# CAMPHOR-DERIVED CHIRAL AUXILIARIES IN ASYMMETRIC SYNTHESIS

THESIS

Submitted in fulfilment of the
requirements for
the degree of
**DOCTOR OF PHILOSOPHY**
of Rhodes University

by

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February 1998

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## ABSTRACT

The investigation has been focussed largely on the chemistry and stereo-directing potential of camphor-derived compounds. The major regioisomer produced on partial hydrolysis of *N*-benzylcamphorimide was identified, by one- and two-dimensional NMR and X-ray crystallography, as (+)-(1*S*,3*R*)-3-(*N*-benzylcarbamoyl)-2,3,3-trimethylcyclopentanecarboxylic acid, the methyl ester of which was shown to undergo an unexpected intramolecular rearrangement during LAH reduction to afford (1*S*,3*R*)-*N*-benzyl-3-hydroxymethyl-2,2,3-trimethylcyclopentane carboxamide.

Several tartrate- and camphor-derived diols have been investigated as chiral auxiliaries in various asymmetric reactions of corresponding acetals of α,β-unsaturated aldehydes. MCPBA epoxidation of the tartrate-derived acetals afforded epoxy acetals in 4-12 % diastereomeric excess. The camphor-derived acetals were obtained solely as the *exo*-substituted diastereomers, the stereochemistry being confirmed by two-dimensional NMR spectroscopy and X-ray crystallography. Simmons-Smith cyclopropanation of these camphor-derived acetals afforded cyclopropyl products with diastereoselectivities of 4% d.e. for the bornane-2,10-diol acetal and 46 - > 99 % d.e. for the bornane-2,3-diol acetals. In order to increase diastereofacial selectivity, a camphor-derived diol having a bulky substituent at C-10 was prepared, *viz.*, phenyl 2,3-dihydroxybornane-10-sulfonate, and α,β-unsaturated acetals of this diol were shown to undergo Simmons-Smith cyclopropanation with complete topological control (> 99% d.e.), the diastereoselectivities being conveniently determined by $^{1}H$ and $^{13}C$ NMR spectroscopy. Computer modelling, with the software package HYPERCHEM®, was used to explore the stereochemical aspects of the Simmons-Smith cyclopropanation, and hydrolysis of one of the cyclopropyl acetals has permitted the diastereoselective bias to be confirmed. (+)-Pinane-2,3-diol was also investigated as a chiral auxiliary in the Simmons-Smith reactions of α,β-unsaturated aldehydes, and moderate diasteroselectivities (20-30 % d.e.) were observed.

In a series of exploratory studies, the Diels-Alder reaction of the 2,3-dihydroxybornane-10-sulfonate acetal of *trans*-cinnamaldehyde with cyclopentadiene afforded a single cycloadduct, while $OsO_4$ dihydroxylation, MCPBA oxidation and alkylation of chiral acetals produced from both bornane-2,3-diol and phenyl 2,3-dihydroxybornane-10-sulfonate were less selective.

# CONTENTS

# ACKNOWLEDGEMENTS

I would like to thank my supervisor, Professor Perry Kaye, for his assistance, guidance and encouragement throughout this project. It has been extremely stimulating and rewarding to work under his supervision and his support has been greatly appreciated.

I would like to thank Mr Aubrey Sonneman for collecting MS data and for his invaluable technical assistance, Mr Andy Soper for assistance with the NMR, Dr Boshoff of the Cape Technikon Mass Spectrometry Unit for collecting high resolution MS data, S. Abboo for HPLC assitance, Professor J. S. Field and Ms N. Ramesar (University of Natal, Pietermaritzburg) for diffraction data collection and Mr J. Bacsa for the X-ray structure solution.

Thank you to Ross Robinson and Jeffry Guthrie-Strachan for proof-reading the manuscript and, together with Melanie Evans and Liezel Sabbagh, for their moral support and advice throughout the years. Thank you to André Daubinet and Paula Antunes for assistance with the computing aspects of this manuscript. I would also like to thank the staff of the Chemistry Department and my colleagues for assistance and moral support throughout my stay at Rhodes.

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

Finally, I would like to thank FRD and Rhodes University for financial support.

# 1. INTRODUCTION

The majority of molecules manufactured for use as medicines or pesticides contain at least one chiral centre and therefore exist in more than one stereoisomeric form. The biological receptors with which these molecules interact may also be chiral and thus provide an asymmetric environment in which these molecules maybe distinguishable. This may result in biological activity being associated with a particular stereoisomer; examples include the antibacterial, chloramphenicol[1] [of which only the (*R*,*R*) diastereomer is active] and the stereoisomers of paclobutrazol[2] [one of which is a fungicide and the other a plant-growth regulator]. Moreover, while one stereoisomer may exhibit beneficial properties the other maybe positively harmful - a situation tragically observed with the use of *racemic* thalidomide. The teratogenic effects of thalidomide[3] have been attributed to one enantiomer, while the other is effective in the treatment of morning sickness. Stereocontrol in synthesis is, therefore, of great importance and constitutes the fundamental challenge in asymmetric synthesis.[4]

In one, widely-used approach a prochiral precursor is converted into a chiral compound by the addition of a chiral group, which is finally removed after the asymmetric synthesis has been carried out. The attached chiral group is responsible for discrimination between the prochiral faces of a functional group allowing for one face to be preferentially attacked; such a chiral group is referred to as a chiral auxiliary. The main requirements of a chiral auxiliary may be summarised as follows:-[5]

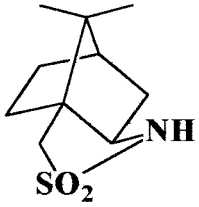
i) it must be readily available in a homochiral form which can be efficiently attached to the prochiral substrate;

ii) it must induce highly stereoselectivity and, preferably, result in crystalline intermediates as this facilitates in separation; and

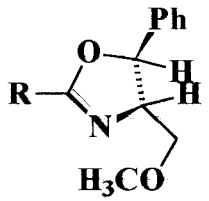
iii) it must be easily removed and recovered in good yield without diminishing its

optical purity or that of the product.

While many chiral auxiliaries are available,[6] such as Oppolzers sultam (**1**) and derivatives of oxazolines (**2**) and menthol (**3**), particular use has been made of chiral acetals in the present study, and the aim of the introduction, which follows, is to highlight the use of such groups as chiral auxiliaries.




(1)

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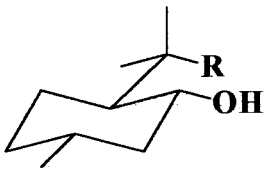
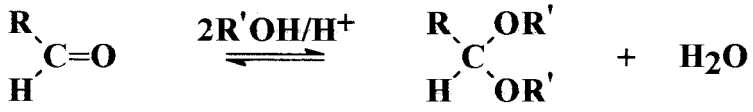



(3)

**FIGURE 1**

## 1.1 APPLICATIONS OF ACETALS AS CHIRAL AUXILIARIES

Protecting groups[7] are often used in the synthesis of target molecules to protect sensitive functional groups. In recent years there has been a move towards the use of protecting groups as chiral auxiliaries, thereby extending their role to include asymmetric induction.

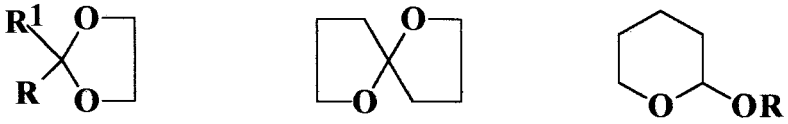



(4) (5)

**SCHEME 1**

Acetals,[8] the most commonly used protecting groups for an aldehyde functionality, are readily formed under mild conditions. Although simple acid-catalysed acetalisation with removal of water (**Scheme 1**) is still widely employed, numerous other methods of forming acetals are available.[9] Acetals maybe acyclic or cyclic and, in the case of the

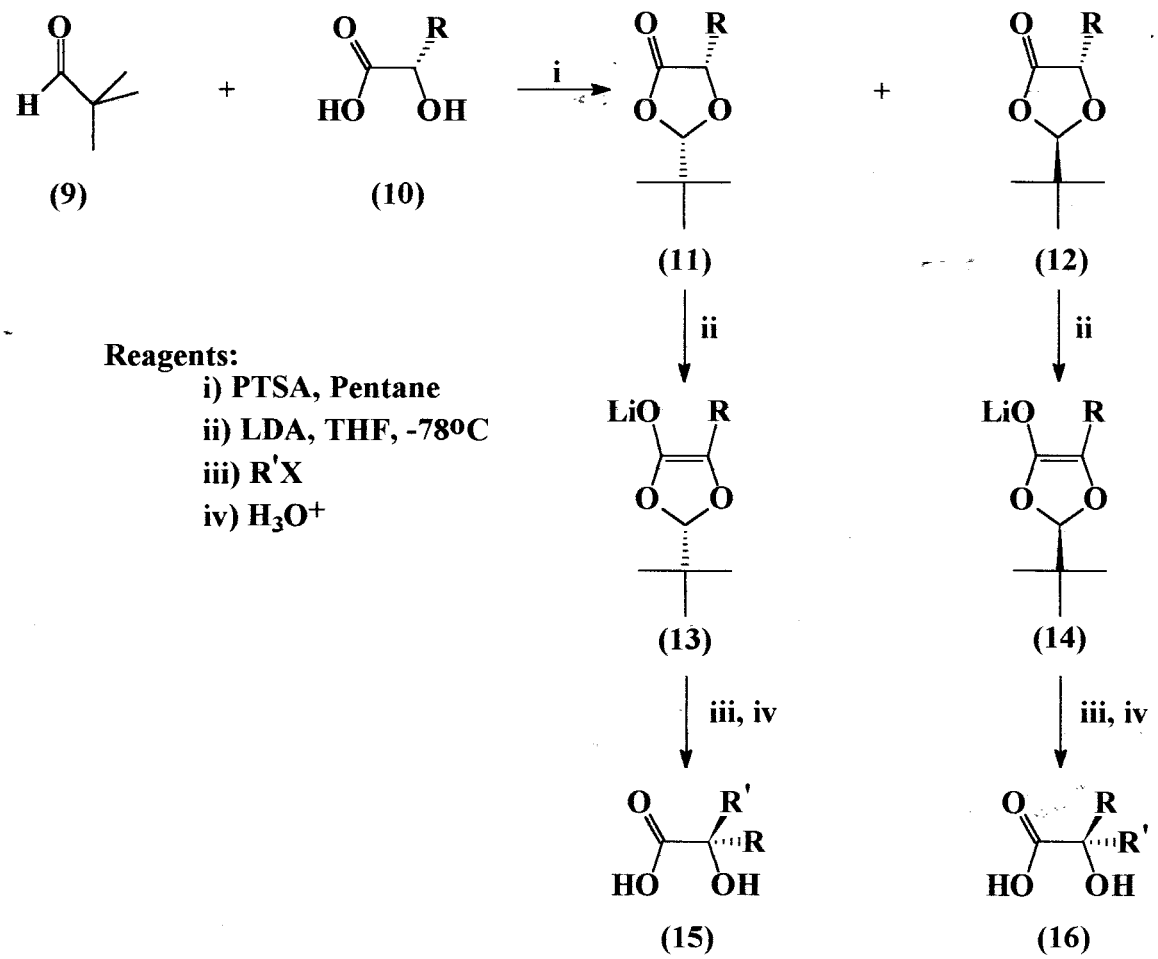
latter, the oxygens may be in the same ring (*e.g.* **6**), in different rings (*e.g.* **7**) or only one oxygen maybe part of the ring system (*e.g.* **8**). In asymmetric synthesis, chiral acetals with both oxygens in the same ring have received most attention with asymmetric induction being achieved either in the heterocyclic ring or at more distant sites.




**(6)** **(7)** **(8)**

**FIGURE 2**

Seebach *et al.*[10, 11] used the 'temporary' chirality of an acetal centre to achieve stereoselective alkylation on the heterocyclic ring. The lactone-acetals formed from pivaldehyde (**9**) and various homochiral α-hydroxy acids (**10**) were deprotonated by a lithium amide (thus converting the original tetrahedral chiral centre to a trigonal centre) and the resulting enolates were reacted with an electrophile. Cleavage of the acetal afforded α-substituted carboxylic acids (**Scheme 2**). Although the *cis*-disubstituted heterocycle (**11**), which yields the α-substituted product (**15**) with retention of configuration at the original chiral centre, is preferentially formed, some of the *trans*-disubstituted analogue (**12**) is also obtained, accounting for the formation of product (**16**). However, after isolating the major acetal (**11**), in each case Seebach *et al.* were able to achieve alkylation of the heterocyclic enolates in greater than 90 % diastereomeric excess (% d.e.). Asymmetric induction in these reactions arises from the fact that attack by the electrophile occurs on the enolate face opposite to the bulky *tert*-butyl group.



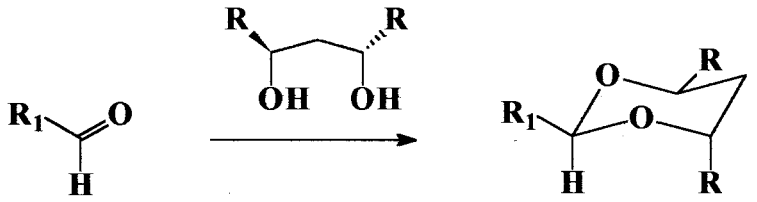

**SCHEME 2**

The need to separate the diastereomeric acetals in such applications can be avoided by using diols having a $C_2$ axis of symmetry,[12] as only a single acetal would be formed. During the past 20 years, a large number of studies have demonstrated the usefulness of $C_2$ chiral acetals as chiral auxiliaries in asymmetric synthesis.

### 1.1.1 Chiral Acetals of diols possessing $C_2$ symmetry

Asymmetric induction at prochiral trigonal systems (C=C, C=O and C=N) accounts for the majority of stereoselective reactions and, since reactions at prochiral tetrahedral centres are relatively rare, this makes the prochiral acetal carbon an attractive centre for

asymmetric synthesis.[13] The prochiral *si*- and *re*-faces of the carbonyl group in a simple aldehyde (**17**), which has no other stereogenic centres, are enantiofacial. However, the formation of cyclic acetals, prepared from diols having a $C_2$ axis of symmetry, renders the acetal carbon chiral, thus permitting asymmetric induction in the aldehyde moiety. In the case of acetal (**18**), one ring substituent is in an equatorial position and the other in an axial position, thus differentiating the two "sides" of the aldehyde moeity. Cyclic acetals may undergo attack at the acetal carbon, leading to cleavage of the heterocyclic ring, or they may control stereoselectivity at the α- and/or β-carbon.

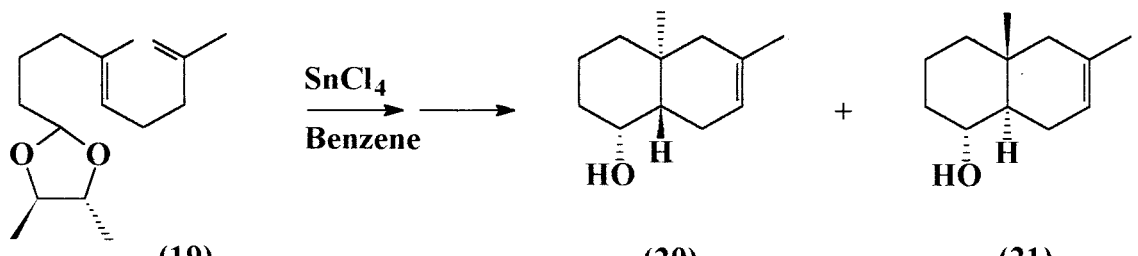



(17) (18)

SCHEME 3

### 1.1.2 Cleavage of Acetals

It was the biomimetic polyolefin cyclization studies of Johnson *et al.*[14, 15] that sparked interest in the use of diols with $C_2$ symmetry as auxiliaries. These authors investigated the tin(IV)chloride catalyzed cyclization of a chiral dienic acetal (**19**), derived from (2*R*,3*R*)-butanediol and a dienal (**Scheme 4**). The octalin alcohols (**20**) and (**21**) were obtained as the major products in high yield and in 83-84 % d.e..



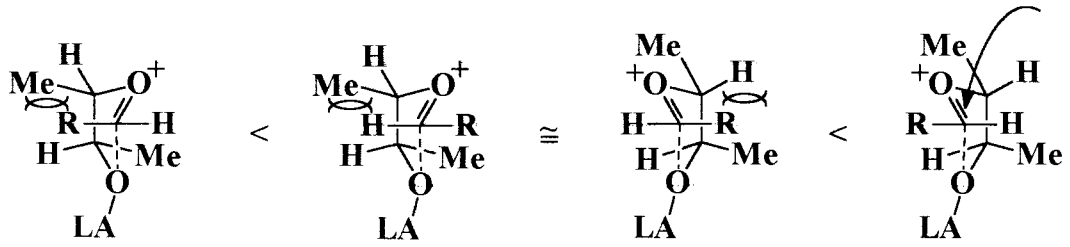

(19) (20) (21)

SCHEME 4

In this case, the observed asymmetric induction has been rationalized in terms of diastereoselective acetal cleavage.

### 1.1.2.1 Mechanism of acetal cleavage

Basically, the above cyclization is a C-C bond-forming reaction, which involves the unidirectional Lewis acid-catalysed ring opening of the acetal to afford an electrophile, and the double bond acting as the nucleophile. The unidirectional opening of the acetal, *via* a Lewis acid complex, is responsible for the observed stereoselection and was rationalized by Johnson *et al.*[15] on steric grounds. Johnson proposed that, in the transition state, the acetal is only partially cleaved and that attack by the double bond electrons occurs in an $S_N2$ manner (*i.e. anti* to the departing oxygen) at the *pseudo*-oxocarbenium ion in one of four possible diastereomeric transition state complexes (**22**)-(**25**) (**Figure 3**). Of these, structure (**25**) is the least sterically hindered and therefore the most favoured, resulting in departure of the *pro-R* oxygen and formation of the experimentally observed *R*-configuration at the acetal carbon. The presence of an oxocarbenium ion intermediate in the asymmetric cleavage of chiral acetals has been proven by Sammakia *et al.*[16] using stereospecifically deuterated acetals.

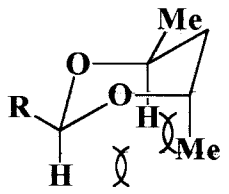



(22) (23) (24) (25)

**FIGURE 3**

The mechanism is not only valid for five-membered dioxolane rings but is also applicable to six-membered dioxane rings (**18**).[17] The dioxane ring favours a chair

conformation in which the 1,3-diaxial interactions are minimised; for example, acetals of 2,4-pentanediol favour conformation (**26**) over conformation (**27**) (**Figure 4**), and coordination of the Lewis acid will occur at the oxygen which best relieves the axial strain. Coordination of the Lewis acid at O(1) results in elongation of the C(2)-O(1) bond (**28**), relieving some of the strain between the acetal hydrogen and the axial 6-methyl group, while coordination at O(3) would shorten the C(2)-O(1) bond (**29**) thus increasing the 1,3-diaxial interaction. Consequently, coordination at O(1) should be favoured, resulting in preferential *anti*-attack by nucleophiles at the acetal carbon.

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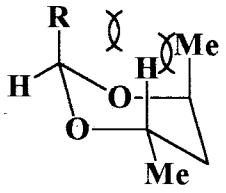


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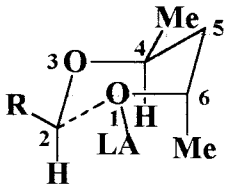


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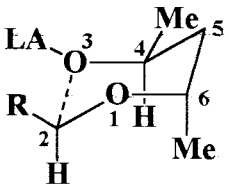


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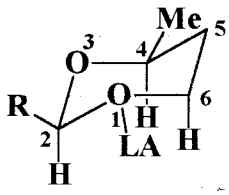
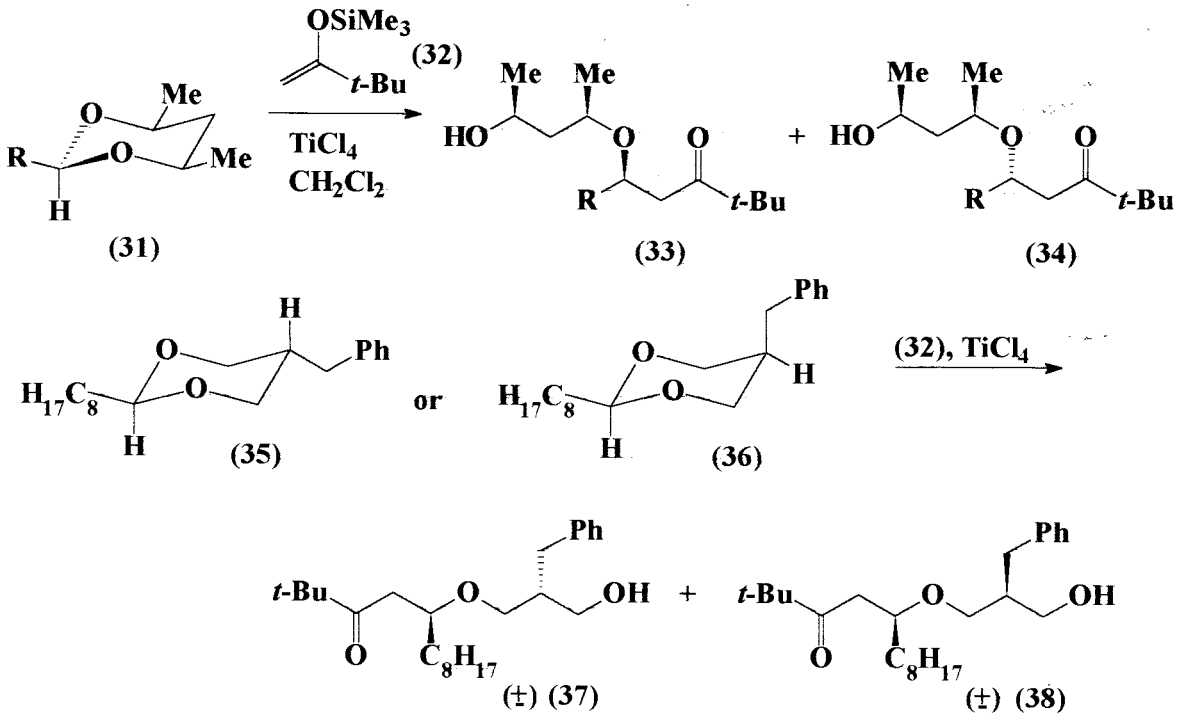



(30)

**FIGURE 4**

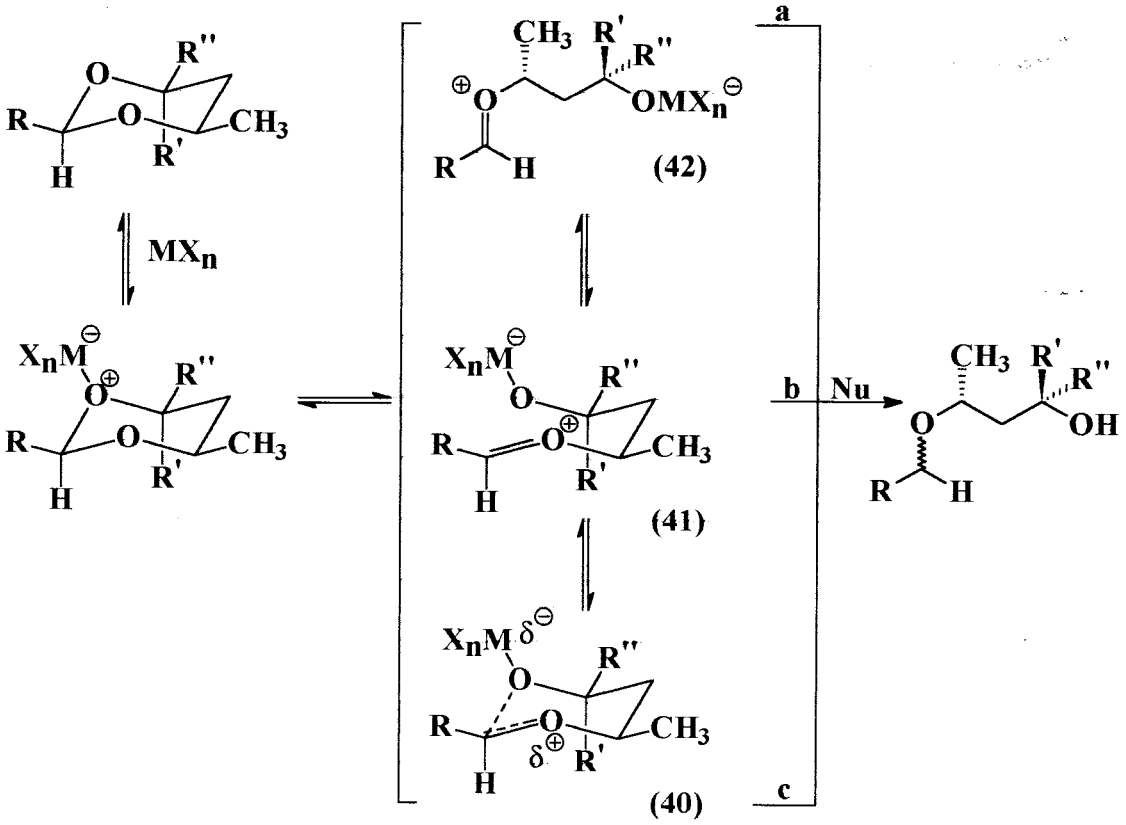
Recent NMR investigations by Denmark *et al.*[18] not only support Johnson's assumptions but also explain the mechanism of cleavage for 1,3-butanediol-derived dioxanes, such as (**30**). The assumption that the oxygen atom, to which the Lewis acid coordinates, rehybridizes to $sp^2$ making it planar or slightly pyramidal would explain why the cleavage occurs at the less hindered O(1)-C(2) bond as the Lewis acid coordinated at O(3) would be more sterically hindered by an equatorial substituent than by an axial substituent.

However, cleavage of the *meso*-2,4,6-trisubstituted dioxanes (**31**) and 2,5-disubstituted dioxane acetals (**35**) and (**36**), studied by Yamamoto *et al.*,[19] cannot be rationalized by the postulated $S_N2$ mechanism discussed above. The *meso*-acetal (**31**) should, if the $S_N2$ mechanism were operating, produce a 1:1 mixture of the diastereomers since the acetal oxygens are enantiotopic; in the event, a mixture of diastereomeric products (**33**) and (**34**) were obtained when the acetal was cleaved with the enol silane (**32**) and $TiCl_4$. Furthemore, $S_N2$ cleavage of either the *cis*- or *trans*-2,5-disubstituted acetals (**35**) and (**36**) should yield the (*R*,*S*) and (*S*,*R*) diastereomers of (**37**) and the (*R*,*R*) and (*S*,*S*) diastereomers of (**38**) respectively; however it was found that the acetals were completely unselective and each gave a 1:1 mixture of the diastereomers (**37**) and (**38**) (**Scheme 5**).




**SCHEME 5**

Yamamoto *et al.*[19] therefore proposed that the Lewis acid-mediated nucleophilic substitution of the acetals proceeds completely, or largely, by an $S_N1$ mechanism *via* rapidly equilibrating oxocarbenium ion pairs, and attributed the high stereoselectivity of the chiral acetals (**26**) to oxocarbenium ion pairs that maintain some of the structural features of an intact 6-membered ring. Denmark *et al.*,[20, 21] on the other hand, proposed a mechanistic scheme which involves three distinct ion pairs (**Scheme 6**), *viz.*, an intimate ion pair (**40**), an "external" ion pair (**41**) and a "separated" ion pair (**42**), to account for the stereoselectivity of acetal cleavage. Although, the structures of the Lewis acid-acetal complexes (**28**), (**29**) and (**30**) have been unambiguosly established by NMR,[18] Denmark *et al.* have proposed that these complexes are not, in fact, the reactive intermediates but are in equilibrium with the true reactive species, *viz.*, the ion pairs (**40-42**).

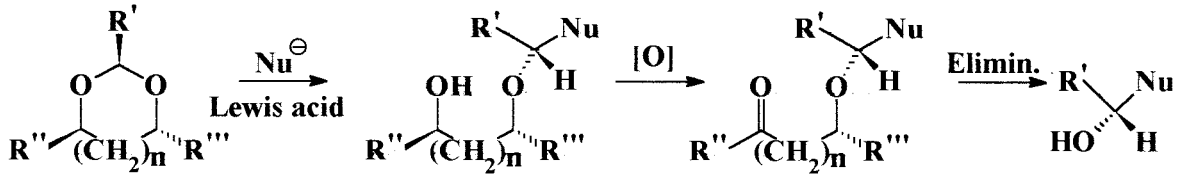



**SCHEME 6**

Structural and enviromental factors determine which ion pair is most stable under the conditions employed and, hence, the preferred pathway. The intimate ion pair (**40**) undergoes highly selective reactions (path c) by $S_N2$ mechanism, and this species is implicated in the reactions of sterically unhindered, aliphatic acetals with weak Lewis acids. Only modest selectivities are observed in reactions of the "external" ion pair species (**41**) as access to the acetal centre is less controlled (path b). Sterically demanding or cation-stabilizing substituents or strong Lewis acids lead to the "external" ion pair being the favoured species. The "separate" ion pair (**42**) reacts without any selectivity as the oxocarbenium is far removed from the influence of the stereogenic centre of the acetal (path a).

In summary, the outcome and mechanism of Lewis acid-catalyzed acetal cleavage is substantially changed by the structure of the acetal involved, but it is generally thought that the more selective chiral acetal cleavages proceed predominantly *via* a direct displacement ($S_N2$-like) mechanism, while the less selective reactions occur *via* an oxocarbenium ion ($S_N1$-like) mechanism.[22]

A wide variety of nucleophiles have been employed in the attack on the acetal carbon with high diastereoselectivity to give the major adducts (**44**) and (**48**) in high yield (**Scheme 7**). Removal of the chiral auxiliary *via* intermediate (**45**) and (**49**) ketones affords the secondary hydroxy compounds (**46**) in high yield and, generally, in




n=0 (43) (44) (45) (46)
n=1 (47) (48) (49)

**SCHEME 7**

enantiomeric excess (e.e.) of 90 % or more. The removal of the chiral auxiliary of α-alkoxy-carbonyl compounds (**45**) was found to be problematic and, although the α-elimination was achieved with sodium in ether,[23] this method is not convenient in the presence of other sensitive functionalities. 2,3-Pentanediol-derived acetals (**49**), however, were found to undergo high-yielding β-elimination of the β-alkoxycarbonyl compounds, usually with weak bases or acids under mild conditions.

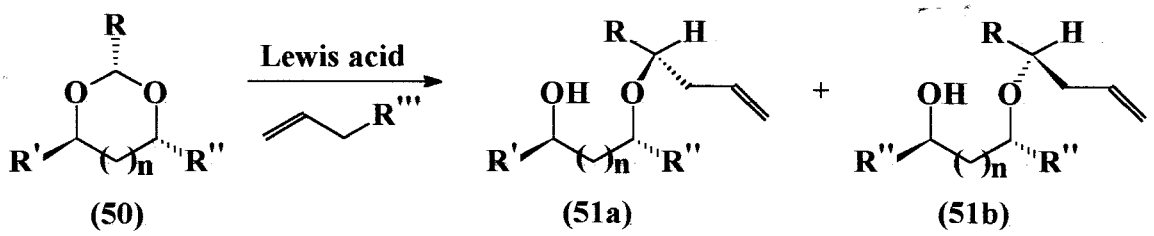
The cleavage of the chiral acetal is an immolative enantioselective synthesis of chiral secondary alcohols as the chiral auxiliary diol is destroyed by removal using the oxidation-elimination sequence. The most utilised auxiliary diols in the cleavage reactions are 2,3-butanediol and 2,4-pentanediol which are readily available and their cost may be overruled by the value of the target secondary alcohols (**46**). Various nucleophiles have been used in the stereoselective ring opening of chiral acetals, and the following sections provide an overview of the relevant literature.

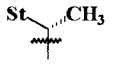
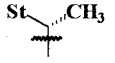
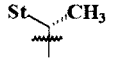
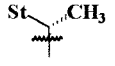
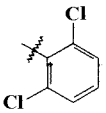
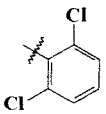
### 1.1.2.2 Diastereoselective allylation and acetylenations

Allylsilanes and silylacetylenes react with acetals in the presence of a Lewis acid to form homoallyl ethers and propargylic ethers respectively. These products are attractive synthetic precursors as they possess an unsaturated bond which can undergo further elaboration. The first example of a diastereoselective allylation was reported by Kishi *et al.*[24] (*cf.* **Table 1**; entry 1). Modifications of the procedure [25] by using 6-membered cyclic acetals and mixed Lewis acid catalysts, *viz.*, $TiCl_4$ and $Ti(OiPr)_4$, was found to improve the diastereoselectivity of the reaction (entries 2 and 3), and was used by Johnson *et al.* to produce (-)-dihydromyoporone[25] and an intermediate in the synthesis of calcitriol lactone.[26] The milder Lewis acids are thought to sufficiently enhance the synchrony between bond forming and bond breaking in the transition state. The

nucleophilicity of the allylating agent also has a marked effect on the diastereoselectivity of the reaction.[27]

**Table 1**: Data for the diastereoselective allylations of various acetals.




| Entry | n | R | R' | R'' | R''' | Lewis acid | Yield/ % | Product 51a:51b |
|---|---|---|---|---|---|---|---|---|
| 1[a] | 0 | Ph | $CH_3$ | $CH_3$ | TMS | $SnCl_4$ | - | 5:1 |
| 2[b] | 1 | n-octyl | $CH_3$ | $CH_3$ | TMS | $TiCl_4$ | 98 | 7:1 |
| 3[b] | 1 | n-octyl | $CH_3$ | $CH_3$ | TMS | $TiCl_2(OiPr)_2$ | 98 | 49:1 |
| 4[c] | 1 |  | $CH_3$ | $CH_3$ | $SnBu_3$ | $TiCl_4$ | 85 | 24:1 |
| 5[c] | 1 |  | (*S*)-$CH_3$ | (*S*)-$CH_3$ | $SnBu_3$ | $TiCl_4$ | 84 | 3:7 |
| 6[c] | 1 |  | $CH_3$ | $CH_3$ | TMS | $TiCl_4$ | 93 | 99:1 |
| 7[c] | 1 |  | (*S*)-$CH_3$ | (*S*)-$CH_3$ | TMS | $TiCl_4$ | 93 | 9:1 |
| 8[d] | 1 | cyclo-hexyl |  | H | TMS | $TiCl_4$ | 98 | 53:1 |
| 9[d] | 1 | Ph |  | H | TMS | $TiCl_4$ | 56 | 6:1 |

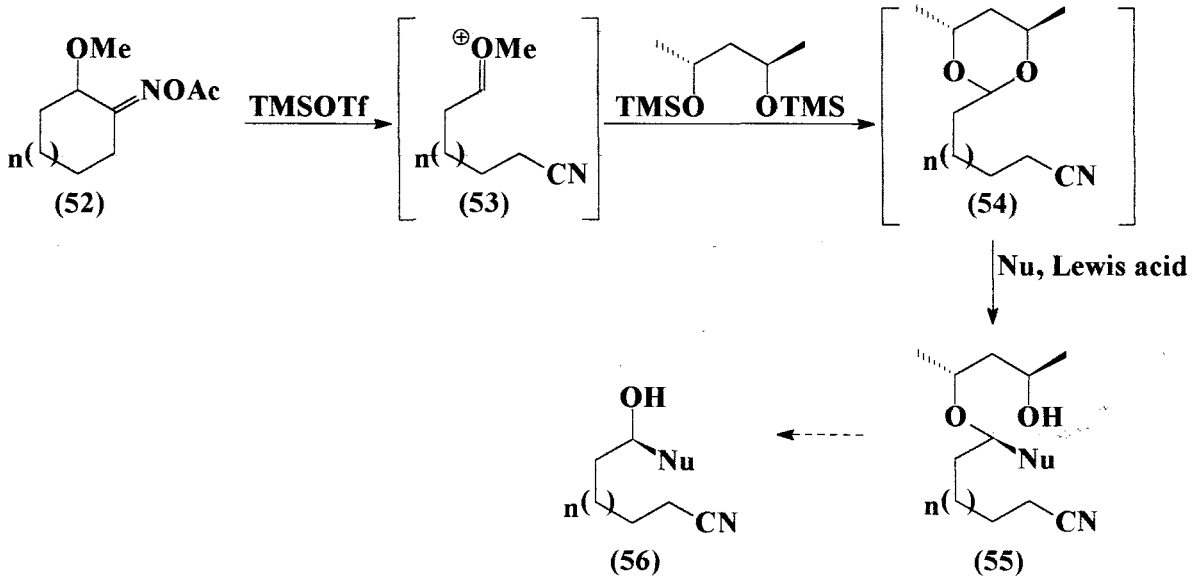
[a] Ref. 24. [b] Ref. 25. [c] Ref. 27 and St is a steroidal moiety derived from pregnenolone. [d] Ref. 28.

When a highly nucleophilic allylating agent is used (entries 4 and 5), nucleophilic attack and ring opening are presumed to be synchronous, and the major homoallylic ether will be the one in keeping with the mechanistic rationalisation of Johnson discussed in section 1.1.2.1. On the other hand, nucleophilic attack by an allylating agent with low nucleophilicity (entries 6 and 7) is thought to occur *after* ring opening and chiral induction is then dictated primarily by the Cram's rule rather than the stereochemistry of the template. Andrus *et al.*[28] made use of 4-(2,6-dichlorophenyl)-1,3-dioxanes (entries 8 and 9) to obtain the allyl ethers; removal of the chiral auxiliary in one step using lithium-ammonia avoids the two step oxidation-elimination sequence (**Scheme 7**) and affords the secondary alcohols (**46**) directly. The low selectivity of the benzaldehyde derived acetal (entry 9) has been proposed to be as a result of an increase in production of the minor *anti*-isomer *via* an oxocarbenium ion ($S_N1$ mechanism) which is stabilised by the phenyl group.

Kellogg *et al.*[29] made use of homochiral mandelic acid to prepare *cis*, *trans* mixtures of 1,3-dioxolan-4-ones, from which the major isomer had to be isolated before reaction with an allylic silane. The yields and diastereoselectivities were, however, lower than those observed using the $C_2$ chiral auxiliaries. Homochiral 1,3-dioxan-4-ones derived from (*R*)-3-hydroxybutanoic acid were studied by Seebach *et al.*[30] and found to undergo highly diastereoselective allylations with milder Lewis acids. Making use of a propargylic silane, Johnson *et al.*[31, 32] were able to synthesise an intermediate for the preparation of vitamin $D_3$ and carry out polyene tetra- and penta-cyclizations using an intramolecular version of the diastereoselective allylation.

Fujioka *et al.*[33] treated racemic α-methoxycycloalkanone oxime acetate (**52**) with (2*R*,4*R*)-2,4-bismethylsiloxypentane in the presence of a catalytic amount of trimethylsilyl triflate to afford the chiral acetal (**54**), *via* the Beckmann fragmentation

intermediate (**53**) (**Scheme 8**). Reaction of chiral acetal (**54**) with silicon-containing nucleophiles under the action of Lewis acids such as $TiCl_4$ and $Ti(OiPr)_4$, affords the ω-cyano compounds (**55**) in both high d.e.'s (68->95 %) and chemical yields. Acetal (**54**) was not isolated and therefore the reaction has the advantage of being a one-pot synthesis. The chiral acetal was removed by the oxidation/β-elimination process to afford the ω-cyano alcohols (**56**).




**SCHEME 8**

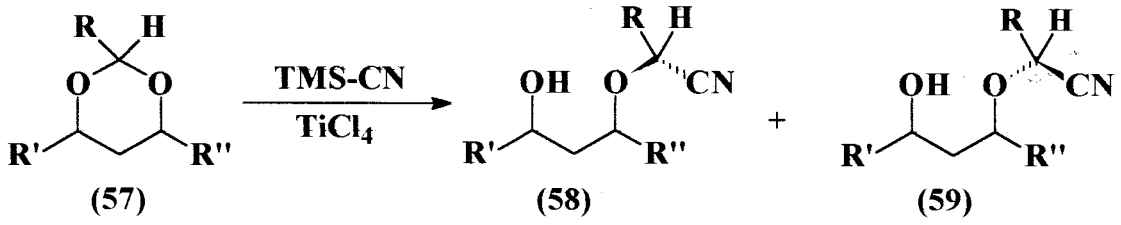
Johnson *et al.*[34] also showed that 2,4-pentanediol acetals undergo coupling with silylacetylenes to produce propargylic ethers with higher diastereoselectivity than the corresponding allylation reaction. The propargylic ethers have been used for the direct synthesis of chiral allenes[35] and as a source of secondary propargylic alcohols, the synthetic utility of which was highlighted by the preparation of the neurotransmitter inhibitor γ-aminobutyric acid (GABA).[36] The use of (*R*)-3-hydroxybutanoic acid acetals in the acetylenations has been reported[30] and the nucleophilicity of the acetylenic agent was shown to have the same effects on diastereoselectivity as the allylating agent in

allylation.[27]

### 1.1.2.3 Diastereoselective cyanations

The enantioselective preparation of cyanohydrins, α-hydroxy esters and β-amino alcohols, with optical purities of greater than 90 %, is readily achieved *via* the cyanohydrin ethers (**58**) and (**59**), which are obtained in excellent yield and diastereoselectivity through the coupling of 2,4-pentanediol acetals (**57**) and cyanotrimethylsilane (*cf.* **Table 2**; entries 1 and 2).[37] The cyanohydrin, obtained after elimination of the chiral auxiliary from the major cyanohydrin ether (entry 3), has

**Table 2**: Data for the diastereoselective cyanations.




(57) (58) (59)

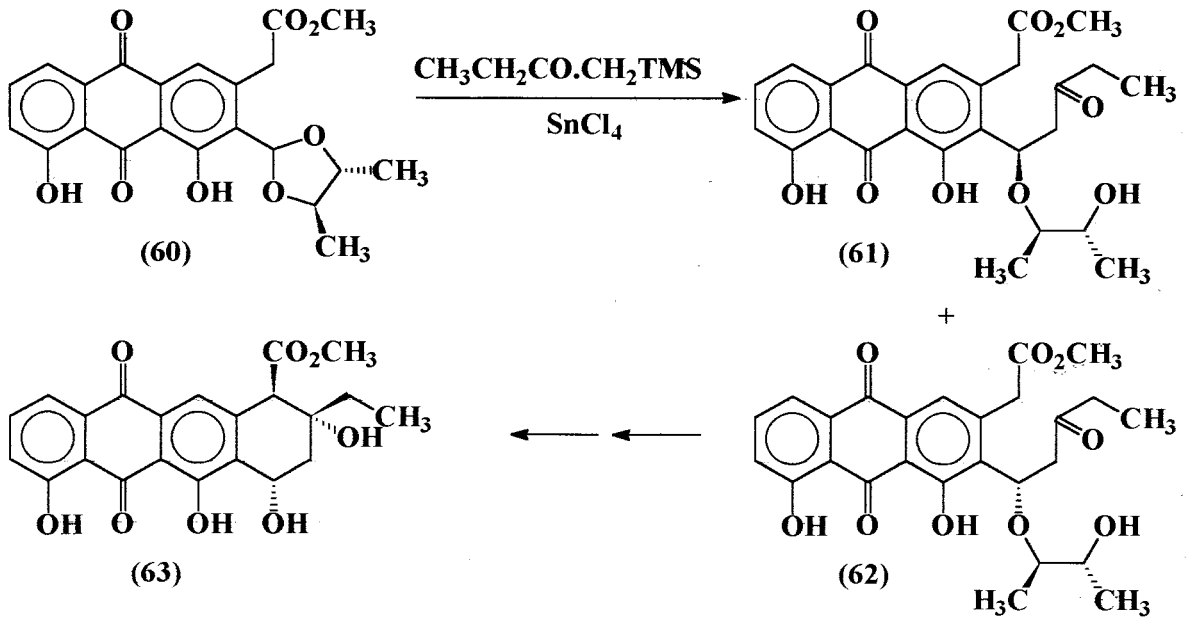
| Entry | R | R' | R'' | Yield/ % | Prod. ratio 58:59 | Ref |
|---|---|---|---|---|---|---|
| 1 | n-Undecyl | (*R*)-$CH_3$ | (*R*)-$CH_3$ | 98 | 19:1 | 37 |
| 2 | n-Octyl | (*R*)-$CH_3$ | (*R*)-$CH_3$ | 100 | 24:1 | 37 |
| 3 | *m*-(Ph)$C_6H_4$ | (*S*)-$CH_3$ | (*S*)-$CH_3$ | 100 | 1:39 | 38 |
| 4 | *m*-(Ph)$C_6H_4$ | (*S*)-$CH_3$ | H | 92 | 1:15 | 38 |
| 5 | Me | (*R*)-$CH_3$ | =O | 65 | 65:1 | 30 |
| 6 | $CH_2CH_2Ph$ | (*R*)-$CH_3$ | =O | 99 | 49:1 | 30 |
| 7 | Ph | (S)-$CH_2OCH_3$ | H | - | 1.6:1 | 39 |

been used as an intermediate in the synthesis of the insecticide, deltamethrin,[38] while Seebach has demonstrated diastereoselective cyanation of homochiral 1,3-dioxan-4-ones derived from (*R*)-3-hydroxybutanoic acid (entries 5 and 6).[30] The use of 1,3-butanediol acetals (entry 4) is interesting in that regioselectivity depends on the rate of addition of reagents and the reaction temperature. Corcoran[39] obtained poor diastereoselectivity in the cyanation on 2-substituted-3-methoxymethyl-1,3-dioxanes (entry 7), but observed that the regioselectivity of cleavage depends on the Lewis acid employed; thus, both enantiomers of the secondary alcohol (**46**) (**Scheme 7**) are available from the same chiral acetal template. Fukuzawa *et al.*[40] prepared chiral acetals, in high yields, from various aldehydes and chiral diols catalysed by scandium(III)triflate [$Sc(OTf)_3$] and successive addition of trimethylsilyl cyanide, without isolation of the acetals, produced the cyanohydrin ethers (**58**) and (**59**) in very high yields and d.e.'s of up to 90 %. The stereochemical outcome of the reaction is in agreement with that of Johnson *et al.*,[37] but the use of $Sc(OTf)_3$, over $TiCl_4$, has the advantage of milder reaction conditions and it is a sequential one-pot synthesis. Solladie-Cavallo *et al.*[41] prepared β-adrenergic blocking agents using $TiCl_4$ induced nucleophilic addition of cyanotrimethylsilane to chiral acetals.

### 1.1.2.4 Diastereoselective crossed aldol condensations

It was the synthesis of optically active aklavinone (**63**), with the aid of an α-silyl carbonyl compound, which first highlighted the asymmetric crossed aldol reaction of chiral acetals. In the synthesis (**Scheme 9**), Kishi *et al.*,[24] treated the (2*R*,3*R*)-2,3-butanediol acetal (**60**) with ethyl trimethylsilylmethyl ketone and tin tetrachloride to obtain a 10:1 mixture of the crossed aldol products (**61**) and (**62**), the configuration of the major diastereoisomer (**62**) being established by conversion to aklavinone (**63**). Kishi *et al.*[42] made use of the same procedure to prepare 11-deoxydaunomycinone and

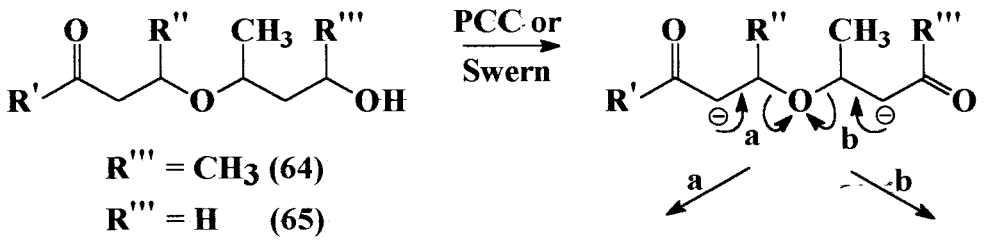
related compounds, and reported that the diastereoselectivity achieved with aromatic acetals is much higher than with simple alphatic acetals. However, Johnson *et al.*,[43] once again using 2,4-pentanediol-derived acetals, carried out Lewis acid-catalyzed crossed aldol reactions on aliphatic systems and obtained diastereoselectivities in excess of 90 % d.e.. Making use of silyl enol ethers and silyl ketene acetals as the nucleophiles, Johnson *et al.* were able to develop procedures for the preparation of a nonactic acid intermediate[44] and (*R*)-(+)-α-lipoic acid.[45]




**SCHEME 9**

Although 2,4-pentanediol-derived acetals may be cleaved with high diastereoselectivity, the subsequent removal of the auxiliary from acyclic intermediates (**64**) is problematic as two carbonyl groups are present after the oxidation, and β-elimination can occur *via* two paths (a and b; **Scheme 10**) with concomitant destruction of the aldol. Although destruction of the aldol (*via* path a) can be avoided when R' is a bulky substituent (*e.g.* *tert*-butyl), the use of 1,3-butanediol acetals (**65**) has proven to be the solution as they form aldehydes on oxidation, which undergo selective β-elimination *via* path b with

dibenzylammonium trifluoroacetate.[45]




$R''' = CH_3$ (64)

$R''' = H$ (65)

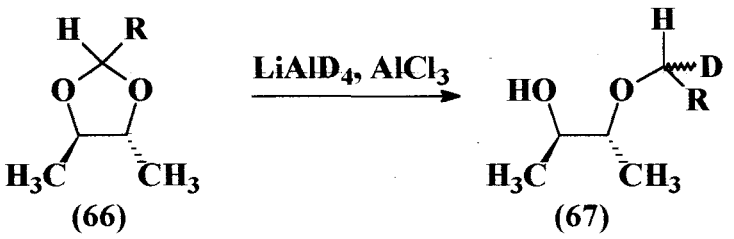
**SCHEME 10**

1,3-Butanediol acetals have been used successfully in the synthesis of mavinolin analogues.[46] Basile *et al.*[47] have used a Reformatsky reagent as the nucleophile to obtain aldol products, the best diastereoselectivities being obtained with 2,4-pentanediol as the chiral auxiliary, while Kellogg[29] has reported aldol reactions of 1,3-dioxolan-4-ones prepared from homochiral mandelic acid.

### 1.1.2.5 Diastereoselective reductions

Metal hydrides, with a Lewis acid character, are able to cleave and reduce acetals as was demonstrated by Richter[48] who made use of "mixed hydride reagents" to reduce chiral acetals. Although the stereochemistry of the products was not established, the diastereoselectivity of the process was determined by $^{1}H$ and $^{2}H$ NMR spectroscopy (**Table 3**).

**Table 3**: Data for the diastereoselective reductive cleavage.




(66) (67)

| Entry | R | Diastereoisomer ratio |
|---|---|---|
| 1 | Me | 49:1 |
| 2 | Et | 99:1 |
| 3 | $CH_2Ph$ | 10:1 |
| 4 | Cyclohexyl | 9:1 |

### 1.1.2.6 Diastereoselective alkylations with organometallic reagents

The use of organocopper reagents in the Lewis acid-catalysed cleavage of chiral acetals, with subsequent alkylation of the acetal carbon, was first achieved by Alexakis *et al.*.[49] These authors, making use of organocopper reagents, found that the selectivity is more dependent on the nature of the Lewis acid than on the type of organometallic reagent (Entries 1-3). The diastereoselectivity was generally found to be greater for dioxanes

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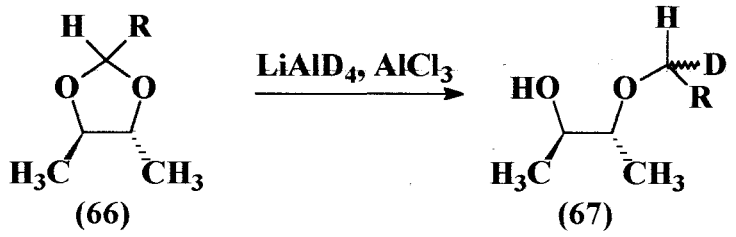


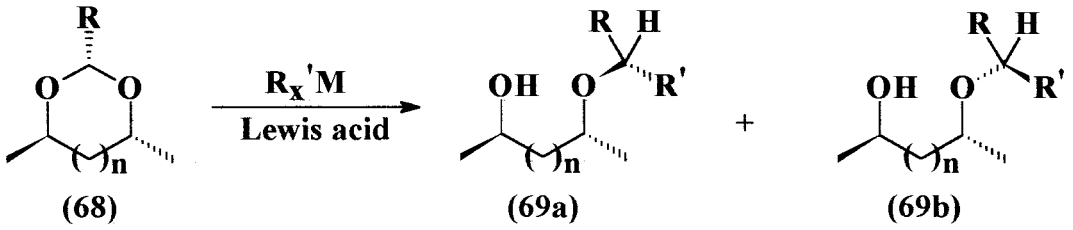

| Entry | R | Diastereoisomer ratio |
|---|---|---|
| 1 | Me | 49:1 |
| 2 | Et | 99:1 |
| 3 | $CH_2Ph$ | 10:1 |
| 4 | Cyclohexyl | 9:1 |

### 1.1.2.6 Diastereoselective alkylations with organometallic reagents

The use of organocopper reagents in the Lewis acid-catalysed cleavage of chiral acetals, with subsequent alkylation of the acetal carbon, was first achieved by Alexakis *et al.*.[49] These authors, making use of organocopper reagents, found that the selectivity is more dependent on the nature of the Lewis acid than on the type of organometallic reagent (Entries 1-3). The diastereoselectivity was generally found to be greater for dioxanes

than for either dioxolanes or dioxepines. However, aliphatic dioxolanes were found to yield a single diastereomer, the configuration of which indicated that the reagent approaches from the *si*-face and in accordance with Johnson's mechanistic proposal.[15]

**Table 4**: Data for the diastereoselective alkylation using organometallic reagents.




(68) (69a) (69b)

| Entry | n | R | R' | $R_X'M$, Lewis acid | Yield/ % | Product ratio 69a:69b | Ref. |
|---|---|---|---|---|---|---|---|
| 1 | 0 | Ph | Me | $Me_2CuLi,BF_3$ | 95 | 5:1 | 49 |
| 2 | 0 | Ph | Me | $MeCu,BF_3$ | 50 | 6:1 | 49 |
| 3 | 0 | Ph | Me | $Me_2CuLi,TiCl_4$ | 48 | 16:1 | 49 |
| 4 | 1 | Ph | Me | $Me_2CuLi,BF_3$ | 93 | 21:1 | 49 |
| 5 | 1 | Hexyl | Me | $Me_2CuLi,BF_3$ | 94 | 100:0 | 49 |
| 6 | 1 | Hexyl | Pr | $Pr_3Al$ | 99 | 1:99 | 53 |
| 7 | 1 | Hexyl | Me | $Me_2AlOC_6F_5$ | 70 | 1:99 | 54 |

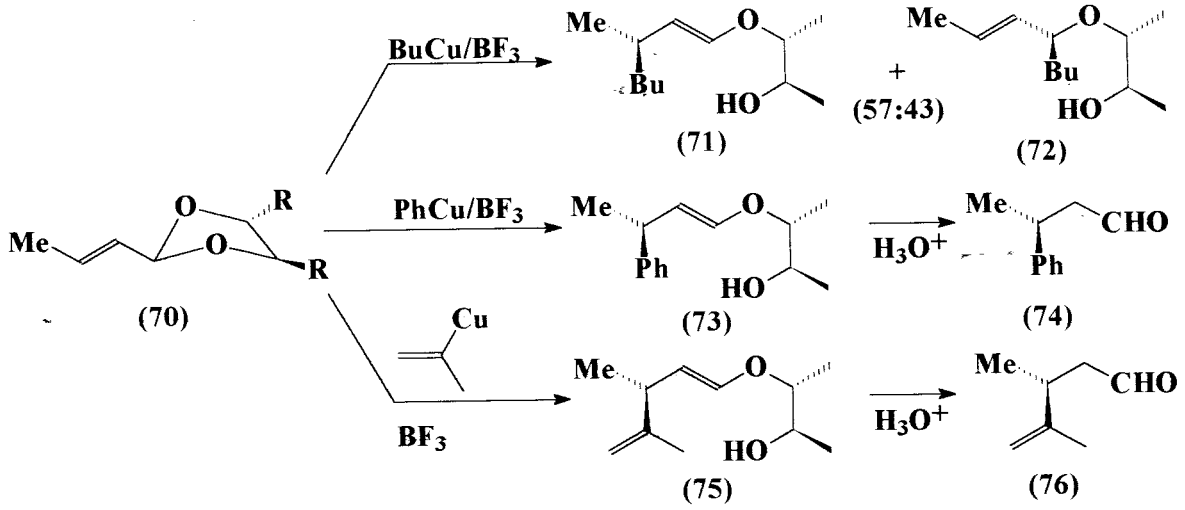
Dioxane acetals of 1,3-butanediol are only cleaved on the non substituted side of the molecule by organometallic reagents, but with low diastereoselectivity. Schreiber *et al.*[50] have reported high diastereoselectivities for the addition of organocopper reagents to homochiral 1,3-dioxan-4-ones derived from (*R*)-3-hydroxybutanoic acid and various aldehydes. Johnson *et al.*[51] have made use of $TiCl_4$ and various organometallic reagents (RLi, RMgX or $R_2CuMgX$) to achieve diastereoselective alkylations, while Yamamoto *et al.*[52] used preformed alkyltitanium halides. Trimethyl- and triethyl-aluminum were

found to be nonselective in reactions with chiral acetals, but higher trialkylaluminum reagents effect alkyl transfers, *via re*-face delivery of the alkyl group, in greater than 95 % selectivity in most cases (entry6).[53] Attack by the alkyl group *syn* to the departing acetal oxygen, has been accounted for by formation of a tight ion-pair between the organoaluminum complex and the oxocarbenium ion. The stereoselective transfer of methyl and ethyl groups has been achieved by a combination of trialkylaluminum reagents and halophenols, such as pentafluorophenol (entry 7), which are thought to increase the nucleophilicity of the reagent by coordination with the aluminum atom. This approach was used in the preparation of (+)-8-hydroxypalmitic acid.[54]

### 1.1.2.7 Reactions of Unsaturated Acetals

(i) α,β-Unsaturated acetals

Cleavage of the α,β-unsaturated acetal (**70**), derived from crotonaldehyde and 2,3-butanediol, with an alkyl copper reagent is not regioselective as nucleophilic attack occurs directly at the acetal carbon (1,2-attack) *via* an $S_N2$ mechanism and at the γ-position (1,4-attack) *via* a $S_N'$ mechanism.[55] However, the products (**71**) and (**72**) were usually obtained with high stereoselectivity (77 % and 63 % d.e. respectively). With aryl[56] and alkenyl [57] copper reagents, however, the reactions were completely regioselective (1,4-attack) and highly stereoselective (**Scheme 11**). The enol ethers (**73**) and (**75**) are readily hydrolysed under acidic conditions to yield the β-substituted aldehydes (**74**) and (**76**), with recovery of the chiral auxiliary. While the size of the acetal ring and the steric bulk of the ring substituents have little effect on the diastereoselectivity of these reactions, other structural features are clearly important.



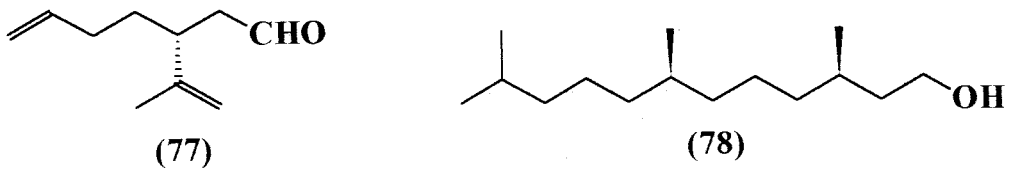

**SCHEME 11**

Thus:-

i) substituents which contain heteroatoms coordinate with the copper reagent leading to stereochemistry reversal; and

ii) the stereochemistry of the double bond is important as the (*E*)- and (*Z*)-aldehydes give final products with opposite absolute configurations.

The presence of a good copper ligand, such as $PBu_3$, significantly increases diastereoselectivity and this approach was successfully used in a synthetic approach to obtain the aldehyde (**77**), a precursor of a pheromone of the California Red scale.[58]

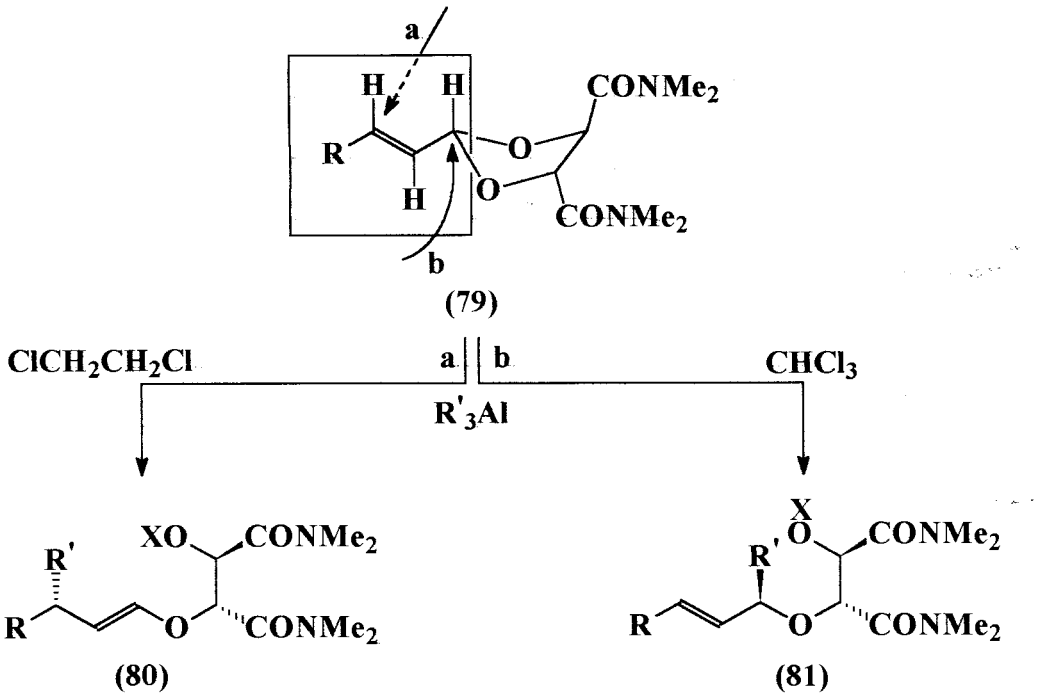


(77) (78)

**FIGURE 5**

Yamamoto *et al.*[58, 59] have used organoaluminum reagents on the acetal (**74**) [derived from citronellal and (*R*,*R*)-(+)-*N*,*N*,*N*',*N*'-tetramethyltartaric acid diamide] to synthesize

the branched alcohol (**78**), which is present in vitamins E and K. These authors found that α,β-unsaturated acetals derived from 2,4-pentanediol resulted in the exclusive formation of the 1,2-adduct, with no diastereoselectivity, when reacted with organoaluminum reagents.[60] However, reactions of acetals derived from (*R,R*)-(+)-*N,N,N',N'*-tetramethyltartaric acid diamide were found to be both more diastereoselective and more regioselective (**Scheme 12**). The regioselectivity is highly dependent on the solvent used; less polar solvents (*e.g.* 1,2-dichloroethane) give the 1,4-adduct (**80**) as the major product (path a), while more polar solvents (*e.g.* chloroform) afford only the 1,2-adduct (**81**) (path b).



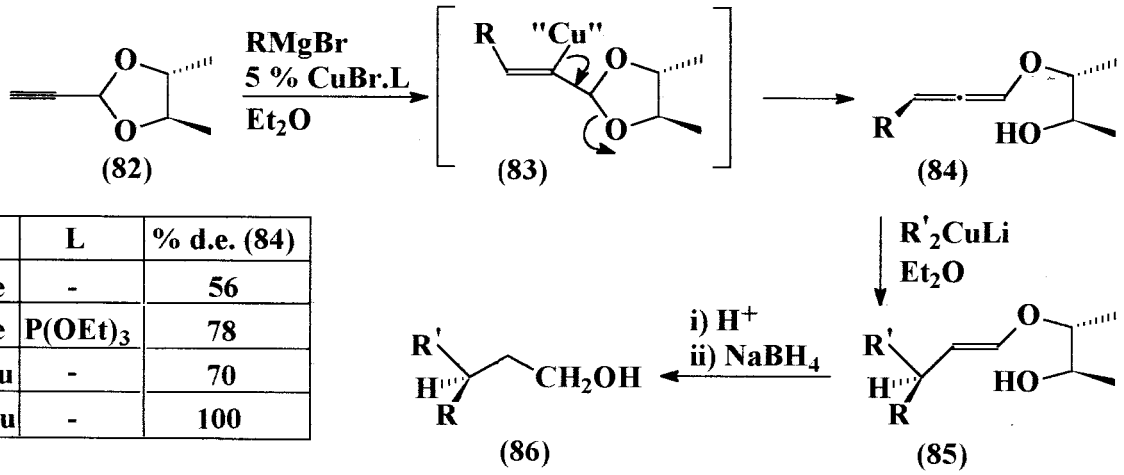

**SCHEME 12**

Formation of the 1,4-adduct is consistent with the mechanistic proposal of Johnson *et al.*[15] and, although the attack is at the γ-position (path a), it is *anti*-$S_N'$. The 1,2-adduct, on the other hand is formed by *syn* attack (path b) at the acetal carbon, in a fashion similar to that discussed in section 1.1.2.6 for the alkylation of chiral acetals with alkylaluminum reagents. In the above cases the α,β-unsaturated acetals react in transoid

conformations to give the observed (*E*)-geometry of the double bond in the enol ethers (**80**) and (**81**). Alkyllithium reagents have also been found to react with 2,3-butanediol acetals in a $S_N'$ manner but, surprisingly, *via* a cisoid intermediate to give mainly the (*Z*)-enol ethers.[55]

(ii) α,β-Acetylenic acetals

Organometallic reagents are known to add across the triple bond of acetylenic acetals to form alkoxyallenes.[61, 62] The first chiral version of this reaction involved use of chiral acetylenic dioxolanes (**82**) derived from 2,3-butanediol (**Scheme 13**); these acetals were reacted with Grignard reagents and a catalytic amount of a copper halide to form chiral alkoxyallenes in high yields, the crucial step being the highly diastereoselective β-elimination reaction of alkenyl copper species (**83**).[63] Complexation of the copper reagent by a donor sigma ligand, such as $P(OEt)_3$, increases the diastereoeselectivity, which is also dependent on the nature of the organic group of the organometallic reagent.




(82) (83) (84) (85) (86)

| R | L | % d.e. (84) |
|---|---|---|
| Me | - | 56 |
| Me | $P(OEt)_3$ | 78 |
| nBu | - | 70 |
| *t*-Bu | - | 100 |

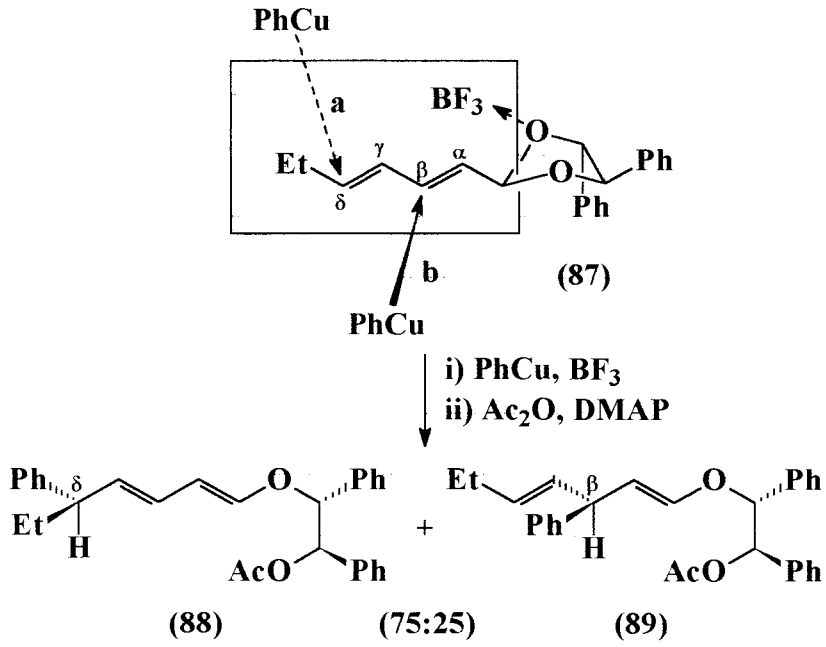
**SCHEME 13**

Dialkyllithium cuprates are known to undergo a *syn* addition reaction with

alkoxyallenes (**84**) and this addition was used to determine the absolute configuration of the alkoxyallenes (**84**) by generating an asymmetric carbon, which was found to be of (*S*)-configuration by conversion to the alcohol (**85**), which suggests the alkoxyallenes (**84**) have an (*R*)-configuration.

(iii) Dienic acetals

Remote asymmetric induction, with cleavage of the chiral acetal, has recently been reported[64] in the addition of a phenylcopper reagent to chiral dienic acetals (**87**) (**Scheme 14**) derived from (*R,R*)-1,2-diphenylethane-1,2-diol and hepta-2,4-dienal. No regioselectivity was observed with alkylcopper reagents but the phenylcopper reagent, in the presence of $BF_3$ afforded the enol ethers (**88**) and (**89**), with regioselective δ-substitution occuring *via* a *syn*-process (path a). The stereochemistry of the $S_N2''$ reaction is therefore opposite to that of the $S_N2'$ reaction, which gives β-substitution in an *anti*-manner (path b).




**SCHEME 14**

The regioselectivity of addition was found to depend on the stereochemistry and substitution pattern of the dienic system. Thus, in the foregoing examples, the observed diastereoselectivities are due to the chirality of the starting auxiliary diol. However, the presence of another stereogenic centre on the aldehyde precursor may alter the diastereoselectivity - as in the cases discussed in section 1.1.2.2 where, following the Cram rule, the α-stereogenic centre dictates asymmetric induction rather than the acetal template. The presence of a silyloxy group [$OSi(CH_3)_2C(CH_3)_3$] at the β-position to the acetal ring results in the dominance of chelation between the Lewis acid and the β-alkoxy group, thus reducing the influence of the acetal template and diminishing the diastereoselectivity.[65] The presence of a heteroatom in the α-position, however, has little influence on the stereochemical course of an addition, as was shown in the ring cleavage of chiral acetals of (*S*)-α-amino aldehydes with allyltrimethylsilane.[66]

The cleavage of chiral acetals, with subsequent nucleophilic attack, can therefore be achieved with high diastereoselectivity by using appropriate acetals and reagents, enantiomers of high purity being obtained after the removal of the chiral auxiliary.

### 1.1.3 Reactions of Acetals without Ring Cleavage

Highly diastereoselective reactions may result in the generation of new chiral centres in acetal derivatives without cleavage of the chiral acetal. The presence of an acetal auxiliary, in various positions relative to a prochiral centre, has been found to influence the face selectivity of the prochiral centre by either steric or chelation factors. The nature of the diol precursor plays a crucial role in reactions in which the acetal ring is not cleaved.

#### 1.1.3.1 Reduction of carbonyls

The LAH reduction of ketones containing a chiral β-acetal group was successfully achieved by Matsumoto *et al.*[67] who, proposed a congested transition state (**90**) involving coordination of the lithium cation ($Li^+$) (**Figure 6**), to give the alcohol (**93**) as the major diastereomer (**Table 5**; entry 1).

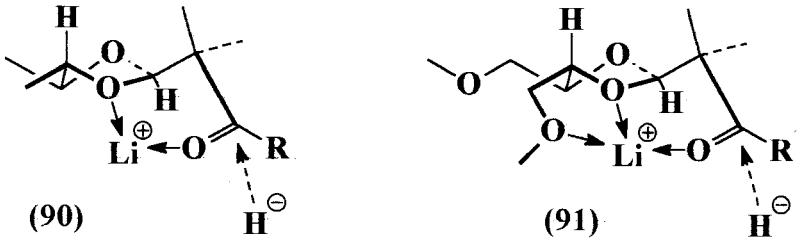
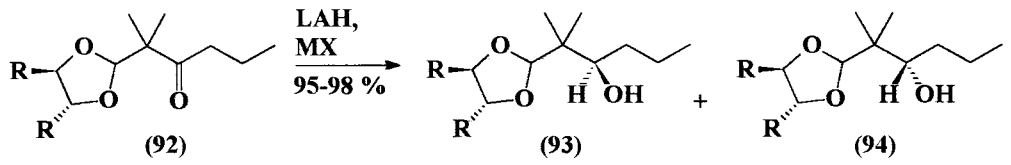



**FIGURE 6**

The interaction between $Li^+$ and the substrate plays an important part in this 1,5-asymmetric induction as was shown by adding 1eq. of LiBr, which increased optical yields (*cf.* entries 1 and 2), while the addition of $MgBr_2$ resulted in the predominance of alcohol (**93a**) (entry 3). The presence of an additional chelating heteroatom on the acetal moiety, as is the case with 1,4-di-*O*-methyl-D-threitol derivative (**92c**) (entries 5 and 6), increases the diastereoselectivity as conformation (**91**) is favoured by the

ketoacetal due to increased chelation. The preparation of (+)-pedamide, an intermediate in the synthesis of the potent insect poison, (+)-pederine, was achieved using this method.[68]

**Table 5**: Data for the diastereoselective reduction of β-carbonyls.




(92) (93) (94)

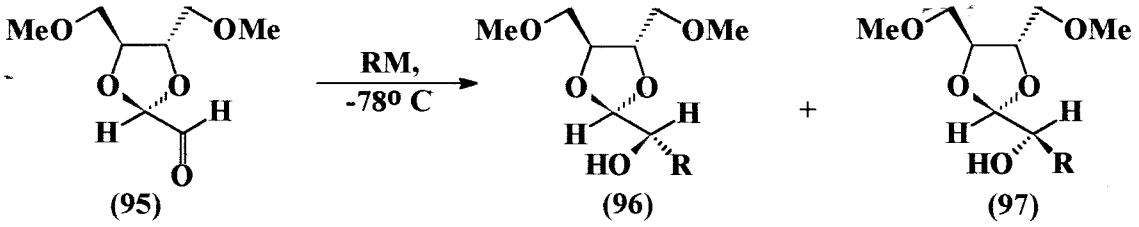
| Entry | Compound | R | MX | Product ratio 93:94 |
|---|---|---|---|---|
| 1 | **92a** | $CH_3$ | - | 4:1 |
| 2 | **92a** | $CH_3$ | LiBr | 5:1 |
| 3 | **92a** | $CH_3$ | $MgBr_2$ | 1:4 |
| 4 | **92b** | Ph | LiBr | 2:1 |
| 5 | **92c** | $CH_2OCH_3$ | - | 5:1 |
| 6 | **92c** | $CH_2OCH_3$ | LiBr | 11:1 |

### 1.1.3.2 Reaction with organometallic reagents

The chiral monoacetal (**95**) of glyoxal has been reacted with a variety of organometallics, with the highest diastereoselectivities (60-80 % d.e.) being recorded using alkyl Grignard reagents (**Table 6**).[69] Addition products, with an *S*-configuration at the new chiral centre, are obtained using alkyl reagents, while aryl- and alkynyl reagents give products having a *R*-configuration, as the major diastereomer. Diastereoselective addition of organometallics to a β- or γ-carbonyl group, however, does not proceed with high selectivity, the exception being the 2,4-pentanediol-derived

acetals of 3-phenyl-1,3-propanedione which give diastereoselectivities in excess of 70 % d.e. when reacted at the β-position with alkyllithium reagents.[17]

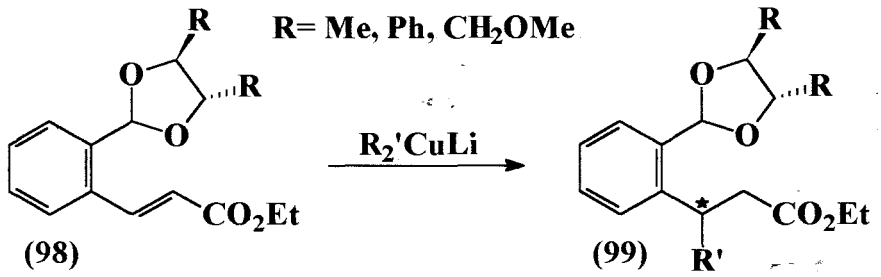
**Table 6**: Data for the diastereoselective alkylation of glyoxal monoacetal (**95**).




(95) (96) (97)

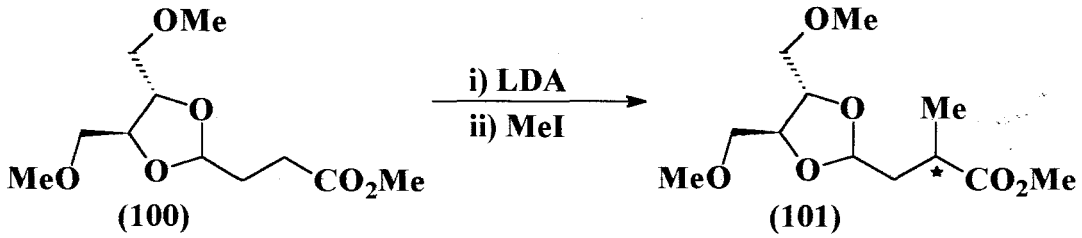
| Entry | RM | Solvent | R | | Yield/ % | Product ratio 96:97 |
|---|---|---|---|---|---|---|
| 1 | MeMgI | $Et_2O$ | Me | a | 70 | 9:1 |
| 2 | BuMgBr | $Et_2O$ | Bu | b | 65 | 87:13 |
| 3 | BuLi | $Et_2O$ | Bu | b | 60 | 52:48 |
| 4 | PhMgBr | $Et_2O$ | Ph | c | 70 | 34:76 |
| 5 | PhC≡CMgBr | THF | PhC≡C | d | 65 | 37:63 |

More remote alkylation at a prochiral centre was achieved by Alexakis *et al.*,[70] who explored the diastereoselective conjugate addition of cuprates to ethyl cinnamate esters bearing a *ortho* acetal appendage (**98**) (**Scheme 15**). Reaction with $Me_2CuLi$, under a variety of conditions , afforded the addition products (**99**) with low diastereoselectivity (15-20 % d.e.). The stereocontrol offered by the acetal group may be due to its chelating ability or its steric bulk, and Alexakis *et al.* found that replacing one or both oxygens of the acetal ring by nitrogen, resulted in stereoselectivity as high as 98 % d.e.. It is uncertain whether this is due to nitrogen being a better sigma donor or providing a more crowded steric centre than oxygen.



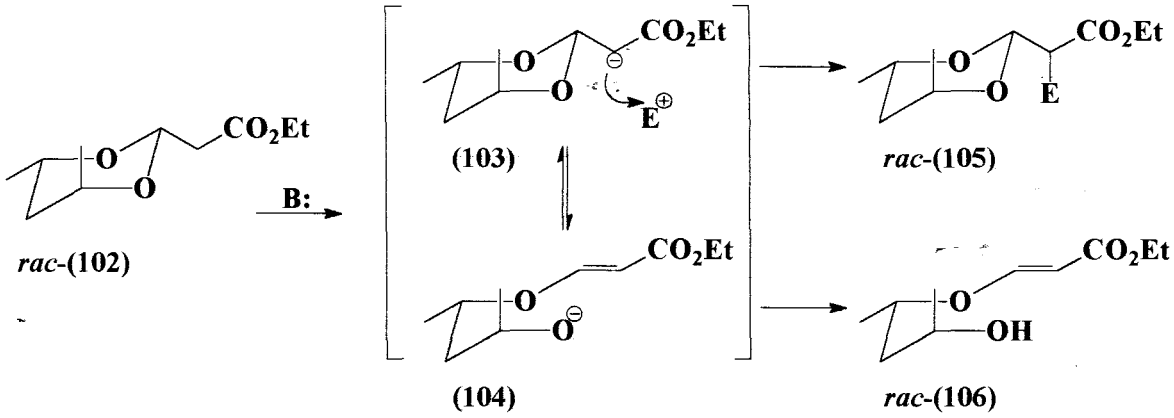

SCHEME 15

In the above examples, the chiral acetal is attached to the electrophile, but it could also be attached to the nucleophile - a scenario which is rare. Alkylation at the β-position, of the chiral acetal (**100**) (**Scheme 16**), has been reported by Alexakis *et al.*[17] to occur with 25 % d.e., and this low selectivity has been ascribed to poor chelation effects since the acetal is not in close proximity to the reactive centre.



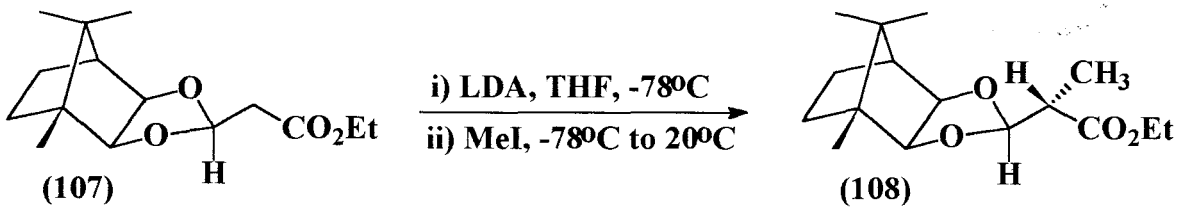

SCHEME 16

Alkylation has been achieved by Pedrosa *et al.*[71] at the α-position of the *meso* 1,3-dioxane, derived from *meso* 2,4-pentanediol and ethyl 3-ethoxyacrylate, in excellent yields, but with no apparent selectivity. However, alkylation of the racemic 1,3-dioxane (**102**) was found to occur without any facial discrimination and to yield mixtures of the alkylation (**105**) and the elimination products (**106**) (**Scheme 17**). The hydroxyalkenes are postulated to form *via* the open oxyanion (**104**), which is generated, in turn by an $E_1$ bc mechanism involving the carbanionic intermediate (**103**). The alkylated product (**105**) was obtained as the sole product in reactions in which TMEDA was used as co-solvent, while the use of magnesium ($Mg^{2+}$) as the counterion led to the exclusive formation of the elimination product (**106**).




**SCHEME 17**

Pedrosa *et al.*[71] also made use of (-)-*exo*-camphanediol as the auxiliary diol and found that the homochiral 2-(β-ethoxycarbonyl)dioxolane (**107**), derived from ethyl 3,3-diethoxypropanoate, may be alkylated with methyl iodide, in the presence of LDA, in good yields but with poor stereoselectivity (20-32 % d.e.) (**Scheme 18**).



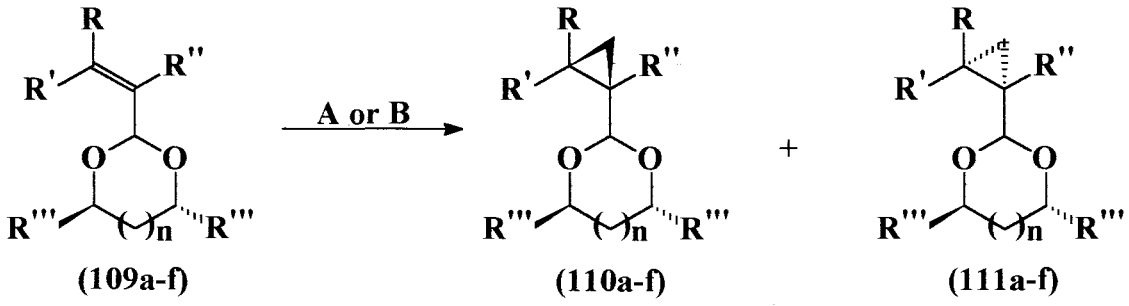

**SCHEME 18**

### 1.1.3.3 Diastereoselective cyclopropanations

Yamamoto *et al.*[72] obtained cyclopropanes from α,β-unsaturated acetals, derived from tartaric acid esters and various α,β-unsaturated aldehydes, in high yield and diastereoselectively (*cf.* **Table 7**, compounds **109a** and **109b**).These authors made use of alkylidene transfer conditions which were found to be superior to the conditions employed by Mash *et al.*,[73] whose use of the Simmon-Smith reagent resulted in little or no stereocontrol (compounds **109c** and **109d**). Zinc has a high affinity for ethereal

oxygen and stereoselectivity is expected to arise from preferential chelation of the organozinc reagent to one of the acetal oxygen atoms, followed by methylene transfer to the nearest face of the double bond.

**Table 7**: Data for diastereoselective cyclopropanations.[72, 73, 74]




(109a-f) (110a-f) (111a-f)

| Cmpd | Cond | R | R' | R'' | R''' | n | Yield/ % | Product ratio 110:111 |
|---|---|---|---|---|---|---|---|---|
| **109a** | A | Me | H | H | $CO_2Pr^i$ | 0 | 90 | 32:1 |
| **109b** | A | Pr | H | H | $CO_2Et$ | 0 | 95 | 16:1 |
| **109c** | B | Me | Me | H | $CH_2OCH_2Ph$ | 0 | 94 | 1:1 |
| **109d** | B | H | *cis*[-$(CH_2)_4$-] | | $CH_2OCH_2Ph$ | 0 | 70 | 2:1 |
| **109e** | A | Et | H | Me | Me | 1 | 69 | 7:1 |
| **109f** | A | Me | Me | H | Me | 1 | 81 | 1:2 |

Conditions: (A) $Et_2Zn$, $CH_2I_2$, Hexanes, -20°C. (B) Zn(Cu), $CH_2I_2$, $Et_2O$, heat.

In dioxane acetals, coordination occurs at the O(1) atom (see **Figure 7**) (for reasons discussed in section 1.1.2.2) which should lead to a *syn* transfer of the methylene group. However, the opposite stereochemical outcome, with low diastereoselectivity, is observed for cyclopropanation of chiral acetals derived from (*R*,*R*)-2,4-pentanediol and *anti* delivery of the methylene moiety appears to take place (compounds **109e** and

**109f**).[74] These observations have been rationalized, *inter alia*, by a change in geometry of the double bond during cyclopropanation (**Figure 7**) - an explanation supported by the cyclopropanation of β,β-disubstituted alkenes (compound **109f**). In this case, the proposed conformation (**I**) is unlikely, due to steric interactions between R' and the axial methyl group, and conformation (**II**) is preferred. This results in the cyclopropane having the opposite stereochemistry to those of acetals where R' is H and conformation (**I**) can be adopted.

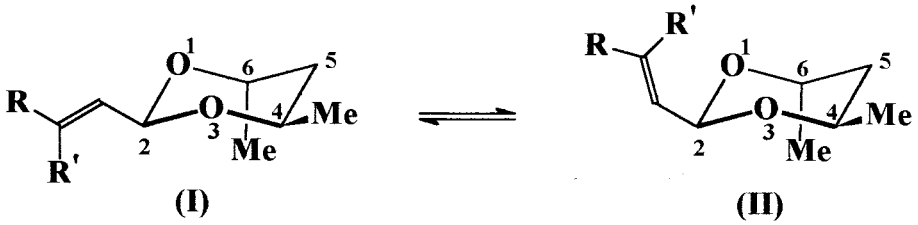
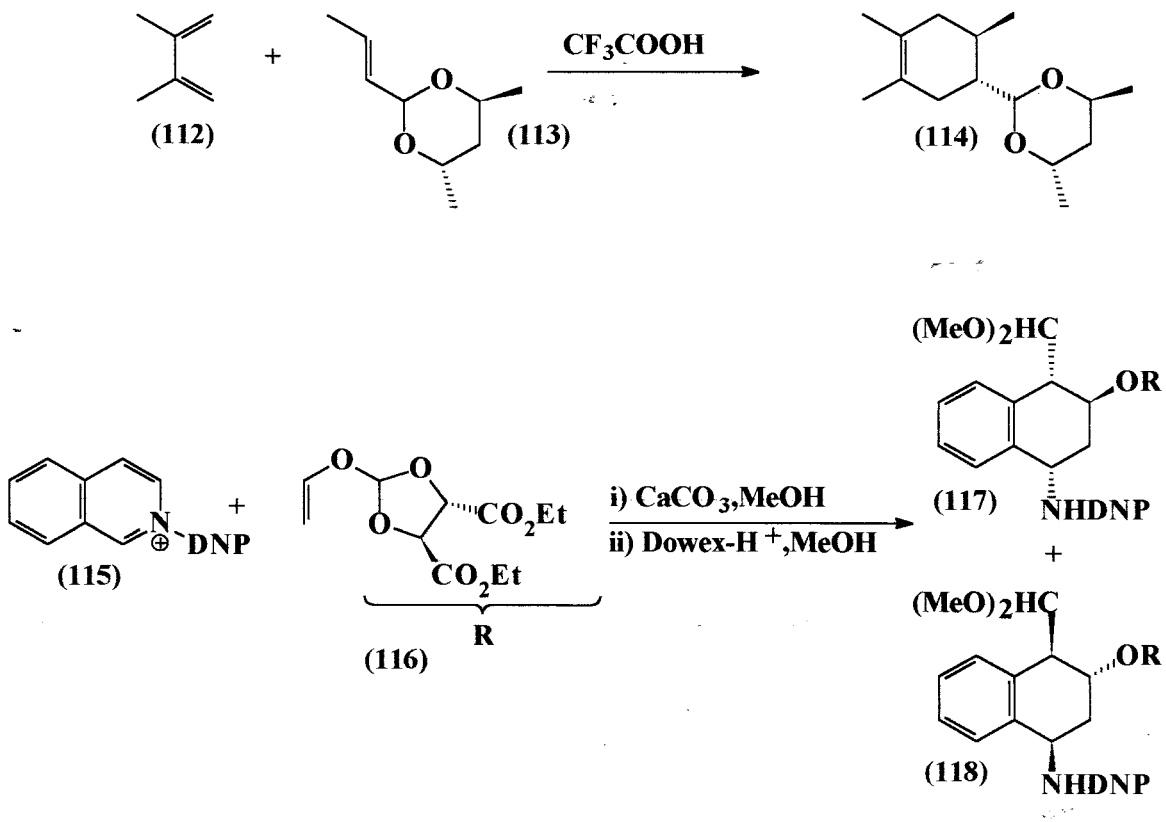



**FIGURE 7**

Yamamoto *et al.*[72] have successfully applied their asymmetric cyclopropanation reaction conditions to prepare a key intermediate for the synthesis of 5,4-methanoleukotriene $A_4$, a leukotriene biosynthesis inhibitor.

### 1.1.3.4 Diastereoselective Diels-Alder reactions

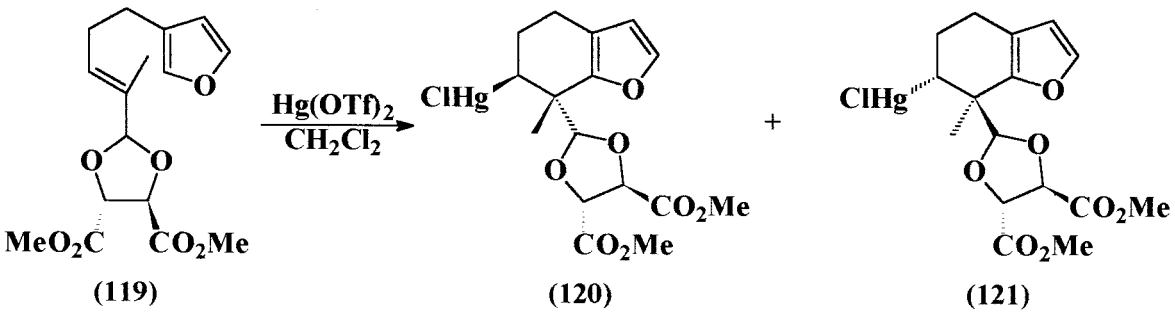
Alexakis *et al.*[17] reported cycloaddition of the chiral acetal (**113**) with 2,3-dimethyl-1,3-butadiene (**112**) and, although high yields of the cycloadduct (**114**) were obtained, low selectivities (13 % d.e.) were observed. Stereoselectivities of 5-20 % d.e. were observed in the inverse-electron-demand cycloaddition of the isoquinolium salts (**115**) with chiral ortho ester vinyl ethers (**116**) to form the homochiral tetralins (**117**) and (**118**) (**Scheme 19**).[75]




SCHEME 19

### 1.1.3.5 Biomimetic olefin cyclization

Chiral acetals , derived from tartaric acid esters, have been used in the cyclization of perillene derivatives (**Scheme 20**).[76] Clean cyclization was achieved by treating the

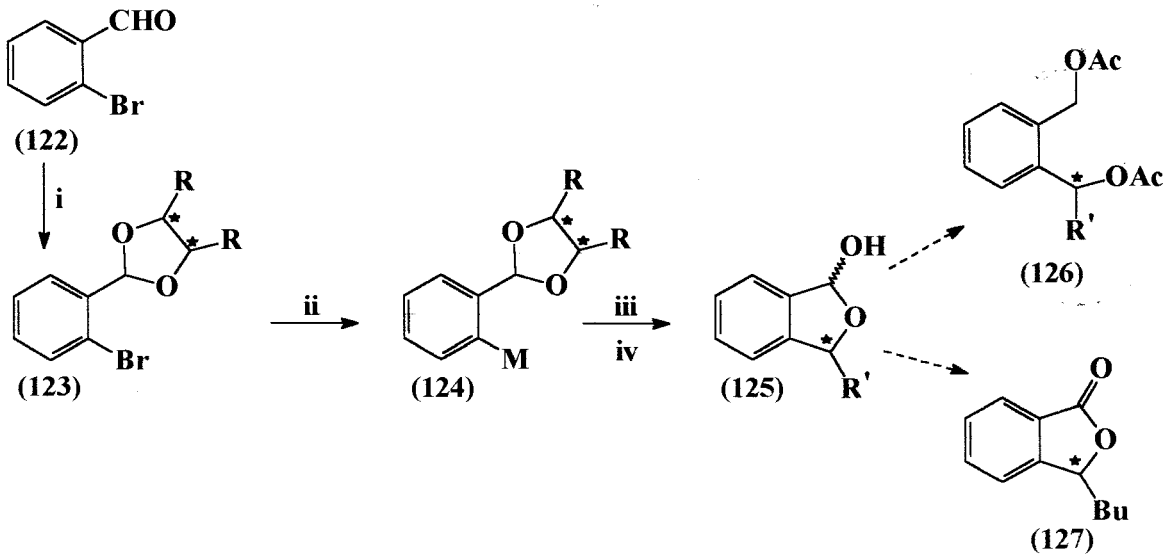



SCHEME 20

chiral acetals (**119**) with $Hg(OTf)_2$ in dichloromethane at -78°C, and the absolute configuration of the major diastereomer (**120**) was determined by X-ray crystallography. Subsequent reductive demercuration and chemical transformations permitted the determination of diastereomeric ratios.

### 1.1.3.6 Organometallic reagents bearing an acetal moiety

The enolates, discussed in section 1.1.3.2, are not the only systems examined in which the chiral acetal auxiliary is linked to the nucleophile. Organometallic derivatives with an acetal appendage have also been studied, the most common being aryl metallic derivatives in which the chiral acetal moiety occupies the *ortho* position, as in structure (**124**) (**Scheme 21**).




**Reagents: i) (2 *S*,3*S*)-1,4-dimethoxy-2,3-butanediol or ( *S*,*S*) 1,2-diphenyl-1,2-ethanediol,**
**ii) BuLi (and $MgBr_2$ for magnesium derivatives),**
**iii) R'CHO, THF or $Et_2O$,**
**iv) $H_3O^+$**

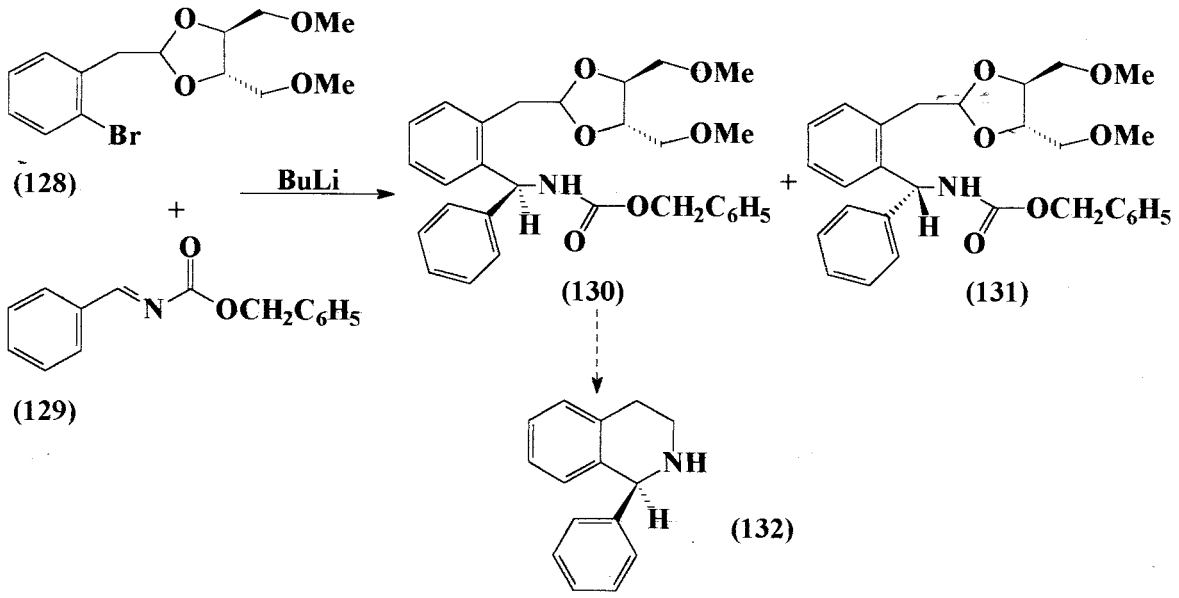
**SCHEME 21**

Such compounds are readily prepared from 2-bromobenzaldehyde (**122**), by acetalization with a diol having $C_2$ symmetry, followed by halogen-metal exchange in the resulting bromo-acetal (**123**). Mangeney *et al.*[77] studied the diastereoselective addition of chiral, aryl metallic reagents to aldehydes (R'CHO) to afford, after removal of the chiral auxiliary, the homochiral lactols (**125**); the enantiomeric excess was determined by $^1$H NMR with the chiral shift reagent [Eu(hfc)$_3$] of the corresponding diacetates (**126**) and the favoured configuration of the new chiral centre by comparison of the optical rotation of the known lactone (**127**).

These authors first made use of acetals derived from (2*S*,3*S*)-1,4-dimethoxy-2,3-butanediol in the hope that one of the methoxy oxygen atoms would chelate with the metal atom to provide stereocontrol. However, relatively poor selectivity was observed (5-37 % e.e.) and the authors suggested that steric control, rather than chelation control, is responsible for selectivity. They therefore increased the steric effects by using aminals prepared from chiral, symmetrical diamines and obtained stereoselectivities of up to 98 % e.e.. Aminals have been widely studied by these authors as alternatives to acetals.[78, 79]

The addition of homochiral, aryl Grignard reagents, bearing an *ortho* dioxane ring, to carbonyl compounds was described by Yamamoto *et al.*;[80] the best diastereoselectivity (88 % d.e.) was achieved with benzaldehyde. Würsch *et al.*[81] made use of lithium derivatives, obtained from (2-bromophenyl)acetaldehyde dioxolane acetals (**128**), in stereoselective addition to acylimines, such as (**129**) (**Scheme 22**). The addition products (**130**) and (**131**) were obtained in high yield with good diastereoselectivity (44 % d.e.). However, the introduction of ester and amide groups into the dioxolane moiety or the use of dioxane or dioxepane acetals failed to give addition products. The transformation of the isolated, major addition product (**130**) into the known 1-

phenyltetrahydroisoquinoline (**132**) permitted determination of the configuration at the new stereogenic centre.



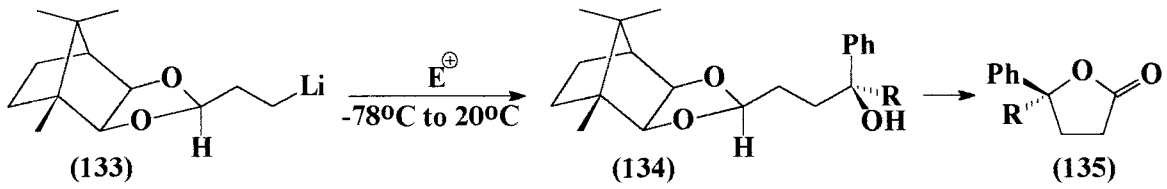

**SCHEME 22**

Pedrosa *et al.*[82] converted 2-(2-bromoethyl)dioxolane, obtained from (-)-*exo*-camphanediol and 3-bromopropanal, into the lithium derivative (**133**) which, on reaction with benzaldehyde and acetophenone, afforded the carbinols (**134**). The carbinols were transformed into known, γ-substituted butyrolactones (**135**) by oxidation with MCPBA to establish the preferred configuration at the new chiral centre and facilitate the estimation of stereoselectivity. The diastereoselectivities were also dertermined by integration of the $^1$H NMR signals of the carbinol mixtures.

It was found that *si*-facial discrimination of the carbonyl was favoured by the camphordiol derivative (**133**), giving the carbinol of *S*-configuration in low diastereomeric excess. In the same study, the lithium dioxolane derived from (-)-1,4-di-*O*-benzyl-*L*-threitol (a diol prepared from tartaric acid) was found not to discriminate

the faces of the carbonyl substrate, affording an equimolar mixture of the epimeric carbinols.

**Table 8**: Data for diastereoselective carbinol formation with organometallic reagents containing an acetal moiety.



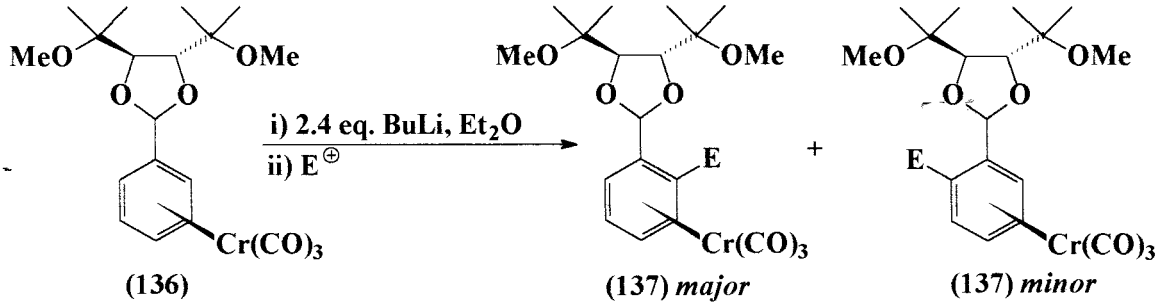

(133) (134) (135)

| Entry | $E^{\oplus}$ | R | Solvent | Compound (134) | |
|---|---|---|---|---|---|
| | | | | Yield/ % | % d.e. |
| 1 | PhCHO | H | $Et_2O$ | 64 | 9 |
| 2 | PhCOMe | Me | $Et_2O$ | 51 | 26 |
| 3 | PhCHO | H | THF | 50 | 3 |
| 4 | PhCOMe | Me | THF | 36 | 8 |

### 1.1.3.7 Reactions of arylaldehyde acetal-chromium tricarbonyl complexes

The deprotonation of the chiral chromium tricarbonyl complex of the benzaldehyde acetal (**136**) derived from diethyl tartrate is readily achieved by treatment with alkyllithium reagents; subsequent reaction with several electrophiles results in unequal mixtures of the corresponding diastereomers (**137**).[83, 84] High yields and selectivities are observed with the *slow* addition of butyllithium at -30°C. Preferential abstraction of the *pro-R* proton by butyllithium was confirmed by :- i) X-ray crystallography of the major product (**137a**) (**Table 9**; entry 1); and ii) hydrolysis of the acetal from the major diastereomer (**137b**) (entry 2) to give a known complex.

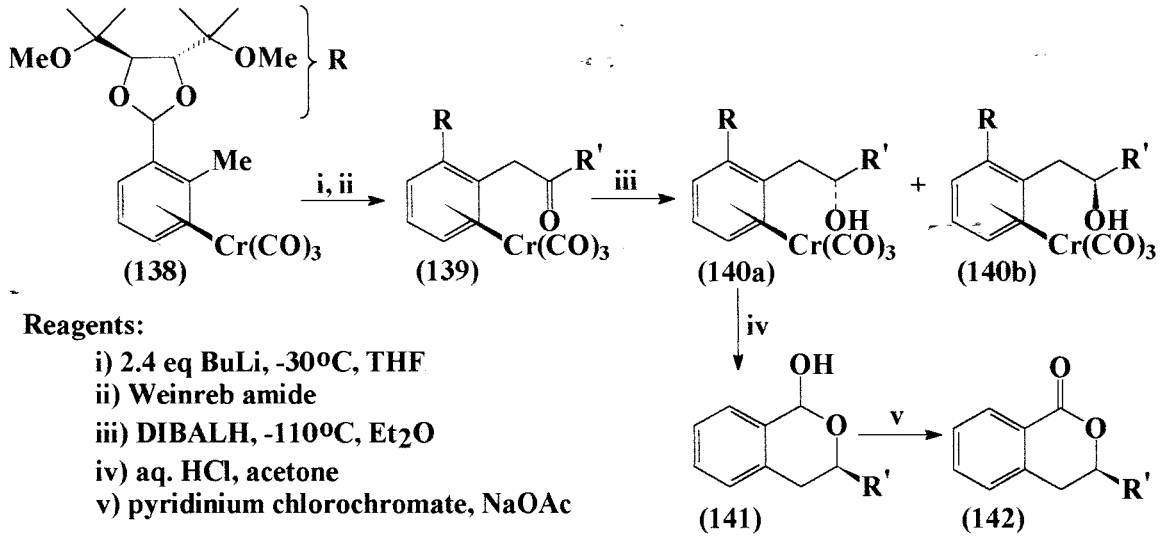
**Table 9**: Data for diastereoselective lithiation of arylaldehyde acetal-chromium tricarbonyl complexes.




(136) (137) *major* (137) *minor*

| Entry | $E^{\oplus}$ | | E | Yield/ % | % d.e. |
|---|---|---|---|---|---|
| 1 | $Me_3SiCl$ | a | $Me_3Si$ | 77 | 86 |
| 2 | MeI | b | Me | 62 | 92 |
| 3 | $Bu_3SnCl$ | c | $Bu_3Sn$ | 73 | 91 |
| 4 | $Ph_2PCl$ | d | $Ph_2P$ | 69 | ≥94 |
| 5 | $BrCH_2CH_2Br$ | e | Br | 64 | 88 |

Green *et al.*[85] used the protected *o*-tolualdehyde complex (**138**) to form the ketone (**139**) (**Scheme 23**); the alkyl chain was attached by benzylic lithiation followed by addition of an *N*-methoxy-*N*-methyl (Weinreb) amide. Reduction of the ketone (**139**; R'= Ph) was successfully achieved with diisobutyl aluminium hydride (DIBALH) at -110°C to give the corresponding alcohol, the major diastereomer (**140a**; R'=Ph) being shown to have an *R*-configuration by X-ray crystallography. The use of substrates where R' is a larger substituent (*e.g.* *t*-Bu) gave the analogous alcohols with the same configuration, but with better diastereoselectivity. Acidic hydrolysis of the acetal group from the major alcohols (**140a**) occurred with decomplexation of the tricarbonylchromium moiety to yield the lactols (**141**); subsequent oxidation afforded the enantiomerically pure dihydroisocoumarins (**142**).

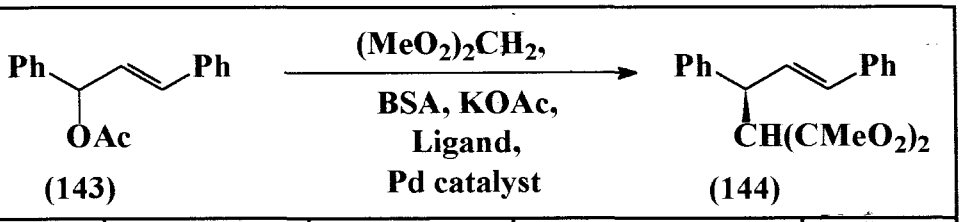


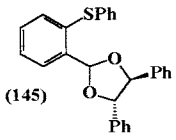
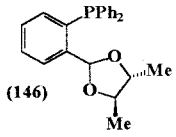
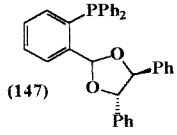

**SCHEME 23**

### 1.1.3.8 Acetals as ligands for asymmetric catalysis

Williams *et al.*[86] reported the ability of chiral acetal ligands (*e.g.* **145-147**) to provide asymmetric induction in palladium catalysed allylic substitution, in which the acetal is attached to an auxiliary donor atom.The acetal ligands are prepared by the reaction of aldehydes with $C_2$-symmetric diols. The absolute configuration of the ligand does not appear to affect the stereochemical outcome of the reaction as ligands (**146**) and (**147**), which have the opposite configurations, both gave the *S*-(-)-enantiomer as the major product. The shift reagent $Eu(hfc)_3$ was used to determine the enantiomeric excess in each case.

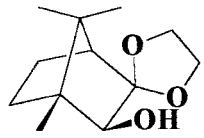
**Table 10**: Data for palladium catalysed allylic substitution using chiral ligands.[86]



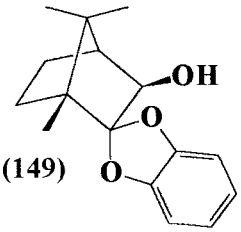

| Entry | Ligand | Time/ h | Yield/ % | % e.e. |
|---|---|---|---|---|
| 1 |  (145) | 24 | 81 | 82 |
| 2 |  (146) | 24 | 75 | 68 |
| 3 |  (147) | 24 | 70 | 88 |

## 1.2 AIMS OF THE INVESTIGATION

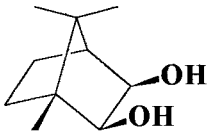
Camphor is readily available in optically pure form and is relatively inexpensive making it ideal as a chiral auxiliary. Moreover, the development of camphor-derived chiral auxiliaries may be attributed to the conformational rigidity of the bicyclic camphor system and the numerous transformations which camphor is capable of undergoing. Numerous studies in these laboratories have investigated camphor-derived compounds as chiral auxiliaries.[87-90] In one such study, Learmont[87] explored the hydrolysis of *N*-benzylcamphorimide (**153**) as a means to provide chiral amines or amino acids *via* an asymmetric Gabriel type synthesis. However, the *N*-benzylcamphorimide (**153**) was found to be remarkably resistant to hydrolysis, although regioselective partial hydrolysis was achieved. Ravindran[88] reported that the steric bulk imparted by the ethylenedioxy group of the ketal (**148**) resulted in moderate stereoselectivities, and so attention was given to the preparation of the bulkier chiral auxiliary (**149**) which, although unsuccessful, aroused our interest in diols possessing a $C_2$ axis of symmetry.



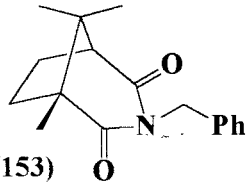
(148)



(149)



(150)



(153)

**FIGURE 8**

The use of cyclic acetals as protecting groups is well-established and, in recent years, chiral cyclic acetals have evolved rapidly as useful chiral auxiliaries in asymmetric synthesis. Acetals derived from diols possessing a $C_2$ axis of symmetry have, by far, received most attention since the formation of a single acetal during acetalization allows for the preparation of asymmetric building blocks with high optical purity. Chiral acetals derived from the *exo*-camphane diol (**150**) are also formed as a single

diastereomer which makes them ideal substrates for asymmetric inductions. To our knowledge, the use of the *exo*-camphane diol (**150**), as a chiral auxiliary, has only recently been reported.[71, 82]

The present investigation has involved the following objectives:

(1) Establishing the structure of the major regioisomeric product from partial hydrolysis of *N*-benzylcamphorimide.

(2) The synthesis of tartrate- and novel camphor-derived diols as potential chiral auxiliaries.

(3) The development of efficient acetalization methods for the preparation of chiral cyclic acetals.

(4) Conformational studies to determine the preferred conformations of the various acetal substrates and hence, the likely orientation of attack.

(5) A study of the asymmetric induction achieved in various reactions of the chiral cyclic acetals.

# 2. DISCUSSION

In the discussion which follows, the development of the research will be described with attention being given, in turn, to the preparation of chiral auxiliaries, the synthesis of chiral acetals and, finally, transformations designed to determine the effectiveness of the chiral auxiliaries.

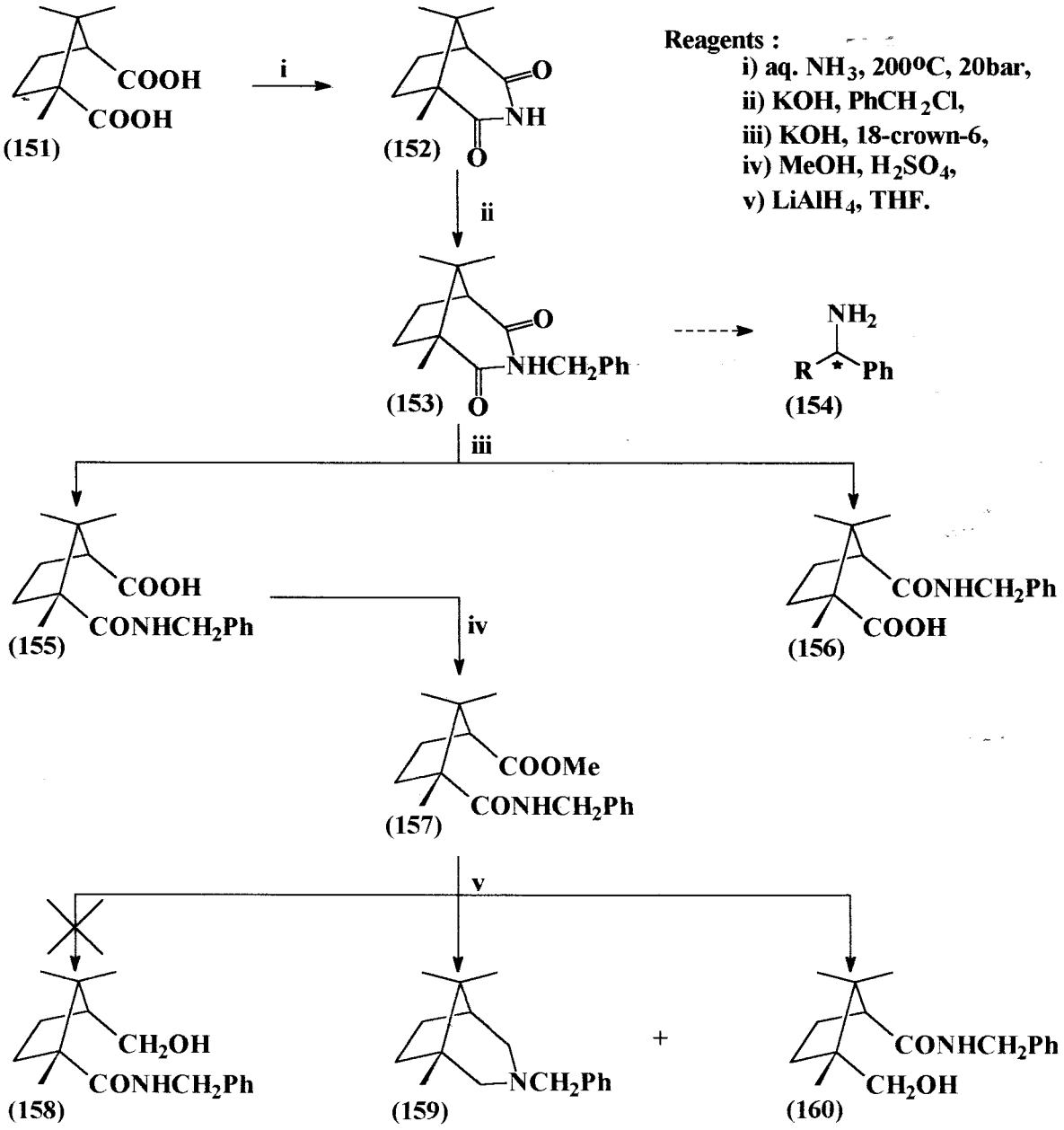
## 2.1 PREPARATION OF CHIRAL AUXILIARIES

### 2.1.1 Investigation of the ring-opening of *N*-benzylcamphorimide (153)

In previous work carried out in these laboratories, Learmonth[87] used the inexpensive camphor derivative, camphoric acid (**151**), as a precursor in a high-yielding reaction with ammonia,[91] at elevated temperature and pressure, to synthesize camphorimide (**152**). It was envisaged that *N*-alkylation of camphorimide and subsequent hydrolysis would afford chiral amines and amino acids (**154**) (**Scheme 24**) *via* an asymmetric Gabriel type synthesis. However, *N*-benzylcamphorimide (**153**), prepared as a model compound, resisted hydrolysis to the free benzylamine under a range of conditions, but partial hydrolysis was achieved with significant regioselectivity, in the presence of crown ethers.

Bell[92] had previously used methanolic sodium hydroxide to effect partial hydrolysis of *N*-benzylcamphorimide (**153**) and identified the carboxy amide (**155**) as the major isomer, on the assumption that preferential attack would occur at the sterically less hindered carbonyl group. Learmonth, however, found that esterification and reduction of the major carboxy amide, which he obtained, led to the formation of the partially reduced product (**160**), strongly suggesting that the major product of the initial

hydrolysis was the carboxy amide (**156**). Preferential formation of this carboxy amide (**156**) would require nucleophilic attack at the more sterically hindered carbonyl group of the imide (**153**) contrary to Bell's assumption.




**SCHEME 24**

The work of Learmonth and Bell was therefore repeated in an attempt to establish unequivocally the structure of the major regioisomer obtained from partial hydrolysis of *N*-benzylcamphorimide (**153**).

One-dimensional NMR studies of the crude mixture of the carboxy amides (**155**) and (**156**), obtained by hydrolysis with KOH and with 18-crown-6 or dibenzo-18-crown-6, showed that the major and minor products were produced in a 7:3 ratio. The ratio was calculated by integration of the well-resolved $^{1}H$ amide peaks at 5.91 and 5.77 ppm (corresponding to the major and minor regioisomers, respectively) and by integration of carbon peaks in the $^{13}C$ NMR spectrum (assuming that the isomers, as for diastereomers, have the same $T_1$ relaxation times).[93] Heteronuclear multiple bond correlation (HMBC) spectroscopy of the crude mixture permitted assignment of structure (**155**) to the major carboxy amide by confirming the locations of the carboxylic acid (C-9) and amide carbonyl (C-10)[b] nuclei (**Figure 10**). The C-10 nucleus was identified by its coupling to the amide hydrogen and the 12-methylene protons, while its coupling to the 8-methyl hydrogens and the *endo* 4-H nucleus clearly indicates that the major regioisomer obtained during hydrolysis is the carboxy amide (**155**). This assignment is supported by the coupling of the C-9 nucleus to the 1-methine proton. A similar study on the crude hydrolysis mixture, obtained using Bell's method (*i.e.* methanolic sodium hydroxide),[92] indicated a 7:3 ratio of the regioisomers with carboxy amide (**155**) again being the major component. Repeated recrystallization from EtOAc-hexane removed sufficient of the minor product to afford crystals of the major product suitable for single crystal X-ray analysis, which confirmed that the major product was, in fact, the carboxy amide (**155**) proposed by Bell[92] (**Figure 9**).

[b] The numbering of the carbon atoms may change to conform with systematic nomenclature.

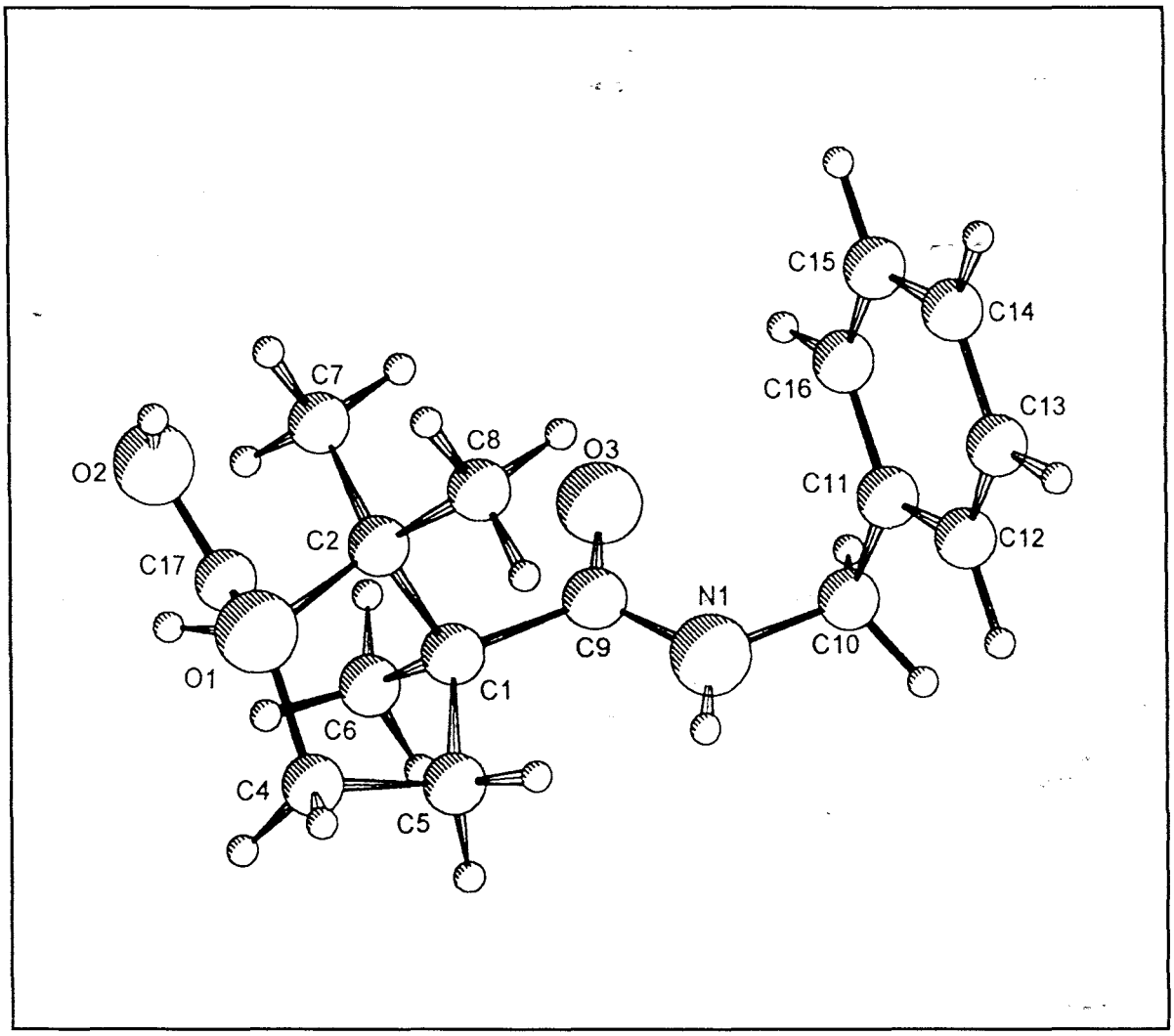



**Figure 9.** X-ray crystal structure of the carboxy amide (**155**), showing crystallographic numbering.

Esterification of the pure carboxy amide (**155**) afforded the *expected* methyl ester derivative (**157**), the structure of which was established by HMBC spectroscopy. This technique revealed coupling of the ester carbonyl carbon (C-9) to both the methoxy hydrogens and to the 1-methine proton, as well as coupling between the amide carbonyl carbon (C-10) and the 8-methyl hydrogens, the amide hydrogen and benzylic methylene protons (**Figure 11**). However, reduction of this ester (**157**) with lithium aluminium hydride (LAH), rather than affording the expected, partially reduced regioisomer (**158**),

gave the regioisomeric hydroxy amide (**160**) together with *N*-benzylcamphidine (**159**). The structure of the hydroxy amide (**160**) was elucidated by HMBC spectroscopy, which showed coupling of the $CH_2OH$ carbon (C-9) with the 8-methyl protons and coupling between the amide carbonyl carbon (C-10) and the 1-methine and benzylmethylene protons (**Figure 12**).

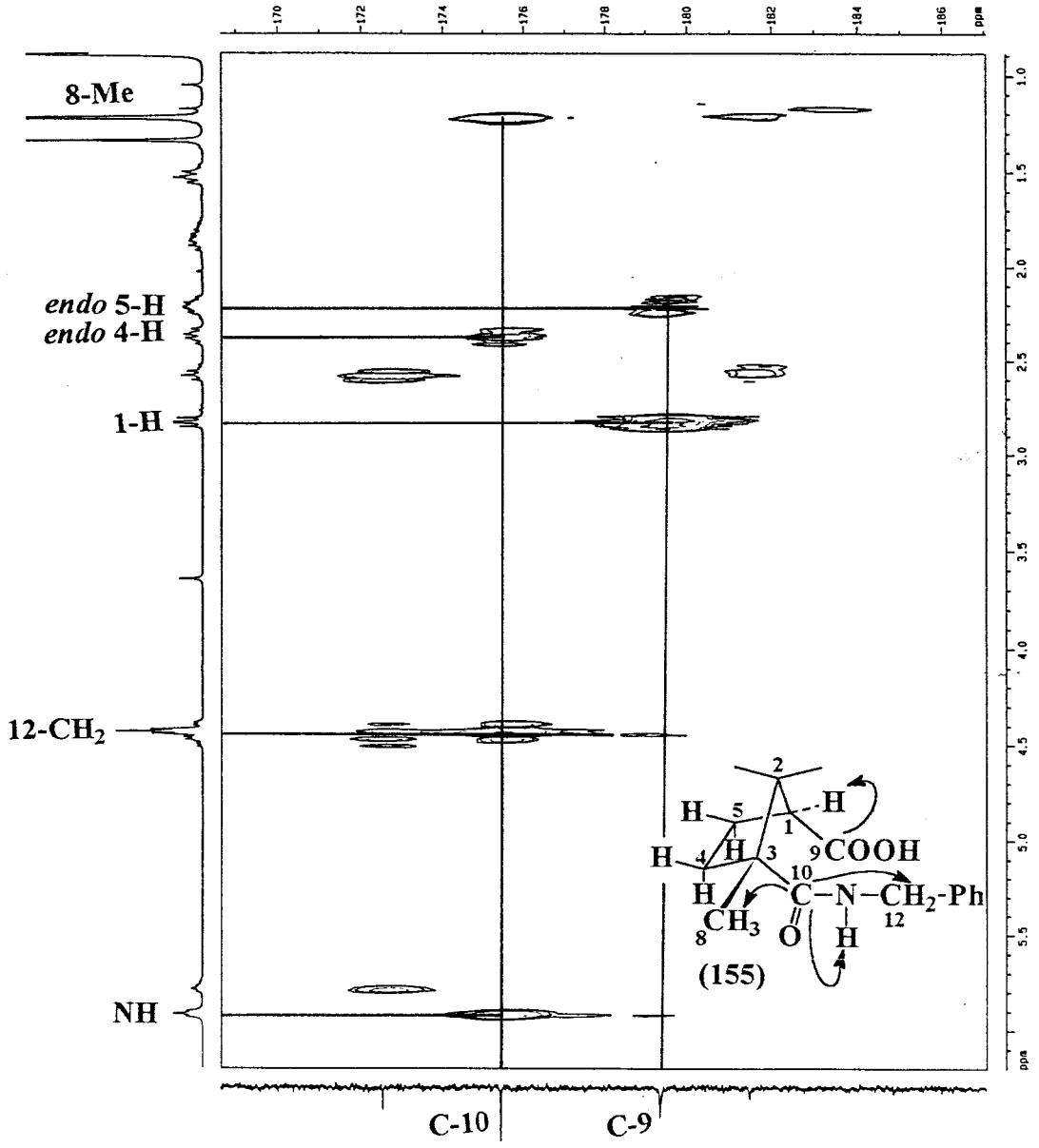



**Figure 10.** Partial HMBC spectrum of the crude mixture of amide acids (**155**) and (**156**), in $CDCl_3$, showing couplings to C-9 and C-10 in (1*S*,3*R*)-3-(*N*-benzylcarbamoyl)-2,2,3-trimethylcyclopentanecarboxylic acid (**155**).

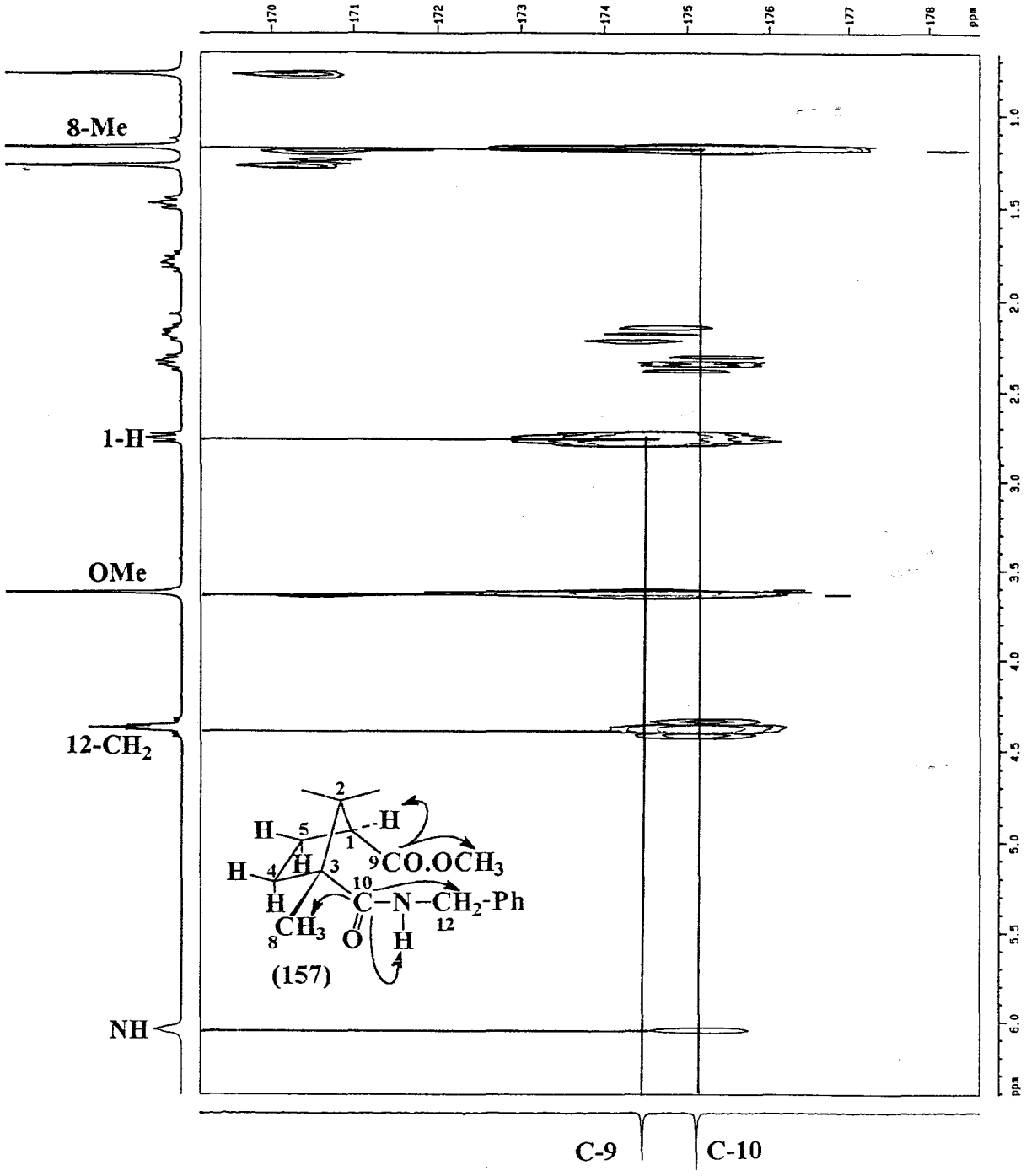



**Figure 11.** The partial HMBC spectra of the methyl ester derivative (**157**) in $CDCl_3$.

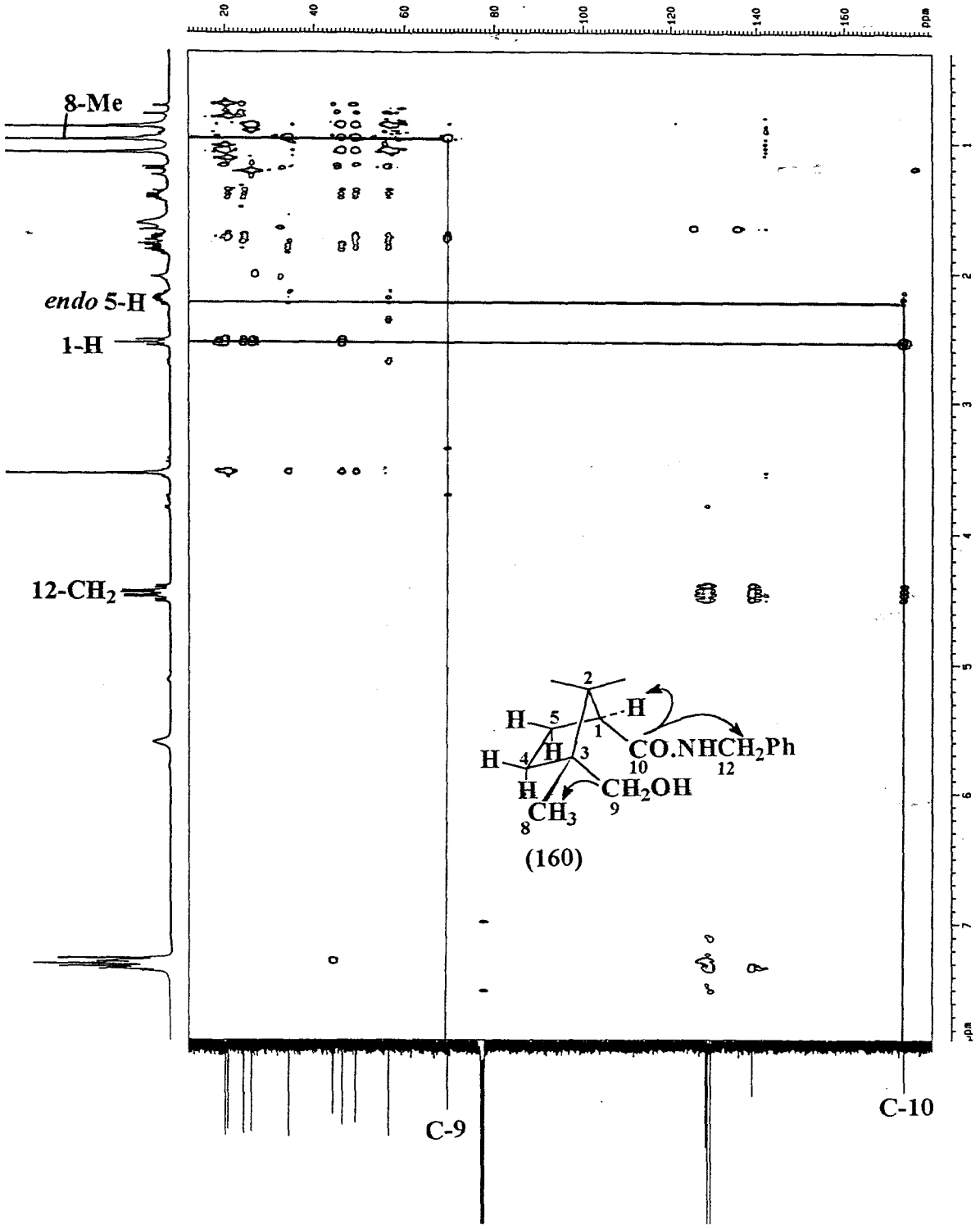
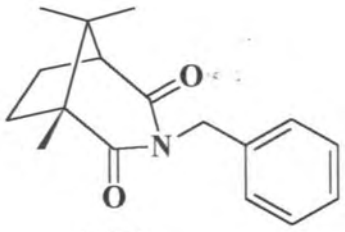



**Figure 12.** The HMBC spectrum of hydroxy amide (**160**) in $CDCl_3$.

Since no rearrangement occurs during esterification of the carboxy amide (**155**), [illegible] partially reduced regioisomer (**160**) must result from an intramolecular rearrangement of the methyl ester derivative (**157**) during LAH reduction of the ester carbonyl (C-9) and/or the amide carbonyl (C-10). However, the LAH reduction of amides to amines has been reported to occur with difficulty.[94] Moreover, the experimental observation that the secondary amide carbonyl group (C-10) is intact in the hydroxy amide (**160**) [the major reduction product (55 %)] and the fact that the reaction order of LAH reduction of carbonyl compounds is expected to follow the sequence:- aldehyde > ester > amide[95] strongly suggest initial reduction of the ester carbonyl group (C-9). The proposed mechanism for the observed rearrangement is therefore based on initial, partial reduction of the ester moiety to afford intermediate (**161**) (**Scheme 25**). The detection of small amounts of the hydroxy amide (**158**) suggests that intermediate (**161**) may be completely reduced at the ester functionality but that this is a minor pathway. Intramolecular nucleophilic attack at C-9 by the amide nitrogen, with displacement of the methoxy group, could then afford the cyclic intermediate (**162**).

Computer modelling of the compound (**153**) reveals unfavourable eclipsing of the 11-methyl group and the adjacent carbonyl group, with a separation of only 2.7 Å, which is significantly less than the sum of their van der Waals radii (3.4 Å) (**Figure 13**).






(153)

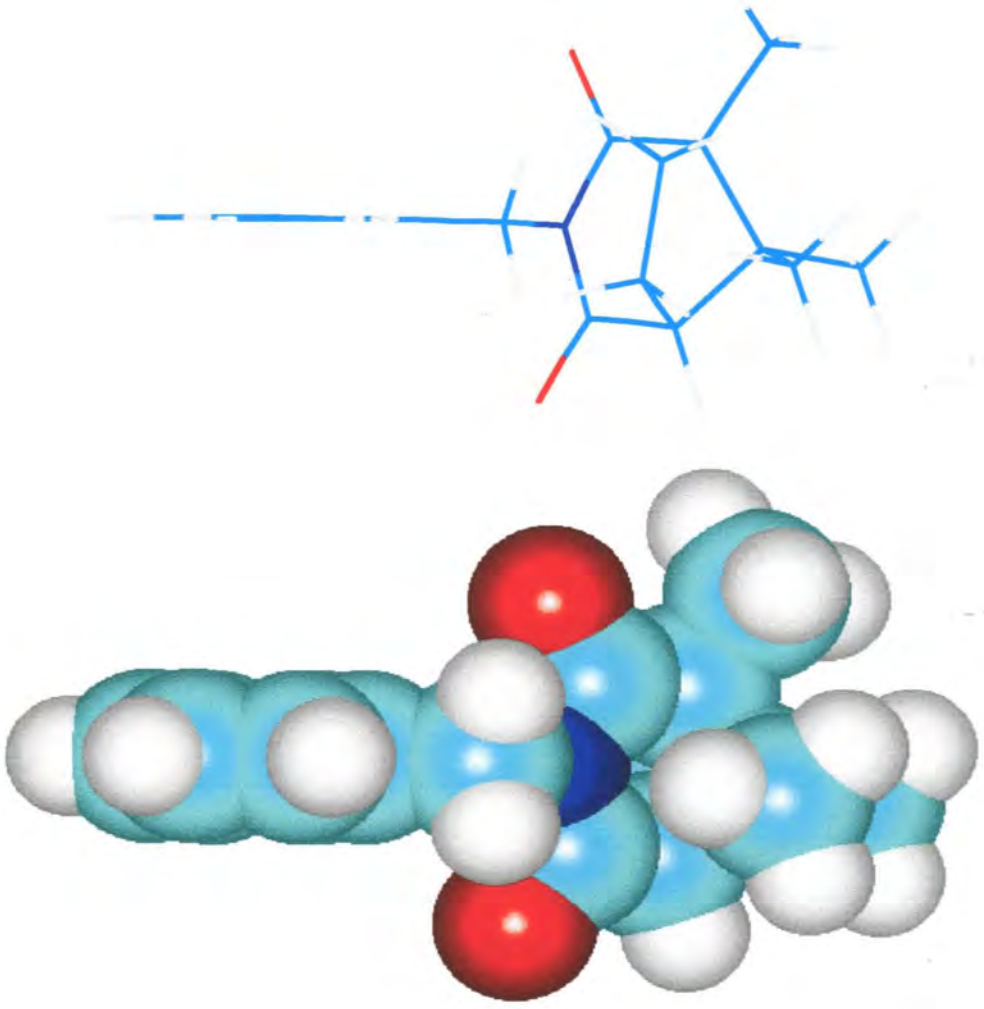
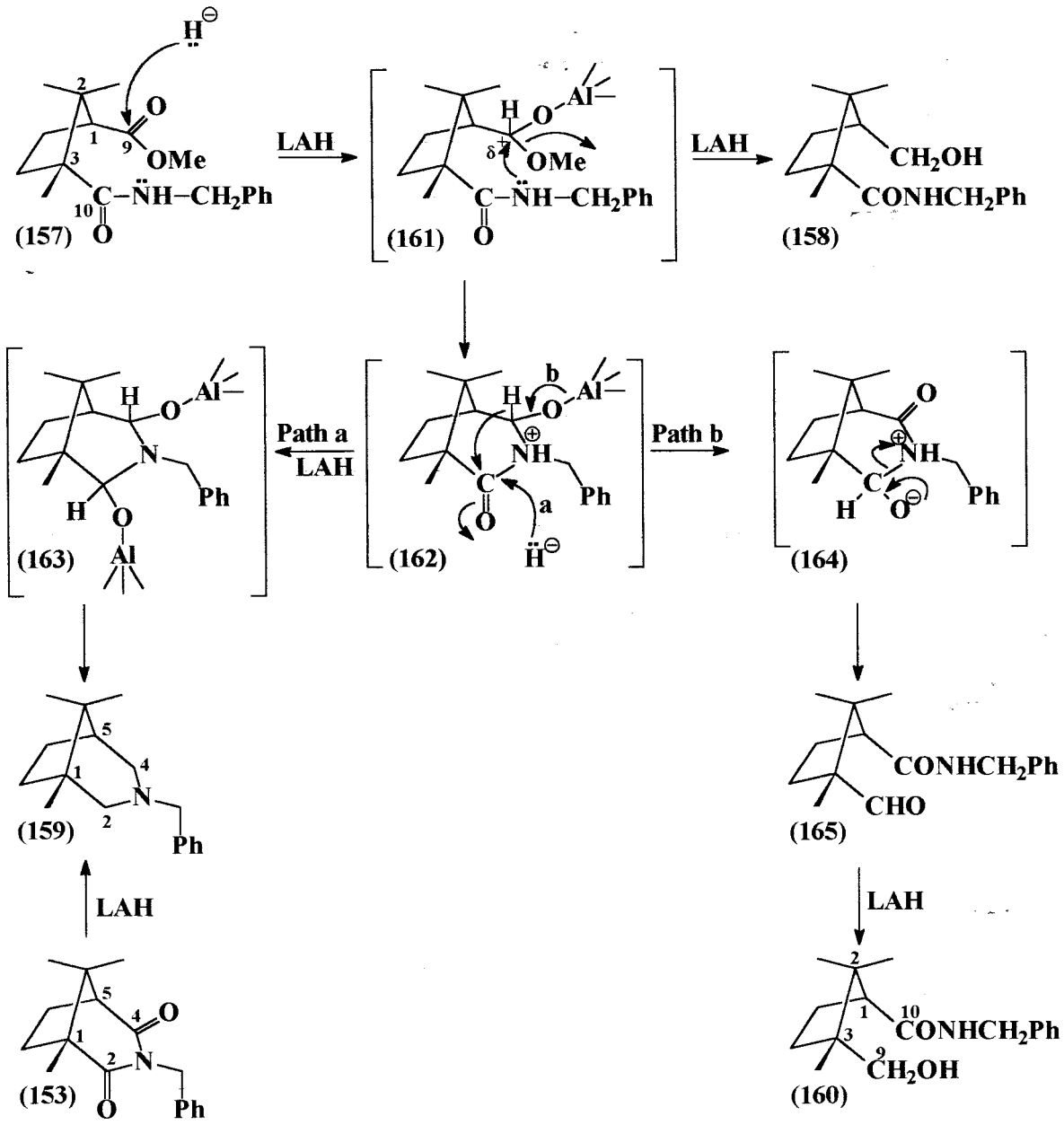


**FIGURE 13.** Computer-generated stick and space-filling models of compound (**153**).




**SCHEME 25**

The resulting steric strain can be relieved if the carbonyl carbon becomes tetrahedral and this can be achieved by formation of intermediates (**163**) and (**164**) *via* path (a) or path (b) respectively. These intermediates may then be transformed, respectively, to *N*-benzylcamphidine (**159**) and the rearranged hydroxy amide (**160**). In path (a), LAH

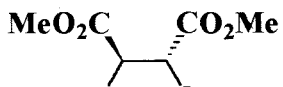
reduction of the amide carbonyl group involves nucleophilic attack by hydride ion to afford intermediate (**163**), further reduction of which leads to *N*-benzylcamphidine (**159**). In path (b), on the other hand, intramolecular hydride attack (a 1,3-hydride shift) at the amide carbonyl and subsequent ring-opening affords the amido aldehyde (**165**), which is then reduced by LAH to the hydroxy amide (**160**). Although the secondary amide carbonyl of both the hydroxy amides (**158**) and (**160**) appear to exhibit resistance to LAH reduction under the reaction conditions, both carbonyl groups of the tertiary amide, *N*-benzylcamphorimide (**153**) can be smoothly reduced. Consequently, it is not unreasonable to expect reduction [*via* path (a)] of the amide carbonyl group in the cyclic intermediate (**162**), which is, in fact, partially reduced *N*-benzylcamphorimide (**153**). Thus, the two divergent paths (a and b) are postulated to account for the experimentally observed products (**159**) and (**160**) respectively.

In summary, the major regioisomer obtained from partial hydrolysis of *N*-benzylcamphorimide (**153**) is the carboxy amide (**155**), which arises from attack by a hydroxide ion at the less hindered carbonyl group, while the formation of the hydroxy amide (**160**), during the LAH reduction of the methyl ester derivative (**157**), can be explained by intramolecular rearrangement. The hydroxy amide (**160**) is a potential chiral auxiliary for asymmetric Baylis-Hillman reactions; however, the difficulties experienced with this reaction (see **Section 2.3.5.3.5**) resulted in such an investigation being set aside for future studies.

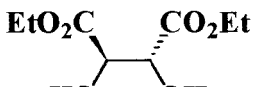
## 2.2

### 2.2.1 Preparation of diols possessing $C_2$ symmetry

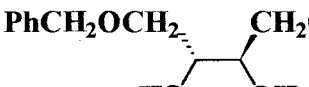
Diols, with a $C_2$ axis of symmetry, are ideal chiral auxiliaries for the formation of chiral acetals as only one stereoisomer of the acetal is produced. Therefore, separation of diastereomers is avoided and the acetals are obtained in high optical purity, making them ideal for asymmetric synthesis. Initially, we decided to use diols derived from tartaric acid, *viz.*, dimethyl tartrate (**166**), diethyl tartrate (**167**) and 1,4-di-*O*-benzyl-D-threitol (**168**).



(166)



(167)

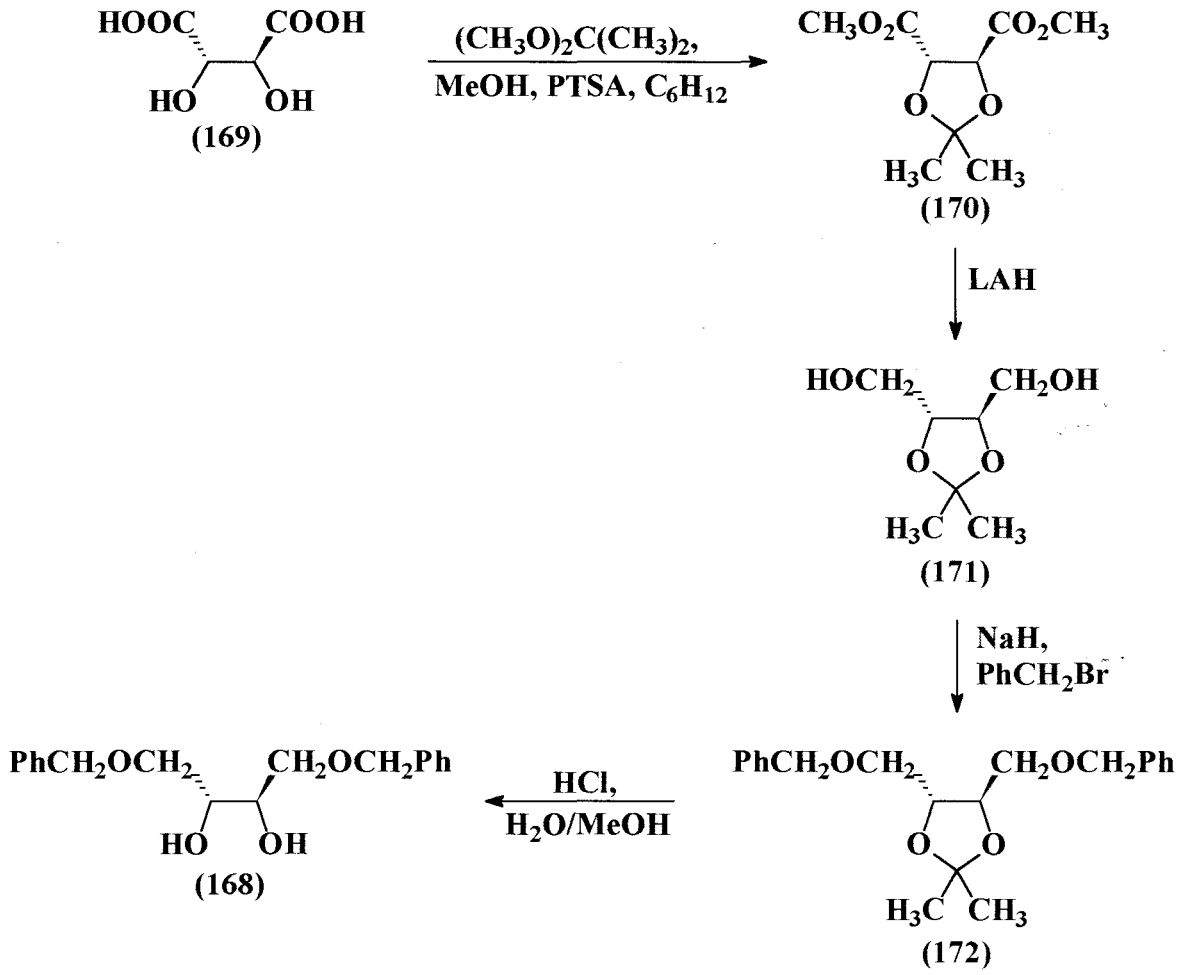


(168)

**FIGURE 14**

Dimethyl and diethyl tartrate are commercially available, while 1,4-di-*O*-benzyl-D-threitol (**168**) was readily prepared, *via* 2,3-di-*O*-isopropylidene-D-threitol (**171**) following the procedure of Mash *et al.*[96] (**Scheme 26**). The 2,3-di-*O*-isopropylidene-D-threitol intermediate (**171**) was prepared by LAH reduction of dimethyl 2,3-di-*O*-isopropylidene-D-tartrate (**170**) which was, itself, synthesised from D-tartaric acid (**169**) and 2,2-dimethoxypropane in the presence of *p*-toluenesulfonic acid (PTSA) and methanol, and using cyclohexane as solvent. Slow distillation of acetone-cyclohexane and methanol-cyclohexane azeotropes, followed by fractional distillation of the residue afforded dimethyl 2,3-di-*O*-isopropylidene-D-tartrate (**170**) in 84 % yield. Alkylation of the D-threitol derivative (**171**), using NaH and benzyl bromide, afforded 1,4-di-*O*-benzyl-2,3-di-*O*-isopropylidene-D-threitol (**172**), which was hydrolysed with 0.5 M HCl in MeOH to afford the target diol (**168**) in an overall yield of 13 %.

The (2*R*,3*R*)-enantiomer of compound (**171**) has been used to prepare a number of useful synthetic derivatives,[97,98,99] all of which are potential chiral auxiliaries possessing $C_2$ symmetry. However, we decided to explore the use of 1,4-di-*O*-benzyl-D-threitol (**168**) since it is a solid, making handling easier, and because the benzyl moieties are relatively large blocking groups and, as UV chromophores, were expected to make the detection of derivatives easier.




**SCHEME 26**

The 1,4-di-*O*-benzyl-D-threitol (**168**) was fully characterised using 1D- and 2D NMR techniques as the reported spectral data,[96] of the (2*R*,3*R*)-enantiomer, did not report $^1H$ and $^{13}C$ signal assignments. The hydroxyl protons were identified by $D_2O$ exchange,

which resulted in a decrease in the intensity of the broad singlet at 2.86 ppm. The COSY spectrum permitted assignment of the multiplet at 3.86 ppm to the 2- and 3-methine groups, coupling of these nuclei to both the 1- and 4-methylene groups (resonating at 3.60 ppm) and to the hydroxyl protons being clearly evident (see **Figure**

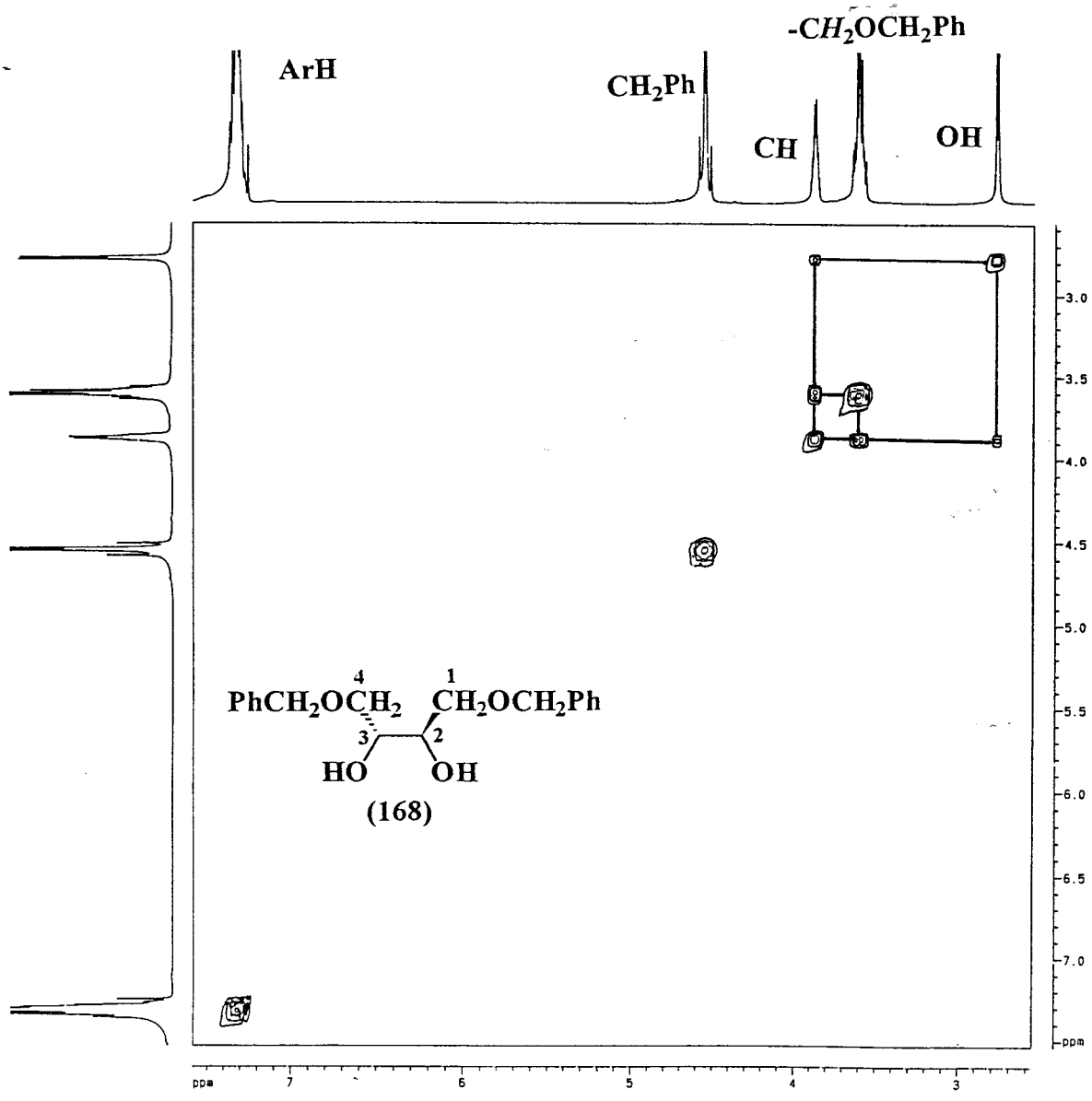
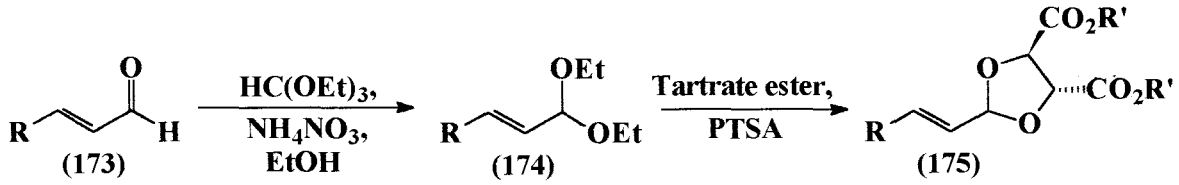



**FIGURE 15.** The COSY spectrum of 1,4-di-*O*-benzyl-*D*-threitol (**168**) in $CDCl_3$.

### 2.2.2 Preparation of acetals of diols possessing $C_2$ symmetry

While many efficient procedures have been developed for the acetalization of saturated aldehydes,[9, 100, 101] methods for preparation of α,β-unsaturated acetals are less common,[102-105] and usually suffer from poor yields, tedious procedures or the use of expensive reagents. Migration of the double bond can occur in the acid catalysed formation of α,β-unsaturated acetals, but this can be avoided by using milder reaction conditions and/or milder acid catalysts.[9]

Yamamoto *et al.*[74] reported that direct acetalization of aldehydes with tartaric acid esters occurs with low yields, whereas transacetalization of the crude dialkoxy derivative (**174**) affords the desired acetals in higher yields (**Scheme 27**). (The dialkoxy acetal (**174**) was obtained after vigorous stirring of the aldehyde with triethyl orthoformate, in the presence of $NH_4NO_3$ for 2 days, in dry ethanol.) Using this method, the cinnamaldehyde diethyl tartrate acetal (**176**) was successfully prepared, albeit in low yields (< 25 %); numerous attempts failed to improve the yield.

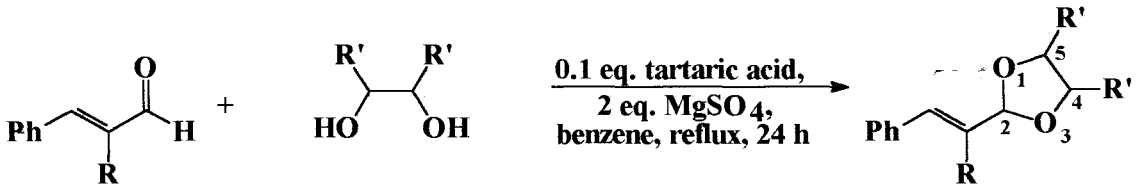



**SCHEME 27**

On the other hand, direct acetalization of various cinnamaldehyde and α-methylcinnamaldehyde with the tartrate-derived diols (**166**), (**167**) and (**168**), using a method developed by Ta-Jung Lu *et al.*,[106] afforded the acetals (**176-179**) (**Table 11**) in higher yields. These authors used mild acid catalysts, such as tartaric acid and oxalic acid, to prevent isomerization of the double bond, and anhydrous $MgSO_4$ to suppress by-product formation and increase yields. In our study, tartaric acid was used as the

acid catalyst and the acetals were obtained in yields ranging from 42 to 77 %.

**Table 11:** Data for the acetalization of tartrate-derived diols.




| Entry | Config. | R | R' | Yield/ %[a] | Acetal |
|---|---|---|---|---|---|
| 1 | (4*R*,5*R*) | H | $CO_2Et$ | 54 | **176** |
| 2 | (4*R*,5*R*) | H | $CO_2Me$ | 48 | **177** |
| 3 | (4*S*,5*S*) | H | $CH_2OCH_2Ph$ | 42 | **178** |
| 4 | (4*R*,5*R*) | $CH_3$ | $CO_2Et$ | 77 | **179** |

[a] Pure isolated yield.

The chiral acetals (**176-179**) were all unambiguously characterised using NMR spectroscopy. It is apparent from the $^1H$ NMR spectra of acetal (**178**) (**Figure 16**), that the double bond has neither migrated (being part of a conjugate system already[107]) nor isomerised, the large coupling between the vinylic protons (16 Hz) being indicative of their *trans* relationship.

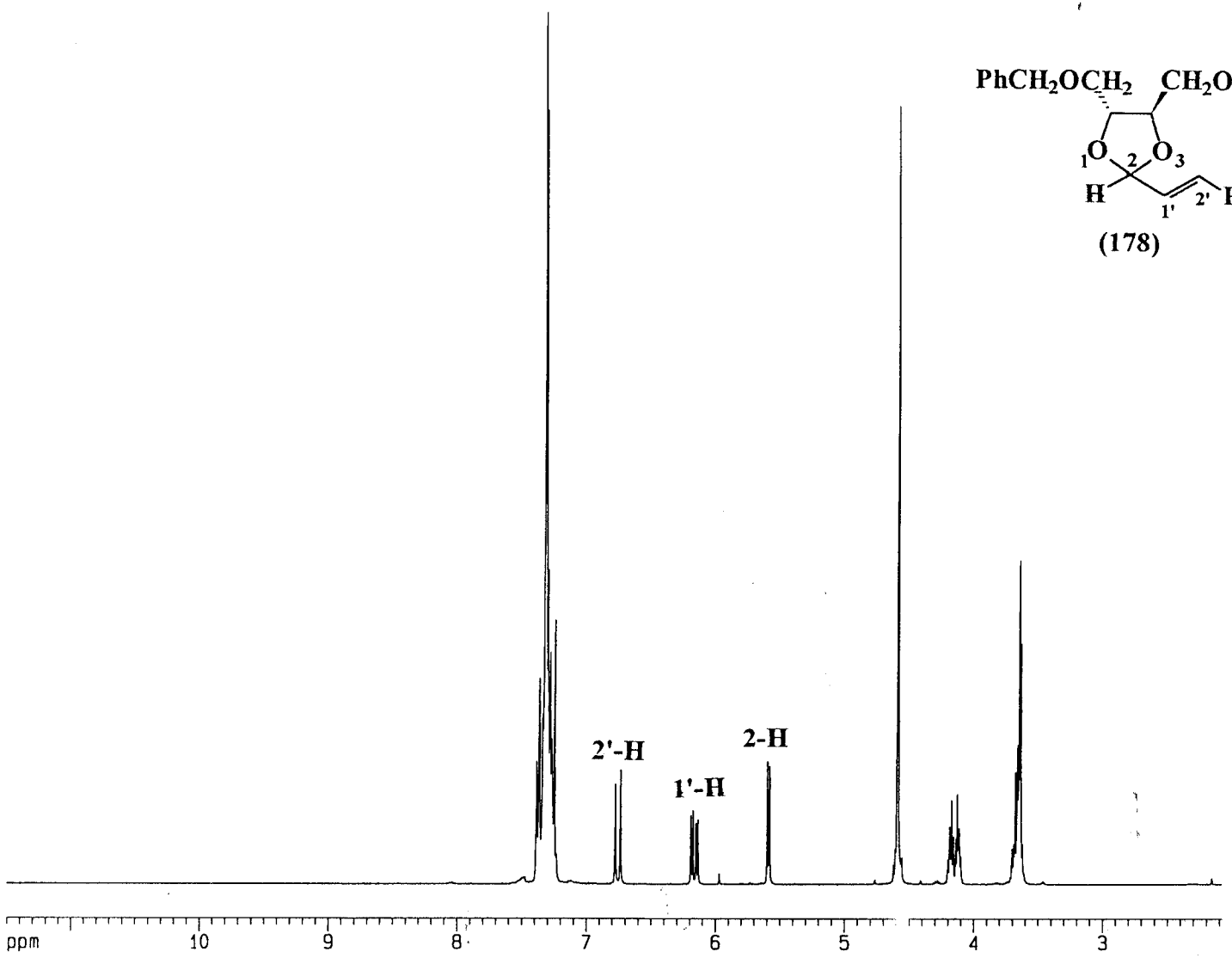



**Figure 16.** The 400 MHz $^{1}H$ NMR spectrum of acetal (**178**) in $CDCl_3$.

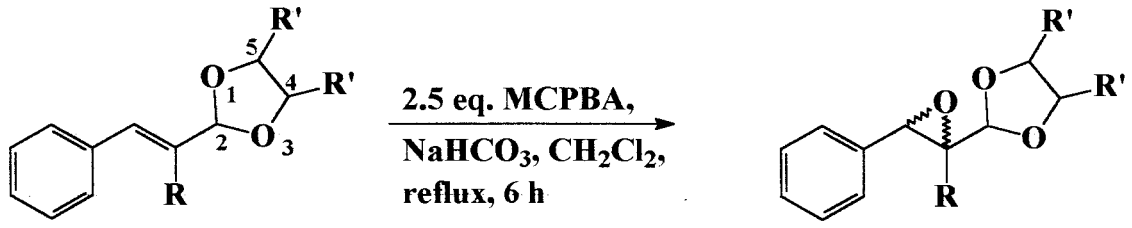
### 2.2.3 Asymmetric epoxidations

Diols containing a $C_2$ axis of symmetry have been used very successfully in asymmetric epoxidation. In the classic Sharpless epoxidation,[108, 109] allylic and homoallylic alcohols are treated with *tert*-butyl hydroperoxide in the presence of $Ti(O\text{-}iPr)_4$ and diethyl tartrate to produce epoxy alcohols of high enantiomeric purity (usually > 90 % e.e.). The high enantioselectivity observed in these reactions is attributed to asymmetric induction by the diethyl tartrate, which acts as an optically active catalyst. Surprisingly, an extensive literature search revealed only one reference to the attempted asymmetric epoxidation of chiral acetals, in which a diol having $C_2$ symmetry behaves as a chiral auxiliary rather than as a chiral catalyst. The attempt, by Alexakis *et al.*, involved MCPBA epoxidation of the crotonaldehyde acetal derived from 2,3-butanediol and gave an inseparable 1:1 mixture of both possible diastereomers.[17] The apparent absence of other reports on the asymmetric epoxidation of chiral acetals prompted us to apply this reaction to various chiral acetals synthesised in the course of this study.

The MCPBA epoxidation of the diethyl tartrate-derived acetal (**176**) was examined first to establish an efficient general procedure for the epoxidation of chiral acetals. The reaction was carried out using $CH_2Cl_2$ as solvent and solid $NaHCO_3$ [110] to prevent cleavage of the acid sensitve acetal group, and solid MCPBA (2.5 eq.) was added to the vigorously stirred two phase system. The reaction temperature was found to affect the rate of epoxidation but not the stereoselectivity of addition. At 4 °C, several days of vigorous stirring was shown, by NMR spectroscopy, to afford very little epoxide, and the yield was not increased by adding a further 2.5 eq. of MCPBA. Epoxidation of the acetal (**176**) at room temperature resulted in an increase in the yield, but NMR spectroscopy indicated that the major component of the crude material, isolated after stirring for two days, was still the unreacted acetal. Total conversion of the acetal (**176**)

to the epoxide (**180**) was finally achieved by boiling the reaction mixture under reflux for six hours. Epoxidation of the tartrate acetals (**177-179**) with MCPBA was therefore carried out under reflux, to produce mixtures of the corresponding diastereomeric epoxides (**180-183**) (**Table 12**), which could not be separated by preparative layer or flash chromatography.

**Table 12** Data for the MCPBA epoxidation of tartrate-derived acetals (**176-179**)




| Acetal | R | R' | Config. | Product no. | Isolated yield/ % | Diastereomeric ratio[a] |
|---|---|---|---|---|---|---|
| **176** | H | $CO_2Et$ | (4*R*,5*R*) | **180** | 46 | 54:46 |
| **177** | H | $CO_2Me$ | (4*R*,5*R*) | **181** | 98 | 52:48 |
| **178** | H | $CH_2OCH_2Ph$ | (4*S*,5*S*) | **182** | 96 | 56:44 |
| **179** | $CH_3$ | $CO_2Et$ | (4*R*,5*R*) | **183** | 88 | 56:44 |

[a] Determined by $^1H$ and $^{13}C$ NMR spectroscopy.

The $^1H$ NMR spectra of the crude reaction mixtures clearly reflected the formation of the acetal epoxides as there are large chemical shift differences between the substrate 2-methine and vinyl proton signals. In the spectrum of the diethyl acetal (**176**), for example, the 1'- and 2'-vinyl protons resonate as a doublet of doublets (6.24 ppm) and a doublet (6.84 ppm) respectively, while the 2-methine nucleus appears as a doublet at 5.81 ppm (**Figure 17a**). In the spectrum of the corresponding epoxide (**180**) (**Figure 17b**), the 1'-H nucleus resonates as a multiplet at 3.29 ppm while the 2'-H and 2-

methine nuclei are observed as doublets at *ca.* 5.34 ppm and *ca.* 3.96 ppm respectively. The diastereomeric ratio was calculated, in each case, by integration of the well-resolved 2'-H signal (*ca.* 5.34 ppm) corresponding to the major and minor diastereomers (see **Table 12**). The diastereomeric ratios were also determined by integration of the $^{13}C$ signals of corresponding carbon atoms in each pair of diastereomers. Differences in NOE and relaxation time for diastereomers are considered negligible[93] and, consequently, signal intensities should be proportional to concentration. The diastereomeric ratios determined using the $^{13}C$ NMR data were, in fact, the same as those determined using the $^{1}H$ NMR data.

Given the low diastereomeric excesses observed (4-12 %), no attempt was made to separate the products. Computer modelling of acetal (**178**) (**Figure 18**) suggests that both faces of the double bond are readily accessible and that the chiral acetal moiety can rotate freely. Increasing the rotational barrier by introducing an α-methyl group, as in acetal (**179**), only effects a marginal improvement in selectivity (**Table 12**; entry 4). There is also a small, but hardly significant, increase in stereocontrol as the steric bulk of the R' is increased (*cf.* entries 1-3).

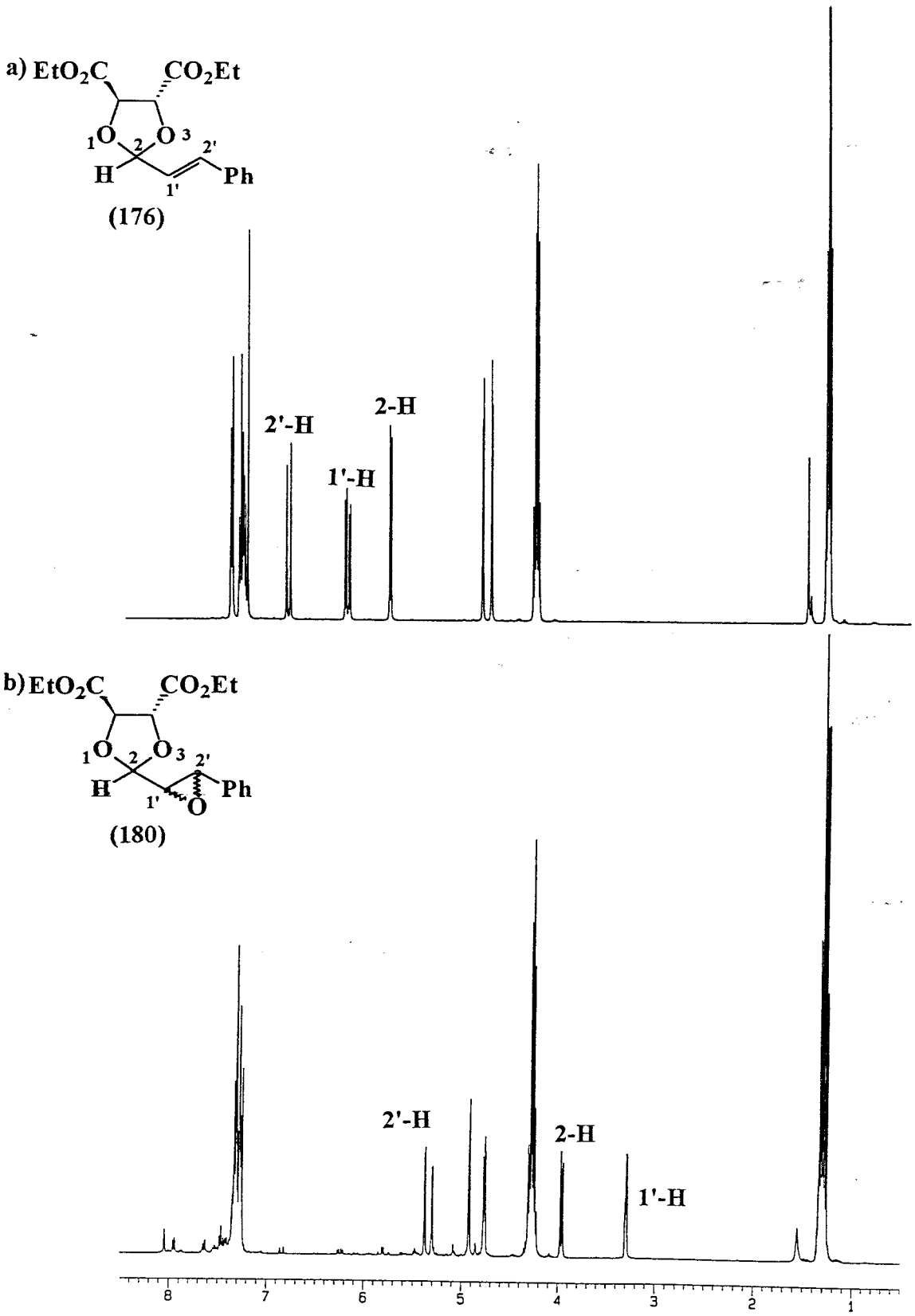
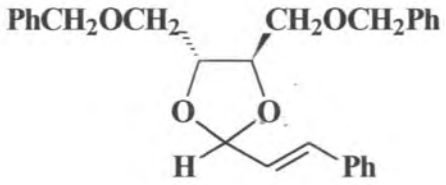



**FIGURE 17.** The 400 MHz $^1$H NMR spectra of **a)** acetal (**176**) and **b)** epoxy acetal (**180**) in $CDCl_3$.




(178)

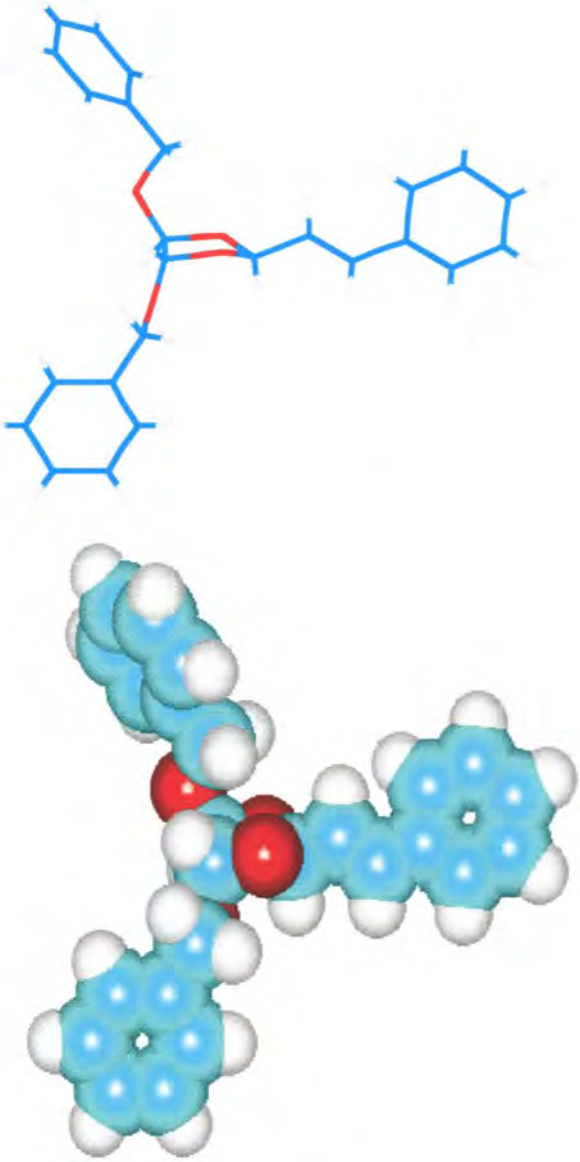


**FIGURE 18.** Computer-generated stick and space-filling models of acetal (**178**).

In an attempt to improve the stereoselectivity of epoxidation attention was given to the use of an epoxidising agent with the ability to chelate to the substrate. Magnesium monoperoxyphthalate hexahydrate (MMPP) was therefore used in the expectation that preferential chelation of the metal atom to one of the acetal oxygens would result in face-selective delivery of the oxygen atom to the double bond. However, under various conditions[111] and using a number of acetals (**Table 13**) epoxidation with MMPP could not be achieved, $^1$H NMR spectroscopy indicating, in each case, the presence of unreacted substrate alone.

**Table 13** Summary of the conditions for the attempted epoxidations of unsaturated acetals (**177**) and (**178**) with MMPP

| Entry | Acetal | Solvent | Ratio Acetal:MMPP | Phase transfer catalyst | Time/ h, temp/ °C |
|---|---|---|---|---|---|
| 1 | **178** | $CH_2Cl_2/H_2O$ | 1:1.2 | BTAC | 7, r.t |
| 2 | **178** | $CHCl_3/H_2O$ | 1:1.2 | BTAC | 3, 53 |
| 3 | **178** | $iPrOH/H_2O$ | 1:1.2 | BTAC | 3, 60 |
| 4 | **177** | $CHCl_3/H_2O$ | 1:1.2 | CTAB | 3, reflux |
| 5 | **177** | $CHCl_3/H_2O$/pyridine | 1:2 | CTAB | 3, reflux |

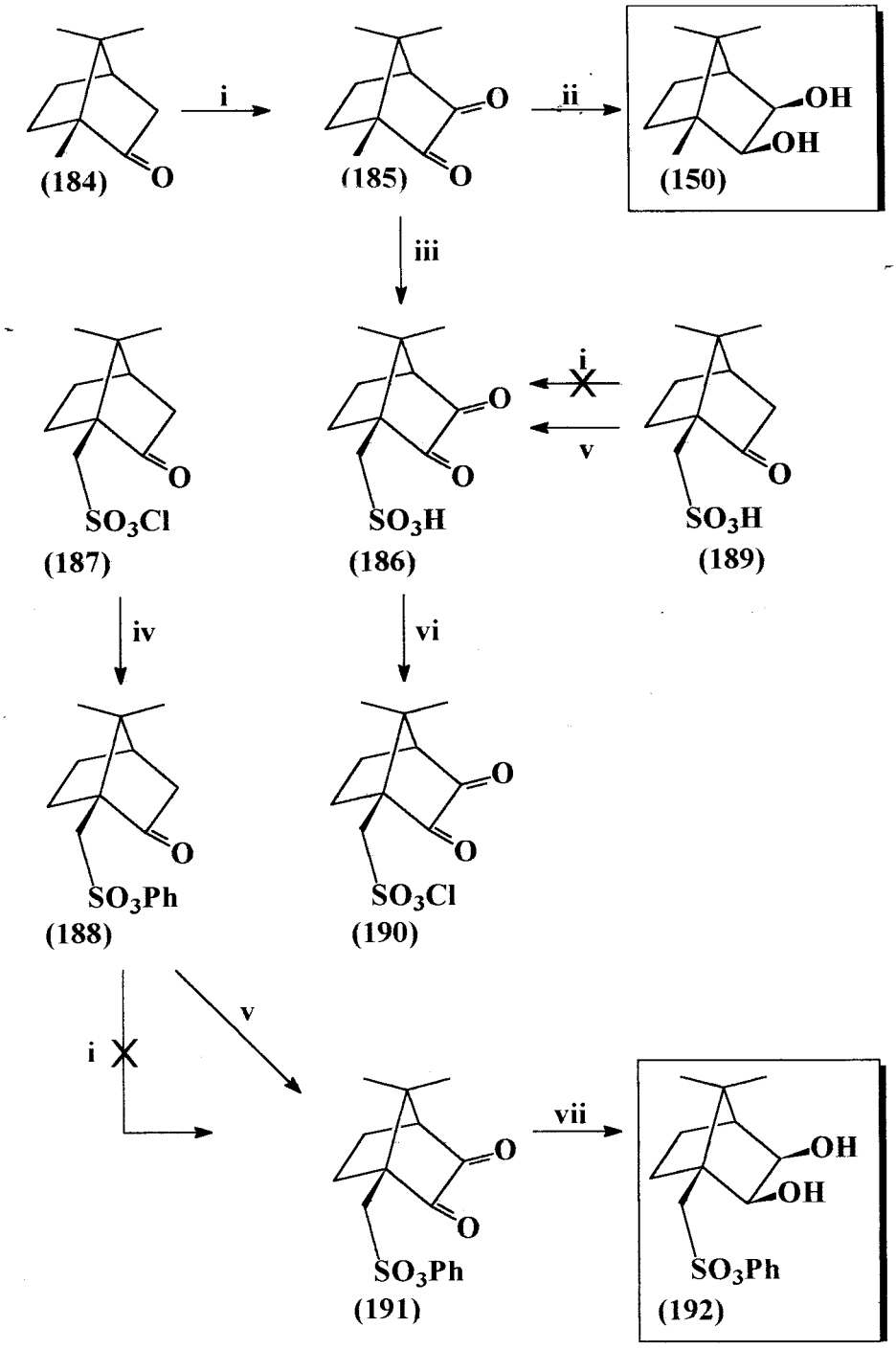
BTAC = benzyltriethylammonium chloride; CTAB = cetyltrimethylammonium bromide.

## 2.3 CAMPHOR-DERIVED DIOLS AS CHIRAL AUXILIARIES

Camphor (**184**) has been studied in our laboratories, for a number of years, as a convenient precursor in the preparation of novel chiral auxiliaries. In the present study, the bornane-2,3-diols (**150**) and (**192**) (**Scheme 28**) were prepared for use in the synthesis of chiral acetals of various aldehydes. Although compound (**150**) has recently been employed in the formation of chiral acetals,[71, 82] the diol (**192**) appears to be a novel compound. Acetal derivatives of the bornane-2,3-diols (**150**) and (**192**) would possess the rigid, bicyclic, camphor skeleton, and the close co-ordination sites provided by the oxygen atoms of the acetal ring, were expected to facilitate the formation of rigid transition states in asymmetric reactions. The diol (**192**) has the further advantage of possessing a relatively large blocking group at C-10 of the camphor skeleton, which, it was hoped, would prevent co-ordination at the proximate acetal oxygen atom or block attack at a prochiral centre from one face.

### 2.3.1 Preparation of bornane-2,3-diols

Camphorquinone (**185**), readily prepared from camphor (**184**) by oxidation with selenium dioxide ($SeO_2$) in acetic anhydride, was reduced by LAH in ether to afford 2-*exo*,3-*exo*-bornanediol (**150**) in high yield (**Scheme 28**). However, analogous oxidation of phenyl bornane-10-sulfonate (**188**) and camphor-10-sulfonic acid (**189**) with $SeO_2$ proved unsuccessful. Camphorquinone-10-sulfonic acid (**186**) was obtained both by sulfonation of camphorquinone (**185**), under conditions similar to those used for the synthesis of Reychlers acid,[112] and by the action of selenous acid ($H_2SeO_3$)[113] on camphor-10-sulfonic acid (**189**), in yields of 23 and 57 %, respectively.




**Reagents : i) $SeO_2$, acetic anhydride, ii) LAH, ether, iii) $H_2SO_4$, acetic anhydride, iv) phenol, pyridine, v) $H_2SeO_3$, dioxane, vi) $SOCl_2$, DMF, vii) $NaBH_4$, MeOH.**

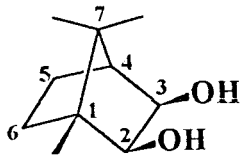
**SCHEME 28**

Formation of camphorquinone-10-sulfonyl chloride (**190**) by reaction of camphorquinone-10-sulfonic acid (**186**) with thionyl chloride[114, 115] in cold DMF was achieved in low yield (27 %) and, moreover, tedious ion-exchange chromatography was required for the purification of camphorquinone-10-sulfonic acid (**186**) derived from the sulfonic acid (**189**). Consequently, an alternative approach to the diol (**192**) was investigated. In this approach, the phenyl ester (**188**) was prepared from the sulfonyl chloride (**187**) and then oxidised directly to the camphorquinone ester (**191**) by gentle reflux for 72 h in the presence of $H_2SeO_3$, in dioxane. Reduction of the quinone (**191**) to afford the phenyl 2-*exo*,3-*exo*-dihydroxybornane-10-sulfonate (**192**) was finally achieved using two equivalents of $NaBH_4$ in methanol at 0°C; use of LAH in $Et_2O$, on the other hand, afforded a dark oil, which was shown by $^1H$ NMR spectroscopy to contain none of the desired diol (**192**).

The bornane-2,3-diols (**150**) and (**192**) were fully characterised by 1D- and 2D-NMR spectroscopy. The pair of doublets at 2.67 and 2.77 ppm in the $^1H$ NMR spectrum (**Figure 19a**) of the diol (**150**) were assigned to the 2- and 3-*exo*-hydroxyl protons since, when $D_2O$ was added to the NMR tube (**Figure 19b**), their signal intensity decreased and their coupling to the 2- and 3-*endo* protons, which resonate as multiplets at 3.59 and 3.82 ppm in **Figure 19a**, but as a pair of doublets in **Figure 19b**. Assignment of the 2- and 3-*exo*-hydroxyl protons of phenyl 2-*exo*,3-*exo*-dihydroxybornane-10-sulfonate (**192**) to the signals at 3.05 and 3.21 ppm (**Figure 20**) was also facilitated by deuterium exchange. This assignment was supported by the inverse HETCOR spectrum (**Figure 21**), in which the hydroxyl proton signals show no correlation with a carbon nucleus. It is also apparent from the HETCOR spectrum that the pair of doublets at 3.13 and 3.78 ppm correspond to the diastereotopic 10-methylene protons. The 2- and 3-*endo* protons, which resonate at 3.88 and 4.16 ppm (**Figure 20a**), collapse to doublets in the presence of $D_2O$ (**Figure 20b**) and each correlates to a

separate carbon nucleus in the HETCOR spectrum.

a)




(150)




b)

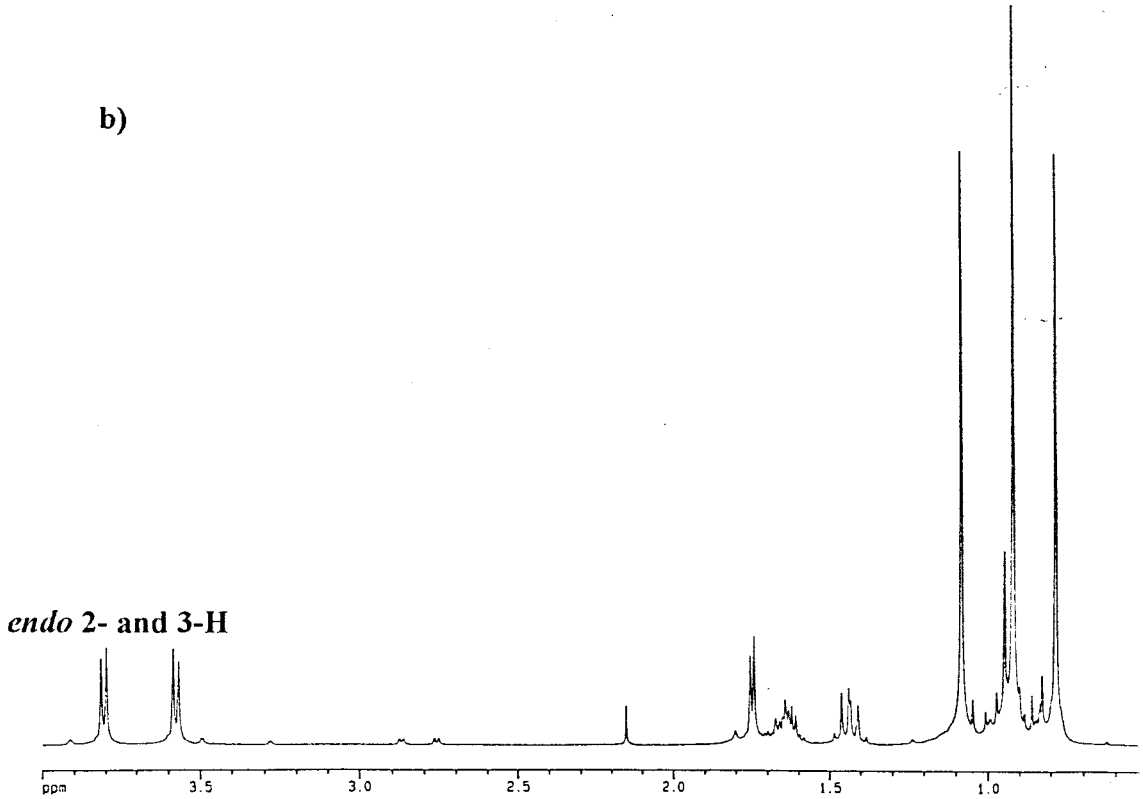



**FIGURE 19.** The 400 MHz $^1$H NMR spectra of the diol (**150**):-(**a**) in $CDCl_3$ and (**b**) after $D_2O$ exchange.

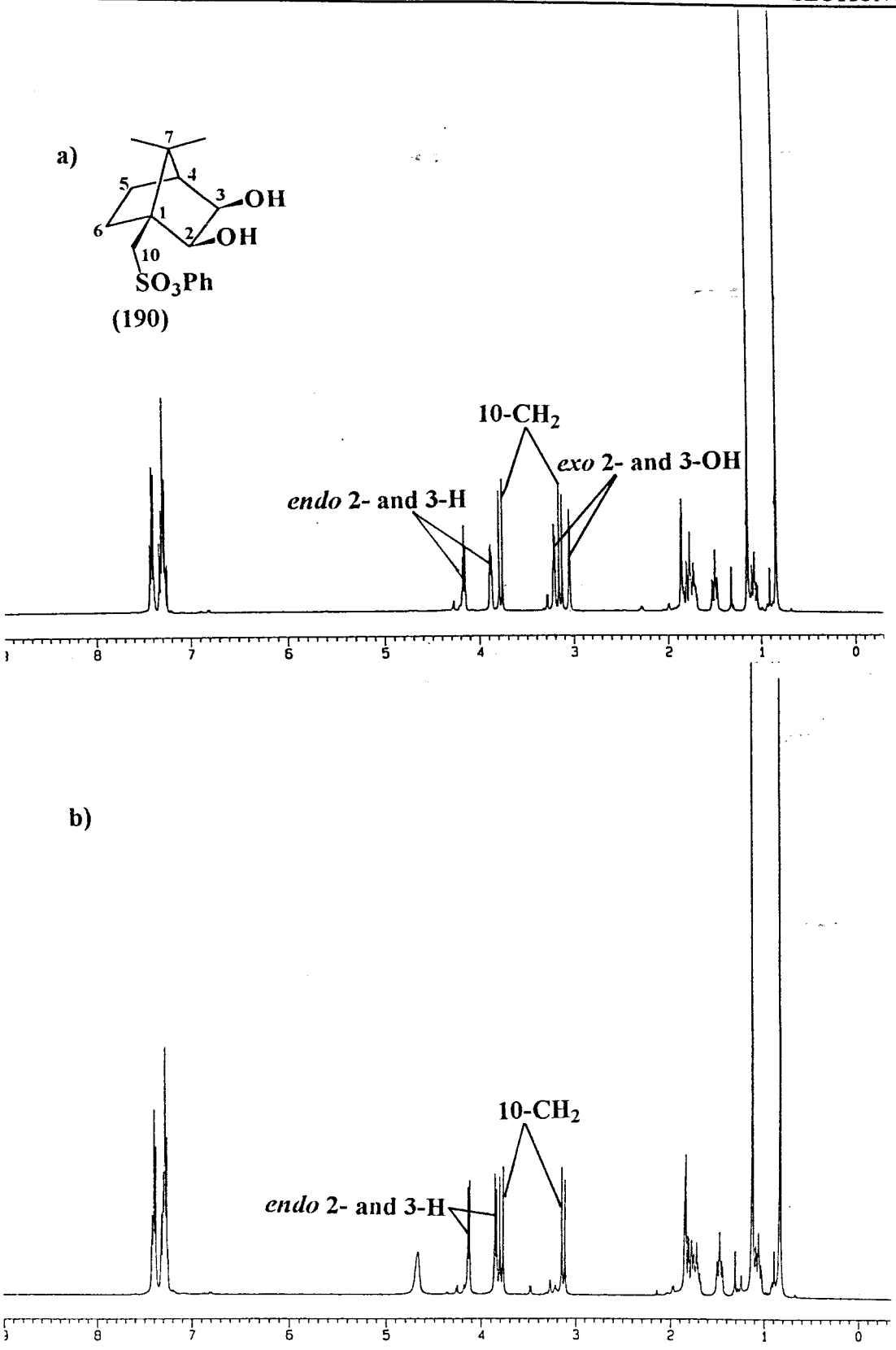



**FIGURE 20.** The 400 MHz $^1H$ NMR spectra of the diol (**190**):-(**a**) in $CDCl_3$ and (**b**) after $D_2O$ exchange.

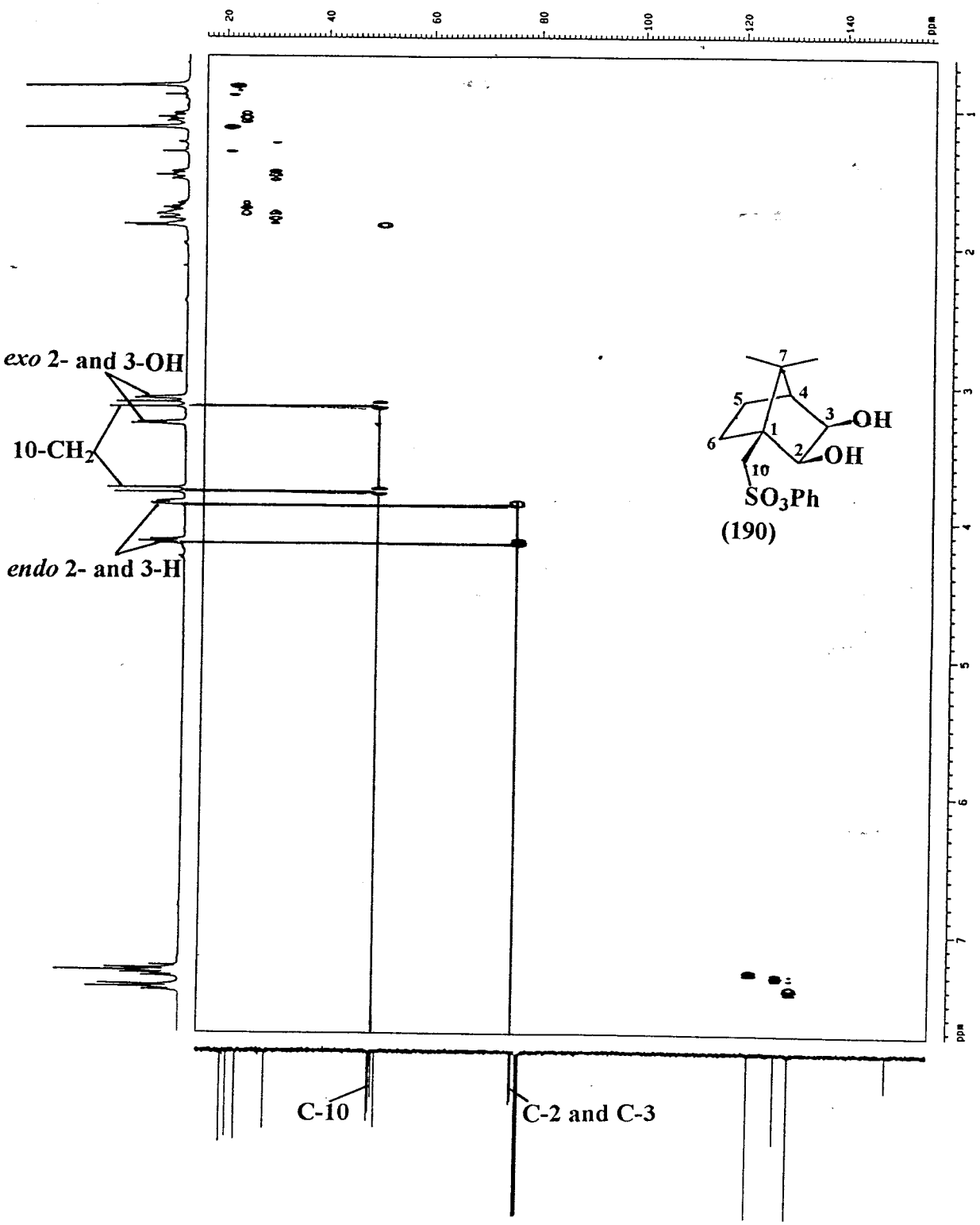
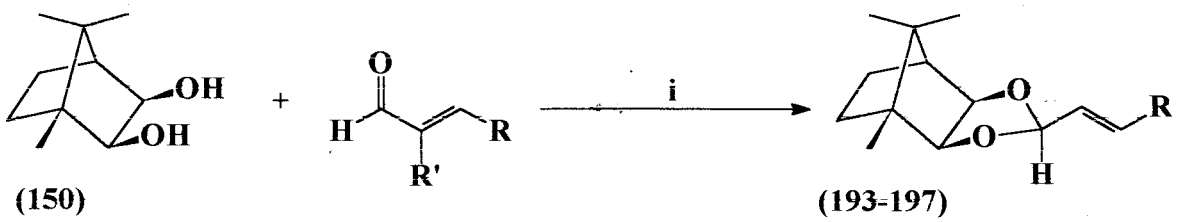



**FIGURE 21.** The inverse HETCOR spectrum of phenyl 2-*exo*,3-*exo*-dihydroxybornane-10-sulfonate (**190**) in $CDCl_3$.

### 2.3.2 Preparation of acetals of the bornane-2-*exo*,3-*exo*-diol

In developing a procedure for the synthesis of α,β-unsaturated acetals from the bornanediol (**150**) we had to bear in mind the possibility of double bond migration if the $pK_a$ of the acid catalyst exceeded 3,[9] and the capacity of the camphor skeleton to undergo rearrangement. The first synthetic procedure attempted involved addition of the diol (**150**) to a mixture of cinnamaldehyde and 0.1 equivalents of tartaric acid, in benzene at room temperature. However, TLC analysis revealed no development of product after several hours - a situation attributed to the mild conditions or the fact that conjugation deactivates[116, 117] the carbonyl group towards acetal formation.

The tartaric acid was therefore replaced by PTSA; the reaction was monitored by TLC and, after stirring at room temperature for 2 h, none of the starting aldehyde could be detected. The addition of anhydrous $MgSO_4$ (to remove water produced during the reaction and to suppress by-product formation) gave marginally improved reaction yield. This method was then used to synthesise a variety of acetals from the bornanediol (**150**) and numerous α,β-unsaturated aldehydes (**Scheme 29**).




(150) (193-197)

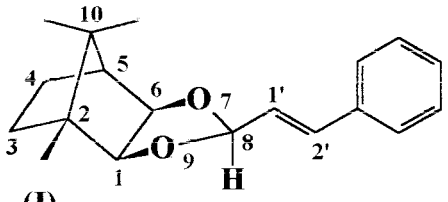
**Reagents: i) PTSA, $MgSO_4$, benzene**

| R | R' | Pure yield/ % | Acetal |
|---|---|---|---|
| H | H | 77 | **193** |
| $CH_3$ | H | 78 | **194** |
| $CH_3(CH_2)_2$ | H | 70 | **195** |
| Ph | H | 69 | **196** |
| Ph | $CH_3$ | 70 | **197** |

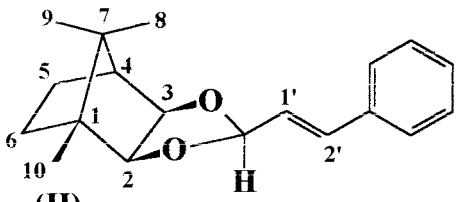
**SCHEME 29**

The acetals (**193-197**) are all new compounds and were all fully characterised by $^1H$ and $^{13}C$ NMR spectroscopy and high resolution mass spectrometry. Although the diol (**150**) does not possess a $C_2$ axis of symmetry, only a single diastereomeric acetal was detectable by NMR spectroscopy, in each case. It is apparent from the $^1H$ NMR spectra of the acetals [illustrated for acetal (**196**)[¥] in (**Figure 22**)] that the camphor skeleton

[¥] The acetal (**196**) maybe systematically named as (1*S*,2*R*,5*S*,6*R*,8*R*)-2,10,10-trimethyl-8-styryl-7,9-dioxatricyclo[4.3.0.$1^{2,5}$]decane (**I**), but for convenience the conventional numbering of the camphor skeleton (**II**) has been retained in the discussion.




(I)




(II)

remained intact and that no rearrangement had occurred during acetalization. The 2- and 3-*endo* protons resonate as a pair of doublets at 3.86 and 4.04 ppm (**Figure 22**), their multiplicity confirming the formation of the acetal (**196**).* The 2'- and 3'-vinyl proton signals resonate at 6.24 (dd) and 6.80 (d) ppm respectively, the large vicinal coupling constant ($J_{2',3'}$ 16 Hz) indicating a *trans* relationship. This coupling is clearly apparent in the COSY spectrum (**Figure 23**), as is the 6.3 Hz coupling between the 2'-vinyl proton and the 1'-methine proton, which resonates as a doublet at 5.21 ppm.

* The 2- and 3-*endo* protons occur as multiplets in the $^1$H NMR spectrum of the diol (**150**) (**Figure 19a**) due to coupling to the hydroxyl protons which, are lost during acetalization.

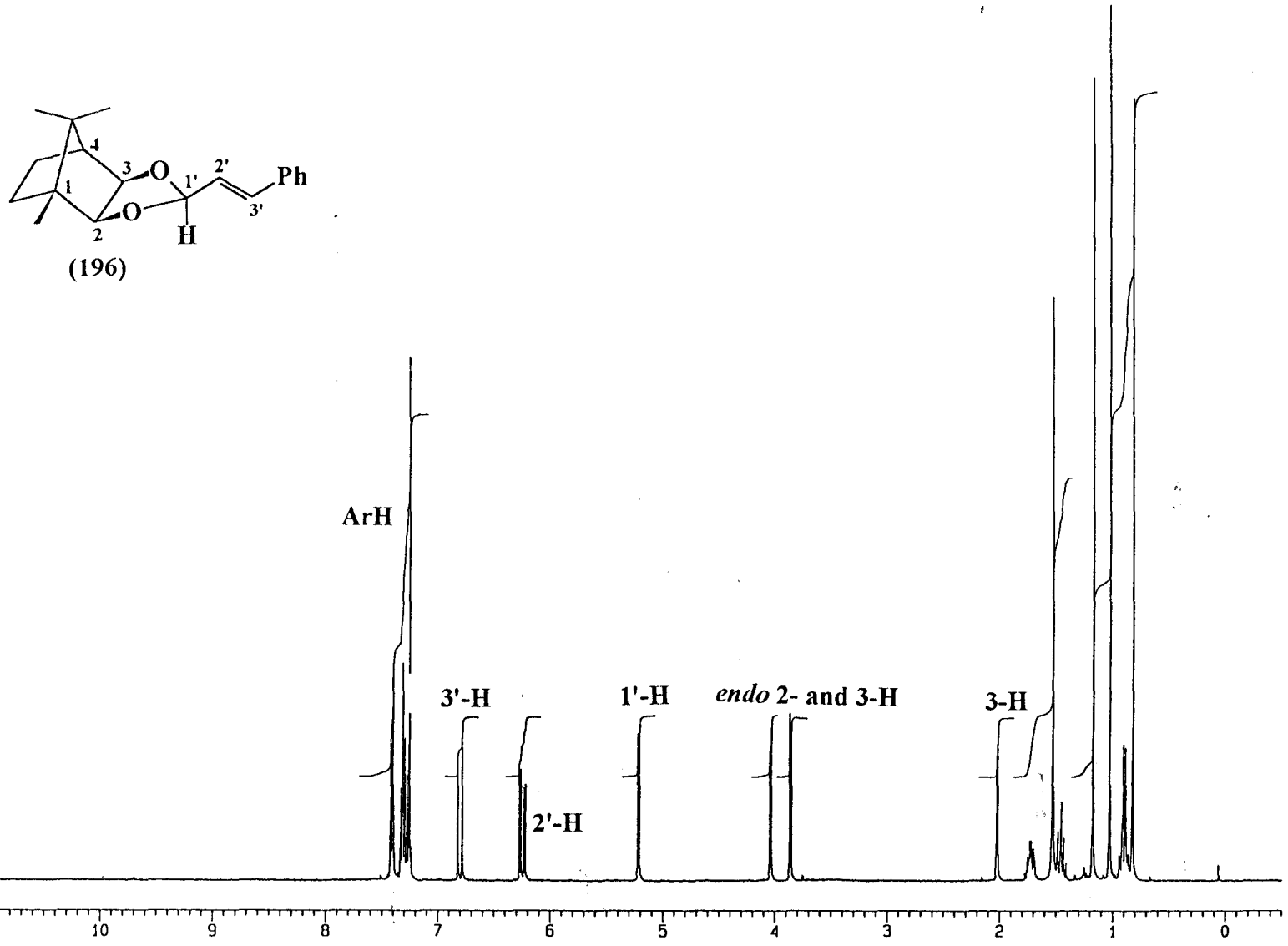



**FIGURE 22.** The 400 MHz $^1$H NMR spectrum of the acetal (**196**) in $CDCl_3$.

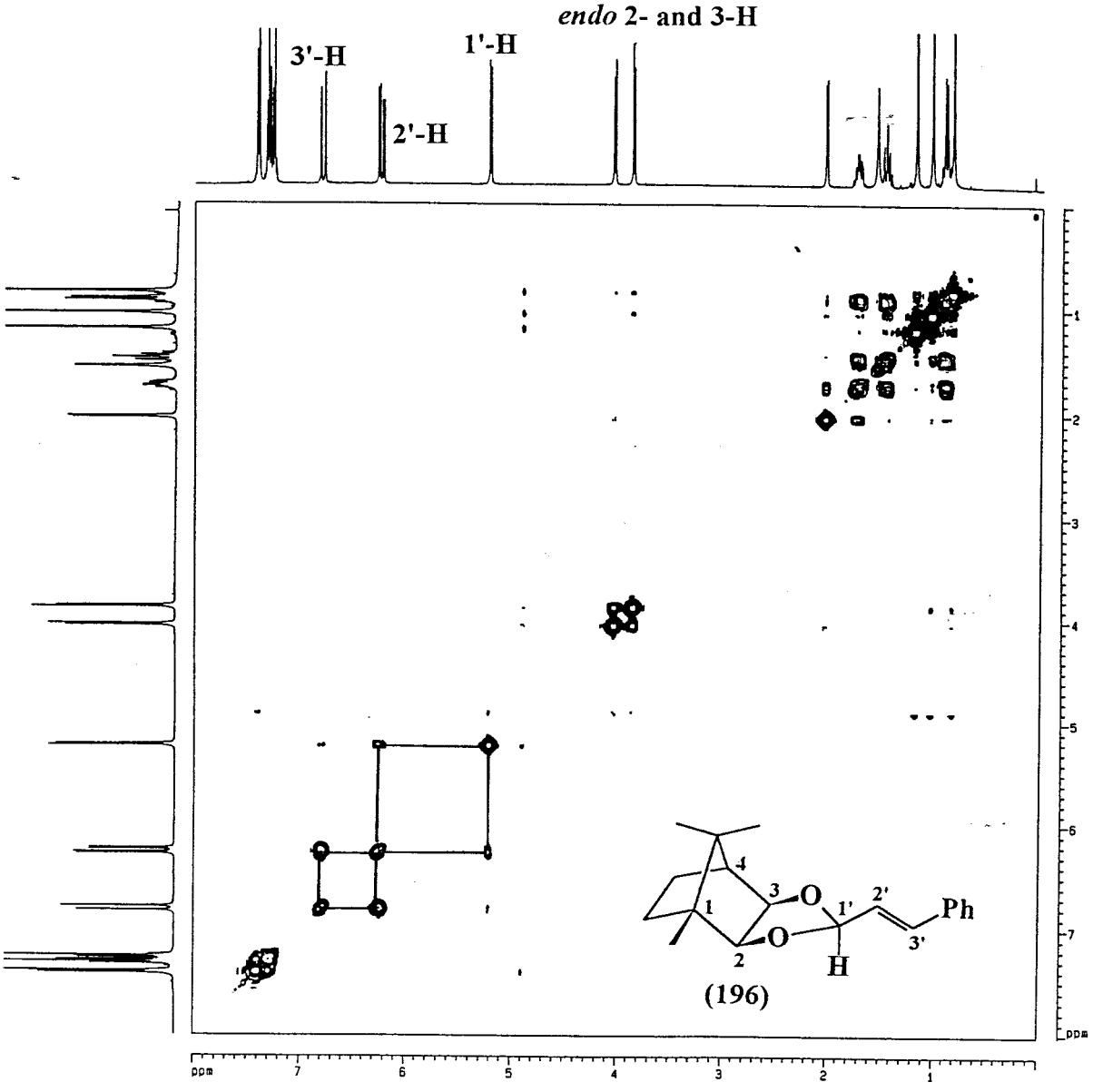
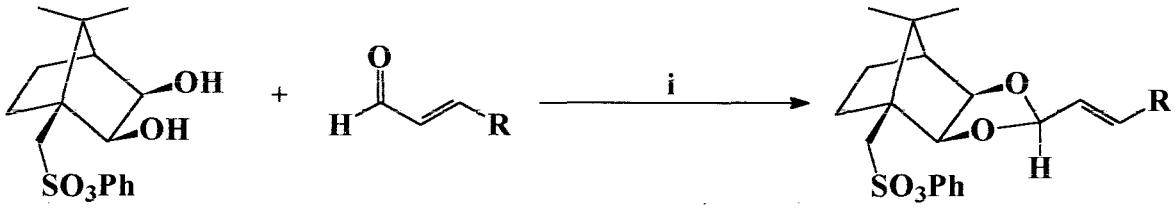



**FIGURE 23.** The COSY spectrum of the acetal (**196**) in $CDCl_3$.

### 2.3.3 Preparation of acetals of phenyl 2-*exo*,3-*exo*-dihydroxybornane-10-sulfonate

The acetals (**198-202**) (**Scheme 30**) were prepared by reacting phenyl 2-*exo*,3-*exo*-dihydroxybornane-10-sulfonate (**192**) with a selection of α,β-unsaturated aldehydes, following the procedure used for the synthesis of the bornane-2,3-diol derived acetals (**193-197**).




**(192)** **(198-202)**

**Reagents: i) PTSA, $MgSO_4$, benzene**

| R | Pure yield/ % | Acetal |
|---|---|---|
| H | 64 | **198** |
| $CH_3$ | 74 | **199** |
| $CH_3(CH_2)_2$ | 76 | **200** |
| Ph | 73 | **201** |
| 2-$NO_2$Ph | 72 | **202** |

**SCHEME 30**

The acetals (**198-202**) are also new compounds and were all fully characterised by $^1H$ and $^{13}C$ NMR spectroscopy and high resolution mass spectrometry. As was the case with the acetals (**193-197**), derived from bornane-2,3-diol (**150**), NMR spectroscopy revealed the formation of diastereomerically pure products, which were readily isolated and purified by flash chromatography. The $^1H$ NMR spectrum of acetal (**201**) (**Figure**

**24**) is typical of the series. In fact, apart from an additional pair of doublets (at 3.20 and 3.84 ppm), due to the diastereotopic 10-methylene protons, and a doubling of the aromatic proton intergrals, indicating the presence of an extra phenyl group, the $^1$H NMR spectrum of the acetal (**201**) is very similar to that of the corresponding cinnamaldehyde acetal (**196**) of the bornane-2,3-diol (**150**) (**Figure 22**).

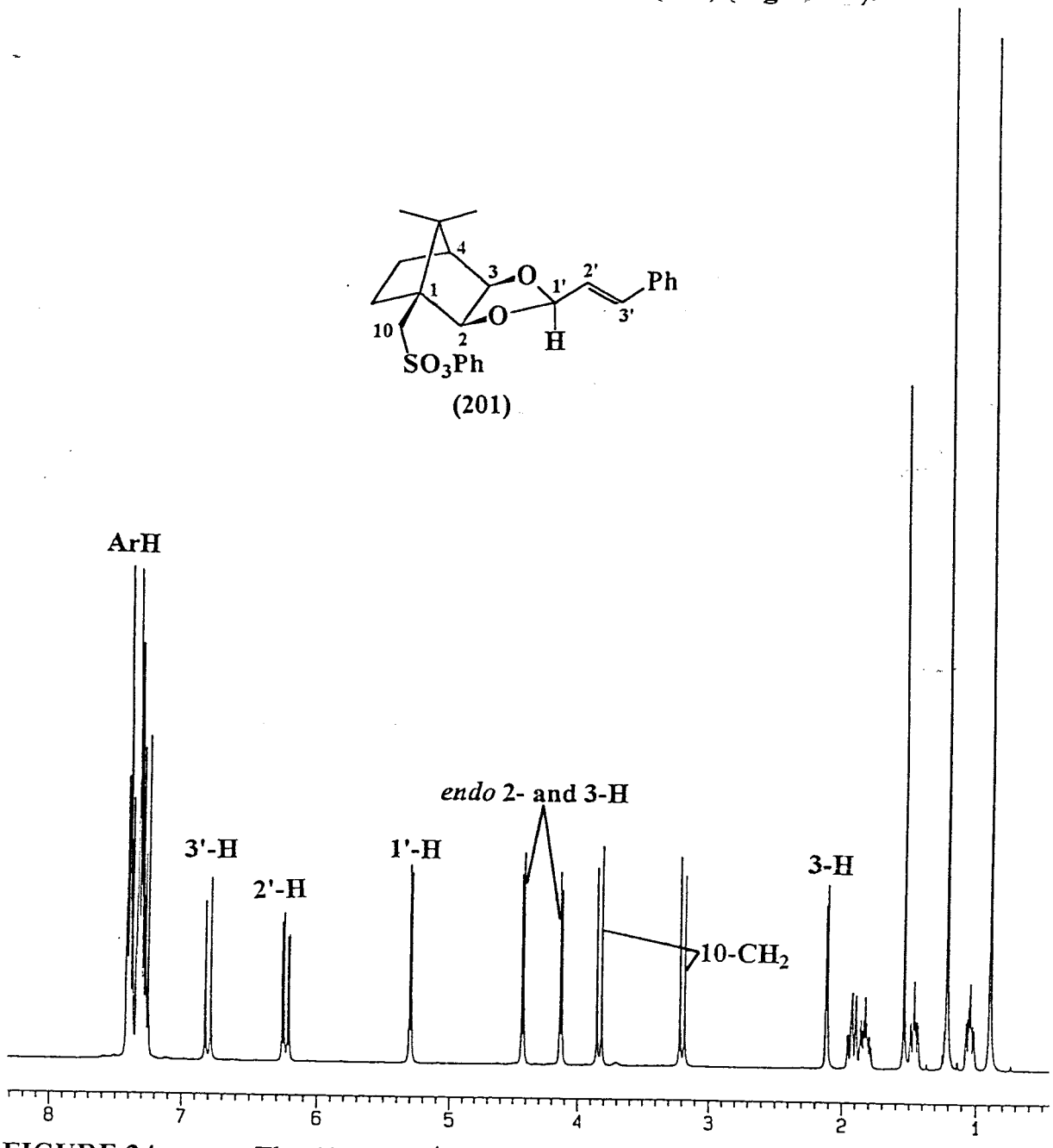
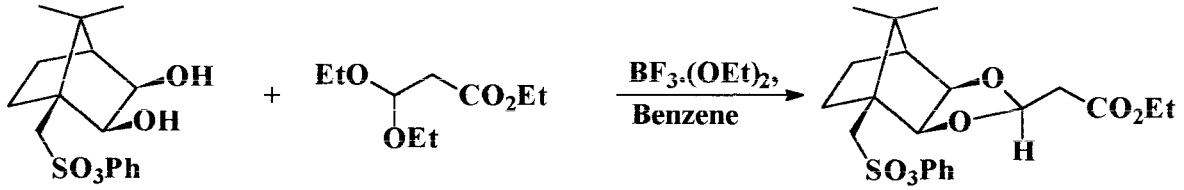



**FIGURE 24.** The 400 MHz $^1$H NMR spectrum of the acetal (**201**) in $CDCl_3$.

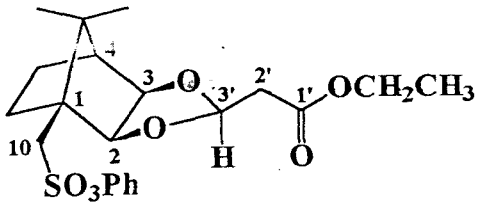
The bornane-2,3-diol (**192**) was also used to prepare carbethoxymethyldioxolane (**204**) in 85 % yield, by reacting equimolar amounts of ethyl 3,3-diethoxypropionate (**203**) and the diol (**192**) in the presence of boron trifluoride etherate, in benzene for 30 min (**Scheme 31**).[71] This acetal (**204**) was prepared as a model substrate to explore the diastereofacial selectivity of electrophilic attack on the carboxylic ester enolate derivative.




**(192)** **(203)** **(204)**

**SCHEME 31**

The acetal (**204**) was purified by preparative layer chromatography and NMR spectroscopy indicated the presence of only one diastereomer, which was fully characterised using 1D- and 2D-NMR techniques. The camphor skeleton, and the C-10 ester moiety, were found to be intact and gave similar spectral characteristics as those observed for the acetal (**201**). The 2'-methylene protons resonate as a multiplet (dq) at 2.69 ppm and their coupling to the 3'-methine proton (5.08 ppm) is clearly visible in the COSY spectrum (**Figure 25**). Correlations are also clearly evident between the ester methyl triplet at 1.19 ppm and methylene quartet at 4.09 ppm, and between the diastereotopic 10-methylene protons at *ca.* 3.40 ppm.




(204)

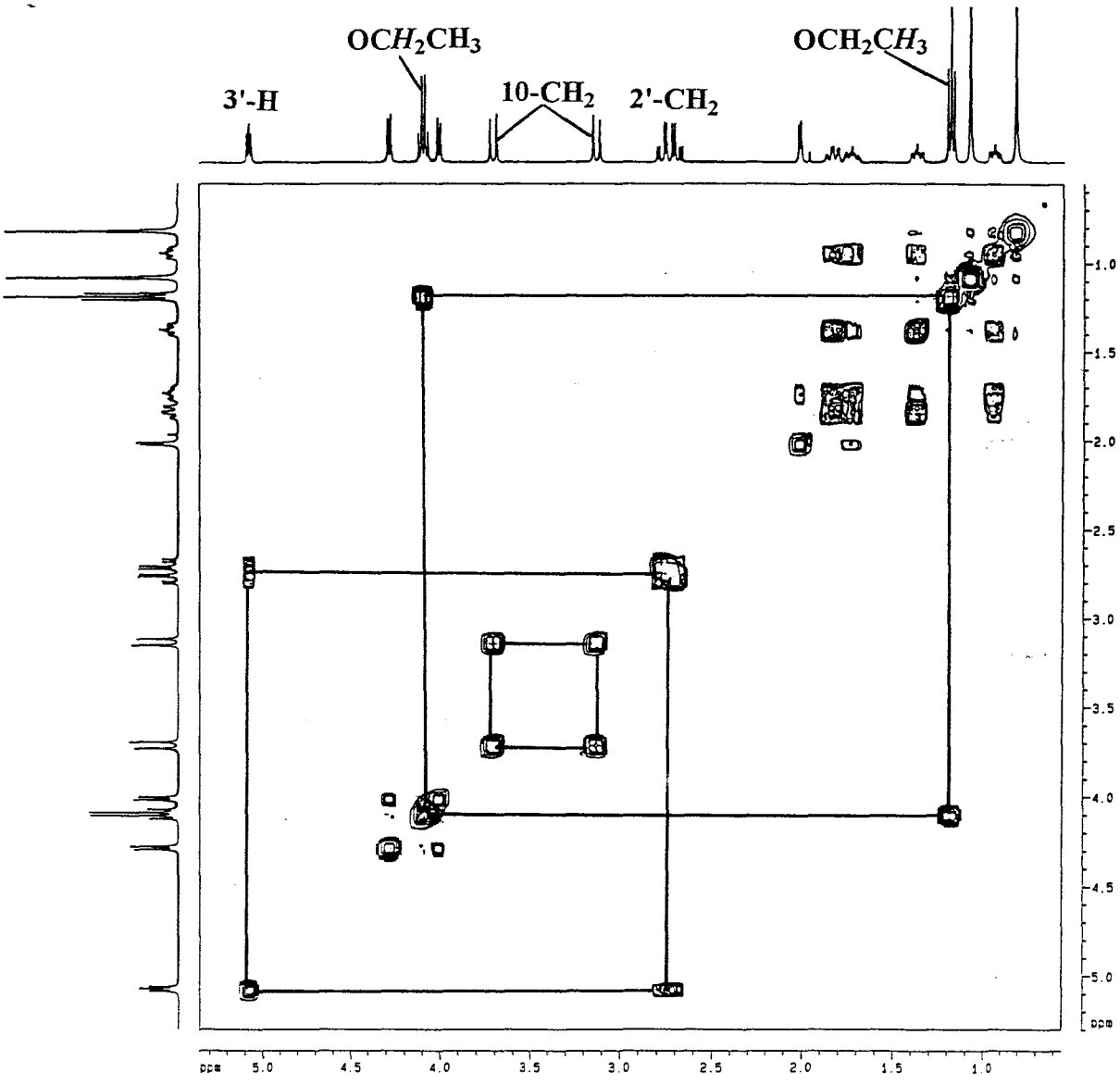



**FIGURE 25.** Partial 400 MHz COSY spectrum of the 2-(carbethoxymethyl)dioxolane (**204**) in $CDCl_3$.

### 2.2.2.5 Conformational analysis of bornane-2,3-diol-derived acetals

Conformational analysis of the acetals (**196**) and (**201**) derived from the bornanediol (**150**) and phenyl 2-*exo*,3-*exo*-dihydroxybornane-10-sulfonate (**192**), using computer modelling, 2D-NMR techniques and X-ray crystallography was undertaken to rationalise the formation, in each case, of a single diastereomeric product during acetalization.

Although five membered rings are highly flexible,[118] both internal substitution, by heteroatoms, and external substitution, by bulky substituents, confine 1,3-dioxolane rings to certain definite energy minima and prevent pseudorotation.[119, 120] In the acetals (**196**) and (**201**), derived from the diols (**150**) and (**192**) respectively, the presence of two heteroatoms and fusion to the rigid bicyclic camphor system serve to lock the ring into an "envelope" conformation. Computer modelling of conformational options available to the two possible stereoisomers (**196a**) and (**196b**) (**Figure 26**), of acetal (**196**) clearly indicated the absence of unfavourable steric interactions in structure (**I**)

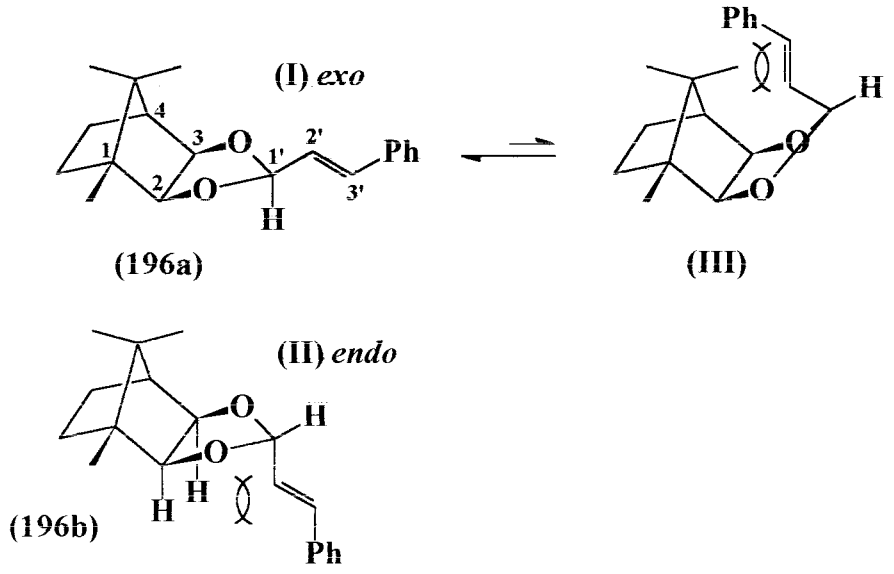
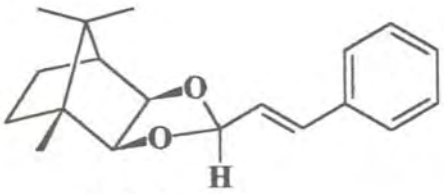



**FIGURE 26**

(**Figure 27**), suggesting that the isolated acetal (**196**) was, in fact, the *exo*-substituted diastereomer. Similar arguments apply to acetal (**201**). Flipping of the dioxolane ring in conformation (**I**) to give the conformer (**III**), is likely to be inhibited by steric repulsion between the bridgehead methyl group and the olefin moiety.




**(196a)**

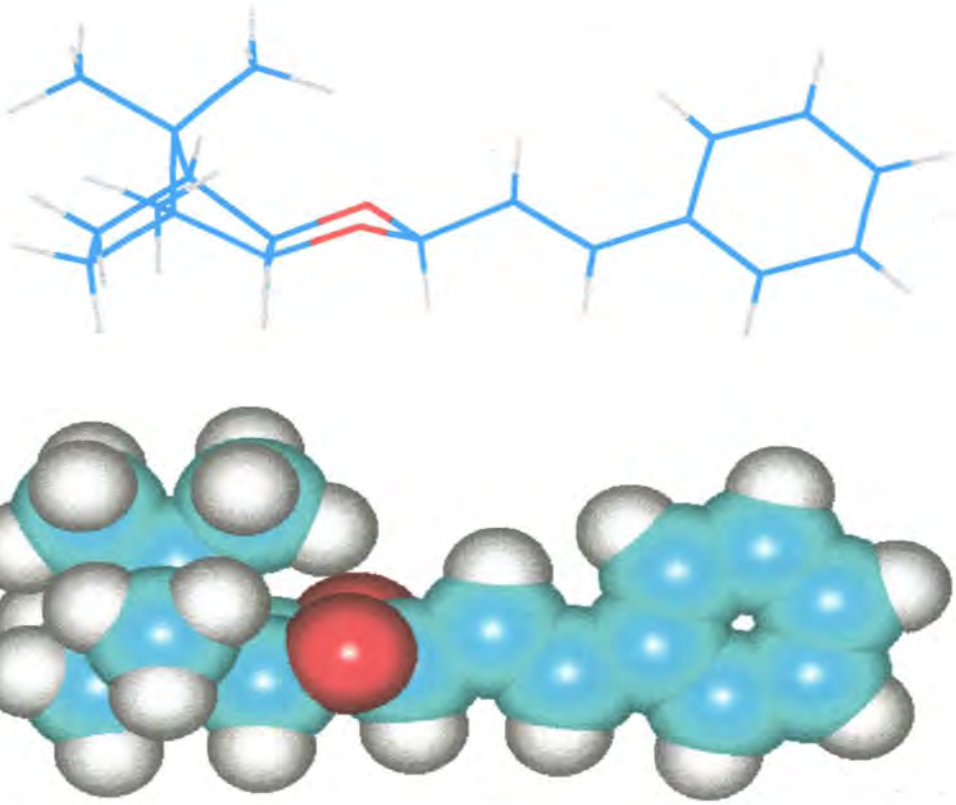


**FIGURE 27.** Computer-generated stick and space-filling models of the conformer (**I**) of acetal (**196a**).

Conformation of the structures of the acetals (**196**) and (**201**) was finally achieved using 2-D NMR spectroscopy. The NOESY spectrum of acetal (**196**) (**Figure 28**) shows correlations between the 2'-vinylic proton and a bridgehead methyl group, and between the 1'-methine proton and the 2-, 3-methine and 3'-vinylic protons. These correlations are clearly consistent with conformation (**I**) of the *exo*-substituted acetal (**196a**). Similar observations in the NOESY spectrum of the acetal (**201**) argue for the formation of the *exo*-substituted analogue.

Crystals of acetal (**201**) suitable for single crystal X-ray analysis, were obtained. The X-ray structure for this compound (**Figure 29**), confirms that the cinnamyl group is *exo*-orientated and that the solid state conformation corresponds to the solution conformation inferred from the NOE.

With the diastereomerically pure acetals (**196**) and (**201**) in hand and their structures well established, attention could be given to their use in asymmetric synthesis. Hoffmann[121] has suggested two conditions for efficient asymmetric induction in open-chain structures :-

i) preferably only one conformation should be available in the transition state of the stereogenic reaction - a condition which can be achieved by restricting the number of energetically favourable conformations of the bonds connecting the reacting prochiral group and the inducing stereocentre; and

ii) the conformation should be such that the diastereotopic faces of the reacting prochiral group are differentiated by the different substituents on the controlling stereocentre.

The differentiation may be provided by a large group which shields approach to one side of the reacting prochiral group (steric control) or by coordination of the incoming

reagent with a suitable group at the controlling stereocentre, directing attack to a particular face of the reacting prochiral group (chelation control). The series of chiral acetals (**193-202**), derived from the diols (**150**) and (**192**) seemed to fulfill these criteria, since rotation about the bond connecting the acetal and the olefin is unlikely due to the proximity of the bulky bicyclic skeleton and since all of them possess suitable coordination sites in the form of the acetal oxygen atoms.

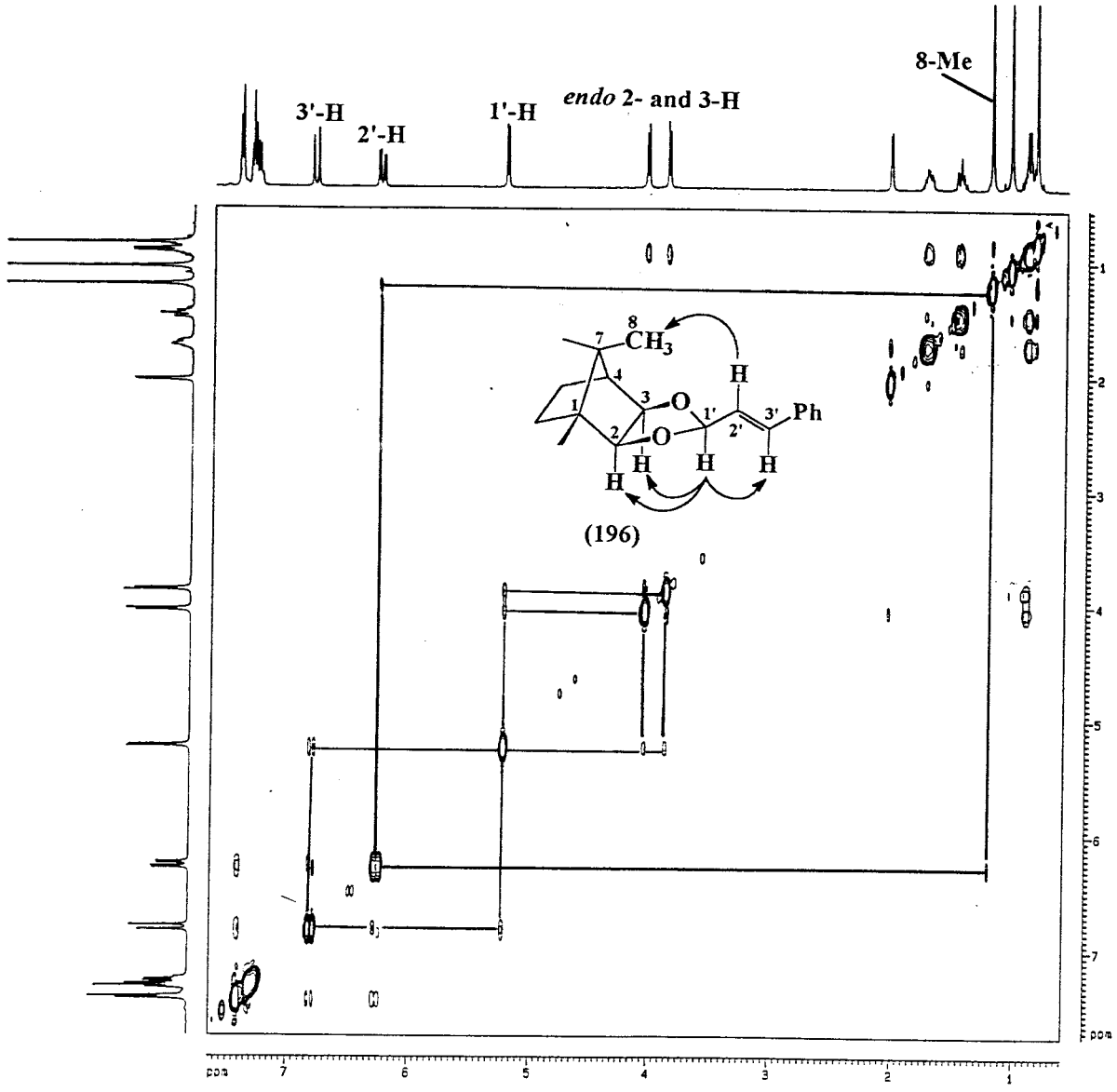



**FIGURE 28.** NOESY spectrum of acetal (**196**), in $CDCl_3$.

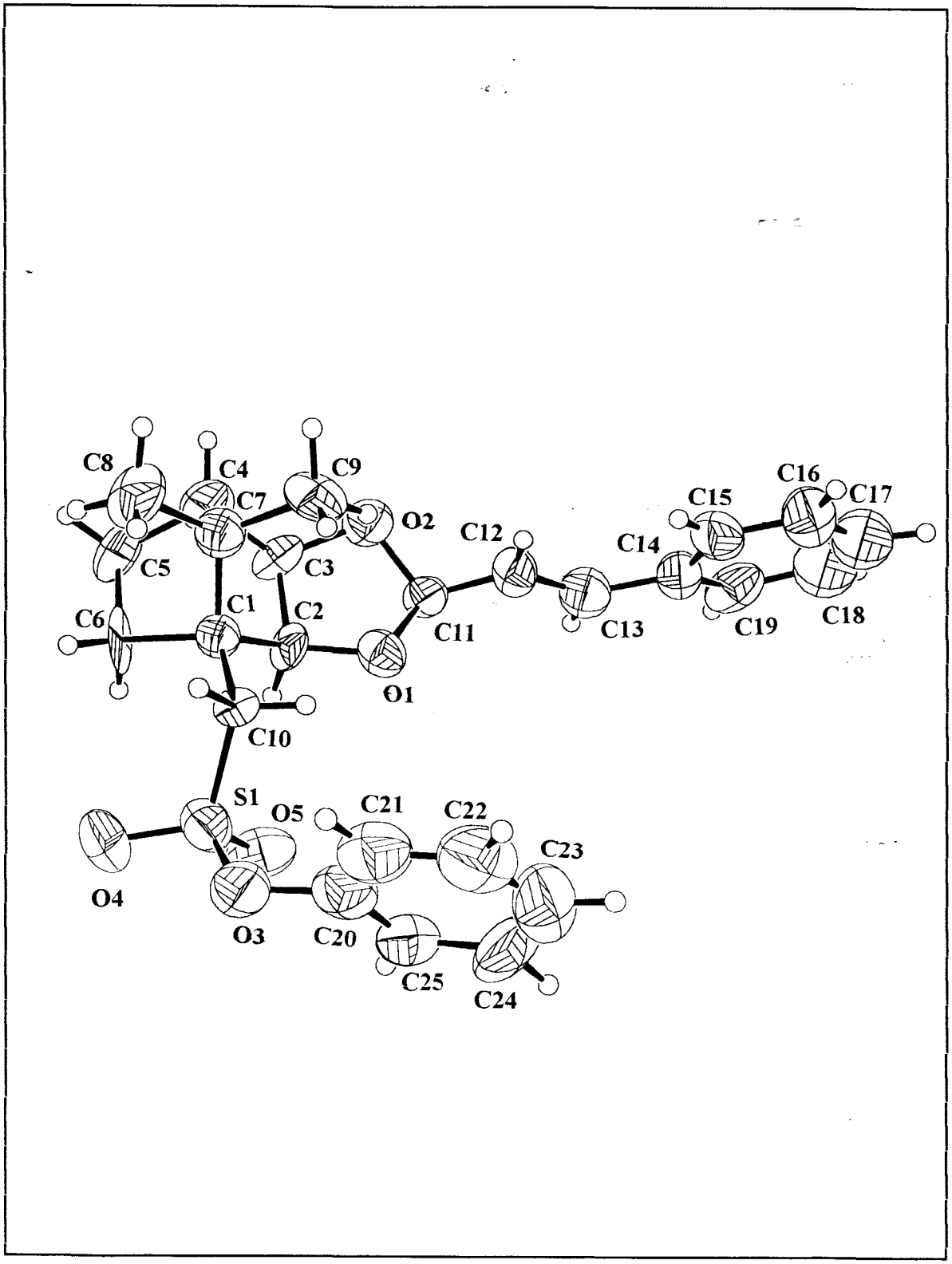



**FIGURE 29.** X-ray crystal structure of the acetal (**201**), showing crystallographic numbering.

## 2.3.5 ASYMMETRIC REACTIONS

### 2.3.5.1 Asymmetric Simmons-Smith Cyclopropanation

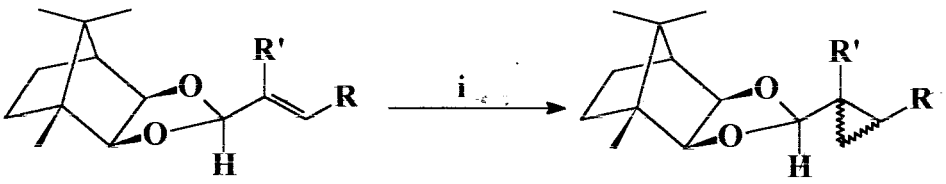
The cyclopropane moiety occurs in a number of natural and unnatural products and is a useful intermediate group in synthesis:[122-127] as a result, there have been intensive efforts to develop efficient methods for the construction of cyclopropane systems. The most widely used method to generate cyclopropanes is the Simmons-Smith cyclopropanation reaction[128] although, until recently, its application to asymmetric reactions was limited. A variety of methods for producing Simmons-Smith reagents are known,[129] all of which generate species containing an (iodomethyl)zinc moiety. The coordination of the reagent to oxygen was recognised early,[130] and this feature of the Simmons-Smith reaction has been used in chiral auxiliary-directed cyclopropanation of chiral acetals[72, 74] and ketals[73, 131] to obtain enantiomerically pure cyclopropanes. A variety of homochiral ketals have been reported to undergo efficient and highly diastereoselective cyclopropanation when treated with a Zn-Cu couple and methylene iodide, and this methodology has been used to synthesize a number of natural products.[132-134] By comparison, however, the use of homochiral acetals in diastereoselective cyclopropanation (**Section 1.1.3.3**) has not attracted as much attention.

In the present study, cyclopropanation of cinnamaldehyde bornane acetal (**196**) was first attempted by addition of the acetal to a mixture of Zn-Cu couple and methylene iodide in dry ether. The Zn-Cu couple was initially prepared using the method of Shank and Schechter,[135] but failed to effect cyclopropanation of the substrate. It has been reported that the procedure is not readily reproducible and that the activity of the couple may vary from batch to batch and, consequently, an attempt was made to prepare the couple

following the method reported by Rawson *et al.*.[136] This procedure involves refluxing a mixture of zinc dust and cuprous chloride in ether, for 30 min, before adding the alkene and methylene iodide. Unfortuntely, this couple also seemed to be inactive, as $^1$H NMR analysis of the crude material isolated from the cyclopropanation reaction indicated the absence of a cyclopropyl product.

The cinnamaldehyde bornane acetal (**196**) was then treated with diethylzinc and methylene iodide in dry hexane, at -20°C, to afford a diastereomeric mixture of the cyclopropyl acetals in very low yields (*ca.* 20 %). The low yields may be attributed to the formation of a white, viscous precipitate, the presence of which is reported to make quantitative methylene transfer impossible.[137] Finally, addition of a solution containing 1 mmol of the acetal (**196**), in dry $CH_2Cl_2$, to a vigorously stirred mixture of diethylzinc (5 mmol) and methylene iodide (10 mmol), in $CH_2Cl_2$ at -10°C (method A), gave a diastereomeric mixture of the cyclopropyl acetals (**208**) in 74 % yield, *after* purification (**Scheme 32**; **Table 14**).

Similar results were obtained by the very slow, dropwise addition of methylene iodide (10 mmol) to a mixture of the acetal (**196**) and diethylzinc in dry $CH_2Cl_2$ at -10°C (method B); however yields obtained for the cyclopropyl product (**208**) under these conditions were, however, slightly higher. Using above methods A and B, the Simmons-Smith cyclopropanantion of the chiral acetals (**193-197**) was achieved with moderate to excellent diastereoselectivity (46-> 99 % d.e.; see **Table 14**).




**(193-197)** **(205-209)**

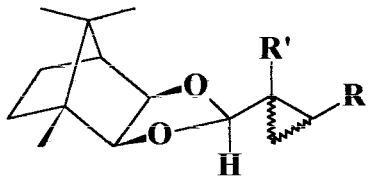
**Reagents: i) $Et_2Zn$, $CH_2I_2$, $CH_2Cl_2$, -10°C**

| Acetal | R | R' | Method[a] | Product |
|---|---|---|---|---|
| **193** | H | H | A | **205** |
| **194** | H | $CH_3$ | A | **206** |
| **195** | H | $(CH_2)_2CH_3$ | A | **207** |
| **196** | H | Ph | A | **208** |
| **196** | H | Ph | B | **208** |
| **197** | $CH_3$ | Ph | A | **209** |

[a] Method A : Addition of a solution of the acetal (1 mmol), in dry $CH_2Cl_2$, to a vigorously stirred mixture of diethylzinc (5 mmol) and methylene iodide (10 mmol), in $CH_2Cl_2$ at -10°C; Method B : Slow, dropwise addition of methylene iodide (10 mmol) to a stirred mixture of the acetal (1 mmol) and diethylzinc (5 mmol) in dry $CH_2Cl_2$ at -10°C.

**SCHEME 32**

**Table 14** Data for the diastereoselective formation of the cyclopropyl acetals (**205-209**) obtained using method A[a].




(205-209)

| Cyclopropyl acetal | R | R' | Yield[b]/ % | % d.e. |
|---|---|---|---|---|
| **205** | H | H | 41 | 100 |
| **206** | H | $CH_3$ | 72 | 62 |
| **207** | H | $(CH_2)_2CH_3$ | 84 | 70 |
| **208** | H | Ph | 74 | 66 |
| **209** | $CH_3$ | Ph | 58 | 46 |

[a] Method A : Addition of a solution of the acetal (1 mmol), in dry $CH_2Cl_2$, to a vigorously stirred mixture of diethylzinc (5 mmol) and methylene iodide (10 mmol), in $CH_2Cl_2$ at -10°C. [b] Purified material.

The cyclopropyl acetals (**205-209**) were all characterised by 1-D and 2-D NMR spectroscopy. The spectra of the cyclopropyl acetal (**207**) are typical and are illustrated in **Figures 30-32**. The most striking features of the $^1H$ NMR spectrum (**Figure 30a**) are the absence of signals in the vinyl region and the appearence of two multiplets at 0.31 and 0.47 ppm, which each integrate for one proton. These signals show correlation to a single carbon nucleus resonating at 8.8 ppm in the inverse HETCOR spectrum (**Figure 31**) and may be assigned to the cyclopropyl methylene protons. This assignment is supported by the fact that the signal at 8.8 ppm corresponds to a methylene carbon in the DEPT spectrum (**Figure 30b**) and appears within the characteristically shielded range reported for cyclopropyl carbons (-5 to 20 ppm).[138] In

the COSY spectrum (**Figure 32**) the cyclopropyl methylene protons show coupling to the broad multiplet at 0.77 ppm which corresponds to the 2'- and 3'-H nuclei which, in turn, show correlations to the methine carbons at 15.5 and 19.1 ppm in the inverse HETCOR spectrum. Coupling between the 2' -H and 1'-H (4.0 ppm) nuclei is also evident in the COSY spectrum.

The diastereomeric ratios, in each case, were determined by intergration of well resolved $^{13}C$ NMR signals for corresponding carbon atoms in each pair of diastereomers, on the assumption that the $T_1$ relaxation times are comparable.[93]

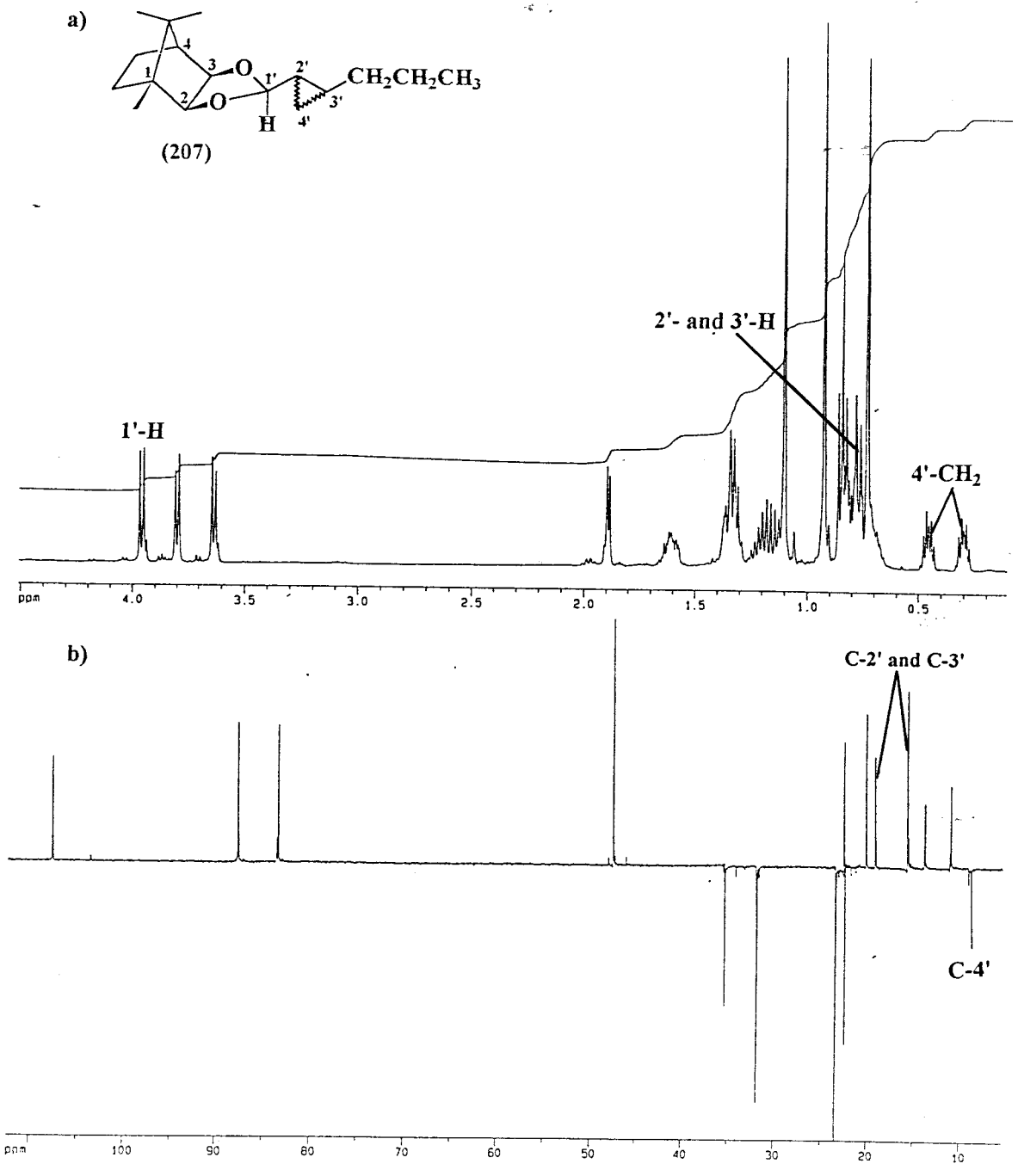



**FIGURE 30.** **a)** The 400 MHz $^1$H NMR and **b)** DEPT spectra of the diastereomeric mixture of cyclopropyl acetals (**207**), in $CDCl_3$.

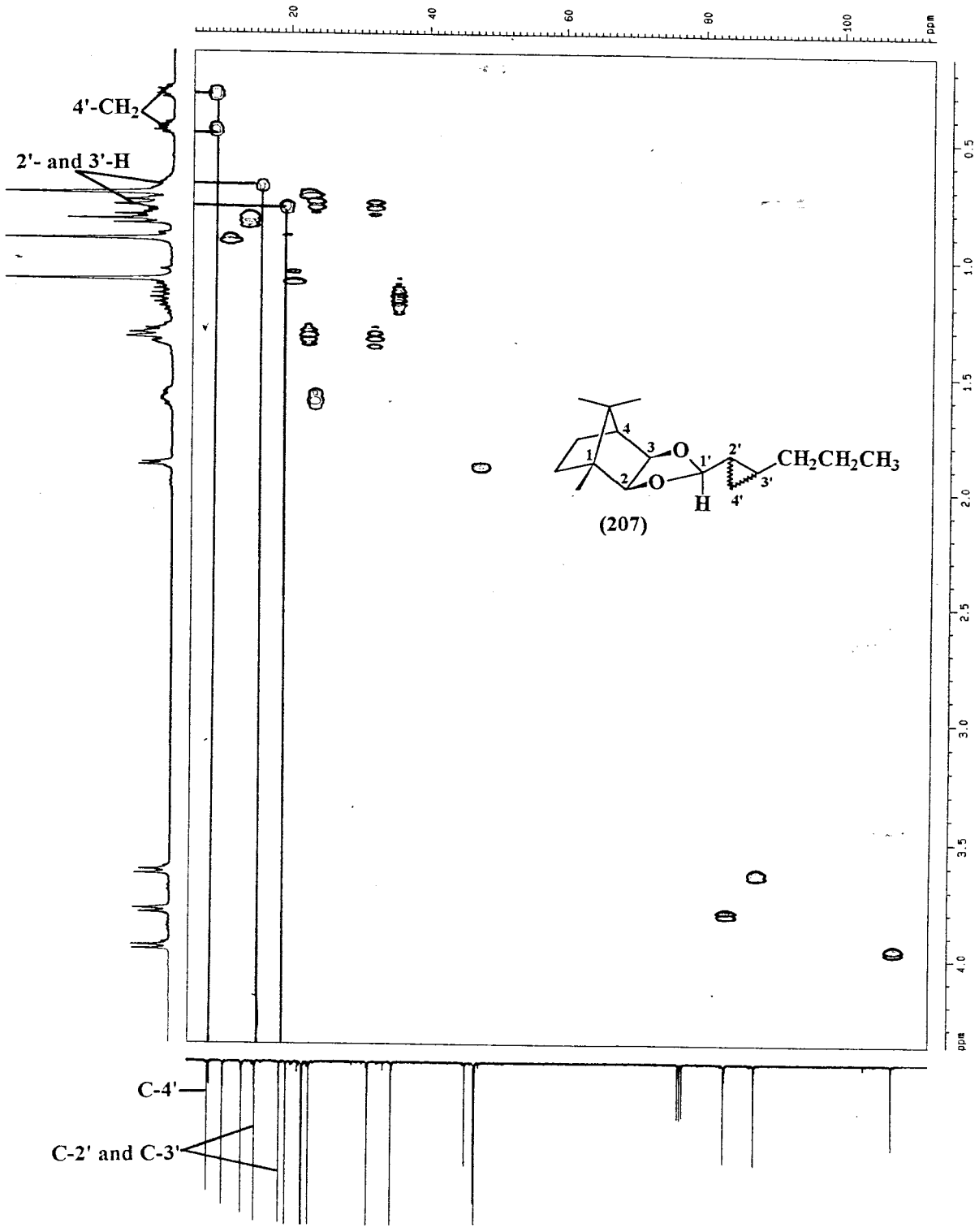
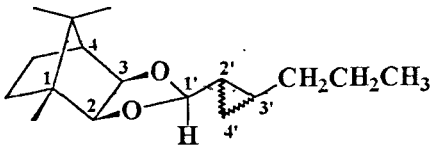



**FIGURE 31.** The HETCOR spectrum of the diastereomeric mixture of cyclopropyl acetals (**207**), in $CDCl_3$.




(207)

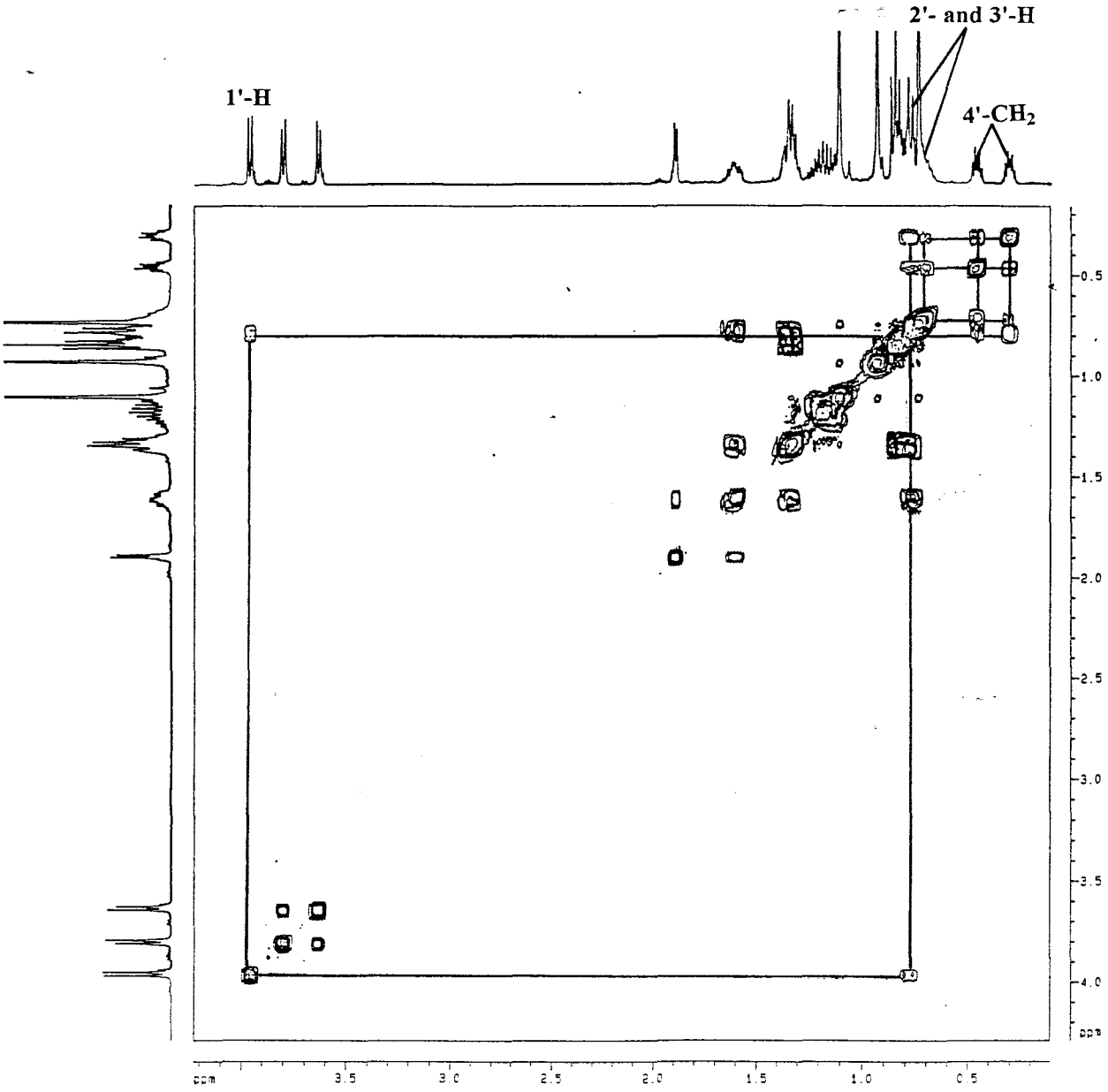
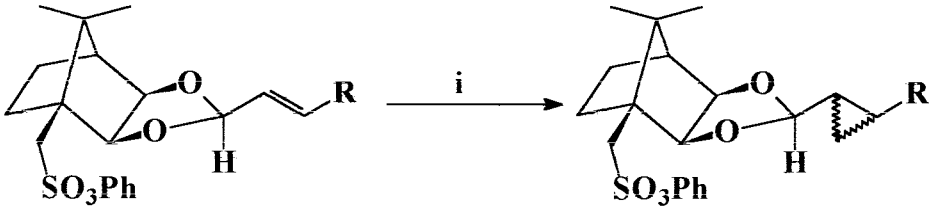



**FIGURE 32.** The 400 MHz COSY spectrum of the diastereomeric mixture of cyclopropyl acetals (**207**), in $CDCl_3$.

The four acetal derivatives (**198-201**) of the chiral diol (**201**) were cyclopropanated using method A, as the yields were generally slightly higher than with method B. From the $^{1}H$ and $^{13}C$ NMR spectra of the crude cyclopropyl acetals (**210-213**), it was immediately apparent that these reactions proceeded with excellent stereocontrol (**Scheme 33**; **Table 15**), the spectra revealing the presence of only one diastereomer in each case.



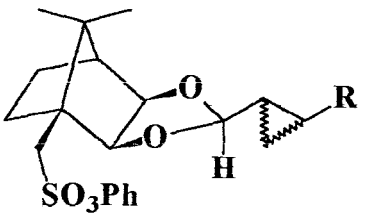

**(198-201)** **(210-213)**

**Reagents: i) $Et_2Zn$, $CH_2I_2$, $CH_2Cl_2$, -10°C**

| Acetal | R | Product |
|---|---|---|
| **198** | H | **210** |
| **199** | $CH_3$ | **211** |
| **200** | $(CH_2)CH_3$ | **212** |
| **201** | Ph | **213** |

**SCHEME 33**

**Table 15** Data for the diastereoselective formation of the cyclopropyl acetals (**210-213**).



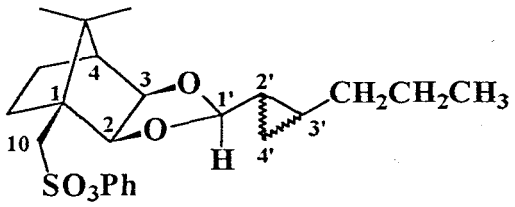

(**210-213**)

| Cyclopropyl acetal | R | Yield / % | % d.e. |
|---|---|---|---|
| **210** | H | 28 | > 99 |
| **211** | $CH_3$ | 80 | > 99 |
| **212** | $(CH_2)CH_3$ | 76 | > 99 |
| **213** | Ph | 95 | > 99 |

The cyclopropyl acetals (**210-213**) were fully characterised by $^1H$ and $^{13}C$ NMR spectroscopy and mass spectrometry. Apart from an additional pair of doublets at 3.16 and 3.79 ppm (due to the diastereotopic 10-methylene protons) and the aromatic signals at 7.25-7.39 ppm, the $^1H$ NMR spectrum of the cyclopropyl acetal (**212**) (**Figure 33**), for example, is very similar to that of the corresponding cyclopropyl acetal (**207**) (**Figure 30a**).

The low yields obtained for the cyclopropanation of the acrolein-derived acetals [(**193**) and (**198**)] in both series may be due to the lack of alkyl substitution, which is known to facilitate methylene transfer in such reactions.[139] On the other hand, excessive substitution may introduce rate-retarding steric effects, which may account for the low yields obtained in the cyclopropanation of α-methyl cinnamaldehyde acetal (**197**). Increasing the reaction time failed to increase the yield of the cyclopropyl acetals, (**193**), (**197**) and (**198**), presumably due to competing decomposition of the zinc reagent.

Charrette *et al.* have reported that the addition of methylene iodide to diethylzinc in $CH_2Cl_2$ at 0°C is highly exothermic and that reagent decomposition is significant after 20 min.[137] The yields were increased, however, by repeating the reaction on the crude products obtained after the first cyclopropanation. This approach did not affect the diastereoselectivity, but the starting acetals, from which the cyclopropanated products could not be isolated, were still present after work-up; reported yields were therefore determined by $^1$H NMR spectroscopy. Attempts to separate the diastereomeric mixtures of the cyclopropyl acetals (**205-209**), using PTLC, flash chromatography or HPLC, also proved unsuccessful.




(212)

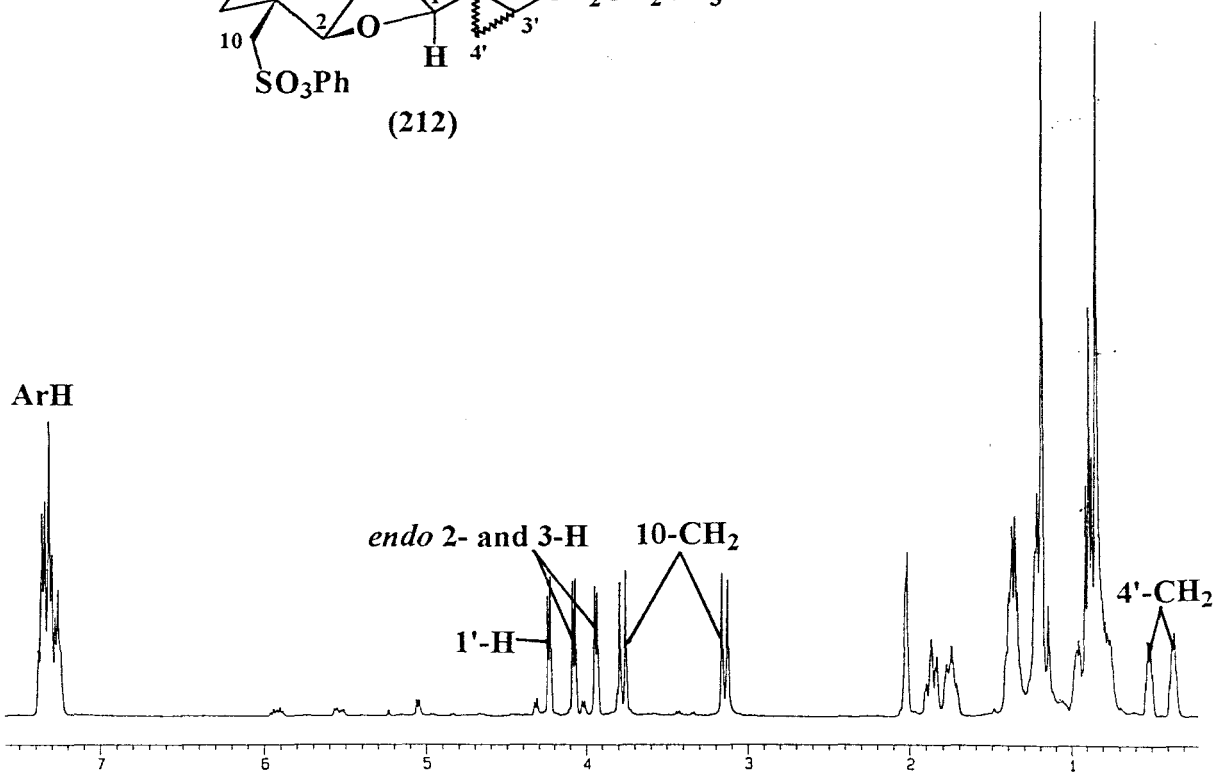
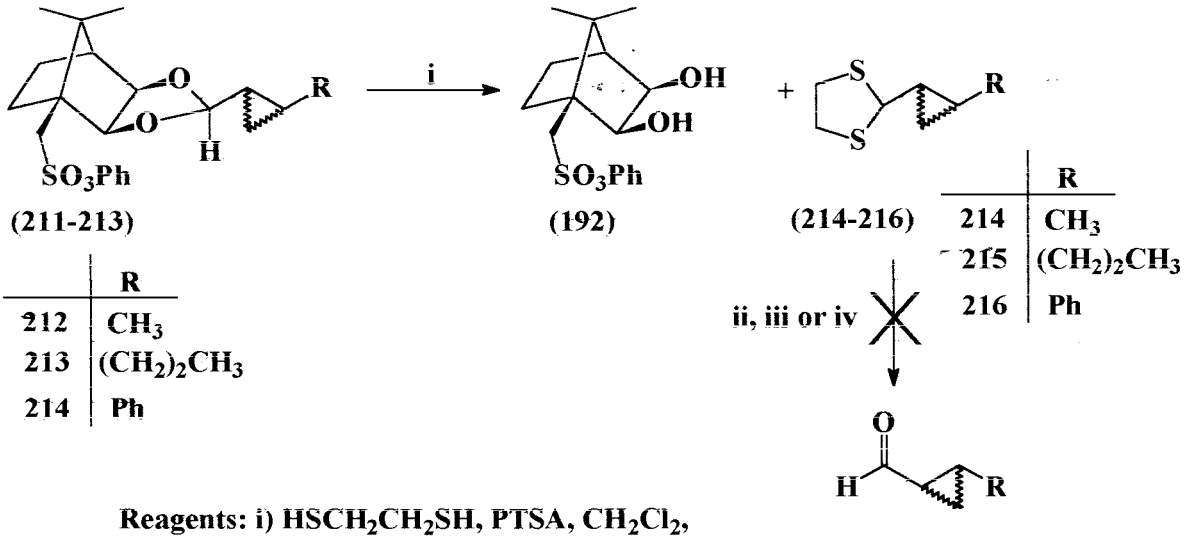



**FIGURE 33.** The 400 MHz $^1$H NMR spectrum of the cyclopropyl acetal (**212**), in $CDCl_3$.

### 2.3.5.1.1 Hydrolysis of camphor-derived acetals

To determine the absolute configuration at the new stereogenic centres, acid-catalysed hydrolysis of the cyclopropyl acetals, (**208**) and (**213**), derived from *trans*-cinnamaldehyde was explored, as the corresponding cyclopropyl aldehydes are known.[72, 140] However, these acetals proved remarkably resistant to hydrolysis. Treatment of the diastereomeric mixture of cyclopropyl acetals (**208**) with 10 % HCl in MeOH was attempted first but, after stirring for several days, $^1$H NMR spectroscopy indicated the presence of starting material alone. An attempt to hydrolyse the cyclopropyl acetals (**208**), by boiling under reflux for 7 hours in a THF-$H_2O$ (5:1) mixture, in the presence of a catalytic amount of PTSA, was similarly unsuccessful. Conia *et al.*[141] have reported the hydrolysis of acetals on wet silica gel to give the corresponding aldehydes in high yield. Following their procedure, the cyclopropyl acetal (**213**) was added to a mixture of wet silica gel and sulfuric acid and the resulting slurry was stirred for several days. However, $^1$H NMR spectroscopy, after work-up, indicated only starting material to be present.

Pedrosa *et al.*[71] hydrolysed the alkylation product (**108**) of the 2-(β-ethoxycarbonyl)-dioxolane (**107**) (**Scheme 18**) by initial transthioacetalization to dithiolane and subsequent hydrolysis using a solution of methyl iodide in acetonitrile, in the presence of calcium carbonate. Following this approach, the cyclopropyl acetals (**211-213**), in dry $CH_2Cl_2$, were treated with 1 equivalent of ethanedithiol in the presence of PTSA, to afford the cyclopropyl dithiolanes (**214-216**) and the diol (**192**) in high yield (**Scheme 34**; **Table 16**).




| | R |
|---|---|
| 212 | $CH_3$ |
| 213 | $(CH_2)_2CH_3$ |
| 214 | Ph |

| | R |
|---|---|
| 214 | $CH_3$ |
| 215 | $(CH_2)_2CH_3$ |
| 216 | Ph |

**Reagents: i) $HSCH_2CH_2SH$, PTSA, $CH_2Cl_2$,**
**ii) MeI, $CaCO_3$, $CH_3CN$,**
**iii) Hg(II)oxide, $BF_3.OEt_2$, THF,**
**iv) glyoxylic acid, acetic acid, conc. HCl.**

**SCHEME 34**

**Table 16** Results of the transthioacetalization of cyclopropyl acetals (**211-213**)

| Cyclopropyl acetal | R | Yield of diol (192)/ % | Dithiolane | Yield of dithiolane/ % |
|---|---|---|---|---|
| **211** | $CH_3$ | 86 | **214** | 87 |
| **212** | $(CH_2)_2CH_3$ | 83 | **215** | 89 |
| **213** | Ph | 87 | **216** | 92 |

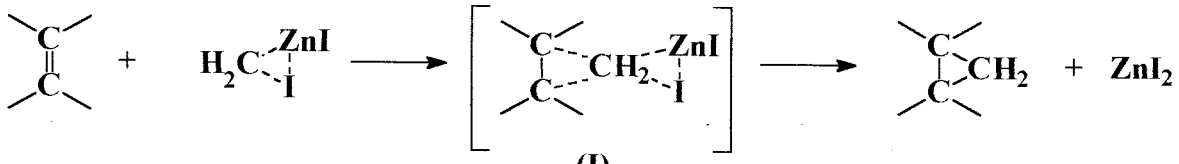
However, application of the method of Pedrosa *et al.* failed to hydrolyse the dithiolane (**215**) and, as the hydrolysis of dithiolanes is based on conversion of the sulfur atoms to better leaving groups,[142] the addition of mercury(II)oxide and $BF_3.OEt_2$ was also explored, following the method reported by Vedejs *et al.*,[143] but no hydrolysis was observed. When the cyclopropyl dithiolane (**216**) was treated with a solution of

glyoxylic acid in acetic acid containing conc. HCl,[144] neither the desired aldehyde nor the starting dithiolane (**216**) could be detected by $^1$H NMR analysis, and it seems that these conditions were too harsh.

Hydrolysis of the cyclopropyl acetal (**216**) was finally achieved, by boiling the mixture under reflux for 3 days in THF-$H_2O$ (5:1), in the presence of 2 equivalents PTSA, to afford the cyclopropyl aldehyde (**217**) in 10 % yield (**Scheme 35**). As the cyclopropyl aldehyde (**217**) is known,[140] it permitted the absolute configuration of the cyclopropyl group to be established by measuring the optical rotation, which was found to be $[\alpha]_D^{26}$ -324° (*c* 0.333 in $CDCl_3$). This value corresponds to an diastereomeric excess of 86 % of the laevorotatory (*R,R*)-aldehyde (**217**) {$[\alpha]_D^{26}$ -378°(*c* 0.374 in $CDCl_3$)[140]} which is less than the > 99% d.e. observed in $^1$H and $^{13}$C NMR spectroscopy and this difference maybe due to the presence of optically active impurities. However, it does unambiguously establish the absolute configuration of the newly created stereogenic centres.

### 2.3.5.1.2 Mechanistic and stereochemical implications of the asymmetric cyclopropanation reactions

Although the Simmons-Smith reaction has been widely used as a convenient and versatile method for the synthesis of cyclopropanes, a detailed study of the mechanism of the process is lacking. A one-step mechanism has been suggested, involving a three-centre transition state (**I**), in which the electrophilic methylene group adds to the alkene π-bond with concerted formation of both carbon-carbon bonds (**Figure 34**).[128, 145]




**(I)**

**FIGURE 34**

Simmons-Smith cyclopropanating reagents have been prepared by a number of methods, all of which generate species containing an iodomethylzinc moiety.[128, 146, 147] It was originally suggested that iodomethylzinc iodide is the initial product in the reaction of methylene iodide with zinc-copper couple (**Equation 1**). Extensive studies by Simmons *et al.*[145, 148] led to the conclusion that the actual organozinc reagent is a bis(halomethyl)zinc.zinc iodide species resulting from a Schlenk-type equilibrium (**Equation 2**); the structure of the complex has been investigated by its complexation with a diether.[129]

$$Zn(Cu) + CH_2I_2 \rightarrow ICH_2ZnI + (Cu) \qquad \textbf{(Equation 1)}$$

$$2ICH_2ZnI \rightleftharpoons (ICH_2)_2Zn\text{-}ZnI_2 \qquad \textbf{(Equation 2)}$$

$$Et_2Zn + CH_2I_2 \rightarrow EtZnCH_2I + EtI \qquad \textbf{(Equation 3)}$$

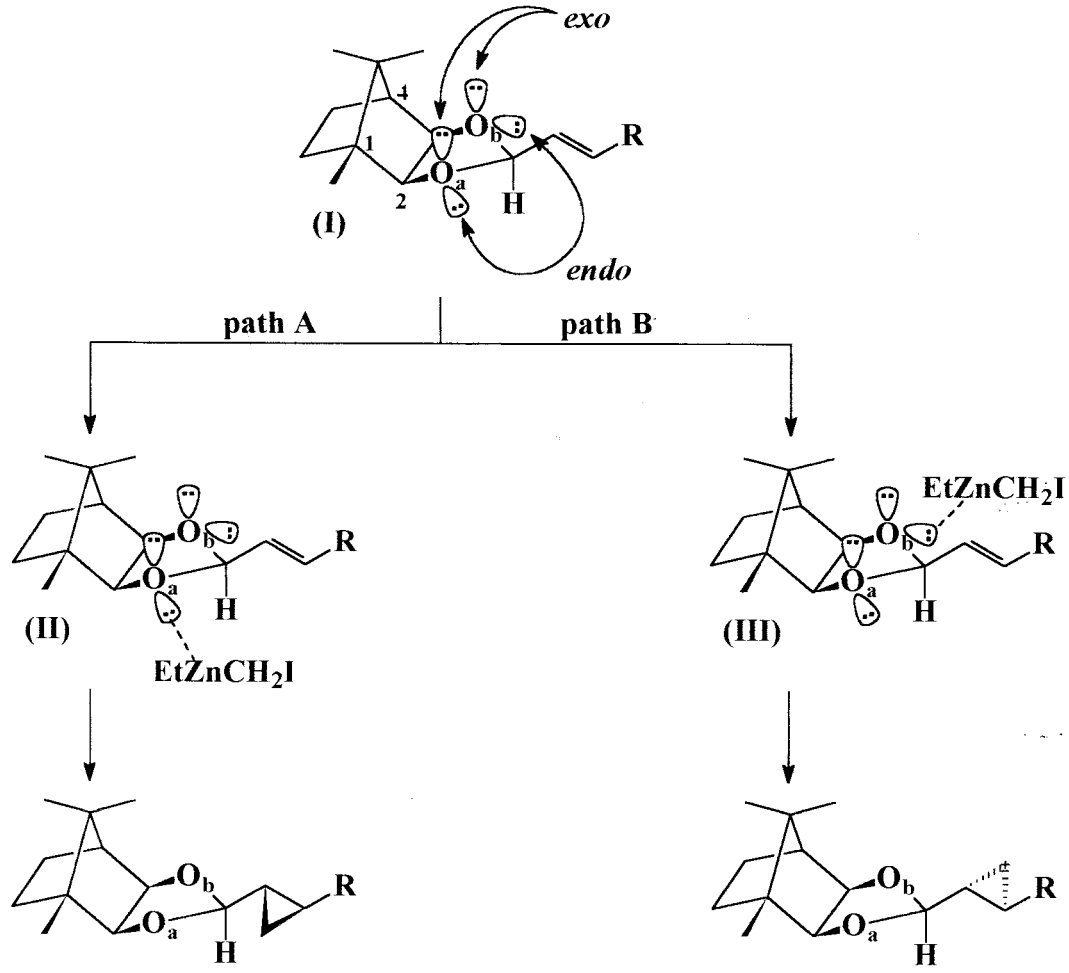
$$EtZnCH_2I + CH_2I_2 \rightarrow (ICH_2)_2Zn + EtI \qquad \textbf{(Equation 4)}$$

The intermediates formed from diethylzinc and methylene iodide are not known with certainty, but it seems likely that they are ethyl iodomethylzinc (**Equation 3**) and a bis(halomethyl)zinc species (**Equation 4**).[149] The zinc iodide complex of the latter species is bis(halomethyl)zinc.zinc iodide - the active cyclopropanating reagent initially proposed by Simmons *et al.*.[145, 148]

The observed stereoselectivities (**Schemes 32** and **33**) maybe ascribed to the high affinity of the organozinc reagent for ethereal oxygen.[139] Coordination of the Simmons-Smith reagent with an oxygen atom influences both the rate and stereochemical outcome of the cyclopropanation reaction (as evidenced by comparative data for reactions of allylic alcohols and ethers relative to simple alkenes) and is followed by methylene transfer to the more accessible face of the double bond.[139, 150, 151] The transition state complex is considered to be very bulky due to the surrounding zinc and iodine atoms and, consequently, the zinc coordinates to the least sterically hindered oxygen atom, thus positioning the reagent for diastereoselective methylene transfer.

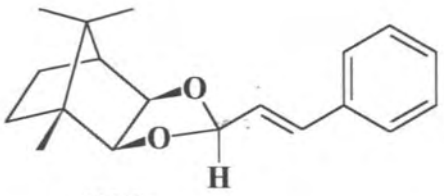
In the acetals (**193-197**), derived from diol (**150**), coordination with the Simmons-Smith reagent may occur at the $O_a$- or $O_b$-dioxolane oxygens *via* either the *endo* or *exo* lone pairs (**Scheme 36**). The computer-generated model of the acetal (**196**) (**Figure 35a**) shows that chelation of the bulky zinc reagent to the *exo* lone pairs of the dioxolane oxygens would be inhibited by unfavourable steric interactions with the bridgehead methyl group, while chelation to the *endo* lone pair of the $O_a$-dioxolane oxygen (**path A**) is likely to be inhibited by the steric bulk of the 10-methyl group (**Figure 35a**). Therefore, it is proposed that the sterically preferred site for coordination of the reagent is the *endo* lone pair of the $O_b$-dioxolane oxygen atom (**path B**) as it is readily accessible to the Simmons-Smith reagent, and the C-4 hydrogen atom offering little or no resistance. Reaction *via* path B is thus expected to be favoured, with methylene

delivery at the *Re* face producing (*R*,*R*)-cyclopropane acetals. The diastereoselectivities (46-100 % d.e.) observed in the cyclopropanation of acetals (**193-197**) clearly indicate the existence of a significant stereochemical bias for methylene transfer, predicted to involve preferential coordination of the organozinc reagent with the *endo* lone pair of the $O_b$-dioxolane oxygen atom.

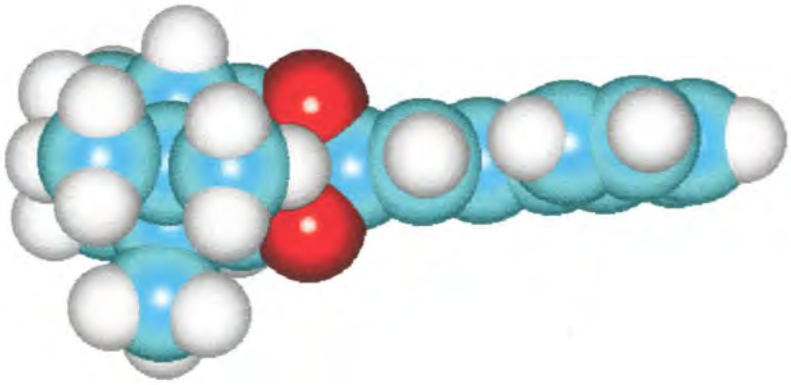



**SCHEME 36**

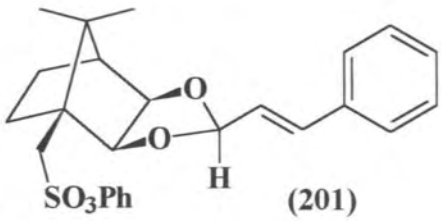
a)




(196)



b)




(201)

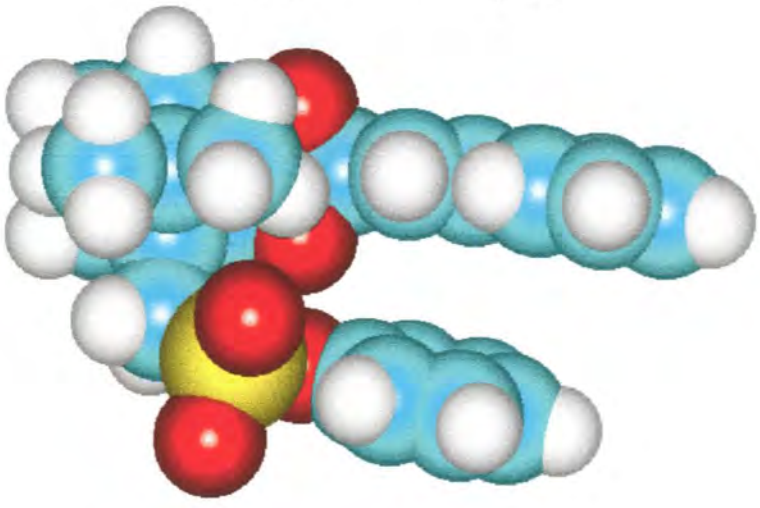
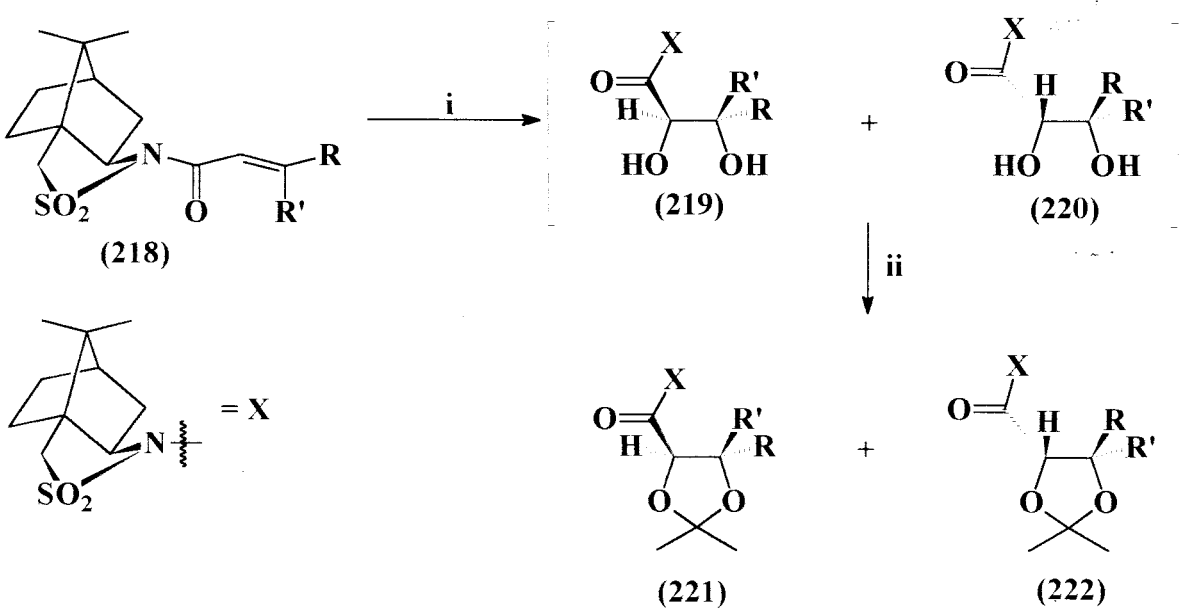


**FIGURE 35.** Computer-generated space-filling models of **a)** acetal (**196**) and **b)** acetal (**201**).

The acetals (**198-201**), prepared from the diol (**192**), possess the phenyl methanesulfonate moeity at C-1 which blocks the $O_a$-dioxolane oxygen atom (**Figure 35b**) even more effectively than the 10-methyl group in the acetals (**193-197**) and, therefore, prevents chelation of the organozinc reagent with either the *endo* or *exo* lone pairs of the $O_a$-dioxolane oxygen atom. Chelation is again proposed to involve the *endo* lone pair of the $O_b$-dioxolane oxygen atom, the diastereoselectivity of methylene transfer being supported by exclusive formation of a single diastereomer in the cyclopropanation of the acetals (**198-201**). These stereochemical arguments are further supported by isolation of the known cyclopropyl aldehyde (**217**), *via* hydrolysis of the cyclopropyl acetal (**213**) with excess PTSA (**Scheme 35**) (see **Section 2.3.5.1.1**).

### 2.3.5.2 Diastereoselective dihydroxylations

The oxidation of alkenes to vicinal diols, using osmium tetroxide ($OsO_4$), favours *syn* addition to the less hindered face of the double bond.[152] Diastereoselective addition of $OsO_4$ to alkenes has been achieved using optically active amines, which not only accelerate the reaction but also bind to the $OsO_4$ as chiral ligands. Oppolzer's sultam, a camphor-derived chiral auxiliary, has been used to prepare the enoylsultams (**218**), which were shown by Oppolzer *et al.* to undergo asymmetric oxidation with $OsO_4$/*N*-methylmorpholine *N*-oxide (**Scheme 37**).[153, 154] Acetalization of the resulting glycols (**219**) and (**220**) allowed for the determination, by capillary GLC, of the product ratios [(**221**):(**222**)], which were found to range from 90:10 to 95:5. In each case, the major component (**221**) was obtained in > 99 % d.e. after purification.

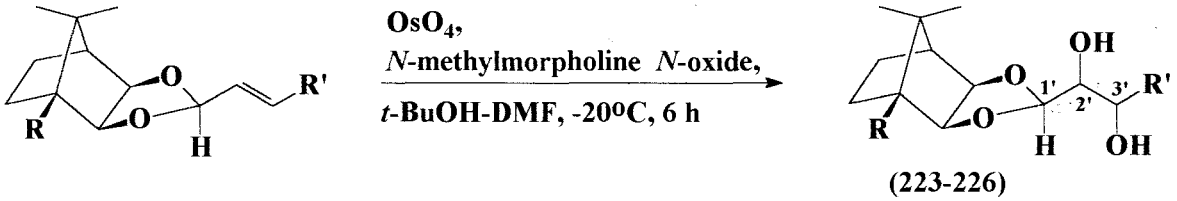



**Reagents : i) $OsO_4$, *N*-methylmorpholine *N*-oxide, DMF-*t*-BuOH (1:1), -20°C, 6 h, ii) $Me_2C(OMe)_2$, $Me_2CO$, PTSA**

**SCHEME 37**

It was proposed that the enoylsultams (**218**) adopt a conformation in which one face of the double bond is blocked by a bridgehead methyl group, resulting in the high selectivities observed. Mash *et al.*, on the other hand, investigated osmylation of the 1,4-di-*O*-benzyl-L-threitol ketal of 2-cyclopenten-1-one and observed poor diastereoselectivity (3:2).[155] These precedents prompted us to explore $OsO_4$ dihydroxylation of various acetals prepared during the course of this study.

The asymmetric dihydroxylation of the acetals (**194-196**) and (**199**) were carried out by adding a solution of $OsO_4$ in *t*-BuOH to a stirred solution of the acetal and *N*-methylmorpholine *N*-oxide in a 1:1 mixture of *t*-BuOH/DMF, at -20°C, and then stirring for 6 h (**Scheme 38; Table 17**).[153]



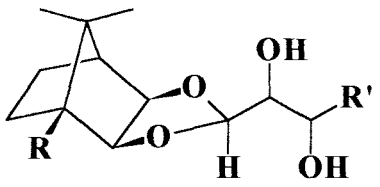

(223-226)

| Acetal | R | R' | Product |
|---|---|---|---|
| **194** | $CH_3$ | $CH_3$ | **223** |
| **195** | $CH_3$ | $(CH_2)_2CH_3$ | **224** |
| **196** | $CH_3$ | Ph | **225** |
| **199** | $CH_2SO_3Ph$ | $CH_3$ | **226** |

**SCHEME 38**

The $^1H$ and $^{13}C$ NMR spectra of the crude reaction mixtures clearly reflected the formation of the diols (**223-226**) as diastereomeric mixtures, the observed doubling of peaks permitting determination of the diastereoselectivities (**Table 17**).

**Table 17** Data for the diastereoselective formation of the diols (**223-226**).




**(223-226)**

| Diol | R | R' | Yield/ % | % d.e. |
|---|---|---|---|---|
| **223** | $CH_3$ | $CH_3$ | 52 | 18 |
| **224** | $CH_3$ | $(CH_2)_2CH_3$ | 59 | 10 |
| **225** | $CH_3$ | Ph | 54 | 13 |
| **226** | $CH_2SO_3Ph$ | $CH_3$ | 61 | 22 |

The diols (**223-226**) were all characterised by 1-D and 2-D NMR spectroscopy. The $^1H$ NMR spectra, illustrated for the diol (**223**) (**Figure 36a**), reveals the absence of the vinyl proton signals but the presence of signals at *ca.* 2.54 and 2.80 ppm, which identified as the 2'- and 3'-hydroxyl protons by $D_2O$ exchange (**Figure 36b**). The hydroxyl protons were assigned from the COSY spectrum (**Figure 37**), the 2'- hydroxyl proton showing coupling to the 2'-methine proton, which couples, in turn, to the 1'-methine and 3'-methine protons, resonating at 4.62 and 3.95 ppm respectively. On the other hand, the 3'-hydroxyl proton (2.54 ppm) couples to the 3'-methine proton (3.95 ppm), which also couples to the 1'-methine and 4'-methyl protons, the latter resonating as a doublet at 1.24 ppm.

The low diastereoselectivities (10-18 %; **Table 17**) observed in the dihydroxylation of the acetals (**194-196**) may be due to the poor blocking effect of the 10-methyl group, permitting addition of the $OsO_4$ from either face of the double bond. It was hoped that the presence of the phenyl sulfonate moiety at C-10 in the acetal (**199**) would

selectively block one face of the double bond but there was only a slight improvement in diastereoselectivity (22 % d.e.).

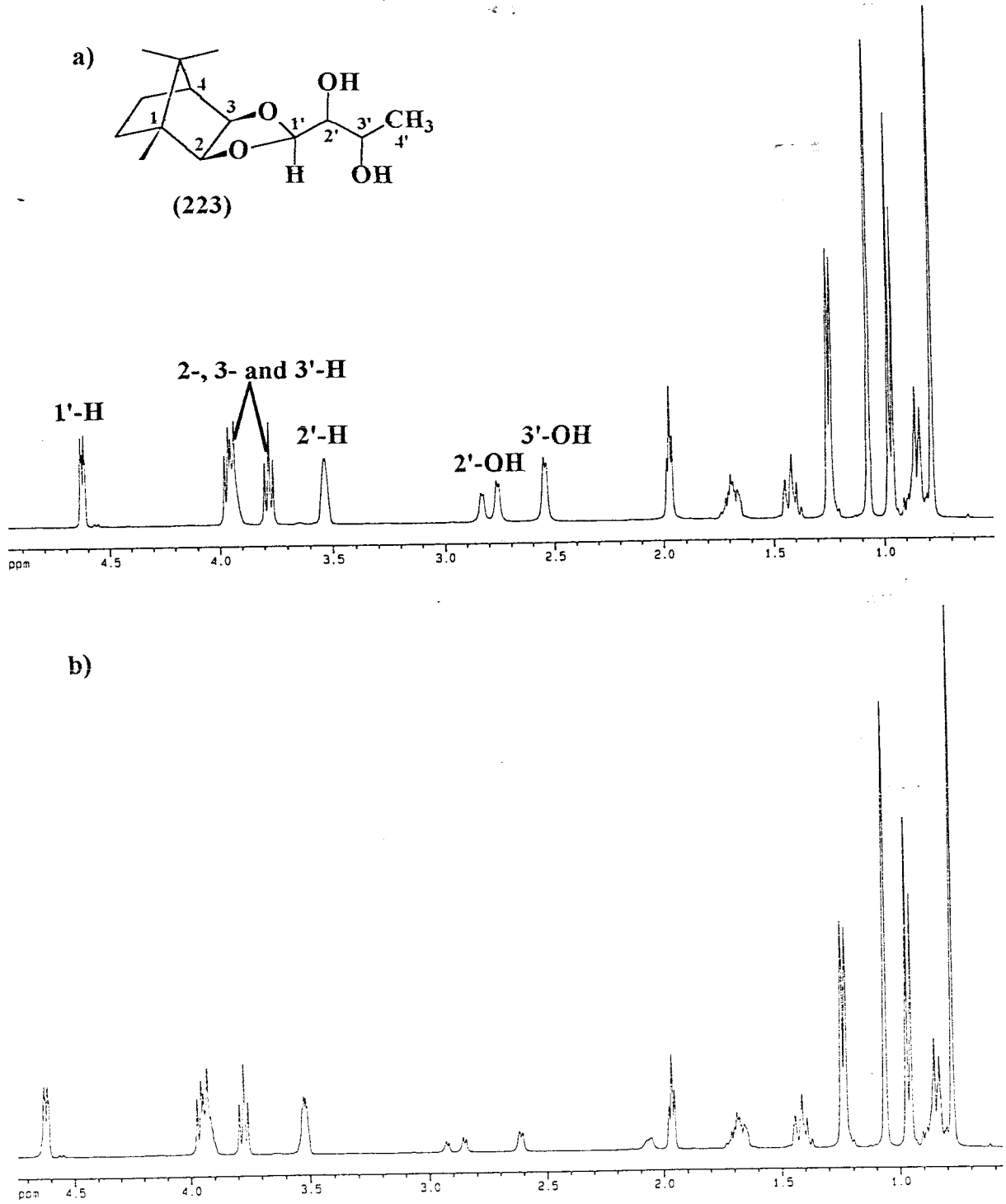
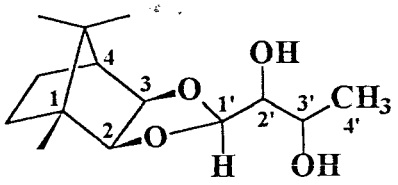



**FIGURE 36.** The 400 MHz $^1$H NMR spectra of the diol (**223**): (**a**) in $CDCl_3$; and (**b**) after $D_2O$ exchange.




(223)

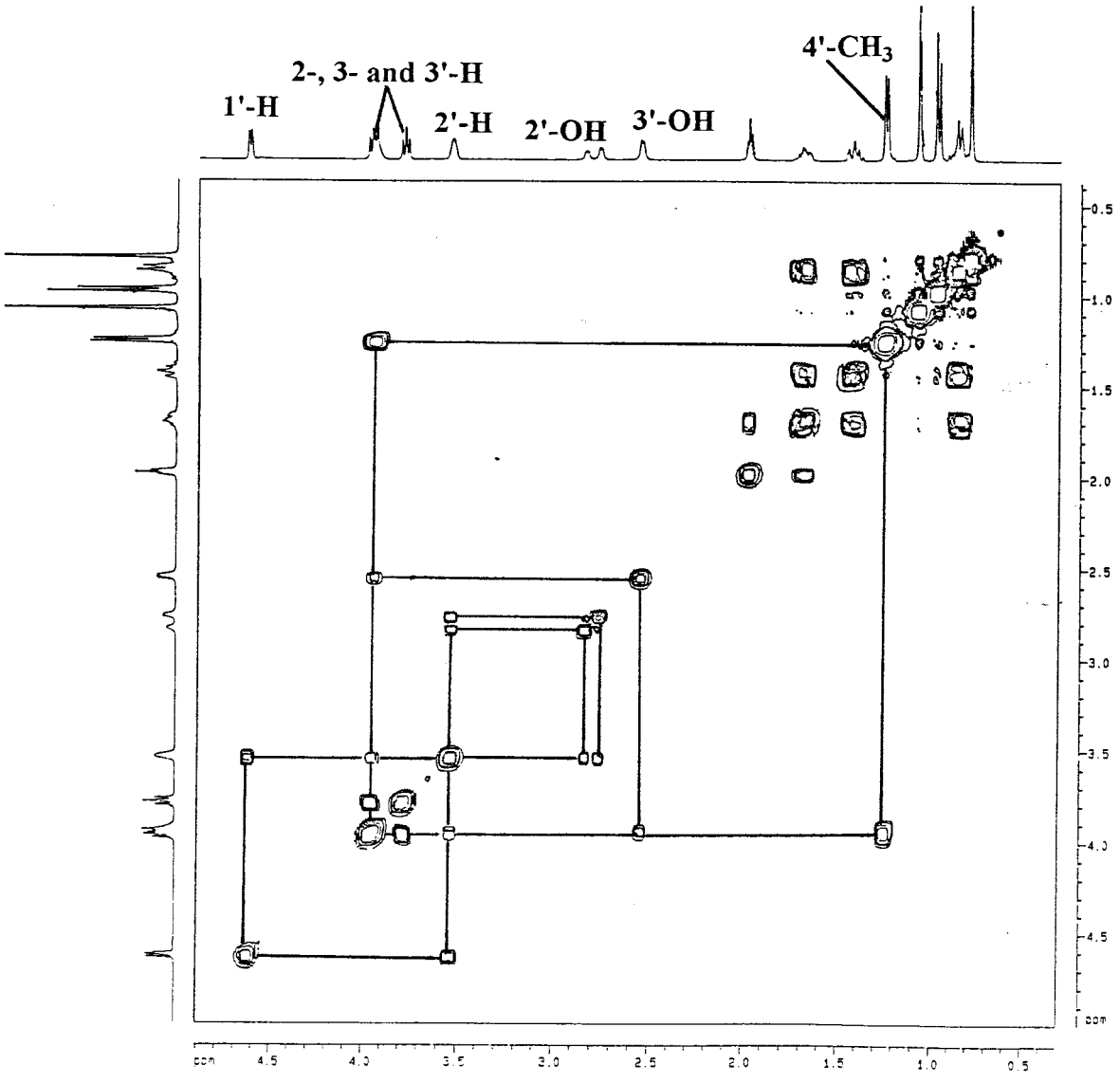


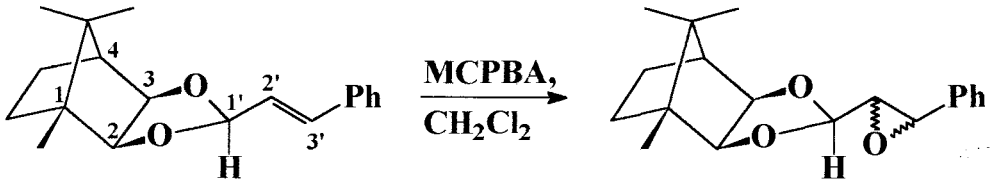

**FIGURE 37.** The COSY spectrum of the diol (**223**) in $CDCl_3$.

### 2.3.5.3 Exploratory studies

Exploratory studies into the asymmetric inductions in the epoxidation, Diels-Alder, cleavage, elimination and Baylis-Hillman reactions of the camphor-derived acetals, were undertaken.

#### 2.3.5.3.1 MCPBA epoxidation

The acetal (**196**) was epoxidised with MCPBA under similar conditions to those used for the tartrate acetals (**177-179**) (**Section 2.2.3**), and the acetal epoxide (**227**) was obtained in 78 % yield (**Scheme 39**).




(196) (227)

**SCHEME 39**

The formation of the acetal epoxide (**227**) is evident from the $^1$H NMR spectrum which reveals significant upfield shifts of the 1'-, 2'- and 3'-proton signals; similar upfield shifts were observed for the corresponding protons of the epoxide acetals (**180-183**). The 1'-methine proton in the product resonates as a multiplet at 4.57 ppm, whereas in the starting acetal (**196**), it appears as a doublet at 5.21 ppm (**Figure 22**); the COSY spectrum shows correlation between the 1'-H signal and the 2'-H multiplet at 3.22 ppm, and between the 2'-H signal and the 3'-H doublet at 3.94 ppm (**Figure 38**).

The ratio of the diastereomeric epoxides (**227**) was calculated by integration of the well-resolved 4-H doublets at *ca.* 2.02 ppm, corresponding to the two diastereomers and was

found to be 1:1 (i.e. 0 % d.e.), suggesting that both faces of the double bond in the alkene substrate (**196**) are equally accessible to the MCPBA.

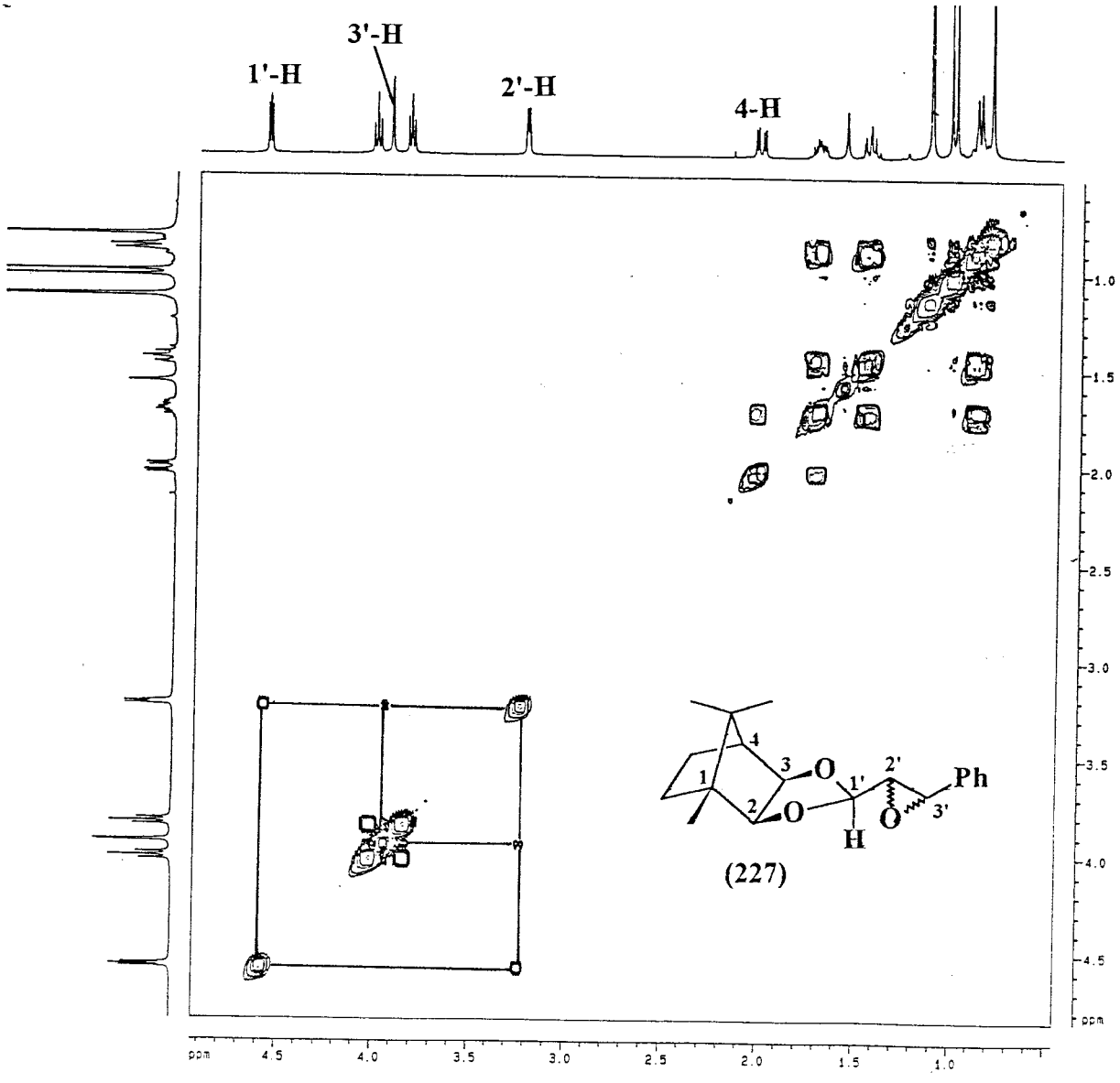



**FIGURE 38.** Partial 400 MHz COSY spectrum of the acetal epoxide (**227**), in $CDCl_3$.

### 2.3.5.3.2 Asymmetric Diels-Alder reactions

The Diels-Alder reaction is a powerful tool for the synthesis of enantiomerically pure, complex molecules, the attractive feature of the reaction being the highly regioselective formation of two bonds with the simultaneous creation of up to four chiral centres. The use of chiral auxiliaries, which are attached to either the diene or the dienophile, and optically active catalysts[156] have been successfully used to carry out asymmetric Diels-Alder reactions. Oppolzer *et al.*[157-159] have used various camphor-derived alcohols, such as compounds (**228**) and (**229**) (**Figure 39**), as chiral auxiliaries, which when attached to the dienophile, as in compound (**230**), produced Diels-Alder adducts with high diastereoselection. The high selectivities observed have been ascribed to the bulky substituents on the camphor molecule which shield the double bond thereby hindering access of the diene to one face of the double bond.

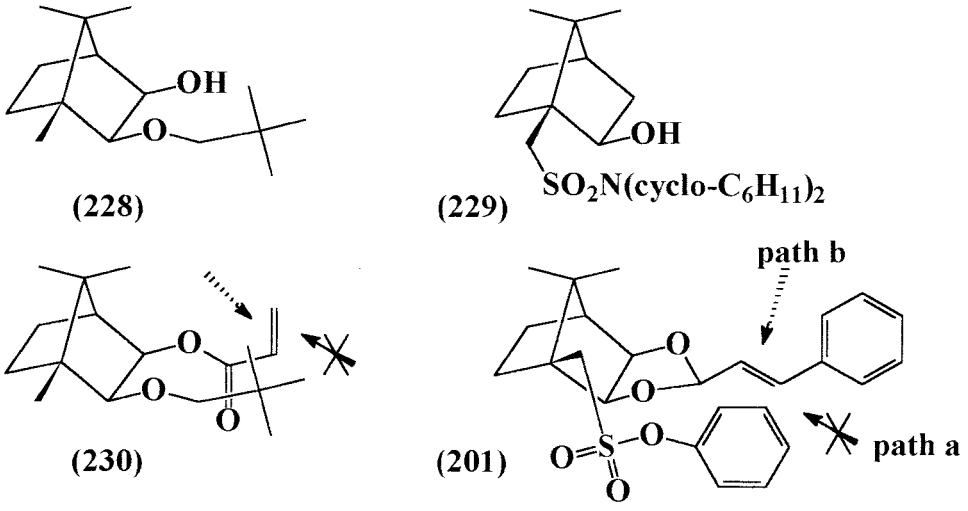
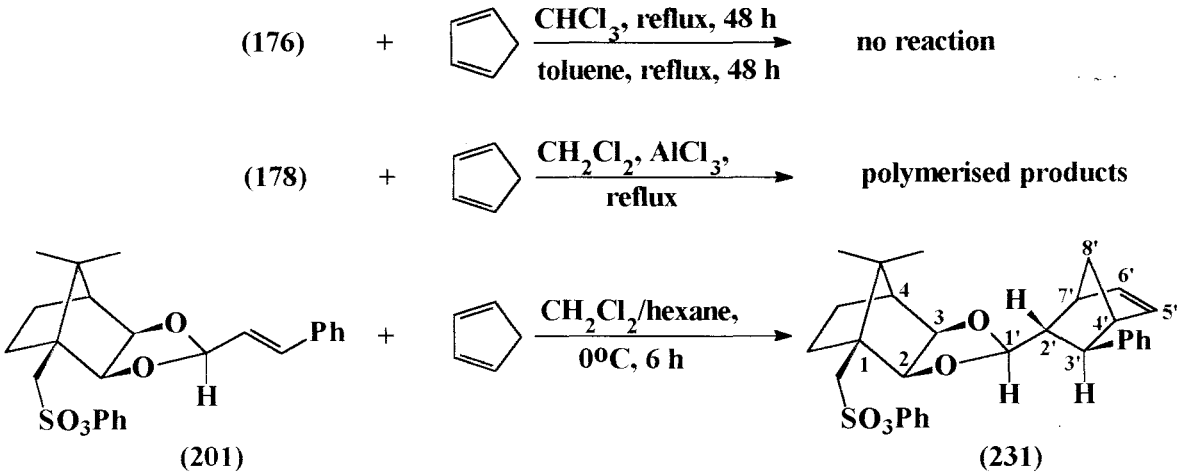



**FIGURE 39**

We hypothesised that the bulky phenyl methanesulfonate substituent at C-1 of acetal (**201**) would effect similar hindrance to the double bond (**Figure 36b**) and thus induce high stereoselectivity. Intramolecular Diels-Alder reactions of ketals of α,β-unsaturated

ketones require long reaction times at high temperatures,[160, 161] whereas the activation of α,β-unsaturated acetals *via* intermediate allylic cations, using the method of Gassman *et al.*,[162] affords the cycloadducts in high yields and at low temperatures. Alexakis *et al.*[17] reported the use of triflic acid to activate the acetal (**113**) (**Section 1.1.3.4**), but no further Diels-Alder reactions of acetals were uncovered in a literature search. Therefore, we attempted to develop an efficient procedure for Diels-Alder reactions of chiral acetals.

The uncatalysed addition of acetal (**176**) to cyclopentadiene was first attempted, but no cycloadduct was formed after heating for 48 h under reflux in either chloroform or toluene (**Scheme 40**). The Lewis acid-catalysed cycloaddition of acetal (**178**) to cyclopentadiene in refluxing dichloromethane was then attempted, but this resulted in the formation of a dark viscous oil, suggesting polymerization of the reaction mixture. Polymerization of dienes is known to be induced by free Lewis acids and may be suppressed by carrying out the reaction in a dichloromethane/hexane mixture.[163]




(201) (231)

**SCHEME 40**

Consequently, acetal (**201**) and cyclopentadiene were reacted in a 5.5:4.5 mixture of dichloromethane and hexane, at 0°C, in the presence of $AlCl_3$ (**Scheme 40**). The

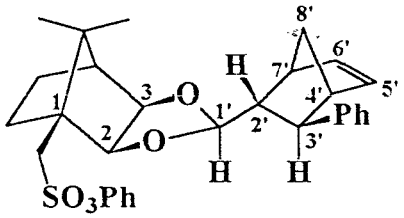
progress of the reaction was monitored by TLC and starting material was still present after 2 h; a further 0.5 equivalents cyclopentadiene was then added and the mixture stirred for a further 6 h. After work-up, purification of the crude product by HPLC yielded the cycloadduct (**231**) in 32 % yield.

The $^1$H NMR spectrum of the isolated cycloadduct (**231**) indicated the camphor skeleton to be intact, while the double bound of the acetal (**201**) was no longer present. The vinyl protons of compound (**231**) resonate as multiplets at 6.14 and 6.32 ppm and their coupling to the 4'- and 7'-methine protons (multiplets at 3.02 and 3.06 ppm) is apparent in the COSY spectrum (**Figure 40**). Both the 4'- and 7'-methine nuclei show coupling to the diastereotopic 8'-methylene protons which are observed as a pair of multiplets at 1.51 and 1.65 ppm. The 2'-proton multiplet at 2.45 ppm, was identified by its coupling to the 7'-proton which, in turn, coupled to the 3'-proton (a multiplet at 2.56 ppm) and to the 1'-methine proton (a doublet at 4.27 ppm).

The correlation of the 2'-proton with one of the 8'-methylene protons in the NOESY spectrum of compound (**231**) (**Figure 41**) suggests that the *exo*-adduct is formed by attack of the cyclopentadiene on the acetal (**201**). This deduction is supported by the absence of any correlation between the 8'-methylene protons and 3'-proton. Attack of the cyclopentadiene on the alkene, as indicated by path a [(see compound (**201**), **Figure 39**], would result in the vinyl protons being close in space to the phenyl protons of the phenyl methanesulphonate blocking group and some correlation between them should be observed; however, this is not the case.

In an attempt to increase the yield of the cycloadduct (**231**), an attempt was made to activate the acetal (**201**) using triflic acid, following the method of Gassman *et al.*;[162] however, $^1$H NMR spectroscopy of the crude product showed very little of the desired

compound (< 10 %).




**(231)**

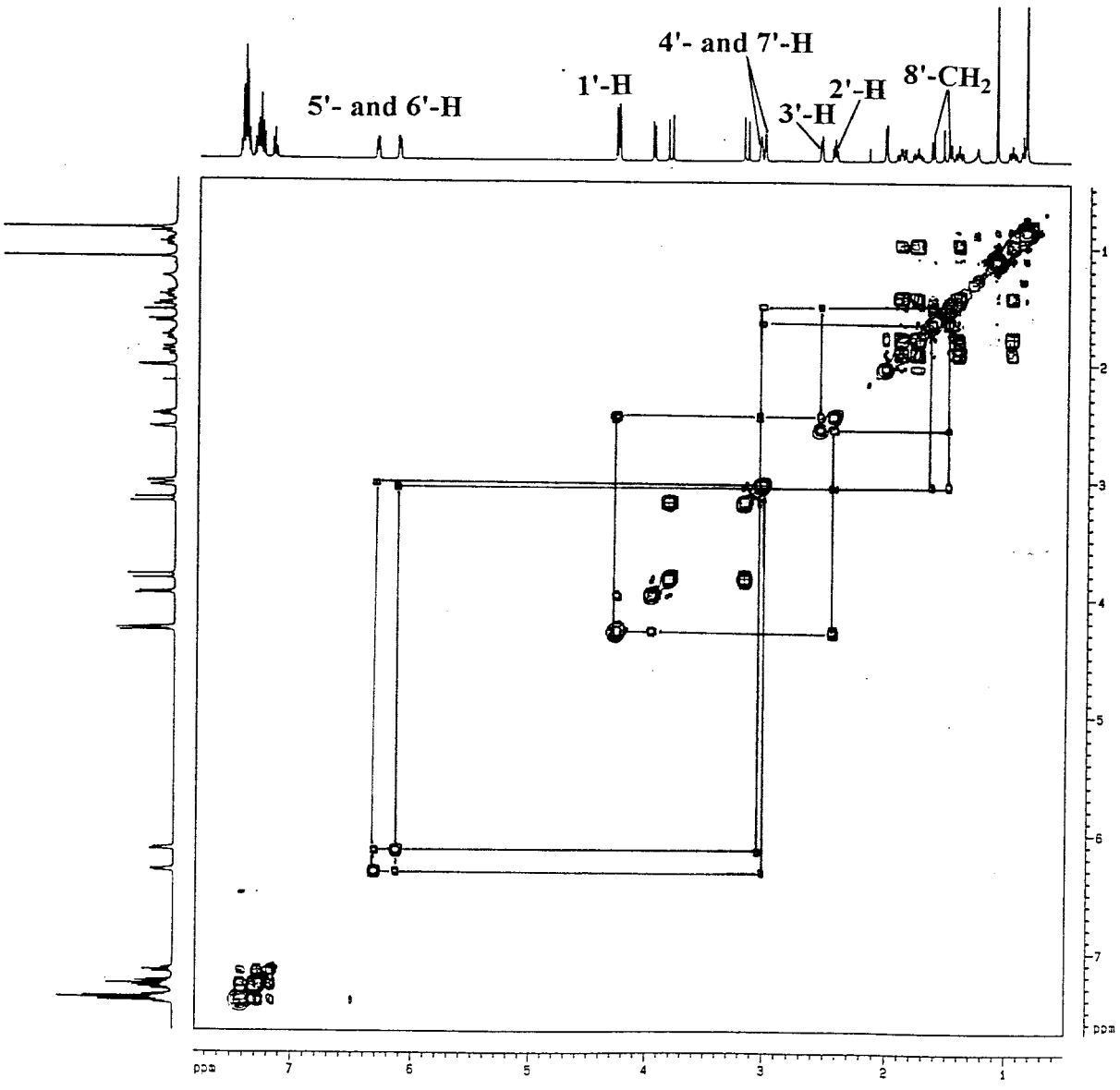
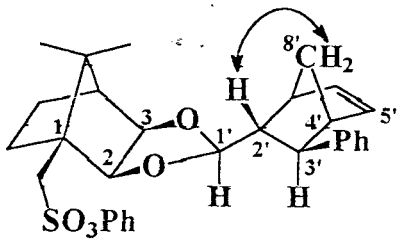



**FIGURE 40.** The 400 MHz COSY spectrum of compound (**231**), in $CDCl_3$.




(231)

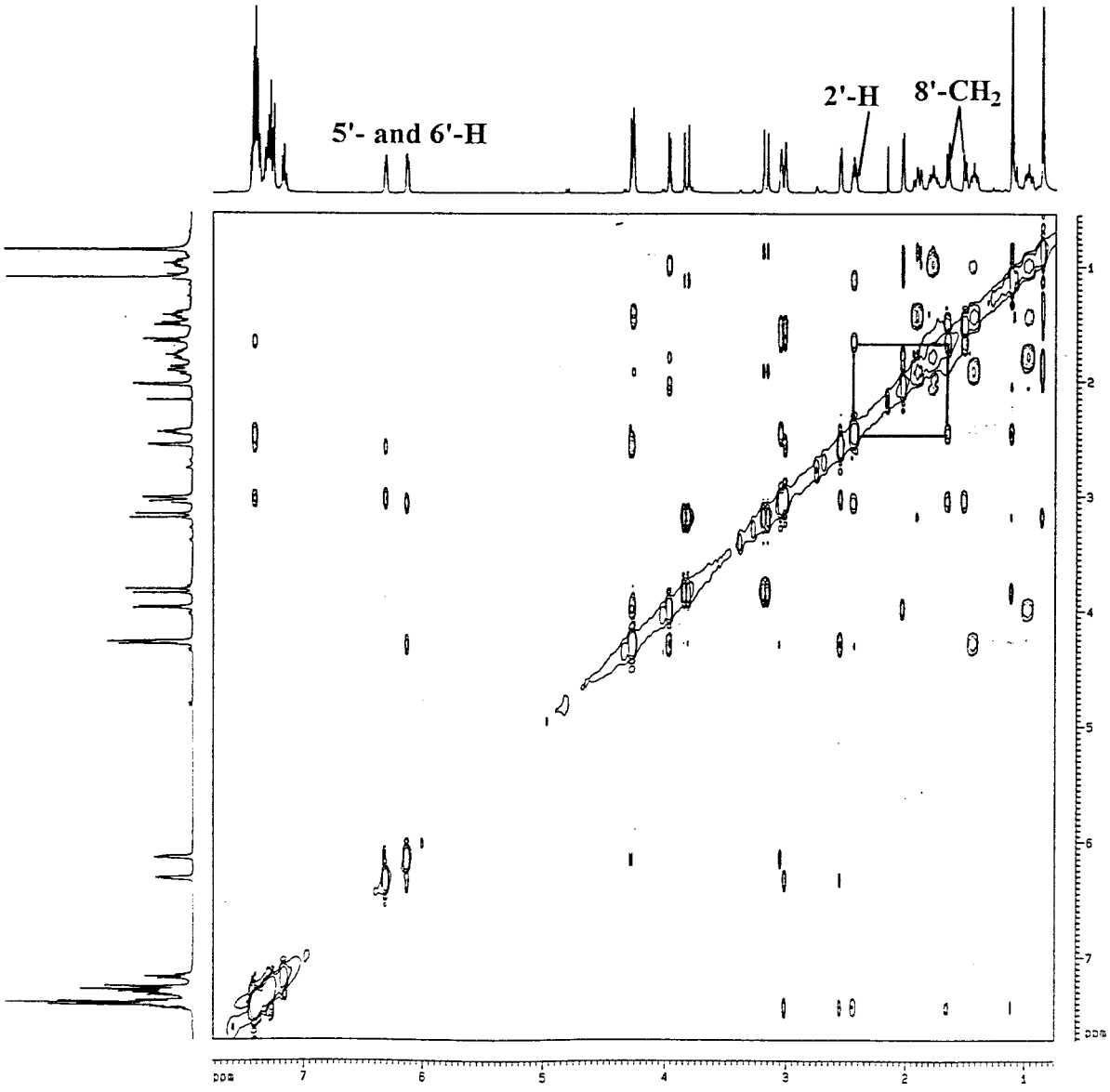
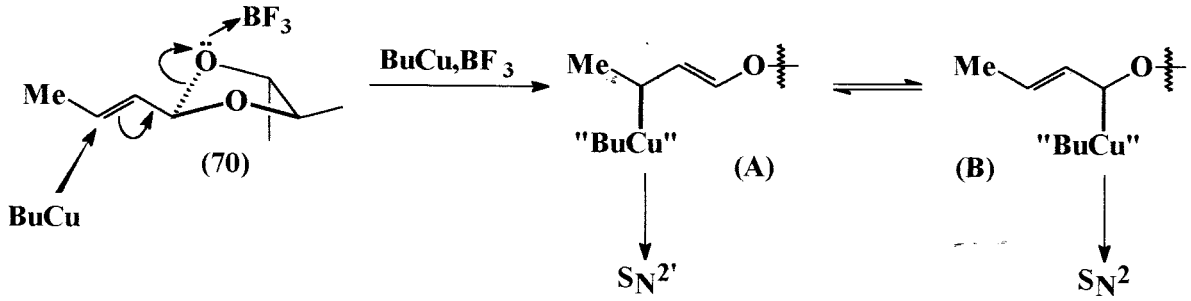



**FIGURE 41.** The NOESY spectrum of compound (**231**) in $CDCl_3$.

### 2.3.5.3.3 Organocopper alkylation

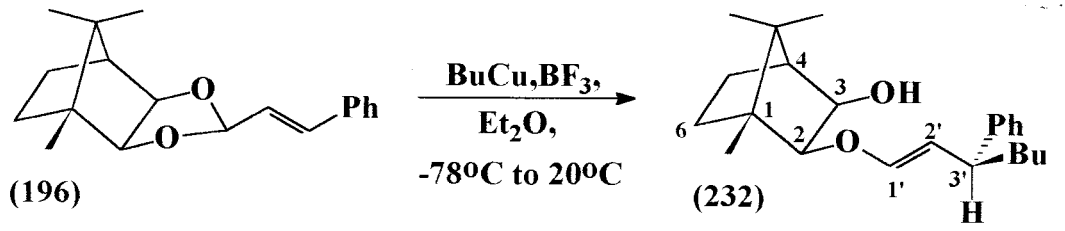
Organocopper reagents have been widely used in organic synthesis because of the useful and unique transformations which they promote, and their combination with Lewis acids has widened their range of applications to include the diastereoselective cleavage of chiral acetals.[164] Aldehydes are commonly protected from nucleophilic attack by transformation to acetals, which are normally stable towards various organometallic reagents.[165] However, organometallic reagents which possess Lewis acid character or which are associated with a Lewis acid are known to cleave chiral acetals with high diastereoselectivity at the acetal centre (**Section 1.1.2**); nucleophilic cleavage of α,β-unsaturated acetals (**Section 1.1.2.7**) is also diastereoselective but not always regioselective, as two products may be formed - one by direct attack at the acetal centre ($S_N2$), the other by $S_N2'$ displacement.[64] The enhanced reactivity of $RM/BF_3$ reagents towards acetals, over organometallic reagents which are not associated with a Lewis acid, is attributed to activation of the acetal by the electrophilic Lewis acid.

Alexakis *et al.* obtained a mixture of $S_N2'$ and $S_N2$ products when the chiral acetal (**70**) was treated with $BuCu/BF_3$ (**Scheme 11**), and rationalized the formation of the products by an initial, *anti* $S_N2'$ process, in which the acetal reacts in a transoid conformation[55] and the leaving group is the $BF_3$-complexed oxygen atom adjacent to the pseudoaxial group. These authors postulated that the resulting σ-allyl complex (**A**) is in equilibrium with (**B**) and, therefore, the regioselectivity depends on the rate of reductive elimination in (**A**) and (**B**) relative to the isomerization (**Scheme 41**). Although the reaction is not regioselective, the products are formed with high diastereoselectivity as a result of preferential coordination of the Lewis acid to the oxygen adjacent to the pseudoaxial group.




**SCHEME 41**

In the preferred conformation of *trans*-cinnamaldehyde bornane acetal (**196**) (**Section 2.3.4**), both acetal oxygen atoms are adjacent to pseudoequatorial groups (in the form of the camphor skeleton), making them unfavourable sites for coordination due to the resultant steric hindrance (**Section 1.1.2.1**). As coordination of the Lewis acid is vital for activation of the acetal, which can then be attacked by the organocopper nucleophile, the efficient diastereoselective cleavage of bornane derived acetals was considered unlikely. In the event, reaction of the *trans*-cinnamaldehyde bornane acetal (**196**) with preformed $BuCu/BF_3$ in diethyl ether, afforded the $S_N2'$ product, the enol ether (**232**), in 17 % yield after flash chromatography on silica gel (**Scheme 42**).

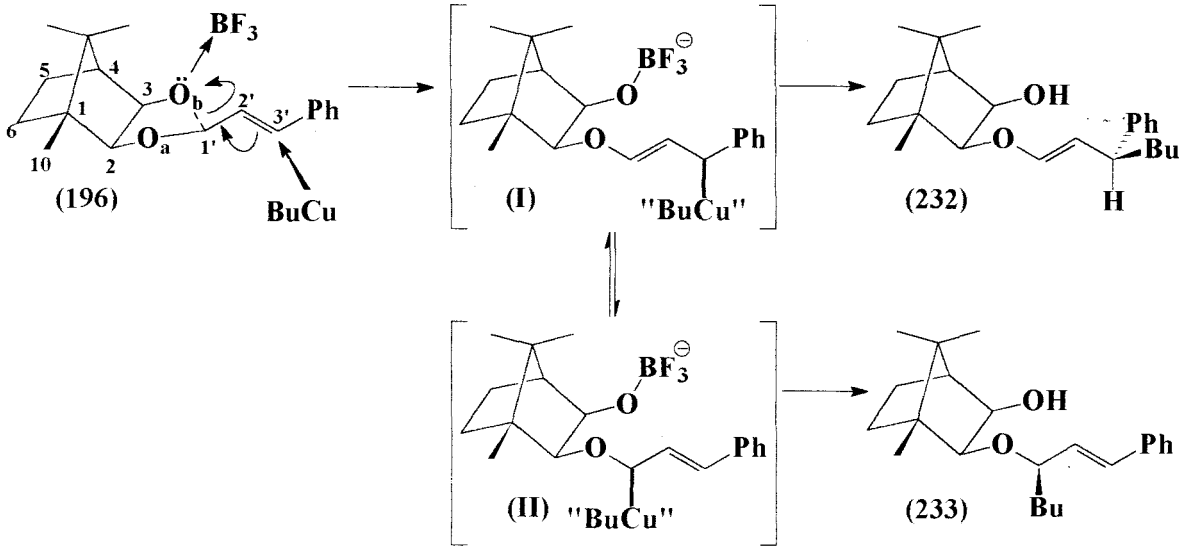



**SCHEME 42**

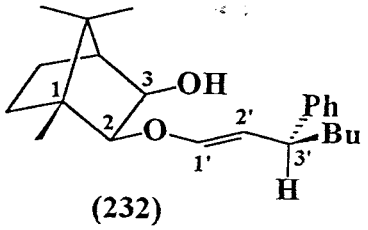
The enol ether (**232**) was obtained as a single diastereomer, as shown by $^1H$ NMR spectroscopy, and the stereochemistry of the double bond was determined to be *E* ( $J_{1',2'}$ = 12.4 Hz). The structure of enol ether (**232**) was confirmed by 2-D NMR spectroscopy. The COSY spectrum of compound (**232**) showed correlation between the vinyl protons.

resonating as a multiplet at 5.04 and a doublet at 6.15 ppm respectively, and coupling of the 2'-vinyl proton to the 3'-methine proton (**Figure 42**). Correlation between the 2-methine doublet at 3.54 ppm and the 3-methine multiplet at 3.83 ppm is also evident, as is the coupling between the 3-methine proton and the 3-hydroxyl proton. The HMBC spectrum of the enol ether (**232**) reveals a three bond correlation between the 1'-vinyl proton and the C-2 nucleus, the assignment of the signal at 88.4 ppm to the latter nucleus being supported by correlations with the 3-hydroxyl proton, the 4-methine proton, the 6-methylene protons and the 10-methyl protons (**Figure 43**).

The formation of enol ether (**232**) is clearly consistent with diastereoselective nucleophilic cleavage of the $BF_3$-activated acetal (**196**) by the organocopper reagent, as indicated in **Scheme 43**. Nucleophilic attack by the cuprate reagent in an *anti* $S_N2'$ process,[64] would afford the σ-allyl complex (**I**), *via* cleavage of the C(1')-$O_b$ bond. This bond is expected to be weakened by preferential coordination of the $BF_3$ to the less hindered $O_b$ dioxolane oxygen atom.




**SCHEME 43**




(232)

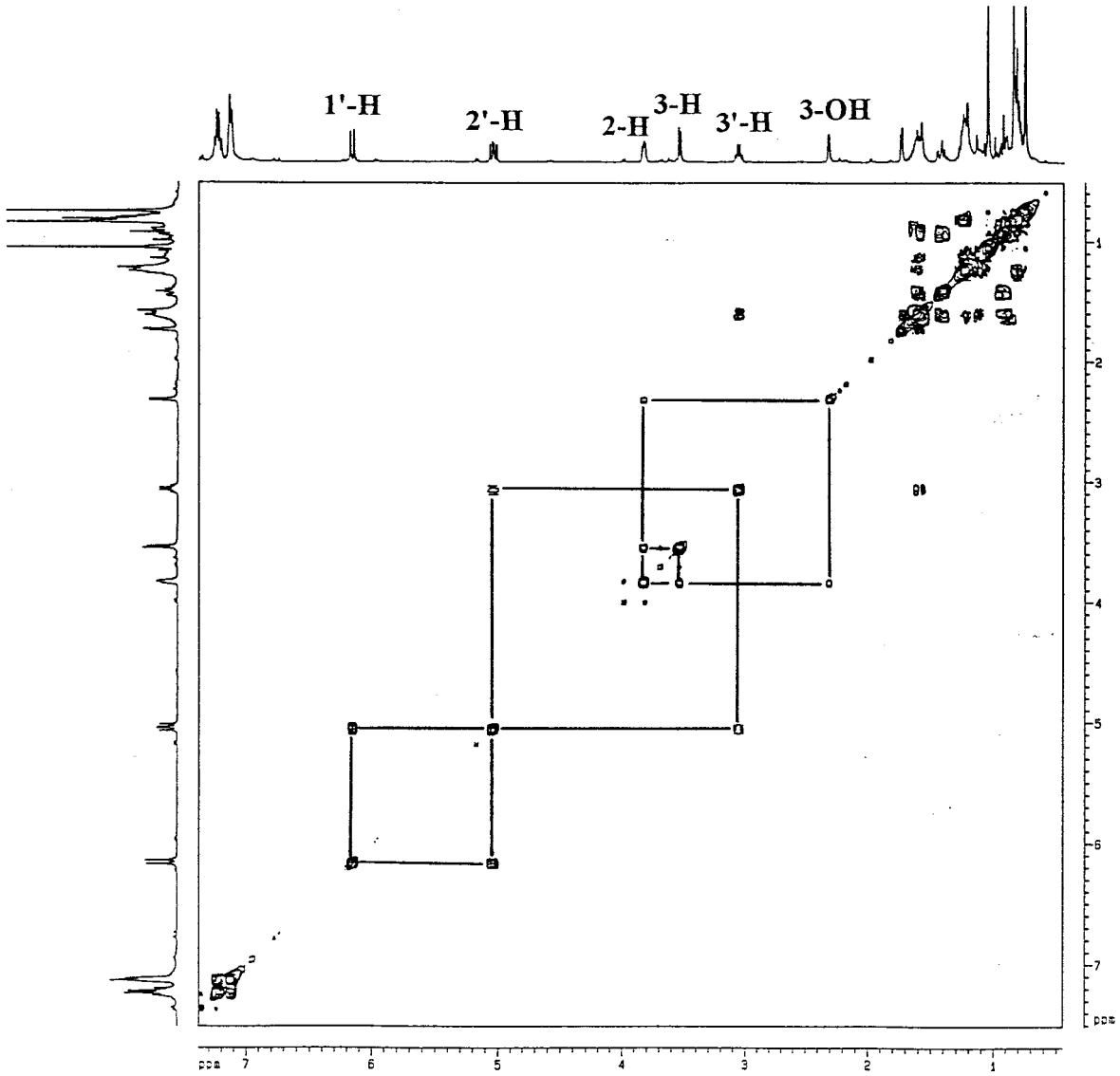



**FIGURE 42.** The COSY spectrum of enol ether (**232**) in $CDCl_3$.

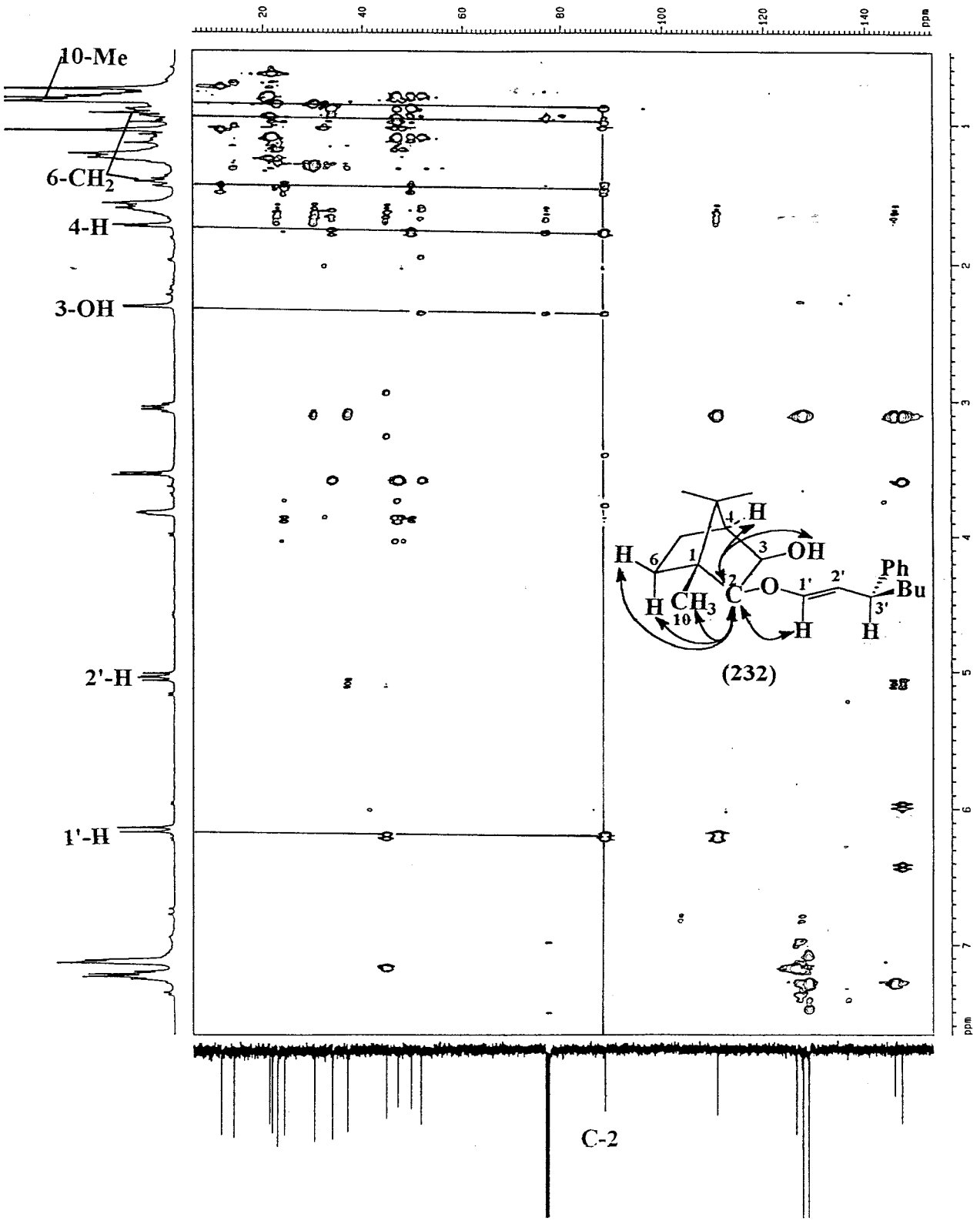



**FIGURE 43.** The HMBC spectrum of enol ether (**232**) in $CDCl_3$.

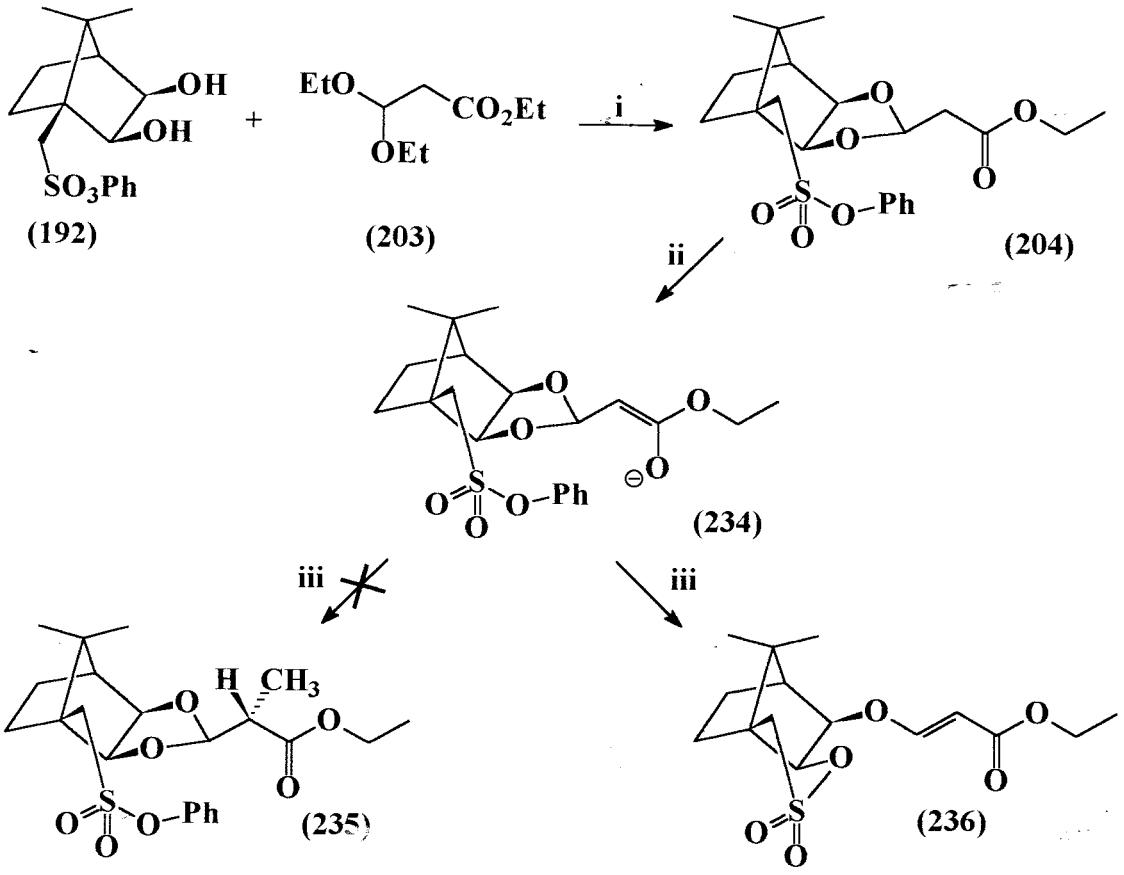
However, the low yield of the enol ether (**232**) suggests that coordination of the Lewis acid, to either of the acetal oxygens, does not occur readily. Alexakis *et al.*[55, 165] observed that *meso* acetals, derived from *meso*-2,4-petanediol, are less reactive when treated with $RCu/BF_3$ reagents than acetals, derived from (+)- or (-)-2,4-pentanediol, and suggested that the absence of axial substituent adjacent to the acetal oxygens was responsible for the decrease in reactivity. The absence of any axial substituents may similarly account for the the low reactivity of the acetal (**196**).

Although complex (**I**) (**Scheme 43**) may undergo isomerization to complex (**II**), which would in turn would result in the formation of the $S_N'$ product (**233**), it undergoes a rapid reductive elimination to give the experimentally observed enol ether (**232**). The overall process, once the auxiliary is removed, may thus be viewed as conjugate addition of BuLi to an α,β-unsaturated aldehyde with high regio- and stereo-selectivity, but unfortunately in poor yield. An attempt to improve the yield of the enol ether (**232**) was made by reacting the acetal (**196**) with $Bu_2CuLi,BF_3$, as organocuprates ($R_2CuLi$) are more reactive than the corresponding organocopper reagents (RCu),[165] but $^1H$ NMR analysis showed very little of the desired compound.

### 2.3.5.3.4 Diastereoselective Elimination

The lithium amide promoted asymmetric alkylation of β-ketoesters has been achieved using ketals[166] and, recently, Pedrosa *et al.* used acetal derivatives[71]. These authors reacted the homochiral 2-(ethoxcarbonyl) dioxolane (**107**), derived from bornane-2,3-diol (**150**), with excess methyl iodide in the presence of lithium di*iso*propylamide (LDA) to obtain the alkylated product in high yield but with poor diastereoselectivity (see **Scheme 18**, p. 31). We envisaged that acetal (**204**) would react similarly but with increased diastereoselectivity, the bulky phenyl sulfonate substituent at C-10 being expected to hinder attack of the electrophile at the pro-*R* face of the enolate (**234**), thereby favouring formation of the alkylated product (**235**) with an *S*-configuration at the new stereogenic centre (**Scheme 44**). The ester derivative (**204**) was obtained by reacting ethyl 3,3-diethoxypropionate (**203**) and the diol (**192**) in the presence of boron trifluoride etherate (see **Scheme 31**, p. 80).[71]

However, under similar conditions to those used by Pedrosa *et al.*,[71] the acetal (**204**) underwent diastereoselective elimination, affording the sultone (**236**), instead of the expected alkylation. Pedrosa *et al.*[71] also observed the formation of an elimination product during the alkylation of the 1,3-dioxane derived from racemic 2,4-pentanediol and 3,3-diethoxypropionate, but obtained the alkylated derivative as the sole product when TMEDA was used as co-solvent (see **Section 1.1.3.2**).




**Reagents: i) $BF_3.(OEt)_2$, benzene, ii) LDA, THF, -78°C, iii) MeI, -78°C to 20°C.**

**SCHEME 44**

Consequently, in an attempt obtain the alkylated product (**235**), TMEDA was used as a co-solvent but the sultone (**236**) was again isolated as the sole product. It is proposed that the sultone (**236**) is formed *via* deprotonation of the acetal (**204**) to give the carbanion (**237**), which rapidly undergoes diastereoselective cleavage of the acetal with concomitant nucleophilic substitution of the sulfonic ester by the proximate acetal oxygen (**Figure 44**). The most striking features of the $^1H$ NMR spectrum, which was used to elucidate the structure of the sultone (**236**), are the absence of an aromatic signal and the appearance of the vinyl proton signals as a pair of doublets at 5.24 and 7.48 ppm (**Figure 45**).

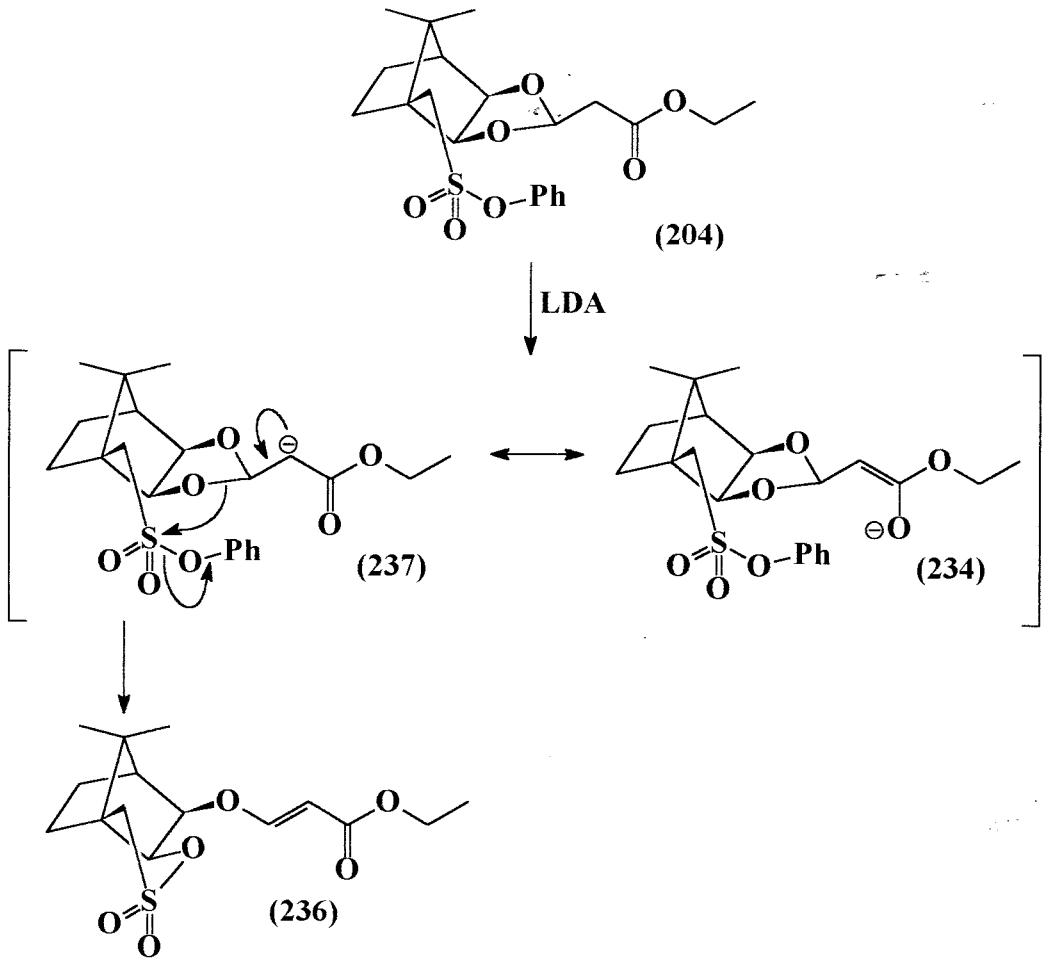
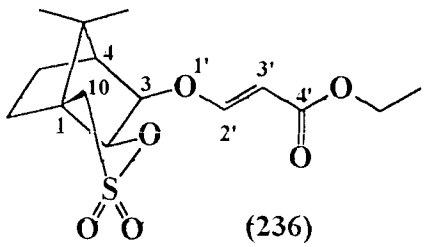



**FIGURE 44**




(236)




**FIGURE 45.** The 400 MHz $^1$H NMR spectrum of sultone (**236**) in $CDCl_3$.

### 2.3.5.3.5 Attempted diastereoselective Baylis-Hillman reactions

The addition of an acrylate to an aldehyde, catalysed by a tertiary amine, is widely referred to as the Baylis-Hillman reaction (**Figure 46**).[167, 168] As a new stereogenic centre is formed in the reaction, various attempts have been made to induce stereoselecetivity by making use of chiral catalysts, aldehydes and acrylate derivatives.

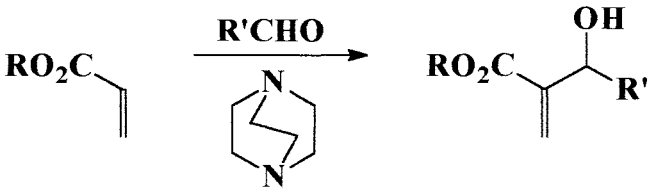



**FIGURE 46**

Acrylate esters, prepared from the camphor-derived chiral auxiliaries (**229**) and (**238**) (**Figure 47**), have not proved to be reliable or highly enantioselective substrates in Baylis-Hillman reactions.[169] However, Leahy *et al.*, using acrylamides derived from Oppolzers sultam (**1**), obtained optically pure products (> 99 % e.e.).[170]

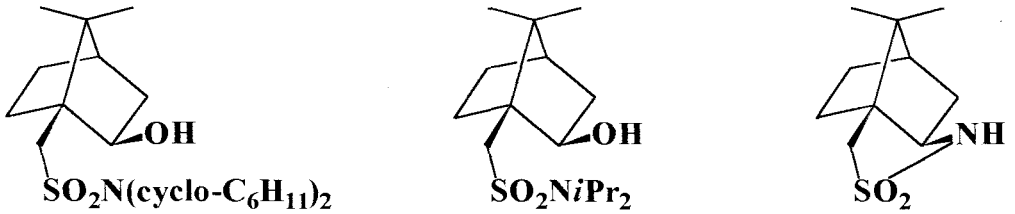
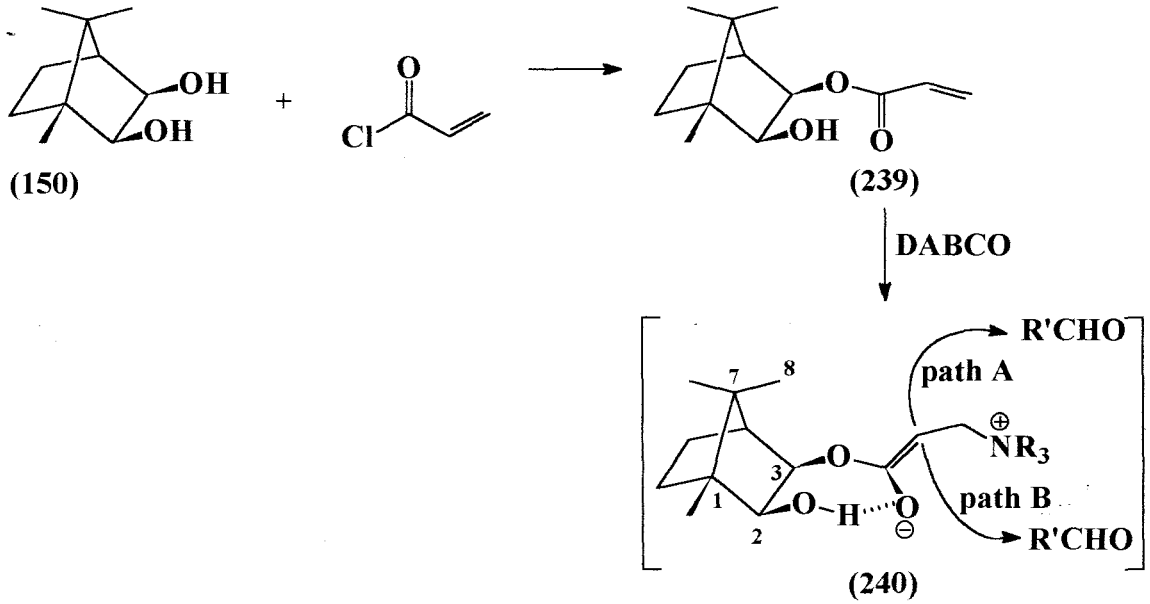



**FIGURE 47**

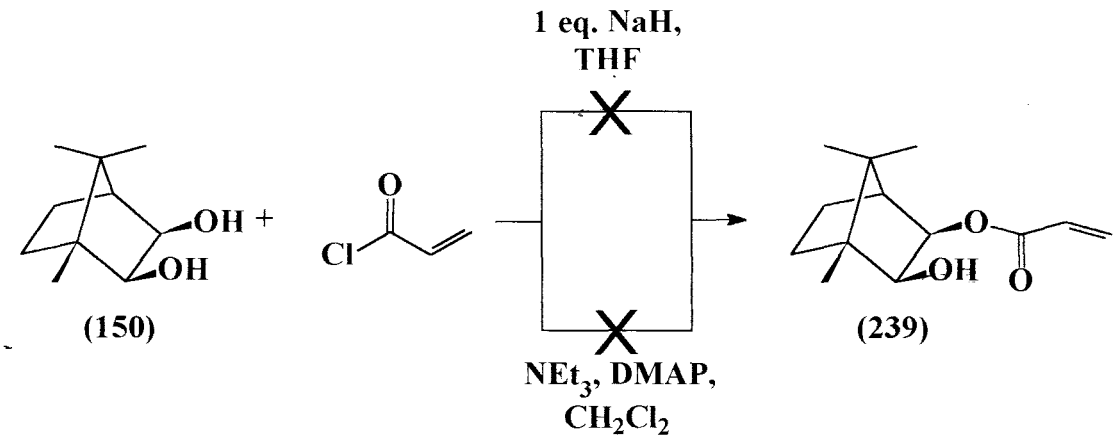
In the present study, the camphor-derived diol (**150**) was investigated as a potential chiral auxiliary for stereoselective Baylis-Hillman reactions. Monoacrylation, using 1 equivalent of acryloyl chloride was expected to afford the chiral acrylic ester (**239**)

which, as a Baylis-Hillman substrate, might permit stabilisation of the zwitterionic enolate species (**240**) *via* intramolecular hydrogen bonding (**Scheme 45**). Subsequent attack by the enolate (**240**) on the aldehyde could then occur preferentially at the less hindered *endo*-face of the double bond (path B); *exo*-face attack is expected to be hindered by the steric bulk of the 8-methyl group.



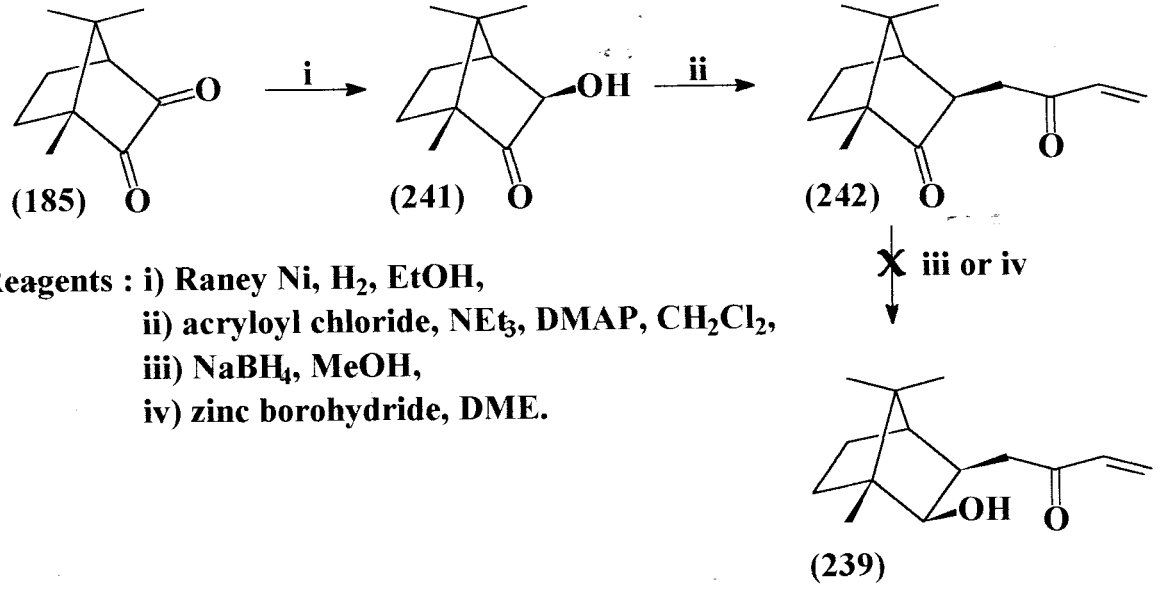

**SCHEME 45**

Preparation of the acrylate (**239**) was first attempted by adding 1 equivalent of NaH to a solution of diol (**150**) in THF; the mixture was then stirred at room temperature for 1 hour to generate the alkoxide anion, followed by the adddition of acryloyl chloride (**Scheme 46**). After boiling the mixture under reflux for 2 hours, $^1$H NMR analysis of the crude product showed none of the desired material. Oppolzer *et al.* have reported the preparation of acrylic esters by treatment of the alcohol with acryloyl chloride, triethylamine and 4-dimethylaminopyridine (DMAP) in $CH_2Cl_2$, at 0°C.[171] This synthetic procedure was followed using the alcohol (**150**), but $^1$H NMR analysis of the crude product revealed a very complex mixture of components which could not be adequately separated by flash column chromatography.




**SCHEME 46**

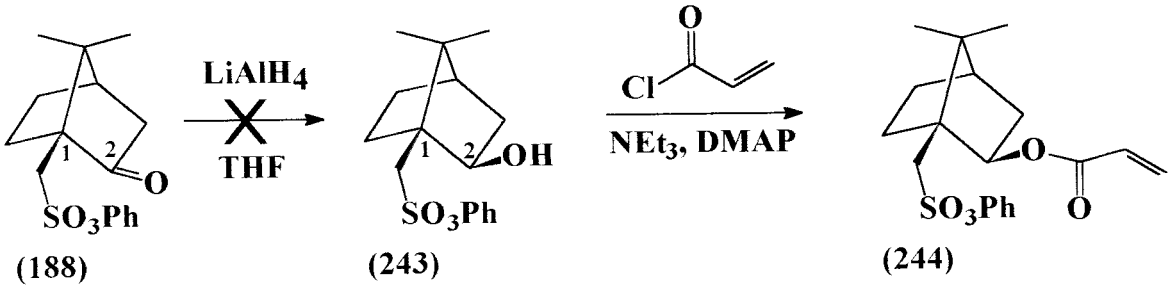
Given the lack of success in preparing the acrylic ester (**239**) directly from the diol (**150**), an alternative approach was explored. It was envisaged that selective reduction of the 2-carbonyl group in the acrylic ester (**242**) would afford the desired acrylate (**239**) (**Scheme 47**). The acrylic ester (**242**) was prepared in 30 % yield using 3-*exo*-hydroxycamphor (**241**) and the method of Oppolzer *et al.*;[171] 3-*exo*-hydroxycamphor (**241**) was obtained in good yield by regio- and stereoselective Raney nickel reduction of camphorquinone (**185**). Reduction of 2-carbonyl group was first attempted by adding $NaBH_4$ to a solution of the acrylic ester (**242**) in methanol; however, work-up resulted in polymerization of the product. Use of zinc borohydride, which has been reported to selectively reduce ketones over conjugated enones,[172] similarly resulted in polymerization.




**Reagents : i) Raney Ni, $H_2$, EtOH,**
**ii) acryloyl chloride, $NEt_3$, DMAP, $CH_2Cl_2$,**
**iii) $NaBH_4$, MeOH,**
**iv) zinc borohydride, DME.**

**SCHEME 47**

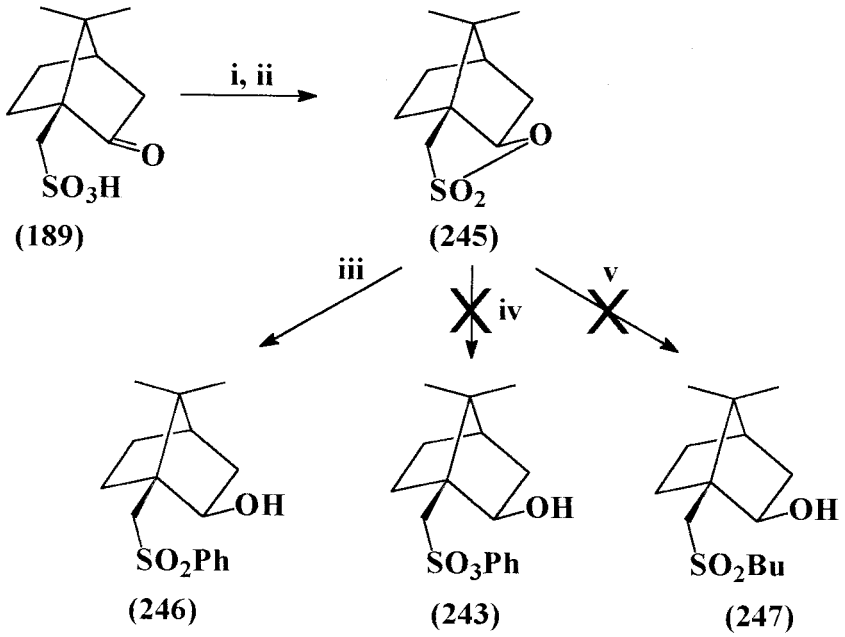
Faced with these difficulties in preparing the chiral acrylic ester (**239**), the acrylic ester (**244**) was targeted as a possible Baylis-Hillman substrate, as it was expected that the phenyl methanesulfonate moiety at C-1 would hinder attack of the "front" face of the double bond. Unfortunately, LAH reduction of the ketone (**188**) gave a complex mixture of products instead of the desired alcohol (**243**) (**Scheme 48**).




**SCHEME 48**

A final approach, utilising the sultone (**245**), was then investigated as a means of obtaining the chiral alcohol (**243**), which could be esterified to afford the desired acrylic

ester (**244**). Oppolzer *et al.*[173] have reported nucleophilic ring opening of the sultone (**245**), with phenyllithium, to afford the sulfone (**246**) in 53 % yield (**Scheme 49**). The sultone (**245**) was obtained by reduction of camphor-10-sulfonic acid (**189**) with sodium borohydride and subsequent cyclisation with *p*-toluenesulfonyl chloride in pyridine.[174] Nucleophilic ring opening of the sultone (**245**) by the phenoxy anion, generated by the reaction of BuLi on phenol, failed to afford the expected alcohol (**243**), $^1$H NMR analysis indicationg the presence of unreacted starting material alone. Having failed to open the sultone (**245**) with phenoxide ion, the use of BuLi as nucleophile was investigated. However, this also proved unsuccessful, $^1$H NMR analysis providing no evidence for the formation of the sulfone (**247**). Due to time constraints, these reactions could not be explored further.




**Reagents : i) $NaBH_4$, $H_2O$, ii) TsCl, pyridine, iii) PhLi, $Et_2O$, iv) phenol, BuLi, THF, v) BuLi, $Et_2O$.**

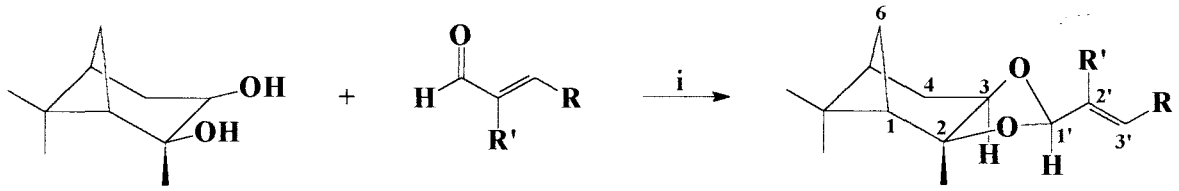
**SCHEME 49**

## 2.4 PINANE-2,3-DIOL AS A CHIRAL AUXILIARY

Encouraged by the moderate to excellent diastereoselectivities (46->99 % d.e.) obtained in the asymmetric Simmons-Smith cyclopropanation of acetals (**193-197**) and (**198-201**), derived from the bornanediols (**150**) and (**192**) respectively, an investigation into the use of commercially available (+)-pinane-2,3-diol (**248**), as the chiral auxiliary, was undertaken.

### 2.4.1 Preparation of acetals of pinane-2,3-diol

Following the procedure used for the preparation of the bornane-2,3-diol-derived acetals (**193-197**), pinane-2,3-diol (**248**) was reacted with a selection of α,β-unsaturated aldehydes to afford the acetals (**249-252**) (**Scheme 50**).



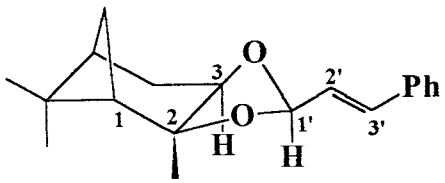

(248) (249-252)

**Reagents : i) PTSA, $MgSO_4$, benzene**

| R | R' | Pure yield/ % | Acetal |
|---|---|---|---|
| $CH_3$ | H | 69 | **249** |
| $(CH_2)_2CH_3$ | H | 54 | **250** |
| Ph | H | 71 | **251** |
| Ph | $CH_3$ | 49 | **252** |

**SCHEME 50**

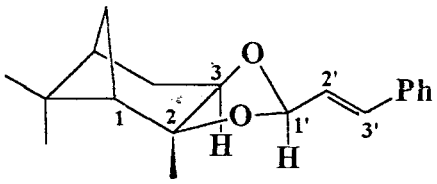
The acetals (**249-252**) are new compounds and were all fully characterised by $^{1}H$ and $^{13}C$ NMR spectroscopy and high resolution mass spectrometry. The NMR spectra of the crude products indicated the presence of a single diastereomer in each case, which was readily isolated and purified by preparative TLC. The $^{1}H$ NMR spectra, of which the spectrum for acetal (**251**) is representative (**Figure 47**), indicated that the pinane skeleton was still intact and had not undergone rearrangement. The 2'- and 3'-vinyl protons resonate as a doublet of doublets and a doublet at 6.27 and 6.83 ppm respectively, their *trans* relationship being indicated by the large vicinal coupling ($J_{2',3'}$ 16 Hz). The COSY spectrum of acetal (**251**) shows the vicinal coupling between the 2'- and 3'-vinyl protons and of the 2'-vinyl proton to the 1'-methine proton (**Figure 48**). Coupling of the 3-methine proton, resonating as a doublet at 4.02 ppm in the $^{1}H$ NMR spectrum, to the 4-methylene protons is also observed in the COSY spectrum.




**(251)**




**FIGURE 47.** The 400 MHz $^{1}H$ NMR spectrum of acetal (**251**) in $CDCl_3$.




(251)

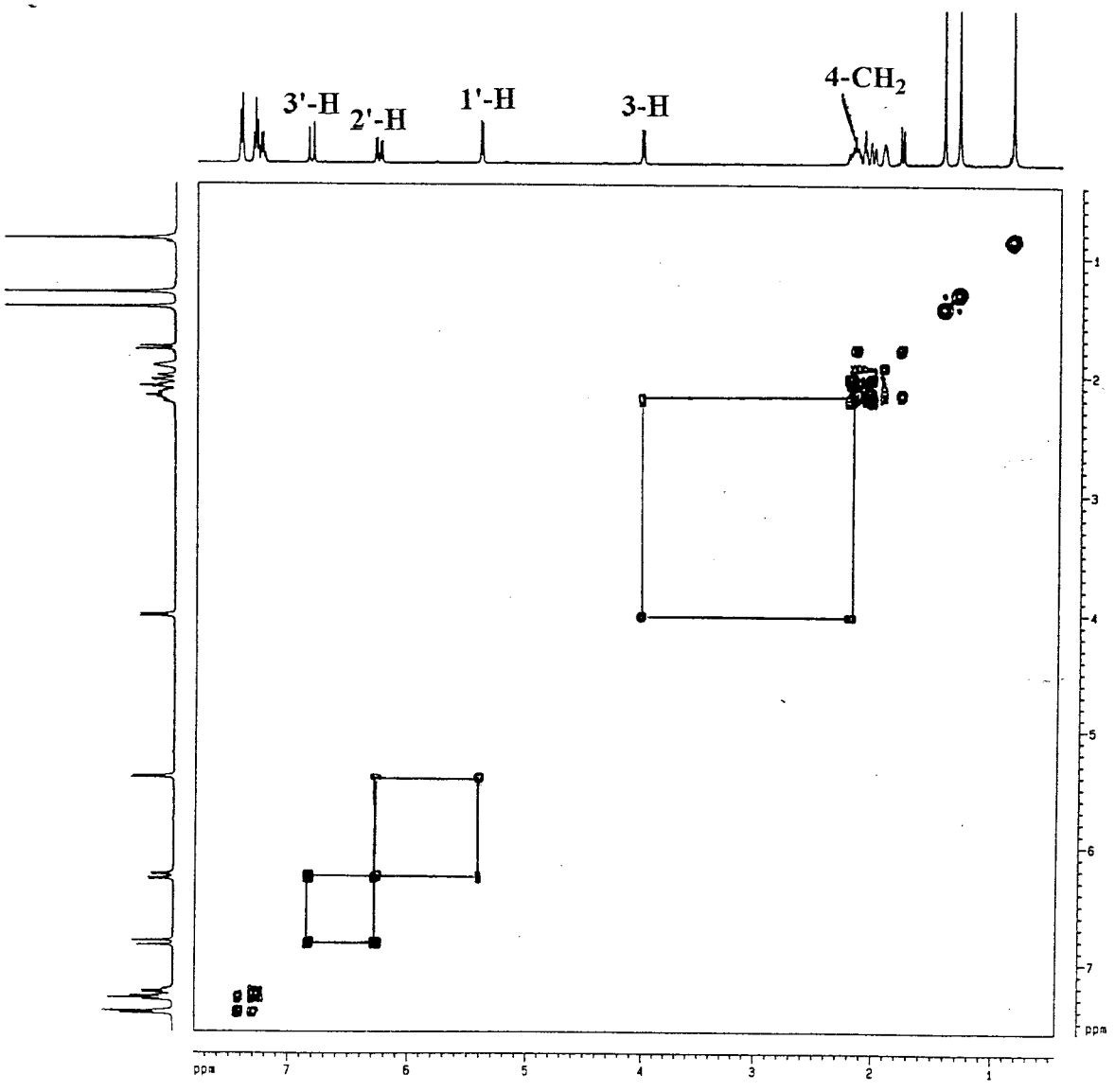
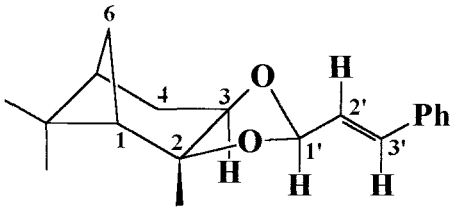


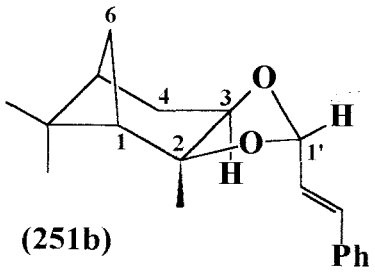

**FIGURE 48.** The 400 MHz COSY spectrum of acetal (**251**) in $CDCl_3$.

### 2.4.2 Conformational analysis of pinane-2,3-diol-derived acetals

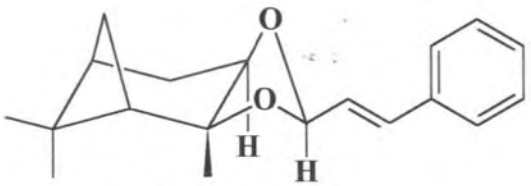
As single diastereomeric products were formed during the acetalization of the various α,β-unsaturated aldehydes with pinane-2,3-diol (**248**), a conformational analysis of acetal (**251**), representative of the series, was undertaken to account for the observed stereoselectivity. Computer modelling of the two possible stereisomers (**251a**) and (**251b**) of acetal (**251**) indicated the *exo*-substituted diastereomer (**251a**) to be less sterically hindered and, hence, more likely (**Figure 49**). Confirmation of the structure (**251a**) was achieved using the NOESY spectrum (**Figure 50**), which shows correlation of the 1'-methine proton to the 3- and 3'-methine protons and the 2-methyl protons, while the 2'-vinyl proton correlates with one of the 6-methylene protons. These correlations confirm the structure of acetal (**251**) as the *exo*-substituted isomer (**251a**).



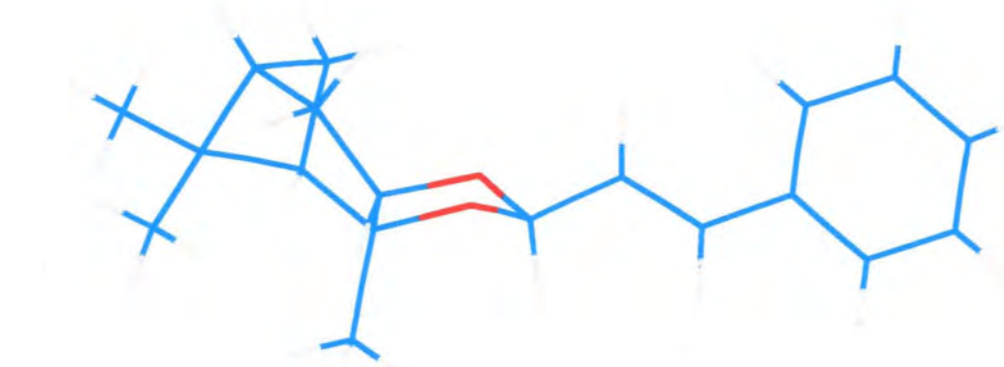

**(251a)**




**(251b)**




**(251a)**



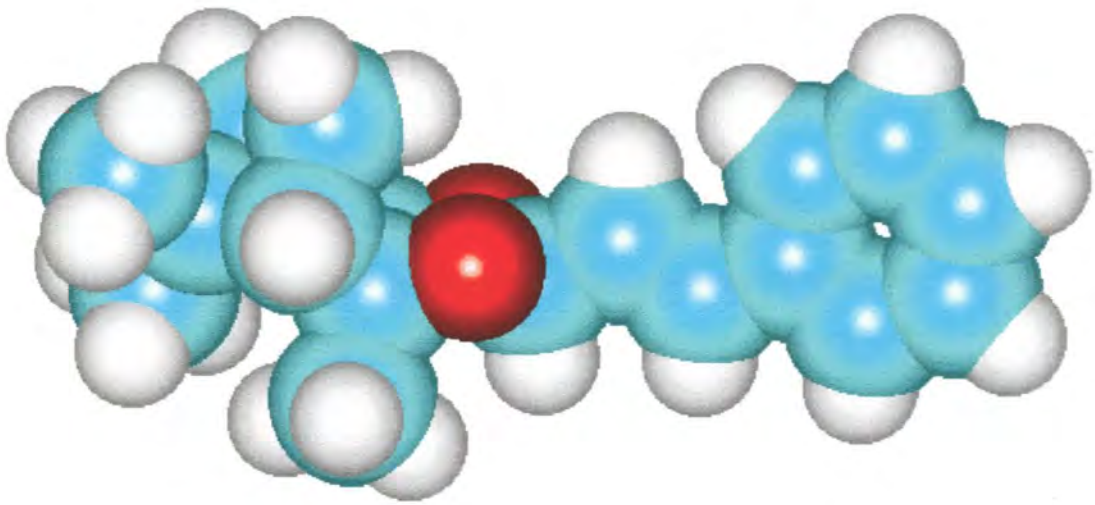
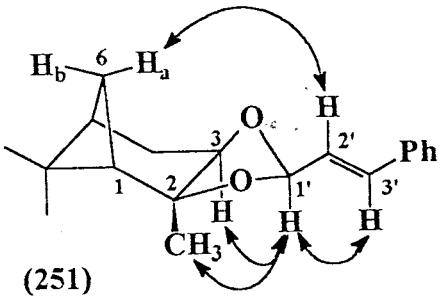


**FIGURE 49.** Computer-generated stick and space-filling models of acetal (**251a**).




(251)

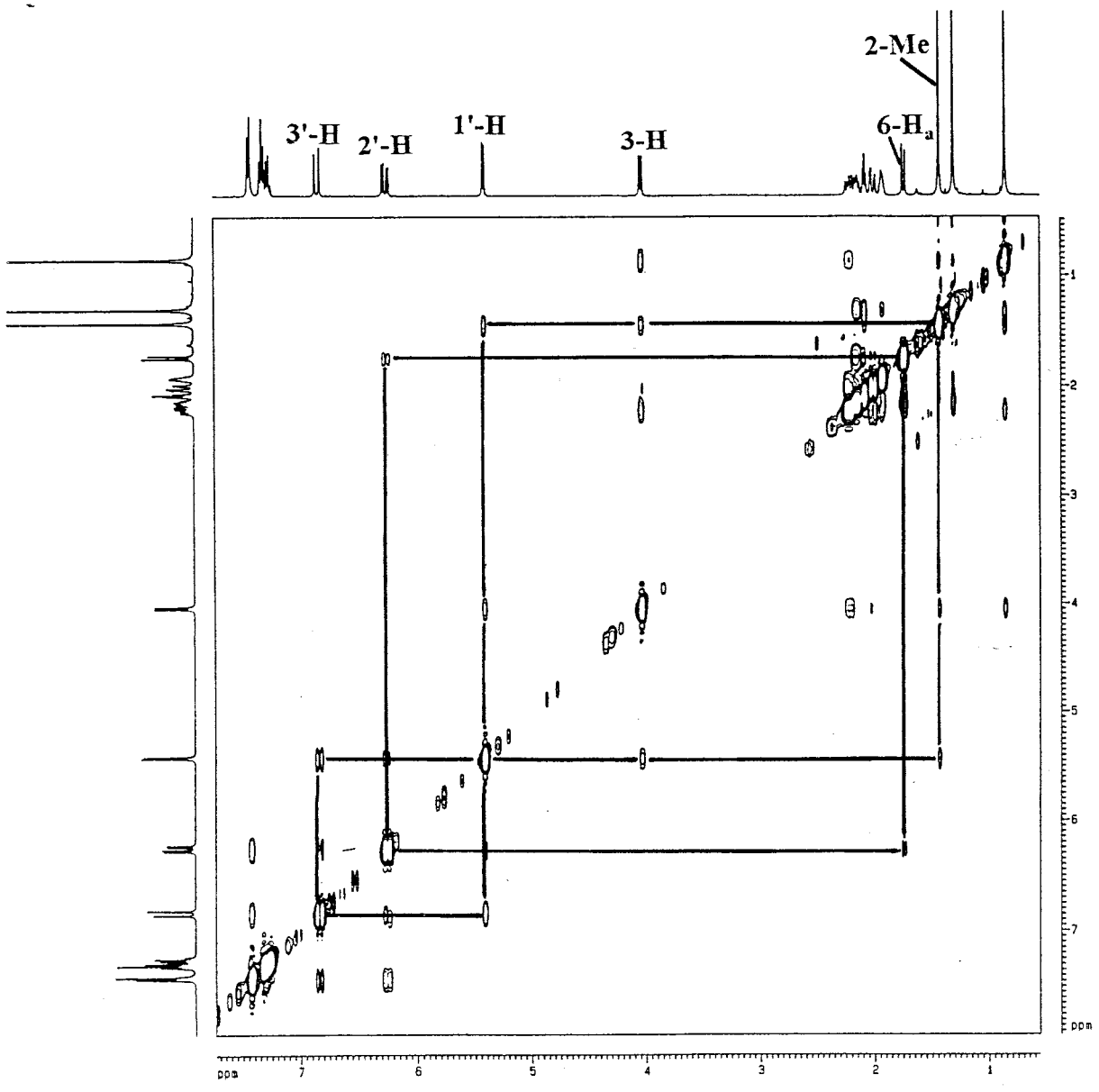
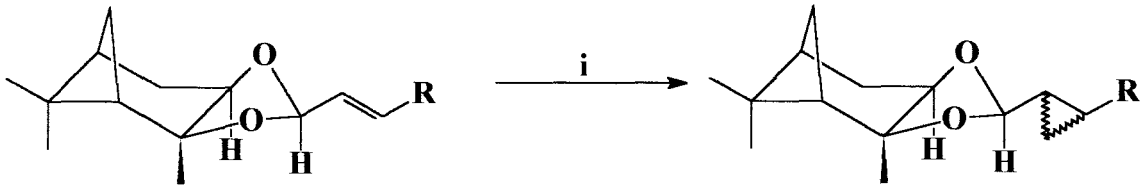



**FIGURE 50.** The 400 MHz NOESY spectrum of acetal (**251**).

### 2.4.3 Asymmetric Simmons-Smith cyclopropanation

The Simmons-Smith cyclopropanation of acetals (**249-251**) was achieved by the slow, dropwise addition of methylene iodide to a mixture of the acetal and diethylzinc in dry $CH_2Cl_2$, at -10°C, to afford the corresponding cyclopropyl acetals (**253-255**), as diastereomeric mixtures, in good yield (71-74 %) (**Scheme 51; Table 18**).




**(249-251)** **(253-255)**

**Reagents: i) $Et_2Zn$, $CH_2I_2$, $CH_2Cl_2$, -10°C**

| Acetal | R | Product |
|---|---|---|
| **249** | $CH_3$ | **253** |
| **250** | $(CH_2)_2CH_3$ | **254** |
| **251** | Ph | **255** |

**SCHEME 51**

The cyclopropyl acetals (**253-255**) were identified by $^1H$ and $^{13}C$ NMR spectroscopy. The $^1H$ NMR spectra [shown for the cyclopropyl acetal (**255**) in (**Figure 51a**)] reveal an absence of signals in the vinyl region and an upfield shift of the 1'-methine doublet to *ca.* 4.7 ppm. The presence of a cyclopropyl ring is supported by the multiplets at 0.90, 1.01, 1.18 and 1.52 ppm, each integrating for a single proton, and by the presence of the characteristically shielded cyclopropyl methylene carbon (11.6 ppm) in the DEPT spectrum (**Figure 51b**).

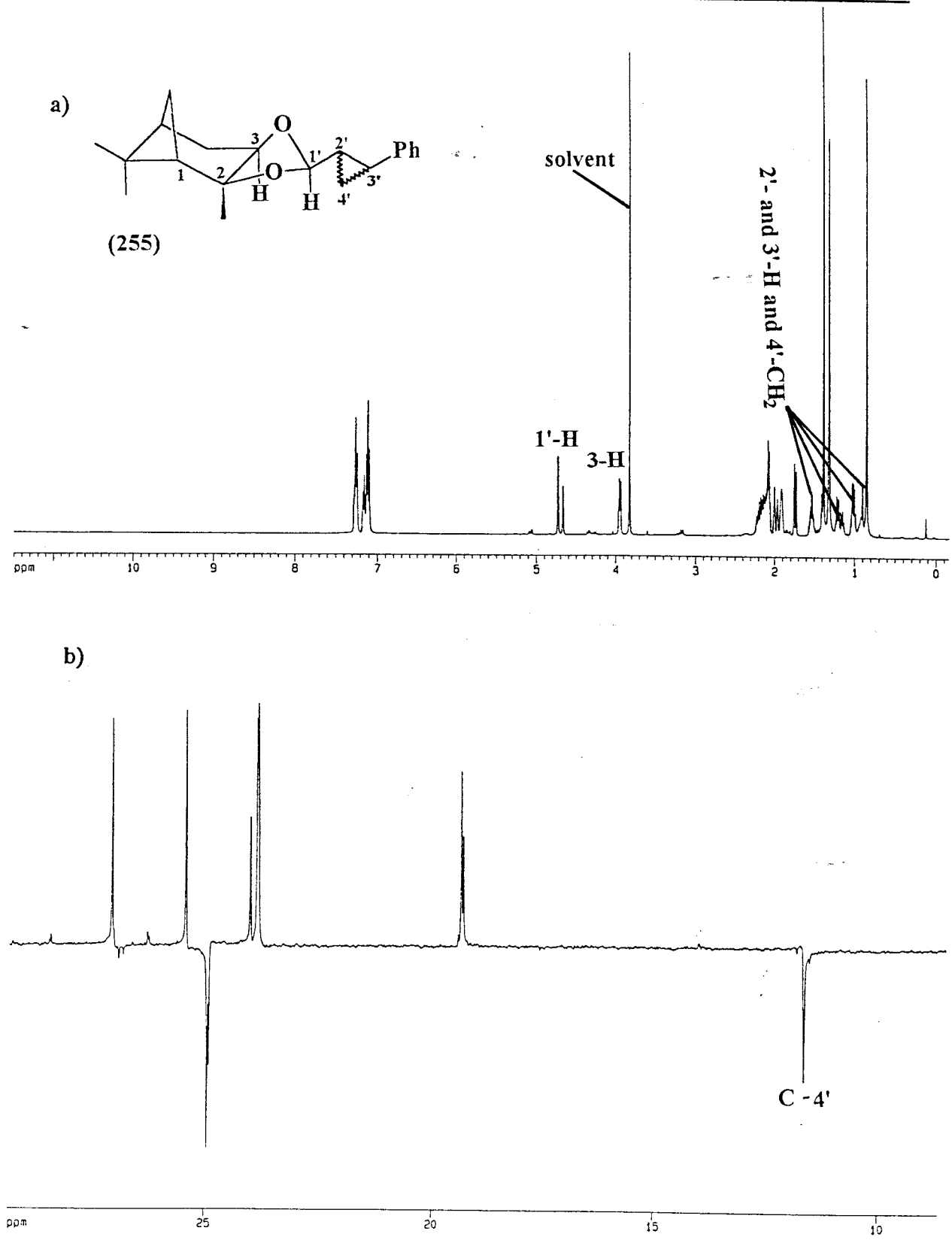
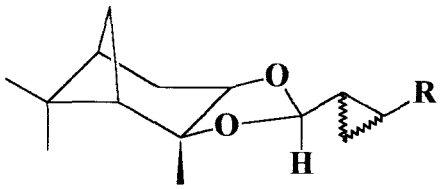



**FIGURE 51.** **a)** The 400 MHz $^1H$ NMR and **b)** partial DEPT spectra of the diastereomeric mixture of the cyclopropyl acetals (**255**) in $CDCl_3$.

It was apparent from the $^{1}H$ and $^{13}C$ NMR spectra of the cyclopropyl acetals (**253-255**) that a pair of diastereomers were formed during the Simmons-Smith cyclopropanation of each of the acetals (**249-251**). The diastereomeric ratio (24 % d.e.) for the cyclopropyl acetal (**251**) was determined by intergration of the well-resolved 1'-methine peaks at 4.67 and 4.73 ppm (corresponding to the minor and major diastereomers, respectively) (**Figure 51a**). On the assumption that diastereomers have the same $T_1$ relaxation times,[93] the diastereomeric ratios of the cyclopropyl acetals (**253**) and (**254**) were determined by integration of well-resolved $^{13}C$ NMR signals for corresponding carbon atoms in each pair of diastereomers (**Table 18**).

**Table 18** Data for the diastereoselective formation of the cyclopropyl acetals (**253-255**).




**(253-255)**

| Cyclopropyl Acetal | R | Pure Yield/ % | % d.e. |
|---|---|---|---|
| **253** | $CH_3$ | 71 | 20 |
| **254** | $(CH_2)_2CH_3$ | 73 | 30 |
| **255** | Ph | 74 | 24 |

The low diastereoselectivities observed (20-30 % d.e.) may be readily explained by assuming the operation of a similar mechanism to that proposed for cyclopropanation of the acetals (**193-197**) and (**198-201**). The organozinc reagent, having a high affinity for ethereal oxygen,[139] could, in principle, coordinate to either the $O_a$- or $O_b$-dioxolane oxygen atoms *via* either the *endo* or *exo* lone pairs (**Figure 52a**). Coordination of the reagent by the *exo* lone pairs on either dioxolane oxygen appears sterically unhindered

(**Figure 52b**), but the consequent spatial orientation of the organozinc reagent relative to the alkene could render methylene transfer inefficient. Therefore, it is proposed that coordination of the organozinc species involves an *endo* lone pair on either of the dioxolane oxygens, with the diastereoselectivity being dependent on the relative accessibility of these sites. Although the *endo* lone pair of the $O_b$-dioxolane oxygen atom is sterically unhindered and could be assumed to be the favoured coordination site, the 10-methyl group does not, in fact, significantly hinder coordination of the organozinc reagent to the $O_a$ *endo* lone pair. Unlike the 10-methyl group in the acetals (**193-197**), which is *syn* to the *endo* lone pair of the $O_a$-dioxolane oxygen atom (**Figure 36a**), the 10-methyl group in the acetals (**249-251**) is in a *pseudo*-axial position and, therefore, its steric bulk does not greatly hinder access to the *endo* lone pair of the $O_a$-dioxolane oxygen atom (see **Figure 52a, b**).

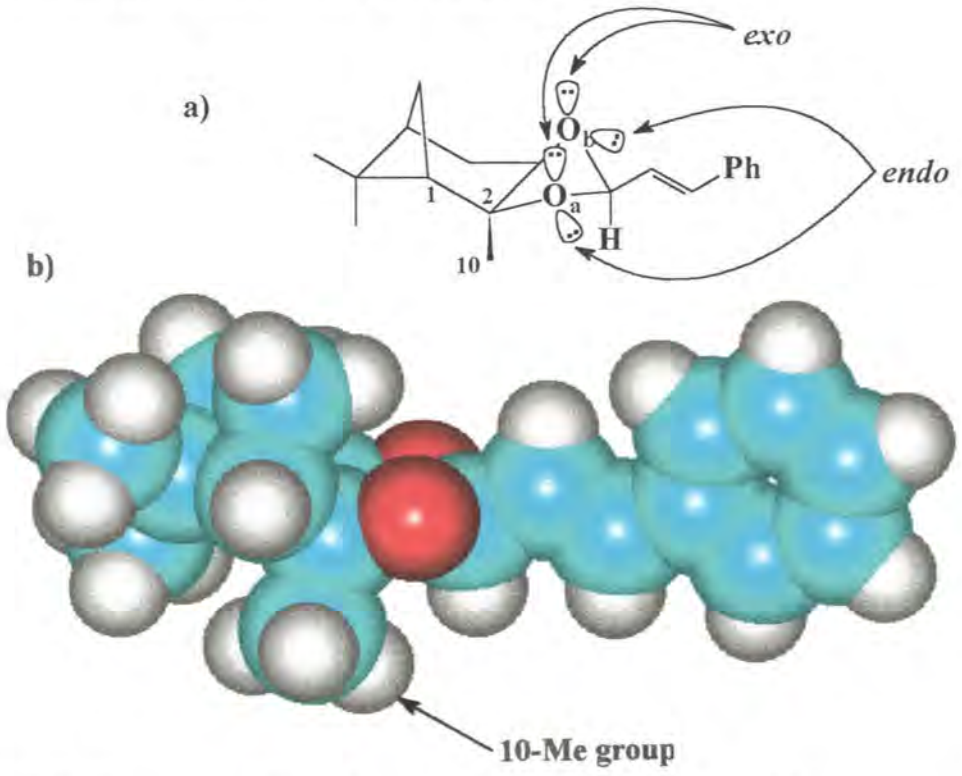
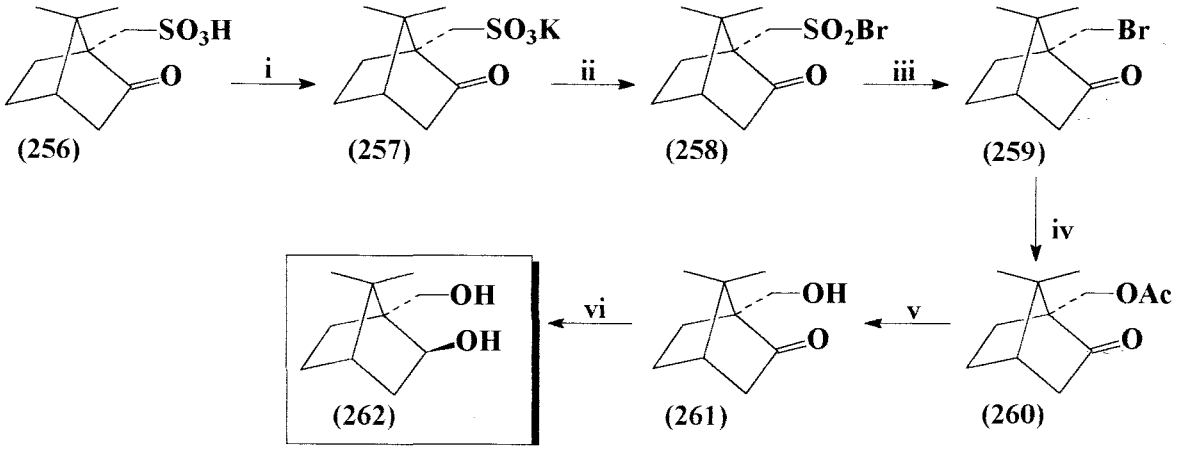



**FIGURE 52.** **a)** Dioxolane oxygen atom lone pairs and **b)** computer generated space-filling model of acetal (**251**).

## 2.5 (-)-BORNANE-2-*EXO*,10-DIOL AS A CHIRAL AUXILIARY

### 2.5.1 Preparation of (-)-bornane-2-*exo*,10-diol (262)

The potassium salt (**257**) of (-)-camphor-10-sulfonic acid (**256**) was reacted with freshly prepared $PBr_5$ to afford the sulfonyl bromide (**258**), which was refluxed in xylene for 3 hours to give 10-bromocamphor (**259**) in 53 % yield. The bromocamphor (**259**) was then dissolved in acetic acid, solid potassium acetate was added and the mixture boiled under reflux to afford 10-acetoxycamphor (**260**). Methanolysis of the acetate (**260**) using methanolic-KOH gave 10-hydroxycamphor (**261**), LAH reduction of which afforded the diol (**262**) (**Scheme 52**).[175]

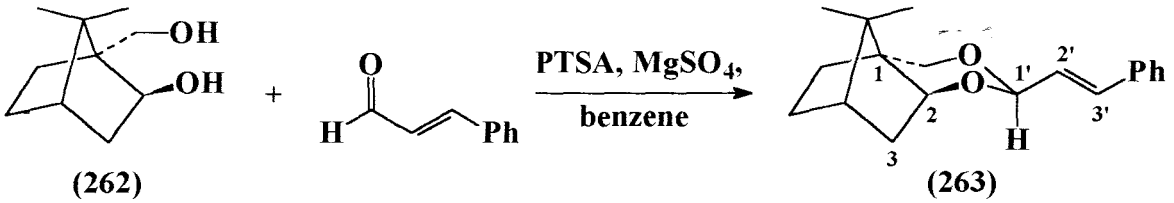



**Reagents: i) KOH, MeOH, ii) $PBr_5$, $Et_2O$, iii) xylene, reflux, iv) KOAc, AcOH, v) 10 % KOH-MeOH, vi) LAH, $Et_2O$.**

**SCHEME 52**

### 2.5.2 Preparation of the cinnamaldehyde acetal (263) from diol (262)

The acetal (**263**) was prepared under similar conditions to those used for the camphor-derived acetals (**193-197**), and was obtained in 74 % yield (**Scheme 53**).



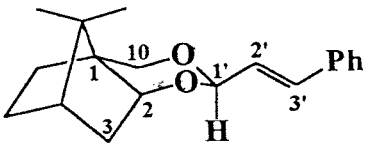

(262) (263)

**SCHEME 53**

The acetal (**263**) was fully characterised by $^{1}H$ and $^{13}C$ NMR spectroscopy and high resolution mass spectrometry. The $^{1}H$ NMR spectrum of the acetal (**263**) confirmed that the camphor skeleton was intact and that no rearrangement had occurred during acetalization. The vinyl protons of the acetal (**263**) exhibit similar chemical shifts to those of the corresponding cinnamaldehyde acetal (**196**) prepared from bornane-2,3-diol (**150**) (**Figure 22**). The COSY spectrum shows coupling correlations between the 2'- and 3'-vinyl protons and between the 2'- and the 1'-protons (**Figure 53**). The diastereotopic 10-methylene protons resonate as a pair of doublets at 3.82 and 4.12 ppm, their correlation to each other being clearly evident in the COSY spectrum; the overlapping 2-methine proton signal, at 3.82 ppm clearly couples to the 3-methylene protons.

### 2.5.3 Conformational analysis of the acetal (263)

During acetalization, acetal (**263**) is formed as a single diastereomer, the conformation of which was elucidated with the aid of computer modelling (**Figure 54**) which suggests that the *exo*-substituted diastereomer (**I**) is isolated.




(263)

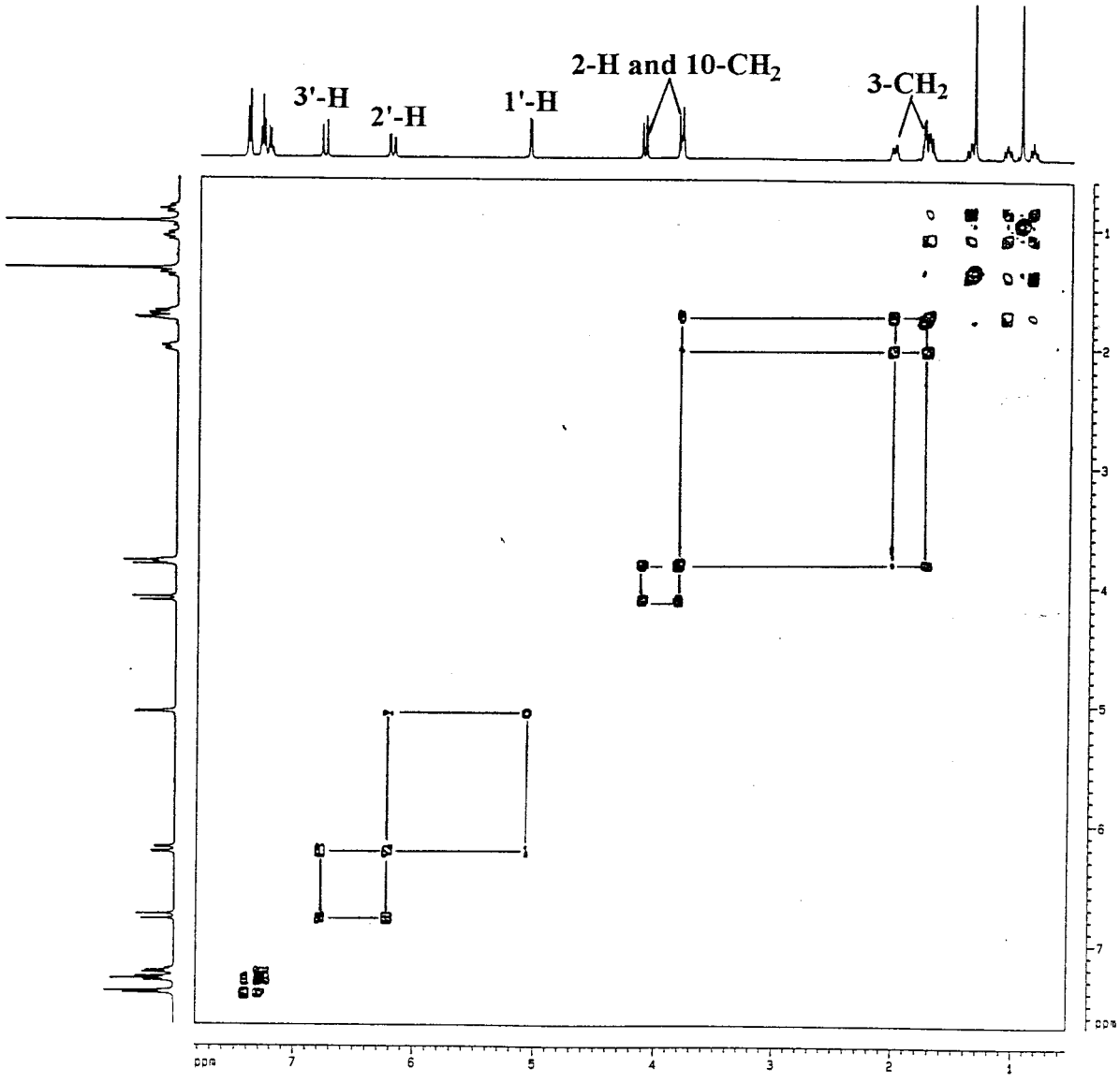



**FIGURE 53.** The 400 MHz COSY spectrum of the acetal (**263**) in $CDCl_3$.

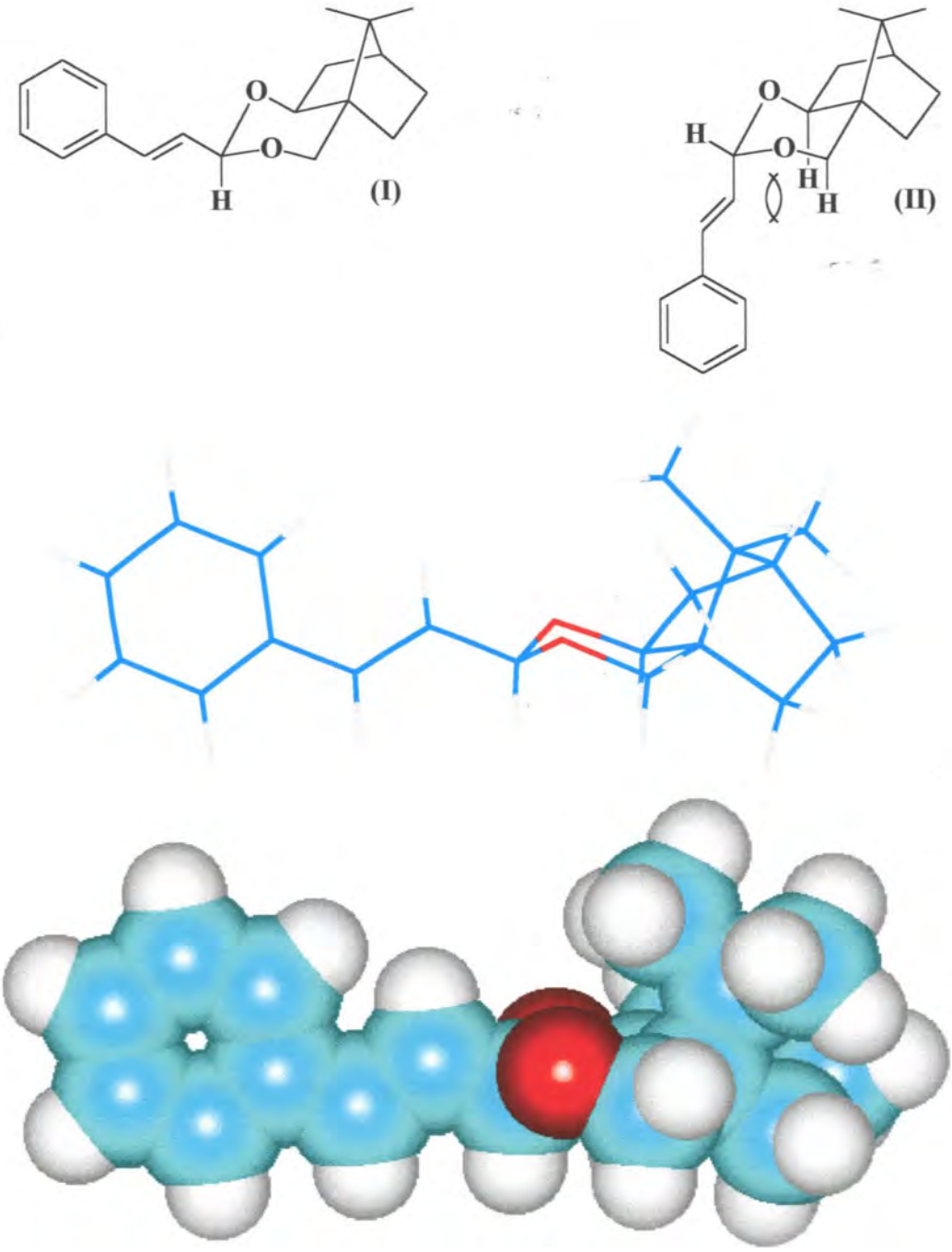
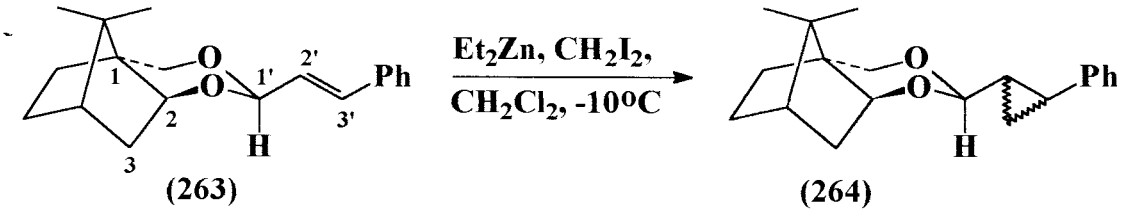



**FIGURE 54.** Computer-generated space-filling models of the conformer ( **I**) of the acetal (**263**).

### 2.5.4 Asymmetric Simmons-Smith cyclopropanation of the acetal (263)

Cyclopropanation of the acetal (**263**) under similar conditions to those used for the pinane-derived acetals (**249-251**) gave the cyclopropyl derivative (**264**) in 78 % yield (**Scheme 54**).




(263) (264)

**SCHEME 54**

The cyclopropyl acetal (**264**) was characterised using the $^{1}H$ and $^{13}C$ NMR data. The $^{1}H$ NMR spectrum reveals a pair of doublets at *ca.* 4.50 ppm, corresponding to the 1'-methine proton, four multiplets at 0.93, 1.18, 1.46 and 2.10 ppm, each of which integrate for one proton, and an absence of signals in the vinyl region (**Figure 55a**). The inverse HETCOR spectrum (**Figure 56**) shows that the multiplets at 0.93 and 1.18 ppm correlate with a single carbon nucleus, which corresponds to a methylene carbon in the DEPT spectrum (**Figure 55b**); these multiplets may thus be assigned to the 4'-cyclopropyl methylene protons. The multiplets at 1.46 and 2.10 ppm correlate with the shielded methine carbons at *ca.* 18.9 and 25.7 ppm in the HETCOR spectrum and were assigned to the 2'- and 3'- methine protons.

The doubling of peaks in the $^{1}H$ NMR spectrum indicates the presence of a diastereomeric mixture, the ratio of which was determined by integration of signals in the $^{13}C$ spectra for corresponding carbon atoms in each diastereomer.[93] In each case the diastereomeric ratios determined were 52:48 (*i.e.* 4 % d.e.).

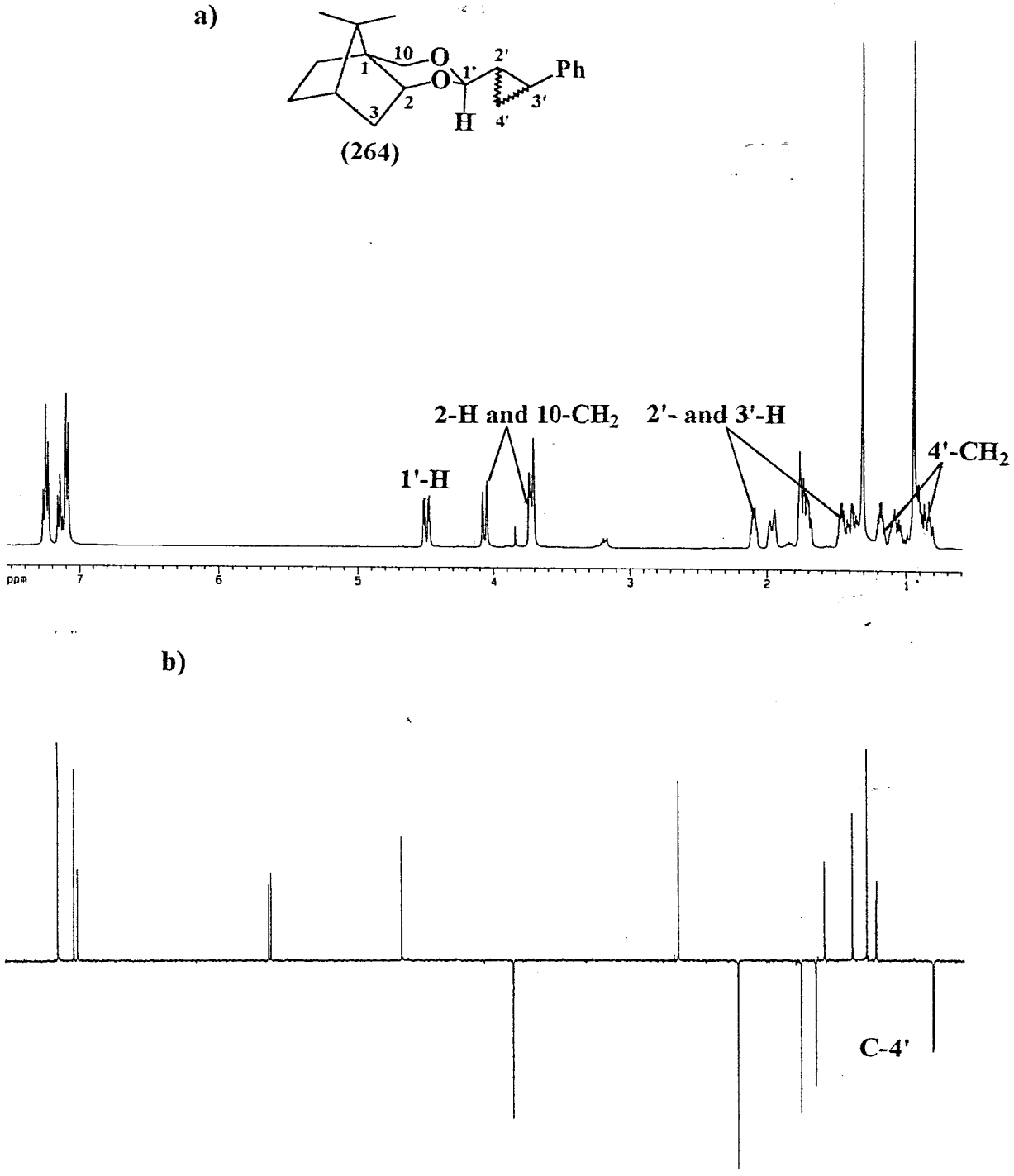



**FIGURE 55.** **a)** The 400 MHz $^1$H NMR and **b)** DEPT spectra of the diastereomeric cyclopropyl acetal (**264**) in $CDCl_3$.

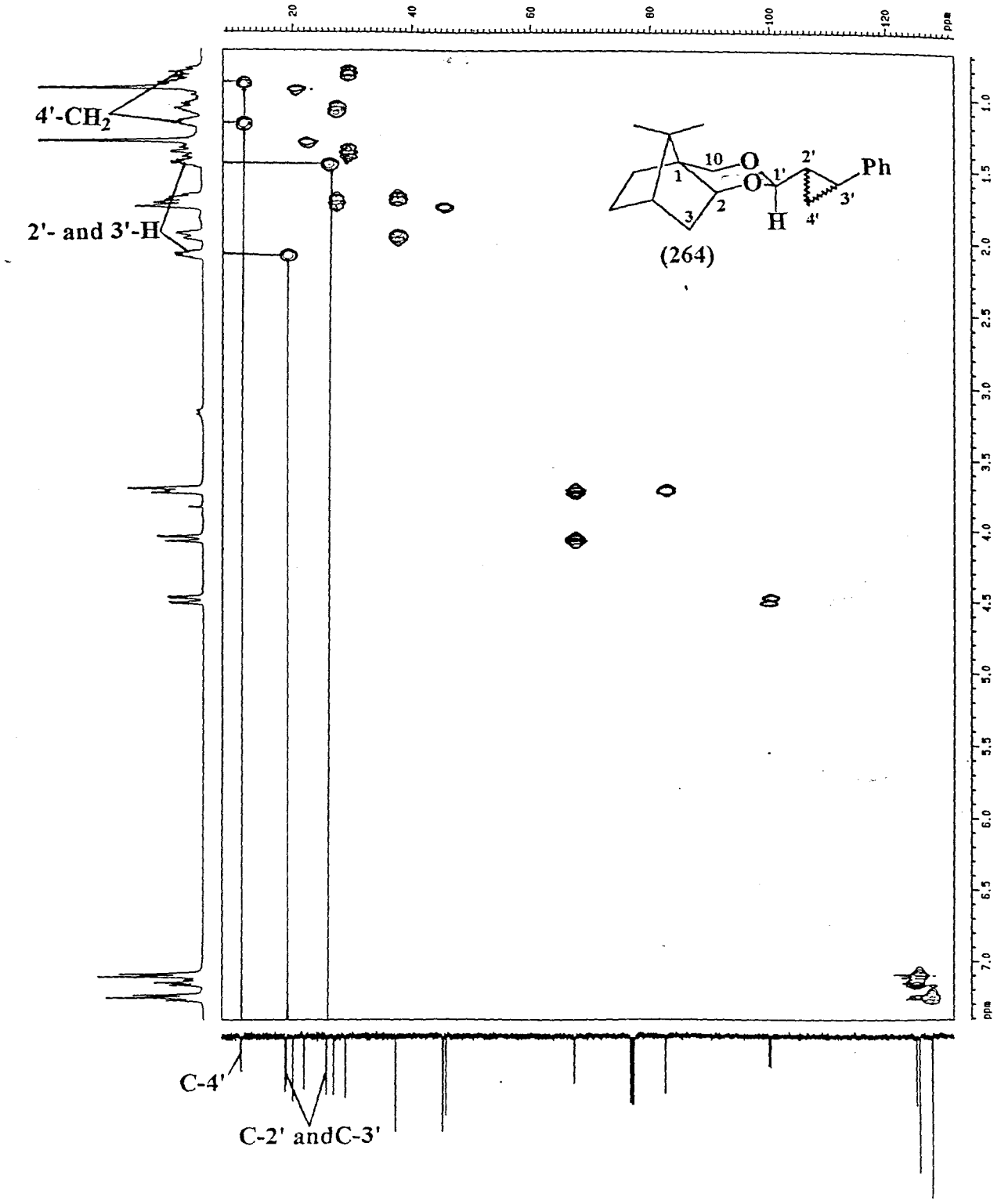
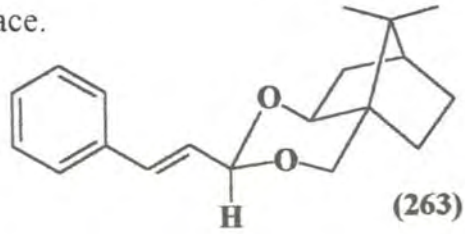



**FIGURE 56.** Inverse HETCOR spectrum of the diastereomeric of cyclopropyl acetals (**264**) in $CDCl_3$.

The low diastereoselectivity in the Simmons-Smith cyclopropanation of acetal (**263**) is readily explained by examining the computer-generated model of the preferred conformation of the acetal (**263**) (**Figure 57**). The model reveals that the dioxolane oxygen atoms are both sterically unhindered and chelation of the organozinc reagent is equally likely at either face.




**(263)**

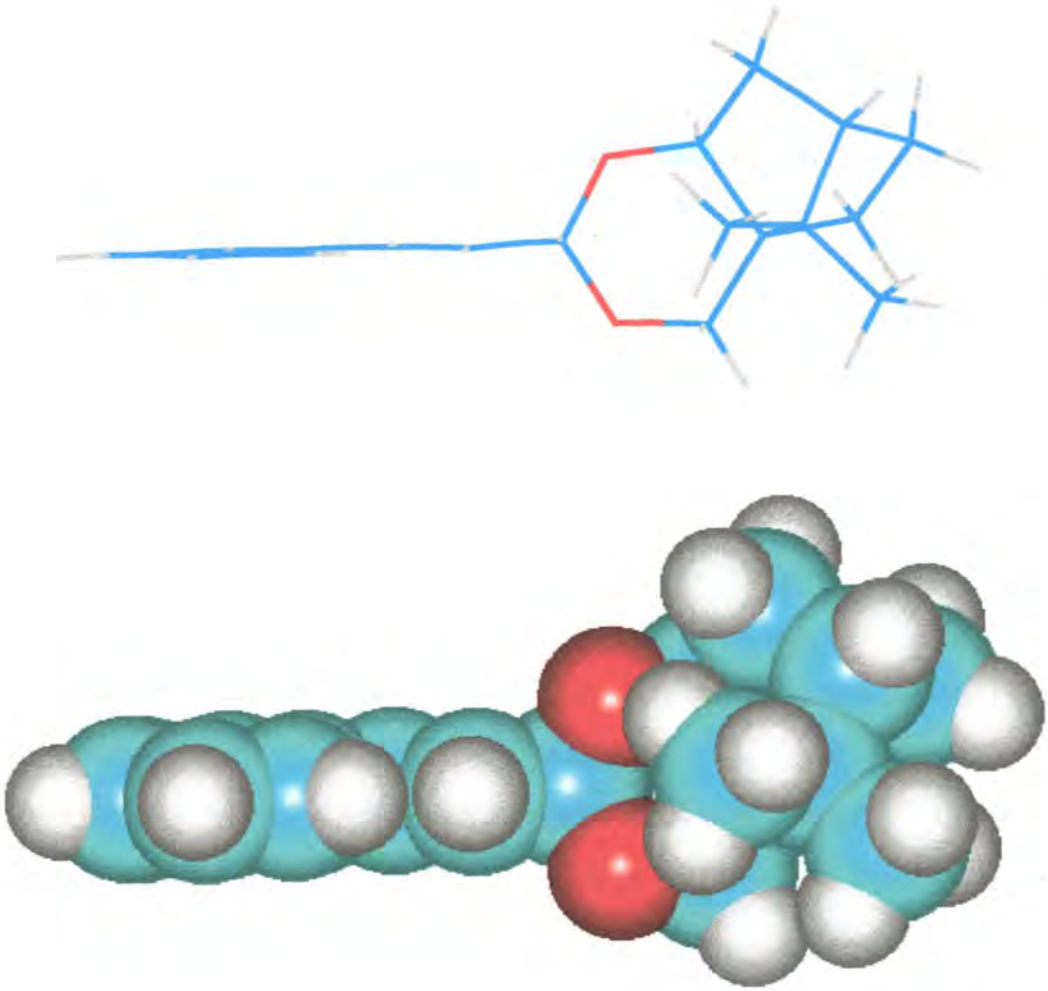


**FIGURE 58.** Computer generated stick and space-filling models of acetal (**263**).

## 2.6 CONCLUSION

From the foregoing discussion, it is apparent the main objectives of this research have been achieved. These have included determining the structure of the major regioisomeric product of partial hydrolysis of *N*-benzylcamphorimide, synthesising several chiral diols and exploring their use as chiral auxiliaries in the preparation and asymmetric reactions of α,β-unsaturated acetals.

In an extension of earlier work,[87] partial hydrolysis of *N*-benzylcamphorimide was shown to occur by nucleophilic attack at the less hindered carbonyl carbon (C-4) to afford (+)-(1*S*,3*R*)-3-(*N*-benzylcarbamoyl)-2,2,3-trimethylcyclopentanecarboxylic acid as the major regioisomer. One- and two-dimensional NMR spectroscopy and X-ray crystallography were used to elucidate the structure of the major regioisomer, the methyl ester derivative of which was shown to undergo an unexpected intramolecular rearrangement during LAH reduction to furnish (1*S*, 3*R*)-*N*-benzyl-3-hydroxymethyl-2,2,3-trimethylcyclopentanecarboxamide.[176]

Initially, attention was given to the use of tartrate-derived diols having $C_2$ symmetry, and 1,4-di-*O*-benzyl-D-threitol and dimethyl- and diethyl tartrate were used to prepare a selection of α,β-unsaturated acetals. However, poor asymmetric inductions were observed in the MCPBA epoxidation of these acetals, and attention was turned to the use of bornane-2,3-diol, pinane-2,3-diol, bornane-2,10-diol and the novel ester, phenyl 2,3-dihydroxybornane-10-sulfonate, as chiral auxiliaries. Reaction of these diols with a selection of α,β-unsaturated aldehydes, under mild conditions, afforded a range of novel camphor-derived acetals, as single diastereomers and in high yields. Two-dimensional NMR spectroscopy, computer modelling and X-ray crystallography indicated preferential formation of *exo*-substituted acetals in all cases.

While Simmons-Smith cyclopropanation of the bornane-2,3-diol-derived acetals proceeded with high diastereoselectivity, the acrolein derivative showing a diastereoselectivity of > 99 % d.e., cyclopropanation of all the acetals derived from phenyl 2,3-dihydroxybornane-10-sulfonate proceeded with total stereocontrol (*i.e.* > 99 % d.e.) with only a single diastereomer being detectable by NMR spectroscopy in each case. The *trans*-cinnamaldehyde acetal derivative of bornane-2,10-diol, however, showed low diastereoselectivity (4 % d.e.), while acetals derived from (+)-pinane-2,3-diol exhibited somewhat better diastereoselectivity (20-30 % d.e.). The cyclopropyl acetals proved remarkably resistant to hydrolysis.

Conformational analysis and computer modelling of the acetals revealed that the phenyl sulfonate moiety at C-10 blocks coordination of the cyclopropanating reagent to the proximate dioxolane oxygen atom more effectively than the 10-methyl group. Hydrolysis of a cyclopropyl acetal of phenyl 2,3-dihydroxybornane-10-sulfonate furnished the known cyclopropyl aldehyde, the optical rotation of which allowed the absolute configuration of the new stereogenic centres to be established. The observed stereochemistry is consistent with the proposal that the reagent coordinates to the less hindered dioxolane oxygen atom.

A series of exploratory studies were also undertaken to evaluate the potential of the camphor-derived acetals in other asymmetric transformations. The most promising of these was the Diels-Alder reaction of the cinnamaldehyde acetal, derived from phenyl 2,3-dihydroxybornane-10-sulfonate, with cyclopentadiene, which afforded a single cycloadduct in 32 % yield; however, disappointing diastereoselectivities were observed in the $OsO_4$ dihydroxylation and MCPBA epoxidation of the bornane-2,3-diol-derived acetals. The organocopper alkylation of cinnamaldehyde acetal, derived from bornane-2,3-diol, gave the expected enol ether, but in poor yield, while attempted α-alkylation of the 8-carbethoxymethyldioxolane of phenyl 2,3-dihydroxybornane-10-sulfonate led

to the isolation of a novel bornane sultone.

From these studies it is apparent that the use of camphor-derived diols as chiral auxiliaries has significant potential in asymmetric reactions of α,β-unsaturated aldehydes, and future research is expected to include:-

i) developing an efficient hydrolysis of the camphor-derived acetals;

ii) exploring the preparation and stereo-directing potential of camphor-derived diols in which the steric bulk and polarity of the C-10 substituent is varied; and

iii) extending the use of the chiral acetals in asymmetric Diels-Alder and other reactions.

# 3. EXPERIMENTAL

## 3.1 GENERAL

A Kofler hot-stage apparatus was used to determine melting points, which are uncorrected. IR spectra were recorded on a Perkin-Elmer 180 spectrometer, using KBr discs or liquid films.

Unless indicated otherwise, $^{1}H$ NMR and $^{13}C$ NMR spectra were recorded on a Bruker AMX400 spectrometer for solutions in $CDCl_3$. Coupling constants (*J*) are given in Hz while chemical shifts are expressed in parts per million (ppm) referenced using the chloroform signals 7.25 ppm for $^{1}H$ spectra and at 77.0 ppm for the centre line of the $CDCl_3$ triplet for $^{13}C$ spectra. Optical rotations were measured on a Perkin-Elmer 141 polarimeter in a 1dm cell, and concentrations are given in g/100 ml. Low-resolution mass spectra were recorded on a Hewlett Packard 5988A mass spectrometer and high-resolution mass spectra on a double-focusing Kratos MS 80RF mass spectrometer (Cape Technikon Mass Spectrometry Unit).

Semi-preparative HPLC was carried out on a Spectra-Physics P100 chromatograph using a 250 x 10 mm Spherisorb 55 W normal phase column. Flash chromatography[177] was performed using Merck Silica gel 60 [particle size 0.040-0.063 mm (230-400 mesh)], while preparative thin layer chromatography (PTLC) was carried out on glass plates coated with Merck Silica gel 60 $F_{254}$. Thin layer chromatography (TLC) analyses were performed on precoated Merck Silica gel 60 $F_{254}$ plastic sheets and compounds detected by inspection under UV light, exposure to iodine vapours or by spraying with 10 % $H_2SO_4$-MeOH and allowing to char in the oven at 80°C for 10 min.

Solvents were dried under $N_2$ using the following methods:-[178, 179]

(1) diethyl ether and THF were distilled from sodium benzophenone ketyl;

(2) hexane was distilled from Na wire;

(3) dichloromethane, petroleum ether (40-60°C), xylene, DME and benzene were distilled from $CaH_2$;

(4) chloroform was dried over $CaCl_2$ and distilled before use; and

(5) *t*-BuOH was stirred in the presence of $KMnO_4$ at room temperature for 2 d, filtered, and distilled from $KMnO_4$.

## 3.2 PREPARATIVE PROCEDURES

### 3.2.1 Preparation of (+)-camphorimide (152) derivatives.[87]

#### 3.2.1.1 *Preparation of (+)-camphorimide* (152)

A stirred slurry of camphoric acid (**151**) (30.0 g, 150 mmol) and 25 % aq. $NH_3$ (20 ml) was heated at 200°C and 15 bar in an autoclave for 5 h. The solid, which formed after cooling overnight, was washed with ice-cold $H_2O$, filtered off and then recrystallised from 10 % acetic acid to yield 1,8,8-trimethyl-2,4-dioxo-3-azabicyclo[3.2.1] octane (**152**) (25.2 g, 93 %), m.p. (sealed tube) 243-246°C (lit.,[91] 243°C); $\nu_{max}$ (KBr)/cm$^{-1}$ 3205 (NH), 1720 and 1680 [C(O)-N-C(O)]; $\delta_H$(400 MHz; $CDCl_3$) 0.94, 0.99 and 1.13 (9H, 3 x s, 9-, 10- and 11-Me), 1.80 (1H, m, 6-$H_{exo}$), 1.92 (2H, m, 7-$H_{exo}$ and 7-$H_{endo}$), 2.17 (1H, m, 6-$H_{endo}$), 2.56 (1H, d, 5-H) and 8.36 (1H, s, NH); $\delta_C$(100 MHz; $CDCl_3$) 13.1, 19.3 and 21.8 (C-9, C-10 and C-11), 25.2 (C-6), 34.2 (C-7), 45.0 (C-1), 53.8 (C-8), 56.0 (C-5), 176.5 and 178.5 (C-2 and C-4); *m/z* 181 ($\mathbf{M}^+$, 63 %) and 95 (100).

#### 3.2.1.2 *Preparation of (+)-N-benzylcamphorimide* (153)

Benzyl chloride (17.2 g, 122 mmol) was added to a stirred solution of (+)-camphorimide (**152**) (22.0 g, 122 mmol) in 1.1 M-ethanolic KOH (120 ml), and the mixture was boiled under reflux for 2 h. After cooling, the ethanol was removed *in vacuo* and the residue diluted with 1 % aq. KOH (100 ml) and extracted with EtOAc (3 x 100 ml). The organic layers were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo*. Flash chromatography [elution with hexane-EtOAc (8:2)] of the residue yielded, as a colourless oil which crystallised on standing, (1*R*,5*S*)-3-benzyl-1,8,8-trimethyl-2,4-dioxo-3-azabicyclo[3.2.1]octane (**153**) (22.1 g, 68 %), m.p. 66-70°C; $\nu_{max}$ (KBr)/cm$^{-1}$ 1720 and 1668 [C(O)-N-C(O)]; $\delta_H$(400 MHz; $CDCl_3$)

0.87, 0.93 and 1.17 (9H, 3 x s, 9-, 10- and 11-Me), 1.69 (1H, m, 6-$H_{exo}$), 1.86 (2H, m, 7-$H_{exo}$ and 7-$H_{endo}$), 2.16 (1H, m, 6-$H_{endo}$), 2.71 (1H, d, 5-H), 4.84 (2H, s, $NCH_2$) and 7.18-7.35 (5H, m, Ar-H); $\delta_C$(100 MHz; $CDCl_3$) 14.0, 19.0 and 21.9 (C-9, C-10 and C-11), 25.2 (C-6), 34.1 (C-7), 42.5 (C-12), 44.2 (C-1), 54.4 (C-8), 56.6 (C-5), 127.3, 128.3, 128.7 and 137.2 (Ar-C) and 176.2 and 178.1 (C-2 and C-4); *m/z* 274 ($\mathbf{M}^+$, 0.14 %) and 271 (100).

### 3.2.1.3 *Preparation of carboxy amides* (155) *and* (156)

Solid KOH (8.90 g, 160 mmol) and 18-crown-6 (4.6 g) were added to a stirred solution of (+)-*N*-benzylcamphorimide (**153**) (22 g, 81 mmol) in toluene (250 ml). The resulting mixture was boiled under reflux for 3 h and then allowed to cool. The two-phase mixture was diluted with $H_2O$ (400 ml) and the aqueous phase isolated once all the solid had dissolved. The aqueous phase was washed with toluene (100 ml) and acidified with 6**M**-HCl to pH 1. The resulting precipitate was dissolved in EtOAc (150 ml) and the aqueous layer extracted with further EtOAc (2 x 100 ml). The combined organic solutions were dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield an oil which became semi-crystalline on standing (16.8 g). This material was found to be a 7:3[§] mixture of the carboxy amides (**155**) and (**156**). Several recrystallizations from EtOAc-hexane removed sufficient of the minor product to permit characterisation of the major product as (1*S*,3*R*)-3-(*N*-benzylcarbamoyl)-2,2,3-trimethylcyclopentanecarboxylic acid (**155**), m.p. 136-140°C (lit.,[92] 144°C); $\nu_{max}$ (KBr)/$cm^{-1}$ 3600-2500 (COOH), 3380 (NH),1700 [CO(OH)] and 1680 [CO(NH)]; $\delta_H$(400 MHz; $CDCl_3$) 0.91, 1.23 and 1.34 (9H, 3 x s, 6-, 7- and 8-Me), 1.54 and 2.37 (2H, 2 x m, 4-$CH_2$), 1.88 and 2.22 (2H, 2 x m, 5-

[§] The $^1$H NMR amide proton signals at 5.79 and 5.91 ppm in the crude material correspond to the minor and major compounds respectively and were integrated to determine the product ratio.

$CH_2$), 2.84 (1H, dd, 1-H), 4.44 (2H, m, $NCH_2$), 5.86 (1H, t, NH) and 7.24-7.35 (5H, m, Ar-H); $\delta_C$(100 MHz; $CDCl_3$) 21.1, 21.7 and 23.6 (C-6, C-7 and C-8), 22.6 (C-5), 32.9 (C-4), 43.7 ($NCH_2$), 47.2 (C-3), 52.9 (C-1), 55.9 (C-2), 127.6, 127.8, 128.8 and 138.3 (Ar-C), 175.4 [C(O)N] and 179.0 [C(O)O]; *m/z* 289 ($\mathbf{M}^+$, 16 %) and 91 (100).

### 3.2.1.4 *Hydrolysis of (+)-N-benzylcamphorimide* (153)[92]

A solution of (+)-*N*-benzylcamphorimide (**153**) (3.16 g, 11.7 mmol) in ethanol (50 ml) and 2.5 M-NaOH (50 ml) was heated on a steam bath until most of the ethanol had boiled off. The mixture was diluted with $H_2O$ (50 ml), shaken with ether (50 ml) and the aqueous layer acidified with 10 M-HCl. The liberated oil was solidified by placing the reaction flask in liquid nitrogen, filtered and washed with cold $H_2O$ (25 ml). $^1$H NMR spectroscopy of the crude material showed a 7:3 mixture of the carboxy amides (**155**) and (**156**) (2.8 g, 83 %), while the HMBC spectrum of the crude mixture indicated that the major product was carboxy amide (**155**).

### 3.2.1.5 *Esterfication of carboxy amides* (155) *and* (156)

Conc. $H_2SO_4$ (1.3 ml) was added to a stirred solution containing a 7:3 mixture of the crude carboxy amides (**155**) and (**156**) (10 g, 35 mmol) in anhydrous MeOH (85 ml) in a flask fitted with a Dean-Stark trap charged with 3Å molecular sieves. The resulting mixture was boiled under reflux for 24 h. The MeOH was removed *in vacuo*, and the residue neutralised with 5 % aq. $Na_2CO_3$ and then extracted with EtOAc (3 x 100 ml). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to yield an oil, flash chromatography [elution with benzene-$Et_2O$ (8:2)] of which yielded, as the major component, a colourless oil, methyl (1*S*,3*R*)-3-(*N*-benzylcarbamoyl)-2,2,3-trimethylcyclopentanecarboxylate (**157**) (7.6 g, 71 %), $\delta_H$(400 MHz; $CDCl_3$) 0.77, 1.18 and 1.28 (9H, 3 x s, 6-, 7- and 8-Me), 1.48, 1.78, 2.18 and 2.35 (4H, 4 x m, 4-$CH_2$ and 5-$CH_2$), 2.76 (1H, dd, 1-H), 3.63

(3H, s, OMe), 4.38 (2H, m, $NCH_2$), 6.04 (1H, m, NH) and 7.20-7.30 (5H, m, Ar-H); $\delta_C$(100 MHz; $CDCl_3$) 21.1, 21.7 and 23.2 (C-6, C-7 and C-8), 22.3 (C-5), 32.5 (C-4), 43.3 ($NCH_2$), 46.9 (C-3), 51.3 (OMe), 52.5 (C-1), 55.7 (C-2), 127.2, 127.5, 128.5 and 138.5 (Ar-C), 174.4 [C(O)O] and 175.1 [C(O)N]; *m/z* 303 (**M**$^+$, 0.9 %) and 90 (100).

### 3.1.2.6 *Reduction of methyl ester derivative* (157)

A solution of the methyl ester (**157**) (11 g, 36 mmol) in dry THF (30 ml) was added to a large excess of LAH (12 g, 0.32 mmol) suspended in dry THF (300 ml), and the resulting mixture boiled under reflux for 36 h, under an $N_2$ atmosphere. After cooling, the reaction flask was placed in an ice bath and *slow*, sequential addition of $H_2O$ (12 ml), 10 % aq. NaOH (12 ml) and $H_2O$ (36 ml) resulted in the formation of a white granular solid. The white solid was removed by filtration and the filtrate dried ($MgSO_4$) and concentrated *in vacuo*. Distillation of the residual oil afforded: (+)-(1*R*,5*S*)-*N*-benzylcamphidine (**159**) (2.97 g, 34 %) [b.p. 90-98°C/0.3 mm Hg (lit.[180] bp 165°C/30 mm Hg); $\delta_H$(400 MHz; $CDCl_3$) 0.79, 0.89 and (9H, 3 x s, 9-, 10- and 11-Me), 1.57 and 1.77 (5H, 2 x m, 5-H, 6- and 7-$CH_2$), 2.29 (2H, dd, $J_{2exo,2endo}$ 10.6, 2-$H_{exo}$ and 2-$H_{endo}$), 2.46 (1H, dd, $J_{4endo,5}$ 3.3, $J_{4endo,4exo}$ 10.6, 4-$H_{endo}$), 2.60 (1H, d, $J_{4endo,4exo}$ 10.6, 4-$H_{exo}$), 3.57 (2H, s, $NCH_2$) and 7.22-7.37 (5H, m, Ar-H); $\delta_C$(100 MHz; $CDCl_3$) 17.9, 18.3 and 24.4 (C-9, C-10 and C-11), 26.8 and 35.6 (C-6 and C-7), 41.7 and 42.8 (C-1 and C-8), 46.1 (C-5), 54.6 (C-4), 61.3 (C-2), 61.9 ($NCH_2$) and 126.6, 128.0, 128.6 and 139.9 (Ar-C); *m/z* 246 (**M**$^+$, 56 %) and 91 (100)]; and, as a glassy residue, (1*S*,3*R*)-*N*-benzyl-3-hydroxymethyl-2,2,3-trimethylcyclopentanecarboxamide (**160**) (5.35 g, 54 %) [m.p. 107-113°C (from EtOH-$H_2O$)(lit.,[87] 142-144°C); $\nu_{max}$ (KBr)/cm$^{-1}$ 3380 (OH and NH) and 1640 (CO); $\delta_H$(400 MHz; $CDCl_3$) 0.88, 0.98 and 1.06 (9H, 3 x s, 6-, 7- and 8-Me), 1.41, 1.78 and 2.21 (4H, 3 x m, 4- and 5-$CH_2$), 1.62 (1H, br s, OH), 2.54 (1H, t, 1-H), 3.52

(2H, s, 9-$CH_2$), 4.45 (2H, m, $NCH_2$), 5.60 (1H, br s, NH) and 7.26-7.35 (5H, m, Ar-H); $\delta_C$(100 MHz; $CDCl_3$) 19.9, 20.5 and 25.7 (C-6, C-7 and C-8), 24.0 and 34.0 (C-4 and C-5), 43.8 ($NCH_2$), 46.0 and 48.9 (C-2 and C-3), 56.3 (C-1), 69.0 (C-9), 127.5, 128.0, 128.7 and 138.5 (Ar-C) and 173.4 (CO); *m/z* 275 (**M**$^+$, 15 %) and 91 (100)].

### 3.1.2.7 *Reduction of (+)-N-benzylcamphorimide* (153)

Following the procdure for the reduction of methyl ester (**157**), a solution of (+)-*N*-benzylcamphorimide (**153**) (1.0 g, 3.7 mmol) in dry THF (5 ml) was added, under $N_2$, to a stirred suspension of LAH (1.3 g, 33 mmol) in dry THF (25 ml) and the mixture boiled under reflux for 10 h. Work-up afforded a mixture (4:1 by $^1H$ and $^{13}C$ NMR spectroscopy) of (+)-*N*-benzylcamphorimide (**153**); and (+)-*N*-benzylcamphidine (**159**).

## 3.2.2 Preparation of Diols

### 3.2.2.1 *Preparation of dimethyl 2,3-O-isopropylidene-D-tartrate* (170)[96]

Solid PTSA (0.20 g, 1.1 mmol) and 2,2-dimethoxypropane (80.5 g, 773 mmol) were added, under $N_2$, to a solution of (+)-D-tartaric acid (50.5 g, 336 mmol) and the resultant mixture was placed on a steam bath and boiled under reflux for 1.5 h. After cooling, 2,2-dimethoxypropane (47 ml) and cyclohexane (225 ml) were added and a 30 cm fractionating column was fitted. The resultant mixture was slowly heated and the acetone-cyclohexane and methanol-cyclohexane azeotropes were removed over a 16 h period, until the temperature at the solvent head was 74°C. Additional 2,2-dimethoxypropane (3 ml) was added and the mixture boiled under reflux for 15 min, cooled and stirred for 2 h after the addition of anhydrous $K_2CO_3$ (0.5 g, 3.6 mmol). Volatiles were removed *in vacuo* and fractional distillation of the residue afforded, as a pale yellow oil, dimethyl 2,3-*O*-isopropylidene-D-tartrate (**170**) (61.7 g, 84 %), b.p. 82-93°C/0.25 mmHg (lit.,[96] 94-101°C/0.5 mmHg); $\delta_H$(400 MHz; $CDCl_3$)1.46 [6H, s, $C(CH_3)_2$], 3.79 (6H, s, 2 x $CO_2CH_3$) and 4.77 (2H, s, 2- and 3-H); $\delta_C$(100 MHz; $CDCl_3$) 26.2 [$C(CH_3)_2$], 52.7 (2 x $CO_2CH_3$), 76.9 (C-2 and C-3), 113.8 [$C(CH_3)_2$] and 170.0 (C-1 and C-4).

### 3.2.2.2 *Preparation of 2,3-di-O-isopropylidene-D-threitol* (171)[96]

A solution of dimethyl 2,3-*O*-isopropylidene-D-tartrate (**170**) (25 g, 115 mmol) in dry ether (60 ml) was added dropwise, under $N_2$, to a stirred suspension of LAH (8.0 g, 210 mmol) in dry ether (120 ml) and the resultant mixture was boiled under reflux for 3 h. After cooling in an ice bath, $H_2O$ (9 ml), 4 M NaOH (9 ml) and $H_2O$ (13 ml) were added sequentially and the resultant mixture was stirred overnight and filtered. The white solid was suspended in EtOAc (250 ml), boiled under reflux for 30 min and filtered. The combined filtrates were concentrated *in vacuo* and the residue

distilled *in vacuo* to afford, as a pale yellow oil, 2,3-di-*O*-isopropylidene-D-threitol (**171**) (10.6 g, 57 %), b.p. 86-96°C/0.3 mmHg (lit.,[96] 94-106°C/0.4 mmHg); $\delta_H$(400 MHz; $CDCl_3$) 1.41 [6H, s, $C(CH_3)_2$], 2.45 (2H, m, 2 x OH), 3.72 (4H, m, 1- and 4-$CH_2$) and 3.96 (2H, m, 2- and 3-H); $\delta_C$(100 MHz; $CDCl_3$) 27.0 [$C(CH_3)_2$], 62.0 (2 x $CH_2OH$), 78.1 (C-2 and C-3) and 109.3 [$C(CH_3)_2$].

### 3.2.2.3 *Preparation of 1,4-di-O-benzyl-2,3-O-isopropylidene-D-threitol* (172)[96]

Fresh NaH (6.12 g of a 55 % dispersion in oil; 3.36 g, 0.14 mol) was washed with dry hexane (3 x 10 ml), under $N_2$, to remove the oil. To a vigorously stirred suspension of the washed NaH, in dry THF (50 ml), was added dropwise, at room temperature *via* a pressure equalising funnel, a solution of 2,3-di-*O*-isopropylidene-*D*-threitol (**171**) (10.0 g, 0.062 mol) in dry THF (50 ml), followed by the dropwise addition of benzyl bromide (18.5 ml, 0.15 mol) *via* the addition funnel. The resultant mixture was stirred at room temperature for 12 h and then under reflux for 2 h, cooled in an ice bath and quenched by the addition of $H_2O$ until a clear solution was obtained. Volatiles were removed *in vacuo* and the residue diluted with $H_2O$ (250 ml) and extracted with ether (3 x 100 ml). The ethereal extracts were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford, as a dark yellow oil, crude 1,4-di-*O*-benzyl-2,3-*O*-isopropylidene-D-threitol (**172**) (24.8 g), which was used directly in the preparation of 1,4-di-*O*-benzyl-D-threitol (**168**).

### 3.2.2.4 *Preparation of 1,4-di-O-benzyl-D-threitol* (168)[96]

Crude 1,4-di-*O*-benzyl-2,3-*O*-isopropylidene-D-threitol (**172**) (24.8 g, 0.0725 mol) was dissolved in methanol (60 ml), 0.5 M HCl (6 ml) added and the resultant mixture was slowly distilled over 3 h to remove acetone and methanol. The mixture was cooled, methanol (10 ml) and 0.5 M HCl (4 ml) added and the resultant mixture

stirred overnight. The mixture was then diluted with sat. $NaHCO_3$ (100 ml) and extracted with ether (3 x 100 ml). The ethereal extracts were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford a yellow oil. Recrystallization from chloroform/hexane afforded, as a white solid, 1,4-di-*O*-benzyl-D-threitol (**168**) (13.2 g, 60 %), m.p. 48-51°C (lit.,[96] 54-55°C); $\delta_H$(400 MHz; $CDCl_3$) 2.86 (2H, br s, 2 x OH), 3.60 (4H, m, 2 x $CH_2OCH_2Ph$), 3.86 (2H, m, 2- and 3-H), 4.54 (4H, m, 2 x $CH_2OCH_2Ph$) and 7.25-7.36 (10H, m, Ar-H) ; $\delta_C$(100 MHz; $CDCl_3$) 70.5 (C-1 and C-4), 71.9 (C-2 and C-3), 73.5 (2 x $CH_2OCH_2Ph$) and 127.7, 127.8, 128.4 and 137.7 (Ar-C).

### 3.2.2.5 *Preparation of (+)-camphorquinone* (185)

Selenium dioxide (50 g, 0.45 mol) was added to a solution of (+)-camphor (40 g, 0.26 mol) in acetic anhydride (40 ml) and the mixture boiled under reflux for 5 h fitted to a NaOH scrubber. On cooling, the precipitated selenium was removed by filtration and the filtrate neutralised with 10 % aq. NaOH. The resulting yellow precipitate was allowed to settle overnight in a cold room, filtered and washed with cold $H_2O$. The semi-dry material was dissolved in petroleum ether (80-100°C) and the residual aqueous layer withdrawn. The organic layer was concentrated *in vacuo* and recrystallization from petroleum ether (40-60°C) afforded, as yellow crystals, (1*R*,4*S*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2,3-dione (**185**) (30.8 g, 71 %), m.p. 178-182°C (lit.,[181] 183-186°C); $\nu_{max}$ (KBr)/$cm^{-1}$ 1765 and 1745 (2 x CO); $\delta_H$(400 MHz; $CDCl_3$) 0.92, 1.05 and 1.09 (3H, 3 x s, 8-, 9- and 10-Me), 1.62, 1.91 and 2.15 (4H, 3 x m, 5-$CH_2$ and 6-$CH_2$) and 2.61 (1H, d, 4-H); $\delta_C$(100 MHz; $CDCl_3$) 8.6, 17.3 and 21.0 (C-8, C-9 and C-10), 22.2 and 29.9 (C-5 and C-6), 42.5 and 58.6 (C-1 and C-7), 57.9 (C-4) and 202.7 and 204.7 (C-2 and C-3).

### 3.2.2.6 *Preparation of bornane-2,3-diol* (150)

A solution of (+)-camphorquinone (**185**) (5.00 g, 30 mmol) in dry ether (50 ml) was added dropwise under $N_2$, to a slurry of LAH (1.25 g, 33 mmol) in dry ether (75 ml). The mixture was boiled under reflux for 1 h and then cooled in an ice bath. The excess LAH was quenched by the slow addition of $H_2O$ (10 ml) and the resulting suspension stirred overnight. The precipitated solid was removed by filtration and washed with ether (100 ml). The filtrate was concentrated *in vacuo* to yield an off-white solid, steam distillation of which afforded, as a white solid, (1*R*,2*S*,3*R*,4*S*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-*exo*,3-*exo*-diol (**150**) (3.76 g, 74 %) m.p. 252-255°C (lit.,[182] 230-231°C); $\nu_{max}$ (KBr)/cm$^{-1}$ 3490; $\delta_H$(400 MHz; $CDCl_3$) 0.77, 0.93 and 1.10 (9H, 3 x s, 8-, 9- and 10-Me), 0.94, 1.45 and 1.62 (4H, 3 x m, 5- and 6-$CH_2$), 1.77 (1H, d, 4-H), 2.52 and 2.62 (2H, 2 x d, 2 x OH) and 3.60 and 3.82 (2H, 2 x m, 2- and 3-H); $\delta_C$(100 MHz; $CDCl_3$) 11.1, 21.0 and 21.8 (C-8, C-9 and C-10), 24.1 and 33.2 (C-5 and C-6), 46.5 and 48.8 (C-1 and C-7), 51.6 (C-4) and 76.3 and 80.0 (C-2 and C-3).

### 3.2.2.7 *Preparation of (+)-camphorquinone-10-sulfonic acid* (186)

***Method 1: Sulfonation of camphorquinone* (185)**

Acetic anhydride (9.54 ml, 101 mmol) was added dropwise to cold conc. $H_2SO_4$ (2.70 ml, 50.5 mmol) at such a rate that the temperature of the reaction mixture did not rise above 20°C. Solid camphorquinone (**185**) (8.40 g, 50.5 mmol) was dissolved in the stirred mixture and the resultant dark mixture was left to stand in a cold room (+4°C) for 72 h. The solid which settled out was filtered and washed with ether to afford, as a yellow solid, 7,7-dimethylbicyclo[2.2.1]heptyl-2,3-dione-methanesulfonic acid (**186**) (2.90 g, 23 %), m.p. 146-150°C (lit.,[113] 155-157°C); $\delta_H$(400 MHz; DMSO) 0.82 and 1.11 (6H, 2 x s, 8- and 9-Me), 1.50, 1.66, 2.13 and 2.74 (4H, 4 x m, 5- and 6-$CH_2$), 2.58 (1H, d, 4-H) and 2.64 and 2.97 (2H, 2 x d, 10-

$CH_2$); $\delta_C$(100 MHz; DMSO) 17.8 and 20.8 (C-8 and C-9), 21.3 and 24.8 (C-5 and C-6), 43.1 and 59.0 (C-1 and C-7), 46.1 (C-4), 57.0 (C-10) and 202.4 and 202.8 (C-2 and C-3).

***Method 2: Oxidation of (+)-camphor-10-sulfonic acid* (189) *with selenous acid***[113]

Solid (+)-camphor sulfonic acid (8.7 g, 38 mmol) and freshly prepared selenous acid ($H_2SeO_3$)[183] (4.9 g, 38 mmol) were dissolved in dioxane (50 ml) and the resultant mixture was boiled under gentle reflux for 72 h, with the exclusion of light and moisture. Precipitated selenium was removed by filtration through celite and the filtrate evaporated *in vacuo* to a viscous yellow oil which was dissolved in $H_2O$ (100 ml), 20 % aq. $H_2SO_4$ (2 ml) added and the mixture boiled under reflux for 3 h. The solution was filtered and the filtrate treated with $BaCO_3$, filtered and concentrated *in vacuo*. The yellow concentrate was passed through a bed (3 x 12 cm) of Dowex 50 WX8 (protonated form) and the eluate was concentrated *in vacuo*. The resultant solid was dissolved in isopropanol and diluted with a large volume of EtOAc and allowed to crystallise at +4°C. Filtration and drying *in vacuo* afforded, as yellow crystals, 7,7-dimethylbicyclo[2.2.1]heptyl-2,3-dione-methanesulfonic acid (**189**) (5.32 g, 57 %).

### 3.2.2.8 *Preparation of (+)-camphorquinone-10-sulfonyl chloride* (187)

Thionyl chloride (26.1 g, 219 mmol) was added to DMF (16 ml) at 0°C and the mixture stirred at this temperature for 5 min before the addition of solid (+)-camphorquinone-10-sulfonic acid (**189**) (3.7 g, 15 mmol). The reaction mixture was stirred for 2 h at 0°C and room temperature for 2 h, before pouring the mixture onto crushed ice (200 g). The yellow precipitate was extracted into ether and the ethereal solution concentrated *in vacuo* to afford a yellow solid which was dissolved in warm ether and decanted from the residual aqueous layer. Concentration of the organic

layer *in vacuo* afforded, as yellow crystals, 7,7-dimethylbicyclo[2.2.1]heptyl-2,3-dione-methanesulfonyl chloride (**187**) (1.12 g, 27 %), m.p. 87-90°C (lit.,[113] 92-93°C); $\delta_H$(400 MHz; $CDCl_3$) 1.01 and 1.22 (6H, 2 x s, 8- and 9-Me), 1.76, 2.02, 2.31 and 2.65 (4H, 4 x m, 5- and 6-$CH_2$), 2.71 (1H, d, 4-H) and 3.85 and 4.33 (2H, 2 x d, 10-$CH_2$); $\delta_C$(100 MHz; $CDCl_3$) 18.3 and 20.9 (C-8 and C-9), 21.9 and 25.5 (C-5 and C-6), 44.3 and 59.6 (C-1 and C-7), 57.4 (C-4), 62.8 (C-10) and 198.5 and 198.6 (C-2 and C-3).

### 3.2.2.9 *Preparation of phenyl (+)-camphor-10-sulfonate* (188)

To a stirred solution of phenol (3.76 g, 40.0 mmol) in pyridine (13 ml) at 0°C was added solid (+)-camphor-10-sulfonyl chloride (**187**) (10 g, 40 mmol) over 20 min. The mixture was stirred at 0°C for 2 h and at room temperature for 1 h. The reaction was quenched by diluting with $H_2O$ (50 ml) and the resulting mixture was shaken with 10% aq. HCl (20 ml) and extracted with ether (3 x 50 ml). The combined organic layers were then washed sequentially with $H_2O$ (50 ml), 10% aq. HCl (20 ml) and $H_2O$ (50 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield, as a colourless oil, phenyl {(1*S*,4*R*)-7,7-dimethylbicyclo[2.2.1]heptyl-2-one}methanesulfonate (**188**) (10.0 g, 81%), (Found: $\mathbf{M}^+$ 308.1070. Calc. for $C_{16}H_{20}O_4S$ *M*, 308.1077); $\nu_{max}$ (liquid film)/$cm^{-1}$ 2980, 1750 (CO), 1490 and 1380 and 1100 ($SO_2$-OPh); $\delta_H$(400 MHz; $CDCl_3$) 0.88 and 1.13 (6H, 2 x s, 8- and 9-Me), 1.43, 1.70, 2.05 and 2.52 (4H, 4 x m, 5-$CH_2$ and 6-$CH_2$), 1.94 (1H, d, $J_{gem}$ 18, 3-$H_{endo}$), 2.09 (1H, m, 4-H), 2.39 (1H, m, 3-$H_{exo}$), 3.49 (2H, dd, *J* 15, 10-$CH_2$) and 7.26-7.40 (5H, m, Ar-H); $\delta_C$(100 MHz; $CDCl_3$) 19.5 and 19.8 (C-8 and C-9), 25.0 and 26.7 (C-5 and C-6), 42.3 (C-3), 42.8 (C-4), 47.5 and 58.0 (C-1 and C-7), 47.8 (C-10), 121.9, 127.0, 129.8 and 149.2 (Ar-C) and 213.9 (CO); *m/z* 308 ($\mathbf{M}^+$, 0.4 %) and 109 (100).

### 3.2.2.10 *Preparation of phenyl (+)-camphorquinone-10-sulfonate* (191)

Phenyl (+)-camphor-10-sulfonate (**188**) (10.0 g, 32.5 mmol) was dissolved in 1,4-dioxane (50 ml) and freshly prepared $H_2SeO_3$ (4.19 g, 32.5 mmol) added. The mixture, protected from light and moisture, was boiled gently under reflux for 72 h. Precipitated selenium was removed by filtration through celite and the filtrate concentrated *in vacuo*. Petroleum ether (40-60°C; 100 ml) was added and the mixture concentrated *in vacuo* to yield a dark solid which was dispersed in $CHCl_3$ (100 ml) and the insoluble material removed by filtration through celite. The $CHCl_3$ was evaporated *in vacuo* and the residue taken up in ether (200 ml) and filtered through fresh celite. The celite was washed with additional ether (100 ml) and the combined ethereal fractions were evaporated to 50 ml on a water bath. On cooling, the solution afforded yellow crystals of *phenyl {(1S,4S)-7,7-dimethylbicyclo[2.2.1]heptyl-2,3-dione}methanesulfonate* (**191**) (4.8 g, 46 %), m.p. 78-82°C; $\nu_{max}$ (KBr)/$cm^{-1}$ 1770 and 1750 (2 x CO), 1480 and 1375 and 1140 ($SO_2$-OPh); (Found: $\mathbf{M}^+$ 322.0846. $C_{16}H_{18}O_5S$ requires *M*, 322.0871); $\delta_H$(400 MHz; $CDCl_3$) 0.99 and 1.23 (6H, 2 x s, 8- and 9-Me), 1.73, 1.98, 2.29 and 2.73 (4H, 4 x m, 5-$CH_2$ and 6-$CH_2$), 2.69 (1H, d, 4-H), 3.60 (2H, dd, *J* 15, 10-$CH_2$) and 7.28-7.44 (5H, m, Ar-H); $\delta_C$(100 MHz; $CDCl_3$) 18.4 and 20.9 (C-8 and C-9), 21.9 and 25.5 (C-5 and C-6), 44.0 and 58.4 (C-1 and C-7), 46.8 (C-10), 57.5 (C-4), 121.9, 127.4, 130.1 and 149.11 (Ar-C) and 199.5 and 199.7 (C-2 and C-3); *m/z* 322 ($\mathbf{M}^+$, 0.6%) and 109 (100).

### 3.2.2.11 *Preparation of phenyl (+)-bornane-2-*exo*,3-*exo*-dihydroxy-10-sulfonate* (192)

To a stirred solution of $NaBH_4$ (0.35 g, 9.21 mmol) in anhydrous MeOH (30 ml) cooled to 0°C and under $N_2$, was added solid phenyl (+)-camphorquinone-10-sulfonate (**191**) (1.00 g, 3.10 mmol) over 20 min. The mixture was stirred overnight

and filtered. The MeOH was removed *in vacuo* and the residue dissolved in $H_2O$ (100 ml). The miture was extracted with ether (3 x 50 ml) and the combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford a colourless oil which crystallised on standing. Recrystallization from $CCl_4$ afforded, as a white solid, *phenyl {(1S,2S,3R,4S)-7,7-dimethylbicyclo[2.2.1]heptyl-2*-exo,*3*-exo-*dihydroxy}methanesulfonate* (**192**) (0.51 g, 51 %), m.p. 126-130°C; (Found: $\mathbf{M}^+$ 326.1194. $C_{16}H_{22}O_5S$ requires *M*, 326.1187); $\nu_{max}$ (KBr)/$cm^{-1}$ 3300 (OH) and 1370 and 1150 ($SO_2$-OPh); $\delta_H$(400 MHz; $CDCl_3$) 0.84 and 1.14 (6H, 2 x s, 8- and 9-Me), 1.08, 1.49 and 1.76 (4H, 3 x m, 5-$CH_2$ and 6-$CH_2$), 1.86 (1H, d, 4-H), 3.05 and 3.21 (2H, 2 x m, 2- and 3-OH), 3.46 (2H, dd, $J_{gem}$ 13.7, 10-$CH_2$), 3.88 and 4.16 (2H, 2 x m, 2- and 3-H) and 7.27-7.43 (5H, m, Ar-H); $\delta_C$(100 MHz; $CDCl_3$) 20.8 and 21.9 (C-8 and C-9), 23.7 and 29.4 (C-5 and C-6), 49.1 and 49.4 (C-1 and C-7), 49.8 (C-10), 50.4 (C-4), 75.7 and 76.1 (C-2 and C-3) and 122.0, 127.3, 130.0 and 149.1 (Ar-C); *m/z* 308 (**M**-$H_2O$, 0.001 %) and 94 (100).

### 3.2.2.12 *Preparation of potassium (-)-camphor-10-sulfonate* (257)[175]

A stirred solution of (-)-camphor-10-sulfonic acid (20 g, 86 mmol) in methanol (60 ml) was cooled in an ice bath and solid KOH (4.8 g, 86 mmol) was added and the resulting suspension stirred for 10 min. The reaction was then stirred at room temperature for 10 min, ether (30 ml) added and stirred for a further 15 min. A white solid, obtained by filtration and washed well with ether, was dried *in vacuo* to afford potassium {(1*R*,4*S*)-7,7-dimethylbicyclo[2.2.1]heptyl-2-one}methanesulfonate (**257**) (21.2 g, 91 %), $\nu_{max}$ (KBr)/$cm^{-1}$ 2980, 1750, 1730, 1220, 1190 and 1050.

### 3.2.2.13 *Preparation of (-)-10-bromocamphor* (259)[175]

Freshly prepared $PBr_5$ (22 g, 74 mmol) was rapidly added to a vigorously stirred suspension of potassium (-)-camphor-10-sulfonate (**257**) (20 g, 74 mmol) in absolute

ether (100 ml) at 0°C and under $N_2$. After the addition the mixture was removed from the cooling bath and stirred for 30 min at room temperature and under gentle reflux for 30 min. On cooling, the mixture was slowly poured into an ice-water slurry (200 ml $H_2O$; 200 g ice), stirred for 10 min and the resulting precipitate was dissolved in ether (200 ml). The ethereal layer was isolated, washed with $H_2O$ (2 x 100 ml), dried ($MgSO_4$) and concentrated *in vacuo* to afford, as a white solid, (-)-camphor-10-sulfinobromide (**258**) (20.1 g, 92 %) which was dissolved in absolute xylene (150 ml) and boiled under reflux for 3 h. The xylene was removed *in vacuo* and the semi-solid residue was steam distilled and the distillate shaken with ether (150 ml). The organic layer was separated, dried ($MgSO_4$) and concentrated *in vacuo*, recrystallization from EtOH-$H_2O$ (1:1) yielded, as a white solid, (1*R*,4*S*)-10-bromo-7,7-dimethylbicyclo[2.2.1]heptan-2-one (**259**) (8.32 g, 53 %), m.p. 72-76°C (lit.,[175] 76°C); $\nu_{max}$ (KBr)/cm$^{-1}$ 1750 (CO); $\delta_H$(400 MHz; $CDCl_3$) 0.91 and 1.06 (6H, 2 x s, 8- and 9-Me), 1.37, 1.51, 2.00 and 2.07 (5H, 4 x m, 4-H, 5- and 6-$CH_2$), 1.86 (1H, d, $J_{3endo,3exo}$ 18.4, 3-$H_{endo}$), 2.36 (1H, m, 3-$H_{exo}$) and 3.47 (2H, dd, 10-$CH_2$); $\delta_C$(100 MHz; $CDCl_3$) 20.2 and 20.4 (C-8 and C-9), 26.7 and 27.6 (C-5 and C-6), 29.2 (C-10), 42.9 (C-3), 43.9 (C-4), 48.1 and 60.2 (C-1 and C-7) and 215.3 (CO); *m/z* 230 (**M**$^+$, 3.9%) and 79 (100).

### 3.2.2.14 *Preparation of (-)-10-acetoxycamphor* (260)[175]

To a stirred solution of (-)-10-bromocamphor (**259**) (8.0 g, 35 mmol) in acetic acid (16 ml) was added solid potassium acetate (23.9 g, 243 mmol) and the mixture boiled under reflux for 20 h. The solid, which formed on cooling, was dissolved in $H_2O$ (100 ml) and neutralised with sat. aq. $NaHCO_3$. The mixture was extracted with ether (3 x 100 ml) and the organic layers combined, dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography [elution with EtOAc-Hexane (60:40)] of the residue afforded, as a pale yellow oil, (1*R*,4*S*)-10-acetoxy-7,7-dimethylbicyclo[2.2.1]heptan-

2-one (**260**) (6.25 g, 85 %), $\nu_{max}$ (liquid film)/cm$^{-1}$ 2960, 1770, 1240 and 1030; $\delta_H$(400 MHz; $CDCl_3$) 0.90 and 0.98 (6H, 2 x s, 8- and 9-Me), 1.36 and 1.89 (4H, 2 x m, 5- and 6-$CH_2$), 1.79 (1H, d, $J_{3endo,3exo}$ 18.3, 3-$H_{endo}$), 1.96 (3H, s, OCO.$CH_3$), 2.01 (1H, m, 4-H), 2.35 (1H, m, 3-$H_{exo}$) and 4.17 (2H, dd, 10-$CH_2$); $\delta_C$(100 MHz; $CDCl_3$) 19.6 and 20.5 (C-8 and C-9), 20.6 (OCO.$CH_3$), 25.5 and 26.6 (C-5 and C-6), 43.1 (C-3), 43.8 (C-4), 46.8 and 59.9 (C-1 and C-7), 60.3 (C-10) and 170.6 and 215.7 (OCO.$CH_3$ and CO).

### 3.2.2.15 *Preparation of (-)-10-hydroxycamphor* (261)[175]

A mixture of (-)-10-acetoxycamphor (**260**) (6.00 g, 29 mmol) and 10 % methanolic KOH (60 ml) was boiled under reflux for 6 h, diluted with $H_2O$ (100 ml) and extracted with ether. The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford a yellow semi-solid material, recrystallization with petroleum ether (40-60°C) yielded, as pale yellow crystals, (1*S*,4*S*)-10-hydroxy-7,7-dimethylbicyclo[2.2.1]heptan-2-one (**261**) (3.5 g, 71 %), m.p. 210-215°C (lit.,[175] 218°C); $\nu_{max}$ (KBr)/cm$^{-1}$ 3480 (OH) and 1730 (CO); $\delta_H$(400 MHz; $CDCl_3$) 0.91 and 0.94 (6H, 2 x s, 8- and 9-Me), 1.31, 1.50, 1.76 and 1.91 (4H, 4 x m, 5- and 6-$CH_2$), 1.79 (1H, d, $J_{3endo,3exo}$ 18.4, 3-$H_{endo}$), 2.00 (1H, t, 4-H), 2.33 (1H, m, 3-$H_{exo}$), 2.62 (1H, br s, OH) and 3.68 (2H, dd, 10-$CH_2$); $\delta_C$(100 MHz; $CDCl_3$) 19.4 and 20.8 (C-8 and C-9), 25.9 and 26.6 (C-5 and C-6), 43.3 (C-3), 43.8 (C-4), 46.6 and 61.5 (C-1 and C-7), 60.3 (C-10) and 220.5 (CO).

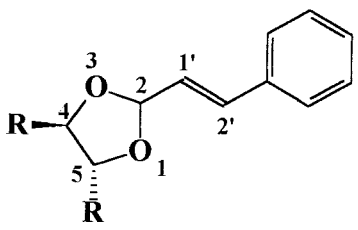
### 3.2.2.16 *Preparation of (-)-bornane-2-*exo*,10-diol* (262)

To a stirred suspension of LAH (0.84 g, 21 mmol) in dry ether (30 ml) a solution of (-)-10-hydroxycamphor (**261**) (3.0 g, 18 mmol) in dry ether (20 ml), was added dropwise. The mixture was boiled under reflux for 1 h, cooled to 0°C and quenched by the slow addition of $H_2O$ (5 ml). The mixture was stirred until it had turned

white, filtered and the filtrate concentrated *in vacuo* to afford a white solid. Recrystallization from a large volume of petroleum ether (60-80°C) yielded, as white crystals, (1*S*,2*S*,4*S*)-7,7-dimethylbicyclo[2.2.1]heptan-2-*exo*,10-diol (**262**) (1.6 g, 52 %), m.p. 84°C; $\nu_{max}$ (KBr)/cm$^{-1}$ 3400 (OH); $\delta_H$(400 MHz; $CDCl_3$) 0.87 and 1.16 (6H, 2 x s, 8- and 9-Me), 1.06, 1.46 and 1.74 (7H, 3 x m, 3-$CH_2$, 4-H, 5- and 6-$CH_2$), 2.70 and 3.04 (2H, 2 x br s, 2 x OH), 3.80 (2H, dd, 10-$CH_2$) and 3.96 (1H, dd, 2-H); $\delta_C$(100 MHz; $CDCl_3$) 20.5 and 20.6 (C-8 and C-9), 26.9 and 30.0 (C-5 and C-6), 40.4 (C-3), 46.1 (C-4), 48.2 and 52.9 (C-1 and C-7), 63.1 (C-10) and 78.4 (C-2); *m/z* 153 (**M**-OH, 0.21%) and 106 (100).

### 3.2.3 Preparation of acetals

#### 3.2.3.1 *Tartaric acid derived acetals*




##### 3.2.3.1.1 *Preparation of cinnamaldehyde dimethyl tartrate acetal* (177)

A solution of dimethyl D-tartrate (10.00 g, 56 mmol), in dry benzene (10 ml), was added to a stirred mixture of *trans*-cinnamaldehyde (4.95 g, 38 mmol), $MgSO_4$ (6.77 g, 56 mmol) and (+)-tartaric acid (0.028 g, 0.19 mmol) in dry benzene (60 ml). A Dean-Stark trap was fitted and the mixture boiled under reflux for 24 h. After cooling, solid $NaHCO_3$ (0.032 g, 0.38 mmol) was added and the resulting mixture was stirred for 30 min and then filtered through a bed of $NaHCO_3$, which was subsequently washed with benzene (100 ml). The combined benzene solutions were evaporated *in vacuo* and flash chromatography [elution with hexane-EtOAc (8:2)] of the residue afforded, as a colourless oil, *dimethyl (4S,5S)-2-styryl-1,3-dioxolane-4,5-dicarboxylate* (**177**) (5.31 g, 48 %), $\delta_H$(400 MHz; $CDCl_3$) 3.83 and 3.84 (6H, 2 x s, 2 x $CO_2CH_3$), 4.80 and 4.90 (2H, 2 x d, 4- and 5-H), 5.79 (1H, d, $J_{1',2}$ 6.7, 2-H), 6.23 (1H, dd, $J_{1',2}$ 6.7 and $J_{1',2'}$ 15.7, 1'-H), 6.89 (1H, d, $J_{1',2'}$ 15.7, 2'-H) and 7.26-7.43 (5H, m, Ar-H); $\delta_C$(100 MHz; $CDCl_3$) 52.79/52.82[*] (2 x $CO_2CH_3$), 77.0 and 77.3 (C-4 and C-5), 107.3 (C-2), 123.5 (C-1'), 127.1, 128.6, 128.7 and 135.4 (Ar-C), 137.0 (C-2') and 169.6 and 169.9 (2 x $CO_2CH_3$).

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[*] Chemical shift values quoted in this format, here and elsewhere, refer to diastereomeric nuclei and such assignments are tentative.

#### 3.2.3.1.2 *Preparation of cinnamaldehyde diethyl tartrate acetal* (176)

Following the procedure described for the synthesis of dimethyl (4*S*,5*S*)-2-styryl-1,3-dioxolane-4,5-dicarboxylate (**177**), a mixture of *trans*-cinnamaldehyde (3.30 g, 25 mmol), $MgSO_4$ (6.60 g, 50 mmol) and (+)-tartaric acid (0.019 g, 0.12 mmol) in dry benzene (50 ml) was reacted with a solution of diethyl D-tartrate (7.72 g, 38 mmol) in dry benzene (10 ml). Work-up and flash chromatography [elution with hexane-ether (4:1)] yielded, as colourless oil, diethyl (4*S*,5*S*)-2-styryl-1,3-dioxolane-4,5-dicarboxylate (**177**) (4.32 g, 54 %), $\delta_H$(400 MHz; $CDCl_3$) 1.33 (6H, m, 2 x $CO_2CH_2CH_3$), 4.30 (4H, m, 2 x $CO_2CH_2CH_3$), 4.76 and 4.86 (2H, 2 x d, 4- and 5-H), 5.81 (1H, d, $J_{1',2}$ 6.7, 2-H), 6.24 (1H, dd, $J_{1',2}$ 6.7 and $J_{1',2'}$ 16, 1'-H), 6.84 (1H, d, $J_{1',2'}$ 16, 2'-H) and 7.26-7.43 (5H, m, Ar-H); $\delta_C$(100 MHz; $CDCl_3$) 14.1 (2 x $CO_2CH_2CH_3$), 62.02/62.03 (2 x $CO_2CH_2CH_3$), 77.2 and 77.5 (C-4 and C-5), 107.2 (C-2), 123.8 (C-1'), 127.1, 128.6, 128.7 and 135.5 (Ar-C), 136.8 (C-2') and 169.2 and 169.6 (2 x $CO_2CH_2CH_3$).

#### 3.2.3.1.3 *Preparation of (Z)-α-methylcinnamaldehyde diethyl tartrate acetal* (179)

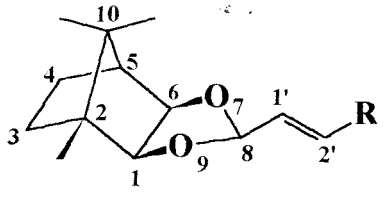
Following the procedure described for the synthesis of dimethyl (4*S*,5*S*)-2-styryl-1,3-dioxolane-4,5-dicarboxylate (**177**), a mixture of α-methylcinnamaldehyde (3.7 g, 25 mmol), $MgSO_4$ (3.0 g, 25 mmol) and (+)-tartaric acid (0.019 g, 0.11 mmol) in dry benzene (25 ml) was reacted with a solution of diethyl D-tartrate (10.3 g, 50 mmol) in dry benzene (10 ml). Work-up and flash chromatography [elution with hexane-EtOAc (9:1)] yielded, as a yellow oil, diethyl (4*S*,5*S*)-2-(1-methylstyryl)-1,3-dioxolane-4,5-dicarboxylate (**179**) (5.38 g, 77 %), $\delta_H$(400 MHz; $CDCl_3$) 1.31 (6H, m, 2 x $CO_2CH_2CH_3$), 1.92 (3H, d, 1'-Me), 4.27 (4H, m, 2 x $CO_2CH_2CH_3$), 4.75 and 4.87 (2H, 2 x d, 4- and 5-H), 5.63 (1H, s, 2-H), 6.73 (1H, s, 2'-H) and 7.21-7.35 (5H, m, Ar-H); $\delta_C$(100 MHz; $CDCl_3$) 11.4 ($CH_3$-1), 14.00/14.06 (2 x $CO_2CH_2CH_3$),

61.92/61.95 (2 x $CO_2CH_2CH_3$), 77.1 and 77.3 (C-4 and C-5), 110.5 (C-2), 127.2, 128.1, 129.0 and 132.2 (Ar-C), 132.4 (C-1'), 136.3 (C-2') and 168.9 and 169.7 (2 x CO).

#### 3.2.3.1.4 *Preparation of cinnamaldehyde 1,4-di-O-benzyl tartrate acetal* (178)

Following the procedure described for the synthesis of dimethyl (4*S*,5*S*)-2-styryl-1,3-dioxolane-4,5-dicarboxylate (**177**), a mixture of *trans*-cinnamaldehyde (1.6 g, 12 mmol), $MgSO_4$ (0.74 g, 6.1 mmol) and (+)-tartaric acid (0.005 g, 0.03 mmol) in dry benzene (50 ml) was reacted with a solution of (2*S*,3*S*)-1,4-di-*O*-benzyl-tartrate (**168**) (3.70 g, 12.5 mmol) in dry benzene (10 ml). Work-up and flash chromatography [elution with hexane-EtOAc (9:1)] yielded, as off white crystals, (4*S*,5*S*)-4,5-bis[(benzyloxy)methyl]-2-styryl-1,3-dioxolane (**178**) (2.78 g, 42 %), $\delta_H$(400 MHz; $CDCl_3$) 3.68 (4H, m, 2 x $CH_2OCH_2Ph$), 4.17 (2H, m, 4- and 5-H), 4.60 (4H, s, 2 x $CH_2OCH_2Ph$), 5.60 (1H, d, $J_{1',2}$ 6.2, 2-H), 6.17 (1H, dd, $J_{1',2}$ 6.2 and $J_{1',2'}$ 16, 1'-H), 6.76 (1H, d, $J_{1',2'}$ 16, 2'-H) and 7.26-7.37 (15H, m, Ar-H); $\delta_C$(100 MHz; $CDCl_3$) 70.3 and 70.5 (2 x $CH_2OCH_2Ph$), 73.52/73.54 (2 x $CH_2OCH_2Ph$), 77.5 and 78.1 (C-4 and C-5), 104.3 (C-2), 125.3 (C-1'), 127.0, 127.6, 127.7, 128.3, 128.4, 128.5, 135.8 and 137.9 (Ar-C) and 135.2 (C-2').

### 3.2.3.2 *Bornane-2,3-diol derived acetals*




#### 3.2.3.2.1 *Preparation of acrolein bornane acetal* (193)

Solid $MgSO_4$ (3.54 g, 29.40 mmol), PTSA (0.28 g, 1.47 mmol) and bornane-2,3-diol (**150**) (2.50 g, 14.70 mmol) were sequentially added to a stirred solution of acrolein (0.82 g, 14.70 mmol) in dry benzene (80 ml). Progress of the reaction was monitored by TLC and after 2 h only a small amount of the aldehyde was detected. $NaHCO_3$ (0.31 g, 3.69 mmol) was added and the mixture stirred for a further 30 min before filtering. The $MgSO_4$ was washed with ether (100 ml) and the combined organic filtrates were washed with $H_2O$ (100 ml), sat. aq. $NaHCO_3$ (100 ml) and sat. aq. NaCl (100 ml), dried $MgSO_4$, filtered and concentrated *in vacuo*. The resultant yellow liquid was purified by flash chromatography [elution with hexane-EtOAc (4:1)] to yield, as a colourless liquid, *(1*S*,2*R*,5*S*,6*R*,8*R*)-2,10,10-trimethyl-8-vinyl-7,9-dioxatricyclo[4.3.0.1$^{2,5}$]decane* (**193**) (2.34 g, 77 %), (Found: $\mathbf{M}^+$ 208.1460. $C_{13}H_{20}O_2$ requires *M*, 208.1462); $\delta_H$(400 MHz; $CDCl_3$) 0.79, 0.99 and 1.10 (9H, 3 x s, 11-, 12- and 13-Me), 0.86, 1.41 and 1.68 (4H, 3 x m, 3- and 4-$CH_2$), 1.97 (1H, d, 5-H), 3.79 and 3.97 (2H, 2 x d, 1- and 6-H), 5.00 (1H, d, 8-H), 5.37 and 5.50 (2H, 2 x d, C=C$H_2$) and 5.93 (1H, m, 1'-H); $\delta_C$(100 MHz; $CDCl_3$) 11.0, 20.0 and 22.5 (C-11, C-12 and C-13), 23.4 and 31.8 (C-3 and C-4), 46.1 and 47.4 (C-2 and C-10), 47.6 (C-5), 83.7 and 87.9 (C-1 and C-6), 103.1 (C-8), 121.3 (C-2') and 133.2 (C-1'); *m z* 208 ($\mathbf{M}^+$, 6 %) and 55 (100).

### 3.2.3.2.2 *Preparation of crotonaldehyde bornane acetal* (194)

Following the procedure described for the synthesis of (1*S*,2*R*,5*S*,6*R*,8*R*)-2,10,10-trimethyl-8-vinyl-7,9-dioxatricyclo[4.3.0.$1^{2,5}$]decane (**193**), bornane-2,3-diol (**150**) (3.40 g, 20 mmol) was added to a stirred mixture of *trans*-crotonaldehyde (1.40 g, 20 mmol), $MgSO_4$ (4.81 g, 40 mmol) and PTSA (0.38 g, 2 mmol) in dry benzene (80 ml). After stirring for 3 h, work-up and flash chromatography [elution with hexane-EtOAc (4:1)] yielded, as a white semi-solid, *(1*S,*2*R,*5*S,*6*R,*8*R*)-2,10,10-trimethyl-8-(1-propenyl)-7,9-dioxatricyclo[4.3.0.$1^{2,5}$]decane* (**194**) (3.44 g, 78 %), (Found: $\mathbf{M}^+$ 222.1609. $C_{14}H_{22}O_2$ requires *M*, 222.1618); $\delta_H$(400 MHz; $CDCl_3$) 0.80, 0.99 and 1.13 (9H, 3 x s, 11-, 12- and 13-Me), 0.86, 1.41 and 1.67 (4H, 3 x m, 3- and 4-$CH_2$), 1.73 (3H, dd, 3'-Me), 1.96 (1H, d, 5-H), 3.77 and 3.95 (2H, 2 x d, 1- and 6-H), 4.98 (1H, d, $J_{4,1'}$ 7, 8-H), 5.59 (1H, m, 1'-H) and 5.96 (1H, m, 2'-H); $\delta_C$(100 MHz; $CDCl_3$) 11.0, 20.1 and 22.5 (C-11, C-12 and C-13), 17.7 (C-3'), 23.4 and 31.9 (C-3 and C-4), 46.1 and 47.4 (C-2 and C-10), 47.6 (C-5), 83.6 and 87.8 (C-1 and C-6), 103.5 (C-8), 126.5 (C-1') and 134.0 (C-2'); *m/z* 222 ($\mathbf{M}^+$, 2 %) and 41 (100).

### 3.2.3.2.3 *Preparation of* trans-*2-hexenal bornane acetal* (195)

Following the procedure described for the synthesis of (1*S*,2*R*,5*S*,6*R*,8*R*)-2,10,10-trimethyl-8-vinyl-7,9-dioxatricyclo[4.3.0.$1^{2,5}$]decane (**193**), bornane-2,3-diol (**150**) (1.70 g, 10.0 mmol) was added to a stirred mixture of *trans*-2-hexenal (0.98 g, 10.0 mmol), $MgSO_4$ (2.40 g, 20.0 mmol) and PTSA (0.19 g, 1.0 mmol) in dry benzene (90 ml). After stirring for 3 h, work-up and flash chromatography [elution with hexane-EtOAc (9:1)] yielded, as a pale yellow oil, *(1*S,*2*R,*5*S,*6*R,*8*R*)-2,10,10-trimethyl-8-(1-pentenyl)-7,9-dioxatricyclo[4.3.0.$1^{2,5}$]decane* (**195**) (1.74 g, 70 %), (Found: $\mathbf{M}^+$ 250.1923. Calc. For $C_{16}H_{25}O_2$ requires *M*, 250.1931); $\delta_H$(400 MHz; $CDCl_3$) 0.77, 0.96 and 1.10 (9H, 3 x s, 11-, 12- and 13-Me), 0.85, 1.39 and 1.65 (9H, 3 x m, 3-, 4-, 4'-$CH_2$ and 5'-Me), 1.93 (1H, m, 5-H), 2.01 (2H, m, 3'-$CH_2$), 3.75

and 3.92 (2H, 2 x m, 1- and 6-H), 4.96 (1H, m, 8-H), 5.53 (1H, m, 1'-H) and 5.90 (1H, m, 2'-H); $\delta_C$(100 MHz; $CDCl_3$) 11.0, 13.6, 20.0 and 22.5 (C-11, C-12, C-13 and C-5'), 21.7, 23.3, 31.8 and 34.1 (C-3, C-4, C-3' and C-4'), 46.0 and 47.3 (C-2 and C-10), 47.5 (C-5), 83.5 and 87.7 (C-1 and C-6), 103.6 (C-8), 125.2 (C-1') and 138.7 (C-2').

### 3.2.3.2.4 *Preparation of* trans-*cinnamaldehyde bornane acetal* (196)

Following the procedure described for the synthesis of (1*S*,2*R*,5*S*,6*R*,8*R*)-2,10,10-trimethyl-8-vinyl-7,9-dioxatricyclo[4.3.0.$1^{2,5}$]decane (**193**), bornane-2,3-diol (**150**) (1.96 g, 11.5 mmol) was added to a stirred mixture of *trans*-cinnamaldehyde (1.52 g, 11.5 mmol), $MgSO_4$ (2.77 g, 23.0 mmol) and PTSA (0.22 g, 1.15 mmol) in dry benzene (100 ml). After stirring for 3 h, work-up and recrystallization yielded, as white crystals, (1*S*,2*R*,5*S*,6*R*,8*R*)-2,10,10-trimethyl-8-styryl-7,9-*dioxatricyclo[4.3.0.1$^{2,5}$]decane* (**196**) (2.25 g, 69 %), m.p. 63-68 °C (from EtOH); (Found: $\mathbf{M}^+$ 284.1789. $C_{19}H_{24}O_2$ requires *M*, 284.1775); $\delta_H$(400 MHz; $CDCl_3$) 0.83, 1.03 and 1.18 (9H, 3 x s, 11-, 12- and 13-Me), 0.89, 1.45 and 1.72 (4H, 3 x m, 3- and 4-$CH_2$), 2.02 (1H, d, 5-H), 3.86 and 4.04 (2H, 2 x d, 1- and 6-H), 5.21 (1H, d, $J_{4,1'}$ 6.3, 8-H), 6.24 (1H, dd, $J_{4,1'}$ 6.3 and $J_{1',2'}$ 16.1, 1'-H), 6.80 (1H, d, $J_{1',2'}$ 16.1, 2'-H) and 7.24-7.42 (5H, m, Ar-H); $\delta_C$(100 MHz; $CDCl_3$) 11.0, 20.3 and 22.5 (C-11, C-12 and C-13), 23.4 and 31.9 (C-3 and C-4), 46.2 and 47.5 (C-2 and C-10), 47.7 (C-5), 83.8 and 88.0 (C-1 and C-6), 103.3 (C-8), 123.9 (C-1'), 127.0, 128.4, 128.5 and 135.9 (Ar-C) and 136.2 (C-2'); *m/z* 284 ($\mathbf{M}^+$, 18.5 %) and 104 (100).

### 3.2.3.2.5 *Preparation of (Z)-α-methylcinnamaldehyde bornane acetal* (197)

Following the procedure described for the synthesis of (1*S*,2*R*,5*S*,6*R*,8*R*)-2,10,10-trimethyl-8-vinyl-7,9-dioxatricyclo[4.3.0.$1^{2,5}$]decane (**193**), bornane-2,3-diol (**150**)

and 3.92 (2H, 2 x m, 1- and 6-H), 4.96 (1H, m, 8-H), 5.53 (1H, m, 1'-H) and 5.90 (1H, m, 2'-H); $\delta_C$(100 MHz; $CDCl_3$) 11.0, 13.6, 20.0 and 22.5 (C-11, C-12, C-13 and C-5'), 21.7, 23.3, 31.8 and 34.1 (C-3, C-4, C-3' and C-4'), 46.0 and 47.3 (C-2 and C-10), 47.5 (C-5), 83.5 and 87.7 (C-1 and C-6), 103.6 (C-8), 125.2 (C-1') and 138.7 (C-2').

#### 3.2.3.2.4 *Preparation of* trans-*cinnamaldehyde bornane acetal* (196)

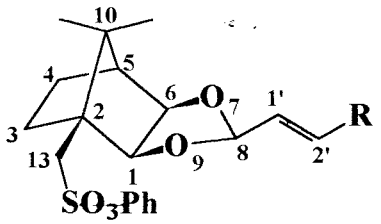
Following the procedure described for the synthesis of (1*S*,2*R*,5*S*,6*R*,8*R*)-2,10,10-trimethyl-8-vinyl-7,9-dioxatricyclo[4.3.0.$1^{2,5}$]decane (**193**), bornane-2,3-diol (**150**) (1.96 g, 11.5 mmol) was added to a stirred mixture of *trans*-cinnamaldehyde (1.52 g, 11.5 mmol), $MgSO_4$ (2.77 g, 23.0 mmol) and PTSA (0.22 g, 1.15 mmol) in dry benzene (100 ml). After stirring for 3 h, work-up and recrystallization yielded, as white crystals, (1*S*,2*R*,5*S*,6*R*,8*R*)-2,10,10-*trimethyl-8-styryl-7,9-dioxatricyclo[4.3.0.1$^{2,5}$]decane* (**196**) (2.25 g, 69 %), m.p. 63-68°C (from EtOH); (Found: $\mathbf{M}^+$ 284.1789. $C_{19}H_{24}O_2$ requires *M*, 284.1775); $\delta_H$(400 MHz; $CDCl_3$) 0.83, 1.03 and 1.18 (9H, 3 x s, 11-, 12- and 13-Me), 0.89, 1.45 and 1.72 (4H, 3 x m, 3- and 4-$CH_2$), 2.02 (1H, d, 5-H), 3.86 and 4.04 (2H, 2 x d, 1- and 6-H), 5.21 (1H, d, $J_{4,1'}$ 6.3, 8-H), 6.24 (1H, dd, $J_{4,1'}$ 6.3 and $J_{1',2'}$ 16.1, 1'-H), 6.80 (1H, d, $J_{1',2'}$ 16.1, 2'-H) and 7.24-7.42 (5H, m, Ar-H); $\delta_C$(100 MHz; $CDCl_3$) 11.0, 20.3 and 22.5 (C-11, C-12 and C-13), 23.4 and 31.9 (C-3 and C-4), 46.2 and 47.5 (C-2 and C-10), 47.7 (C-5), 83.8 and 88.0 (C-1 and C-6), 103.3 (C-8), 123.9 (C-1'), 127.0, 128.4, 128.5 and 135.9 (Ar-C) and 136.2 (C-2'); *m/z* 284 ($\mathbf{M}^+$, 18.5 %) and 104 (100).

#### 3.2.3.2.5 *Preparation of (Z)-α-methylcinnamaldehyde bornane acetal* (197)

Following the procedure described for the synthesis of (1*S*,2*R*,5*S*,6*R*,8*R*)-2,10,10-trimethyl-8-vinyl-7,9-dioxatricyclo[4.3.0.$1^{2,5}$]decane (**193**), bornane-2,3-diol (**150**)

(2.32 g, 13.7 mmol) was added to a stirred mixture of α-methylcinnamaldehyde (2.00 g, 13.7 mmol), $MgSO_4$ (3.27 g, 27.2 mmol) and PTSA (0.26 g, 1.37 mmol) in dry benzene (80 ml). After stirring for 3 h, work-up and flash chromatography [elution with hexane-EtOAc (4:1)] yielded, as a yellow oil, *(1S,2R,5S,6R,8R)-2,10,10-trimethyl-8-(1-methylstyryl)-7,9-dioxatricyclo[4.3.0.$1^{2,5}$]decane* (**197**) (2.84 g, 70 %), (Found: $\mathbf{M}^+$ 298.1933. $C_{20}H_{26}O_2$ requires *M*, 298.1931); $\delta_H$(400 MHz; $CDCl_3$) 0.83, 1.06 and 1.16 (9H, 3 x s, 11-, 12- and 13-Me), 0.92, 1.47 and 1.75 (4H, 3 x m, 3- and 4-$CH_2$), 1.96 (3H, s, 1'-Me), 2.05 (1H, d, 5-H), 3.88 and 4.06 (2H, 2 x d, 1- and 6-H), 5.09 (1H, s, 8-H), 6.86 (1H, s, 2'-H) and 7.21-7.36 (5H, m, Ar-H); $\delta_C$(100 MHz; $CDCl_3$) 11.1, 20.5 and 22.6 (C-11, C-12 and C-13), 14.5 [C(1')Me], 23.5 and 32.0 (C-3 and C-4), 46.2 and 47.5 (C-2 and C-10), 47.6 (C-5), 83.7 and 87.8 (C-1 and C-6), 104.6 (C-8), 126.7, 128.0, 129.1 and 132.3 (Ar-C), 127.9 (C-2') and 137.1 (C-1'); *m/z* 298 ($\mathbf{M}^+$, 2.76 %) and 194 (100).

### 3.2.3.3 *Bornane-2,3-dihydroxy-10-sulfonate derived acetals*




#### 3.2.3.3.1 *Preparation of acrolein bornane-10-sulfonate acetal* (198)

Following the procedure described for the synthesis of (1*S*,2*R*,5*S*,6*R*,8*R*)-2,10,10-trimethyl-8-vinyl-7,9-dioxatricyclo[4.3.0.$1^{2,5}$]decane (**193**), the bornane-10-sulfonate diol (**192**) (0.49 g, 1.5 mmol) was added to a stirred mixture of acrolein (0.084 g, 1.5 mmol), $MgSO_4$ (0.36 g, 3.0 mmol) and PTSA (0.03 g, 1.5 mmol) in dry benzene (25 ml). After stirring for 5 h, work-up and separation by PTLC [hexane-EtOAc (4:1)] yielded an oil which on standing afforded, as white crystals, *phenyl {(1S,2S,5S,6R,8R)-10,10-dimethyl-8-vinyl-7,9-dioxatricyclo[4.3.0.$1^{2,6}$]dec-2-yl}methanesulfonate* (**198**) (0.35 g, 64 %), m.p. 84-86°C; (Found: $\mathbf{M}^+$ 364.1347. $C_{19}H_{24}O_5S$ requires *M*, 364.1339); $\nu_{max}$ (liquid film)/$cm^{-1}$ 1480, 1370 and 1140; $\delta_H$(400 MHz; $CDCl_3$) 0.86 and 1.14 (6H, 2 x s, 11- and 12-Me), 0.99, 1.42, 1.78 and 1.87 (4H, 4 x m, 3- and 4-$CH_2$), 2.06 (1H, d, 5-H), 3.17 and 3.79 (2H, 2 x d, 13-$CH_2$), 4.06 and 4.36 (2H, 2 x d, 1- and 6-$CH_2$), 5.39 and 5.51 (1H, 2 x d, 2'-$CH_2$), 5.93 (1H, m, 1'-H) and 7.25-7.39 (5H, m, Ar-H); $\delta_C$(100 MHz; $CDCl_3$) 19.9 and 22.6 (C-11 and C-12), 23.1 and 27.7 (C-3 and C-4), 46.7 (C-5), 47.6 and 48.7 (C-2 and C-10), 49.3 (C-13), 83.3 and 83.7 (C-1 and C-6), 103.2 (C-8), 121.4 (C-2'), 121.9, 126.9, 129.7 and 149.1 (Ar-C) and 132.5 (C-1'); *m/z* 364 ($\mathbf{M}^+$, 3.8 %) and 271 (100).

### 3.2.3.3.2 *Preparation of* trans-*crotonaldehyde bornane-10-sulfonate acetal* (199)

Following the procedure described for the synthesis of (1*S*,2*R*,5*S*,6*R*,8*R*)-2,10,10-trimethyl-8-vinyl-7,9-dioxatricyclo[4.3.0.$1^{2,5}$]decane (**193**), the bornane-10-sulfonate diol (**192**) (0.49 g, 1.5 mmol) was added to a stirred mixture of *trans*-crotonaldehyde (0.11 g, 1.5 mmol), $MgSO_4$ (0.36 g, 3.0 mmol) and PTSA (0.03 g, 1.5 mmol) in dry benzene (25 ml). After stirring for 5 h, work-up and separation by PTLC [hexane-EtOAc (9:1)] yielded, as a pale yellow oil, *phenyl {(1*S*,2*R*,5*S*,6*R*,8*R*)-10,10-dimethyl-8-(1-propenyl)-7,9-dioxatricyclo[4.3.0.$1^{2,5}$]dec-2-yl}methanesulfonate* (**199**) (0.42 g, 74 %), (Found: $\mathbf{M}^+$ 378.1490. $C_{20}H_{26}O_5S$ requires *M*, 378.1495); $\nu_{max}$ (liquid film)/$cm^{-1}$ 1480, 1360 and 1140; $\delta_H$(400 MHz; $CDCl_3$) 0.86 and 1.17 (6H, 2 x s, 11- and 12-Me), 0.99, 1.42, 1.78 and 1.89 (4H, 4 x m, 3- and 4-$CH_2$), 1.74 (3H, m, 3'-Me), 2.05 (1H, d, 5-H), 3.17 and 3.79 (2H, 2 x d, 13-$CH_2$), 4.04 and 4.34 (2H, 2 x d, 1- and 6-$CH_2$), 5.06 (1H, d, 8-H), 5.58 (1H, m, 1'-H), 5.97 (1H, m, 2'-H) and 7.25-7.40 (5H, m, Ar-H); $\delta_C$(100 MHz; $CDCl_3$) 17.6 (C-3'), 19.9 and 22.6 (C-11 and C-12), 23.1 and 27.8 (C-3 and C-4), 46.7 (C-5), 47.6 and 48.7 (C-2 and C-10), 49.3 (C-13), 83.2 and 83.7 (C-1 and C-6), 103.8 (C-8), 122.0, 126.9, 129.8 and 149.1 (Ar-C), 125.9 (C-1') and 134.2 (C-2'); *m/z* 378 ($\mathbf{M}^+$, 8.9 %) and 149 (100).

### 3.2.3.3.3 *Preparation of* trans-*2-hexenal bornane-10-sulfonate acetal* (200)

Following the procedure described for the synthesis of (1*S*,2*R*,5*S*,6*R*,8*R*)-2,10,10-trimethyl-8-vinyl-7,9-dioxatricyclo[4.3.0.$1^{2,5}$]decane (**193**), the bornane-10-sulfonate diol (**192**) (0.49 g, 1.5 mmol) was added to a stirred mixture of *trans*-2-hexenal (0.147 g, 1.5 mmol), $MgSO_4$ (0.36 g, 3.0 mmol) and PTSA (0.03 g, 1.5 mmol) in dry benzene (30 ml). After stirring for 5 h, work-up and separation by PTLC [hexane-

EtOAc (4:1)] yielded, as a colourless oil, *phenyl {(1S,2R,5S,6R,8R)-10,10-dimethyl-8-(1-pentenyl)-7,9-dioxatricyclo[4.3.0.1$^{2,5}$]dec-2-yl}methanesulfonate* (**200**) (0.46 g, 76 %), (Found: **M**$^+$ 406.1809. $C_{20}H_{30}O_5S$ requires *M*, 420.1963); $\delta_H$(400 MHz; $CDCl_3$) 0.88 and 1.18 (6H, 2 x s, 11- and 12-Me), 0.90 (3H, t, 5'-H), 1.00, 1.42, 1.79 and 1.89 (5H, 4 x m, 3-, 4 and 4'-$CH_2$), 2.06 (3H, m, 5-H and 3'-$CH_2$), 3.17 and 3.81 (2H, 2 x d, 13-$CH_2$), 4.05 and 4.35 (2H, 2 x d, 1- and 6-$CH_2$), 5.08 (1H, d, 8-H), 5.56 (1H, m, 1'-H), 5.96 (1H, m, 2'-H) and 7.27-7.41 (5H, m, Ar-H); $\delta_C$(100 MHz; $CDCl_3$) 13.6 (C-5'), 20.0 and 22.7 (C-11 and C-12), 21.8 (C-4'), 23.2 and 27.9 (C-3 and C-4), 34.2 (C-3'), 46.8 (C-5), 47.8 and 48.9 (C-2 and C-10), 49.5 (C-13), 83.3 and 83.8 (C-1 and C-6), 104.0 (C-8), 122.1, 127.0, 129.8 and 149.2 (Ar-C), 124.6 (C-1') and 139.3 (C-2'); *m/z* 406 (**M**$^+$, 3 %) and 149 (100).

### 3.2.3.3.4 *Preparation of* trans-*cinnamaldehyde bornane-10-sulfonate acetal* (201)

Following the procedure described for the synthesis of (1*S*,2*R*,5*S*,6*R*,8*R*)-2,10,10-trimethyl-8-vinyl-7,9-dioxatricyclo[4.3.0.1$^{2,5}$]decane (**193**), the bornane-10-sulfonate diol (**192**) (0.49 g, 1.5 mmol) was added to a stirred mixture of *trans*-cinnamaldehyde (0.20 g, 1.5 mmol), $MgSO_4$ (0.36 g, 3.0 mmol) and PTSA (0.03 g, 1.5 mmol) in dry benzene (30 ml). After stirring for 5 h, work-up and separation by PTLC [hexane-EtOAc (4:1)] yielded a colourless oil which on standing afforded, as white crystals, *phenyl {(1S,2R,5S,6R,8R)-10,10-dimethyl-8-styryl-7,9-dioxatricyclo[4.3.0.1$^{2,5}$]dec-2-yl}methanesulfonate* (**201**) (0.48 g, 73 %), m.p. 120-124 °C; (Found: **M**$^+$ 440.1663. $C_{25}H_{28}O_5S$ requires *M*, 440.1657); $\delta_H$(400 MHz; $CDCl_3$) 0.90 and 1.21 (6H, 2 x s, 11- and 12-Me), 1.04, 1.46 and 1.87 (4H, 3 x m, 3- and 4-$CH_2$), 2.12 (1H, d, 5-H), 3.20 and 3.84 (2H, 2 x d, 13-$CH_2$), 4.13 and 4.43 (2H, 2 x d, 1- and 6-$CH_2$), 5.30 (1H, d, $J_{4,1'}$ 5.9, 8-H), 6.23 (1H, dd, $J_{4,1'}$ 5.9 and $J_{1',2'}$ 16, 1'-H), 6.80 (1H, d, $J_{1',2'}$ 16, 2'-H) and 7.28-7.46 (10H, m, Ar-H); $\delta_C$(100 MHz;

$CDCl_3$) 20.2 and 22.7 (C-11 and C-12), 23.2 and 27.9 (C-3 and C-4), 46.9 (C-5), 47.8 and 48.9 (C-2 and C-10), 49.4 (C-13), 83.5 and 83.9 (C-1 and C-6), 103.5 (C-8), 122.1, 126.9, 127.0, 128.5, 128.6, 129.9, 135.7 and 149.2 (Ar-C), 123.2 (C-1') and 136.3 (C-2'); *m/z* 440 ($\mathbf{M}^+$, 10.1 %) and 104 (100).

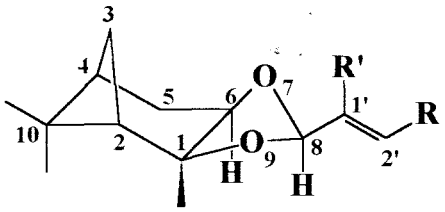
### 3.2.3.3.5 *Preparation of* trans-*2-nitrocinnamaldehyde bornane-10-sulfonate acetal* (202)

Following the procedure described for the synthesis of (1*S*,2*R*,5*S*,6*R*,8*R*)-2,10,10-trimethyl-8-vinyl-7,9-dioxatricyclo[4.3.0.$1^{2,5}$]decane (**193**), the bornane-10-sulfonate diol (**192**) (0.49 g, 1.5 mmol) was added to a stirred mixture of *trans*-2-nitrocinnamaldehyde (0.18 g, 1.5 mmol), $MgSO_4$ (0.36 g, 3.0 mmol) and PTSA (0.03 g, 1.5 mmol) in dry benzene (30 ml). After stirring for 5 h, work-up and separation by PTLC [hexane-EtoOAc (4:1)] yielded, as a dark yellow oil, *phenyl {(1S,2R,5S,6R,8R)-10,10-dimethyl-8-(2-nitrostyryl)-7,9-dioxatricyclo[4.3.0.$1^{2,5}$]dec-2-yl}methanesulfonate* (**202**) (0.53 g, 72 %), (Found: $\mathbf{M}^+$ 485.1518. $C_{25}H_{27}NO_7S$ requires *M*, 485.1507); $\delta_H$(400 MHz; $CDCl_3$) 0.87 and 1.19 (6H, 2 x s, 11- and 12-Me), 1.02, 1.43, 1.80 and 1.91 (4H, 4 x m, 3- and 4-$CH_2$), 2.08 (1H, d, 5-H), 3.20 and 3.82 (2H, 2 x d, 13-$CH_2$), 4.11 and 4.41 (2H, 2 x d, 1- and 6-$CH_2$), 5.28 (1H, m, 8-H), 6.19 (1H, dd, 1'-H) and 7.26-7.91 (5H, m, 2'- and Ar-H); $\delta_C$(100 MHz; $CDCl_3$) 20.0 and 22.5 (C-11 and C-12), 23.0 and 27.6 (C-3 and C-4), 46.6 (C-5), 47.6 and 48.7 (C-2 and C-10), 49.2 (C-13), 83.4 and 83.8 (C-1 and C-6), 102.1 (C-8), 121.8, 124.4, 126.9, 128.1, 128.9, 129.7, 129.8, 130.9, 131.4, 133.1, 147.7 and 149.0 (Ar-C and C-2') and 128.8 (C-1'); *m/z* 485 ($\mathbf{M}^+$, 3 %) and 94 (100).

### 3.2.3.3.6 *Preparation of the carbethoxymethyldioxolane* (204)

Ethyl 3,3-diethoxypropionate (**203**) (0.19 g, 1.0 mmol) and the bornane-10-sulfonate diol (**192**) (0.33 g, 1.0 mmol) were stirred, in the presence of $BF_3.Et_2O$ (0.38 ml, 3.0 mmol) for 30 min, in benzene (10 ml). The mixture was neutralized with sat. aq. $NaHCO_3$ (50 ml) and extracted with EtOAc (3 x 50 ml). The combined organic layers were dried ($Na_2SO_4$), filtered, concentrated *in vacuo* and PTLC [hexane-EtOAc (7:3)] of the residue afforded, as a colourless oil, *phenyl {(1S,2S,5S,6R,8R) -8-carbethoxymethyl-10,10-dimethyl-7,9-dioxatricyclo[4.3.0.1$^{2,5}$]dec-2-yl}methanesulfonate* (**204**) (0.46 g, 85 %), $\nu_{max}$ (liquid film)/cm$^{-1}$ 1760; $\delta_H$(400 MHz; $CDCl_3$) 0.82 and 1.08 (6H, 2 x s, 11- and 12-Me), 0.94, 1.37, 1.73 and 1.82 (4H, 4 x m, 3-and 4-$CH_2$), 1.19 (3H, t, 5'-Me), 2.01 (1H, d, 5-H), 2.69 (2H, m, 1'-H), 3.13 and 3.71 (2H, 2 x d, 13-$CH_2$), 4.00 and 4.28 (2H, 2 x d, 1- and 6-$CH_2$), 4.09 (1H, q, 4'-H), 5.08 (1H, dd, 8-H) and 7.21-7.36 (5H, m, Ar-H); $\delta_C$(100 MHz, $CDCl_3$) 13.9 (C-5'), 19.6 and 22.4 (C-11 and C-12), 22.9 and 27.6 (C-3 and C-4), 38.0 (C-1'), 46.4 (C-5), 47.4 and 48.5 (C-2 and C-10), 49.1 (C-13), 60.5 (C-4'), 83.4 and 83.6 (C-1 and C-6), 100.3 (C-8), 121.8, 126.8, 129.6 and 149.0 (Ar-C) and 168.7 (CO).

### 3.2.3.4 (+)-*Pinane-2,3-diol derived acetals*




#### 3.2.3.4.1 *Preparation of* trans-*crotonaldehyde pinane acetal* (249)

Following the procedure described for the synthesis of (1*S*,2*R*,5*S*,6*R*,8*R*)-2,10,10-trimethyl-8-vinyl-7,9-dioxatricyclo[4.3.0.$1^{2,5}$]decane (**193**), (+)-pinane-2,3-diol (**248**) (0.600 g, 3.53 mmol) was added to a stirred mixture of *trans*-crotonaldehyde (0.247 g, 3.53 mmol), $MgSO_4$ (0.850 g, 7.06 mmol) and PTSA (0.067 g, 0.35 mmol) in dry benzene (80 ml). After stirring for 5 h, work-up and separation by PTLC [hexane-EtOAc (4:1)] yielded, as a colourless oil, *(1*S,*2*S,*4*S,*6*R,*8*R*)-1,10,10-trimethyl-8-(1-propenyl)-7,9-dioxatricyclo[4.3.0.$1^{2,4}$]decane* (**249**) (0.54 g, 69 %), (Found: **M**$^+$ 222.1615. $C_{14}H_{22}O_2$ requires *M*, 222.1620); $\delta_H$(400 MHz; $CDCl_3$) 0.77, 1.22 and 1.31 (9H, 3 x s, 11-, 12- and 13-Me), 1.61, 1.88 and 2.00-2.14 (4H, 3 x m, 3- and 5-$CH_2$), 1.67 (3H, dd, 3'-Me), 1.82 and 1.95 (2H, 2x m, 2- and 4-H), 3.88 (1H, d, 6-H), 5.12 (1H, d, 8-H), 5.52 (1H, m, 1'-H) and 5.92 (1H, m, 2'-H); $\delta_C$(100 MHz; $CDCl_3$) 17.4 (C-3'), 23.7, 25.4 and 27.0 (C-11, C-12 and C-13), 24.9 and 32.5 (C-3 and C-5), 37.5 and 83.3 (C-1 and C-10), 39.8 and 50.5 (C-2 and C-4), 76.9 (C-6), 100.5 (C-8), 127.3 (C-1') and 132.8 (C-2'); *m/z* 222 (**M**$^+$, 1.26 %) and 43 (100).

#### 3.2.3.4.2 *Preparation of* trans-*2-hexenal pinane acetal* (250)

Following the procedure described for the synthesis of (1*S*,2*R*,5*S*,6*R*,8*R*)-2,10,10-trimethyl-8-vinyl-7,9-dioxatricyclo[4.3.0.$1^{2,5}$]decane (**193**), (+)-pinane-2,3-diol (**248**) (0.600 g, 3.53 mmol) was added to a stirred mixture of *trans*-2-hexenal (0.346 g, 3.53 mmol), $MgSO_4$ (0.850 g, 7.06 mmol) and PTSA (0.067 g, 0.35 mmol) in dry

benzene (80 ml). After stirring for 5 h, work-up and separation by PTLC [hexane-EtOAc (4:1)] yielded, as a colourless oil, *(1*S,*2*S,*4*S,*6*R,*8*R*)-1,10,10-trimethyl-8-(1-pentenyl)-,9-dioxatricyclo[4.3.0.1$^{2,4}$]decane* (**250**) (0.48 g, 54 %), (Found: **M**$^+$ 250.1948. $C_{16}H_{26}O_2$ requires *M*, 250.1933); $\delta_H$(400 MHz; $CDCl_3$) 0.78, 1.23 and 1.32 (9H, 3 x s, 11-, 12- and 13-Me), 0.85 (3H, t, 5'-H), 1.38 (2H, m, 4'-H), 1.62, and 1.76-2.14 (8H, 2 x m, 2- and 4-H and 3-, 5- and 3'-$CH_2$), 3.89 (1H, d, 6-H), 5.13 (1H, d, 8-H), 5.50 (1H, dd, 1'-H) and 5.91 (1H, m, 2'-H); $\delta_C$(100 MHz; $CDCl_3$) 13.5 (C-5'), 21.6 (C-4'), 23.8, 25.4 and 27.0 (C-11, C-12 and C-13), 24.9, 32.6 and 34.0 (C-3, C-5 and C-3'), 37.6 and 83.3 (C-1 and C-10), 39.8 and 50.6 (C-2 and C-4), 76.9 (C-6), 100.8 (C-8), 126.0 (C-1') and 138.0 (C-2'); *m/z* 250 (**M**$^+$, 0.45 %) and 43 (100).

### 3.2.3.4.3 *Preparation of* trans-*cinnamaldehyde pinane acetal* (251)

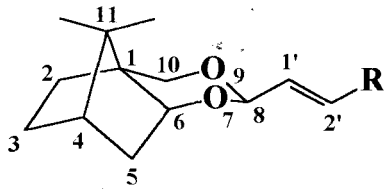
Following the procedure described for the synthesis of (1*S*,2*R*,5*S*,6*R*,8*R*)-2,10,10-trimethyl-8-vinyl-7,9-dioxatricyclo[4.3.0.1$^{2,5}$]decane (**193**), (+)-pinane-2,3-diol (**248**) (0.60 g, 3.5 mmol) was added to a stirred mixture of *trans*-cinnamaldehyde (0.47 g, 3.5 mmol), $MgSO_4$ (0.85 g, 7.1 mmol) and PTSA (0.067 g, 0.35 mmol) in dry benzene (80 ml). After stirring for 5 h, work-up and separation by PTLC [hexane-EtOAc (4:1)] yielded, as a colourless oil, *(1*S,*2*S,*4*S,*6*R,*8*R*)-1,10,10-trimethyl-8-styryl-7,9-dioxatricyclo[4.3.0.1$^{2,4}$]decane* (**251**) (0.72 g, 71 %), (Found: **M**$^+$ 284.1773. $C_{19}H_{24}O_2$ requires *M*, 284.1776); $\delta_H$(400 MHz; $CDCl_3$) 0.85, 1.31 and 1.43 (9H, 3 x s, 11-, 12- and 13-Me), 1.78, 2.03 and 2.18 (4H, 3 x m, 3- and 5-$CH_2$), 1.93 and 2.10 (2H, 2x m, 2- and 4-H), 4.02 (1H, d, 6-H), 5.41 (1H, d, $J_{4,1'}$ 6.3, 8-H), 6.27 (1H, dd, $J_{4,1'}$ 6.3 and $J_{1',2'}$ 16.1, 1'-H), 6.83 (1H, d, $J_{1',2'}$ 16.1, 2'-H) and 7.22-7.43 (5H, m, Ar-H); $\delta_C$(100 MHz; $CDCl_3$) 23.7, 25.4 and 27.0 (C-11, C-12 and C-13), 25.0 and 32.5 (C-3 and C-5), 37.5 and 83.5 (C-1 and C-10), 39.8 and 50.5 (C-2 and C-4), 77.0 (C-6), 100.4 (C-8), 124.7 (C-1'), 126.7, 128.0, 128.2 and 135.7 (Ar-C)

and 135.2 (C-2').

### 3.2.3.4.4 *Preparation of (Z)-α-methylcinnamaldehyde pinane acetal* (252)

Following the procedure described for the synthesis of (1*S*,2*R*,5*S*,6*R*,8*R*)-2,10,10-trimethyl-8-vinyl-7,9-dioxatricyclo[4.3.0.$1^{2,5}$]decane (**193**), (+)-pinane-2,3-diol (**248**) (0.600 g, 3.53 mmol) was added to a stirred mixture of α-methylcinnamaldehyde (0.516 g, 3.53 mmol), $MgSO_4$ (0.850 g, 7.06 mmol) and PTSA (0.067 g, 0.35 mmol) in dry benzene (60 ml). After stirring for 5 h, work-up and separation by PTLC [hexane-EtOAc (4:1)] yielded, as a pale yellow oil, *(1*S,*2*S,*4*S,*6*R,*8*R*)-1,10,10-trimethyl-8-(1-methylstyryl)-7,9-dioxatricyclo[4.3.0.$1^{2,4}$]decane* (**252**) (0.46 g, 49 %), $\delta_H$(400 MHz; $CDCl_3$) 0.89, 1.33 and 1.46 (9H, 3 x s, 11-, 12- and 13-Me), 1.88, 1.94, 2.07, 2.18 and 2.26 (6H, 5 x m, 2- and 4-H and 3- and 5-$CH_2$), 2.03 (3H, s, 1'-Me), 4.07 (1H, d, 6-H), 5.30 (1H, s, 8-H), 6.77 (1H, s, 2'-H) and 7.22-7.37 (5H, m, Ar-H); $\delta_C$(100 MHz; $CDCl_3$) 12.2 [C(1')Me], 23.9, 25.4 and 27.0 (C-11, C-12 and C-13), 24.9 and 32.8 (C-3 and C-5), 37.9 and 83.1 (C-1 and C-10), 39.8 and 50.7 (C-2 and C-4), 77.1 (C-6), 104.0 (C-8), 126.7 (C-2'), 127.9, 128.9, 130.6 and 133.7 (Ar-C) and 136.6 (C-1'); *m/z* 298 (**M**$^+$, 0.68 %) and 93 (100).

### 3.2.3.5 (-)-*Bornane-2,10-diol derived acetals*




#### 3.2.3.5.1 *Preparation of acetal* (263)

Following the procedure described for the synthesis of (1*S*,2*R*,5*S*,6*R*,8*R*)-2,10,10-trimethyl-8-vinyl-7,9-dioxatricyclo[4.3.0.$1^{2,5}$]decane (**193**), bornane-2,10-diol (**262**) (0.40 g, 2.4 mmol) was added to a stirred mixture of *trans*-cinnamaldehyde (0.26 g, 2.0 mmol), $MgSO_4$ (0.48 g, 4.0 mmol) and PTSA (0.04 g, 0.2 mmol) in dry benzene (40 ml). After stirring for 5 h, work-up and separation by PTLC [hexane-EtOAc (4:1)] yielded, a colourless oil, *(1*S,*4*S,*6*S,*8*R*)-11,11-dimethyl-8-styryl-7,8-dioxatricyclo[4.4.0.$1^{1,4}$]undecane* (**263**) (0.42 g, 74 %), (Found: $\mathbf{M}^+$ 284.1770. $C_{19}H_{24}O_2$ requires *M*, 284.1776); $\delta_H$(400 MHz; $CDCl_3$) 0.96 and 1.36 (6H, 2 x s, 12- and 13-Me), 0.86, 1.08, 1.39, 1.74 and 2.02 (7H, 5 x m, 3-, 5- and 2-$CH_2$ and 4-H), 3.82 and 4.12 [2H, 2 x d, 10-$CH_2$ overlapping at 3.81 (1H, dd, 6-H)], 5.07 (1H, d, $J_{4,1'}$ 4.9, 8-H), 6.22 (1H, dd, $J_{4,1'}$ 4.9 and $J_{1',2'}$ 16.1, 1'-H), 6.78 (1H, d, $J_{1',2'}$ 16.1, 2'-H) and 7.22-7.43 (5H, m, Ar-H); $\delta_C$(100 MHz; $CDCl_3$) 20.0 and 21.9 (C-12 and C-13), 26.8, 28.8 and 37.0 (C-2, C-3 and C-5), 44.9 (C-4), 45.0 and 45.6 (C-1 and C-11), 67.2 (C-10), 82.4 (C-6), 99.1 (C-8), 125.8 (C-1'), 126.5, 127.7, 128.2 and 136.0 (Ar-C) and 132.7 (C-2').

## 3.2.4 Asymmetric Reactions

### 3.2.4.1 *Epoxidations with MCPBA*

#### 3.2.4.1.1 *Epoxidation of cinnamaldehyde diethyl tartrate acetal* (176)

Solid MCPBA (0.67 g, 3.9 mmol) was slowly added to a stirred mixture of diethyl tartrate acetal (**176**) (0.32 g, 1.0 mmol) and $NaHCO_3$ (0.33 g, 3.9 mmol) in $CH_2Cl_2$ (40 ml) and the resultant mixture was boiled under reflux for 6 h. The cooled reaction mixture was washed sequentially with 1 M NaOH (30 ml) and $H_2O$ (30 ml), dried ($Na_2SO_4$), filtered and concentrated in vacuo to afford, as a yellow oil, a diastereomeric mixture (8 % d.e. by $^1H$ and $^{13}C$ NMR) of *diethyl 2-(1,2-epoxy-2-phenylethyl)-1,3-dioxolane-4,5-dicarboxylate* (**180**) (0.32 g, 98 %), $\delta_H$(400 MHz; $CDCl_3$) 1.31 (6H, m, 2 x $COCH_2CH_3$), 3.29 (1H, m, 1'-H), 3.95/3.97 (1H, d, 2-H), 4.27 (4H, m, 2 x $CO_2CH_2CH_3$), 4.75/4.77 and 4.91/4.92 (2H, 2 x d, 4- and 5-H), 5.30/5.37 (1H, d, 2'-H) and 7.26-7.35 (5H, m, Ar-H); $\delta_C$(100 MHz; $CDCl_3$) 13.93/13.99 (2 x $CO_2CH_2CH_3$), 55.24/55.30 (C-1'), 60.48/60.71 (C-2'), 61.96/61.99 (2 x $CO_2CH_2CH_3$), 77.15/77.38 and 77.49/77.77 (C-4 and C-5), 105.52/106.16 (C-2), 125.68/125.75, 128.3, 128.4 and 135.75/135.77 (Ar-C) and 168.70/168.74 and 168.90/168.91 (2 x CO).

#### 3.2.4.1.2 *Epoxidation of cinnamaldehyde dimethyl tartrate acetal* (177)

Following the procedure described for the epoxidation of diethyl (4*S*,5*S*)-2-styryl-1,3-dioxolane-4,5-dicarboxylate (**176**), solid MCPBA (1.33 g, 7.71 mmol) was added to a stirred mixture of cinnamaldehyde dimethyl tartrate acetal (**177**) (0.58 g, 2.0 mmol) and $NaHCO_3$ (0.97 g, 11.5 mmol) in $CH_2Cl_2$ (40 ml). After boiling the mixture under reflux for 6 h, work-up afforded, as a white oil, a diastereomeric mixture (4 % d.e. by $^1H$ and $^{13}C$ NMR) of *dimethyl (4S,5S)-2-(1,2-epoxy-2-phenylethyl)-1,3-dioxolane-4,5-dicarboxylate* (**181**) (0.28 g, 46 %), $\delta_H$(400 MHz;

$CDCl_3$) 3.29 (1H, m, 1'-H), 3.81 (6H, m, 2 x $CO_2CH_3$), 3.95/3.97 (1H, d, 2'-H), 4.80/4.81 and 4.96/4.97 (2H, 2 x d, 4- and 5-H), 5.30/5.39 (1H, d, 2-H) and 7.26-7.36 (5H, m, Ar-H); $\delta_C$(100 MHz; $CDCl_3$) 52.87/52.91 (2 x $CO_2CH_3$), 55.34/55.47 (C-1'), 60.44/60.69 (C-2'), 77.14/77.32 and 77.44/77.71 (C-4 and C-5), 105.49/106.28 (C-2), 125.87/125.79, 128.5, 129.77/130.24 and 134.46/135.76 (Ar-C) and 169.18/169.21 and 169.41/169.44 (2 x CO).

#### 3.2.4.1.3 *Epoxidation of cinnamaldehyde 1,4-di-O-benzyl tartrate acetal* (178)

Following the procedure described for the epoxidation of diethyl (4*S*,5*S*)-2-styryl-1,3-dioxolane-4,5-dicarboxylate (**176**), solid MCPBA (0.33 g, 1.9 mmol) was added to a stirred mixture of cinnamaldehyde 1,4-di-*O*-benzyl tartrate acetal (**178**) (0.21 g, 0.5 mmol) and $NaHCO_3$ (0.16 g, 1.9 mmol) in $CH_2Cl_2$ (40 ml). After boiling the mixture under reflux for 6 h, work-up afforded, as a white oil, a diastereomeric mixture (12 % d.e. by $^1H$ and $^{13}C$ NMR) of *4,5-bis[(benzyloxy)methyl]-2-(1,2-epoxy-2-phenylethyl)-1,3-dioxolane* (**182**) (0.21 g, 96 %), $\delta_H$(400 MHz; $CDCl_3$) 3.17 (1H, m, 1'-H), 3.65 (4H, 2 x m, 2 x $CH_2OCH_2Ph$), 3.87/3.93 (1H, m, 2'-H), 4.17 (2H, m, 4- and 5-H), 4.59 (4H, s, 2 x $CH_2OCH_2Ph$), 5.15 (1H, m, 2-H) and 7.26-7.35 (Ar-H); $\delta_C$(100 MHz; $CDCl_3$) 55.17/55.52 (C-1'), 61.32/61.34 (C-2'), 69.93/69.98 and 70.24 (2 x $CH_2OCH_2Ph$), 77.95/78.03 and 78.06/ 78.12 (C-4 and C-5), 103.2 (C-2), 125.8, 127.60/127.64, 127.68, 128.3, 128.38/128.40, 128.4, 128.5, 136.22/136.25, 137.8 and 137.82/137.86 (Ar-C).

#### 3.2.4.1.4 *Epoxidation of (Z)-α-methylcinnamaldehyde diethyl tartrate acetal* (179)

Following the procedure described for the epoxidation of diethyl (4*S*,5*S*)-2-styryl-1,3-dioxolane-4,5-dicarboxylate (**176**), solid MCPBA (0.66 g, 3.9 mmol) was added

to a stirred mixture of α-methylcinnamaldehyde diethyl tartrate acetal (**179**) (0.33 g, 1.0 mmol) and $NaHCO_3$ (0.17 g, 1.9 mmol) in $CH_2Cl_2$ (40 ml). After boiling under reflux for 6 h, work-up afforded, as a white oil, a diastereomeric mixture (12 % d.e.) of *diethyl 2-(1,2-epoxy-1-methyl-2-phenylethyl)-1,3-dioxolane-4,5-dicarboxylate* (**183**) (0.31 g, 88 %), $\delta_H$(400 MHz; $CDCl_3$) 1.13/1.15 (3H, s, 1'-Me), 1.32 (6H, m, 2 x $CO_2CH_2CH_3$), 4.18/4.20 (1H, s, 2'-H), 4.28 (4H, m, 2 x $CO_2CH_2CH_3$), 4.73 and 4.94 (2H, 2 x m, 4- and 5-H), 5.23/5.28 (1H, s, 2-H) and 7.27-7.33 (5H, m, Ar-H); $\delta_C$(100 MHz; $CDCl_3$) 10.62/10.72 [C(1')Me], 14.05/14.10 (2 x $CO_2CH_2CH_3$), 59.94/60.18 (C-1'), 61.95/62.03 (2 x $CO_2CH_2CH_3$), 62.16/62.22 (C-2'), 77.25/77.32 and 77.78/77.82 (C-4 and C-5), 107.87/108.26 (C-2). 126.6, 128.0, 129.76/130.23, 134.45/134.74 and 134.77/135.15 (Ar-C) and 168.45/168.72 and 169.28/169.30 (2 x CO).

### 3.2.4.1.5 *Epoxidation of* trans-*cinnamaldehyde bornane acetal* (196)

Following the procedure described for the epoxidation of diethyl (4*S*,5*S*)-2-styryl-1,3-dioxolane-4,5-dicarboxylate (**176**), solid MCPBA (0.44 g, 2.6 mmol) was added to a stirred mixture of *trans*-cinnamaldehyde bornane acetal (**196**) (0.28 g, 1.0 mmol) and $NaHCO_3$ (0.17 g, 1.9 mmol) in $CH_2Cl_2$ (40 ml). After boiling under reflux for 6 h, work-up afforded, as a colourless oil, a diastereomeric mixture (0 % d.e.) of *8-(1,2-epoxy-2-phenylethyl)-2,10,10-trimethyl-7,9-dioxatricyclo[4.3.0.1$^{2,5}$]decane* (**227**) (0.24 g, 79 %), $\delta_H$(400 MHz; $CDCl_3$) 0.82, 1.00/1.03 and 1.13/1.14 (9H, 3 x s, 11-, 12- and 13-Me), 0.88, 1.45 and 1.70 (4H, 3 x m, 3- and 4-$CH_2$), 2.00/2.04 (1H, d, 5-H), 3.22 (1H, m, 1'-H), 3.84 and 4.02 (2H, 2 x m, 1- and 6-H), 3.94 (1H, d, 2'-H), 4.57 (1H, m, 8-H) and 7.22-7.41 (5H, m, Ar-H); $\delta_C$(100 MHz; $CDCl_3$) 11.0, 20.2/20.3 and 22.5 (C-11, C-12 and C-13), 23.3/23.4 and 31.7/31.8 (C-3 and C-4), 46.2 and 47.4 (C-2 and C-10), 47.6 (C-5), 55.6 (C-2'), 59.9 (C-1'), 84.0 and 88.2 (C-1 and C-6), 102.4/ 102.5 (C-8) and 125.7/125.8, 128.4,

128.5 and 138.2 (Ar-C).

### 3.2.4.2 *Epoxidations with MMPP*

For conditions of attempted epoxidations with MMPP see **Table 13** (Section 2.2.1.3 p.66).

### 3.2.4.2 *Asymmetric Cyclopropanation*

#### 3.2.4.2.1 *Cyclopropanation of cinnamaldehyde bornane acetal* (196)

**Method 1**: To a vigorously stirred solution of *trans*-cinnamaldehyde bornane acetal (**196**) (0.28 g, 1.0 mmol) in dry hexane (10 ml), at -20°C and under a nitrogen atmosphere, was added a solution of diethylzinc (5.0 ml of a 1 **M** hexane solution, 5.0 mmol) followed by the *slow*, dropwise addition of methylene iodide (0.86 ml, 10 mmol) and the resultant mixture stirred for 4 h and for a further 4 h at 0°C. The mixture was poured into cold sat. aq. $NH_4Cl$ (100 ml), extracted with ether (4 x 50 ml) and the combined ethereal extracts were washed with sat. aq. $Na_2S_2O_3$ (100 ml) and $H_2O$ (100 ml), dried ($Na_2SO_4$) and concentrated *in vacuo*. HPLC [hexane-EtOAc (9:1)] of the residue afforded, as a colourless oil, a diastereomeric mixture (60 % d.e. by $^1H$ and $^{13}C$ NMR) of *2,10,10-trimethyl-8-(2-phenylcyclopropyl)-7,9-dioxatricyclo[4.3.0.1$^{2,5}$]decane* (**208**) (0.59 g, 20 %), (Found: $\mathbf{M}^+$ 298.1924. $C_{20}H_{26}O_2$ requires *M*, 298.1933); $\delta_H$(400 MHz; $CDCl_3$) 0.82, 1.00 and 1.19 (9H, 3 x s, 11-, 12- and 13-Me), 0.87, 1.46 and 1.72 (5 H, 3 x m, 3- and 4-$CH_2$ and 1'-H), 1.06 (2H, m, 3'-$CH_2$), 2.00 [1H, d, 5-H overlapping m (2'-H)], 3.78 and 3.94 (2H, 2 x d, 1- and 6-H), 4.28 (1H, d, 8-H) and 7.08-7.27 (5H, m, Ar-H); $\delta_C$(100 MHz; $CDCl_3$) 11.04/11.12, 20.3 and 22.5 (C-11, C-12 and C-13), 12.16/12.38 (C-3'), 20.2 (C-2'), 23.22/23.26 (C-1'), 23.5 and 31.9 (C-3 and C-4), 46.2 (C-5), 47.4 and 47.5 (C-2 and C-10), 83.5 and 87.9 (C-1 and C-6), 106.7 (C-8) and 125.7, 126.17/126.21, 128.3 and 141.7 (Ar-C); *m/z* 298 ($\mathbf{M}^+$, 0.8 %) and 93 (100).

**Method 2**: To a vigorously stirred solution of diethylzinc (5.0 ml of a 1 **M** hexane solution, 5.0 mmol) was *slowly* added, dropwise, methylene iodide (0.86 ml, 10 mmol) at -10°C, under a nitrogen atmosphere. A solution of *trans*-cinnamaldehyde bornane acetal (**196**) (0.28 g, 1.0 mmol) in dry $CH_2Cl_2$ (10 ml) was added and the

resultant mixture was stirred for 30 min at -10°C, warmed to room temperature over 1.5 h and poured into sat. aq. $NH_4Cl$ (100 ml) and extracted with ether (2 x 50 ml). The combined ethereal extracts were washed with sat. aq. $Na_2S_2O_3$ (50 ml) and $H_2O$ (50 ml), dried ($Na_2SO_4$) and concentrated *in vacuo*. PTLC [hexane-$CH_2Cl_2$ (60:40)] of the residue afforded, as a colourless oil, a diastereomeric mixture (66 % d.e. by $^1H$ and $^{13}C$ NMR) of *2,10,10-trimethyl-8-(2-phenylcyclopropyl)-7,9-dioxatricyclo[4.3.0.1$^{2,5}$]decane* (**208**) (0.22 g, 74 %).

**Attempt 1**:[135] To a stirred suspension of freshly prepared Zn-Cu couple[❂] (0.55 g) in dry ether (20 ml) was added an iodine crystal and the mixture boiled under reflux for 30 min. The mixture was cooled and a solution of *trans*-cinnamaldehyde bornane acetal (**196**) (0.28 g, 1 mmol) in dry ether (2 ml), was added dropwise and the mixture boiled under reflux for 30 min. After cooling to 0°C, $H_2O$ (1 ml) was added and the reaction mixture stirred for 30 min at room temperature after which the grey/black precipitate was removed by filtration and washed with ether (20 ml). The filtrate was washed sequentially with sat. aq. $NH_4Cl$ (20 ml), sat. aq. $Na_2CO_3$ (20 ml) and sat. aq. NaCl (20 ml), dried ($MgSO_4$) and concentrated *in vacuo*. $^1H$ NMR spectroscopy of the crude reaction mixture showed the presence of unreacted *trans*-cinnamaldehyde bornane acetal (**196**).

**Attempt 2**:[136] A stirred suspension of zinc dust (0.85 g, 13 mmol) and cuprous chloride (1.3 g, 13 mmol) in dry ether (20 ml) were boiled under reflux for 30 min, under a nitrogen atmosphere. The suspension was cooled and a solution of *trans*-cinnamaldehyde bornane acetal (**196**) (1.4 g, 5.0 mmol) in dry ether (5 ml) added and methylene iodide (1.7 g, 6.5 mmol) and the resultant mixture boiled under reflux

[❂] Zn-Cu couple was prepared according to the method of Shank and Shechter[135] immediately before use.

for 24 h. After cooling to 0°C, $H_2O$ (1 ml) was added and the reaction mixture stirred for 30 min at room temperature and the grey/black precipitate was removed by filtration and washed with ether (20 ml). The filtrate was washed sequentially with sat. aq. $NH_4Cl$ (20 ml), sat. aq. $Na_2CO_3$ (20 ml) and sat. aq. NaCl (20 ml), dried ($MgSO_4$) and concentrated *in vacuo*. $^1H$ NMR spectroscopy revealed none of the desired product.

#### 3.2.4.2.2 *Cyclopropanation of acrolein bornane acetal* (193)

Following the procedure (method 2) described for the synthesis of 2,10,10-trimethyl-8-(2-phenylcyclopropyl)-7,9-dioxatricyclo[4.3.0.$1^{2,5}$]decane (**208**), methylene iodide (0.86 ml, 10 mmol) was added *slowly*, dropwise, under nitrogen to a vigorously stirred solution of diethylzinc (5.0 ml of a 1 **M** hexane solution, 5.0 mmol) at -10°C and a solution of acrolein bornane acetal (**193**) (0.21 g, 1.0 mmol) in $CH_2Cl_2$ (10 ml) added to the resultant mixture. Work-up and PTLC [hexane-EtOAc (9:1)] afforded, as a colourless oil, an inseparable mixture (1:1 by $^1H$ NMR), of (1*S*,2*R*,5*S*,6*R*,8*R*)-2,10,10-trimethyl-8-vinyl-7,9-dioxatricyclo[4.3.0.$1^{2,5}$]decane (**193**) (0.092 g, 44 %); and

*2,10,10-trimethyl-8-cyclopropyl-7,9-dioxatricyclo[4.3.0.$1^{2,5}$]decane* (**205**) (0.092 g, 41 %), $\delta_H$(400 MHz; $CDCl_3$) 0.35 and 0.58 (4H, 2 x m, 2'- and 3'-$CH_2$), 0.77, 0.96 and 1.15 (9H, 3 x s, 11-, 12- and 13-Me), 1.10 (1H, m, 1'-H), 0.83, 1.40 and 1.66 (4H, m, 3- and 4-$CH_2$),[†] 1.95 (1H, d, 5-H),[†] 3.70 and 3.86 (2H, 2 x d, 1- and 6-H) and 3.90 (1H, d, 8-H); $\delta_C$(100 MHz; $CDCl_3$) 1.6 and 2.0 (C-2' and C-3'), 11.1, 20.0 and 22.5 (C-11, C-12 and C-13), 11.8 (C-1'), 23.4 and 31.9 (C-3 and C-4), 46.1 and 47.3 (C-2 and C-10), 47.5 (C-5) and 108.5 (C-8).

[†] Signal overlaps corresponding signal for the starting material.

### 3.2.4.2.3 *Cyclopropanation of crotonaldehyde bornane acetal* (194)

Following the procedure (method 2) described for the synthesis of 2,10,10-trimethyl-8-(2-phenylcyclopropyl)-7,9-dioxatricyclo[4.3.0.$1^{2,5}$]decane (**208**), methylene iodide (0.86 ml, 10 mmol) was added *slowly*, dropwise, under $N_2$ to a vigorously stirred solution of diethylzinc (5.0 ml of a 1 M hexane solution, 5.0 mmol) at -10°C and a solution of *trans*-crotonaldehyde bornane acetal (**194**) (0.22 g, 1.0 mmol) in $CH_2Cl_2$ (10 ml) added to the resultant mixture. Work-up and PTLC [hexane-EtOAc (4:1)] afforded, as a colourless oil, a diastereomeric mixture (62 % d.e. by $^1H$ and $^{13}C$ NMR) of *2,10,10-trimethyl-8-(2-methylcyclopropyl)-7,9-dioxatricyclo[4.3.0.$1^{2,5}$]decane* (**206**) (0.17 g, 72 %), $\delta_H$(400 MHz; $CDCl_3$) 0.32 and 0.50 (2H, 2 x m, 3'-$CH_2$), 0.77, 0.97 and 1.14 (9H, 3 x s, 11-, 12- and 13-Me), 0.80, 1.38 and 1.66 (6H, 3 x m, 3- and 4-$CH_2$ and 1'- and 2'-H), 1.03 (3H, d, 2'-Me), 1.93 (1H, d, 5-H), 3.68 and 3.83 (2H, 2 x d, 1- and 6-H) and 3.96 (1H, d, 8-H); $\delta_C$(100 MHz; $CDCl_3$) 9.79/9.92 (C-3'), 10.2 [C(2')Me], 11.0 and 18.0 (C-1' and C-2'), 20.03/20.08, 20.2 and 22.5 (C-11, C-12 and C-13), 23.4 and 31.82/31.88 (C-3 and C-4), 46.1 and 47.29/47.32 (C-2 and C-10), 47.4 (C-5), 83.19/83.48 and 87.52/87.79 (C-1 and C-6) and 107.7 (C-4).

### 3.2.4.2.4 *Cyclopropanation of* trans-*2-hexenal bornane acetal* (195)

Following the procedure (method 2) described for the synthesis of 2,10,10-trimethyl-8-(2-phenylcyclopropyl)-7,9-dioxatricyclo[4.3.0.$1^{2,5}$]decane (**208**), methylene iodide (0.86 ml, 10 mmol) was added *slowly*, dropwise, under $N_2$ to a vigorously stirred solution of diethylzinc (5.0 ml of a 1 M hexane solution, 5.0 mmol) at -10°C and a solution of *trans*-2-hexenal bornane acetal (**195**) (0.25 g, 1.0 mmol) in $CH_2Cl_2$ (10 ml) added to the resultant mixture. Work-up afforded, as a yellow oil, a diastereomeric mixture (70 % d.e. by $^1H$ and $^{13}C$ NMR) of *2,10,10-trimethyl-8-(2-propylcyclopropyl)-7,9-dioxatricyclo[4.3.0.$1^{2,5}$]decane* (**207**) (0.22 g, 84 %),

(Found: $\mathbf{M}^+$ 264.2078. Calc. For $C_{17}H_{28}O_2S$ requires *M*, 264.2089);$\delta_H$(400 MHz; $CDCl_3$) 0.31 and 0.47 (2H, 2 x m, 3'-$CH_2$), 0.73, 0.93 and 1.10 (9H, 3 x s, 11-, 12- and 13-Me), 0.77, 1.18, 1.33 and 1.62 (13H, 4 x m, 3- and 4-$CH_2$, 1'- and 2'-H, 2'-$CH_2CH_2CH_3$, 2'-$CH_2CH_2CH_3$ and 2'-$CH_2CH_2CH_3$ ), 1.89 (1H, d, 5-H), 3.64 and 3.80 (2H, 2 x d, 1- and 6-H) and 3.96 (1H, d, 8-H); $\delta_C$(100 MHz; $CDCl_3$) 8.67/8.98 (C-3'), 10.89/11.00, 20.0 and 22.4 (C-11, C-12 and C-13), 13.65/ 13.72 [C(2')-$CH_2CH_2CH_3$], 15.42/15.52 and 19.01/19.08 (C-1' and C-2'), 22.3 [C(2')-$CH_2CH_2CH_3$], 23.3 and 31.77/ 31.84 (C-3 and C-4), 35.3 [C(2')-$CH_2CH_2CH_3$], 46.0 and 47.2 (C-2 and C-10), 47.4 (C-5), 83.22/83.37 and 87.48/87.55 (C-1 and C-6) and 107.6 (C-8); *m/z* 264 ($\mathbf{M}^+$, 8 %) and 55 (100).

### 3.2.4.2.5 *Cyclopropanation of (Z)-α-methylcinnamaldehyde bornane acetal* (197)

Following the procedure (method 2) described for the synthesis of 2,10,10-trimethyl-8-(2-phenylcyclopropyl)-7,9-dioxatricyclo[4.3.0.$1^{2,5}$]decane (**208**), methylene iodide (0.86 ml, 10 mmol) was added *slowly*, dropwise, under $N_2$ to a vigorously stirred solution of diethylzinc (5.0 ml of a 1 **M** hexane solution, 5.0 mmol) at -10°C and a solution of α-methylcinnamaldehyde bornane acetal (**197**) (0.30 g, 1.0 mmol) in $CH_2Cl_2$ (10 ml) added to the resultant mixture. Work-up and PTLC [hexane-EtOAc (9:1)] afforded, as a colourless oil, an inseparable mixture (1:2 by $^1$H NMR) of (1*S*,2*R*,5*S*,6*R*,8*R*)-2,10,10-trimethyl-8-(1-methylstyryl)-7,9-dioxatricyclo[4.3.0.$1^{2,5}$]decane (**197**) (0.091 g, 31 %); and a diastereomeric mixture (46 % d.e. by $^1$H and $^{13}$C NMR) of *2,10,10-trimethyl-8-(1-methyl-2-phenylcyclopropyl)-7,9-dioxatricyclo[4.3.0.$1^{2,5}$]decane* (**209**) (0.18 g, 58 %), $\delta_H$(400 MHz; $CDCl_3$) 0.87, 0.93 and 1.06 (9H, 3 x s, 11-, 12- and 13-Me), 0.94, 1.50 and 1.76 (4H, 3 x m, 3- and 4-$CH_2$),† 0.86 and 1.25 (2H, 2 x m, 3'-$CH_2$), 1.31/1.32 (3H, s, 1'-Me), 2.05 (1H, d, 5-H), 2.50 (1H, m, 2'-H), 3.79 and 3.97 (2H, 2

x d, 1- and 6-H), 4.59/4.64 (1H, s, 8-H) and 7.19-7.38 (5H, m, Ar-H);† $\delta_C$(100 MHz; $CDCl_3$) 10.97/11.02 [C(1')Me], 14.35/14.38 (C-3'), 15.10/15.31 and 22.81/22.88 (C-1' and C-2'), 21.03/21.08, 22.5 and 24.99/25.08 (C-11, C-12 and C-13), 23.60/23.67 and 32.11/32.14 (C-3 and C-4), 46.04/46.06 (C-5), 47.3 and 47.35/47.38 (C-2 and C-10), 83.6 and 87.6 (C-1 and C-6), 106.09/106.40 (C-8) and 125.8,-127.83/127.88, 129.13/129.14 and 138.56/138.64 (Ar-C).

### 3.2.4.2.6 *Cyclopropanation of* trans-*cinnamaldehyde bornane-10-sulfonate acetal* (**201**)

To a vigorously stirred solution of *trans*-cinnamaldehyde bornane-10-sulfonate acetal (**201**) (0.44 g, 1.0 mmol) in dry $CH_2Cl_2$ (10 ml), at -18 °C and under $N_2$, was added a solution of diethylzinc (5.0 ml of a 1 M hexane solution, 5.0 mmol) followed by the *slow*, dropwise addition of methylene iodide (0.86 ml, 10 mmol) and the resultant mixture was placed in an ice bath and stirred for 1.5 h and allowed to warm to room temperature over 4 h. The mixture was poured into cold sat. aq. $NH_4Cl$ (100 ml), stirred for 10 min and the organic layer isolated, washed with sat. aq. $Na_2S_2O_3$ (50 ml) and sat. aq. NaCl (50 ml), dried ($Na_2SO_4$) and concentrated *in vacuo*. PTLC [hexane-EtOAc (9:1)] of the residue afforded, as a colourless oil, *phenyl {10,10-dimethyl-8-(2-phenylcyclopropyl)-7,9-dioxatricyclo[4.3.0.$1^{2,5}$]dec-2-yl}methanesulfonate* (**213**) (0.43 g, 95 %), (Found: $\mathbf{M}^+$ 454.1808. $C_{26}H_{30}O_5S$ requires *M*, 454.1813); $\delta_H$(400 MHz; $CDCl_3$) 0.90 and 1.26 (3H, 2 x s, 11- and 12-Me), 1.06, 1.51, 1.81 and 1.92 (7H, 4 x m, 3-, 4- and 3'-$CH_2$ and 1'-H), 2.05 (1H, m, 2'-H), 2.10 (1H, d, 5-H), 3.18 and 3.82 (2H, 2 x d, 13-$CH_2$), 4.04 and 4.38 (2H, 2 x d, 1- and 6-H overlapping at 4.38, d, 8-H) and 7.09-7.43 (10H, m, Ar-H); $\delta_C$(100 MHz; $CDCl_3$) 12.1 (C-3'), 20.0 and 22.5 (C-11 and C-12), 20.1 (C-2'), 22.9 (C-1'), 23.1 and 27.7 (C-3 and C-4), 46.6 (C-5), 47.6 and 48.7 (C-2 and C-10), 49.2 (C-13), 83.1 and 83.6 (C-1 and C-6), 107.0 (C-8) and 121.9, 125.8, 126.1, 126.8, 128.2, 129.7, 141.3 and

149.3 (Ar-C); *m/z* 454 ($\mathbf{M}^+$, 1.7 %) and 91 (100).

### 3.2.4.2.7 *Cyclopropanation of acrolein bornane-10-sulfonate acetal* (198)

Following the procedure described for the synthesis of phenyl {10,10-dimethyl-8-(2-phenylcyclopropyl)-7,9-dioxatricyclo[4.3.0.$1^{2,5}$]dec-2-yl}methanesulfonate (**213**), a solution of diethylzinc (5.0 ml of a 1 **M** hexane solution, 5.0 mmol) was added, under $N_2$, to a solution of acrolein bornane-10-sulfonate acetal (**198**) (0.25 g, 0.69 mmol) in $CH_2Cl_2$ (10ml) at -10°C, followed by the *slow*, dropwise addition of $CH_2I_2$ (0.86 ml, 10 mmol). Work-up and PTLC [hexane-EtOAc (4:1)] afforded, as a colourless oil, a mixture (1.6:1) of phenyl {(1*S*,2*S*,5*S*,6*R*,8*R*)-10,10-dimethyl-8-vinyl-7,9-dioxatricyclo[4.3.0.$1^{2,5}$]dec-2-yl}methanesulfonate (**198**) (0.12 g, 48 %); and

*phenyl {8-cyclopropyl-10,10-dimethyl-7,9-dioxatricyclo[4.3.0.$1^{2,5}$]dec-2-yl}methanesulfonate* (**210**) (0.074 g, 28 %), (Found: $\mathbf{M}^+$ 378.1490. $C_{20}H_{26}O_5S$ requires *M*, 378.1495); $\delta_H$(400 MHz; $CDCl_3$) 0.39 and 0.62 (4H, 2 x m, 2'- and 3'-$CH_2$), 0.86 and 1.16 (6H, 2 x s, 11- and 12-Me),† 1.00, 1.22, 1.80 and 1.87 (4H, 4 x m, 3- and 4-$CH_2$ and 1'-H),† 2.07 (1H, d, 5-H),† 3.17 and 3.79 (2H, 2 x d, 13-$CH_2$),† 3.98 and 4.28 (2H, 2 x d, 1- and 6-$CH_2$), 4.02 (1H, 2 x d, 8-H) and 7.25-7.40 (5H, m, Ar-H);† $\delta_C$(100 MHz; $CDCl_3$) 1.8 and 2.0 (C-2' and C-3'), 11.7 (C-1'), 19.9 and 22.6 (C-11 and C-12), 23.1 and 27.8 (C-3 and C-4), 46.6 (C-5), 47.6 and 48.7 (C-2 and C-10), 49.7 (C-13), 83.1 and 83.6 (C-1 and C-6), 108.6 (C-8), and 121.9, 126.9, 129.7 and 149.2 (Ar-C); *m/z* 378 ($\mathbf{M}^+$, 8.9 %) and 149 (100).

### 3.2.4.2.8 *Cyclopropanation of* trans-*crotonaldehyde bornane-10-sulfonate acetal* (199)

Following the procedure described for the synthesis of phenyl {10,10-dimethyl-8-(2-phenylcyclopropyl)-7,9-dioxatricyclo[4.3.0.$1^{2,5}$]dec-2-yl}methanesulfonate (**213**), a

solution of diethylzinc (5.0 ml of a 1 M hexane solution, 5.0 mmol) was added, under $N_2$, to a solution of *trans*-crotonaldehyde bornane-10-sulfonate acetal (**199**) (0.38 g, 1.0 mmol) in $CH_2Cl_2$ (10ml) at -10°C, followed by the *slow*, dropwise addition of $CH_2I_2$ (0.86 ml, 10 mmol). Work-up and PTLC [hexane-EtOAc (4:1)] afforded, as a colourless oil, *phenyl {10,10-dimethyl-8-(2-methylcyclopropyl)-7,9-dioxatricyclo[4.3.0.1$^{2,5}$]dec-2-yl}methanesulfonate* (**211**) (0.31 g, 80 %), (Found: **M**$^+$ 392.1670. $C_{21}H_{28}O_5S$ requires *M*, 392.1657); $\delta_H$(400 MHz; $CDCl_3$) 0.34 and 0.53 (2H, 2 x m, 3'-$CH_2$), 0.81 (2H, m, 1'- and 2'-H), 0.85 and 1.20 (6H, 2 x s, 11- and 12-Me), 0.96, 1.40, 1.75 and 1.85 (4H, m, 3- and 4-$CH_2$), 1.04 (3H, d, 2'-Me), 2.02 (1H, d, 5-H), 3.15 and 3.80 (2H, 2 x d, 13-$CH_2$), 3.93 and 4.25 (2H, 2 x d, 1- and 6-H), 4.05 (1H, d, 8-H) and 7.26-7.39 (5H, m, Ar-H); $\delta_C$(100 MHz; $CDCl_3$) 9.9 (C-3'), 10.1 (C-1'), 17.9 [C(2')Me], 19.9 (C-2'), 20.0 and 22.5 (C-11 and C-12), 23.1 and 27.7 (C-3 and C-4), 46.5 (C-5), 47.5 and 48.7 (C-2 and C-10), 49.3 (C-13), 82.9 and 83.5 (C-1 and C-6), 107.9 (C-8) and 121.9, 126.8, 129.6 and 149.3 (Ar-C); *m/z* 392 (**M**$^+$, 0.5 %) and 41 (100).

### 3.2.4.2.9 *Cyclopropanation of* trans*-2-hexenal bornane-10-sulfonate acetal* (200)

Following the procedure described for the synthesis of phenyl {10,10-dimethyl-8-(2-phenylcyclopropyl)-7,9-dioxatricyclo[4.3.0.1$^{2,5}$]dec-2-yl}methanesulfonate (**213**), a solution of diethylzinc (5.0 ml of a 1 M hexane solution, 5.0 mmol) was added, under $N_2$, to a solution of *trans*-2-hexenal bornane-10-sulfonate acetal (**200**) (0.39 g, 0.95 mmol) in $CH_2Cl_2$ (10ml) at 0°C, followed by the *slow*, dropwise addition of $CH_2I_2$ (0.86 ml, 10 mmol). Work-up and PTLC [hexane-EtOAc (95:5)] afforded, as a yellow oil, *phenyl {10,10-dimethyl-8-(2-propylcyclopropyl)-7,9-dioxatricyclo[4.3.0.1$^{2,5}$]dec-2-yl}methanesulfonate* (**212**) (0.30 g, 76 %), (Found: **M**$^+$ 420.1979. $C_{23}H_{32}O_5S$ requires *M*, 420.1969); $\delta_H$(400 MHz; $CDCl_3$) 0.38 and 0.53

(2H, 2 x m, 3'-$CH_2$), 0.83 (2H, m, 1'- and 2'-H), 0.86 and 1.21 (6H, 2 x s, 11- and 12-Me overlapping at 1.21, m, 2'-C*H*$_2$CH$_2$CH$_3$), 0.90 (3H, t, 2'-$CH_2CH_2CH_3$ ), 0.97, 1.38, 1.76 and 1.88 (4H, 4 x m, 3- and 4-$CH_2$ overlapping at 1.38, m, 2'-$CH_2CH_2CH_3$), 2.04 (1H, d, 5-H), 3.16 and 3.79 (2H, 2 x d, 13-$CH_2$), 3.95 and 4.24 (2H, 2 x d, 1- and 6-H), 4.08 (1H, d, 8-H) and 7.25-7.39 (5H, m, Ar-H); $\delta_C$(100 MHz; $CDCl_3$) 8.8 (C-3'), 13.6 [C(2')-$CH_2CH_2CH_3$], 15.6 and 18.9 (C-1' and C-2'), 19.0 and 22.6 (C-11 and C-12), 22.2 [C(2')-$CH_2CH_2CH_3$], 23.1 and 27.6 (C-3 and C-4), 35.2 [C(2')-$CH_2CH_2CH_3$], 46.6 (C-5), 47.5 and 48.6 (C-2 and C-10), 49.2 (C-13), 83.0 and 83.4 (C-1 and C-6), 107.8 (C-8) and 121.9, 126.8, 129.6 and 149.3 (Ar-C); *m/z* 420 (**M**$^+$, 1.5 %) and 133 (100).

### 3.2.4.2.10 *Cyclopropanation of* trans-*crotonaldehyde pinane acetal* (249)

Following the procedure described for the synthesis of phenyl {10,10-dimethyl-8-(2-phenylcyclopropyl)-7,9-dioxatricyclo[4.3.0.$1^{2,5}$]dec-2-yl}methanesulfonate (**213**), a solution of diethylzinc (5.0 ml of a 1 M hexane solution, 5.0 mmol) was added, under $N_2$, to a solution of *trans*-crotonaldehyde pinane acetal (**249**) (0.2 g, 0.9 mmol) in $CH_2Cl_2$ (10ml) at -10°C, followed by the *slow*, dropwise addition of $CH_2I_2$ (0.86 ml, 10 mmol). Work-up and PTLC [hexane-EtOAc (95:5)] afforded, as a colourless oil, a diastereomeric mixture (20 % d.e. by $^1$H and $^{13}$C NMR) of *1,10,10-trimethyl-8-(2-methylcyclopropyl)-7,9-dioxatricyclo[4.3.0.$1^{2,4}$]decane* (**253**) (0.15 g, 71 %), $\delta_H$(400 MHz; $CDCl_3$) 0.31 and 0.55 (2H, 2 x m, 3'-$CH_2$), 0.77, 1.03, 1.23 and 1.28 (12H, 4 x m, 11-, 12-, 13- and 2'-Me overlapping at 0.77 and 1.03, 2 x m, 1'- and 2'-H), 1.64, 1.87, 1.99 and 2.07 (6H, 4 x m, 2- and 4-H and 3- and 5-$CH_2$), 3.82 (1H, m, 6-H) and 4.66 (1H, m, 8-H); $\delta_C$(100 MHz; $CDCl_3$) 9.54/9.59 (C-3'), 15.0 and 19.8 (C-1' and C-2'), 18.10/18.13, 23.9, 25.5 and 27.2 (C-11, C-12, C-13 and C(2')$CH_3$), 25.0 and 32.7 (C-3 and C-5), 37.7 and 82.94/83.21 (C-1 and C-10), 39.9 and 50.69/50.73 (C-2 and C-4), 76.66/76.93 (C-6) and 103.95/103.99 (C-8).

### 3.2.4.2.11 *Cyclopropanation of* trans-*2-hexenal pinane acetal* (250)

Following the procedure described for the synthesis of phenyl {10,10-dimethyl-8-(2-phenylcyclopropyl)-7,9-dioxatricyclo[4.3.0.$1^{2,5}$]dec-2-yl}methanesulfonate (**213**), a solution of diethylzinc (5.0 ml of a 1 **M** hexane solution, 5.0 mmol) was added, under $N_2$, to a solution of *trans*-2-hexenal pinane acetal (**250**) (0.31 g, 1.2 mmol) in $CH_2Cl_2$ (10ml) at -10°C, followed by the *slow*, dropwise addition of $CH_2I_2$ (0.86 ml, 10 mmol). Work-up and PTLC [hexane-EtOAc (95:5)] afforded, as a colourless oil, a diastereomeric mixture (30 % d.e. by $^1H$ and $^{13}C$ NMR) of *1,10,10-trimethyl-8-(2-propylcyclopropyl)-7,9-dioxatricyclo[4.3.0.$1^{2,4}$]decane* (**253**) (0.24 g, 73 %), $\delta_H$(400 MHz; $CDCl_3$) 0.30 and 0.56 (2H, 2 x m, 3'-$CH_2$), 0.77, 1.23 and 1.27 (9H, 3 x s, 11-, 12- and 13-Me), 0.87, 1.03 and 1.33 (9H, 3 x m, 1'- and 2'-H, 2'-C*H*$_2$CH$_2$CH$_3$, 2'-CH$_2$C*H*$_2$CH$_3$ and 2'-CH$_2$CH$_2$C*H*$_3$), 1.63, 1.87, 1.97 and 2.06 (6H, 4 x m, 2- and 4-H and 3- and 5-$CH_2$), 3.83 (1H, m, 6-H) and 4.37 (1H, d, 8-H); $\delta_C$(100 MHz; $CDCl_3$) 8.04/8.28 (C-3'), 14.99/15.07 [C(2)-$CH_2CH_2CH_3$], 18.1 and 19.76/19.87 (C-1' and C-2'), 22.34/22.38 [C(2)-$CH_2CH_2CH_3$], 23.9, 25.5 and 27.2 (C-11, C-12 and C-13), 25.0 and 32.69/32.74 (C-3 and C-5), 35.32/35.35 [C(2)-$CH_2CH_2CH_3$], 37.7 and 82.86/83.00 (C-1 and C-10), 39.9 and 50.7 (C-2 and C-4), 76.55/76.78 (C-6) and 103.52/103.99 (C-8); *m/z* 264 (**M**$^+$, 4.4 %) and 135 (100).

### 3.2.4.2.12 *Cyclopropanation of* trans-*cinnamaldehyde pinane acetal* (251)

Following the procedure described for the synthesis of phenyl {10,10-dimethyl-8-(2-phenylcyclopropyl)-7,9-dioxatricyclo[4.3.0.$1^{2,5}$]dec-2-yl}methanesulfonate (**213**), a solution of diethylzinc (5.0 ml of a 1 **M** hexane solution, 5.0 mmol) was added, under $N_2$, to a solution of *trans*-cinnamaldehyde pinane acetal (**251**) (0.28 g, 1.0 mmol) in $CH_2Cl_2$ (10ml) at 0°C, followed by the *slow*, dropwise addition of $CH_2I_2$ (0.86 ml, 10 mmol). Work-up and PTLC [hexane-EtOAc (95:5)] afforded, as a colourless oil, a diastereomeric mixture (24 % d.e. by $^1H$ and $^{13}C$ NMR) of *1,10,10-*

*trimethyl-8-(2-phenylcyclopropyl)-7,9-dioxatricyclo[4.3.0.1$^{2,4}$]decane* (**255**) (0.22 g, 74 %), $\delta_H$(400 MHz; $CDCl_3$) 0.85, 1.31 and 1.38 (9H, 3 x s, 11-, 12- and 13-Me), 0.90, 1.01, 1.18 and 1.52 (4H, 4 x m, 1'- and 2'-H and 3'-$CH_2$), 1.74, 1.91, 2.00 and 2.12 (6H, 4 x m, 2- and 4-H and 3- and 5-$CH_2$), 3.94 (1H, d, 6-H), 4.67/4.73 (1H, d, 8-H) and 7.09-7.28 (5H, m, Ar-H); $\delta_C$(100 MHz; $CDCl_3$) 11.6 (C-3'), 19.31/19.35 and 24.0 (C-1' and C-2'), 23.84/23.86, 24.92/24.96 and 27.1 (C-11, C-12 and C-13), 25.4 and 32.58/32.62 (C-3 and C-5), 37.6 and 83.00/83.13 (C-1 and C-10), 39.8 and 50.56/50.59 (C-2 and C-4), 76.59/76.80 (C-6), 101.85/102.33 (C-8) and 125.44/125.47, 125.86/125.91, 128.03/128.05 and 141.75/141.81 (Ar-C); *m/z* 298 (**M**$^+$, 0.90 %) and 93 (100).

### 3.2.4.2.13 *Cyclopropanation of acetal* (263)

Following the procedure described for the synthesis of phenyl {10,10-dimethyl-8-(2-phenylcyclopropyl)-7,9-dioxatricyclo[4.3.0.1$^{2,5}$]dec-2-yl}methanesulfonate (**213**), a solution of diethylzinc (5.0 ml of a 1 **M** hexane solution, 5.0 mmol) was added, under $N_2$, to a solution of acetal (**263**) (0.28 g, 1.0 mmol) in $CH_2Cl_2$ (10ml) at 0°C, followed by the *slow*, dropwise addition of $CH_2I_2$ (0.86 ml, 10 mmol). Work-up and PTLC [hexane-EtOAc (9:1)] afforded, as a colourless oil, a diastereomeric mixture (50:50 by $^1$H and $^{13}$C NMR) of *11,11-dimethyl-8-(2-phenylcyclopropyl)-7,9-dioxatricyclo[4.4.0.1$^{1,4}$]undecane* (**264**) (0.23 g, 78 %), $\delta_H$(400 MHz; $CDCl_3$) 0.84, 1.08, 1.39, 1.73 and 1.97 (6H, 5 x m, 2-, 3- and 5-$CH_2$ overlapping at 1.73, m, 4-H), 0.93 and 1.18 (2H, 2 x m, 3'-$CH_2$), 1.46 and 2.10 (2H, 2 x m, 1'- and 2'-H), 3.73 (1H, m, 6-H), 3.73 and 4.07 (2H, 2 x d, 10-$CH_2$ overlapping), 4.47/4.51 (1H, d, 8-H) and 7.09/7.28 (5H, m, Ar-H); $\delta_C$(100 MHz; $CDCl_3$) 11.41/11.54 (C-3'), 18.84/19.00 and 25.75/25.77 (C-1' and C-2'), 20.1 and 22.01/22.04 (C-12 and C-13), 26.92/26.93, 28.88/28.90 and 37.2 (C-2, C-3 and C-5), 45.1 (C-4), 45.2 and 45.7 (C-1 and C-11), 67.36/67.39 (C-10), 82.54/82.55 (C-6), 99.88/100.19 (C-8) and 125.4, 125.9, 128.1

and 142.41/142.52 (Ar-C).

### 3.2.4.3 *Hydrolysis of cyclopropyl acetals*

#### 3.2.4.3.1 *Hydrolysis of cyclopropyl acetal* (213)

An excess of PTSA (0.20 g, 1.1 mmol) was added to a stirred solution of phenyl {10,10-dimethyl-8-(2-phenylcyclopropyl)-7,9-dioxatricyclo[4.3.0.$1^{2,5}$]dec-2-yl}methanesulfonate (**213**) (0.30 g, 0.66 mmol) in a 5:1 mixture of THF-$H_2O$ (5 ml) and the resultant mixture boiled under reflux for 72 h. The cooled mixture was poured into sat. aq. $NaHCO_3$ (50 ml) and extracted with hexane (2 x 50 ml). The extracts were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo*. PTLC [hexane EtOAc (9:1)] of the residue afforded, as a yellow oil, 2-phenylcyclopropane aldehyde (0.010 g, 10 %), $[\alpha]_D^{26}$ -324° (*c*. 0.333 in $CHCl_3$)[lit.,[140] -340°(*c*. 0.363 in $CHCl_3$)]; $\delta_H$(400 MHz; $CDCl_3$) 1.52 and 1.72 (2H, 2 x m, 3-H), 2.16 (1H, 1 x m, 1-H), 2.62 (1H, 1 x m, 2-H), 7.19-7.30 (5H, m, Ar-H) and 9.32 (1H, d, CHO); $\delta_C$(100 MHz; $CDCl_3$) 16.4 (C-3), 26.6 (C-2), 33.7 (C-1), 126.8, 128.6, 128.7 and 139.0 (Ar-C) and 200.0 (CHO).

#### 3.2.4.3.2 *Attempted hydrolysis of cyclopropyl acetals*

**Attempt 1**: To a stirred solution of a diastereomeric mixture of 2,10,10-trimethyl-8-(2-phenylcyclopropyl)-7,9-dioxatricyclo[4.3.0.$1^{2,5}$]decane (**208**) (0.17 g, 0.57 mmol) was added 10 % HCl and the resultant mixture was stirred for 72 h, poured into sat. aq. $NaHCO_3$ (20 ml) and extracted with pentane (2 x 30 ml). The combined pentane layers were dried ($MgSO_4$) and concentrated *in vacuo*. $^1$H NMR spectroscopy showed the presence of 2,10,10-trimethyl-8-(2-phenylcyclopropyl)-7,9-dioxatricyclo[4.3.0.$1^{2,5}$]decane (**208**).

**Attempt 2**: Solid PTSA (0.1 g, 0.5 mmol) was added to a diastereomeric mixture of 2,10,10-trimethyl-8-(2-phenylcyclopropyl)-7,9-dioxatricyclo[4.3.0.$1^{2,5}$]decane (**208**)

(0.18 g, 0.60 mmol) in THF-$H_2O$ [5 ml; (5:1)] and the mixture refluxed for 24 h. After cooling, the mixture was poured into sat. aq. $NaHCO_3$ (20 ml) and extracted with pentane (2 x 30 ml). The combined pentane layers were dried ($MgSO_4$) and concentrated *in vacuo*. $^1H$ NMR spectroscopy showed the presence of 2,10,10-trimethyl-8-(2-phenylcyclopropyl)-7,9-dioxatricyclo[4.3.0.$1^{2,5}$]decane (**208**).

**Attempt 3**:[141] To a stirred suspension of silica gel (1.5 g,Merck Silica gel 60, 230-400 mesh) in $CH_2Cl_2$ (2 ml) was added15 % sulfuric acid (8 drops) and the mixture stirred for 5 min. A solution of phenyl {10,10-dimethyl-8-(2-phenylcyclopropyl)-7,9-dioxatricyclo[4.3.0.$1^{2,5}$]dec-2-yl}methanesulfonate (**213**) (0.454 g, 1.00 mmol) in $CH_2Cl_2$ (2 ml) was added and the reaction mixture stirred for several days after which the mixture was filtered and the solid washed with $CH_2Cl_2$ (3 x 10 ml). The combined organic filtrates were concentrated *in vacuo* and $^1H$ NMR spectroscopy revealed unreacted cyclopropyl acetal (**213**).

### 3.2.4.3.3 *Preparation of 2-(2-methylcyclopropyl)-1,3-dithiolane* (214)

Ethanedithiol (0.079 g, 0.84 mmol) was added, under $N_2$, to a stirred mixture of phenyl {10,10-dimethyl-8-(2-methylcyclopropyl)-7,9-dioxatricyclo[4.3.0.$1^{2,5}$]dec-2-yl}methanesulfonate (**211**) (0.33 g, 0.84 mmol) and PTSA (0.025 g, 0.13 mmol) in dry $CH_2Cl_2$ (10 ml) and the resultant mixture boiled under reflux for 30 min, cooled, filtered and concentrated *in vacuo*. PTLC [hexane-EtOAc (4:1)] of the residue, afforded as a colourless oil, 2-(2-methylcyclopropyl)-1,3-dithiolane (**214**) (0.117 g, 87 %), $\delta_H$(400 MHz; $CDCl_3$) 0.38 and 0.51 (2H, 2 x m, 3'-$CH_2$), 0.74 (1H, m, 2'-H), 0.91 (1H, m, 1'-H), 1.02 (3H, d, 2'-Me), 3.15 and 3.26 (4H, 2 x m, 4- and 5-$CH_2$) and 4.04 (1H, d, 2-H); $\delta_C$(100 MHz; $CDCl_3$) 14.4 (C-3'), 14.6 (C-2'), 18.3 [C(2')-Me], 27.1 (C-1'), 38.7 and 38.9 (C-4 and C-5) and 58.9 (C-2); *m/z* 160 (**M**$^+$, 12 %) and 117 (100).

### 3.2.4.3.4 *Preparation of 2-(2-propylcyclopropyl)-1,3-dithiolane* (215)

Following the procedure described for the synthesis of 2-(2-methylcyclopropyl)-1,3-dithiolane (**214**), ethanedithiol (0.047 g, 0.50 mmol) was added, under $N_2$, to a stirred mixture of phenyl {10,10-dimethyl-8-(2-propylcyclopropyl)-7,9-dioxatricyclo[4.3.0.$1^{2,5}$]dec-2-yl}methanesulfonate (**212**) (0.21 g, 0.50 mmol) and PTSA (0.015 g, 0.080 mmol) in dry $CH_2Cl_2$ and the resultant mixture boiled under reflux for 30 min, cooled, filtered and concentrated *in vacuo*. PTLC [hexane-EtOAc (4:1)] of the residue, afforded as a colourless oil, 2-(2-propylcyclopropyl)-1,3-dithiolane (**215**) (0.084 g, 89 %), $\delta_H$(400 MHz; $CDCl_3$) 0.41 and 0.50 (2H, 2 x m, 3'-$CH_2$), 0.73 (1H, m, 2'-H), 0.89 (3H, t, 2'-$CH_2CH_2CH_3$ overlapping m, 1'-H), 1.12 and 1.25 (2H, 2 x m, 2'-$CH_2CH_2CH_3$), 1.37 (2H, m, 2'-$CH_2CH_2CH_3$), 3.16 and 3.26 (4H, 2 x m, 4- and 5-$CH_2$) and 4.03 (1H, d, 2-H); $\delta_C$(100 MHz; $CDCl_3$) 13.3 (C-3'), 13.9 [C(2')$CH_2CH_2CH_3$], 20.3 (C-2'), 22.4 [C(2')$CH_2CH_2CH_3$], 25.8 (C-1'), 35.6 [C(2')$CH_2CH_2CH_3$], 38.7 and 38.8 (C-4 and C-5) and 60.0 (C-2); *m/z* 188 ($M^+$, 3.7 %) and 111 (100).

### 3.2.4.3.5 *Preparation of 2-(2-phenylcyclopropyl)-1,3-dithiolane* (216)

Following the procedure described for the synthesis of 2-(2-methylcyclopropyl)-1,3-dithiolane (**214**), ethanedithiol (0.047 g, 0.50 mmol) was added, under $N_2$, to a stirred mixture of phenyl {10,10-dimethyl-8-(2-phenylcyclopropyl)-7,9-dioxatricyclo[4.3.0.$1^{2,5}$]dec-2-yl}methanesulfonate (**213**) (0.21 g, 0.50 mmol) and PTSA (0.015 g, 0.080 mmol) in dry $CH_2Cl_2$ and the resultant mixture boiled under reflux for 30 min, cooled, filtered and concentrated *in vacuo*. PTLC [hexane-EtOAc (4:1)] of the residue, afforded as a colourless oil, 2-(2-propylcyclopropyl)-1,3-dithiolane (**216**) (0.084 g, 89 %), $\delta_H$(400 MHz; $CDCl_3$) 1.09 (2H, m, 3'-$CH_2$), 1.55 (1H, m, 2'-H), 1.99 (3H, m, 1'-H), 3.20 and 3.29 (4H, 2 x m, 4- and 5-$CH_2$) and 4.32 (1H, d, 2-H); $\delta_C$(100 MHz; $CDCl_3$) 12.3 (C-3'), 21.1 (C-2'), 23.9 (C-1'), 38.1 and

37.6 (C-4 and C-5), 62.0 (C-2) and 124.5, 126.3, 129.1 and 140.7 (Ar-C); *m/z* 222 ($\mathbf{M}^+$, 0.01 %) and 117 (100).

### 3.2.4.3.6 *Attempted hydrolysis of cyclopropyldithiolanes*

**Attempt 1**:[71] To a solution of 2-(2-propylcyclopropyl)-1,3-dithiolane (**215**) (0.080 g, 0.43 mmol) in 80 % aq. $CH_3CN$ (5 ml) was added $CaCO_3$ (0.40 g, 0.40 mmol) and MeI (150 µl; 2.40 mmol). The resultant mixture was stirred for 72 h, diluted with $CH_2Cl_2$ (10 ml) and filtered over silica gel, which was washed well with $CH_2Cl_2$ (20 ml). The solvent was removed *in vacuo* and $^1$H NMR spectroscopy of the residue showed the presence of unhydrolysed 2-(2-propylcyclopropyl)-1,3-dithiolane (**215**).

**Attempt 2**:[143] To vigorously stirred suspension of mercury(II)oxide (0.18 g, 0.85 mmol) in 15 % aq. THF (1 ml) was added $BF_3.OEt_2$ (0.12 g, 0.85 mmol) and a solution of cyclopropyl dithiolane (**216**) (0.80 g, 0.43 mmol) and the resultant mixture stirred for 30 min. The mixture was diluted with ether (5 ml), filtered and washed with sat. aq. $Na_2CO_3$ (25 ml). The organic layer was separated, dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford, as a pale yellow oil, 2-(2-propylcyclopropyl)-1,3-dithiolane (**216**).

**Attempt 3**:[144] Cyclopropyl dithiolane (**216**) (0.158 g, 0.850 mmol) was added to a stirred solution of glyoxylic acid (3.77 g, 40.9 mmol) in glacial acetic acid (30 ml) followed by the addition of conc. HCl (3.9 ml, 40.9 mmol) at room temperature and the reaction mixture stirred for 2 h. The reaction mixture was neutralised with sat. aq. $NaHCO_3$ and extracted with chloroform (3 x 20 ml). The organic layers were combined, washed with sat. aq. $NaHCO_3$ (50 ml), dried ($MgSO_4$) and concentrated *in vacuo*. $^1$H NMR showed no desired product or starting material.

### 3.2.4.4 *Asymmetric dihydroxylations*

#### 3.2.4.4.1 *Dihydroxylation of crotonaldehyde bornane acetal* (194)

To a stirred mixture of crotonaldehyde bornane acetal (**194**) (0.22 g, 1 mmol) and *N*-methylmorpholine *N*-oxide (0.23 g, 2 mmol) in *t*-BuOH/DMF 1:1 (10 ml) at -20°C was added a 0.4 M solution of $OsO_4$ (0.75 ml, 0.3 mmol; stabilized by the addition of a few drops of 30 % aq. $H_2O_2$ solution) in *t*-BuOH and the resultant mixture stirred for 6 h. The reaction was quenched by the addition of aq. sat. $NaHSO_3$ (50 ml), extracted with EtOAc (2 x 50 ml), the combined organic phases dried ($MgSO_4$) and concentrated *in vacuo* to afford, as a yellow oil, a diastereomeric mixture (18 % d.e. by $^1H$ and $^{13}C$ NMR) of *8-(1,2-dihydroxypropyl)-2,10,10-trimethyl-7,9-dioxatricyclo[4.3.0.1$^{2,5}$]decane* (**233**) (0.13 g, 52 %), $\delta_H$(400 MHz; $CDCl_3$) 0.78, 0.96/0.98 and 1.07 (9H, 3 x s, 11-, 12- and 13-Me), 1.24 (3H, d, 3'-Me), 0.83, 1.42 and 1.68 (4H, 3 x m, 3- and 4-$CH_2$), 1.97 (1H, m, 5-H), 2.54 (1H, d, 2'-OH), 2.76/2.83 (1H, d, 1'-OH), 3.53 (1H, br s, 1'-H), 3.77 and 3.95 (2H, 2 x m, 1- and 6-H overlapping at 3.95, m, 2'-H) and 4.62 (1H, m, 8-H); $\delta_C$(100 MHz; $CDCl_3$) 10.89/11.00, 20.15/20.16 and 22.5 (C-11, C-12 and C-13), 19.3 (C-3'), 23.4 and 31.81/31.86 (C-3 and C-4), 46.1 and 47.5 (C-2 and C-10), 47.4 (C-5), 67.16/67.23 (C-2'), 74.17/74.27 (C-1'), 83.51/84.20 and 87.69/88.31 (C-1 and C-6) and 103.1 (C-8).

#### 3.2.4.4.2 *Dihydroxylation of* trans-*2-hexenal bornane acetal* (195)

Following the procedure described for the synthesis of 8-(1,2-dihydroxypropyl)-2,10,10-trimethyl-7,9-dioxatricyclo[4.3.0.1$^{2,5}$]decane (**233**), a 0.4 M solution of $OsO_4$ (0.75 ml, 0.3 mmol) in *t*-BuOH was added to a mixture of *trans*-2-hexenal bornane acetal (**195**) (0.25 g, 1 mmol) and *N*-methylmorpholine *N*-oxide (0.23 g, 2 mmol) in *t*-BuOH/DMF 1:1 (10 ml). Work-up afforded, as a yellow oil, a diastereomeric

mixture (10 % d.e. by $^{1}H$ and $^{13}C$ NMR) of *8-(1,2-dihydroxypentyl)-2,10,10-trimethyl-7,9-dioxatricyclo[4.3.0.1$^{2,5}$]decane* (**234**) (0.17 g, 59 %), $\delta_H$(400 MHz; $CDCl_3$) 0.79, 0.96/0.98and 1.07 (9H, 3 x s, 11-, 12- and 13-Me), 0.92 (3H, t, 5'-Me), 0.85, 1.37-1.56 and 1.67-1.74 (8H, 3 x m, 3-, 4-, 3'- and 4'-$CH_2$), 1.97 (1H, m, 5-H), 2.33 (1H, d, 2'-OH), 2.61/2.67 (1H, d, 1'-OH), 3.60 (1H, br s, 1'-H), 3.79 and 3.96 (2H, 2 x m, 1- and 6-H overlapping at 3.79, m, 2'-H) and 4.65 (1H, m, 8-H); $\delta_C$(100 MHz; $CDCl_3$) 10.91/11.00, 20.12/20.14 and 22.5 (C-11, C-12 and C-13), 13.9 (C-5'), 18.81/18.84 and 35.44/35.48 (C-3' and C-4'), 23.4 and 31.83/31.87 (C-3 and C-4), 46.1 and 47.4 (C-2 and C-10 overlapping at 47.4, C-5), 70.64/70.71 (C-2'), 72.9 (C-1'), 83.62/84.18 and 87.78/88.27 (C-1 and C-6) and 103.3 (C-8).

### 3.2.4.4.3 *Dihydroxylation of* trans-*cinnamaldehyde bornane acetal* (196)

Following the procedure described for the synthesis of 8-(1,2-dihydroxypropyl)-2,10,10-trimethyl-7,9-dioxatricyclo[4.3.0.1$^{2,5}$]decane (**233**), a 0.4 **M** solution of $OsO_4$ (0.75 ml, 0.3 mmol) in *t*-BuOH was added to a mixture of *trans*-cinnamaldehyde bornane acetal (**196**) (0.28 g, 1 mmol) and *N*-methylmorpholine *N*-oxide (0.23 g, 2 mmol) in *t*-BuOH/DMF 1:1 (10 ml). Work-up afforded, as a yellow oil, a diastereomeric mixture (13 % d.e. by $^{1}H$ and $^{13}C$ NMR) of *8-(1,2-dihydroxy-2-phenylethyl)-2,10,10-trimethyl-7,9-dioxatricyclo[4.3.0.1$^{2,5}$]decane* (**235**) (0.17 g, 54 %), $\delta_H$(400 MHz; $CDCl_3$) 0.80/0.81, 0.97/1.00 and 1.11/1.13 (9H, 3 x s, 11-, 12- and 13-Me), 0.87, 1.44 and 1.70 (4H, 3 x m, 3- and 4-$CH_2$), 1.96/2.00 (1H, d, 5-H), 2.51/2.62 (1H, d, 1'-OH), 3.00 (1H, br s, 2'-OH), 3.78/3.79 and 3.95/3.97 (2H, 2 x d, 1- and 6-H), 3.91 (1H, m, 1'-H), 4.63/4.65 (1H, d, 8-H), 4.91 (1H, m, 2'-H) and 7.20-7.40 (5H, m, Ar-H); $\delta_C$(100 MHz; $CDCl_3$) 10.90/11.01, 20.20/20.22 and 22.51/22.53 (C-11, C-12 and C-13), 23.5 and 31.85/31.89 (C-3 and C-4), 46.08/46.11 and 47.45/47.49 (C-2 and C-10), 47.36/47.42 (C-5), 72.95/73.11 (C-2'), 74.43/74.46 (C-1'), 83.81/84.13 and 87.96/88.19 (C-1 and C-6), 102.51/102.54 (C-8)

and 126.36/126.45, 127.67/127.69, 128.3 and 140.74/140.76 (Ar-C).

#### 3.2.4.4.4 *Dihydroxylation of* trans-*crotonaldehyde bornane-10-sulfonate acetal* (199)

Following the procedure described for the synthesis of 8-(1,2-dihydroxypropyl)-2,10,10-trimethyl-7,9-dioxatricyclo[4.3.0.$1^{2,5}$]decane (**233**), a 0.4 M solution of $OsO_4$ (0.75 ml, 0.3 mmol) in *t*-BuOH was added to a mixture of *trans*-crotonaldehyde bornane-10-sulfonate acetal (**199**) (0.37 g, 1 mmol) and *N*-methylmorpholine *N*-oxide (0.23 g, 2 mmol) in *t*-BuOH/DMF 1:1 (10 ml). Work-up afforded, as a yellow oil, a diastereomeric mixture (22 % d.e. by $^{1}H$ and $^{13}C$ NMR) of *phenyl {8-(1,2-dihydroxypropyl)-10,10-dimethyl-7,9-dioxatricyclo[4.3.0.$1^{2,5}$]dec-2-yl}methanesulfonate* (**236**) (0.25 g, 61 %), $\delta_H$(400 MHz; $CDCl_3$) 0.86 and 1.13 (6H, 2 x s, 11- and 12-Me), 0.99, 1.42, 1.79 and 1.88 (4H, 4 x m, 3- and 4-$CH_2$), 1.22/1.24 (3H, d, 3'-H), 2.07 (1H, d, 5-H), 2.87 and 2.93 (2H, 2 x m, 1'- and 2'-OH), 3.16/3.18 and 3.71/3.75 (2H, 2 x d, 13-$CH_2$), 3.52 (1H, m, 1'-H), 3.91 (1H, m, 2'-H), 4.05 and 4.33 (2H, 2 x m, 1- and 6-H), 4.66/4.69 (1H, d, 8-H) and 7.25-7.41 (5H, m, Ar-H); $\delta_C$(100 MHz; $CDCl_3$) 19.3 (C-3'), 20.1 and 22.7 (C-11 and C-12), 23.2 and 27.83/27.92 (C-3 and C-4), 46.56/46.58 (C-5), 47.7 and 48.8 (C-2 and C-10), 49.15/49.29 (C-13), 67.1 (C-2'), 74.07/74.18 (C-1'), 83.33/83.70 and 83.92/84.19 (C-1 and C-6), 103.39/103.54 (C-8) and 115.4, 121.88/121.93, 127.07/127.09, 129.88/129.90 and 149.14/149.20 (Ar-C).

### 3.2.4.5 *Asymmetric Diels-Alder reactions*

#### 3.2.4.5.1 *Diels-Alder reaction of* trans-*cinnamaldehyde bornane-10-sulfonate acetal* (201)

Cyclopentadiene [0.63 ml of a 1 M solution in $CH_2Cl_2$-petroleum ether (4.5:5.5), 0.63 mmol] and $AlCl_3$ (0.05 g, 0.38 mmol) were added, at 0°C, to a stirred solution of acetal (**201**) (0.22 g, 0.5 mmol) in a 4.5:5.5 mixture of $CH_2Cl_2$-petroleum ether (10 ml) and the reaction monitored by TLC. After 6 h no acetal was detected by TLC and the mixture was poured onto crushed ice (10 g) and stirred for 10 min before extracting with $CH_2Cl_2$ (3 x 20 ml). The combined organic extracts were dried ($MgSO_4$), concentrated *in vacuo* and the residue purified by HPLC [elution with hexane-EtOAc (9:1)] afforded, as a colourless oil, phenyl{(1*S*,2*R*,5*S*,6*R*,8*R*)-10,10-dimethyl-8-styryl-7,9-dioxatricyclo[4.3.0.$1^{2,5}$]dec-2-yl}methanesulfonate (**201**) (0.57 g, 26 %); and

as a yellow oil, *phenyl {10,10-dimethyl-8-(3-phenylbicyclo[2.2.1]hept-5-en-2-yl)-7,9-dioxatricyclo[4.3.0.$1^{2,5}$]dec-2-yl}methanesulfonate* (**231**) (0.80 g, 32 %), $\delta_H$(400 MHz; $CDCl_3$) 0.86 and 1.11 (6H, 2 x s, 11- and 12-Me), 0.98, 1.43, 1.77 and 1.91 (4H, 4 x m, 3- and 4-$CH_2$), 1.51 and 1.65 (2H, 2 x m, 7'-$CH_2$), 2.04 (1H, d, 5-H), 2.45 (1H, m, 2'-H), 2.56 (1H, m, 3'-H), 3.02 and 3.06 (2H, 2 x m, 1'- and 4'-H), 3.18 and 3.83 (2H, 2 x d, 13-$CH_2$), 3.97 and 4.27 (2H, 2 x d, 1- and 6-H overlapping at 4.27, d, 8-H), 6.14 and 6.32 (2H, 2 x m, 5'- and 6'-H) and 7.13-7.48 (10H, m, Ar-H); $\delta_C$(100 MHz; $CDCl_3$) 20.1 and 22.7 (C-11 and C-12), 23.2 and 27.8 (C-3 and C-4), 45.0 (C-1'), 46.7 (overlapping C-5, C-3' and C-7'), 47.7 and 48.7 (C-2 and C-10), 48.6 (C-4'), 49.4 (C-2'), 49.5 (C-13), 83.5 and 83.6 (C-1 and C-6), 108.4 (C-8), 121.9, 125.6, 127.0, 127.8, 128.1, 129.8, 144.6 and 150.0 (Ar-C) and 135.0 and 138.0 (C-5' and C-6').

**Attempt 1**: ***Uncatalysed reaction***

Solid cinnamaldehyde diethyl tartrate acetal (**176**) (0.32 g, 1.0 mmol) was added to a stirred solution of freshly distilled cyclopentadiene (0.066 g, 1.0 mmol) in $CHCl_3$ (5 ml) or toluene (5 ml) and the resultant mixture boiled under reflux for 48 h, cooled and concentrated *in vacuo*. $^1H$ NMR spectroscopy of the residue showed only the presence of acetal (**176**).

**Attempt 2**: ***Catalysed reaction***

Freshly distilled cyclopentadiene (0.033 g, 0.5 mmol) was added dropwise to a stirred mixture of cinnamaldehyde 1,4-di-*O*-benzyl tartrate acetal (**178**) (0.21 g, 0.5 mmol) and $AlCl_3$ (0.0.67 g, 0.5 mmol) in $CH_2Cl_2$ and the resultant dark orange mixture boiled under reflux for 24 h. The cooled mixture was poured onto crushed ice (50 g) and the organic layer separated. The aqueous layer was extracted with $CH_2Cl_2$ (3 x 20 ml) and these extracts, combined with the separated organic layer, were dried ($Na_2SO_4$), filtered and concentrated *in vacuo* to yield a black, viscous oil due to polymerization of the reaction material.

### 3.2.4.6 *Organocopper alkylation of* trans-*cinnamaldehyde bornane acetal* (196)

BuLi (0.32 g, 5 mmol) was added, under $N_2$, to a suspension of CuI (0.95 g, 5 mmol) in dry ether (5 ml) at -30°C and the resultant mixture stirred for 10 min before being cooled to -78°C and $BF_3.OEt_2$ (0.71 g, 5 mmol) added. A solution of *trans*-cinnamaldehyde bornane acetal (**196**) (1.42 g, 5 mmol) in dry ether (5 ml), was added after 10 min and the resultant mixture was stirred for 1 h at -78°C and at room temperature for 2 h before sat. aq. $NaHCO_3$ (50 ml) was added. The mixture was stirred for 2 h, poured into $H_2O$ (50 ml), filtered, extracted with ether (2 x 50 ml), the ethereal layers combined, dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography [elution with hexane-EtOAc (95:5)] of the residue afforded, as a colourless oil, 2,10,10-trimethyl-8-styryl-7,9-dioxatricyclo[4.3.0.$1^{2,5}$]decane (**196**) (0.53 g, 37 %); and

as a colourless oil, *3*-exo-*hydroxy-2-(1-oxa-4-phenyl-hept-2-ene)-1,10,10-trimethylbicyclo[2.2.1]heptane* (**232**) (0.29 g, 17 %), $\delta_H$(400 MHz; $CDCl_3$) 0.75, 0.84 and 1.05 (9H, 3 x s, 8-, 9- and 10-Me), 0.77-1.66 (13H, complex of multiplets, 5-, 6-, 5'-, 6'- and 7'-$CH_2$ and 8'-Me), 1.73 (1H, d, 4-H), 2.32 (1H, d, OH), 3.06 (1H, m, 4'-H), 3.54 (1H, d, 2-H), 3.83 (1H, m, 3-H), 5.04 (1H, m, 3'-H), 6.15 (1H, d, 2'-H) and 7.11-7.37 (5H, m, Ar-H); $\delta_C$(100 MHz; $CDCl_3$) 11.5 (C-8'), 14.0, 21.0 and 21.5 (C-8, C-9 and C-10), 22.5, 29.8 and 36.6 (C-5', C-6' and C-7'), 23.9 and 33.4 (C-5 and C-6), 44.4 (C-4'), 46.7 and 49.4 (C-1 and C-7), 51.3 (C-4), 76.8 (C-3), 88.4 (C-2), 110.5 (C-3'), 126.0, 127.3, 128.4 and 145.7 (Ar-C) and 147.2 (C-2'); *m/z* 342 ($\mathbf{M}^+$, 0.63 %) and 133 (100).

### 3.2.4.7 *Alkylation of carbethoxymethyldioxolane* (204)

BuLi (0.065 g, 1.0 mmol) was added, under $N_2$, to a stirred solution of di*iso*propylamine (0.10 g, 1.0 mmol) in dry THF (5 ml) at -78 °C and the resultant mixture was stirred for 30 min before a solution of 8-carbethoxymethyldioxolane (**204**) (0.35 g, 0.83 mmol) in dry THF (1 ml) was added dropwise, followed by the addition of methyl iodide (0.14 g, 1.0 mmol). The resultant mixture was allowed to warm to room temperature and sat. aq. $NaHCO_3$ (50 ml) added. The mixture was stirred for 10 min, extracted with EtOAc (3 x 50 ml) and the combined organic extracts dried ($Na_2SO_4$) and concentrated *in vacuo*. PTLC [hexane-EtOAc (7:3)] of the residue afforded 8-carbethoxymethyldioxolane (**204**) (0.13 g, 38 %); and *3-(4-phenyl-1-oxaprop-2-enyl)bornanesultone* (**236**) (0.13 g, 49 %), $\delta_H$(400 MHz; $CDCl_3$) 0.92 and 1.23 (4H, 2 x s, 8- and 9-Me), 1.20, 1.39 and 1.92 (4H, 3 x m, 5- and 6-$CH_2$), 1.25 (3H, t, 6'-Me), 2.19 (1H, d, 4-H), 3.27 (2H, m, 10-$CH_2$), 4.14 (2H, q, 5'-$CH_2$), 4.29 and 4.39 (2H, 2 x d, 2- and 3-H), 5.24 (1H, d, 2'-H) and 7.48 (1H, d, 1'-H); $\delta_C$(100 MHz; $CDCl_3$) 14.3 (C-6'), 20.3 and 20.8 (C-8 and C-9), 23.6 and 27.9 (C-5 and C-6), 48.1 and 55.7 (C-1 and C-7), 48.5 (C-4), 48.8 (C-10), 59.9 (C-5'), 83.1 and 86.0 (C-2 and C-3), 98.7 (C-2'), 160.3 (C-1') and 167.1 (C-3'); *m/z* 330 ($\mathbf{M}^+$, 8.5 %) and 41 (100).

### *3.2.4.8 Attempted asymmetric Baylis-Hillman reactions.*

#### *3.2.4.8.1 Attempted synthesis of 2-hydroxy-3-acryl-bornane* (239)

**Method 1:** NaH (0.14 g, 5.9 mmol) was washed with dry THF (2 x 10 ml), the washings removed *via* a cannula and the freshly washed NaH suspended in THF (20 ml). A solution of bornane-2,3-diol (**150**) (1.0 g, 5.9 mmol) in dry THF (10 ml) was added, *via* a pressure equalising funnel, to the stirred suspension and the mixture was stirred at room temperature for 1 h. To the resulting mixture, a solution of acryloyl chloride (0.53 g, 5.9 mmol) in dry THF was added and the mixture was boiled under reflux for 2 h. The reaction mixture was cooled to room temperature, concentrated *in vacuo*, diluted with ether (50 ml), washed with sat. aq. $NaHCO_3$ (20 ml), $H_2O$ (20 ml), sat. aq. brine (10 ml) and the organic layer separated, dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford a very viscous oil. None of the desired product was detected by $^1H$ NMR spectroscopy.

**Method 2 :**[171] To a solution of bornane-2,3-diol (**150**) (1.7 g, 10 mmol) in dry $CH_2Cl_2$ (40 ml) under $N_2$, at 0°C, was added $NEt_3$ (1.0 g, 10 mmol) and DMAP (0.17 g, 1.4 mmol), the resultant mixture was stirred for 5 min and acryloyl chloride (0.91 g, 10 mmol) added dropwise. The reaction mixture was stirred for 1 h, diluted with $H_2O$ (50 ml), the organic layer isolated, dried ($MgSO_4$) and concentrated *in vacuo* to afford a dark orange oil. None of the desired product was detected by $^1H$ NMR spectroscopy.

#### *3.2.4.8.2 Preparation of 3-exo-hydroxybornane* (241)

Raney Ni (4.5 g) was suspended in absolute ethanol and stirred under a $H_2$ atmosphere for 2 h. To the slurry was added camphorquinone (**185**) (6.0 g, 36 mmol) and the mixture stirred for 4 h, filtered and the solid washed with EtOAc (50 ml).

The combined organic filtrates were concentrated *in vacuo* and flash chromatography [benzene:ether (9:1)] of the residue afforded, as a white solid, (*1R,3R,4S*)-3-*exo*-hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (**241**) (3.3 g, 55 %) m.p. 216-219°C (lit.,[184] 226-229°C); *v*max (KBr)/cm-1 1740 (CO).

### *3.2.4.8.3 Preparation of bornane-3-acrylate* (242)

To a stirred solution of 3-hydroxy bornane (**241**) (3.0 g, 18 mmol) in dry $CH_2Cl_2$ (50 ml) was added triethylamine (3.6 g, 36 mmol) and DMAP (0.31 g, 2.5 mmol) and the mixture stirred under $N_2$, at 0°C, for 5 min. Acryloyl chloride (3.2 g, 36 mmol) was added dropwise and the resultant mixture stirred for 1 h before the addition of $H_2O$ (50 ml). The organic layer was isolated, dried ($MgSO_4$) and concentrated in vacuo to afford a dark orange oil. The oil was taken up in a hexane:EtOAc (7:3) mixture (10 ml) which resulted in some of the material polymerizing and the remaining material was isolated and concentrated *in vacuo*. Flash chromatography [hexane:EtOAc (7:3)] of the residue afforded, as a pale yellow oil, bornane-3-acrylate (**242**) (1.2 g, 30 %) $\delta_H$(400 MHz; $CDCl_3$) 0.88, 0.89 and 0.90 (9H, 3 x s, 8-, 9- and 10-Me), 1.45, 1.62 and 1.98 (4H, 3 x m, 5- and 6-$CH_2$), 2.07 (1H, d, 4-H), 4.78 (1H, s, 3-H), 5.79 and 6.30 (2H, 2 x dd, CH=C$H_2$) and 6.03 (1H, dd, C*H*=$CH_2$); $\delta_C$(100 MHz; $CDCl_3$) 9.2, 18.6 and 20.6 (C-8, C-9 and C-10), 24.7 and 28.4 (C-5 and C-6), 43.4 and 57.1 (C-1 and C-10), 48.3 (C-4), 76.7 (C-3), 127.8 and 131.3 (*C*=$CH_2$) and 165.0 and 214.0 (2 x CO).

### *3.2.4.8.4 Attempted reduction of bornane-3-acrylate* (242)

**Method 1 :** To a solution of bornane-3-acrylate (**242**) (1.0 g, 4.5 mmol) in MeOH (20 ml), at 0°C, was added solid $NaBH_4$ (0.17 g, 4.5 mmol) and the mixture stirred for 2 h. The mixture was concentrated *in vacuo*, diluted with $H_2O$ (50 ml) and extracted with EtOAc (2 x 20 ml). The organic extracts were combined, dried

($MgSO_4$) and concentrated *in vacuo* to yield a viscous yellow oil, which polymerized on standing.

**Method 2 :** Freshly prepared zinc borohydride[172] (16 ml of a ~0.5 **M** DME solution, 8 mmol) was added to a solution of bornane-3-acrylate (**242**) (1.8 g, 8 mmol) in dry DME, at -10°C, and the resultant mixture stirred for 30 min. The reaction mixture was diluted with $H_2O$ (50 ml) and extracted with ether (2 x 50 ml). The ethereal layers were combined, washed with $H_2O$ (50 ml), dried ($MgSO_4$) and concentrated *in vacuo* to yield a colourless oil which rapidly polymerised.

### *3.2.4.8.5 Attempted reduction of phenyl camphor-10-sulfonate* (188)

A solution of phenyl camphor-10-sulfonate (**188**) (1.0 g, 3.2 mmol) in dry THF (10 ml) was added dropwise, under $N_2$, to a stirred suspension of LAH (0.12 g, 3.2 mmol) in dry THF (20 ml), at -78°C, and the resultant mixture stirred. When the mixture had warmed to 0°C, $H_2O$ (10 ml) was added dropwise and the mixture allowed to warm to room temperature, filtered and the solid washed with ether. The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. $^1H$ NMR analysis showed no desired product.

### *3.2.4.8.6 Preparation of sultone* (245)

A solution of camphor-10-sulfonic acid (**189**) (4.6 g, 20 mmol) in $H_2O$ (10 ml) was slowly added to stirred solid $NaBH_4$ (1.4 g, 37 mmol) and the mixture stirred for a further 10 min. The mixture was concentrated *in vacuo* and the white residue placed in an oven for 2 h at 110°C. The solid was placed in a cellulose thimble and in a Soxhlet extractor and extracted for 8 h with absolute EtOH. The EtOH was removed *in vacuo* and the white residue dried in an oven for 2 h at 110°C. The crude solid (3.8 g) was dissolved in dry pyridine (8 ml) and freshly recrystallised *p*-

toluenesulfonyl chloride (4.5 g, 24 mmol) added. The resultant mixture was vigorously stirred under $N_2$ for 5 h before a slurry of 1 g ice and 1 ml $H_2O$ was added. $H_2O$ (20 ml) was added and the mixture stirred for a further 20 min before being stored at 4°C overnight. The precipitate was filtered and recrystallised from hexane to afford, as white needles, sultone (**245**) (1.1 g, 27 %) m.p. 108-111°C (from hexane)(lit.,[174] 114-116°C); $\delta_H$(400 MHz; $CDCl_3$) 0.91and 1.10 (6H, 3 x s, 8- and 9-Me), 1.25, 1.38 and 1.85-1.97 (6H, 3 x m, 3-, 5- and 6-$CH_2$), 2.23-2.31 (1H, m, 4-H), 3.20 (2H, dd, 10-$CH_2$) and 4.38 (1H, dd, 2-H).

### *3.2.4.8.7 Attempted nucleophilic opening of sultone* (245)

**Method 1:** To a solution of phenol (1.7 g, 18 mmol) in dry THF (30 ml), under $N_2$, was added BuLi (11 ml of a 15 % hexane solution; 18 mmol) and the mixture stirred for 30 min, at 0°C, to generate the phenoxy anion. A solution of the sultone (**245**) (1.1 g, 5 mmol) in THF (5 ml) was added and the mixture stirred for 48 h at room temperature. The reaction mixture was poured into sat. aq. $NaHCO_3$ (100 ml) and extracted with ether (2 x 50 ml). The combined ethereal layers were dried ($MgSO_4$) and concentrated *in vacuo* to afford a colourless oil. $^1$H NMR analysis of the oil showed no new product development.

**Method 2:** To a stirred solution of sultone (**245**) (1.1 g, 5 mmol) in dry ether (30 ml), under $N_2$ at room temperature, was added BuLi (10.7 ml of a 15 % hexane solution; 18 mmol) and the resultant mixture stirred for 5 h. The reaction mixture was poured into sat. aq. $NaHCO_3$ (100 ml) and extracted with ether (2 x 50 ml). The combined ethereal layers were dried ($MgSO_4$) and concentrated *in vacuo* to afford a white, semi solid residue. $^1$H NMR analysis showed none of the desired product.

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# 5. APPENDIX

## 5.1 CRYSTALLOGRAPHIC DATA FOR (1*S*,3*R*)-3-(*N*-BENZYLCARBAMOYL)-2,3,3-TRIMETHYLCYCLOPENTANECARBOXYLIC ACID (151).

### *Crystal data*

$C_{17}H_{23}NO_3$, $M$ = 289.17, Monoclinic, $a$ = 10.100(4), $b$ = 11.341(4), $c$ = 14.456(4) Å, $\beta$ = 101.096(28)°, V = 1624.79(99)Å$^3$, $\lambda$ = 0.70930 Å, space group $P2_1/n$, Z = 4, $D_x$ = 1.177 g cm$^{-3}$, $\mu$ = 0.46 cm$^{-1}$, crystal dimensions 0.85 x 0.69 x 0.5 mm.

### *Data collection and processing*

$CAD_4$ diffractometer, $\omega$-2$\theta$ mode with $\omega$ scan width = 0.66 + 0.35 tan $\theta$, variable $\omega$ scan speed (max. = 5.49° min$^{-1}$), graphite-monochromated Mo-K$\alpha$ radiation; 5122 reflections measured ($2 \leq \theta \leq 30°$, $h$: 14-14, $k$: 0-15, $l$: 0-20) 4001 observed with $I > \sigma(I)$.

### *Structure analysis and refinement*

Direct methods[185] followed by full-matrix least-squares refinement with all non-hydrogen atoms anisotropic, and hydrogen atoms (with the exception of the amide hydrogen) in calculated positions with common isotropic temperature factors. A unit weights refinement gave a very small variation in the mean value of $(F_o-F_o)^2$ as a function of the magnitude of $F_o$. Application of a weighting scheme was consequently considered unnecessary. The final $R$ factor was 0.0726 (211 parameters).

**Table 19** Fractional coordinates (x $10^4$) for (1*S*,3*R*)-3-(*N*-benzylcarbamoyl)-2,2,3-trimethylcyclopentanecarboxylic acid (**151**).[a,b]

| Atom | *x/a* | *y/b* | *z/c* |
|---|---|---|---|
| N(1) | 6464(2) | 3556(2) | 7154(1) |
| O(1) | 2140(2) | 4762(2) | 3965(1) |
| O(2) | 704(2) | 3568(2) | 4483(2) |
| O(3) | 5023(2) | 2498(1) | 7832(1) |
| C(1) | 4089(2) | 4182(2) | 6941(1) |
| C(2) | 3075(2) | 3540(2) | 6140(1) |
| C(3) | 2227(2) | 4599(2) | 5643(1) |
| C(4) | 3135(2) | 5700(2) | 5818(2) |
| C(5) | 4465(2) | 5285(2) | 6433(2) |
| C(6) | 3421(3) | 4559(3) | 7760(1) |
| C(7) | 2180(2) | 2634(2) | 6508(2) |
| C(8) | 3838(2) | 2904(2) | 5467(1) |
| C(9) | 5241(2) | 3350(2) | 7348(1) |
| C(10) | 7601(2) | 2743(2) | 7420(1) |
| C(11) | 7667(2) | 1875(2) | 6645(1) |
| C(12) | 8497(2) | 2093(2) | 5999(2) |
| C(13) | 8527(3) | 1318(3) | 5268(2) |
| C(14) | 7713(3) | 329(3) | 5168(2) |
| C(15) | 6891(3) | 110(2) | 5799(2) |
| C(16) | 6869(3) | 877(2) | 6540(2) |
| C(17) | 1711(2) | 4348(2) | 4611(1) |

[a]For atom labelling, see Fig.9.[b]Estimated standard deviations in parentheses.

**Table 20** Selected bond lengths/Å and angles/° for (1*S*,3*R*)-3-(*N*-benzylcarbamoyl)-2,2,3-trimethylcyclopentanecarboxylic acid (**151**).[a,b]

| | | | |
|---|---|---|---|
| N(1)-H(1) | 0.891(25) | C(2)-C(3) | 1.567(2) |
| N(1)-C(9) | 1.338(3) | C(3)-C(4) | 1.541(3) |
| N(1)-C(10) | 1.465(3) | C(3)-C(17) | 1.510(2) |
| O(1)-C(17) | 1.198(2) | C(4)-C(5) | 1.535(3) |
| O(2)-C(17) | 1.333(2) | C(10)-C(11) | 1.502(3) |
| O(3)-C(9) | 1.237(2) | C(11)-C(12) | 1.392(3) |
| C(1)-C(2) | 1.570(2) | C(11)-C(16) | 1.381(3) |
| C(1)-C(5) | 1.534(3) | C(12)-C(13) | 1.378(3) |
| C(1)-C(6) | 1.532(3) | C(13)-C(14) | 1.372(4) |
| C(1)-C(9) | 1.526(3) | C(14)-C(15) | 1.382(4) |
| C(2)-C(7) | 1.530(3) | C(15)-C(16) | 1.384(3) |
| C(2)-C(8) | 1.532(3) | | |
| | | | |
| C(10)-N(1)-C(9) | 122.9(2) | C(4)-C(5)-C(1) | 104.9(2) |
| C(5)-C(1)-C(2) | 102.2(1) | O(3)-C(9)-N(1) | 121.8(2) |
| C(6)-C(1)-C(2) | 112.2(2) | C(1)-C(9)-N(1) | 118.5(2) |
| C(6)-C(1)-C(5) | 109.2(2) | C(1)-C(9)-O(3) | 119.7(2) |
| C(9)-C(1)-C(2) | 109.7(1) | C(11)-C(10)-N(1) | 111.3(2) |
| C(9)-C(1)-C(5) | 116.6(2) | C(12)-C(11)-C(10) | 120.2(2) |
| C(3)-C(2)-C(1) | 101.7(1) | C(16)-C(11)-C(10) | 120.7(2) |
| C(7)-C(2)-C(1) | 113.5(2) | C(16)-C(11)-C(12) | 119.1(2) |
| C(7)-C(2)-C(3) | 111.5(2) | C(13)-C(12)-C(11) | 120.4(3) |
| C(8)-C(2)-C(1) | 110.5(2) | C(14)-C(13)-C(12) | 120.2(3) |
| C(8)-C(2)-C(3) | 111.6(2) | C(15)-C(14)-C(13) | 119.9(3) |

**Table 20** Continued.

| | | | |
|---|---|---|---|
| C(8)-C(2)-C(7) | 107.9(2) | C(16)-C(15)-C(14) | 120.1(3) |
| C(4)-C(3)-C(2) | 106.9(1) | C(15)-C(16)-C(11) | 120.2(2) |
| C(17)-C(3)-C(2) | 111.2(2) | C(3)-C(17)-O(1) | 126.0(2) |
| C(17)-C(3)-C(4) | 113.4(2) | C(3)-C(17)-O(2) | 111.8(2) |
| C(5)-C(4)-C(3) | 105.9(2) | O(2)-C(17)-O(1) | 122.2(2) |

[a]For atom labelling, see Fig. 9. [b]Estimated standard deviations in parentheses.

**Table 21** Anisotropic Temperature Factors ($Å^2$ x $^3$10 ) for (1*S*,3*R*)-3-(*N*-benzylcarbamoyl)-2,2,3-trimethylcyclopentanecarboxylic acid (**151**).[a,b]

| Atom | U(11) | U(22) | U(33) | U(23) | U(13) | U(12) |
|---|---|---|---|---|---|---|
| N(1) | 51(1) | 50(1) | 49(1) | -1(1) | -1(1) | 4(1) |
| O(1) | 80(1) | 77(1) | 42(1) | 5(1) | 4(1) | -15(1) |
| O(2) | 57(1) | 78(1) | 48(1) | -8(1) | 1(1) | -17(1) |
| O(3) | 68(1) | 69(1) | 55(1) | 22(1) | 0(1) | 6(1) |
| C(1) | 51(1) | 45(1) | 35(1) | -3(1) | -1(1) | 3(1) |
| C(2) | 51(1) | 41(1) | 39(1) | -2(1) | 1(1) | -1(1) |
| C(3) | 47(1) | 47(1) | 39(1) | -3(1) | 0(1) | 4(1) |
| C(4) | 63(1) | 43(1) | 56(1) | -1(1) | -9(1) | 2(1) |
| C(5) | 58(1) | 43(1) | 61(1) | 4(1) | -10(1) | -4(1) |
| C(6) | 89(2) | 88(2) | 42(1) | -12(1) | 9(1) | 20(2) |
| C(7) | 65(1) | 68(2) | 75(2) | 18(1) | -4(1) | -19(1) |
| C(8) | 73(1) | 58(1) | 46(1) | -14(1) | -3(1) | 16(1) |
| C(9) | 56(1) | 49(1) | 36(1) | 0(1) | -4(1) | 3(1) |
| C(10) | 49(1) | 67(1) | 50(1) | -4(1) | -6(1) | 10(1) |
| C(11) | 52(1) | 58(1) | 46(1) | 5(1) | -3(1) | 13(1) |
| C(12) | 59(1) | 76(2) | 65(1) | -1(1) | 9(1) | 3(1) |
| C(13) | 92(2) | 95(2) | 65(2) | -4(2) | 28(1) | 5(2) |
| C(14) | 132(3) | 73(2) | 60(2) | -9(1) | 28(2) | 8(2) |
| C(15) | 116(2) | 56(1) | 71(2) | -3(1) | 20(2) | -6(2) |
| C(16) | 89(2) | 55(1) | 59(1) | 3(1) | 18(1) | 2(1) |
| C(17) | 47(1) | 51(1) | 43(1) | -1(1) | -2(1) | 3(1) |

[a]For atom labelling, see Fig. 9. [b]Estimated standard deviations in parentheses.

## 5.2 CRYSTALLOGRAPHIC DATA FOR PHENYL {(1*S*,2*S*,5*S*,6*R*,8*S*)-10,10-DIMETHYL-8-STYRYL-7,9-DIOXATRICYCLO[4.3.0.$1^{2,5}$]DEC-2-YL}METHANESULFONATE (201).

**TABLE 22** Crystal data and structure refinement for acetal (**201**).

| | |
|---|---|
| Temperature | 293 (2) K |
| Wavelength | 0.71070 Å |
| Space group | $P2_12_12_1$ |
| Crystal type | Orthorhombic |
| Unit cell dimensions | a = 6.841 (4) Å, $\alpha = 90°$ |
| | b = 13.196 (4) Å, $\beta = 90°$ |
| | c = 25.222 (6) Å, $\gamma = 90°$ |
| Volume | 2277 (2) $Å^3$ |
| Z | 4 |
| Density (calculated) | 1.372 $mg/m^3$ |
| Absorption coefficent | 0.179 $mm^{-1}$ |
| F(000) | 1054 |
| $\theta$ range for data collection | 2.23 to 29.95° |
| Index range | $-1 \leq h \leq 9$, $-1 \leq k \leq 18$, $-1 \leq l \leq 35$ |
| Reflections collected | 4794 |
| Independent reflections | 4546 [R(int) = 0.1483] |
| Refinement method | Full-matrix least squares on $F^2$ |
| Data/ restraints/ parameters | 4546/ 0/ 282 |
| Goodness-of-fit on $F^2$ | 1.096 |

**Table 22** Continued

| | |
|---|---|
| Final R indices [I>2ϕ(I)] | R1 = 0.1605, wR2 = 0.4223 |
| R indices (all data) | R1 = 0.2412, wR2 = 0.4602 |
| Absolute structure parameters | 0.3(5) |
| Largest diff. Peak and hole | 0.758 and -0.424 e.Å$^{-3}$ |

**Table 23** Fractional coordinates (x $10^4$) for acetal **(201)**.[a,b]

| Atom | *x/a* | *y/b* | *z/c* |
|---|---|---|---|
| S(1) | 1713(6) | 6806(3) | 6707(1) |
| O(1) | 2605(13) | 9460(6) | 6161(3) |
| C(12) | 3509(25) | 10797(8) | 5581(4) |
| C(14) | 3355(28) | 11559(8) | 4660(5) |
| C(11) | 2480(20) | 10544(8) | 6066(4) |
| C(1) | 3518(18) | 8612(9) | 7003(3) |
| C(15) | 2287(29) | 12166(10) | 4334(6) |
| C(13) | 2628(20) | 11235(8) | 5174(5) |
| O(5) | 1408(19) | 6339(9) | 7209(4) |
| O(2) | 3408(16) | 10969(6) | 6520(3) |
| C(10) | 3749(11) | 7620(9) | 6709(4) |
| O(3) | 2414(18) | 5885(7) | 6344(4) |
| C(3) | 2723(21) | 1038(19) | 6963(5) |
| C(9) | 6640(17) | 9467(11) | 6634(6) |
| O(4) | 114(14) | 7274(9) | 6458(4) |
| C(5) | 3122(28) | 9586(11) | 7813(4) |
| C(4) | 4205(26) | 10138(12) | 7373(5) |
| C(7) | 5386(13) | 9198(12) | 7123(5) |
| C(2) | 2193(17) | 9353(9) | 6698(4) |
| C(6) | 2610(20) | 8563(12) | 7584(3) |
| C(20) | 2877(30) | 6061(12) | 5804(7) |
| C16 | 3037(40) | 11645(11) | 4023(6) |
| C18 | 5914(29) | 12215(7) | 3689(4) |

**Table 23** Continued

| | | | |
|---|---|---|---|
| C17 | 4714(35) | 12215(7) | 3689(4) |
| C22 | 1939(49) | 6333(15) | 4921(7) |
| C21 | 1421(27) | 6266(11) | 5454(6) |
| C25 | 4730(35) | 5920(14) | 5654(8) |
| C23 | 3863(56) | 6268(16) | 4770(9) |
| C19 | 5194(29) | 11358(11) | 4497(6) |
| C8 | 6769(28) | 8696(13) | 7523(6) |
| C24 | 5230(39) | 6008(16) | 5136(10) |

[a]For atom labelling, see Fig.29.[b]Estimated standard deviations in parentheses.

**Table 24** Bond lengths/Å and angles/° for acetal (**201**).[a,b]

| | | | |
|---|---|---|---|
| S(1)-O(4) | 1.404(11) | C(9)-C(7) | 1.54(2) |
| S(1)-O(5) | 1.423(10) | C(11)-O(2) | 1.424(13) |
| S(1)-O(3) | 1.596(10) | C(12)-C(11) | 1.45(2) |
| S(1)-C(10) | 1.759(10) | C(12)-C(13) | 1.32(2) |
| O(1)-C(2) | 1.390(12) | C(14)-C(13) | 1.45(2) |
| O(1)-C(11) | 1.454(13) | C(14)-C(15) | 1.36(2) |
| O(2)-C(3) | 1.44(2) | C(14)-C(19) | 1.35(2) |
| O(3)-C(20) | 1.42(2) | C(15)-C(16) | 1.43(2) |
| C(3)-C(4) | 1.48(2) | C(16)-C(17) | 1.28(3) |
| C(1)-C(2) | 1.54(2) | C(18)-C(17) | 1.40(2) |
| C(1)-C(6) | 1.593(10) | C(18)-C(19) | 1.35(2) |
| C(1)-C(7) | 1.52(2) | C(20)-C(21) | 1.36(2) |
| C(1)-C(10) | 1.51(2) | C(20)-C(25) | 1.34(3) |
| C(3)-C(2) | 1.56(2) | C(22)-C(21) | 1.39(3) |
| C(4)-C(7) | 1.61(2) | C(22)-C(23) | 1.37(4) |
| C(5)-C(6) | 1.51(2) | C(23)-C(24) | 1.36(3) |
| C(5)-C(4) | 1.52(2) | C(25)-C(24) | 1.36(3) |
| C(7)-C(8) | 1.53(2) | | |
| | | | |
| O(4)-S(1)-O(5) | 118.3(7) | C(4)-C(3)-C(2) | 105.7(10 |
| O(4)-S(1)-O(3) | 108.2(6) | C(6)-C(5)-C(4) | 105.2(9 |
| O(5)-S(1)-O(3) | 103.0(7) | C(3)-C(4)-C(5) | 106.2(14 |
| O(4)-S(1)-C(10) | 110.5(6) | C(3)-C(4)-C(7) | 103.7(9 |
| O(5)-S(1)-C(10) | 112.2(6) | C(5)-C(4)-C(7) | 99.3(12 |

**Table 24** Continued

| | | | |
|---|---|---|---|
| O(3)-S(1)-C(10) | 103.2(6) | C(1)-C(7)-C(8) | 115.4(13) |
| C(2)-O(1)-C(11) | 104.4(9) | C(1)-C(7)-C(9) | 115.0(9) |
| C(13)-C(12)-C(11) | 122.2(14) | C(8)-C(7)-C(9) | 106.3(10) |
| C(19)-C(14)-C(15) | 116(2) | C(1)-C(7)-C(4) | 92.8(9) |
| C(19)-C(14)-C(13) | 122(2) | C(8)-C(7)-C(4) | 112.7(12) |
| C(15)-C(14)-C(13) | 122(2) | C(9)-C(7)-C(4) | 114.5(13) |
| O(2)-C(11)-C(12) | 111.8(11) | O(1)-C(2)-C(1) | 115.5(9) |
| O(2)-C(11)-O(1) | 103.2(8) | O(1)-C(2)-C(3) | 106.5(9) |
| C(12)-C(11)-O(1) | 109.7(10) | C(1)-C(2)-C(3) | 101.7(8) |
| C(10)-C(1)-C(7) | 116.7(10) | C(5)-C(6)-C(1) | 103.0(10) |
| C(10)-C(1)-C(2) | 111.6(8) | C(25)-C(20)-C(21) | 123(2) |
| C(7)-C(1)-C(2) | 105.7(9) | C(25)-C(20)-O(3) | 117(2) |
| C(10)-C(1)-C(6) | 117.1(9) | C(21)-C(20)-O(3) | 120(2) |
| C(7)-C(1)-C(6) | 99.4(9) | C(17)-C(16)-C(15) | 118(2) |
| C(2)-C(1)-C(6) | 104.8(9) | C(19)-C(18)-C(17) | 118(2) |
| C(14)-C(15)-C(16) | 122(2) | C(16)-C(17)-C(18) | 121.4(13) |
| C(12)-C(13)-C(14) | 131.6(14) | C(23)-C(22)-C(21) | 121(2) |
| C(11)-O(2)-C(3) | 105.5(9) | C(20)-C(21)-C(22) | 117(2) |
| C(1)-C(10)-S(1) | 116.6(7) | C(20)-C(25)-C(24) | 120(2) |
| C(20)-O(3)-S(1) | 119.6(9) | C(24)-C(23)-C(22) | 119(2) |
| O(2)-C(3)-C(4) | 115.8(12) | C(14)-C(19)-C(18) | 124(2) |
| O(2)-C(3)-C(2) | 102.2(8) | C(25)-C(24)-C(23) | 120(2) |

[a]For atom labelling, see Fig.29.[b]Estimated standard deviations in parentheses.

**Table 25** Anisotropic Temperature Factors ($Å^2 \times 10^3$) for acetal (**201**).[a,b]

| Atom | U(11) | U(22) | U(33) | U(23) | U(13) | U(12) |
|---|---|---|---|---|---|---|
| S(1) | 67(2) | 73(2) | 77(2) | 15(2) | 3(2) | -8(2) |
| O(1) | 63(5) | 53(4) | 71(5) | 9(4) | -1(4) | 2(4) |
| O(2) | 86(6) | 56(5) | 74(5) | -1(4) | -11(5) | -1(6) |
| O(3) | 117(9) | 54(5) | 86(6) | 1(4) | -18(7) | 1(6) |
| O(4) | 54(5) | 100(7) | 115(8) | -23(6) | -12(6) | 1(6) |
| O(5) | 108(9) | 105(8) | 85(6) | 30(6) | 14(7) | -26(8) |
| C(1) | 75(7) | 73(7) | 10(3) | 10(4) | 34(4) | 0(7) |
| C(2) | 51(6) | 71(7) | 43(5) | 14(5) | -21(5) | 9(6) |
| C(3) | 67(8) | 60(7) | 61(6) | -17(6) | -25(7) | 14(7) |
| C(4) | 100(12) | 81(10) | 62(7) | -27(7) | 5(8) | -9(9) |
| C(5) | 106(12) | 98(11) | 44(5) | -25(6) | -12(8) | 24(11) |
| C(6) | 73(8) | 133(12) | 22(4) | 34(6) | 32(5) | 5(9) |
| C(7) | 7(3) | 116(11) | 80(7) | 4(8) | -30(5) | 4(6) |
| C(8) | 95(12) | 104(11) | 92(9) | 18(9) | -43(10) | 16(12) |
| C(9) | 32(5) | 88(9) | 106(10) | 9(8) | 10(7) | -6(7) |
| C(10) | 10(3) | 73(7) | 60(5) | 17(6) | -22(4) | -3(4) |
| C(11) | 72(8) | 40(5) | 61(6) | 5(5) | -15(7) | 0(6) |
| C(12) | 94(10) | 40(6) | 61(6) | 9(5) | -5(8) | 6(7) |
| C(13) | 93(9) | 64(7) | 85(8) | -47(6) | 35(7) | 79(7) |
| C(14) | 113(12) | 40(6) | 59(6) | -8(5) | 9(8) | -6(8) |
| C(15) | 114(13) | 57(7) | 90(9) | -18(7) | -27(10) | 12(9) |
| C(16) | 319(29) | 18(4) | 39(5) | -25(4) | 0(11) | 47(11) |
| C(17) | 267(22) | 7(3) | 45(5) | -43(4) | 27(10) | -6(8) |
| C(18) | 124(15) | 61(8) | 81(9) | -11(8) | 22(10) | 3(10) |

**Table 25** Continued

| | | | | | | |
|---|---|---|---|---|---|---|
| C(19) | 114(14) | 64(8) | 82(9) | -8(7) | 14(10) | -28(10) |
| C(20) | 98(13) | 56(8) | 101(11) | 0(8) | -7(11) | -4(9) |
| C(21) | 84(11) | 73(9) | 94(10) | -14(8) | -4(10) | -12(10) |
| C(22) | 193(26) | 102(14) | 79(11) | -39(10) | -24(15) | -7(19) |
| C(23) | 208(30) | 81(12) | 92(13) | -13(10) | 40(17) | 4(17) |
| C(24) | 126(18) | 101(15) | 131(17) | -39(14) | 42(16) | -17(14) |
| C(25) | 114(16) | 81(11) | 116(15) | -14(11) | -6(13) | -7(13) |

[a]For atom labelling, see Fig.29.[b]Estimated standard deviations in parentheses.