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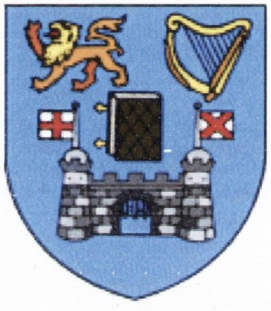
# Studies on Novel Chiral Sulfones



by

**Frank Lewis**

A thesis submitted to the University of Dublin for the degree of

Doctor of Philosophy

March 2008

Trinity College Dublin

*"The strongest oak of the forest is not the one that is protected from the storm and hidden from the sun. It's the one that stands in the open where it is compelled to struggle for its existence against the winds and rains and the scorching sun. Effort only fully releases its reward after a person refuses to quit."*

**Napoleon Hill**

## Declaration

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# Summary

The research carried out in the present study focuses mainly on the synthesis of some novel chiral sulfones and the studies of their potential applications as chiral auxiliaries in asymmetric synthesis. This thesis is divided into four chapters:

Chapter 1 summarises the different approaches to asymmetric synthesis with a particular focus on the chiral auxiliary approach. The most important chiral auxiliaries, including those derived from the chiral pool element camphor, are introduced and their modes of action and some illustrative applications in asymmetric synthesis are discussed. In addition, the chemistry of the sulfonyl functional group is summarised.

Chapter 2 is concerned with the synthesis of camphor-derived chiral allyl and benzyl sulfones and the reactions of their derived carbanions with aldehydes. These camphorsulfonyl compounds were found to undergo stereospecific cyclisation on treatment with base. Their derived isobornyl analogues successfully reacted with benzaldehyde, but with virtually no stereoselectivity. Studies on analogous achiral sulfones show that these compounds can be used as masked carbanion equivalents in reactions with benzaldehyde.

Chapter 3 describes the synthesis of some novel chiral vinyl sulfones and studies on their nucleophilic epoxidation reactions. With the camphorsulfonyl compounds, promising levels of stereoselectivity were observed which were dependent on the conditions used. Additional studies suggest coordination effects do not account for the observed stereoselectivity. Studies on the hydrolysis of achiral sulfonyloxiranes and the dihydroxylation of achiral vinyl sulfones failed to afford the target α-hydroxyaldehydes.

Chapter 4 reports on the synthesis of novel camphor-derived chiral benzyl sulfones which utilises the carbocation rearrangement chemistry exhibited by camphor to install the sulfonyl functionality into its methyl groups. In addition, a novel route to 10-iodocamphor is presented. Extension of this work led to the development of new facile routes to the 10-halocamphors.

## Acknowledgements

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Finally, I would like to thank my family for their love and support through these last four years and indeed throughout my whole life. Thank you Mum, for believing in me. I would not be here without you.

*Thank you!*

# Abbreviations

| | |
|---|---|
| Ac | acetyl |
| acac | acetylacetonate |
| AD mix | asymmetric dihydroxylation mixture |
| AIBN | 2,2'-azobisisobutyronitrile |
| BINAP | 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl |
| Bn | benzyl |
| b.p. | boiling point |
| BuLi | *n*-butyllithium |
| CAN | ceric ammonium nitrate |
| Cbz | benzyloxycarbonyl |
| CI | chemical ionisation |
| COD | 1,5-cyclooctadiene |
| COSY | correlation spectroscopy |
| DABCO | 1,4-diazabicyclo[2.2.2]octane |
| DCM | dichloromethane |
| de | diastereomeric excess |
| DEPT | distortionless enhancement by polarisation transfer |
| DET | diethyltartrate |
| DIBAL-H | diisobutylaluminium hydride |
| DHQ | dihydroquinine |
| DMAP | 4-(dimethylamino)pyridine |
| DMF | *N*,*N*-dimethylformamide |

| | |
|---|---|
| DMSO | dimethylsulfoxide |
| ee | enantiomeric excess |
| $E^+$ | electrophile |
| Et | ethyl |
| EtOAc | ethyl acetate |
| EWG | electron withdrawing group |
| FTIR | fourier transform infra red |
| Hex | hexyl |
| HMPA | hexamethylphosphoramide |
| HRMS | high resolution mass spectrometry |
| Hz | hertz |
| IR | infra red |
| LDA | lithium diisopropylamide |
| LICA | lithium isopropylcyclohexylamide |
| LiHMDS | lithium hexamethyldisilazide |
| MAD | methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide) |
| MCPBA | *m*-chloroperbenzoic acid |
| Me | methyl |
| MoOPH | oxodiperoxymolybdenum(pyridine)(hexamethylphosphoric triamide) |
| m.p. | melting point |
| NMO | *N*-methylmorpholine-*N*-oxide |
| NMR | nuclear magnetic resonance |
| NOE | nuclear overhauser effect |

| | |
|---|---|
| $Nu^-$ | nucleophile |
| [O] | oxidation |
| PCC | pyridinium chlorochromate |
| Pd/C | palladium on activated charcoal |
| Ph | phenyl |
| ppm | parts per million |
| py | pyridine |
| RAMP | (2*R*)-2-(methoxymethyl)pyrrolidin-1-amine |
| rt | room temperature |
| SAMP | (2*S*)-2-(methoxymethyl)pyrrolidin-1-amine |
| TBS | tri-*n*-butylsilyl |
| $^t$BuOK | potassium *tert*-butoxide |
| TFA | trifluoroacetic acid |
| TFAA | trifluoroacetic anhydride |
| THF | tetrahydrofuran |
| TLC | thin layer chromatography |
| TMSCl | chlorotrimethylsilane |
| $TolSO_2$ | *p*-toluenesulfonyl |
| TosMIC | *p*-toluenesulfonylmethylisocyanide |
| TsCl | *p*-toluenesulfonyl chloride |
| TsOH | *p*-toluenesulfonic acid |

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# Chapter 1

# Introduction

## 1.1 Approaches to Asymmetric Synthesis

### 1.1.1 Brief Overview of Asymmetric Synthesis

Advances in the field of asymmetric synthesis have been considerable in the past 50 years.[1] The increasing demand for enantiomerically pure compounds by the chemical and pharmaceutical industries will ensure that new methods will continue to be developed. The various approaches to the synthesis of enantiomerically enriched compounds range from simple resolution of racemates to the use of chiral templates and auxiliaries to asymmetric synthesis using chiral reagents in either stoichiometric or catalytic amounts.

The resolution of racemic mixtures involves reaction of the racemate with an enantiomerically pure compound to form diastereomeric adducts which can be separated by crystallisation or chromatography. Although this approach leads to considerable waste if only one enantiomer is required, it remains a viable option if both enantiomers can be used. A more recent approach is dynamic kinetic resolution, in which racemisation of the racemic substrate leads to replenishment of the faster reacting enantiomer at the expense of the slower reacting enantiomer, resulting in a quantitative theoretical yield of the desired product.

The chiral template approach involves the direct incorporation of an enantiomerically pure compound derived from nature (the 'chiral pool') into the structure of the target compound. Although this approach has the advantage of guaranteeing enantiomeric purity in the product, the lack of availability of both enantiomers of the chiral pool element in most cases and the structural limitations imposed on the choice of target compound mean this approach has been largely superseded by more efficient methods.

The chiral auxiliary approach involves the attachment of an enantiomerically pure compound to a prochiral substrate. A reaction is carried out on the substrate whose stereochemistry is influenced by the auxiliary. The auxiliary is then removed from the enantiomerically enriched product and preferably recovered. This approach often gives high enantiomeric excesses and in many cases this can be raised by recrystallisation prior to removal of the auxiliary.

A more recent approach to asymmetric synthesis involves the reaction of a prochiral substrate with a chiral reagent which may be used in either stoichiometric or catalytic amounts. The chiral reagent is typically derived from a transition metal or main group metal complex, from a chiral organic compound (organocatalysis) or from an enzyme (biocatalysis). This method is often more economical than the auxiliary approach, avoiding the need for extra steps to introduce and remove the auxiliary, although it has only been applied successfully to a few reactions.

### 1.1.2 Chiral Auxiliaries in Asymmetric Synthesis

Even today, the use of chiral auxiliaries ranks as one of the most reliable, well understood and widespread methods in asymmetric synthesis.[2] This approach requires additional synthetic steps for both the introduction and subsequent removal of the auxiliary as well as stoichiometric amounts of auxiliary, rendering it less attractive compared to other methods like asymmetric catalysis. However, for many reactions, no catalytic enantioselective method exists, and chiral auxiliaries remain the only stereoselective method available. Some of the most important chiral auxiliaries not derived from camphor are shown in **Figure 1.1**.

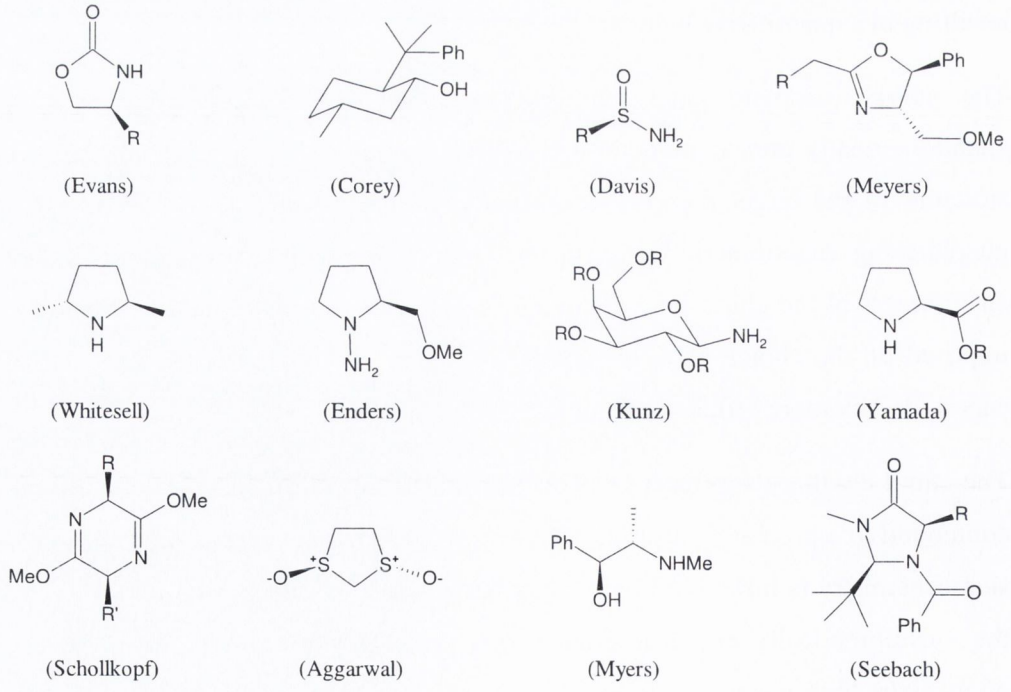
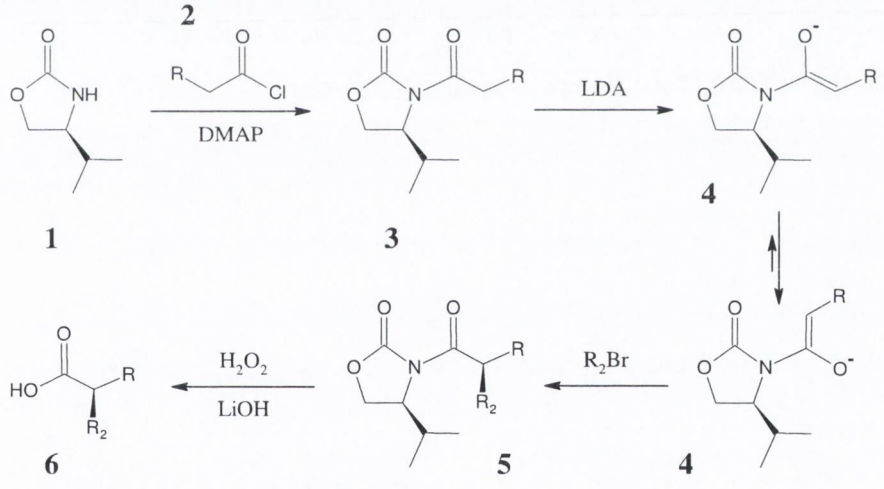



**Figure 1.1**

**Important non-camphor-derived chiral auxiliaries**

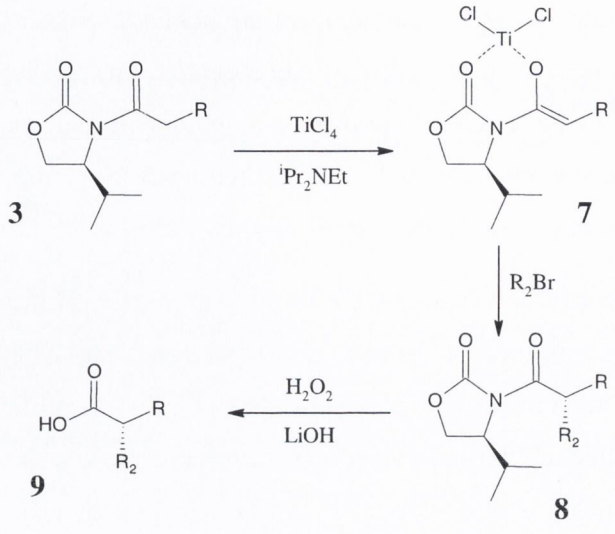
For a chiral auxiliary to be successful, there are generally two structural features it must possess to achieve high levels of stereocontrol; (a) face-shielding group in close proximity to the reacting prochiral centre, and (b) control of the rotamer population in the side-chain bearing the reacting prochiral centre. These principles will be illustrated below for some of these auxiliaries.

Chiral oxazolidinones developed by Evans *et al.* are a powerful class of auxiliaries which have been employed in a wide variety of reactions, including asymmetric aldol reactions, alkylations and pericyclic reactions.[3] Oxazolidinone **1** (R = $^{i}$Pr), derived from valine, confers high levels of stereocontrol in enolate alkylations and aldol reactions on its *N*-acyl derivatives. In the absence of chelation control, *cis*-enolate **4** adopts an *anti* conformation to minimise dipolar interactions, resulting in efficient shielding of the *si*-face by the isopropyl group. Approach of an electrophile from the less hindered *re*-face leads to enantiomerically enriched derivative **6** after cleavage of the auxiliary (**Scheme 1.1**).



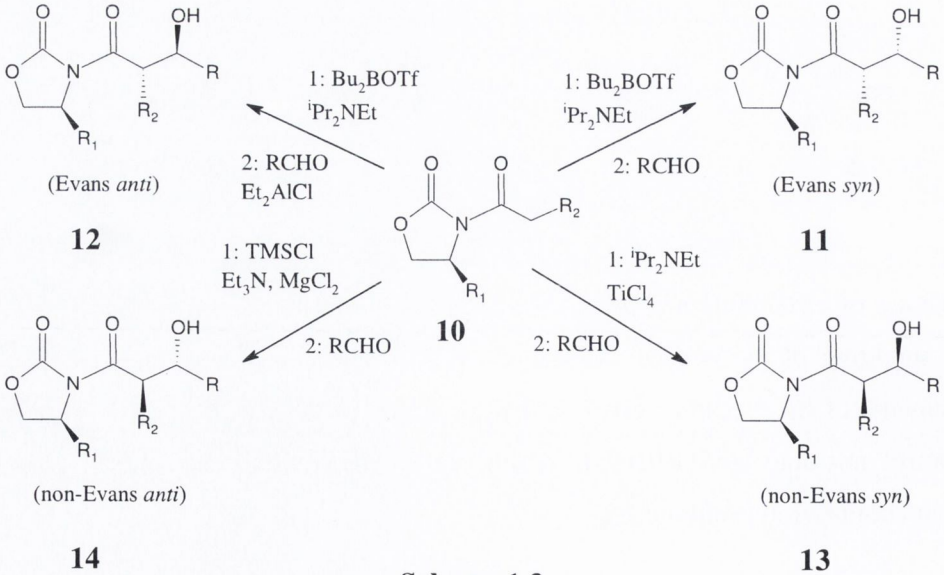

**Scheme 1.1**

The use of a chelating metal ion enforces a *syn* conformation on enolate **7**, resulting in shielding of the *re*-face. Attack of an electrophile on the *si*-face, followed by cleavage of the auxiliary gives the enantiomeric product **9**. Thus, it is possible to control absolute stereochemistry using the same auxiliary by careful choice of metal counterion (**Scheme 1.2**).




**Scheme 1.2**

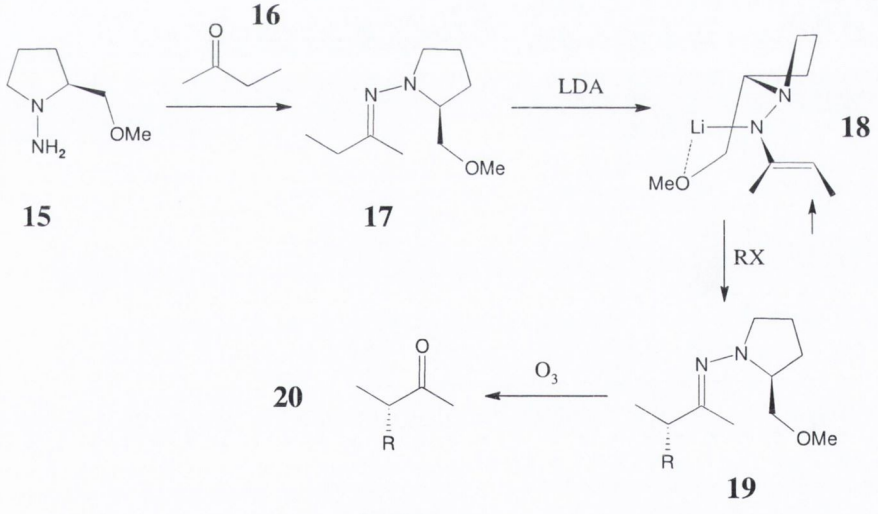
Control of relative and absolute stereochemistry is also possible in aldol-reactions of *N*-acyl derivatives of oxazolidinone **1** by careful choice of conditions. In the absence of chelating metals, *syn*-aldols **11** ('Evans *syn*-aldol') are obtained when *Z*-boron enolates of **10** react with aldehydes,[4] while the additional use of a Lewis acid allows *anti*-aldols **12** ('Evans *anti*-aldol') to be accessed.[5] Chelate-controlled methods result in the formation of 'non-Evans' products. Titanium enolates give rise to 'non-Evans *syn*' products **13**. The synthesis of 'non-Evans *anti*' aldols **14** by magnesium chloride-catalysed aldol reaction was recently reported (**Scheme 1.3**).[6]




**Scheme 1.3**

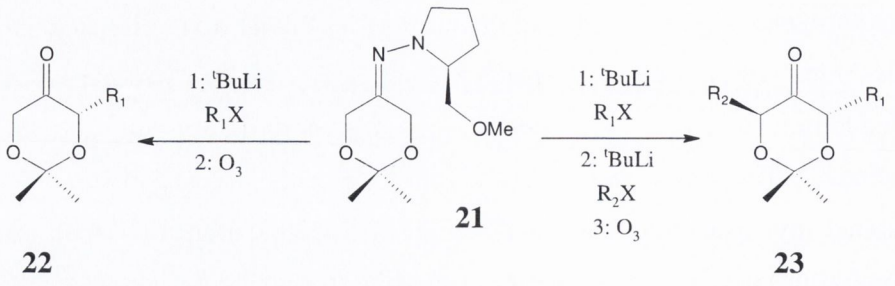
Oxazolidinones **1** have also found applications as chiral auxiliaries in asymmetric Diels-Alder reactions,[7] Reformatsky reactions,[8] singlet oxygen [2 + 2] cycloaddition reactions[9] and heterogeneous hydrogenations of alkenes[10] and pyridines.[11] The ready availability[12] and high level of conformational control exhibited by oxazolidinones **1** (through metal chelation or dipole moment minimisation) have resulted in their extensive use in natural product synthesis.

The (*S*)-pyrrolidine **15** ('SAMP') and its (*R*)-enantiomer ('RAMP') introduced by Enders *et al.* have become widely used chiral auxiliaries.[13] SAMP is available from (*S*)-proline while RAMP is derived from glutamic acid. Reaction with aldehydes or ketones yields chiral hydrazones which have been used in α-alkylations, aldol reactions, Michael additions and Diels-Alder reactions. Deprotonation of SAMP-derived hydrazone **17** yields aza-enolate **18** as a monomeric chelate whose top-face is efficiently shielded by the auxiliary. Approach of the electrophile from the bottom face leads to hydrazone **19.** Cleavage of the auxiliary by ozonolysis affords ketone **20** (**Scheme 1.4**).



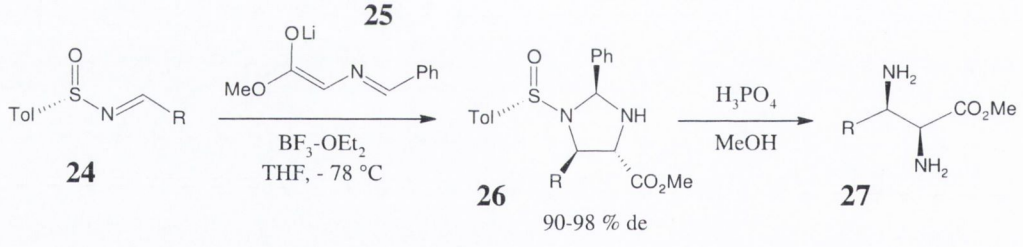

**Scheme 1.4**

Hydrazones like **21** have been used as chiral dihydroxyacetone synthons. Mono or bis-alkylation of **21** with various electrophiles proceeds with high enantio-and diastereoselectivity to afford the dihydroxyacetones **22** or **23** (**Scheme 1.5**).[14]



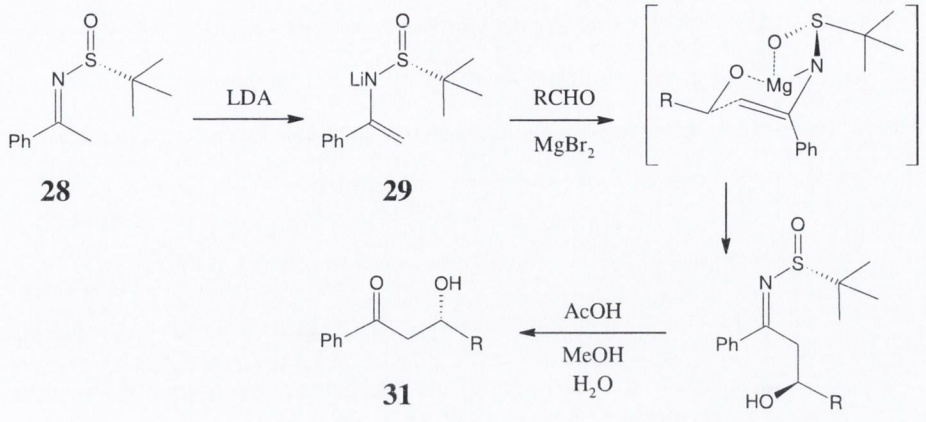

**Scheme 1.5**

Chiral sulfinamides are often employed in the form of their *N*-sulfinylimines. These are obtained by condensation of the enantiopure (*R*) or (*S*)-sulfinamides with the appropriate aldehyde or ketone.[15] Most applications of these sulfinylimines involve stereoselective additions of various nucleophiles to the sulfinyl-activated C=N bond, followed by destructive cleavage of the auxiliary to give a chiral amine. Cycloaddition reactions with 1,3-dipoles is also possible. Cycloaddition of sulfinylimine **24** with azomethine ylide **25** generated an enantiopure imidazoline **26** which upon hydrolysis and cleavage of the auxiliary afforded diaminoester **27** (**Scheme 1.6**).[16]




**Scheme 1.6**

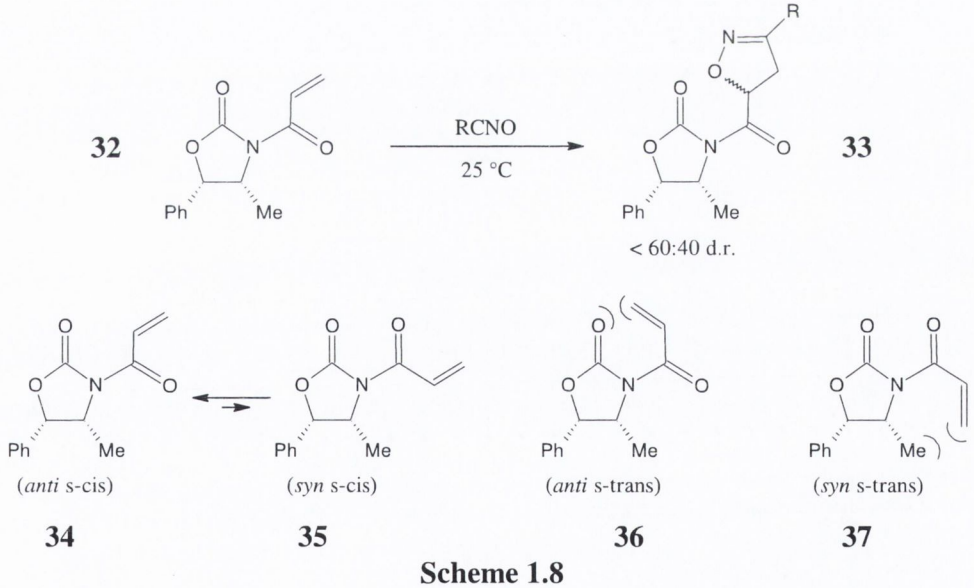
Aldols can also be obtained from sulfinylimines *via* their derived aza-enolates. Deprotonation of sulfinylimine **28** generates aza-enolate **29** which forms a six-membered transition state with the aldehyde in the presence of magnesium bromide. The β-hydroxy imine product **30** may be hydrolysed with non-destructive removal of the auxiliary to generate the aldol product **31** (**Scheme 1.7**).[17] Furthermore, **30** may be reduced in a highly diastereoselective fashion generating either *syn*- or *anti*-1,3-amino alcohols depending on the reducing agent used.




**28** **29** **30** **31**

**Scheme 1.7**

Although the above auxiliaries have been successfully used in many reactions involving metal ion chelation, in some cases poor levels of stereocontrol are observed in reactions carried out in the absence of a metal ion.[18] Acrylamide **32** derived from the Evans auxiliary for example gives virtually no stereocontrol in thermal dipolar cycloaddition reactions (**Scheme 1.8**).




**32** **33** **34** **35** **36** **37**

**Scheme 1.8**

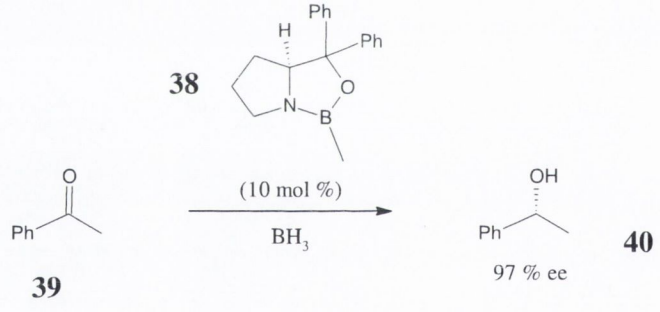
Of the four possible acrylimide rotamers, the s-*trans* rotamers **36** and **37** are disfavoured due to steric interactions between the alkene and the substituents on the auxiliary (see **Scheme 1.8**). Between the two s-*cis* rotamers **34** and **35**, the *anti* s-*cis* rotamer **34** is more favoured due to the unfavourable dipole alignment in **35**. Of these two rotamers, the favoured rotamer **34** has the methyl group of the auxiliary in a poor position to influence the face selectivity of the reaction, whereas in the

disfavoured rotamer **35**, the methyl group is well positioned to affect face selectivity. Assuming the rotamer populations in th ground state will be reflected in the transition state, it is believed that rotamer **34** leads primarily to product formation with subsequent low levels of stereocontrol.

### 1.1.3 Chiral Reagents and Catalysts in Asymmetric Synthesis

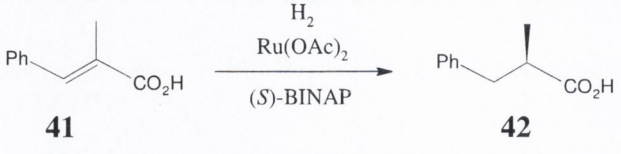
For many reactions, the use of chiral auxiliaries has steadily been replaced by methods which employ chiral reagents and catalysts, particularly those used in industry.[19] A brief overview of some of the most important of these is given below.

One of the best methods for the asymmetric reduction of prochiral ketones was developed by Corey *et al.* in 1987. In the presence of borane, boron heterocycle **38** derived from proline reduces ketones **39** to secondary alcohols **40** with excellent enantioselectivities (**Scheme 1.9**).[20]




**Scheme 1.9**

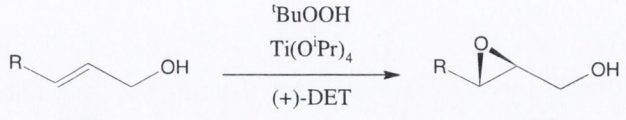
Noyori *et al.* pioneered the asymmetric homogeneous hydrogenation of alkenes using rhodium and ruthenium complexes of chiral diphosphine ligands (**Scheme 1.10**).[21] The reaction works best when the alkene bears an additional heteroatom which can coordinate with the metal (e.g.: enones, allylic alcohols).




**Scheme 1.10**

Two of the most important asymmetric oxidation reactions are the asymmetric epoxidation and asymmetric dihydroxylation reactions developed by Sharpless and co-workers. Discovered in 1981, the Sharpless asymmetric epoxidation reaction

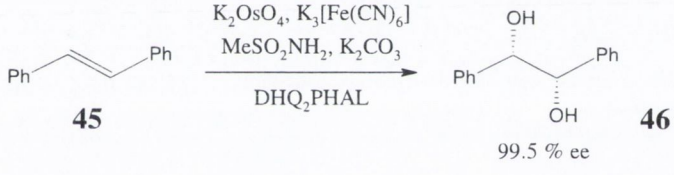
allows the preparation of enantiomerically enriched epoxy-alcohols **44** from allylic alcohols **43** using *tert*-butylhydroperoxide and a chiral complex derived from diethyl tartrate and titanium (IV) isopropoxide (**Scheme 1.11**).[22]




**43** **44**

**Scheme 1.11**

The Sharpless asymmetric dihydroxylation reaction is perhaps the most important method in asymmetric catalysis.[23] Diols such as **46** may be obtained in very high enantiomeric excesses from a wide range of alkenes, both electron rich and electron poor, by reaction with catalytic osmium tetroxide and a stoichiometric co-oxidant in the presence of a chiral phthalazine-based ligand derived from dihydroquinidine (DHQD) or dihydroquinine (DHQ) (**Scheme 1.12**).

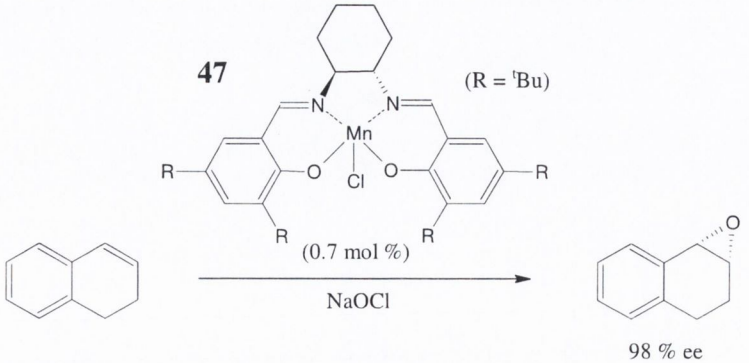



**45** **46**

99.5 % ee

**Scheme 1.12**

One of the best methods for the asymmetric epoxidation of unfunctionalised olefins is the Jacobsen-Katsuki asymmetric epoxidation.[24] The oxidant is a μ-oxo complex of the chiral $C_2$-symmetric manganese-salen complex **47** which is regenerated after each catalytic cycle by the stoichiometric co-oxidant (**Scheme 1.13**).




98 % ee

**48** **49**

**Scheme 1.13**

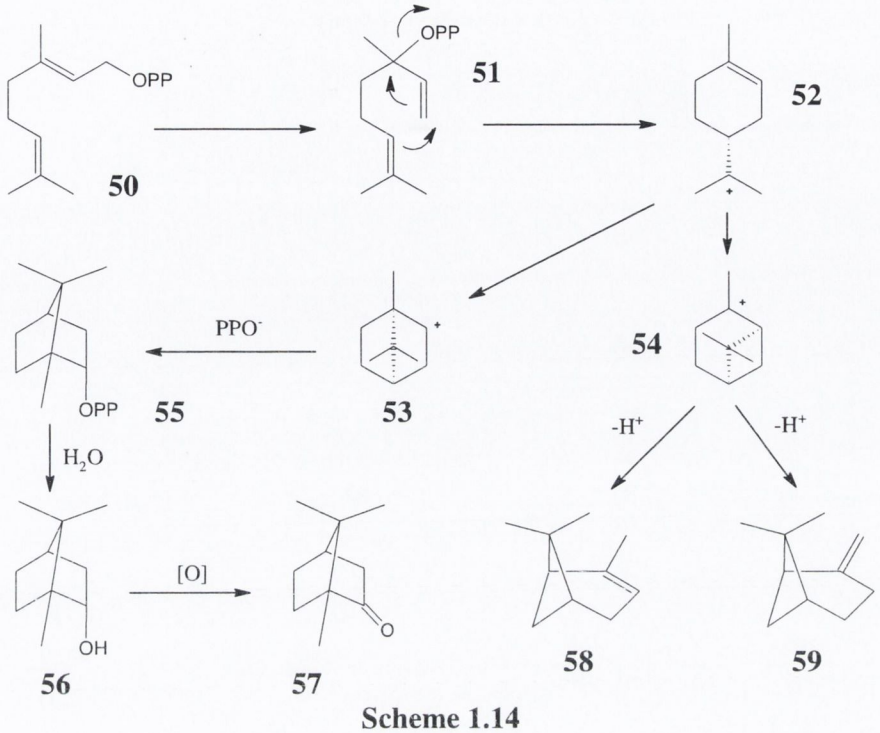
As well as the above-mentioned methods, many other methods have been developed for asymmetric synthesis. Some of the most notable include the asymmetric allylation of aldehydes and ketones using chiral allylboranes,[25] the use of chiral copper (II) bis-oxazolines and other chiral Lewis acids in Diels-Alder reactions, Michael additions and related reactions,[26] palladium and iridium-catalysed asymmetric allylic substitutions,[27] asymmetric epoxidation of olefins by dioxiranes derived from chiral ketones,[28] the asymmetric epoxidation of electron deficient olefins catalysed by polyamino acids (Julia-Colonna) or by phase transfer catalysts and the use of chiral organocatalysts based on proline and DMAP.[29]

## 1.2 Camphor Derivatives in Asymmetric Synthesis

### 1.2.1 Origins and Biosynthesis of Camphor

Camphor is a bicyclic monoterpenoid isolated from the camphor laurel tree (*cinnamonum camphora*) found in Borneo, Taiwan and other parts of Asia.[30] It can also be isolated from oil of turpentine. Camphor has found use as an antimicrobial substance, decongestant, moth repellent and is widely used in cooking in India. Camphor was first prepared synthetically by Komppa in 1903.[31]

The biosynthesis of (+)-camphor **57** is shown in **Scheme 1.14**. Condensation of isopentenylpyrophosphate and dimethylallylpyrophosphate forms geranyl-pyrophosphate **50** which undergoes allylic isomerisation to linaloylpyrophosphate **51**. Cationic cyclisation forms cation **52** which can form one of two possible bicyclic cations **53** and **54**. Cation **53** is trapped to form bornylpyrophosphate **55** which is hydrolysed to borneol **56** and finally oxidised to (+)-camphor **57**. The regioisomeric cation **54** forms α-pinene **58** or β-pinene **59** after proton loss.




**Scheme 1.14**

Many different derivatives of camphor have been prepared.[32] As a result, camphor and its derivatives have found widespread use as sources of chirality in natural product synthesis and asymmetric synthesis. These applications will be discussed in the next section.

### 1.2.2 Camphor Derivatives as Chiral Auxiliaries

The rigid bicyclic structure of the camphor backbone is an attractive structural feature for chiral auxiliary applications. As a result, many derivatives of camphor have been successfully used as chiral auxiliaries in asymmetric synthesis.[33] The most important of these are shown in **Figure 1.2**.

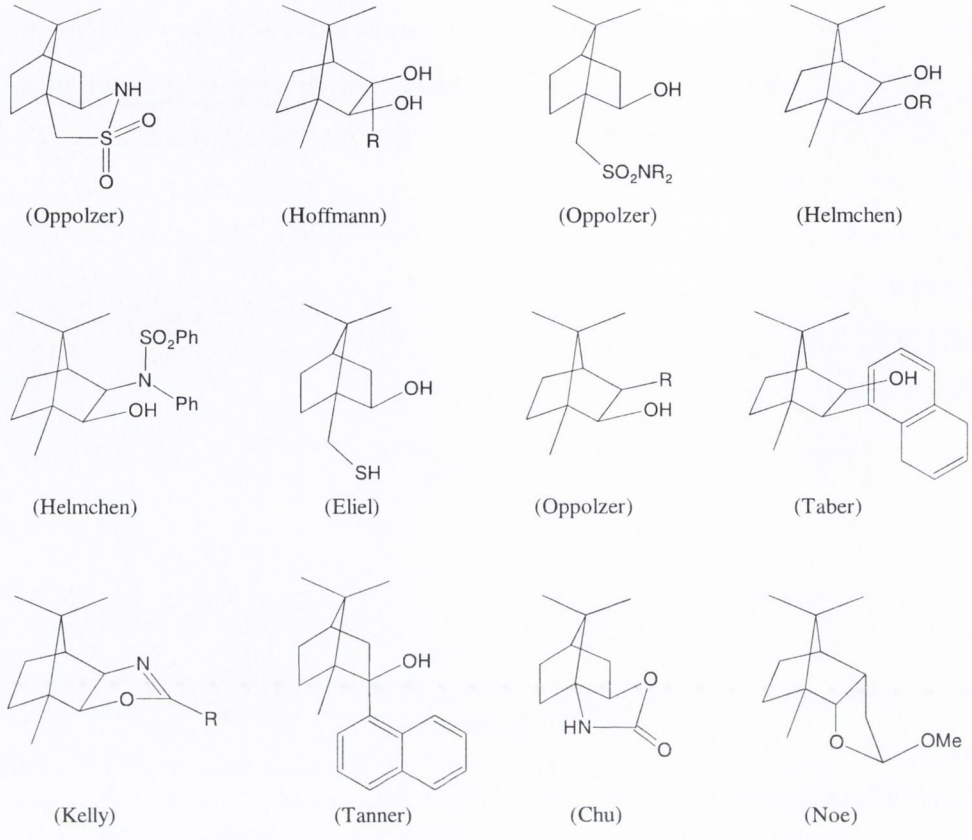


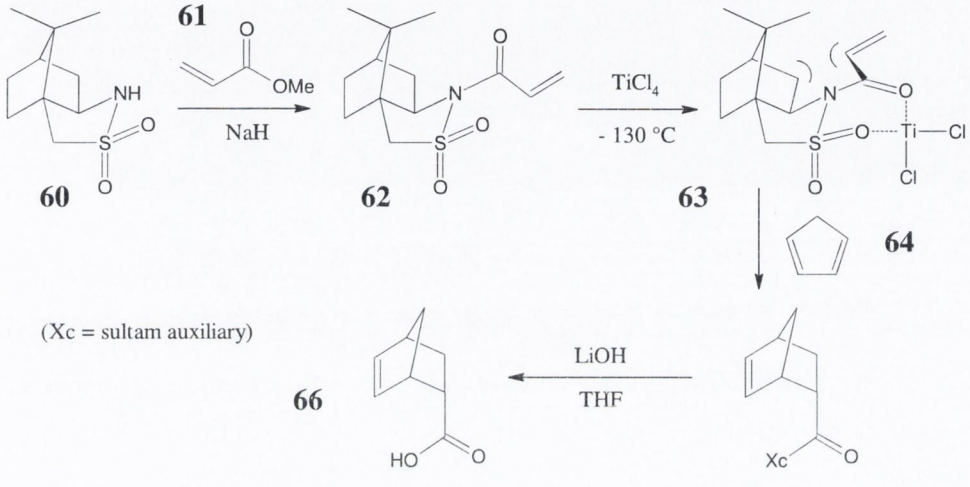

**Figure 1.2**

**Important camphor-derived chiral auxiliaries**

Perhaps the most well known and widely used of these auxiliaries is Oppolzer's sultam **60**, first introduced in 1984.[34] This auxiliary is usually attached to substrates by acylation of the sultam nitrogen, with removal being effected by mild alkaline hydrolysis or reduction. Sultam **60** has been applied to an impressive variety of reactions, both with and without chelating metals, with good to excellent stereocontrol which in most cases can be raised by recrystallisation prior to auxiliary removal.[35] In many cases, the face selectivity for metal catalysed reactions is the same as that found in thermal reactions involving no metal-ion chelation.

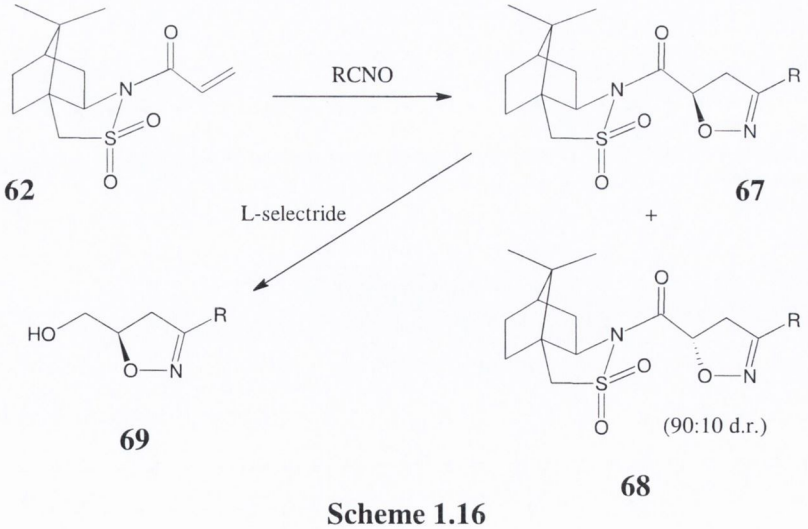
Acryloyl sultam **62** gave adducts **65** with very high *endo* and π-face selectivities in Diels-Alder reactions with cyclopentadiene **64** catalysed by Lewis acids (**Scheme 1.15**).[34] These adducts were obtained pure following crystallisation. Removal of the auxiliary afforded enantiopure acid **66**. Similar results were obtained with

butadiene and isoprene as well as in intramolecular Diels-Alder reactions. The face selectivity is rationalised by invoking approach of the diene toward the C(α)-*Re* face opposite the $C_3$-methylene group of chelated intermediate **63**. The same cycloadduct **65** is obtained by thermal Diels-Alder reaction of acryloyl sultam **62** with cyclopentadiene **64**, albeit with lower face selectivity (83:17 d.r.).[36]



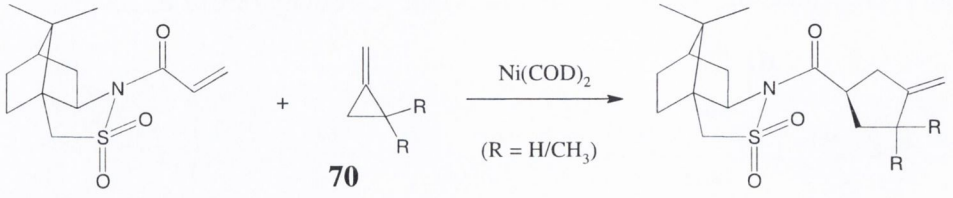

**Scheme 1.15**

In dipolar cycloaddition reactions with nitrile oxides, acryloyl sultam **62** formed adducts **67** and **68** with good diastereoselectivity (90:10 **67**:**68**). Chromatographic separation, followed by reduction with *L*-selectride furnished the isoxazoline **69** (**Scheme 1.16**).[37] Although these levels of asymmetric induction were not exceptional, various other auxiliaries were found to be ineffective in this reaction.[38]




**Scheme 1.16**

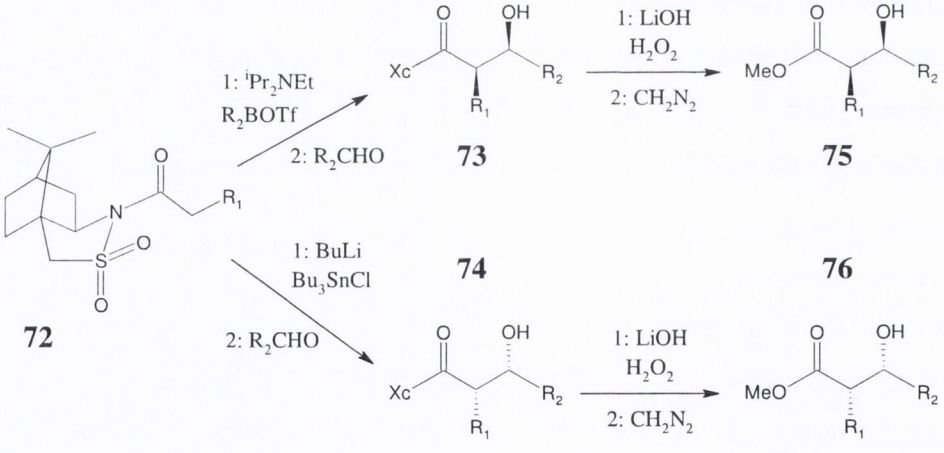
In nickel-catalysed [3 + 2] cycloadditions of methylenecyclopropanes **70**, acryloyl sultam **62** gave adducts **71** with face-selectivities ranging from 82:18 to 99:1 (**Scheme 1.17**). Once again out of several auxiliaries examined, sultam **60** provided the highest levels of stereocontrol.[39]




**62** **70** **71**

**Scheme 1.17**

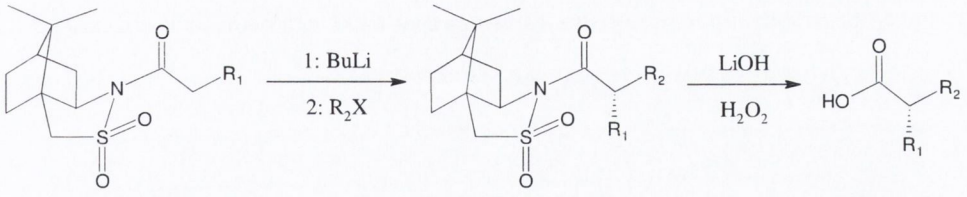
Chiral enolates derived from sultam **60** have also given excellent results in aldol reactions. The *cis*-enolates derived from *N*-acyl sultams **72** react with aldehydes to give diastereomerically pure *syn*-aldol products whose absolute stereochemistry depends on the choice of metal ion. The use of a boron enolate leads to aldol **73** whereas the lithium or tin enolate gives the diastereomeric aldol **74**. Mild hydrolysis and esterification leads to enantiopure β-hydroxyesters **75** and **76** (**Scheme 1.18**).[40]




**72** **73** **74** **75** **76**

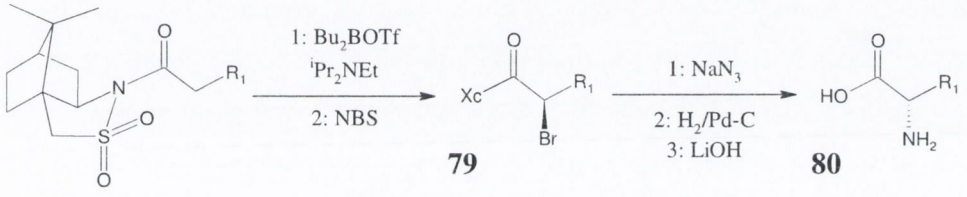
**Scheme 1.18**

Analogous alkylations of chelated enolates derived from **72** gives virtually diastereomerically pure adducts **77** which, following crystallisation and hydrolysis furnished enantiopure carboxylic acids **78** (**Scheme 1.19**).[41]



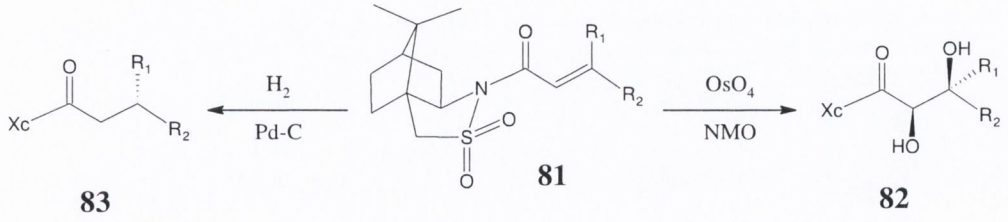

**Scheme 1.19**

Sultam enolates have also been used in the asymmetric synthesis of α-amino acids. Reaction of boron enolate derived from **72** with *N*-bromosuccinimide gave **79** in high diastereomeric purity. Displacement of **79** with azide, followed by hydrogenolysis and cleavage of the auxiliary gave the optically active (*S*)-amino acids **80** (**Scheme 1.20**).[42] Alternatively, direct α-amination of the chiral enolate can be carried out using 1-chloro-1-nitrosocyclohexane.




**Scheme 1.20**

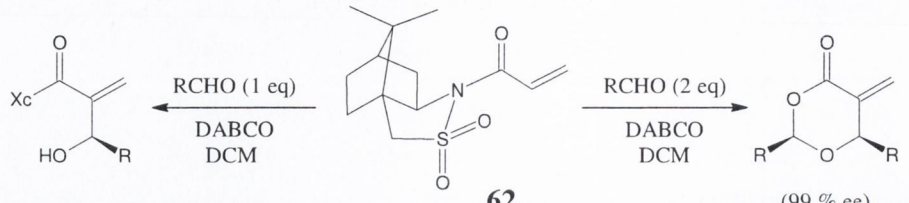
Asymmetric oxidation and reduction reactions have also been carried out on enoyl sultams. Dihydroxylation of sultam **81** with osmium tetroxide/*N*-methylmorpholine-*N*-oxide provided diol **82** as the major isomer with diastereomer ratio's as high as 95:5 (**Scheme 1.21**).[43] This method has been applied to the synthesis of the fungal metabolite (+)-LLP-880β. In addition, simple hydrogenation of enoyl sultams **81** gave saturated sultams **83** with very high π-face selectivity.[44]




**Scheme 1.21**

More recently, Oppolzer's sultam has also been used as a chiral auxiliary in the Baylis-Hillman reaction. Reaction of enoyl sultam **62** with aliphatic aldehydes leads to the expected products **84**. The use of two equivalents of aldehyde however

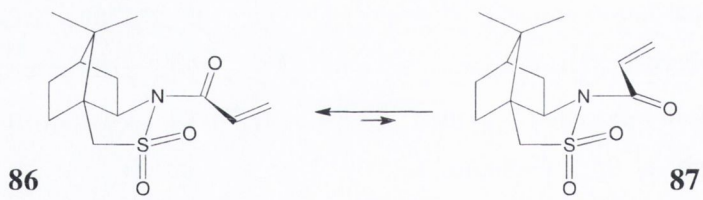
leads to the *in situ* cleavage of the auxiliary and the formation of the cyclic product **85** with very high enantiomeric excess (**Scheme 1.22**).[45]




**84** **62** **85**

**Scheme 1.22**

Why is the observed face selectivity the same in derivatives of Oppolzer's sultam **60** in both thermal reactions (no metal ions) and reactions involving metal-ion chelation? This observation is analogous to the behaviour of $C_2$-symmetric auxiliaries which effectively react through only one rotamer. A model has been proposed in which **60** can be effectively considered to be a 2,5-dialkylpyrrolidine 'in disguise'.[18] Of the four possible planar rotamers of *N*-acryloyl derivatives of **60**, the *anti* s-*cis* rotamer **86** can be considered the most highly populated in the ground state (*cf* Evans auxiliary, see **Scheme 1.8**). This analysis is supported by crystal structures of many derivatives of **60** (**Scheme 1.23**).[46]




**86** (*anti* s-cis) (*syn* s-cis) **87**

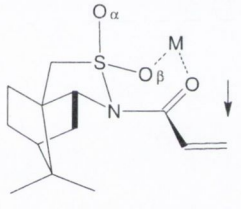
(*anti* s-trans) (*syn* s-trans)

**88** **89**

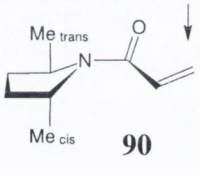
**Scheme 1.23**

Assuming these conformational preferences are reflected in the transition state, the results of thermal reactions dictate that the attacking reagents approach the top face of rotamer **86**. In Oppolzer's chelate model,[34] metal chelation forces the carbonyl

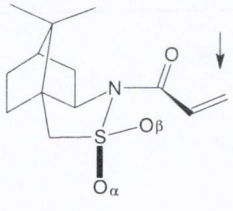
and sulfonyl oxygens into a *syn* alignment, and reagents approach the bottom face of **86** opposite the $C_3$-methylene group. The analogy of chelated and non-chelated derivatives of sultam **60** with *N*-acryloyl derivatives of 2,5-dimethylpyrrolidine[47] **90** is shown in **Figure 1.3**. In thermal reactions, the non-chelate model applies in which the sulfonyl Oα plays the role of the *cis*-methyl group of **90** in shielding the bottom face of the acryloyl unit. In metal chelated reactions, the chelate model can be used. In this model, the sulfonyl Oα is now in the same approximate location as the *trans*-methyl group of **90** and is too far away from the acryloyl unit. Instead, it is the $C_2$-$C_3$ bond of the camphor ring which effectively acts as the *cis*-methyl group of **90** in shielding the bottom face. In agreement with the results, both models predict that chelated and non-chelated reactions will produce the same stereoisomers. The model also predicts why Oppolzer's sultam **60** is a good auxiliary in thermal reactions (e.g.: dipolar cycloadditions, radical reactions) while other imide based auxiliaries (e.g.: Evans auxiliary) are not.




(chelate model) **92**




**90** (2,5-dimethylpyrrolidine)

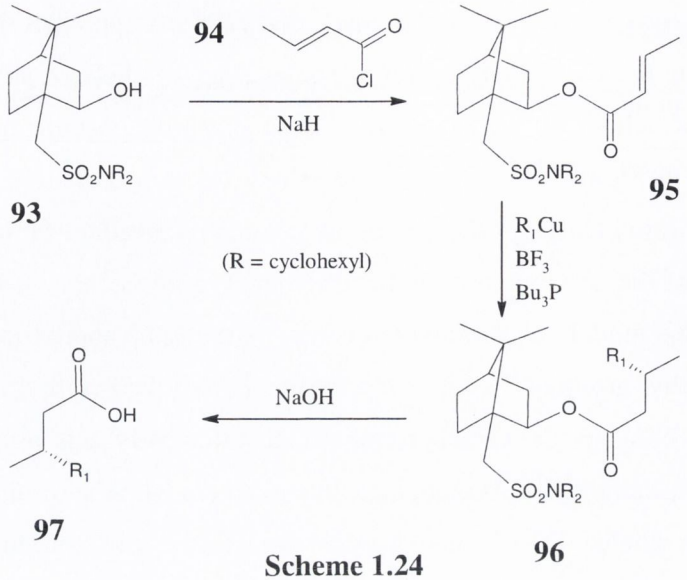



(non-chelate model) **91**

**Figure 1.3**

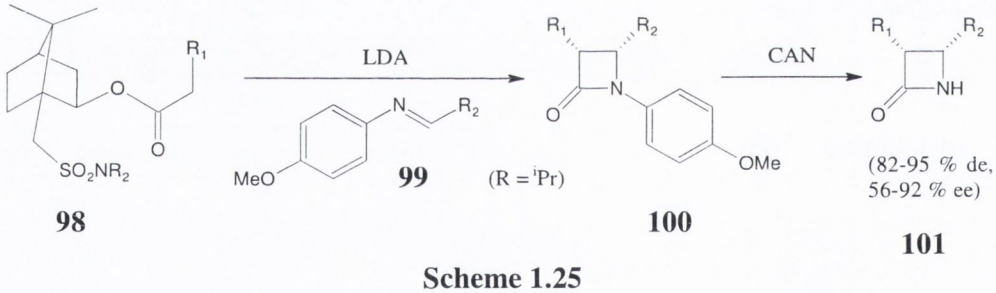
**Analogy of derivatives of sultam 60 with 2,5-dimethylpyrrolidine 90**

Oppolzer's sulfonamide **93** has also proven to be an effective auxiliary in many reactions, including cycloaddition reactions, Michael additions, alkylations and aldol reactions. For example, acylation of **93** with **94** gave enoate **95**. Conjugate addition of an organocopper reagent occurred from the π face opposite the sulfonamido group to give adduct **96** which after saponification afforded the acid **97** in 94-98 % ee (**Scheme 1.24**).[48]



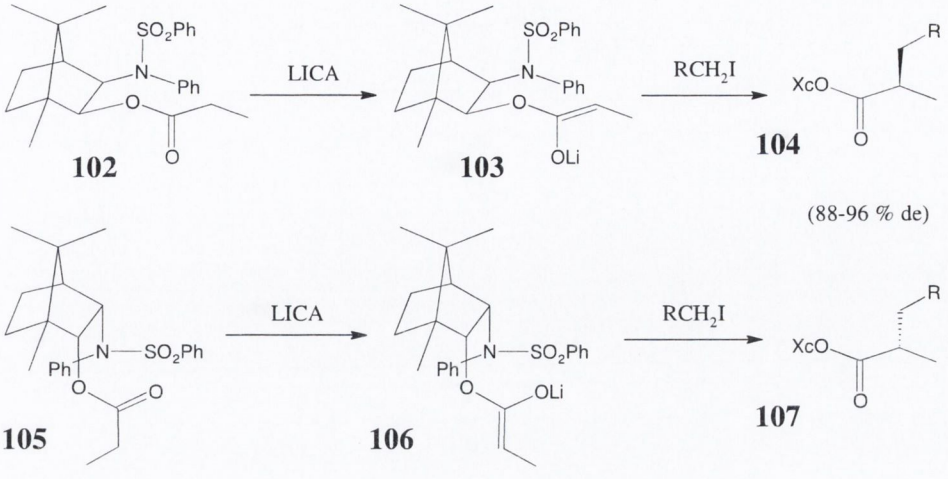

**Scheme 1.24**

Lithium enolates derived from *O*-acyl sulfonamides **98** reacted with imines **99** to afford lactams **100** with *in situ* cleavage of the auxiliary. Treatment of lactams **100** with ceric ammonium nitrate furnished the β-lactams **101** with good control of both absolute and relative stereochemistry (**Scheme 1.25**).[49]



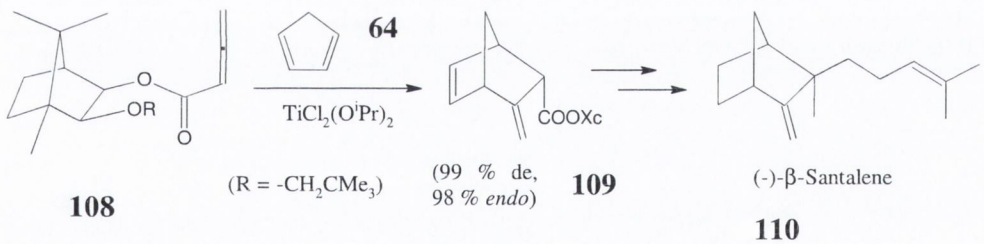

**Scheme 1.25**

The 3-*N*-arylsulfonamidoisoborneol auxiliary developed by Helmchen *et al.* is an effective auxiliary in a number of electrophilic α-substitution reactions of its *O*-acyl derivatives. For example, alkylation of enolate **103** derived from **102** gives **104** *via* attack from the face opposite the $C_3$-sulfonamido group. Interestingly, the epimeric product **107** is obtained when the corresponding bornyl derivative **105** is employed (**Scheme 1.26**).[50]



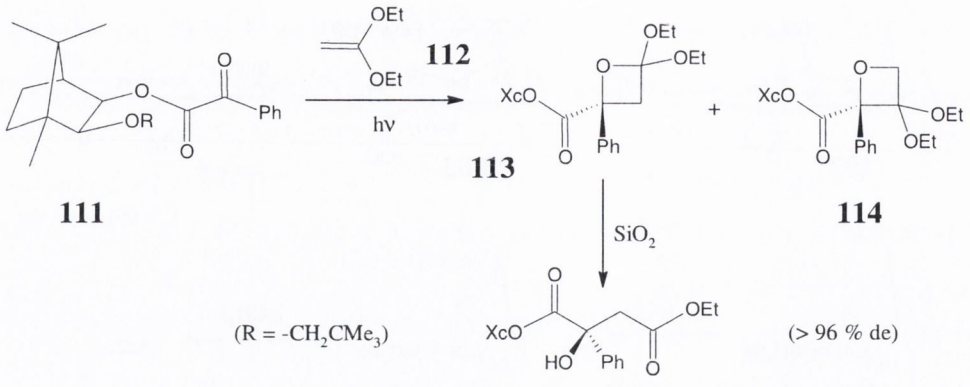

**Scheme 1.26**

Neopentyl derivatives of Helmchen's 3-hydroxyisoborneol auxiliary have been applied to asymmetric Diels-Alder and related reactions. Lewis acid-catalysed Diels-Alder reaction of allenic ester **108** with cyclopentadiene **64** afforded cycloadduct **109** with high *endo* and diastereoselectivity. Further elaboration of **109** and auxiliary removal gave (-)-β-santalene **110** (**Scheme 1.27**).[51]



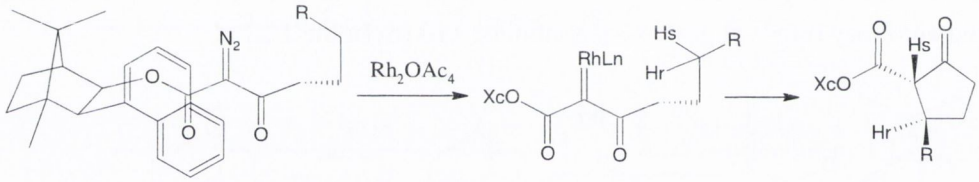

**Scheme 1.27**

Similarly derived glyoxalates have been used in asymmetric Paterno-Büchi reactions. For example, photoaddition of 1,1-diethoxyethene **112** to glyoxalate **111** gave rise to the regioisomeric adducts **113** and **114** each in > 96 % diastereomeric excess. Further treatment of **113** gave the acyclic derivative **115** (**Scheme 1.28**).[52]




**Scheme 1.28**

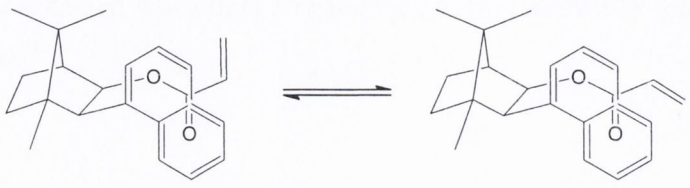
The naphthalene-based auxiliary developed by Taber *et al.* has been employed in asymmetric rhodium catalysed C-H insertion reactions. Auxiliary acylation afforded diazoketoester **116** whose side-chain is folded toward the back by the face shielding naphthalene group. Intramolecular C-H insertion afforded cyclopentanone **118** in 66-86 % diastereomeric excess (**Scheme 1.29**).[53]




**116** **117** **118**

**Scheme 1.29**

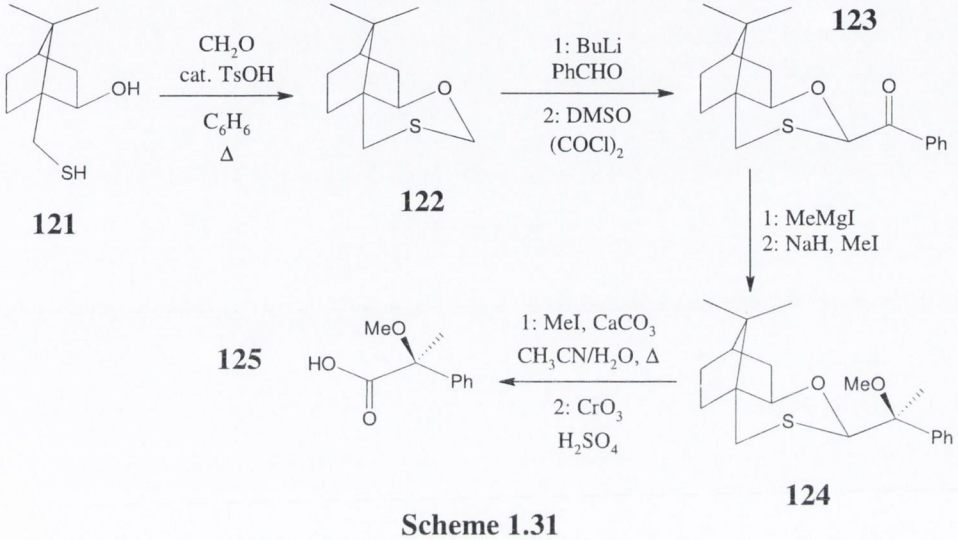
On the other hand, analogous acrylate esters give poor levels of stereocontrol in thermal reactions, such as dipolar cycloadditions and radical reactions.[18] The origin of this poor selectivity is believed to be a lack of rotamer control in the acrylate unit, with both s-*trans* and s-*cis* rotamers **119** and **120** participating in the reaction (**Scheme 1.30**). Thus, despite the presence of an excellent face-shielding group in close proximity to the prochiral acrylate, diastereomeric mixtures are obtained.



(s-trans) **119** (s-cis) **120**

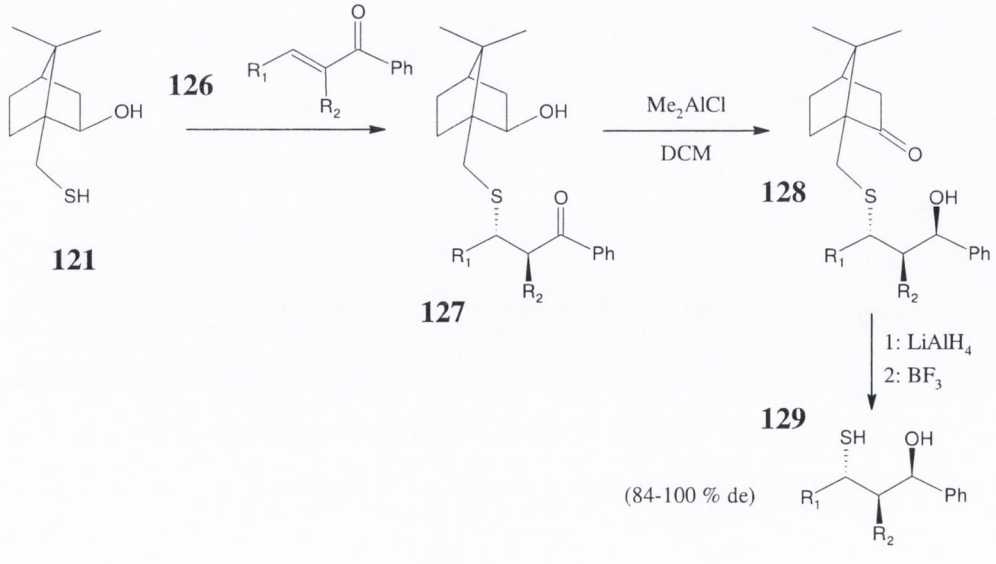
**Scheme 1.30**

Conformationally locked 1,3-oxathianes derived from 10-mercaptoisoborneol **121** were converted into equatorially substituted ketones **123**. Chelation-controlled addition of methylmagnesium iodide occurred from the side opposite the sulfur atom. Subsequent methyl ether formation, cleavage of the auxiliary and oxidation furnished acid **125** in high enantiomeric purity (**Scheme 1.31**).[54]



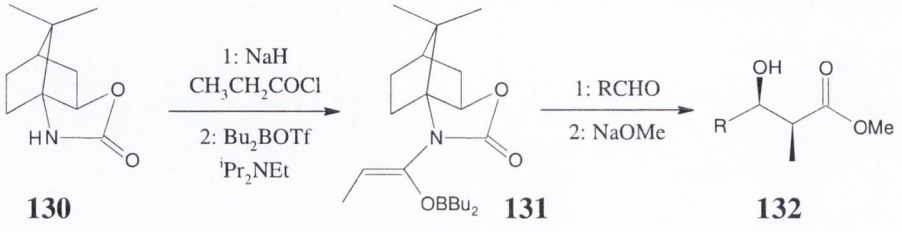

**Scheme 1.31**

More recently, auxiliary **121** has been used in a tandem Michael addition Meerwein-Ponndorf-Verley (MPV) reduction with enones. Michael addition of **121** to enone **126**, followed by MPV reduction afforded alcohol **128** in high diastereomeric excess. Destructive cleavage of the auxiliary with transfer of the sulfur atom occurred to give mercaptoalcohol **129** (**Scheme 1.32**).[55]



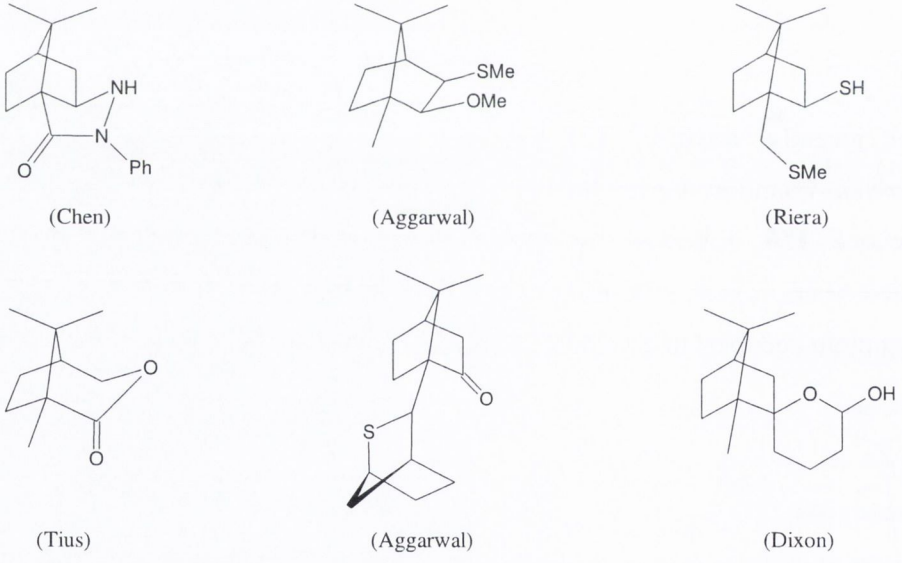

**Scheme 1.32**

Oxazolidinone **130** has been employed as a chiral auxiliary in asymmetric aldol reactions by Chu *et al.* Boron enolates of *N*-acyl derivatives of **130** react with aldehydes with virtually complete stereoselectivity to afford the *syn* β-hydroxyester **132** as a single stereoisomer after removal of the auxiliary (**Scheme 1.33**).[56]




**Scheme 1.33**

In addition to the auxiliaries mentioned above, a number of camphor derived chiral auxiliaries have been recently developed within the last seven years. Some of these are shown in **Figure 1.4**.



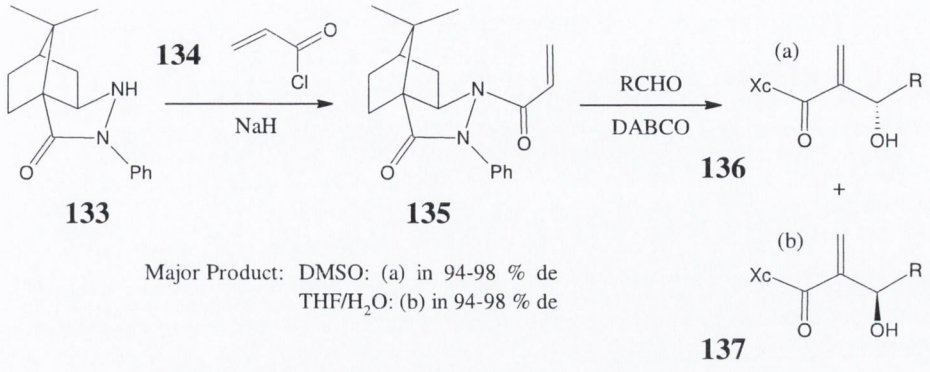

(Chen) (Aggarwal) (Riera)

(Tius) (Aggarwal) (Dixon)

**Figure 1.4**

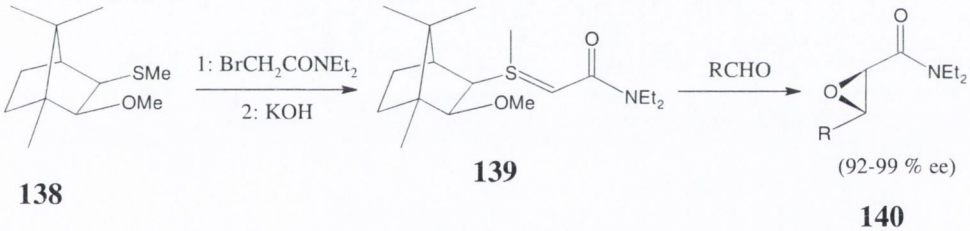
**Recent camphor-derived chiral auxiliaries**

Auxiliary **133** has been developed by Chen *et al.* for asymmetric Baylis-Hillman reactions. Acrylate **135** derived from **133** reacted with aldehydes in the presence of DABCO to give one of two diastereomeric adducts depending on the choice of solvent. In DMSO, diastereomer **136** predominated whereas in THF/water **137** was the major product (**Scheme 1.34**).[57]



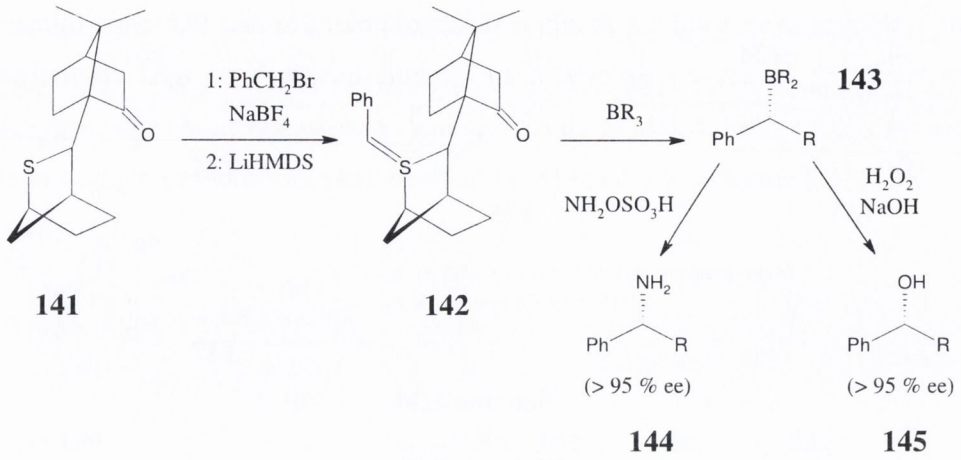

**Scheme 1.34**

Sulfur ylides derived from sulfide **138** have been used in asymmetric Darzens reactions. Alkylation of sulfide **138** and deprotonation produced ylide **139** which reacts with aldehydes to afford epoxides **140** with high enantioselectivities, particularly with aromatic aldehydes (**Scheme 1.35**).[58] Ylides derived from auxiliary **138** have also been used in the asymmetric cyclopropanation of electron deficient alkenes.[59]



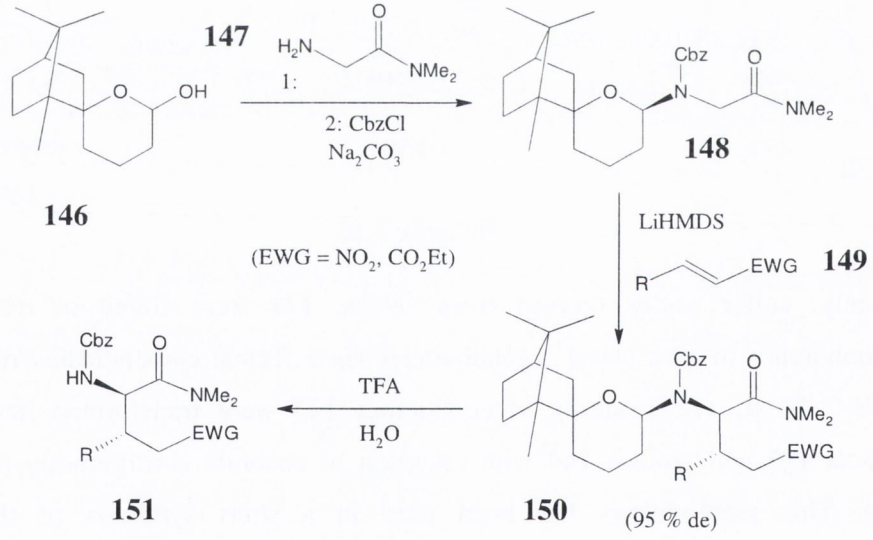

**Scheme 1.35**

Recently, sulfur ylides derived from sulfide **141** were found to react with organoboranes to give chiral organoboranes *via* a formal carbenoid insertion into the B-C bond. The resulting organoboranes **143** were transformed into chiral alcohols **145** and amines **144** with retention of absolute configuration (**Scheme 1.36**). This methodology has been used in a short synthesis of the anti-inflammatory agents neobenodine and cetirizine.[60]




**Scheme 1.36**

Lactol auxiliary **146** can be converted into glycinamide derivatives **148** by direct condensation with an α-amino amide **147**. Lithium enolates derived from **148** react with Michael acceptors **149** with high stereoselectivity to afford the derivatives **150**. Acidic hydrolysis of **150** regenerates the auxiliary **146** and yields protected amino acid derivatives **151** with two newly formed stereocentres (**Scheme 1.37**).[61]

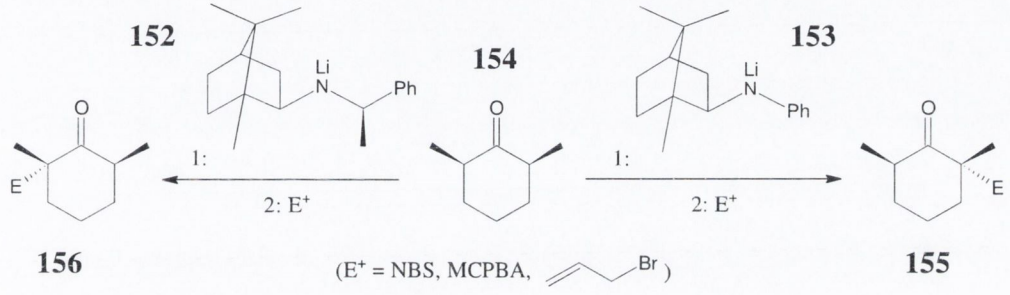



**Scheme 1.37**

### 1.2.3 Camphor Derivatives as Chiral Reagents and Catalysts

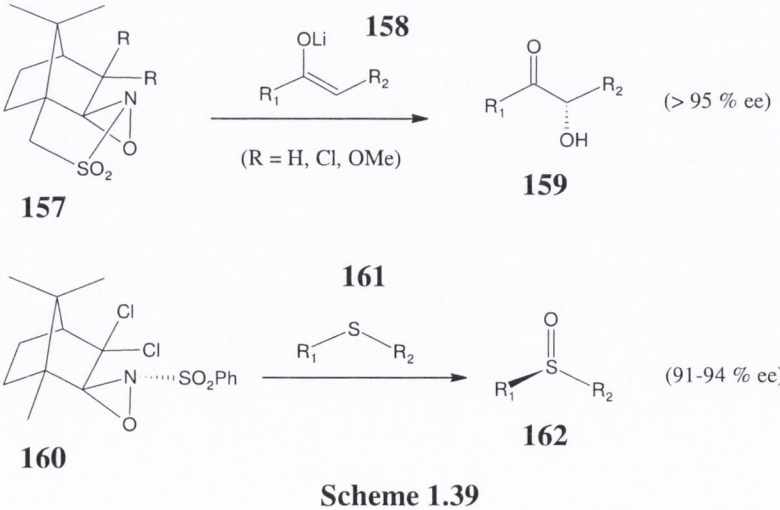
In addition to the widespread use of derivatives of camphor as chiral auxiliaries, many derivatives have been employed as chiral reagents or as chiral ligands in metal-catalysed reactions.[62] Some of these examples are illustrated below.

Chiral camphor-derived lithium amide bases **152** and **153** have been developed by Simpkins *et al.* for the enantioselective deprotonation of prochiral ketones.[63] Deprotonation of ketone **154** with amide base **152** and subsequent trapping of the chiral enolate with an electrophile gave the ketone **156** with good enantioselectivity. The enantiomeric ketone **155** was obtained *via* deprotonation of **154** using amide base **153** (**Scheme 1.38**).



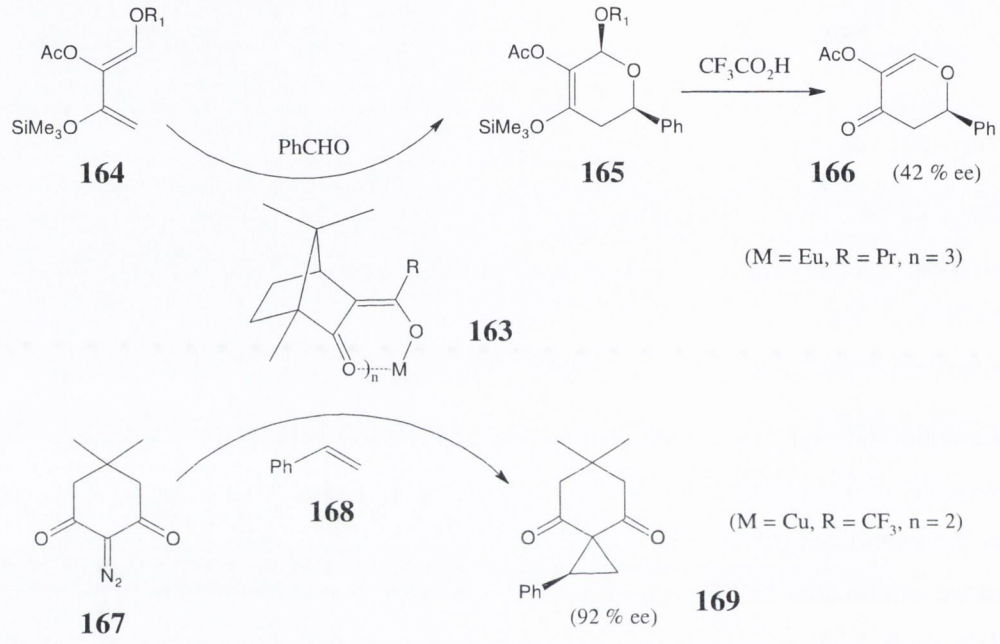

**Scheme 1.38**

Camphorsulfonyl oxaziridines **157** (prepared from the camphorsulfonyl imines) are versatile chiral electrophilic oxidising reagents. The most widely used application is the enantioselective oxidation of enolates to α-hydroxycarbonyl compounds. A range of enolates **158** have been oxidised to chiral α-hydroxycarbonyl compounds **159** with high enantiomeric excesses (**Scheme 1.39**).[64] A related *N*-sulfonyl oxaziridine **160** has also been applied to the stoichiometric synthesis of enantiomerically enriched sulfoxides **162** from sulfides **161**.[65]



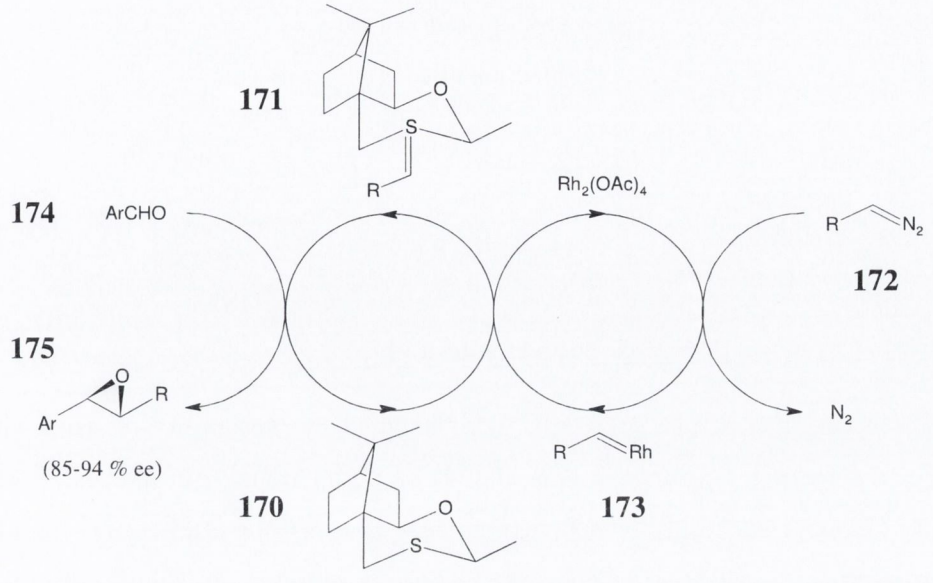

**Scheme 1.39**

Danishefsky *et al.* found that europium complexes of 3-acyl camphor derivative **163** catalysed hetero Diels-Alder reactions of ienes **164** and aromatic aldehydes.[66] The dihydropyran products **165** were transformed into products **166** albeit with only modest enantioselectivity (**Scheme 1.40**). Similarly, copper complexes of bidentate ligand **163** catalyse the asymmetric cyclopropanation of alkenes to form cyclopropanes **169** with good enantioselectivity.[67]



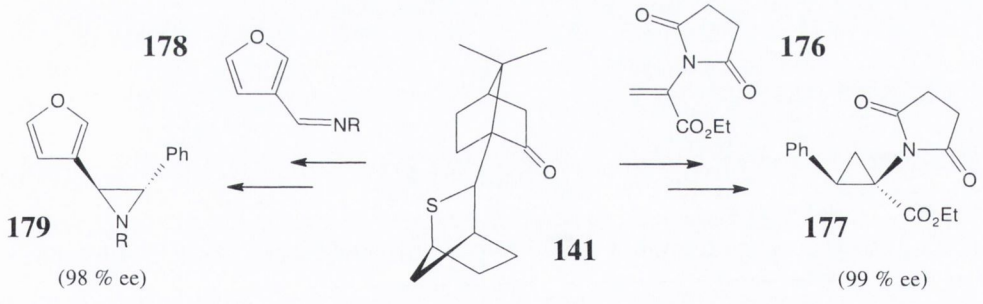

**Scheme 1.40**

Catalytic variants of the stoichiometric sulfur ylide carbonyl epoxidation reactions (see **Scheme 1.35**) have been developed by Aggarwal *et al.* Sub-stoichiometric amounts of sulfide **170** react with rhodium carbenes **173** generated *in situ* from diazo-compounds **172** to form ylides **171**. Reaction of aldehydes **174** with **171** furnishes epoxides **175** and regenerates sulfide **170** which re-enters the catalytic cycle (**Scheme 1.41**).[68] Additionally, the diazo-compounds are more safely generated *in situ* by thermal decomposition of tosylhydrazone salts.[69]



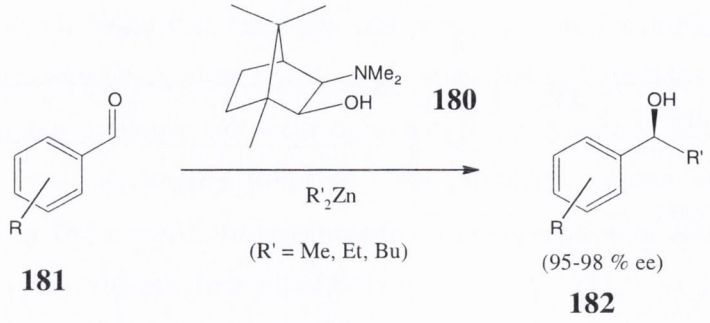

**Scheme 1.41**

The same catalytic cycle has been used for the epoxidation of carbonyl compounds using sulfide **141**, available from (+)-camphor-10-sulfonyl chloride in four steps.[70] Sulfide **141** also catalyses the cyclopropanation of electron deficient alkenes (e.g.: **176**) and the aziridination of imines (e.g.: **178**) using this protocol (**Scheme 1.42**).[71]



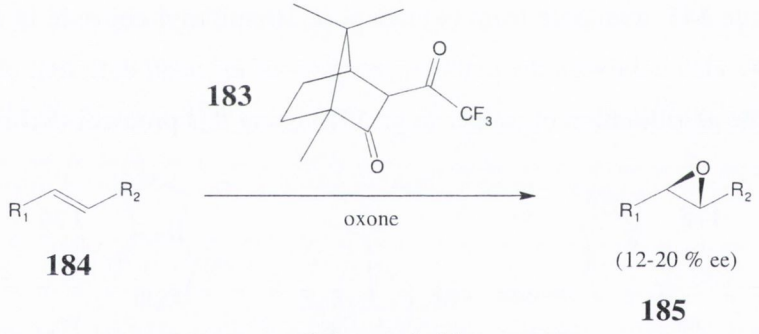

**Scheme 1.42**

Camphor-derived β-aminoalcohol **180** has been used as a chiral ligand in the asymmetric addition of dialkylzinc reagents to aldehydes. Noyori *et al.* obtained chiral alcohols **182** in high yield and enantiomeric excess by the addition of dialkylzinc reagents to aromatic aldehydes **181** in the presence of **180** (**Scheme 1.43**).[72] More recently, **180** gave high levels of stereoinduction as a ligand in asymmetric Reformatsky reactions.[73]




**Scheme 1.43**

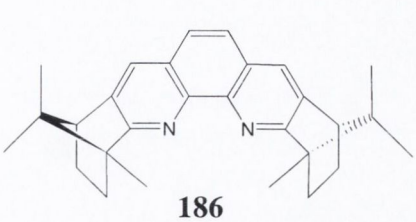
The pioneering work of Curci *et al.* demonstrated the possibility of using chiral dioxiranes for the asymmetric epoxidation of unfunctionalised alkenes. Various chiral ketones, including (+)-3-(trifluoroacetyl) camphor **183** were found to catalyse the epoxidation of alkenes **184** by oxone, although the enantioselectivities were low (**Scheme 1.44**).[74] A range of superior ketone catalysts have since been developed for this reaction.



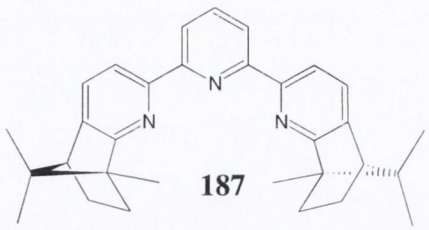

**Scheme 1.44**

In recent years, many camphor based pyridine ligands have been synthesised and used in asymmetric catalysis (**Figure 1.5**).[75] Some of these ligands have displayed good enantioselectivities in various reactions, including allylic substitutions, allylic oxidations, additions of organozinc reagents to carbonyl compounds and hydrogenations. For example, bidentate ligand **190** gave up to 96 % enantiomeric excess in the iridium-catalysed hydrogenation of alkenes **193** (**Scheme 1.45**).[76]

Various other N, P and S-containing camphor-derived ligands have been developed for metal-catalysed reactions.[77] Ligand **195** gave high enantioselectivities in palladium-catalysed allylic substitutions, while ligand **196** has been applied to the nickel-catalysed enantioselective addition of diethylzinc to chalcones.




**186**

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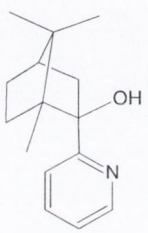


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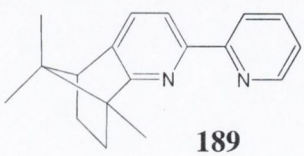


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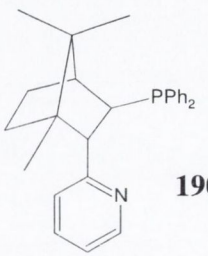


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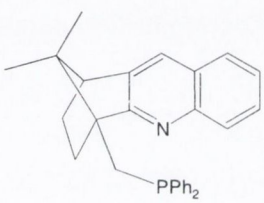


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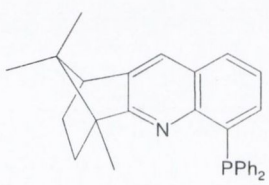
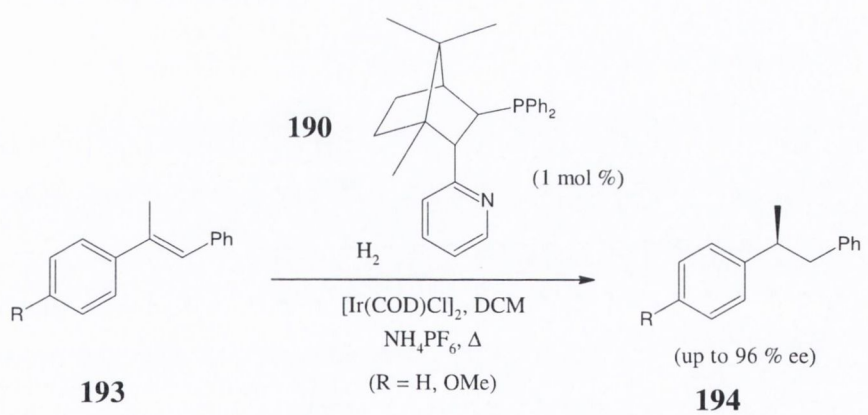



**192**

**Figure 1.5**

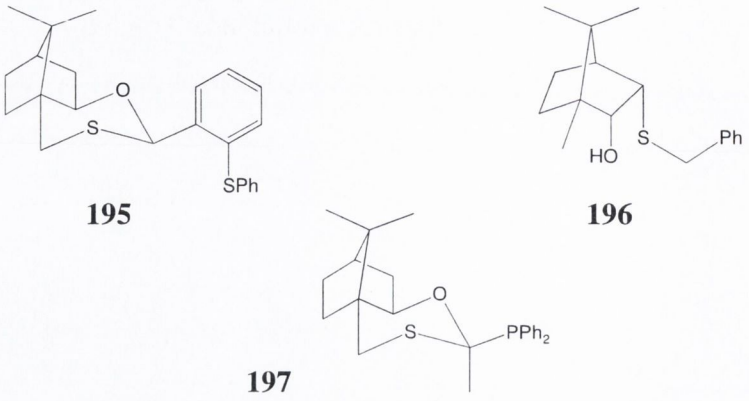
**Camphor-derived chiral pyridine ligands**




**193** **194**

**Scheme 1.45**

Phosphine ligand **197** ('MeCamPHOS') was recently used in the asymmetric Pauson-Khand reactions of terminal alkynes with norbornadiene (**Figure 1.6**).




**195** **196** **197**

**Figure 1.6**

**Camphor-derived N, P and S-containing ligands**

It is clear from the above examples that camphor and its derivatives have occupied a premier place as natural sources of chirality in the field of asymmetric synthesis. Its rigid bicyclic structure lends it to numerous applications as auxiliaries, reagents and ligands in a manner which often allows the rational prediction of face selectivity. Further applications are to be anticipated, especially as ligands and perhaps also as organocatalysts.

## 1.3 Sulfones in Organic Synthesis

Over the last three decades, there has been a dramatic increase in the use of the sulfonyl functional group in organic synthesis.[78] Sulfones have been employed in many synthetic methodologies, enabling the preparation of a great many functionalised products, as well as proving invaluable as synthetic intermediates in the total synthesis of natural products. The synthetic versatility of the sulfonyl group now arguably rivals that of the carbonyl group.

In many respects, the chemistry of the sulfonyl group parallels that of the carbonyl group but there are also important differences. Both functionalities stabilise carbanions in the α-position, allowing a wide range of carbon-carbon bond forming reactions to be carried out. The structural nature of the stabilised anion however, differs between the two functional groups. Another similarity is the electron withdrawing effect both groups exert on conjugated unsaturated systems (alkenes,

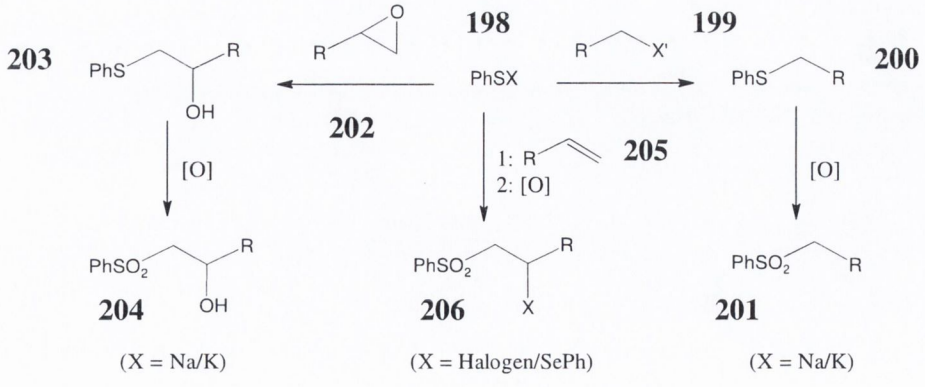
alkynes, arenes, allenes, etc). An important difference between the two groups is that, unlike the carbonyl group, the sulfonyl group is capable of acting as a leaving group in elimination and substitution reactions. In addition, although the carbonyl group readily undergoes nucleophilic addition reactions, the sulfonyl group does not react with nucleophiles at the sulfur atom. Finally, in organic synthesis, the role of the sulfonyl group differs from that of the carbonyl group. Although the carbonyl group is almost always desired in the target compound of a synthesis, the sulfonyl group, with few exceptions, must be removed from the final target.

### 1.3.1 Introduction and Removal of the Sulfonyl Group

A wide variety of methods exists for the introduction of the sulfonyl group into molecules. The necessity to remove the sulfonyl group also means many methods are available for cleavage of the sulfonyl group. The most important of these methods are summarised below.

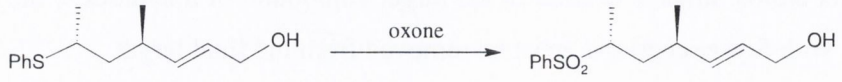
*(a) Introduction of the Sulfonyl Group*

One of the most widely used methods for the introduction of the sulfonyl group is the oxidation of the corresponding sulfides and a variety of reagents are used for this purpose. The sulfides **200** are available through alkylation of metal thiolates **198** with various electrophiles such as halides, tosylates and epoxides, or by addition of sulfenyl halides and selenides **198** to alkenes. Thus the two-step sequence of thiolate alkylation followed by sulfide oxidation constitutes a broadly applicable method for sulfone preparation (**Scheme 1.46**).




**Scheme 1.46**

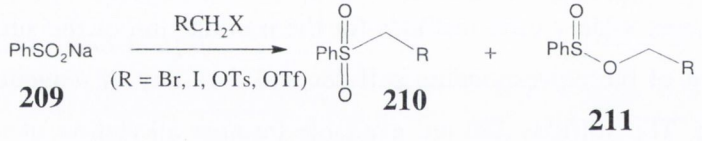
The most common oxidants used for the sulfide-sulfone conversion include MCPBA, urea-hydrogen peroxide complex, peracetic acid (generated *in situ* from hydrogen peroxide and acetic acid), magnesium monoperoxyphthalate, oxone®, sodium perborate and potassium permanganate. For example, chemoselective oxidation of sulfide **207** to sulfone **208** was accomplished using oxone without oxidation of either the alkene or the hydroxyl group (**Scheme 1.47**).[79]




**207** **208**

**Scheme 1.47**

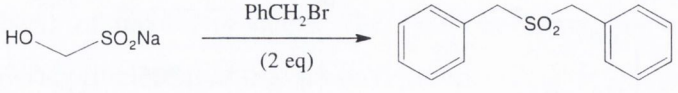
Another popular method for sulfone preparation is alkylation of sulfinic acids or their metal salts (e.g.: **209**). The weaker nucleophilicity of sulfinates compared to thiolates, combined with the ambident nature of the sulfinate nucleophile mean this method has less scope and is best employed with reactive electrophiles such as allylic and benzylic halides and triflates (**Scheme 1.48**).




**209** **210** **211**

**Scheme 1.48**

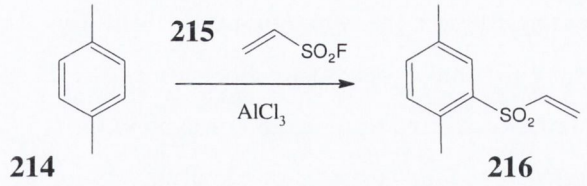
Symmetrical sulfones may be prepared in a single step in moderate yield by treatment of two equivalents of electrophile with sodium formaldehyde sulfoxylate **212**. Formaldehyde adduct **212** essentially acts as an '$SO_2$' dianion equivalent with two successive alkylations occurring at sulfur (**Scheme 1.49**).[80]




**212** **213**

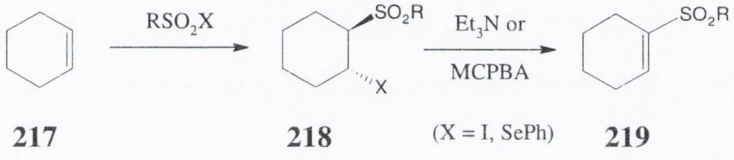
**Scheme 1.49**

In some cases, sulfonic acid derivatives may be used in sulfone preparations. Sulfonyl fluorides and sulfonic anhydrides for example, undergo Friedel-Crafts-type reactions with arenes. Reaction of *p*-xylene **214** with vinylsulfonyl fluoride **215** afforded sulfone **216** in high yield (**Scheme 1.50**).[81]



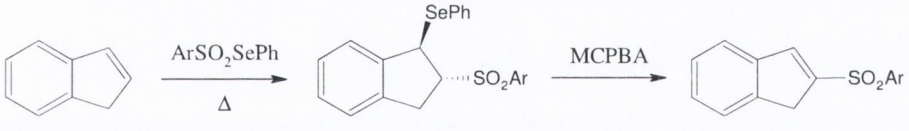

**Scheme 1.50**

The ionic or free radical addition of sulfonyl halides, selenides and related compounds to alkenes, alkynes and allenes is a widely applicable method for preparing unsaturated sulfones. The initial addition produces β-functionalised sulfones which subsequently undergo base-mediated elimination (**Scheme 1.51**).



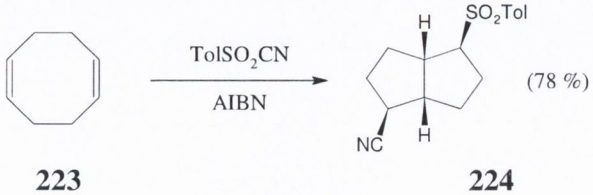

**Scheme 1.51**

For example, selenosulfonylation of **220** affords β-selenosulfone **221**. Oxidation of **221** to the selenoxide and thermal *syn*-elimination generates the vinyl sulfone **222** (**Scheme 1.52**).[82] The same route can be employed for the preparation of alkynyl sulfones from terminal alkynes.



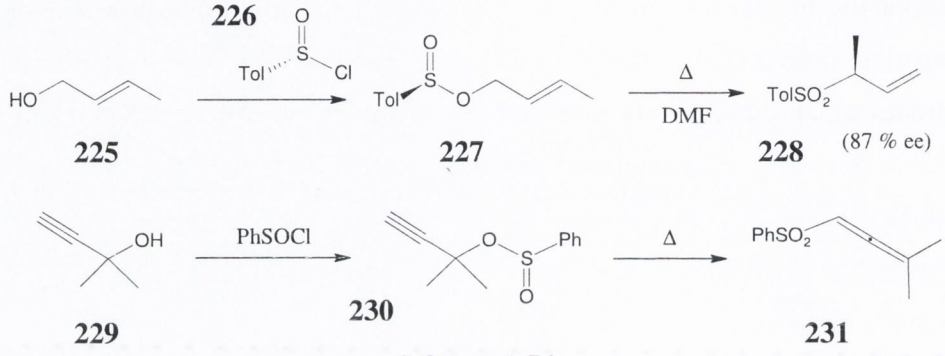

**Scheme 1.52**

Arenesulfonyl cyanides undergo analogous cyanosulfonylation reactions with alkenes under free-radical conditions. This reaction is particularly useful when the intermediate radical can be trapped, as illustrated by the formation of bicyclic cyanosulfone **224** by transannular cyclisation of cyclooctadiene (**Scheme 1.53**).[83]




**Scheme 1.53**

Another useful method for the introduction of the sulfonyl group is the [2,3]-sigmatropic shift of allylic and propargylic sulfinate esters. These sulfinate esters **227** and **230**, prepared by sulfinylation of the corresponding alcohols **225** and **229**, undergo thermal sigmatropic rearrangement with allylic inversion and in the case of optically active allylic sulfinates **227**, with high fidelity of chirality transfer from sulfur to carbon (**Scheme 1.54**).[84]



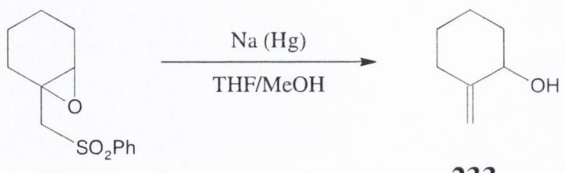

**225** **227** **228** **229** **230** **231**

**Scheme 1.54**

*(b) Removal of the Sulfonyl Group*

Removal of the sulfonyl group can be accomplished with a variety of methods, ranging from reductive desulfonylation (replacement of the sulfonyl group with hydrogen) to methods involving the replacement of the sulfone functionality with carbon or heteroatom groups. The method used often depends on the presence of additional functionality.

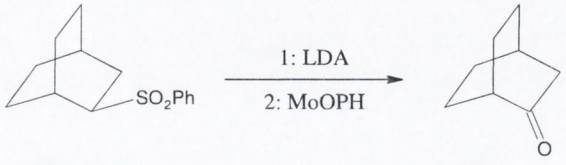
One of the best methods for the reductive desulfonylation of simple alkyl sulfones is sodium amalgam in methanol, although other alkali metal reductants can be used (e.g.: lithium in ethylamine, potassium graphite). Reduction of the carbon-sulfur bond generates a carbanion which is protonated by solvent. In some cases, this anion may be further exploited in synthesis, for example in the conversion of epoxysulfone **232** to allylic alcohol **233** (**Scheme 1.55**).[85]




**232** **233**

**Scheme 1.55**

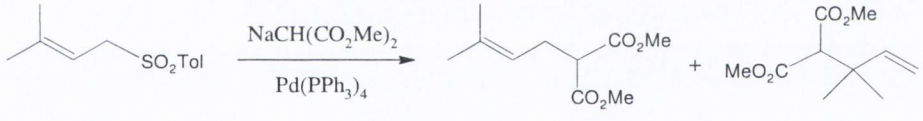
Oxidative desulfonylation of simple sulfones may be accomplished by reaction of their derived carbanions with an electrophilic oxygen source. The resulting geminal α-sulfonyl oxyanion eliminates sulfinate ion to form an aldehyde or ketone. The reagents most commonly used for the oxidation of the sulfonyl carbanion are MoOPH[86] and bis(trimethylsilyl) peroxide (**Scheme 1.56**).[87]




**234** **235**

**Scheme 1.56**

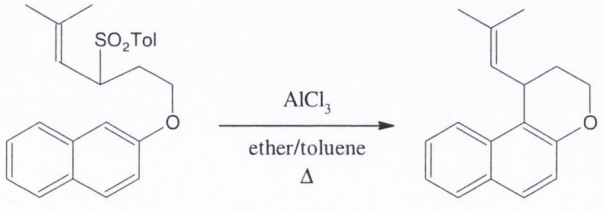
Allylic sulfones are more reactive towards reducing agents than simple alkyl sulfones. In addition, their desulfonylation can be catalysed by palladium, generating π-allyl palladium complexes which react with nucleophiles. Thus for example, the palladium-catalysed desulfonylation of allyl sulfone **236** can be accompanied by carbon-carbon bond formation (**Scheme 1.57**).[88]




**236** **237** (60 : 40) **238**

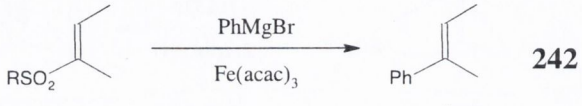
**Scheme 1.57**

Certain allylic sulfones do not require palladium catalysis to react with nucleophiles and in some cases, strong Lewis acids can activate the sulfone toward displacement. Trost and co-workers showed for example how activation of allylic sulfones like **239** allows sulfone displacement by intramolecular Friedel-Crafts reaction (**Scheme 1.58**).[89]




**239** **Scheme 1.58** **240**

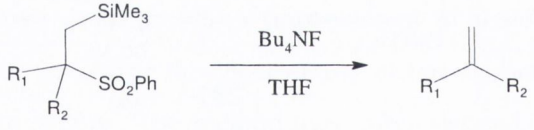
Both reductive and alkylative desulfonylation routes have been applied to vinyl sulfones. A widely used method for reductive desulfonylation of vinyl sulfones introduced by Julia *et al.* involves treatment of the vinyl sulfone with sodium dithionite and sodium hydrogencarbonate.[90] Alkylative desulfonylation may be accomplished using Grignard reagents under nickel or iron catalysis (**Scheme 1.59**).




**241** **242**

**Scheme 1.59**

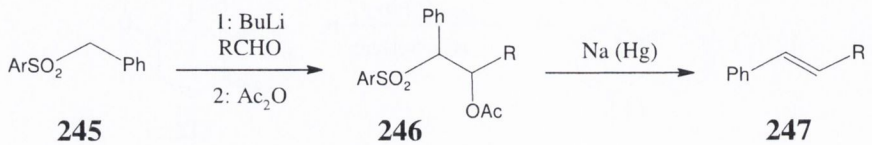
Sulfones possessing electron withdrawing groups in the β-position can undergo base-catalysed elimination of sulfinate anion to furnish alkenes. A closely related method developed by Kocienski *et al.* involves the treatment of β-silyl sulfones **243** with fluoride ion.[91] This method allows the formation of alkenes **244** under mild conditions without the need for base (**Scheme 1.60**).




**243** **244**

**Scheme 1.60**

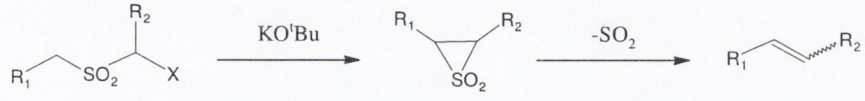
One of the most fundamental methods of generating alkenes connectively from separate partners is the Julia reaction.[92] This reaction involves the reductive elimination of a β-hydroxysulfone or its derivative (usually an acetate or benzoate ester) to form primarily (*E*)-alkenes. The β-hydroxysulfones **246** are readily obtained by reactions of sulfonyl carbanions with aldehydes and ketones. The method is complementary to the Wittig reaction and is frequently used in synthesis (**Scheme 1.61**).




**245** **246** **247**

**Scheme 1.61**

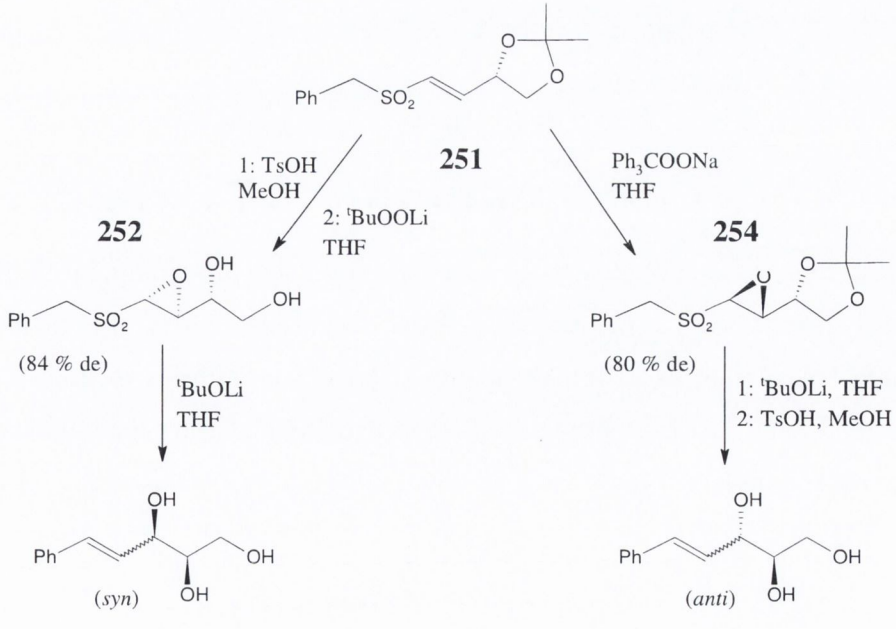
Another well known method for the generation of alkenes by desulfonylation is the Ramberg-Bäcklund reaction. This reaction involves the extrusion of sulfur dioxide from an episulfone **249** (thiirane 1,1-dioxide) which is formed by intramolecular reaction of a sulfonyl carbanion bearing a leaving group in the α-position (**Scheme 1.62**).[93] The α-halosulfones **248** (X = Cl) are often formed *in situ* by treatment of the sulfone with base and carbon tetrachloride.




**248** **249** (X = Cl, I, $OSO_2R$, OSOR) **250**

**Scheme 1.62**

A useful variation of this reaction is the epoxy-Ramberg-Bäcklund reaction, developed recently by Evans and Taylor.[94] In this reaction the leaving group is an epoxide ring which generates an allylic alcohol upon base-catalysed ring opening. The starting sulfonyloxiranes are readily obtained by nucleophilic epoxidation of the corresponding vinyl sulfones. Using chiral pool derived vinyl sulfone **251**, optically active allylic alcohols **253** and **255** may be generated from the sulfonyloxiranes obtained *via* substrate-controlled *syn* or *anti* epoxidation (**Scheme 1.63**).

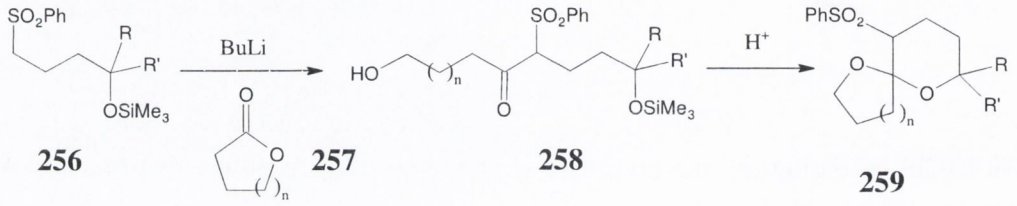



**253** **255**

**Scheme 1.63**

### 1.3.2 Organic Synthesis Involving the Sulfonyl Group

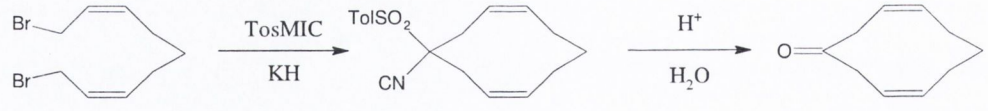
One of the most important aspects of the chemistry of sulfones is the reactions of their derived carbanions with electrophiles. Sulfones can act as masked carbanion equivalents through the sequence of electrophilic quenching of a sulfonyl carbanion, followed by removal of the sulfonyl group. An illustrative example of the utility of sulfones in carbon-carbon forming reactions is the reaction of sulfone **256** with lactones **257** in the synthesis of spiroketals **259** by Brimble *et al.* (**Scheme 1.64**).[95]




**256** **257** **258** **259**

**Scheme 1.64**

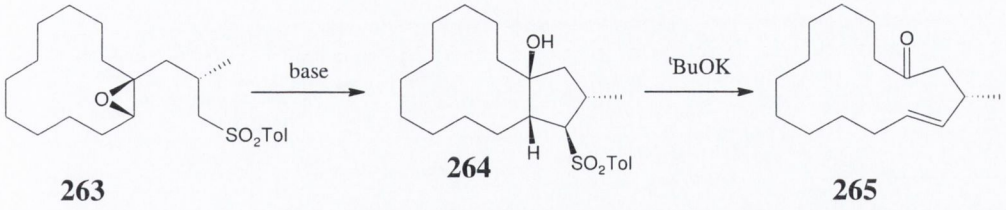
In some cases, the presence of additional functionality on the sulfone or the electrophile allows facile removal of the sulfonyl group or conversion into another functionality. For example, double alkylation of tosylmethylisocyanide (TosMIC) with dibromide **260** yields **261** which is subsequently converted into ketone **262** by hydrolysis (**Scheme 1.65**).[96]




**260** **261** **262**

**Scheme 1.65**

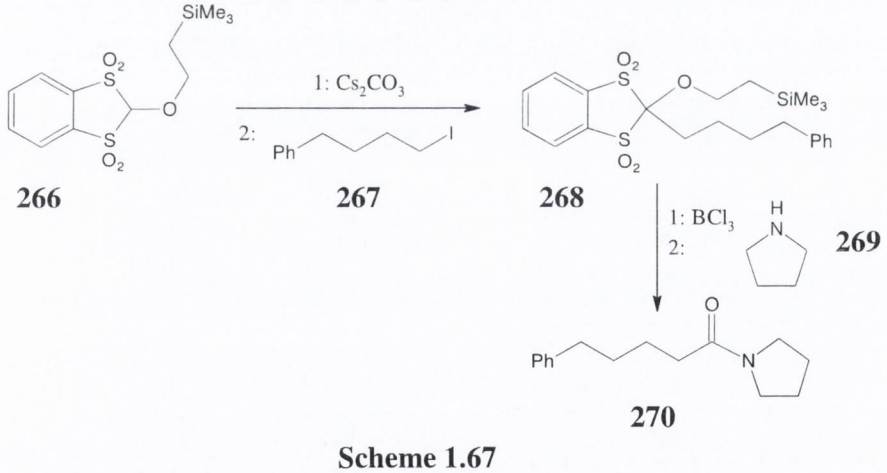
The sulfonyl group has also been employed as a leaving group in Grob-type fragmentation reactions of bicyclic γ-hydroxysulfones which are themselves prepared by reaction of a sulfonyl-stabilised carbanion with an epoxide. This is illustrated by the formation of macrocyclic ketone **265** by Grob-type fragmentation of sulfone **264** (**Scheme 1.66**).[97]




**263** **264** **265**

**Scheme 1.66**

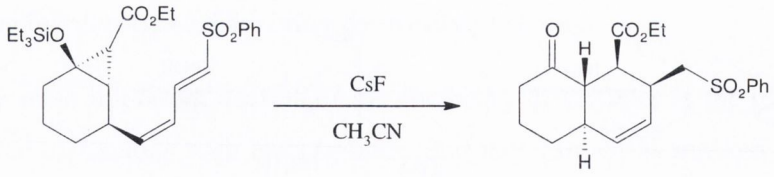
The Michael addition of sulfonyl carbanions to unsaturated esters yields cyclopropane products. In these reactions, the sulfonyl bearing carbon can be considered as a formal '1,1-dipole' or ucleophilic carbenoid. Trost aptly describes sulfones as chemical chameleons for their dual reactivity as both nucleophiles and electrophiles.[98] Manipulation of a sulfonyl carbanion can often be followed by Lewis-acid or transition metal mediated displacement of the sulfonyl group. Trost *et al.* employed alkoxybis(sulfonyl)methane **266** as an effective carbonyl 1,1-dipole synthon in such reactions. For example, Lewis-acid catalysed displacement of adduct **268** with pyrrolidine **269** afforded amide **270** (**Scheme 1.67**).[99]




**266** **267** **268** **269** **270**

**Scheme 1.67**

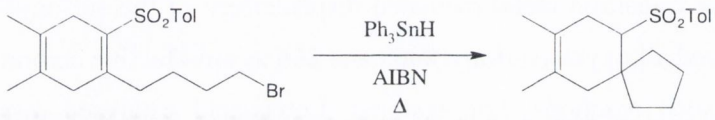
The reactivity of α,β-unsaturated sulfones as Michael acceptors has also been exploited in synthesis. Both carbon and heteroatom nucleophiles undergo additions to vinyl, alkynyl and allenyl sulfones to give addition products. An elegant example of a stereoselective intramolecular enolate addition to a vinyl sulfone **271** is shown in **Scheme 1.68**. The product sulfone **272** was required as an intermediate for dihydrocompactin synthesis.[100]




**271** **272**

**Scheme 1.68**

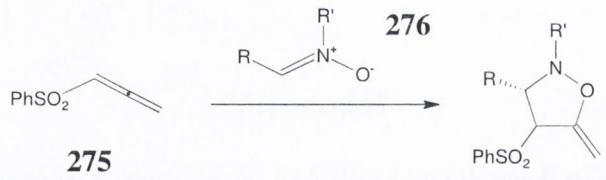
The Michael addition of radical species to vinyl sulfones is also a synthetically useful procedure. The intramolecular addition of carbon-based radicals is particularly effective for the formation of cyclopentanes on account of the extremely rapid 5-*exo-trig* ring closure. An illustrative example is the tin-mediated formation of spirocycle **274** from **273** (**Scheme 1.69**).[101]




**273** **274**

**Scheme 1.69**

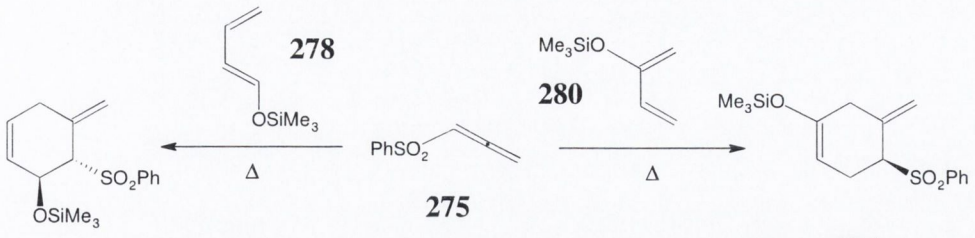
Unsaturated sulfones also display rich cycloaddition chemistry. Vinyl, alkynyl and allenyl sulfones undergo photochemical [2 + 2] cycloadditions as well as thermal [4 + 2] cycloadditions with unsaturated partners. Additionally, [3 + 2] cycloadditions with 1,3-dipoles leads to useful sulfonyl-functionalised heterocycles. For example, allenyl sulfone **275** reacts chemoselectively and regioselectively with nitrones **276** to give cycloadducts **277** (**Scheme 1.70**).[102]




**275** **276** **277**

**Scheme 1.70**

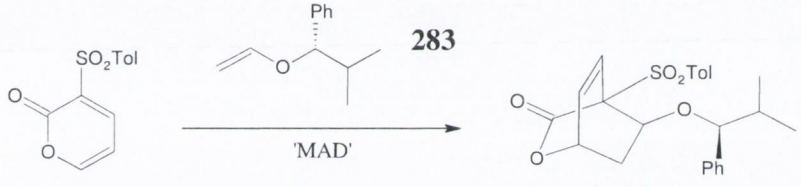
The Diels-Alder reactions of allenyl sulfones with electronically biased dienes also proceed both chemoselectively and regioselectively to furnish cyclohexene products bearing *exo*-methylene groups. An example is the formation of cycloadducts **279** and **281** by reaction of the sulfone-activated double bond of allenyl phenyl sulfone **275** with dienes **278** and **280** (**Scheme 1.71**).[103]




**279** **281**

**Scheme 1.71**

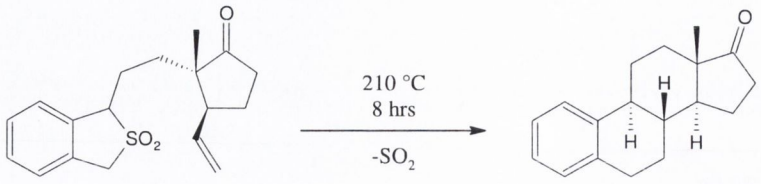
Sulfonyl-substituted dienes participate in Diels-Alder reactions with both electron rich and electron poor olefins. With electron rich partners the reactions are often highly regioselective with the orientation of substituents depending on the location of the sulfonyl group in the diene. An example in synthesis is the cycloaddition of sulfonyl pyrone **282** with a chiral vinyl ether **283** to form **284** which was subsequently converted to a known A-ring precursor for 1α,25-dihydroxyvitamin $D_3$ (**Scheme 1.72**).[104]




**282** **284**

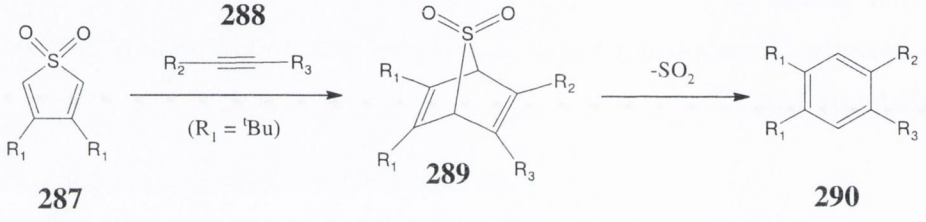
**Scheme 1.72**

The chemistry of cyclic sulfones closely parallels that of their acyclic counterparts, although in some cases cyclic sulfones exhibit unique reactivity. The extrusion of sulfur dioxide from thiirane 1,1-dioxides ('episulfones') has already been mentioned in the discussion of the Ramberg-Bäcklund reaction. Similarly, dihydrothiophene 1,1-dioxides ('sulfolenes') undergo thermolytic extrusion of sulfur dioxide, a reaction which has typically been used in synthesis to generate dienes which are subsequently trapped by Diels-Alder reaction. An illustrative example is the synthesis of estra-1,3,5(10)-trien-17-one **286** from **285** by Nicolaou *et al.* (**Scheme 1.73**).[105]




**285** **Scheme 1.73** **286**

In related reactions, bicyclic sulfolenes can be formed by Diels-Alder reactions of thiophene 1,1-dioxides with 2π partners. Subsequent extrusion of sulfur dioxide generates 6-membered ring products. This two-step sequence has been exploited by Nakayama *et al.* for the synthesis of highly substituted aromatic compounds **290** by cycloaddition of **287** with internal alkynes **288** (**Scheme 1.74**).[106]



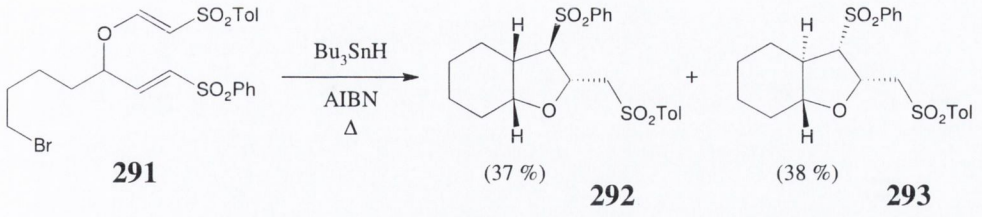

**287** **290**

**Scheme 1.74**

### 1.3.3 Tandem Reactions Involving the Sulfonyl Group

The synthetic utility of the sulfonyl group in organic synthesis can often be extended considerably by their use in tandem reaction processes. These may be classified as those reactions where two or more sequential reactions occur in a single synthetic step. Unsaturated sulfones are particularly amenable to such tandem sequences, as Michael addition of a suitable species can often be followed by subsequent reactions of the resulting α-sulfonyl anion or radical formed *in situ*. Some illustrative examples are shown below.

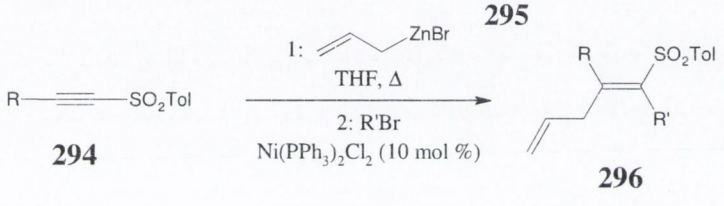
Carretero *et al.* described the radical cascade cyclisation of a number of suitably functionalised γ-oxygenated vinyl sulfones.[107] In this sequence, the initial intramolecular radical addition to the vinyl sulfone generates an α-sulfonyl radical which undergoes a second cyclisation in the presence of a suitable trap. The utility of the process in synthesis was demonstrated by the preparation of separable mixtures of bicyclic *cis* and *trans*-fused tetrahydrofurans **292** and **293** from acyclic precursors **291** (**Scheme 1.75**).




**291** **292** **293**

**Scheme 1.75**

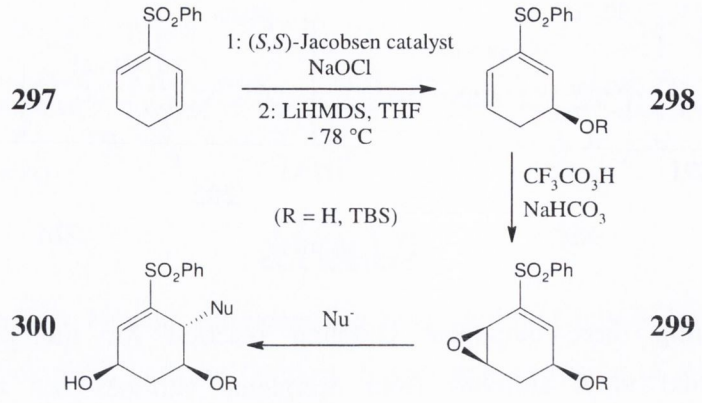
An interesting three-component coupling reaction for the preparation of tetrasubstituted vinyl sulfones from acetylenic sulfones has been recently reported.[108] Michael addition of an organozinc reagent to an acetylenic sulfone **169** generates a vinylzinc species which undergoes Negishi cross-coupling with an alkylbromide, resulting in a highly regio-and stereoselective synthesis of tetrasubstituted alkenes **170** (**Scheme 1.76**).




**294** **296**

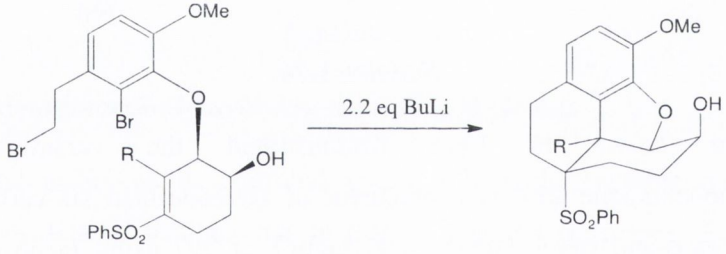
**Scheme 1.76**

Fuchs and co-workers have demonstrated the versatility of 2-sulfonylcyclohexadiene **297** as a precursor of stereodefined six-carbon building blocks.[109] Regio-and stereoselective epoxidation of **297** using Jacobsen's catalyst followed by eliminative ring opening generates **298** which undergoes substrate-controlled epoxidation with pertrifluoroacetic acid forming epoxyvinyl sulfone **299**. The reactions of **299** with various nucleophiles proceeds in a stereoselective and regiospecific fashion to furnish products **300** bearing three asymmetric centres *via* a tandem Michael addition-epoxide opening sequence (**Scheme 1.77**). Chiral acyclic products may also be accessed by ozonolysis of products **300**.



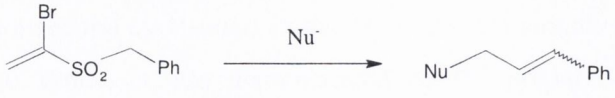

**Scheme 1.77**

A striking example of the application of a tandem vinyl sulfone Michael addition-electrophilic trapping sequence is shown in **Scheme 1.78**. Treatment of vinyl sulfone **301** with BuLi affords the aryllithium derivative which undergoes tandem intramolecular Michael addition-sulfonyl carbanion alkylation to generate the tetracyclic sulfone **302**, a key intermediate in the total synthesis of morphine.[110]




**301** **Scheme 1.78** **302**

Finally, certain α-bromovinyl sulfones undergo tandem Michael addition-Ramberg-Bäcklund rearrangements on treatment with various nucleophiles.[111] This reaction proceeds efficiently with benzylic bromovinyl sulfones whose labile α-protons permit rapid proton transfer to the anion formed on conjugate addition of the nucleophile. The new anion is then set up for standard Ramberg-Bäcklund rearrangement, leading to functionalised allylic alkenes **304** (**Scheme 1.79**).




**303** ($Nu^-$ = MeONa, BnSK, $RNH_2$, $NaCMe(CO_2Me)_2$) **304**

**Scheme 1.79**

## 1.4 Strategy

It is clear that the synthetic versatility of the sulfonyl group has been developed to a considerably high degree. Despite this rich chemistry, relatively little work has been carried out on the use of chiral sulfones in asymmetric synthesis. This is in marked contrast to the sulfoxide group which has enjoyed widespread use in asymmetric synthesis,[112] although this functionality has the obvious advantage of sulfur-based chirality easily introduced by asymmetric sulfide oxidation.

It was considered that a chiral auxiliary approach to chiral sulfones would be a particularly attractive option, based on the variety of methods for the introduction of the sulfonyl group and the frequent necessity to remove it after the asymmetric synthetic step has been performed. The present work is concerned with exploring certain potential applications in asymmetric synthesis of chiral pool based sulfones derived from inexpensive (+)-or (-)-camphor-10-sulfonic acid.

The primary focus of Chapter 2 is the exploration of reactions of stabilised anions derived from chiral camphor-based allyl and benzyl sulfones with aldehydes with a view to preparing optically active homoallyl and homobenzyl alcohols after desulfonylation. This synthetic route has been verified in the achiral series with the corresponding arylsulfonyl compounds.

Chapter 3 is concerned with studies on the nucleophilic epoxidation chemistry of chiral vinyl sulfones and its potential application to the enantioselective synthesis of 3-*O*-benzylglyceraldehyde. In addition, an achiral study is presented as well as the synthesis of a chiral sulfonyldiene, a potential precursor to the 4-carbon tetrose sugars.

Chapter 4 covers the synthesis of novel chiral benzyl sulfones from (+)-camphor with a view to exploring their applications in asymmetric synthesis. The well known carbocationic rearrangement chemistry of the camphor framework is utilised to selectively introduce the sulfonyl group onto either the 7-*syn* or 7-*anti* methyl groups.

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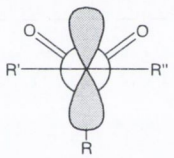
# Chapter 2

# Synthesis and Reactions of Some Chiral Allyl and Benzyl Sulfones

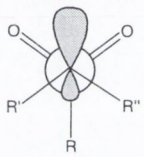
## 2.1 Introduction

### 2.1.1 Chemistry of Sulfonyl Carbanions

The utility of sulfones in organic synthesis stems largely from the ability of the sulfonyl group to stabilise α-carbanions. The reactivity of these anions toward a wide range of electrophiles, combined with the various methods of desulfonylation available has led to the widespread use of sulfones in synthesis. The structures of sulfonyl carbanions have been the focus of extensive study and there is a large body of evidence to suggest that α-sulfonyl carbanions can adopt either a planar $sp^2$ hybridised structure **305** or a pyramidal $sp^3$ structure **306**, depending on the structure of the sulfone.[1] In benzylic anions, the α-carbon is rather flattened, whereas in non-benzylic anions, the α-carbon is significantly pyrimidalised. In each case, as verified by X-ray crystal structures of α-lithiosulfones, the carbanion lone pair is approximately *gauche* to the two sulfone oxygen atoms.

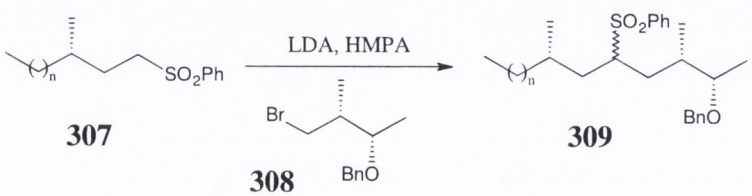



**305**




**306**

Sulfonyl carbanions are frequently used in C-C bond forming reactions with many electrophiles, including alkyl halides and tosylates, epoxides, aldehydes and ketones, enones, and carboxylic acid derivatives. Alkylation of a sulfonyl carbanion, followed by desulfonylation allows sulfones to be used as masked carbanion equivalents and this strategy has found extensive use in natural product synthesis.[2] For example, coupling of two homochiral fragments led to sulfone **180**, a key intermediate in the synthesis of the pheromones of the pine sawfly[3] (**Scheme 2.1**).




**307** **308** **309**

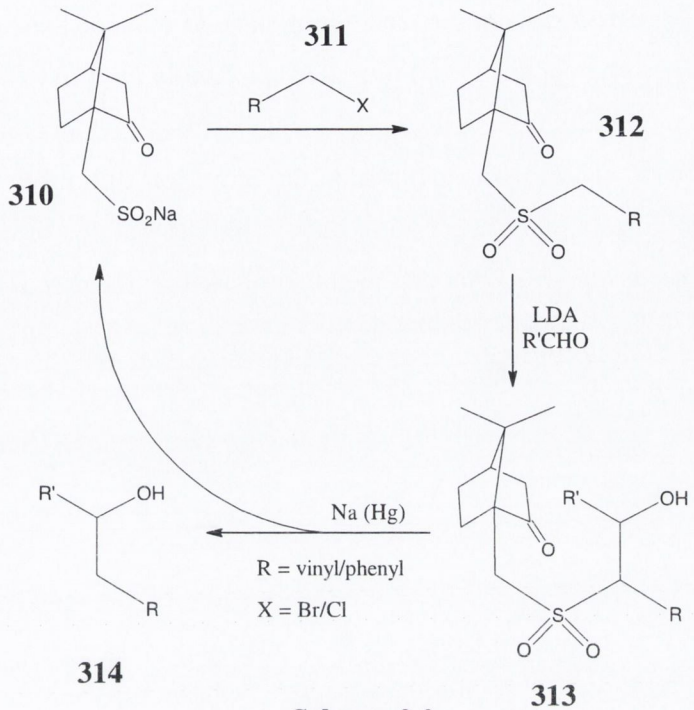
**Scheme 2.1**

The reactions of sulfonyl carbanions with aldehydes and ketones lead to β-hydroxysulfones. These compounds can be converted into alkenes by acylation, followed by desulfonylation with sodium amalgam (Julia reaction),[4] allowing connective olefin synthesis from two separate fragments. The β-hydroxysulfone products can also be converted into vinyl sulfones by derivatisation, followed by basic elimination.

### 2.1.2 Proposed Synthesis of Homoallylic and Homobenzylic Alcohols

The present study focuses on the reactions of sulfonyl carbanions with aldehydes. Although there are a few isolated reports on the reductive desulfonylation of β-hydroxy sulfones which do not result in olefin formation,[5] there appears to have been no general studies carried out on the reductive desulfonylation of β-hydroxy sulfones as a method for the preparation of secondary alcohols. With this in mind, the aim of the present study was to examine the reactions of the derived anions of homochiral camphor based allylic and benzylic sulfones with aldehydes, and then to examine the reductive desulfonylation of the derived adducts as a means of preparing homoallylic and homobenzylic alcohols. Thus, alkylation of sodium camphor-10-sulfinate **310** with an allylic or benzylic halide **311** would afford sulfone **312**. Treatment of **312** with a suitable base, followed by an aldehyde may afford diastereomeric adducts **313**. Desulfonylation with a suitable reagent, such as sodium amalgam, would potentially yield the product homoallylic or homobenzylic alcohol **314**, together with metal sulfinate (**Scheme 2.2**).

If successful, these synthetic routes would allow chiral sulfones **312** to be used as masked and potentially chiral allyl and benzyl anion equivalents in organic synthesis. In addition, the metal sulfinate produced in the final desulfonylation step may be recovered and recycled back for further use, thereby allowing sulfinate **310** to be used as a recyclable chiral auxiliary.




**Scheme 2.2**

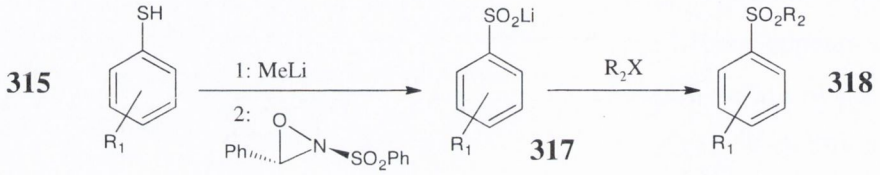
In addition to the above mentioned problems regarding the desulfonylation step, other potential drawbacks exist. Firstly, the carbonyl group of the auxiliary may react with the sulfonyl carbanion, rather than the aldehyde, to generate tricyclic products. Secondly, the β-hydroxysulfones generated by reaction of the sulfonyl carbanions with aldehydes may revert back to starting materials by a retro-aldol reaction, establishing an equilibrium between the β-hydroxysulfone adduct and the free sulfonyl carbanion. Field reported an example of a retro-aldol reaction of a β-hydroxysulfone on treatment with potassium hydroxide which afforded phenyl methyl sulfone and benzaldehyde.[6]

## 2.2 Studies on the Anion Chemistry of Chiral Allyl and Benzyl Sulfones 326 and 328

### 2.2.1 Preparation of Sodium Camphor Sulfinate 310

Of the many methods available for the preparation of sulfones, as outlined in Chapter 1, sodium sulfinate alkylation was chosen for the preparation of the sulfones required in this study.

Sulfones can be obtained from the reaction of sulfinic acids or their derived metal salts with various electrophiles. Sulfinic acids are usually unstable and decompose, and so they are typically used and stored as their metal salts. Standard methods for the preparation of metal sulfinates include the reduction of sulfonyl halides (eg: with metals or with sodium or potassium sulfite) and the reaction of organometallic reagents with sulfur dioxide.[7] Another method reported by Field *et al.*[8] involves the reaction of sulfonyl halides with thiols. More recently, Perrio *et al.* prepared a number of lithium arenesulfinates **317** by direct oxidation of the corresponding lithium thiolates with 2-(phenylsulfonyl)-3-phenyloxaziridine **316** (**Scheme 2.3**).[9]

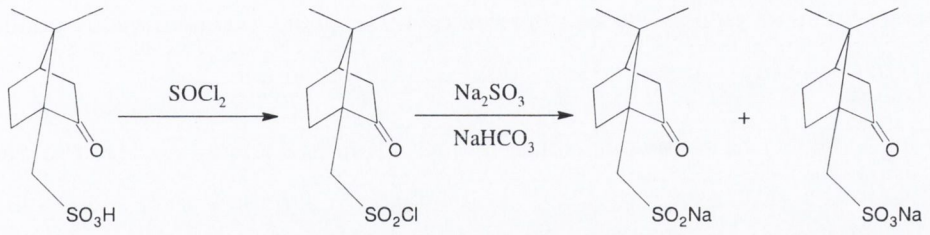



**Scheme 2.3**

The required sodium sulfinate **310** should be obtainable from commercially available (+)-camphor-10-sulfonic acid (historically known as Reychler's acid[10]) by the two-step sequence of conversion to the sulfonyl chloride, followed by reduction with sodium sulfite in basic conditions. A similar sequence starting from *p*-chlorobenzenesulfonic acid had been reported by Kulka *et al.*[11]

The preparation of (+)-camphor-10-sulfonyl chloride from (+)-camphor-10-sulfonic acid was first reported by Smiles and Hilditch in 3297.[12] Thionyl chloride was found to give higher yields and shorter reaction times than phosphorus pentachloride. The authors also prepared the sodium and zinc sulfinate salts. Additionally the preparation of sodium sulfinate **310** from (+)-camphor-10-sulfonyl chloride was recently reported by Lacour *et al.*[13]

Taking this precedent into account, this two-step method for the preparation of sulfinate **310** has been optimised to high yield by Grayson *et al.*[14] Following this procedure, (+)-camphor-10-sulfonic acid **319** was treated with excess thionyl chloride (3 equiv.) which furnished the sulfonyl chloride **320**. Reduction of **320** by dropwise addition of an acetone solution of **320** over 2 hours to aqueous sodium sulfite in the presence of sodium hydrogen carbonate at 70 °C afforded the sodium sulfinate **310** in high yield (**Scheme 2.4**).




**319** **320** **310** **321**

**Scheme 2.4**

The $^{1}$H NMR spectrum of **310** showed a pair of doublets at δ 2.13 and 2.57 ppm, corresponding to the diastereotopic methylene protons adjacent to sulfur, as well as a doublet at δ 1.88 ppm assigned to the *endo* proton at C-3. The $^{1}$H and $^{13}$C NMR details of **310** were in good agreement with those published by Lacour *et al.*[13] Closer inspection of the $^{1}$H NMR spectrum revealed that the corresponding sodium sulfonate **321** was also present, as evidenced by a pair of doublets at δ 2.79 and 3.21 ppm which were identical with those of an authentic sample. The sodium sulfonate is clearly formed by competing hydrolysis of the sulfonyl chloride **320** on addition to the aqueous solution. The ratio of sulfinate **310** to sulfonate **321** was determined by integration of the relevant signals in the $^{1}$H NMR spectrum to be ca. 7:1. In a subsequent experiment in which the dropwise addition of an acetone solution of **320** was carried out over 4 hours instead of 2, a ca. 20 : 1 ratio of sulfinate **310** to sulfonate **321** was obtained, corresponding to ca. 5 % by weight of sodium sulfonate **321** present in the crude product. Thus it is necessary to prolong the addition of sulfonyl chloride **320** to the aqueous sodium sulfite solution in order to avoid contamination of the product by appreciable amounts of sodium sulfonate **321** and the resulting detrimental yields obtained in subsequent alkylation reactions.

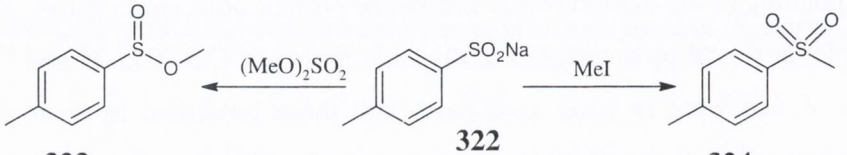
### 2.2.2 Preparation of Allyl Sulfone 326 and Benzyl Sulfone 328

With the sodium sulfinate **310** in hand, the next goal was the preparation of the corresponding chiral allyl and benzyl sulfones.

There are many methods that have been developed for the preparation of sulfones by alkylation of metal sulfinates. Most applications involve alkylation of commercially available sodium benzenesulfinate or sodium *p*-toluenesulfinate with electrophiles in polar aprotic solvents such as DMF. The reactions of sodium *p*-

toluenesulfinate with a variety of electrophiles under phase transfer conditions using tetra-*n*-butylammonium salts have also been reported.[15]

In some cases, the ambident nature of the sulfinate nucleophile leads to varying amounts of sulfinate ester products obtained *via* *O*-alkylation of the metal sulfinate. As a general rule, hard electrophiles (eg: dimethyl sulfate) lead to sulfinate esters, while soft electrophiles (eg: methyl iodide) lead to sulfones. This has been neatly illustrated by Meek and Fowler (**Scheme 2.5**).[16]

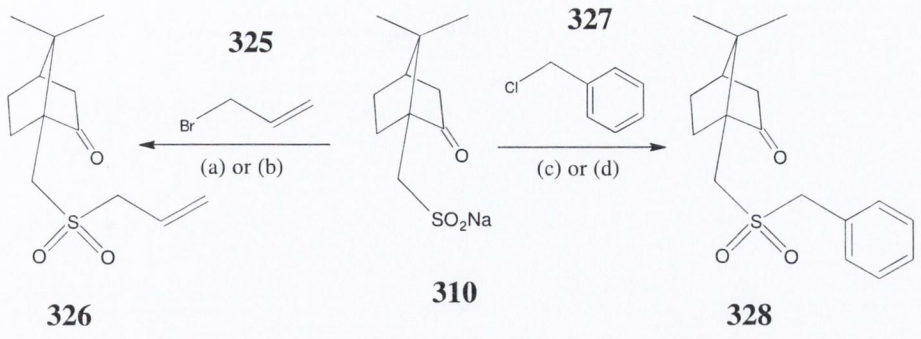



**323** **322** **324**

**Scheme 2.5**

For the reactions of sodium sulfinate **310** with allyl bromide and benzyl chloride, DMSO was chosen as the solvent, owing to the solubility of sodium sulfinates in DMSO at elevated temperature. Thus, treatment of sodium sulfinate **310** with allyl bromide in DMSO at 60 °C afforded, after standard work-up, the novel allyl sulfone **326** in modest yield. Similarly, treatment of sodium sulfinate **310** with benzyl chloride in DMSO at 80 °C gave the novel benzyl sulfone **328** in good yield. Slightly better yields were achieved by the addition of a catalytic (20 mol %) amount of sodium iodide, presumably by the formation of the more reactive allyl and benzyl iodides *via* an *in situ* Finkelstein reaction. Under these conditions, sulfones **326** and **328** were obtained in 65 % and 74 % yields respectively, following purification by chromatography or recrystallisation. None of the corresponding sulfinate esters were observed.

Sulfones **326** and **328** were also prepared by alkylation of sulfinate **310** with the appropriate electrophile in acetonitrile in the presence of a phase transfer catalyst. Masson *et al.* obtained various phenyl benzylic sulfones in near quantitative yield by alkylation of sodium benzenesulfinate with benzylic halides in acetonitrile with tetrapropylammonium bromide as phase transfer catalyst.[17] Using this procedure with triethylhexylammonium bromide as phase transfer agent, sulfones **326** and **328** were obtained in 74 % and 75 % yield respectively (**Scheme 2.6**).




(a) NaI, DMSO, 60 °C.
(b) $Et_3HexNBr$, $CH_3CN$, reflux.

(c) NaI, DMSO, 80 °C.
(d) $Et_3HexNBr$, $CH_3CN$, reflux.

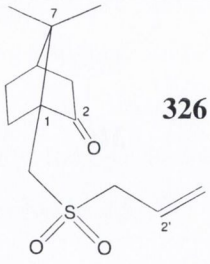
**Scheme 2.6**

The reduced yields obtained in these reactions compared to those for sodium benzenesulfinate may be attributed to the presence of some inorganic salts (sodium sulfate/sodium chloride) in the crude sodium sulfinate **310**.

The novel sulfones **326** and **328** were characterised from their $^1H$ and $^{13}C$ NMR spectra. In the $^1H$ NMR spectrum of **326**, the chemical shifts and signal multiplicities of the camphor ring protons were assigned by comparison to those published for camphor.[18] The characteristic signals for the *endo* methylene proton at C-3 (doublet at ca. δ 1.8) and the methine proton at C-4 (triplet at ca. δ 2.1) in camphor were observed at δ 1.95 and 2.14 ppm respectively. The signal corresponding to the *exo* methylene proton at C-3 (double triplet at ca. δ 2.3) could not be assigned due to signal overlapping. The methylene protons at C-5 and C-6 could not be assigned unambiguously. In addition to these signals, a pair of doublets at δ 2.75 and 3.47 ppm was observed, each with a coupling constant consistent with geminal coupling (15 Hz). These were assigned to the pair of diastereotopic methylene protons adjacent to the sulfur and C-1. The diastereotopic allylic protons appeared as a pair of double doublets at δ 3.80 and 4.12 ppm with a lower separation than that observed above for the protons next to C-1. The vinylic protons gave rise to resonances at δ 5.52 and 6.01 ppm. Similarly, the $^{13}C$ NMR spectrum of **326** was assigned by comparison with the published data for camphor.[19] The $^1H$ and $^{13}C$ NMR data for **326** are summarised in **Table 2.1**.

**Table 2.1**

**NMR spectroscopic details for allyl sulfone 326 in $CDCl_3$**



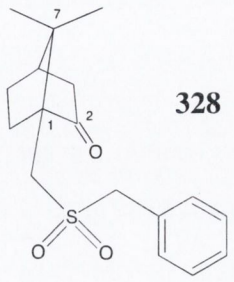

**326**

| $^1$H (ppm) | Multiplicity (Hz) | $^{13}$C (ppm) | Assignment |
|---|---|---|---|
| 1.07 | s | 19.2 | 7-$CH_3$ |
| 0.89 | s | 19.3 | 7-$CH_3$ |
| not assigned | - | 24.9 | C-5 |
| not assigned | - | 26.6 | C-6 |
| 2.14 | t, *J* 4.5 | 42.1 | C-4 |
| 1.95 | d, *J* 18.4 | 42.2 | C-3 |
| not assigned | - | | |
| - | - | 48.2 | C-7 |
| 2.75 | d, *J* 15.0 | 48.6 | $CH_2SO_2$ |
| 3.47 | d, *J* 15.0 | | |
| - | - | 58.5 | C-1 |
| 3.80 | dd, *J* 14.0, 7.5 | 59.9 | C-1' |
| 4.12 | dd, *J* 14.0, 7.5 | | |
| 5.52 | m | 124.4 | C-3' |
| 6.01 | ddt, *J* 17.3, 10.0, 7.5 | 124.8 | C-2' |
| - | - | 215.0 | C-2 |

Similarly, the $^1$H and $^{13}$C NMR spectra of **328** were assigned. In the $^1$H NMR spectrum of **328**, the signals for the *endo* methylene proton at C-3 and the methine proton at C-4 were observed at δ 1.97 and 2.13 ppm respectively, while a pair of AB systems was observed, corresponding to the diastereotopic methylene protons adjacent to the sulfur and C-1 (δ 2.68 and 3.40), and the diastereotopic benzylic protons (δ 4.36 and 4.72). The $^1$H and $^{13}$C NMR data for **328** are summarised in **Table 2.2**.

**Table 2.2**

**NMR spectroscopic details for benzyl sulfone 328 in $CDCl_3$**

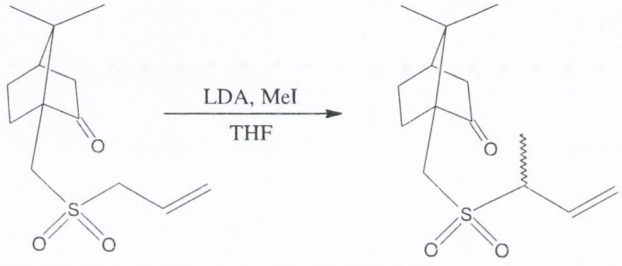



**328**

| $^1$H (ppm) | Multiplicity (Hz) | $^{13}$C (ppm) | Assignment |
|---|---|---|---|
| 1.02 | s | 19.2 | 7-$CH_3$ |
| 0.85 | s | 19.3 | 7-$CH_3$ |
| not assigned | - | 25.2 | C-5 |
| not assigned | - | 26.6 | C-6 |
| 2.13 | t, *J* 4.5 | 42.1 | C-4 |
| 1.97 | d, *J* 18.5 | 42.2 | C-3 |
| not assigned | - | | |
| - | - | 48.2 | C-7 |
| 2.68 | d, *J* 15.0 | 48.9 | alkyl $CH_2SO_2$ |
| 3.40 | d, *J* 15.0 | | |
| - | - | 58.7 | C-1 |
| 4.36 | d, *J* 13.5 | 61.6 | benzyl $CH_2SO_2$ |
| 4.72 | d, *J* 13.5 | | |
| - | - | 127.9 | Ar C-1 |
| 7.38-7.49 | m | 128.4 | Ar C-3 |
| 7.38-7.49 | m | 128.4 | Ar C-4 |
| 7.38-7.49 | m | 130.5 | Ar C-2 |
| - | - | 215.1 | C-2 |

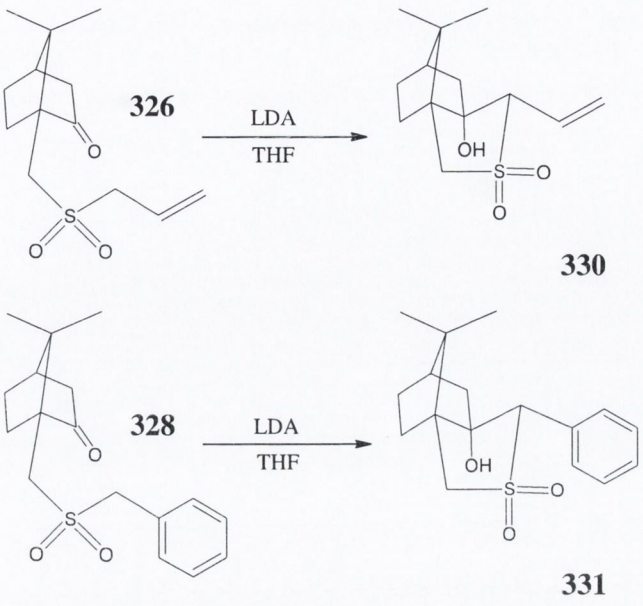
### 2.2.3 Anion Chemistry of Allyl Sulfone 326 and Benzyl Sulfone 328

The reactions of sulfonyl-stabilised carbanions derived from allyl sulfone **326** and benzyl sulfone **328** were next examined. Treatment of allyl sulfone **326** with LDA at – 60 °C, followed by the addition of benzaldehyde gave, after acidic quench and standard work up, a crude product whose $^1$H NMR spectrum showed an intractable mixture of products. These could not be cleanly separated by column chromatography. Similar treatment of benzyl sulfone **328** also gave an intractable mixture. Minor amounts of both diastereomers of α-methyl allyl sulfone **329** were formed when allyl sulfone **326** was treated with LDA at – 60 °C for 1 hour, followed by the addition of a large excess of methyl iodide and warming to room temperature for 5 hours (**Scheme 2.7**).




**326** **Scheme 2.7** **329**

In order to verify if the anions derived from these sulfones were reacting intramolecularly with the carbonyl group of the auxiliary, thereby forming anions unreactive toward external electrophiles, these reactions were repeated in the absence of an electrophile. Thus, treatment of allyl sulfone **326** with LDA at – 60 °C gave, after the usual work up, tricyclic sulfone **330** as a single diastereomer in good yield (70 %), together with a small amount of unchanged starting sulfone **326** after column chromatography. Similar treatment of benzyl sulfone **328** under identical conditions gave tricyclic sulfone **331** also as a single diastereomer in lower yield, together with a significant amount (52 %) of unreacted starting sulfone **328** (**Scheme 2.8**).




**Scheme 2.8**

The differing extents of cyclisation of **326** and **328** may probably be attributed to a steric effect which is more pronounced in **328** than in **326**, owing to the more bulky phenyl group. It is unlikely to be a result of the relative pKa's of the allylic and benzylic protons in **326** and **328**. In the analogous phenylsulfonyl compounds phenyl allyl sulfone and phenyl benzyl sulfone, the pKa's (in DMSO) are 22.5 and 23.4 respectively.[20] Assuming the relative pKa's to be similar in **326** and **328**, this would imply a greater acidity for **326** and therefore lower reactivity of its derived anion compared to that derived from **328**. Sulfone **331** was obtained in higher yield (76 %) by allowing the solution of the anion derived from **328** to warm to room temperature for 3 hours, prior to acidic quench.

In the $^1$H NMR spectrum of **330**, a partially-collapsed AB quartet was observed at δ 3.10, corresponding to the methylene protons adjacent to sulfur. The allylic methine proton came into resonance as a doublet at δ 3.74 ppm, while the *endo* methylene proton adjacent to the hydroxyl group had shifted upfield to δ 1.48 ppm. In the $^1$H NMR spectrum of **331,** the methylene protons adjacent to sulfur formed a collapsed AB quartet at δ 3.20 ppm while the benzylic methine proton gave a singlet at δ 4.38 ppm. These signals were observed in the spectra of the crude products obtained in the above reactions of **326** and **328** with benzaldehyde. The $^1$H NMR spectra of sulfones **330** and **331** are shown in **Figure 2.1** and **Figure 2.2**, respectively.

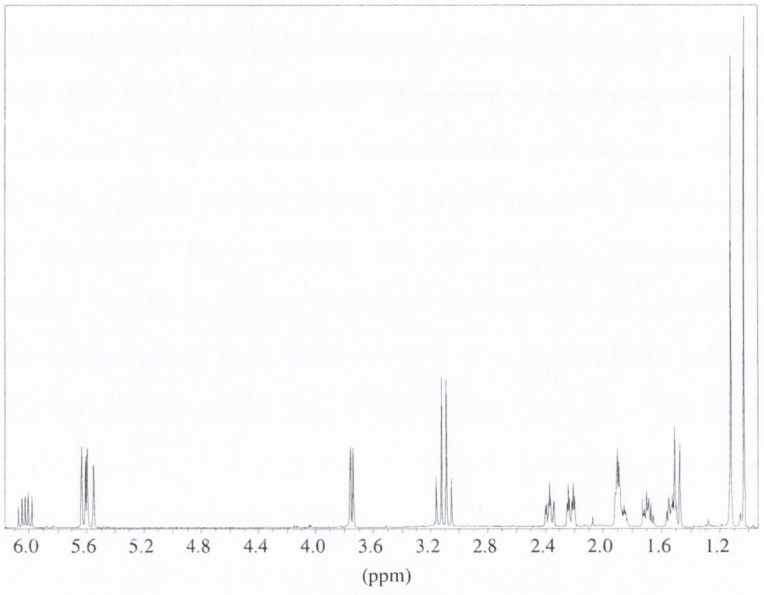



**Figure 2.1**

**$^1$H NMR spectrum of tricyclic allyl sulfone 330 in $CDCl_3$**

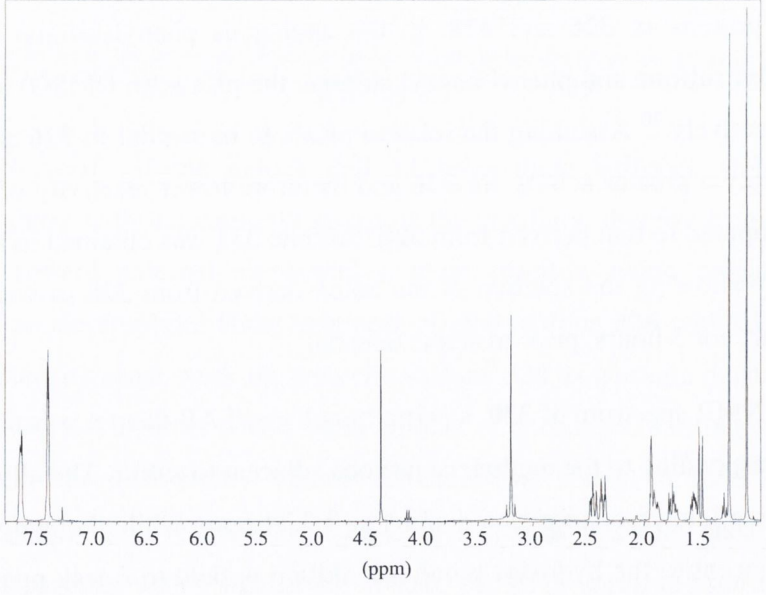



**Figure 2.2**

**$^1$H NMR spectrum of tricyclic benzyl sulfone 331 in $CDCl_3$**

Although these intramolecular cyclisations were a 'dead end' in the context of forming adducts with electrophiles, the finding that the products were obtained as

single stereoisomers prompted a further investigation into the chemistry of these novel compounds. Tricyclic allyl sulfone **330** in particular was of interest by virtue of the potential additional functionalisation of its double bond. Henbest and co-workers discovered that epoxidation of cyclic allylic alcohols such as cyclohex-2-enol with perbenzoic acid occurs on the side *cis* to the hydroxyl group to give *cis* epoxy alcohols.[21] A similar hydroxyl group directing effect may be possible in sulfone **330**. Treatment of **330** with MCPBA in chloroform gave the epoxide **332** as a single diastereomer. The same diastereomer was obtained when ether was used as the solvent. The $^{1}H$ NMR spectrum of epoxide **332** is shown in **Figure 2.3**. Assignments of the signals in the $^{1}H$ and $^{13}C$ NMR spectra of **332** were verified by $^{1}H$-$^{1}H$ and $^{13}C$-$^{1}H$ COSY experiments.

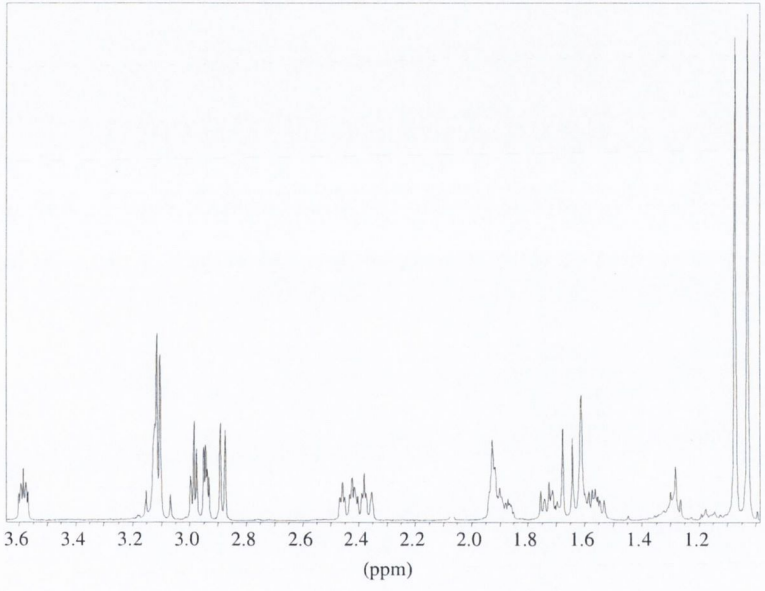



**Figure 2.3**

**$^{1}H$ NMR spectrum of epoxide 332 in $CDCl_3$**

The epoxide **332** underwent regiospecific ring opening when treated with sodium thiophenoxide to yield diol **333** as a single stereoisomer in good yield. The $^{1}H$ NMR spectrum of diol **333** is shown in **Figure 2.4**. Assignments of the signals in the $^{1}H$ and $^{13}C$ NMR spectra of **333** were verified by $^{1}H$-$^{1}H$ and $^{13}C$-$^{1}H$ COSY experiments.

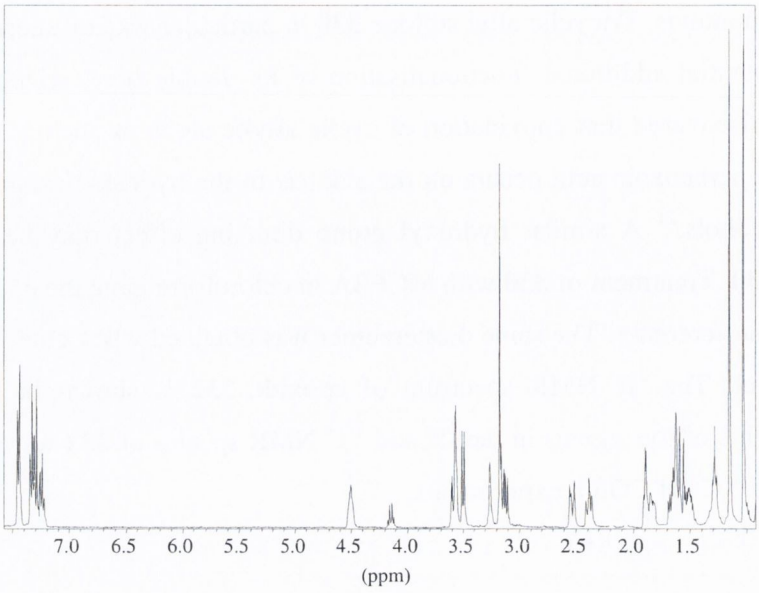
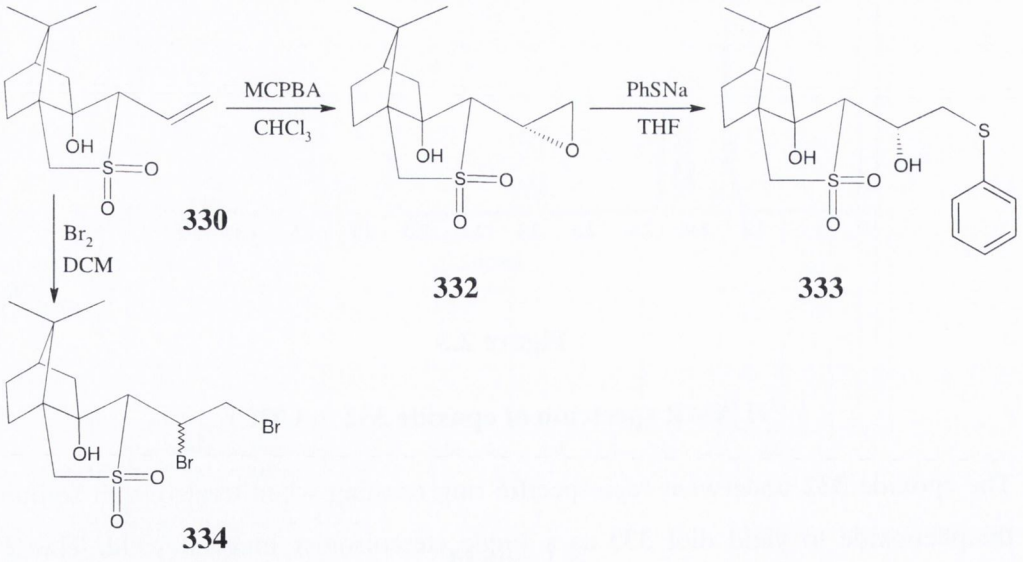



**Figure 2.4**

**$^1$H NMR spectrum of diol 333 in $CDCl_3$**

In contrast to the above stereospecific epoxidation, treatment of **330** with bromine in DCM gave both diastereomers of dibromide **334** in ca. 1:1 ratio (**Scheme 2.9**).




**Scheme 2.9**

The absolute stereochemistry at the newly formed asymmetric centres in epoxide **332** and tricyclic benzyl sulfone **331** were determined by X-ray diffraction. The molecular structure in the crystal of epoxide **332**, shown in **Figure 2.5**, allowed the

stereochemistry of cyclisation of **326** to be determined, as well as the stereochemistry of epoxidation of the tricyclic product **330**. Surprisingly, the hydroxyl group of **332** was in the *endo* configuration, indicating the carbanion derived from **326** had attacked the carbonyl group exclusively from the top face. This is in contrast to the known precedent for stereoselective additions of metal hydrides and organometallic reagents to camphor which give predominantly *exo*-configured products *via* axial attack from the less hindered bottom face.[22] Also evident is the configuration of the oxiranyl group at C-4, held away from the bulky 10-*syn* methyl group in a *pseudo*-equatorial configuration. The configuration of the oxiranyl oxygen indicates that epoxidation of **330** occurred from the side of the double bond closest to the hydroxyl group.

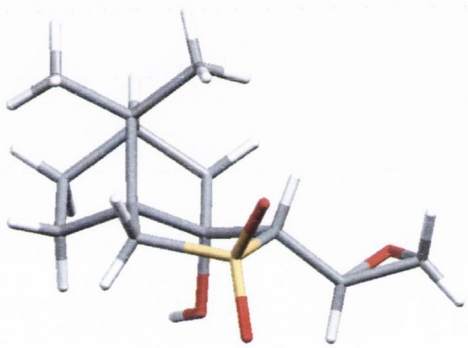


**Figure 2.5**

**Molecular structure in the crystal of epoxide 332**

The molecular structure in the crystal of **331**, shown in **Figure 2.6**, shows that **331** has the same absolute configuration as **330** at its two newly formed asymmetric centres, with the hydroxyl group in the *endo* configuration and the phenyl group *pseudo*-equatorial on the new 5-membered ring.

It is clear that the carbonyl group of the auxiliary in sulfones **326** and **328** will need to be manipulated in order to obtain adducts with electrophiles. Prior to this, a brief study on the retro-aldol chemistry of the tricyclic sulfones **330** and **331** was carried out in order to ascertain the position of equilibrium of the anions (**Scheme 2.10**). Treatment of sulfones **330** and **331** with a suitable base would yield an oxyanion

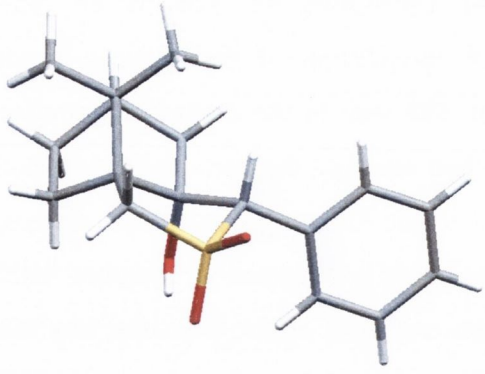
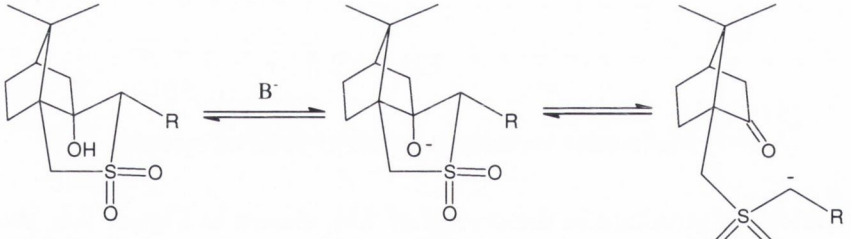


**Figure 2.6**

**Molecular structure in the crystal of benzyl sulfone 331**

**335** which can equilibrate with its sulfonyl stabilised carbanion **336**. The product distribution obtained after acidic quenching and work-up should be a reflection of the position of equilibrium of these anions, and thus an indication of the feasibility of trapping the sulfonyl carbanion with an electrophile (other than $H^+$). If the equilibrium favours the sulfonyl carbanion, this could be trapped by reaction with an electrophile, such as methyl iodide. The results of these studies will be covered in the next section.




**330** R = vinyl
**331** R = phenyl

**335**

**336**

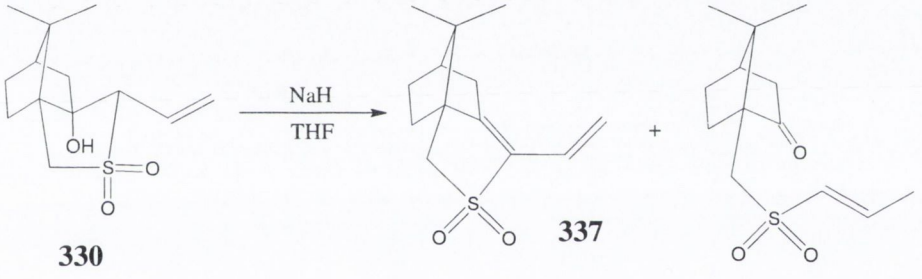
**Scheme 2.10**

## 2.3 Studies on the Retro-Aldol Chemistry of Tricyclic Sulfones 330 and 331

### 2.3.1 Retro-Aldol Chemistry of Tricyclic Sulfone 330

*(a) With Sodium Hydride*

The reaction of sulfone **330** with sodium hydride in THF in the absence of an electrophile was first explored in order to provide an indication of the position of equilibrium of the anion derived from **330**. Treatment of **330** with sodium hydride in THF at 0 °C, followed by warming to room temperature and acidic quenching gave two products. Separation by column chromatography yielded sulfonyldiene **337** as the major product (83 %), followed by a minor amount of (*E*)-vinyl sulfone **338** (**Scheme 2.11**).




**330** **337** **338**

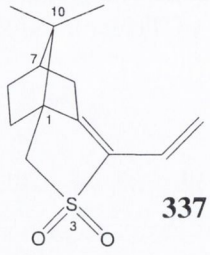
**Scheme 2.11**

Vinyl sulfone **338** is clearly formed *via* retro-aldol reaction of the initially formed oxyanion of **330** and subsequent double bond isomerisation prior to quenching with acid. Sulfonyldiene **337** may be formed either by deprotonation at the allylic position followed by β-elimination of hydroxide ion, or by deprotonation of the hydroxyl group followed by intermolecular proton transfer to form the same allylic carbanion leading to β-elimination.

In the $^{1}$H NMR spectrum of sulfonyldiene **337**, the methylene protons adjacent to sulfur appeared as a collapsed AB quartet at δ 3.14 ppm, while the vinylic methine proton had collapsed to a double doublet which came into resonance at δ 6.25 ppm. The $^{1}$H and $^{13}$C NMR details for **337** are summarised in **Table 2.3**. The $^{1}$H NMR spectrum of vinyl sulfone **338** displayed a pair of double quartets at δ 6.55 and 6.89 ppm corresponding to the vinylic protons, and a 3-proton double doublet for the terminal allylic methyl group at δ 1.96 ppm.

**Table 2.3**

**NMR spectroscopic details for sulfonyldiene 337 in $CDCl_3$**



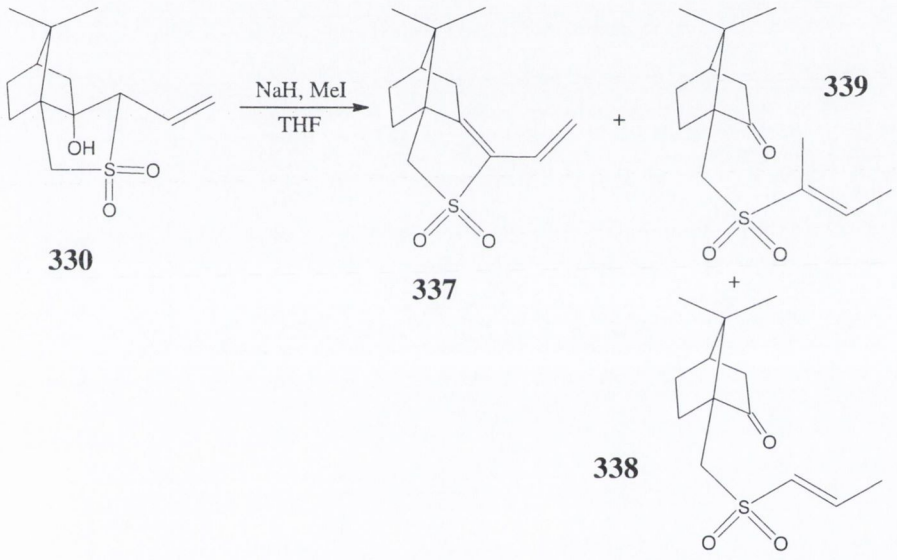

**337**

| $^1$H (ppm) | Multiplicity (Hz) | $^{13}$C (ppm) | Assignment |
|---|---|---|---|
| 1.04 | s | 18.4 | 10-$CH_3$ |
| 0.83 | s | 18.5 | 10-$CH_3$ |
| not assigned | - | 26.6 | C-8 |
| not assigned | - | 30.6 | C-9 |
| 2.19 | d, *J* 18.5 | 32.8 | C-6 |
| 2.63 | dd, *J* 18.5, 4.5 | | |
| 2.11 | t, *J* 4.5 | 44.8 | C-7 |
| - | - | 47.9 | C-10 |
| 3.11 | d, *J* 13.5 | 53.1 | C-2 |
| 3.16 | d, *J* 13.5 | | |
| - | - | 54.2 | C-1 |
| 5.45 | d, *J* 11.0 | 118.6 | CH=*C*$H_2$ |
| 5.83 | d, *J* 18.0 | | |
| 6.25 | dd, *J* 18.0, 11.0 | 121.2 | *C*H=$CH_2$ |
| - | - | 129.5 | C-4 |
| - | - | 157.3 | C-5 |

The fact that vinyl sulfone **338** is obtained as the minor product in the above reaction would seem to indicate that the anion equilibrium in **Scheme 2.10** lies with the oxyanion **335** (assuming initial deprotonation occurs at the hydroxyl group). Despite this, the retro-aldol reactions of **330** with sodium hydride were repeated in the presence of an electrophile.

*(b) With Sodium Hydride/Methyl Iodide*

The above reaction was repeated in the presence of methyl iodide. A solution of **330** and a large excess of methyl iodide were added dropwise to a suspension of sodium hydride in THF. Work-up and column chromatography gave three products. The first fraction consisted of an intractable mixture of several products of which sulfonyldiene **337** was the major product, as judged by $^{1}H$ NMR integration of the relevant signals. The other products obtained in this fraction could not be identified. The second and third fractions consisted of pure samples of trisubstituted vinyl sulfone **339** and vinyl sulfone **338** respectively (**Scheme 2.12**).



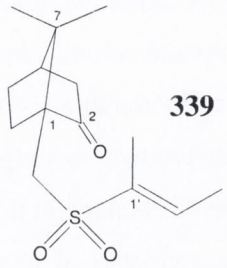

**Scheme 2.12**

The trisubstituted vinyl sulfone **339** is presumably formed *via* retro-aldol reaction of the oxyanion **335** (**Scheme 2.10**) to form allylic sulfonyl carbanion **336** which is trapped by methyl iodide. Subsequent double bond migration into a more favourable trisubstitution pattern yields **339**.

In the $^{1}H$ NMR spectrum of **339**, the single vinylic proton appeared as an apparent quartet of doublets at $\delta$ 6.77 ppm. The terminal allylic methyl group $\beta$ to the sulfone appeared as an apparent double doublet at $\delta$ 1.84 ppm, while the allylic methyl $\alpha$ to the sulfone gave an apparent triplet at $\delta$ 2.12 ppm. The $^{1}H$ and $^{13}C$ NMR details of **339** are summarised in **Table 2.4**.

**Table 2.4**

**NMR spectroscopic details for vinyl sulfone 339 in $CDCl_3$**



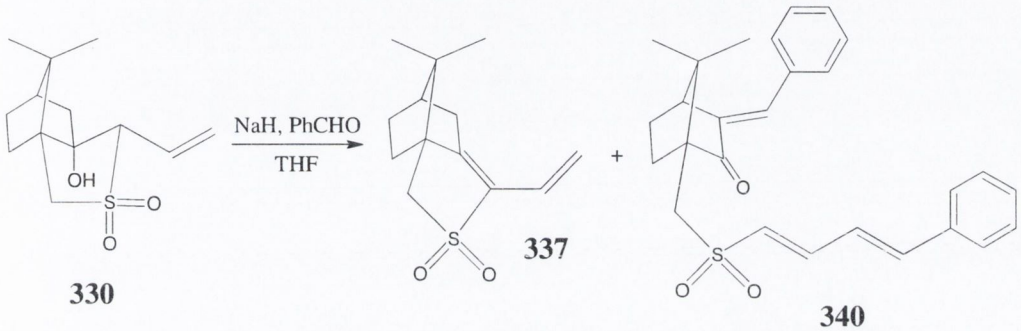

**339**

| $^1$H (ppm) | Multiplicity (Hz) | $^{13}$C (ppm) | Assignment |
|---|---|---|---|
| 1.84 | app dd, *J* 7.0, 1.5 | 11.4 | C-3' |
| 2.12 | app t, *J* 1.5, 1.0 | 13.6 | 1'-$CH_3$ |
| 1.12 | s | 19.3 | 7-$CH_3$ |
| 0.87 | s | 19.5 | 7-$CH_3$ |
| not assigned | - | 23.9 | C-5 |
| not assigned | - | 26.5 | C-6 |
| 2.11 | m | 42.0 | C-4 |
| 1.92 | d, *J* 18.5 | 42.1 | C-3 |
| 2.36 | dt, *J* 18.5, 4.0 | | |
| - | - | 47.7 | C-7 |
| 2.73 | d, *J* 15.0 | 48.0 | $CH_2SO_2$ |
| 3.45 | d, *J* 15.0 | | |
| - | - | 58.1 | C-1 |
| 6.77 | app qd, *J* 7.0, 1.5 | 136.6 | C-2' |
| - | - | 137.7 | C-1' |
| - | - | 214.5 | C-2 |

*(c) With Sodium Hydride/Benzaldehyde*

The above reaction was repeated in the presence of benzaldehyde. A solution of **330** was added to a suspension of sodium hydride in THF prior to the addition of benzaldehyde. The crude product obtained after work-up showed an intractable mixture of products in its $^1$H NMR spectrum. The signals attributed to sulfonyldiene **337** could be observed as well as a large amount of benzyl alcohol. Column chromatography yielded four fractions. Three of these fractions gave intractable mixtures which could not be identified, in addition to varying amounts of benzyl alcohol. The remaining fraction consisted of sulfonyldiene **337** as the

major product, together with a small amount of another product which was identified as sulfonyldiene **340** (**Scheme 2.13**). The $^1$H NMR and mass spectra of this fraction were consistent with this assignment. Sulfonyldiene **340** was also obtained by a different route and is discussed in Chapter 3, pg 329. Its $^1$H NMR spectrum was identical with the signals observed for the crude product obtained in this fraction. The $^1$H NMR spectrum of this fraction is shown in **Figure 2.7**.




**Scheme 2.13**

The formation of **340** may be explained by a retro-aldol/carbanion trapping sequence similar to that observed in the above reaction with methyl iodide.

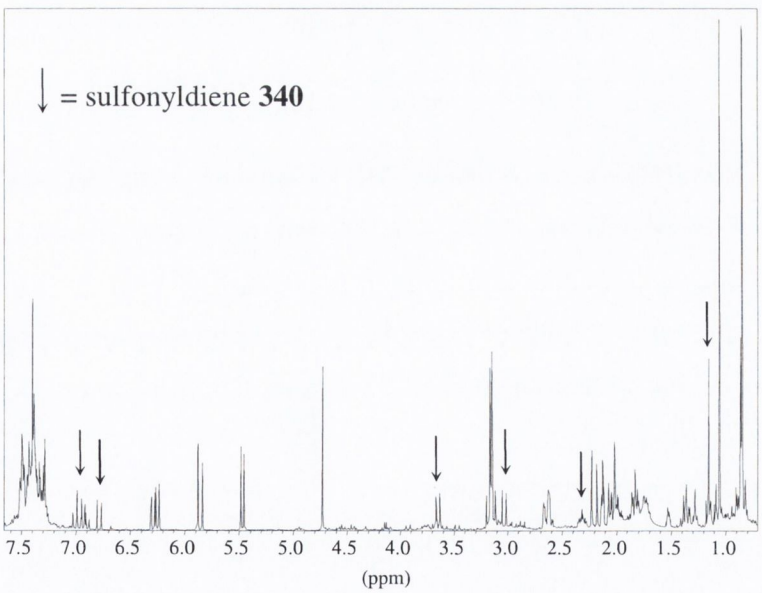
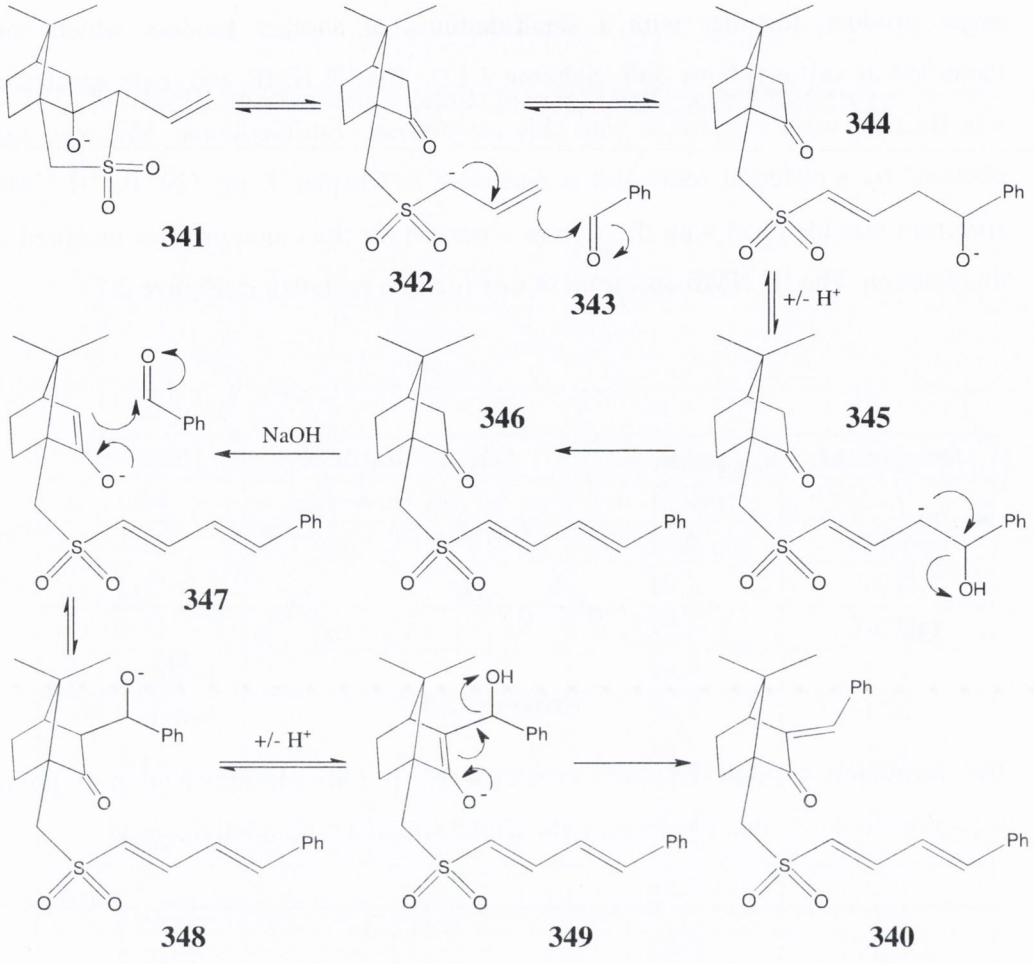



**Figure 2.7**

**$^1$H NMR spectrum of fraction containing sulfonyldienes**

**337 and 340 in $CDCl_3$**




**Scheme 2.14**

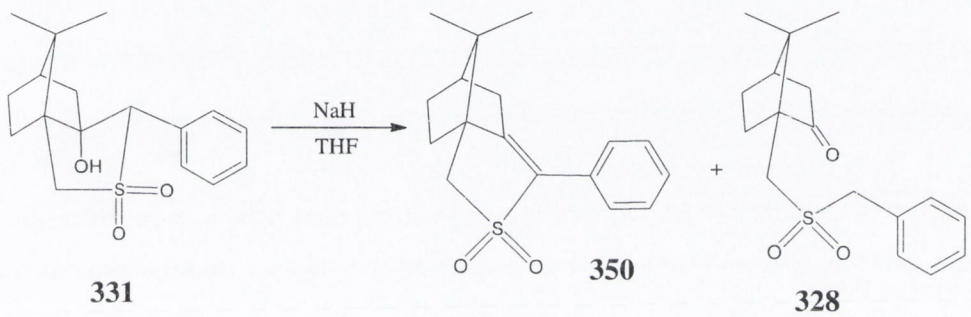
Thus the initially formed oxyanion **341** equilibrates with the allylic sulfonyl carbanion **342** which isomerises and is then trapped by benzaldehyde **343**. Intermolecular or intramolecular proton transfer, followed by elimination of hydroxide ion furnishes the diene side chain. Deprotonation of the auxiliary, presumably by the sodium hydroxide liberated in the formation of **337**, yields an enolate **347** which reacts with benzaldehyde. Further proton transfer and elimination gives the sulfonyldiene **340** (**Scheme 2.14**). The benzyl alcohol observed in this reaction is probably formed by Cannizzaro reaction of benzaldehyde with the sodium hydroxide liberated in the formation of **337**.

It is clear from the above reactions that β-elimination is the dominant reaction when **330** is treated with sodium hydride. The minor amounts of adducts obtained with methyl iodide and benzaldehyde and the different regioselectivities obtained with each make these reactions unsuitable from a synthetic point of view.

### 2.3.2 Retro-Aldol Chemistry of Tricyclic Sulfone 331

*(a) With Sodium Hydride*

The reaction of **330** with sodium hydride was repeated with the tricyclic benzyl sulfone **331** under identical conditions. Again two products were formed in this reaction. Purification by column chromatography yielded a minor amount of vinyl sulfone **350**, formed *via* β-elimination, together with the major product, benzyl sulfone **328**, formed by retro-aldol reaction followed by quenching of the benzylic carbanion (**Scheme 2.15**).




**331** **350** **328**

**Scheme 2.15**

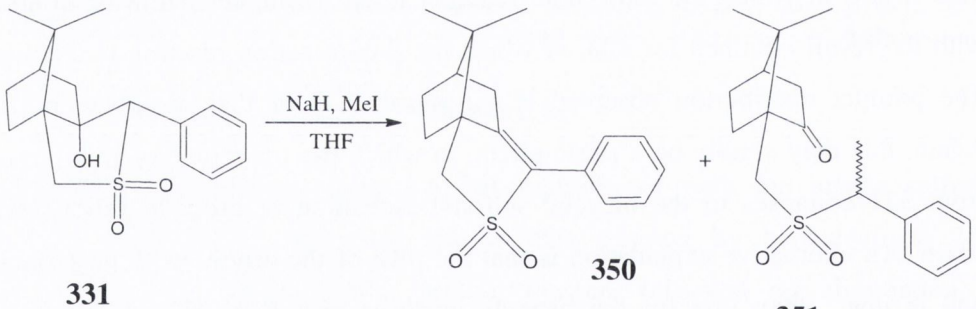
This result, in which the retro-aldol reaction is the dominant pathway, contrasts with the result obtained for **330**, in which the β-elimination reaction is dominant. The product distribution observed is a near reversal of that observed for **330**. Again, this may simply be a steric effect, in which the tricyclic oxyanion derived from **331** collapses to the bicyclic sulfonyl carbanion in order to relieve steric strain. An alternative explanation is that the pKa of the allylic methine proton in **330** is lower than that for the benzylic methine proton in **331**. As mentioned previously[20], the pKa (in DMSO) of phenyl allyl sulfone is lower than that for phenyl benzyl sulfone. If the pKa of the allyl proton in **330** is lower than that for the benzyl proton in **331**, a higher concentration of the allylic carbanion (leading to **337** *via* β-elimination) would be formed compared to the corresponding benzylic carbanion (leading to **350**).

The $^1$H NMR spectrum of **350** showed a collapsed AB quartet at δ 3.25 ppm corresponding to the methylene protons adjacent to sulfur. The *endo* methylene proton adjacent to the double bond appeared as a doublet at δ 2.40 ppm, while the

*exo* methylene proton on the same carbon appeared as a double triplet at δ 2.85 ppm.

*(b) With Sodium Hydride/Methyl Iodide*

The result obtained in the above reaction of **331** with sodium hydride is more promising than that obtained from the corresponding allyl compound **330**, from the point of view of obtaining adducts with electrophiles. The reaction of **331** with sodium hydride in the presence of methyl iodide was subsequently examined. Addition of **331** and a large excess of methyl iodide to a suspension of sodium hydride in THF, followed by the usual work-up gave a crude product whose $^1$H NMR spectrum showed the presence of vinyl sulfone **350**, formed *via* β-elimination, as well as both diastereomers of α-methyl benzyl sulfone **351** in ca. 1.3:1 ratio. Integration of the relevant signals showed that **351** and **350** were present in ca. 1.1:1 ratio, indicating that β-elimination had occurred to a greater extent in this reaction. Column chromatography yielded the minor diastereomer of **351** pure, while the major diastereomer eluted with vinyl sulfone **350** (**Scheme 2.16**).




**331** **350** **351**

**Scheme 2.16**

The mechanism for the formation of **351** is analogous to that for the corresponding reaction of allylic sulfone **330** with methyl iodide. The oxyanion formed on deprotonation of **331** undergoes retro-aldol reaction to form the more reactive sulfonyl carbanion which is trapped by the electrophile.

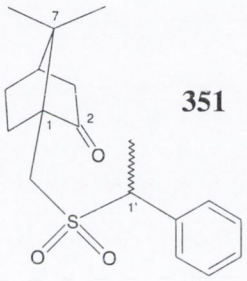
In the NMR spectrum of the mixture, the signals for the major diastereomer of **351** were obtained by subtracting the signals due to vinyl sulfone **350**. The $^1$H NMR spectrum of the major diastereomer of α-methyl benzyl sulfone **351** was characterised by the presence of a quartet at δ 4.81 ppm, corresponding to the

benzylic methine proton, as well as a 3 proton doublet at δ 1.80 ppm, assigned to the new methyl group. Similarly, the $^{1}$H NMR spectrum of the minor diastereomer displayed a quartet at δ 4.42 ppm for the benzylic methine proton, as well as a 3 proton doublet at δ 1.85 ppm corresponding to the new methyl group. The $^{1}$H and $^{13}$C NMR details for the minor diastereomer of **351** are shown in **Table 2.5**.

**Table 2.5**

**NMR spectroscopic details for the minor diastereomer**

**of sulfone 351 in $CDCl_3$**

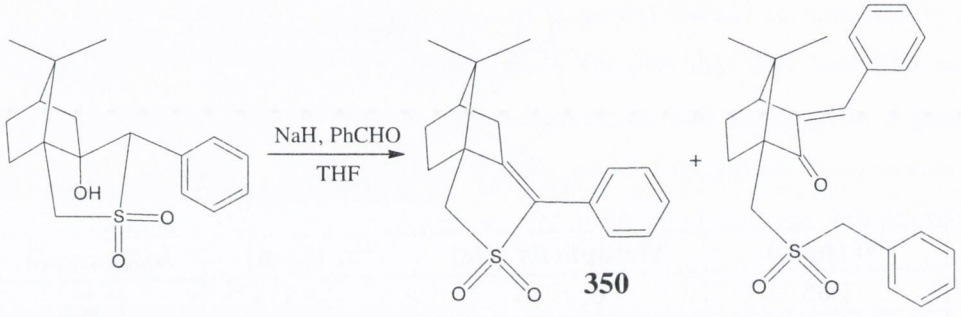



**351**

| $^{1}$H (ppm) | Multiplicity (Hz) | $^{13}$C (ppm) | Assignment |
|---|---|---|---|
| 1.85 | d, *J* .0 | 14.5 | C-2' |
| 1.08 | s | 19.4 | 7-$CH_3$ |
| 0.87 | s | 19.5 | 7-$CH_3$ |
| not assigned | - | 24.7 | C-5 |
| not assigned | - | 26.4 | C-6 |
| 1.92 | d, *J* 18.7 | 42.2 | C-3 |
| 2.38 | dt, *J* 18.7, 4.1 | | |
| 2.09 | t, *J* 4.6 | 42.2 | C-4 |
| 2.72 | d, *J* 14.6 | 46.3 | $CH_2SO_2$ |
| 3.34 | d, *J* 14.6 | | |
| - | - | 47.7 | C-7 |
| - | - | 58.4 | C-1 |
| 4.81 | q, *J* 7.5 | 64.9 | C-1' |
| 7.34-7.54 | m | 128.3 | Ar C-3 |
| 7.34-7.54 | m | 128.5 | Ar C-4 |
| 7.34-7.54 | m | 128.9 | Ar C-2 |
| - | - | 133.3 | Ar C-1 |
| - | - | 214.7 | C-2 |

*(c) With Sodium Hydride/Benzaldehyde*

Tricyclic sulfone **331** was treated with sodium hydride, followed by benzaldehyde using similar conditions employed for the tricyclic allyl sulfone **330**. Addition of **331** to sodium hydride in THF, followed by addition of excess benzaldehyde and work-up gave a crude product with a relatively clean $^1$H NMR spectrum. The spectrum consisted of the product of β-elimination, vinyl sulfone **350**, along with a second product which was identified as benzylidene sulfone **352** (**Scheme 2.17**). This compound was the major product (ca. 1.4:1 ratio) as judged by $^1$H NMR integration. The two products could not be separated by column chromatography and eluted together as a viscous oil.

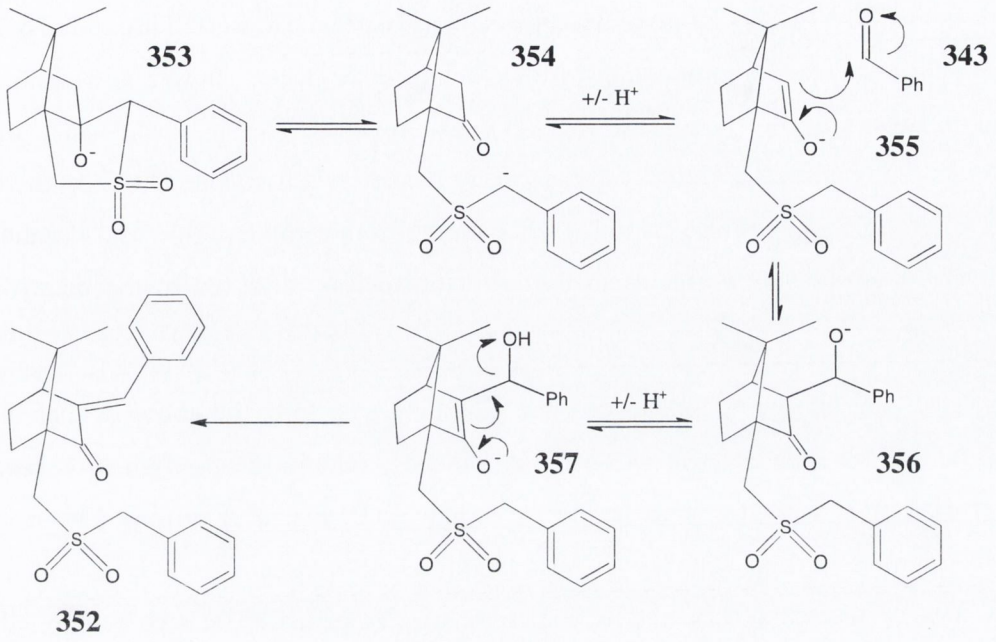



**331** **352**

**Scheme 2.17**

The regiospecificity of this reaction is in contrast with the above reaction of **331** with methyl iodide. The mechanism for the formation of **352** is analogous to that proposed for the formation of **340** (**Scheme 2.14**). Retro-aldol reaction of the initially formed oxyanion **353** yields a benzylic sulfonyl carbanion **354** which presumably undergoes inter or intramolecular proton transfer to yield an enolate **355**. Reaction of this enolate with benzaldehyde **343** occurs with concomitant elimination of hydroxide ion, giving **352** (**Scheme 2.18**).

The $^1$H NMR spectrum of **352** could be characterised by subtraction of the signals for vinyl sulfone **350** from the spectrum of the crude product. The $^1$H NMR spectrum of **352** displayed a pair of doublets at δ 2.78 and 3.55 ppm for the methylene protons adjacent to sulfur and C-1, and another pair at δ 4.43 and 4.87 ppm corresponding to the benzylic methylene protons.




**Scheme 2.18**

The methine proton at C-4 appeared as a doublet at δ 3.15 ppm. The $^{1}H$ NMR spectrum of benzylidene sulfone **352** is shown in **Figure 2.8**.

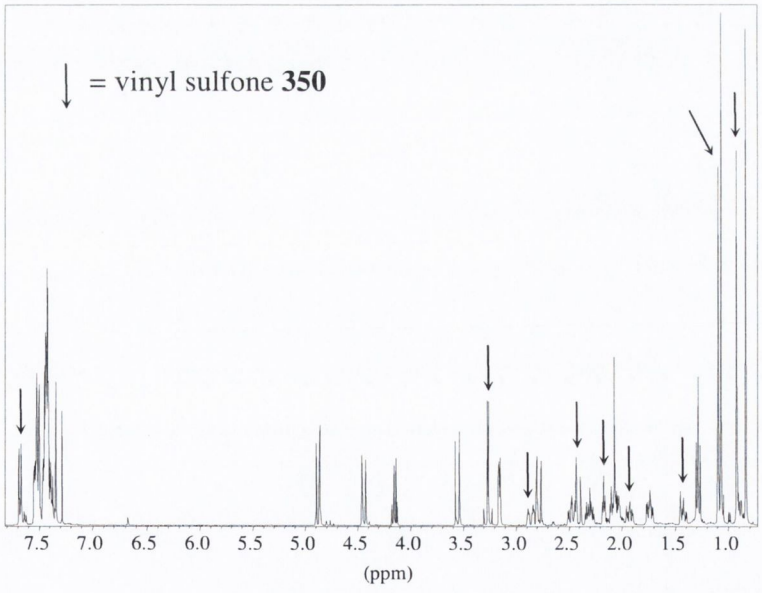



**Figure 2.8**

**$^{1}H$ NMR spectrum of benzylidene sulfone 352 in $CDCl_3$**

In the $^{13}C$ NMR spectrum of **352**, the carbonyl carbon had shifted upfield to δ 347.2 ppm as a result of conjugation with the benzylidene group. These assignments were verified by $^{1}H$-$^{1}H$ and $^{13}C$-$^{1}H$ COSY experiments. The stereochemistry of the double bond in the benzylidene group was tentatively assigned as (*E*) on the basis of an NOE experiment, in which irradiation of the methine proton at C-4 enhanced the intensity of the signals in the aromatic region attributed to the benzylidene group.

There are two main conclusions that may be drawn from the above studies on the retro-aldol chemistry of sulfones **330** and **331**. Firstly, the β-elimination reaction occurs to different extents in the two compounds. For allyl sulfone **330**, it is the dominant reaction whereas for benzyl sulfone **331**, it occurs to a lesser extent. As mentioned earlier, this may be due to the relative pKa's of the two compounds, or the greater steric effect of the phenyl group encountered in the formation of **331** relative to **330**, or both. The β-elimination reaction may also be facilitated by the *anti* periplanar relationship between the hydroxyl group and the α proton in **330** and **331** as revealed in their crystal structures. Secondly, the regioselectivity of adduct formation varies between the two electrophiles. With methyl iodide, alkylation occurred regioselectively α to the sulfonyl group in both compounds. With benzaldehyde, reaction occurs at the auxiliary and γ to the sulfonyl group in **330** and occurs exclusively at the auxiliary in **331**. This may be rationalised by assuming that the reactions with methyl iodide give kinetic products by irreversible trapping of the sulfonyl carbanions liberated in the retro-aldol step, whereas any initially formed adducts of these sulfonyl carbanions with benzaldehyde can reversibly proceed through a series of steps eventually giving vinyl ketones, rather than vinyl sulfones as the thermodynamic products. The results of these studies on the retro-aldol chemistry of **330** and **331** are summarised in **Table 2.6**.

**Table 2.6**

**Summary of retro-aldol reactions of tricyclic sulfones 330 and 331**

| Sulfone | Electrophile | β-Elimination (%)[a] | Retro-aldol (%)[a] | Regioselectivity |
|---|---|---|---|---|
| **330** | $H^+$ | 83[b] | 17[b] | α-sulfonyl |
| **330** | MeI | 74[c, d] | 12[b] | α-sulfonyl |
| **330** | PhCHO | 70[c, d] | 9[d] | γ-sulfonyl and α-carbonyl |
| **331** | $H^+$ | 21[b] | 79[b] | α-sulfonyl |
| **331** | MeI | 45[d] | 55[d] | α-sulfonyl |
| **331** | PhCHO | 35[d] | 65[d] | α-carbonyl |

[a] % by weight. [b] isolated yield after chromatography. [c] major product contaminated with minor amounts of unidentified products. [d] estimated by $^1$H NMR integration.

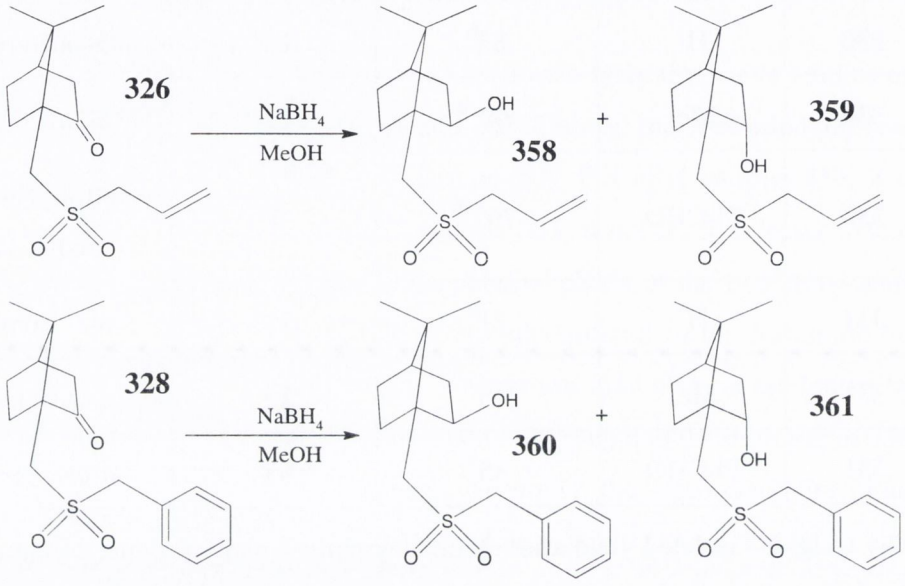
## 2.4 Synthesis and Aldol Reactions of Isobornyl Sulfones 358 and 360

### 2.4.1 Synthesis of Isobornyl Sulfones 358 and 360

The intramolecular cyclisations of sulfones **326** and **328** and the ineffectiveness of the retro-aldol approach of the tricyclic compounds **330** and **331** prompted a new approach wherein the carbonyl group was manipulated prior to anion generation. This may be achieved either by protection as its acetal, or by reduction with a metal hydride, forming the corresponding isobornyl sulfones.

It is well known that camphor is reduced with metal hydrides in a highly stereoselective manner to yield isoborneol as the major product, formed *via* axial attack form the less hindered bottom face.[23] This strategy was chosen for the

removal of the carbonyl group in sulfones **326** and **328**. Treatment of **326** with excess sodium borohydride in methanol gave a mixture of isobornyl sulfone **358** and its *endo* configured bornyl isomer **359** in 16.5:1 diastereomer ratio respectively, as determined by $^{1}$H NMR spectroscopy. Similarly, reduction of **328** gave isobornyl sulfone **360** and bornyl sulfone **361** in 15.7:1 diastereomer ratio. These mixtures were separated by column chromatography (**Scheme 2.19**).




**Scheme 2.19**

The signals in the $^{1}$H NMR spectra of the isobornyl sulfones **358** and **360** and their bornyl isomers **359** and **361** corresponding to the protons and carbon atoms of the chiral auxiliary were assigned by comparison to the known values for isoborneol and borneol.[24] Similarly, assignments of the $^{13}$C NMR spectra were aided by comparison with literature values.[25] The $^{1}$H NMR spectra of **358** and **360** were characterised by the appearance of a double doublet at ca. δ 4.15 ppm corresponding to the *endo* methine proton at C-2, as well as a 5-proton multiplet at ca. δ 1.7-1.9 ppm for the isobornyl ring protons. The $^{1}$H NMR spectra of the isobornyl sulfones **358** and **360** are shown in **Figure 2.9**.

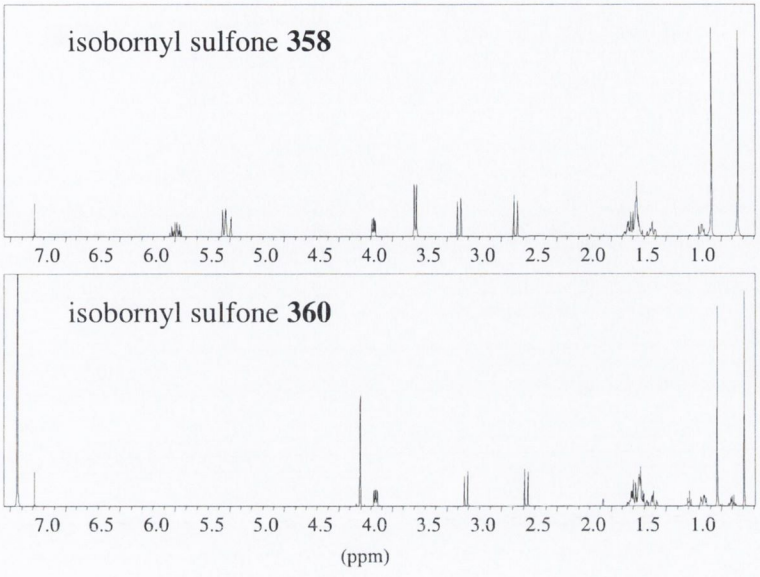



**Figure 2.9**

**$^1$H NMR spectra of isobornyl sulfones 358 and 360 in $CDCl_3$**

The bornyl isomers **359** and **361** displayed a double triplet at ca. δ 4.3 ppm for the *exo* methine proton at C-2. The characteristic signals for the *endo* methylene proton at C-3 (double doublet) and the methine proton at C-4 (triplet), unresolved in the isobornyl isomers **358** and **360**, were observed at ca. δ 1.15 and 1.66 ppm respectively in both compounds. The $^1$H NMR spectra of the bornyl sulfones **359** and **361** are shown in **Figure 2.10**.

### 2.4.2 Anion Chemistry of Isobornyl Sulfones 358 and 360

Initially, the isobornyl sulfone **360** was used in the next step. Truce and Klinger obtained a number of diastereomeric β-hydroxysulfones by reactions of sulfonyl carbanions with aldehydes.[26] Mixtures of *erythro* and *threo* diastereomers were obtained. These were distinguished from the magnitude of the vicinal coupling constant between the methine protons on the adjacent asymmetric centres. Similar mixtures of diastereomers may be anticipated in the reaction of **360** with benzaldehyde. In addition, the pre-existing chirality in **360** ensures the *erythro* and *threo* diastereomers will each be obtained as diastereomers, rather than racemic enantiomers.

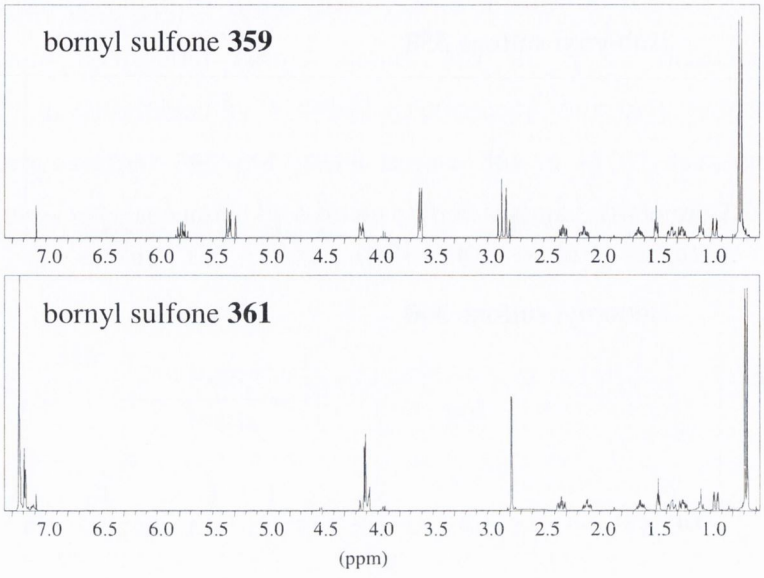
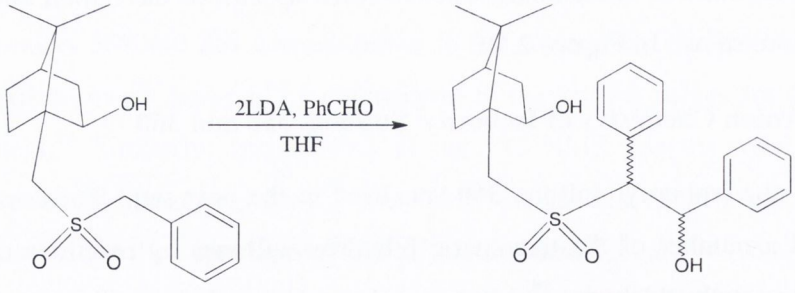



**Figure 2.10**

**$^1$H NMR spectra of bornyl sulfones 359 and 361 in $CDCl_3$**

Treatment of **360** with 2 equivalents of LDA, followed by benzaldehyde gave a crude product whose $^1$H NMR spectrum showed the presence of four diastereomers of β-hydroxysulfone **362**, in addition to a small amount of unreacted starting material (**Scheme 2.20**).

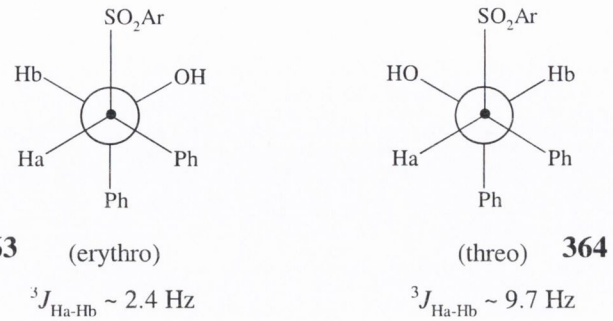



**360** **362** 1.5:1 threo:erythro (threo: ca. 1:1 d.r., erythro: ca. 3.8:1 d.r.)

**Scheme 2.20**

It has been shown that the analogous phenyl and *p*-tolylsulfonyl compounds reside in a preferred conformation in which the arylsulfonyl group and the phenyl group

on the adjacent carbon are antiperiplanar,[27] enabling the two diastereomers to be distinguished from the magnitude of the vicinal coupling constants[28] (**Figure 2.11**).




**363** (erythro) $^{3}J_{Ha\text{-}Hb}$ ~ 2.4 Hz

(threo) **364** $^{3}J_{Ha\text{-}Hb}$ ~ 9.7 Hz

**Figure 2.11**

**Newman projections of *erythro* and *threo* β-hydroxysulfones**

The $^{1}$H NMR spectrum of **362** showed a pair of closely spaced doublets at ca. δ 5.6 ppm, each with a coupling constant of 9.5 Hz and another pair at ca. δ 6.0 ppm, each with a coupling constant of 3.5 Hz. These signals were assigned to the pairs of *pseudo*-enantiomeric *threo* and *erythro* isomers of **362** respectively. Three of the four diastereomers of **362** were separated by careful column chromatography (the minor *erythro* diastereomer could not be isolated), enabling assignment of the remaining signals in the crude product. Integration of the relevant signals showed that the reaction was mildly *threo* selective (1.5:1 ratio), in agreement with previous observations.[29] In addition, the *pseudo*-enantiomeric *threo* isomers were present in ca. 1:1 ratio, whereas the *erythro* isomers were present in ca. 3.8:1 ratio.

The absolute configuration of one of the *threo* diastereomers, last to be eluted from the column and obtained free from starting material, was determined by X-ray crystallography. The molecular structure in the crystal, shown in **Figure 2.12**, revealed that the absolute configuration at the two newly formed asymmetric centres was 1'*S*, 2'*S*. With this information, and the relative stereochemistry known from the *vicinal* coupling constant in the $^{1}$H NMR spectrum, the absolute configuration of the second *threo* diastereomer was determined as 1'*R*, 2'*R*. The isobornylsulfonyl group and the phenyl group on the adjacent carbon were *anti*, placing the *vicinal* methine protons in an antiperiplanar relationship, in agreement with the conformational preference[27] exhibited by the analogous arylsulfonyl

compounds and the large *vicinal* coupling constant observed in the $^{1}H$ NMR spectrum.

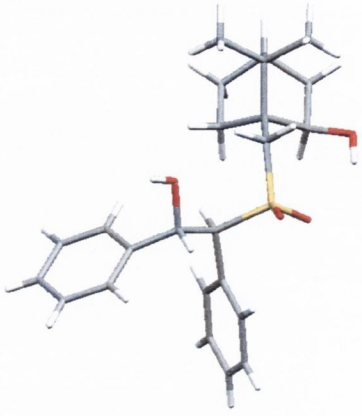


**Figure 2.12**

**Molecular structure in the crystal of *threo* β-hydroxysulfone 362**

Similarly, the absolute configuration of the major *erythro* diastereomer of **362** was determined by X-ray crystallography. The molecular structure in the crystal, shown in **Figure 2.13** shows that the absolute configuration of the sulfonyl side-chain is 1'*S*, 2'*R*. Hence the absolute configuration of the minor *erythro* diastereomer (which is *pseudo*-enantiomeric at the sulfonyl side-chain) is 1'*R*, 2'*S*.

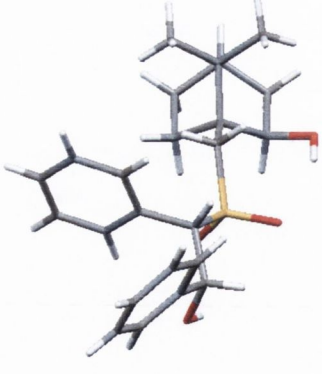


**Figure 2.13**

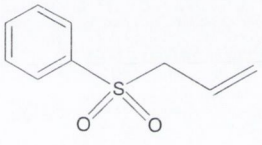
**Molecular structure in the crystal of *erythro* β-hydroxysulfone 362**

Following the work described in section 2.5, samarium iodide/HMPA was chosen as the reagent for the desulfonylation of the chiral β-hydroxysulfones **362**. Disappointingly, each of the diastereomers of **362** failed to react on treatment with excess (10 equivalents) samarium iodide in THF/HMPA and was recovered.

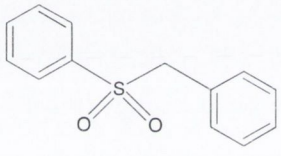
## 2.5 Studies on Achiral Allyl and Benzyl Sulfones 366, 369 and 370

### 2.5.1 Anion Reactions of 366, 369 and 370 with Benzaldehyde

At this point it was deemed appropriate to carry out analogous reactions on the achiral phenylsulfonyl compounds **365** and **366**, due to concerns regarding the desulfonylation step.



**365**



**366**

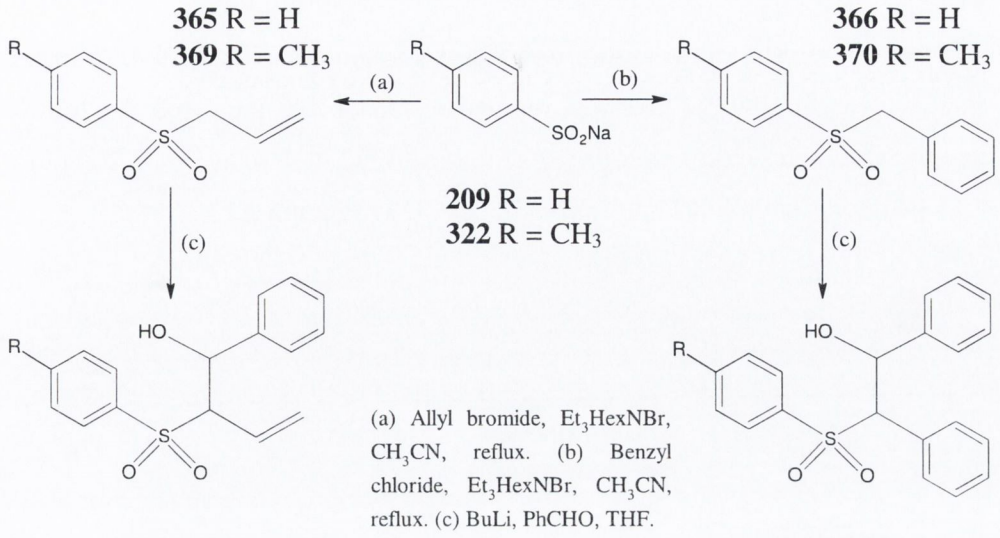
There are only a few reports in the literature on the desulfonylation of β-hydroxysulfones which do not result in olefin formation (Julia reaction). Kotake *et al.* reported that β-tosylhomoallylic alcohols underwent desulfonylation on treatment with $Pd(PPh_3)_4/NaBH_4$ giving regioselectively homoallylic alcohols.[30] It was also disclosed that these desulfonylations were accompanied by double bond migration or retro-aldol reaction when reagents such as Al(Hg), Na(Hg) or Li-$EtNH_2$ were used. Samarium iodide in THF/HMPA was also found to be an effective reagent for the desulfonylation of a variety of phenylsulfonyl compounds, including β-hydroxysulfones.[31] Samarium iodide in THF has also been used in the Julia olefination of a series of β-hydroxy imidazolyl sulfones.[32] Additionally, β-acetoxy glycosyl phenyl sulfones and β-acetoxy glycosyl 2-pyridylsulfones undergo Julia-type olefination on treatment with samarium iodide in THF/HMPA.[33] Ueno *et al.* reported that alkylated allylic *p*-tolyl sulfones undergo regioselective desulfonylation by reaction with tri-*n*-butyltin hydride under free-radical conditions, followed by protolysis of the resulting allylic stannanes with HCl or

acetic acid.[34] The desulfonylation step appears to be compatible with the presence of a hydroxyl group in the β-position of the allylic sulfone.[35] These reports prompted a study on the desulfonylations of the achiral β-hydroxysulfones derived from **365** and **366** using these procedures.

Phenyl benzyl sulfone **366** was prepared in near quantitative yield by reaction of sodium benzenesulfinate **209** with benzyl chloride using triethylhexylammonium bromide as phase transfer catalyst, according to the procedure of Masson *et al.*[17] The same procedure was used for the preparation of phenyl allyl sulfone **365**. The reaction of the anion of **366** with benzaldehyde gave a very low yield of adducts, presumably due to the stability of the benzylic anion of **366** and the reversibility of the β-alkoxide formation step. Similar observations were reported for this reaction by Kingsbury *et al.*,[36] as well as for reactions of benzyl *p*-tolyl sulfones with aromatic aldehydes.[37] The *erythro* and *threo* diastereomers of **368** could not be cleanly separated by chromatography. The reaction of **365** with benzaldehyde failed to produce any adducts **367** and starting material was recovered. Better results were obtained with the *p*-tolyl analogues **369** and **370**. Allyl *p*-tolyl sulfone **369** and benzyl *p*-tolyl sulfone **370** were obtained in high yield as described above from sodium *p*-toluenesulfinate **322**. Benzyl *p*-tolyl sulfone **370** reacted with benzaldehyde to form β-hydroxysulfone adducts **372** as a mixture of *threo*:*erythro* diastereomers in ca. 2.2:1 ratio. These could not be separated by recrystallisation and were obtained in good yield contaminated with a minor amount of unreacted sulfone **370**. Allyl *p*-tolyl sulfone **369** formed a mixture of diastereomeric adducts **371** in fair yield in ca. 2.6:1 ratio. These were separated by chromatography. A significant amount of double bond isomerisation occurred during this reaction giving rise to the corresponding vinyl sulfone **373** (**Scheme 2.21**).

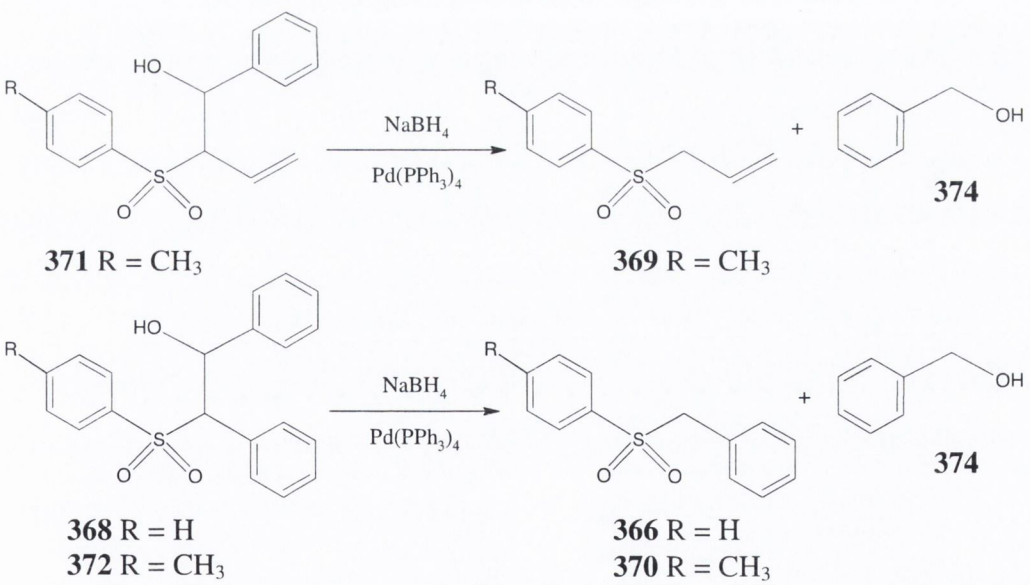
### 2.5.2 Desulfonylation Reactions of β-Hydroxysulfones 368, 371 and 372

The palladium-catalysed desulfonylation procedure using sodium borohydride reported by Kotake *et al.*[30] was carried out on **368**. Disappointingly, **368** underwent retro-aldol reaction under these conditions giving phenyl benzyl sulfone **366** and benzyl alcohol as products.




**Scheme 2.21**

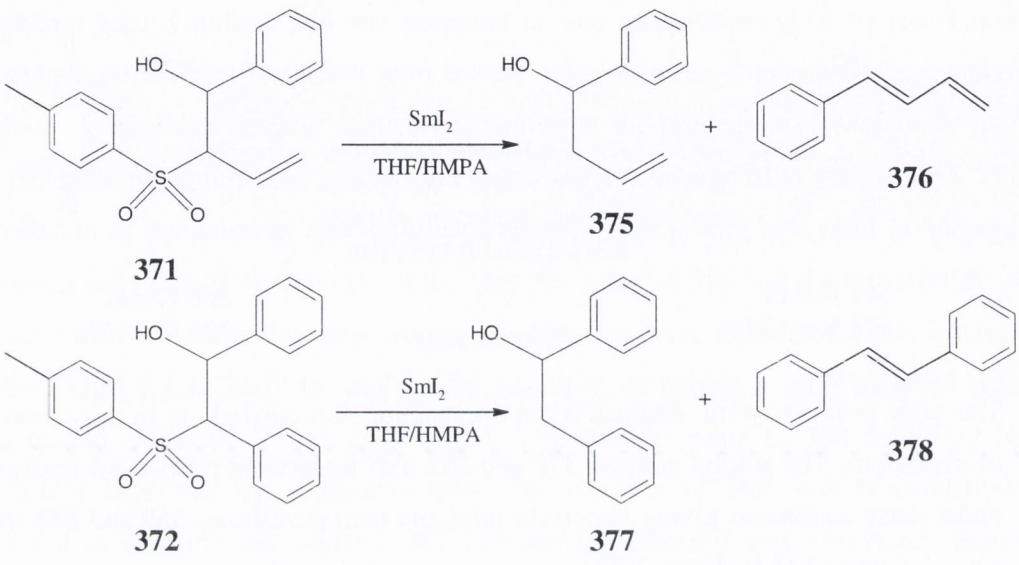
The same products were obtained when the reaction was carried out in the absence of palladium. The *p*-tolyl adducts **371** and **372** also underwent retro-aldol reaction under these conditions giving rise to the allyl and benzyl sulfones **369** and **370** and benzyl alcohol **374** (**Scheme 2.22**).




**Scheme 2.22**

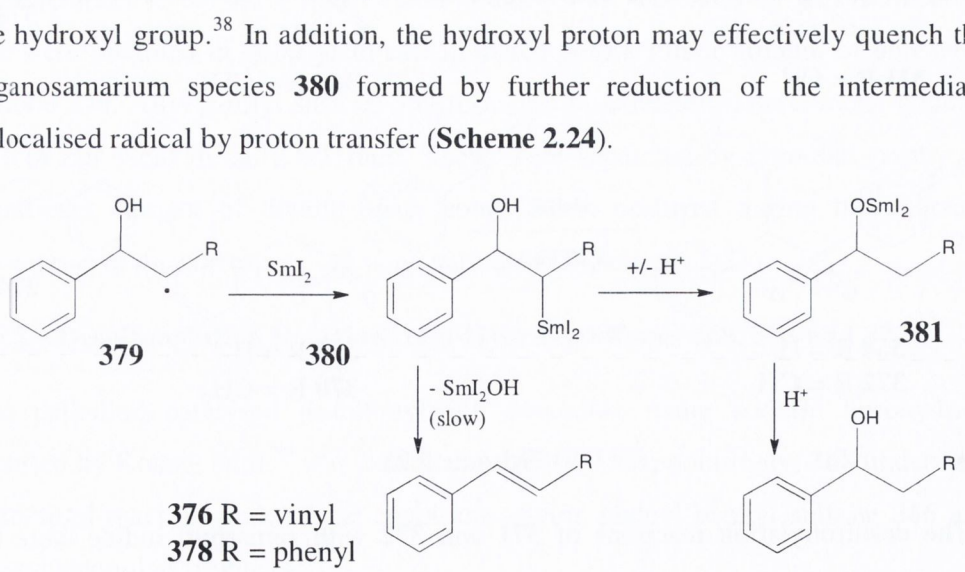
The desulfonylation reactions of **371** and **372** with samarium iodide were then examined. Treatment of **371** with excess samarium iodide in THF/HMPA at – 20 $^{o}$C for 5 hrs gave a crude product whose $^{1}$H NMR spectrum showed the presence of the desired homoallylic alcohol **375** and 1-phenylbuta-1,3-diene **376** (the product of

Julia olefination) in ca. 4:1 ratio, in addition to some unreacted starting material. The homoallylic alcohol **375** was isolated in reasonable yield (63 %) following column chromatography. Similar treatment of **372** led to a ca. 1.2:1 ratio of homobenzylic alcohol **377** and *trans* stillbene **378** (**Scheme 2.23**).




**Scheme 2.23**

The relative success of this desulfonylation procedure in giving rise to the homoallylic/homobenzylic alcohols (and with minor amounts of β-elimination products in the case of **371**) may be attributed to the poor leaving group ability of the hydroxyl group.[38] In addition, the hydroxyl proton may effectively quench the organosamarium species **380** formed by further reduction of the intermediate delocalised radical by proton transfer (**Scheme 2.24**).




**Scheme 2.24**

The free-radical desulfonylation procedure[34] using tri-*n*-butyltin hydride in the presence of AIBN was then carried out on **371**. Unfortunately, no reaction occurred on treatment of **371** with tri-*n*-butyltin hydride/AIBN in either benzene or toluene at reflux, and starting material was recovered.

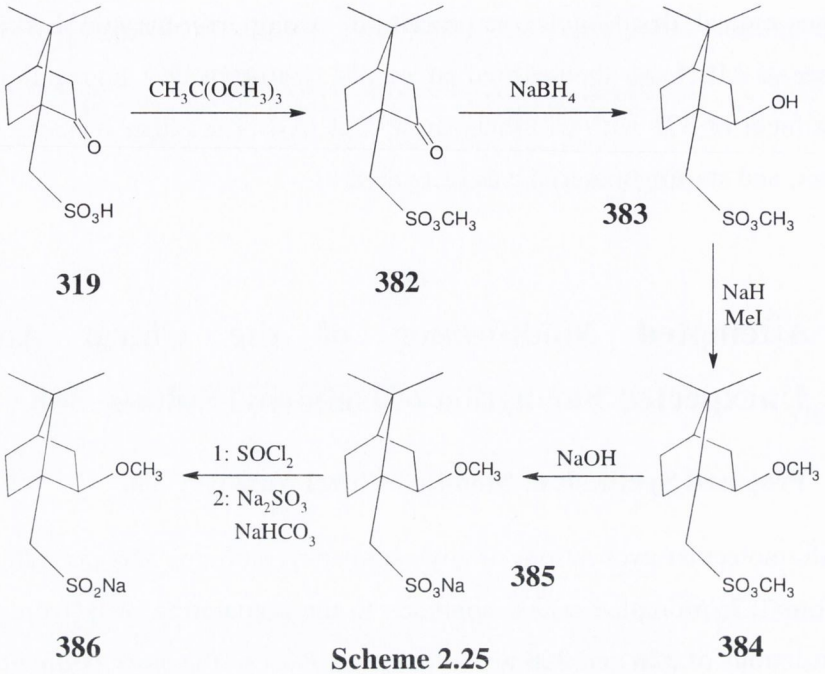
## 2.6 Attempted Modification of the Chiral Auxiliary; Unexpected Formation of Isobornyl Sultone 388

### 2.6.1 Proposed Synthesis of Modified Chiral Auxiliary 386

The intramolecular cyclisations of allyl and benzyl sulfones **326** and **328**, discussed in section 2.2, prompted a new approach to the preparation of β-hydroxysulfones from reactions of **326** and **328** with aldehydes. Prior to the work outlined in section 2.4, the preparation of a new chiral auxiliary was attempted, in which the carbonyl group of (+)-camphorsulfonic acid was replaced by a methoxy group, prior to sulfone preparation. Thus, conversion of (+)-camphorsulfonic acid **319** into the known methyl sulfonate ester **382**,[39] followed by reduction with sodium borohydride should yield primarily the *exo* alcohol **383**. Conversion of **383** to its methyl ether **384**, followed by hydrolysis of the sulfonate ester should afford sodium sulfonate **385**, which could be converted into its corresponding sodium sulfinate **386** by the usual two-step procedure (**Scheme 2.25**).

### 2.6.2 Unexpected Formation of Isobornyl Sultone 388

Following the procedure of Gopalan and co-workers,[40] sulfonate ester **382** was conveniently obtained by treating the acid **319** with trimethyl orthoacetate. Reduction of **382** with excess sodium borohydride in methanol afforded the *exo*-alcohol **383** along with ca. 10 % of its *endo* isomer **387** as judged by $^1$H NMR. This was used without further purification. The *exo* alcohol displayed a double doublet at ca. δ 4.1 ppm for the *endo* methine proton at C-2 as well as a pair of doublets at ca. δ 3.0 and 3.6 ppm corresponding to the methylene protons adjacent to the sulfonate ester group. The $^1$H NMR spectrum of **383** is shown in **Figure 2.14**.




**Scheme 2.25**

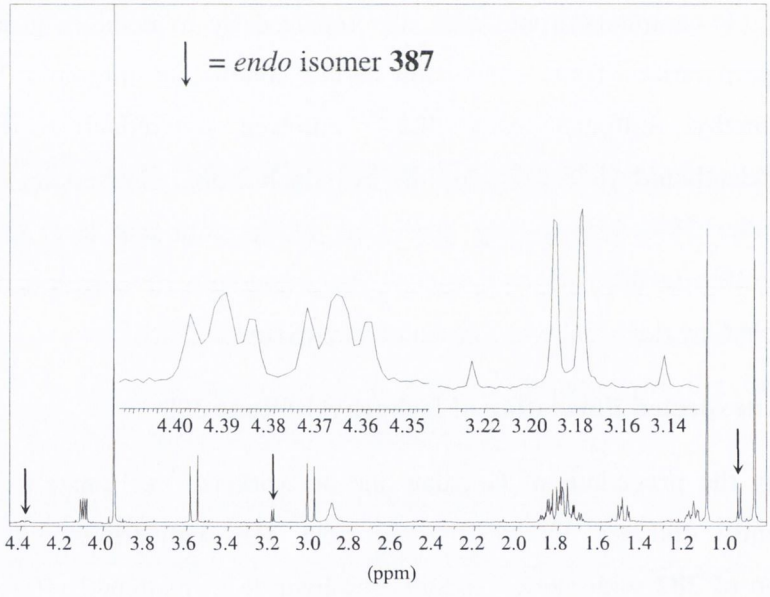


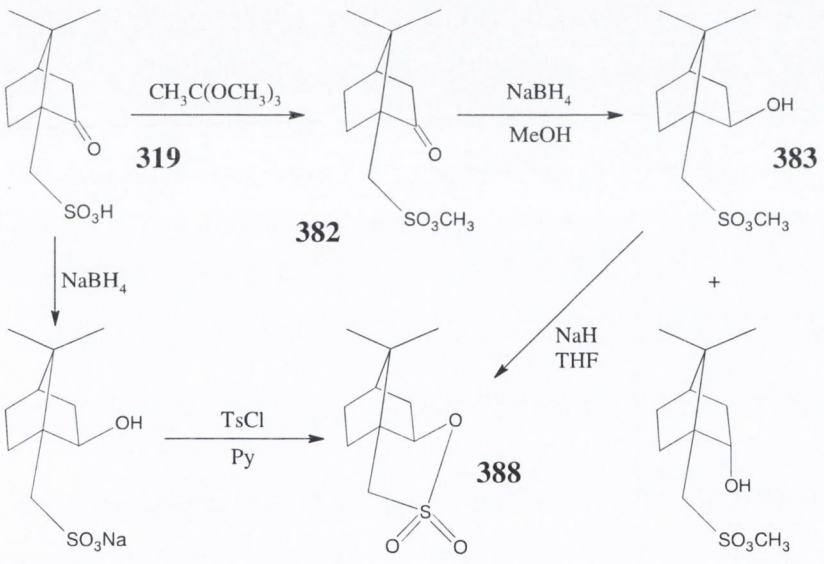

**Figure 2.14**

**$^1$H NMR spectrum of 383 with signal enlargements of *endo* isomer 387 ($CDCl_3$)**

Treatment of **383** with sodium hydride/methyl iodide afforded isobornyl sultone **388,** rather than the expected methyl ether **384.** When the reaction was repeated without methyl iodide, sultone **388** was obtained in 60 % yield. The NMR

spectroscopic details of **388** were identical to those published by Melo *et al.*[41] Sultone **388** has been synthesised by the sulfonation of camphene with sulfuric acid/acetic anhydride,[42] and also by the reduction of acid **319** with sodium borohydride, followed by cyclisation with *p*-toluenesulfonyl chloride in pyridine[43] (**Scheme 2.26**). Thus, an alternative route to sultone **388** has been realised which, although requiring an extra step, avoids the need for Soxhlet extraction of the sulfonate salt **389** with hot ethanol.

The acid catalysed methylation of **383** with methyl-2,2,2-trichloroacetimidate[44] was subsequently examined. However, no reaction occurred on treatment of **383** with this reagent in the presence of trifluoromethanesulfonic acid in DCM and starting material was recovered. This line of work was subsequently aborted in favour of the approach discussed in section 2.4.




**Scheme 2.26**

## 2.7 Summary and Concluding Remarks

This chapter has focused on the anion chemistry of the chiral allyl and benzyl sulfones **326** and **328** derived from sodium camphorsulfinate **310**. These chiral sulfones undergo 5-*exo* trig cyclisation in a completely stereoselective fashion on treatment with LDA, giving single diastereomers whose absolute configurations have been determined from their X-ray crystal structures.

Attempted retro-aldol reactions of these tricyclic products with methyl iodide or benzaldehyde gave both the corresponding tricyclic vinyl sulfones **337** and **350** formed *via* β-elimination, and products arising from retro-aldol reaction, followed by trapping with the electrophile, with different product distributions observed for each compound.

Reduction of sulfones **326** and **328** leads predominantly to their isobornyl analogues **358** and **360**. Reaction of **360** with benzaldehyde proceeds in a non-stereoselective fashion to give adducts **362** as a mixture of all four possible diastereomers which can be separated by careful chromatography. The absolute configurations of these diastereomers were determined by X-ray crystallography and $^{1}$H NMR. These adducts did not undergo desulfonylation when treated with samarium iodide/HMPA.

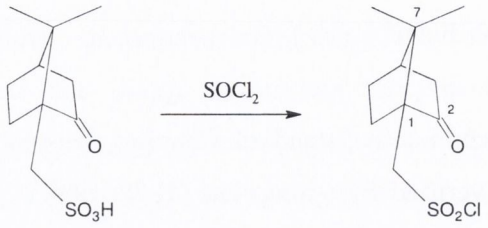
Similar studies on achiral arylsulfonyl compounds **366**, **369** and **370** showed that these compounds can be used as masked carbanion equivalents *via* the sequence of sulfonyl carbanion aldol reaction/desulfonylation. Allylic sulfones have also been used as masked allylic carbanion equivalents in the reverse sequence; zinc or samarium mediated desulfonylation to form an allylic organometallic species, followed by reaction with a carbonyl compound.[45]

Finally, a novel 3-step route to isobornylsultone **388** has been discovered. Future work in this area could involve the examination of Lewis acids in the reactions of isobornyl sulfones **358** and **360** with aldehydes to determine if chelation has any beneficial effect on the stereochemical outcome of the reaction. The use of other reagents for the desulfonylation of these adducts and subsequent recovery of the auxiliary will also need to be addressed.

## 2.8 Experimental

NMR spectra were recorded at 20 °C for solutions in $CDCl_3$ unless stated otherwise on a Bruker AVANCE DPX 400 MHz spectrometer. Proton and carbon chemical shifts are reported in parts per million (ppm) and are measured relative to tetramethylsilane as an internal standard. Coupling constants (*J*) are recorded in Hz. Assingments were verified by appropriate $^{1}H$-$^{1}H$ COSY, $^{13}C$-$^{1}H$ COSY and $^{13}C$-DEPT experiments. Multiplicities are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), quintet (qu), sextet (sx), septet (sp), multiplet (m), double doublet (dd), double triplet (dt), double quartet (dq), double septet (dsp), triple doublet (td), triple triplet (tt), triple quartet (tq), broad (br) and apparent (app). Mass spectra were obtained for solutions in methanol unless otherwise stated using VG Alto Spec (HRMS) and Kratos (FAB) instruments. IR spectra were recorded for Nujol mulls (N) or for neat liquid films (L) between sodium chloride plates using a Matteson Genesis II FTIR spectrometer and were processed using WinFirst software. Uncorrected melting points were measured in unsealed capillary tubes using a Griffin melting point apparatus. Thin layer chromatography was carried out under gravity using Merck Kieselgel 60 $F_{254}$ 0.2 mm silica gel plates. Optical rotations were determined at the temperature stated for solutions of concentration *c* in a 1 dm cell using a Perkin-Elmer 141 polarimeter; specific rotations are given in units of $10^{-1}$ deg $cm^2$ $g^{-1}$. Evaporation was performed under reduced pressure in a Heidolph laborota 4000 rotary evaporator. Organic extracts of reaction products were dried over anhydrous magnesium sulfate unless stated otherwise. Ether refers to the use of diethyl ether. Tetrahydrofuran (THF) solvent was refluxed over potassium hydroxide, stored under a nitrogen atmosphere over sodium wire/benzophenone and was freshly distilled before use. Acetone, benzene, toluene, dichloromethane and chloroform were dried and distilled over anhydrous calcium chloride. Diisopropylamine was stored over calcium hydride and was freshly distilled before use. All other solvents and reagents were used as received from Aldrich Chemical Co.

**(1*S*, 4*R*)-(7,7-Dimethyl-2-oxobicyclo[2.2.1]hept-1-yl)methanesulfonyl chloride 320**[12, 46]




**319** **320**

Thionyl chloride (37.7 mls, 516 mmol) was added to (+)-camphor-10-sulfonic acid **319** (40 g, 172 mmol) in a 1L flask. The mixture was stirred at rt for 1 hr, warmed at 40 °C for a further 6 hrs and then cooled back to rt and left stirring overnight. The mixture was diluted with ether (400 mls) and quenched over ice/$H_2O$. The aqueous layer was extracted with ether (400 mls). The combined organic extracts were washed with $H_2O$ (200 mls) and satd. sodium hydrogen carbonate soln. (4 × 100 mls) until the evolution of $CO_2$ had ceased, and then dried and evaporated to afford the title compound as a white solid (38 g, 89 %).

m.p.: 62-63 °C (from ether); Lit.[12]: 67-68 °C

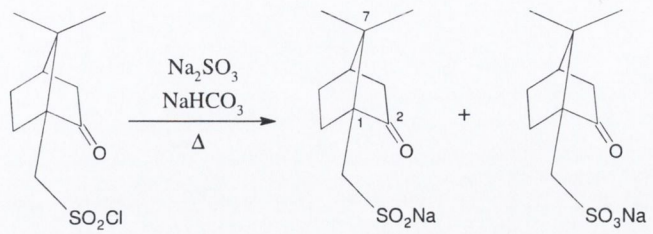
$[\alpha]_D$ (*c* 1.29, $CHCl_3$, 27 °C) +30.9; Lit[46]: (*c* 4.2, $CHCl_3$) +28.8

IR: $\nu_{max}$ (N) 2921, 1741 (C=O), 1459, 1368, 1279, 1171, 1132, 1102, 1045 ($SO_2$), 854, 768 $cm^{-1}$

$^1H$ NMR (400.1 MHz): δ 0.94 (3H, s, 7-C*H*$_3$), 1.16 (3H, s, 7-C*H*$_3$), 1.47-1.54 (1H, m), 1.76-1.83 (1H, m), 2.01 (1H, d, $^2J$ = 18.4, 3-C*H*$_2$ *endo*), 2.08-2.16 (1H, m), 2.18 (1H, t, $^3J$ = 4.7, 4-C*H*), 2.42-2.52 (2H, m), 3.74 (1H, d, $^2J$ = 14.3, C*H*$_2$SO$_2$Cl), 4.32 (1H, d, $^2J$ = 14.3, C*H*$_2$SO$_2$Cl) ppm

$^{13}C$ NMR (100.6 MHz): δ 19.2 (7-*C*H$_3$), 19.3 (7-*C*H$_3$), 24.8 (C-5), 26.4 (C-6), 41.8 (C-3), 42.3 (C-4), 47.7 (C-7), 59.2 (C-1), 63.7 (*C*H$_2$SO$_2$Cl), 212.3 (C-2) ppm

**Sodium (1*S*, 4*R*)-(7,7-dimethyl-2-oxobicyclo[2.2.1]hept-1-yl)methanesulfinate 310**[12, 13]




**320** **310** **321**

(+)-Camphor-10-sulfonyl chloride **320** (36.3 g, 144 mmol) in dry acetone (80 ml) was added dropwise over 4 hrs to a solution of sodium sulfite (35.29 g, 280 mmol) and sodium hydrogen carbonate (23.52 g, 280 mmol) in water (200 ml) maintained at 70 °C. The mixture was stirred for an additional 1 hr at 70 °C and was then allowed to cool to rt and left stirring overnight. The mixture was evaporated to yield a white residue which was taken up in boiling methanol and filtered through celite. The filtrate was evaporated to afford the title compound as a white solid (31.43 g, 94 %) together with *ca.* 5 % of the corresponding sodium sulfonate **321**.

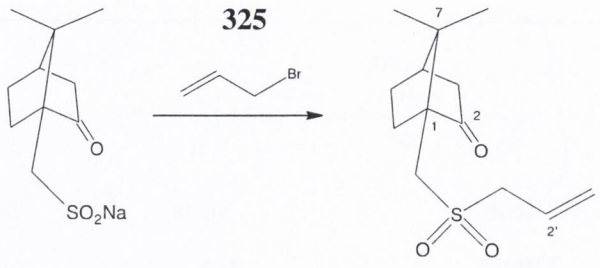
$[\alpha]_D$ (*c* 0.76, $H_2O$, 22 °C) -41.8; Lit[12]: (*c* 0.885, $H_2O$, 19 °C) -58.2

IR: $\nu_{max}$ (N) 3358, 2918, 1741 (C=O), 1460, 1375, 1278, 1197, 1020, 973, (S=O), 851, 816, 723 $cm^{-1}$

$^1H$ NMR in $D_2O$ (400.1 MHz): δ 0.80 (3H, s, 7-C*H*$_3$), 0.93 (3H, s, 7-C*H*$_3$), 1.33-1.40 (1H, m), 1.43-1.51 (1H, m), 1.88 (1H, d, $^2J$ = 19.0, 3-C*H*$_2$ *endo*), 1.92-2.00 (1H, m), 2.00-2.06 (1H, dd, $^2J$ = 12.0, $^3J$ = 2.5), 2.10 (1H, t, $^3J$ = 4.5, 4-C*H*), 2.13 (1H, d, $^2J$ = 13.5, C*H*$_2$SO$_2$Na), 2.35-2.42 (1H, ddd, $^2J$ = 19.0, $^3J_1$ = 4.5, $^3J_2$ = 3.0, 3-C*H*$_2$ *exo*), 2.57 (1H, d, $^2J$ = 13.5, C*H*$_2$SO$_2$Na) ppm

$^{13}C$ NMR in $D_2O$ (100.6 MHz): δ 18.3 (7-*C*H$_3$), 18.7 (7-*C*H$_3$), 25.6 (C-5), 25.9 (C-6), 42.0 (C-4), 42.3 (C-3), 47.6 (C-7), 58.5 (C-1), 59.5 (*C*H$_2$SO$_2$Na), 223.8 (C-2) ppm

**(1*S*, 4*R*)-1-({[Prop-2'-enyl]sulfonyl}methyl)-7,7-dimethylbicyclo[2.2.1]heptan-2-one 326**




**310** **326**

Method A:

Sodium (+)-camphor-10-sulfinate **310** (5.36 g, 22 mmol) and sodium iodide (0.67 g, 20 mol %) were dissolved in DMSO (50 mls). The mixture was warmed to 40 °C to dissolve the solids and allyl bromide **325** (2.92 ml, 33 mmol) was added. The solution was warmed at 60 °C for 6 hrs. The solution was then allowed to cool to rt, diluted with water (200 mls) and extracted with ether (3 × 100 mls). The combined organic extracts were washed with satd. aq. $Na_2SO_3$ (100 ml) and brine (50 ml), dried and evaporated to yield an oil. Column chromatography on silica gel using EtOAc:Hexane(1:2) afforded the title compound as a colourless oil (3.77 g, 65 %).

Method B: [17]

Sodium (+)-camphor-10-sulfinate **310** (0.94 g, 3.9 mmol) was suspended in acetonitrile (15 ml) and triethylhexylammonium bromide (0.21 g, 20 mol %) was added. Allyl bromide **325** (0.38 ml, 4.3 mmol) was added and the mixture was heated under reflux for 24 hrs. The mixture was allowed to cool to rt, diluted with $H_2O$ (50 ml) and extracted with ether (3 × 50 ml). The combined organic extracts were washed with brine (50 ml), dried and evaporated to yield an oil. Column chromatography on silica gel using EtOAc:Hexane(1:2) afforded the title compound as a colourless oil (0.75 g, 74 %).

$[\alpha]_D$ (*c* 0.51, MeOH, 22 °C) +19.2

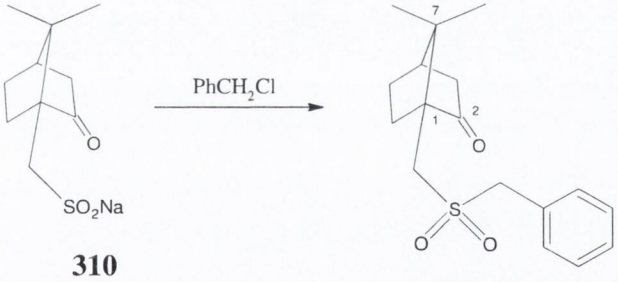
IR $\nu_{max}$ (L) 3087, 2961, 1744 (C=O), 1638 (C=C), 1455, 1417, 1394, 1317 ($SO_2$), 1245, 1201, 1133 ($SO_2$), 1051, 994, 937, 876, 820, 773, 676 $cm^{-1}$

$^1$H NMR (400.1 MHz): δ 0.89 (3H, s, 7-C*H*$_3$), 1.07 (3H, s, 7-C*H*$_3$), 1.44-1.50 (1H, m), 1.81-1.89 (1H, m), 1.95 (1H, d, $^2J$ = 18.4, 3-C*H*$_2$ *endo*), 2.01-2.11 (1H, m), 2.14 (1H, t, $^3J$ = 4.5, 4-C*H*), 2.36-2.45 (2H, m), 2.75 (1H, d, $^2J$ = 15.0, C*H*$_2$SO$_2$), 3.47 (1H, d, $^2J$ = 15.0, C*H*$_2$SO$_2$), 3.80 (1H, dd, $^2J$ = 14.0, $^3J$ = 7.5, 1'-C*H*$_2$), 4.12 (1H, dd, $^2J$ = 14.0, $^3J$ = 7.5, 1'-C*H*$_2$), 5.52 (2H, m, 3'-C*H*$_2$), 6.01 (1H, ddt, $^3J_1$ = 17.3, $^3J_2$ = 10.0, $^3J_3$ = 7.5, 2'-C*H*$_2$) ppm

$^{13}$C NMR (100.6 MHz): δ 19.2 (7-*C*H$_3$), 19.3 (7-*C*H$_3$), 24.9 (C-5), 26.6 (C-6), 42.1 (C-4), 42.2 (C-3), 48.2 (C-7), 48.6 (*C*H$_2$SO$_2$), 58.5 (C-1), 59.9 (C-1'), 124.4 (C-3'), 124.8 (C-2'), 215.0 (C-2) ppm

HRMS (CI) *m/z* 279.1027: *calculated for* $[C_{13}H_{20}O_3S + Na]^+$ 279.1030

**(1*S*, 4*R*)-1-[(Benzylsulfonyl)methyl]-7,7-dimethylbicyclo[2.2.1]heptan-2-one 328**




**310** **328**

Method A:

Sodium (+)-camphor-10-sulfinate **310** (5 g, 21 mmol) and sodium iodide (0.6 g, 20 mol %) were dissolved in DMSO (75 ml). The flask was warmed to 40 °C to dissolve the solid and benzyl chloride (3.14 ml, 27.2 mmol) was added. The solution was warmed at 80 °C for 12 hrs. The solution was then allowed to cool to rt, diluted with water (200 ml) and extracted with ether (2 × 200 ml). The combined organic extracts were washed with satd. aq. $Na_2SO_3$ (100 mls) and brine (50 ml), dried and evaporated to yield an oil which later crystallized. Recrystallisation from ethyl acetate afforded the title compound as a white solid (5.01 g, 78 %).

Method B: [17]

Sodium (+)-camphor-10-sulfinate **310** (0.94 g, 3.9 mmol) was suspended in acetonitrile (15 ml) and triethylhexylammonium bromide (0.21 g, 20 mol %) was added. Benzyl chloride (0.5 ml, 4.3 mmol) was added and the mixture was heated under reflux for 24 hrs. The mixture was allowed to cool to rt, diluted with $H_2O$ (50 ml) and extracted with ether (3 × 50 ml). The combined organic extracts were washed with brine (50 ml), dried and evaporated to yield an oil which later crystallized. Recrystallisation from ethyl acetate afforded the title compound as a white solid (0.91 g, 75 %).

m.p.: 68-69 °C (from EtOAc)

$[\alpha]_D$ (*c* 0.48, MeOH, 22 °C) +21.0

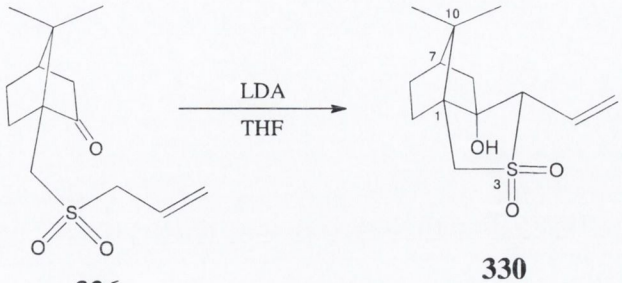
IR $\nu_{max}$ (N) 2945, 1737 (C=O), 1455, 1411, 1375, 1314 ($SO_2$), 1263, 1198, 1153, 1118 ($SO_2$), 1052, 1029, 965, 931, 879, 857, 793, 744, 720, 701 $cm^{-1}$

$^1H$ NMR (400.1 MHz): δ 0.85 (3H, s, 7-C*H*$_3$), 1.02 (3H, s, 7-C*H*$_3$), 1.44-1.51 (1H, m), 1.89-1.97 (1H, m), 1.97 (1H, d, $^2J$ = 18.5, 3-C*H*$_2$-*endo*), 2.02-2.09 (1H, m), 2.13 (1H, t, $^3J$ = 4.5, 4-C*H*), 2.32-2.45 (2H, m), 2.68 (1H, d, $^2J$ = 15.0, alkyl C*H*$_2$SO$_2$), 3.40 (1H, d, $^2J$ = 15.0, alkyl C*H*$_2$SO$_2$), 4.36 (1H, d, $^2J$ = 13.5, benzyl C*H*$_2$SO$_2$), 4.72 (1H, d, $^2J$ = 13.5, benzyl C*H*$_2$SO$_2$), 7.38-7.41 (3H, m, Ar*H*), 7.46-7.49 (2H, m, Ar*H*) ppm

$^{13}C$ NMR (100.6 MHz): δ 19.2 (7-*C*H$_3$), 19.3 (7-*C*H$_3$), 25.2 (C-5), 26.6 (C-6), 42.1 (C-4), 42.2 (C-3), 48.2 (C-7), 48.9 (alkyl *C*H$_2$SO$_2$), 58.7 (C-1), 61.6 (benzyl *C*H$_2$SO$_2$), 127.9 (Ar C-1), 128.4 (Ar C-3), 128.4 (Ar C-4), 130.5 (Ar C-2), 215.1 (C-2) ppm

HRMS (CI) *m/z* 329.1173: *calculated for* $[C_{17}H_{22}O_3S + Na]^+$ 329.1187

**(1*S*, 4*S*, 5*S*, 7*R*)-10,10-Dimethyl-4-vinyl-3-thiatricyclo[5.2.1.0$^{1,5}$]decan-5-ol 3,3-dioxide 330**




**326** **330**

*n*-Butyllithium (0.8 ml, 2.5 M, 1.9 mmol) was added to a solution of dry diisopropylamine (0.36 ml, 2.5 mmol) in dry THF (5 ml) at – 60 °C under an atmosphere of nitrogen. The solution was allowed to warm to 0 °C and then recooled to – 60 °C. A solution of sulfone **326** (0.51 g, 1.9 mmol) in dry THF (4 ml) was added dropwise *via* syringe and the solution was stirred at – 60 °C for 90 mins. The solution was then allowed to warm to rt, quenched with satd. aq. $NH_4Cl$ (50 ml) and extracted with ether (3 × 50 ml). The combined organic extracts were washed with brine (50 ml), dried and evaporated to yield an oil (0.41 g). Column chromatography on silica gel using EtOAc:hexane (1:2) afforded the title compound as a white solid (0.36 g, 70 %), followed by unchanged starting sulfone **326** (0.03 g).

m.p.: 89-91 °C (from EtOAc/hexane)

$[\alpha]_D$ (*c* 1.11, MeOH, 22 °C) -74.8

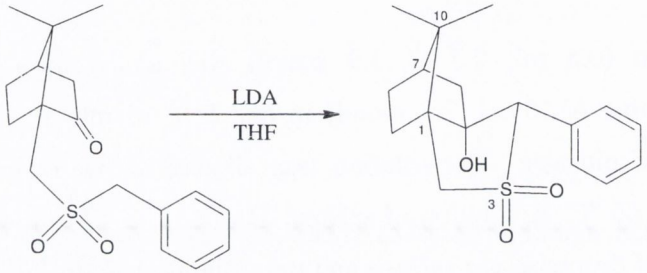
IR $\nu_{max}$ (N) 3507 (O-H), 3465 (O-H), 2918, 1634 (C=C), 1461, 1409, 1375, 1300 ($SO_2$), 1221, 1182, 1116 ($SO_2$), 1023, 994, 931, 859, 831, 786, 741, 645 $cm^{-1}$

$^1$H NMR (400.1 MHz): δ 1.02 (3H, s, 10-C$H_3$), 1.12 (3H, s, 10-C$H_3$), 1.48 (1H, d, $^2J$ = 13.5, 6-C$H_2$ *endo*), 1.49-1.56 (1H, m), 1.66-1.72 (1H, m), 1.84-1.91 (2H, m), 2.22 (1H, dt, $^2J$ = 13.5, $^3J$ = 3.5, 6-C$H_2$ *exo*), 2.33-2.39 (1H, m), 3.06 (1H, d, $^2J$ = 14.5, 2-C$H_2$), 3.13 (1H, d, $^2J$ = 14.5, 2-C$H_2$), 3.74 (1H, d, $^3J$ = 8.5, 4-C*H*), 5.57 (1H, d, $^3J$ = 17.0, CH=C$H_2$), 5.61 (1H, d, $^3J$ = 10.5, CH=C$H_2$), 6.02 (1H, ddd, $^3J_1$ = 17.0, $^3J_2$ = 10.5, $^3J_3$ = 8.5, C*H*=CH$_2$) ppm

$^{13}C$ NMR (100.6 MHz): δ 21.4 (10-$CH_3$), 21.4 (10-$CH_3$), 26.1 (C-8), 26.7 (C-9), 41.9 (C-6), 43.7 (C-7), 50.3 (C-10), 51.0 (C-2), 56.5 (C-1), 72.7 (C-4), 82.1 (C-5), 122.7 ($CH$=$CH_2$), 125.2 (CH=$CH_2$) ppm

HRMS (CI) *m/z* 279.1035: *calculated for* $[C_{13}H_{20}O_3S + Na]^+$ 279.1030

**(1*S*, 4*S*, 5*S*, 7*R*)-10,10-Dimethyl-4-phenyl-3-thiatricyclo[5.2.1.0$^{1,5}$]decan-5-ol 3,3-dioxide 331**




**328** **331**

*n*-Butyllithium (2.61 ml, 2.5 M, 6.5 mmol) was added to a solution of dry diisopropylamine (1.19 ml, 8.5 mmol) in dry THF (10 ml) at – 60 °C under an atmosphere of nitrogen. The solution was allowed to warm to 0 °C and then recooled to – 60 °C. A solution of sulfone **328** (2 g, 6.5 mmol) in dry THF (15 ml) was added dropwise *via* syringe and the solution was stirred at – 60 °C for 15 mins and then allowed to warm to rt and stirred for a further 3 hrs. The solution was then quenched with satd. aq. $NH_4Cl$ (50 ml) and extracted with ether (3 × 50 ml). The combined organic extracts were washed with brine (50 ml), dried and evaporated to yield an oil (1.89 g). Column chromatography on silica gel using EtOAc:hexane (1:3) afforded the title compound as a white solid (1.53 g, 76 %), followed by unchanged starting sulfone **328** (0.28 g).

m.p.: 83 °C (from EtOAc/hexane)

$[\alpha]_D$ (*c* 0.93, MeOH, 22 °C) +4.4

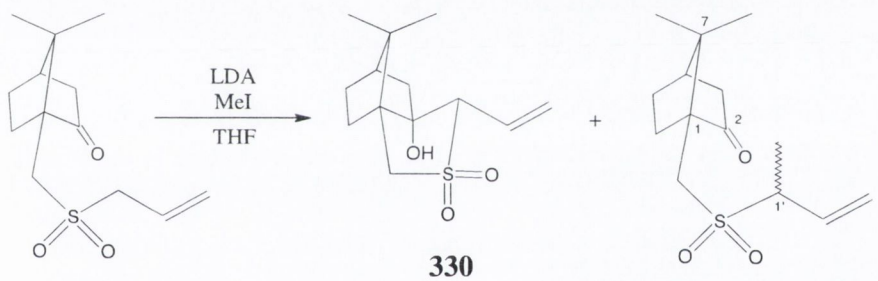
IR: $\nu_{max}$ (N) 3515 (O-H), 2929, 1601 (Ar C-C), 1499, 1455, 1376, 1300 ($SO_2$), 1247, 1222, 1183, 1117 ($SO_2$), 1077, 1027, 944, 832, 794, 738, 716, 694 $cm^{-1}$

$^1$H NMR (400.1 MHz): δ 1.07 (3H, s, 10-C*H*$_3$), 1.23 (3H, s, 10-C*H*$_3$), 1.49 (1H, d, $^2J$ = 13.5, 6-C*H*$_2$ *endo*), 1.53-1.58 (1H, m), 1.70-1.77 (1H, m), 1.87-1.90 (1H, m), 1.93 (1H, t, $^3J$ = 3.5, 7-C*H*), 2.36 (1H, dt, $^2J$ = 13.5, $^3J$ = 3.5, 6-C*H*$_2$ *exo*), 2.44 (1H, m), 3.17 (1H, d, $^2J$ = 14.5, 2-C*H*$_2$), 3.21 (1H, d, $^2J$ = 14.5, 2-C*H*$_2$), 4.38 (1H, s, 4-C*H*), 7.41 (3H, t, $^3J$ = 2.5, Ar-*H*), 7.64-7.67 (2H, m, Ar-*H*) ppm

$^{13}$C NMR (100.6 MHz): δ 21.6 (10-*C*H$_3$), 21.6 (10-*C*H$_3$), 26.1 (C-8), 26.9 (C-9), 42.3 (C-6), 43.9 (C-7), 50.3 (C-10), 51.4 (C-2), 56.2 (C-1), 71.9 (C-4), 81.9 (C-5), 126.8 (Ar C-1), 128.2(Ar C-3), 128.5 (Ar C-4), 130.2 (Ar C-2) ppm

HRMS (CI) *m/z* 329.1196: *calculated for* $[C_{17}H_{22}O_3S + Na]^+$ 329.1186

**(1*S*, 4*R*)-1-{[(1'-Methylprop-2'-enyl)sulfonyl]methyl}-7,7-dimethylbicyclo[2.2.1]heptan-2-one 329**




**326** **330** **329**

*n*-Butyllithium (0.51 ml, 2.5 M, 1.2 mmol) was added to a solution of dry diisopropylamine (0.23 ml, 1.6 mmol) in dry THF (4 ml) at – 60 °C under an atmosphere of nitrogen. The solution was allowed to warm to 0 °C and then recooled to – 60 °C. A solution of sulfone **326** (0.33 g, 1.2 mmol) in dry THF (4 ml) was added dropwise *via* syringe and the solution was stirred at – 60 °C for 1 hr. Methyl iodide (1.6 ml, 25 mmol) was added *via* syringe and the solution was allowed to warm to rt and stirred for a further 5 hrs. The solution was then quenched with satd. aq. $NH_4Cl$ (50 ml) and extracted with ether (3 × 50 ml). The combined organic extracts were washed with brine (50 ml), dried and evaporated to yield an oil (0.31 g). The crude product was purified over silica gel, eluting with EtOAc:hexane (1:2) to yield three products. The first product to elute was sulfone **330** as an oil (0.15 g) contaminated with ca. 23 % of one diastereomer of sulfone

**329**. The second product to elute was another diastereomer of sulfone **329** (0.03 g) as an oil (described below). The third product to elute was unchanged starting sulfone **326** (0.03 g) as an oil.

$[\alpha]_D$ (*c* 0.27, MeOH, 26 °C) +47.0

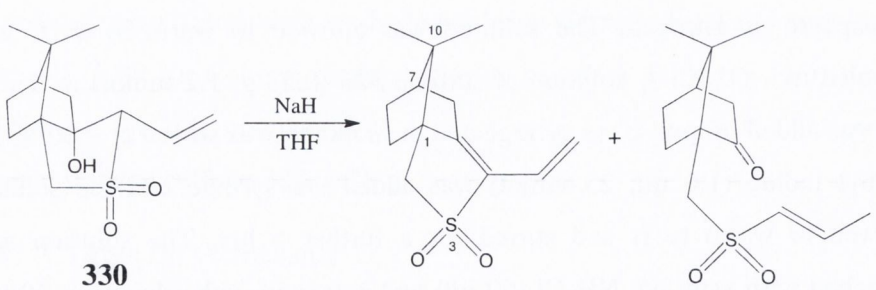
IR: $\nu_{max}$ (L) 3087, 2955, 1743 (C=O), 1637 (C=C), 1454, 1416, 1375, 1313 ($SO_2$), 1132 ($SO_2$), 1049, 997, 936, 853, 776, 732, 679 $cm^{-1}$

$^1H$ NMR (400.1 MHz): δ 0.90 (3H, s, 7-C*H*$_3$), 1.12 (3H, s, 7-C*H*$_3$), 1.40-1.47 (1H, m), 1.55 (3H, d, $^3J$ = 7.3, 1'-C*H*$_3$), 1.70-1.77 (1H, m), 1.94 (1H, d, $^2J$ = 18.3, 3-C*H*$_2$ *endo*), 2.01-2.09 (1H, m), 2.11 (1H, t, $^3J$ = 4.4, 4-C*H*), 2.40 (1H, dt, $^2J$ = 18.3, $^3J$ = 4.4, 3-C*H*$_2$ *exo*), 2.50-2.57 (1H, m), 2.72 (1H, d, $^2J$ = 14.6, C*H*$_2$SO$_2$), 3.50 (1H, d, $^2J$ = 14.6, C*H*$_2$SO$_2$), 3.79 (1H, qu, $^3J_1$ = 8.0, $^3J_2$ = 7.3, 1'-C*H*), 5.45 (2H, dd, $^3J_1$ = 16.8, $^3J_2$ = 10.2, 3'-C*H*$_2$), 6.00 (1H, ddd, $^3J_1$ = 16.8, $^3J_2$ = 10.2, $^3J_3$ = 8.0, 2'-C*H*) ppm

$^{13}C$ NMR (100.6 MHz): δ 12.5 (1'-*C*H$_3$), 19.4 (7-*C*H$_3$), 19.5 (7-*C*H$_3$), 24.6 (C-5), 26.5 (C-6), 42.1 (C-3), 42.2 (C-4), 45.3 (*C*H$_2$SO$_2$), 47.7 (C-7), 58.2 (C-1), 63.5 (C-1'), 121.4 (C-3'), 131.2 (C-2'), 214.6 (C-2) ppm

HRMS (CI) *m/z* 293.1185: *calculated for* $[C_{14}H_{22}O_3S + Na]^+$ 293.1186

**(1*S*, 7*R*)-10,10-Dimethyl-4-vinyl-3-thiatricyclo[5.2.1.0$^{1,5}$]dec-4-ene 3,3-dioxide 337**




**330** **337** **338**

A solution of sulfone **330** (0.13 g, 0.50 mmol) in dry THF (4 ml) was added dropwise to a suspension of sodium hydride (0.022g, 60 %, 0.55 mmol) in dry THF (3 ml) at 0 °C under an atmosphere of nitrogen. The mixture was stirred at 0 °C for

30 mins and then allowed to warm to rt and stirred for an additional 90 mins. The mixture was then quenched with satd. aq. $NH_4Cl$ (50 ml) and extracted with ether (3 × 50 ml). The combined organic extracts were washed with brine (50 ml), dried and evaporated to yield an oil. Column chromatography on silica gel using EtOAc:hexane (1:2) afforded the title compound as a white solid (0.1 g, 83 %), followed by vinyl sulfone **338** (0.02 g, see page 110).

m.p.: decomposes at 137 °C

$[\alpha]_D$ (*c* 0.29, $CHCl_3$, 26 °C) -62.7

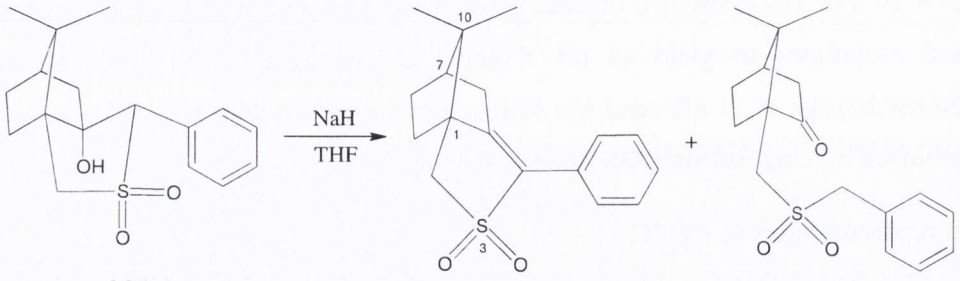
IR: $\nu_{max}$ (N) 2923, 1666 (C=C), 1457, 1375, 1288 ($SO_2$), 1155, 1116 ($SO_2$), 981, 923, 742 $cm^{-1}$

$^1H$ NMR (400.1 MHz): δ 0.83 (3H, s, 10-C*H*$_3$), 1.04 (3H, s, 10-C*H*$_3$), 1.31-1.36 (1H, m), 1.78-1.83 (1H, m), 1.92-2.06 (2H, m), 2.11 (1H, t, $^3J$ = 4.5, 7-C*H*), 2.19 (1H, d, $^2J$ = 18.5, 6-C*H*$_2$ *endo*), 2.63 (1H, dd, $^2J$ = 18.5, $^3J$ = 4.5, 6-C*H*$_2$ *exo*), 3.11 (1H, d, $^2J$ = 13.5, 2-C*H*$_2$), 3.16 (1H, d, $^2J$ = 13.5, 2-C*H*$_2$), 5.45 (1H, d, $^3J$ = 11.0, CH=C*H*$_2$), 5.83 (1H, d, $^3J$ = 18.0, CH=C*H*$_2$), 6.25 (1H, dd, $^3J_1$ = 18.0, $^3J_2$ = 11.0, C*H*=CH$_2$) ppm

$^{13}C$ NMR (100.6 MHz): δ 18.4 (10-*C*H$_3$), 18.5 (10-*C*H$_3$), 26.6 (C-8), 30.6 (C-9), 32.8 (C-6), 44.8 (C-7), 47.9 (C-10), 53.1 (C-2), 54.2 (C-1), 118.68 (CH=*C*H$_2$), 121.2 (*C*H=CH$_2$), 129.5 (C-4), 157.3 (C-5) ppm

HRMS (CI) *m/z* 261.0936: *calculated for* $[C_{13}H_{18}O_2S + Na]^+$ 261.0924

**(1*S*, 7*R*)-10,10-Dimethyl-4-phenyl-3-thiatricyclo[5.2.1.0$^{1,5}$]dec-4-ene 3,3-dioxide 350**




**331** **350** **328**

A solution of sulfone **331** (0.3 g, 0.98 mmol) in dry THF (8 ml) was added dropwise to a suspension of sodium hydride (0.043g, 60 %, 1.07 mmol) in dry THF (6 ml) at 0 °C under an atmosphere of nitrogen. The mixture was stirred at 0 °C for 30 mins and then allowed to warm to rt and stirred for an additional 90 mins. The mixture was then quenched with satd. aq. $NH_4Cl$ (50 ml) and extracted with ether (3 × 50 ml). The combined organic extracts were washed with brine (50 ml), dried and evaporated to yield an oil. Column chromatography on silica gel using EtOAc:hexane (1:3) afforded the title compound as a white solid (0.06 g, 21 %), followed by benzyl sulfone **328** (0.24 g).

m.p.: 97-99 °C (from EtOAc/hexane)

$[\alpha]_D$ (*c* 0.53, MeOH, 25 °C) -69.2

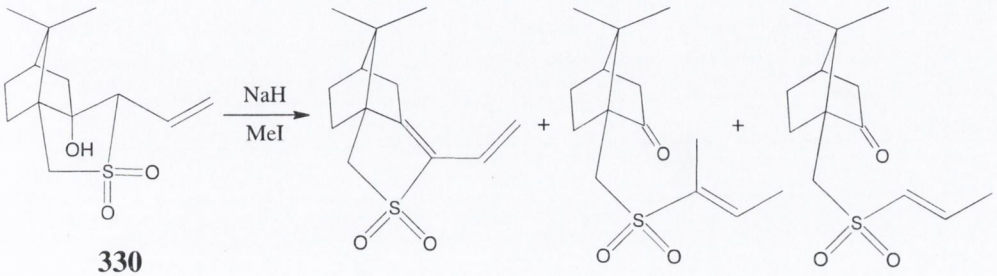
IR: $\nu_{max}$ (N) 2919, 1720, 1649 (C=C), 1598 (Ar C-C), 1459, 1410, 1376, 1293 ($SO_2$), 1209, 1153, 1120 ($SO_2$), 756, 686 cm$^{-1}$

$^1$H NMR (400.1 MHz): δ 0.91 (3H, s, 10-C*H*$_3$), 1.09 (3H, s, 10-C*H*$_3$), 1.38-1.44 (1H, m), 1.89-1.95 (1H, m), 1.98-2.13 (2H, m), 2.16 (1H, t, $^3J$ = 4.5, 7-C*H*), 2.40 (1H, d, $^2J$ = 18.0, 6-C*H*$_2$ *endo*), 2.85 (1H, dt, $^2J$ = 18.0, $^3J$ = 3.5, 6-C*H*$_2$ *exo*), 3.23 (1H, d, $^2J$ = 13.0, 2-C*H*$_2$), 3.28 (1H, d, $^2J$ = 13.0, 2-C*H*$_2$), 7.33-7.38 (1H, m, Ar-*H*), 7.41-7.44 (2H, m, Ar-*H*), 7.66-7.68 (2H, m, Ar-*H*) ppm

$^{13}$C NMR (100.6 MHz): δ 18.5 (10-*C*H$_3$), 18.6 (10-*C*H$_3$), 26.7 (C-8), 30.9 (C-9), 34.4 (C-6), 44.9 (C-7), 47.7 (C-10), 53.1 (C-2), 54.4 (C-1), 126.7 (Ar C-3), 127.6 (Ar C-1), 128.2 (Ar C-4), 128.4 (Ar C-2) 130.6 (C-4), 156.3 (C-5) ppm

HRMS (CI) *m/z* 311.1079: *calculated for* $[C_{17}H_{20}O_2S + Na]^+$ 311.1080

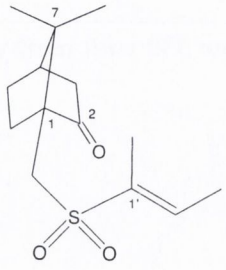
**Retro-aldol reaction of sulfone 330 with methyl iodide**




**330** **337** **339** **338**

A solution of sulfone **330** (0.3 g, 1.17 mmol) and methyl iodide (1.45 ml, 23.4 mmol) in dry THF (8 ml) was added dropwise to a suspension of sodium hydride (0.051g, 60 %, 1.28 mmol) in dry THF (3 ml) at 0 °C under an atmosphere of nitrogen. The mixture was stirred at 0 °C for 30 mins and then allowed to warm to rt and stirred for an additional 3 hrs. The mixture was then quenched with satd. aq. $NH_4Cl$ (50 ml) and extracted with ether (3 × 50 ml). The combined organic extracts were washed with brine (50 ml), dried and evaporated to yield an oil. The crude product was purified over silica gel, eluting with EtOAc:hexane (1:2) to yield three products. The first product to elute was a waxy solid (0.16 g) whose $^1H$ NMR spectrum showed it to contain sulfone **337** among other products. The second product to elute was vinyl sulfone **339** (0.04 g, 12 %) as a white solid. The third product to elute was vinyl sulfone **338** (0.04 g, 13 %) as an oil.

**(1*S*, 4*R*)-1-({[(1'*E*)-1'-Methylprop-1'-enyl]sulfonyl}methyl)-7,7-dimethylbicyclo[2.2.1]heptan-2-one 339**




**339**

m.p.: 66-68 °C (from EtOAc/hexane)

$[\alpha]_D$ (*c* 0.16, MeOH, 26 °C) +21.2

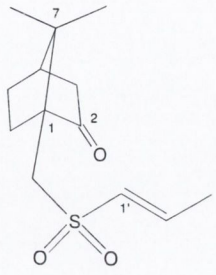
IR: $\nu_{max}$ (N) 2924, 2854, 1744 (C=O), 1646 (C=C), 1456, 1376, 1294 ($SO_2$), 1167, 1118 ($SO_2$), 1053, 998, 907, 865, 775, 744, 698 $cm^{-1}$

$^1H$ NMR (400.1 MHz): δ 0.87 (3H, s, 7-C$H_3$), 1.12 (3H, s, 7-C$H_3$), 1.40-1.47 (1H, m), 1.62-1.69 (1H, m), 1.84 (3H, app dd, $^3J$ = 7.0, $^5J$ = 1.5, 3'-C$H_3$), 1.92 (1H, d, $^2J$ = 18.5, 3-C$H_2$ *endo*), 2.02-2.10 (1H, m), 2.11 (1H, m, 4-C*H*), 2.12 (3H, app t, $^4J$ = 1.5, $^5J$ = 1.0, 1'-C$H_3$), 2.36 (1H, dt, $^2J$ = 18.5, $^3J$ = 4.0, 3-C$H_2$ *exo*), 2.55-2.62 (1H, m), 2.73 (1H, d, $^2J$ = 15.0, C$H_2SO_2$), 3.45 (1H, d, $^2J$ = 15.0, C$H_2SO_2$), 6.77 (1H, app qd, $^3J$ = 7.0, $^4J$ = 1.5, 2'-C*H*) ppm

$^{13}C$ NMR (100.6 MHz): δ 11.4 (C-3'), 13.6 (1'-*C*$H_3$), 19.3 (7-*C*$H_3$), 19.5 (7-*C*$H_3$), 23.9 (C-5), 26.5 (C-6), 42.0 (C-4), 42.1 (C-3), 47.7 (C-7), 48.0 (*C*$H_2SO_2$), 58.1 (C-1), 136.6 (C-2'), 137.7 (C-1'), 214.5 (C-2) ppm

HRMS (CI) *m/z* 293.1191: *calculated for* $[C_{14}H_{22}O_3S + Na]^+$ 293.1186

**(1*S*, 4*R*)-1-({[(1'*E*)-Prop-1'-enyl]sulfonyl}methyl)-7,7-dimethylbicyclo[2.2.1]heptan-2-one 338**




**338**

$[\alpha]_D$ (*c* 0.9, MeOH, 25 °C) +34.5

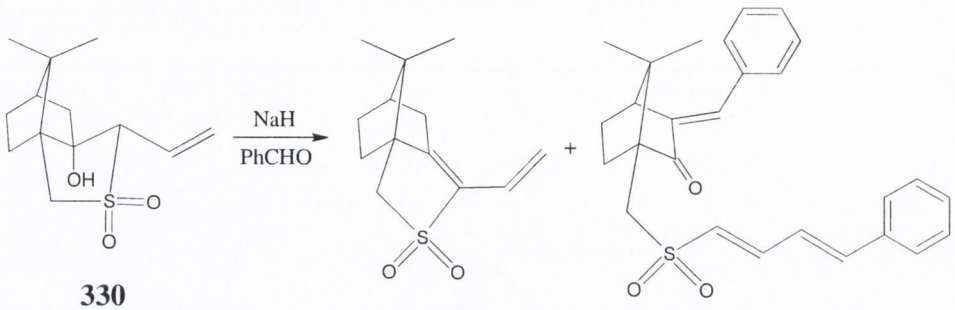
IR: $\nu_{max}$ (L) 2960, 1744 (C=O), 1641 (C=C), 1440, 1393, 1315 ($SO_2$), 1216, 1131 ($SO_2$), 1051, 956, 828, 806, 678 $cm^{-1}$

$^1$H NMR (400.1 MHz): δ 0.87 (3H, s, 7-C*H*$_3$), 1.09 (3H, s, 7-C*H*$_3$), 1.42-1.49 (1H, m), 1.68-1.75 (1H, m), 1.93 (1H, d, $^2J$ = 18.5, 3-C*H*$_2$ *endo*), 1.96 (3H, dd, $^3J$ = 7.0, $^4J$ = 1.5, 3'-C*H*$_3$), 2.01-2.10 (1H, m), 2.13 (1H, t, $^3J$ = 4.5, 4-C*H*), 2.38 (1H, dt, $^2J$ = 18.5, $^3J$ = 4.0, 3-C*H*$_2$ *exo*), 2.46-2.53 (1H, m), 2.84 (1H, d, $^2J$ = 15.0, C*H*$_2$SO$_2$), 3.43 (1H, d, $^2J$ = 15.0, C*H*$_2$SO$_2$) 6.55 (1H, dq, $^3J$ = 15.0, $^4J$ = 1.5, 1'-C*H*), 6.89 (1H, dq, $^3J_1$ = 15.0, $^3J_2$ = 7.0, 2'-C*H*) ppm

$^{13}$C NMR (100.6 MHz): δ 16.8 (C-3'), 19.2 (7-*C*H$_3$), 19.3 (7-*C*H$_3$), 24.2 (C-5), 26.6 (C-6), 42.0 (C-4), 42.1 (C-3), 47.9 (C-7), 51.4 (*C*H$_2$SO$_2$), 58.2 (C-1), 131.3 (C-1'), 142.5 (C-2'), 214.5 (C-2) ppm

HRMS (CI) *m/z* 279.1021: *calculated for* $[C_{13}H_{20}O_3S + Na]^+$ 279.1030

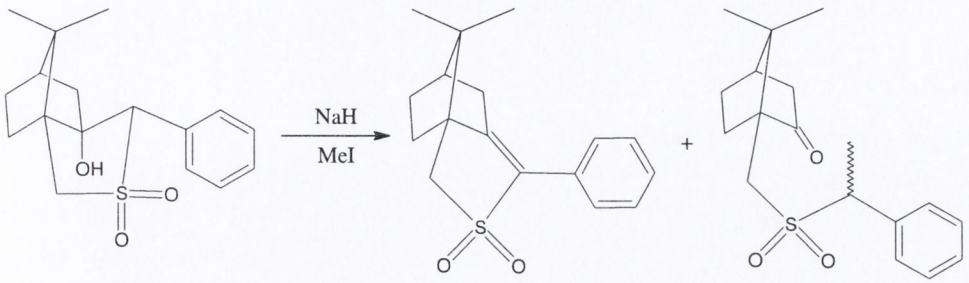
**Retro-aldol reaction of sulfone 330 with benzaldehyde**




**330** **337** **340**

A solution of sulfone **330** (0.25 g, 0.97 mmol) in dry THF (7 ml) was added dropwise to a suspension of sodium hydride (0.043g, 60 %, 1.07 mmol) in dry THF (3 ml) at 0 °C under an atmosphere of nitrogen. After the evolution of $H_2$ had ceased (ca. 5 min), freshly distilled benzaldehyde (0.1 ml, 1.07 mmol) was added. The mixture was stirred at 0 °C for 30 mins and then allowed to warm to rt and stirred for an additional 24 hrs. The mixture was then quenched with satd. aq. $NH_4Cl$ (50 ml) and extracted with ether (3 × 50 ml). The combined organic extracts were washed with brine (50 ml), dried and evaporated to yield an oil (0.41 g). The crude product was purified over silica gel, eluting with EtOAc:hexane (1:3) to yield three fractions. The first fraction to elute was an oil (0.02 g) whose $^1H$ NMR spectrum showed an intractable mixture. The second fraction to elute was an oil (0.08 g) whose $^1H$ NMR spectrum showed it to contain sulfone **337** and sulfone **340** in approx. 2.5 : 1 ratio. The third fraction to elute was an oil (0.15 g) whose $^1H$ NMR spectrum showed an intractable mixture. Sulfone **340** is described in Chapter 3, page 190.

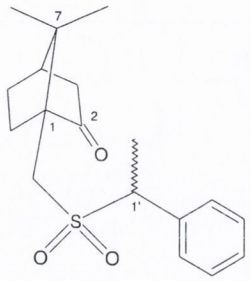
**Retro-aldol reaction of sulfone 331 with methyl iodide**




**331** **350** **351**

A solution of sulfone **331** (0.31 g, 1.01 mmol) and methyl iodide (1.26 ml, 20.2 mmol) in dry THF (8 ml) was added dropwise to a suspension of sodium hydride (0.044g, 60 %, 1.11 mmol) in dry THF (5 ml) at 0 °C under an atmosphere of nitrogen. The mixture was stirred at 0 °C for 30 mins and then allowed to warm to rt and stirred for an additional 3 hrs. The mixture was then quenched with satd. aq. $NH_4Cl$ (50 ml) and extracted with ether (3 × 50 ml). The combined organic extracts were washed with brine (50 ml), dried and evaporated to yield an oil (0.31 g) whose $^1H$ NMR spectrum showed it to contain both diastereomers of sulfone **351** in approx. 1.3 : 1 ratio together with sulfone **350**. The crude product was purified over silica gel, eluting with EtOAc:hexane (1:5) to yield two products. The first product to elute was an oil (0.19 g) which contained sulfone **350** and the major diastereomer of sulfone **351** in approx. 1.6 : 1 ratio. The second product to elute was the minor diastereomer of sulfone **351** as an oil (0.1 g, 30 %).

**(1*S*, 4*R*)-1-{[(1'-Phenylethyl)sulfonyl]methyl}-7,7-dimethylbicyclo[2.2.1]heptan-2-one 351**




**351**

Major diastereomer:

$^{1}$H NMR (400.1 MHz): δ 0.72 (3H, s, 7-C$H_3$), 0.94 (3H, s, 7-C$H_3$), 1.80 (3H, d, $^{3}J$ = 7.5, 2'-C$H_3$), 1.94 (1H, d, $^{2}J$ = 18.5, 3-C$H_2$ *endo*), 2.44 (1H, d, $^{2}J$ = 15.0, C$H_2$SO$_2$), 3.26 (1H, d, $^{2}J$ = 15.0, C$H_2$SO$_2$), 4.81 (1H, q, $^{3}J$ = 7.5, 1'-C*H*), 7.34-7.45 (3H, m, Ar-*H*), 7.51-7.54 (2H, m, Ar-*H*) ppm

$^{13}$C NMR (100.6 MHz): δ 13.0 (C-2'), 19.1 (7-*C*H$_3$), 19.2 (7-*C*H$_3$), 25.2 (C-5), 26.6 (C-6), 42.0 (C-4), 42.2 (C-3), 47.0 (*C*H$_2$SO$_2$), 48.0 (C-7), 58.8 (C-1), 64.7 (C-1'), 128.4 (Ar C-3), 128.4 (Ar C-4), 128.8 (Ar C-2), 135.0 (Ar C-1), 214.7 (C-2) ppm

Minor diastereomer:

$[\alpha]_D$ (*c* 0.52, MeOH, 27 °C) -13.0

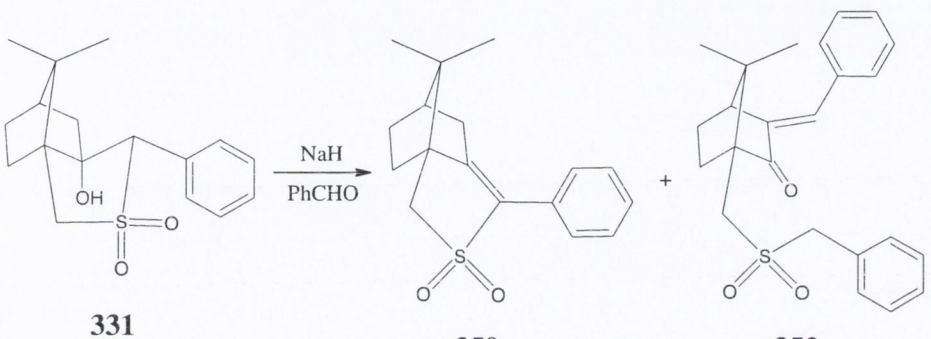
IR: $\nu_{max}$ (L) 3063, 3032, 2959, 2254, 1958, 1890, 1744 (C=O), 1602 (Ar C-C), 1494, 1454, 1393, 1312 (SO$_2$), 1131 (SO$_2$), 1051, 964, 916, 853, 791, 732, 699, 609 cm$^{-1}$

$^{1}$H NMR (400.1 MHz): δ 0.87 (3H, s, 7-C$H_3$), 1.08 (3H, s, 7-C$H_3$), 1.38-1.44 (1H, m), 1.64-1.71 (1H, m), 1.85 (3H, d, $^{3}J$ = 7.0, 2'-C$H_3$), 1.92 (1H, d, $^{2}J$ = 18.7, 3-C$H_2$ *endo*), 1.98-2.07 (1H, m), 2.09 (1H, t, $^{3}J$ = 4.6, 4-C*H*), 2.38 (1H, dt, $^{2}J$ = 18.7, $^{3}J$ = 4.1, 3-C$H_2$ *exo*), 2.45 (1H, m), 2.72 (1H, d, $^{2}J$ = 14.6, C$H_2$SO$_2$), 3.34 (1H, d, $^{2}J$ = 14.6, C$H_2$SO$_2$), 4.42 (1H, q, $^{3}J$ = 7.0, 1'-C*H*), 7.37-7.43 (3H, m, Ar-*H*), 7.45-7.48 (2H, m, Ar-*H*) ppm

$^{13}$C NMR (100.6 MHz): δ 14.5 (C-2'), 19.4 (7-*C*H$_3$), 19.5 (7-*C*H$_3$), 24.7 (C-5), 26.4 (C-6), 42.2 (C-3), 42.2 (C-4), 46.3 (*C*H$_2$SO$_2$), 47.7 (C-7), 58.4 (C-1), 64.9 (C-1'), 128.3 (Ar C-3), 128.5 (Ar C-4), 128.9 (Ar C-2), 133.3 (Ar C-1), 214.7 (C-2) ppm

HRMS (CI) *m/z* 343.1335: *calculated for* [$C_{18}H_{24}O_3S$ + Na]$^+$ 343.1343

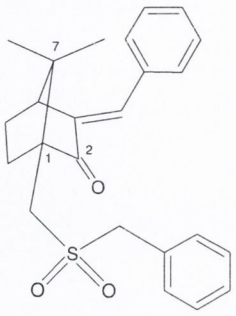
**Retro-aldol reaction of sulfone 331 with benzaldehyde**




**331** **350** **352**

A solution of sulfone **331** (0.28 g, 0.91 mmol) in dry THF (7 ml) was added dropwise to a suspension of sodium hydride (0.040g, 60 %, 1.00 mmol) in dry THF (5 ml) at 0 °C under an atmosphere of nitrogen. After 10 mins, freshly distilled benzaldehyde (0.37 ml, 3.66 mmol) was added. The mixture was stirred at 0 °C for 30 mins and then allowed to warm to rt and stirred for an additional 24 hrs. The mixture was then quenched with satd. aq. $NH_4Cl$ (50 ml) and extracted with ether (3 × 50 ml). The combined organic extracts were washed with brine (50 ml), dried and evaporated to yield an oil (0.69 g). The crude product was purified over silica gel, eluting with EtOAc:hexane (1:3) to yield an oil (0.23 g) whose $^1$H NMR spectrum showed it to contain sulfone **352** and sulfone **350** in approx. 1.4 : 1 ratio.

**(1*S*, 4*S*)-(3*E*)-3-Benzylidene-1-[(benzylsulfonyl)methyl]-7,7-dimethylbicyclo[2.2.1]heptan-2-one 352**




**352**

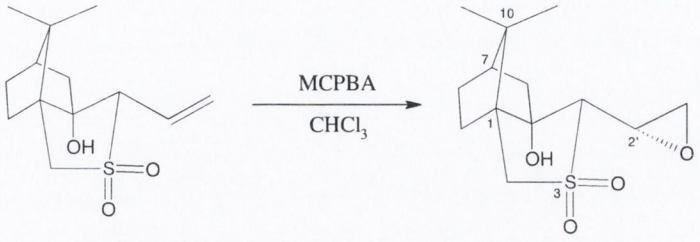
IR: $\nu_{max}$ (L) 3060 (Ar-H), 2959, 1958, 1891, 1723 (C=O), 1643 (C=C), 1494, 1450, 1374, 1315 ($SO_2$), 1259, 1122 ($SO_2$), 1056, 947, 882, 761, 697 $cm^{-1}$

$^1H$ NMR (400.1 MHz): δ 0.83 (3H, s, 7-C*H*$_3$), 1.06 (3H, s, 7-C*H*$_3$), 1.70-1.76 (1H, m), 2.00-2.10 (1H, m), 2.25-2.33 (1H, m), 2.44-2.50 (1H, m), 2.78 (1H, d, $^2J$ = 15.0, alkyl C*H*$_2$SO$_2$), 3.15 (1H, d, $^3J$ = 4.0, 4-C*H*), 3.55 (1H, d, $^2J$ = 15.0, alkyl C*H*$_2$SO$_2$), 4.43 (1H, d, $^2J$ = 13.5, benzyl C*H*$_2$SO$_2$), 4.87 (1H, d, $^2J$ = 13.5, benzyl C*H*$_2$SO$_2$), 7.33 (1H, s, benzylidene C=C*H*), 7.36-7.46 (6H, m, Ar-*H*), 7.49-7.54 (4H, m, Ar-*H*) ppm

$^{13}C$ NMR (100.6 MHz): δ 18.4 (7-*C*H$_3$), 20.0 (7-*C*H$_3$), 25.5 (C-5), 26.2 (C-6), 48.2 (C-4), 49.1 (alkyl *C*H$_2$SO$_2$), 58.0 (C-7), 59.9 (C-1), 61.6 (benzyl *C*H$_2$SO$_2$), 128.0 (benzyl Ar-*C*), 128.3 (benzyl Ar-*C*), 128.4 (benzyl Ar-*C*), 128.8 (benzylidene C=*C*H), 129.2 (benzylidene Ar-*C*), 129.4 (benzylidene Ar-*C*), 130.6 (benzylidene Ar-*C*), 133.2 (benzyl Ar-*C*), 134.5 (C-3), 139.6 (benzylidene Ar-*C*), 204.2 (C-2) ppm

HRMS (CI) *m/z* 417.1512: *calculated for* $[C_{24}H_{26}O_3S + Na]^+$ 417.1500

**(1*S*, 4*S*, 5*S*, 7*R*, 2'*S*)-10,10-Dimethyl-4-oxiran-2'-yl-3-thiatricyclo[5.2.1.0$^{1,5}$]decan-5-ol 3,3-dioxide 332**




**330** **332**

Sulfone **330** (0.25 g, 0.97 mmol) was dissolved in chloroform (5 ml) and a solution of MCPBA (0.48 g, 70 %, 1.95 mmol) in chloroform (5 ml) was added dropwise. The solution was heated under reflux for 4 hrs and then allowed to cool to rt and left stirring overnight. The mixture was diluted with chloroform (100 ml) and then washed with satd. aq. $NaHCO_3$ (2 × 50 ml) and brine (50 ml), dried and evaporated to yield a white solid (0.32 g). Column chromatography on silica gel using EtOAc:hexane (1:2) afforded the title compound as a white solid (0.12 g, 45 %).

m.p.: 152 °C (from EtOAc/hexane)

$[\alpha]_D$ (*c* 0.09, MeOH, 26 °C) -40.0

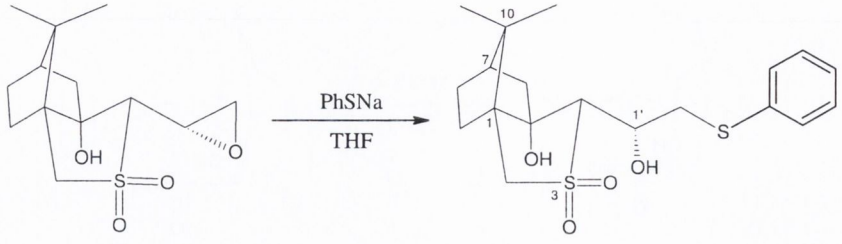
IR: $\nu_{max}$ (N) 3506 (O-H), 2908, 1461, 1376, 1303 ($SO_2$), 1253, 1179, 1125 ($SO_2$), 1037, 878, 732 $cm^{-1}$

$^1$H NMR (400.1 MHz): δ 1.02 (3H, s, 10-C*H*$_3$), 1.07 (3H, s, 10-C*H*$_3$), 1.52-1.58 (1H, m), 1.66 (1H, d, $^2J$ = 13.5, 6-C*H*$_2$ *endo*), 1.69-1.75 (1H, m), 1.85-1.89 (1H, m), 1.92 (1H, t, $^3J$ = 4.0, 7-C*H*), 2.35-2.41 (1H, m), 2.44 (1H, dt, $^2J$ = 13.5, $^3J$ = 3.5, 6-C*H*$_2$ *exo*), 2.88 (1H, d, $^3J$ = 7.0, 4-C*H*), 2.94 (1H, dd, $^2J$ = 4.5, $^3J$ = 2.5, 3'-C*H*$_2$ *anti*), 2.98 (1H, t, $^2J$ = 4.5, $^3J$ = 4.0, 3'-C*H*$_2$ *syn*), 3.08 (1H, d, $^2J$ = 14.5, 2-C*H*$_2$), 3.12 (1H, br s, O*H*), 3.13 (1H, d, $^2J$ = 14.5, 2-C*H*$_2$), 3.58 (1H, qu, 2'-C*H*) ppm

$^{13}$C NMR (100.6 MHz): δ 21.2 (10-*C*H$_3$), 21.4 (10-*C*H$_3$), 26.0 (C-8), 26.6 (C-9), 42.9 (C-6), 44.1 (C-3'), 44.1 (C-7), 44.5 (C-2'), 50.3 (C-10), 51.9 (C-2), 56.8 (C-1), 71.1 (C-4), 81.8 (C-5) ppm

HRMS (CI) *m/z* 295.0985: *calculated for* $[C_{13}H_{20}O_4S + Na]^+$ 295.0979

**(1*S*, 4*S*, 5*S*, 7*R*, 1'*S*)-10,10-Dimethyl-4-[1'-hydroxy-2'-(phenylthio)ethyl]-3-thiatricyclo[5.2.1.0$^{1,5}$]decan-5-ol 3,3-dioxide 333**




**332** **333**

Thiophenol (0.076 ml, 0.73 mmol) was added to a suspension of sodium hydride (0.03 g, 60 %, 0.73 mmol) in dry THF (3 ml) at 0 °C under an atmosphere of nitrogen. After the evolution of $H_2$ had ceased (ca. 5 min), a solution of sulfone **332** (0.1 g, 0.36 mmol) in dry THF (4 ml) was added dropwise. The solution was allowed to warm to rt and stirred for 5 hrs. The solution was quenched with satd. aq. $NH_4Cl$ (50 ml) and extracted with ether (3 × 50 ml). The combined organic extracts were washed with brine (50 ml), dried and evaporated to yield a semi-solid (0.27 g). Column chromatography on silica gel using EtOAc:hexane (1:2) afforded the title compound as a white solid (0.1 g, 71 %).

m.p.: 124 °C (from EtOAc/hexane)

$[\alpha]_D$ (*c* 0.35, MeOH, 26 °C) -93.7

IR: $\nu_{max}$ (N) 3407 (O-H), 2922, 1582 (Ar C-C), 1460, 1376, 1280 ($SO_2$), 1214, 1118 ($SO_2$), 1076, 984, 804, 735, 692 cm$^{-1}$

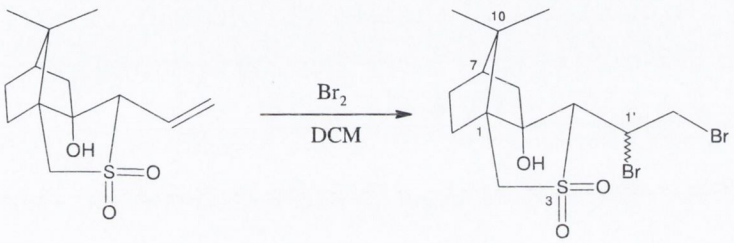
$^1$H NMR (400.1 MHz): δ 1.02 (3H, s, 10-C$H_3$), 1.15 (3H, s, 10-C$H_3$), 1.47-1.53 (1H, m), 1.57 (1H, d, $^2J$ = 14.0, 6-C$H_2$ *endo*), 1.61-1.68 (1H, m), 1.81-1.85 (1H, m), 1.89 (1H, t, $^3J$ = 4.5, 7-C*H*), 2.38 (1H, m), 2.52 (1H, dt, $^2J$ = 14.0, $^3J$ = 3.0, 6-C$H_2$ *exo*), 3.12 (1H, dd, $^2J$ = 14.3, $^3J$ = 7.5, 2'-C$H_2$), 3.17 (2H, s, 2-C$H_2$), 3.25 (1H, br s, O*H*), 3.49 (1H, d, $^3J$ = 8.0, 4-C*H*), 3.56 (1H, br s, O*H*), 3.58 (1H, dd, $^2J$ = 14.3, $^3J$ = 3.5, 2'-C$H_2$), 4.50 (1H, m, 1'-C*H*), 7.23 (1H, t, $^3J$ = 7.5, Ar 4-C*H*), 7.32 (2H, t, $^3J$ = 7.5, Ar 3-C*H*), 7.44 (2H, d, $^3J$ = 7.5, Ar 2-C*H*) ppm

$^{13}$C NMR (100.6 MHz): δ 21.2 (10-*C*H$_3$), 21.3 (10-*C*H$_3$), 25.9 (C-8), 26.3 (C-9), 38.8 (C-2'), 44.7 (C-7), 46.0 (C-6), 49.7 (C-10), 52.9 (C-2), 56.7 (C-1), 65.9 (C-1'),

71.5 (C-4), 83.1 (C-5), 126.4 (Ar C-4), 128.7 (Ar C-2), 129.3 (Ar C-3), 133.6 (Ar C-1) ppm

HRMS (CI) *m/z* 405.1154: *calculated for* $[C_{19}H_{26}O_4S_2 + Na]^+$ 405.1169

**(1*S*, 4*R*, 5*S*, 7*R*)-10,10-Dimethyl-4-(1',2'-dibromoethyl)-3-thiatricyclo[5.2.1.0$^{1,5}$]decan-5-ol 3,3-dioxide 334**




**330** **334**

Sulfone **330** (0.2 g, 0.78 mmol) was dissolved in DCM (5 ml) and the solution was cooled to 0 °C using an ice bath. A solution of bromine in DCM (2.2 ml, 0.39 M, 0.85 mmol) was added dropwise and the solution was stirred at 0 °C for 30 mins and then allowed to warm to rt and stirred for an additional 3 hrs. $H_2O$ (50 ml) was added and the mixture was extracted with ether (3 × 50 ml). The combined organic extracts were washed with satd. aq. $Na_2SO_3$ (50 ml) and brine (50 ml), dried and evaporated to yield a white solid (0.29 g) whose $^1H$ NMR spectrum showed it to contain two diastereomers of **334** in approx. 1:1 ratio. The crude product was purified over silica gel, eluting with EtOAc:hexane (1:2) to yield two products. The first product to elute was diastereomer A as a white solid (0.1 g). The second product to elute was diastereomer B as a white solid (0.12 g).

Diastereomer A:

m.p.: 134 °C (from EtOAc/hexane)

$[\alpha]_D$ (*c* 0.33, MeOH, 27 °C) -5.4

IR: $\nu_{max}$ (N) 3419 (O-H), 2924, 1607, 1461, 1376, 1308 ($SO_2$), 1246, 1178, 1120 ($SO_2$), 1028, 740 $cm^{-1}$

$^{1}$H NMR (400.1 MHz): δ 1.03 (3H, s, 10-C$H_3$), 1.18 (3H, s, 10-C$H_3$), 1.46-1.52 (1H, m), 1.59 (1H, d, $^{2}J$ = 14.5, 6-C$H_2$ *endo*), 1.64-1.72 (1H, m), 1.82-1.88 (1H, m), 1.91 (1H, t, $^{3}J$ = 4.5, 7-C*H*), 2.36 (1H, m), 2.66 (1H, dt, $^{2}J$ = 14.5, $^{3}J$ = 3.5, 6-C$H_2$ *exo*), 2.81 (1H, br s, O*H*), 3.16 (1H, d, $^{2}J$ = 14.0, 2-C$H_2$), 3.21 (1H, d, $^{2}J$ = 14.0, 2-C$H_2$), 3.83 (1H, d, $^{3}J$ = 10.5, 4-C*H*), 4.02 (1H, dd, $^{2}J$ = 12.0, $^{3}J$ = 2.5, 2'-C$H_2$), 4.12 (1H, dd, $^{2}J$ = 12.0, $^{3}J$ = 4.5, 2'-C$H_2$), 4.78 (1H, ddd, $^{3}J_1$ = 10.5, $^{3}J_2$ = 4.5, $^{3}J_3$ = 2.5, 1'C*H*) ppm

$^{13}$C NMR (100.6 MHz): δ 21.1 (10-*C*H$_3$), 21.1 (10-*C*H$_3$), 25.7 (C-8), 26.9 (C-9), 37.7 (C-6), 44.2 (C-7), 45.4 (C-1'), 47.2 (C-2'), 49.8 (C-10), 52.7 (C-2), 56.7 (C-1), 71.6 (C-4), 83.6 (C-5) ppm

HRMS (CI) *m/z* 438.9332: *calculated for* [$C_{13}H_{20}O_3SBr_2$ + Na]$^{+}$ 439.1598

Diastereomer B:

m.p.: 172 °C (from EtOAc/hexane)

$[\alpha]_D$ (*c* 0.36, MeOH, 27 °C) -58.8

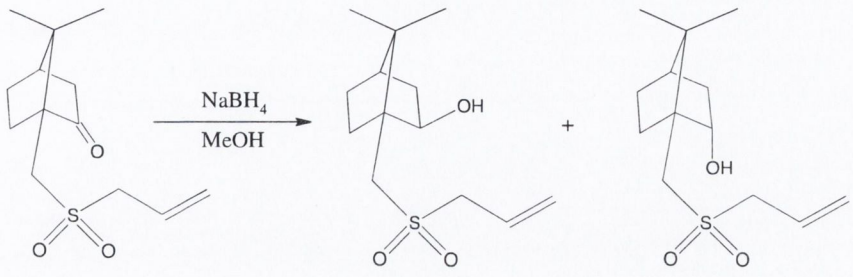
IR: $\nu_{max}$ (N) 3419 (O-H), 2924, 1607, 1461, 1376, 1308 ($SO_2$), 1246, 1178, 1120 ($SO_2$), 1028, 740 cm$^{-1}$

$^{1}$H NMR (400.1 MHz): δ 1.01 (3H, s, 10-C$H_3$), 1.15 (3H, s, 10-C$H_3$), 1.45-1.50 (1H, m), 1.51 (1H, d, $^{2}J$ = 13.0, 6-C$H_2$ *endo*), 1.66-1.74 (1H, m), 1.82-1.90 (1H, m), 1.93 (1H, t, $^{3}J$ = 4.5, 7-C*H*), 2.18-2.24 (1H, m), 2.82 (1H, dt, $^{2}J$ = 13.0, $^{3}J$ = 3.5, 6-C$H_2$ *exo*), 3.16 (1H, d, $^{2}J$ = 14.5, 2-C$H_2$), 3.20 (1H, d, $^{2}J$ = 14.5, 2-C$H_2$), 3.74 (1H, d, $^{3}J$ = 10.5, 4-C*H*), 3.95 (1H, dd, $^{2}J$ = 11.5, $^{3}J$ = 3.0, 2'-C$H_2$), 4.02 (1H, dd, $^{2}J$ = 11.5, $^{3}J$ = 3.0, 2'-C$H_2$), 4.80 (1H, dt, $^{3}J_1$ = 10.5, $^{3}J_2$ = 3.0, 1'-C*H*) ppm

$^{13}$C NMR (100.6 MHz): δ 20.9 (10-*C*H$_3$), 21.2 (10-*C*H$_3$), 25.9 (C-8), 26.6 (C-9), 38.4 (C-6), 43.1 (C-7), 43.4 (C-2'), 44.1 (C-1'), 50.4 (C-10), 52.2 (C-2), 55.4 (C-1), 71.7 (C-4), 83.6 (C-5) ppm

HRMS (CI) *m/z* 438.9332: *calculated for* [$C_{13}H_{20}O_3SBr_2$ + Na]$^{+}$ 439.1598

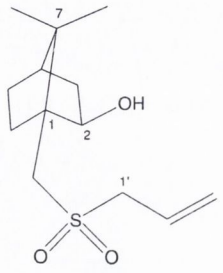
**Reduction of sulfone 326 with sodium borohydride**




**326** **358** **359**

Sulfone **326** (0.43 g, 1.67 mmol) was dissolved in methanol (10 ml) and sodium borohydride (0.25 g, 6.71 mmol) was added. The solution was stirred at rt for 6 hrs. The solution was then diluted with satd. aq. $NH_4Cl$ (50 ml) and extracted with ether (3 × 50 ml). The combined organic extracts were washed with brine (50 ml), dried and evaporated to yield an oil (0.39 g) whose $^1H$ NMR spectrum showed it to contain two diastereomers in approx. 16.5:1 ratio. The crude product was purified over silica gel, eluting with EtOAc:hexane (1:2) to yield two products. The first product to elute was sulfone **358** as a white solid (0.33 g, 76 %). The second product to elute was sulfone **359** as an oil (0.02 g, 4 %).

**(1*S*, 2*R*, 4*R*)-1-({[Prop-2'-enyl]sulfonyl}methyl)-7,7-dimethylbicyclo[2.2.1]heptan-2-ol 358**




**358**

m.p.: 49-50 °C (from EtOAc/hexane)

$[\alpha]_D$ (*c* 0.25, MeOH, 26 °C) -26.4

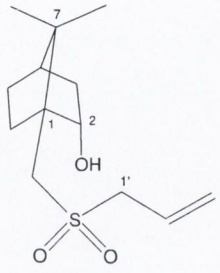
IR: $\nu_{max}$ (N) 3424 (O-H), 2927, 1638 (C=C), 1456, 1374, 1312 ($SO_2$), 1240, 1197, 1122 ($SO_2$), 1075, 1027, 996, 943, 879, 829, 721 $cm^{-1}$

$^1H$ NMR (400.1 MHz): δ 0.84 (3H, s, 7-C$H_3$), 1.08 (3H, s, 7-C$H_3$), 1.14-1.19 (1H, m), 1.59-1.66 (1H, m), 1.70-1.88 (5H, m), 2.86 (1H, d, $^2J$ = 13.0, alkyl C$H_2SO_2$), 3.38 (1H, d, $^2J$ = 13.0, alkyl C$H_2SO_2$), 3.78 (2H, d, $^3J$ = 7.5, 1'-C$H_2$), 4.17 (1H, dd, $^3J_1$ = 8.0, $^3J_2$ = 4.0, 2-C*H*), 5.51 (1H, dd, $^3J$ = 17.3, $^2J$ = 1.0, 3'-C$H_2$ *trans*), 5.55 (1H, dd, $^3J$ = 10.0, $^2J$ = 1.0, 3'-C$H_2$ *cis*), 5.99 (1H, ddt, $^3J_1$ = 17.3, $^3J_2$ = 10.0, $^3J_3$ = 7.5, 2'-C*H*) ppm

$^{13}C$ NMR (100.6 MHz): δ 19.8 (7-*C*$H_3$), 20.5 (7-*C*$H_3$), 27.4 (C-5), 30.4 (C-6), 38.9 (C-3), 44.0 (C-4), 49.1 (C-7), 50.0 (alkyl *C*$H_2SO_2$), 50.3 (C-1), 60.0 (C-1'), 76.1 (C-2), 124.9 (C-3'), 125.0 (C-2') ppm

HRMS (CI) *m/z* 281.1188: *calculated for* $[C_{13}H_{22}O_3S + Na]^+$ 281.1186

**(1*S*, 2*S*, 4*R*)-1-({[Prop-2'-enyl]sulfonyl}methyl)-7,7-dimethylbicyclo[2.2.1]heptan-2-ol 359**




**359**

$[\alpha]_D$ (*c* 0.16, MeOH, 26 °C) +22.5

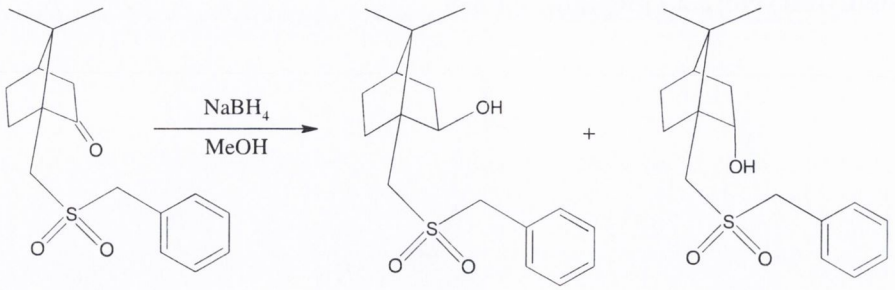
IR: $\nu_{max}$ (L) 3483 (O-H), 2953, 1639 (C=C), 1452, 1391, 1310 ($SO_2$), 1262, 1126 ($SO_2$), 1069, 1020, 938, 874, 792 $cm^{-1}$

$^1$H NMR (400.1 MHz): δ 0.91 (3H, s, 7-*C*H$_3$), 0.93 (3H, s, 7-*C*H$_3$), 1.14 (1H, dd, $^2J$ = 13.0, $^3J$ = 3.0, 3-C*H*$_2$ *endo*), 1.41-1.47 (1H, m), 1.50-1.58 (1H, m), 1.68 (1H, t, $^3J$ = 4.5, 4-C*H*), 1.79-1.88 (1H, m), 2.29-2.36 (1H, m), 2.48-2.54 (1H, m), 3.01 (1H, d, $^2J$ = 13.5, alkyl C*H*$_2$SO$_2$), 3.08 (1H, d, $^2J$ = 13.5, alkyl C*H*$_2$SO$_2$), 3.80 (2H, d, $^3J$ = 7.5, 1'-C*H*$_2$), 4.34 (1H, dt, $^3J_1$ = 9.8, $^3J_2$ = 2.5, 2-C*H*), 5.50 (1H, dd, $^3J$ = 17.0, $^2J$ = 1.0, 3'-C*H*$_2$ *trans*), 5.55 (1H, dd, $^3J$ = 10.0, $^2J$ = 1.0, 3'-C*H*$_2$ *cis*), 5.97 (1H, ddt, $^3J_1$ = 17.0, $^3J_2$ = 10.0, $^3J_3$ = 7.5, 2'-C*H*) ppm

$^{13}$C NMR (100.6 MHz): δ 18.4 (7-*C*H$_3$), 20.0 (7-*C*H$_3$), 23.3 (C-5), 27.8 (C-6), 37.5 (C-3), 43.3 (C-4), 50.8 (C-7), 51.6 (C-1), 54.2 (alkyl *C*H$_2$SO$_2$), 59.1 (C-1'), 74.5 (C-2), 124.4 (C-2'), 124.6 (C-3') ppm

HRMS (CI) *m/z* 281.1183: *calculated for* $[C_{13}H_{22}O_3S + Na]^+$ 281.1186

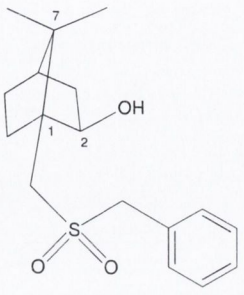
**Reduction of sulfone 328 with sodium borohydride**




**328** **360** **361**

Sulfone **328** (1.00 g, 3.26 mmol) was dissolved in methanol (25 ml) and sodium borohydride (0.49 g, 13.0 mmol) was added. The solution was stirred at rt for 6 hrs. The solution was then diluted with satd. aq. $NH_4Cl$ (50 ml) and extracted with ether (3 × 50 ml). The combined organic extracts were washed with brine (50 ml), dried and evaporated to yield a white solid (0.86 g) whose $^1H$ NMR spectrum showed it to contain two diastereomers in approx. 15.7:1 ratio. The crude product was purified over silica gel, eluting with EtOAc:hexane (1:3) to yield two products. The first product to elute was sulfone **360** as a white solid (0.72 g, 71 %). The second product to elute was sulfone **361** as an oil (0.1 g, 9 %) which later crystallized on standing overnight.

**(1*S*, 2*R*, 4*R*)-1-[(Benzylsulfonyl)methyl]-7,7-dimethylbicyclo[2.2.1]heptan-2-ol 360**




**360**

m.p.: 107-108 °C (from EtOAc/hexane)

$[\alpha]_D$ (*c* 0.44, MeOH, 26 °C) -38.4

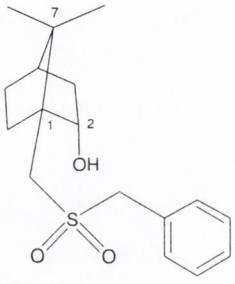
IR: $\nu_{max}$ (N) 3494 (O-H), 2919, 1456, 1376, 1299 ($SO_2$), 1267, 1208, 1143, 1106 ($SO_2$), 1029, 982, 884, 792, 698 $cm^{-1}$

$^1H$ NMR (400.1 MHz): δ 0.78 (3H, s, 7-C*H*$_3$), 1.02 (3H, s, 7-C*H*$_3$), 1.12-1.17 (1H, m), 1.57-1.62 (1H, m), 1.65-1.84 (5H, m), 2.76 (1H, d, $^2J$ = 13.0, alkyl C*H*$_2$SO$_2$), 3.31 (1H, d, $^2J$ = 13.0, alkyl C*H*$_2$SO$_2$), 4.15 (1H, dd, $^3J_1$ = 8.0, $^3J_2$ = 4.5, 2-C*H*), 4.28 (1H, d, $^2J$ = 14.5, benzyl C*H*$_2$SO$_2$), 4.31 (1H, d, $^2J$ = 14.5, benzyl C*H*$_2$SO$_2$), 7.44 (5H, s, Ar-*H*) ppm

$^{13}C$ NMR (100.6 MHz): δ 19.3 (7-*C*H$_3$), 20.0 (7-*C*H$_3$), 26.9 (C-5), 29.9 (C-6), 38.5 (C-3), 43.6 (C-4), 48.6 (C-7), 49.7 (alkyl *C*H$_2$SO$_2$), 50.0 (C-1), 61.3 (benzyl *C*H$_2$SO$_2$), 75.7 (C-2), 127.3 (Ar C-1), 128.6 (Ar C-3), 128.7 (Ar C-4), 130.1 (Ar C-2) ppm

HRMS (CI) *m/z* 331.1333: *calculated for* $[C_{17}H_{24}O_3S + Na]^+$ 331.1343

**(1*S*, 2*S*, 4*R*)-1-[(Benzylsulfonyl)methyl]-7,7-dimethylbicyclo[2.2.1]heptan-2-ol 361**




**361**

m.p.: 88-90 °C (from EtOAc/hexane)

$[\alpha]_D$ (*c* 0.27, MeOH, 26 °C) +19.6

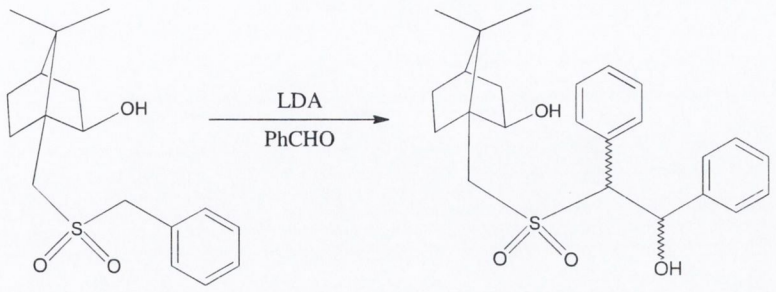
IR: $\nu_{max}$ (N) 3513, 3433 (O-H), 2925, 2855, 1456, 1375, 1296 ($SO_2$), 1259, 1113 ($SO_2$), 1066, 1020, 770, 696 $cm^{-1}$

$^1H$ NMR (400.1 MHz): δ 0.86 (3H, s, 7-C*H*$_3$), 0.88 (3H, s, 7-C*H*$_3$), 1.14 (1H, dd, $^2J$ = 13.3, $^3J$ = 3.0, 3-C*H*$_2$ *endo*), 1.40-1.47 (1H, m), 1.50-1.58 (1H, m), 1.66 (1H, t, $^3J$ = 4.5, 4-C*H*), 1.78-1.87 (1H, m), 2.26-2.34 (1H, m), 2.50-2.56 (1H, m), 2.96 (1H, d, $^2J$ = 14.0, alkyl C*H*$_2$SO$_2$), 2.99 (1H, d, $^2J$ = 14.0, alkyl C*H*$_2$SO$_2$), 4.29 (1H, dt, $^3J_1$ = 10.0, $^3J_2$ = 2.5, 2-C*H*), 4.29 (1H, d, $^2J$ = 13.5, benzyl C*H*$_2$SO$_2$), 4.33 (1H, d, $^2J$ = 13.5, benzyl C*H*$_2$SO$_2$), 7.43 (5H, s, Ar-*H*) ppm

$^{13}C$ NMR (100.6 MHz): δ 18.4 (7-*C*H$_3$), 20.0 (7-*C*H$_3$), 23.4 (C-5), 27.8 (C-6), 37.5 (C-3), 43.3 (C-4), 50.9 (C-7), 51.6 (C-1), 54.4 (alkyl *C*H$_2$SO$_2$), 60.8 (benzyl *C*H$_2$SO$_2$), 74.5 (C-2), 128.0 (Ar C-1), 128.6 (Ar C-3), 128.8 (Ar C-4), 130.3 (Ar C-2) ppm

HRMS (CI) *m/z* 331.1328: *calculated for* $[C_{17}H_{24}O_3S + Na]^+$ 331.1343

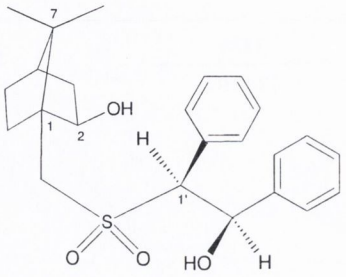
**Aldol reaction of sulfone 360 with benzaldehyde**




**360** **362**

*n*-Butyllithium (0.6 ml, 2.5 M, 1.49 mmol) was added to a solution of dry diisopropylamine (0.23 ml, 1.64 mmol) in dry THF (6 ml) at – 60 °C under an atmosphere of nitrogen. The solution was allowed to warm to 0 °C and then recooled to – 60 °C. A solution of sulfone **360** (0.22 g, 0.71 mmol) in dry THF (8 ml) was added dropwise *via* syringe. After 20 mins, freshly distilled benzaldehyde (0.08 ml, 0.78 mmol) was added and the solution was stirred at – 60 °C for 3 hrs. The solution was then allowed to warm to rt, quenched with satd. aq. $NH_4Cl$ (50 ml) and extracted with ether (3 × 50 ml). The combined organic extracts were washed with brine (50 ml), dried and evaporated to yield an oil. The crude product was purified over silica gel, eluting with EtOAc:hexane (1:3) to yield three diastereomers. The first diastereomer to elute was sulfone **362a** as an oil (0.08 g, 27 %) which later crystallised. The second diastereomer to elute was sulfone **362b** as an oil (0.1 g, 33 %). The third diastereomer to elute was sulfone **362c** as a white solid (0.08 g, 27 %). Sulfones **362a** and **362b** were contaminated with minor amounts of unreacted starting sulfone **360**.

**(1*S*, 2*R*, 4*R*, 1'*S*, 2'*R*)-1-{[(1',2'-Diphenyl-2'-hydroxyethyl)sulfonyl]methyl}-7,7-dimethylbicyclo[2.2.1]heptan-2-ol 362a**




**362a**

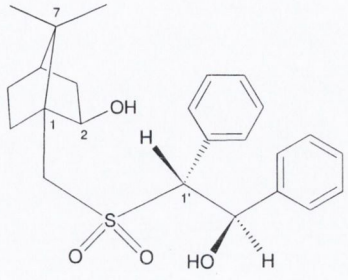
IR: $\nu_{max}$ (N) 3485 (O-H), 3432 (O-H), 2924, 1602 (Ar C-C), 1455, 1375, 1309 ($SO_2$), 1248, 1126 ($SO_2$), 1056, 1025, 877, 805, 697 $cm^{-1}$

$^1H$ NMR (400.1 MHz): δ 0.62 (3H, s, 7-C$H_3$), 0.90 (3H, s, 7-C$H_3$), 1.54-1.80 (7H, m), 2.62 (1H, d, $^2J$ = 13.0, C$H_2SO_2$), 3.03 (1H, d, $^2J$ = 13.0, C$H_2SO_2$), 4.14 (1H, dd, $^3J_1$ = 7.8, $^3J_2$ = 4.5, 2-C*H*), 4.23 (1H, d, $^3J$ = 3.5, 1'-C*H*), 5.96 (1H, d, $^3J$ = 3.5, 2'-C*H*), 7.17-7.28 (5H, m, Ar-*H*), 7.33-7.46 (5H, m, Ar-*H*) ppm

$^{13}C$ NMR (100.6 MHz): δ 19.2 (7-*C*$H_3$), 19.9 (7-*C*$H_3$), 26.9 (C-5), 29.9 (C-6), 38.5 (C-3), 43.5 (C-4), 48.6 (C-7), 50.1 (C-1), 50.3 (*C*$H_2SO_2$), 70.6 (C-1'), 75.7 (C-2), 75.8 (C-2'), 125.8 (Ar C-3), 127.6 (Ar C-4), 127.9 (Ar C-3), 128.1 (Ar C-2), 128.7 (Ar C-1), 128.8 (Ar C-4), 130.2 (Ar C-2), 139.2 (Ar C-1) ppm

HRMS (CI) *m/z* 437.1770: *calculated for* $[C_{24}H_{30}O_4S + Na]^+$ 437.1761

**(1*S*, 2*R*, 4*R*, 1'*R*, 2'*R*)-1-{[(1',2'-Diphenyl-2'-hydroxyethyl)sulfonyl]methyl}-7,7-dimethylbicyclo[2.2.1]heptan-2-ol 362b**




**362b**

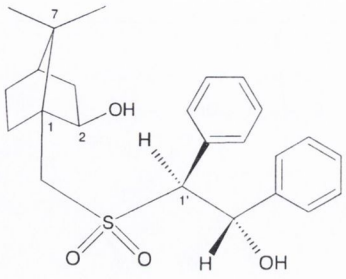
IR: $\nu_{max}$ (L) 3482 (O-H), 3063, 3031, 2954, 1953, 1890, 1804, 1719, 1602 (Ar C-C), 1493, 1455, 1390, 1292 ($SO_2$), 1117 ($SO_2$), 1056, 1026, 912, 879, 790, 731, 698 $cm^{-1}$

$^1H$ NMR (400.1 MHz): δ 0.82 (3H, s, 7-C$H_3$), 1.00 (3H, s, 7-C$H_3$), 1.08-1.19 (1H, m), 1.57-1.83 (6H, m), 3.35 (1H, d, $^2J$ = 14.0, C$H_2SO_2$), 3.39 (1H, d, $^2J$ = 14.0, C$H_2SO_2$), 4.14 (1H, dd, $^3J_1$ = 7.8, $^3J_2$ = 4.5, 2-C*H*), 4.44 (1H, d, $^3J$ = 9.5, 1'-C*H*), 5.57 (1H, d, $^3J$ = 9.5, 2'-C*H*), 7.16 (5H, s, Ar-*H*), 7.22 (5H, s, Ar-*H*) ppm

$^{13}C$ NMR (100.6 MHz): δ 19.3 (7-*C*$H_3$), 20.1 (7-*C*$H_3$), 27.0 (C-5), 29.8 (C-6), 38.5 (C-3), 43.6 (C-4), 48.8 (C-7), 50.6 (C-1), 53.3 (*C*$H_2SO_2$), 74.2 (C-1'), 75.8 (C-2), 76.1 (C-2') 126.5 (Ar C-3), 127.8 (Ar C-4), 127.8 (Ar C-3), 128.3 (Ar C-2), 128.7 (Ar C-4), 129.4 (Ar C-2), 130.0 (Ar C-1), 139.5 (Ar C-1) ppm

HRMS (CI) *m/z* 437.1770: *calculated for* $[C_{24}H_{30}O_4S + Na]^+$ 437.1761

**(1*S*, 2*R*, 4*R*, 1'*S*, 2'*S*)-1-{[(1',2'-Diphenyl-2'-hydroxyethyl)sulfonyl]methyl}-7,7-dimethylbicyclo[2.2.1]heptan-2-ol 362c**




**362c**

m.p.: 168 °C (from EtOAc/hexane)

$[\alpha]_D$ (*c* 0.25, $CHCl_3$, 22 °C) -10.4

IR: $\nu_{max}$ (N) 3473 (O-H), 3345 (O-H), 2924, 1954, 1887, 1803, 1601 (Ar C-C), 1455, 1375, 1299 ($SO_2$), 1249, 1119 ($SO_2$), 1047, 942, 880, 826, 762, 698 $cm^{-1}$

$^1H$ NMR (400.1 MHz): δ 0.77 (3H, s, 7-C*H*$_3$), 1.06 (3H, s, 7-C*H*$_3$), 1.10-1.16 (1H, m), 1.56-1.61 (1H, m), 1.69-1.78 (5H, m), 2.93 (1H, d, $^2J$ = 13.5, C*H*$_2$SO$_2$), 3.92 (1H, d, $^2J$ = 13.5, C*H*$_2$SO$_2$), 4.21 (1H, dd, $^3J_1$ = 7.8, $^3J_2$ = 4.5, 2-C*H*), 4.44 (1H, d, $^3J$ = 9.5, 1'-C*H*), 5.58 (1H, d, $^3J$ = 9.5, 2'-C*H*), 7.17 (5H, s, Ar-*H*), 7.23 (5H, s, Ar-*H*) ppm

$^{13}C$ NMR (100.6 MHz): δ 19.4 (7-*C*H$_3$), 20.0 (7-*C*H$_3$), 27.0 (C-5), 30.0 (C-6), 38.3 (C-3), 43.7 (C-4), 48.7 (C-7), 50.6 (C-1), 53.8 (*C*H$_2$SO$_2$), 74.4 (C-1'), 76.0 (C-2), 76.0 (C-2'), 126.5 (Ar C-3), 127.7 (Ar C-4), 127.8 (Ar C-3), 128.2 (Ar C-2), 128.4 (Ar C-4), 129.4 (Ar C-2), 129.9 (Ar C-1), 139.6 (Ar C-1) ppm

HRMS (CI) *m/z* 437.1757: *calculated for* $[C_{24}H_{30}O_4S + Na]^+$ 437.1761

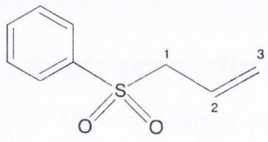
**Attempted desulfonylation of chiral β-hydroxysulfone 362c with samarium iodide**[31, 33]

The starting sulfone **362c** (0.08 g) was placed in an oven-dried flask and sealed under nitrogen. The flask was cooled to – 20 °C and a solution of samarium iodide in THF (9.66 ml, 0.1 M, 5 equiv.) was added *via* syringe. HMPA (1 ml) was added and the solution was stirred at – 20 °C for 2.5 hrs. The solution was then allowed to warm to rt, a solution of samarium iodide in THF (9.66 ml, 0.1 M, 5 equiv.) was added *via* syringe and the solution was stirred for an additional 5.5 hrs. The solution was then diluted with satd. aq. ammonium chloride (50 ml) and extracted with DCM (3 × 50 ml). The combined organic extracts were dried and evaporated to afford unchanged starting sulfone.

**Preparation of allyl and benzyl sulfones 365, 366, 369 and 370. General procedure**[17]

Sodium arenesulfinate **209** or **322** (60.4 mmol) was suspended in acetonitrile (50 ml) and triethylhexylammonium bromide (2.14 g, 20 mol %) was added. The appropriate electrophile (40.3 mmol) was added and the mixture was heated under reflux for 24 hrs. The mixture was allowed to cool to rt, diluted with $H_2O$ (50 ml) and extracted with ether (3 × 50 ml) and DCM (50 ml). The combined organic extracts were dried and evaporated to afford the allyl or benzyl sulfone in the yields mentioned individually below.

**(Prop-2-enylsulfonyl)benzene 365**[47]




**365**

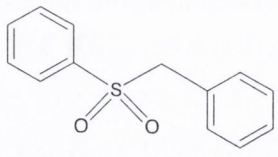
Obtained from sodium benzenesulfinate **209** and allyl bromide as an oil (6.16 g, 84 %).

IR: $\nu_{max}$ (L) 3066, 2977, 2920, 1639 (C=C), 1584 (Ar C-C), 1478, 1447, 1397, 1311 ($SO_2$), 1241, 1196, 1146 ($SO_2$), 1084, 994, 938, 874, 790, 754, 690, 626 $cm^{-1}$

$^1H$ NMR (400.1 MHz): δ 3.83 (2H, d, $^3J$ = 7.5, 1-C*H*$_2$), 5.16 (1H, d, $^3J$ = 17.0, 3-C*H*$_2$ *trans*), 5.35 (1H, d, $^3J$ = 10.0, 3-C*H*$_2$ *cis*), 5.81 (1H, ddt, $^3J_1$ = 17.0, $^3J_2$ = 10.0, $^3J_3$ = 7.5, 2-C*H*), 7.57 (2H, t, $^3J$ = 7.5, *m*-Ar*H*), 7.67 (1H, t, $^3J$ = 7.5, *p*-Ar*H*), 7.89 (2H, d, $^3J$ = 7.5, *o*-Ar*H*) ppm

$^{13}C$ NMR (100.6 MHz): δ 60.4 (C-1), 124.1 (C-2), 124.3 (C-3), 128.0 (Ar C-3), 128.6 (Ar C-2), 133.3 (Ar C-4), 137.7 (Ar C-1) ppm

**(Benzylsulfonyl)benzene 366**[17, 48]




**366**

Obtained from sodium benzenesulfinate **209** and benzyl chloride as a white solid (9.16 g, 98 %).

m.p.: 144 °C (from ether); Lit.[49]: 144-145 °C

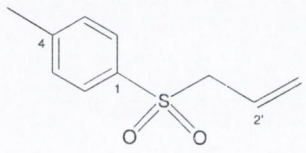
IR: $\nu_{max}$ (N) 3029, 2921, 1584 (Ar C-C), 1448, 1413, 1376, 1291 ($SO_2$), 1263, 1201, 1153, 1127 ($SO_2$), 1082, 1028, 998, 921, 885, 795, 758, 730, 688, 599 $cm^{-1}$

$^{1}$H NMR (400.1 MHz): δ 4.33 (2H, s, benzyl-C*H*$_2$), 7.09 (2H, d, $^{3}J$ = 7.0, Ar-*H*), 7.25-7.29 (2H, m, Ar-*H*), 7.31-7.39 (1H, m, Ar-*H*), 7.46 (2H, t, $^{3}J$ = 7.5, Ar-*H*), 7.60-7.65 (3H, m, Ar-*H*) ppm

$^{13}$C NMR (100.6 MHz): δ 62.4 (benzyl *C*H$_2$), 127.6 (Ar C-1), 128.1 (Ar C-3), 128.1 (Ar C-3), 128.3 (Ar C-4), 128.4 (Ar C-2), 130.3 (Ar C-2), 133.2 (Ar C-4), 137.3 (Ar C-1) ppm

HRMS (CI) *m/z* 255.0462: *calculated for* $[C_{13}H_{12}O_2S + Na]^+$ 255.0455

**1-(Prop-2'-enylsulfonyl)-4-methylbenzene 369**[50]




**369**

Obtained from sodium *p*-toluenesulfinate **322** and allyl bromide as a white solid (7.42 g, 93 %).

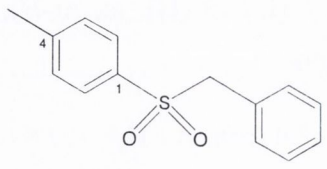
m.p.: 55 °C (from ether); Lit.[50]: 59 °C

IR: $\nu_{max}$ (N) 2923, 1639 (C=C), 1593 (Ar C-C), 1460, 1379, 1289 ($SO_2$), 1244, 1206, 1141 ($SO_2$), 1083, 993, 939, 871, 808, 776, 706, 643, 615 cm$^{-1}$

$^{1}$H NMR (400.1 MHz): δ 2.45 (3H, s, 4-C*H*$_3$), 3.80 (2H, d, $^{3}J$ = 7.5, 1'-C*H*$_2$), 5.16 (1H, dd, $^{3}J$ = 17.0, $^{2}J$ = 1.0, 3'-C*H*$_2$ *trans*), 5.34 (1H, d, $^{3}J$ = 10.0, 3'-C*H*$_2$ *cis*), 5.80 (1H, ddt, $^{3}J_1$ = 17.0, $^{3}J_2$ = 10.0, $^{3}J_3$ = 7.5, 2'-C*H*), 7.35 (2H, d, $^{3}J$ = 8.0, 3 and 5-C*H*), 7.75 (2H, d, $^{3}J$ = 8.0, 2 and 6-C*H*) ppm

$^{13}$C NMR (100.6 MHz): δ 21.2 (4-*C*H$_3$), 60.4 (C-1'), 124.1 (C-3'), 124.3 (C-2'), 128.0 (C-3 and C-5), 129.2 (C-2 and C-6), 134.8 (C-1), 144.3 (C-4) ppm

**1-(Benzylsulfonyl)-4-methylbenzene 370**[51]



**370**

Obtained from sodium *p*-toluenesulfinate **322** and benzyl chloride as a white solid (9.67 g, 97 %).

m.p.: 144 °C (from ether); Lit.[51]: 142-144 °C

IR: $\nu_{max}$ (N) 2926, 1592 (Ar C-C), 1456, 1378, 1306 ($SO_2$), 1150 ($SO_2$), 1081, 1033, 818, 775, 722, 698, 665 $cm^{-1}$

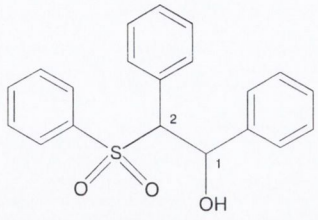
$^1H$ NMR (400.1 MHz): δ 2.43 (3H, s, 4-C*H*$_3$), 4.31 (2H, s, benzyl C*H*$_2$), 7.11 (2H, d, $^3J$ = 8.0, 3 and 5-C*H*), 7.24-7.36 (5H, m, benzyl Ar*H*), 7.52 (2H, d, $^3J$ = 8.0, 2 and 6-C*H*) ppm

$^{13}C$ NMR (100.6 MHz): δ 21.2 (4-*C*H$_3$), 62.4 (benzyl *C*H$_2$), 127.8 (Ar C-1), 128.0 (Ar C-3), 128.1 (C-3 and C-5), 128.2 (Ar C-4), 129.0 (C-2 and C-6), 130.3 (Ar C-2), 134.4 (C-1), 144.2 (C-4) ppm

**Aldol-type reactions of sulfones 366, 369 and 370 with benzaldehyde. General procedure**[37]

*n*-Butyllithium (1.1 equiv.) was added dropwise to a solution of the allyl or benzyl sulfone (1 equiv.) in dry THF (25 ml) at - 40 °C under an atmosphere of nitrogen. After 10 mins, freshly distilled benzaldehyde (1.1 equiv.) was added dropwise. The solution was then stirred at the temperature and for the time period indicated individually below. The solution was then allowed to warm to rt, quenched with satd. aq. $NH_4Cl$ (50 ml) and extracted with DCM (3 × 50 ml). The combined organic extracts were dried and evaporated to yield a crude product which was purified as described individually below.

***threo*-1,2-Diphenyl-2-(phenylsulfonyl)ethanol 368**[28, 29]




**368**

Obtained from sulfone **366** (1.3 g, 5.60 mmol). The reaction mixture was stirred at – 20 °C for 3.5 hrs. Work up gave a crude product whose $^1$H NMR spectrum showed it to contain unreacted sulfone **366** and the adducts **368** (as two diastereomers) in ca. 3:1 ratio. The crude product was purified over silica gel, eluting with EtOAc:hexane (1:3.5) to yield three products. The first product to elute was unreacted sulfone **366** as a white solid (0.86 g). The second product to elute was a mixture of two diastereomers of **368** as a white solid (0.16 g, 8 %) contaminated with minor amounts of unreacted sulfone **366**. The third product to elute was a single diastereomer (*threo*) of **368** as a white solid (0.36 g, 19 %).

m.p.: 107-108 °C (from EtOAc/hexane); Lit.[28]: 112-113 °C

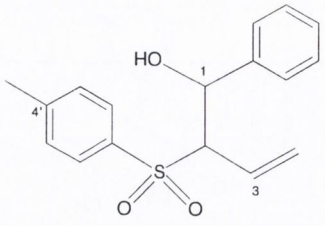
IR: $\nu_{max}$ (N) 3462 (O-H), 2926, 2855, 1601 (Ar C-C), 1456, 1376, 1308 ($SO_2$), 1141 ($SO_2$), 1084, 1040, 995, 921, 800, 758, 697 $cm^{-1}$

$^1$H NMR (400.1 MHz): δ 4.48 (1H, d, $^3J$ = 10.0, 2-C*H*), 5.78 (1H, d, $^3J$ = 10.0, 1-C*H*), 6.90 (2H, br s, Ar-*H*), 7.02 (2H, t, $^3J$ = 7.5, Ar-*H*), 7.07-7.15 (4H, m, Ar-*H*), 7.19-7.21 (2H, m, Ar-*H*), 7.39 (2H, t, $^3J$ = 7.5, Ar-*H*), 7.54-7.57 (3H, m, Ar-*H*) ppm

$^{13}$C NMR (100.6 MHz): δ 73.4 (C-2), 77.0 (C-1), 126.9 (Ar C-3), 127.6 (Ar C-3), 127.7 (Ar C-4), 128.1 (Ar C-4), 128.2 (Ar C-3), 128.4 (Ar C-2), 129.7 (Ar C-4), 129.8 (Ar C-2), 130.2 (Ar C-1), 133.4 (Ar C-2), 137.0 (Ar C-1), 139.0 (Ar C-1) ppm

HRMS (CI) *m/z* 361.0884: *calculated for* $[C_{20}H_{18}O_3S + Na]^+$ 361.0873

**2-[(4'-Methylphenyl)sulfonyl]-1-phenylbut-3-en-1-ol 371**[52]




**371**

Obtained from sulfone **369** (1.5 g, 7.65 mmol). The reaction mixture was allowed to warm to 0 °C during 4.5 hrs. The crude product was purified over silica gel, eluting with EtOAc:hexane (1:3) to yield three products. The first product to elute was a single diastereomer (diastereomer A) of **371** as a white solid (0.81 g, 35 %) contaminated with minor amounts of unreacted sulfone **369**. The second product to elute was a single diastereomer (diastereomer B) of **371** as a white solid (0.07 g, 3 %). The third product to elute was vinyl sulfone **373** as a white solid (0.39 g, 16 %).

Diastereomer A:

m.p.: 86 °C (from EtOAc/hexane); Lit.[52]: 88-89 °C

IR: $\nu_{max}$ (N) 3499 (O-H), 3063, 3031, 2927, 1637 (C=C), 1597 (Ar C-C), 1494, 1456, 1403, 1376, 1290 ($SO_2$), 1191, 1141 ($SO_2$), 1084, 993, 937, 875, 816, 755, 704, 668, 607 $cm^{-1}$

$^1H$ NMR (400.1 MHz): δ 2.47 (3H, s, 4'-C*H*$_3$), 3.62 (1H, d, $^3J$ = 10.5, 2-C*H*), 4.71 (1H, d, $^3J$ = 17.5, 4-C*H*$_2$ *trans*), 5.25 (1H, d, $^3J$ = 11.0, 4-C*H*$_2$ *cis*), 5.76 (1H, s, 1-C*H*), 6.08 (1H, app dt, $^3J_1$ = 17.5, $^3J_2$ = 10.0, 3-C*H*), 7.26-7.33 (5H, m, Ar*H*), 7.37 (2H, d, $^3J$ = 8.0, 3' and 5'-C*H*), 7.79 (2H, d, $^3J$ = 8.0, 2' and 6'-C*H*) ppm

$^{13}C$ NMR (100.6 MHz): δ 21.2 (4'-*C*H$_3$), 69.8 (C-1), 75.1 (C-2), 124.1 (C-3), 125.5 (Ar C-3), 125.7 (C-4), 127.4 (Ar C-4), 127.8 (Ar C-2), 128.6 (C-3' and C-5'), 129.2 (C-2' and C-6'), 133.6 (C-1'), 139.3 (Ar C-1), 144.7 (C-4') ppm

HRMS (CI) *m/z* 325.0884: *calculated for* $[C_{17}H_{18}O_3S + Na]^+$ 325.0873

Diastereomer B:

m.p.: 67 °C (from EtOAc/hexane); Lit.[52]: 67-68 °C

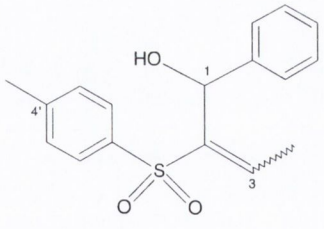
IR: $\nu_{max}$ (N) 3515 (O-H), 3029, 2922, 2861, 1639 (C=C), 1597 (Ar C-C), 1492, 1452, 1380, 1286 ($SO_2$), 1208, 1141 ($SO_2$), 1085, 1044, 929, 814, 748, 697 $cm^{-1}$

$^1$H NMR (400.1 MHz): δ 2.48 (3H, s, 4'-C*H*$_3$), 3.86 (1H, app t, $^3J$ = 9.5, 2-C*H*), 4.64 (1H, d, $^3J$ = 17.0, 4-C*H*$_2$ *trans*), 4.94 (1H, dd, $^3J$ = 10.0, $^2J$ = 1.0, 4-C*H*$_2$ *cis*), 5.29 (1H, d, $^3J$ = 9.0, 1-C*H*), 5.32 (1H, app dt, $^3J_1$ = 17.0, $^3J_2$ = 10.0, 3-C*H*), 7.28-7.34 (5H, m, Ar*H*), 7.38 (2H, d, $^3J$ = 8.0, 3' and 5'-C*H*), 7.78 (2H, d, $^3J$ = 8.0, 2' and 6'-C*H*) ppm

$^{13}$C NMR (100.6 MHz): δ 21.2 (4'-*C*H$_3$), 72.1 (C-1), 75.6 (C-2), 123.6 (C-4), 126.5 (C-3), 126.8 (Ar C-3), 127.0 (Ar C-4), 128.0 (Ar C-2), 128.9 (C-3' and C-5'), 129.1 (C-2' and C-6'), 133.4 (C-1'), 138.9 (Ar C-1), 144.9 (C-4') ppm

HRMS (CI) *m/z* 325.0886: *calculated for* $[C_{17}H_{18}O_3S + Na]^+$ 325.0873

**2-[(4'-Methylphenyl)sulfonyl]-1-phenylbut-2-en-1-ol 373**




**373**

m.p.: 89 °C (from EtOAc/hexane)

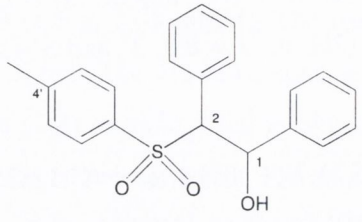
IR: $\nu_{max}$ (N) 3477 (O-H), 3029, 2921, 1638 (C=C), 1596 (Ar C-C), 1453, 1376, 1297 ($SO_2$), 1241, 1133 ($SO_2$), 1082, 1060, 1014, 871, 811, 758, 696 $cm^{-1}$

$^1$H NMR (400.1 MHz): δ 1.89 (3H, d, $^3J$ = 7.5, 4-C*H*$_3$), 2.39 (3H, s, 4'-C*H*$_3$), 5.83 (1H, s, 1-C*H*), 7.16 (2H, d, $^3J$ = 8.0, 3' and 5'-C*H*), 7.17 (5H, s, Ar*H*), 7.23 (1H, q, $^3J$ = 7.5, 3-C*H*), 7.50 (2H, d, $^3J$ = 8.0, 2' and 6'-C*H*) ppm

$^{13}$C NMR (100.6 MHz): δ 14.1 (C-4), 21.0 (4'-*C*H$_3$), 68.3 (C-1), 125.0 (Ar C-3), 126.7 (Ar C-4), 127.3 (Ar C-2), 127.7 (C-3' and C-5'), 129.1 (C-2' and C-6'), 136.9 (C-1'), 139.4 (C-2), 141.0 (C-3), 143.4 (Ar C-1), 143.6 (C-4') ppm

HRMS (CI) *m/z* 325.0872: *calculated for* [$C_{17}H_{18}O_3S$ + Na]$^+$ 325.0873

***erythro* and *threo*-2-[(4'-Methylphenyl)sulfonyl]-1,2-diphenylethanol 372**[27, 53]




**372**

Obtained from sulfone **370** (1.6 g, 6.50 mmol). The reaction mixture was allowed to warm to 0 °C during 4 hrs. The crude product which crystallized after 2 days was recrystallised from EtOAc:hexane (2:1) to yield a mixture of *erythro* and *threo* **372** (ca. 1:2.2 ratio) as a white solid (1.63 g, 71 %) contaminated with minor amounts of unreacted sulfone **370**.

m.p.: 104 °C (from EtOAc/hexane); Lit.[27, 53]: 156-157 °C (*erythro*), 151-152 °C (*threo*)

IR: $\nu_{max}$ (N) 3493 (O-H), 2924, 1595 (Ar C-C), 1456, 1378, 1307 ($SO_2$), 1139 ($SO_2$), 1084, 1057, 919, 814, 776, 699, 665 cm$^{-1}$

$^1$H NMR (400.1 MHz): δ 2.38 (3H, s, 4'-C*H*$_3$ *erythro*), 2.39 (3H, s, 4'-C*H*$_3$ *threo*), 4.17 (1H, d, $^3J$ = 2.0, 2-C*H erythro*), 4.45 (1H, d, $^3J$ = 9.5, 2-C*H threo*), 5.75 (1H, d, $^3J$ = 9.5, 1-C*H threo*), 6.01 (1H, d, $^3J$ = 2.0, 1-C*H erythro*), 6.90 (4H, br s, Ar-*H erythro* and *threo*), 7.00-7.36 (16H, m, Ar-*H erythro* and *threo*), 7.11 (4H, d, $^3J$ = 8.5, 3' and 5'-C*H erythro* and *threo*), 7.43 (2H, d, $^3J$ = 8.5, 2' and 6'-C*H threo*), 7.55 (2H, d, $^3J$ = 8.5, 2' and 6'-C*H erythro*) ppm

$^{13}$C NMR (100.6 MHz): δ 21.1 (4'-*C*H$_3$ *erythro*), 21.2 (4'-*C*H$_3$ *threo*), 70.7 (C-2 *erythro*), 73.4 (C-2 *threo*), 75.9 (C-1 *erythro*), 77.0 (C-1 *threo*), 125.6 (Ar C), 126.9

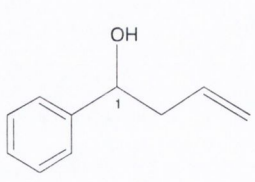
(Ar C), 127.3 (Ar C), 127.5 (Ar C), 127.6 (Ar C), 127.6 (Ar C), 128.0 (C-3' and C-5' *erythro*), 128.2 (Ar C), 128.5 (C-3' and C-5' *threo*), 128.9 (C-2' and C-6' *threo*), 129.0 (C-2' and C-6' *erythro*), 129.8 (Ar C), 130.9 (Ar C), 134.0 (C-1' *threo*), 134.2 (C-1' *erythro*), 139.0 (Ar C), 144.3 (C-4' *erythro*), 144.5 (C-4' *threo*) ppm

HRMS (CI) *m/z* 375.1021: *calculated for* $[C_{21}H_{20}O_3S + Na]^+$ 375.1030

**Desulfonylation of β-hydroxysulfones 371 and 372 with samarium iodide. General procedure**[31, 33]

The starting sulfone (1 equiv.) was placed in an oven-dried flask and sealed under nitrogen. The flask was cooled to – 20 °C and a solution of samarium iodide in THF (0.1 M, 4 equiv.) was added *via* syringe. HMPA (1 ml) was added and the solution was stirred at – 20 °C for 5 hrs during which time the deep purple solution became colourless. The solution was allowed to warm to rt, diluted with satd. aq. ammonium chloride (50 ml) and extracted with ether (3 × 50 ml). The combined organic extracts were dried and evaporated to afford a crude product which was purified by column chromatography on silica gel (EtOAc:hexane; 1:3) to afford the purified products described individually below.

**1-Phenylbut-3-en-1-ol 375**[54]




**375**

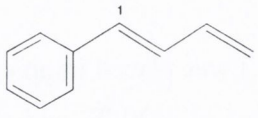
Obtained from sulfone **371** (0.13 g) as an oil (0.04 g, 63 %). **375** was the second product to elute from the column. Unreacted sulfone **371** (0.03 g) was also eluted.

IR: $\nu_{max}$ (L) 3473 (O-H), 3061, 3027, 2926, 2854, 1641 (C=C), 1597 (Ar C-C), 1493, 1453, 1377, 1302, 1144, 1086, 967, 915, 814, 750, 700 $cm^{-1}$

$^{1}$H NMR (400.1 MHz): δ 1.91 (1H, br s, O-*H*), 2.52-2.57 (2H, m, 2-C$H_2$), 4.77 (1H, dd, $^{3}J_1$ = 7.7, $^{3}J_2$ = 5.5, 1-C*H*), 5.16-5.22 (2H, m, 4-C$H_2$ *cis* and *trans*), 5.69-5.89 (1H, m, 3-C*H*), 7.29-7.39 (5H, m, Ar*H*) ppm

$^{13}$C NMR (100.6 MHz): δ 43.9 (C-2), 73.7 (C-1), 118.5 (C-4), 126.1 (C-3), 127.7 (Ar C-3), 128.6 (Ar C-4), 134.7 (Ar C-2), 144.2 (Ar C-1) ppm

**(1*E*)-1-Phenylbuta-1,3-diene 376**[55]




**376**

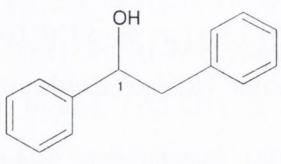
Obtained from sulfone **371** (0.13 g) as an oil (0.01 g, 18 %). **376** was the first product to elute from the column.

IR: $\nu_{max}$ (L) 3082, 3057, 3029, 1801, 1641 (C=C), 1593 (Ar C-C), 1492, 1448, 998, 953, 897, 746, 685 cm$^{-1}$

$^{1}$H NMR (400.1 MHz): δ 5.16 (1H, d, $^{3}J$ = 10.0, 4-C$H_2$ *cis*), 5.31 (1H, d, $^{3}J$ = 17.0, 4-C$H_2$ *trans*), 6.49 (1H, app dt, $^{3}J_1$ = 17.0, $^{3}J_2$ = 10.0, 3-C*H*), 6.56 (1H, d, $^{3}J$ = 16.5, 1-C*H*), 6.80 (1H, dd, $^{3}J_1$ = 16.5, $^{3}J_2$ = 10.0, 2-C*H*), 7.18-7.45 (5H, m, Ar*H*) ppm

$^{13}$C NMR (100.6 MHz): δ 116.8 (C-4), 126.4 (C-2), 127.1 (C-3), 128.8 (C-1), 129.6 (Ar C-2), 132.3 (Ar C-4), 136.8 (Ar C-3), 137.2 (Ar C-1) ppm

**1,2-Diphenylethanol 377**[56]




**377**

Obtained from sulfone **372** (0.19 g) as a white solid (0.04 g, 40 %). **377** was the second product to elute from the column. Unreacted sulfone **372** (0.05 g) was also eluted.

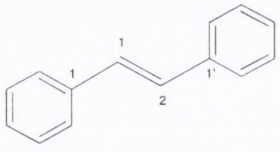
m.p.: 64 °C (from EtOAc/hexane); Lit.[57]: 65-66 °C

IR: $\nu_{max}$ (N) 3302 (O-H), 3024, 2924, 1596 (Ar C-C), 1454, 1377, 1313, 1272, 1208, 1149, 1071, 1027, 952, 917, 814, 760, 697 $cm^{-1}$

$^1H$ NMR (400.1 MHz): δ 1.88 (1H, br s, O-*H*), 3.02 (1H, dd, $^2J$ = 13.5, $^3J$ = 8.5, 2-C$H_2$), 3.08 (1H, dd, $^2J$ = 13.5, $^3J$ = 4.5, 2-C$H_2$), 4.93 (1H, dd, $^3J_1$ = 8.5, $^3J_2$ = 4.5, 1-C*H*), 7.17-7.39 (10H, m, Ar*H*) ppm

$^{13}C$ NMR (100.6 MHz): δ 45.6 (C-2), 74.9 (C-1), 125.4 (Ar C-3), 126.1 (Ar C-4), 127.1 (Ar C-4), 127.9 (Ar C-3), 128.0 (Ar C-2), 129.0 (Ar C-2), 137.5 (Ar C-1), 143.3 (Ar C-1) ppm

**(*E*)-1,1'-(Ethene-1,2-diyl)dibenzene 378**[58]




**378**

Obtained from sulfone **372** (0.19 g) as a yellow solid (0.03 g, 31 %). **378** was the first product to elute from the column.

m.p.: 125 °C (from EtOAc/hexane); Lit.[59]: 127 °C

IR: $\nu_{max}$ (N) 3019, 2922, 1949, 1876, 1816, 1597 (Ar C-C), 1577, 1494, 1451, 1377, 1299, 1263, 1154, 1072, 1028, 962, 909, 873, 765, 692 $cm^{-1}$

$^1H$ NMR (400.1 MHz): δ 7.14 (2H, s, 1 and 2-C*H*), 7.27-7.31 (2H, m, Ar 4 and 4'-C*H*), 7.39 (4H, t, $^3J$ = 7.0, Ar 3 and 3'-C*H*), 7.55 (4H, d, $^3J$ = 7.0, Ar 2 and 2'-C*H*) ppm

$^{13}C$ NMR (100.6 MHz): δ 126.0 (Ar C-2 and C-2'), 127.1 (Ar C-4 and C-4'), 128.1 (C-1 and C-2), 128.2 (Ar C-3 and C-3'), 136.8 (Ar C-1 and C-1') ppm

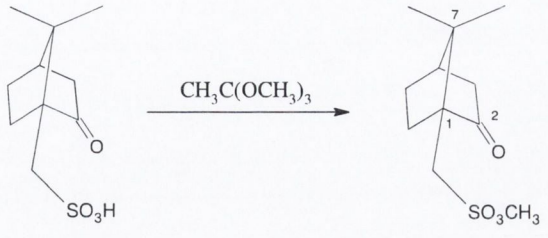
**Attempted desulfonylation of β-hydroxysulfones 368, 371 and 372 with tetrakis(triphenylphosphine)palladium(0)/sodium borohydride. General procedure**[30]

Sodium borohydride (0.27 g, 7.15 mmol) was added to a solution of the β-hydroxysulfone **368**, **371** or **372** (1.19 mmol) in dry THF (8 ml) and isopropanol (5 ml) at - 20 °C under an atmosphere of nitrogen. A solution of tetrakis(triphenylphosphine)palladium(0) (0.068 g, 5 mol %) in dry THF (2 ml) was added dropwise *via* syringe and the solution was stirred at - 20 °C for 3 hrs and then allowed to warm to rt and stirred for an additional 5 hrs. The solution was then diluted with $H_2O$ (50 ml) and extracted with ether (3 × 50 ml). The combined organic extracts were dried and evaporated to yield a dark solid whose $^1H$ NMR spectrum showed it to contain allyl or benzyl sulfone **366** (from **368**), **369** (from **371**) or **370** (from **372**) and benzyl alcohol.

**Attempted desulfonylation of β-hydroxysulfone 371 with tri-*n*-butyltin hydride/2,2'-azobis(isobutyronitrile)**[34]

Tri-*n*-butyltin hydride (0.35 ml, 1.32 mmol) was added *via* syringe to a solution of sulfone **371** (0.2 g, 0.66 mmol) in dry benzene (5 ml) under an atmosphere of nitrogen. 2,2'-Azobis(isobutyronitrile) (0.005 g, 5 mol %) was then added and the solution was heated under reflux for 6 hrs. The solution was then allowed to cool to rt, acetic acid (2 ml) was added and the solution was stirred for an additional 18 hrs. The solution was then diluted with $H_2O$ (50 ml) and extracted with ether (3 × 50 ml). The combined organic extracts were washed with $H_2O$ (50 ml), dried and evaporated to afford a crude product (1.2 g) whose $^1H$ NMR spectrum showed it to consist of unreacted sulfone **371**.

**(1*S*, 4*R*)-Methyl (7,7-dimethyl-2-oxobicyclo[2.2.1]hept-1-yl)methanesulfonate 382**[39]




**319** **382**

Following the procedure of Gopalan,[40] (+)-camphor-10-sulfonic acid **319** (3.0g, 12.9 mmol) was suspended in DCM (50 ml) and trimethyl orthoacetate (8.21 ml, 64.5 mmol) was added. The resulting solution was stirred at rt for 90 mins. The solution was then evaporated to yield an oil. Removal of excess trimethyl orthoacetate on an oil pump afforded the title compound as a pale pink solid (2.88 g, 90 %).

m.p.: 107-109 °C (from DCM); Lit.[39]: 61 °C

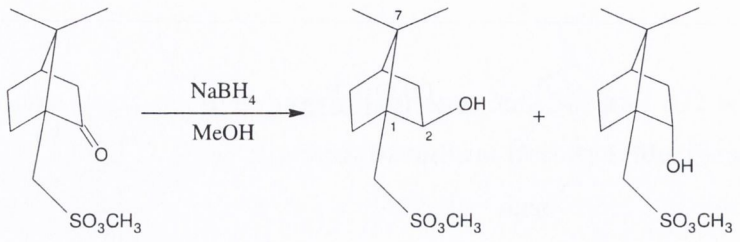
$[\alpha]_D$ (*c* 1.61, $CHCl_3$, 22 °C) +42.7; Lit.[39]: (*c* 5 %, $CHCl_3$, 23 °C) +43.6

IR: $\nu_{max}$ (N) 2923, 2723, 2669, 1741 (C=O), 1456, 1376, 1301, 1269, 1170 (S=O), 1054, 989 (S=O), 808, 747 $cm^{-1}$

$^1H$ NMR (400.1 MHz): δ 0.88 (3H, s, 7-C*H*$_3$), 1.10 (3H, s, 7-C*H*$_3$), 1.41-1.48 (1H, m), 1.63-1.70 (1H, m), 1.95 (1H, d, $^2J$ = 18.5, 3-C*H*$_2$ *endo*), 2.01-2.10 (1H, m), 2.13 (1H, t, $^3J$ = 4.5, 4-C*H*), 2.39 (1H, dt, $^2J$ = 18.5, $^3J$ = 4.5, 3-C*H*$_2$ *exo*), 2.43-2.50 (1H, m), 2.98 (1H, d, $^2J$ = 15.0, C*H*$_2$SO$_3$CH$_3$), 3.59 (1H, d, $^2J$ = 15.0, C*H*$_2$SO$_3$CH$_3$), 3.95 (3H, s, SO$_3$C*H*$_3$) ppm

$^{13}C$ NMR (100.6 MHz): δ 19.2 (7-*C*H$_3$), 19.2 (7-*C*H$_3$), 24.3 (C-5), 26.4 (C-6), 42.0 (C-3), 42.2 (C-4), 45.5 (*C*H$_2$SO$_3$CH$_3$), 47.5 (C-7), 55.7 (SO$_3$*C*H$_3$), 57.3 (C-1), 214.1 (C-2) ppm

**(1*S*, 2*R*, 4*R*)-Methyl (2-hydroxy-7,7-dimethylbicyclo[2.2.1]hept-1-yl)methanesulfonate 383**




**382** **383** **387**

Methyl sulfonate ester **382** (0.25 g, 1.01 mmol) was dissolved in methanol (10 mls) and sodium borohydride (0.115 g, 3.04 mmol) was added. The solution was stirred at rt for 1 hr. Acetic acid (2 mls) was added and sodium carbonate was added until the pH was neutral. The mixture was diluted with ethyl acetate (100 mls) and washed with water (50 mls) and satd. aq. $NaHCO_3$ (2 × 50 mls), dried and evaporated to afford the title compound as a clear oil (0.24 g, 95 %) contaminated with ca. 10 % of its corresponding *endo* isomer **387**.

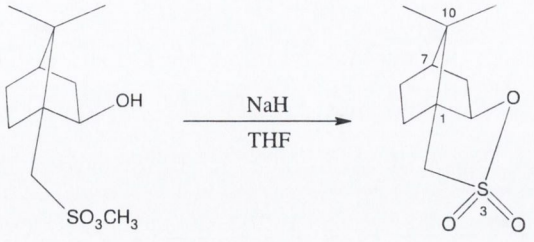
IR: $\nu_{max}$ (L) 3554 (O-H), 2957, 2883, 1456, 1352 (S=O), 1257, 1166 (S=O), 1076, 992, 879, 807, 746 $cm^{-1}$

$^1H$ NMR (400.1 MHz): δ 0.86 (3H, s, 7-C$H_3$), 1.09 (3H, s, 7-C$H_3$), 1.13-1.17 (1H, m), 1.45-1.51 (1H, m), 1.69-1.88 (5H, m), 2.83 (1H, br s, O-*H*), 2.99 (1H, d, $^2J$ = 14.0, C$H_2$SO$_3$CH$_3$), 3.56 (1H, d, $^2J$ = 14.0, C$H_2$SO$_3$CH$_3$), 3.94 (3H, s, SO$_3$C$H_3$), 4.09 (1H, dd, $^3J_1$ = 7.5, $^3J_2$ = 4.5, 2-C*H*) ppm

$^{13}C$ NMR (100.6 MHz): δ 19.3 (7-*C*H$_3$), 20.0 (7-*C*H$_3$), 26.8 (C-5), 29.7 (C-6), 38.7 (C-3), 43.9 (C-4), 48.3 (C-7), 48.5 (*C*H$_2$SO$_3$CH$_3$), 49.3 (C-1), 54.9 (SO$_3$*C*H$_3$), 75.7 (C-2) ppm

HRMS (CI) *m/z* 249.1153: *calculated for* $[C_{11}H_{20}O_4S + H]^+$ 249.1161

**(1*S*, 5*R*, 7*R*)-10,10-Dimethyl-4-oxa-3-thiatricyclo[5.2.1.0$^{1,5}$] decane 3,3-dioxide 388**[41, 43]




**383** **388**

A solution of the sulfonate ester **383** (0.24 g, 0.96 mmol) in dry THF (5 ml) was added to a suspension of sodium hydride (0.0425 g, 60 %, 1.06 mmol) in dry THF (5 ml) at 0 °C under an atmosphere of nitrogen. The mixture was stirred at 0 °C for 1 hr. The mixture was then allowed to warm to rt, quenched with $H_2O$ (50 ml) and extracted with ether (3 × 50 ml). The combined organic extracts were washed with brine (50 ml), dried and evaporated to yield a semi-solid material which was placed on the oil pump where it later crystallised to afford the title compound as a white solid (0.12 g, 60 %).

m.p.: 111-112 °C (from ether); Lit.[43]: 114-116 °C

$[\alpha]_D$ (*c* 0.33, $CCl_4$, 27 °C) -3.7; Lit.[43]: (*c* 10, $CCl_4$, 25 °C) -4.05

IR: $\nu_{max}$ (N) 2920, 1459, 1412, 1375, 1345 (S=O), 1258, 1227, 1177 (S=O), 1149, 1111, 1079, 1026, 990, 940, 893, 864, 815, 737, 683 cm$^{-1}$

$^1$H NMR (400.1 MHz): δ 0.95 (3H, s, 10-C*H*$_3$), 1.12 (3H, s, 10-C*H*$_3$), 1.24-1.29 (1H, m), 1.38-1.43 (1H, m), 1.86-1.97 (4H, m), 2.28 (1H, dd, $^2J$ = 14.0, $^3J$ = 3.5), 3.19 (1H, d, $^2J$ = 13.5, 2-C*H*$_2$), 3.29 (1H, d, $^2J$ = 13.5, 2-C*H*$_2$), 4.38 (1H, dd, $^3J_1$ = 7.7, $^3J_2$ = 3.5, 5-C*H*) ppm

$^{13}$C NMR (100.6 MHz): δ 19.3 (10-*C*H$_3$), 19.4 (10-*C*H$_3$), 26.2 (C-8), 28.6 (C-9), 35.3 (C-6), 43.9 (C-7), 46.9 (C-10), 48.6 (C-2), 55.0 (C-1), 87.5 (C-5) ppm

HRMS (CI) *m/z* 217.0898: *calculated for* $[C_{10}H_{16}O_3S + H]^+$ 217.0899

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57. See reference (c) in 56 above.

58. (a) L. Djakovitch and K. Koehler, *J. Am. Chem. Soc.*, 2001, **123**, 5990. (b) M. Mahesh, J. A. Murphy and H. P. Wessel, *J. Org. Chem.*, 2005, **70**, 4118. (c) K. Hamza, R. Abu-Reziq, D. Avnir and J. Blum, *Org. Lett.*, 2004, **6**, 925.

59. See reference (c) in 58 above.

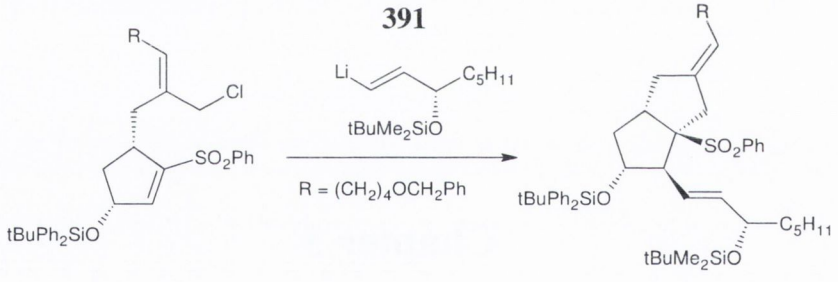
# Chapter 3

# Synthesis and Nucleophilic Epoxidation Reactions of Some Chiral Vinyl Sulfones

# 3.1 Introduction

## 3.1.1 Chemistry of Vinyl Sulfones

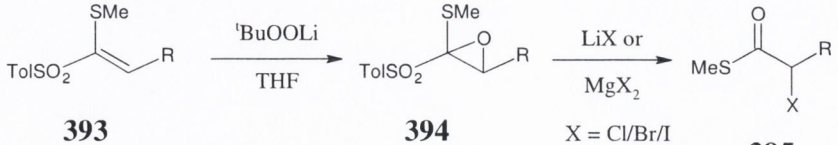
Vinyl sulfones are versatile intermediates in organic synthesis, acting as both electron deficient olefins in a wide range of 2 + 2, 3 + 2 and 4 + 2 cycloaddition processes, and as Michael acceptors with a number of carbon and heteroatom nucleophiles.[1] In contrast to the Michael addition chemistry of unsaturated carbonyl compounds, competing addition of nucleophiles to the sulfonyl function does not occur. The sequence of Michael addition, followed by electrophilic trapping of the resulting sulfonyl carbanion is particularly useful for the generation of two carbon-carbon bonds in a single step. This is demonstrated during the course of Fuchs' elegant total synthesis of (+)-carbacyclin, in which Michael addition of vinyllithium **391** is followed by intramolecular trapping of the carbanion, generating the fused bicyclopentane ring system **392** (**Scheme 3.1**).[2]




**390** **392**

**Scheme 3.1**

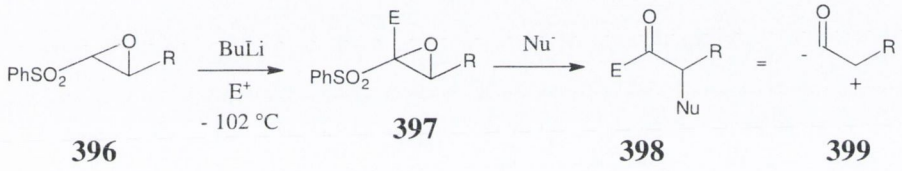
Vinyl sulfones can also act as synthetic precursors to α-functionalised carbonyl compounds. Nucleophilic epoxidation of vinyl sulfones generates sulfonyloxiranes which react at the β-position with nucleophiles. The resulting oxyanion eliminates sulfinate anion generating the carbonyl group. This chemistry has been utilised by Jackson *et al.* for the preparation of α-halothioesters **395** from α-thioalkyl vinyl sulfones **393** (**Scheme 3.2**).[3]




**393** **394** X = Cl/Br/I **395**

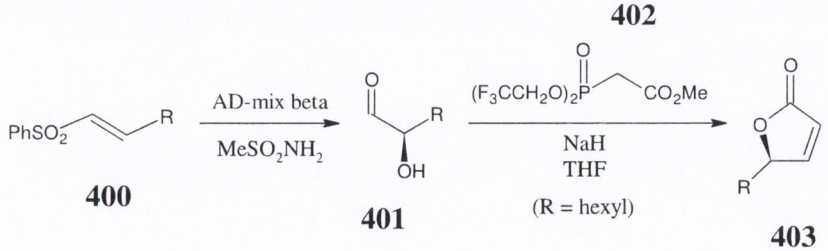
**Scheme 3.2**

Sulfonyloxiranes are readily obtained by Meth-Cohn epoxidation of vinyl sulfones using a metal alkyl peroxide,[4] or by Darzens condensations of α-haloalkyl sulfones with aldehydes and ketones.[5] These and the related sulfinyloxiranes react regiospecifically at the β-position with a range of heteroatom nucleophiles generating carbonyl compounds.[6] The reactivity and regiospecificity of these oxiranes toward nucleophiles is believed to arise from an anomeric effect. X-ray crystal structures of some sulfonyloxiranes show a pronounced shortening of the C-O bond adjacent to the sulfonyl group and a lengthening of the C-O bond distant from the sulfonyl group.[7] Sulfonyloxiranes are also capable of additional functionalization prior to nucleophilic cleavage, by lithiation and electrophilic quenching at low temperature, hence acting as masked acyl-anion equivalents **399** (**Scheme 3.3**).[8]




**Scheme 3.3**

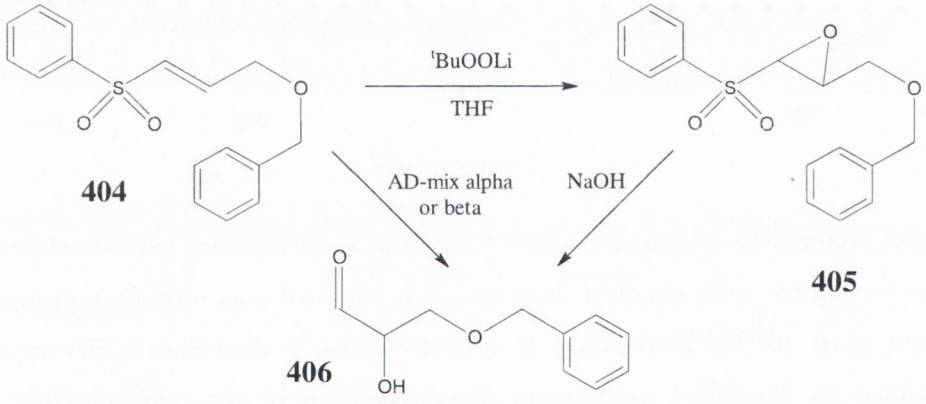
Direct preparation of α-hydroxyaldehydes from vinyl sulfones can be achieved by dihydroxylation with osmium tetroxide. This protocol was recently employed by Evans *et al.* for the preparation of optically active 5-alkylfuran-2(5*H*)-ones **403**, obtained by Sharpless asymmetric dihydroxylation of the corresponding vinyl sulfone **400**, followed by *cis*-selective Horner-Wadsworth-Emmons reaction of the resulting α-hydroxyaldehyde **401** and lactonisation (**Scheme 3.4**).[9] Chiral α-hydroxyaldehydes obtained by this method have recently been used in the asymmetric synthesis of (−)-swainsonine.[10]




**Scheme 3.4**

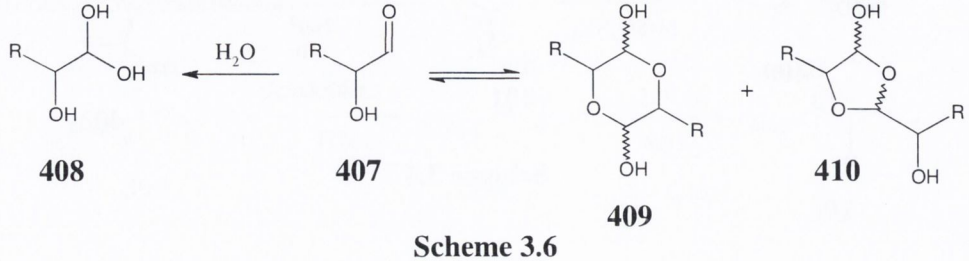
### 3.1.2 Proposed Synthesis of 3-*O*-Benzylglyceraldehyde 406

The above mentioned precedent for the preparation of α-functionalised aldehydes from vinyl sulfones prompted a study directed at the asymmetric synthesis of a derivative of glyceraldehyde, the simplest of the monosaccharide sugars. The realization that the α-hydroxyaldehyde functionality common to all the monosaccharides could be obtained in principle from the corresponding vinyl sulfones led to the examination of these routes for the preparation of α-hydroxyaldehydes. For TLC analysis and lipophilicity, 3-*O*-benzylglyceraldehyde[11] **406** was chosen as the target, and the aim of the present study was to examine its preparation from the corresponding γ-functionalized vinyl sulfone **404** either by direct Sharpless asymmetric dihydroxylation,[12] or by hydrolytic ring opening of the derived sulfonyloxirane **405** (**Scheme 3.5**).



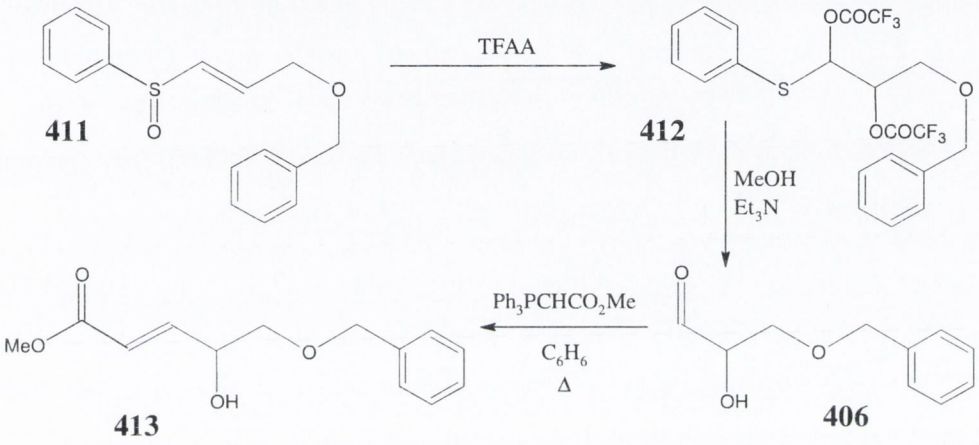

**Scheme 3.5**

Hydroxyaldehydes such as **407** in their unprotected form are particularly prone to dimerisation to form diastereomeric 1,4-dioxanes **409** and/or 1,3-dioxolanes **410** as well as water-soluble hydrates **408**, often leading to difficulties in characterisation and low isolated yields (**Scheme 3.6**).[13]



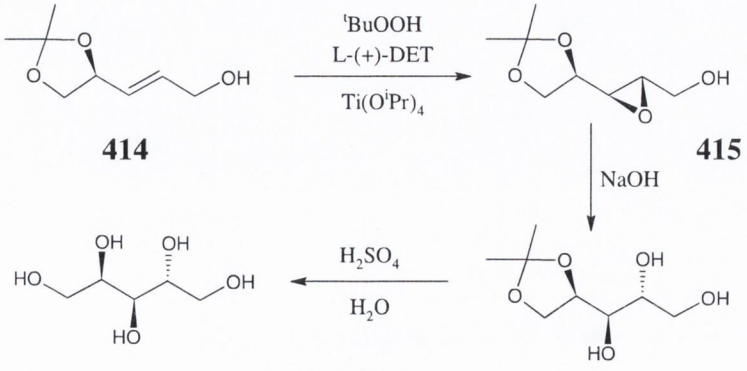

**Scheme 3.6**

Fortunately these mixtures of hemi-acetals can be converted to more easily characterisable alkene derivatives *via* Horner-Wadsworth-Emmons or Wittig reaction.[9,14] The desired target aldehyde **406** was previously prepared by Craig *et al.* in racemic form by additive Pummerer rearrangement of vinyl sulfoxide **411** in trifluoroacetic anhydride, followed by cleavage of the trifluoroacetate esters **412** with methanol and catalytic triethylamine. The aldehyde was charachterised as the unsaturated ester **413** formed by a Wittig reaction with methoxycarbonylmethylenetriphenylphosphorane (**Scheme 3.7**).[14]




**Scheme 3.7**

Previous syntheses of the carbohydrates have typically involved the Sharpless asymmetric epoxidation reaction of allylic alcohols to build up the polyhydroxylated chain.[15] For example, allylic alcohol **414** underwent Sharpless asymmetric epoxidation affording epoxyalcohol **415**. Payne rearrangement followed by hydrolysis gave **416** which on deprotection yielded D-lyxitol **417** (**Scheme 3.8**).



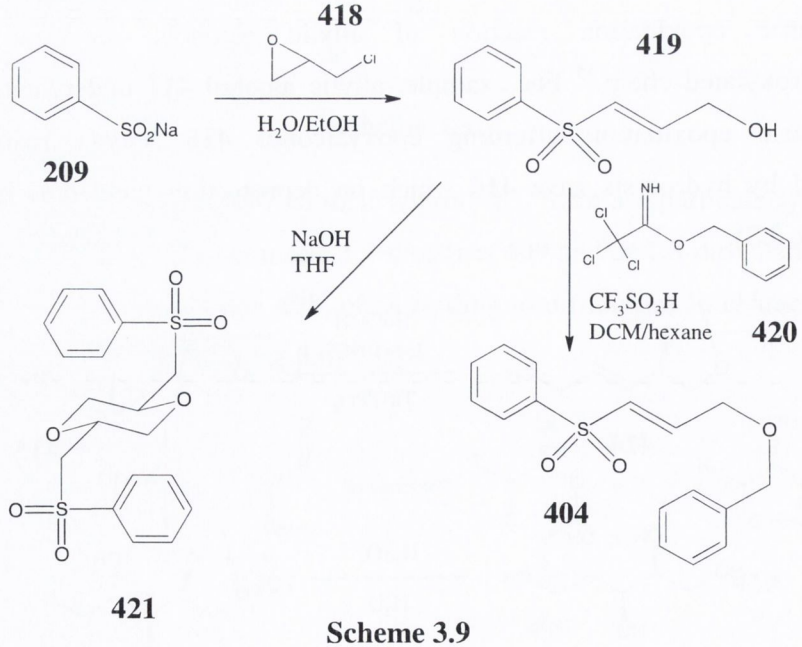

**Scheme 3.8**

## 3.2 Studies on Achiral γ-Functionalised Vinyl Sulfone 404

### 3.2.1 Preparation of γ-Functionalised Vinyl Sulfone 404

The desired vinyl sulfone **404** has been previously reported by Jackson *et al.*[16] Rather than follow the published three-step route to **404** which produces a mixture of *E* and *Z*-isomers, it was decided to prepare **404** in two steps as its pure *E*-isomer by benzyl ether formation of the corresponding free alcohol, itself obtained by reaction of sodium benzenesulfinate **209** with epichlorohydrin.[17] Following this procedure, the γ-hydroxyvinyl sulfone **419** was obtained in 90 % yield exclusively as its (*E*)-isomer. A standard Williamson ether route to the benzyl ether **404** is ruled out on account of the known conversion of the free alcohol **419** to the *bis*-sulfonylmethyl-1,4-dioxane **421** on treatment with base.[14] Indeed, this compound was readily obtained by exposure of **419** to NaOH in THF.

Bundle and co-workers reported that both allyl and benzyl-2,2,2-trichloroacetimidate could be used for the acid-catalysed allylation and benzylation of hydroxyl groups in non-polar solvents.[18] Following this procedure, the desired benzyl ether **404** was prepared by treatment of the alcohol **419** with benzyl-2,2,2-trichloroacetimidate **420** and a catalytic amount of trifluoromethanesulfonic acid in 80 % yield (**Scheme 3.9**).

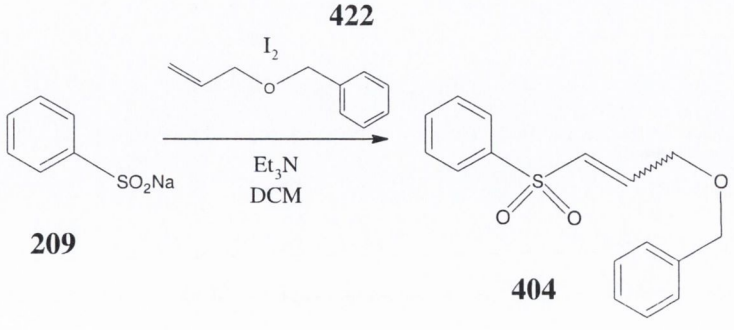



**Scheme 3.9**

The iodosulfonylation reaction constitutes a convenient method for the preparation of vinyl sulfones from the corresponding alkenes in a single step.[19] The ionic or free-radical addition of an arenesulfonyl iodide to an alkene generates an intermediate β-iodosulfone which on treatment with base furnishes vinyl sulfones. The sulfonyl iodide is often generated *in situ* from sodium arenesulfinate and iodine. This method has been employed by Mori *et al.* for the preparation of the toluenesulfonyl analogue of **404**.[20] Subsequently, this route was also examined for the preparation of **404** by iodosulfonylation of allyl benzyl ether.

Initial experiments in which allyl benzyl ether was treated with sodium benzenesulfinate/iodine or sodium p-toluenesulfinate/iodine in $H_2O$/THF mixtures failed to produce synthetically useful yields of the corresponding vinyl sulfone and significant quantities of unreacted allyl benzyl ether were recovered. The use of excess sodium sulfinate (1.5 - 2 equiv.) and iodine (1.5 – 4 equiv.) and prolonged reaction times, or the use of triethylhexylammonium bromide as phase-transfer catalyst did not have any significant effect on the yields of product. The use of methanol as solvent resulted in lower conversions of product.

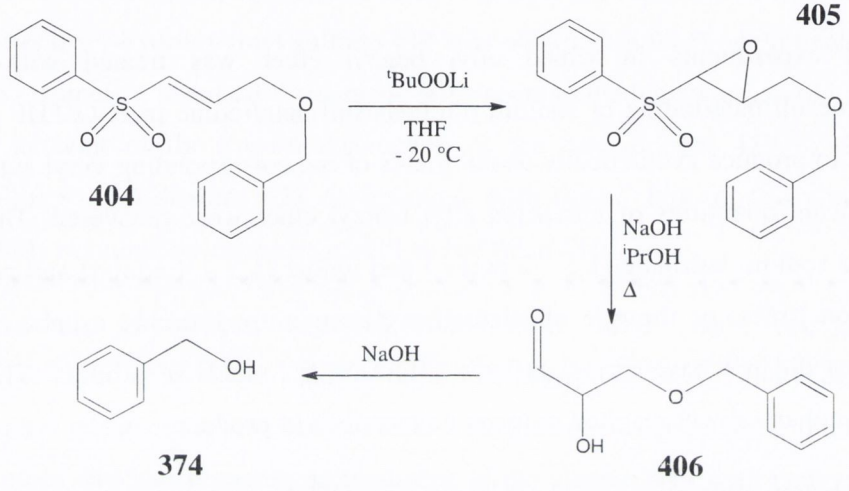
Much better conversions were achieved using DCM as solvent under heterogeneous conditions.[21] A slight modification of the published procedures in which a homogeneous solution of benzenesulfonyl iodide was generated by admixture of a DCM solution of iodine with an aqueous solution of sodium benzenesulfinate prior to addition of allyl benzyl ether **422** gave the best conversions. Using these conditions, **404** was obtained as a 3.6:1 inseparable mixture of *E* and *Z* isomers in 62 % yield following chromatography (**Scheme 3.10**). Attempts to increase the *E*:*Z* ratio by irradiation in the presence of iodine,[22] or by treatment with DABCO[23] met with no success.




**Scheme 3.10**

### 3.2.2 Studies on the Hydrolysis of Sulfonyloxirane 405

The γ-functionalised vinyl sulfone **404** was converted to the known sulfonyloxirane **405** on treatment with lithium *tert*-butylperoxide in THF at – 20 °C. The $^{1}H$ and $^{13}C$ NMR data of **405** were consistent with those reported by Jackson *et al.*[16] When **405** was hydrolysed using NaOH in $^{i}PrOH$ at reflux, benzyl alcohol **374** was obtained as the sole product, presumably arising *via* β-elimination from the target aldehyde **406** formed *in situ* (**Scheme 3.11**).




**Scheme 3.11**

It is clear from this result that milder conditions for the base-catalysed hydrolysis of sulfonyloxirane are necessary. There are few reports in the literature on the hydrolysis of sulfonyloxiranes. Steroid based sulfonyloxiranes were successfully hydrolysed with potassium hydroxide, generated *in situ* by addition of water to potassium *tert*-butoxide in THF.[24] Reaction of these sulfonyloxiranes with hydroxide ion under various other conditions afforded intractable mixtures. Sekiya *et al.* showed that chloromethylsulfonyloxiranes can be hydrolysed by treatment with titanium (IV) chloride in DCM, followed by water.[25]

Treatment of **405** with potassium *tert*-butoxide/water failed to generate any hydroxyaldehyde product and starting material was recovered. The use of Sekiya's procedure[25] gave an intractable mixture whose $^{1}H$ NMR spectrum bore no resemblance to aldehyde **406** or its dioxane/dioxolane dimers.[14] Treatment of this crude product with excess methoxycarbonylmethylenetriphenylphosphorane in benzene at reflux according to the procedure of Craig *et al.*[14] failed to afford the

expected unsaturated ester **413**. The only signals visible in the $^{1}$H NMR spectrum of the crude product were those attributed to the Wittig reagent. Similarly, when **405** was treated with conc. sulfuric acid in THF/water at reflux, an intractable mixture was obtained. Attempted Wittig reaction again failed to generate the ester **413** (see **Scheme 3.7**).

Although the methodologies for sulfonyloxirane hydrolysis were limited to those mentioned above, several methods exist for the ring opening of unfunctionalised oxiranes with water and other nucleophiles under mild conditions.[26] Carbon tetrabromide has recently been found to catalyse the ring opening of epoxides with alcohols and water under mild conditions (60 °C).[27] Various metal salts such as lithium and magnesium perchlorate promote the alcoholysis of epoxides in acetonitrile.[28] Iron (III) chloride was found to catalyse the ring opening of epoxides by alcohols by a one-electron transfer mechanism.[29] Other one-electron transfer agents such as ceric ammonium nitrate[30] and 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ)[31] also catalyse this reaction. Additionally, alumina catalyses the ring opening of epoxides by alcohols and other nucleophiles under very mild conditions.[32]

Application of these various methods to the ring opening of sulfonyloxirane **405** did not lead to any observable products and in each case starting material was recovered quantitatively. Finely powdered lithium hydroxide in THF at 40 °C also failed to generate the aldehyde **406**.

At this stage it was reasoned that the use of a silanolate nucleophile, rather than hydroxide ion, could provide access to the aldehyde **406** in protected form. This method, if successful would allow the isolation of **406** in monomeric form as its silyl ether, which would effectively circumvent the problems associated with dimerisation and water solubility of the unprotected aldehyde. Silanolates have recently been used as masked hydroxide equivalents in iridium-catalysed asymmetric allylic substitution reactions for the enantioselective synthesis of allylic alcohols.[33] Unfortunately, no reaction occurred on treatment of **405** with potassium trimethylsilanolate in either DCM or THF at reflux, even in the presence of magnesium chloride. The results from these various reactions on the hydrolysis of sulfonyloxirane **405** are summarised in **Table 3.1**.

**Table 3.1**

**Studies on the hydrolysis and silanolysis of sulfonyloxirane 405**

| Entry | Reagent | Conditions | Product |
|---|---|---|---|
| 1 | NaOH | $^{i}$PrOH/$H_2O$, reflux, 24 hours | benzyl alcohol |
| 2 | $H_2O$ | KO$^{t}$Bu, THF, 40 °C, 5 days | no reaction[a] |
| 3 | $H_2O$ | $TiCl_4$, DCM, rt, 1 hour | ?[b] |
| 4 | $H_2O$ | $H_2SO_4$, THF, reflux, 72 hours | ?[b] |
| 5 | $H_2O$ | $CBr_4$, THF, 60 °C, 48 hours | no reaction[a] |
| 6 | $H_2O$ | $LiClO_4$, $CH_3CN$, reflux, 48 hours | no reaction[a] |
| 7 | $H_2O$ | $FeCl_3$, $^{t}$BuOH, reflux, 24 hours | no reaction[a] |
| 8 | $H_2O$ | alumina, THF, 60 °C, 72 hours | no reaction[a] |
| 9 | LiOH | THF, 40 °C, 72 hours | no reaction[a] |
| 10 | $Me_3SiOK$ | DCM, reflux, 24 hours | no reaction[a] |
| 11 | $Me_3SiOK$ | $MgCl_2$, THF, reflux, 24 hours | no reaction[a] |

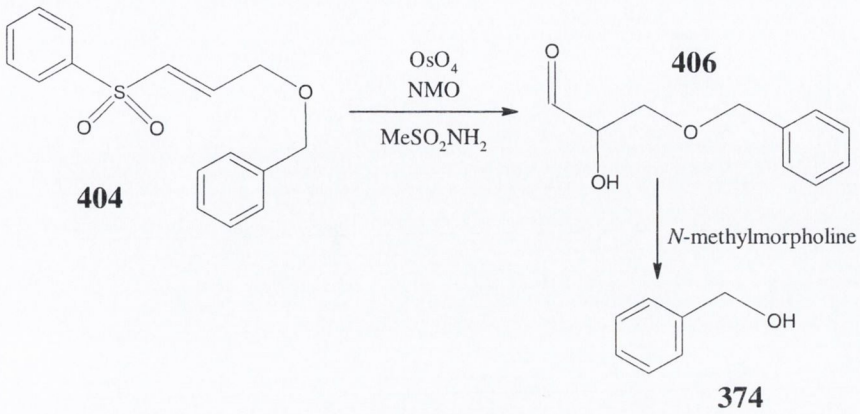
[a] Starting material was recovered. [b] Intractable mixture.

It is clear that a more extensive examination of conditions for the hydrolysis of **405** is required. Development of conditions for the silanolysis of **405** and related oxiranes would be a promising addition to this methodology.

### 3.2.3 Studies on the Dihydroxylation of γ-Functionalised Vinyl Sulfone 404

The non-asymmetric dihydroxylation of vinyl sulfone **404** was initially explored under Upjohn conditions.[34] Treatment of **404** with osmium tetroxide using *N*-methylmorpholine-*N*-oxide as co-oxidant in acetone/$H_2O$ yielded benzyl alcohol as product. As with the hydrolysis of sulfonyloxirane **405**, this result can be rationalised by assuming that the *in situ* formed aldehyde **406** undergoes β-

elimination, presumably catalysed by the spent co-oxidant *N*-methylmorpholine (**Scheme 3.12**).




**Scheme 3.12**

Yamamoto *et al.* reported that potassium hexacyanoferrate(III) could be used as stoichiometric co-oxidant in the dihydroxylation of olefins catalysed by osmium tetroxide, although no examples involving electron deficient olefins were reported.[35] Sulfone **404** was unreactive under these conditions, even on prolonged standing (1 week) and starting material was recovered.

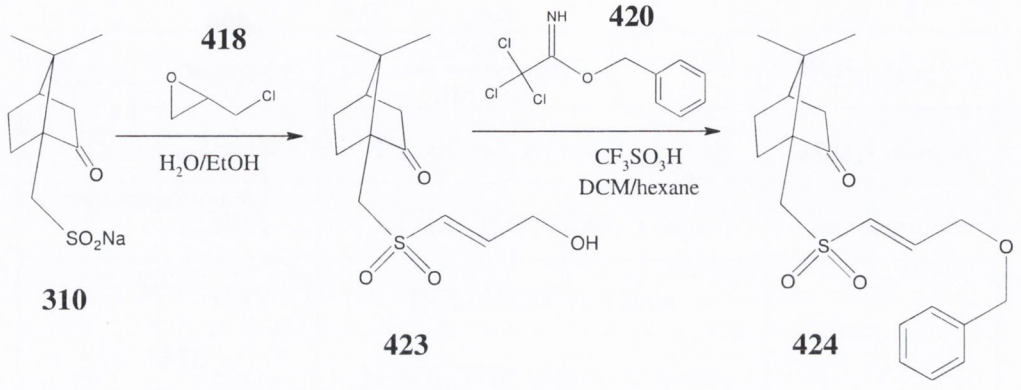
Finally, the Sharpless asymmetric dihydroxylation procedure reported by Evans *et al.*[9] was carried out. No reaction occurred under these conditions, even after 3 weeks and starting material was recovered.

## 3.3 Studies on Chiral Camphorsulfonyl Compound 424

### 3.3.1 Preparation of Chiral Vinyl Sulfone 424

The same two-step procedure which had been employed for the preparation of the achiral vinyl sulfone **404** (see **Scheme 3.8**), was used for the preparation of its chiral camphorsulfonyl analogue from sodium camphorsulfinate **310**. The novel γ-hydroxy vinyl sulfone **423** was prepared in 73 % yield by treatment of sodium camphorsulfinate **310** with epichlorohydrin according to the published procedure.[17] A higher overall yield was obtained when an excess (2 equiv.) of epichlorohydrin was used. Jackson *et al.* had obtained the phenylsulfonyl compound **419** by treatment of sodium benzenesulfinate with epichlorohydrin in $H_2O$/DMF at

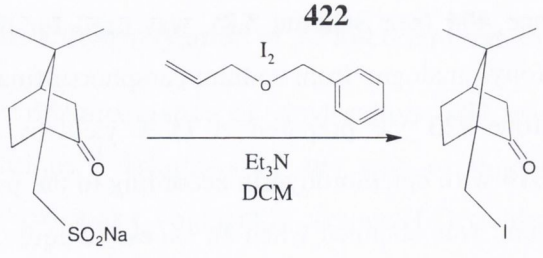
reflux.[36] This procedure was employed for the preparation of **423** in comparable yield. The free alcohol **423** was subsequently converted into its benzyl ether **424** using benzyl-2,2,2-trichloroacetimidate under acidic conditions (**Scheme 3.13**).




**Scheme 3.13**

The $^{1}H$ NMR spectrum of **424** was characterised by the appearance of a pair of double triplets at δ 6.85 and 6.92 ppm, corresponding to the α and β vinylic protons respectively. The allylic methylene protons gave rise to a double doublet at δ 4.24 ppm while the methylene protons adjacent to sulfur appeared as a pair of doublets at δ 2.86 and 3.45 ppm. The $^{1}H$ and $^{13}C$ NMR details of **424** are summarised in **Table 3.2**.

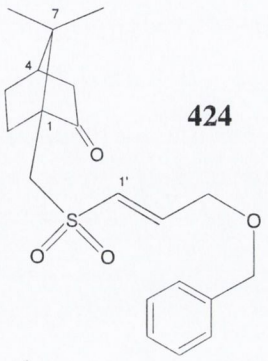
The modified iodosulfonylation procedure which had been successfully used for the preparation of **404** was examined for the preparation of **424** from sodium camphorsulfinate **310**. Surprisingly, the only products obtained from this reaction were 10-iodocamphor **425** and recovered allyl benzyl ether (**Scheme 3.14**). The mechanism of this transformation and the implication of this result for the preparation of the 10-halocamphors will be discussed in detail in Chapter 4, section 4.4.




**Scheme 3.14**

**Table 3.2**

**NMR spectroscopic details for vinyl sulfone 424 in $CDCl_3$**




**424**

| $^1$H (ppm) | Multiplicity (Hz) | $^{13}$C (ppm) | Assignment |
|---|---|---|---|
| 1.09 | s | 19.2 | 7-$CH_3$ |
| 0.87 | s | 19.3 | 7-$CH_3$ |
| not assigned | - | 24.3 | C-5 |
| not assigned | - | 26.6 | C-6 |
| 2.12 | t, *J* 4.5 | 42.0 | C-4 |
| 1.93 | d, *J* 18.5 | 42.1 | C-3 |
| 2.38 | dt, *J* 18.5, 4.5 | | |
| - | - | 47.9 | C-7 |
| 2.86 | d, *J* 15.0 | 51.3 | $CH_2SO_2$ |
| 3.45 | d, *J* 15.0 | | |
| - | - | 58.2 | C-1 |
| 4.24 | dd, *J* 3.0, 1.5 | 67.1 | C-3' |
| 4.60 | s | 72.5 | benzyl $CH_2$ |
| 7.31-7.38 | m | 127.2 | Ar C-3 |
| 7.31-7.38 | m | 127.5 | Ar C-4 |
| 7.31-7.38 | m | 128.0 | Ar C-2 |
| 6.85 | dt, *J* 15.0, 1.5 | 129.9 | C-1' |
| - | - | 136.9 | Ar C-1 |
| 6.92 | dt, *J* 15.0, 3.0 | 142.7 | C-2' |
| - | - | 214.3 | C-2 |

### 3.3.2 Studies on the Nucleophilic Epoxidation of Chiral Vinyl Sulfone 424

A number of studies was carried out on the nucleophilic epoxidation of **424** in order to probe the diastereoselectivity of the reaction and to examine the feasibility of employing the camphorsulfonyl group as a chiral auxiliary for the asymmetric

synthesis of 3-*O*-benzylglyceraldehyde and related α-functionalised aldehydes. Initial experiments conducted on a small scale using excess (4 equiv.) lithium *tert*-butylperoxide in THF gave the product sulfonyloxiranes **426** as 1:1 mixtures of diastereomers, as determined by $^1$H NMR. The diastereomers of **426** could not be separated by column chromatography. When the reaction was conducted on a larger scale using a smaller excess (3 equiv.) of lithium *tert*-butylperoxide, a 5.8:1 ratio of diastereomers was obtained (**Scheme 3.15**). The $^1$H NMR spectrum of this mixture is shown in **Figure 3.1**.

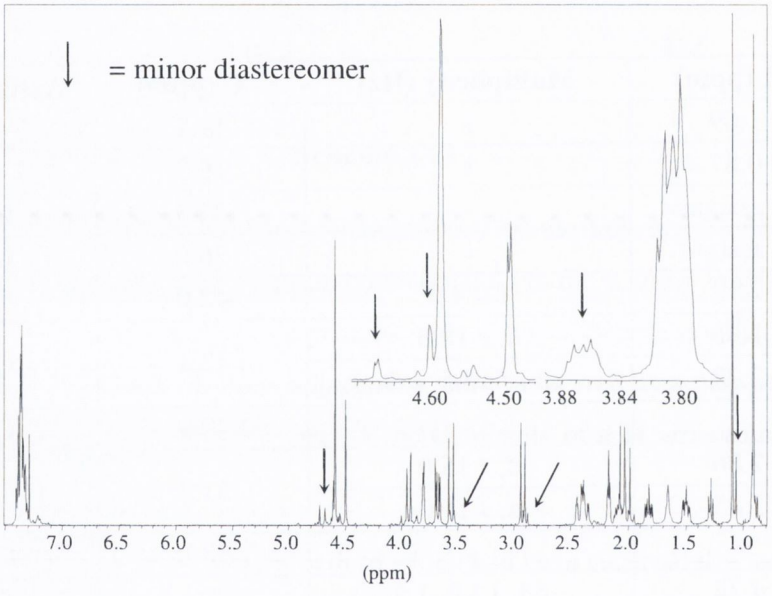
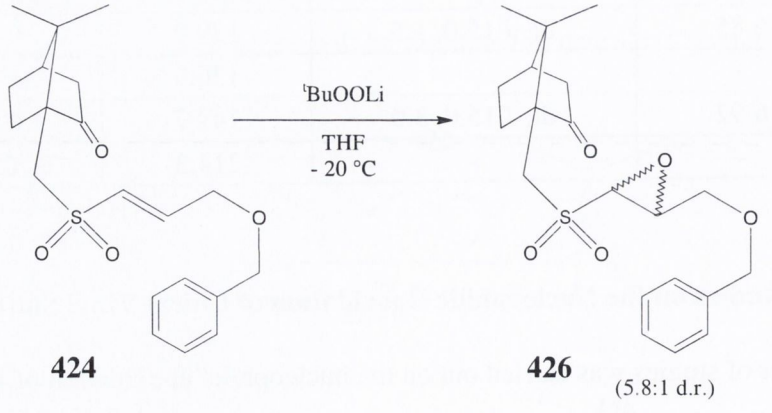



**Figure 3.1**

**$^1$H NMR spectrum of diastereomeric sulfonyloxiranes 426 in $CDCl_3$**

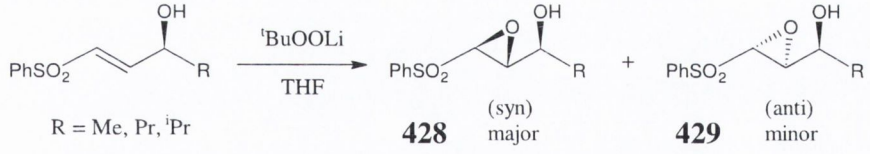



**424** **426** (5.8:1 d.r.)

**Scheme 3.15**

This result was broadly duplicated in a subsequent experiment under the same conditions, giving a diastereomeric ratio of 5.1:1. In another experiment using two equivalents of reagent, a 2.1:1 diastereomer ratio was obtained. The diastereomers of **426** were recovered in poor yield (45 %) following chromatography. No side-products arising from Baeyer-Villiger reaction of the carbonyl group were observed.

The origins of this variable diastereoselectivity in the Meth-Cohn epoxidation of **424** are unclear. Most examples of diastereoselective epoxidation of chiral electron deficient olefins involve substrates bearing allylic asymmetric centres. The observed diastereoselectivity is then influenced by a number of factors, including the conformational preferences of the substrate, coordination and solvent effects and the steric bulk and metal counter ion used in the epoxidising reagent. For example, Jackson *et al.* observed high *syn*-diastereoselectivity in the nucleophilic epoxidation of sulfones **427** using lithium *tert*-butylperoxide in THF.[37] This result is ascribed to coordination of the lithium ion of the reagent to the allylic oxygen prior to delivery of the oxygen atom to the olefin (**Scheme 3.16**). Exclusive *syn*-diastereoselectivity was also observed in the epoxidation of enantiomerically pure γ-hydroxy-1-arylthio-1-nitroalkenes.[38]




R = Me, Pr, $^{i}$Pr

**427**

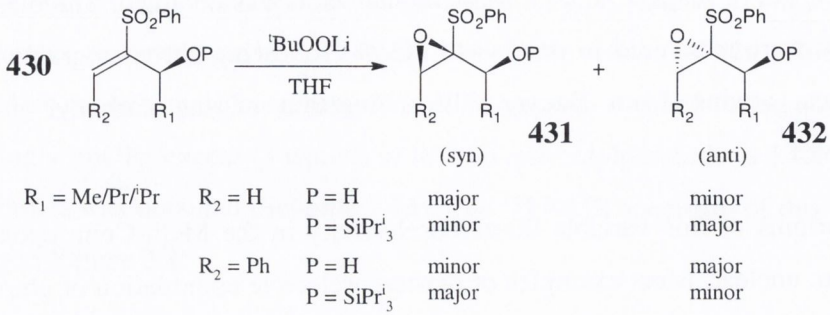
**428** (syn) major

**429** (anti) minor

**Scheme 3.16**

Similarly, epoxidation of sulfone **430** ($R_2$ = H) gave the *syn*-oxiranes **431** as the major diastereomers (P = H). In contrast, epoxidation of the silyl ethers gave predominantly the *anti*-oxiranes **432** (P = $SiPr^{i}_3$), a result attributed to approach of the reagent from the opposite face of the protecting group, rather than prior coordination to the allylic oxygen.[39] When the substrates contained a bulky β-substituent ($R_2$ = Ph), 1,3-allylic strain[40] changes the conformational preference resulting in a reversal of the diastereoselectivity. Thus the free alcohol (P = H) gave the *anti*-oxirane **432** selectively while the silyl ether (P = $SiPr^{i}_3$) gave the *syn*-

oxirane **431**. These effects of competing 1,2 vs. 1,3-allylic strain are also observed in the corresponding vinyl sulfoxides[41] (**Scheme 3.17**).




**Scheme 3.17**

Variations in the extent of *syn*-diastereoselectivity were observed by Jackson *et al.* in the epoxidation of γ-oxygenated vinylsulfoximines depending on the steric bulk of the reagent ($^t$BuOOH v $Ph_3COOH$) and the metal counter ion used ($Li^+$ v $Na^+$ v $K^+$), with the highest selectivities being observed with lithium triphenylmethyl peroxide.[42]

Although sulfone **424** possesses a γ-oxygen substituent, it is too distant from the chirality of the auxiliary. A chelation model **433** in which the lithium ion coordinates to the carbonyl oxygen and the sulfone oxygen prior to epoxidation, as in **Figure 3.2** could account for the observed results.

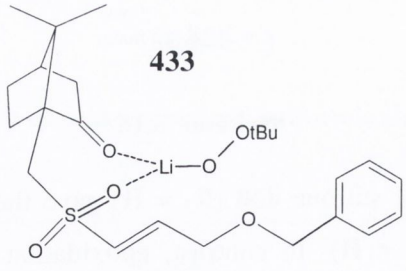



**Figure 3.2**

**Possible mode of chelation 433 between lithium *tert*-butyl peroxide and vinyl sulfone 424**

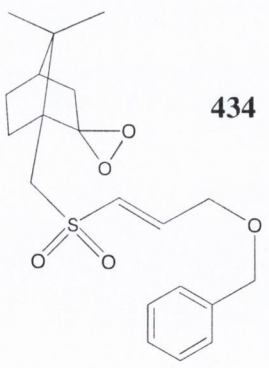
In order to verify if coordination and/or hydrogen bonding effects were responsible for the diastereoselectivity observed in the epoxidation of **424**, the reaction was carried out in toluene, a solvent in which the effects of coordination would be

expected to be enhanced. Higher levels of *syn*-diastereoselectivity were observed by Jackson *et al.* in the nucleophilic epoxidation of γ-oxygenated-1-arylthio-1-nitroalkenes with lithium *tert*-butylperoxide when toluene was used as the solvent rather than THF.[43] In the event, epoxidation of **424** in toluene gave a 1:1 mixture of diastereomers, suggesting that coordination and/or hydrogen bonding effects were not responsible for the diastereoselectivity observed in THF.

The epoxidation of **424** in THF was then carried out using lithium triphenylmethyl peroxide, a more sterically bulky reagent which would be expected to give higher levels of diastereoselectivity compared to lithium *tert*-butylperoxide.[44] Surprisingly, a 1:1 mixture of diastereomers was obtained with this reagent, a result which contrasts with that obtained using lithium *tert*-butylperoxide.

The epoxidations in THF were carried out in the presence of Lewis acids in an attempt to enforce chelation control by coordination of the carbonyl and sulfone oxygens to the Lewis acid. With magnesium chloride or titanium (IV) isopropoxide as Lewis acids, 1:1 diastereomer ratios were obtained. No reaction occurred when titanium (IV) chloride was used as the Lewis acid.

The epoxidation of **424** was also carried out under classical Weitz-Scheffer conditions, using alkaline hydrogen peroxide.[45] Again, a 1:1 ratio of diastereomers was observed on treatment of **424** with sodium hydroperoxide in acetone. Attempts to epoxidise **424** intramolecularly by *in situ* conversion of the auxiliary into a dioxirane **434** using either oxone/acetonitrile[46] or hydrogen peroxide/acetonitrile[47] were unsuccessful and starting material was recovered (**Figure 3.3**).




**434**

**Figure 3.3**

**Chiral dioxirane 434 derived from vinyl sulfone 424**

This lack of reactivity of vinyl sulfones toward electrophilic epoxidising reagents was also observed by Evans *et al.*[48] The results of these studies on the nucleophilic epoxidation of vinyl sulfone **424** are summarised in **Table 3.3**.

**Table 3.3**

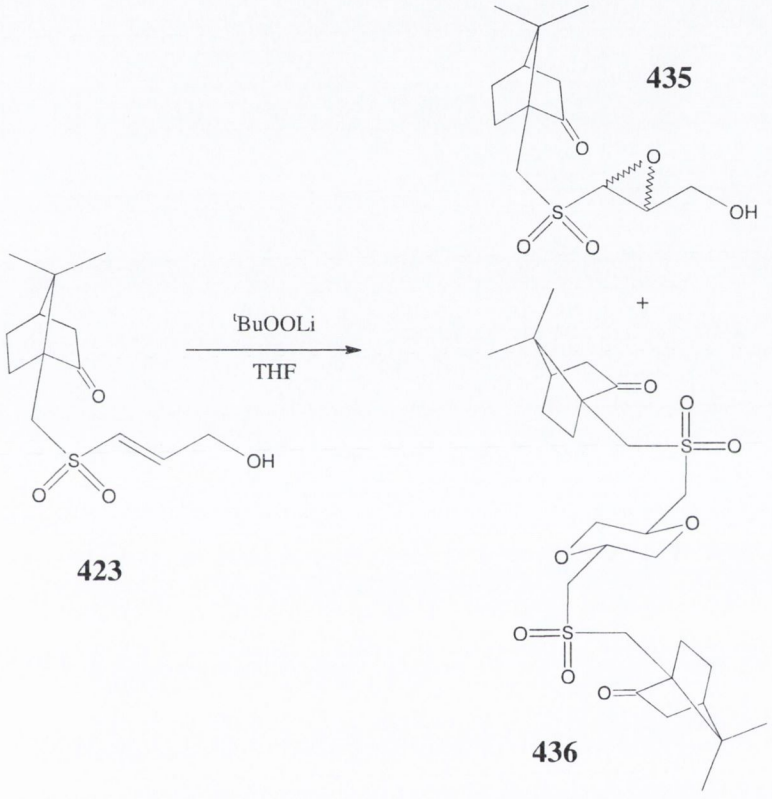
**Studies on the nucleophilic epoxidation of vinyl sulfone 424**

| **Diastereomer ratio of 426**[a] | **Reagent (equivalents)** | **Solvent** | **Conditions** |
|---|---|---|---|
| 1 : 1 | $^t$BuOOLi (4) | THF | - 20 °C, 3 hrs |
| 5.8 : 1 | $^t$BuOOLi (3) | THF | - 20 °C, 3 hrs |
| 2.1 : 1 | $^t$BuOOLi (2) | THF | - 20 °C, 2.5 hrs |
| 1 : 1 | $Ph_3COOLi$ (2) | THF | - 20 °C, 6 hrs |
| 1 : 1 | $^t$BuOOLi (3) | toluene | - 20 °C, 4 hrs |
| 1 : 1 | $^t$BuOOLi (4) | THF | $Ti(O^iPr)_4$, - 20 °C, 2 hrs |
| 1 : 1 | $^t$BuOOLi (4) | THF | $MgCl_2$, - 20 °C, 2.5 hrs |
| 1 : 1 | HOONa (3) | acetone | 40 °C, 3 hrs |
| no reaction[b] | oxone (4) | $CH_3CN/H_2O$ | $NaHCO_3$, rt, 24 hrs |
| no reaction[b] | $H_2O_2$ (4) | $CH_3CN/H_2O$ | $K_2CO_3$, rt, 48 hrs |

[a] determined from $^1$H NMR of crude product. [b] starting material was recovered.

A brief study was also carried out on the nucleophilic epoxidation of the free alcohol **423**. Under standard Meth-Cohn conditions, **423** afforded the corresponding sulfonyloxirane **435** as a 4.7:1 mixture of diastereomers, as judged by $^1$H NMR. The diastereomers were inseparable by chromatography and were recovered in very low yield (15 %). The possibility that the unprotected hydroxyl

group of **435** undergoes Payne rearrangement may account for the low yield of the oxirane.[49] A significant quantity of the bis-camphorsulfonylmethyl-1,4-dioxane **436** was obtained as a pair of diastereomers (ca. 1:1 d.r.) from the crude reaction product (although not enough to account for the poor yields of the oxiranes). This is clearly formed by intermolecular Michael addition of the oxyanion of **423** formed under the basic conditions of the epoxidation reaction (**Scheme 3.18**).




**Scheme 3.18**

The $^{1}H$ NMR spectrum of the diastereomers of sulfonyloxirane **435** is shown in **Figure 3.4**. Following a complete spectroscopic analysis of the dioxane **436** ($^{1}H$, $^{13}C$, $^{1}H$-$^{1}H$ and $^{13}C$-$^{1}H$ COSY), its structure and conformation were assigned as being *trans*-diequatorial at the dioxane ring for both diastereomers, on the basis of the large coupling constant (11.5 Hz) observed between the *trans*-diaxial protons for each diastereomer. A coupling constant of 10.5 Hz was observed between these protons for the corresponding phenylsulfonyl compound **421** (**Figure 3.5**).

As with its benzyl ether, the diastereoselection observed in the epoxidation of **423** is unlikely to be controlled by coordination of the lithium ion to the allylic hydroxyl

group. A possible explanation involves participation of the carbonyl group of the auxiliary in the mechanism of the epoxidation reaction. The sulfonyl carbanion formed on Michael addition of the reagent to the double bond of either **423** or its benzyl ether **424** could cyclise with the auxiliary, forming a tricyclic oxyanion

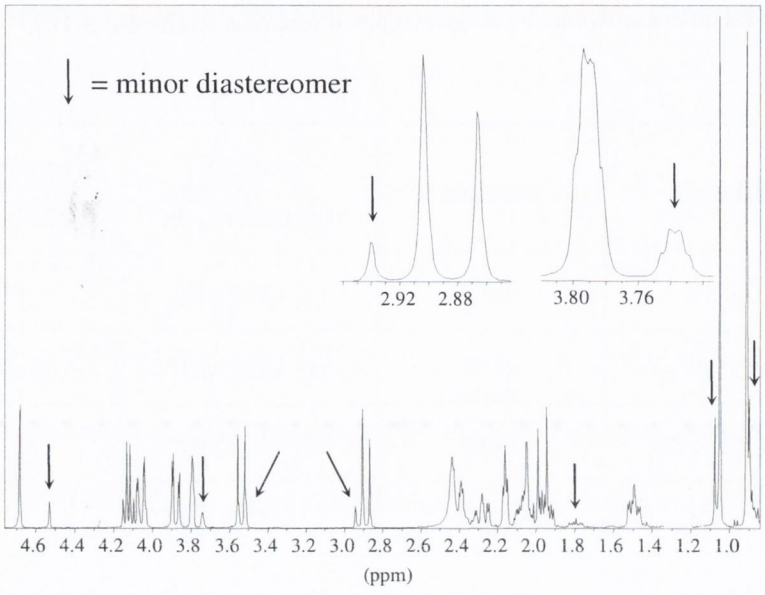
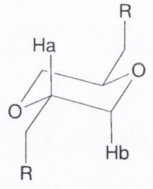



**Figure 3.4**

**$^1$H NMR spectrum of diastereomeric sulfonyloxiranes 435 in $CDCl_3$**




**437**

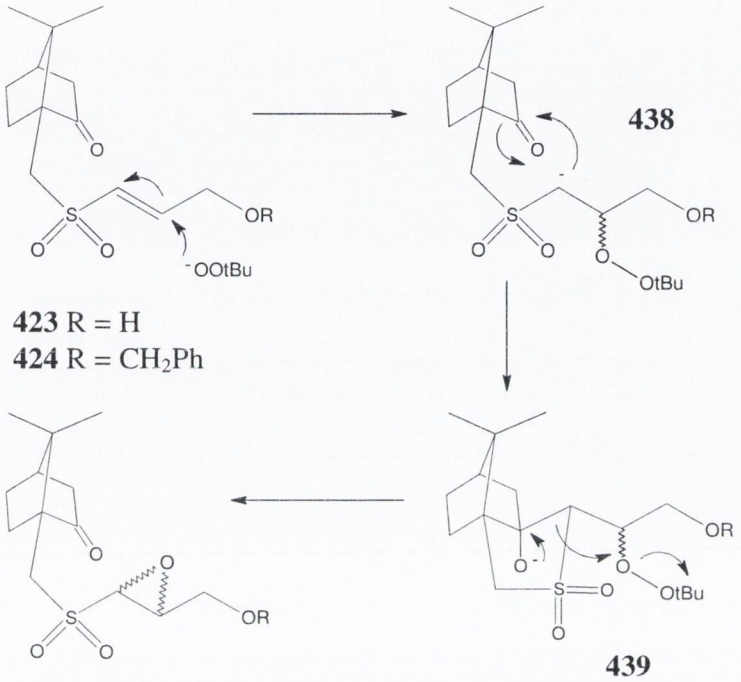
R = Phenylsulfonyl: $J_{Ha\text{-}Hb}$ = 10.5 Hz

R = 10-Camphorsulfonyl: $J_{Ha\text{-}Hb}$ = 11.5 Hz

**Figure 3.5**

**Vicinal coupling constants between *trans*-diaxial protons in 1,4-dioxane's 421 and 436**

intermediate **439** as one of two possible diastereomers (assuming attack of the sulfonyl carbanion on the carbonyl group is stereospecific, as was observed with the allyl/benzyl sulfones discussed in Chapter 2). Collapse of this intermediate and subsequent elimination of lithium *tert*-butoxide affords the oxiranes (**Scheme 3.19**).




**423** R = H
**424** R = $CH_2Ph$

**435** R = H
**426** R = $CH_2Ph$

**Scheme 3.19**

The conformational lock imposed in intermediate **439** may serve to destabilise one of these intermediates relative to its epimer, or it may be that only one of the diastereomeric sulfonyl carbanions cyclises to form **439**, whilst the other undergoes more rapid "background" epoxidation without participation of the carbonyl group. Under conditions of kinetic control, this would lead to the major diastereomer, whilst epoxidation *via* the tricyclic intermediate **439** would eventually give rise to the minor diastereomer.

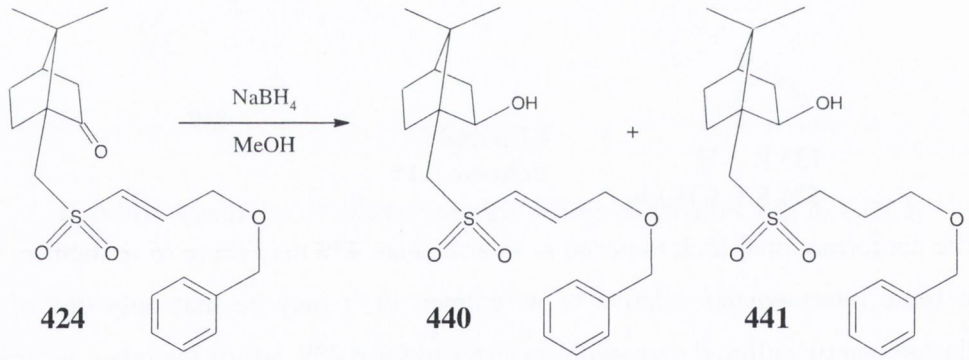
In order to shed more light on the role of the camphor auxiliary in the nucleophilic epoxidation of **424**, the epoxidation of the isobornyl derivative of **424**, formed by reduction of its carbonyl group, was next studied.

## 3.4 Studies on Chiral Isobornylsulfonyl Compound 440

### 3.4.1 Preparation of Chiral Vinyl Sulfone 440

Following on from the above studies on the camphorsulfonyl compound **424**, the Meth-Cohn epoxidation of its isobornylsulfonyl derivative was subsequently examined. Although removal of the carbonyl group would provide a probe as to its influence in the epoxidation reaction, the presence of a hydroxyl group could provide the possibility of coordination-controlled diastereoselection.

Accordingly, sulfone **424** was reduced with sodium borohydride in methanol to afford two products, the desired vinyl sulfone **440**, together with the saturated alkyl sulfone **441** formed by reduction of the double bond of **440**. Both products were separated by chromatography. No traces of the corresponding bornylsulfonyl (*endo*-) isomers were detected in the crude product or in the purified material (**Scheme 3.20**).

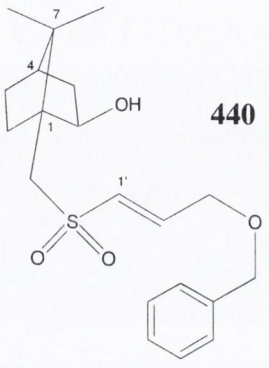



**Scheme 3.20**

The $^{1}H$ NMR spectrum of vinyl sulfone **440** was characterised by the appearance of a double doublet at δ 4.18 ppm assigned to the *endo*-methine proton at C-2, as well as by a pair of double triplets at δ 6.75 and 6.98 ppm corresponding to the vinylic protons. The methylene protons adjacent to sulfur appeared as a pair of doublets at δ 2.86 and 3.41 ppm. The $^{1}H$ and $^{13}C$ NMR details of **440** are summarised in **Table 3.4**.

**Table 3.4**

**NMR spectroscopic details for vinyl sulfone 440 in $CDCl_3$**




**440**

| $^1$H (ppm) | Multiplicity (Hz) | $^{13}$C (ppm) | Assignment |
|---|---|---|---|
| 1.08 | s | 19.3 | 7-$CH_3$ |
| 0.82 | s | 20.0 | 7-$CH_3$ |
| not assigned[a] | - | 27.0 | C-5 |
| not assigned[a] | - | 30.2 | C-6 |
| not assigned[a] | - | 38.5 | C-3 |
| not assigned[a] | - | 43.6 | C-4 |
| - | - | 48.6 | C-7 |
| - | - | 50.3 | C-1 |
| 2.86 | d, *J* 13.5 | 53.7 | $CH_2SO_2$ |
| 3.41 | d, *J* 13.5 | | |
| 4.27 | dd, *J* 3.0, 2.0 | 67.0 | C-3' |
| 4.62 | s | 72.8 | benzyl $CH_2$ |
| 4.18 | dd, *J* 8.0, 4.0 | 75.8 | C-2 |
| 7.28-7.43 | m | 127.2 | Ar C-3 |
| 7.28-7.43 | m | 127.6 | Ar C-4 |
| 7.28-7.43 | m | 128.1 | Ar C-2 |
| 6.75 | dt, *J* 15.0, 2.0 | 128.9 | C-1' |
| - | - | 136.6 | Ar C-1 |
| 6.98 | dt, *J* 15.0, 3.0 | 143.8 | C-2' |

[a] Five of the isobornyl ring protons form an overlapping multiplet at δ 1.68-1.84.

The saturated sulfone **441** was characterised by a triplet at δ 3.62 ppm corresponding to the methylene protons adjacent to the ether oxygen and an apparent double doublet at δ 3.19 ppm for the propyl methylene protons adjacent to sulfur. The β-methylene protons appeared as a complex multiplet at δ 2.14-2.21 ppm.

The conditions of the above reaction were varied in order to minimise formation of the over-reduced compound **441**. In general, it was found that when less than 4 equivalents of sodium borohydride were used, the reaction favoured the vinyl sulfone **440** over the saturated sulfone **441** but did not go to completion and substantial amounts of starting material **424** were recovered. Raising the reaction temperature from ambient temperature to 40 °C resulted in substantial over-reduction to **441** even when less reductant (1.5 equiv.) was used.

It was reasoned that an electrophilic reductant would be more chemoselective in the reduction of **424**. Diisobutylaluminum hydride[50] was subsequently examined for the reduction of **424**. The use of 1.1 equivalents in THF gave the vinyl sulfone **440** together with a significant amount of starting material. Prolonging the reaction time had no effect on the extent of reaction. Surprisingly, when 1.8 equivalents were used, substantial amounts of the over-reduced sulfone **441** were also obtained, with complete consumption of starting material **424**. In summary, both reagents proved unselective in the reduction of **424**, and no further studies were carried out. The results of these studies on the reduction of **424** are summarised in **Table 3.5**.

### 3.4.2 Studies on the Nucleophilic Epoxidation of Chiral Vinyl Sulfone 440

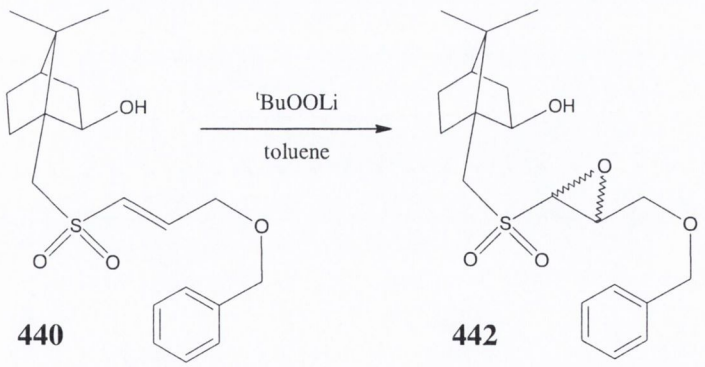
A brief study was carried out on the nucleophilic epoxidation of **440**. Toluene was chosen as the solvent on account of the previously mentioned precedent for enhanced coordination controlled diastereoselection in the Meth-Cohn epoxidation in toluene compared to THF.[43] The reaction of **440** with lithium *tert*-butylperoxide in toluene was extremely slow, taking over 48 hrs to reach completion. The product oxiranes **442** were isolated in excellent yield (95 %) as a 1:1 mixture of diastereomers following chromatography (**Scheme 3.21**). The $^{1}$H NMR spectrum of the mixture of oxiranes **442** is shown in **Figure 3.6**.

**Table 3.5**

**Studies on the reduction of vinyl sulfone 424**

| Ratio of 440 : 441[a] | Reagent (equivalents) | Conditions | Extent of reaction[c] |
|---|---|---|---|
| 1.38 : 1 | $NaBH_4$ (4) | MeOH, rt, 3.5 hrs | complete |
| 1 : 0[b] | $NaBH_4$ (1) | MeOH, 0 °C, 2 hrs | incomplete |
| 1 : 2.2 | $NaBH_4$ (1.5) | MeOH, 40 °C, 5 hrs | incomplete |
| 1.5 : 1 | $NaBH_4$ (2) | MeOH, rt, 2 hrs | incomplete |
| 1 : 0[b] | DIBAL-H (1.1) | THF, 0 °C – rt, 2.5 hrs | incomplete |
| 1 : 1.6 | DIBAL-H (1.8) | THF, 0 °C – rt, 5 hrs | complete |
| 3.2 : 1 | DIBAL-H (1.2) | THF, 0 °C – rt, 21 hrs | incomplete |
| 2.6 : 1 | DIBAL-H (1.1) | DCM, - 20 °C – rt, 29 hrs | incomplete |

[a] As judged by $^1$H NMR. [b] None of **441** detected. [c] As judged by presence/absence of starting material in $^1$H NMR.




**440** **442**

(1:1 d.r.)

**Scheme 3.21**

This result appears to support the hypothesis that the carbonyl group was the causative factor in the diastereoselection observed in the epoxidation of the ketone **424** in THF, although the reaction is clearly sensitive to the conditions. The lack of

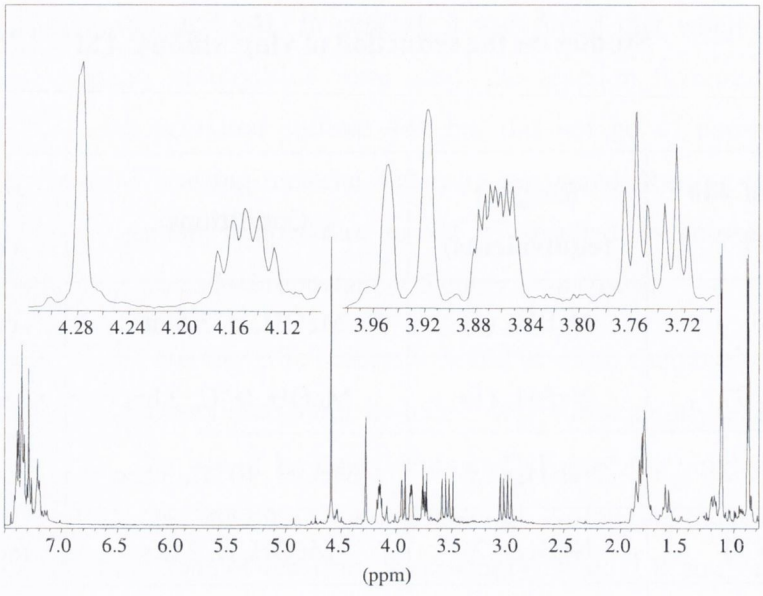
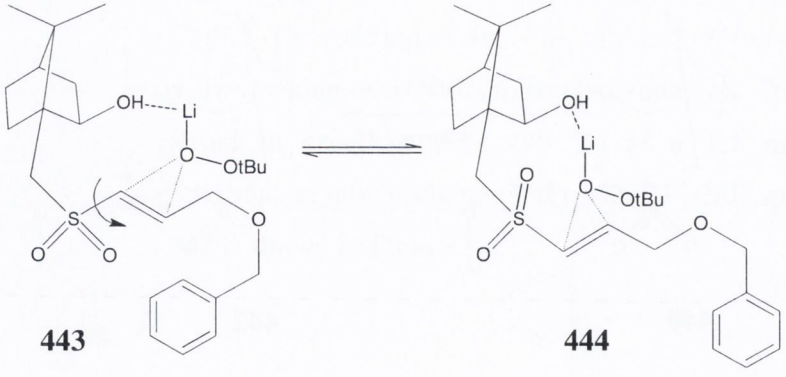



**Figure 3.6**

**$^1$H NMR spectrum of diastereomeric sulfonyloxiranes 442 in $CDCl_3$**

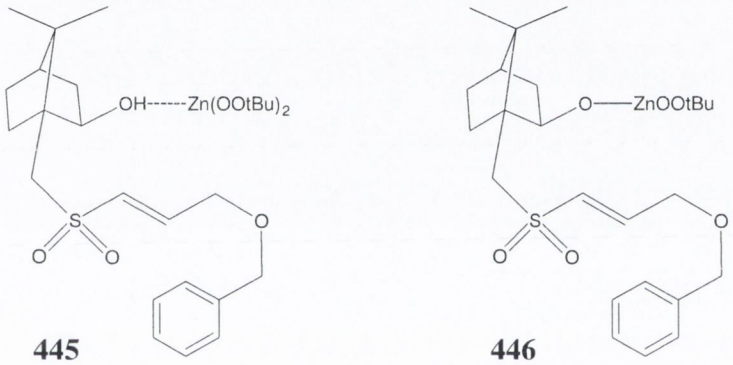
diastereoselection observed in the epoxidation of the alcohol **440** in toluene does not necessarily indicate that no coordination occurred between the lithium ion and the hydroxyl group. Coordinatio could have occurred, but lack of rotamer control in the sulfonyl side-chain may lead to the observed lack of diastereoselection (**Scheme 3.22**).




**Scheme 3.22**

Other metal-based epoxidising methods were subsequently examined in an attempt to make use of the hydroxyl group in **440**. Enders *et al.* reported that enones underwent asymmetric epoxidation on treatment with diethylzinc/oxygen in the

presence of *N*-methylpseudoephedrine.[51] The epoxidising reagent is apparently a chiral alkoxy(ethylperoxy)zinc species derived from reaction of the chiral alcohol with diethylzinc followed by insertion of molecular oxygen into the carbon-zinc bond. Additionally, Jackson *et al.* found that a chirally modified magnesium *tert*-butylperoxide derived from (+)-diethyl tartrate or from (+)-di-*tert*-butyl tartrate and dibutylmagnesium epoxidised enones with excellent enantioselectivities.[52] The possibility that the hydroxyl group of sulfone **440** could be tethered to a magnesium or zinc peroxide species, either by coordination as in **445**, or by deprotonation as in **446** prior to intramolecular epoxidation, prompted a study of the reaction between **440** and the zinc salt of *tert*-butylhydroperoxide (**Figure 3.7**).[53]




**445** **446**

**Figure 3.7**

**Possible modes of interaction between zinc *tert*-butyl peroxide species and sulfone 440**

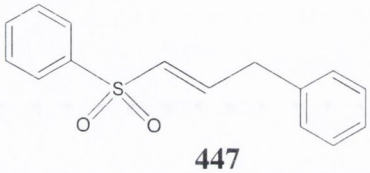
Addition of diethylzinc to a toluene solution of **440**, followed by addition of *tert*-butylhydroperoxide failed to afford any product however, and starting material was recovered. A subsequent experiment in which diethylzinc (1 equiv.) was added to a toluene solution of *tert*-butylhydroperoxide (2 equiv.) prior to addition of **440**, also failed to proceed and starting material was again recovered. Based on these results, the above reactions were not repeated using dibutylmagnesium.

Finally, the possibility of coordinating a titanium peroxide species to **440**, akin to the Sharpless asymmetric epoxidation of allylic alcohols, was examined.[54] However, no reaction occurred on treatment of **440** with titanium (IV) isopropoxide/*tert*-butylhydroperoxide under standard Sharpless conditions, even on prolonged standing (7 days) at room temperature. This result is not surprising in

view of the previously mentioned non-reactivity of vinyl sulfones toward electrophilic epoxidising reagents.

## 3.5 Studies on Achiral Unfunctionalised Vinyl Sulfone 447

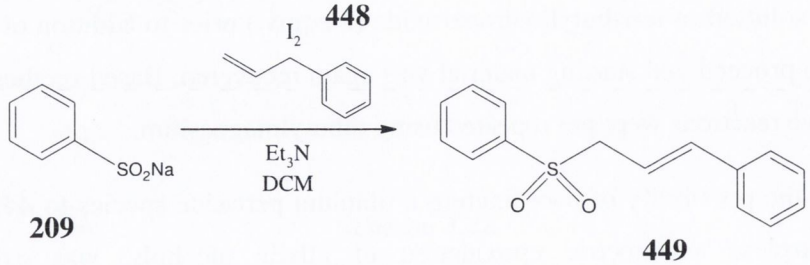
The β-elimination of benzyl alcohol observed in the hydrolysis of sulfonyloxirane **405** (see section 3.2.2) and in the Upjohn dihydroxylation of γ-functionalised vinyl sulfone **404** (see section 3.2.3) prompted a new study on a vinyl sulfone which lacks oxygen functionality in the γ-position. For these studies, sulfone **447** was chosen as the target, accessible in principle by iodosulfonylation of allyl benzene.



**447**

### 3.5.1 Preparation of Vinyl Sulfone 447

The modified iodosulfonylation procedure which had been successfully applied to the synthesis of the γ-functionalised vinyl sulfone **404** (see section 3.2.1) was examined for the synthesis of **447**. Iodosulfonylation of allyl benzene **448**, followed by treatment of the intermediate β-iodosulfone with triethylamine yielded the known allylic isomer **449**, presumably formed by deconjugation of the vinyl sulfone formed *in situ* (**Scheme 3.23**). The spectroscopic details of **449** were identical to those already published.[55]



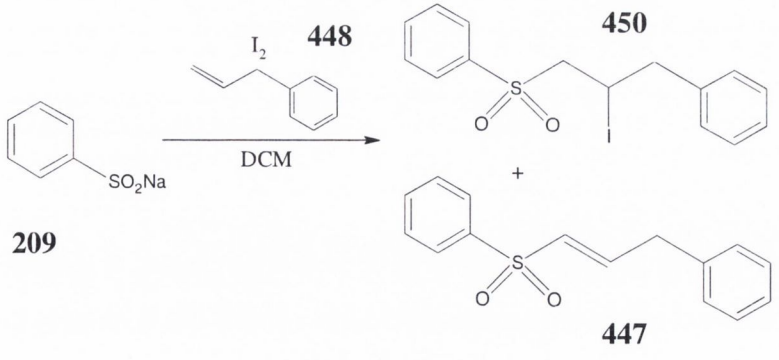

**209** **449**

**Scheme 3.23**

In order to determine if there was a sufficient time window within which the vinyl sulfone **447** could be isolated from the reaction mixture prior to its isomerisation to

the allyl isomer **449**, the reaction was repeated with the modification that immediately after the addition of triethylamine, the reaction mixture was divided into six equal portions. Each of these was worked up after different time intervals; 5 mins, 15 mins, 30 mins, 1 hour, 2 hours and 4 hours. The $^1$H NMR spectra of the crude products from each aliquot were analysed for the presence of the vinyl and allyl isomers **447** and **449**, as well as the intermediate β-iodosulfone. The results of this experiment showed that the β-iodosulfone was completely consumed after 4 hours exposure to triethylamine, by which time the proportion of the allyl isomer **449** exceeded that of the vinyl isomer **447** (ca. 1.3:1 ratio). After 2 hours, more of the vinyl isomer **447** was present (ca. 1.5:1 ratio of **447**:**449**), although a significant quantity of β-iodosulfone remained. The vinyl isomer becomes visible after 15 mins. Deconjugation of **447** to its allyl isomer becomes visible after only 30 mins, by which time only a small amount of the β-iodosulfone had reacted. These results indicate that the desired vinyl sulfone **447** undergoes base-catalysed deconjugation as it is formed, and so triethylamine is an unsuitable base for its preparation.

An NMR study was subsequently carried out on the β-iodosulfone intermediate in order to identify suitable bases for the preparation of **447**. The intermediate β-iodosulfone **450** was prepared by iodosulfonylation of allyl benzene **448** without exposure to base. Iodosulfone **450** was isolated in 71 % yield following chromatography, together with a small amount of the vinyl sulfone **447**, presumably formed by spontaneous elimination during column chromatography (**Scheme 3.24**).




**Scheme 3.24**

In order to slow down the deconjugation step, it was deemed necessary to choose bases with a lower pKa than triethylamine (pKa = 10.75).[56] Four bases were examined in this study; pyridine (pKa = 5.23), imidazole (pKa = 6.99) and *N*-methylmorpholine (pKa = 7.38).[56] Diisopropylamine (pKa = 11.05) was also examined on account of its steric hindrance. The β-iodosulfone **450** was dissolved in deuteriochloroform and the appropriate base (2 equiv.) was added. NMR spectra were obtained at regular time intervals for each base.

With pyridine, the elimination reaction was very slow, and the vinyl sulfone **447** was present in only trace amounts after 3.5 hrs. Even after 5 days the reaction had not reached completion (ca. 1.3:1 ratio of **450**:**447**). None of the deconjugated isomer **449** was detected. The $^1$H NMR spectra from this experiment are shown in **Figure 3.8**.

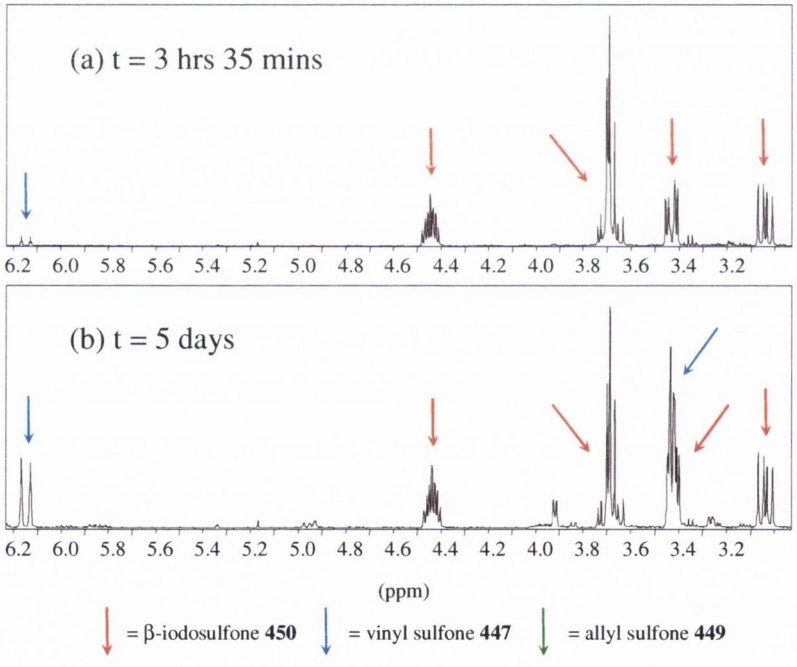



**Figure 3.8**

**$^1$H NMR study of the reaction of β-iodosulfone 450 with pyridine in $CDCl_3$**

With imidazole the reaction was more rapid. After 20 hrs, the reaction was 50 % complete (ca. 1:1 ratio of **450**:**447**) with no traces of the allylic isomer present. Trace amounts of **449** were visible after 2 days by which time the β-iodosulfone **450** was almost completely consumed. After 3 days 3 hrs, the reaction was

complete, and an 8:1 ratio of **447**:**449** was present. The deconjugation of **447** to **449** was extremely slow and **447** was the major product, even after 9 days. The $^{1}H$ NMR spectra from this experiment are shown in **Figure 3.9**.

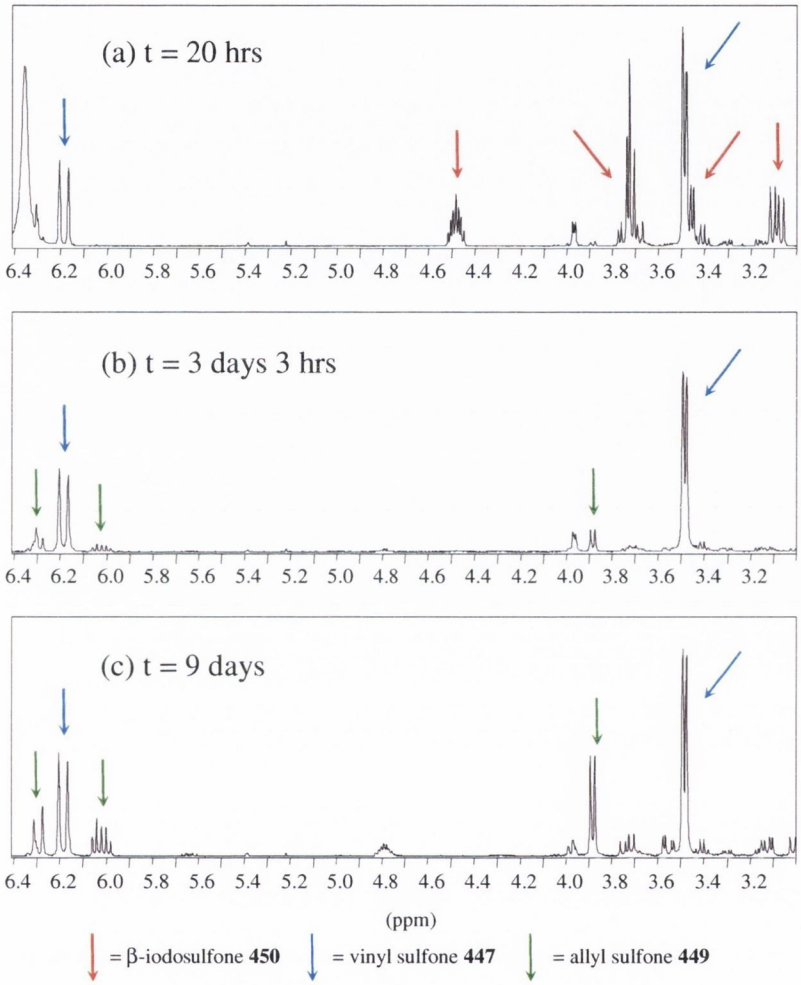



**Figure 3.9**

**$^{1}H$ NMR study of the reaction of β-iodosulfone 450 with imidazole in $CDCl_3$**

With *N*-methylmorpholine as base, deconjugation was visible after only 1.5 hrs. The elimination reaction reached completion after 19.5 hrs, by which time the ratio of **447**:**449** was ca. 1:1. Deconjugation of **447** proceeded slowly and after 4 days 4 hrs, the vinyl sulfone **447** was almost completely consumed (ca. 17:1 ratio of **449**:**447**). The $^{1}H$ NMR spectra from this experiment are shown in **Figure 3.10**.

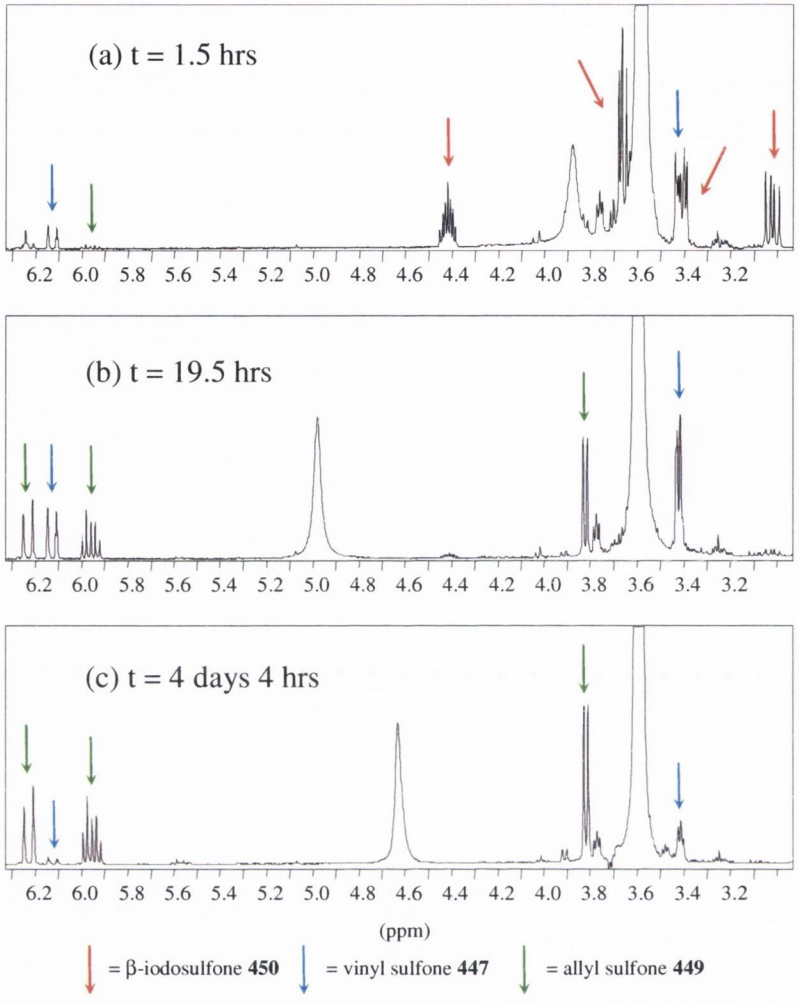



**Figure 3.10**

**$^1$H NMR study of the reaction of β-iodosulfone 450 with *N*-methylmorpholine in $CDCl_3$**

With diisopropylamine as base, the β-elimination of **450** proceeded at a rate similar to that observed with triethylamine, and the reaction was complete after 3.5 hrs. The ratio of **447** to its allyl isomer **449** at this stage was ca. 3.5:1 (compared to 1:1.3 for triethylamine), indicating that the rate of deconjugation had indeed been slowed down. After 1 day 5 hrs, the deconjugation of **447** had almost reached completion. The $^1$H NMR spectra from this experiment are shown in **Figure 3.11**.

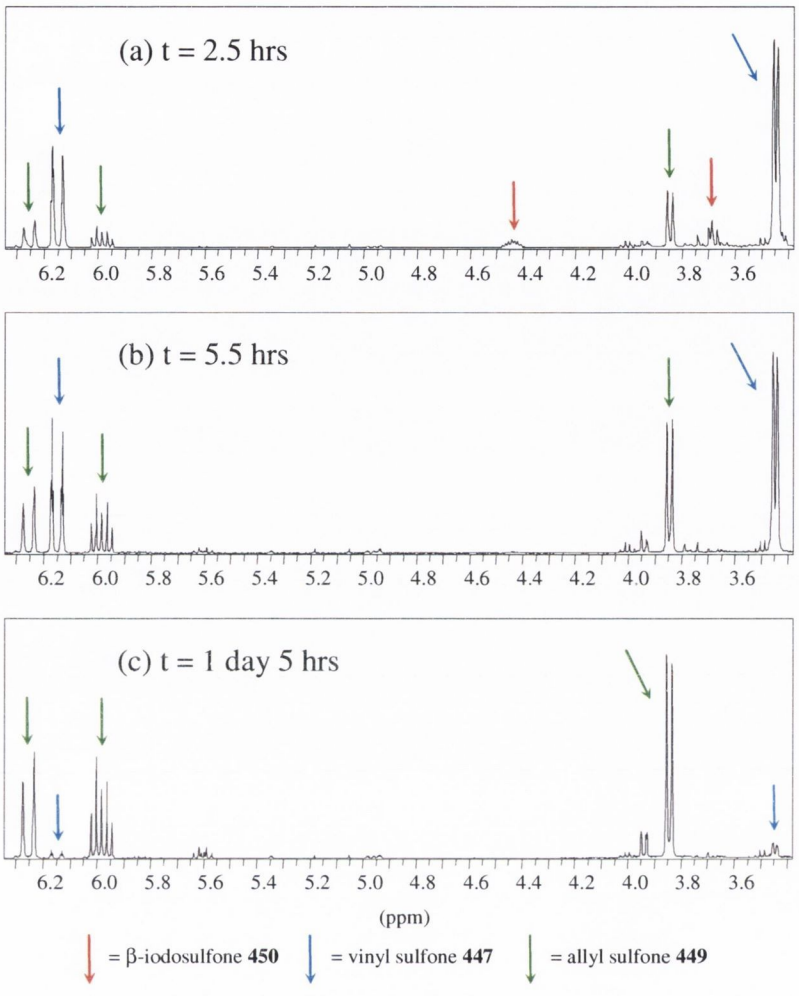



**Figure 3.11**

**$^1$H NMR study of the reaction of β-iodosulfone 450**

**with diisopropylamine in $CDCl_3$**

The above results show that the order of pKa's for the four bases correlate well with the rates of both β-elimination of the iodosulfone **450**, and deconjugation of the vinyl sulfone **447**, with imidazole emerging as the most promising base for the synthesis of **447**. The results obtained in the above experiments are summarised in **Table 3.6**.

**Table 3.6**

**NMR studies of the reaction of β-iodosulfone 450 with different bases**

| Base | pKa[56] | β-elimination[a] reaction time | 447 : 449[b] ratio | Deconjugation reaction time[c] |
|---|---|---|---|---|
| pyridine | 5.23 | > 5 days | 1 : 0[d] | none observed |
| imidazole | 6.99 | 3 days 3 hrs | 8 : 1 | > 9 days |
| *N*-methyl-morpholine | 7.38 | 19.5 hrs | 1 : 1 | 4 days 4 hrs[e] |
| diisopropyl -amine | 11.05 | 3.5 hrs | 3.5 : 1 | 1 day 5 hrs[e] |

[a] As judged by disappearance of β-iodosulfone **450**. [b] Ratio at completion of β-elimination reaction. [c] As judged by disappearance of vinyl sulfone **447**. [d] No allyl isomer **449** detected. [e] Trace amounts of vinyl sulfone **447** present.

A number of small-scale iodosulfonylation reactions was carried out to determine the best conditions for the preparation of vinyl sulfone **447**. Pyridine failed to effect β-elimination in the iodosulfonylation of allyl benzene in DCM, even at reflux, although addition of silica gel to the refluxing solution caused complete elimination to form the vinyl sulfone **447**. Similarly, evaporation of the reaction mixture and dissolution of the crude β-iodosulfone in pyridine effected elimination to the vinyl sulfone **447**, with a small amount of deconjugation to the allyl isomer **449**. Heating this pyridine solution at ca. 80 °C resulted in complete deconjugation.

The β-elimination reaction with imidazole as base failed to reach completion after 3 days at ambient temperature. The reaction reached completion after 4 days at reflux, with minor amounts of the allyl isomer **449** present. Using chloroform as solvent, the reaction reached completion after 7 days at ambient temperature. Recently, Wolff and co-workers reported that neutral alumina can be used to effect dehydroiodination in the iodosulfonylation of alkenes with benzenesulfinic acid/*N*-iodosuccinimide in DCM.[57] Using this procedure, rapid β-elimination occurred.

Surprisingly, the allylic isomer **449** was obtained exclusively, even on brief exposure to alumina (1 hour). The results obtained from these reactions are summarised in **Table 3.7**.

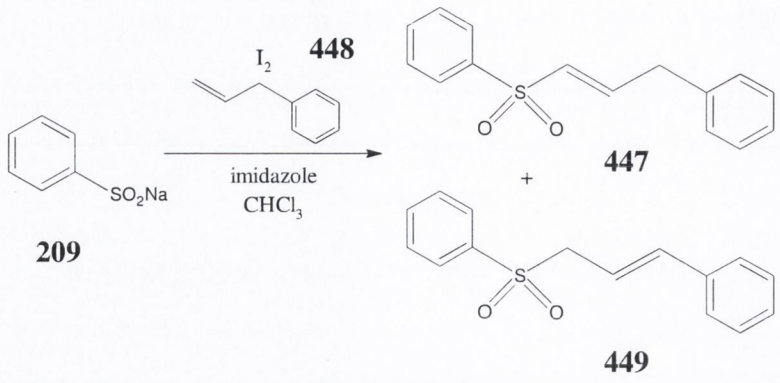
**Table 3.7**

**Studies on the iodosulfonylation of allyl benzene**

| **Base (equivalents)** | **Solvent**[a] | **Conditions** | **Reaction time**[b] |
|---|---|---|---|
| pyridine (1) | DCM | 40 °C, 90 mins | no reaction |
| pyridine (4) | DCM | silica, 40 °C, 24 hrs | 24 hrs |
| pyridine (-) | pyridine | rt, 5.5 hrs | 5.5 hrs |
| imidazole (2) | DCM | 40 °C, 4 days | 4 days |
| imidazole (4) | $CHCl_3$ | rt, 7 days | 7 days |
| alumina (-) | DCM | rt, 1 hr | 1 hr |

[a] Solvent used in β-elimination step. [b] Reaction time of β-elimination step as judged by TLC.

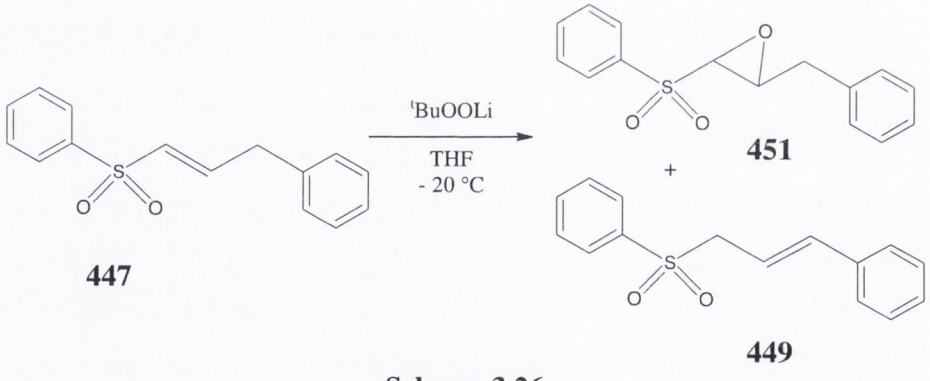
From the above results, imidazole in chloroform was chosen as the base/solvent system for the large scale preparation of the desired vinyl sulfone **447**. Iodosulfonylation of allyl benzene, followed by treatment with imidazole for 7 days gave the vinyl sulfone **447** and its allyl isomer **449** in ca. 2:1 ratio from which the vinyl sulfone was obtained reasonably pure by recrystallisation (**Scheme 3.25**). The greater extent of deconjugation which had occurred compared to the small scale reaction may be attributed to a concentration effect (double the concentration was used in the scaled-up reaction).




**Scheme 3.25**

### 3.5.2 Studies on the Hydrolysis of Sulfonyloxirane 451

Having obtained the vinyl sulfone **447** its Meth-Cohn epoxidation to form the desired sulfonyloxirane was next examined. Epoxidation of **447** with lithium *tert*-butylperoxide in THF afforded a ca. 1:1.3 mixture of the sulfonyloxirane **451** and the allyl sulfone **449**, formed by deconjugation of **447** under the basic reaction conditions. Sulfonyloxirane **451** was obtained pure following chromatography (**Scheme 3.26**).

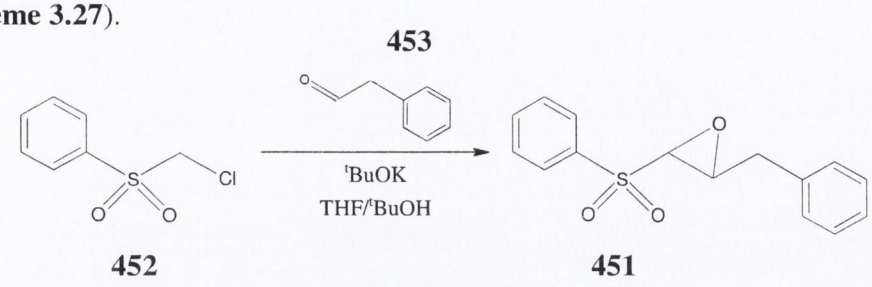



**Scheme 3.26**

The novel sulfonyloxirane **451** exhibited a pair of double doublets at δ 2.97 and 3.13 ppm assigned to the benzylic methylene protons, and a doublet at δ 3.90 ppm for the α-sulfonyloxiranyl proton. The β-sulfonyloxiranyl proton appeared as a multiplet at δ 3.91-3.94 ppm.

Owing to the extensive deconjugation observed in the epoxidation of **447**, an alternative route to the sulfonyloxirane **451** involving Darzens reaction[5] of phenyl chloromethylsulfone **452** with phenylacetaldehyde was examined. The desired sulfonyloxirane **451** was obtained in good yield on treatment of phenyl

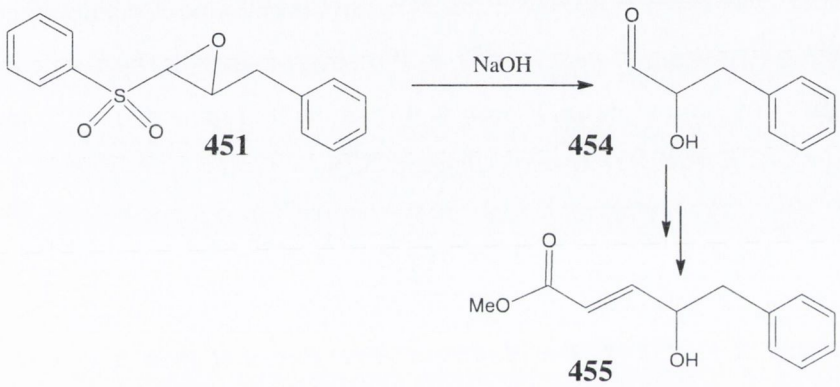
chloromethylsulfone **452** with phenylacetaldehyde **453** and potassium *tert*-butoxide (**Scheme 3.27**).




**452** **451**

**Scheme 3.27**

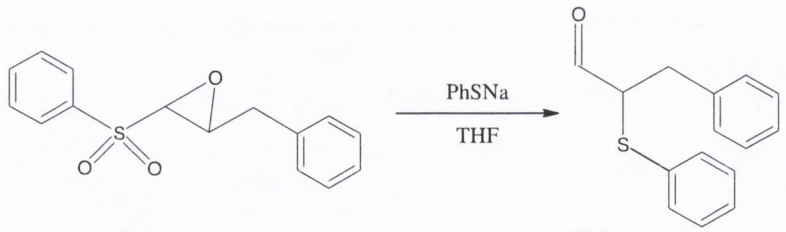
A brief study was carried out on the hydrolysis of **451** with a view to preparing the known hydroxyaldehyde **454** and its ester derivative **455** (**Scheme 3.28**).[58]




**Scheme 3.28**

Treatment of **451** with potassium hydroxide in the presence of potassium *tert*-butoxide[24] gave an intractable mixture which could not be characterised. Treatment of this crude product with methoxycarbonylmethylenetriphenylphosphorane in benzene failed to afford the known γ-hydroxy unsaturated ester **455**.[59] Similarly disappointing results were obtained using Sekiya's procedure.[25] The intractable mixture obtained in this case could not be derivatised and the only characterisable product was the Wittig reagent. No reaction occurred on treatment of **451** with aqueous sodium hydroxide in THF at reflux and starting material was recovered.

Following these disappointing results on the hydrolysis of **451**, its reactivity toward a softer nucleophile (thiolate) was examined.[60] Ring opening of **451** with sodium thiophenoxide in THF afforded the known α-phenylthio aldehyde **456** in good yield (**Scheme 3.29**).[61]

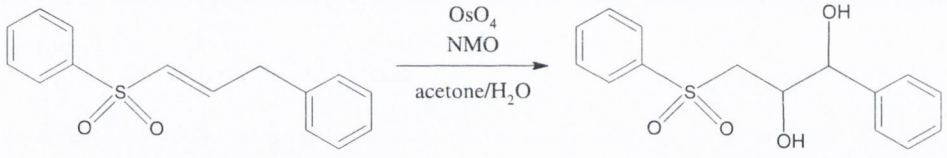



**451** **456**

**Scheme 3.29**

### 3.5.3 Studies on the Dihydroxylation of Vinyl Sulfone 447

For comparison with the results obtained in the dihydroxylation of γ-functionalised vinyl sulfone **404** (section 3.2.3), the dihydroxylation of **447** was examined. Upjohn dihydroxylation of **447** using *N*-methylmorpholine-*N*-oxide as co-oxidant afforded the known sulfonyldiol **457** as the only product.[62] The formation of **457** presumably occurs by deconjugation of **447** to the more reactive allyl isomer prior to reaction with osmium tetroxide (**Scheme 3.30**).




**447** **457**

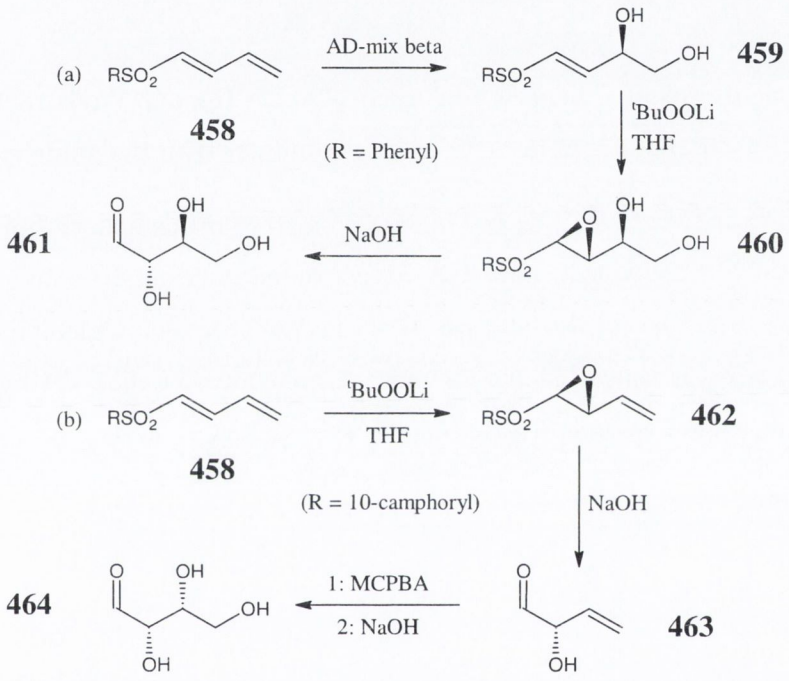
**Scheme 3.30**

It is clear from the above studies that vinyl sulfone **447** is an unsuitable substrate for the preparation of the corresponding α-hydroxyaldehyde, owing to its susceptibility to deconjugation, and no further studies on the dihydroxylation of **447** were carried out.

## 3.6 Studies on the Synthesis of Chiral Sulfonyldiene 474

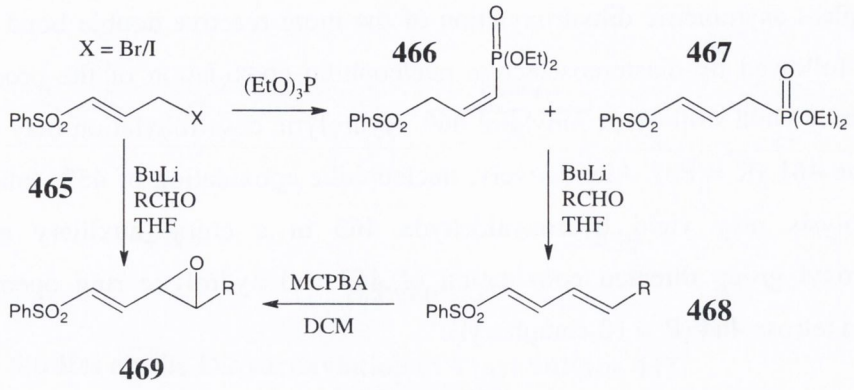
In line with the above studies aimed at the asymmetric synthesis of 3-*O*-benzylglyceraldehyde **406** using a γ-functionalised vinyl sulfone as the precursor, the synthesis of a chiral camphorsulfonyl substituted 1,3-diene was carried out as a potential precursor to the tetrose sugars. Plausible routes to the tetroses from 1-sulfonyl-1,3-dienes are illustrated in **Scheme 3.31**, involving chemoselective oxidations of each double bond followed by desulfonylation. For example,

Sharpless asymmetric dihydroxylation of the more reactive double bond of diene **458**, followed by diastereoselective nucleophilic epoxidation of the product diol **459** may yield sulfonyloxiranyldiol **460**. Hydrolytic desulfonylation may yield the tetrose **461** (R = Ph). Alternatively, nucleophilic epoxidation of **458**, followed by hydrolysis may yield hydroxyaldehyde **463** in a chiral auxiliary approach. Hydroxyl group directed epoxidation of **463** and hydrolytic ring opening may afford tetrose **464** (R = 10-camphoryl).




**Scheme 3.31**

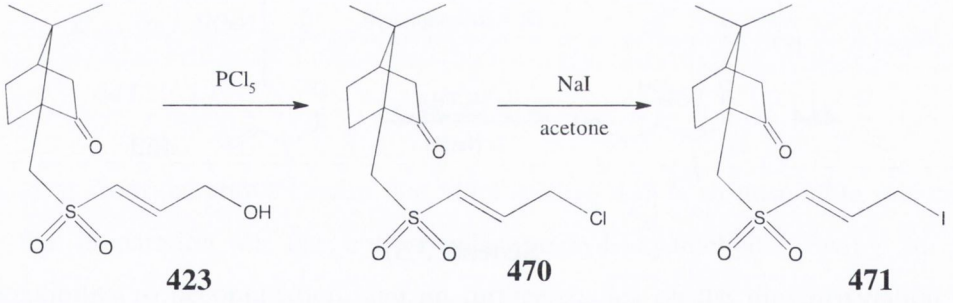
1-Sulfonyl-1,3-dienes are versatile intermediates in organic synthesis which are typically prepared by condensations of sulfones with carbonyl compounds, or by additions of sulfonyl halides/selenides to dienes.[63] A potential drawback in some cases is the formation of mixtures of *E,E* and either *E,Z* or *Z,E* isomers. Grayson *et al.* obtained 1-Sulfonyl-1,3-dienes as pure *E,E* isomers by Horner-Wadsworth-Emmons reactions of the sulfonylphosphonates **466** with a variety of aldehydes.[64] The phosphonates **466** were obtained by Arbuzov reaction of the known allylic bromide/iodide **465**.[17] Additionally, these same allylic halides undergo Darzens reactions with aromatic aldehydes affording diene monoepoxides[65] **469** which can be obtained in principle by electrophilic epoxidation of diene **468** (**Scheme 3.32**).[66]




**Scheme 3.32**

### 3.6.1 Synthesis of Chiral Sulfonyldiene 474 *via* Horner-Wadsworth-Emmons Reaction of Camphorsulfonylphosphonates with Benzaldehyde

The above procedure was applied to the synthesis of the camphorsulfonyl analogue of **468** (R = Ph). Allylic alcohol **423** was converted to the allylic chloride **470** using phosphorus pentachloride. Sulfone **470** failed to react with triethylphosphite on heating, and was converted into the more reactive allylic iodide **471** by Finkelstein reaction with sodium iodide in acetone (**Scheme 3.33**).

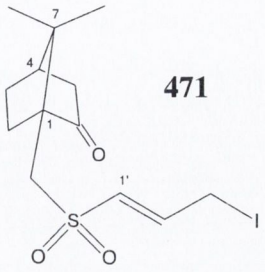



**Scheme 3.33**

The iodide was characterised by a doublet at δ 3.95 ppm corresponding to the allylic methylene protons, and by a double triplet at δ 6.91 ppm assigned to the β-vinyl proton. The allylic carbon came into resonance at δ -1.9 ppm in the $^{13}C$ NMR spectrum. The $^{1}H$ and $^{13}C$ NMR details of **471** are shown in **Table 3.8**.

**Table 3.8**

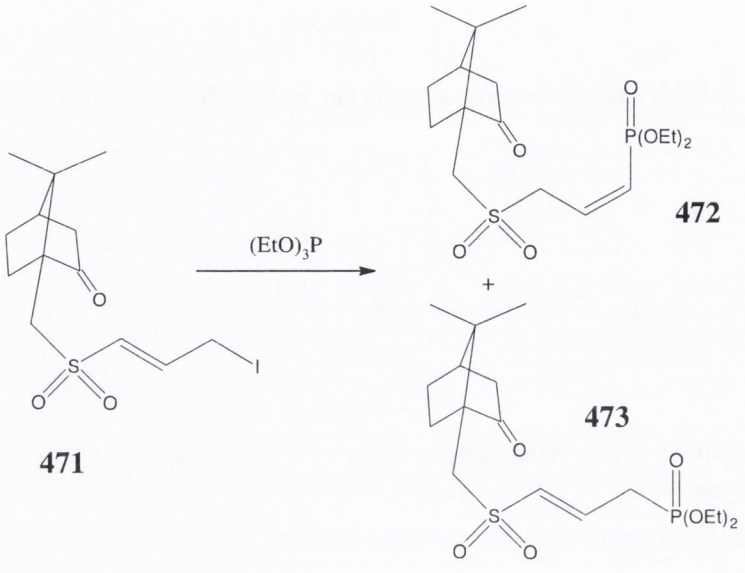
**NMR spectroscopic details for iodosulfone 471 in $CDCl_3$**




**471**

| $^1$H (ppm) | Multiplicity (Hz) | $^{13}$C (ppm) | Assignment |
|---|---|---|---|
| 3.95 | d, *J* 8.0 | -1.9 | C-3' |
| 1.05 | s | 19.1 | 7-$CH_3$ |
| 0.86 | s | 19.2 | 7-$CH_3$ |
| not assigned | - | 24.1 | C-5 |
| not assigned | - | 26.5 | C-6 |
| 2.12 | t, *J* 4.5 | 41.9 | C-4 |
| 1.92 | d, *J* 18.5 | 42.1 | C-3 |
| not assigned | - | | |
| - | - | 48.1 | C-7 |
| 2.84 | d, *J* 14.5 | 51.6 | $CH_2SO_2$ |
| 3.41 | d, *J* 14.5 | | |
| - | - | 58.0 | C-1 |
| 6.68 | d, *J* 15.0 | 131.5 | C-1' |
| 6.91 | dt, *J* 15.0, 8.0 | 141.0 | C-2' |
| - | - | 214.4 | C-2 |

The allylic iodide **471** underwent Arbuzov reaction with triethylphosphite to give a mixture of phosphonates which, by comparison with the data for the phenylsulfonyl compounds and from $^1$H-$^1$H and $^{13}$C-$^1$H COSY experiments was assigned as a ca. 2.2:1 ratio of (*Z*)-vinylic and (*E*)-allylic phosphonates **472** and **473**. These could not be separated by chromatography (**Scheme 3.34**).




**Scheme 3.34**

In its $^{1}H$ NMR spectrum, the (*Z*)-vinylic phosphonate **472** was characterised by a pair of diastereotopic allylic methylene protons at δ 3.98 and 4.33 ppm and by an apparent triplet at δ 6.15 ppm with a coupling to phosphorus of 17.8 Hz corresponding to the α-vinylic proton. In the $^{13}C$ spectrum, the α-vinylic carbon appeared as a doublet at δ 127.0 ppm with a coupling to phosphorus of 185.6 Hz. The (*E*)-allylic phosphonate **473** displayed a double doublet at δ 2.81 ppm for the allylic α-protons in the $^{1}H$ NMR spectrum, and a doublet at δ 28.8 ppm ($^{1}J_{P\text{-}C}$ = 138.9 Hz) for the allylic α-carbon. The $^{1}H$ NMR spectrum of the phosphonates **472** and **473** is shown in **Figure 3.12**.

The mixture of phosphonates **472** and **473** underwent Horner-Wadsworth-Emmons reaction with benzaldehyde on treatment with LDA in THF to afford two sulfonyldienes. The desired (*E,E*)-sulfonyldiene **474** was obtained as the major product, together with the benzylidene sulfonyldiene **340**. Both products were separable by chromatography (**Scheme 3.35**). The benzylidene compound **340** is clearly formed either by condensation of the enolate of **474** with excess benzaldehyde, or by a Knöevenagel type reaction catalysed by diisopropylamine.

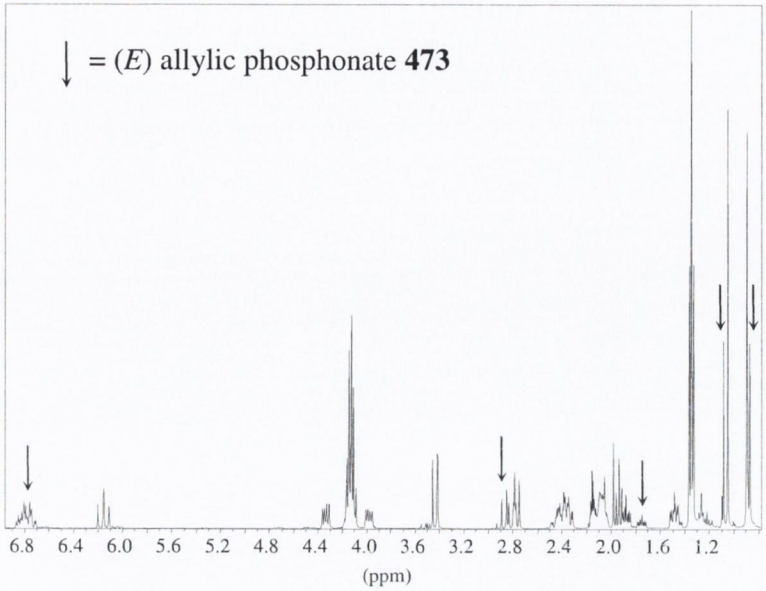
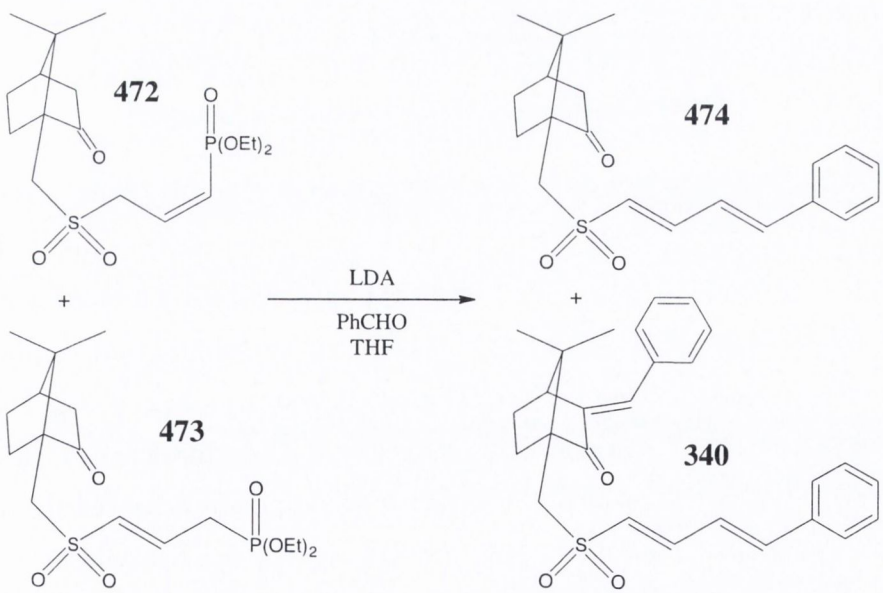



**Figure 3.12**

**$^1$H NMR spectrum of the mixture of phosphonates**

**472 and 473 in $CDCl_3$**




**Scheme 3.35**

The dienes **474** and **340** were assigned by comparison of their spectroscopic data with those of the phenylsulfonyl analogues.[64] In the $^1$H NMR spectrum of diene **474**, the vinylic α and δ protons each appeared as doublets at δ 6.68 and 6.99 ppm

respectively, with coupling constants (14.5-15.5 Hz) consistent with *E,E* stereochemistry.[67] The β and γ protons appeared as double doublets at δ 7.33 and 6.87 ppm. These assignments were verified by $^{1}H$-$^{1}H$ and $^{13}C$-$^{1}H$ COSY experiments. The $^{1}H$ NMR spectrum of **474** is shown in **Figure 3.13**.

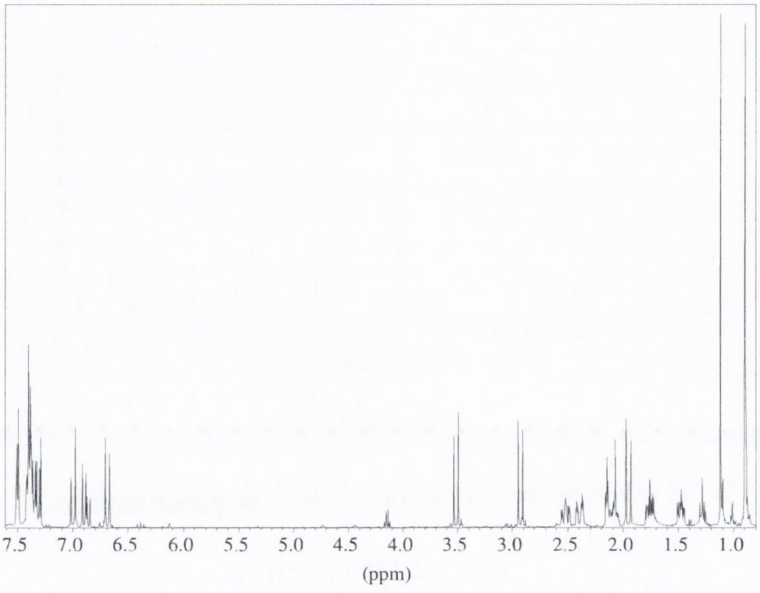



**Figure 3.13**

**$^{1}H$ NMR spectrum of sulfonyldiene 474 in $CDCl_3$**

In the $^{1}H$ NMR spectrum of diene **340**, the characteristic signals for the methylene protons adjacent to the carbonyl group were absent, and the methine proton at C-4, appeared as a doublet at δ 3.15 ppm (the same proton appears as a triplet at δ 2.14 in diene **474**). In the $^{13}C$ NMR spectrum, the carbonyl carbon had shifted upfield (δ 203.8) relative to diene **474** (δ 214.6). The stereochemistry of the double bond of the benzylidene group was tentatively assigned as *E* on the basis of an NOE experiment in which irradiation of the C-4 methine proton enhanced the signal intensity of the benzylidene aromatic protons but not the benzylidene vinylic proton. The $^{1}H$ NMR spectrum of **340** is shown in **Figure 3.14**.

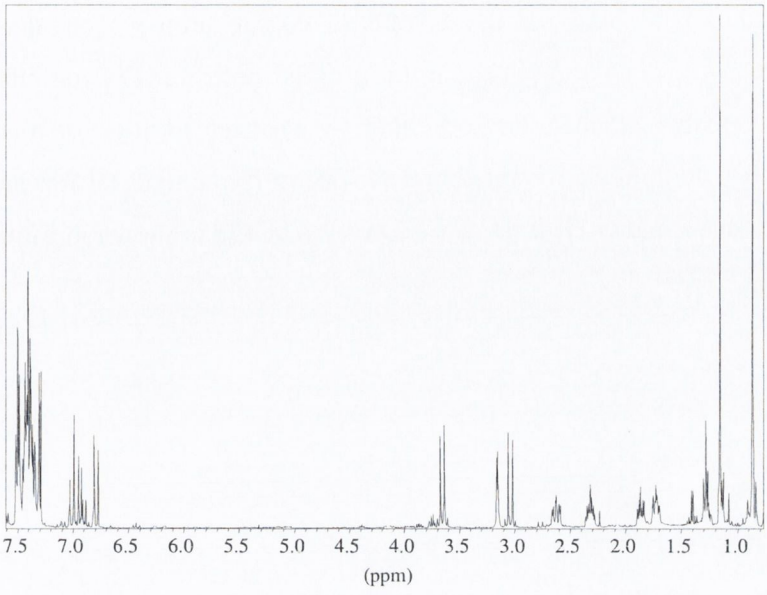
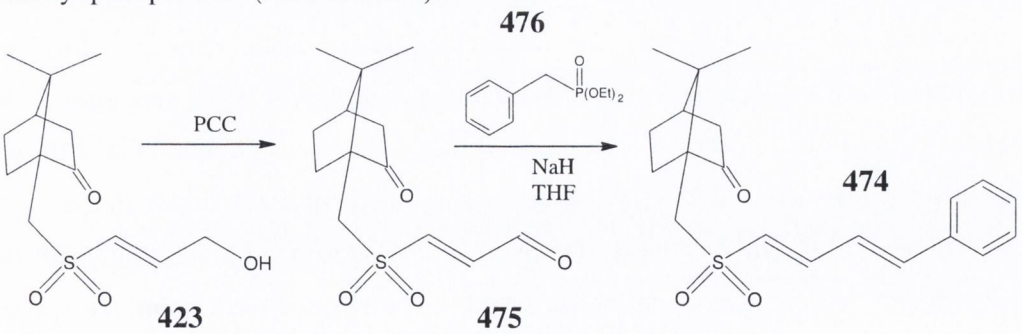



**Figure 3.14**

**$^1$H NMR spectrum of sulfonyldiene 340 in $CDCl_3$**

### 3.6.2 Synthesis of Chiral Sulfonyldiene 474 *via* Wittig Reaction of Aldehyde 475 with Benzylidenetriphenylphosphorane

Although the above route to the chiral sulfonyldiene **474** allows scope for the preparation of different dienes by appropriate choice of aldehyde, the formation of the benzylidene compound **340** as a side-product led to the examination of an alternative route to **474** in two steps involving oxidation of allylic alcohol **423** to its aldehyde **475** followed by Horner-Wadsworth-Emmons reaction with diethyl benzyl phosphonate (**Scheme 3.36**).




**Scheme 3.36**

Accordingly, alcohol **423** was oxidised to aldehyde **475** in reasonable yield (58 % after chromatography) using pyridinium chlorochromate.[68] Aldehyde **475** displayed

a double doublet at δ 6.89 ppm corresponding to the β-sulfonyl vinylic proton and a doublet at δ 7.64 ppm for the α-sulfonyl vinylic proton. The aldehyde proton appeared as a doublet at δ 9.84 ppm. In its mass spectrum, **475** was characterised as its adduct with methanol, formed either by Michael addition of methanol to the highly electron deficient double bond of **475**, or by hemiacetal formation with the aldehyde functionality. The $^1$H NMR spectrum of **475** is shown in **Figure 3.15**.

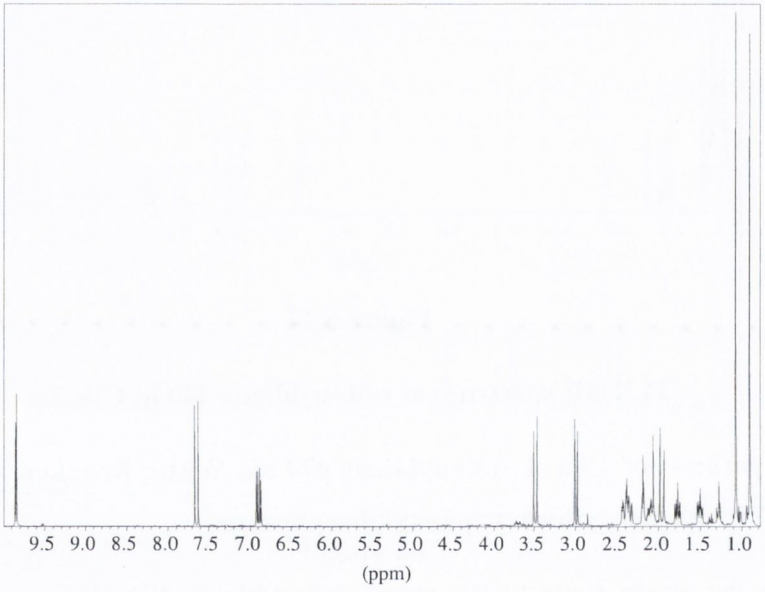


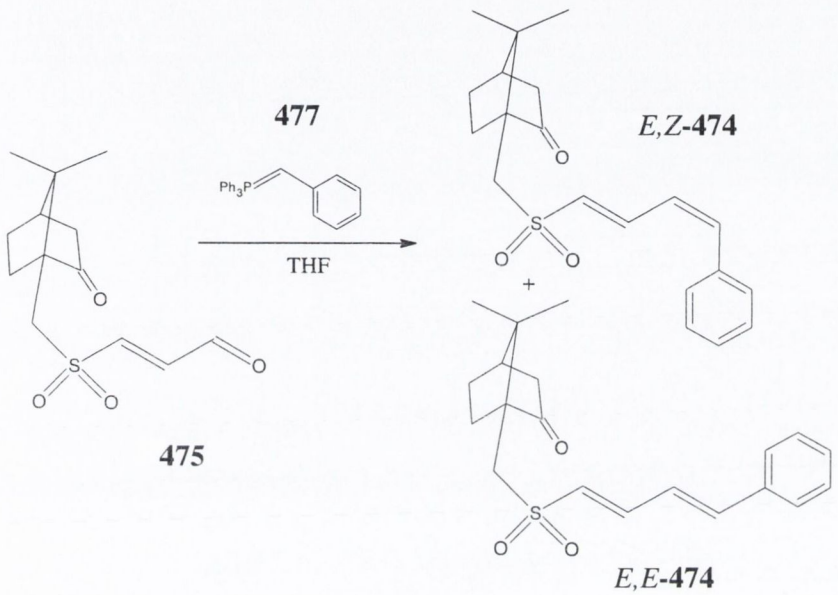

**Figure 3.15**

**$^1$H NMR spectrum of aldehyde 475 in $CDCl_3$**

The Horner-Wadsworth-Emmons reaction of the aldehyde **475** with diethyl benzyl phosphonate failed to afford the desired sulfonyldiene **474**. The only product recovered on work-up was the unreacted phosphonate reagent. However, evaporation of the aqueous layer and examination of the $^1$H NMR spectrum of the resulting solid in deuterium oxide showed that sodium camphorsulfinate **310** was present. Clearly, the aldehyde had undergone decomposition under the reaction conditions (TLC analysis during the reaction indicated its absence), although the absence of any other reaction products makes it difficult to determine the species responsible and the mechanism of the reaction.

Following this disappointing outcome, the Wittig reaction of aldehyde **475** with benzylidenetriphenylphosphorane was examined.[69] Although this non-stabilised

ylid would be expected to affect *E/Z* selectivity,[70] it would provide a synthetic route to the diene **474** from the sensitive aldehyde **475** using non-basic conditions. Treatment of **475** with benzylidenetriphenylphosphorane in THF gave the desired diene **474** as a ca. 1.4:1 ratio of *E,Z* and *E,E* isomers in good yield. These were inseparable by chromatography (**Scheme 3.37**).




**Scheme 3.37**

The $^{1}H$ and $^{13}C$ NMR spectra of the *E,Z* isomer of **474** were assigned by subtraction of the signals due to the *E,E* isomer from the spectrum of the mixture. The $^{1}H$ NMR spectrum of the *E,Z* isomer displayed a triplet at δ 6.38 ppm and a doublet at δ 6.96 ppm which were assigned to the γ and δ protons respectively. Both protons had coupling constants consistent with *Z*-double bond stereochemistry (11.5 Hz). The $^{1}H$ NMR spectrum of the mixture of *E,Z* and *E,E* isomers is shown in **Figure 3.16**.

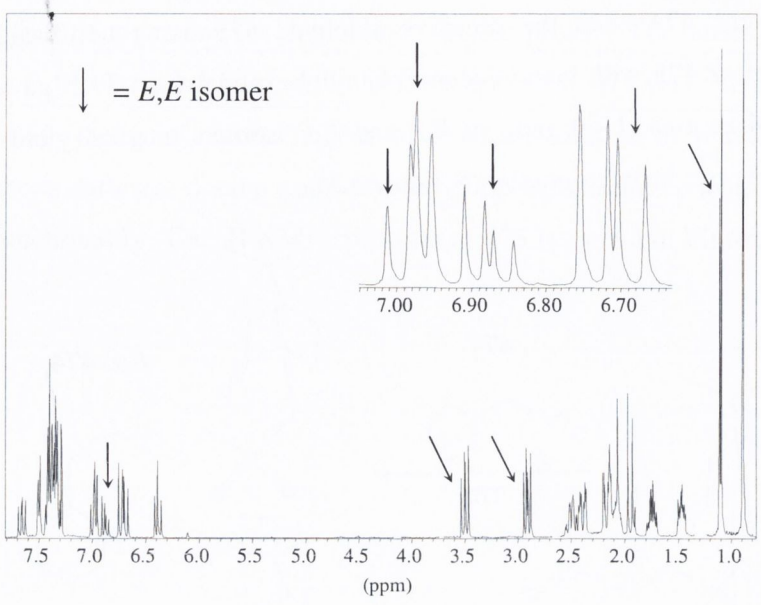



**Figure 3.16**

**$^1$H NMR spectrum of the mixture of *E,E* and *E,Z* sulfonyldienes 474 in $CDCl_3$**

## 3.7 Summary and Concluding Remarks

It is clear that a more extensive investigation into the hydrolysis of sulfonyloxirane **405** under mild conditions will need to be carried out. In particular, changing the nature of the arylsulfonyl group or replacing it with a better leaving group (e.g.: nitro) may have a beneficial effect on reactivity. Nitrooxiranes have been shown to be reactive toward weak nucleophiles such as trifluoroacetic acid and methanesulfonic acid.[71] The failure of vinyl sulfone **404** to afford aldehyde **406** directly by asymmetric dihydroxylation is disappointing.

Studies into the nucleophilic epoxidation of the chiral vinyl sulfone **424** seem to indicate that the choice of conditions (particularly the amount of epoxidising reagent used) is important to achieve stereocontrol. Indeed given the lack of conformational control in the sulfonyl side-chain (in comparison to Oppolzer's sultam for example), it was surprising that stereoselectivity was observed when 3 equivalents of lithium *tert*-butylperoxide were used. Studies conducted in toluene

and on the isobornyl analogue **440** suggest that coordination does not play a role in controlling the stereoselectivity. A mechanism to explain the observed stereoselectivity has been postulated. Studies on the cyclopropanation of **424** would be an interesting reaction worthy of future investigation.

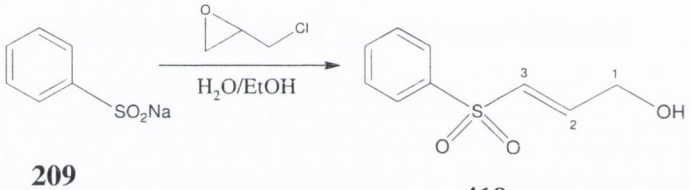
The preparation of the unfunctionalised vinyl sulfone **447** by iodosulfonylation proved troublesome and a relatively weak base (imidazole) was necessary to avoid extensive deconjugation to the allyl isomer **449**. Again disappointing results were obtained on the hydrolysis of sulfonyloxirane **451**, more conveniently obtained by Darzens reaction. However, **451** reacted cleanly with sodium thiophenoxide.

Finally, a novel route to the chiral *E,E* sulfonyldiene **474** has been achieved, involving Horner-Wadsworth-Emmons reaction of camphorsulfonylphosphonates **472** and **473** with benzaldehyde.

## 3.8 Experimental

Anhydrous solutions of *tert*-butyl hydroperoxide in benzene were obtained by azeotropic distillation of commercially available 70 % solutions of *tert*-butyl hydroperoxide in water according to the procedure of Sharpless.[72] Concentrations were estimated by $^1$H NMR. Triphenylmethyl hydroperoxide was prepared according to the procedure of Eberhard.[44] Methoxycarbonyl-methylenetriphenylphosphorane was prepared according to the procedure of Lugtenburg.[73] Pyridinium chlorochromate was prepared according to the procedure of Corey.[68] Chloromethyl phenyl sulfone **452** was prepared according to the procedure of Makosza.[74] All other general experimental conditions as for Chapter 2.

**(2*E*)-3-(Phenylsulfonyl)prop-2-en-1-ol 419**[36,57,75]




**209** **419**

Following the procedure of Culvenor, Davies and Savige,[17] sodium benzenesulfinate **209** (15.0 g, 91.3 mmol) was dissolved in water (45 ml) and ethanol (11.25 ml) and epichlorohydrin (7.14 ml, 91.3 mmol) was added. The solution was stirred at rt for 2 days. The precipitated solid was filtered and washed with water and hexane and left to dry in the air for a day to yield the title compound as a white solid (16.36 g, 90 %).

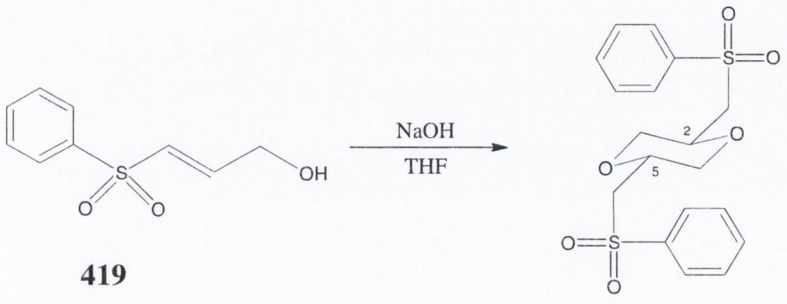
m.p.: 138 °C (from EtOAc); Lit.[75]: 139-141 °C

IR: $\nu_{max}$ (N) 3479 (O-H), 2897, 1628 (C=C), 1581 (Ar C-C), 1453, 1376, 1276 ($SO_2$), 1196, 1141 ($SO_2$), 1081, 1016, 940, 843, 762, 718, 687, 633 cm$^{-1}$

$^1$H NMR (400.1 MHz): δ 4.43 (2H, app t, $^3J$ = 2.5, 1-C*H*$_2$), 6.69 (1H, dt, $^3J$ = 15.0, $^4J$ = 2.0, 3-C*H*), 7.08 (1H, dt, $^3J_1$ = 15.0, $^3J_2$ = 3.0, 2-C*H*), 7.56 (2H, t, $^3J$ = 7.5, *m*-Ar*H*), 7.65 (1H, t, $^3J$ = 7.5, *p*-Ar*H*), 7.91 (2H, d, $^3J$ = 7.5, *o*-Ar*H*) ppm

$^{13}$C NMR (100.6 MHz): δ 60.5 (C-1), 127.2 (C-3), 128.8 (C-2), 129.2 (Ar C), 133.0 (Ar C), 139.7 (Ar C), 144.6 (Ar C) ppm

**2,5-*bis*[(Phenylsulfonyl)methyl]-1,4-dioxane 421**[17]




**419** **421**

Sulfone **419** (1 g, 5.0 mmol) was dissolved in THF (15 ml) and a aqueous solution of sodium hydroxide (5 ml, 1 M, 5.0 mmol) was added. The solution was stirred at rt for 4 hrs. The solution was then diluted with satd. aq. ammonium chloride (50 ml) and the resulting precipitate was filtered and washed with water (50 ml) and ether (5 ml) to yield a white solid (0.67 g, 67 %).

m.p.: 238 °C (from ether); Lit.[17]: 244 °C

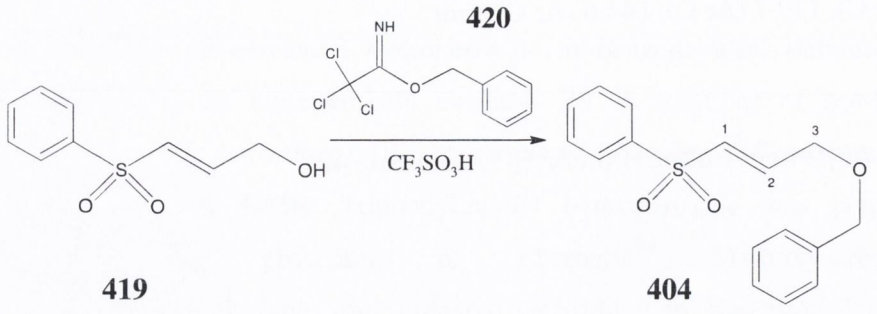
IR: $\nu_{max}$ (N) 2927, 1584 (Ar C-C), 1450, 1376, 1304 ($SO_2$), 1245, 1146 ($SO_2$), 1084, 1025, 997, 914, 862, 812, 750, 686, 659 cm$^{-1}$

$^1$H NMR (400.1 MHz): δ 3.05 (2H, dd, $^2J$ = 14.5, $^3J$ = 5.0, 2 and 5-C$H_2$SO$_2$), 3.27 (2H, dd, $^2J$ = 14.5, $^3J$ = 6.5, 2 and 5-C$H_2$SO$_2$), 3.34 (2H, app t, $^2J$ = 11.5, $^3J$ = 11.5, 3 and 6-C$H_2$ *axial*), 3.81 (2H, dd, $^2J$ = 11.5, $^3J$ = 2.5, 3 and 6-C$H_2$ *equatorial*), 3.98-4.04 (2H, m, 2 and 5-C*H*), 7.58 (4H, t, $^3J$ = 7.0, *m*-Ar*H*), 7.69 (2H, t, $^3J$ = 7.0, *p*-Ar*H*), 7.92 (4H, d, $^3J$ = 7.0, *o*-Ar*H*) ppm

$^{13}$C NMR (100.6 MHz): δ 57.2 (2 and 5-*C*H$_2$SO$_2$), 69.0 (C-2 and C-5), 69.3 (C-3 and C-6), 127.5 (Ar C-2), 128.8 (Ar C-3), 133.5 (Ar C-4), 139.0 (Ar C-1) ppm

HRMS (CI) *m/z* 419.0601: *calculated for* $[C_{18}H_{20}O_6S_2 + Na]^+$ 419.0598

**{[(1*E*)-3-(Benzyloxy)prop-1-enyl]sulfonyl}benzene 404**[16]




**419** **404**

Following the procedure of Bundle,[18] sulfone **419** (5.0 g, 25 mmol) was dissolved in dry DCM (80 ml) and dry hexane (80 ml) and benzyl-2,2,2-trichloroacetimidate **420** (7 ml, 37 mmol) was added. Trifluoromethanesulfonic acid (2 ml) was added dropwise and the solution was stirred at rt for 24 hrs. Hexane (150 ml) was added and the precipitated trichloroacetamide was filtered. The filtrate was washed with satd. aq. sodium hydrogen carbonate (50 ml) and brine (50 ml), dried and evaporated to yield an oil. Column chromatography on silica gel using EtOAc:Hexane(1:3) afforded the title compound as a clear oil (5.84 g, 80 %).

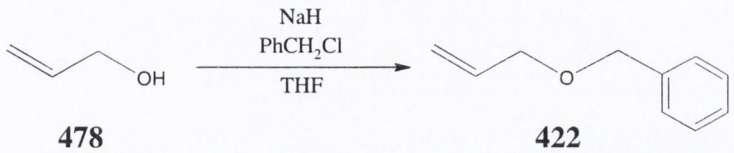
IR: $\nu_{max}$ (L) 3062, 3031, 2860, 1631 (C=C), 1585 (Ar C-C), 1495, 1447, 1359, 1307 ($SO_2$), 1200, 1145 ($SO_2$), 1085, 1024, 944, 828, 753, 688 $cm^{-1}$

$^1H$ NMR (400.1 MHz): δ 4.23 (2H, dd, $^3J$ = 3.5, $^4J$ = 2.5, 3-C$H_2$), 4.56 (2H, s, benzyl C$H_2$), 6.70 (1H, dt, $^3J$ = 15.0, $^4J$ = 2.5, 1-C*H*), 7.03 (1H, dt, $^3J_1$ = 15.0, $^3J_2$ = 3.5, 2-C*H*), 7.30-7.38 (5H, m, benzyl Ar*H*), 7.56 (2H, t, $^3J$ = 7.5, $PhSO_2$ *m*-Ar*H*), 7.64 (1H, t, $^3J$ = 7.5, $PhSO_2$ *p*-Ar*H*), 7.91 (2H, d, $^3J$ = 7.5, $PhSO_2$ *o*-Ar*H*) ppm

$^{13}C$ NMR (100.6 MHz): δ 67.1 (C-3), 72.7 (benzyl *C*$H_2$), 127.2 (C-1), 127.2 (benzyl Ar C), 127.6 (benzyl Ar C), 128.0 (benzyl Ar C), 128.8 (C-2), 129.8 ($PhSO_2$ Ar C), 132.9 ($PhSO_2$ Ar C), 136.6 ($PhSO_2$ Ar C), 139.7 (benzyl Ar C), 142.0 ($PhSO_2$ Ar C) ppm

HRMS (CI) *m/z* 311.0717: *calculated for* $[C_{16}H_{16}O_3S + Na]^+$ 311.0717

**Preparation of allyl benzyl ether 422**[76]




**478** **422**

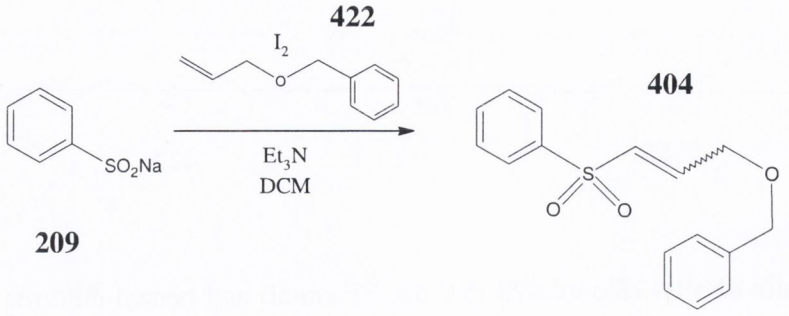
A mixture of allyl alcohol **478** (5.0 ml, 73 mmol) and benzyl chloride (9.2 ml, 80 mmol) was added dropwise *via* syringe to a suspension of sodium hydride (3.2 g, 60 %, 80 mmol) in dry THF (50 ml) at 0 °C under an atmosphere of nitrogen. The solution was stirred at 0 °C for 30 mins and triethylhexylammonium bromide (1.9 g, 10 mol %) and sodium iodide (1.1 g, 10 mol %) were then added and the solution was allowed to warm to rt and stirred for an additional 24 hrs. The solution was diluted with water (150 ml) and extracted with ether (3 × 100 ml). The combined organic extracts were washed with brine (100 ml), dried and evaporated to yield a liquid. Distillation under reduced pressure afforded the title compound (10.5 g, 97 %) as a clear liquid (b.p. 81 °C at 10-20 mm/Hg).

IR: $\nu_{max}$ (L) 3065, 3031, 2923, 2857, 1646 (C=C), 1601 (Ar C-C), 1495, 1453, 1358, 1267, 1204, 1073, 1025, 926, 824, 740, 698 $cm^{-1}$

$^1H$ NMR (400.1 MHz): δ 4.08 (2H, dd, $^3J$ = 5.4, $^4J$ = 1.3, allyl C$H_2$), 4.58 (2H, s, benzyl C$H_2$), 5.26 (1H, dd, $^3J$ = 10.9, $^2J$ = 1.3, CH=C$H_2$ *cis*), 5.37 (1H, app dd, $^3J$ = 17.4, $^4J$ = 1.3, $^2J$ = 1.3, CH=C$H_2$ *trans*), 6.01 (1H, app ddd, $^3J_1$ = 17.4, $^3J_2$ = 10.9, $^3J_3$ = 5.4, C*H*=CH$_2$), 7.30-7.44 (5H, m, Ar*H*) ppm

$^{13}C$ NMR (100.6 MHz): δ 70.7 (allyl *C*H$_2$), 71.6 (benzyl *C*H$_2$), 116.7 (CH=*C*H$_2$), 127.1 (*C*H=CH$_2$), 127.3 (Ar C-3), 127.9 (Ar C-2), 134.3 (Ar C-4), 137.8 (Ar C-1) ppm

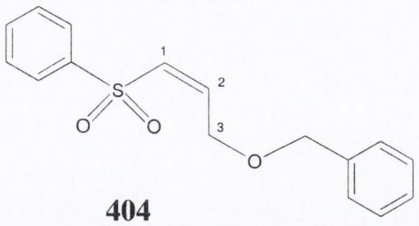
**Iodosulfonylation of allyl benzyl ether 422**




**209**

A solution of iodine (2 g, 7.8 mmol) in DCM (200 ml) was vigorously mixed with a solution of sodium benzenesulfinate **209** (1.42 g, 8.6 mmol) in water (100 ml) in a separating funnel. The yellow organic phase was placed in a round bottomed flask and allyl benzyl ether **422** (1.16 g, 7.8 mmol) was added. The solution was stirred at rt for 3 days. Triethylamine (4.36 ml, 31 mmol) was added and the solution was stirred for a further 24 hrs. The solution was then washed with water (50 ml) and the aqueous layer was extracted with ether (50 ml). The combined organic extracts were dried and evaporated to yield an oil (2.17 g) whose $^1$H NMR spectrum showed it to contain sulfone **404** as a mixture of *E* and *Z* isomers in ca. 3.6 : 1 ratio. The crude product was purified over silica gel, eluting with EtOAc:hexane (1:4) to yield two products. The first product to elute was *Z*-vinyl sulfone **404** (0.07 g) as a clear oil. The second product to elute was *E*-vinyl sulfone **404** (0.78 g) as a clear oil. Also eluted was a mixture of *E* and *Z*-vinyl sulfones **404** (0.55 g). Total yield; 1.4 g (62 %).

**{[(1Z)-3-(Benzyloxy)prop-1-enyl]sulfonyl}benzene 404**[16]

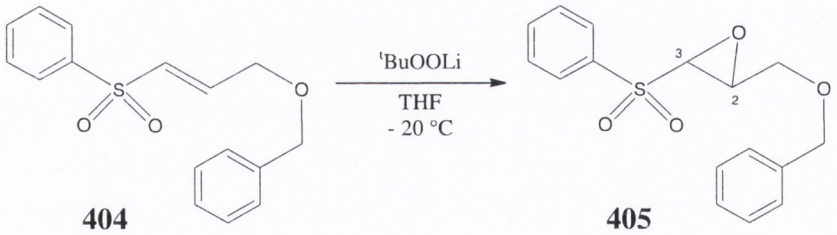


**404**

$^1$H NMR (400.1 MHz): δ 4.57 (2H, s, benzyl C*H*$_2$), 4.75 (2H, dd, $^3J$ = 5.0, $^4J$ = 2.0, 3-C*H*$_2$), 6.29 (1H, dt, $^3J$ = 11.5, $^4J$ = 2.0, 1-C*H*), 6.47 (1H, dt, $^3J_1$ = 11.5, $^3J_2$ = 5.0, 2-C*H*), 7.30-7.40 (5H, m, benzyl Ar*H*), 7.57 (2H, t, $^3J$ = 7.5, PhSO$_2$ *m*-Ar*H*), 7.64 (1H, t, $^3J$ = 7.5, PhSO$_2$ *p*-Ar*H*), 7.89 (2H, d, $^3J$ = 7.5, PhSO$_2$ *o*-Ar*H*) ppm

$^{13}$C NMR (100.6 MHz): δ 65.6 (C-3), 72.6 (benzyl *C*H$_2$), 126.8 (C-1), 127.4 (benzyl Ar C), 127.5 (benzyl Ar C), 128.0 (benzyl Ar C), 128.9 (C-2), 129.1 (PhSO$_2$ Ar C), 133.2 (PhSO$_2$ Ar C), 136.9 (PhSO$_2$ Ar C), 140.2 (benzyl Ar C), 143.9 (PhSO$_2$ Ar C) ppm

***trans*-2-[(Benzyloxy)methyl]-3-(phenylsulfonyl)oxirane 405**[16]




**404** **405**

*n*-Butyllithium (5 ml, 2.5 M, 12.6 mmol) was added dropwise *via* syringe to a solution of *tert*-butylhydroperoxide (10.7 ml, 1.17 M in benzene, 12.6 mmol) in dry THF (7 ml) at -78 °C under an atmosphere of nitrogen. The solution was allowed to warm to -20 °C and a solution of sulfone **404** (1.46 g, 5.0 mmol) in dry THF (14 ml) was added dropwise *via* syringe. The solution was stirred at -20 °C for 2.5 hrs. The solution was allowed to warm to rt, quenched with satd. aq. sodium sulfite (50 ml) and extracted with ether (3 × 50 ml). The combined organic extracts were dried

over sodium sulfate and evaporated to yield an oil. Column chromatography on silica gel using EtOAc:Hexane(1:3) afforded the title compound as a clear oil (1.25 g, 81 %).

IR: $\nu_{max}$ (L) 3064, 3029, 2863, 1585 (Ar C-C), 1496, 1448, 1324 ($SO_2$), 1215, 1155 ($SO_2$), 1087, 1024, 914, 826, 747, 687 $cm^{-1}$

$^1H$ NMR (400.1 MHz): δ 3.68 (1H, dd, $^2J$ = 12.5, $^3J$ = 4.5, 2-C$H_2$OC$H_2$Ph), 3.87-3.89 (1H, m, 2-C*H*), 3.90 (1H, dd, $^2J$ = 12.5, $^3J$ = 2.0, 2-C$H_2$OC$H_2$Ph), 4.23 (1H, d, $^3J$ = 1.0, 3-C*H*), 4.54 (2H, s, benzyl C$H_2$), 7.28-7.38 (5H, m, benzyl Ar*H*), 7.62 (2H, t, $^3J$ = 7.5, $PhSO_2$ *m*-Ar*H*), 7.73 (1H, t, $^3J$ = 7.5, $PhSO_2$ *p*-Ar*H*), 7.96 (2H, d, $^3J$ = 7.5, $PhSO_2$ *o*-Ar*H*) ppm

$^{13}C$ NMR (100.6 MHz): δ 55.9 (C-2), 65.1 (C-3), 65.6 (2- *C*$H_2$OC$H_2$Ph), 73.0 (benzyl *C*$H_2$), 127.3 (benzyl Ar C), 127.5 (benzyl Ar C), 128.0 ($PhSO_2$ Ar C), 128.3 (benzyl Ar C), 128.9 ($PhSO_2$ Ar C), 134.0 ($PhSO_2$ Ar C), 136.3 ($PhSO_2$ Ar C), 136.6 (benzyl Ar C) ppm

HRMS (CI) in ether *m/z* 327.0680: *calculated for* $[C_{16}H_{16}O_4S + Na]^+$ 327.0666

**Attempted preparation of 3-(benzyloxy)-2-hydroxypropanal 406**[11,14,77]

Method A: By hydrolysis of sulfonyloxirane **405** with NaOH

Sulfonyloxirane **405** (0.44 g, 1.4 mmol) was dissolved in isopropanol (5 ml) and sodium hydroxide (3.2 ml, 1M, 3.2 mmol) was added. The solution was heated under reflux for 24 hrs. The mixture was allowed to cool to rt, diluted with water (50 ml) and extracted with DCM (4 × 50 ml). The combined organic extracts were dried over sodium sulfate and evaporated to yield a brown liquid (0.22 g) whose $^1H$ NMR spectrum showed it to be benzyl alcohol.

Method B: By hydrolysis of sulfonyloxirane **405** with KOH/KO$^t$Bu[24]

Water (0.03 ml, 1.77 mmol) was added *via* syringe to a solution of potassium *tert*-butoxide (0.66 g, 5.92 mmol) in dry THF (5 ml) and *tert*-butanol (0.5 ml) at rt under an atmosphere of nitrogen. The solution was stirred for 10 mins and then a solution of sulfonyloxirane **405** (0.18 g, 0.59 mmol) in dry THF (5 ml) was added

*via* syringe. The solution was stirred at rt for 3 days and then at ca. 40 °C for a further 2 days. The solution was then diluted with water (30 ml) and extracted with DCM (3 × 50 ml). The combined organic extracts were dried over sodium sulfate and evaporated to afford the starting sulfonyloxirane **405** (0.17 g).

Method C: By hydrolysis of sulfonyloxirane **405** with $TiCl_4/H_2O$[25]

Titanium (IV) chloride (0.11 ml, 1.05 mmol) was added *via* syringe to a solution of sulfonyloxirane **405** (0.16 g, 0.52 mmol) in dry DCM (10 ml) at rt under an atmosphere of nitrogen. The solution was stirred at rt for 1 hour. Water (20 ml) was then added and the solution was stirred for a further 2 hours. The phases were separated and the aqueous phase was extracted with DCM (4 × 25 ml). The combined organic extracts were dried over sodium sulfate and evaporated to yield a dark brown oil (0.1 g).

Method D: By Upjohn dihydroxylation of vinyl sulfone **404**[34]

Vinyl sulfone **404** (0.18 g, 0.63 mmol) and methanesulfonamide (0.06 g, 0.63 mmol) were dissolved in acetone (5 ml) and water (1 ml) and *N*-methylmorpholine-*N*-oxide (0.22 g, 1.9 mmol) was added. Osmium tetroxide (0.2 ml, 2.5 wt. % soln. in *tert*-butanol, 2.5 mol %) was added and the mixture was stirred at rt for 6 days. The mixture was diluted with DCM (100 ml) and solid sodium sulfite (0.5 g) and sodium hydrogen carbonate (0.05 g, 0.63 mmol) were added and the mixture was vigorously stirred for 15 min. The mixture was filtered through celite and washed with water and DCM. The filtrate was transferred to a separating funnel and the phases were mixed and separated. The aqueous phase was extracted with DCM (50 ml). The combined organic extracts were dried over sodium sulfate and evaporated to yield a brown oil (0.11 g) whose $^1$H NMR spectrum showed it to be benzyl alcohol.

Method E: By Sharpless asymmetric dihydroxylation of vinyl sulfone **404**[9]

Vinyl sulfone **404** (1.36 g, 4.72 mmol) was dissolved in *tert*-butanol (20 ml) and water (20 ml) and methanesulfonamide (0.56 g, 5.90 mmol) was added. AD-mix α (8.88 g, 18.88 mmol of $K_3[Fe(CN)_6]$) was then added and the mixture was vigorously stirred at rt for 3 weeks. The mixture was then partitioned between DCM (100 ml) and water (50 ml) with vigorous stirring for 30 mins. The phases

were separated and the aqueous phase was extracted with DCM (4 × 25 ml). The combined organic extracts were dried over sodium sulfate and evaporated to afford the starting sulfone **404** as an oil (1.16 g).

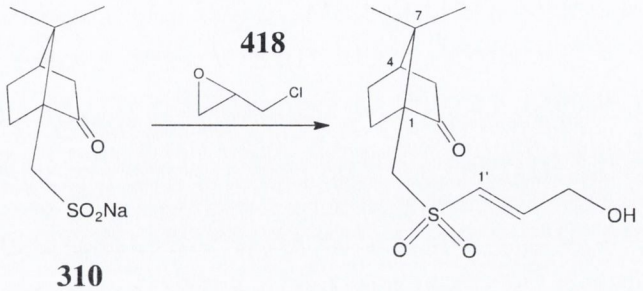
**Attempted silanolysis of sulfonyloxirane 405 with potassium trimethylsilanolate**

Magnesium chloride (0.051 g, 0.54 mmol) was added to a solution of potassium trimethylsilanolate (0.069 g, 0.54 mmol) in dry THF (5 ml) under an atmosphere of nitrogen. The solution was stirred for 10 mins and then a solution of sulfonyloxirane **405** (0.15 g, 0.49 mmol) in dry THF (5 ml) was added *via* syringe. The solution was stirred at rt for 17 hrs and then heated under reflux for a further 26 hrs. The solution was then allowed to cool to rt, diluted with water (50 ml) and extracted with ether (3 × 50 ml). The combined organic extracts were dried over sodium sulfate and evaporated to afford the starting sulfonyloxirane **405** (0.14 g).

**Attempted Wittig reaction of the crude product from Method C above with methoxycarbonylmethylenetriphenylphosphorane**[14]

The crude product (0.1 g) and methoxycarbonylmethylenetriphenylphosphorane (0.74 g, 2.22 mmol) were dissolved in dry benzene (20 ml) under an atmosphere of nitrogen. The solution was heated under reflux for 24 hrs. The solution was then allowed to cool to rt and diluted with DCM (100 ml). The solution was then washed with water (50 ml), dried over sodium sulfate and evaporated to afford a pale brown solid whose $^{1}$H NMR spectrum showed it to consist of the unreacted phosphorane.

**(1*S*, 4*R*)-1-({[(1'*E*)-3'-Hydroxyprop-1'-enyl]sulfonyl}methyl)-7,7-dimethylbicyclo[2.2.1]heptan-2-one 423**




**310** **423**

Method A:[17]

Sodium sulfinate **310** (9.5 g, 39 mmol) was dissolved in water (42 ml) and ethanol (10.5 ml) and epichlorohydrin **418** (6.2 ml, 79 mmol) was added. The solution was stirred at rt for 10 days. The solution was then diluted with water (100 ml) and extracted with ethyl acetate (3 × 100 ml). The combined organic extracts were washed with brine (50 ml), dried and evaporated to yield an oil. Removal of excess epichlorohydrin on an oil pump afforded an oil (9.65 g, 88 %) which slowly crystallised after several days. A small portion of the product was triturated with a small volume of ether to afford the title compound as a white solid.

Method B:[36]

Sodium sulfinate **310** (0.95 g, 3.9 mmol) was dissolved in water (10 ml) and DMF (0.5 ml) and epichlorohydrin **418** (0.62 ml, 7.9 mmol) was added. The solution was heated under reflux for 6 hrs. The mixture was then allowed to cool to rt, diluted with water (50 ml) and extracted with ethyl acetate (3 × 50 ml). The combined organic extracts were dried and evaporated to yield an oil. Removal of excess epichlorohydrin on an oil pump afforded an oil (0.92 g, 85 %) which slowly crystallised after several days.

m.p.: 71 °C (from ether)

$[\alpha]_D$ (*c* 0.5, MeOH, 26 °C) +26.8

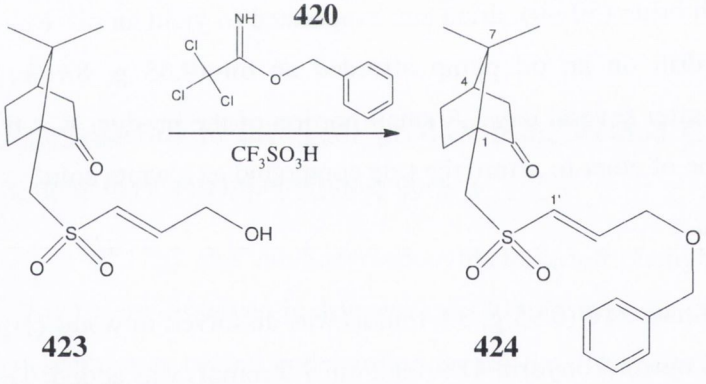
IR: $\nu_{max}$ (N) 3523 (O-H), 3061, 2923, 1740 (C=O), 1635 (C=C), 1454, 1414, 1375, 1310 ($SO_2$), 1199, 1130 ($SO_2$), 1104, 1052, 1018, 943, 837, 788, 674 $cm^{-1}$

$^1$H NMR (400.1 MHz): δ 0.86 (3H, s, 7-C*H*$_3$), 1.07 (3H, s, 7-C*H*$_3$), 1.42-1.48 (1H, m), 1.70-1.77 (1H, m), 1.93 (1H, d, $^2J$ = 18.4, 3-C*H*$_2$ *endo*), 2.02-2.08 (1H, m), 2.12 (1H, t, $^3J$ = 4.5, 4-C*H*), 2.37 (1H, dt, $^2J$ = 18.4, $^3J$ = 4.5, 3-C*H*$_2$ *exo*), 2.46 (1H, m), 2.87 (1H, d, $^2J$ = 15.0, C*H*$_2$SO$_2$), 3.44 (1H, d, $^2J$ = 15.0, C*H*$_2$SO$_2$), 4.40 (2H, dd, $^3J$ = 3.4, $^4J$ = 2.7, 3'-C*H*$_2$), 6.83 (1H, dt, $^3J$ = 15.0, $^4J$ = 2.7, 1'-C*H*), 6.96 (1H, dt, $^3J_1$ = 15.0, $^3J_2$ = 3.4, 2'-C*H*) ppm

$^{13}$C NMR (100.6 MHz): δ 19.2 (7-*C*H$_3$), 19.2 (7-*C*H$_3$), 24.3 (C-5), 26.5 (C-6), 41.9 (C-4), 42.1 (C-3), 48.1 (C-7), 51.4 (*C*H$_2$SO$_2$), 58.2 (C-1), 60.3 (C-3'), 128.8 (C-1'), 146.0 (C-2'), 214.9 (C-2) ppm

HRMS (CI) *m/z* 295.0930: *calculated for* [$C_{13}H_{20}O_4S$ + Na]$^+$ 295.0979

**(1*S*, 4*R*)-1-({[(1'*E*)-3'-Benzyloxyprop-1'-enyl]sulfonyl}methyl)-7,7-dimethylbicyclo[2.2.1]heptan-2-one 424**




Following the procedure of Bundle,[18] sulfone **423** (2.5 g, 9.1 mmol) was dissolved in dry DCM (40 ml) and dry hexane (80 ml) and benzyl-2,2,2-trichloroacetimidate **420** (2.5 ml, 13.6 mmol) was added. Trifluoromethanesulfonic acid (1 ml) was added dropwise and the solution was stirred at rt for 48 hrs. Hexane (100 ml) was added and the precipitated trichloroacetamide was filtered. The filtrate was diluted with ether (100 ml) and washed with satd. aq. sodium hydrogen carbonate (50 ml) and brine (50 ml), dried and evaporated to yield an oil. Column chromatography on silica gel using EtOAc:Hexane(1:2) afforded the title compound as a clear oil (2.2 g, 66 %).

$[\alpha]_D$ (*c* 0.57, MeOH, 26 °C) +27.3

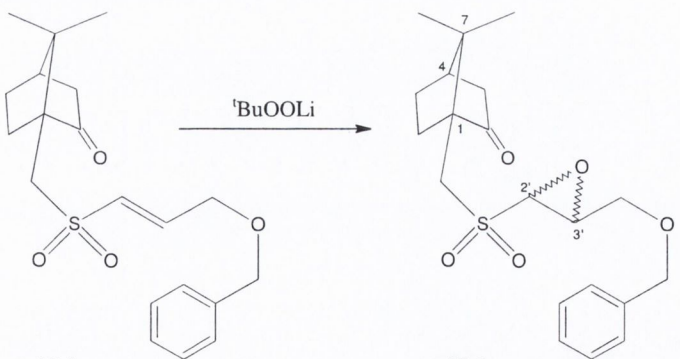
IR: $\nu_{max}$ (L) 3062, 3029, 2959, 1740 (C=O), 1639 (C=C), 1601 (Ar C-C), 1495, 1454, 1392, 1360, 1314 ($SO_2$), 1279, 1201, 1121 ($SO_2$), 1051, 1026, 945, 908, 831, 784, 739, 699 $cm^{-1}$

$^1H$ NMR (400.1 MHz): δ 0.87 (3H, s, 7-C*H*$_3$), 1.09 (3H, s, 7-C*H*$_3$), 1.41-1.47 (1H, m), 1.69-1.74 (1H, m), 1.93 (1H, d, $^2J$ = 18.5, 3-C*H*$_2$ *endo*), 2.01-2.08 (1H, m), 2.12 (1H, t, $^3J$ = 4.5, 4-C*H*), 2.38 (1H, dt, $^2J$ = 18.5, $^3J$ = 4.5, 3-C*H*$_2$ *exo*), 2.50 (1H, m), 2.86 (1H, d, $^2J$ = 15.0, C*H*$_2$SO$_2$), 3.45 (1H, d, $^2J$ = 15.0, C*H*$_2$SO$_2$), 4.24 (2H, dd, $^3J$ = 3.0, $^4J$ = 1.5, 3'-C*H*$_2$), 4.60 (2H, s, benzyl C*H*$_2$), 6.85 (1H, dt, $^3J$ = 15.0, $^4J$ = 1.5, 1'-C*H*), 6.92 (1H, dt, $^3J_1$ = 15.0, $^3J_2$ = 3.0, 2'-C*H*), 7.31-7.38 (5H, m, Ar*H*) ppm

$^{13}C$ NMR (100.6 MHz): δ 19.2 (7-*C*H$_3$), 19.3 (7-*C*H$_3$), 24.3 (C-5), 26.6 (C-6), 42.0 (C-4), 42.1 (C-3), 47.9 (C-7), 51.3 (*C*H$_2$SO$_2$), 58.2 (C-1), 67.1 (C-3'), 72.5 (benzyl *C*H$_2$), 127.2 (Ar C-3), 127.5 (Ar C-4), 128.0 (Ar C-2), 129.9 (C-1'), 136.9 (Ar C-1), 142.7 (C-2'), 214.3 (C-2) ppm

HRMS (CI) *m/z* 385.1455: *calculated for* $[C_{20}H_{26}O_4S + Na]^+$ 385.1449

**(1*S*, 4*R*)-1-({[3'-(Benzyloxymethyl)oxiran-2'-yl]sulfonyl}methyl)-7,7-dimethylbicyclo[2.2.1]heptan-2-one 426**




**424** **426**

Method A:

*n*-Butyllithium (3.8 ml, 2.5 M, 9.5 mmol) was added dropwise *via* syringe to a solution of *tert*-butylhydroperoxide (8 ml, 1.17 M in benzene, 9.5 mmol) in dry

THF (7 ml) at -78 °C under an atmosphere of nitrogen. The solution was allowed to warm to -20 °C and a solution of sulfone **424** (1.15 g, 3.1 mmol) in dry THF (14 ml) was added dropwise *via* syringe. The solution was stirred at -20 °C for 2.5 hrs. The solution was allowed to warm to rt, quenched with satd. aq. sodium sulfite (50 ml) and extracted with ether (3 × 100 ml). The combined organic extracts were washed with brine (50 ml), dried over sodium sulfate and evaporated to yield an oil (0.84 g) whose $^1$H NMR spectrum showed it to consist of two diastereomers of sulfone **426** in ca. 5.8:1 ratio. Column chromatography on silica gel using EtOAc:Hexane (1:2) afforded the title compound (both diastereomers in ca. 5.8:1 diastereomer ratio) as a colourless oil (0.55 g, 45 %).

IR: $\nu_{max}$ (L) 3029, 2959, 1744 (C=O), 1601 (Ar C-C), 1454, 1393, 1323 ($SO_2$), 1273, 1216, 1139 ($SO_2$), 1051, 965, 917, 825, 741, 699 cm$^{-1}$

Major diastereomer:

$^1$H NMR (400.1 MHz): δ 0.91 (3H, s, 7-C*H*$_3$), 1.09 (3H, s, 7-C*H*$_3$), 1.46-1.52 (1H, m), 1.78-1.85 (1H, m), 2.00 (1H, d, $^2J$ = 18.5, 3-C*H*$_2$ *endo*), 2.04-2.11 (1H, m), 2.16 (1H, t, $^3J$ = 4.5, 4-C*H*), 2.33-2.44 (2H, m), 2.92 (1H, d, $^2J$ = 15.0, C*H*$_2$SO$_2$), 3.55 (1H, d, $^2J$ = 15.0, C*H*$_2$SO$_2$), 3.67 (1H, dd, $^2J$ = 12.0, $^3J$ = 4.5, C*H*$_2$OCH$_2$Ph), 3.80 (1H, app qu, $^3J$ = 2.0, 3'-C*H*), 3.93 (1H, dd, $^2J$ = 12.0, $^3J$ = 2.0, C*H*$_2$OCH$_2$Ph), 4.49 (1H, d, $^3J$ = 1.5, 2'-C*H*), 4.58 (2H, s, CH$_2$OC*H*$_2$Ph), 7.28-7.40 (5H, m, Ar*H*) ppm

$^{13}$C NMR (100.6 MHz): δ 19.1 (7-*C*H$_3$), 19.2 (7-*C*H$_3$), 24.6 (C-5), 26.5 (C-6), 42.0 (C-3), 42.1 (C-4), 48.0 (C-7), 49.8 (*C*H$_2$SO$_2$), 54.6 (C-3'), 57.9 (C-1), 64.6 (C-2'), 66.2 (*C*H$_2$OCH$_2$Ph), 73.0 (CH$_2$O*C*H$_2$Ph), 127.3 (Ar C-3), 127.5 (Ar C-4), 128.0 (Ar C-2), 136.7 (Ar C-1), 214.4 (C-2) ppm

Minor diastereomer:

$^1$H NMR (400.1 MHz): δ 0.91 (3H, s, 7-C*H*$_3$), 1.05 (3H, s, 7-C*H*$_3$), 1.34-1.52 (2H, m), 1.96 (1H, d, $^2J$ = 18.5, 3-C*H*$_2$ *endo*), 2.00-2.11 (1H, m), 2.15 (1H, t, $^3J$ = 4.5, 4-C*H*), 2.24-2.31 (1H, m), 2.36-2.45 (1H, m), 2.89 (1H, d, $^2J$ = 15.0, C*H*$_2$SO$_2$), 3.53 (1H, d, $^2J$ = 15.0, C*H*$_2$SO$_2$), 3.65 (1H, dd, $^2J$ = 12.0, $^3J$ = 4.5, C*H*$_2$OCH$_2$Ph), 3.85 (1H, app qu, $^3J$ = 2.0, 3'-C*H*), 3.92 (1H, dd, $^2J$ = 12.0, $^3J$ = 2.0, C*H*$_2$OCH$_2$Ph), 4.59 (2H, s, CH$_2$OC*H*$_2$Ph), 4.66 (1H, d, $^3J$ = 2.0, 2'-C*H*), 7.29-7.39 (5H, m, Ar*H*) ppm

$^{13}$C NMR (100.6 MHz): δ 19.1 (7-*C*H$_3$), 19.3 (7-*C*H$_3$), 25.4 (C-5), 26.6 (C-6), 42.1 (C-3), 42.1 (C-4), 48.3 (C-7), 49.4 (*C*H$_2$SO$_2$), 55.7 (C-3'), 58.6 (C-1), 65.3 (C-2'), 66.2 (*C*H$_2$OCH$_2$Ph), 73.0 (CH$_2$O*C*H$_2$Ph), 127.3 (Ar C-3), 127.5 (Ar C-4), 128.0 (Ar C-2), 136.7 (Ar C-1), 214.4 (C-2) ppm

HRMS (CI) *m/z* 401.1401: *calculated for* [$C_{20}H_{26}O_5S$ + Na]$^+$ 401.1398

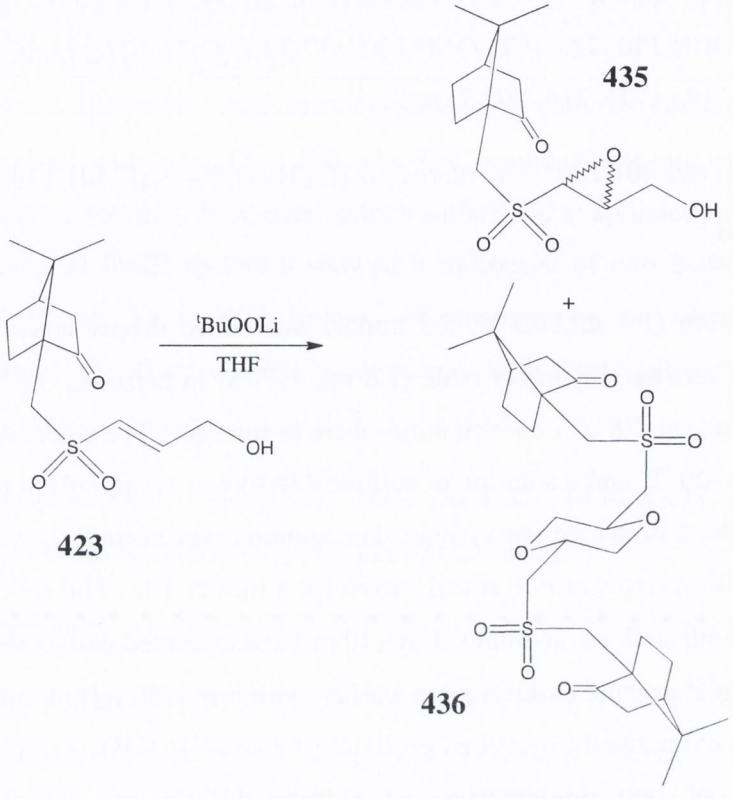
Method B[43]:

*n*-Butyllithium (1.3 ml, 2.5 M, 3.3 mmol) was added dropwise *via* syringe to a solution of *tert*-butylhydroperoxide (2.8 ml, 1.17 M in benzene, 3.3 mmol) in dry toluene (4 ml) at -78 °C under an atmosphere of nitrogen. The solution was allowed to warm to -20 °C and a solution of sulfone **424** (0.4 g, 1.1 mmol) in dry toluene (6 ml) was added dropwise *via* syringe. The solution was stirred at -20 °C for 3 hrs and then allowed to warm to rt and stirred for a further 1 hr. The solution was then quenched with satd. aq. sodium sulfite (40 ml) and extracted with ether (3 × 50 ml). The combined organic extracts were washed with brine (50 ml), dried over sodium sulfate and evaporated to yield an oil (0.32 g) whose $^1$H NMR spectrum showed it to consist of two diastereomers of sulfone **426** in ca. 1:1 ratio. Column chromatography on silica gel using EtOAc:Hexane (1:2) afforded the title compound (ca. 1:1 diastereomer ratio) as a colourless oil (0.21 g, 51 %).

**Attempted intramolecular epoxidation of sulfone 424 with oxone[46]**

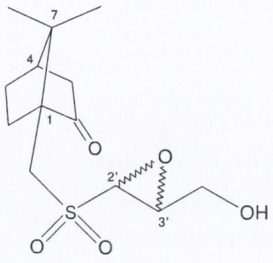
Sulfone **424** (0.2 g, 0.55 mmol) and triethylhexylammonium bromide (0.02 g, 20 mol %) were dissolved in acetonitrile (5 ml) and warmed to 40 °C. A solution of oxone (1.35 g, 4.41 mmol) and sodium hydrogen carbonate (0.37 g, 4.41 mmol) in aq. $Na_2$[EDTA] soln. (20 ml, 0.4 mM) was added dropwise and the mixture was stirred at 40 °C for 6 days. The mixture was diluted with water (20 ml) and extracted with ether (3 × 50 ml). The combined organic extracts were washed with brine (50 ml), dried and evaporated to yield unchanged starting sulfone **424** (0.16 g) as an oil.

**Nucleophilic epoxidation of sulfone 423**




*n*-Butyllithium (2.4 ml, 2.5 M, 6.0 mmol) was added dropwise *via* syringe to a solution of *tert*-butylhydroperoxide (5 ml, 1.17 M in benzene, 6.0 mmol) in dry THF (6 ml) at -78 °C under an atmosphere of nitrogen. The solution was allowed to warm to -20 °C and a solution of sulfone **423** (0.55 g, 3.1 mmol) in dry THF (8 ml) was added dropwise *via* syringe. The solution was stirred at -20 °C for 2 hrs. The solution was then allowed to warm to rt, quenched with satd. aq. sodium sulfite (40 ml) and extracted with ethyl acetate (3 × 50 ml). The combined organic extracts were dried over sodium sulfate and evaporated to yield an oil (0.27 g) whose $^1$H NMR spectrum showed it to consist of two diastereomers of sulfone **435** in ca. 4.7:1 ratio. Column chromatography on silica gel using EtOAc:Hexane (1:1) afforded sulfone **435** (ca. 4.7:1 diastereomer ratio) as a colourless oil (0.09 g, 15 %). A white solid precipitated from the crude product on addition of the chromatography solvent system and was identified as dioxane **436** (0.15 g, 27 %).

**(1*S*, 4*R*)-1-({[3'-(Hydroxymethyl)oxiran-2'-yl]sulfonyl}methyl)-7,7-dimethylbicyclo[2.2.1]heptan-2-one 435**




**435**

IR: $\nu_{max}$ (L) 3504 (O-H), 2960, 1739 (C=O), 1454, 1394, 1320 ($SO_2$), 1274, 1216, 1137 ($SO_2$), 1054, 916, 881, 826, 734, 678 $cm^{-1}$

Major diastereomer:

$^1$H NMR (400.1 MHz): δ 0.90 (3H, s, 7-C*H*$_3$), 1.04 (3H, s, 7-C*H*$_3$), 1.46-1.52 (1H, m), 1.90-2.01 (1H, m), 1.96 (1H, d, $^2J$ = 18.5, 3-C*H*$_2$ *endo*), 2.02-2.10 (1H, m), 2.16 (1H, t, $^3J$ = 4.0, 4-C*H*), 2.24-2.31 (1H, m), 2.41 (1H, dt, $^2J$ = 18.5, $^3J$ = 4.0, 3-C*H*$_2$ *exo*), 2.88 (1H, d, $^2J$ = 15.0, C*H*$_2$SO$_2$), 3.53 (1H, d, $^2J$ = 15.0, C*H*$_2$SO$_2$), 3.78-3.80 (1H, m, 3'-C*H*), 3.87 (1H, dd, $^2J$ = 13.5, $^3J$ = 3.0, C*H*$_2$OH), 4.05 (1H, dd, $^2J$ = 13.5, $^3J$ = 2.0, C*H*$_2$OH), 4.68 (1H, d, $^3J$ = 1.5, 2'-C*H*) ppm

$^{13}$C NMR (100.6 MHz): δ 19.0 (7-*C*H$_3$), 19.3 (7-*C*H$_3$), 25.3 (C-5), 26.6 (C-6), 42.1 (C-4), 42.1 (C-3), 48.4 (C-7), 49.4 (*C*H$_2$SO$_2$), 56.9 (C-3'), 58.5 (*C*H$_2$OH), 58.6 (C-1), 65.2 (C-2'), 215.0 (C-2) ppm

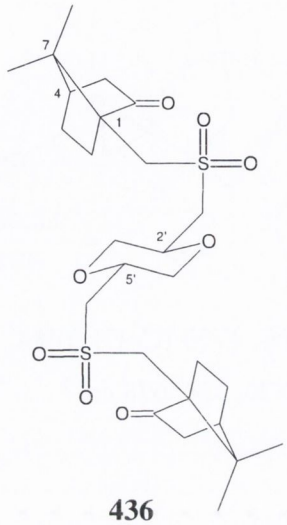
Minor diastereomer:

$^1$H NMR (400.1 MHz): δ 0.89 (3H, s, 7-C*H*$_3$), 1.07 (3H, s, 7-C*H*$_3$), 1.46-1.52 (1H, m), 1.75-1.82 (1H, m), 1.90-2.01 (1H, m), 1.96 (1H, d, $^2J$ = 18.5, 3-C*H*$_2$ *endo*), 2.02-2.10 (1H, m), 2.16 (1H, t, $^3J$ = 4.0, 4-C*H*), 2.41 (1H, dt, $^2J$ = 18.5, $^3J$ = 4.0, 3-C*H*$_2$ *exo*), 2.92 (1H, d, $^2J$ = 15.0, C*H*$_2$SO$_2$), 3.53 (1H, d, $^2J$ = 15.0, C*H*$_2$SO$_2$), 3.73-3.75 (1H, m, 3'-C*H*), 3.87 (1H, dd, $^2J$ = 13.5, $^3J$ = 3.0, C*H*$_2$OH), 4.05 (1H, dd, $^2J$ = 13.5, $^3J$ = 2.0, C*H*$_2$OH), 4.53 (1H, d, $^3J$ = 1.5, 2'-C*H*) ppm

$^{13}$C NMR not observed

HRMS (CI) *m/z* 311.0917: *calculated for* $[C_{13}H_{20}O_5S + Na]^+$ 311.0928

**(1*S*, 4*R*)-1-[({[5'-({[(7,7-Dimethyl-2-oxobicyclo[2.2.1]hept-1-yl)methyl]sulfonyl}methyl)-1',4'-dioxan-2'-yl]methyl}sulfonyl)methyl]-7,7-dimethylbicyclo[2.2.1]heptan-2-one 436**



**436**

m.p.: 211 °C (from ether)

IR: $\nu_{max}$ (N) 2919, 1728 (C=O), 1458, 1376, 1306 ($SO_2$), 1120 ($SO_2$), 1053, 1020, 921, 790, 723, 663 $cm^{-1}$

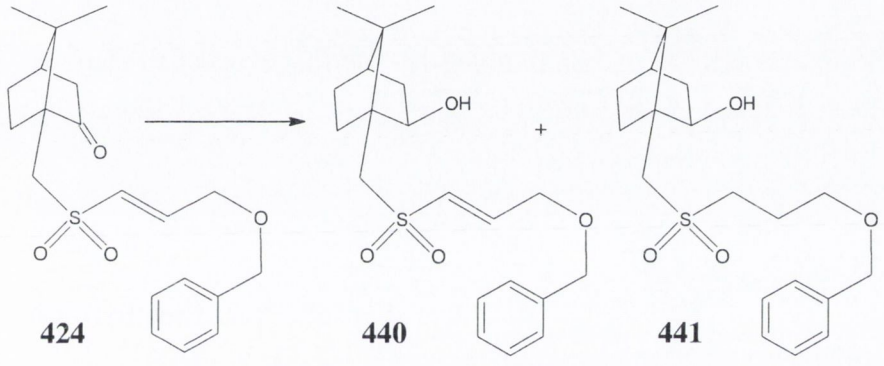
Diastereomers A and B:

$^1$H NMR (400.1 MHz): δ 0.90 (12H, s, 7-C*H*$_3$), 1.06 (6H, s, 7-C*H*$_3$), 1.09 (6H, s, 7-C*H*$_3$), 1.45-1.51 (4H, m), 1.77-1.84 (2H, m), 1.90-1.97 (2H, m), 1.95 (2H, d, $^2J$ = 18.0, 3-C*H*$_2$ *endo*), 1.96 (2H, d, $^2J$ = 18.5, 3-C*H*$_2$ *endo*), 2.03-2.11 (4H, m), 2.13-2.16 (4H, m, 4-C*H*), 2.29-2.48 (8H, m), 2.89 (2H, d, $^2J$ = 15.0, 1- C*H*$_2$SO$_2$), 2.96 (2H, dd, $^2J$ = 14.5, $^3J$ = 4.0, 2' and 5'- C*H*$_2$SO$_2$), 2.97 (2H, d, $^2J$ = 15.0, 1-C*H*$_2$SO$_2$), 3.11 (2H, dd, $^2J$ = 14.5, $^3J$ = 4.0, 2' and 5'- C*H*$_2$SO$_2$), 3.29 (2H, dd, $^2J$ = 14.5, $^3J$ = 7.5 , 2' and 5'- C*H*$_2$SO$_2$), 3.58 (4H, app t, $^2J$ = 11.5, $^3J$ = 11.5, 3' and 6'-C*H*$_2$ *axial*), 3.64 (4H, d, $^2J$ = 15.0, 1- C*H*$_2$SO$_2$), 3.76 (2H, dd, $^2J$ = 14.5, $^3J$ = 9.0, 2' and 5'- C*H*$_2$SO$_2$), 3.91 (2H, dd, $^2J$ = 11.5, $^3J$ = 2.5, 3' and 6'-C*H*$_2$ *equatorial*), 3.96 (2H, dd, $^2J$ = 11.5, $^3J$ = 2.5, 3' and 6'-C*H*$_2$ *equatorial*), 4.18-4.23 (2H, m, 2' and 5'-C*H*), 4.23-4.29 (2H, m, 2' and 5'-C*H*) ppm

$^{13}$C NMR (100.6 MHz): δ 19.2 (7-*C*H$_3$), 19.3 (7-*C*H$_3$), 19.3 (7-*C*H$_3$), 19.3 (7-*C*H$_3$), 24.5 (C-5), 25.2 (C-5), 26.6 (C-6), 26.7 (C-6), 42.0 (C-4), 42.1 (C-4), 42.1 (C-3), 42.2 (C-3), 48.0 (C-7), 48.2 (C-7), 51.6 (1- *C*H$_2$SO$_2$), 52.8 (1- *C*H$_2$SO$_2$), 56.4 (2' and 5'- *C*H$_2$SO$_2$), 56.4 (2' and 5'- *C*H$_2$SO$_2$), 58.3 (C-1), 58.8 (C-1), 69.1 (C-3' and C-6'), 69.1 (C-3' and C-6'), 69.2 (C-2' and C-5'), 69.7 (C-2' and C-5'), 214.6 (C-2), 214.6 (C-2) ppm

HRMS (CI) *m/z* 567.2039: *calculated for* $[C_{26}H_{40}O_8S_2 + Na]^+$ 567.2061

**Reduction of vinyl sulfone 424**




**424** **440** **441**

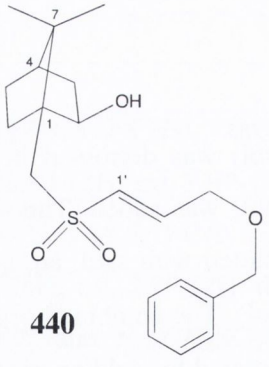
Method A:

Sulfone **424** (0.4 g, 1.1 mmol) was dissolved in methanol (20 ml) and sodium borohydride (0.16 g, 4.4 mmol) was added. The solution was stirred at rt for 3.5 hrs. The solution was then diluted with satd. aq. ammonium chloride (50 ml) and extracted with ether (3 × 50 ml). The combined organic extracts were washed with brine (50 ml), dried and evaporated to yield an oil (0.36 g). The crude product was purified over silica gel, eluting with EtOAc:hexane (1:3) to yield two products. The first product to elute was sulfone **440** (0.18 g, 45 %) as a colourless oil. The second product to elute was sulfone **441** (0.13 g, 32 %) as a colourless oil.

Method B:[78]

Sulfone **424** (1.04 g, 2.8 mmol) was dissolved in dry THF (8 ml) under an atmosphere of nitrogen and cooled to 0 °C. Diisobutylaluminium hydride (3.43 ml, 1.5 M in toluene, 5.1 mmol) was added *via* syringe and the solution was stirred at 0 °C for 1 hr ant then allowed to warm to rt and stirred for an additional 4 hrs. The solution was then diluted with ammonium hydroxide (50 ml) and DCM (100 ml) and stirred vigorously for 1.5 hrs. The combined phases were filtered through Celite$^{R}$ and the filtrate was transferred to a separating funnel. The phases were mixed and separated and the aqueous layer was extracted with DCM (50 ml). The combined organic extracts were washed with brine (50 ml), dried and evaporated to yield an oil (1 g). The crude product was purified over silica gel, eluting with EtOAc:hexane (1:3) to yield two products. The first product to elute was sulfone **440** (0.34 g, 32 %) as a colourless oil. The second product to elute was sulfone **441** (0.50 g, 48 %) as a colourless oil.

**(1*S*, 2*R*, 4*R*)-1-({[(1'*E*)-3'-Benzyloxyprop-1'-enyl]sulfonyl}methyl)-7,7-dimethylbicyclo[2.2.1]heptan-2-ol 440**




**440**

$[\alpha]_D$ (*c* 0.7, MeOH, 25 °C) -23.7

IR: $\nu_{max}$ (L) 3517 (O-H), 2954, 2879, 1640 (C=C), 1601 (Ar C-C), 1495, 1454, 1389, 1307 ($SO_2$), 1123 ($SO_2$), 1075, 1027, 949, 880, 825, 737, 698 $cm^{-1}$

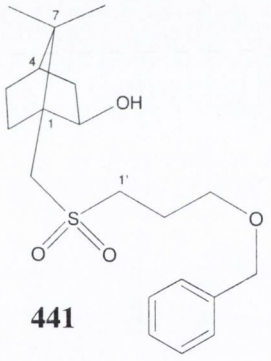
$^1$H NMR (400.1 MHz): δ 0.82 (3H, s, 7-C*H*$_3$), 1.08 (3H, s, 7-C*H*$_3$), 1.13-1.18 (1H, m), 1.55-1.63 (1H, m), 1.68-1.84 (5H, m), 2.86 (1H, d, $^2J$ = 13.5, C*H*$_2$SO$_2$), 3.41

(1H, d, $^2J$ = 13.5, C$H_2$SO$_2$), 4.18 (1H, dd, $^3J_1$ = 8.0, $^3J_2$ = 4.0, 2-C*H*), 4.27 (2H, dd, $^3J$ = 3.0, $^4J$ = 2.0, 3'-C$H_2$), 4.62 (2H, s, benzyl C$H_2$), 6.75 (1H, dt, $^3J$ = 15.0, $^4J$ = 2.0, 1'-C*H*), 6.98 (1H, dt, $^3J_1$ = 15.0, $^3J_2$ = 3.0, 2'-C*H*), 7.28-7.43 (5H, m, Ar*H*) ppm

$^{13}$C NMR (100.6 MHz): δ 19.3 (7-*C*H$_3$), 20.0 (7-*C*H$_3$), 27.0 (C-5), 30.2 (C-6), 38.5 (C-3), 43.6 (C-4), 48.6 (C-7), 50.3 (C-1), 53.7 (*C*H$_2$SO$_2$), 67.0 (C-3'), 72.8 (benzyl *C*H$_2$), 75.8 (C-2), 127.2 (Ar C-3), 127.6 (Ar C-4), 128.1 (Ar C-2), 128.9 (C-1'), 136.6 (Ar C-1), 143.8 (C-2') ppm

HRMS (CI) *m/z* 387.1606: *calculated for* [$C_{20}H_{28}O_4S$ + Na]$^+$ 387.1605

**(1*S*, 2*R*, 4*R*)-1-({[3'-Benzyloxypropyl]sulfonyl}methyl)-7,7-dimethylbicyclo[2.2.1]heptan-2-ol 441**




**441**

[α]$_D$ (*c* 0.13, MeOH, 25 °C) -20.0

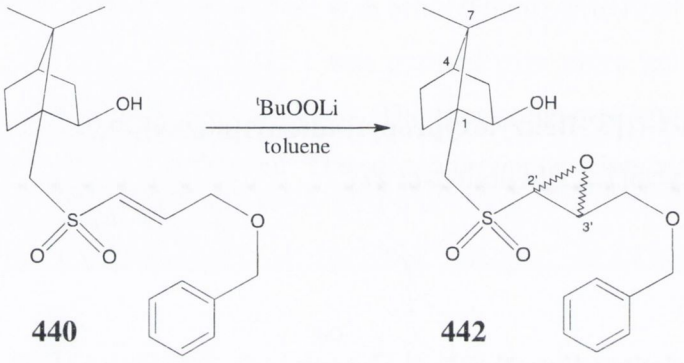
IR: $\nu_{max}$ (L) 3512 (O-H), 2954, 2878, 1602 (Ar C-C), 1454, 1370, 1307 (SO$_2$), 1124 (SO$_2$), 1075, 1027, 879, 830, 738, 698 cm$^{-1}$

$^1$H NMR (400.1 MHz): δ 0.83 (3H, s, 7-C$H_3$), 1.08 (3H, s, 7-C$H_3$), 1.13-1.18 (1H, m), 1.57-1.62 (1H, m), 1.70-1.87 (5H, m), 2.14-2.21 (2H, m, 2'-C$H_2$), 2.85 (1H, d, $^2J$ = 13.5, C$H_2$SO$_2$), 3.19 (2H, app dd, $^3J_1$ = 7.5, $^3J_2$ = 6.0, 1'-C$H_2$), 3.40 (1H, d, $^2J$ = 13.5, C$H_2$SO$_2$), 3.62 (2H, t, $^3J$ = 6.0, 3'-C$H_2$), 4.16 (1H, dd, $^3J_1$ = 8.5, $^3J_2$ = 4.0, 2-C*H*), 4.53 (2H, s, benzyl C$H_2$), 7.31-7.39 (5H, m, Ar*H*) ppm

$^{13}$C NMR (100.6 MHz): δ 19.4 (7-*C*H$_3$), 20.1 (7-*C*H$_3$), 22.3 (C-2'), 27.0 (C-5), 30.0 (C-6), 38.5 (C-3), 43.6 (C-4), 48.6 (C-7), 50.0 (C-1), 51.2 (C-1'), 52.0 (*C*H$_2$SO$_2$), 67.3 (C-3'), 72.6 (benzyl *C*H$_2$), 75.7 (C-2), 127.2 (Ar C-3), 127.4 (Ar C-4), 128.0 (Ar C-2), 137.3 (Ar C-1) ppm

HRMS (CI) *m/z* 389.1743: *calculated for* [$C_{20}H_{30}O_4S$ + Na]$^+$ 389.1762

**(1*S*, 2*R*, 4*R*)-1-({[3'-(Benzyloxymethyl)oxiran-2'-yl]sulfonyl}methyl)-7,7-dimethylbicyclo[2.2.1]heptan-2-ol 442**




**440** **442**

*n*-Butyllithium (0.46 ml, 2.5 M, 1.1 mmol) was added dropwise *via* syringe to a solution of *tert*-butylhydroperoxide (0.98 ml, 1.17 M in benzene, 1.1 mmol) in dry toluene (4 ml) at -78 °C under an atmosphere of nitrogen. The solution was allowed to warm to -20 °C and a solution of sulfone **440** (0.21 g, 0.55 mmol) in dry toluene (4 ml) was added dropwise *via* syringe. The solution was stirred at -20 °C for 4 hrs and then allowed to warm to rt and stirred for a further 48 hrs. The solution was then quenched with satd. aq. sodium sulfite (40 ml) and extracted with ether (3 × 50 ml). The combined organic extracts were washed with brine (50 ml), dried over sodium sulfate and evaporated to yield an oil (0.23 g) whose $^1$H NMR spectrum showed it to consist of two diastereomers of sulfone **442** in ca. 1:1 ratio. Column chromatography on silica gel using EtOAc:Hexane (1:2) afforded the title compound (ca. 1:1 diastereomer ratio) as a colourless oil (0.21 g, 95 %).

IR: $\nu_{max}$ (L) 3537 (O-H), 2955, 2880, 1601 (Ar C-C), 1455, 1390, 1372, 1318 ($SO_2$), 1251, 1134 ($SO_2$), 1075, 1026, 916, 878, 739, 699 cm$^{-1}$

Diastereomers A and B:

$^{1}$H NMR (400.1 MHz): δ 0.86 (3H, s, 7-C*H*$_3$), 0.87 (3H, s, 7-C*H*$_3$), 1.09 (3H, s, 7-C*H*$_3$), 1.10 (3H, s, 7-C*H*$_3$), 1.14-1.19 (2H, m), 1.54-1.61 (2H, m), 1.75-1.88 (10H, m), 2.98 (1H, d, $^{2}J$ = 13.5, C*H*$_2$SO$_2$), 3.04 (1H, d, $^{2}J$ = 13.5, C*H*$_2$SO$_2$), 3.50 (1H, d, $^{2}J$ = 13.5, C*H*$_2$SO$_2$), 3.56 (1H, d, $^{2}J$ = 13.5, C*H*$_2$SO$_2$), 3.74 (2H, app dt, $^{2}J$ = 12.0, $^{3}J$ = 3.5, C*H*$_2$OCH$_2$Ph), 3.84-3.87 (2H, m, 3'-C*H*), 3.93 (2H, d, $^{2}J$ = 12.0, C*H*$_2$OCH$_2$Ph), 4.15 (2H, dd, $^{3}J_1$ = 8.5, $^{3}J_2$ = 4.0, 2-C*H*), 4.27 (2H, s, 2'-C*H*), 4.58 (4H, s, CH$_2$OC*H*$_2$Ph), 7.32-7.40 (10H, m, Ar*H*) ppm

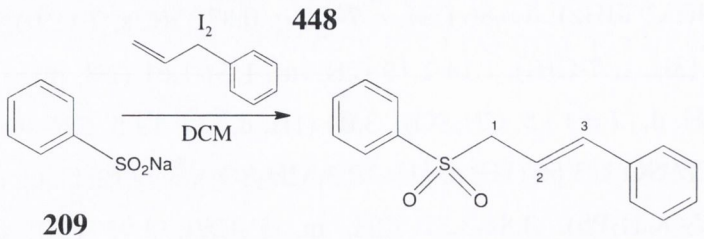
$^{13}$C NMR (100.6 MHz): δ 19.4 (7-*C*H$_3$), 19.4 (7-*C*H$_3$), 20.0 (7-*C*H$_3$), 20.0 (7-*C*H$_3$), 27.0 (C-5), 27.0 (C-5), 30.0 (C-6), 30.0 (C-6), 38.7 (C-3), 38.7 (C-3), 43.6 (C-4), 43.6 (C-4), 48.7 (C-7), 48.7 (C-7), 49.8 (C-1), 50.0 (C-1), 50.2 (*C*H$_2$SO$_2$), 50.4 (*C*H$_2$SO$_2$), 54.8 (C-3'), 55.3 (C-3'), 64.0 (C-2'), 64.1 (C-2'), 65.4 (*C*H$_2$OCH$_2$Ph), 65.4 (*C*H$_2$OCH$_2$Ph), 73.1 (CH$_2$O*C*H$_2$Ph), 73.1 (CH$_2$O*C*H$_2$Ph), 75.7 (C-2), 75.8 (C-2), 127.3 (Ar C-3), 127.3 (Ar C-3), 127.6 (Ar C-4), 127.6 (Ar C-4), 128.1 (Ar C-2), 128.1 (Ar C-2), 136.5 (Ar C-1), 136.6 (Ar C-1) ppm

HRMS (CI) *m/z* 403.1550: *calculated for* $[C_{20}H_{28}O_5S + Na]^+$ 403.1554

**Attempted intramolecular epoxidation of sulfone 440 with titanium (IV) isopropoxide/*tert*-butyl hydroperoxide**[54]

Sulfone **440** (0.1 g, 0.27 mmol) was dissolved in dry DCM (5 ml) under an atmosphere of nitrogen and cooled to – 20 °C. Titanium (IV) isopropoxide (0.08 ml, 0.27 mmol) was added *via* syringe and the solution was allowed to warm to rt. After 1 hr, the solution was recooled to – 20 °C and *tert*-butylhydroperoxide (0.46 ml, 1.17 M in benzene, 0.54 mmol) was added *via* syringe. The solution was stirred at – 20 °C for 1 hr and then allowed to warm to rt and stirred for an additional 7 days. The solution was diluted with water (50 ml) and extracted with ether (3 × 50 ml). The combined organic extracts were washed with brine (50 ml), dried and evaporated to yield unchanged starting sulfone **440** (0.09 g) as an oil.

**{[(2*E*)-3-Phenylprop-2-enyl]sulfonyl}benzene 449**[55]




Method A:[21]

A solution of iodine (2 g, 7.8 mmol) in DCM (200 ml) was vigorously mixed with a solution of sodium benzenesulfinate **209** (1.42 g, 8.6 mmol) in water (100 ml) in a separating funnel. The yellow organic phase was placed in a round bottomed flask and allyl benzene **448** (1.04 ml, 7.8 mmol) was added. The solution was stirred at rt for 3 days. Triethylamine (1.1 ml, 7.8 mmol) was added and the solution was stirred for a further 24 hrs. The solution was then washed with water (50 ml) and the aqueous layer was extracted with ether (50 ml). The combined organic extracts were dried and evaporated to yield a semi-solid material (2.05 g) which was recrystallised from EtOAc:hexane (ca. 1:1) to yield the title compound (1.62 g, 80 %) as a white solid.

Method B:[57]

A solution of iodine (0.25 g, 0.98 mmol) in DCM (50 ml) was vigorously mixed with a solution of sodium benzenesulfinate **209** (0.17 g, 1.08 mmol) in water (25 ml) in a separating funnel. The yellow organic phase was placed in a round bottomed flask and allyl benzene **448** (0.13 ml, 0.98 mmol) was added. The solution was stirred at rt for 3 days. Alumina (ca. 50 ml, neutral) was added and the mixture was stirred for an additional 1 hr. The alumina was filtered and washed with DCM (100 ml) and the filtrate was dried and evaporated to yield the title compound as a white semi-solid (0.22 g, 88 %).

m.p.: 109-110 °C (from EtOAc/hexane); Lit.[79]: 115 °C

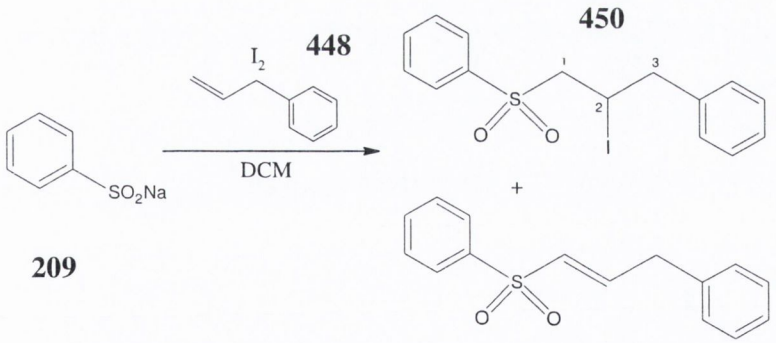
IR: $\nu_{max}$ (N) 3056, 2925, 1974, 1901, 1839, 1773, 1649 (C=C), 1585 (Ar C-C), 1446, 1402, 1376, 1292 ($SO_2$), 1238, 1134 ($SO_2$), 1083, 1025, 981, 906, 813, 738, 688 $cm^{-1}$

$^1H$ NMR (400.1 MHz): δ 3.98 (2H, d, $^3J$ = 7.5, 1-C*H*$_2$), 6.12 (1H, dt, $^3J_1$ = 15.5, $^3J_2$ = 7.5, 2-C*H*), 6.39 (1H, d, $^3J$ = 15.5, 3-C*H*), 7.28-7.35 (5H, m, Ph Ar*H*), 7.56 (2H, t, $^3J$ = 7.5, $PhSO_2$ *m*-Ar*H*), 7.66 (1H, t, $^3J$ = 7.5, $PhSO_2$ *p*-Ar*H*), 7.90 (2H, d, $^3J$ = 7.5, $PhSO_2$ *o*-Ar*H*) ppm

$^{13}C$ NMR (100.6 MHz): δ 60.0 (C-1), 114.6 (C-2), 126.1 (Ph Ar*C*), 128.0 ($PhSO_2$ Ar*C*), 128.0 (Ph Ar*C*), 128.2 (Ph Ar*C*), 128.6 ($PhSO_2$ Ar*C*), 133.3 ($PhSO_2$ Ar*C*), 135.2 ($PhSO_2$ Ar*C*), 137.8 (Ph Ar*C*), 138.7 (C-3) ppm

HRMS (CI) *m/z* 281.0612: *calculated for* $[C_{15}H_{14}O_2S + Na]^+$ 281.0611

**[(2-Iodo-3-phenylpropyl)sulfonyl]benzene 450**




447

A solution of iodine (0.5 g, 1.9 mmol) in DCM (100 ml) was vigorously mixed with a solution of sodium benzenesulfinate **209** (0.35 g, 2.1 mmol) in water (50 ml) in a separating funnel. The yellow organic phase was placed in a round bottomed flask and allyl benzene **448** (0.26 ml, 1.9 mmol) was added. The solution was stirred at rt for 3 days. The solution was then washed with water (50 ml) and the aqueous layer was extracted with ether (50 ml). The combined organic extracts were washed with satd. aq. sodium sulfite (50 ml), dried and evaporated to yield an oil (0.73 g). Column chromatography on silica gel using EtOAc:Hexane (1:3)

afforded the title compound as an oil (0.54 g, 71%) which later crystallized. Also eluted was vinyl sulfone **447** (0.09 g) as a white solid. Sulfone **447** is described on page 223.

m.p.: 51 °C (from EtOAc/hexane)

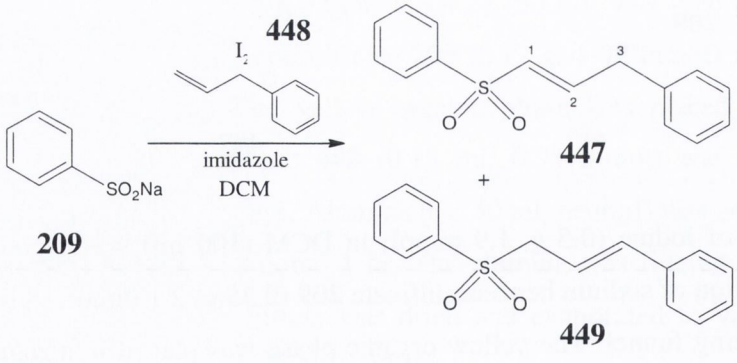
IR: $\nu_{max}$ (N) 3057, 3027, 2966, 2929, 1947, 1900, 1809, 1771, 1603 (Ar C-C), 1583 (Ar C-C), 1496, 1452, 1408, 1307 ($SO_2$), 1240, 1151 ($SO_2$), 1112, 1082, 1024, 996, 927, 867, 770, 730, 686, 630, 584 $cm^{-1}$

$^1H$ NMR (400.1 MHz): δ 3.18 (1H, dd, $^2J$ = 14.5, $^3J$ = 9.0, 3-C$H_2$), 3.57 (1H, dd, $^2J$ = 14.5, $^3J$ = 4.5, 3-C$H_2$), 3.80 (1H, dd, $^2J$ = 14.3, $^3J$ = 8.5, 1-C$H_2$), 3.85 (1H, dd, $^2J$ = 14.3, $^3J$ = 5.5, 1-C$H_2$) 4.58 (1H, app sp, 2-C*H*), 7.22-7.37 (5H, m, Ph Ar*H*), 7.62 (2H, t, $^3J$ = 7.5, $PhSO_2$ *m*-Ar*H*), 7.72 (1H, t, $^3J$ = 7.5, $PhSO_2$ *p*-Ar*H*), 7.96 (2H, d, $^3J$ = 7.5, $PhSO_2$ *o*-Ar*H*) ppm

$^{13}C$ NMR (100.6 MHz): δ 20.8 (C-2), 45.0 (C-3), 64.3 (C-1), 126.8 (Ph Ar*C*), 127.6 ($PhSO_2$ Ar*C*), 128.1 (Ph Ar*C*), 128.7 (Ph Ar*C*), 129.1 ($PhSO_2$ Ar*C*), 133.8 ($PhSO_2$ Ar*C*), 137.8 (Ph Ar*C*), 138.7 ($PhSO_2$ Ar*C*) ppm

HRMS (CI) *m/z* 408.9744: *calculated for* $[C_{15}H_{15}O_2SI + Na]^+$ 408.9734

**{[(1*E*)-3-Phenylprop-1-enyl]sulfonyl}benzene 447**[80]




A solution of iodine (5 g, 19.6 mmol) in chloroform (500 ml) was vigorously mixed with a solution of sodium benzenesulfinate **209** (3.54 g, 21.6 mmol) in water (200 ml) in a separating funnel. The yellow organic phase was placed in a round

bottomed flask and allyl benzene **448** (2.6 ml, 19.6 mmol) was added. The solution was stirred at rt for 3 days. Imidazole (5.36 g, 78.7 mmol) was added and the solution was stirred for a further 7 days. The solution was then washed with water (250 ml) and the aqueous layer was extracted with ether (150 ml). The combined organic extracts were washed with aq. HCl (100 ml, 1 M) and satd. aq. sodium sulfite (50 ml), dried and evaporated to yield a semi-solid material (5.14 g) whose $^1$H NMR spectrum showed it to contain sulfone **447** and sulfone **449** in ca. 2:1 ratio. Recrystallization from EtOAc:hexane (ca. 4:1) afforded the title compound (2.79 g) as a white solid. A second batch of crystals (0.63 g) was collected from the mother liquor after 1 day. Total yield: 3.42 g, 68 %.

m.p.: 105 °C (from EtOAc/hexane); Lit.[81]: 107-109 °C

IR: $\nu_{max}$ (N) 2925, 2854, 1630 (C=C), 1596 (Ar C-C), 1453, 1376, 1303 ($SO_2$), 1143 ($SO_2$), 1083, 974, 926, 846, 796, 755, 699 cm$^{-1}$

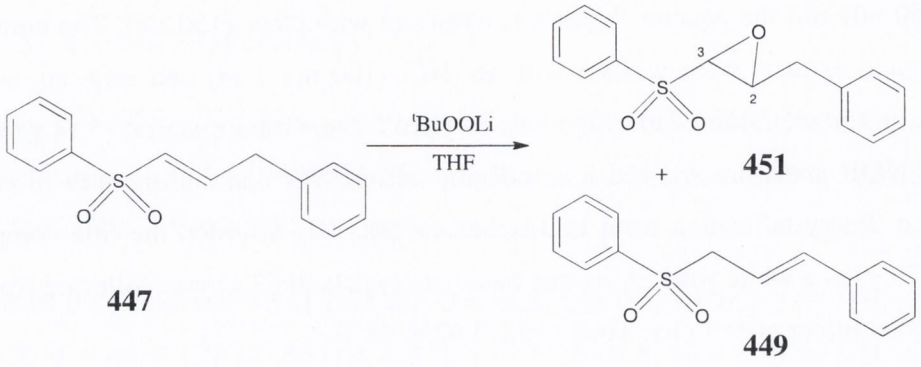
$^1$H NMR (400.1 MHz): δ 3.58 (2H, dd, $^3J$ = 6.5, $^4J$ = 1.5, 3-$CH_2$), 6.28 (1H, dt, $^3J$ = 15.0, $^4J$ = 1.5, 1-C*H*), 7.14-7.16 (2H, m, Ph Ar*H*), 7.17 (1H, dt, $^3J_1$ = 15.0, $^3J_2$ = 6.5, 2-C*H*), 7.25-7.35 (3H, m, Ph Ar*H*), 7.55 (2H, t, $^3J$ = 7.5, $PhSO_2$ *m*-Ar*H*), 7.63 (1H, t, $^3J$ = 7.5, $PhSO_2$ *p*-Ar*H*), 7.88 (2H, d, $^3J$ = 7.5, $PhSO_2$ *o*-Ar*H*) ppm

$^{13}$C NMR (100.6 MHz): δ 37.1 (C-3), 126.6 (Ph Ar*C*), 127.1 ($PhSO_2$ Ar*C*), 128.3 (Ph Ar*C*), 128.4 (Ph Ar*C*), 128.8 ($PhSO_2$ Ar*C*), 131.0 (C-1), 132.9 ($PhSO_2$ Ar*C*), 135.7 (Ph Ar*C*), 139.9 ($PhSO_2$ Ar*C*), 145.0 (C-2) ppm

HRMS (CI) *m/z* 281.0612: *calculated for* $[C_{15}H_{14}O_2S + Na]^+$ 281.0611

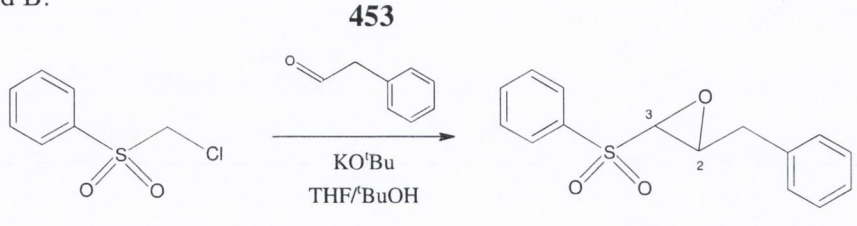
***trans*-2-Benzyl-3-(phenylsulfonyl) oxirane 451**

Method A:[4]




*n*-Butyllithium (3.87 ml, 2.5 M, 9.68 mmol) was added dropwise *via* syringe to a solution of *tert*-butylhydroperoxide (9.85 ml, 1.17 M in benzene, 11.62 mmol) in dry THF (6 ml) at -78 °C under an atmosphere of nitrogen. The solution was allowed to warm to -20 °C and a solution of sulfone **447** (1 g, 3.87 mmol) in dry THF (10 ml) was added dropwise *via* syringe. The solution was stirred at -20 °C for 3 hrs. The solution was then allowed to warm to rt, quenched with satd. aq. sodium sulfite (50 ml) and extracted with ether (3 × 50 ml). The combined organic extracts were dried over sodium sulfate and evaporated to yield an oil (1.39 g). The crude product was purified over silica gel, eluting with EtOAc:hexane (1:4) to yield two products. The first product to elute was sulfone **451** (0.51 g, 48 %) as a white solid. The second product to elute was sulfone **449** (0.51 g, 51 %) as a white solid.

Method B:[5]




Solid potassium *tert*-butoxide (1.176 g, 10.49 mmol) was added in small portions to a solution of phenyl chloromethylsulfone **452** (2.00 g, 10.49 mmol) in dry THF (40 ml) and *tert*-butanol (2 ml) at 0 °C under an atmosphere of nitrogen. A solution of

phenylacetaldehyde **453** (1.22 ml, 10.49 mmol) in dry THF (10 ml) was added dropwise *via* syringe and the solution was allowed to warm to rt and stirred for a total of 5 hrs. The solution was then quenched with satd. aq. ammonium chloride (50 ml) and extracted with ether (3 × 50 ml). The combined organic extracts were dried over sodium sulfate and evaporated to yield an oil (2.79 g). The crude product was purified over silica gel, eluting with EtOAc:hexane (1:3) to yield two products. The first product to elute was sulfone **451** (2.31 g, 80 %) as an oil which later crystallized on standing overnight. The second product to elute was unchanged phenyl chloromethylsulfone **452** (0.33 g) as a white solid.

m.p.: 83 °C (from EtOAc/hexane)

IR: $\nu_{max}$ (N) 2922, 1582 (Ar C-C), 1452, 1376, 1308 ($SO_2$), 1214, 1150 ($SO_2$), 1084, 1023, 931, 897, 833, 740, 705, 686 $cm^{-1}$

$^1H$ NMR (400.1 MHz): δ 2.97 (1H, dd, $^2J$ = 15.0, $^3J$ = 5.5, 2-C$H_2$Ph), 3.13 (1H, dd, $^2J$ = 15.0, $^3J$ = 4.5, 2-C$H_2$Ph), 3.90 (1H, d, $^3J$ = 1.5, 3-C*H*), 3.91-3.94 (1H, m, 2-C*H*), 7.20-7.22 (2H, m, Ph Ar*H*), 7.27-7.35 (3H, m, Ph Ar*H*), 7.59 (2H, t, $^3J$ = 7.5, $PhSO_2$ *m*-Ar*H*), 7.71 (1H, t, $^3J$ = 7.5, $PhSO_2$ *p*-Ar*H*), 7.92 (2H, d, $^3J$ = 7.5, $PhSO_2$ *o*-Ar*H*) ppm

$^{13}C$ NMR (100.6 MHz): δ 35.7 (2-*C*$H_2$Ph), 57.1 (C-2), 67.3 (C-3), 126.8 (Ph Ar*C*), 128.3 (Ph Ar*C*), 128.3 ($PhSO_2$ Ar*C*), 128.6 (Ph Ar*C*), 128.7 (Ph Ar*C*), 128.9 ($PhSO_2$ Ar*C*), 134.0 ($PhSO_2$ Ar*C*), 134.1 ($PhSO_2$ Ar*C*) ppm

HRMS (CI) *m/z* 297.0558: *calculated for* $[C_{15}H_{14}O_3S + Na]^+$ 297.0560

**Attempted preparation of 2-hydroxy-3-phenylpropanal 454**[58]

Method A: By hydrolysis of sulfonyloxirane **451** with KOH/KO$^t$Bu[24]

Water (0.06 ml, 3.28 mmol) was added *via* syringe to a solution of potassium *tert*-butoxide (1.22 g, 10.94 mmol) in dry THF (7 ml) and *tert*-butanol (1 ml) at rt under an atmosphere of nitrogen. The solution was stirred for 10 mins and then a solution of sulfonyloxirane **451** (0.3 g, 1.09 mmol) in dry THF (8 ml) was added *via* syringe. The solution was stirred at rt for 3 days and then at ca. 40 °C for a further 2 days. The solution was then diluted with water (30 ml) and extracted with DCM (3

× 50 ml). The combined organic extracts were dried over sodium sulfate and evaporated to yield a brown oil (0.11 g).

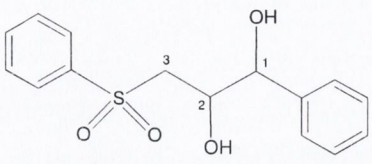
Method B: By hydrolysis of sulfonyloxirane **451** with $TiCl_4/H_2O$[25]

Titanium (IV) chloride (0.22 ml, 2.04 mmol) was added *via* syringe to a solution of sulfonyloxirane **451** (0.28 g, 1.02 mmol) in dry DCM (10 ml) at rt under an atmosphere of nitrogen. The solution was stirred at rt for 1 hour. Water (20 ml) was then added and the solution was stirred for a further 2 hours. The phases were separated and the aqueous phase was extracted with DCM (2 × 25 ml) and ethyl acetate (2 × 25 ml). The combined organic extracts were dried over sodium sulfate and evaporated to yield a black oil (0.29 g).

Method C: By Upjohn dihydroxylation of vinyl sulfone **447**[34]

Vinyl sulfone **447** (0.28 g, 1.08 mmol) and methanesulfonamide (0.1 g, 1.08 mmol) were dissolved in acetone (5 ml) and water (1 ml) and *N*-methylmorpholine-*N*-oxide (0.38 g, 3.25 mmol) was added. Osmium tetroxide (0.35 ml, 2.5 wt. % soln. in *tert*-butanol, 2.5 mol %) was added and the mixture was stirred at rt for 6 days. The mixture was diluted with DCM (100 ml) and solid sodium sulfite (0.5 g) and sodium hydrogen carbonate (0.09 g, 1.08 mmol) were added and the mixture was vigorously stirred for 15 min. The mixture was filtered through celite and washed with water and DCM. The filtrate was transferred to a separating funnel and the phases were mixed and separated. The aqueous phase was extracted with DCM (50 ml). The combined organic extracts were dried over sodium sulfate and evaporated to yield a brown oil (0.26 g) which was taken up in DCM (100 ml) and washed with aq. HCl (100 ml, 1 M) and dried and evaporated to yield diol **457** (0.18 g, 58 %) as a light brown solid.

**1-Phenyl-3-(phenylsulfonyl)propane-1,2-diol 457**[62]




**457**

m.p.: 129-130 °C (from DCM); Lit.[62]: 133 °C

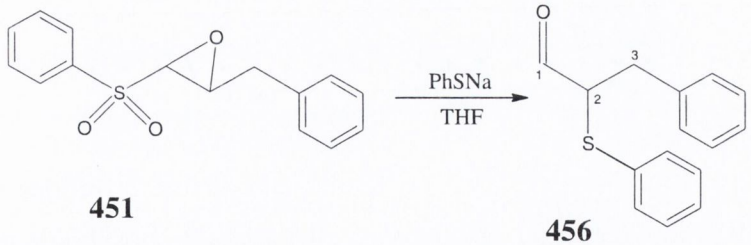
IR: $\nu_{max}$ (N) 3505 (O-H), 3059, 3027, 2923, 1601 (Ar C-C), 1450, 1380, 1279 ($SO_2$), 1237, 1146 ($SO_2$), 1085, 1042, 905, 841, 740, 688 $cm^{-1}$

$^1H$ NMR (400.1 MHz): δ 3.18 (1H, dd, $^2J$ = 14.5, $^3J$ = 2.0, 3-C$H_2$), 3.28 (1H, dd, $^2J$ = 14.5, $^3J$ = 9.5, 3-C$H_2$), 4.26-4.31 (1H, m, 2-C*H*), 4.61 (1H, d, $^3J$ = 6.0, 1-C*H*), 7.26-7.35 (5H, m, Ph Ar*H*), 7.56 (2H, t, $^3J$ = 7.5, $PhSO_2$ *m*-Ar*H*), 7.68 (1H, t, $^3J$ = 7.5, $PhSO_2$ *p*-Ar*H*), 7.86 (2H, d, $^3J$ = 7.5, $PhSO_2$ *o*-Ar*H*) ppm

$^{13}C$ NMR (100.6 MHz): δ 58.2 (C-3), 69.9 (C-2), 75.6 (C-1), 125.4 (Ph Ar*C*), 126.3 (Ph Ar*C*), 127.4 (Ph Ar*C*), 128.0 ($PhSO_2$ Ar*C*), 128.2 (Ph Ar*C*), 128.9 ($PhSO_2$ Ar*C*), 133.5 ($PhSO_2$ Ar*C*), 133.5 ($PhSO_2$ Ar*C*) ppm

HRMS (CI) *m/z* 315.0670: *calculated for* $[C_{15}H_{16}O_4S + Na]^+$ 315.0666

**3-Phenyl-2-(phenylthio)propanal 456**[61]




**451** **456**

Thiophenol (0.08 ml, 0.80 mmol) was added dropwise *via* syringe to a suspension of sodium hydride (0.032 g, 60 %, 0.80 mmol) in dry THF (4 ml) at 0 °C under an atmosphere of nitrogen. After the evolution of hydrogen had ceased, a solution of sulfonyloxirane **451** (0.2 g, 0.72 mmol) in dry THF (6 ml) was added dropwise and

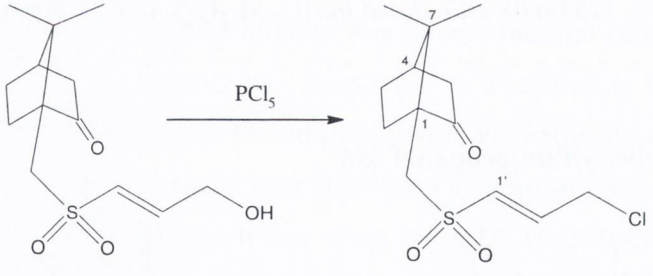
the solution was stirred at 0 °C for 1 hr and then allowed to warm to rt and stirred for a further 24 hrs. The solution was diluted with water (50 ml) and extracted with ether (3 × 50 ml). The combined organic extracts were dried over sodium sulfate and evaporated to yield an oil (0.34 g). Column chromatography on silica gel using EtOAc:Hexane (1:4) afforded the title compound as an oil (0.14 g, 79%).

IR: $\nu_{max}$ (L) 3058, 2923, 2853, 1948, 1877, 1800, 1719 (C=O), 1579 (Ar C-C), 1476, 1439, 1386, 1306, 1154, 1069, 1024, 901, 835, 739, 691 $cm^{-1}$

$^1$H NMR (400.1 MHz): δ 3.00 (1H, dd, $^2J$ = 14.5, $^3J$ = 7.0, 3-C$H_2$), 3.22 (1H, dd, $^2J$ = 14.5, $^3J$ = 8.0, 3-C$H_2$), 3.85 (1H, app td, $^3J_1$ = 8.0, $^3J_2$ = 3.5, 2-C*H*), 7.16-7.41 (10H, m, Ar*H*), 9.50 (1H, d, $^3J$ = 3.5, 1-C*H*) ppm

$^{13}$C NMR (100.6 MHz): δ 33.7 (C-3), 57.5 (C-2), 125.1 (Ar *C*), 126.5 (Ar *C*), 128.2 (Ar *C*), 128.6 (Ar *C*), 128.7 (Ar *C*), 128.9 (Ar *C*), 132.8 (Ar *C*), 136.7 (Ar *C*), 193.6 (C-1) ppm

**(1*S*, 4*R*)-1-({[(1'*E*)-3'-Chloroprop-1'-enyl]sulfonyl}methyl)-7,7-dimethylbicyclo[2.2.1]heptan-2-one 470**




**423** **470**

Following the procedure of Culvenor, Davies and Savige,[17] Sulfone **423** (3.76 g, 13.8 mmol) was placed in a round bottomed flask and phosphorus pentachloride (2.87 g, 13.8 mmol) was added. The mixture of solids was agitated with a spatula until the reaction commenced. After the evolution of hydrogen chloride had ceased, the oily mixture was warmed to 50 °C for 1 hr and then diluted with water (50 ml) and extracted with ether (3 × 50 ml). The combined organic extracts were washed with water (50 ml) and satd. aq. sodium hydrogen carbonate (50 ml), dried and

evaporated to yield an oil (3 g) which later crystallized. Recrystallization from EtOAc/hexane (1:1) afforded the title compound as a white solid (2.55 g, 63 %).

m.p.: 70-72 °C (from EtOAc/hexane)

$[\alpha]_D$ (*c* 0.56, MeOH, 27 °C) +28.3

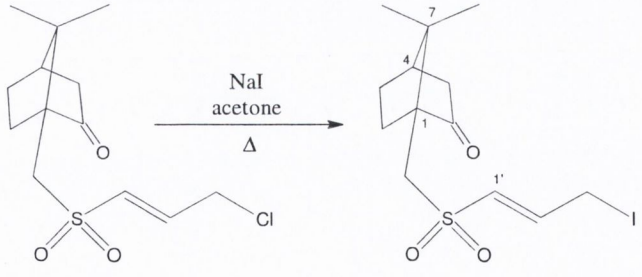
IR: $\nu_{max}$ (N) 3056, 2921, 2855, 1747 (C=O), 1639 (C=C), 1458, 1376, 1318 ($SO_2$), 1294, 1268, 1122 ($SO_2$), 1066, 1047, 966, 933, 845, 777, 722 $cm^{-1}$

$^1H$ NMR (400.1 MHz): δ 0.88 (3H, s, 7-C*H*$_3$), 1.09 (3H, s, 7-C*H*$_3$), 1.44-1.50 (1H, m), 1.71-1.79 (1H, m), 1.95 (1H, d, $^2J$ = 18.5, 3-C*H*$_2$ *endo*), 2.03-2.11 (1H, m), 2.14 (1H, t, $^3J$ = 4.5, 4-C*H*), 2.36-2.47 (2H, m), 2.90 (1H, d, $^2J$ = 14.5, C*H*$_2$SO$_2$), 3.45 (1H, d, $^2J$ = 14.5, C*H*$_2$SO$_2$), 4.24 (2H, d, $^3J$ = 3.0, 3'-C*H*$_2$), 6.92 (2H, s, 1'-C*H* and 2'-C*H*) ppm

$^{13}C$ NMR (100.6 MHz): δ 19.2 (7-*C*H$_3$), 19.2 (7-*C*H$_3$), 24.4 (C-5), 26.6 (C-6), 40.9 (C-3'), 42.0 (C-4), 42.1 (C-3), 48.1 (C-7), 51.7 (*C*H$_2$SO$_2$), 58.2 (C-1), 133.0 (C-1'), 139.7 (C-2'), 214.4 (C-2) ppm

HRMS (CI) *m/z* 313.0649: *calculated for* $[C_{13}H_{19}O_3SCl + Na]^+$ 313.0640

**(1*S*, 4*R*)-1-({[(1'*E*)-3'-Iodoprop-1'-enyl]sulfonyl}methyl)-7,7-dimethylbicyclo[2.2.1]heptan-2-one 471**




**470** **471**

Following the procedure of Culvenor, Davies and Savige,[17] Sulfone **470** (0.1 g, 0.34 mmol) and sodium iodide (0.16 g, 1.06 mmol) were dissolved in dry acetone (20 ml) and heated under reflux for 4 hrs. The solution was allowed to cool to rt and then diluted with water (50 ml) and extracted with ether (3 × 50 ml). The

combined organic extracts were washed with satd. aq. sodium sulfite (50 ml), dried and evaporated to yield an oil which was taken up in ether/DCM (10 ml) and evaporated to yield the title compound as a yellow solid (0.11 g, 83 %).

m.p.: 82-84 °C (from ether/DCM)

$[\alpha]_D$ (*c* 0.64, $CHCl_3$, 27 °C) +21.4

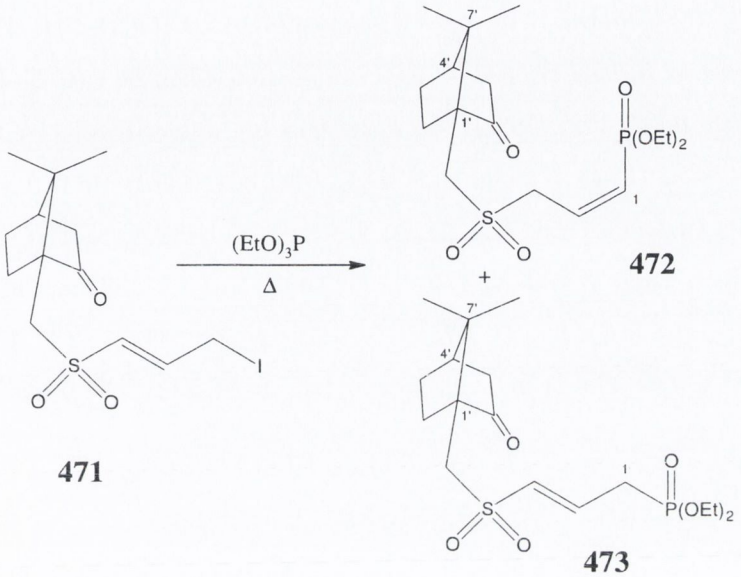
IR: $\nu_{max}$ (N) 3051, 2923, 2854, 1745 (C=O), 1627 (C=C), 1457, 1376, 1316 ($SO_2$), 1290, 1269, 1168, 1130 ($SO_2$), 1047, 960, 909, 838, 774 $cm^{-1}$

$^1H$ NMR (400.1 MHz): δ 0.86 (3H, s, 7-C*H*$_3$), 1.05 (3H, s, 7-C*H*$_3$), 1.42-1.48 (1H, m), 1.68-1.75 (1H, m), 1.92 (1H, d, $^2J$ = 18.5, 3-C*H*$_2$ *endo*), 2.00-2.09 (1H, m), 2.12 (1H, t, $^3J$ = 4.5, 4-C*H*), 2.33-2.42 (2H, m), 2.84 (1H, d, $^2J$ = 14.5, C*H*$_2$SO$_2$), 3.41 (1H, d, $^2J$ = 14.5, C*H*$_2$SO$_2$), 3.95 (2H, d, $^3J$ = 8.0, 3'-C*H*$_2$), 6.68 (1H, d, $^3J$ = 15.0, 1'-C*H*), 6.91 (1H, dt, $^3J_1$ = 15.0, $^3J_2$ = 8.0, 2'-C*H*) ppm

$^{13}C$ NMR (100.6 MHz): δ -1.9 (C-3'), 19.1 (7-*C*H$_3$), 19.2 (7-*C*H$_3$), 24.1 (C-5), 26.5 (C-6), 41.9 (C-4), 42.1 (C-3), 48.1 (C-7), 51.6 (*C*H$_2$SO$_2$), 58.0 (C-1), 131.5 (C-1'), 141.0 (C-2'), 214.4 (C-2) ppm

HRMS (CI) *m/z* 404.9983: *calculated for* $[C_{13}H_{19}O_3SI + Na]^+$ 404.9996

**(1'*S*, 4'*R*)-Diethyl[(1*Z*)-3-{[(7',7'-dimethyl-2'-oxobicyclo[2.2.1]hept-1'-yl)methyl]sulfonyl}prop-1-enyl] phosphonate 472 and (1'*S*, 4'*R*)-diethyl[(2*E*)-3-{[(7',7'-dimethyl-2'-oxobicyclo[2.2.1]hept-1'-yl)methyl]sulfonyl}prop-2-enyl] phosphonate 473**




Following the procedure of Grayson,[64] sulfone **471** (0.87 g, 2.27 mmol) and triethyl phosphite (0.4 ml, 2.27 mmol) were heated together at ca. 100 °C for 12 hrs. The oily mixture was allowed to cool to rt to yield a brown oil (0.87 g, 97 %) whose $^1$H NMR spectrum showed it to consist of phosphonate **472** and phosphonate **473** in ca. 2.2:1 ratio.

IR: $\nu_{max}$ (L) 2980, 1745 (C=O), 1636 (C=C), 1445, 1393, 1320 ($SO_2$), 1250 (P=O), 1129, 1027 ($SO_2$), 966, 796, 703 cm$^{-1}$

$^1$H NMR (400.1 MHz): δ 0.86 (3H, s, 7'-C*H*$_3$ **473**), 0.89 (3H, s, 7'-C*H*$_3$ **472**), 1.04 (3H, s, 7'-C*H*$_3$ **472**), 1.08 (3H, s, 7'-C*H*$_3$ **473**), 1.34 (12H, t, $^3J$ = 7.0, OCH$_2$C*H*$_3$ **472** and **473**), 1.42-1.51 (2H, m, **472** and **473**), 1.71-1.78 (1H, m, **473**), 1.83-1.90 (1H, m, **472**), 1.93 (1H, d, $^2J$ = 18.0, 3'-C*H*$_2$ *endo* **473**), 1.95 (1H, d, $^2J$ = 18.5, 3'-C*H*$_2$ *endo* **472**), 2.03-2.11 (4H, m, **472** and **473**), 2.13 (1H, t, $^3J$ = 4.5, 4'-C*H* **473**), 2.15 (1H, t, $^3J$ = 4.5, 4'-C*H* **472**), 2.30-2.48 (4H, m, **472** and **473**), 2.76 (1H, d, $^2J$ = 15.0, 1'-C*H*$_2$SO$_2$ **472**), 2.81 (2H, dd, $^2J_{H\text{-}P}$ = 22.8, $^3J$ = 7.5, 1-C*H*$_2$ **473**), 2.86 (1H, d, $^2J$ = 15.5, 1'-C*H*$_2$SO$_2$ **473**), 3.43 (2H, d, $^2J$ = 15.0, 1'-C*H*$_2$SO$_2$ **472** and **473**), 3.98

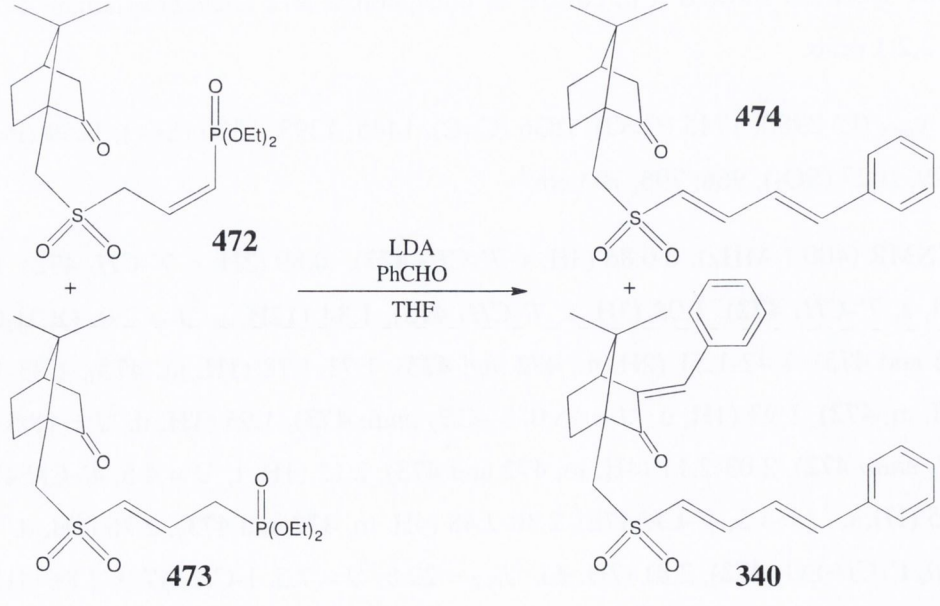
(1H, dd, $^{2}J$ = 13.8, $^{3}J$ = 7.0, 3-C$H_2$ **472**), 4.12 (8H, qu, $^{3}J$ = 7.0, $^{3}J_{H\text{-}P}$ = 7.0, OC$H_2$CH$_3$ **472** and **473**), 4.33 (1H, dd, $^{2}J$ = 13.8, $^{3}J$ = 8.0, 3-C$H_2$ **472**), 6.15 (1H, app t, $^{2}J_{H\text{-}P}$ = 17.8, $^{3}J$ = 17.5, 1-C*H* **472**), 6.70-6.86 (3H, m, 2-C*H* **472**, 2-C*H* **473** and 3-C*H* **473**) ppm

$^{13}$C NMR (100.6 MHz): δ 15.8 (OCH$_2$*C*H$_3$ **473**), 15.9 (OCH$_2$*C*H$_3$ **472**), 19.0 (7'-*C*H$_3$ **472** and **473**), 19.2 (7'-*C*H$_3$ **473**), 19.3 (7'-*C*H$_3$ **472**), 24.1 (C-5' **473**), 25.0 (C-5' **472**), 26.6 (C-6' **473**), 26.6 (C-6' **472**), 29.3 (d, $^{1}J_{C\text{-}P}$ = 138.9, 1-*C*H$_2$ **473**), 41.9 (C-4' **473**), 42.1 (C-4' **472** and C-3' **473**), 42.2 (C-3' **472**), 48.0 (C-7' **473**), 48.4 (C-7' **472**), 50.3 (1'-*C*H$_2$SO$_2$ **472**), 51.5 (1'-*C*H$_2$SO$_2$ **473**), 58.1 (C-1' **473**), 58.6 (C-1' **472**), 59.6 (d, $^{3}J_{C\text{-}P}$ = 24.2, 3-*C*H **472**), 61.7 (d, $^{2}J_{C\text{-}P}$ = 5.8, O*C*H$_2$CH$_3$ **473**), 61.7 (d, $^{2}J_{C\text{-}P}$ = 5.8, O*C*H$_2$CH$_3$ **472**), 126.9 (d, $^{1}J_{C\text{-}P}$ = 185.6, 1-*C*H **472**), 134.1 (d, $^{3}J_{C\text{-}P}$ = 14.5, 3-*C*H **473**), 136.0 (d, $^{2}J_{C\text{-}P}$ = 10.6, 2-*C*H **473**), 136.9 (d, $^{2}J_{C\text{-}P}$ = 6.8, 2-*C*H **472**), 214.3 (C-2' **473**), 215.2 (C-2' **472**) ppm

$^{31}$P NMR (161.9 MHz): δ 9.71 (*P* **472**), 10.24 (*P* **473**) ppm

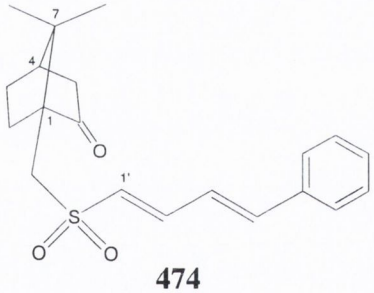
HRMS (CI) *m/z* 415.1331: *calculated for* $[C_{17}H_{29}O_6SP + Na]^+$ 415.1319

**Horner-Wadsworth-Emmons reaction of phosphonates 472 and 473 with benzaldehyde**



*n*-Butyllithium (1.18 ml, 2.5 M, 2.9 mmol) was added to a solution of dry diisopropylamine (0.53 ml, 3.8 mmol) in dry THF (6 ml) at – 60 °C under an atmosphere of nitrogen. The solution was allowed to warm to 0 °C and then recooled to – 60 °C. A solution of phosphonates **472** and **473** (1.16 g, 2.9 mmol) in dry THF (10 ml) was added dropwise *via* syringe. After 15 mins, freshly distilled benzaldehyde (0.3 ml, 2.9 mmol) was added dropwise *via* syringe. The solution was stirred at – 60 °C for 90 mins and then allowed to warm to rt and stirred for an additional 2.5 hrs. The solution was then quenched with satd. aq. ammonium chloride (50 ml) and extracted with ether (3 × 50 ml). The combined organic extracts were washed with brine (50 ml), dried and evaporated to yield an oil (1 g). The crude product was purified over silica gel, eluting with EtOAc:hexane (1:3) to yield two products. The first product to elute was sulfone **340** as a yellow solid (0.17 g, 13 %). The second product to elute was sulfone **474** as a white solid (0.39 g, 38 %).

**(1*S*, 4*R*)-1-({[(1'*E*, 3'*E*)-4'-Phenylbuta-1',3'-dien-1'-yl]sulfonyl}methyl)-7,7-dimethylbicyclo[2.2.1]heptan-2-one 474**




**474**

m.p.: 110 °C (from EtOAc/hexane)

$[\alpha]_D$ (*c* 0.48, MeOH, 27 °C) +48.7

IR: $\nu_{max}$ (N) 3059, 2923, 1743 (C=O), 1624 (C=C), 1601 (Ar C-C), 1454, 1376, 1307 ($SO_2$), 1178, 1122 ($SO_2$), 1046, 1007, 912, 857, 832, 752, 689 $cm^{-1}$

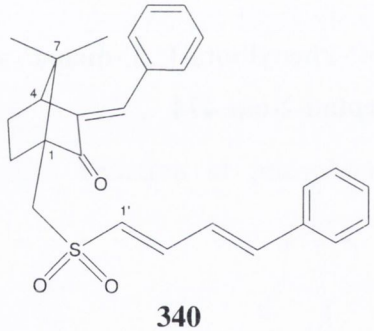
$^1H$ NMR (400.1 MHz): δ 0.89 (3H, s, 7-C$H_3$), 1.11 (3H, s, 7-C$H_3$), 1.43-1.50 (1H, m), 1.71-1.78 (1H, m), 1.94 (1H, d, $^2J$ = 18.5, 3-C$H_2$ *endo*), 2.03-2.12 (1H, m), 2.14

(1H, t, $^3J$ = 4.5, 4-C*H*), 2.39 (1H, dt, $^2J$ = 18.5, $^3J$ = 4.0, 3-C$H_2$ *exo*), 2.47-2.55 (1H, m), 2.92 (1H, d, $^2J$ = 15.0, C$H_2$SO$_2$), 3.51 (1H, d, $^2J$ = 15.0, C$H_2$SO$_2$), 6.68 (1H, d, $^3J$ = 14.5, 1'-C*H*), 6.87 (1H, dd, $^3J_1$ = 15.5, $^3J_2$ = 11.0, 3'-C*H*), 6.99 (1H, d, $^3J$ = 15.5, 4'-C*H*), 7.33 (1H, dd, $^3J_1$ = 14.5, $^3J_2$ = 11.0, 2'-C*H*), 7.35-7.41 (3H, m, Ar*H*), 7.48-7.50 (2H, m, Ar*H*) ppm

$^{13}$C NMR (100.6 MHz): δ 19.3 (7-*C*H$_3$), 19.3 (7-*C*H$_3$), 24.2 (C-5), 26.6 (C-6), 41.9 (C-4), 42.1 (C-3), 48.0 (C-7), 52.0 (*C*H$_2$SO$_2$), 58.2 (C-1), 123.2 (C-3'), 127.0 (Ar C-2), 128.4 (Ar C-3), 128.9 (Ar C-4), 129.1 (C-1'), 134.9 (Ar C-1), 142.2 (C-4'), 142.3 (C-2'), 214.6 (C-2) ppm

HRMS (CI) *m/z* 367.1335: *calculated for* [$C_{20}H_{24}O_3S$ + Na]$^+$ 367.1343

**(1*S*, 4*S*)-(3*E*)-3-Benzylidene-1-({[(1'*E*, 3'*E*)-4'-phenylbuta-1',3'-dien-1'-yl]sulfonyl}methyl)-7,7-dimethylbicyclo[2.2.1]heptan-2-one 340**




**340**

m.p.: 124-125 °C (from EtOAc/hexane)

[α]$_D$ (*c* 1.01, MeOH, 27 °C) +186.3

IR: $\nu_{max}$ (N) 2918, 1719 (C=O), 1639 (C=C), 1587 (Ar C-C), 1451, 1376, 1309 (SO$_2$), 1120 (SO$_2$), 1056, 996, 955, 855, 807, 748, 691 cm$^{-1}$

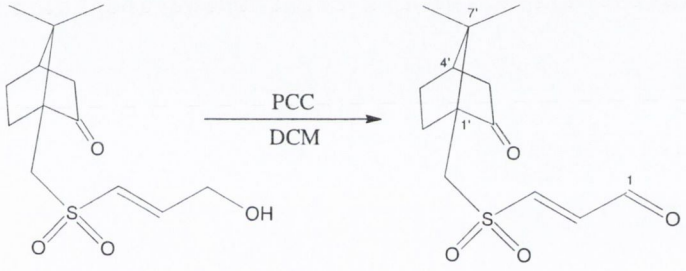
$^1$H NMR (400.1 MHz): δ 0.86 (3H, s, 7-C*H*$_3$), 1.15 (3H, s, 7-C*H*$_3$), 1.69-1.75 (1H, m), 1.82-1.89 (1H, m), 2.27-2.35 (1H, m), 2.58-2.65 (1H, m), 3.03 (1H, d, $^2J$ = 15.0, C$H_2$SO$_2$), 3.15 (1H, d, $^3J$ = 4.0, 4-C*H*), 3.65 (1H, d, $^2J$ = 15.0, C$H_2$SO$_2$), 6.78 (1H, d, $^3J$ = 15.0, 1'-C*H*), 6.91 (1H, dd, $^3J_1$ = 15.5, $^3J_2$ = 10.5, 3'-C*H*), 7.00 (1H, d,

$^{3}J$ = 15.5, 4'-C*H*), 7.29 (1H, s, benzylidene C*H*), 7.33-7.44 (7H, m, 2'-C*H* and Ar*H*), 7.47-7.51 (4H, m, Ar*H*) ppm

$^{13}$C NMR (100.6 MHz): δ 18.5 (7-*C*H$_3$), 20.0 (7-*C*H$_3$), 25.2 (C-5), 25.4 (C-6), 48.0 (C-4), 48.1 (C-7), 52.1 (*C*H$_2$SO$_2$), 57.5 (C-1), 123.3 (C-3'), 127.0 (Ar *C*), 128.3 (Ar *C*), 128.4 (Ar *C*), 128.8 (Ar *C*), 128.9 (benzylidene *C*H), 129.0 (Ar *C*), 129.1 (C-1'), 129.4 (Ar *C*), 134.5 (C-3), 134.9 (Ar *C*), 139.6 (Ar *C*), 142.1 (C-4'), 142.3 (C-2'), 203.8 (C-2) ppm

HRMS (CI) *m/z* 455.1672: *calculated for* [$C_{27}H_{28}O_3S$ + Na]$^+$ 455.1656

**(1'*S*, 4'*R*)-(2*E*)-3-{[(7',7'-Dimethyl-2'-oxobicyclo[2.2.1]hept-1'-yl)methyl]sulfonyl}prop-2-enal 475**




**423** **475**

Sulfone **423** (4.02 g, 14.7 mmol) was dissolved in dry DCM (100 ml) and solid pyridinium chlorochromate (6.37 g, 29.5 mmol) was added in small portions. The mixture was stirred at rt for 4 hrs. The supernatant was then decanted and the remaining black residue was triturated with ether (2 × 50 ml). The combined organic extracts were twice filtered through Celite$^R$ and the filtrate was washed with water (50 ml), dried over sodium sulfate and evaporated to yield a dark oil (2.84 g). Column chromatography on silica gel using EtOAc:Hexane (1:2) afforded the title compound as a pale red solid (2.32 g, 58%).

m.p.: 58 °C (from EtOAc/hexane)

$[\alpha]_D$ (*c* 0.47, $CHCl_3$, 27 °C) +25.1

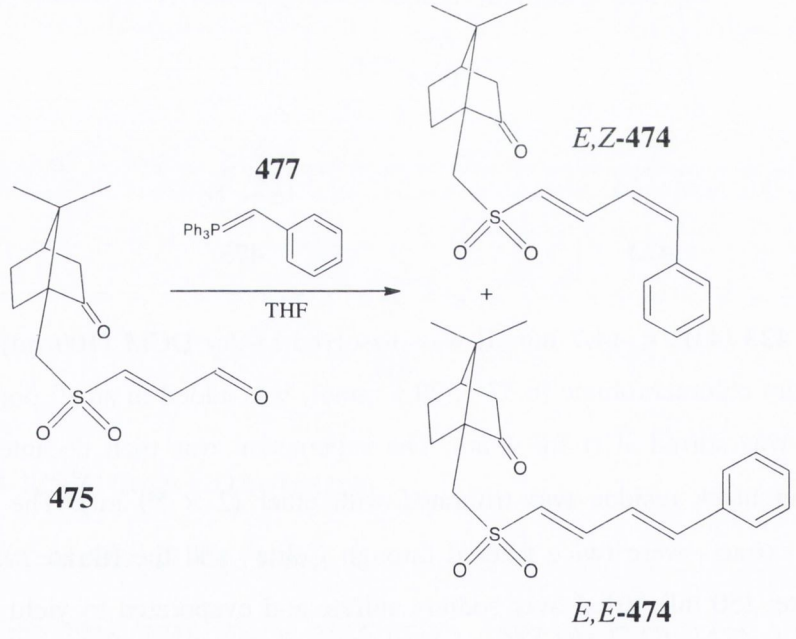
IR: $\nu_{max}$ (N) 3046, 2961, 1741 (C=O), 1692 (HC=O), 1455, 1375, 1314 ($SO_2$), 1275, 1125 ($SO_2$), 1084, 971, 911, 832, 782, 686 cm$^{-1}$

$^1$H NMR (400.1 MHz): δ 0.90 (3H, s, 7'-C*H*$_3$), 1.07 (3H, s, 7'-C*H*$_3$), 1.46-1.53 (1H, m), 1.73-1.80 (1H, m), 1.95 (1H, d, $^2J$ = 18.5, 3'-C*H*$_2$ *endo*), 2.04-2.13 (1H, m), 2.18 (1H, t, $^3J$ = 4.5, 4'-C*H*), 2.31-2.39 (1H, m), 2.40 (1H, dt, $^2J$ = 18.5, $^3J$ = 4.0, 3'-C*H*$_2$ *exo*), 2.99 (1H, d, $^2J$ = 15.0, C*H*$_2$SO$_2$), 3.48 (1H, d, $^2J$ = 15.0, C*H*$_2$SO$_2$), 6.89 (1H, dd, $^3J_1$ = 15.5, $^3J_2$ = 7.0, 2-C*H*), 7.64 (1H, d, $^3J$ = 15.5, 3-C*H*), 9.84 (1H, d, $^3J$ = 7.0, 1-C*H*) ppm

$^{13}$C NMR (100.6 MHz): δ 19.0 (7'-*C*H$_3$), 19.2 (7'-*C*H$_3$), 24.7 (C-5'), 26.6 (C-6'), 42.0 (C-4'), 42.1 (C-3'), 48.5 (C-7'), 52.5 (*C*H$_2$SO$_2$), 58.4 (C-1'), 136.0 (C-2), 147.9 (C-3), 189.8 (C-1), 214.9 (C-2') ppm

HRMS (CI) *m/z* 325.1081: *calculated for* [$C_{13}H_{18}O_4S$ + $CH_4O$ + Na]$^+$ 325.1084

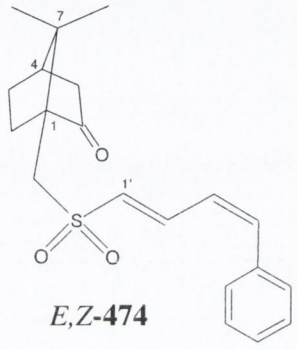
**Wittig reaction of sulfone 475 with benzylidenetriphenylphosphorane**




*n*-Butyllithium (0.7 ml, 2.5 M, 1.75 mmol) was added to a suspension of benzyltriphenylphosphonium chloride (0.928 g, 2.38 mmol) in dry THF (10 ml) at – 60 °C under an atmosphere of nitrogen. The solution was stirred at – 60 °C for 30 mins and then cooled to – 78 °C. A solution of sulfone **475** (0.43 g, 1.59 mmol) in dry THF (10 ml) was added dropwise *via* syringe. The solution was allowed to warm to rt and stirred for 24 hrs. The solution was quenched with satd. aq.

ammonium chloride (50 ml) and extracted with ether (3 × 50 ml). The combined organic extracts were dried and evaporated to yield a yellow oil. Column chromatography on silica gel using EtOAc:Hexane (1:3) afforded sulfone **474** (mixture of *E,Z* and *E,E* isomers in ca. 1.4:1 ratio) as an oil (0.44 g, 80 %).

**(1*S*, 4*R*)-1-({[(1'*E*, 3'*Z*)-4'-Phenylbuta-1',3'-dien-1'-yl]sulfonyl}methyl)-7,7-dimethylbicyclo[2.2.1]heptan-2-one 474**




*E,Z*-**474**

$^{1}$H NMR (400.1 MHz): δ 0.88 (3H, s, 7-C*H*$_3$), 1.09 (3H, s, 7-C*H*$_3$), 1.42-1.50 (1H, m), 1.69-1.78 (1H, m), 1.95 (1H, d, $^{2}J$ = 18.5, 3-C*H*$_2$ *endo*), 2.02-2.11 (1H, m), 2.13 (1H, t, $^{3}J$ = 4.5, 4-C*H*), 2.39 (1H, dt, $^{2}J$ = 18.5, $^{3}J$ = 4.5, 3-C*H*$_2$ *exo*), 2.44-2.55 (1H, m), 2.90 (1H, d, $^{2}J$ = 15.0, C*H*$_2$SO$_2$), 3.48 (1H, d, $^{2}J$ = 15.0, C*H*$_2$SO$_2$), 6.38 (1H, t, $^{3}J$ = 11.5, 3'-C*H*), 6.73 (1H, d, $^{3}J$ = 15.0, 1'-C*H*), 6.96 (1H, d, $^{3}J$ = 11.5, 4'-C*H*), 7.29-7.43 (5H, m, Ar*H*), 7.65 (1H, dd, $^{3}J_1$ = 15.0, $^{3}J_2$ = 11.5, 2'-C*H*) ppm

$^{13}$C NMR (100.6 MHz): δ 19.3 (7-*C*H$_3$), 19.3 (7-*C*H$_3$), 24.3 (C-5), 26.6 (C-6), 42.0 (C-4), 42.1 (C-3), 48.0 (C-7), 51.9 (*C*H$_2$SO$_2$), 58.2 (C-1), 124.4 (C-3'), 128.1 (Ar C-4), 128.2 (Ar C-2), 128.8 (Ar C-3), 131.4 (C-1'), 135.1 (Ar C-1), 137.9 (C-4'), 139.8 (C-2'), 214.5 (C-2) ppm

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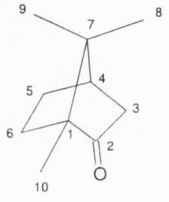
# Chapter 4

# Synthesis of Sulfones by Wagner-Meerwein Rearrangements of the Camphor Framework

## 4.1 Introduction

There has been widespread interest in the chemistry of camphor and its derivatives throughout the history of natural product chemistry. This is largely due to the wide variety of transformations and rearrangements that this readily available natural product undergoes. These rearrangements permit the functionalisation of camphor **57** at each of its C-10, C-9 and C-8 methyl groups.[1]

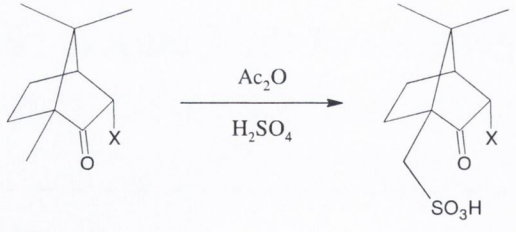



**57**

In addition, functionality can be installed at the methylene groups at C-5 and C-3. Cleavage of the C(1)-C(2), C(2)-C(3) and C(1)-C(7) bonds under various conditions give rise to useful chiral intermediates. As a result, camphor **57** and its derivatives have found widespread use in the synthesis of natural products.[2]

### 4.1.1 Remote Functionalisation of Camphor at C-10

In 1898, it was discovered that treatment of (+)-camphor **57** or *endo*-(+)-3-bromocamphor **479** with acetic anhydride/sulfuric acid gives rise to the corresponding 10-sulfonic acids **319** and **480** with retention of absolute configuration (**Scheme 4.1**).[3]



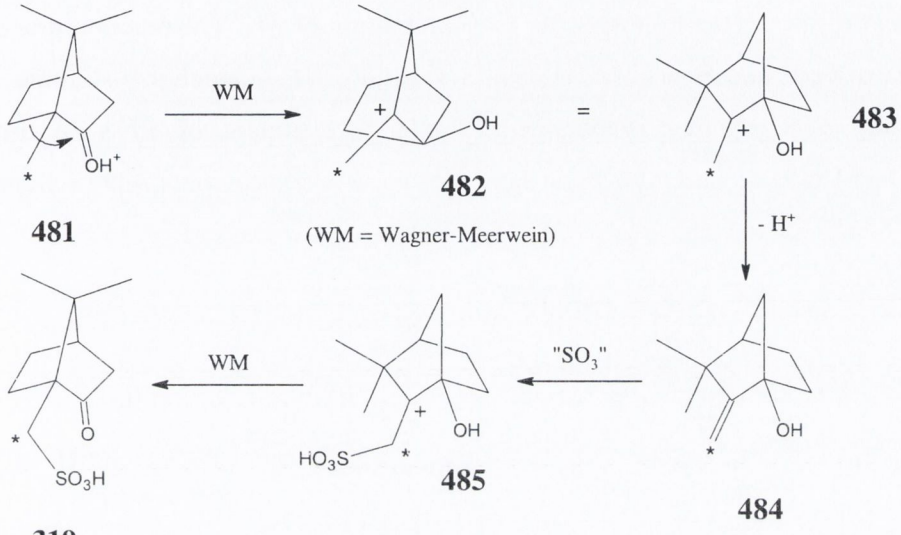

**57** X = H
**479** X = Br

**Scheme 4.1**

**319** X = H
**480** X = Br

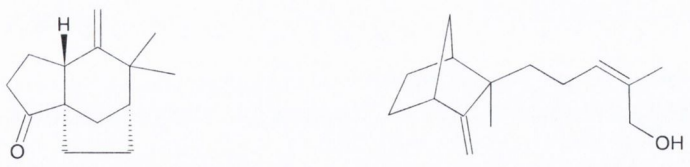
The mechanism proposed for this transformation[4] involves Wagner-Meerwein rearrangement of protonated camphor, followed by proton loss from the resulting carbocation intermediate to produce alkene intermediate **484** in which the original C-10 methyl group is now an *exo*-methylene group. Interception of this

intermediate with the electrophile ("$SO_3$") affords a new carbocation intermediate which undergoes a reversal of the original Wagner-Meerwein rearrangement to generate the acid **319** (**Scheme 4.2**). The position of the original C-10 methyl group is shown throughout for clarity.




**Scheme 4.2**

(+)-Camphor-10-sulfonic acid **319** (historically known as Reychler's acid) in addition to its use as a chiral resolving agent[5] is the precursor of a large variety of C-10 substituted camphor derivatives. Some of these have been used in the enantiospecific total synthesis of natural products, such as (–) Khusimone[6] **486** and (+)-β-Santalol[7] **487** (**Figure 4.1**). In addition, many C-10 substituted camphor derivatives have found use as chiral auxiliaries and chiral reagents in asymmetric synthesis (see Chapter 1, section 1.2).




(–)-Khusimone

**486**

(+)-β-Santalol

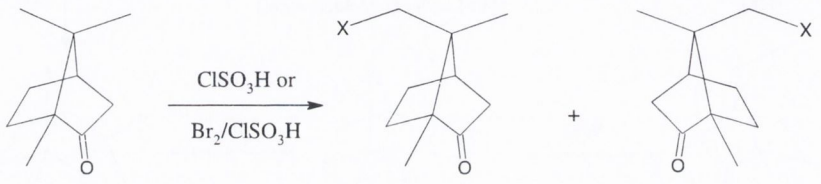
**487**

**Figure 4.1**

**(–)-Khusimone 486 and (+)-β-Santalol 487**

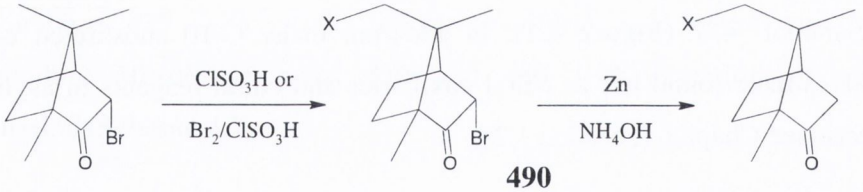
### 4.1.2 Remote Functionalisation of Camphor at C-9

When the conditions normally used to sulfonate camphor at C-10 are changed, a different regiochemical outcome is obtained. Kipping and Pope discovered in 1893 that treatment of (+)-camphor **57** with fuming sulfuric acid or with chlorosulfonic acid results in the regiospecific C-9 sulfonation of **57**.[8] The reaction proceeds with partial racemisation however, and a mixture of (+)-camphor-9-sulfonic acid **488** and its enantiomer is obtained. Similarly, treatment of **57** with bromine in chlorosulfonic acid affords partially racemic 9-bromocamphor **489** (**Scheme 4.3**).[9]




**57** **Scheme 4.3** **488** X = $SO_3H$
**489** X = Br

The loss of enantiomeric purity in the sulfonation/bromination of (+)-camphor **57** at C-9 reduces the usefulness of these reactions. However, **488** and **489** can be obtained in enantiomerically pure form by sulfonation[10] or bromination[11] of *endo*-(+)-3-bromocamphor **479**, followed by removal of the C-3 bromo substituent (**Scheme 4.4**).

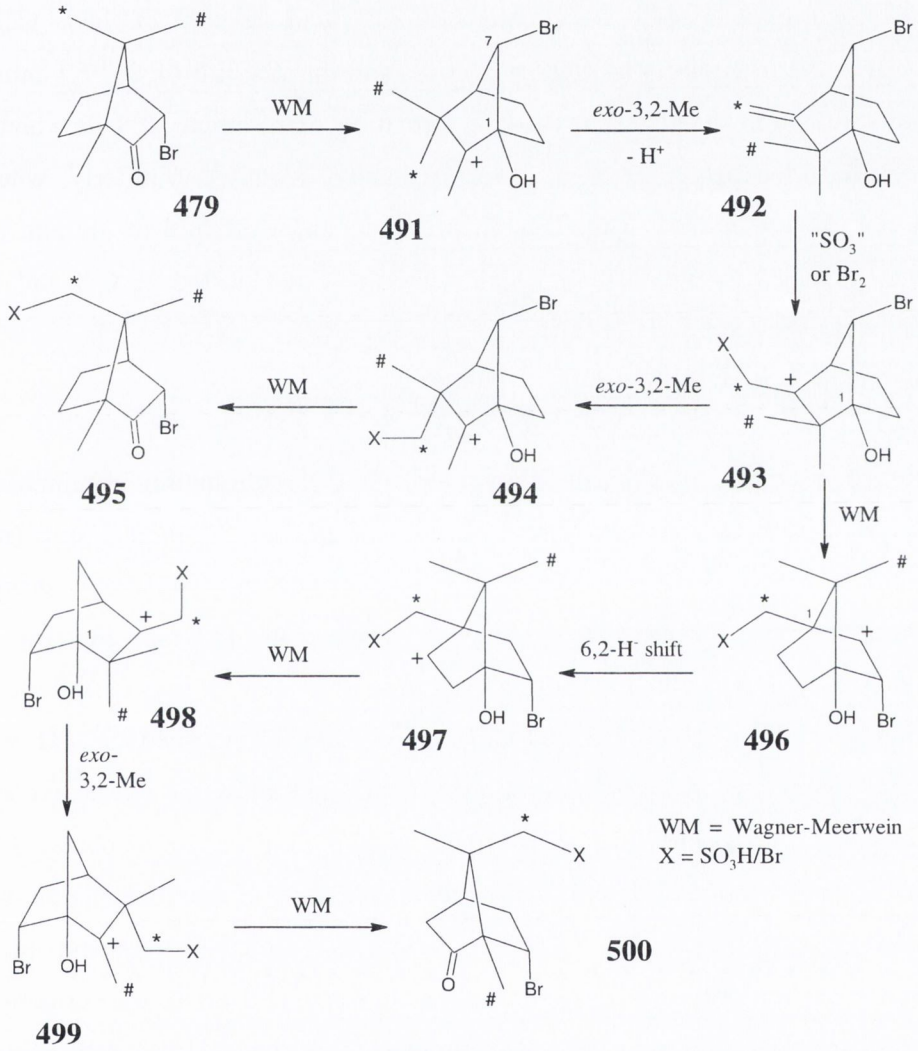



**490**

**479** **Scheme 4.4** **488** X = $SO_3H$
**489** X = Br

The mechanism proposed for the C-9 sulfonation[12] and bromination of *endo*-(+)-3-bromocamphor **479** is related to that proposed for the acid-catalysed partial racemisation of (+)-camphor[13] and the interconversion of 3,9-dibromocamphor with 6,9-dibromocamphor on exposure to fuming sulfuric acid.[14] Initial Wagner-Meerwein rearrangement generates a carbocation intermediate **491** which undergoes *exo*-3,2-methyl shift (Nametkin shift). Proton loss from the resulting carbocation generates alkene intermediate **492** in which the original C-9 methyl group of **479** becomes the *exo*-methylene group of **492**. Trapping of this

intermediate with the electrophile ("$SO_3$" or $Br_2$) generates cation **493** which undergoes a reversal of the *exo*-3,2-methyl shift, followed by a reversal of the original Wagner-Meerwein rearrangement to regenerate the camphor skeleton of the product **495** (**Scheme 4.5**). The positions of the original C-8 (#) and C-9 (*) methyl groups are shown throughout for clarity.




**Scheme 4.5**

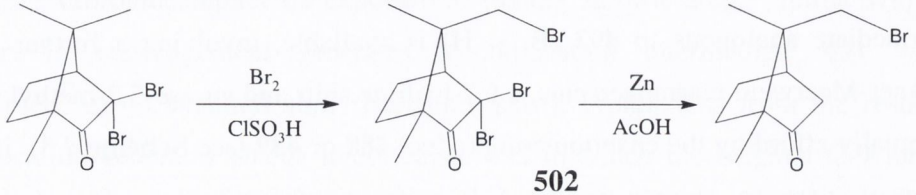
In order to explain the loss of optical purity when the C-9 sulfonation/bromination is carried out on (+)-camphor **57**, it is assumed that an alternative pathway from the intermediate analogous to **493** (Br = H) is available, involving a further three Wagner-Meerwein rearrangements, a 6,2-hydride shift and an *exo*-3,2-methyl shift, eventually affording the enantiomeric product **488** or **489** (see **Scheme 4.3**). If this pathway were to operate in the C-9 sulfonation/bromination of *endo*-(+)-3-

bromocamphor **479**, *endo*-6-bromocamphor-9-sulfonic acid or *endo*-6,9-dibromocamphor **500** would be formed (see **Scheme 4.5**). These compounds are structural isomers of **495** and not enantiomers, hence the formation of enantiopure C-9 substituted derivatives **495** is assured.

Support for this mechanism is provided by the observation that treatment of *endo*-(+)-3-bromocamphor **479** with chlorosulfonic acid results in low yielding rearrangement to *endo*-(-)-6-bromocamphor[15] and that the use of 8-[$^{14}$C]-camphor in the sulfonation reaction leads to the formation of racemate **488** in which the radiolabel is located at the C-8 and C-10 methyl groups.[13] Similarly, when 8-deuteriocamphor is used in the bromination reaction, a mixture of (+) and (-)-9-bromocamphor was obtained in which deuterium was located at C-8 and C-10 respectively.[16]

### 4.1.3 Remote Functionalisation of Camphor at C-8

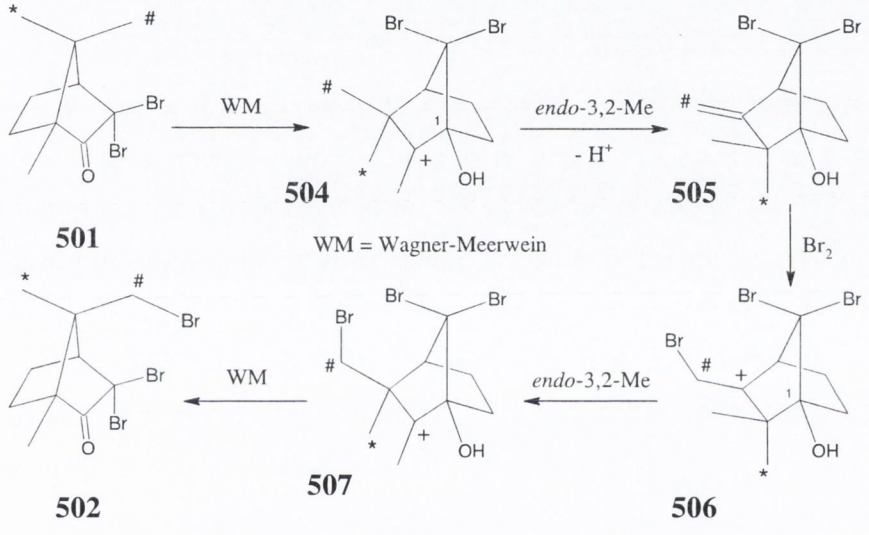
From the proposed mechanism above for the C-9 sulfonation/bromination of camphor, it was postulated that the occurrence of an *endo*-3,2-methyl shift (rather than the observed *exo*-3,2-methyl shift) would convert the C-8 methyl group of camphor into the *exo*-methylene group of intermediate **492** (see **Scheme 4.5**), eventually leading to a C-8 substituted camphor derivative. It was considered that placing a bromine substituent at the 7-*syn* position of intermediate **491** would sterically block the preferred *exo*-3,2-methyl shift and allow the alternative *endo*-3,2-methyl shift to occur. Such an intermediate could in principle be obtained from 3,3-dibromocamphor and this realisation led to the study of the bromination of this compound with bromine/chlorosulfonic acid. As predicted, treatment of 3,3-dibromocamphor **501** with bromine in chlorosulfonic acid led to the formation of (+)-3,3,8-tribromocamphor **502** and subsequent regiospecific C-3 debromination gave enantiomerically pure (+)-8-bromocamphor **503** in 35-40 % overall yield (**Scheme 4.6**).[17]




**501** **502** **503**

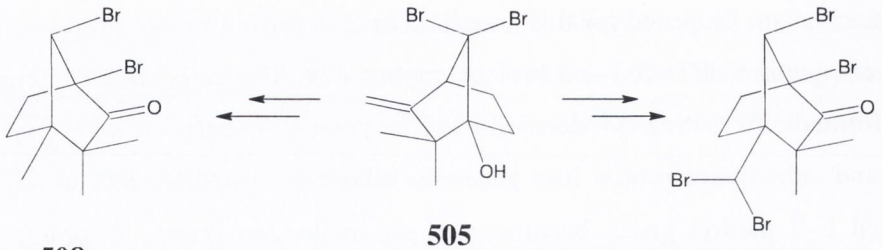
**Scheme 4.6**

The mechanism proposed for this transformation is related to that proposed for the C-9 bromination of *endo*-(+)-3-bromocamphor **479**. The carbocation intermediate **504** formed after Wagner-Meerwein rearrangement undergoes *endo*-3,2-methyl shift and subsequent proton loss generates alkene intermediate **505** in which the original C-8 methyl group becomes the *exo*-methylene group. Trapping of this intermediate **505** with bromine, followed by a reversal of the *endo*-3,2-methyl shift and a reversal of the original Wagner-Meerwein rearrangement regenerates the camphor skeleton of the product **502** (**Scheme 4.7**). Again, the positions of the original C-8 and C-9 methyl groups are indicated throughout.




**Scheme 4.7**

Although the development of this simple three-step process for the conversion of (+)-camphor to (+)-8-bromocamphor **503** does not prove that an *endo*-3,2-methyl shift had occurred, subsequent studies using 8 and 9-deuteriocamphor provided results consistent with this mechanistic proposal. When 9-deuteriocamphor is subjected to the C-3 bromination/C-8 bromination/C-3 debromination sequence, the deuterium is located exclusively at the C-9 position in the product. Similarly, 8-deuteriocamphor gave exclusively 8-bromo-8-[$^2$H]-camphor.[18] In addition, 1,7-dibromo-4-methylcamphenilone **508** and 1,7-dibromo-4-dibromomethyl-camphenilone **509** have been isolated as by-products in the C-8 bromination reaction and it is proposed that these compounds arise from intermediate **505** (**Scheme 4.8**).[19]




**508** **505** **509**

**Scheme 4.8**

This three-step sequence for the 8-bromination of (+)-camphor has opened the door to the utilisation of (+)-8-bromocamphor **503** and its derivatives in natural product synthesis, including the enantiospecific synthesis of (+)-longiborneol and (+)-longifolene.[20]

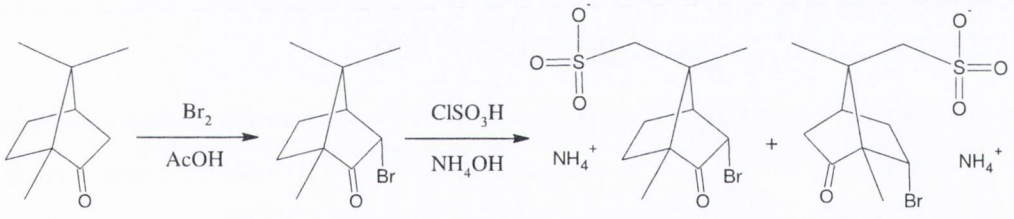
In connection with the work described in Chapters 2 and 3, it was envisaged that this chemistry could be utilised to prepare various sulfones regioisomeric with those previously described in which the sulfonyl group is attached to the 8 or 9-position of the camphor framework, rather than the 10-position. Ultimately, this would lead to studies on the viability of these sulfones (which posess an additional asymmetric centre) in asymmetric synthesis. The application of the above-mentioned chemistry to the synthesis of sulfones of this type is illustrated by the preparation of two benzyl sulfones and these studies are described in the next section.

## 4.2 Preparation of Benzylsulfone 516 *via* 9-Functionalisation of Camphor

Since both the C-9 sulfonation and C-9 bromination of (+)-camphor is known, either of these routes could be used in principle for the preparation of the corresponding sulfones. (+)-Camphor-9-sulfonic acid (usually isolated as its sodium or ammonium salt) could be converted by the usual two-step sequence (see Chapter 2) into its sodium sulfinate salt. Alkylation with appropriate electrophiles would afford the sulfones. Alternatively, sulfones could be obtained from (+)-9-bromocamphor *via* nucleophilic substitution with a thiolate, followed by oxidation of the resulting sulfide. It was decided to use the sulfonation procedure originally

described by Kipping and Pope, who also obtained (+)-camphor-9-sulfonyl chloride in optically active form using the sequence described in section 4.1.2.[21]

Accordingly, *endo*-(+)-3-bromocamphor **479** was prepared from (+)-camphor **57** according to the procedure of Albizati[42] and subjected to the sulfonation conditions of Kipping and Pope. Neutralisation with calcium carbonate followed by addition of ammonium sulfate and filtration gave a crude ammonium salt whose $^1$H NMR spectrum showed the presence of two products in ca. 2:1 ratio. Recrystallisation afforded ammonium *endo*-(+)-3-bromocamphor-9-sulfonate **510** as the major product whose $^1$H NMR spectrum was identical with that of an authentic sample.[22] Numerous attempts to isolate the minor isomeric product, either by fractional recrystallisation or by washing the crude product with acetone, failed to yield a product which could be characterised. From the proposed mechanism (see **Scheme 4.5**), it is likely that it is ammonium *endo*-6-bromocamphor-9-sulfonate **511** formed by rearrangement of the camphor framework during sulfonation (**Scheme 4.9**).




**57** **479** **510** **511**

**Scheme 4.9**

Numerous attempts were made to isolate the corresponding sulfonyl chloride, allegedly formed *in situ* from the acid, by extracting the crude reaction mixture with ether. In all cases intractable oils were obtained in low yield. The $^1$H NMR spectrum of the mixture of ammonium salts **510** and **511** is shown in **Figure 4.2**.

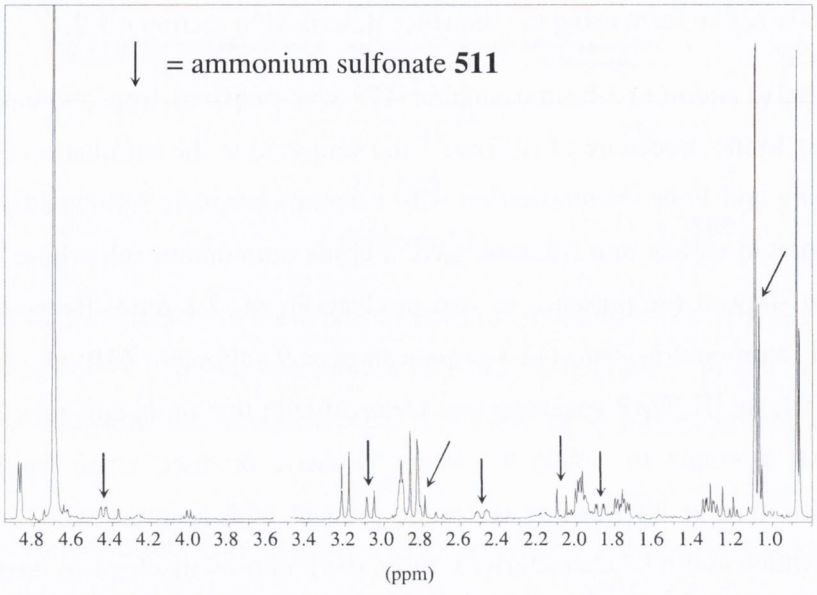



**Figure 4.2**

**$^1$H NMR spectrum of ammonium sulfonates**

**510 and 511 in $D_2O$**

A number of small-scale experiments was performed in order to find conditions under which the observed rearrangement leading to **511** would be minimised, by varying the reaction temperature, reaction time and the amount of chlorosulfonic acid used. These studies are summarised in **Table 4.1** below. Overall, it was found that a reduction in any one of these parameters (with the other two held constant) resulted in less rearrangement and a higher ratio of the desired product **510** to the rearranged product **511**. For example, using less chlorosulfonic acid resulted in an increase in the ratio of **510**:**511** from 2.1:1 to 2.8:1 (entry 6 vs. entry 7). Reducing the reaction temperature from 70 °C to 20 °C caused a change in this ratio from 1.8:1 to 3.3:1 (entry 3 vs. entry 4). Reducing the reaction time from 25 hours to 1 hour also caused an increase in this ratio from 2.1:1 to 3.3:1 (entry 4 vs. entry 5). However, in many cases the reaction failed to go to completion, particularly when the reaction was carried out below 40 °C. In these cases, unreacted *endo*-(+)-3-bromocamphor **479** was recovered unchanged by extraction of the reaction mixture with ether after basic neutralisation with ammonium hydroxide.

**Table 4.1**

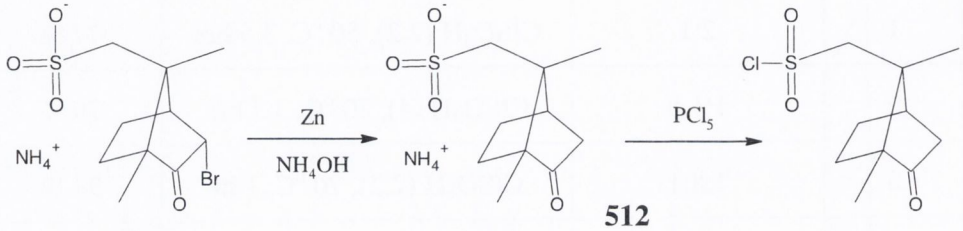
**Studies on the sulfonation of *endo*-(+)-3-bromocamphor 479**

| Entry | 510:511 Ratio[a] | Conditions (equivalents) | Yield[b] |
|---|---|---|---|
| 1 | 2:1 | $ClSO_3H$ (2.2), 50 °C, 3.5 hrs | 77 % |
| 2 | 1:1.5 | $ClSO_3H$ (4), 30 °C, 3.5 hrs | 79 % |
| 3 | 1.8:1 | $ClSO_3H$ (2.2), 70 °C, 1 hr | 94 % |
| 4 | 3.3:1 | $ClSO_3H$ (2.2), 20 °C, 1 hr | 12 % |
| 5 | 2.1:1 | $ClSO_3H$ (2.2), 20 °C, 25 hrs | 79 % |
| 6 | 2.1:1 | $ClSO_3H$ (2.2), 40 °C, 1 hr | 50 % |
| 7 | 2.8:1 | $ClSO_3H$ (1.1), 40 °C, 1 hr | 38 % |
| 8 | 2.5:1 | $ClSO_3H$ (1.1), 20 °C, 24 hrs | 38 % |
| 9 | 2.7:1 | $ClSO_3H$ (1.1), 40 °C, 3 hrs | 52 % |
| 10 | 2.3:1 | $ClSO_3H$ (1.5), 50 °C, 3 hrs | 77 % |
| 11 | 2.5:1 | $ClSO_3H$ (1.1), 50 °C, 3 hrs | 72 % |

[a]: Ratio determined from $^1H$ NMR. [b]: Total yield of **510** and **511**.

From these studies, the conditions in entry 10 were used for the scaled-up synthesis of the ammonium salt **510**. Treatment of *endo*-(+)-3-bromocamphor **479** with chlorosulfonic acid gave a mixture of **510** and **511** in ca. 2.3:1 ratio from which the desired ammonium salt **510** was obtained pure in 22 % yield following recrystallisation. A significant quantity of unreacted starting material **479** (7.75 g) was recovered in this reaction.

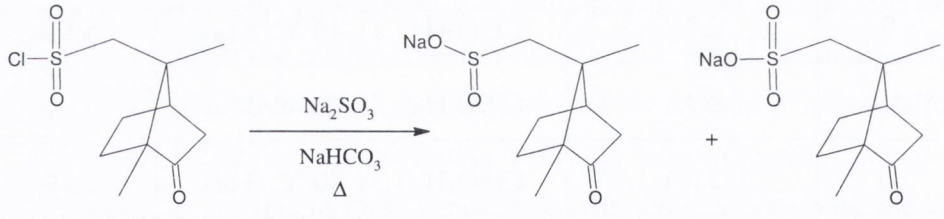
The ammonium salt **510** underwent C-3 debromination with zinc in ammonium hydroxide solution to afford ammonium sulfonate **512** which was converted into the sulfonyl chloride **513** on treatment with phosphorus pentachloride.[21] The use of thionyl chloride in this reaction failed to afford the sulfonyl chloride (**Scheme 4.10**).




**510** **512** **513**

**Scheme 4.10**

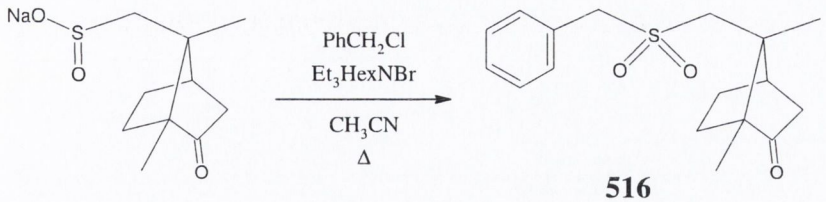
The sulfonyl chloride **513** was reduced to the corresponding sodium sulfinate **514** using the same procedure described in Chapter 2 for the reduction of (+)-camphor-10-sulfonyl chloride. The sodium sulfinate **514** was prepared in 96 % yield contaminated with ca. 10 % of the corresponding sodium sulfonate **515** formed by hydrolysis of the sulfonyl chloride **513** (**Scheme 4.11**).




**513** **514** **515**

**Scheme 4.11**

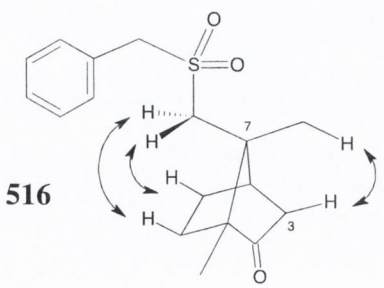
In its $^1$H NMR spectrum, the novel sulfinate salt **514** displayed a pair of doublets at δ 2.17 and 2.45 ppm, each with a coupling constant of 13.5 Hz. These were assigned to the diastereotopic methylene protons adjacent to sulfur. The doublet at δ 1.89 ppm ($J$ = 19.0 Hz) was assigned to the *endo* proton at C-3. Alkylation of sodium sulfinate **514** with benzyl chloride under phase-transfer conditions described by Masson *et al.*[23] afforded the novel benzyl sulfone **516** in good yield following chromatography (**Scheme 4.12**).




**514** **516**

**Scheme 4.12**

The $^1$H NMR details of sulfone **516** were broadly similar to those of the regioisomeric 10-substituted benzyl sulfone described in Chapter 2. The AB system for the methylene protons adjacent to sulfur appeared as doublets at δ 2.72 and 3.07 ppm. In contrast, the benzylic protons formed an almost completely collapsed AB system at ca. δ 4.27 ppm. Further confirmation of the regiospecificity of the C-9 sulfonation reaction was obtained from NOE experiments. The $^1$H NMR spectrum of **516** and the NOE experiments are shown in **Figure 4.4**. Irradiation of each of the diastereotopic protons adjacent to sulfur failed to enhance the signal intensity of the *exo*-proton at C-3 but enhanced the signals attributed to the protons at C-5 and C-6 (**Figure 4.4** (a) and (b)). Irradiation of the C-7-methyl protons however, did enhance the signal intensity of the C-3 *exo* proton indicating this methyl group was *syn* to the carbonyl group (**Figure 4.4** (c)). The most important NOE effects of **516** are shown in **Figure 4.3**.




**516**

**Figure 4.3**

**Summary of the important NOE effects of benzyl sulfone 516**

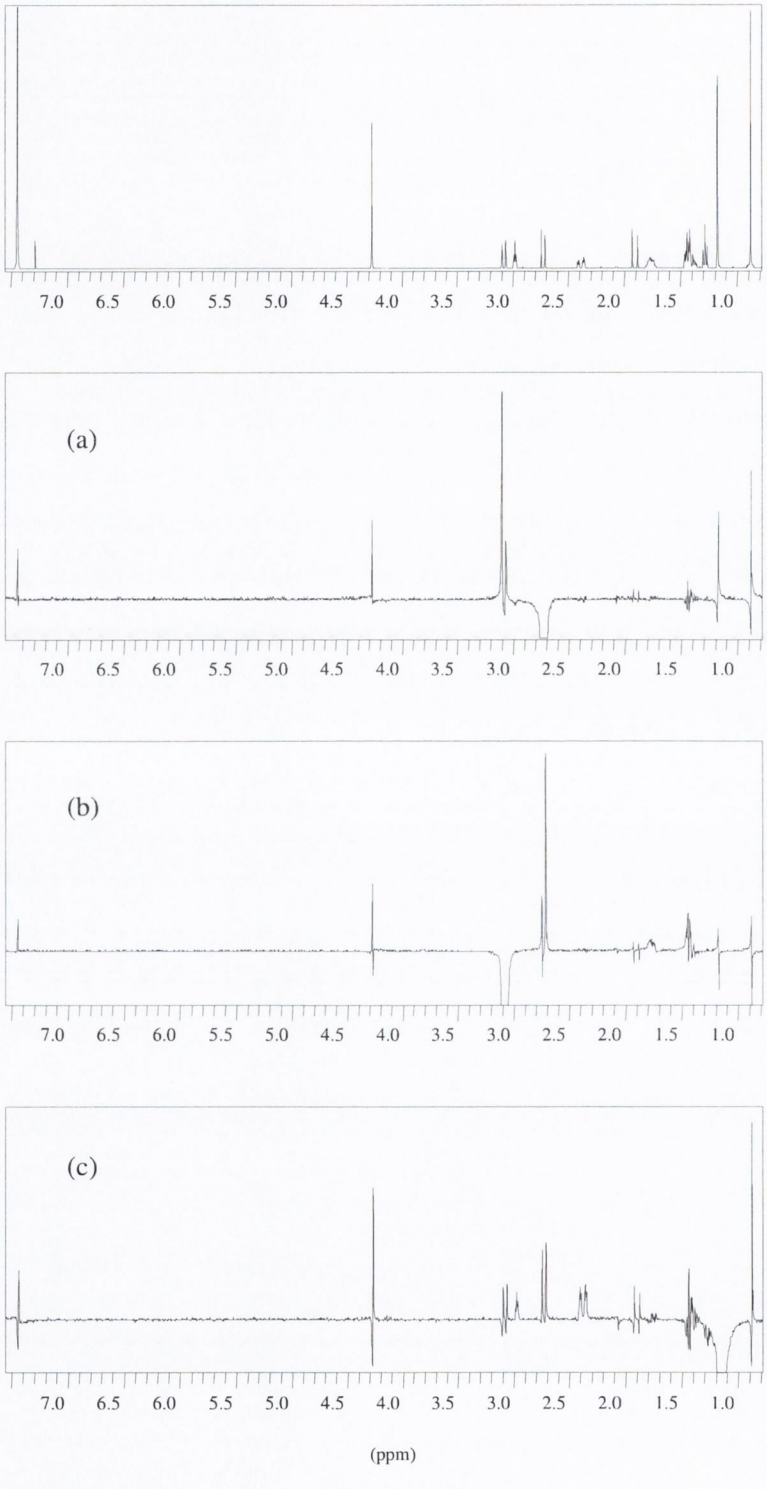


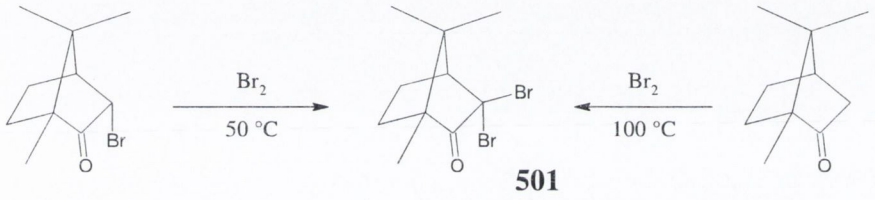

**Figure 4.4**

**$^1$H NMR and NOE spectra of benzyl sulfone 516 in $CDCl_3$**

## 4.3 Preparation of Benzylsulfone 518 *via* 8-Functionalisation of Camphor

Since there are no reports on the C-8 sulfonation of camphor, the only available route to 8-functionalised camphor derivatives is *via* the 8-bromination reaction discussed in section 4.1.3. Synthesis of these sulfones would involve displacement of the bromo group with a thiolate, followed by oxidation of the resulting sulfide.

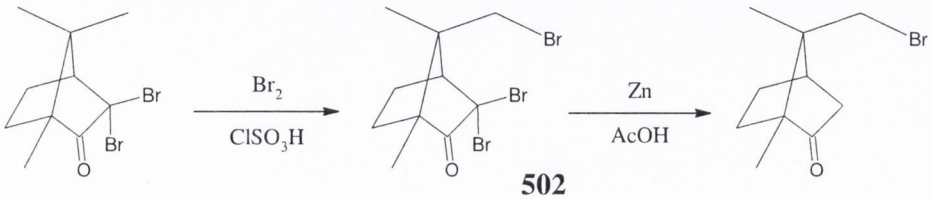
(+)-3,3-Dibromocamphor **501** was prepared in 84 % yield from *endo*-(+)-3-bromocamphor **479** according to the procedure of Money *et al.*[24] This compound has also been prepared directly from (+)-camphor **57** by heating at ca. 100 °C with excess bromine.[25] Using this procedure, **501** was also obtained from (+)-camphor **57** in 98 % yield (**Scheme 4.13**).




**479** **501** **57**

**Scheme 4.13**

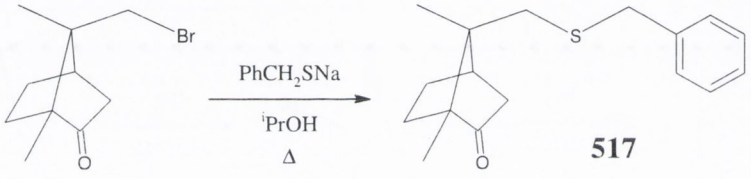
(+)-3,3-Dibromocamphor **501** was then subjected to the C-8 bromination conditions described by Money *et al.*[19,24] Examination of the $^1$H NMR spectrum of the crude product revealed the presence of the expected product **502** in addition to at least one other major product. The $^1$H NMR details of this product were consistent with those provided by Money *et al.*[19] for 1,7-dibromo-4-dibromomethyl-camphenilone **509** (see **Scheme 4.8**). These two compounds were inseparable by column chromatography and vacuum distillation led only to a partial separation. Treatment of this crude product with zinc dust in acetic acid effected regiospecific C-3 debromination to afford (+)-8 bromocamphor **503** obtained in 62 % yield following purification by chromatography (**Scheme 4.14**).




**501** **502** **503**

**Scheme 4.14**

Despite its neopentyl structure, there are some reports on the displacement of the bromo substituent in both 8 and 9-bromocamphor with sulfur nucleophiles. A two-step preparation of 9-mercaptocamphor from (+)-9-bromocamphor has been reported, involving $S_N2$ displacement of bromine with potassium thioacetate.[26] Additionally, Komarov *et al.* showed that both (+)-8-bromocamphor **503** and (+)-9-bromocamphor **489** successfully react with 2-mercaptoethanol to give substitution products.[27] With this precedent, (+)-8-bromocamphor **503** was treated with the sodium salt of benzyl mercaptan in refluxing isopropanol for 24 hours. A good yield (62 %) of the sulfide **517** was obtained, together with unreacted (+)-8-bromocamphor **503** following chromatography. Extending the reaction time to 4 days resulted in almost complete conversion and the sulfide **517** was isolated in 93 % yield (**Scheme 4.15**).



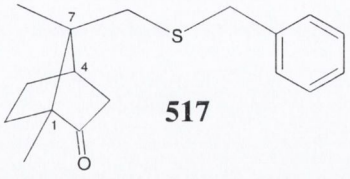

**503** **517**

**Scheme 4.15**

In its $^1H$ NMR spectrum, sulfide **517** displayed a pair of doublets at δ 2.14 and 2.30 ppm, corresponding to the diastereotopic methylene protons adjacent to sulfur at the neopentyl position. The benzylic protons formed a partially collapsed AB system at ca. δ 3.69 ppm. The $^1H$ and $^{13}C$ NMR details of **517** are summarised in **Table 4.2**.

**Table 4.2**

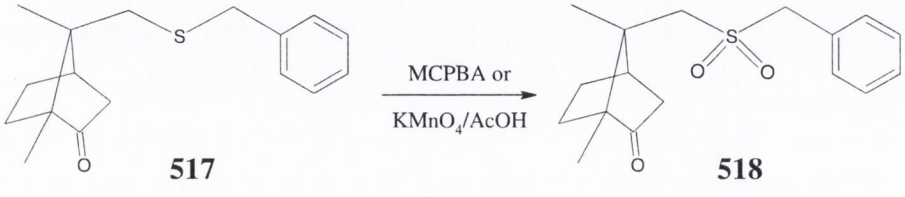
**NMR spectroscopic details for sulfide 517 in $CDCl_3$**




**517**

| $^1H$ (ppm) | Multiplicity (Hz) | $^{13}C$ (ppm) | Assignment |
|---|---|---|---|
| 0.89 | s | 8.8 | 1-$CH_3$ |
| 1.04 | s | 15.6 | 7-$CH_3$ |
| not assigned | - | 26.2 | C-5 |
| not assigned | - | 29.8 | C-6 |
| 2.14 | d, *J* 12.0 | 36.8 | alkyl $CH_2S$ |
| 2.30 | d, *J* 12.0 | | |
| 3.66 | d, *J* 13.5 | 37.1 | benzyl $CH_2S$ |
| 3.71 | d, *J* 13.5 | | |
| 2.35 | t, *J* 4.5 | 39.8 | C-4 |
| 1.82 | d, *J* 18.5 | 42.2 | C-3 |
| 2.11-2.18 | m | | |
| - | - | 49.8 | C-7 |
| - | - | 58.4 | C-1 |
| 7.24-7.37 | m | 126.6 | Ar C-4 |
| 7.24-7.37 | m | 128.0 | Ar C-3 |
| 7.24-7.37 | m | 128.2 | Ar C-2 |
| - | - | 137.6 | Ar C-1 |
| - | - | 218.4 | C-2 |

The sulfide **517** was oxidised to the corresponding sulfone **518** in good yield using either MCPBA in DCM,[28] or alternatively using potassium permanganate in DCM/acetic acid (**Scheme 4.16**).[29]



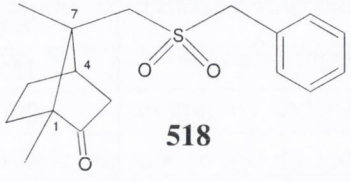

**517** **518**

**Scheme 4.16**

Sulfone **518** displayed a pair of doublets at δ 2.54 and 2.74 ppm corresponding to the neopentyl alkyl protons adjacent to sulfur. The benzylic protons did not display any diastereotopicity, and came into resonance as a singlet at δ 4.20 ppm. The $^{1}H$ and $^{13}C$ NMR details of **518** are shown in **Table 4.3**.

**Table 4.3**

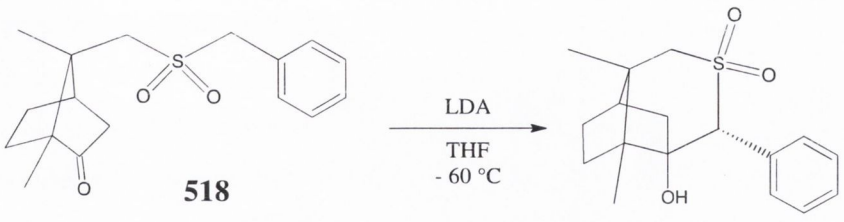
**NMR spectroscopic details for sulfone 518 in $CDCl_3$**




**518**

| $^{1}H$ (ppm) | Multiplicity (Hz) | $^{13}C$ (ppm) | Assignment |
|---|---|---|---|
| 0.87 | s | 8.7 | 1-$CH_3$ |
| 1.25 | s | 16.0 | 7-$CH_3$ |
| not assigned | - | 26.5 | C-5 |
| not assigned | - | 27.8 | C-6 |
| 2.95 | t, *J* 4.5 | 39.4 | C-4 |
| 1.90 | d, *J* 19.0 | 42.5 | C-3 |
| 2.27 | dt, *J* 19.0, 4.0 | | |
| - | - | 48.6 | C-7 |
| 2.54 | d, *J* 14.0 | 53.2 | alkyl $CH_2SO_2$ |
| 2.74 | d, *J* 14.0 | | |
| - | - | 60.2 | C-1 |
| 4.20 | s | 61.9 | benzyl $CH_2SO_2$ |
| - | - | 127.4 | Ar C-1 |
| 7.36-7.43 | m | 128.7 | Ar C-3 |
| 7.36-7.43 | m | 128.8 | Ar C-4 |
| 7.36-7.43 | m | 130.0 | Ar C-2 |
| - | - | 217.6 | C-2 |

Based on the proximal relationship between the sulfonyl side-chain and the carbonyl group in **518**, it was decided to examine if **518** would undergo base-mediated 6-*exo* trig cyclisation in a stereospecific fashion analogous to the allylic and benzylic sulfones discussed in Chapter 2. Accordingly, **518** was treated with LDA at – 60 °C in THF to afford the *endo*-configured tricyclic alcohol **519** in 75 % yield (**Scheme 4.17**).




**518** **519**

**Scheme 4.17**

Examination of the $^{1}H$ and $^{13}C$ NMR spectra of **519** showed that only a single diastereomer was present, indicating the cyclisation reaction was completely stereoselective as was the case for the sulfones described in Chapter 2. The $^{1}H$ NMR spectrum of **519** is shown in **Figure 4.5**.

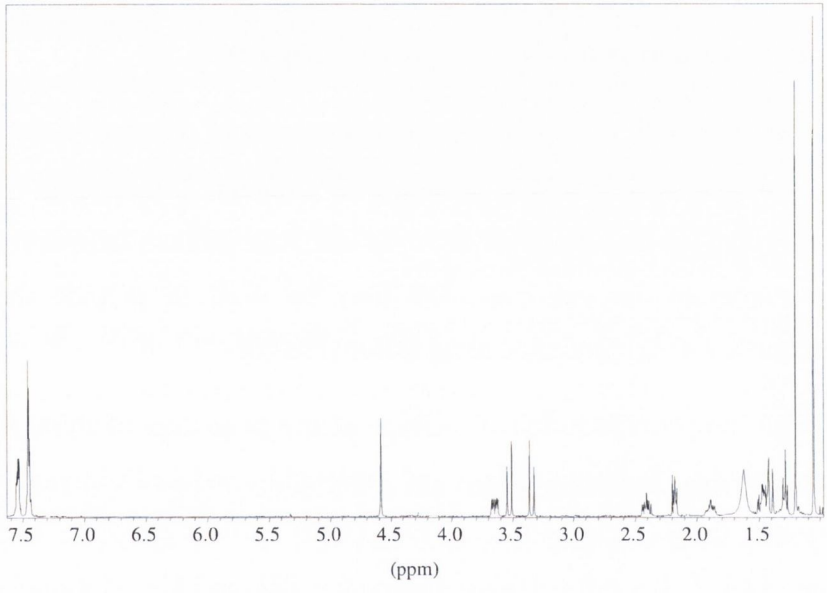



**Figure 4.5**

**$^{1}H$ NMR spectrum of tricyclic sulfone 519 in $CDCl_3$**

The absolute configuration at the new stereocentres in **519** was determined by X-ray crystallography. Apart from the expected *endo*-configuration of the hydroxyl group, a notable feature is the configuration at the benzylic carbon in which the bulky phenyl group is held away from the C-1 methyl group. The epimeric structure would place the phenyl group and the C-1 methyl group in close proximity in an almost *syn*-periplanar arrangement. The molecular structure in the crystal of **519** is shown in **Figure 4.6**.

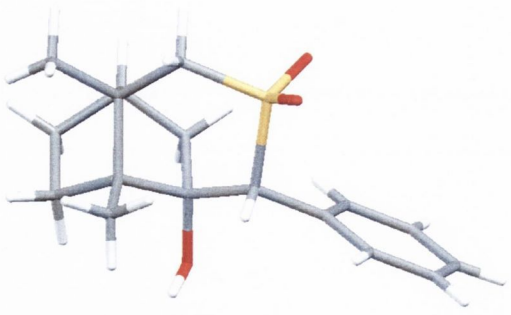


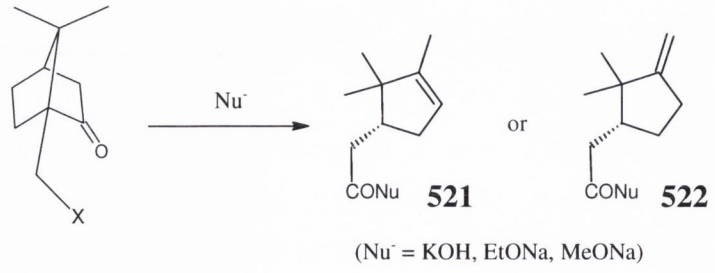
**Figure 4.6**

**Molecular structure in the crystal of tricyclic sulfone 519**

## 4.4 Preparation of the 10-Halocamphors

During the course of the attempted iodosulfonylation of allyl benzyl ether using sodium camphorsulfinate **310** discussed in Chapter 3 (see page 160), it was discovered that 10-iodocamphor **425** was the sole product of this reaction. This finding suggested that sulfinate **310** may be used to prepare the other 10-halocamphors *via* their corresponding sulfonyl halides.

The 10-halocamphors have found widespread use as sources of chiral intermediates in natural product synthesis.[2] Base and nucleophile induced cleavage of the C(1)-C(2) bond in these compounds leads to optically active cyclopentenes **521** and **522** (**Scheme 4.18**).[30] Recently, 10-bromocamphor **520** and 10-iodocamphor **425** have been used in the preparation of bidentate phosphine ligands for asymmetric catalysis.[31]




**520** X = Br
**425** X = I

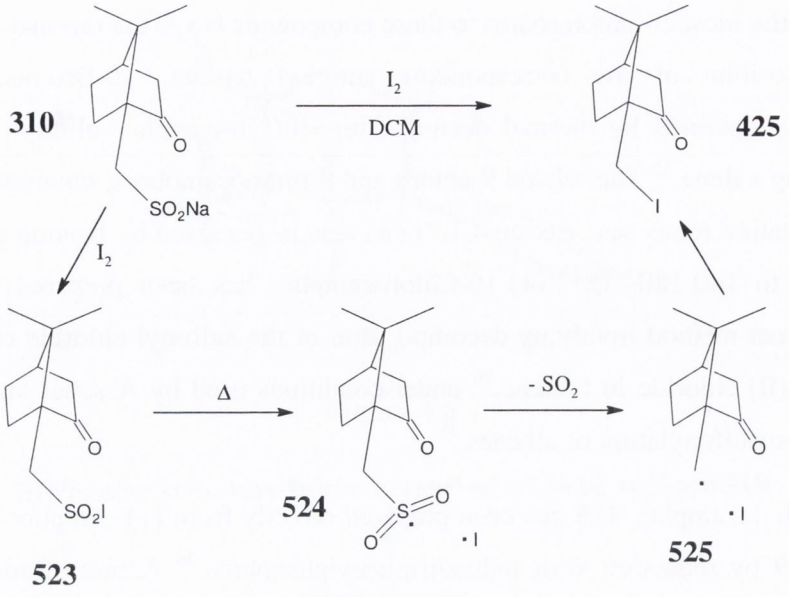
**Scheme 4.18**

One of the most common routes to these compounds is *via* the thermal free-radical decomposition of the corresponding sulfonyl halides. 10-Bromocamphor is normally obtained by thermal decomposition of 10-camphorsulfonyl bromide in refluxing xylene.[32] The related 9-chloro and 9-bromocamphors, obtained *via* the C-9 sulfonation route (see section 4.1.2) can also be accessed by heating the sulfonyl halides to 140-180 °C.[33] (+)-10-Chlorocamphor has been prepared by a more convenient method involving decomposition of the sulfonyl chloride catalysed by copper (II) chloride in toluene,[34] under conditions used by Asscher and Vofsi for the chlorosulfonylation of alkenes.[35]

(+)-10-Iodocamphor **425** has been prepared directly from (+)-camphor-10-sulfonic acid **319** by reduction with iodine/triphenylphosphine.[36] Arenesulfonic acids can also be reduced to the corresponding arenethiols using this system. This procedure does not appear to have been used for the preparation of 10-bromocamphor or 10-chlorocamphor however. More recently, 10-chloro, 10-bromo and 10-iodocamphor have all been obtained from (+)-camphor in a two-step procedure involving C-10 functionalisation by Wagner-Meerwein rearrangement promoted by triflic anhydride, followed by treating the derived 2-methylenenorbornan-1-ol with the corresponding *N*-halosuccinimide.[37] Other miscellaneous routes to these compounds include the preparation of 10-bromocamphor from camphene,[38] and the conversion of 10-bromocamphor to 10-chlorocamphor using lithium chloride.[39]

### 4.4.1 Preparation of 10-Iodocamphor 425

Using the same procedure as the attempted iodosulfonylation reaction mentioned above (simple admixture of a DCM solution of iodine and an aqueous solution of sodium sulfinate **310**) with omission of the alkene, (−)-10-iodocamphor **425** was prepared from sodium camphorsulfinate **310** in 65 % yield. This reaction may be rationalised by invoking a free-radical mechanism where the reactive sulfonyl iodide **523** undergoes homolytic fission generating a camphorsulfonyl radical **524**. Loss of sulfur dioxide generates the neopentyl 10-camphoryl radical **525**. Radical recombination with the iodo radical generates the product (**Scheme 4.19**).

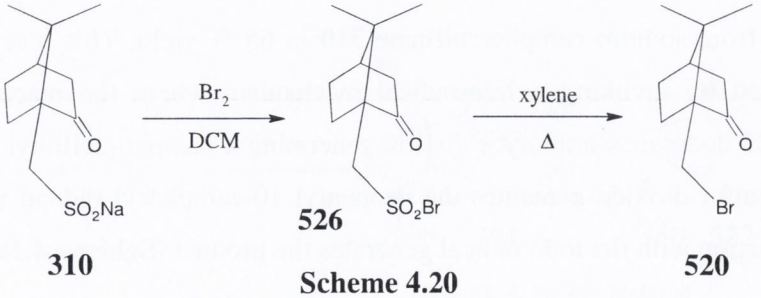



**Scheme 4.19**

The decomposition of the sulfonyl iodide **523** appears to be a rapid process which occurs at ambient temperature (TLC). On the other hand, β-iodosulfones can be generated from **523** in the presence of certain alkenes such as norbornene and 1,5-cyclooctadiene.[34] It appears that the product distribution depends on the relative rates of sulfur dioxide extrusion from the camphorsulfonyl radical **524** and of addition of **524** to an alkene.

### 4.4.2 Preparation of 10-Bromocamphor 520

Using the same procedure described above, (+)-10-camphorsulfonyl bromide **526** was prepared from sodium sulfinate **310** and bromine. Using the published procedure,[32] the less reactive sulfonyl bromide **526** was heated in xylene at reflux to generate (+)-10-bromocamphor **520** in 72 % overall yield (**Scheme 4.20**).

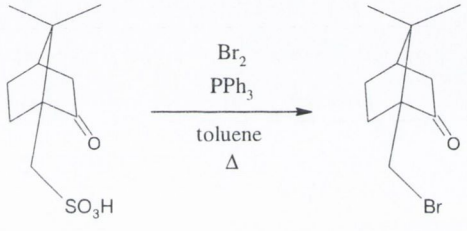



**Scheme 4.20**

Use of the Asscher-Vofsi conditions[35] for the preparation of **520** (catalytic copper (II) chloride and triethylammonium chloride in refluxing toluene) did not give a

promising result. The $^1$H NMR spectrum of the crude product, obtained in low yield, showed the presence of **520** as well as numerous other products which could not be identified. However, a control experiment in which the sulfonyl bromide **526** was heated in toluene in the absence of the copper catalyst resulted in complete decomposition to (+)-10-bromocamphor **520**.

It was reasoned that a synthetic route to (+)-10-bromocamphor **520** directly from the sulfonic acid **319** would be a useful and convenient procedure for the preparation of **520** in a single step. The procedure used by Oae *et al.*[40] for the preparation of (−)-10-iodocamphor **425** from (+)-camphor-10-sulfonic acid **319** was subsequently examined. Treatment of acid **319** with excess bromine/triphenylphosphine in refluxing toluene led to the formation of **520** in 78 % yield after column chromatography (**Scheme 4.21**).

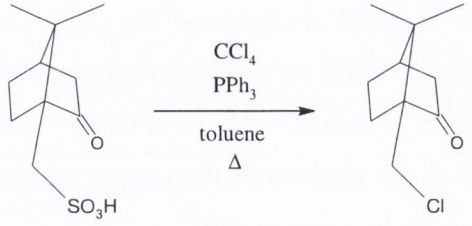



**319** **520**

**Scheme 4.21**

### 4.4.3 Preparation of 10-Chlorocamphor 527

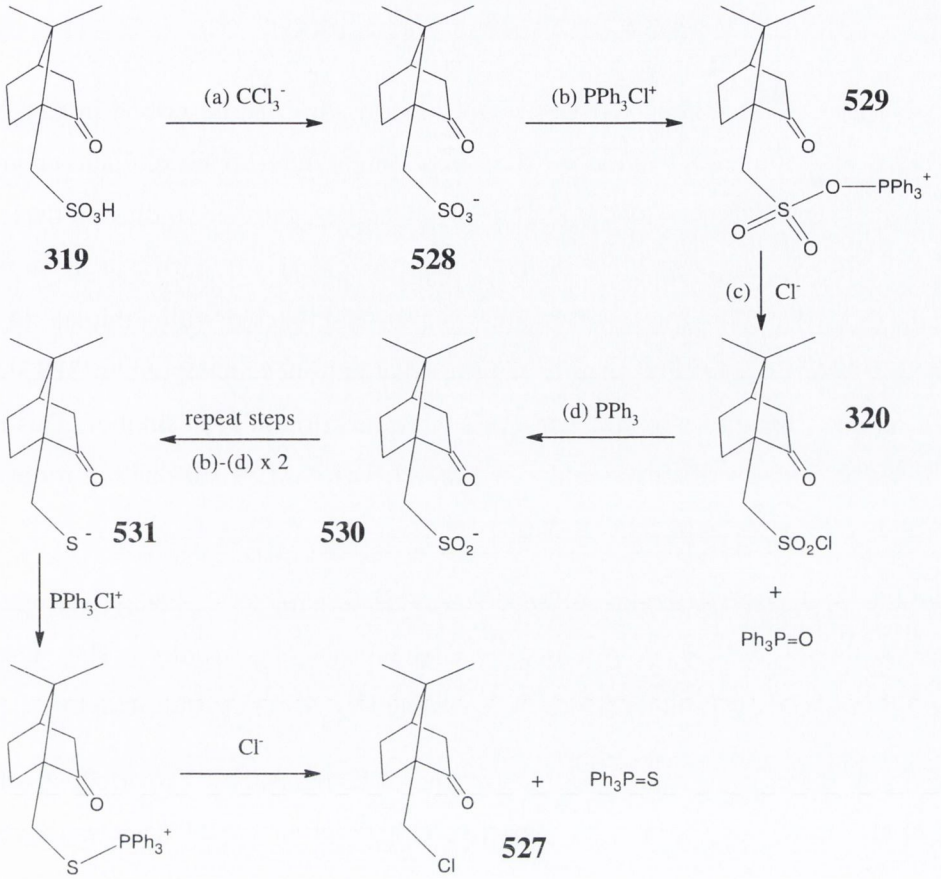
Encouraged by the above result, the preparation of (+)-10-chlorocamphor from (+)-camphor-10-sulfonic acid **319** was then undertaken. It was decided to use carbon tetrachloride as the c lorine source, since the combination of carbon tetrachloride/triphenylphosphine is frequently employed in the preparation of alkyl chlorides from alcohols (the Appel reaction).[41] Using this reagent combination, (+)-10-chlorocamphor **527** was prepared from acid **319** in 66 % yield following chromatography (**Scheme 4.22**).




**319** **527**

**Scheme 4.22**

The likely mechanism of this transformation is analogous to that proposed by Oae and co-workers[40] for the formation of 10-iodocamphor **425**. Reaction of the sulfonate anion **528** with the chlorotriphenylphosphonium ion generated *in situ*, affords **529** which reacts with chloride ion to generate sulfonyl chloride **320** and triphenylphosphine oxide. Reaction of the sulfonyl chloride **320** with triphenylphosphine forms sulfinate **530** and regenerates chlorotriphenylphosphonium ion. The sulfinate **530** is then further reduced (steps (b)-(d)) to the corresponding sulfenate and then to the thiolate **531**. Reaction of thiolate **531** with chlorotriphenylphosphonium ion, followed by displacement of triphenylphosphine sulfide generates 10-chlorocamphor **527** (**Scheme 4.23**).




**Scheme 4.23**

Based on the free-radical decomposition reactions of 10-camphorsulfonyl iodide **523** and 10-camphorsulfonyl bromide **526** mentioned previously, it might be reasonable to assume that, in the case of the reduction of (+)-camphor-10-sulfonic acid **319** with iodine/triphenylphosphine,[40] the sulfonyl iodide formed *in situ* undergoes homolytic fission with subsequent loss of sulfur dioxide to generate 10-iodocamphor **425**. It appears that this pathway is not operative in this case (at least not as the sole pathway) as 10-mercaptocamphor may be isolated in up to 15 % yield from the reaction mixture when shorter reaction times are used. Thus, it is likely that the reactive sulfonyl iodide **523** reacts with triphenylphosphine more rapidly than it undergoes homolytic fission.

## 4.5 Summary and Concluding Remarks

In summary, two benzylic sulfones regioisomeric with that described in Chapter 2 have been prepared, utilising the rich and stereospecific, acid-catalysed rearrangement chemistry that (+)-camphor undergoes. Further studies on these and related sulfones may establish their potential as chiral auxiliaries in asymmetric synthesis. The finding that (+)-8-bromocamphor **503** reacted with a thiolate in high yield, despite its neopentyl nature, suggests that sulfones analogous to **518** should be available through a similar route *via* C-9 bromination of (+)-camphor. This route to C-9 substituted sulfones would avoid the alternative C-9 sulfonation route with the numerous associated aqueous work-up's.

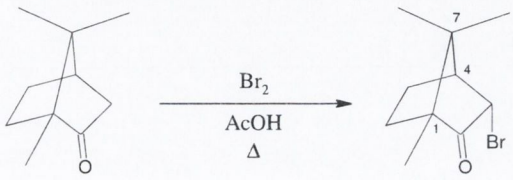
Like the allylic and benzylic sulfones discussed in Chapter 2, benzyl sulfone **518** was found to cyclise in a completely stereoselective fashion. The absolute configuration of the product has been determined by X-ray crystallography.

Finally, a novel route to (−)-10-iodocamphor **425** has been discovered, involving free-radical decomposition of the reactive sulfonyl iodide **523** made *in situ* from sodium sulfinate **310**. (+)-10-Bromocamphor **520** may also be obtained by the same route. Both (+)-10-bromocamphor **520** and (+)-10-chlorocamphor **527** may also be obtained directly from (+)-camphor-10-sulfonic acid **319** by Appel-type reaction with excess triphenylphosphine and an appropriate electrophilic halogen source.

## 4.6 Experimental

All general experimental conditions as for Chapter 2.

**(1*R*, 3*S*, 4*S*)-3-Bromo-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one 479**[11]




**57** **479**

Following the procedure of Albizati,[42] acetic acid (50 ml) was added to (+)-camphor **57** (20 g, 131 mmol) in a 3-neck flask. The solution was heated under reflux at 80-90 °C and a solution of bromine (8 ml, 155 mmol) in acetic acid (8 ml) was added slowly in small aliquots to prevent the deep red colour of excess bromine building up. The solution was heated under reflux at 80-90 °C for a further 2 hrs and then allowed to cool to rt and stirred overnight. The mixture was then added dropwise with stirring to ice/water (120 ml). The resulting precipitate was filtered off and washed with 20 ml portions of water until the filtrate was colourless. The solid was sucked dry on the Buchner funnel and left to dry in the air for a day. The solid was then taken up in ether, dried, filtered and concentrated under reduced pressure to afford the title compound as a white solid (24.85 g, 82 %).

m.p.: 75 °C (from ether); Lit.[43]: 76 °C

$[\alpha]_D$ (*c* 1.01, MeOH, 22 °C) +125.7; Lit.[43]: (*c* 1.0, 23 °C) +125

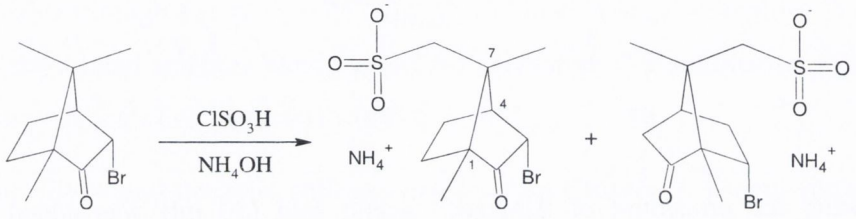
IR: $\nu_{max}$ (N) 2921, 1761 (C=O), 1459, 1375, 1318, 1274, 1208, 1105, 1034, 1003, 911, 808, 767, 691 $cm^{-1}$

$^1$H NMR (400.1 MHz): δ 0.95 (3H, s, 1-C*H*$_3$), 0.99 (3H, s, 7-C*H*$_3$), 1.09 (3H, s, 7-C*H*$_3$), 1.41-1.48 (1H, m), 1.65-1.74 (1H, m), 1.85-1.94 (1H, m), 2.07-2.13 (1H, m), 2.32 (1H, t, $^3J$ = 4.7, 4-C*H*), 4.64 (1H, d, $^3J$ = 4.7, 3-C*H exo*) ppm

$^{13}C$ NMR (100.6 MHz): δ 9.1 (1-*C*$H_3$), 19.4 (7-*C*$H_3$), 19.5 (7-*C*$H_3$), 21.9 (C-5), 30.0 (C-6), 45.4 (C-7), 49.1 (C-4), 53.4 (C-3), 57.1 (C-1), 212.1 (C-2) ppm

HRMS (CI) *m/z* 253.0213: *calculated for* $[C_{10}H_{15}OBr + Na]^+$ 253.0203

**Ammonium (1*R*, 3*S*, 4*S*, 7*R*)-(3-bromo-1,7-dimethyl-2-oxobicyclo[2.2.1]hept-7-yl)methanesulfonate 510**[8,10]




**479** **510** **511**

Following the procedure of Kipping and Pope,[21] chlorosulfonic acid (7.88 ml, 119 mmol) was added to *endo*-(+)-3-bromocamphor **479** (18.35 g, 79 mmol) in a 3 neck flask. After the initial evolution of hydrogen chloride had ceased the solution was heated at 50 °C with stirring for 3 hrs. The solution was then allowed to cool to rt, carefully quenched with water (100 ml) and then carefully neutralized with conc. ammonium hydroxide soln. until basic to litmus. The solution was extracted with ether (100 ml) and the aqueous phase was evaporated to dryness. The resulting solid was triturated with boiling ethanol (ca. 200 ml) and filtered and the insoluble solids were washed with boiling ethanol. The filtrate was evaporated to yield a light brown solid (13.3 g). Recrystallization from water afforded the title compound as a white solid (4.68 g). Evaporation of the mother liquor and recrystallization of the resulting solid from water yielded an additional 1.17 g of product. Total yield: 5.85 g, 22 %. The organic phase was dried and evaporated to yield unreacted *endo*-(+)-3-bromocamphor **479** (7.75 g).

m.p.: 278-280 °C (from $H_2O$); Lit.[22]: 284 °C

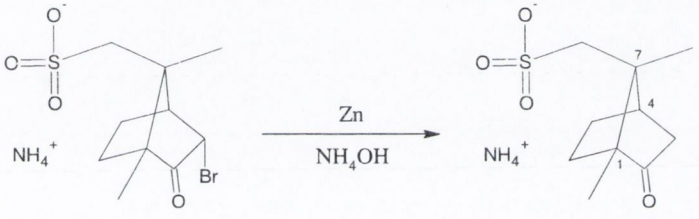
$[\alpha]_D$ (*c* 1.14, $H_2O$, 25 °C) +82.8; Lit.[44]: (*c* 2 g in 50 ml, $H_2O$, 22 °C) +85.2

IR $\nu_{max}$ (N) 3174 ($NH_4^+$), 2917, 1752 (C=O), 1460, 1376, 1292, 1257, 1185, 1160 ($SO_2$), 1042 ($SO_2$), 1006, 837, 757, 725 $cm^{-1}$

$^1$H NMR in $D_2O$ (400.1 MHz): δ 0.86 (3H, s, 1-C$H_3$), 1.07 (3H, s, 7-C$H_3$), 1.26-1.33 (1H, m), 1.70-1.78 (1H, m), 1.90-2.02 (2H, m), 2.82 (1H, d, $^2J$ = 14.5, C$H_2$SO$_3$NH$_4$), 2.89 (1H, t, $^3J$ = 4.0, 4-C*H*), 3.18 (1H, d, $^2J$ = 14.5, C$H_2$SO$_3$NH$_4$), 4.86 (1H, d, $^3J$ = 4.5, 3-C*H exo*) ppm

$^{13}$C NMR in $D_2O$ (100.6 MHz): δ 8.2 (1-*C*H$_3$), 16.4 (7-*C*H$_3$), 21.0 (C-5), 29.3 (C-6), 46.4 (C-4), 46.6 (C-7), 52.7 (C-3), 53.3 (*C*H$_2$SO$_3$NH$_4$), 59.8 (C-1), 217.6 (C-2) ppm

**Ammonium (1*R*, 4*R*, 7*R*)-(1,7-dimethyl-2-oxobicyclo[2.2.1]hept-7-yl)methanesulfonate 512**[21]




**510** **512**

Following the procedure of Kipping and Pope,[21] ammonium sulfonate **510** (4.0 g, 12.2 mmol) was dissolved in conc. ammonium hydroxide soln. (40 ml) and zinc dust (1.59 g, 24.4 mmol) was added in small portions over 30 mins. The mixture was stirred at rt for 2.5 hrs and then heated at 50 °c for 1.5 hrs. The mixture was then allowed to cool to rt and the excess zinc dust was filtered. The filtrate was evaporated to dryness. The resulting solid was triturated with boiling ethanol (ca. 100 ml) and filtered and the insoluble solids were washed with boiling ethanol and the filtrate was evaporated to yield a white solid (2.43 g, 80 %).

m.p.: 252-254 °C (from EtOH)

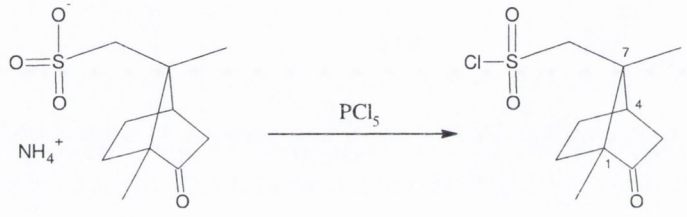
$[\alpha]_D$ (*c* 0.94, $H_2O$, 22 °C) +42.1

IR $\nu_{max}$ (N) 3448, 3162 ($NH_4^+$), 2900, 1734 (C=O), 1459, 1376, 1302, 1212, 1159 ($SO_2$), 1090, 1043 ($SO_2$), 948, 792, 716 cm$^{-1}$

$^1$H NMR in $D_2O$ (400.1 MHz): δ 0.78 (3H, s, 1-C$H_3$), 0.96 (3H, s, 7-C$H_3$), 1.28-1.39 (2H, m), 1.66-1.74 (1H, m), 1.90 (1H, d, $^2J$ = 19.0, 3-C$H_2$ *endo*), 1.94-2.01 (1H, m), 2.36 (1H, dt, $^2J$ = 19.0, $^3J$ = 4.5, 3-C$H_2$ *exo*), 2.66 (1H, t, $^3J$ = 4.5, 4-C*H*), 2.71 (1H, d, $^2J$ = 14.5, C$H_2SO_3NH_4$), 3.08 (1H, d, $^2J$ = 14.5, C$H_2SO_3NH_4$) ppm

$^{13}$C NMR in $D_2O$ (100.6 MHz): δ 7.9 (1-*C*$H_3$), 16.0 (7-*C*$H_3$), 25.3 (C-5), 28.3 (C-6), 39.7 (C-4), 41.9 (C-3), 47.7 (C-7), 52.9 (*C*$H_2SO_3NH_4$), 59.9 (C-1), 225.1 (C-2) ppm

**(1*R*, 4*R*, 7*R*)-(1,7-Dimethyl-2-oxobicyclo[2.2.1]hept-7-yl)methanesulfonyl chloride 513**[8,21]




**512** **513**

Following the procedure of Kipping and Pope,[21] ammonium sulfonate **512** (4.45 g, 17.8 mmol) was placed in a round bottomed flask and phosphorus pentachloride (4.84 g, 23.2 mmol) was added. The mixture of solids was agitated with a spatula until the reaction commenced. After 3 hrs at rt, the oily mixture was taken up in ether (150 ml) and the solution was washed with water (100 ml) and satd. aq. sodium hydrogen carbonate (50 ml), dried and evaporated to yield a semi-solid (2.99 g). The crude product was triturated with a small volume of ether (ca. 2 ml) and the resulting solid was filtered to yield the title compound as a white solid (0.86 g, 19 %).

m.p.: 136 °C (from ether); Lit.[21]: 137.5 °C

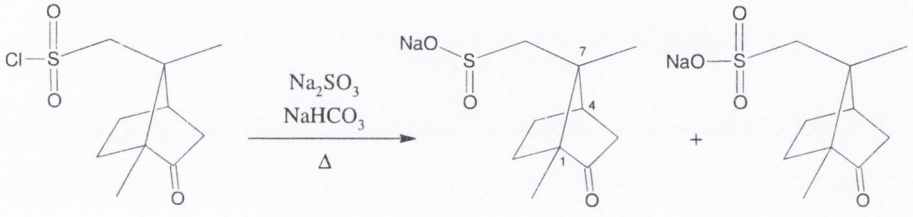
$[\alpha]_D$ (*c* 2.19, $CHCl_3$, 22 °C) +128.1; Lit.[8]: (*c* 1.33 g in 25 ml, $CHCl_3$, 14 °C) +128.7

IR $\nu_{max}$ (N) 2932, 1739 (C=O), 1460, 1417, 1362, 1205, 1164 ($SO_2$), 1073, 1044 ($SO_2$), 951, 873, 708, 669 cm$^{-1}$

$^1$H NMR (400.1 MHz): δ 0.99 (3H, s, 1-C$H_3$), 1.25 (3H, s, 7-C$H_3$), 1.56-1.65 (2H, m), 1.67-1.73 (1H, m), 2.02 (1H, d, $^2J$ = 18.5, 3-C$H_2$ *endo*), 2.16-2.25 (1H, m), 2.44 (1H, dt, $^2J$ = 18.5, $^3J$ = 4.0, 3-C$H_2$ *exo*), 2.86 (1H, t, $^3J$ = 4.5, 4-C*H*), 3.74 (1H, d, $^2J$ = 13.5, C$H_2$SO$_2$Cl), 4.03 (1H, d, $^2J$ = 13.5, C$H_2$SO$_2$Cl) ppm

$^{13}$C NMR (100.6 MHz): δ 8.9 (1-C$H_3$), 17.0 (7-C$H_3$), 26.0 (C-5), 28.5 (C-6), 40.5 (C-4), 42.0 (C-3), 50.0 (C-7), 59.8 (C-1), 70.7 (C$H_2$SO$_2$Cl), 214.4 (C-2) ppm

**Sodium (1*R*, 4*R*, 7*R*)-(1,7-dimethyl-2-oxobicyclo[2.2.1]hept-7-yl)methanesulfinate 514**




**513** **514** **515**

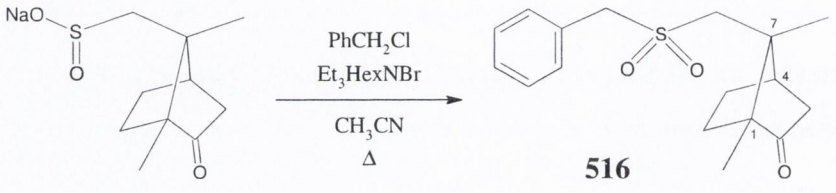
Sulfonyl chloride **513** (0.63 g, 2.5 mmol) in dry acetone (10 ml) was added dropwise over 1 hr to a solution of sodium sulfite (0.63 g, 5.0 mmol) and sodium hydrogen carbonate (0.42 g, 5.0 mmol) in water (10 ml) maintained at 70 °C. The mixture was stirred for an additional 1 hr at 70 °C and was then allowed to cool to rt and left stirring overnight. The mixture was evaporated to yield a white solid which was taken up in boiling ethanol (ca. 50 ml) and filtered through Celite$^R$. The filtrate was evaporated to afford the title compound as a white solid (0.58 g, 96 %) together with *ca.* 10 % of the corresponding sodium sulfonate **515**.

IR $\nu_{max}$ (N) 3344, 3188, 2921, 1739 (C=O), 1458, 1377, 1204, 1026 (S=O), 971 (S=O), 850, 721 cm$^{-1}$

$^1$H NMR in D$_2$O (400.1 MHz): δ 0.77 (3H, s, 1-C$H_3$), 0.92 (3H, s, 7-C$H_3$), 1.27-1.38 (2H, m), 1.65-1.73 (1H, m), 1.89 (1H, d, $^2J$ = 19.0, 3-C$H_2$ *endo*), 1.94-2.01 (1H, m), 2.17 (1H, d, $^2J$ = 13.5, C$H_2$SO$_2$Na), 2.36 (1H, dt, $^2J$ = 19.0, $^3J$ = 4.5, 3-C$H_2$ *exo*), 2.45 (1H, d, $^2J$ = 13.5, C$H_2$SO$_2$Na), 2.55 (1H, t, $^3J$ = 4.5, 4-C*H*) ppm

$^{13}$C NMR in $D_2O$ (100.6 MHz): δ 7.9 (1-*C*$H_3$), 16.5 (7-*C*$H_3$), 25.3 (C-5), 28.5 (C-6), 39.9 (C-4), 41.9 (C-3), 47.6 (C-7), 59.6 (C-1), 64.7 (*C*$H_2SO_2Na$), 225.8 (C-2) ppm

**(1*R*, 4*R*, 7*R*)-7-[(benzylsulfonyl)methyl]-1,7-dimethylbicyclo[2.2.1]heptan-2-one 516**




**514** **516**

According to the procedure of Masson,[23] sodium sulfinate **514** (0.36 g, 1.51 mmol) was suspended in acetonitrile (10 ml) and triethylhexylammonium bromide (0.08 g, 20 mol %) was added. Benzyl chloride (0.19 ml, 1.66 mmol) was added and the mixture was heated under reflux for 24 hrs. The mixture was allowed to cool to rt, diluted with water (50 ml) and extracted with ether (3 × 50 ml). The combined organic extracts were dried and evaporated to yield an oil. Column chromatography on silica gel using EtOAc:hexane (1:3) afforded the title compound as a white solid (0.32 g, 69 %).

m.p.: 93-94 °C (from EtOAc/hexane)

$[\alpha]_D$ (*c* 0.39, $CHCl_3$, 19 °C) +75.8

IR $\nu_{max}$ (N) 2923, 1737 (C=O), 1602 (Ar C-C), 1459, 1377, 1296 ($SO_2$), 1203, 1132 ($SO_2$), 1078, 1044, 950, 828, 753, 727, 698 cm$^{-1}$

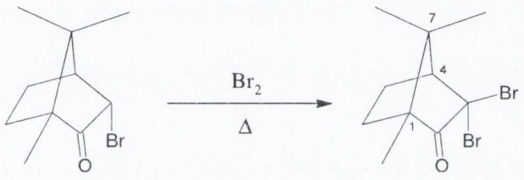
$^1$H NMR (400.1 MHz): δ 0.87 (3H, s, 1-C$H_3$), 1.16 (3H, s, 7-C$H_3$), 1.35-1.46 (3H, m), 1.72-1.80 (1H, m), 1.90 (1H, d, $^2J$ = 18.5, 3-C$H_2$ *endo*), 2.38 (1H, dt, $^2J$ = 18.5, $^3J$ = 4.5, 3-C$H_2$ *exo*), 2.72 (1H, d, $^2J$ = 13.5, alkyl C$H_2SO_2$), 2.97 (1H, t, $^3J$ = 4.5, 4-C*H*), 3.07 (1H, d, $^2J$ = 13.5, alkyl C$H_2SO_2$), 4.25 (1H, d, $^2J$ = 14.0, benzyl C$H_2SO_2$), 4.28 (1H, d, $^2J$ = 14.0, benzyl C$H_2SO_2$), 7.44 (5H, s, Ar*H*) ppm

$^{13}$C NMR (100.6 MHz): δ 8.9 (1-*C*H$_3$), 17.0 (7-*C*H$_3$), 25.9 (C-5), 28.8 (C-6), 39.9 (C-4), 42.0 (C-3), 48.5 (C-7), 52.1 (alkyl *C*H$_2$SO$_2$), 59.5 (C-1), 62.3 (benzyl *C*H$_2$SO$_2$), 127.8 (Ar C-1), 128.6 (Ar C-3), 128.7 (Ar C-4), 130.0 (Ar C-2), 216.0 (C-2) ppm

HRMS (CI) *m/z* 329.1187: *calculated for* [$C_{17}H_{22}O_3S$ + Na]$^+$ 329.1186

**(1*R*, 4*S*)-3,3-Dibromo-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one 501**[20,24,25,45]

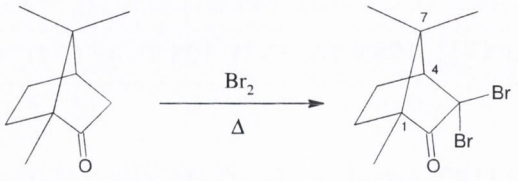
Method A:[24]




**479** **501**

Following the procedure of Money,[24] *endo*-(+)-3-bromocamphor **479** (10 g, 43.4 mmol) was placed in a flask wrapped in tin foil to exclude light and bromine (3.28 ml, 64.1 mmol) was added. The flask was heated at ca. 50 °C for 24 hrs. The flask was allowed to cool to rt and diluted with ether (200 ml). The solution was washed with water (100 ml) and the aqueous phase was extracted with ether (2 × 50 ml). The combined organic extracts were washed with satd. aq. sodium sulfite (2 × 100 ml) until colorless, and dried and evaporated to yield an oil which was taken up in acetic acid (60 ml) and added dropwise to ice/water (ca. 600 ml). The resulting precipitate was filtered and washed with water to afford the title compound as a yellow solid (11.39 g, 84 %).

Method B:[25,45]




**57** **501**

Following the procedure of Lu,[25] (+)-camphor **57** (3 g, 19.7 mmol) was placed in a flask wrapped in tin foil to exclude light and bromine (3.03 ml, 59.2 mmol) was added. The flask was heated at ca. 100 °C for 24 hrs. The flask was allowed to cool to rt and diluted with ether (100 ml). The solution was washed with water (50 ml) and the aqueous phase was extracted with ether (2 × 50 ml). The combined organic extracts were washed with satd. aq. sodium sulfite (50 ml), dried and evaporated to yield an oil which later crystallized (6.01 g, 98 %).

m.p.: 50-51 °C (from acetic acid); Lit.[45]: 54-55 °C

$[\alpha]_D$ (*c* 1.72, 95 % EtOH, 27 °C) +36.2; Lit.[24]: (*c* 1.67, 95 % EtOH, 25 °C) +37.1

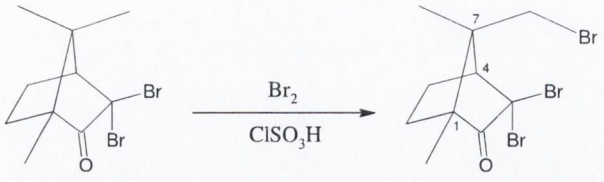
IR $\nu_{max}$ (N) 2924, 1765 (C=O), 1459, 1375, 1315, 1294, 1262, 1236, 1180, 1142, 1112, 1019, 1001, 940, 911, 859, 811, 775, 696, 647 $cm^{-1}$

$^1H$ NMR (400.1 MHz): δ 1.01 (3H, s, 1-C*H*$_3$), 1.11 (3H, s, 7-C*H*$_3$), 1.23 (3H, s, 7-C*H*$_3$), 1.61-1.66 (2H, m), 2.03-2.12 (1H, m), 2.28-2.35 (1H, m), 2.82 (1H, d, $^3J$ = 4.0, 4-C*H*) ppm

$^{13}C$ NMR (100.6 MHz): δ 9.9 (1-*C*H$_3$), 22.0 (7-*C*H$_3$), 23.6 (7-*C*H$_3$), 28.5 (C-5), 28.5 (C-6), 45.6 (C-7), 57.2 (C-1), 58.8 (C-4), 63.0 (C-3), 206.2 (C-2) ppm

HRMS (CI) *m/z* 332.9292: *calculated for* $[C_{10}H_{14}OBr_2 + Na]^+$ 332.9289

**(1*R*, 4*S*, 7*S*)-3,3-Dibromo-7-(bromomethyl)-1,7-dimethylbicyclo[2.2.1]heptan-2-one 502**[17,19]




**501** **502**

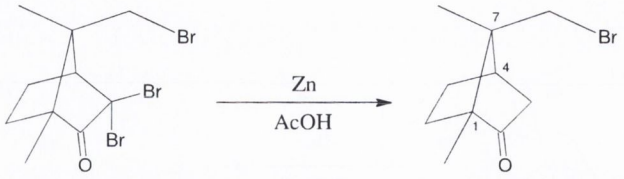
Following the procedure of Money,[20,24] 3,3-dibromocamphor **501** (8.82 g, 28.4 mmol) was added in small portions to a stirred solution of bromine (2.18 ml, 42.6 mmol) in chlorosulfonic acid (13.2 ml, 199 mmol) cooled to 0 °C. The solution was allowed to warm to rt and stirred for 4 hrs. The solution was then added dropwise to ice/water (ca. 200 ml) and extracted with ether (3 × 100 ml). The combined organic extracts were washed with satd. aq. sodium sulfite (100 ml) and satd. aq. sodium hydrogen carbonate (100 ml), dried and evaporated to yield an orange oil (10.65 g). Distillation under reduced pressure using a short Vigreux column afforded crude 3,3,8-tribromocamphor **502** (6.6 g) as a yellow oil (b.p. 140 °C at 0.1 mm/Hg).

IR $\nu_{max}$ (L) 2967, 1763 (C=O), 1450, 1384, 1249, 1154, 1068, 1018, 915, 817, 779, 703, 648 $cm^{-1}$

$^1$H NMR (400.1 MHz): δ 1.05 (3H, s, 1-C*H*$_3$), 1.31 (3H, s, 7-C*H*$_3$), 1.78-1.82 (2H, m), 2.01-2.10 (1H, m), 2.32-2.40 (1H, m), 3.11 (1H, d, $^3J$ = 4.0, 4-C*H*), 3.31 (1H, d, $^2J$ = 11.0, C*H*$_2$Br), 3.74 (1H, d, $^2J$ = 11.0, C*H*$_2$Br) ppm

$^{13}$C NMR (100.6 MHz): δ 10.0 (1-*C*H$_3$), 19.8 (7-*C*H$_3$), 27.9 (C-5), 30.6 (C-6), 40.7 (*C*H$_2$Br), 50.3 (C-7), 56.0 (C-4), 57.0 (C-1), 60.5 (C-3), 205.1 (C-2) ppm

**(1*R*, 4*R*, 7*S*)-7-(Bromomethyl)-1,7-dimethylbicyclo[2.2.1]heptan-2-one 503**[17,19]




**502** **503**

Following the procedure of Money,[19,20] crude 3,3,8-tribromocamphor **502** (5.15 g, 13.2 mmol) was dissolved in acetic acid (25 ml) and cooled to 0 °C. Zinc dust (2.6 g, 39.7 mmol) was added in small portions over 30 mins. The mixture was allowed to warm to rt and stirred for an additional 2 hrs. The mixture was diluted with ether (50 ml) and the excess zinc dust was filtered. The filtrate was washed with water (2 × 50 ml) and satd. aq. sodium hydrogen carbonate (2 × 50 ml), dried and evaporated to yield an oil. Column chromatography on silica gel using EtOAc:hexane (1:9) afforded the title compound as a white solid (1.91 g, 62 %).

m.p.: 81-82 °C (from EtOAc/hexane); Lit.[19]: 82-83 °C

$[\alpha]_D$ (*c* 0.31, 95 % EtOH, 22 °C) +74.1; Lit.[24]: (*c* 1.17, 95 % EtOH, 25 °C) +73.1

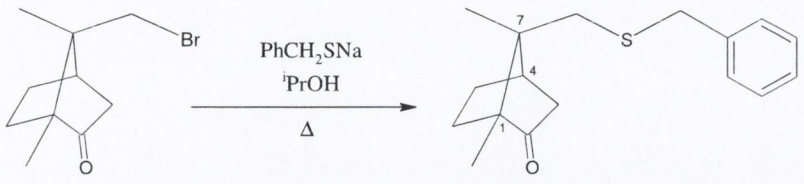
IR $\nu_{max}$ (N) 2964, 2927, 1744 (C=O), 1445, 1382, 1376, 1275, 1246, 1041, 927, 809, 756, 723, 657 $cm^{-1}$

$^1H$ NMR (400.1 MHz): δ 0.94 (3H, s, 1-C$H_3$), 1.16 (3H, s, 7-C$H_3$), 1.37-1.44 (1H, m), 1.55-1.61 (1H, m), 1.79-1.86 (1H, m), 1.92-1.98 (1H, m), 1.97 (1H, d, $^2J$ = 18.5, 3-C$H_2$ *endo*), 2.39 (1H, dt, $^2J$ = 18.5, $^3J$ = 4.0, 3-C$H_2$ *exo*), 2.46 (1H, t, $^3J$ = 4.5, 4-C*H*), 3.12 (1H, d, $^2J$ = 10.5, C$H_2$Br), 3.19 (1H, d, $^2J$ = 10.5, C$H_2$Br) ppm

$^{13}C$ NMR (100.6 MHz): δ 8.9 (1-*C*$H_3$), 15.1 (7-*C*$H_3$), 25.8 (C-5), 31.3 (C-6), 39.0 (*C*$H_2$Br), 40.9 (C-4), 41.9 (C-3), 51.0 (C-7), 57.7 (C-1), 217.3 (C-2) ppm

HRMS (CI) *m/z* 253.0215: *calculated for* $[C_{10}H_{15}OBr + Na]^+$ 253.0203

**(1*R*, 4*R*, 7*S*)-7-[(Benzylthio)methyl]-1,7-dimethylbicyclo[2.2.1]heptan-2-one 517**




**503** **517**

Following the procedure of Komarov,[27] freshly cut sodium metal (0.1 g, 4.67 mmol) was dissolved in isopropanol (10 ml) and benzyl mercaptan (0.73 ml, 6.23 mmol) was added. A solution of 8-bromocamphor **503** (0.36 g, 1.55 mmol) in isopropanol (5 ml) was added and the solution was heated under reflux for 4 days. The solution was allowed to cool to rt, diluted with water (50 ml) and extracted with ether (3 × 50 ml). The combined organic extracts were washed with dil. potassium hydroxide (2 × 50 ml, 0.1 M), dried over sodium sulfate and evaporated to yield an oil. Column chromatography on silica gel using EtOAc:hexane (1:10) afforded the title compound as a clear oil (0.4 g, 93 %).

$[\alpha]_D$ (*c* 1.01, $CHCl_3$, 21 °C) +19.7

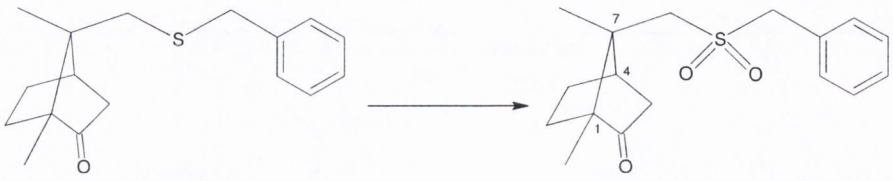
IR $\nu_{max}$ (L) 3060, 3027, 2958, 1741 (C=O), 1601 (Ar C-C), 1492, 1450, 1413, 1380, 1282, 1240, 1200, 1154, 1069, 1040, 924, 759, 701 $cm^{-1}$

$^1$H NMR (400.1 MHz): δ 0.89 (3H, s, 1-C*H*$_3$), 1.04 (3H, s, 7-C*H*$_3$), 1.31-1.46 (2H, m), 1.67-1.74 (1H, m), 1.82 (1H, d, $^2J$ = 18.5, 3-C*H*$_2$ *endo*), 1.86-1.93 (1H, m), 2.11-2.18 (1H, m, 3-C*H*$_2$ *exo*), 2.14 (1H, d, $^2J$ = 12.0, alkyl C*H*$_2$S), 2.30 (1H, d, $^2J$ = 12.0, alkyl C*H*$_2$S), 2.35 (1H, t, $^3J$ = 4.5, 4-C*H*), 3.66 (1H, d, $^2J$ = 13.5, benzyl C*H*$_2$S), 3.71 (1H, d, $^2J$ = 13.5, benzyl C*H*$_2$S), 7.24-7.37 (5H, m, Ar*H*) ppm

$^{13}$C NMR (100.6 MHz): δ 8.8 (1-*C*H$_3$), 15.6 (7-*C*H$_3$), 26.2 (C-5), 29.8 (C-6), 36.8 (alkyl *C*H$_2$S), 37.1 (benzyl *C*H$_2$S), 39.8 (C-4), 42.2 (C-3), 49.8 (C-7), 58.4 (C-1), 126.6 (Ar C-4), 128.0 (Ar C-3), 128.2 (Ar C-2), 137.6 (Ar C-1), 218.4 (C-2) ppm

HRMS (CI) *m/z* 297.1297: *calculated for* $[C_{17}H_{22}OS + Na]^+$ 297.1288

**(1*R*, 4*R*, 7*S*)-7-[(Benzylsulfonyl)methyl]-1,7-dimethylbicyclo[2.2.1]heptan-2-one 518**




**517** **518**

Method A:[28]

Sulfide **517** (0.15 g, 0.54 mmol) was dissolved in DCM (10 ml) and cooled to 0 °C. A solution of MCPBA (0.296 g, 70 %, 1.2 mmol) in DCM (5 ml) was added dropwise over 15 mins. The solution was stirred at 0 °C for 4 hrs. The solution was allowed to warm to rt and diluted with DCM (100 ml). The solution was washed with satd. aq. sodium sulfite (50 ml) and satd. aq. sodium hydrogen carbonate (50 ml), dried and evaporated to yield an oil. Column chromatography on silica gel using EtOAc:hexane (1:3) afforded the title compound as an oil (0.14 g, 83 %) which later crystallized on standing overnight.

Method B:[29]

Sulfide **517** (0.33 g, 1.2 mmol) was dissolved in DCM (10 ml) and acetic acid (2 ml) and finely powdered potassium permanganate (0.38 g, 2.4 mmol) was added in small portions over 5 mins. The mixture was stirred at rt for 5 hrs. The mixture was then diluted with DCM (100 ml) and filtered and the filtrate was washed with water (3 × 50 ml), satd. aq. sodium sulfite (50 ml) and satd. aq. sodium hydrogen carbonate (50 ml) and then dried and evaporated to yield an oil (0.32 g, 87 %) which later crystallized on standing overnight.

m.p.: 78-79 °C (from EtOAc/hexane)

$[\alpha]_D$ (*c* 0.33, $CHCl_3$, 15 °C) +21.8

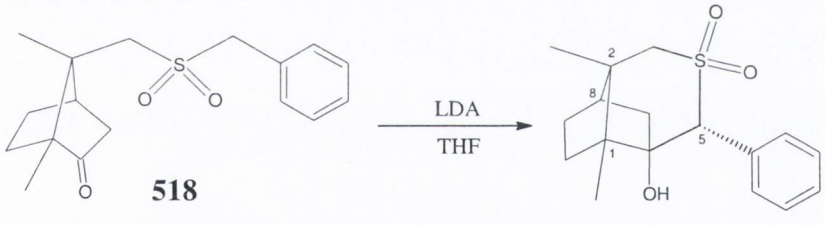
IR $\nu_{max}$ (N) 2923, 2854, 1732 (C=O), 1603 (Ar C-C), 1459, 1376, 1313 ($SO_2$), 1263, 1202, 1120 ($SO_2$), 1073, 927, 888, 787, 723, 696 $cm^{-1}$

$^1$H NMR (400.1 MHz): δ 0.87 (3H, s, 1-C$H_3$), 1.25 (3H, s, 7-C$H_3$), 1.38-1.45 (1H, m), 1.62-1.71 (2H, m), 1.90 (1H, d, $^2J$ = 19.0, 3-C$H_2$ *endo*), 1.95-2.00 (1H, m), 2.27 (1H, dt, $^2J$ = 19.0, $^3J$ = 4.0, 3-C$H_2$ *exo*), 2.54 (1H, d, $^2J$ = 14.0, alkyl C$H_2$SO$_2$), 2.74 (1H, d, $^2J$ = 14.0, alkyl C$H_2$SO$_2$), 2.95 (1H, t, $^3J$ = 4.5, 4-C*H*), 4.20 (2H, s, benzyl C$H_2$SO$_2$), 7.36-7.43 (5H, m, Ar*H*) ppm

$^{13}$C NMR (100.6 MHz): δ 8.7 (1-*C*H$_3$), 16.0 (7-*C*H$_3$), 26.5 (C-5), 27.8 (C-6), 39.4 (C-4), 42.5 (C-3), 48.6 (C-7), 53.2 (alkyl *C*H$_2$SO$_2$), 60.2 (C-1), 61.9 (benzyl *C*H$_2$SO$_2$), 127.4 (Ar C-1), 128.7 (Ar C-3), 128.8 (Ar C-4), 130.0 (Ar C-2), 217.6 (C-2) ppm

HRMS (CI) *m/z* 329.1185: *calculated for* [$C_{17}H_{22}O_3S$ + Na]$^+$ 329.1186

**(1*R*, 2*S*, 5*R*, 6*S*, 8*R*)-1,2-Dimethyl-5-phenyl-4-thiatricyclo[4.4.0.0$^{2,8}$]decan-6-ol 4,4-dioxide 519**




**518** **519**

*n*-Butyllithium (0.42 ml, 2.5 M, 1.04 mmol) was added to a solution of dry diisopropylamine (0.2 ml, 1.35 mmol) in dry THF (5 ml) at – 60 °C under an atmosphere of nitrogen. The solution was allowed to warm to 0 °C and then re-cooled to – 60 °C. A solution of sulfone **518** (0.32 g, 1.04 mmol) in dry THF (6 ml) was added dropwise *via* syringe and the solution was stirred at – 60 °C for 30 mins and then allowed to warm to rt and stirred for a further 3.5 hrs. The solution was then quenched with satd. aq. $NH_4Cl$ (50 ml) and extracted with ether (3 × 50 ml). The combined organic extracts were washed with brine (50 ml), dried and evaporated to yield a yellow solid (0.27 g). Column chromatography on silica gel using EtOAc:hexane (1:2) afforded the title compound as a white solid (0.24 g, 75 %). Also eluted was unchanged starting sulfone **518** (0.02 g, 6 %).

m.p.: 171 °C (from EtOAc/hexane)

$[\alpha]_D$ (*c* 0.37, $CHCl_3$, 15 °C) + 37.5

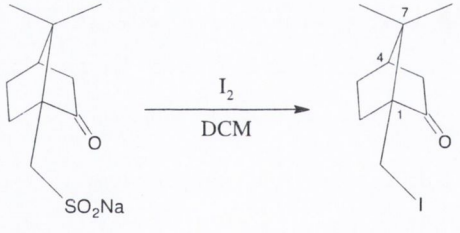
IR $\nu_{max}$ (N) 3435 (O-H), 2921, 1600 (Ar C-C), 1459, 1377, 1289 ($SO_2$), 1217, 1105 ($SO_2$), 1055, 983, 924, 855, 786, 732, 693 $cm^{-1}$

$^1H$ NMR (400.1 MHz): δ 1.05 (3H, s, 1-C*H*$_3$), 1.20 (3H, s, 2-C*H*$_3$), 1.40 (1H, d, $^2J$ = 14.0, 7-C*H*$_2$ *endo*), 1.44-1.50 (2H, m), 1.84-1.92 (1H, m), 2.17 (1H, t, $^3J$ = 4.5, 8-C*H*), 2.37-2.44 (1H, m), 3.34 (1H, d, $^2J$ = 15.0, 3-C*H*$_2$), 3.52 (1H, d, $^2J$ = 15.0, 3-C*H*$_2$), 3.64 (1H, ddd, $^2J$ = 14.0, $^3J$ = 4.5, $^4J$ = 3.5, 7-C*H*$_2$ *exo*), 4.58 (1H, s, 5-C*H*), 7.43-7.46 (3H, m, Ar*H*), 7.52-7.55 (2H, m, Ar*H*) ppm

$^{13}C$ NMR (100.6 MHz): δ 11.1 (1-*C*H$_3$), 19.3 (2-*C*H$_3$), 28.1 (C-9), 29.7 (C-10), 39.6 (C-7), 45.0 (C-8), 50.2 (C-2), 50.5 (C-1), 60.7 (C-3), 72.0 (C-5), 79.0 (C-6), 128.7 (Ar C-3), 129.2 (Ar C-2), 131.0 (Ar C-4), 131.1 (Ar C-1) ppm

HRMS (CI) *m/z* 329.1174: *calculated for* $[C_{17}H_{22}O_3S + Na]^+$ 329.1186

**(1*S*, 4*R*)-1-(Iodomethyl)-7,7-dimethylbicyclo[2.2.1]heptan-2-one 425**[36]




**310** **425**

A solution of iodine (0.5 g, 1.97 mmol) in DCM (100 ml) was vigorously mixed with a solution of sodium sulfinate **310** (0.54 g, 2.16 mmol) in water (50 ml) in a separating funnel. The yellow organic phase was placed in a round bottomed flask and stirred at rt for 1.5 hrs. The solution was then washed with water (50 ml) and the aqueous layer was extracted with ether (50 ml). The combined organic extracts were washed with satd. aq. sodium sulfite (50 ml), dried and evaporated to yield a white solid (0.36 g, 65 %).

m.p.: 69 °C (from DCM); Lit.[31]: 71 °C

$[\alpha]_D$ (*c* 1.28, $CHCl_3$, 23 °C) -20.1; Lit.[31]: (*c* 1, $CHCl_3$, 23 °C) -20.4

IR $\nu_{max}$ (N) 2921, 1743 (C=O), 1456, 1417, 1375, 1297, 1213, 1188, 1163, 1063, 1038, 955, 891, 766 $cm^{-1}$

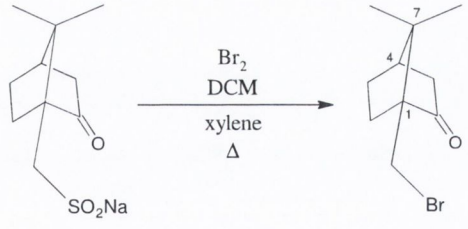
$^1H$ NMR (400.1 MHz): δ 0.91 (3H, s, 7-C*H*$_3$), 1.08 (3H, s, 7-C*H*$_3$), 1.40 (1H, t, *J* = 9.5, 5-C*H*$_2$ *endo*), 1.62 (1H, t, *J* = 9.5, 6-C*H*$_2$ *endo*), 1.92 (1H, d, $^2J$ = 18.5, 3-C*H*$_2$ *endo*), 1.96-2.05 (2H, m, 5-C*H*$_2$ *exo* and 6-C*H*$_2$ *exo*), 2.17 (1H, app dd, $^3J_1$ = 5.5, $^3J_2$ = 2.5, 4-C*H*), 2.41 (1H, ddd, $^2J$ = 18.5, $^3J$ = 5.0, $^4J$ = 2.0, 3-C*H*$_2$ *exo*), 3.13 (1H, d, $^2J$ = 11.0, C*H*$_2$I), 3.32 (1H, d, $^2J$ = 11.0, C*H*$_2$I) ppm

$^{13}C$ NMR (100.6 MHz): δ 0.3 (*C*H$_2$I), 19.6 (7-*C*H$_3$), 19.8 (7-*C*H$_3$), 26.2 (C-5), 30.0 (C-6), 42.5 (C-3), 43.5 (C-4), 47.8 (C-7), 58.6 (C-1), 214.7 (C-2) ppm

HRMS (CI) *m/z* 301.0077: *calculated for* $[C_{10}H_{15}OI + Na]^+$ 301.0064

**(1*S*, 4*R*)-1-(Bromomethyl)-7,7-dimethylbicyclo[2.2.1]heptan-2-one 520**[31,32]

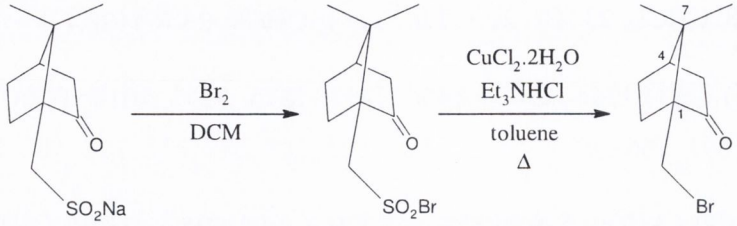
Method A:[31]




**310** **520**

A solution of bromine (0.1 ml, 1.97 mmol) in DCM (100 ml) was vigorously mixed with a solution of sodium sulfinate **310** (0.54 g, 2.16 mmol) in water (50 ml) in a separating funnel. The organic phase was removed and evaporated and the resulting solid was dissolved in xylene (15 ml). The solution was heated under reflux for 6 hrs. The solution was allowed to cool to rt, water (50 ml) was added and the mixture was extracted with ether (3 × 50 ml). The combined organic extracts were dried and evaporated to yield an oil. Column chromatography on silica gel using EtOAc:hexane (1:3) afforded the title compound as a white solid (0.33 g, 72 %).

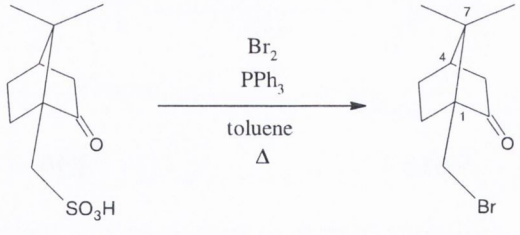
Method B:[34]




**310** **526** **520**

A solution of bromine (0.1 ml, 1.97 mmol) in DCM (100 ml) was vigorously mixed with a solution of sodium sulfinate **310** (0.54 g, 2.16 mmol) in water (50 ml) in a separating funnel. The organic phase was removed and evaporated and the resulting solid sulfonyl bromide **526** was dissolved in toluene (25 ml). Copper (II) chloride dihydrate (0.004 g, 0.02 mmol) and triethylammonium chloride (0.005 g, 0.03 mmol) were added and the mixture was heated under reflux for 24 hrs. The mixture was allowed to cool to rt, water (50 ml) was added and the mixture was extracted with ether (3 × 50 ml). The combined organic extracts were washed with satd. aq. sodium hydrogen carbonate (50 ml), dried and evaporated to yield a solid (0.2 g) whose $^1$H NMR spectrum showed it to consist mainly of (+)-10-bromocamphor **520** among other unidentified products.

Method C:[40]




**319** **520**

(+)-Camphor-10-sulfonic acid **319** (1.00 g, 4.30 mmol) and triphenylphosphine (5.64 g, 21.5 mmol) were dissolved in dry toluene (20 ml) under an atmosphere of nitrogen. Bromine (0.66 ml, 12.91 mmol) was added dropwise *via* syringe and the solution was heated under reflux for 36 hrs. The solution was then allowed to cool to rt and diluted with water (50 ml). The phases were mixed and separated and the aqueous phase was extracted with DCM (2 × 50 ml). The combined organic

extracts were washed with water (50 ml), dried and evaporated to afford a brown solid (7.31 g). The crude product was triturated with ether (ca. 20 ml) and filtered and the filtrate was evaporated to yield a brown solid which was purified by column chromatography on silica gel, eluting with ether:hexane (1:2) to afford two products. The first product to elute was (+)-10-bromocamphor **520** as a white solid (0.78 g, 78 %). The second product to elute was triphenylphosphine sulfide (0.47 g, 37 %) as a white solid.

m.p.: 75 °C (from EtOAc/hexane); Lit.[46]: 76-77 °C

$[\alpha]_D$ (*c* 1.12, $CHCl_3$, 23 °C) +24.8; Lit.[31]: (*c* 1, $CHCl_3$, 23 °C) +25.7

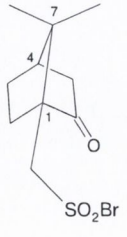
IR $\nu_{max}$ (N) 2923, 2854, 1747 (C=O), 1457, 1375, 1328, 1275, 1234, 1165, 1066, 1044, 963, 906, 851, 774, 706, 669, 634 $cm^{-1}$

$^1H$ NMR (400.1 MHz): δ 0.96 (3H, s, 7-C*H*$_3$), 1.12 (3H, s, 7-C*H*$_3$), 1.40-1.46 (1H, m, 5-C*H*$_2$ *endo*), 1.54-1.61 (1H, m, 6-C*H*$_2$ *endo*), 1.93 (1H, d, $^2J$ = 18.5, 3-C*H*$_2$ *endo*), 2.00-2.08 (1H, m), 2.11-2.15 (1H, m), 2.12 (1H, t, $^3J$ = 4.0, 4-C*H*), 2.43 (1H, dt, $^2J$ = 18.5, $^3J$ = 4.0, 3-C*H*$_2$ *exo*), 3.42 (1H, d, $^2J$ = 11.5, C*H*$_2$Br), 3.64 (1H, d, $^2J$ = 11.5, C*H*$_2$Br) ppm

$^{13}C$ NMR (100.6 MHz): δ 19.8 (7-*C*H$_3$), 20.0 (7-*C*H$_3$), 26.2 (C-5), 27.2 (C-6), 28.9 (*C*H$_2$Br), 42.5 (C-3), 43.4 (C-4), 47.8 (C-7), 59.8 (C-1), 215.1 (C-2) ppm

HRMS (CI) *m/z* 253.0200: *calculated for* $[C_{10}H_{15}OBr + Na]^+$ 253.0203

**(1*S*, 4*R*)-(7,7-Dimethyl-2-oxobicyclo[2.2.1]hept-1-yl)methanesulfonyl bromide 526**[31,47]




**526**

m.p.: 89 °C (from DCM); Lit.[47]: 93 °C

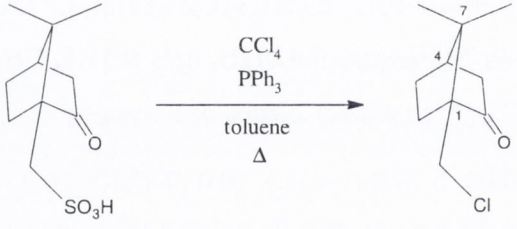
$[\alpha]_D$ (*c* 0.86, $CHCl_3$, 22 °C) +25.4; Lit.[47]: (*c* 10 g in 100 ml, $CHCl_3$, 18 °C) +26.0

IR $\nu_{max}$ (N) 2923, 1742 (C=O), 1459, 1376, 1353 ($SO_2$), 1152 ($SO_2$), 1051, 720, 665 $cm^{-1}$

$^1H$ NMR (400.1 MHz): δ 0.94 (3H, s, 7-C*H*$_3$), 1.15 (3H, s, 7-C*H*$_3$), 1.46-1.53 (1H, m), 1.77-1.85 (1H, m), 2.01 (1H, d, $^2J$ = 18.5, 3-C*H*$_2$ *endo*), 2.06-2.14 (1H, m), 2.17 (1H, t, $^3J$ = 4.5, 4-C*H*), 2.45 (1H, dt, $^2J$ = 18.5, $^3J$ = 4.0, 3-C*H*$_2$ *exo*), 2.49 (1H, m), 3.92 (1H, d, $^2J$ = 14.5, C*H*$_2$SO$_2$Br), 4.49 (1H, d, $^2J$ = 14.5, C*H*$_2$SO$_2$Br) ppm

$^{13}C$ NMR (100.6 MHz): δ 19.2 (7-*C*H$_3$), 19.3 (7-*C*H$_3$), 25.0 (C-5), 26.5 (C-6), 41.8 (C-3), 42.3 (C-4), 47.7 (C-7), 60.1 (C-1), 68.6 (*C*H$_2$SO$_2$Br), 212.1 (C-2) ppm

**(1*S*, 4*R*)-1-(Chloromethyl)-7,7-dimethylbicyclo[2.2.1]heptan-2-one 527**[39,48]




**319** **527**

(+)-Camphor-10-sulfonic acid **319** (1.00 g, 4.30 mmol) and triphenylphosphine (5.64 g, 21.5 mmol) were dissolved in dry toluene (20 ml) under an atmosphere of nitrogen. Carbon tetrachloride (1.25 ml, 12.91 mmol) was added dropwise *via* syringe and the solution was heated under reflux for 45 hrs. The solution was then allowed to cool to rt and diluted with water (50 ml). The phases were mixed and separated and the aqueous phase was extracted with DCM (2 × 50 ml). The combined organic extracts were washed with water (50 ml), dried and evaporated to afford a brown solid (6.25 g). The crude product was triturated with ether (ca. 20 ml) and filtered and the filtrate was evaporated to yield a brown solid which was purified by column chromatography on silica gel, eluting with ether:hexane (1:2) to afford two products. The first product to elute was (+)-10-chlorocamphor **527** as a

white solid (0.53 g, 66 %). The second product to elute was triphenylphosphine sulfide (0.25 g, 20 %) as a white solid.

m.p.: 129 °C (from ether/hexane); Lit.[39]: 131-132 °C

$[\alpha]_D$ (*c* 1.16, EtOH, 16 °C) +39.7; Lit.[39]: (*c* 0.96, EtOH, 20 °C) +41.8

IR $\nu_{max}$ (N) 2925, 1744 (C=O), 1455, 1414, 1375, 1301, 1219, 1168, 1101, 1053, 1006, 982, 934, 853, 762, 716, 639 $cm^{-1}$

$^1H$ NMR (400.1 MHz): δ 0.99 (3H, s, 7-C*H*$_3$), 1.13 (3H, s, 7-C*H*$_3$), 1.39-1.46 (1H, m, 5-C*H*$_2$ *endo*), 1.48-1.54 (1H, m, 6-C*H*$_2$ *endo*), 1.92 (1H, d, $^2J$ = 18.5, 3-C*H*$_2$ *endo*), 2.01-2.07 (1H, m), 2.10 (1H, t, $^3J$ = 4.5, 4-C*H*), 2.18 (1H, td, $^2J$ = 12.0, $^3J$ = 4.0), 2.43 (1H, dt, $^2J$ = 18.5, $^3J$ = 4.5, 3-C*H*$_2$ *exo*), 3.62 (1H, d, $^2J$ = 12.0, C*H*$_2$Cl), 3.81 (1H, d, $^2J$ = 12.0, C*H*$_2$Cl) ppm

$^{13}C$ NMR (100.6 MHz): δ 19.9 (7-*C*H$_3$), 20.0 (7-*C*H$_3$), 25.6 (C-5), 26.2 (C-6), 40.9 (*C*H$_2$Cl), 42.6 (C-3), 43.3 (C-4), 47.3 (C-7), 60.6 (C-1), 215.5 (C-2) ppm

HRMS (CI) *m/z* 187.0892: *calculated for* $[C_{10}H_{15}OCl + H]^+$ 187.0890

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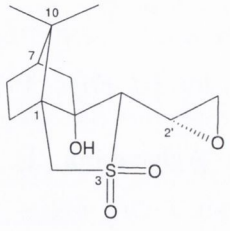
# Appendix of Crystal Structure Data

**1. Crystal structure determination of (1*S*, 4*S*, 5*S*, 7*R*, 2'*S*)-10,10-dimethyl-4-oxiran-2'-yl-3-thiatricyclo[5.2.1.$0^{1,5}$]decan-5-ol 3,3-dioxide 332**




**332**

Data were collected on a Bruker SMART APEX diffractometer with CCD detector. The diffractometer utilized graphite-monochromated Mo-Kα radiation (λ = 0.71073 Å). The omega scan method was used to collect a full sphere of data for each crystal with detector-to-crystal distance of 5 cm at – 150 °C. Data were collected, processed and corrected from Lorentz and polarization effects using SMART[1] and SAINT-NT[2] software. Absorption corrections for single crystals were applied using SADABS.[3] The structures were solved using direct methods and refined on HKLF4 data with the SHELXTL program package.[4] All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were assigned to calculated positions using a riding model with appropriately fixed isotropic thermal parameters. Figures were drawn using MERCURY[5] and ORTEP3[6] (**Figure 1**). The crystallographic details and experimental parameters are given in **Table 1**. Bond lengths are found in **Table 2**. Bond angles are found in **Table 3**.

[1] Bruker SMART, Version 5.625, 1997-2001, Bruker-AXS Inc.

[2] Bruker SAINT-NT, Version 6.02a, 1997-2001, Bruker-AXS Inc.

[3] SADABS, Version 2.03, 1999, Bruker-AXS Inc.

[4] G. M. Sheldrick, SHELXTL, Version 5.1, 1998, Bruker-AXS Inc.

[5] Free download from the CCDC website (www.ccdc.cam.ac.uk)

[6] L. J. Farrugia, *J. Appl. Cryst.*, 1997, **30**, 565.

**Table 1. Crystallographic data and structure refinement for sulfone 332**

| | |
|---|---|
| empirical formula | $C_{13}H_{20}O_4S$ |
| formula weight | M = 272.10 g $mol^{-1}$ |
| crystal system | orthorhombic |
| space group | P2(1)2(1)2(1) |
| cell constants | a = 6.9004(13) Å $\alpha = 90^{\circ}$<br>b = 10.778(2) Å $\beta = 90^{\circ}$<br>c = 17.373(3) Å $\gamma = 90^{\circ}$ |
| temperature | T = 396(2) K |
| wavelength | $\lambda$ = 0.71073 Å |
| cell volume | V = 1292.0(4) $Å^3$ |
| formula units | Z = 3 |
| density (calculated) | $\sigma$ = 1.400 $Mg/m^3$ |
| crystal size | 0.34 × 0.11 × 0.05 $mm^3$ |
| absorption coeffecient | $\mu$ = 0.255 $mm^{-1}$ |
| range for data collection | $2.22^{\circ} \leq \Theta \leq 25.00^{\circ}$ |
| hkl range | $-8 \leq h \leq 8, -12 \leq k \leq 12, -20 \leq l \leq 20$ |
| collected reflections | 9950 |
| independent reflections | 2277 [$R_{int}$ = 0.0664] |
| data / restraints / parameter | 2277 / 0 / 167 |
| R values [$I > 2\sigma(I)$] | R1 = 0.0610, wR2 = 0.1289 |
| R values [all data] | R1 = 0.0654, wR2 = 0.1289 |
| Flack parameter | 0.12(16) |
| residual electron density | max. 0.476 e $Å^{-3}$<br>min. – 0.339 e $Å^{-3}$ |
| absorption correction | semi-empirical from equivalents |
| refinement method | full-matrix least-squares on $F^2$ |
| max. and min. transmission | 1.00000 and 0.576787 |
| completeness to theta = $25.00^{\circ}$ | 100.0 % |
| goodness-of-fit on $F^2$ | 1.208 |
| F (000) | 584 |

**Table 2. Bond lengths for sulfone 332**

| | | | |
|---|---|---|---|
| S(1) - O(2) | 1.416(3) Å | C(5) - C(4) | 1.561(6) Å |
| S(1) - O(1) | 1.437(3) Å | C(5) - C(7) | 1.574(5) Å |
| S(1) - C(9) | 1.791(4) Å | C(3) - C(6) | 1.528(6) Å |
| S(1) - C(8) | 1.826(4) Å | C(3) - C(1) | 1.544(6) Å |
| O(4) - C(10) | 1.445(5) Å | C(3) - C(4) | 1.557(6) Å |
| O(4) - C(15) | 1.446(5) Å | C(7) - C(6) | 1.532(5) Å |
| O(3) - C(7) | 1.426(5) Å | C(10) - C(15) | 1.455(6) Å |
| C(8) - C(10) | 1.485(5) Å | C(2) - C(1) | 1.550(6) Å |
| C(8) - C(7) | 1.535(5) Å | C(4) - C(13) | 1.534(6) Å |
| C(5) - C(9) | 1.516(6) Å | C(4) - C(12) | 1.534(6) Å |
| C(5) - C(2) | 1.527(5) Å | | |

**Table 3. Bond angles for sulfone 332**

| | | | |
|---|---|---|---|
| O(2)-S(1)-O(1) | 117.37(19) ° | O(3)-C(7)-C(6) | 114.60(3) ° |
| O(2)-S(1)-C(9) | 111.30(2) ° | O(3)-C(7)-C(8) | 103.70(3) ° |
| O(1)-S(1)-C(9) | 110.29(19) ° | C(6)-C(7)-C(8) | 116.80(3) ° |
| O(2)-S(1)-C(8) | 109.83(18) ° | O(3)-C(7)-C(5) | 112.30(3) ° |
| O(1)-S(1)-C(8) | 109.13(18) ° | C(6)-C(7)-C(5) | 102.00(3) ° |
| C(9)-S(1)-C(8) | 97.03(18) ° | C(8)-C(7)-C(5) | 107.60(3) ° |
| C(10)-O(4)-C(15) | 60.50(3) ° | O(4)-C(10)-C(15) | 59.80(2) ° |
| C(10)-C(8)-C(7) | 115.50(3) ° | O(4)-C(10)-C(8) | 112.70(3) ° |
| C(10)-C(8)-S(1) | 110.90(3) ° | C(15)-C(10)-C(8) | 121.70(4) ° |
| C(7)-C(8)-S(1) | 105.30(3) ° | C(5)-C(2)-C(1) | 103.10(3) ° |
| C(9)-C(5)-C(2) | 114.10(3) ° | C(3)-C(1)-C(2) | 102.80(3) ° |
| C(9)-C(5)-C(4) | 119.70(3) ° | C(3)-C(6)-C(7) | 104.40(3) ° |
| C(2)-C(5)-C(4) | 101.70(3) ° | C(13)-C(4)-C(12) | 105.90(4) ° |
| C(9)-C(5)-C(7) | 109.50(3) ° | C(13)-C(4)-C(3) | 113.20(4) ° |
| C(2)-C(5)-C(7) | 107.60(3) ° | C(12)-C(4)-C(3) | 114.40(4) ° |

| | | | |
|---|---|---|---|
| C(4)-C(5)-C(7) | 103.10(3) ° | C(13)-C(4)-C(5) | 119.40(3) ° |
| C(5)-C(9)-S(1) | 107.90(3) ° | C(12)-C(4)-C(5) | 112.20(4) ° |
| C(6)-C(3)-C(1) | 107.90(3) ° | C(3)-C(4)-C(5) | 91.90(3) ° |
| C(6)-C(3)-C(4) | 102.20(3) ° | O(4)-C(15)-C(10) | 59.70(3) ° |
| C(1)-C(3)-C(4) | 102.70(3) ° | | |

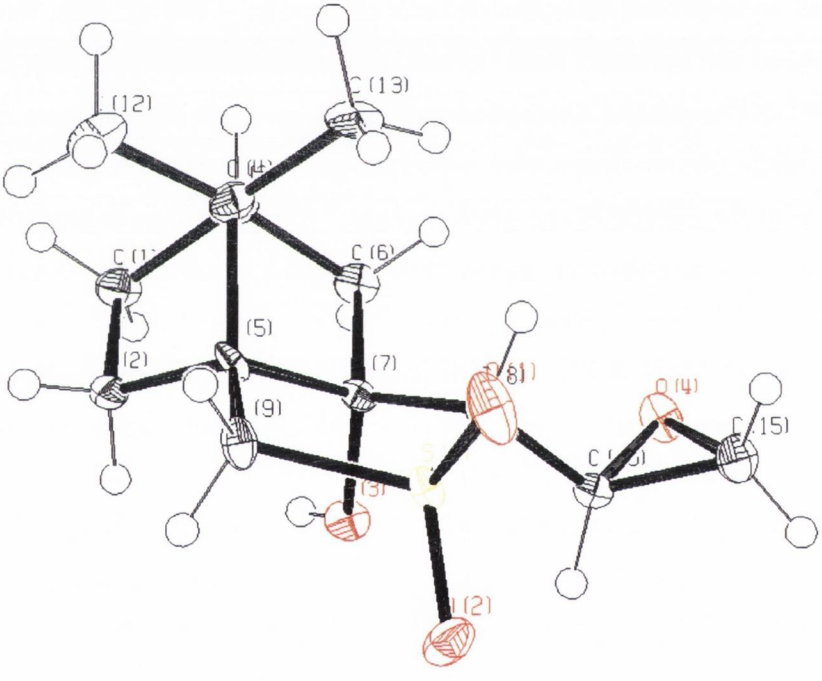
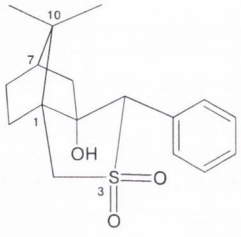



**Figure 1. X-ray crystal structure of sulfone 332**

**2. Crystal structure determination of (1*S*, 4*S*, 5*S*, 7*R*)-10,10-dimethyl-4-phenyl-3-thiatricyclo[5.2.1.0$^{1,5}$]decan-5-ol 3,3-dioxide 331**




**331**

Data were collected on a Bruker SMART APEX diffractometer with CCD detector. The diffractometer utilized graphite-monochromated Mo-Kα radiation (λ = 0.71073 Å). The omega scan method was used to collect a full sphere of data for each crystal with detector-to-crystal distance of 5 cm at – 150 °C. Data were collected, processed and corrected from Lorentz and polarization effects using SMART[1] and SAINT-NT[2] software. Absorption corrections for single crystals were applied using SADABS.[3] The structures were solved using direct methods and refined on HKLF4 data with the SHELXTL program package.[4] All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were assigned to calculated positions using a riding model with appropriately fixed isotropic thermal parameters. Figures were drawn using MERCURY[5] and ORTEP3[6] (**Figure 2**). The crystallographic details and experimental parameters are given in **Table 4**. Bond lengths are found in **Table 5**. Bond angles are found in **Table 6**.

[1] Bruker SMART, Version 5.625, 1997-2001, Bruker-AXS Inc.

[2] Bruker SAINT-NT, Version 6.02a, 1997-2001, Bruker-AXS Inc.

[3] SADABS, Version 2.03, 1999, Bruker-AXS Inc.

[4] G. M. Sheldrick, SHELXTL, Version 5.1, 1998, Bruker-AXS Inc.

[5] Free download from the CCDC website (www.ccdc.cam.ac.uk)

[6] L. J. Farrugia, *J. Appl. Cryst.*, 1997, **30**, 565.

**Table 4. Crystallographic data and structure refinement for sulfone 331**

| | |
|---|---|
| empirical formula | $C_{17}H_{22}O_3S$ |
| formula weight | M = 306.41 g mol $^{-1}$ |
| crystal system | triclinic |
| space group | P1 |
| cell constants | a = 7.4577(8) Å  α = 69.631(2) °<br>b = 8.8390(9) Å  β = 84.447(2) °<br>c = 12.2989(13) Å  γ = 85.449(2) ° |
| temperature | T = 396(2) K |
| wavelength | λ = 0.71073 Å |
| cell volume | V = 755.56(14) Å$^3$ |
| formula units | Z = 2 |
| density | σ = 1.347 Mg/m$^3$ |
| crystal size | 0.40 × 0.40 × 0.10 mm$^3$ |
| absorption coeffecient | μ = 0.222 mm$^{-1}$ |
| range for data collection | 2.46 ° ≤ Θ ≤ 28.21 ° |
| hkl range | −9 ≤ h ≤ 9, −11 ≤ k ≤ 11, −16 ≤ l ≤ 16 |
| collected reflections | 7626 |
| independent reflections | 6162 [$R_{int}$ = 0.0176] |
| data / restraints / parameter | 6162 / 3 / 385 |
| R values [I > 2σ(I)] | R1 = 0.0312, wR2 = 0.0806 |
| R values [all data] | R1 = 0.0314, wR2 = 0.0808 |
| Flack parameter | 0.03(4) |
| residual electron density | max. 0.302 e Å$^{-3}$<br>min. − 0.239 e Å$^{-3}$ |
| absorption correction | semi-empirical from equivalents |
| refinement method | full-matrix least-squares on $F^2$ |
| max. and min. transmission | 1.00000 and 0.858128 |
| completeness to theta = 28.21 ° | 98.8 % |
| goodness-of-fit on $F^2$ | 1.113 |
| F (000) | 328 |

**Table 5. Bond lengths for sulfone 331**

| | | | |
|---|---|---|---|
| S(1) - O(4) | 1.4402(14) Å | C(21) - C(18) | 1.551(3) Å |
| S(1) - O(5) | 1.4466(15) Å | C(21) - C(25) | 1.574(3) Å |
| S(1) - C(8) | 1.7895(18) Å | C(4) - C(3) | 1.393(3) Å |
| S(1) - C(7) | 1.8048(16) Å | C(10) - C(11) | 1.545(2) Å |
| S(2) - O(1) | 1.4404(13) Å | C(25) - C(27) | 1.532(2) Å |
| S(2) - O(2) | 1.4450(14) Å | C(25) - C(26) | 1.539(2) Å |
| S(2) - C(27) | 1.7868(18) Å | C(30) - C(31) | 1.387(3) Å |
| S(2) - C(28) | 1.8039(16) Å | C(30) - C(29) | 1.399(3) Å |
| O(3) - C(24) | 1.419(2) Å | C(14) - C(13) | 1.532(3) Å |
| O(6) - C(10) | 1.427(2) Å | C(14) - C(11) | 1.535(3) Å |
| C(28) - C(29) | 1.501(2) Å | C(14) - C(15) | 1.553(3) Å |
| C(28) - C(24) | 1.546(2) Å | C(18) - C(23) | 1.533(3) Å |
| C(7) - C(5) | 1.516(2) Å | C(18) - C(19) | 1.545(3) Å |
| C(7) - C(10) | 1.549(2) Å | C(29) - C(34) | 1.392(3) Å |
| C(24) - C(23) | 1.549(2) Å | C(13) - C(12) | 1.559(3) Å |
| C(24) - C(25) | 1.580(2) Å | C(3) - C(2) | 1.381(3) Å |
| C(9) - C(8) | 1.524(2) Å | C(15) - C(16) | 1.531(3) Å |
| C(9) - C(12) | 1.538(2) Å | C(15) - C(17) | 1.538(3) Å |
| C(9) - C(15) | 1.572(2) Å | C(2) - C(1) | 1.385(3) Å |
| C(9) - C(10) | 1.582(2) Å | C(34) - C(33) | 1.382(3) Å |
| C(5) - C(4) | 1.389(2) Å | C(6) - C(1) | 1.376(3) Å |
| C(5) - C(6) | 1.404(2) Å | C(26) - C(19) | 1.557(2) Å |
| C(21) - C(22) | 1.532(3) Å | C(32) - C(31) | 1.385(3) Å |
| C(21) - C(20) | 1.544(3) Å | C(32) - C(33) | 1.391(3) Å |

**Table 6. Bond angles for sulfone 331**

| | | | |
|---|---|---|---|
| O(4)-S(1)-O(5) | 117.42(9) ° | C(11)-C(10)-C(7) | 117.14(15) ° |
| O(4)-S(1)-C(8) | 111.28(9) ° | O(6)-C(10)-C(9) | 112.56(14) ° |
| O(5)-S(1)-C(8) | 109.07(9) ° | C(11)-C(10)-C(9) | 102.28(13) ° |
| O(4)-S(1)-C(7) | 113.06(8) ° | C(7)-C(10)-C(9) | 107.12(13) ° |
| O(5)-S(1)-C(7) | 107.14(8) ° | C(27)-C(25)-C(26) | 116.87(15) ° |
| C(8)-S(1)-C(7) | 96.87(8) ° | C(27)-C(25)-C(21) | 117.06(15) ° |
| O(1)-S(2)-O(2) | 117.56(8) ° | C(26)-C(25)-C(21) | 101.45(13) ° |
| O(1)-S(2)-C(27) | 111.66(9) ° | C(27)-C(25)-C(24) | 110.52(13) ° |
| O(2)-S(2)-C(27) | 108.50(9) ° | C(26)-C(25)-C(24) | 105.90(14) ° |
| O(1)-S(2)-C(28) | 112.22(8) ° | C(21)-C(25)-C(24) | 103.62(13) ° |
| O(2)-S(2)-C(28) | 109.17(8) ° | C(31)-C(30)-C(29) | 121.11(18) ° |
| C(27)-S(2)-C(28) | 95.46(8) ° | C(13)-C(14)-C(11) | 107.88(17) ° |
| C(29)-C(28)-C(24) | 119.68(15) ° | C(13)-C(14)-C(15) | 103.05(16) ° |
| C(29)-C(28)-S(2) | 115.82(11) ° | C(11)-C(14)-C(15) | 102.41(14) ° |
| C(24)-C(28)-S(2) | 101.53(11) ° | C(23)-C(18)-C(19) | 108.50(16) ° |
| C(5)-C(7)-C(10) | 118.01(14) ° | C(23)-C(18)-C(21) | 102.22(14) ° |
| C(5)-C(7)-S(1) | 110.69(11) ° | C(19)-C(18)-C(21) | 102.77(15) ° |
| C(10)-C(7)-S(1) | 101.40(11) ° | C(34)-C(29)-C(30) | 118.51(17) ° |
| O(3)-C(24)-C(28) | 110.85(14) ° | C(34)-C(29)-C(28) | 124.16(17) ° |
| O(3)-C(24)-C(23) | 106.24(14) ° | C(30)-C(29)-C(28) | 117.32(16) ° |
| C(28)-C(24)-C(23) | 116.52(14) ° | C(18)-C(23)-C(24) | 102.78(14) ° |
| O(3)-C(24)-C(25) | 114.66(14) ° | C(14)-C(13)-C(12) | 103.83(16) ° |
| C(28)-C(24)-C(25) | 105.92(13) ° | C(25)-C(27)-S(2) | 106.34(12) ° |
| C(23)-C(24)-C(25) | 102.68(14) ° | C(14)-C(11)-C(10) | 103.42(14) ° |
| C(8)-C(9)-C(12) | 116.79(15) ° | C(2)-C(3)-C(4) | 120.65(18) ° |
| C(8)-C(9)-C(15) | 116.96(15) ° | C(16)-C(15)-C(17) | 105.91(17) ° |
| C(12)-C(9)-C(15) | 101.69(14) ° | C(16)-C(15)-C(14) | 114.97(17) ° |
| C(8)-C(9)-C(10) | 110.51(13) ° | C(17)-C(15)-C(14) | 114.54(16) ° |
| C(12)-C(9)-C(10) | 105.72(14) ° | C(16)-C(15)-C(9) | 117.23(15) ° |
| C(15)-C(9)-C(10) | 103.76(14) ° | C(17)-C(15)-C(9) | 112.22(17) ° |
| C(4)-C(5)-C(6) | 117.99(16) ° | C(14)-C(15)-C(9) | 91.97(13) ° |

| | | | |
|---|---|---|---|
| C(4)-C(5)-C(7) | 122.23(15) ° | C(3)-C(2)-C(1) | 119.20(19) ° |
| C(6)-C(5)-C(7) | 119.78(15) ° | C(33)-C(34)-C(29) | 120.64(19) ° |
| C(22)-C(21)-C(20) | 105.37(16) ° | C(1)-C(6)-C(5) | 121.09(17) ° |
| C(22)-C(21)-C(18) | 115.08(16) ° | C(25)-C(26)-C(19) | 101.89(14) ° |
| C(20)-C(21)-C(18) | 114.30(15) ° | C(9)-C(12)-C(13) | 101.99(16) ° |
| C(22)-C(21)-C(25) | 117.61(14) ° | C(6)-C(1)-C(2) | 120.46(17) ° |
| C(20)-C(21)-C(25) | 112.48(16) ° | C(31)-C(32)-C(33) | 120.10(19) ° |
| C(18)-C(21)-C(25) | 92.12(14) ° | C(34)-C(33)-C(32) | 120.20(2) ° |
| C(9)-C(8)-S(1) | 106.50(12) ° | C(32)-C(31)-C(30) | 119.45(19) ° |
| C(5)-C(4)-C(3) | 120.54(17) ° | C(18)-C(19)-C(26) | 103.87(14) ° |
| O(6)-C(10)-C(11) | 108.01(14) ° | O(6)-C(10)-C(7) | 109.65(13) ° |

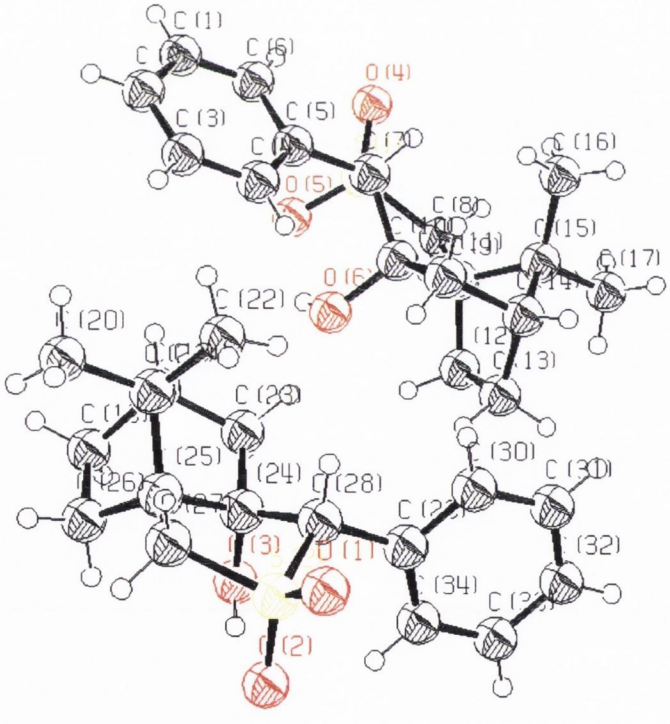
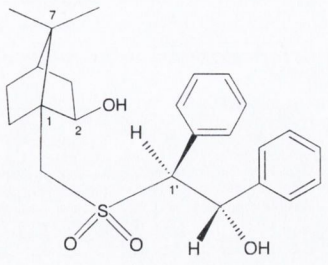



**Figure 2. X-ray crystal structure of sulfone 331**

**3. Crystal structure determination of (1*S*, 2*R*, 4*R*, 1'*S*, 2'*S*)-1-{[(1',2'-diphenyl-2'-hydroxyethyl)sulfonyl]methyl}-7,7-dimethylbicyclo[2.2.1]heptan-2-ol 362c**




**362c**

Data were collected on a Bruker SMART APEX diffractometer with CCD detector. The diffractometer utilized graphite-monochromated Mo-Kα radiation (λ = 0.71073 Å). The omega scan method was used to collect a full sphere of data for each crystal with detector-to-crystal distance of 5 cm at – 150 °C. Data were collected, processed and corrected from Lorentz and polarization effects using SMART[1] and SAINT-NT[2] software. Absorption corrections for single crystals were applied using SADABS.[3] The structures were solved using direct methods and refined on HKLF4 data with the SHELXTL program package.[4] All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were assigned to calculated positions using a riding model with appropriately fixed isotropic thermal parameters. Figures were drawn using MERCURY[5] and ORTEP3[6] (**Figure 3**). The crystallographic details and experimental parameters are given in **Table 7**. Bond lengths are found in **Table 8**. Bond angles are found in **Table 9**.

[1] Bruker SMART, Version 5.625, 1997-2001, Bruker-AXS Inc.

[2] Bruker SAINT-NT, Version 6.02a, 1997-2001, Bruker-AXS Inc.

[3] SADABS, Version 2.03, 1999, Bruker-AXS Inc.

[4] G. M. Sheldrick, SHELXTL, Version 5.1, 1998, Bruker-AXS Inc.

[5] Free download from the CCDC website (www.ccdc.cam.ac.uk)

[6] L. J. Farrugia, *J. Appl. Cryst.*, 1997, **30**, 565.

**Table 7. Crystallographic data and structure refinement for sulfone 362c**

| | |
|---|---|
| empirical formula | $C_{24}H_{30}O_4S$ |
| formula weight | M = 414.54 g mol $^{-1}$ |
| crystal system | monoclinic |
| space group | P2(1) |
| cell constants | a = 6.9192(10) Å  α = 90 °<br>b = 17.748(2) Å  β = 92.641(3) °<br>c = 8.6534(12) Å  γ = 90 ° |
| temperature | T = 396(2) K |
| wavelength | λ = 0.71073 Å |
| cell volume | V = 1061.5(3) Å$^3$ |
| formula units | Z = 2 |
| density | σ = 1.297 Mg/m$^3$ |
| crystal size | 0.38 × 0.16 × 0.16 mm$^3$ |
| absorption coeffecient | μ = 0.180 mm$^{-1}$ |
| range for data collection | 2.30 ° ≤ Θ ≤ 25.00 ° |
| hkl range | −8 ≤ h ≤ 8, −20 ≤ k ≤ 21, −10 ≤ l ≤ 10 |
| collected reflections | 8391 |
| independent reflections | 3525 [$R_{int}$ = 0.0166] |
| data / restraints / parameter | 3525 / 1 / 266 |
| R values [I > 2σ(I)] | R1 = 0.0260, wR2 = 0.0740 |
| R values [all data] | R1 = 0.0268, wR2 = 0.0750 |
| Flack parameter | − 0.03(5) |
| residual electron density | max. 0.252 e Å$^{-3}$<br>min. − 0.153 e Å$^{-3}$ |
| absorption correction | semi-empirical from equivalents |
| refinement method | full-matrix least-squares on F$^2$ |
| max. and min. transmission | 1.00000 and 0.871121 |
| completeness to theta = 25.00 ° | 100.0 % |
| goodness-of-fit on F$^2$ | 0.981 |
| F (000) | 444 |

**Table 8. Bond lengths for sulfone 362c**

| | | | |
|---|---|---|---|
| S(1)-O(2) | 1.4425(12) Å | C(6)-C(1) | 1.395(2) Å |
| S(1)-O(3) | 1.4464(13) Å | C(6)-C(7) | 1.511(2) Å |
| S(1)-C(24) | 1.7827(18) Å | C(9)-C(14) | 1.394(2) Å |
| S(1)-C(8) | 1.8187(15) Å | C(9)-C(10) | 1.387(2) Å |
| O(4)-C(7) | 1.427(2) Å | C(5)-C(4) | 1.389(2) Å |
| O(1)-C(22) | 1.432(2) Å | C(19)-C(16) | 1.525(2) Å |
| C(23)-C(24) | 1.524(2) Å | C(19)-C(21) | 1.532(2) Å |
| C(23)-C(15) | 1.544(2) Å | C(14)-C(13) | 1.391(3) Å |
| C(23)-C(22) | 1.559(2) Å | C(1)-C(2) | 1.384(3) Å |
| C(23)-C(18) | 1.570(2) Å | C(3)-C(4) | 1.371(3) Å |
| C(8)-C(9) | 1.512(2) Å | C(3)-C(2) | 1.390(3) Å |
| C(8)-C(7) | 1.539(2) Å | C(10)-C(11) | 1.384(3) Å |
| C(18)-C(17) | 1.530(2) Å | C(13)-C(12) | 1.378(3) Å |
| C(18)-C(20) | 1.532(2) Å | C(22)-C(21) | 1.543(2) Å |
| C(18)-C(19) | 1.540(2) Å | C(11)-C(12) | 1.379(3) Å |
| C(6)-C(5) | 1.383(2) Å | C(15)-C(16) | 1.558(3) Å |

**Table 9. Bond angles for sulfone 362c**

| | | | |
|---|---|---|---|
| O(2)-S(1)-O(3) | 117.07(7) $^{o}$ | O(4)-C(7)-C(6) | 110.73(13) $^{o}$ |
| O(2)-S(1)-C(24) | 107.90(8) $^{o}$ | O(4)-C(7)-C(8) | 107.81(12) $^{o}$ |
| O(3)-S(1)-C(24) | 108.00(7) $^{o}$ | C(6)-C(7)-C(8) | 111.29(13) $^{o}$ |
| O(2)-S(1)-C(8) | 108.81(7) $^{o}$ | C(14)-C(9)-C(10) | 119.31(17) $^{o}$ |
| O(3)-S(1)-C(8) | 107.52(7) $^{o}$ | C(14)-C(9)-C(8) | 121.24(15) $^{o}$ |
| C(24)-S(1)-C(8) | 107.14(7) $^{o}$ | C(10)-C(9)-C(8) | 119.36(15) $^{o}$ |
| C(24)-C(23)-C(15) | 117.63(13) $^{o}$ | C(6)-C(5)-C(4) | 121.02(17) $^{o}$ |
| C(24)-C(23)-C(22) | 116.23(13) $^{o}$ | C(16)-C(19)-C(21) | 107.23(16) $^{o}$ |
| C(15)-C(23)-C(22) | 103.51(13) $^{o}$ | C(16)-C(19)-C(18) | 103.57(14) $^{o}$ |
| C(24)-C(23)-C(18) | 112.89(13) $^{o}$ | C(21)-C(19)-C(18) | 102.18(13) $^{o}$ |
| C(15)-C(23)-C(18) | 101.49(13) $^{o}$ | C(9)-C(14)-C(13) | 119.97(18) $^{o}$ |

| | | | |
|---|---|---|---|
| C(22)-C(23)-C(18) | 103.07(12) ° | C(2)-C(1)-C(6) | 119.93(17) ° |
| C(23)-C(24)-S(1) | 119.93(12) ° | C(4)-C(3)-C(2) | 119.82(16) ° |
| C(9)-C(8)-C(7) | 111.69(13) ° | C(11)-C(10)-C(9) | 120.22(18) ° |
| C(9)-C(8)-S(1) | 110.84(10) ° | C(12)-C(13)-C(14) | 120.15(19) ° |
| C(7)-C(8)-S(1) | 111.00(11) ° | O(1)-C(22)-C(21) | 109.62(14) ° |
| C(17)-C(18)-C(20) | 107.14(16) ° | O(1)-C(22)-C(23) | 114.99(13) ° |
| C(17)-C(18)-C(19) | 113.38(14) ° | C(21)-C(22)-C(23) | 103.21(13) ° |
| C(20)-C(18)-C(19) | 113.57(13) ° | C(3)-C(4)-C(5) | 119.86(17) ° |
| C(17)-C(18)-C(23) | 114.08(13) ° | C(19)-C(21)-C(22) | 103.29(13) ° |
| C(20)-C(18)-C(23) | 115.33(13) ° | C(3)-C(2)-C(1) | 120.45(17) ° |
| C(19)-C(18)-C(23) | 93.13(13) ° | C(12)-C(11)-C(10) | 120.36(19) ° |
| C(5)-C(6)-C(1) | 118.90(15) ° | C(23)-C(15)-C(16) | 103.22(14) ° |
| C(5)-C(6)-C(7) | 119.97(15) ° | C(19)-C(16)-C(15) | 103.13(14) ° |
| C(1)-C(6)-C(7) | 120.92(15) ° | C(13)-C(12)-C(11) | 120.00(2) ° |

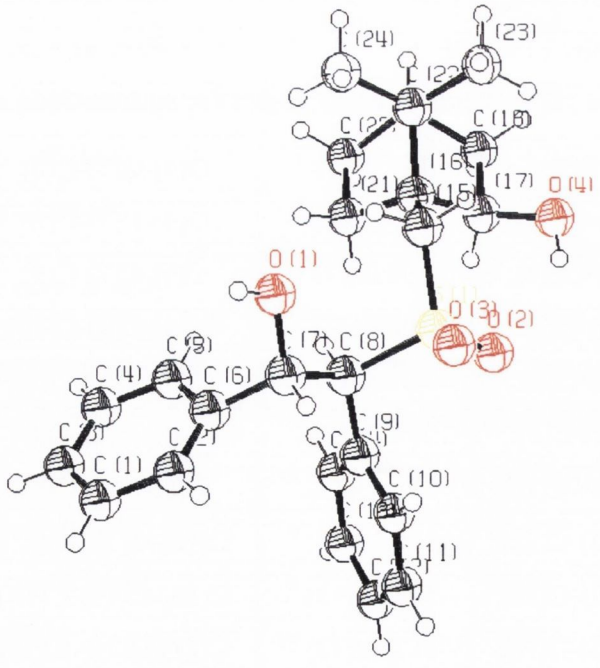
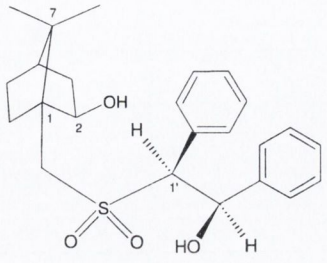



**Figure 3. X-ray crystal structure of sulfone 362c**

**4. Crystal structure determination of (1*S*, 2*R*, 4*R*, 1'*S*, 2'*R*)-1-{[(1',2'-diphenyl-2'-hydroxyethyl)sulfonyl]methyl}-7,7-dimethylbicyclo[2.2.1]heptan-2-ol 362a**




**362a**

Data were collected on a Bruker SMART APEX diffractometer with CCD detector. The diffractometer utilized graphite-monochromated Mo-Kα radiation (λ = 0.71073 Å). The omega scan method was used to collect a full sphere of data for each crystal with detector-to-crystal distance of 5 cm at – 150 °C. Data were collected, processed and corrected from Lorentz and polarization effects using SMART[1] and SAINT-NT[2] software. Absorption corrections for single crystals were applied using SADABS.[3] The structures were solved using direct methods and refined on HKLF4 data with the SHELXTL program package.[4] All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were assigned to calculated positions using a riding model with appropriately fixed isotropic thermal parameters. Figures were drawn using MERCURY[5] and ORTEP3[6] (**Figure 4**). The crystallographic details and experimental parameters are given in **Table 10**. Bond lengths are found in **Table 11**. Bond angles are found in **Table 12**.

[1] Bruker SMART, Version 5.625, 1997-2001, Bruker-AXS Inc.

[2] Bruker SAINT-NT, Version 6.02a, 1997-2001, Bruker-AXS Inc.

[3] SADABS, Version 2.03, 1999, Bruker-AXS Inc.

[4] G. M. Sheldrick, SHELXTL, Version 5.1, 1998, Bruker-AXS Inc.

[5] Free download from the CCDC website (www.ccdc.cam.ac.uk)

[6] L. J. Farrugia, *J. Appl. Cryst.*, 1997, **30**, 565.

**Table 10. Crystallographic data and structure refinement for sulfone 362a**

| | |
|---|---|
| empirical formula | $C_{24}H_{30}O_4S$ |
| formula weight | M = 414.54 g mol $^{-1}$ |
| crystal system | monoclinic |
| space group | P2(1) |
| cell constants | a = 11.906(4) Å  α = 90 °<br>b = 6.684(2) Å  β = 104.413(7) °<br>c = 13.515(5) Å  γ = 90 ° |
| temperature | T = 396(2) K |
| wavelength | λ = 0.71073 Å |
| cell volume | V = 1041.7(6) Å$^3$ |
| formula units | Z = 1 |
| density | σ = 1.225 Mg/m$^3$ |
| crystal size | 0.20 × 0.13 × 0.10 mm$^3$ |
| absorption coeffecient | μ = 0.180 mm$^{-1}$ |
| range for data collection | 1.77 ° ≤ Θ ≤ 28.29 ° |
| hkl range | −15 ≤ h ≤ 15, −8 ≤ k ≤ 8, −16 ≤ l ≤ 17 |
| collected reflections | 9965 |
| independent reflections | 5026 [$R_{int}$ = 0.1146] |
| data / restraints / parameter | 5026 / 1 / 263 |
| R values [I > 2σ(I)] | R1 = 0.1486, wR2 = 0.2817 |
| R values [all data] | R1 = 0.1678, wR2 = 0.2817 |
| Flack parameter | 0.3(4) |
| residual electron density | max. 2.848 e Å$^{-3}$<br>min. − 0.901 e Å$^{-3}$ |
| absorption correction | sadabs |
| refinement method | full-matrix least-squares on $F^2$ |
| completeness to theta = 28.29 ° | 99.3 % |
| goodness-of-fit on $F^2$ | 1.147 |
| F (000) | 384 |

**Table 11. Bond lengths for sulfone 362a**

| | | | |
|---|---|---|---|
| S(1)-O(4) | 1.410(10) Å | C(8)-C(10) | 1.508(16) Å |
| S(1)-O(2) | 1.425(8) Å | C(11)-C(17) | 1.515(17) Å |
| S(1)-C(11) | 1.768(11) Å | C(11)-C(12) | 1.516(18) Å |
| S(1)-C(10) | 1.802(10) Å | C(12)-C(14) | 1.392(19) Å |
| O(1)-C(9) | 1.467(15) Å | C(12)-C(13) | 1.379(17) Å |
| O(3)-C(17) | 1.426(15) Å | C(13)-C(24) | 1.408(19) Å |
| C(1)-C(2) | 1.537(18) Å | C(14)-C(15) | 1.386(18) Å |
| C(1)-C(7) | 1.580(2) Å | C(15)-C(16) | 1.410(3) Å |
| C(2)-C(5) | 1.491(17) Å | C(16)-C(24) | 1.400(3) Å |
| C(2)-C(3) | 1.553(17) Å | C(17)-C(18) | 1.524(17) Å |
| C(3)-C(9) | 1.580(2) Å | C(18)-C(23) | 1.406(17) Å |
| C(4)-C(5) | 1.614(19) Å | C(18)-C(19) | 1.447(19) Å |
| C(5)-C(8) | 1.513(16) Å | C(19)-C(20) | 1.387(19) Å |
| C(5)-C(6) | 1.551(19) Å | C(20)-C(21) | 1.360(2) Å |
| C(7)-C(8) | 1.544(16) Å | C(21)-C(22) | 1.470(3) Å |
| C(8)-C(9) | 1.504(16) Å | C(22)-C(23) | 1.370(2) Å |

**Table 12. Bond angles for sulfone 362a**

| | | | |
|---|---|---|---|
| O(4)-S(1)-O(2) | 118.90(5) ° | O(1)-C(9)-C(3) | 107.20(10) ° |
| O(4)-S(1)-C(11) | 110.60(6) ° | C(8)-C(9)-C(3) | 102.40(10) ° |
| O(2)-S(1)-C(11) | 107.10(6) ° | C(8)-C(10)-S(1) | 114.30(8) ° |
| O(4)-S(1)-C(10) | 110.20(6) ° | C(17)-C(11)-C(12) | 114.30(9) ° |
| O(2)-S(1)-C(10) | 107.00(5) ° | C(17)-C(11)-S(1) | 110.80(9) ° |
| C(11)-S(1)-C(10) | 101.70(6) ° | C(12)-C(11)-S(1) | 112.50(10) ° |
| C(2)-C(1)-C(7) | 102.80(11) ° | C(14)-C(12)-C(13) | 119.30(12) ° |
| C(5)-C(2)-C(3) | 101.70(10) ° | C(14)-C(12)-C(11) | 122.90(12) ° |
| C(5)-C(2)-C(1) | 102.10(11) ° | C(13)-C(12)-C(11) | 117.80(14) ° |
| C(3)-C(2)-C(1) | 106.30(11) ° | C(12)-C(13)-C(24) | 122.10(15) ° |
| C(2)-C(3)-C(9) | 102.40(11) ° | C(12)-C(14)-C(15) | 120.40(13) ° |

| | | | |
|---|---|---|---|
| C(2)-C(5)-C(8) | 96.30(10) ° | C(14)-C(15)-C(16) | 119.80(14) ° |
| C(2)-C(5)-C(6) | 113.50(10) ° | C(24)-C(16)-C(15) | 120.70(13) ° |
| C(8)-C(5)-C(6) | 112.60(11) ° | O(3)-C(17)-C(11) | 114.10(10) ° |
| C(2)-C(5)-C(4) | 112.00(11) ° | O(3)-C(17)-C(18) | 106.40(10) ° |
| C(8)-C(5)-C(4) | 116.10(10) ° | C(11)-C(17)-C(18) | 110.60(9) ° |
| C(6)-C(5)-C(4) | 106.40(11) ° | C(23)-C(18)-C(19) | 119.80(12) ° |
| C(8)-C(7)-C(1) | 101.70(10) ° | C(23)-C(18)-C(17) | 123.40(12) ° |
| C(9)-C(8)-C(5) | 104.20(10) ° | C(19)-C(18)-C(17) | 116.70(11) ° |
| C(9)-C(8)-C(10) | 116.60(9) ° | C(20)-C(19)-C(18) | 119.00(13) ° |
| C(5)-C(8)-C(10) | 113.20(9) ° | C(21)-C(20)-C(19) | 121.70(16) ° |
| C(9)-C(8)-C(7) | 105.10(10) ° | C(20)-C(21)-C(22) | 119.70(14) ° |
| C(5)-C(8)-C(7) | 102.30(9) ° | C(23)-C(22)-C(21) | 119.50(14) ° |
| C(10)-C(8)-C(7) | 114.00(9) ° | C(18)-C(23)-C(22) | 120.30(14) ° |
| O(1)-C(9)-C(8) | 115.10(10) ° | C(16)-C(24)-C(13) | 117.60(14) ° |

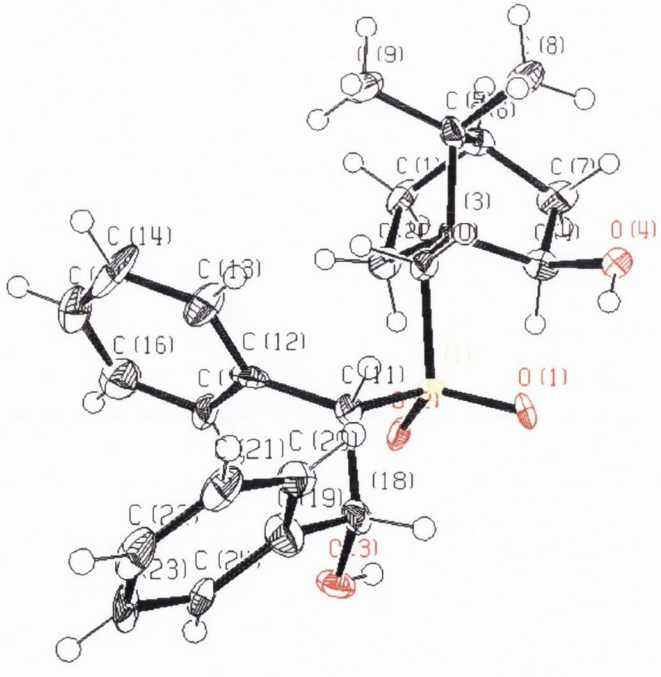
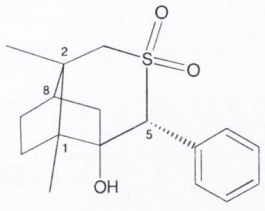



**Figure 4. X-ray crystal structure of sulfone 362a**

**5. Crystal structure determination of (1*R*, 2*S*, 5*R*, 6*S*, 8*R*)-1,2-dimethyl-5-phenyl-4-thiatricyclo[4.4.0.0$^{2,8}$]decan-6-ol 4,4-dioxide 519**




**519**

Data were collected on a Bruker SMART APEX diffractometer with CCD detector. The diffractometer utilized graphite-monochromated Mo-Kα radiation (λ = 0.71073 Å). The omega scan method was used to collect a full sphere of data for each crystal with detector-to-crystal distance of 5 cm at – 150 °C. Data were collected, processed and corrected from Lorentz and polarization effects using SMART[1] and SAINT-NT[2] software. Absorption corrections for single crystals were applied using SADABS.[3] The structures were solved using direct methods and refined on HKLF4 data with the SHELXTL program package.[4] All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were assigned to calculated positions using a riding model with appropriately fixed isotropic thermal parameters. Figures were drawn using MERCURY[5] and ORTEP3[6] (**Figure 5**). The crystallographic details and experimental parameters are given in **Table 13**. Bond lengths are found in **Table 14**. Bond angles are found in **Table 15**.

[1] Bruker SMART, Version 5.625, 1997-2001, Bruker-AXS Inc.

[2] Bruker SAINT-NT, Version 6.02a, 1997-2001, Bruker-AXS Inc.

[3] SADABS, Version 2.03, 1999, Bruker-AXS Inc.

[4] G. M. Sheldrick, SHELXTL, Version 5.1, 1998, Bruker-AXS Inc.

[5] Free download from the CCDC website (www.ccdc.cam.ac.uk)

[6] L. J. Farrugia, *J. Appl. Cryst.*, 1997, **30**, 565.

**Table 13. Crystallographic data and structure refinement for sulfone 519**

| | |
|---|---|
| empirical formula | $C_{17}H_{22}O_3S$ |
| formula weight | M = 306.41 g mol $^{-1}$ |
| crystal system | orthorhombic |
| space group | P2(1)2(1)2(1) |
| cell constants | a = 13.2824(18) Å $\alpha = 90^{\circ}$<br>b = 19.706(3) Å $\beta = 90^{\circ}$<br>c = 35.169(5) Å $\gamma = 90^{\circ}$ |
| temperature | T = 396(2) K |
| wavelength | $\lambda$ = 0.71073 Å |
| cell volume | V = 9205(2) Å$^3$ |
| formula units | Z = 24 |
| density | $\sigma$ = 1.327 Mg/m$^3$ |
| crystal size | 0.40 × 0.16 × 0.13 mm$^3$ |
| absorption coeffecient | $\mu$ = 0.219 mm$^{-1}$ |
| range for data collection | $1.16^{\circ} \leq \Theta \leq 25.00^{\circ}$ |
| hkl range | $-15 \leq h \leq 15$, $-22 \leq k \leq 23$, $-41 \leq l \leq 41$ |
| collected reflections | 73460 |
| independent reflections | 16246 [$R_{int}$ = 0.0472] |
| data / restraints / parameter | 16246 / 0 / 1153 |
| R values [$I > 2\sigma(I)$] | R1 = 0.0492, wR2 = 0.1204 |
| R values [all data] | R1 = 0.0610, wR2 = 0.1285 |
| Flack parameter | – 0.03(5) |
| residual electron density | max. 0.782 e Å$^{-3}$<br>min. – 0.460 e Å$^{-3}$ |
| absorption correction | semi-empirical from equivalents |
| refinement method | full-matrix least-squares on $F^2$ |
| max. and min. transmission | 1.00000 and 0.834852 |
| completeness to theta = 25.00 $^{\circ}$ | 100.0 % |
| goodness-of-fit on $F^2$ | 1.039 |
| F (000) | 3936 |

**Table 14. Bond lengths for sulfone 519**

| | | | |
|---|---|---|---|
| S(3)-O(5) | 1.439(2) Å | C(36)-C(35) | 1.547(5) Å |
| S(3)-O(42) | 1.456(2) Å | C(53)-C(52) | 1.536(5) Å |
| S(3)-C(42) | 1.778(3) Å | C(53)-C(57) | 1.536(5) Å |
| S(3)-C(44) | 1.814(3) Å | C(53)-C(54) | 1.542(5) Å |
| S(4)-O(7) | 1.439(3) Å | C(51)-C(52) | 1.545(6) Å |
| S(4)-O(8) | 1.443(3) Å | C(51)-C(58) | 1.547(5) Å |
| S(4)-C(56) | 1.789(3) Å | C(35)-C(39) | 1.520(5) Å |
| S(4)-C(61) | 1.812(3) Å | C(63)-C(64) | 1.390(5) Å |
| S(5)-O(11) | 1.438(2) Å | C(20)-C(24) | 1.531(5) Å |
| S(5)-O(12) | 1.454(2) Å | C(20)-C(21) | 1.538(5) Å |
| S(5)-C(77) | 1.778(3) Å | C(56)-C(54) | 1.544(5) Å |
| S(5)-C(78) | 1.811(3) Å | C(24)-C(25) | 1.568(4) Å |
| S(2)-O(2) | 1.428(2) Å | C(2)-C(3) | 1.522(5) Å |
| S(2)-O(3) | 1.441(2) Å | C(2)-C(1) | 1.547(6) Å |
| S(2)-C(23) | 1.792(3) Å | C(67)-C(66) | 1.386(5) Å |
| S(2)-C(28) | 1.807(3) Å | C(29)-C(30) | 1.379(5) Å |
| S(6)-O(41) | 1.436(3) Å | C(29)-C(34) | 1.394(5) Å |
| S(6)-O(40) | 1.442(3) Å | C(75)-C(74) | 1.512(4) Å |
| S(6)-C(6) | 1.784(3) Å | C(75)-C(70) | 1.543(4) Å |
| S(6)-C(11) | 1.812(3) Å | C(75)-C(68) | 1.555(4) Å |
| O(1)-C(8) | 1.435(4) Å | C(43)-C(129) | 1.559(4) Å |
| O(4)-C(25) | 1.416(4) Å | C(5)-C(4) | 1.540(5) Å |
| O(9)-C(60) | 1.420(4) Å | C(55)-C(54) | 1.524(5) Å |
| O(6)-C(43) | 1.431(4) Å | C(48)-C(50) | 1.376(6) Å |
| C(44)-C(45) | 1.514(4) Å | C(48)-C(46) | 1.379(5) Å |
| C(44)-C(43) | 1.543(4) Å | C(47)-C(49) | 1.392(5) Å |
| C(73)-O(10) | 1.422(4) Å | C(47)-C(45) | 1.393(5) Å |
| C(73)-C(72) | 1.552(4) Å | C(60)-C(57) | 1.557(4) Å |
| C(73)-C(75) | 1.559(4) Å | C(60)-C(58) | 1.558(4) Å |
| C(73)-C(78) | 1.565(4) Å | C(31)-C(32) | 1.383(6) Å |
| C(26)-C(27) | 1.525(4) Å | C(31)-C(30) | 1.397(5) Å |

| | | | |
|---|---|---|---|
| C(26)-C(18) | 1.539(5) Å | C(23)-C(21) | 1.548(5) Å |
| C(26)-C(21) | 1.550(4) Å | C(64)-C(65) | 1.374(6) Å |
| C(26)-C(25) | 1.555(5) Å | C(46)-C(45) | 1.401(5) Å |
| C(41)-C(40) | 1.529(5) Å | C(4)-C(3) | 1.539(5) Å |
| C(62)-C(63) | 1.394(5) Å | C(15)-C(14) | 1.384(5) Å |
| C(62)-C(67) | 1.392(5) Å | C(14)-C(13) | 1.392(5) Å |
| C(62)-C(61) | 1.516(4) Å | C(39)-C(129) | 1.554(5) Å |
| C(77)-C(70) | 1.537(4) Å | C(33)-C(32) | 1.373(6) Å |
| C(11)-C(12) | 1.520(4) Å | C(33)-C(34) | 1.385(5) Å |
| C(11)-C(8) | 1.544(4) Å | C(66)-C(65) | 1.371(6) Å |
| C(38)-C(37) | 1.514(4) Å | C(70)-C(76) | 1.530(5) Å |
| C(72)-C(71) | 1.534(5) Å | C(12)-C(13) | 1.392(5) Å |
| C(6)-C(4) | 1.541(5) Å | C(12)-C(17) | 1.393(5) Å |
| C(7)-C(3) | 1.531(5) Å | C(58)-C(54) | 1.550(4) Å |
| C(7)-C(8) | 1.556(4) Å | C(68)-C(69) | 1.554(5) Å |
| C(37)-C(36) | 1.546(4) Å | C(80)-C(82) | 1.385(5) Å |
| C(37)-C(40) | 1.555(4) Å | C(49)-C(50) | 1.375(5) Å |
| C(37)-C(43) | 1.565(4) Å | S(1)-O(67) | 1.427(3) Å |
| C(40)-C(42) | 1.534(4) Å | S(1)-O(68) | 1.437(3) Å |
| C(40)-C(39) | 1.544(5) Å | S(1)-C(126) | 1.766(4) Å |
| C(28)-C(29) | 1.514(4) Å | S(1)-C(103) | 1.808(3) Å |
| C(28)-C(25) | 1.543(4) Å | C(100)-O(66) | 1.540(5) Å |
| C(61)-C(60) | 1.565(4) Å | C(100)-C(121) | 1.544(5) Å |
| C(19)-C(20) | 1.544(5) Å | C(100)-C(123) | 1.551(5) Å |
| C(19)-C(18) | 1.547(5) Å | C(100)-C(124) | 1.558(5) Å |
| C(71)-C(69) | 1.528(5) Å | C(123)-C(130) | 1.414(4) Å |
| C(71)-C(70) | 1.551(4) Å | C(123)-C(103) | 1.547(4) Å |
| C(9)-C(10) | 1.519(5) Å | C(123)-C(122) | 1.558(4) Å |
| C(9)-C(1) | 1.539(5) Å | C(104)-C(127) | 1.388(5) Å |
| C(9)-C(4) | 1.549(5) Å | C(104)-C(131) | 1.392(5) Å |
| C(9)-C(8) | 1.566(4) Å | C(104)-C(103) | 1.514(5) Å |
| C(79)-C(81) | 1.385(5) Å | C(105)-C(120) | 1.531(6) Å |

| | | | |
|---|---|---|---|
| C(79)-C(80) | 1.393(5) Å | C(105)-C(122) | 1.543(5) Å |
| C(79)-C(78) | 1.511(4) Å | C(105)-C(124) | 1.552(5) Å |
| C(16)-C(15) | 1.366(6) Å | C(127)-C(128) | 1.367(5) Å |
| C(16)-C(17) | 1.383(5) Å | C(125)-C(124) | 1.530(5) Å |
| C(22)-C(21) | 1.532(5) Å | C(121)-C(120) | 1.558(5) Å |
| C(59)-C(58) | 1.527(5) Å | C(124)-C(126) | 1.547(5) Å |
| C(84)-C(83) | 1.371(6) Å | C(128)-C(133) | 1.379(6) Å |
| C(84)-C(81) | 1.396(5) Å | C(131)-C(132) | 1.379(6) Å |
| C(83)-C(82) | 1.387(6) Å | C(132)-C(133) | 1.370(6) Å |

**Table 15. Bond angles for sulfone 519**

| | | | |
|---|---|---|---|
| O(5)-S(3)-O(42) | 116.38(14) ° | O(9)-C(60)-C(57) | 110.20(2) ° |
| O(5)-S(3)-C(42) | 110.05(15) ° | O(9)-C(60)-C(58) | 112.80(2) ° |
| O(42)-S(3)-C(42) | 106.58(14) ° | C(57)-C(60)-C(58) | 102.30(3) ° |
| O(5)-S(3)-C(44) | 110.36(14) ° | O(9)-C(60)-C(61) | 107.00(2) ° |
| O(42)-S(3)-C(44) | 107.85(13) ° | C(57)-C(60)-C(61) | 112.60(2) ° |
| C(42)-S(3)-C(44) | 104.94(14) ° | C(58)-C(60)-C(61) | 112.10(2) ° |
| O(7)-S(4)-O(8) | 117.19(16) ° | C(32)-C(31)-C(30) | 120.20(4) ° |
| O(7)-S(4)-C(56) | 108.52(15) ° | C(21)-C(23)-S(2) | 120.70(2) ° |
| O(8)-S(4)-C(56) | 107.91(16) ° | C(65)-C(64)-C(63) | 120.60(4) ° |
| O(7)-S(4)-C(61) | 110.06(14) ° | C(40)-C(42)-S(3) | 120.30(2) ° |
| O(8)-S(4)-C(61) | 107.13(15) ° | C(79)-C(78)-C(73) | 117.10(3) ° |
| C(56)-S(4)-C(61) | 105.39(15) ° | C(79)-C(78)-S(5) | 109.60(2) ° |
| O(11)-S(5)-O(12) | 116.55(14) ° | C(73)-C(78)-S(5) | 109.90(2) ° |
| O(11)-S(5)-C(77) | 110.32(15) ° | C(29)-C(30)-C(31) | 120.70(4) ° |
| O(12)-S(5)-C(77) | 105.92(14) ° | C(48)-C(46)-C(45) | 119.50(4) ° |
| O(11)-S(5)-C(78) | 110.27(14) ° | C(5)-C(4)-C(3) | 113.30(3) ° |
| O(12)-S(5)-C(78) | 108.17(14) ° | C(5)-C(4)-C(6) | 103.50(3) ° |
| C(77)-S(5)-C(78) | 104.89(15) ° | C(3)-C(4)-C(6) | 117.10(3) ° |
| O(2)-S(2)-O(3) | 116.03(15) ° | C(5)-C(4)-C(9) | 114.80(3) ° |

| | | | |
|---|---|---|---|
| O(2)-S(2)-C(23) | 109.17(15) ° | C(3)-C(4)-C(9) | 94.20(3) ° |
| O(3)-S(2)-C(23) | 108.55(16) ° | C(6)-C(4)-C(9) | 114.50(3) ° |
| O(2)-S(2)-C(28) | 110.60(14) ° | C(16)-C(15)-C(14) | 119.40(3) ° |
| O(3)-S(2)-C(28) | 107.20(15) ° | C(22)-C(21)-C(20) | 113.50(3) ° |
| C(23)-S(2)-C(28) | 104.68(15) ° | C(22)-C(21)-C(23) | 104.30(3) ° |
| O(41)-S(6)-O(40) | 116.74(18) ° | C(20)-C(21)-C(23) | 116.20(3) ° |
| O(41)-S(6)-C(6) | 108.59(17) ° | C(22)-C(21)-C(26) | 115.40(3) ° |
| O(40)-S(6)-C(6) | 107.96(17) ° | C(20)-C(21)-C(26) | 93.90(2) ° |
| O(41)-S(6)-C(11) | 110.34(15) ° | C(23)-C(21)-C(26) | 113.90(3) ° |
| O(40)-S(6)-C(11) | 107.75(15) ° | C(15)-C(14)-C(13) | 120.70(3) ° |
| C(6)-S(6)-C(11) | 104.78(16) ° | C(35)-C(39)-C(40) | 102.40(3) ° |
| C(45)-C(44)-C(43) | 117.60(2) ° | C(35)-C(39)-C(129) | 106.00(3) ° |
| C(45)-C(44)-S(3) | 108.90(2) ° | C(40)-C(39)-C(129) | 103.30(3) ° |
| C(43)-C(44)-S(3) | 109.90(2) ° | C(32)-C(33)-C(34) | 120.50(4) ° |
| O(10)-C(73)-C(72) | 111.00(2) ° | C(65)-C(66)-C(67) | 120.60(4) ° |
| O(10)-C(73)-C(75) | 112.10(3) ° | C(26)-C(18)-C(19) | 105.40(3) ° |
| C(72)-C(73)-C(75) | 101.90(2) ° | C(76)-C(70)-C(77) | 104.30(3) ° |
| O(10)-C(73)-C(78) | 106.90(2) ° | C(76)-C(70)-C(75) | 115.30(3) ° |
| C(72)-C(73)-C(78) | 111.80(3) ° | C(77)-C(70)-C(75) | 114.20(3) ° |
| C(75)-C(73)-C(78) | 113.20(2) ° | C(76)-C(70)-C(71) | 112.80(3) ° |
| C(27)-C(26)-C(18) | 111.90(3) ° | C(77)-C(70)-C(71) | 116.80(3) ° |
| C(27)-C(26)-C(21) | 117.50(3) ° | C(75)-C(70)-C(71) | 93.90(2) ° |
| C(18)-C(26)-C(21) | 101.10(3) ° | C(53)-C(57)-C(60) | 103.80(3) ° |
| C(27)-C(26)-C(25) | 116.50(3) ° | C(2)-C(3)-C(7) | 106.70(3) ° |
| C(18)-C(26)-C(25) | 107.20(3) ° | C(2)-C(3)-C(4) | 102.40(3) ° |
| C(21)-C(26)-C(25) | 100.90(2) ° | C(7)-C(3)-C(4) | 103.10(3) ° |
| C(63)-C(62)-C(67) | 118.30(3) ° | O(4)-C(25)-C(28) | 103.10(2) ° |
| C(63)-C(62)-C(61) | 124.00(3) ° | O(4)-C(25)-C(26) | 112.90(2) ° |
| C(67)-C(62)-C(61) | 117.70(3) ° | C(28)-C(25)-C(26) | 110.70(3) ° |
| C(70)-C(77)-S(5) | 120.40(2) ° | O(4)-C(25)-C(24) | 113.80(3) ° |
| C(12)-C(11)-C(8) | 118.10(3) ° | C(28)-C(25)-C(24) | 114.10(2) ° |
| C(12)-C(11)-S(6) | 108.20(2) ° | C(26)-C(25)-C(24) | 102.60(3) ° |

| C(8)-C(11)-S(6) | 110.30(2) ° | C(13)-C(12)-C(17) | 118.60(3) ° |
|---|---|---|---|
| C(71)-C(72)-C(73) | 104.30(3) ° | C(13)-C(12)-C(11) | 123.40(3) ° |
| C(4)-C(6)-S(6) | 120.40(2) ° | C(17)-C(12)-C(11) | 117.90(3) ° |
| C(3)-C(7)-C(8) | 104.00(3) ° | C(53)-C(52)-C(51) | 102.00(3) ° |
| C(38)-C(37)-C(36) | 112.30(3) ° | C(59)-C(58)-C(51) | 112.40(3) ° |
| C(38)-C(37)-C(40) | 117.60(3) ° | C(59)-C(58)-C(54) | 117.20(3) ° |
| C(36)-C(37)-C(40) | 101.50(2) ° | C(51)-C(58)-C(54) | 101.90(3) ° |
| C(38)-C(37)-C(43) | 116.40(3) ° | C(59)-C(58)-C(60) | 116.50(3) ° |
| C(36)-C(37)-C(43) | 106.70(2) ° | C(51)-C(58)-C(60) | 106.10(3) ° |
| C(40)-C(37)-C(43) | 100.50(2) ° | C(54)-C(58)-C(60) | 100.90(2) ° |
| C(41)-C(40)-C(42) | 103.90(3) ° | C(12)-C(13)-C(14) | 119.90(3) ° |
| C(41)-C(40)-C(39) | 113.10(3) ° | C(33)-C(34)-C(29) | 120.80(4) ° |
| C(42)-C(40)-C(39) | 117.40(3) ° | C(47)-C(45)-C(46) | 118.40(3) ° |
| C(41)-C(40)-C(37) | 114.60(3) ° | C(47)-C(45)-C(44) | 118.30(3) ° |
| C(42)-C(40)-C(37) | 114.40(3) ° | C(46)-C(45)-C(44) | 123.20(3) ° |
| C(39)-C(40)-C(37) | 94.00(2) ° | C(75)-C(68)-C(69) | 104.60(3) ° |
| C(29)-C(28)-C(25) | 118.60(3) ° | C(82)-C(80)-C(79) | 120.70(4) ° |
| C(29)-C(28)-S(2) | 108.70(2) ° | C(71)-C(69)-C(68) | 101.60(3) ° |
| C(25)-C(28)-S(2) | 109.90(2) ° | C(66)-C(65)-C(64) | 119.60(3) ° |
| C(62)-C(61)-C(60) | 117.90(3) ° | C(50)-C(49)-C(47) | 120.10(4) ° |
| C(62)-C(61)-S(4) | 108.30(2) ° | C(79)-C(81)-C(84) | 121.00(3) ° |
| C(60)-C(61)-S(4) | 110.20(2) ° | C(55)-C(54)-C(53) | 113.50(3) ° |
| C(20)-C(19)-C(18) | 101.20(3) ° | C(55)-C(54)-C(56) | 103.70(3) ° |
| C(69)-C(71)-C(72) | 106.00(3) ° | C(53)-C(54)-C(56) | 117.50(3) ° |
| C(69)-C(71)-C(70) | 102.10(3) ° | C(55)-C(54)-C(58) | 114.40(3) ° |
| C(72)-C(71)-C(70) | 103.60(2) ° | C(53)-C(54)-C(58) | 93.90(2) ° |
| C(10)-C(9)-C(1) | 112.60(3) ° | C(56)-C(54)-C(58) | 114.40(3) ° |
| C(10)-C(9)-C(4) | 117.20(3) ° | C(16)-C(17)-C(12) | 120.60(3) ° |
| C(1)-C(9)-C(4) | 101.40(3) ° | C(9)-C(1)-C(2) | 104.90(3) ° |
| C(10)-C(9)-C(8) | 116.80(3) ° | C(49)-C(50)-C(48) | 119.10(3) ° |
| C(1)-C(9)-C(8) | 106.70(3) ° | C(80)-C(82)-C(83) | 120.40(4) ° |
| C(4)-C(9)-C(8) | 100.30(2) ° | C(33)-C(32)-C(31) | 119.40(4) ° |

| C(81)-C(79)-C(80) | 118.30(3) ° | O(67)-S(1)-O(68) | 117.26(19) ° |
|---|---|---|---|
| C(81)-C(79)-C(78) | 118.80(3) ° | O(67)-S(1)-C(126) | 109.40(2) ° |
| C(80)-C(79)-C(78) | 122.90(3) ° | O(68)-S(1)-C(126) | 107.96(18) ° |
| O(1)-C(8)-C(11) | 107.30(2) ° | O(67)-S(1)-C(103) | 110.16(16) ° |
| O(1)-C(8)-C(7) | 110.00(2) ° | O(68)-S(1)-C(103) | 107.85(18) ° |
| C(11)-C(8)-C(7) | 113.30(3) ° | C(126)-S(1)-C(103) | 103.27(16) ° |
| O(1)-C(8)-C(9) | 112.00(2) ° | O(66)-C(100)-C(121) | 111.90(3) ° |
| C(11)-C(8)-C(9) | 112.20(2) ° | O(66)-C(100)-C(123) | 116.40(3) ° |
| C(7)-C(8)-C(9) | 102.20(3) ° | C(121)-C(100)-C(123) | 107.00(3) ° |
| C(15)-C(16)-C(17) | 120.80(4) ° | O(66)-C(100)-C(124) | 117.40(3) ° |
| C(83)-C(84)-C(81) | 120.10(4) ° | C(121)-C(100)-C(124) | 101.30(3) ° |
| C(84)-C(83)-C(82) | 119.50(3) ° | C(123)-C(100)-C(124) | 101.10(3) ° |
| C(37)-C(36)-C(35) | 104.80(3) ° | C(130)-C(123)-C(103) | 102.40(3) ° |
| C(52)-C(53)-C(57) | 106.10(3) ° | C(130)-C(123)-C(100) | 112.00(3) ° |
| C(52)-C(53)-C(54) | 102.60(3) ° | C(103)-C(123)-C(100) | 112.30(3) ° |
| C(57)-C(53)-C(54) | 103.10(2) ° | C(130)-C(123)-C(122) | 115.20(3) ° |
| C(52)-C(51)-C(58) | 104.70(3) ° | C(103)-C(123)-C(122) | 113.10(3) ° |
| C(39)-C(35)-C(36) | 102.20(3) ° | C(100)-C(123)-C(122) | 102.20(3) ° |
| C(64)-C(63)-C(62) | 120.30(3) ° | C(127)-C(104)-C(131) | 117.80(3) ° |
| C(24)-C(20)-C(21) | 103.30(3) ° | C(127)-C(104)-C(103) | 123.80(3) ° |
| C(24)-C(20)-C(19) | 107.10(3) ° | C(131)-C(104)-C(103) | 118.50(3) ° |
| C(21)-C(20)-C(19) | 102.80(3) ° | C(120)-C(105)-C(122) | 105.60(3) ° |
| C(54)-C(56)-S(4) | 120.10(2) ° | C(120)-C(105)-C(124) | 101.90(3) ° |
| C(20)-C(24)-C(25) | 103.10(3) ° | C(122)-C(105)-C(124) | 103.90(3) ° |
| C(3)-C(2)-C(1) | 102.00(3) ° | C(104)-C(103)-C(123) | 118.00(3) ° |
| C(66)-C(67)-C(62) | 120.60(3) ° | C(104)-C(103)-S(1) | 107.90(2) ° |
| C(30)-C(29)-C(34) | 118.40(3) ° | C(123)-C(103)-S(1) | 110.50(2) ° |
| C(30)-C(29)-C(28) | 124.10(3) ° | C(105)-C(122)-C(123) | 103.90(3) ° |
| C(34)-C(29)-C(28) | 117.50(3) ° | C(39)-C(129)-C(43) | 103.60(3) ° |
| C(74)-C(75)-C(70) | 117.70(3) ° | C(128)-C(127)-C(104) | 121.20(4) ° |
| C(74)-C(75)-C(68) | 112.30(3) ° | C(100)-C(121)-C(120) | 105.10(3) ° |
| C(70)-C(75)-C(68) | 101.70(3) ° | C(125)-C(124)-C(126) | 104.60(3) ° |

| | | | |
|---|---|---|---|
| C(74)-C(75)-C(73) | 116.30(3) ° | C(125)-C(124)-C(105) | 114.00(3) ° |
| C(70)-C(75)-C(73) | 101.40(2) ° | C(126)-C(124)-C(105) | 117.00(3) ° |
| C(68)-C(75)-C(73) | 105.70(2) ° | C(125)-C(124)-C(100) | 114.30(3) ° |
| O(6)-C(43)-C(44) | 106.30(2) ° | C(126)-C(124)-C(100) | 113.70(3) ° |
| O(6)-C(43)-C(129) | 110.50(2) ° | C(105)-C(124)-C(100) | 93.70(3) ° |
| C(44)-C(43)-C(129) | 112.40(3) ° | C(124)-C(126)-S(1) | 120.60(2) ° |
| O(6)-C(43)-C(37) | 112.00(2) ° | C(105)-C(120)-C(121) | 101.40(3) ° |
| C(44)-C(43)-C(37) | 113.40(2) ° | C(127)-C(128)-C(133) | 121.00(4) ° |
| C(129)-C(43)-C(37) | 102.30(2) ° | C(132)-C(131)-C(104) | 120.20(4) ° |
| C(50)-C(48)-C(46) | 122.00(4) ° | C(133)-C(132)-C(131) | 121.50(4) ° |
| C(49)-C(47)-C(45) | 120.90(3) ° | C(132)-C(133)-C(128) | 118.20(4) ° |

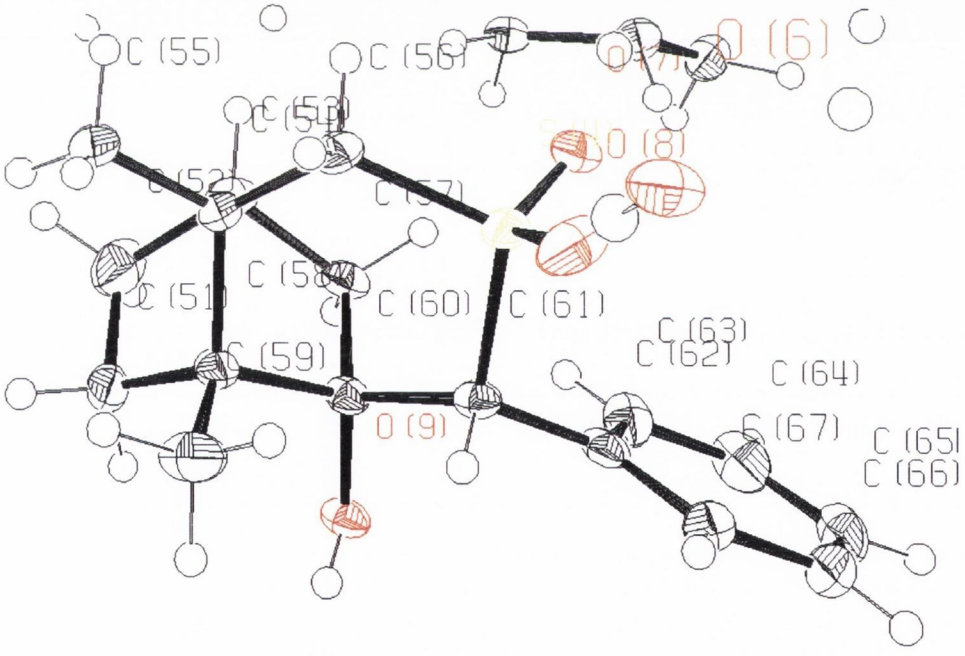



**Figure 5. X-ray crystal structure of sulfone 519 (a single asymmetric unit is shown for clarity)**