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THURPE, H.R.
Chemistry of Allene Oxides

by

Heidi Ruth Thorpe

A Doctorial Thesis

Submitted in partial fulfilment of the requirements for the award of

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Abstract

Chapter One reviews aspects of the chemistry of allene oxides reported in the chemical literature. The review is organised into three sections describing the available methods for the preparation of allene oxides, the reactions of allene oxides and allene oxides in biological systems.

Chapter Two discusses attempts to develop new methods for the generation and trapping of allene oxides. Firstly, an unsuccessful attempt to employ a selenoxide elimination to generate an allene oxide is described. This is followed by a section detailing an improved method for the generation and in situ capture of allene oxides with alcohols. Sodium alkoxides were found to trigger elimination in β,γ-epoxy-β-trimethylsilyl mesylates to afford allene oxides and also act as the nucleophilic trapping component. This methodology was used to synthesise a range of α-alkoxyketones. Attempts to employ other nucleophiles in this process are also discussed.

Chapter Three describes how the successful chemistry described in Chapter Two was modified in order to generate and trap chiral, non-racemic allene oxides. The preparation of homochiral β,γ-epoxy-β-trimethylsilyl mesylates and their subsequent reaction with potassium alkoxides at low temperature under aprotic conditions is described. The α-alkoxyketone products were found to be of high enantiomeric excess and the absolute configuration of the product was determined in one case. Finally, attempts to effect a three-component coupling of an allene oxide, by reaction of an allene oxide with a nucleophile and subsequently an electrophile, are discussed.

Chapter Four describes pioneering work towards a general method for the preparation of methylene cyclic sulfites as potential allene oxide equivalents is presented. A series of such compounds were prepared by reaction of α-hydroxyketones with thionyl chloride and via selenoxide elimination chemistry.

Chapter Five describes the detailed experimental work undertaken in this thesis.
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Abbreviations

Ar  aryl
bp  boiling point
n-BuLi  n-butyllithium
t-Bu  tert-butyl
t-BuOOH  tert-butylhydroperoxide
C.l.  chemical ionisation
m-CPBA  3-chloroperbenzoic acid
18-crown-6  1,4,7,10,13,16-hexaoxacyclo-octadecane
DBU  1,8-diazabicyclo[5.4.0]undec-7-ene
DIBAL  di-iso-butylaluminium hydride
DMSO  dimethylsulfoxide
L-(+)-DET  L-(+)-diethyl tartrate
e.e.  enantiomeric excess
E.I.  electron impact
Et  ethyl
GC  gas chromatography
HPLC  high pressure liquid chromatography
I.R.  infra-red
Me  methyl
mp  melting point
Ms  mesyl
NMR  nuclear magnetic resonance
Ph  phenyl
i-Pr  iso-propyl
THF  tetrahydrofuran
TLC  thin layer chromatography
TMS  trimethylsilyl
Chapter One

The Chemistry of Allene Oxides
1.1 Introduction.

This chapter will review the methods for preparation and the chemistry of the allene oxide ring system. In 1980, Chan and Ong published a comprehensive review on this topic and so this review will focus on more recent literature. Key developments prior to 1980 have been included for completeness.

Allene oxide is a highly strained and reactive oxygen heterocycle, closely related to cyclopropanone and oxyallyl. Allene oxide, oxyallyl and cyclopropanone are thought to exist in equilibrium in solution as opposed to being just resonance forms (Scheme 1). It has been shown that both substitution patterns and reaction conditions can result in the predominance of one tautomer over the other two. Quantum mechanical calculations have shown that all three tautomers are of similar energy but the energy content increases in the order cyclopropanone < allene oxide < oxyallyl.

\[ \text{allene oxide} \]
\[ \text{cyclopropanone} \]
\[ \text{oxyallyl} \]

Scheme 1

Between the three closely related structures of allene oxide, cyclopropanone and oxyallyl there is a rich diversity of chemical reactivity. All three can be utilised individually but often the presence of the other two in solution cannot be completely ruled out. Sterically hindered allene oxides and cyclopropanones have been isolated and successfully characterised. Oxyallyls and more reactive allene oxides and cyclopropanones have been generated in the presence of a reagent to trap them and have therefore only been characterised by analysis of their product mixtures.

This review is organised into three sections. Firstly, the available methods for the preparation of an allene oxides are presented. The second section describes the chemical reactions of allene oxides. Since allene oxides mostly exist only as transient species it should be noted
that there is a considerable amount of overlap in discussion of the first two sections. Finally, research into naturally occurring allene oxides will be briefly reviewed.

1.2 Methods for the Preparation of Allene Oxides

There are three main methods for the preparation of allene oxides: epoxidation of allenes, elimination reactions of appropriately functionalised epoxides and thermal decomposition of fulvene endoperoxides.

1.2.1 Epoxidation of Allenes

Perhaps the most direct route to an allene oxide is by epoxidation of the corresponding allene. However, under most oxidative conditions, allenes react to produce mixtures of products. Such mixtures arise from mono- and diepoxidation and further reactions of the resulting allene oxide and allene diepoxide with acidic or nucleophilic species present in the reaction mixture. Despite this, the oxidation of allenes has been a widely studied area and a diverse range of chemical transformations have been reported. Perhaps not surprisingly, it has been found that the substitution pattern of the allene and the exact nature of the oxidative conditions have a profound influence on the outcome of such reactions.6

Allene itself has been oxidised in the gas phase by oxygen atoms,8 ozone9 and by visible light-induced oxygen transfer from nitrogen dioxide.10 The parent allene oxide has been identified in the resulting mixtures by infra-red spectroscopy. The high stretching band (1823.4 cm⁻¹) is characteristic of the carbon-carbon double bond of allene oxides.9

Oxidation of tetramethylallene 1 with peracetic acid resulted in a complex mixture of products.11 It was postulated that tetramethylallene oxide 2 was the initial intermediate which reacted with residual acetic acid to give the α-substituted ketone 3 and was oxidised further to 2,2,5,5-tetramethyl-1,4-dioxaspiro[2.2]pentane 4. This allene diepoxide 4 also reacted with acetic acid to form the more highly substituted ketone 5, and rearranged to give more stable products 6 and 7 (Scheme 2).
The first uses of steric stabilisation to isolate the reactive intermediates in this type of reaction were reported in a series of papers that appeared in a single issue of the Journal of the American Chemical Society in 1968. Camp and Greene reported the monoepoxidation of 1,3-di-tert-butylallene 8 with m-chloroperbenzoic acid (m-CPBA) which resulted in the isolation and characterisation of an allene oxide for the first time (Scheme 3). 1,3-Di-tert-butylallene oxide 9 was isolated as a colourless liquid and a single geometrical isomer. $^1$H NMR (CCl₄) showed signals at 4.82 (1H, s) and 3.25 (1H, s) which are consistent with the olefinic and epoxide protons. The I.R. spectrum contained a C=C stretching band at 1795 cm⁻¹, known to be characteristic of allene oxides and a molecular ion was observed in the mass spectrum. Later work by Crandall and co-workers showed that the (E)-allene oxide 9 is formed preferentially. 12

$^5$-tert-Butyl-2,2-dimethyl-1,4-dioxaspiro[2.2]pentane 12 was isolated from the epoxidation of 1,1-dimethyl-3-tert-butylallene 10 with peracetic acid, which was shown to subsequently rearrange to a 1:1 mixture of 13 and 14 upon addition of hydrochloric acid (Scheme 4). 13,14
The allene diepoxide 12 was formed as the anti diastereomer exclusively because of the initial stereoselective formation of the (E)-allene oxide\textsuperscript{12}. Attempts to isolate the intermediate 1,1-dimethyl-3-\textit{tert}-butylallene oxide 11, or derivatives of it, by slow addition of the peracid were unsuccessful. One can conclude that oxidation of the intermediate allene oxide with this substitution pattern is extremely rapid and probably faster than oxidation of the allene starting material.

In related work, Crandall and co-workers oxidised 1,1-di-\textit{tert}-butylallene 15 to find that the sole product was the exceptionally stable 2,2-di-\textit{tert}-butylcyclopropanone 17 which was obtained as a waxy solid (m.p. 41-43°C).\textsuperscript{6} 1,1-Di-\textit{tert}-butylallene oxide 16 is thought to be formed initially and subsequently rearrange to the corresponding cyclopropanone. Even with excess peracetic acid, diepoxidation of the allene did not occur suggesting that, in this case, rearrangement is rapid and faster than oxidation of the allene oxide double bond (Scheme 5).

Interestingly, allene oxide 18, produced by vanadium catalysed epoxidation, was found to be stable and was converted to the corresponding acetate 19, including purification by flash silica gel chromatography, with the allene oxide moiety still intact (Scheme 6).\textsuperscript{15} The authors suggested that this stability could be attributed to the presence of the dimethylphenylsilyl substituent on the allene oxide as collapse to a zwitter-ionic oxyallyl, thought to be involved in the rearrangement of allene oxide to cyclopropanone, would be highly disfavoured in the presence of the electropositive silicon substituent.
The understanding gained from epoxidation of allenes with sterically bulky substituents and subsequent reaction of the isolated product has been used to rationalise the outcome of the epoxidation reactions of other allenes which are presumed to proceed via allene oxide intermediates. For example, oxidation of vinylideneadamantane 20 with m-CPBA gave a complex mixture of products from which β-lactone 22 and ester 23 were isolated (Scheme 7).\textsuperscript{15} The β-lactone 22 can be attributed to the prior rearrangement of the initially formed allene oxide to the corresponding cyclopropanone followed by Baeyer-Villiger oxidation with m-CPBA. This bears clear analogy to the work of Crandall and co-workers on 1,1-di-tert-butylallene oxide. The trace amount of ester 23 is probably the result of nucleophilic ring-opening of the initially formed allene oxide with m-chlorobenzoic acid (m-CBA).
Recently, a number of simple allenes have been oxidised with hydrogen peroxide catalysed by cetylpyridinium peroxotungstophosphate (PCWP). Oxidation of terminal allene 1,2-undecadiene with 4 equivalents of 35% H$_2$O$_2$ and PCWP (2 mol%) in a 3:2 mixture of ethanol/dichloromethane afforded 3-ethoxy-2-undecanone 25 in 71% yield (Scheme 8). The oxidation catalyst PCWP has phase-transfer properties therefore allowing the oxidation to occur in the biphasic mixture. The authors suggest that allene oxide 24 is formed initially which subsequently undergoes nucleophilic ring-opening by the alcoholic solvent to form the α-alkoxyketone 25 possibly, via the corresponding enol. Due to the catalytic nature of the oxidation, further oxidation of the allene oxide does not compete with this ring-opening reaction.

Unsymmetrically substituted allene 2,3-nonadiene gave two regioisomeric products 28 and 29 when oxidised with the PCWP/H$_2$O$_2$ system (Scheme 9). These two regioisomers are presumably formed from the two possible allene oxide intermediates 26 and 27 indicating that there is little regioselectivity in the allene oxidation.

A considerable amount of research into the oxidation of allenes capable of undergoing subsequent intramolecular trapping reactions has been undertaken. Indeed, oxidative cyclisation reactions of allenes encompasses a diverse range of transformations. In 1976, Bertrand and co-workers accomplished the cyclisation of β-allenic alcohols 30 and 33 under Payne oxidation conditions. They found that alcohol 30, with only a single substituent at
the tether end of the allene, would cyclise via the initially formed allene oxide 31 to give tetrahydropyranone 32 (Scheme 10). Disubstituted allenic alcohol 33, where $R^3 = CH_3$, was found to cyclise via the corresponding cyclopropanone 34 to give tetrahydrofuranone 35 (Scheme 10). The cyclopropanone intermediate 34 is presumably formed by rearrangement of the corresponding allene oxide formed initially by oxidation of the most nucleophilic double bond of the allene. In these intramolecular reactions, the pattern of reactivity and substitution does not always parallel that of intermolecular reactions. The formation of a five- or six-membered ring can be a strong driving force for cyclisation prior to further rearrangement of the allene oxide.

**Scheme 10**

$\beta$-Allenic alcohols 36 and 38 substituted with a trimethylsilyl group at the 1- or 3-position of the allene, respectively, were found to cyclise via the corresponding cyclopropanone. It was proposed that the silicon substituent enhanced the regioselectivity of carbon-carbon bond cleavage of the cyclopropanone ring by stabilising the resultant carbanion to produce tetrahydropyranone 37 or tetrahydrofuranone 39 (Scheme 11). Therefore, the position of the silicon substituent determined the nature of the product formed.
Crandall later worked on the oxidative cyclisation of allenic alcohols and reported the use of the mild and neutral oxidant dimethyldioxirane (DMD).\textsuperscript{19, 20} In a cold acetone solution of the oxidant, both α-allenic alcohol 40 and β-allenic alcohol 41 were found to be doubly oxidised to the corresponding allene diepoxides which then cyclised to hydroxytetrahydrofuranone 42 and hydroxytetrahydropyranone 43 respectively (Scheme 12). Trapping of the initially formed allene oxide under the neutral reaction conditions was found not to be competitive with further oxidation to the allene diepoxide. However, a change in the course of these reactions was observed on addition of p-toluenesulfonic acid (40 mol%) to the oxidation mixture resulting in the formation of the simple tetrahydrofuranone 45 or tetrahydropyranone 46 (Scheme 12). This shift in the product distribution, when acidic conditions are employed, was rationalised by protonation of the allene oxide resulting in ring-opening to form hydroxyallyl cation 44 which cyclises to the observed products.
Cyclisations onto allene oxides in acidic solutions of dimethyldioxirane have recently been reported by Crandall and co-workers using aldehydes and sulfonamides as the nucleophilic components producing, for example, pyranone 47 and piperidone 48, respectively (Scheme 13). In each case, under neutral conditions the allene diepoxides were produced which were converted into the corresponding more highly substituted products.

Scheme 13

Cyclisation of allenic carboxylic acids via allene oxide intermediates to give even more highly oxygenated rings was accomplished with the formation of DMD in situ (Oxone®, acetone, aqueous NaHCO₃) to keep the concentration of oxidant to a minimum (Scheme 14). The oxidation and cyclisation of allenic phosphoric acids with peracetic acid has also been reported.

Scheme 14

In a similar manner, isolable allene oxide 50 cyclised to furanone 51 at 120°C (Scheme 15). This cyclisation is thought to involve the corresponding oxyallyl species. The allene oxide was formed by stereospecific oxidation of allenic ketone 49 with m-CPBA. The stereoselectivity of the oxidation is thought to be due to steric hindrance of the tert-butyl group on the allene as for the formation of the (E)-allene oxide by oxidation of 1,1-dimethyl-3-tert-butyl allene (Vide Supra). It was suggested that the unusual stability of allene oxide 50 may be due to conjugation with the carbonyl group. We believe this is the only example of an intramolecular cyclisation via a stable allene oxide.
Monoepoxidations of vinyl allenes result in cyclisation by nucleophilic attack of the α,β-double bond on the allene oxide to furnish cyclopentenones. In 1977, Bertrand, Dulcere and Gil oxidised 4-methyl-2,3,5-hexatriene with m-CPBA and alternatively with H₂O₂/C₆H₅CN to give cyclopentenone 52 which the authors reasoned was formed via an allene oxide intermediate (Scheme 16).²⁶

Kim and Cha used a vanadium catalysed epoxidation to convert allene 53 into cyclopentanone 56 (Scheme 17).²⁷ It seems that the hydroxyl group directed the oxidation process but did not interfere with the cyclisation of the vinylallene oxide as products formed from intramolecular nucleophilic attack of the hydroxyl group on allene oxide 54 were not isolated. The cyclisation is thought to proceed via the oxypentadienyl zwitterion 55 and the geometry of the allene double bond is relayed into the relative stereochemistry of the cyclopentenone product. The authors suggest that this is a successful biomimetic demonstration of the lipoxygenase pathway that exists in some plant and marine species and is known to involve allene oxide intermediates in the formation of cyclopentenones (Vide Infra).
Mizuno and co-workers have reported an efficient synthesis of 2-diphenylmethylene-cyclobutan-1-ones by the oxidation of diphenylethlyidene cyclopropanes with m-CPBA and subsequent rearrangement (Scheme 18). Allene 57 is oxidised regiospecifically to give allene oxide 58, substituted with a spirocyclopropane ring at the $sp^3$ epoxide carbon. The regioselectivity in this oxidation is due to the presence of phenyl groups on the allene which cannot lie planar to the allene, thus blocking oxidation of that double bond. Allene oxide 58 is subsequently protonated and undergoes ring-expansion by bond migration to the $sp^2$ ring carbon. A difference in the migratory aptitudes of the two bonds of the cyclopropane ring is observed when one is substituted by an electron donating group or, to a lesser extent, an aromatic ring. Mixtures of regioisomers, such as 59 and 60, were observed with unsymmetrically alkyl substituted cyclopropane rings.
1.2.2 Elimination

Exocyclic β-elimination of an epoxide can give rise to the generation of an allene oxide as illustrated below (Scheme 19). Chan and Ong developed this alternative methodology for allene oxide generation using the Chan group's expertise in organosilicon chemistry. This chemistry has the considerable advantage that it can be performed under essentially neutral non-oxidative conditions.

\[
\begin{align*}
R^1 & \xrightarrow{X} R^2 \\
\text{Scheme 19}
\end{align*}
\]

The mildness of this new process was established when Chan and Ong were able to isolate 1-\textit{tert}-butylallene oxide 62 by elimination of the elements of chlorotrimethylsilane from silyl epoxide 61.\textsuperscript{29} The reaction was performed in diglyme using caesium fluoride as the source of fluoride ion to trigger the elimination (Scheme 20). The allene oxide was isolated by driving it into a cold trap (-78°C) with a stream of nitrogen gas passed through the reaction mixture. 1-\textit{tert}-Butylallene oxide is a colourless liquid that is only stable for ca. 1.5 h at 25°C as it is prone to polymerisation. In the \textsuperscript{1}H NMR spectrum the two vinyl protons are non-equivalent giving an AB pattern at 4.15 ppm with a geminal coupling of 4 Hz. The \textsuperscript{13}C NMR data shows signals at 144.3 ppm and 70.5 ppm for the quaternary olefinic carbon and the terminal olefinic carbon respectively.\textsuperscript{3}

\[
\begin{align*}
t-\text{Bu} & \xrightarrow{\text{CsF}} \text{t-Bu} \\
\text{Scheme 20}
\end{align*}
\]

Allene oxides that do not possess sterically bulky groups and only exist as transient species have been prepared using this methodology. When a nucleophile was added to the reaction mixture an α-(substituted)-methylketone 63 was produced via ring-opening of the allene oxide by the additional nucleophile (Scheme 21).\textsuperscript{3} In the absence of an additional nucleophile α-chloroketones 64 were isolated, the result of ring-opening of the allene oxide by chloride ion generated in these reactions (60-70%) (Scheme 21).\textsuperscript{3}
In an investigation into the formation of cyclopropane 66 from the reaction of amino acetonitrile derivative 65 and epibromohydrin with lithium di-iso-propylamide (LDA) at -70°C, Aitken and co-workers described the formation of an alternative product, namely α-(substituted)-methylketone 67. They optimised the conditions for this alternative reaction and suggested the formation of an allene oxide intermediate to account for the behaviour of epibromohydrin as an acetonyl synthon (Scheme 22). It is thought that the parent allene oxide is formed by elimination of the elements of HBr from epibromohydrin triggered by initial deprotonation of the epoxide CH by the base. The highly reactive nature of this allene oxide makes it capable of undergoing nucleophilic attack at such low temperatures. Competitive formation of 66 is suppressed by using an excess of both epibromohydrin and LDA with respect to nitrile 65. In the absence of a nucleophile, such as the carbanion of 65, epibromohydrin undergoes deprotonation at the methylene carbon to furnish 1-bromo-1-propen-3-ol. To prevent this, epibromohydrin and 65 were mixed prior to the addition of LDA.
This reaction is found to be specific to halohydrins with reactivity decreasing in the order I \(\approx\) Br > Cl > F. When glycidyl benzenesulfonate 68 was used in place of epibromohydrin, under the same reaction conditions, only allylic alcohol 69 was isolated, even in the presence of 65 (Scheme 23).

In 1993, Kabat described the use of a variation on Chan's elimination method for the generation and reaction of homochiral allene oxides.\(^{31}\) In his version of this chemistry, mesylates were used instead of chloride anion as the leaving group (Scheme 24). Anhydrous tetra-\(n\)-butylammonium fluoride (TBAF) was used both to trigger the elimination of epoxy mesylate 70 and as the external trapping nucleophile. Under these conditions \(\alpha\)-fluoroketones 71 were formed in yields ranging from 82-87\% with little or no racemisation.

Similarly, this methodology was used in the stereoselective synthesis of \(\gamma\)-hydroxy-\(\beta\)-keto phosphonates.\(^{32}\) In this instance, precursor 72 is treated with TBAF but the external nucleophile was water. The resulting trapped allene oxide products, \(\gamma\)-hydroxy-\(\beta\)-keto phosphonates 73, were produced in reasonable yields (ca. 74\%) and 96-97\% enantiomeric excess (Scheme 25).
Kabat has used allene oxide chemistry in a novel route to 2-fluoromethyl- and 2-hydroxymethyl-4-alkylfurans.\textsuperscript{33} Epoxy mesylate 74 is treated with fluoride ion to generate the allene oxide which subsequently reacts with either an excess of fluoride ion or added water depending on whether a fluoromethyl or hydroxymethyl product is required. The \( \alpha,\beta \)-epoxy enol formed from ring-opening of the allene oxide rearranges to the furan product 75 (Scheme 26). This methodology was also used to synthesise steroidal fluoromethyl and hydroxymethylfurans.\textsuperscript{33}

\begin{align*}
\text{OMs} & \quad \text{a or b} \\
\text{R} & \quad \text{a, TBAF (2 eq) for } X = \text{F} \\
& \quad \text{b, TBAF (1 eq), H}_2\text{O (10 eq) for } X = \text{OH}
\end{align*}

Scheme 26

Direct evidence for the existence of homochiral allene oxides was reported by Konoike and co-workers who isolated (S)-1-\textit{tert}-butylallene oxide.\textsuperscript{5} They implemented a different method of \( \beta \)-elimination using stannyl epoxy alcohol 76. The chirality was introduced into 76 by use of a Sharpless asymmetric epoxidation reaction of the corresponding allylic alcohol (79\%, 97\% ee). Deoxystannylation was achieved under standard conditions for mesylation of the hydroxyl group (methanesulfonyl chloride, tri-\( n \)-butylamine, triglyme, 0\^\circ\text{C}-R.T.) where on formation of the mesylate, chloride ion present in the reaction mixture spontaneously triggered the E2 elimination. (S)-1-\textit{tert}-Butylallene oxide was isolated from the reaction mixture, in 29\% yield, by removing it in a stream of argon and condensing it onto a cold finger at -78\^\circ\text{C} (Scheme 27).
1.2.3 Thermal Decomposition of Fulvene Endoperoxides

6,6-Dimethylfulvene 77 forms the unstable endoperoxide 78 under photo-oxidation conditions. Thermal isomerisation of this endoperoxide gives 3,3-dimethyl-2(\(H\))-oxepinone 81 as the primary product.\(^{34}\) The intermediates involved in this isomerisation reaction are thought to be allene oxide 79 and cyclopropanone 80 (Scheme 28).

In 1987, Erden and Amputch worked on the thermal decomposition of the partially saturated fulvene endoperoxide, 7-iso-propylidene-2,3-dioxabicyclo[2.2.1]heptane 82.\(^{35}\) This endoperoxide was formed by photo-oxidation of 77 and subsequent \textit{in situ} reduction with diazene. Thermolysis of endoperoxide 82 in CCl\(_4\) at 60°C for 30 min gave a mixture of products. The keto aldehyde 83 was believed to be formed by heterolytic cleavage of the oxygen-oxygen (O-O) bond followed by a 1,2-hydride shift (Scheme 29). The other two products are postulated to arise from initial homolytic cleavage of the O-O bond to furnish the intermediate diradical 84 which rearranges to give epoxy alcohol 85 and cycloadduct 87. The rearrangement of 84 to 87 is thought to proceed via allene oxide 86 which in turn can isomerise to the corresponding cyclopropanone and undergo intramolecular 1,3-dipolar
cycloaddition with the aldehyde to give 87 (Scheme 29). It is possible that the corresponding oxyallyl species is involved in this 1,3-dipolar cycloaddition step. Recently similar products have been isolated from an unsaturated fulvene endoperoxide in which the two methyl groups of 82 were substituted for an adamantyl group to enhance its stability.

Allene oxide 89 was isolated from the photo-oxidation of 6-tert-butylfulvene followed by thermal isomerisation of the resulting moderately stable endoperoxide 88 (characterised by $^1$H and $^{13}$C NMR). The stability of allene oxide 89 is uncharacteristic of an allene oxide possessing sterically bulky groups at only the terminal $sp^2$ carbon atom. Allene oxide 89 rearranged to the corresponding cyclopropanone upon heating to 120°C which then cyclised to produce two products 90 and 91. These products presumably arose from cyclisation across the C2-C3 bond and the C2-O bond of the cyclopropanone respectively (Scheme 30).
Thermolysis of endoperoxide 82 in the presence of a diene such as furan furnished adduct 92 in which the allene oxide or cyclopropanone intermediate had been trapped by the intermolecular Diels-Alder reaction as opposed to intramolecular 1,3-dipolar cycloaddition to afford aldehyde 92 (Scheme 31). The allene oxide intermediate was captured, by addition of acetic acid, to give acetate 93.
The endoperoxide decomposition method for the generation of allene oxides was used in the synthesis of functionalised cyclopentenones. Allene oxide 94 was trapped intramolecularly by a vinyl group conjugated with the allene oxide double bond. It has been suggested that this reaction proceeds via a cyclopropanone and an oxypentadienyl zwitterion. Erden and co-workers illustrated that this method would tolerate a variety of substituents, including a cyclohexenyl group which enabled the construction of quite complex bicyclic systems such as 95 (Scheme 32).

\[ R_1 = R_2 = R_4 = H, R_3 = \text{Ph} \]
\[ R_1 = R_4 = H, R_2 = \text{Me}, R_3 = \text{Ph} \]

Scheme 32
1.3 Reactions of Allene Oxides

Allene oxides contain the structural elements of a double bond, an epoxide and an enol ether and undergo a variety of transformations. The most common reaction of allene oxides reported in the literature is nucleophilic ring opening which proceeds regiospecifically by attack at the $sp^3$ ring carbon both intermolecularly and intramolecularly to give a wide range of products.\(^3\)

The nucleophilic ring-opening reaction of allene oxides was observed directly using 1-tert-butylallene oxide 62 which was found to be borderline between isolable and non-isolable allene oxides, bearing just one sterically bulky substituent at the $sp^3$ ring carbon. This single tert-butyl group does not shield the allene oxide from nucleophilic attack to any extent as 1-tert-butylallene oxide 62 reacted with a variety of nucleophiles to produce $\alpha$-(substituted)-2,2-dimethylpentan-4-ones 96 in good yields (70\%) (Scheme 33).\(^3\)

\[ \text{Scheme 33} \]

Allene oxides that did not possess sterically bulky groups existed as transient species. These allene oxides reacted with nucleophiles already present in the reaction mixture to produce $\alpha$-(substituted)-ketone products (60-70\%) and in the absence of an additional nucleophile to form $\alpha$-chloroketones (60-70\%) by reaction with chloride anion (Vide Supra).\(^1\) Reaction of the two isomeric epoxides 97 and 99 with caesium fluoride and methanol gave the two isomeric ketones 98 and 100 (Scheme 34). This regiospecificity of nucleophilic attack provides additional evidence to support the assumption that these reactions proceed via an allene oxide intermediate.\(^4,4^1\)

\[ \text{Scheme 34} \]
The rearrangement of an allene oxide to the corresponding cyclopropanone has also been observed directly. 1,3-Di-tert-butylallene oxide 9 rearranged to 1,3-di-tert-butylcyclopropanone 101 (half life ca. 5 h) on heating to 100°C (Scheme 35).

![Scheme 35]

It has been shown that allene oxides with an aryl or two alkyl substituents at the $sp^3$ ring carbon rapidly rearrange to the corresponding cyclopropanones. Crandall and co-workers observed that oxidation of 1,1-di-tert-butylallene 15 gave the exceptionally stable 2,2-di-tert-butylcyclopropanone 17 as the sole product (Scheme 36).

![Scheme 36]

Characteristically, fluoride induced elimination of 1-aryl-epoxide 102 and 1,1-disubstituted epoxide 105 produce products derived from the corresponding cyclopropanones and not allene oxides (Schemes 37 and 38). The ester products formed, 104 and 107, are the result of nucleophilic attack at the carbonyl carbon of the more stable cyclopropanones 103 and 106 respectively.
The substituent effect observed in these reactions also manifests itself in the reaction of an allene oxide generated in the presence of a cyclic 1,3-diene. An allene oxide with a single alkyl substituent at the sp\(^3\) ring carbon reacts with cyclopentadiene to give the \(\alpha\)-substituted product 108 presumably via a zwitterionic intermediate (Scheme 39).\(^{42}\)

However, 1-phenyllallene oxide rearranges to the corresponding cyclopropanone 103 and then undergoes a [3 + 4] cycloaddition with the 1,3-diene to give the bridged 7-membered ring cycloadduct 109 (Scheme 40).\(^{1,43}\) Cyclopropanones have been shown to undergo cycloaddition reactions with a wide range of cyclic dienes leading to a diverse range of synthetically important structures.\(^{36}\) It has been suggested that the cycloaddition reactions of cyclopropanones occur via formation of the corresponding oxyallyl. Cyclic adducts such as 109 are commonly associated with the generation of oxyallyl zwitterions in the presence of a 1,3-diene.\(^{44}\)
Crandall and co-workers worked on the intramolecular trapping of allene oxides, generated via allene epoxidation, with alcohols to form a variety of oxygen heterocycles (Vide Supra).\textsuperscript{19,20} The intramolecular trapping of an allene oxide with a double bond to form cyclopentenones has been accomplished using various methods for allene oxide generation. For example, in 1987, Corey and co-workers used Chan's elimination chemistry in a biomimetic synthesis of a preclavalone A model.\textsuperscript{45} Silyl epoxide 110, with a $\beta$-trifluoroacetate as the leaving group, was used as the precursor for allene oxide 111. When this material was treated with caesium fluoride in acetonitrile, cyclopentenone 113 was produced in 20-25\% yield via an oxypentadienyl zwitterion 112 (Scheme 41).

\begin{center}
\textbf{Scheme 41}
\end{center}

A similar biomimetic synthesis has also been reported by Kim and Cha using the epoxidation of a vinyl allene as the method for allene oxide generation (Vide Supra).\textsuperscript{27} Cyclopentanones have also been formed from allene oxides generated by thermal decomposition of fulvene endoperoxides.\textsuperscript{40} Allene oxides occur as intermediates in the biosynthesis of natural products such as the prostaglandin family. Formation of these prostaglandin-type cyclopentenones is believed to parallel this type of rearrangement (Vide Infra).

When allene oxide 89 was treated with tetra-$n$-butylammonium fluoride in THF, an unexpected intramolecular reaction occurred furnishing the disubstituted cyclopropane 114.\textsuperscript{37} The reaction is thought to be initiated by the formation of an enolate anion which subsequently attacks the allene oxide moiety intramolecularly (Scheme 42). This type of reaction has also been observed with naturally-occurring allene oxides incubated with enzyme preparations of Sea Whip coral.\textsuperscript{39}
It has been reported that cycloadducts can be formed by the reaction of an allene oxide with alkyl acrylates. When a mono-alkyl-substituted allene oxide is generated in the presence of an alkyl acrylate the product is a cyclopentanone (Scheme 43). The reaction is regiospecific, forming only 2,4-disubstituted cyclopentanones 115. A simple concerted mechanism of cycloaddition can therefore be discounted as this would most probably furnish the 2,3-disubstituted product.

Hydroboration of (S)-1-tert-butylallene oxide with borane is the only example of the seemingly electron-rich enol moiety of an allene oxide undergoing an electrophilic addition reaction (Scheme 44). Subsequent oxidative work-up gave (R)-4,4-dimethylpentane-1,3-diol 116 (50%) which was established to be of high enantiomeric purity (97% ee) by derivatisation of the primary alcohol function to the Mosher's MPTA ester. This chemistry was used to establish the enantiomeric purity of (S)-1-tert-butylallene oxide.
1.4 Allene Oxides in Biological Systems

1.4.1 Allene Oxides in Plant Lipid Metabolism

Allene oxides have been implicated in a number of biological systems including plant lipid metabolism and marine prostaglandin biosynthesis. In 1978, Zinnerman and Feng described the conversion of \( \alpha \)-linolenic acid into the cyclopentanone derivative 12-oxo-10,15(\( Z \))-phytodienoic acid (12-oxo-PDA) and suggested that it was a precursor to the plant growth regulator jasmonic acid.\(^{46} \) Initially \( \alpha \)-linolenic acid is converted to (13\( S \))-hydroperoxy-9(\( Z \)),11(\( E \)),15(\( Z \))-octadecatrienoic acid [(13\( S \))-HPOT] by a \textit{lipoxygenase} catalysed oxidation. Conversion of (13\( S \))-HPOT to 12-oxo-PDA was assumed to take place under the catalysis of a single \textit{hydroperoxide cyclase} enzyme (Scheme 45).

\[
\begin{align*}
\text{HO}_2\text{C}(\text{H}_2\text{C})_7 & \quad \text{HO}_2\text{C}(\text{H}_2\text{C})_7 \\
\text{Lipoxygenase} & \quad \text{Hydroperoxide cyclase?} \\
\text{HO}_2\text{C}(\text{H}_2\text{C})_7 & \quad \text{Isomerase?} \\
\text{a-Linolenic acid} & \quad \text{(13\( S \))-HPOT} \\
\text{OH} & \quad \text{(12\( S \))-PDA} \\
\text{a-ketol 117} & \quad \text{12-oxo-13-hydroxy-9(\( Z \)),15(\( Z \))-octadecadienoic acid 117}
\end{align*}
\]

\textbf{Scheme 45}

The transformation of (13\( S \))-HPOT to (12\( S \))-PDA was studied in acetone powder preparations of flaxseed and it was found that fatty acid chain lengths of 18, 20 and 22 carbons atoms were tolerated and that the 15(\( Z \))-double bond was essential.\(^{47,48} \) An \( \alpha \)-ketol by-product, 12-oxo-13-hydroxy-9(\( Z \)),15(\( Z \))-octadecadienoic acid 117 was observed which stimulated further research into the detailed mechanism of this transformation.\(^{49,50} \)
In 1987, Hamberg demonstrated the existence of an unstable allene oxide intermediate in an analogous pathway starting from α-linoleic acid. The hydroperoxide, (13S)-hydroperoxy-9(Z),11(E)-octadecadienoic acid [(13S)-HPOD] was briefly incubated with an enzyme preparation of corn resulting in the generation of (12,13S)-epoxy-9(Z),11-octadecadienoic acid [(12,13S)-EOD] (Scheme 46). The process was thought to involve enzymatic dehydration. The allene oxide (12,13S)-EOD was not isolated but was characterised by ultraviolet spectrometry, isotope studies and, most convincingly, trapping experiments. For example, in aqueous media the allene oxide rapidly hydrolysed to the α-ketol 118, analogous to that isolated from the flaxseed incubation of (13S)-HPOT, and also γ-ketol 119 in smaller amounts. In the presence of methanol and other alcohols α-alkoxyketones 120 resulted. This is a classic transformation of allene oxides and therefore a good indication of their presence (Scheme 46).1

\[
\begin{align*}
\text{HO}_2\text{C}(\text{H}_2\text{C})_7&\xrightarrow{\text{H}_2\text{O}}\text{(12,13S)-EOD} \\
\text{HO}_2\text{C}(\text{H}_2\text{C})_7&\xrightarrow{\text{ROH}}\text{OH} + \text{HO}_2\text{C}(\text{H}_2\text{C})_7\xrightarrow{\text{OH}}\text{(12,13S)-EOD}
\end{align*}
\]

**Scheme 46**

In the absence of water and alcohols, the nucleophilic carboxylate group of (12,13S)-EOD attacked the allene oxide (12,13S)-EOD, to form two isomeric macrolactones 121 and 122, which may explain why this allene oxide could not be isolated. Treatment of (12,13S)-EOD with sodium borohydride gave the allylic alcohol 12-hydroxy-9-octadecenoic acid 123 (Scheme 47). The mechanism was elucidated by deuterium labelling experiments which suggested that the reaction proceeded by initial addition of hydrdride to the epoxide ring at C-13 of (12,13S)-EOD followed by further reduction of the C-12 carbonyl by another equivalent of reducing agent.
The allene oxide (12,13S)-EOD was stabilised in the presence of vertebral Serum albumin increasing the half-life from 33 s to ca. 14 min at 0°C in an aqueous medium. The allene oxide is thought to bind to a hydrophobic site on the albumin thus protecting it from hydrolysis. When bound in this way, (12,13S)-EOD was found to form cyclopentenone 124 (Scheme 47). The cyclopentanone 124, 3-oxo-2-pentylcyclopentyl-4-en-1-octanoic acid was found to possess \textit{atrans} side chain configuration and to be a racemate.

In 1988, Brash and co-workers isolated the methyl ester of (12,13S)-EOD and (12,13S)-EOT, the allene oxide derived from (13S)-HPOT and the immediate precursor of 12-oxo-PDA. These allene oxides were characterised by $^1$H NMR with the aid of 2-dimensional correlation spectroscopy (COSY). The $^1$H NMR data was found to be characteristic of an allene oxide when compared to data for chemically synthesised allene oxides. Together with UV and CD spectra and oxygen-labelling experiments the authors were convinced of the allene oxide structures of (12,13S)-EOD methyl ester and (12,13S)-EOT methyl ester (Figure 1).
Allene oxide $(12,13S)$-EOT methyl ester was subsequently found to cyclise spontaneously in buffer to furnish 12-oxo-PDA methyl ester (15-20% yield) in an analogous manner to the cyclisation of $(12,13S)$-EOD when bound to Serum albumin. The 12-oxo-PDA methyl ester from this experiment was again found to be a racemic mixture suggesting that it is formed by chemical cyclisation and not by way of enzymatic catalysis. Similarly, when $(13S)$-HPOT was incubated with acetone powder preparations of flaxseed, a 1:1 mixture of the $(9S,13S)$- and $(9R,13R)$-enantiomers of 12-oxo-PDA resulted. The chemical cyclisation via $(12,13S)$-EOT is thought to proceed via oxapentadienyl zwitterion $125$ (Scheme 48).

Incubation of $(13S)$-HPOT with an ammonium sulfate corn preparation afforded 12-oxo-PDA in 82% yield and 80% ee, predominately as the $(9S,13S)$-enantiomer. This suggests that the transformation was catalysed enzymatically. Soon after, the enzyme that specifically
catalysed this conversion was isolated and named *allene oxide cyclase*. It was found to be present in the soluble fraction of the homogenate of a large number of plants, notably in spinach leaves and potato tubers.57

Indentification of an allene oxide intermediate represents the final piece of the jigsaw puzzle in the *lipoxygenase* pathway from α-linolenic acid to 7-*iso*-jasmonic acid (Scheme 49).

![Chemical Reaction Diagram](attachment:image.png)
1.4.2 Allene Oxides as Intermediates in the Biosynthesis of Prostaglandins.

The species of Sea Whip coral *Plexaura homomalla* is an abundant natural source of prostaglandins of the A and E series. The prostaglandin PGA₂ methyl ester constitutes 2-3% of the dry weight of the coral. PGE₂ is also present in significant amounts as the methyl ester. The conversion of the arachidonic acid derivative, 15-hydroxyeicosatetraenoic acid (15-HETE) to PGA₂ is thought to proceed via the hydroperoxide, (8R)-hydroperoxy-15-hydroxyeicosatetraenoic acid 126 formed by the action of (8R)-lipoxygenase on 15-HETE. The hydroperoxide 126 is thought to be subsequently converted to the allene oxide (8R,9)-epoxyeicosa-5,9,11,14-tetraenoic acid 127 (Scheme 50).

Allene oxide 127 has been found to react non-enzymatically to give prostaglandin analogues and α-ketol products (Scheme 51). In an analogous fashion to plant systems, the non-enzymatic reactions of allene oxide 127 give racemic prostaglandin type structures 128 and 129 with incorrect side chain geometry (cis). The reaction also produced the products of allene oxide hydrolysis, α-ketols 130 and 131, which undergo a further non-enzymatic oxidation to give triols 132. To date, the enzyme that is believed to catalyse this cyclisation in living systems to give chiral prostaglandin PGA₂ has not been isolated.
Metabolism of arachidonic acid has been studied in a similar manner. In this series, arachidonic acid is oxidised by (8R)-lipoxygenase to (8R)-8-hydroperoxyeicosatetraenoic acid (8R)-HPETE which subsequently undergoes enzymatic conversion to an allene oxide intermediate. Similar cyclisation products have been isolated but, perhaps more importantly, in this case the allene oxide (8R)-8,9-epoxyeicosa-5(Z),9,11(Z),14(Z)-tetraenoic acid has been isolated and characterised by $^1$H NMR as the methyl ester derivative (Figure 2). It is thought unlikely, however, that such a pathway relates directly to prostaglandin biosynthesis as the 15-hydroxyl functionality is lacking in this series.
Metabolism of arachidonic acid has been observed in starfish oocytes but the allene oxide formed is thought to have a different fate to that in plants and coral.\textsuperscript{62} Arachidonic acid and (8\textit{R})-HETE have been linked to maturation of starfish mimicking the hormone 1-methyladenine.

This short review has highlighted the main and more recent aspects of the chemistry of allene oxides reported in the chemical literature. The work presented in this thesis describes our attempts to develop new methods for the synthesis and subsequent reaction of allene oxides with an express aim to widen the utility of this interesting class of molecules in organic synthesis.
Chapter Two

New Methodology for the Generation and Capture of Allene Oxides
2.1 Generation of an Allene Oxide via Selenoxide Elimination.

2.1.1 Introduction

We began our research studies by examining a novel method for the generation of allene oxides. In an analogous fashion to the fluoride ion induced elimination method developed by Chan and co-workers (Scheme 52, 1), we proposed to introduce a double bond adjacent to an epoxide ring using selenoxide elimination based strategy (Scheme 52, 2). We envisaged that an elimination reaction based on an alkylaryl selenoxide would occur under essentially neutral reaction conditions providing a mild method for the generation of allene oxides.

\[
\text{R}^1\text{SiMe}_3\text{Cl} \xrightarrow{\text{CsF}} \text{R}^1\text{O} \quad (1)
\]

\[
\text{R}^0\text{O}^+ - \text{Se-Ar} \xrightarrow{} \text{R}^1\text{O} + \text{ArSeOH} \quad (2)
\]

Scheme 52

It has long been known that selenoxides with a β-carbon bearing a hydrogen atom are thermally unstable and decompose to olefins. Elimination of the selenic acid occurs in a syn fashion via an essentially concerted process (Scheme 53). Quantum mechanical calculations have shown that selenoxides eliminate via a cyclic five-membered transition state and that the breaking of the C-H bond occurs prior to breaking of the C-Se bond.

\[
\text{RSeO}^+\text{H} \xrightarrow{} \text{R}^1\text{R}^2\text{R}^3\text{R}^4 + \text{RSeOH}
\]

Scheme 53

Selenoxides that are not suitably substituted for β-elimination can be stable compounds. For example, dimethyl-, diaryl- and arylmethyl selenoxides do not possess a β-hydrogen and have been isolated. Selenoxides have also been isolated where conformational constraints do not allow syn elimination or if the selenoxide oxygen is hydrogen bonded to a nearby acidic hydrogen.
Interestingly, selenoxides exhibit a tendency to eliminate away from substituents containing a heteroatom.\textsuperscript{71} This regioselectivity has been used advantageously to prepare allylic alcohols.\textsuperscript{72} For example, treatment of (E)-octene oxide with phenyl selenate anion, formed from the reduction of diphenyl diselenide with sodium borohydride, gave hydroxy selenide 133. Selenide 133 was not isolated but was immediately oxidised, by an excess of hydrogen peroxide, to the corresponding unstable selenoxide which subsequently decomposed to give the (E)-allylic alcohol 134 in 98% yield (Scheme 54).

\[
\begin{align*}
\text{n-Pr} & \quad \text{PhSeSePh} \\
\text{NaBH}_4, \text{EtOH} & \quad \text{n-Pr} \\
\text{H}_2\text{O}_2 (\text{excess}) & \quad \text{HO} \quad \text{n-Pr} \\
\text{Et} & \quad \text{134}
\end{align*}
\]

\textbf{Scheme 54}

Terminal \(\beta\)-oxyselenoxides, in which elimination can only occur towards a substituent containing an oxygen atom, are usually stable and can be isolated. However, elimination can be facilitated by adopting more forcing conditions such as high temperatures. The addition of an organic base, to neutralise the selenic acid produced in the elimination process, has been found to be beneficial by helping to drive the reaction to completion.\textsuperscript{73} Elimination of terminal \(\beta\)-oxyselenoxides is promoted if the \(\beta\)-oxygen atom is also linked to an electron-withdrawing group such as a carbon-oxygen, carbon-nitrogen or a carbon-carbon double bond or an aromatic ring. Terminal \(\beta\)-oxyselenides 135 and 136 both have the \(\beta\)-oxygen atom in conjugation with an electron withdrawing group making elimination of the corresponding selenoxides possible in refluxing benzene containing sodium hydrogen carbonate (Scheme 55).\textsuperscript{73,74}

\[
\begin{align*}
\text{135} & \quad \text{C}_6\text{H}_{13} \\
\text{i, 5 h; ii, 3 h} & \quad \text{67\%} \\
\text{136} & \quad \text{C}_6\text{H}_{13} \\
\text{EtO}_2\text{C} & \quad \text{Ph} \\
\text{i, 19 h; ii, 6 h} & \quad \text{71\%}
\end{align*}
\]

\textit{Reagents and Conditions:} i, \text{H}_2\text{O}_2, \text{MeOH}, \text{R.T.}; ii, \text{benzene, reflux}, 10\% \text{NaHCO}_3.

\textbf{Scheme 55}
The rate of elimination of alkylaryl selenoxides can be enhanced by an electron-withdrawing group on the aromatic ring whereas electron-donating substituents decrease the rate of elimination.\textsuperscript{75, 76} For example, by the inclusion of an ortho or para electron-withdrawing group on the aromatic ring of alkylaryl selenide 137 both the rate of elimination and the isolated yield of methylene cyclohexane were increased (Scheme 56/Table 1).

![Scheme 56]

### Table 1

<table>
<thead>
<tr>
<th>X</th>
<th>Temp, °C</th>
<th>Time, h</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>25</td>
<td>48</td>
<td>46</td>
</tr>
<tr>
<td>4-Cl</td>
<td>25</td>
<td>9.5</td>
<td>85</td>
</tr>
<tr>
<td>2-NO(_2)</td>
<td>25</td>
<td>9.5</td>
<td>92</td>
</tr>
</tbody>
</table>

Interestingly, selenoxide 138 is stable to elimination and could not be used to prepare cyclopropene 139 (Scheme 57).\textsuperscript{77} However, selenoxides have been shown to eliminate to afford highly strained ring systems. For example selenide 140 was oxidised with ozone and the resulting selenoxide eliminated in pyridine to give the cyclobutene 141 (Scheme 57).\textsuperscript{78}

![Scheme 57]
2.1.2 Preparation of an Alkylaryl Selenoxide as an Allene Oxide Precursor

On the basis of the discussion above, selenoxide 146 was chosen for initial studies to establish whether the strained allene oxide ring system could be generated using a selenoxide elimination strategy. A terminal $\beta$-epoxy selenoxide was chosen to ensure that elimination would only occur in one direction. The electron-withdrawing $o$-nitro group on the aromatic ring should help promote elimination towards an oxygen atom. The long chain alkyl group on the epoxide ring was included to prevent problems with product isolation due to volatility.

![Chemical Structure](image)

We prepared the corresponding epoxyaryl selenide 145 by the route outlined below (Scheme 58). A modified Horner-Wadsworth-Emmons olefination procedure developed by Masamune and Roush was used to prepare exclusively (E)-ethyl-2-dodecenoate 142 in 71% yield. Reduction of 142 with di-iso-butylaluminium hydride gave allylic alcohol 143 which was epoxidised to (2R*,3R*)-epoxydodecan-1-ol 144 in 66% yield over the two steps. (2-Nitrophenyl)-selenocyanate 147 was prepared by diazotization of 2-nitroaniline and subsequent reaction with potassium selenocyanate according to the literature procedure. Treatment of epoxy alcohol 144 with (2-nitrophenyl)selenocyanate 147 and tri-$n$-butylphosphine gave epoxyaryl selenide 145 in 36% yield. No attempts were made to optimise this process, the low yield for this step was probably due to problems associated with product isolation.

![Reagent and Conditions](image)

Reagents and Conditions: i, DBU, LiCl, MeCN, R.T.; ii, DIBAL, toluene, -78°C; iii, $t$-BuOOH, VO(acac)$_2$, R.T.; iv, $n$-Bu$_3$P, THF, R.T.

Scheme 58
We next turned our attention to oxidation of selenide \textbf{145} to the corresponding selenoxide \textbf{146}. Oxidation with \textit{m}-chloroperbenzoic acid in dichloromethane buffered with potassium carbonate furnished the desired selenoxide in 62\% yield, isolated by column chromatography as an orange solid and as an inseparable mixture of diastereomers \textbf{146a} and \textbf{146b} (Scheme 59). An accurate mass measurement under C.I. conditions indicated formation of the desired selenoxide. To support this the \textsuperscript{1}H NMR spectrum of this material showed a down field shift in some of the aromatic signals and some signals in the \textsuperscript{1}H and \textsuperscript{13}C NMR spectra of this material were doubled due to the formation of diastereomers.

\begin{center}
\includegraphics[width=0.8\textwidth]{scheme59}
\end{center}

\textbf{Scheme 59}

In view of the known instability of allene oxides, we elected to thermolyse this mixture of selenoxides \textbf{146a} and \textbf{146b} in the presence of a trapping agent so that if allene oxide \textbf{148} was generated it would be captured as an \( \alpha \)-\( \text{substituted} \)-ketone. Using benzyl alcohol we expected the captured allene oxide product would \( \alpha \)-benzylxyxketone \textbf{149} (Scheme 60). The thermolysis experiments were carried out in three different solvents of increasing boiling points containing pyridine as a base to sequester the (2-nitrophenyl)selenic acid by-product from the reaction mixture (Scheme 60).

\begin{center}
\includegraphics[width=0.8\textwidth]{scheme60}
\end{center}

\textbf{Scheme 60}

Refluxing the selenoxides \textbf{146a} and \textbf{146b} in THF (67\(^\circ\)C) for 48 h failed to facilitate any significant decomposition and the \textsuperscript{1}H NMR spectrum of the crude product showed only the presence of returned starting material. At higher temperatures, by refluxing the selenoxides...
in toluene (110°C) and 1,2-dichlorobenzene (167°C), the material decomposed after 48 h and in each case a mixture of products was observed in the ¹H NMR of the crude product. The mixtures contained mainly an aromatic residue, probably corresponding to (2-nitrophenyl)selenic acid and its disproportionation products. Unfortunately, there was no evidence for the existence of 3-benzyloxy-2-dodecanone 149 in these mixtures. It is possible that the selenoxides 146a and 146b did eliminate in the desired way to produce 1-nonyllallene oxide 148 but this subsequently decomposed before it could be trapped by benzyl alcohol.

We later discovered that benzyl alcohol is not a good trapping agent for allene oxides (Vide Infra). As there seemed little hope of this method being viable for the generation and in situ capture of allene oxides we elected not to take this investigation any further. However, it might be prudent to re-examine this elimination in the presence of more powerful trapping agents, such as an alkoxide anion, in view of our subsequent findings (vide infra).
2.2 An Improved Method for the Generation and \textit{in situ} Trapping of Allene Oxides with Alcohols.

2.2.1. Introduction

It was anticipated that new chemical applications for allene oxides could be devised despite the fact that these heterocycles have been known for some time and a quite diverse range of chemistry has already been accomplished. The work described in this section focuses on nucleophilic ring-opening reactions of allene oxides. We speculated that if allene oxides could be generated under aprotic conditions and captured by nucleophilic ring-opening at the \( sp^3 \) epoxide carbon atom this would give rise to an enolate anion as the initial product. Such methodology would represent a novel route to such enolates. Interestingly, we envisaged that the geometry of the allene oxide double bond would determine the geometry of the enolate anion generated (Scheme 61).

![Scheme 61](image)

To date, nucleophilic ring-opening reactions of allene oxides have been studied under conditions where a proton source is present and so the enolate, we postulate is formed, is quenched to give only methyl ketone products. Capture of the enolate with other electrophiles would furnish more synthetically useful ketone products (Scheme 62).

![Scheme 62](image)
As we have already seen, there are few reliable methods for the generation and *in situ* capture of an allene oxide with nucleophiles. All of the examples mentioned below were discussed in Chapter One but are briefly discussed again in the context of the generation and *in situ* capture of allene oxides under aprotic conditions.

Chan and Ong's method involved generation of the allene oxide ring system by elimination adjacent to the epoxide ring within β-chlorosilyl epoxides such as 97 and 99. Treatment of these precursors with caesium fluoride facilitated elimination to generate the corresponding allene oxides which were captured *in situ* with a protic nucleophile, such as methanol, to give α-substituted ketones 98 and 100 (Scheme 62). Although this chemistry has been widely explored, it would not be directly suitable for aprotic reactions as the alcohol nucleophile also provides a proton source.

\[
\begin{align*}
\text{CsF} & \quad \text{MeOH} \\
97 & \quad 98 \\
99 & \quad 100
\end{align*}
\]

*Scheme 63*

Allene oxides generated by the epoxidation of allenes have also been captured by protic nucleophiles to give α-substituted ketones as the major products. Oxidation of simple allenes, such as 1,2-undecadiene, with hydrogen peroxide catalysed with cetylpyridinium peroxotungstophosphate (PWCP) in a protic solvent, such as ethanol, gave α-ethoxyketone 25 (Scheme 64). Unfortunately, lack of regioselectivity in the oxidation of unsymmetrical disubstituted allenes and the use of protic reaction conditions make this procedure unsuitable for the controlled production and alkylation of an enolate intermediate.

\[
\begin{align*}
\text{PWCP (2 mol%)} & \quad \text{EtOH/CH}_2\text{Cl}_2 \\
\text{EtOH} & \quad 71\%
\end{align*}
\]

*Scheme 64*
Chiral allene oxides have been generated under seemingly aprotic conditions by Kabat. Treatment of epoxy mesylate 150 with 1.95 equivalents of anhydrous tetra-\textit{n}-butylammonium fluoride (TBAF) resulted in the generation of an allene oxide intermediate which underwent nucleophilic attack by fluoride ion to give \( \alpha \)-fluoroketone 151 in 87\% yield and 97\% enantiomeric excess (Scheme 65).

\[ \text{n-C}_{10}\text{H}_{21}\text{O}^+\text{SiMe}_3 \xrightarrow{\text{MsCl/Py}} \text{n-C}_{10}\text{H}_{21}\text{O}^+\text{SiMe}_3 \xrightarrow{\text{TBAF, 1.95 eq}} \text{n-C}_{10}\text{H}_{21}\text{O}^+\text{SiMe}_3 \]

\[ \text{n-C}_{10}\text{H}_{21}\text{CO}^+\text{Me} \xrightarrow{87\%} \text{n-C}_{10}\text{H}_{21}\text{O}^+\text{SiMe}_3 \]

Scheme 65

We are aware of only one other example of allene oxide generation under truly aprotic conditions. Epibromohydrin and (\( R \))-3-cyanomethyl-4-phenyloxazoline 65 were treated with lithium di-\textit{iso}-propylamide (LDA) and tetramethylethylenediamine (TMEDA) at \(-110^\circ\text{C}\). This resulted in the formation of \( \alpha \)-substituted ketone 67, isolated in 75\% yield. The presence of an allene oxide as an intermediate in this reaction is implied by the formation of an \( \alpha \)-substituted ketone product. The transformation is thought to proceed by deprotonation of epibromohydrin at the epoxide methine carbon and subsequent dehalogenation to produce the parent allene oxide which undergoes nucleophilic attack by the carbanion of 65 (Scheme 66).

\[ \text{O} \xrightarrow{\text{LDA, TMEDA -110 \, ^\circ\text{C}}} \text{CN} \text{O} \xrightarrow{\text{H}^+\text{H}_2\text{O}} \text{CN} \text{O} \]

Scheme 66
2.2.2 Initial Experiments

Our initial aim was to devise aprotic conditions for the generation of allene oxides so that the chemistry depicted in Scheme 62 could be explored. We chose to use an elimination strategy and in order to familiarise ourselves with this chemistry we attempted to repeat some of the transformations described by Chan and Ong.\(^3\) Racemic β-Chloro-α-silylepoxide 97 was prepared in three steps and in moderate yield according to the literature procedure (Scheme 67).\(^3\) Generation of 1-decylallene oxide 152 by treatment of this material with caesium fluoride in the absence of any additional nucleophiles gave 3-chloro-2-tridecanone 153 in 65% yield (Scheme 67). This result compares well with the 68% yield reported by Chan and Ong.\(^3\)

\[
\begin{align*}
\text{Me}_3\text{Si} & \quad \xrightarrow{\text{i}} \quad n\text{-C}_{10}\text{H}_{21} \quad \text{Br} \quad \text{SiMe}_3 \quad \xrightarrow{\text{ii}} \quad n\text{-C}_{10}\text{H}_{21} \quad \text{Cl} \\
\text{Me} & \quad \xrightarrow{\text{iii}} \quad n\text{-C}_{10}\text{H}_{21} \quad \text{Cl} \quad \xrightarrow{\text{iv}} \quad n\text{-C}_{10}\text{H}_{21} \quad \text{O} \quad \text{SiMe}_3
\end{align*}
\]

*Reagents and Conditions:* i, t-BuLi, C\(_{10}\)H\(_{21}\)CHO, -78°C to R.T.; ii, SOCl\(_2\), Et\(_2\)O, R.T.; iii, m-CPBA, NaOAc, CH\(_2\)Cl\(_2\), R.T.; iv, CsF (1.1 eq), CH\(_3\)CN, R.T.

Scheme 67

However, generation of allene oxide 152 in the presence of methanol (3.0 eq) did not give 3-methoxy-2-tridecanone 98 as described in the literature.\(^1,3\) Instead, we found this reaction to be extremely problematic resulting in the isolation of a mixture of α-(substituted) ketones. The mixture was found to comprise of 3-chloro-2-tridecanone 153 (71%), 3-fluoro-2-tridecanone 154 (23%) and a small amount of 3-methoxy-2-tridecanone 98 (6%) (Scheme 68). The individual compounds were fully characterised and their relative amounts were determined by gas chromatography. 3-Fluoro-2-tridecanone 154 showed a 'double double doublet' at 4.55 ppm in the \(^1\)H NMR spectrum which was assigned as the methine hydrogen on the carbon directly bonded to the carbonyl group. A diagnostic \(^1\)H-\(^19\)F spin-spin coupling constant was detected (50.3 Hz) for this resonance.
Since the major product was found to be 3-chloro-2-tridecanone 153 it is reasonable to assume that the highly nucleophilic chloride ion produced as a by-product of allene oxide generation, must be reacting with allene oxide 152 more efficiently than any other nucleophile present in the reaction mixture. The formation of 3-fluoro-2-tridecanone 154 can be explained by the increase in solubility of caesium fluoride in acetonitrile in the presence of added methanol. Caesium fluoride is normally quite insoluble in acetonitrile but is completely soluble in methanol.

In order to prevent the formation of 3-chloro-2-tridecanone 153 we reasoned that a less nucleophilic leaving group in the allene oxide precursor was required. The corresponding epoxy mesylate 155, originally synthesised by Kabat as a homochiral compound, reacted under the same conditions to produce a mixture of 3-methoxy-2-tridecanone 98 and 3-fluoro-2-tridecanone 154 (Scheme 69). The preparation of this precursor is discussed later in this chapter.

This method removed all trace of 3-chloro-2-tridecanone 153 and gave a vastly improved yield of the methanol trapped allene oxide product, 3-methoxy-2-tridecanone 98. Unfortunately, 3-fluoro-2-tridecanone 154 was still produced in large quantities. We studied the behaviour of epoxy mesylate 155 under a variety of different conditions for elimination
and subsequent nucleophilic ring-opening to try to optimise the amount of α-alkoxyketones produced. These experiments and the product ratios are summarised in Scheme 70/Table 2.

![Scheme 70](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>F⁻</th>
<th>solvent</th>
<th>ROH</th>
<th>ROH eq</th>
<th>156%*</th>
<th>154%*</th>
<th>155%*</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>CsF</td>
<td>CH₃CN</td>
<td>MeOH</td>
<td>3</td>
<td>34</td>
<td>66</td>
<td>0</td>
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<tr>
<td>2</td>
<td>CsF</td>
<td>CH₃CN</td>
<td>MeOH</td>
<td>12</td>
<td>34</td>
<td>66</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>CsF</td>
<td>MeOH</td>
<td>MeOH</td>
<td>-</td>
<td>0</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>4</td>
<td>CsF</td>
<td>CH₃CN</td>
<td>EtOH</td>
<td>12</td>
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<td>CH₃CN</td>
<td>BnOH</td>
<td>3</td>
<td>25</td>
<td>75</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>TBAF</td>
<td>THF</td>
<td>MeOH</td>
<td>10</td>
<td>34</td>
<td>66</td>
<td>0</td>
</tr>
</tbody>
</table>

* ratio of products 156 and 154 and unreacted starting material 155 was estimated by G.C. analysis of the crude mixtures and is expressed as a percentage.

Table 2

Unfortunately, changing the nature of or increasing the quantity of alcohol (ROH) or by changing the source of fluoride ion did not shift the product ratio in favour of the α-(substituted)-ketone 156. In order to increase the nucleophilicity of the alcohol we examined the use of methoxide anion in these reactions (Scheme 71/Table 3). A catalytic amount of sodium hydride in the presence of three equivalents of methanol gave only a slightly better product ratio with respect to 3-methoxy-2-tridecanone 98 (Table 3, entry 1). However, when caesium fluoride (1.0 eq) and sodium methoxide (1.0 eq) were employed, prepared by the addition of methanol (10.0 eq) to sodium hydride (1.0 eq) in acetonitrile, clean conversion to 3-methoxy-2-tridecanone 98 was observed (Table 3, entry 2).
To our surprise, when caesium fluoride was omitted conversion to 3-methoxy-2-tridecanone 98 did occur but 50% of the epoxy mesylate 155 was recovered unchanged (Table 3, entry 3). This suggested that the alkoxide anion was both facilitating the elimination to generate the allene oxide and acting as the nucleophilic trapping component. Hence, increasing the amount of sodium methoxide to 2 eq in the absence of caesium fluoride and in a more suitable solvent effected clean conversion of 155 to 98 (Table 3, entry 4).

In summary, after much experimentation, conversion of the epoxy mesylate 155 to 3-methoxy-2-tridecanone 98 was accomplished with a twofold excess of sodium methoxide (Scheme 72). The sodium methoxide was prepared by the addition of sodium hydride (2 eq) to an excess of methanol (10 eq) in tetrahydrofuran and the epoxy mesylate 155 was added to the mixture at 0°C. The reaction was allowed to warm gradually to room temperature and was complete after 2.5 h. 3-Methoxy-2-tridecanone 98 was isolated in 63% yield following aqueous work-up and column chromatography.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>eq. CsF</th>
<th>Nu</th>
<th>98%*</th>
<th>154%*</th>
<th>155%*</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>CH₃CN</td>
<td>1</td>
<td>#cat. MeO⁻</td>
<td>50</td>
<td>50</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>CH₃CN</td>
<td>1</td>
<td>1 eq MeO⁻</td>
<td>100</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>CH₃CN</td>
<td>0</td>
<td>1 eq MeO⁻</td>
<td>50</td>
<td>0</td>
<td>50</td>
</tr>
<tr>
<td>4</td>
<td>THF</td>
<td>0</td>
<td>2 eq MeO⁻</td>
<td>100</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

* Ratio of products 98, 154 and of remaining unreacted starting material 155 was estimated by ¹H NMR of crude mixture and is expressed as a percentage.

# Catalytic amount (10%) of NaH added to 3 eq of Methanol.
We believe that the conversion of epoxy mesylate 155 to 3-methoxy-2-tridecanone 98 under these conditions proceeds by initial attack of methoxide anion on the silicon atom thus facilitating elimination to generate allene oxide 152. The second equivalent of methoxide anion then acts as the nucleophilic trap for this allene oxide. This mechanism and other possibilities are discussed later in this chapter. The method we have discovered overcomes the problems we encountered with similar chemistry described by Chan and Ong and, equally important, has the potential to be used for the generation of allene oxides under aprotic conditions (Vide Infra).

2.2.3 The Scope and Limitations of this New Method

Having discovered a new method for the generation and capture of an allene oxide with alcohol nucleophiles, we studied this reaction in more detail to assess its scope and limitations. A series of mesylate precursors were prepared in four steps from suitably substituted terminal acetylenes 156-160. The reaction sequence involved deprotonation of the terminal acetylenes 156-160 with n-butyllithium and subsequent reaction with chlorotrimethylsilane to give the corresponding 1-trimethylsilyl-2-(substituted)-acetylenes 161-165 (Scheme 73). Hydroalumination of these acetylenes in refluxing diethyl ether followed by addition of methyllithium and reaction with formaldehyde gas furnished (Z)-allylic alcohols 166-170 in reasonable yields (50-70%). The hydroalumination of silyl acteylenes is reported to give exclusively (Z)-1-alumino-1-alkenylsilanes when performed in ether, and indeed we observed only one product, the remainder being unreacted starting material. This reaction was problematic at first but was optimised by studying the rate of the hydroalumination step by G.C. analysis of the reaction mixture. Reaction of the lithium alkenylalanate, formed on addition of methyllithium, with formaldehyde was found to be most efficient if formaldehyde gas was passed into the reaction mixture at a fairly rapid rate. Care should be taken with the cracking of paraformaldehyde at 150-156°C! Allylic alcohols 166-170 were converted to epoxy alcohols 171-175 with tert-butyl hydroperoxide and a catalytic amount of vanadyl acetoacetonate (VO(acac)₂). As expected, epoxidation of allylic alcohol 168 occurred exclusively at the alkene double bond adjacent to the carbon bearing the hydroxyl group. Epoxy alcohols 171-175 were treated with methanesulfonyl chloride in dichloromethane containing an excess of triethylamine at 0°C to afford epoxy mesylates 155 and 176-179 (Scheme 73).
Reagents and conditions: i, n-BuLi, -78°C, Me₃SiCl; ii, DIBAL, MeLi, CH₂O; iii, VO(acac)₂, t-BuOOH, CH₂Cl₂, R.T.; iv, MeSO₂Cl, Et₃N, 0°C

Scheme 73

It was discovered that epoxy mesylates 155 and 176-179 were not stable to flash column chromatography and furthermore exhibited a propensity to decompose over a period of time. We found, however, when doing these studies that these compounds can be stored for 24 h or more in a freezer (ca. -5°C). The crude epoxy mesylates 155 and 176-179 were found to be of sufficient purity by ¹H NMR to be used in subsequent reactions without purification.

A sample of epoxy mesylate 155 left to stand at room temperature overnight decomposed by rearrangement to the mesyl ketone 180. Speculating that this rearrangement was acid catalysed we treated epoxy mesylate 155 with methanesulfonic acid in dichloromethane at room temperature for a few hours. This gave ketone 180 in 46% yield after aqueous work-up and column chromatography. Acyclic silyl epoxides are known to undergo acid catalysed rearrangement to carbonyl compounds where the carbonyl group appears on the carbon atom originally bearing the silicon group. We speculate that such a transformation could proceed via the mechanism proposed below (Scheme 74).
The epoxy mesylates 155, 176, 177 and 179 were reacted with a variety of alcohols using our modified reaction conditions (Scheme 75/Table 4). The reactions were generally performed by preparing the sodium alkoxide in tetrahydrofuran at 0°C from the appropriate alcohol R₂OH (3 - 10 eq depending of the volatility of the alcohol) and sodium hydride (2.1 eq). The appropriate epoxy mesylate was dissolved in a small amount of tetrahydrofuran and added to the sodium alkoxide at 0°C then the reaction mixture was allowed to gradually warm to room temperature. The reactions were followed by thin-layer chromatography and were generally complete within 2-3 h.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Mesylate</th>
<th>R²</th>
<th>Ketone</th>
<th>% Yield*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>155</td>
<td>Me</td>
<td>98</td>
<td>63</td>
</tr>
<tr>
<td>2</td>
<td>155</td>
<td>PhCH₂</td>
<td>181</td>
<td>66</td>
</tr>
<tr>
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<td>i-Pr</td>
<td>182</td>
<td>55</td>
</tr>
<tr>
<td>4</td>
<td>155</td>
<td>H₂C=CHCH₂</td>
<td>183</td>
<td>31</td>
</tr>
<tr>
<td>5</td>
<td>176</td>
<td>Me</td>
<td>184</td>
<td>61</td>
</tr>
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<td>176</td>
<td>PhCH₂</td>
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<td>7</td>
<td>177</td>
<td>Me</td>
<td>186</td>
<td>55</td>
</tr>
<tr>
<td>8</td>
<td>177</td>
<td>PhCH₂</td>
<td>187</td>
<td>54</td>
</tr>
<tr>
<td>9</td>
<td>179</td>
<td>PhCH₂</td>
<td>188</td>
<td>&lt;20%</td>
</tr>
</tbody>
</table>

* Yield of pure isolated material after column chromatography.
We found that a variety of alcohols, including primary, secondary and benzylic alcohols, can be employed giving the corresponding 3-alkoxy-2-ketones (Table 4, Entries 1-3 and 5-8) in reasonable and consistent yields. The reaction of epoxy mesylate 155 with allyl alcohol was not clean and only a low yield of ketone 183 was obtained (Table 4, Entry 4). The reaction of sodium tert-butoxide with epoxy mesylate 155 was attempted but was inefficient giving only a low conversion to 3-tert-butoxytridecan-2-one. We found that differences in the nature of the side-chain on the allene oxide could be incorporated without detrimental effects on the process (Table 3, entries 5-8). However, epoxy mesylate 179 bearing a sterically encumbering tert-butyl group gave a mixture of products from which only a small amount of the desired ketone 188 was detected.

Reaction of epoxy mesylate 155 with two equivalents of sodium phenoxide gave only $S_N2$ displacement of the mesylate group by the phenoxide anion to afford epoxide 190 (31%) (Scheme 76). This reaction did not go to completion in the usual reaction time which is reflected in the rather modest yield of epoxide 190.

To further test the scope of this chemistry we prepared secondary alcohol 192. This alcohol was made by oxidation of epoxy alcohol 171 with the tetra-$n$-propylammonium perruthenate (TPAP) / $N$-methylmorpholine-$N$-oxide (NMO) system to the corresponding aldehyde 191, followed by reaction with methylmagnesium iodide (Scheme 77). We found that oxidation of 171 with pyridinium chlorochromate in dichloromethane, as reported by Kabat, resulted in a mixture of products. Similarly Swern oxidation failed to give clean conversion to the aldehyde.

Reagents and Conditions: i, TPAP, NMO, 4Å molecular sieves, CH$_2$Cl$_2$, R.T.; ii, MeMgl, Et$_2$O, 0°C-R.T.

Scheme 77
Only one diastereomer of 3,4-epoxy-3-(trimethylsilyl)-tetradecan-2-ol 192 was isolated from the conversion of 191 with methylmagnesium iodide. However, in view of the very low yield of product obtained we are unable to state with any conviction that this process is stereospecific. The relative stereochemistry of 192 was assigned as (2S*,3R*,4S*) by comparison of the $^1$H NMR chemical shifts of protons $H_a$ and $H_b$ with literature values. We prepared a mixture of $syn$ and $anti$ diastereomers of 192 by the addition of methyl lithium to 191, for comparison with literature data for similar compounds (Figure 3). A mixture of the $syn$ and $anti$ diastereomers of 193 and the $anti$ diastereomer of 194 have been described by other researchers (Figure 3). Homochiral alcohol 194 was prepared via a kinetic resolution process of the corresponding racemic olefin using a Sharpless asymmetric epoxidation and assignment of the absolute configuration was made from the absolute configuration of the unreacted enantiomer of the olefin and the configuration of the tartrate ester used. The relative stereochemistry of the mixture of $anti$ and $syn$ diastereomers of 193 was assigned by comparison with a single diastereomer of a crystalline analogue, prepared under the same reaction conditions, of which the relative stereochemistry was established by single-crystal X-ray diffraction.

Protons $H_a$ and $H_b$ in the $^1$H NMR spectrum of 194, a close analogue of 192, have almost identical chemical shifts to $H_a$ and $H_b$ in 192. The $^1$H NMR data for the mixtures of $syn$ and $anti$ diastereomers of 192 and 193 were compared and it became apparent that signals for $H_a$
and H_b in both _syn_ diastereomers were upfield of those for the _anti_ diastereomers. Hence, the relative stereochemistry of 192 was assigned as (2S*, 3R*, 4S*). The assignment is consistent with the fact that the addition of Grignard reagents to epoxy aldehydes favours the formation of the (2S*, 3R*, 4S*) diastereomer. 87

Secondary epoxy alcohol 192 was mesylated to give epoxy mesylate 195 which was treated with sodium methoxide in tetrahydrofuran. The reaction was clean and efficient as for the primary epoxy mesylates, furnishing 4-methoxy-3-tetradecanone 196. This example is important to our studies as it shows that our method can be used to prepare carbonyl compounds other than just methyl ketones via the corresponding 1,3-disubstituted allene oxide (Scheme 78). We speculate that E2 elimination of the epoxy mesylate 195 would furnish the (E)-allene oxide, assuming that elimination takes place via an _anti_-periplanar arrangement. No studies were undertaken to determine whether this hypothesis is correct.

Further studies to vary the nature of the substituent at C-1 of the mesylate precursor were unsuccessful. Ethyl-substituted epoxy mesylate 198 was successfully prepared from the corresponding secondary alcohol 197, however, reaction with sodium benzyloxide produced a mixture of at least three products. One of the products could be assigned as 3-benzyloxy-3-quindecane 199 by 1H NMR but was inseparable from the other components by column chromatography (Scheme 79). Phenyl-substituted secondary alcohol 200 was prepared using a similar route but was found to yield a mixture of products under the mesylation conditions (Scheme 79). This mesylate being benzylic, secondary and _β_- to silicon shows a high propensity to ionise to the corresponding carbocation which presumably promotes decomposition.
2.2.4 Mechanistic Studies.

We suggest that the transformation of an epoxy mesylate such as 201 to an α-alkoxyketone 204 by reaction with two equivalents of a sodium alkoxide proceeds via initial attack of the alkoxide anion (RO⁻) on the silicon atom of 201 which facilitates E2 elimination to form the corresponding allene oxide 202. The formation of the strong silicon-oxygen (Si-O) bond (530 kJ mol⁻¹) provides a powerful driving force for this reaction. This allene oxide is subsequently attacked by another molecule of alkoxide anion at the sp³ epoxide ring carbon causing the epoxide ring to open furnishing enolate 203. Quenching of this enolate with either excess alcohol present in the reaction mixture or on aqueous work-up would account for the formation of the observed α-alkoxyketone 204 (Scheme 80).

Of course, one can envisage alternative mechanisms for this interconversion that do not involve an allene oxide intermediate. Nucleophilic opening of the epoxide ring of 201 with alkoxide anion would give α-silyl alkoxide 205 which could undergo a Brook type rearrangement to give the isomeric silyloxy carbanion 206.⁸⁸ Expulsion of the mesylate group would furnish silyl enol ether 207.⁸⁹ Hydrolysis of this silyl enol ether during aqueous work-up would then furnish the observed α-alkoxyketone product 204 (Scheme 81).
However, it is known that $\alpha,\beta$-epoxy silanes tend to undergo nucleophilic attack at the $\alpha$- rather than the $\beta$-carbon. Ring-opening of epoxy mesylate 201 at the $\alpha$-position by alkoxide anion would, most likely, be followed by a Peterson type elimination to afford enol ether 208. The enol ether is likely to be hydrolysed on aqueous work up to give ketone 209 or to undergo displacement of the mesylate group by excess alkoxide anion to afford, on hydrolysis, ketone 210 (Scheme 82). In any case, we cannot perceive any mechanism by which the observed $\alpha$-alkoxyketone products could be formed by nucleophilic attack of alkoxide anion at the $\alpha$-carbon of epoxy mesylate 201.

Attempts were made to gain direct evidence for an allene oxide intermediate in the reaction. Subsequent studies established that treatment of epoxy mesylate 155 in tetrahydrofuran containing 18-crown-6 (2.0 eq) at -78°C with potassium methoxide (2.0 eq) also effects clean
conversion to 3-methoxy-2-tridecanone 98 (Vide Infra). We envisaged that this modified procedure may enable us to observe a transient allene oxide using low temperature $^1$H NMR. Hence, epoxy mesylate 155 dissolved in $d_8$-tetrahydrofuran containing 18-crown-6 was treated with potassium methoxide in an NMR tube at -70°C. $^1$H NMR spectra of the reaction mixture were acquired at -70°C at 20 min intervals. Unfortunately no signals were detected that could be assigned to allene oxide 152 (Scheme 67).

Strong indirect evidence for the involvement of an allene oxide in our process was provided by the reaction of mesylate precursor 178 with sodium methoxide. Unlike the 3-alkyl-substituted precursors the reaction of this phenyl-substituted epoxy mesylate 178 formed a 2:3 mixture of ketone 211 and ester 104 respectively (Scheme 83). These two products were separated by column chromatography and fully characterised. The $^1$H NMR data for ester 104 was consistent with data reported by Chan and Ong. Allene oxides substituted at the $sp^3$ carbon with an aryl group have been reported to rapidly rearrange to the corresponding cyclopropanone (Chapter One, Scheme 37). Subsequent nucleophilic attack occurs at the carbonyl carbon of the cyclopropanone producing dihydrocinnamate derivatives. The isolation of ester 104 in the reaction of aryl-substituted epoxy mesylate 178 with sodium methoxide suggests that this reaction proceeds via an allene oxide which is in equilibrium with the corresponding cyclopropanone (Scheme 83). The alternative mechanistic proposals presented (Schemes 81 and 82) cannot readily account for the formation of this ester.

![Scheme 83](image-url)
2.3 Experimentation with Other Nucleophiles

In order to extend the scope of this chemistry we examined the use of a variety of different nucleophiles that would incorporate different heteroatoms into the desired ketone products. Epoxy mesylate precursor 155 was used in all of these studies.

2.3.1 Nitrogen Nucleophiles

A series of experiments were undertaken in an effort to produce α-azidoketones via an allene oxide. Azide anion was chosen as the nitrogen nucleophile, in the first instance, as it is highly nucleophilic and can be readily converted to the amino functionality by reduction. Simple replacement of sodium alkoxide with excess sodium azide failed to produce any of the desired α-azidoketone. This may be rationalised by the poor solubility of sodium azide in tetrahydrofuran.

Next, we experimented with sodium azide in dimethylsulfoxide in the presence of one equivalent of caesium fluoride. This reaction was sluggish and did not reach completion after 20 h. Epoxide 212 was isolated in 46% yield, the result of direct nucleophilic attack at C-1 of the epoxy mesylate giving net substitution of the mesylate group (Scheme 84). Failure of azide anion to trigger the allene oxide generation by attack at the silicon atom may be rationalised in terms of the strength of the silicon-nitrogen (Si-N) and silicon-oxygen (Si-O) bonds formed. For example, the Si-O bond in methoxytrimethylsilane is reported to have a bond dissociation energy of 531 kJ mol\(^{-1}\) and so, as we have previously suggested, its formation may provide the driving force for the alkoxide triggered elimination. The corresponding Si-N bond (320 kJ mol\(^{-1}\)) is considerably weaker.

\[
\begin{align*}
\text{n-C}_{10}\text{H}_{21} & \text{SiMe}_{3} \quad \text{OMs} \\
\text{NaN}_3 (3 \text{ eq.), CsF (1.5 eq)} & \quad \text{DMSO, 46\%} \\
\text{n-C}_{10}\text{H}_{21} & \text{SiMe}_{3} \quad \text{N}_3
\end{align*}
\]

Scheme 84

When the solvent was changed to acetonitrile, two azide containing products were obtained in approximately equal amounts. However, the reaction was slow and did not reach completion after 3 days. \(^1\)H NMR of the isolated mixture of the two products indicated the presence of epoxide 212 and the desired product 3-azido-2-tridecanone 213 (Scheme 85).
We presume that 3-azido-2-tridecanone 213 is the product of nucleophilic ring-opening by azide anion of the allene oxide which is generated by attack of fluoride at silicon atom of the epoxy mesylate. Competitive formation of the α-fluoroketone 154 was not observed because azide anion is a good nucleophile. In order to promote the reaction of the epoxy mesylate with fluoride ion, over the reaction of epoxy mesylate with azide, a tenfold excess of caesium fluoride was used with a threefold excess of sodium azide. This reaction reached completion after 3 h to give one major product. This was identified as 3-azido-2-tridecanone 213 and was isolated by column chromatography in 33% yield (Scheme 86). 1H NMR data was consistent with 3-azido-2-tridecanone 213 and the I.R. showed absorbances at 2104 and 1725 cm⁻¹ which are consistent with the proposed structure. Unfortunately this material was not very stable and we have been unable to fully characterise it. Not surprisingly, with the large excess of caesium fluoride employed, a minor product (5%) was identified as 3-fluorotridecan-2-one 151.

By analogy with the alkoxide anion experiments, we reasoned that a lithium amide might furnish the corresponding α-amino ketone via an allene oxide. Benzylamine was treated with n-butyllithium at 0°C in tetrahydrofuran to produce a solution of lithium benzyl amide. A twofold excess of this solution was added to epoxy mesylate 155 dissolved in tetrahydrofuran at 0°C. All of the epoxy mesylate was consumed at 0°C in 1.5 h to give two products which were separated by column chromatography. The least polar fraction was identified as alcohol 171 (22%) and further elution gave epoxy alcohol 214 (32%). Alcohol 171 had previously been prepared and fully characterised (Vide Supra) and alcohol 214 was identified.
by $^1$H and $^{13}$C NMR in comparison with the homologue ($R = C_9H_{19}$) 144 which had also been previously prepared (Vide Supra) (Scheme 87).

We believe alcohol 171 is produced as a result of nucleophilic attack of the amide anion at the sulfur atom of the mesylate group of 155. We found that alcohol 214 was formed when alcohol 171 was stirred with lithium benzylamide in tetrahydrofuran at 0°C with gradual warming to room temperature. After 16 h this reaction had not gone to completion by thin layer chromatography and subsequent aqueous work-up and column chromatography gave epoxy alcohol 214 in 28% yield, the remainder being unreacted starting material. This result suggests that alcohol 171 is the initial product formed, upon treatment of epoxy mesylate 155 with lithium benzylamide, and subsequently undergoes nucleophilic attack by the amide anion at silicon, resulting in desilylation to give alcohol 214.

\[
\begin{align*}
\text{n-C}_{10}\text{H}_{21} & \quad \text{O} \quad \text{SiMe}_{3} \\
\text{OMs} & \quad \xrightarrow{(\text{PhCH}_{2})\text{HNLi}} \\
\text{THF, 0°C} & \quad \text{171} \\
\text{OH} & \quad \text{155} \\
\end{align*}
\]

Scheme 87

2.3.2 Sulfur Nucleophiles

Thiolate anions were found to react efficiently with the epoxy mesylates in tetrahydrofuran but unfortunately not in the expected manner. Reaction of epoxy mesylate 155 with two equivalents of sodium phenylthiolate gave only $S_N2$ displacement of the mesylate group by the thiolate anion to afford epoxide 215 (67%) (Scheme 88). This can be compared to the reaction of sodium phenoxide with epoxy mesylate 155 (Vide Supra). Phenoxide and phenylthiolate anions are known to be less nucleophilic than their aliphatic counter-parts due to delocalisation of the lone pair of electrons on the heteroatom into the aromatic system. This may account for these aryl anions showing a propensity to attack the epoxy mesylate at carbon rather than silicon.

\[
\begin{align*}
\text{n-C}_{10}\text{H}_{21} & \quad \text{O} \quad \text{SiMe}_{3} \\
\text{OMs} & \quad \xrightarrow{\text{NaSPh, THF, 0°C}} \\
\text{68%} & \quad \text{215} \\
\end{align*}
\]

Scheme 88
The reaction of sodium ethylthiolate with the epoxy mesylate gave an inseparable mixture containing two major products one of which was identified as β-thioepoxide 216. Again, epoxide 216 is the product of direct SN2 displacement of the mesylate group (Scheme 89). None of the desired α-alkyl thioketone was detected by 1H NMR spectroscopy. This can be explained by the fact that sulfur nucleophiles are known to be 'softer' than oxygen nucleophiles as they are less electronegative, highly polarisable and easy to oxidise.

\[ \text{NaSEt, THF} \quad n-\text{ClOH}_2 \quad \text{SiMe}_3 \quad \xrightarrow{\text{mix}} \quad n-\text{C}_{10}\text{H}_{21} \quad \text{SiMe}_3 \quad \text{SEt} + \text{mixture} \]

Scheme 89

### 2.3.3 Carbon Nucleophiles

Experiments were performed using sodium cyanide in an attempt to incorporate additional carbon atoms into the ketone product. In the absence of caesium fluoride using sodium cyanide (2.0 eq) in tetrahydrofuran no reaction occurred with epoxy mesylate 155. This could be rationalised by the insolubility of sodium cyanide in tetrahydrofuran. Unlike with alkoxide anions, the formation of the Si-C bond, which has a bond dissociation energy of 318 kJ mol\(^{-1}\) may not be a sufficient driving force to trigger this elimination reaction. In an analogous manner to the experiments performed with sodium azide we attempted to overcome this problem by treating 155 with caesium fluoride (1.0 eq) and sodium cyanide (1.5 eq) in dimethyl sulfoxide. However, after stirring for 2 days at room temperature only starting material was recovered, as indicated by the 1H NMR of the crude product. To date there is only one example of the use of a carbon nucleophile to attack an allene oxide in the literature (Vide Supra). 30

In summary, the incorporation of other heteroatoms in our process has proven to be problematic due to differences in the nature of the anions and their propensity to attack the epoxy mesylate precursor at either silicon, carbon or sulfur. In most cases attack of these different nucleophiles at silicon in order to trigger elimination is not a favourable process because the formation of the silicon-heteroatom bonds is not a sufficient driving force for the reaction to occur. The Si-N, Si-S and Si-C bonds are relatively weaker and have smaller bond dissociation energies (ca. 300 kJ mol\(^{-1}\)) compared with the Si-O (531 kJ mol\(^{-1}\)) and Si-F (807
kJ mol$^{-1}$) bonds. The formation of these strong bonds, Si-O and Si-F, clearly provides a driving force for the reaction of alkoxide and fluoride anions with an epoxy mesylate such as 155 to furnish allene oxides.
Chapter Three

The Chemistry of Chiral, Non-Racemic Allene Oxides
3.1 Introduction

We were interested in establishing if we could extend our methodology to the synthesis of homochiral α-alkoxyketones. In view of the quite basic reaction conditions we were uncertain as to whether the conversion of a homochiral epoxy mesylate to a homochiral α-alkoxyketone by treatment with an alkoxide anion could be accomplished without product racemisation (Scheme 90).

There are just three reports in the literature on the generation and capture of chiral allene oxides. Kabat successfully converted chiral epoxy mesylate 150, prepared from the corresponding epoxy alcohol 217 (97% ee), into α-fluoroketone 151 in 87% yield and 97% enantiomeric excess (Scheme 91).31

Perhaps more interestingly, this author subsequently reported that epoxymesylate 72 produced as a mixture of diastereomers (97% ee), upon treatment with tetra-n-butylammonium fluoride (1.0 eq), and a tenfold excess of water furnished (R)-γ-hydroxy-β-keto phosphonates 73 in ca. 74% yields and 96-97% enantiomeric excess (Scheme 92).32
Direct evidence for the existence of a homochiral allene oxide has been provided by the isolation of \((S)-1\text{-}\text{tert}-\text{butylallene oxide}\) by Konoike and co-workers. This was accomplished by implementing the \(\beta\)-elimination of a epoxy mesylate \(76\) (Scheme 93). Deoxystannylation was achieved under conditions for mesylation of the hydroxyl group where chloride ion present in the reaction mixture triggered the E2 elimination.

3.2 Initial Experiments

Chiral mesylate precursor \(150\) was prepared from the corresponding chiral epoxy alcohol \(217\) which, in turn, was prepared from \((Z)\)-allylic alcohol \(166\) via the Sharpless asymmetric epoxidation. Using L-(+)-diethyl tartrate, \((2R,3S)\)-epoxy alcohol \(217\) was produced in reasonable yield and high enantiomeric excess (84\% ee) (Scheme 94). The absolute configuration of this epoxide was assigned on the basis of literature precedent. The enantiomeric excess of this epoxy alcohol, and all other examples described in this chapter, was determined by derivatisation of a small quantity of the alcohol with \((R)-(\text{-})\text{\alpha}-\text{methoxy-}\text{-\alpha}-\text{(trifluoromethyl)phenylacetyl chloride}\) (MPTA-Cl). The relative amounts of
the two resulting diastereomeric MPTA esters (Figure 3) were measured from integrals of the epoxide signals in the $^1$H NMR spectrum (Appendix 1).

![Figure 3](image)

Chiral epoxy alcohol 217 was converted to the corresponding epoxy mesylate 150 under standard conditions. This mesylate 150 was treated with exactly two equivalents of sodium methoxide by addition of a precise volume of a 1.0 M stock solution. The reaction was started at 0°C and then allowed to gradually warm to room temperature. After 2 h the reaction was complete and 3-methoxy-2-tridecanone was isolated by column chromatography following aqueous work-up. The enantiomeric excess for this product was estimated from the $^1$H NMR spectrum of a sample containing 0.4 equivalents (with respect to the ketone) europium tris[3-(heptafluoropropyl-hydroxymethylene)-(+-)camphorate], [(+-)-Eu-(hfc)$_3$]. The $^1$H NMR spectrum of racemic 3-methoxy-2-tridecanone 98 containing (+)-Eu-(hfc)$_3$ showed two signals centered at 3.36 ppm that corresponded to the methyl group adjacent to the carbonyl. Hence, the relative amounts of the two enantiomers of 3-methoxy-2-tridecanone could be estimated from the integration of these two signals. Unfortunately, the material produced in this experiment was found to be essentially racemic (Scheme 95).

![Scheme 95](image)

Reagents and Conditions: i, MeSO$_2$Cl, Et$_3$N, DCM; ii, NaOMe (2 eq), THF, 0°C-R.T.

Racemisation at C-3 of 3-methoxy-2-tridecanone suggests that, under these reaction conditions, the proton at this position was abstracted by a base to give the thermodynamic enolate which was subsequently re-protonated from both the Re face and Si face of the enolate. A number of control experiments were performed to test the ability of methoxide anion to abstract the protons from both C-1 and C-3 of 3-methoxy-2-tridecanone. Racemic samples of 3-methoxy-2-tridecanone 98 and epoxy mesylate 155 were treated with sodium methoxide and an excess of $d_1$-methanol in tetrahydrofuran at 0°C with gradual warming to
room temperature. The reaction of epoxy mesylate 155, gave 3-methoxytridecan-2-one which had almost complete deuterium incorporation at both C-1 and C-3 (Scheme 96). When 3-methoxy-2-tridecanone 98 (racemic) was stirred under the same conditions for a similar period of time it underwent proton deuterium exchange to the extent that deuterium was almost completely incorporated at C-1 and C-3 (Scheme 96). The level of deuterium incorporation was estimated from the reduction in size of the integrals for appropriate signals in the $^1H$ NMR spectrum. An accurate mass ion for 3-methoxy-2-tridecanone that was substituted with four deuterium atoms was obtained; observed (MH$^+$); 233.2419, C$_{14}$H$_{25}$O$_2$D$_4$ requires; 233.24187.

From these experiments it can be deduced that sodium methoxide is capable of proton abstraction from C-1 and C-3 of 3-methoxy-2-tridecanone either by direct reaction with the ketone or when it is formed in situ from epoxy mesylate 155.

It is reasonable to assume that the kinetic enolate is formed initially as a result of ring-opening of the allene oxide by methoxide anion. Direct interconversion of the kinetic to the thermodynamic enolate would seem unlikely. It is likely that equilibribration between the enolates proceeds via the ketone suggesting protonation of the initially formed enolate. Hence, a proton source must be available under the reaction conditions to facilitate racemisation (Scheme 97).

![Scheme 96](image)

Scheme 96

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![Scheme 97](image)

Scheme 97

63
In a further control experiment a sample of enantiomerically enriched 3-methoxy-2-tridecanone 218 (ca. 80%ee) was treated with sodium methoxide (2.00 equivalents) in anhydrous tetrahydrofuran at 0°C and gradually warmed to room temperature over 4 h (Scheme 98). The re-isolated ketone was found to be racemic indicating that these reactions are inappropriate for the synthesis of homochiral α-alkoxyketones.

![Scheme 98](image)

We concluded that using sodium methoxide for conversion of chiral, non-racemic epoxy mesylate 150 to enantiomerically enriched 3-methoxy-2-tridecanone via a homochiral allene oxide was not feasible as at some stage during this interconversion racemisation of the product was occurring.
3.3 Experimentation with Lithium and Potassium Counter Ions.

To try to overcome product racemisation in these reactions, the effects of reaction temperature and different metal counter ions were investigated. The results of these experiments are summarised in Scheme 99/Table 5.

\[
\begin{align*}
\text{n-C}_{10}H_{21} \text{O} & \overset{\text{NaOMe, T'C, THF}}{\text{SiMe}_3} \text{OMes} & \overset{\text{LiOMe, T'C, THF}}{\text{n-C}_{10}H_{21} \text{O} \text{Me}} \\
\end{align*}
\]

Scheme 99

<table>
<thead>
<tr>
<th>+M'OMe</th>
<th>T'C</th>
<th>time</th>
<th>218 (% yield)*</th>
<th>218 (% ee)#</th>
</tr>
</thead>
<tbody>
<tr>
<td>NaOMe</td>
<td>0 to R.T.</td>
<td>2-4 h</td>
<td>63</td>
<td>0</td>
</tr>
<tr>
<td>KOMe</td>
<td>0 to R.T.</td>
<td>2-4 h</td>
<td>54</td>
<td>0</td>
</tr>
<tr>
<td>LiOMe</td>
<td>R.T.</td>
<td>7 days</td>
<td>8</td>
<td>ca.50</td>
</tr>
<tr>
<td>NaOMe</td>
<td>-78</td>
<td>6 h</td>
<td>&lt;5</td>
<td>-</td>
</tr>
<tr>
<td>KOMe</td>
<td>-78</td>
<td>6 h</td>
<td>26</td>
<td>ca. 80</td>
</tr>
</tbody>
</table>

* Isolated yield after column chromatography.

# Enantiomeric excess was estimated from the integration of the \(^1\text{H}\) NMR spectrum in the presence of (+)-Eu-(hfc)\(_3\) (CDCl\(_3\)). Racemic material 98 was used for comparison.

Table 5

A 1.0 M solution of sodium methoxide was prepared as previously described and potassium methoxide was prepared in a similar way using potassium hydride. Lithium methoxide was prepared by the addition of \(n\)-butyllithium to methanol in tetrahydrofuran to form a 1.0 M solution. From the table it can be seen that racemisation in these reactions occurs at higher temperatures with sodium and potassium counter ions and to some extent at room temperature with a lithium counter ion. At low temperature (-78°C) sodium methoxide did not react with epoxy mesylate 150 to any extent. However, potassium methoxide did react with this epoxy mesylate at -78°C and importantly 3-methoxy-2-tridecanone 218 isolated from this reaction was found to be enantiomerically enriched. The enantiomeric excess was estimated by \(^1\text{H}\) NMR in the presence of (+)-Eu-(hfc)\(_3\) to be of a similar magnitude (ca. 80% ee) to that of the epoxy alcohol 217 (84% ee) from which it was derived. It should be noted that this successful low temperature reaction was also quenched at -78°C with diethyl ether containing 1% acetic acid.
Unfortunately, the reaction of potassium methoxide with epoxy mesylate 150 at -78°C was very sluggish and produced 218 in only 26% yield after 6 h. In order to increase the reactivity of the methoxide anion, a similar experiment was performed in which 18-crown-6 (2 equivalents) was added to the reaction mixture. This crown ether is known to solvate potassium cations leaving a 'naked' and more nucleophilic anion. We found that under these conditions, the yield of 218 increased to 52% without eroding the enantiomeric excess (Scheme 100). It was interesting to observe that a threefold excess of the pre-prepared potassium methoxide solution can be employed at this temperature without causing product racemisation.

\[
\begin{align*}
\text{n-C}_{10}\text{H}_{21} & \quad \text{OMs} & \quad \text{KOMe (2.0 eq), THF} & \quad \text{n-C}_{10}\text{H}_{21} \\
\text{150} & \quad \text{OMe} & \quad 18\text{-crown-6 (2.0 eq), -78 °C} & \quad 218 \\
\end{align*}
\]

* Enantiomeric excess was determined from the integration of epoxide signals in the $^1$H NMR spectrum of the MPTA ester of the corresponding epoxy alcohol. Racemic material 171 was used for comparison.

† Enantiomeric excess was estimated from the integration of the $^1$H NMR spectrum in the presence of (+)-Eu(hfc)$_3$ (CDCl$_3$). Racemic material 98 was used for comparison.

\textbf{Scheme 100}

Experiments were performed in the presence and absence of 18-crown-6 using potassium 1-naphthalmethoxide at -78°C (Scheme 101). In each case the enantiomerically enriched 3-(1-naphthalenemethoxy)-2-tridecanone 219 was analysed using chiral HPLC in order to obtain more accurate measurements of the enantiomeric excess (Appendix 2). This showed that there was a slight reduction in the enantiomeric excess when the crown ether was employed. However, the small erosion in selectivity is acceptable in light of the much improved isolated yield of the homochiral 3-alkoxy-2-tridecanone 219.
Chiral epoxy alcohols 220 and 221 were prepared by epoxidation of the corresponding (Z)-allylic alcohols 167 and 168 using the Sharpless asymmetric epoxidation in reasonable yields and high enantiomeric excess (Scheme 102). L-(+)-diethyl tartrate was used in each case and the absolute configurations were be assigned as (2R,3S)-220 and (2R,3S)-221 on the basis of literature precedent.92

* Enantiomeric excess was determined from the integration of epoxide signals in the \(^1\)H NMR spectrum of the MPTA ester. Racemic materials 172 and 173 were used for comparison.

Scheme 102
Epoxy alcohols 220 and 221 were converted to the corresponding epoxy mesylates 222 and 223 under standard conditions. Epoxy mesylate 222 was treated with potassium 1-naphthalenemethoxide (2.0 eq) and 18-crown-6 (2.0 eq) at -78°C to furnish α-alkoxyketone 224 in 53% yield and 83% enantiomeric excess. Similarly, epoxy mesylate 223 was treated with potassium benzyloxide (2.0 eq) and 18-crown-6 (2.0 eq) at -78°C to give α-alkoxyketone 225 in 52% yield and 82% enantiomeric excess (Scheme 103).114

![Chemical structures](image)

# Enantiomeric excess was determined by chiral HPLC [Chiralcel OD HPLC column, λ = 254 nm, 2.0% iso-propanol/hexane, 2.0 ml/min: 9.83 min (major), 11.21 min (minor)]. Racemic material was used for comparison.

† Enantiomeric excess was estimated by 1H NMR in the presence of (+)-Eu(hfc)₃ (CDCl₃) Racemic material 187 was used for comparison.

Scheme 103
3.4 Determination of the Absolute Configuration of the α-Alkoxyketone Products

A sample of homochiral α-benzyloxyketone 225 (82% ee) produced by reaction of homochiral epoxy mesylate 223 with potassium benzyloxide and 18-crown-6 (Vide Supra) was reduced by palladium catalysed hydrogenation to give 3-hydroxyoctan-2-one 226, albeit in rather poor yield (15%). No attempts were made to optimise this process as sufficient material was produced for our purposes. The optical rotation of this material was measured on the J-line (mercury, 578 nm), [α]$_D^{25}$ = -40 (c 0.03, CHCl$_3$), and was compared with the literature value for (+)-(3S)-hydroxyoctan-2-one (98%ee) [α]$_D^{25}$ = +91 (c 0.03, CHCl$_3$).95 This literature assignment was made on the basis of chiral G.C. analysis of the corresponding diol as compared with an authentic sample of the (2S, 3S)-diol. Our observed optical rotation was of opposite sign to the literature value for (+)-(3S)-hydroxyoctan-2-one and thus it was concluded that 3-hydroxyoctan-2-one 226 possessed the (3R) configuration (Scheme 104).

We cannot account for the discrepancy in the magnitude of our rotation in comparison with the literature value, and it may indicate partial racemisation during the hydrogenation step. However, this does not effect the outcome of this absolute configuration determination. From these studies we conclude that nucleophilic opening of the allene oxide by the potassium alkoxides proceeds with net stereochemical inversion.

In summary, Sharpless asymmetric epoxidation of (Z)-2-(trimethylsilyl)-2,7-octadien-1-ol 168 with L-(+)-diethyl tartrate gave (2R,3S)-epoxy-3-(trimethylsilyl)-7-octen-1-ol 221 in 85% enantiomeric excess which when converted to epoxy mesylate 223 and treated with potassium benzozone and 18-crown-6 at -78°C gave (3R)-benzyloxy-7-octen-2-one in 82% enantiomeric excess via a homochiral allene oxide intermediate (Scheme 105).
Our investigation into the nucleophilic ring-opening reactions of allene oxides has shown that chiral allene oxides can be generated and trapped by alcohol nucleophiles under the simple reaction conditions to give chiral, non-racemic α-alkoxyketones and α-hydroxyketones. Hence, our methodology represents an unusual but potentially useful approach to these classes of compound.

**3.5 Attempts to Effect a Three Component Coupling of an Allene Oxide**

Having successfully devised an asymmetric variant of the allene oxide nucleophilic ring opening reaction, we next chose to examine whether three component couplings could be achieved using this methodology. At the stage in the reaction when the generation and *in situ* nucleophilic ring-opening of the allene oxide by methoxide anion is complete, we speculate that a potassium enolate should be present in solution. Byproducts from the initial reaction MeSO₂O⁻ K⁺ and MeO-SiMe₃ should also be present in this solution. Quenching of this enolate intermediate with an electrophile (E⁺) added to the reaction mixture would result in the construction of an additional chemical bond (Scheme 106). We hoped that addition of a reasonably strong alkylating agent at this point would result in C-alkylation of the α-methoxyketone product.
We undertook a series of experiments in which a variety of simple electrophiles were added to the reaction mixture upon consumption of the racemic epoxy mesylate 155. Firstly, the addition of simple alkyl halides to the reaction mixture at -78°C was examined. Unfortunately, C-alkylation was not observed and in each case the only product identified by 1H NMR analysis of the crude reaction mixture, was α-methoxyketone 98 formed by protonation of the proposed enolate intermediate (Scheme 107).

Scheme 107

Reaction of an enolate anion with a silylating agent such as trimethylsilyl chloride (TMS-Cl) usually results in the formation of the corresponding silyl enol ether, which are often stable and can be isolated. Several attempts were made to isolate the corresponding silyl enol ether of the proposed enolate intermediate by addition of TMS-Cl to the reaction mixture at the appropriate time. After stirring for a further 2-3 h, the reactions were quenched by addition of saturated sodium hydrogen carbonate or triethylamine at -78°C. However, with either of these work-up procedures only the α-methoxyketone 98 was isolated (Scheme 108). The expected silyl enol ether 227 was successfully prepared in 46% yield directly from 3-methoxy-2-tridecanone 98 using a literature procedure that incorporated a similar triethylamine work-up, thus ruling out the possibility of this work-up procedure preventing the isolation of 227.96

Scheme 108
Addition of benzaldehyde (1.2 equivalents) to the reaction mixture resulted in a more promising outcome. A new spot appeared by TLC of the reaction mixture of similar polarity to the α-methoxyketone 98. Subsequent consumption of the α-methoxyketone 98 was extremely slow and as a result the reaction mixture was gradually allowed to warm up overnight. After 20 h the temperature had reached 0°C and all of the ketone had been consumed. The reaction was quenched with saturated sodium hydrogen carbonate. The dehydrated aldol product 228 was isolated in 50% yield after column chromatography and as a single geometrical isomer (Scheme 109). The geometry of this enone 228 was assigned as trans by 1H NMR on the basis of the magnitude of the spin-spin coupling constant between the two olefinic protons (J = 16.0 Hz). This material was fully characterised by the usual spectroscopic techniques. It appears that the initial aldol product is not stable under the reaction conditions or the following work-up and so dehydrates spontaneously to give the observed enone 228. Repetition of this reaction with constant sampling and analysis by TLC showed that the aldol reaction did not take place to any great extent until the temperature reached at least -5°C.

This reaction was performed on chiral epoxy mesylate 150 but, disappointingly, the enantiomeric excess was determined to be only 35% by chiral HPLC. This is perhaps not surprising since it has been observed that racemisation occurs in the reaction of potassium methoxide and epoxy mesylate 150 at 0°C (Vide Supra). As the aldol reaction also does not occur very rapidly at temperatures below -5°C, racemisation of the α-methoxyketone 218 could be occurring prior to or after the aldol reaction takes place. Unfortunately time constraints on this project prevented further exploration of this three component coupling reaction.
3.6 Mechanistic Possibilities

The failure to alkylate or trap the proposed enolate as the corresponding silyl enol ether 227, together with the racemisation that occurred in the aldol reaction (Scheme 109), make the existence of a stable potassium enolate in these low temperature reactions, questionable. Re-examination of the proposed contents of the solution, once all of the epoxy mesylate 150/155 (chiral or racemic) is consumed, may allude to a possible explanation of the above results. There are three possible species that could exist in solution, the potassium enolate 229, the α-methoxyketone 218/98 or the trimethylsilyl enol ether 227 or a mixture of them all (Figure 4).

If the potassium enolate 229 exists, as we originally proposed, then it is difficult to explain why we cannot alkylate it or trap it as the corresponding trimethylsilyl enol ether. However, to effect C-alkylation of this enolate may be more difficult than was originally envisaged as we learnt that the use of potassium as a counter ion is not ideal. It is reported that potassium enolates are less 'tightly chelated' anions than, say, lithium, often promoting α-alkylation over C-alkylation in non-polar solvents. The presence of the crown ether, 18-crown-6, reinforces this effect by solvating the potassium counter ion. The effect of totally free enolate anion, such as the enolate anion of cyclohexanone, in the gas phase is reported to give exclusively O-alkylation. However if O-alkylation of the enolate anion did occur we might have expected to isolate the corresponding alkyl enol ether.

It is possible that the trimethylsilyl enol ether 227 is formed under these reaction conditions. This could occur by reaction of the potassium enolate anion, prone to reaction at oxygen rather than carbon, with trimethylsilylmethanol that we propose is present in the reaction mixture (Scheme 110).
Potassium methoxide would be generated by formation of the silyl enol ether 227 which could play a part in the racemisation that was observed at higher temperatures. Since essentially neutral conditions were used for the work-up of alkylation reactions, one would expect to isolate quantities of the silyl enol ether 227. However, this compound has never been detected by $^1$H NMR analysis of crude material isolated from these experiments.

Our negative results for alkylation of the proposed enolate 229 suggest that the $\alpha$-methoxyketone is in fact the species present in the reaction mixture at -78°C. This would suggest that somehow the enolate anion produced by nucleophilic attack on the allene oxide had been quenched by a proton. All proton sources were excluded from these reactions and it is highly unlikely that the enolate anion could abstract a proton ($\text{pK}_a$ of corresponding ketone $\approx 20$) from tetrahydrofuran, the solvent.

It is possible, of course, that reactions of epoxy mesylate 150/155 with potassium alkoxides do not proceed via an allene oxide at all and we are instead observing the effects of an entirely different mechanism, possibly by direct attack on the epoxide ring of the precursor. If this was the case, however, we would also expect to observe formation of the silyl enol ether 227 by nucleophilic ring-opening at the $\beta$-carbon of the epoxy mesylate (Vide Supra) (Scheme 111). Formation of an allene oxide does account for the regioselectivity of these
reactions and we have presented indirect evidence for their presence in these reactions (Vide Supra).

![Scheme 111](image)

In summary, we have successfully developed a method for the preparation of chiral non-racemic $\alpha$-alkoxyketones using the nucleophilic ring-opening reactions of chiral allene oxides generated *in situ* by novel elimination methodology. The absolute configuration of one of the chiral $\alpha$-alkoxyketones produced by this methodology was determined and indicates that the reaction of chiral epoxy mesylates 150, 223 and 225 with potassium alkoxides proceeds with stereochemical inversion. It has also been shown that further elaboration of the enolate intermediate, which we suggest is initially formed during these reactions, is possible by aldol reaction with benzaldehyde and affords enone 228. We have attempted to rationalise the mechanism for these reactions in light of our studies on the three component coupling reactions, but must admit to not completely understanding it.
Chapter Four

The Synthesis of
Methylene Cyclic Sulfites as
Potential Allene Oxide Equivalents
4.1 Introduction

In view of the problems encountered with the instability of allene oxides, development of compounds that would react in a similar manner and be easier to prepare and handle seemed an attractive goal. It is well known that the cyclic sulfite or sulfate ring reacts with nucleophiles in a similar way to epoxides.\textsuperscript{99, 100} We thought it feasible that methylene cyclic sulfites (1,3,2-dioxathiolane-4-methylene-2-oxides) 230 and methylene cyclic sulfates (1,3,2-dioxathiolane-4-methylene-2,2-dioxides) 231 might behave as allene oxide equivalents (Figure 5). We reasoned that such compounds would contain less angular strain than the corresponding allene oxide and should therefore be more stable materials.

\[
\text{or} \quad \begin{array}{c}
\text{O} \quad \text{S} \quad \text{O} \\
\text{230}
\end{array} \\
\begin{array}{c}
\text{O} \quad \text{S} \quad \text{O} \\
\text{231}
\end{array} \quad \equiv \quad \begin{array}{c}
\text{O} \\
\text{232}
\end{array}
\]

Figure 5

The reaction of methylene cyclic sulfites or sulfates with nucleophiles might proceed in an SN2 manner at the $sp^3$ ring carbon with ring-opening to give the enol ether 232. Extrusion of sulfur dioxide or sulfur trioxide respectively would produce the $\alpha$-(substituted)-ketones in an analogous fashion to the nucleophilic ring opening reactions of allene oxides (Scheme 112).

\[
\begin{array}{c}
\text{O} \quad \text{S} \quad \text{O} \\
\text{230} \\
\underset{\text{Nu}}{\xrightarrow{\text{Nu}}} \\
\text{O} \quad \text{S} \quad \text{O} \\
\text{232} \quad \underset{\text{H}^+}{\underset{-\text{SO}_2}{\xrightarrow{\text{Nu}}}} \\
\text{O} \quad \text{CH}_3
\end{array}
\]

Scheme 112

Methylene cyclic sulfite 4,4-dimethyl-5-methylene-1,3,2-dioxathiolane-2-oxide 234 is a known compound. It was prepared by the treatment of 2,2-dimethylcyclopropanone with sulfur dioxide (Scheme 113).\textsuperscript{34} We did not consider this procedure to be ideal for a general method of preparation of methylene cyclic sulfites as the number of cyclopropanone starting materials that are stable compounds is very limited. As far as we are aware, no other methylene cyclic sulfites or sulfates are known and so new approaches for the preparation of such compounds were explored.
The most synthetically useful method for the preparation of a cyclic sulfite is by the dehydrochlorination of diols with thionyl chloride, a process that is used on an industrial scale (Scheme 114). Cyclic sulfates are commonly prepared by oxidation of the corresponding cyclic sulfites. Sharpless and co-workers developed a one-pot synthesis from a diol in which the initially formed cyclic sulfite is oxidised \textit{in situ} with catalytic ruthenium tetroxide (Scheme 113).

4.2 New Methods for the Preparation of Methylene Cyclic Sulfites.

4.2.1 Reaction of \(\alpha\)-Hydroxy ketones with Thionyl Chloride.

We reasoned that a methylene cyclic sulfite might be prepared by the treatment of an \(\alpha\)-hydroxyketone with thionyl chloride. In order to attempt this transformation we chose, in the first instance, to use 2-hydroxy-2-methyl-butan-3-one \textbf{233} as the corresponding methylene cyclic sulfite \textbf{234} is a known compound (\textit{Vide Supra}). Treatment of \textbf{233} with thionyl chloride at room temperature in dichloromethane containing two equivalents of triethylamine for 1 h followed by aqueous work-up gave a black viscous residue. However, \(^1\)H NMR analysis of this crude material showed that it was consistent with 5,5-dimethyl-4-methylene-1,3,2-dioxathiolane-2-oxide \textbf{234} and matched the \(^1\)H NMR data reported by Turro.\(^{36}\) Lowering the temperature of the reaction to -78°C followed by quenching of the reaction at this temperature gave, after column chromatography, methylene cyclic sulfite \textbf{234} as a colourless liquid in
58% yield (Scheme 115). Our material was further characterised by $^{13}$C NMR and I.R. spectroscopy but unfortunately we were unable to obtain a good molecular ion for this volatile compound.

Perhaps not surprisingly, attempts to convert 1-hydroxypropan-2-one 235, a primary alcohol, to the corresponding methylene cyclic sulfite using this method resulted in the formation of chloropropanone, a known compound, via an $S_N2$ or $S_Ni$ substitution (Scheme 116).

The two other commercially available tertiary $\alpha$-hydroxyketones were treated with thionyl chloride at -78°C in an attempt to isolate the corresponding methylene cyclic sulfites. Acetyl cyclohexanol 236 was cleanly converted to the corresponding methylene cyclic sulfite 237 in 53% yield after column chromatography (Scheme 117).

However, under similar reaction conditions 2-hydroxy-2-phenylbutan-3-one 238 gave a 2:1 mixture of two products after aqueous work-up. The major product was assigned as a 50:50 mixture of diastereomers of the corresponding methylene cyclic sulfite 239 and the minor product was consistent with the decomposition product 240 (Scheme 118). The assignment of the minor product as 3-phenyl-3-buten-2-one 240 was confirmed by comparison of the $^1$H NMR data with literature values for this compound.
Unfortunately, these compounds could not be separated by column chromatography as this led to further decomposition of 239.

Scheme 118
We speculate that the formation of 240 occurs by ring-opening of the methylene cyclic sulfite to give carbocation 241 which is both secondary and benzylic. Loss of a proton and sulfur dioxide from this intermediate accounts for the formation of 3-phenyl-3-buten-2-one 240.

Scheme 119
Attempts were made to prepare the corresponding methylene cyclic sulfate directly from α-hydroxy ketone 233 by treatment with sulfuryl chloride but, unfortunately this produced a complex mixture of products. Preparation of the corresponding methylene cyclic sulfates by oxidation of 4,4-disubstituted methylene cyclic sulfites was anticipated to be difficult as the double bonds of these compounds would be vulnerable to oxidation. Indeed, attempts to oxidise 234 with ruthenium tetroxide, according to the procedure described by Sharpless, gave a complex mixture of products.102
4.2.2 Preparation of Methylene Cyclic Sulfites by Selenoxide Elimination

In order to develop a more general method for the preparation of methylene cyclic sulfites, the possibility of a selenoxide elimination to generate the exocyclic double bond of the cyclic sulfite ring was investigated. Although previous studies to prepare allene oxides using this type of strategy have been unsuccessful (Vide supra), we were hopeful that a selenoxide elimination adjacent to a cyclic sulfite ring may be more successful (Scheme 120). Formation of a methylene cyclic sulfite would again involve selenoxide elimination towards an oxygen atom, however the resulting five-membered heterocyclic ring system was anticipated to be much less strained than that of an allene oxide.

![Scheme 120](image)

The β-(2-nitrophenylseleno)cyclic sulfite 243 was prepared from commercially available solketal (2,2-dimethyl-1,3-dioxolane-4-methanol) in three steps and in 35% overall yield (Scheme 121). When 243 was oxidised with hydrogen peroxide the selenoxide 244 was identified by $^1$H NMR as a mixture of four diastereomers in approximately equal quantities. Elimination over a number of days, in deuterochloroform at 20°C, gave a mixture of products. These were assigned, by $^1$H NMR as the parent methylene cyclic sulfite 230 and (2-nitrophenyl)selenic acid residues. Unfortunately, it was impossible to isolate 230 (an extremely volatile compound) from the reaction mixture by standard column chromatography methods. A sequence of $^1$H NMR spectra showed, in the region 5.65-2.75 ppm, disappearance of the signals corresponding to the aliphatic protons of selenoxide 244 and appearance of signals corresponding to protons of the methylene cyclic sulfite 230.
These findings suggested that the syn elimination of an alkylaryl selenoxide could be used to generate the exocyclic double bond of a methylene cyclic sulfite. To overcome the difficulties encountered with the isolation of this unsubstituted methylene cyclic sulfite 230, we chose to prepare a range of more highly substituted and less volatile derivatives.

We planned to prepare a selection of 3-(arylseleno)-1,2-diols by asymmetric dihydroxylation of the corresponding allylaryl selenides. We were aware that asymmetric dihydroxylations were unknown for this type of compound although the corresponding allylic sulfides had been successfully dihydroxylated.\textsuperscript{105, 106}

The allylphenyl selenides 245 and 256 were prepared by addition of the appropriate commercially available allylic chloride to a solution of the phenylselenate anion, prepared by reduction of diphenyl diselenide with sodium borohydride, in 83\% and 48\% yields respectively (Scheme 122).
The allyl-(2-nitrophenyl)selenides 247 and 248 were prepared from the corresponding allylic alcohols by reaction with (2-nitrophenyl)selenocyanate in tetrahydrofuran containing tri-\(n\)-butylphosphine in 76% and 83% yield respectively (Scheme 123).

![Scheme 123]

Allylic selenides 245-248 were successfully converted to the corresponding diols 249-253 using Sharpless asymmetric dihydroxylation protocol albeit in only moderate yields. The low yields for these asymmetric dihydroxylation reactions probably reflect the degree of competitive oxidation on selenium, though no by-products were isolated. This is supported by the fact that alkylaryl selenoxides possessing an ortho-nitro substituent were produced in higher yields. The yields and configurations of the 1,1-(disubstituted)-3-(arylseleno)-1,2-diols produced are summarised (Scheme 124/Table 5). The absolute configurations were assigned solely on the Sharpless mnemonic model.\(^{105,107}\) Preliminary attempts to determine the enantiomeric excesses of these diols by chiral HPLC were unsuccessful, however, all of these compounds exhibited substantial optical rotations.

![Scheme 124]

<table>
<thead>
<tr>
<th>Compound</th>
<th>(R^1)</th>
<th>(R^2)</th>
<th>Ar</th>
<th>AD-mix</th>
<th>% yield</th>
<th>Config.</th>
</tr>
</thead>
<tbody>
<tr>
<td>249</td>
<td>Ph</td>
<td>H</td>
<td>C(_6)H(_5)</td>
<td>(\alpha)</td>
<td>39</td>
<td>1(S),2(R)</td>
</tr>
<tr>
<td>250</td>
<td>Ph</td>
<td>H</td>
<td>C(_6)H(_5)</td>
<td>(\beta)</td>
<td>38</td>
<td>1(R),2(S)</td>
</tr>
<tr>
<td>251</td>
<td>Ph</td>
<td>H</td>
<td>2-NO(_2)-C(_6)H(_4)</td>
<td>(\beta)</td>
<td>57</td>
<td>1(R),2(S)</td>
</tr>
<tr>
<td>252</td>
<td>Me</td>
<td>Me</td>
<td>C(_6)H(_5)</td>
<td>(\alpha)</td>
<td>12</td>
<td>2(R)</td>
</tr>
<tr>
<td>253</td>
<td>Me</td>
<td>Me</td>
<td>2-NO(_2)-C(_6)H(_4)</td>
<td>(\beta)</td>
<td>50</td>
<td>2(S)</td>
</tr>
</tbody>
</table>

Table 5
Reaction of diols 249 and 252, both produced using AD-mix-α, with thionyl chloride in dichloromethane containing triethylamine at -78°C gave the corresponding cyclic sulfites 254 and 255 in good yields (71% and 61%). These were treated with 30% hydrogen peroxide in tetrahydrofuran at 20°C for 2-3 h and yielded the corresponding selenoxides 256 and 257.

Reagents and Conditions: i, SOCl₂, Et₃N, CH₂Cl₂, -78°C; ii, 30% H₂O₂, THF, R.T.

Scheme 125

The selenoxides 256 and 257 were identified by ¹H NMR as a mixtures of four diastereomers due to the presence of both a chiral sulfur atom and a chiral selenium atom in both molecules. However, further characterisation proved impossible as these materials began to decompose almost immediately in the NMR solvent (CDCl₃). In both cases a solution of the selenoxide dissolved in deuterochloroform was gently heated (ca. 50°C) and the decomposition process was followed to completion by ¹H NMR. Remarkably, decomposition of selenoxides 256 and 257 gave the starting cyclic sulfites 254 and 255, respectively, as the final products with a considerable reduction in the mass balance (Scheme 126). We are unable to account for these results but hypothesise that some kind of disproportionation reaction of these selenoxides is occurring.

Scheme 126
Cyclic sulfites 258 and 259 prepared from the corresponding diols 251 and 253 in 61% and 93% yield respectively were subsequently oxidised to the corresponding selenoxides 260 and 261 as described above. Selenoxides 260 and 261 began to eliminate immediately (observed by $^1$H NMR) and after heating for 2-3 h in CDCl$_3$, elimination was complete. The desired methylene cyclic sulfites 262 and 234 were isolated by column chromatography, albeit in rather poor yields (28% with respect to the starting selenide in both cases) (Scheme 127).

Scheme 127

The $^1$H NMR, $^{13}$C NMR and I.R. data for methylene cyclic sulfite 234 matched data for this compound which we prepared earlier using different methodology and also matched the data in the literature.$^{34}$ The $^1$H NMR and I.R. data for methylene cyclic sulfite 262 were consistent with corresponding data for other methylene cyclic sulfites we have prepared but unfortunately, this compound decomposed rapidly. The $^1$H NMR showed this material was a 9:1 mixture of diastereomers.

In summary we have found that the use of selenoxide elimination methodology is, in principle, suitable for the preparation of methylene cyclic sulfites. Unfortunately time constraints did not allow us to optimise this method or explore the chemistry of this novel class of compounds.
Chapter Five

Experimental
5.1 General Information

Sodium hydride was purchased as a 60% dispersion in mineral oil which was removed by repeated washing with light petroleum which in turn was removed slowly under reduced pressure to give 100% sodium hydride which was stored under nitrogen. Potassium hydride was purchased as a 35% dispersion in mineral oil and was purified and stored in a similar manner to sodium hydride to give 100% potassium hydride. All other commercially available solvents and reagents were used throughout without further purification unless otherwise stated. Light petroleum (which refers to petroleum ether b.p.40-60°C) and ethyl acetate were distilled from CaCl₂ prior to use. Dichloromethane and toluene were distilled from phosphorus pentoxide prior to use. Acetonitrile and pyridine were distilled from calcium hydride and kept over 4Å molecular sieves. Diethyl ether was purchased as reagent grade and used without further purification for column chromatography. Anhydrous tetrahydrofuran and diethyl ether were prepared by distillation from sodiumbenzophenone ketyl under nitrogen immediately prior to use. Alternatively, anhydrous solvents were purchased from Aldrich in Sure/Seal™ bottles. All other commercially available solvents and reagents were used throughout without further purification unless otherwise stated. All reactions were performed using oven dried glassware under an atmosphere of nitrogen unless otherwise stated.

Analytical thin-layer chromatography was performed on pre-coated aluminium or plastic backed plates (Merck Kieselgel 60 F₂₅₄) and were visualised using ultra-violet light or by staining with iodine, acidic ammonium molybdate (IV) (with heating) or potassium permanganate (with heating) as appropriate. Preparative column chromatography was performed at low positive pressure on Fisons Matrex 60 (30-70mm) flash silica. Samples were applied as a saturated solution in an appropriate solvent.

¹H and ¹³C NMR spectra were recorded at 250 MHz and 62.9 MHz respectively on a Bruker AC-250 instrument or at 400 MHz and 100 MHz respectively on a Bruker DPX-400 instrument. Some ¹H NMR spectra were recorded at 360 MHz on a Varian NMR spectrometer by Astra Charnwood, Loughborough. Spectra were recorded in deuterochloroform unless otherwise stated and residual protic solvent at 7.265 ppm was used as the internal standard unless otherwise stated. Signals in ¹H NMR spectra are described as singlets (s), doublets (d), triplets (t) and so forth, which refer to the spin-spin coupling pattern observed. Signals in ¹³C NMR spectra are also described as singlets (s), doublets (d), triplets (t) and quartets (q) and this information was obtained from DEPT 135 experiments. Infra-red
spectra were recorded in the range 4000-600 cm\(^{-1}\) using a Nicolet FT-205 spectrometer or a Perkin-Elmer Paragon 1000 spectrometer with internal calibration. Spectra were recorded as thin films, as solutions in chloroform or as Nujol\(^\text{®}\) mulls. High and low resolution mass spectra conditions were recorded on a Kratos 80 mass spectrometer, under E.I.\(^+\). Mass spectra under C.I.\(^+\) (thermospray) conditions were recorded by Glaxo Wellcome Research and Development Ltd, Medicines Research Centre, Stevenage. High resolution mass spectra recorded under C.I.\(^+\) conditions were performed by Dr J. A. Ballantine and his staff at the EPSRC Mass Spectrometry Centre, Swansea. Melting points were determined on an Electrothermal digital melting point apparatus. Boiling points refer to the oven temperature for Kugelrohr short-path distillations. Optical rotations on the sodium D-line (598 nm) were recorded on an Optical Activity AA100 polarimeter, or an Opical Activity PolAAr2001 digital polarimeter. The optical rotation on the mercury J-line (578 nm) for compound 226 was kindly recorded for us by Dr D. S. Ennis at SmithKline Beecham Pharmaceuticals, Old Powder Mills, Tonbridge.
5.2 Experimental for Chapter 2

Preparation of \((E)-\text{ethyl 2-dodecenoate (142)}\).\(^{79}\)

\[
n-C_9H_{19}CHO \quad \rightarrow \quad n-C_9H_{19}CO_2Et
\]

To a stirred solution of lithium chloride (2.55 g, 60.0 mmol) dissolved in acetonitrile (300 ml) at room temperature were added in the following order: triethyl phosphonoacetate (13.45 g, 60.0 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (7.60 g, 50.0 mmol) and decylaldehyde (7.80 g, 50.0 mmol). The mixture was stirred for 1.5 h and then diluted with water (400 ml) and extracted with diethyl ether (4 x 200 ml). The combined organic extracts were washed with brine (100 ml) and dried (MgSO\(_4\)). The solvent was removed under reduced pressure and the residue was purified by column chromatography (20% diethyl ether/light petroleum) to give \((E)-\text{ethyl 2-dodecenoate (8.10 g, 71%)}\) as a colourless oil; \(v_{\text{max}}\) (film) 2979, 2927, 2855, 1724, 1655, 1466, 1367, 1266, 1045, 982 cm\(^{-1}\); \(\delta_H\) (250 MHz, CDCl\(_3\)) 6.95 (1H, dt, 15.5, 7.0 Hz), 5.80 (1H, dt, 15.5, 1.5 Hz), 4.14 (2H, q, 11.5 Hz), 2.14 (2H, dq, 11.5, 7.1 Hz), 1.44 (2H, m), 1.28 (15H, m), 0.87 (3H, t, 6.3 Hz); \(\delta_C\) (62.9 MHz, CDCl\(_3\)) 166.7 (s), 149.4 (d), 121.1 (d), 60.0 (t), 32.1 (t), 31.8 (t), 29.4 (t), 29.3 (t), 29.2 (t), 29.1 (t), 27.9 (t), 22.6 (t), 14.2 (q), 14.0 (q); \(m/z\) (C.I.\(^{+}\), thermospray) 227 (MH\(^{+}\)), 244 (MNH\(_4^{+}\)); Observed (MNH\(_4^{+}\)): 244.2277, C\(_{14}\)H\(_{30}\)NO\(_2\) requires: 244.2276.

Preparation of \((E)-2\text{-dodecen-1-ol (143)}\).

\[
n-C_9H_{19}CO_2Et \quad \rightarrow \quad n-C_9H_{19}OH
\]

To a stirred solution of \((E)-\text{ethyl 2-dodecenoate 142 (7.91 g, 35.0 mmol)}\) dissolved in toluene (350 ml) at -78°C was added di-iso-butylaluminium hydride (1.5 M in toluene, 49.0 ml, 73.0 mmol). The mixture was stirred for 2 h during which the temperature was allowed to rise gradually to 0°C. The reaction was quenched with water (35 ml), ethyl acetate (175 ml) and an excess of anhydrous Na\(_2\)SO\(_4\) then stirred for a further 30 min while warming to room temperature. The granular white solid formed was filtered off and the solvent removed under
reduced pressure. The residue was purified by column chromatography (50% diethyl ether/light petroleum) to give (E)-2-dodecen-1-ol 143 (4.56 g, 71%) as a colourless oil; $\nu_{\text{max}}$ (film) 3450 (OH), 2956, 2854, 1650, 1378, 1090, 1003, 967 cm$^{-1}$; $\delta_{\text{H}}$ (250 MHz, CDCl$_3$) 5.66 (2H, m), 4.07 (2H, d, 4.6 Hz), 2.04 (2H, q, 6.6 Hz), 1.56 (1H, br s), 1.26 (14H, m), 0.90 (3H, t, 6.3 Hz); $\delta_{\text{C}}$ (62.9 MHz, CDCl$_3$) 133.5 (d), 128.7 (d), 63.8 (t), 32.1 (t), 31.8 (t), 29.5 (t), 29.4 (t), 29.2 (t), 29.1 (t), 29.05 (t), 22.6 (t), 14.01 (q); m/z (C.I. $^+$, thermospray) 202 (MNH$_4^+$), 184 (M$^+$); Observed (MNH$_4^+$-H$_2$O): 184.1830; C$_{12}$H$_{24}$O requires: 184.1827.

**Preparation of (2S*,3S*)-2,3-epoxydodecan-1-ol (144).**

![Chemical structure](image)

To a stirred solution of (E)-2-dodecen-1-ol 143 (4.42 g, 24.0 mmol) and vanadyl acetoacetate (0.15 g, 0.54 mmol) in dichloromethane (140 ml) at 0°C was added dropwise a solution of tert-butyl hydroperoxide (70% in water, 6.95 g, 54.0 mmol) in dichloromethane (100 ml). The mixture was allowed to warm to room temperature and was stirred overnight (16 h) then diluted with water (400 ml). The layers were separated and the dichloromethane layer was washed with a 10% solution of ferrous sulfate (100 ml) and water (2 x 100 ml). The combined aqueous washings were extracted with dichloromethane (2 x 50 ml) and the combined organic extracts were dried over MgSO$_4$. The solvent was removed under reduced pressure to give (2S*,3S*)-2,3-epoxydodecan-1-ol (4.47 g, 93%) as a white solid, m.p. 49°C [lit., 108 for the (2R,3R)-enantiomer, m.p. = 60°C]; $\nu_{\text{max}}$ (Nujol®) 3130, 2953, 2879, 1025, 885 cm$^{-1}$; $\delta_{\text{H}}$ (250 MHz, CDCl$_3$) 3.82 (1H, m), 3.61 (1H, m), 2.92 (2H, m), 2.22 (1H, br s), 1.60 (2H, m), 1.45 (14H, m), 0.88 (3H, t, 6.3 Hz); $\delta_{\text{C}}$ (62.9 MHz, CDCl$_3$) 61.6 (t), 58.3 (d), 55.9 (d), 31.8 (t), 31.5 (t), 29.4 (t), 29.3 (t), 29.2 (t), 25.8 (t), 22.6 (t), 14.0 (q) (one carbon of the alkyl chain was not resolved); m/z (C.I. $^+$, thermospray) 218 (MNH$_4^+$); Observed (MNH$_4^+$): 218.2120; C$_{12}$H$_{28}$NO$_2$ requires 218.2120.
Preparation of \((2R^*,3S^*)\)-2,3-epoxy-1-(2-nitrophenylseleno)dodecane (145).80

\[
\begin{align*}
 &\text{n-C}_9\text{H}_19 \quad \text{O} \quad \text{OH} \quad \text{n-C}_9\text{H}_19 \\
 &\text{144} \quad \text{145}
\end{align*}
\]

\((2\text{-Nitrophenyl})\text{selenocyanate} \text{147 was prepared according to a literature procedure,}\,75,81\) To a stirred solution of \((2S^*,3S^*)\)-2,3-epoxydodecan-1-ol 144 (1.00 g, 5.00 mmol) and \((2\text{-nitrophenyl})\text{selenocyanate} \text{(1.35 g, 6.00 mmol)}\) in tetrahydrofuran (16 ml) at room temperature was added freshly distilled tri-\(n\)-butylphosphine (1.20 g, 6.00 mmol). The mixture was stirred for a further 30 min and then the solvent was removed under reduced pressure. The brown residue was purified by column chromatography (50\% diethyl ether/light petroleum) then subsequent recrystallisation [light petroleum/ethyl acetate (minimum)] gave \((2R^*,3S^*)\)-2,3-epoxy-1-(2-nitrophenylseleno)dodecane 145 (695 mg, 36\%) as a yellow solid, m.p. 61°C; \(\nu_{\text{max}}\) (Nujol\(®\)) 2747, 2852, 1592, 1565, 1507, 1466, 1449, 1376, 1330, 1247, 1093, 890, 780, 726 cm\(^{-1}\); \(\delta_{\text{H}}\) (250 MHz, CDCl\(_3\)) 8.28 (1H, d, 8.2 Hz), 7.65 (1H, dd, 8.1, 0.5 Hz), 7.50 (1H, t, 7.1 Hz), 7.35 (1H, dt, 7.1, 1.4 Hz), 3.17 (1H, m), 3.00 (2H, m), 2.88 (1H, m), 1.55 (2H, m), 1.27 (14H, m), 0.89 (3H, t, 6.3 Hz); \(\delta_{\text{C}}\) (100 MHz, CDCl\(_3\)) 147.5 (s), 133.6 (d), 132.8 (s), 129.3 (d), 126.3 (d), 125.8 (d), 60.1 (d), 56.6 (d), 31.8 (t), 31.6 (t), 29.4 (t), 29.3 (t), 29.2 (t), 27.8 (t), 25.7 (t), 22.6 (t), 14.0 (q) (one methylene carbon of the alkyl chain was not resolved); \(m/z\) (C.I.\(^{+}\), thermospray) 403 (MNH\(_4^+\)), 385 (MH\(^+\)); Observed (M\(^+\)): 385.1159; C\(_{18}\)H\(_{27}\)NO\(_3\)Se requires: 385.1158.

Preparation of \((2R^*,3S^*)\)-2,3-epoxy-1-[(2-nitrophenyl)selenoxymethyl]dodecane (146).

\[
\begin{align*}
 &\text{n-C}_9\text{H}_19 \quad \text{Se} \quad \text{O} \quad \text{n-C}_9\text{H}_19 \\
 &\text{145} \quad \text{146}
\end{align*}
\]

To a stirred solution of \((2R^*,3S^*)\)-2,3-epoxy-1-(2-nitrophenylseleno)dodecane 145 (231 mg, 0.60 mmol) dissolved in dichloromethane (5 ml), buffered with an excess of potassium carbonate at 0°C, was added 3-chloroperoxybenzoic acid (207 mg, 50\%, 0.60 mmol)
dissolved in dichloromethane (10 ml). The mixture was gradually allowed to warm to room temperature and after 2 h the reaction was estimated to be complete by TLC. The reaction mixture was poured into 5% sodium metabisulfite solution (30 ml) and the layers separated. The dichloromethane layer was washed with saturated NaHCO₃ (2 x 30 ml) and brine (3 x 30 ml) then dried (MgSO₄) and the solvent removed under reduced pressure to give an orange solid. Recrystallisation [light petroleum/ethyl acetate (minimum)] gave (2R*,3S*)-2,3-epoxy-1-[(2-nitrophenylselenoxymethyl)doedcane (146 mg, 62%) as an orange powder and as a 1:1 mixture of diastereomers (m.p. 69-71°C); νmax(CHCl₃) 3024, 2959, 2929, 2858, 1597, 1530, 1465, 1340, 1250, 1047 cm⁻¹; δH (250 MHz, CDCl₃) 8.46 (1H, m), 8.36 (1H, m), 7.95 (1H, m), 7.75 (1H, m), 3.62-2.97 (3H, m), 2.72 (1H, m), 1.47-1.10 (16H, m), 0.84 (3H, t, 5.6 Hz); δC (62.9 MHz, CDCl₃) 135.8 (d), 135.6 (d), 135.0 (s), 132.04 (d), 132.00 (d), 131.5 (s), 128.5 (d), 128.0 (d), 127.5 (s), 126.3 (s), 125.1 (d), 125.0 (d), 59.8 (d), 58.2 (d), 56.1 (t), 53.1 (t), 52.4 (d), 52.3 (t), 31.7 (t), 31.5 (t), 31.3 (t), 29.3 (t), 29.2 (t), 29.1 (t), 25.52 (t), 25.0 (t), 22.5 (t), 14.0 (q) (only one carbon of the alkyl chain is resolved into two signals for the two diastereomers); m/z 402 (MH⁺); Observed (MH⁺): 402.1184: CsH₂₈N₂O₄Se requires: 402.1183.

Reaction of (2S*,3S*)-1-chloro-2,3-epoxy-2-(trimethylsilyl)tridecane (97) with caesium fluoride and methanol.⁹

\[
\begin{align*}
\text{Caesium fluoride (46.0 mg, 0.30 mmol) was weighed directly into a round bottom flask that had been oven-dried and cooled under an atmosphere of nitrogen. (2S*,3S*)-1-Chloro-2,3-} \\
\text{epoxy-2-(trimethylsilyl)tridecane}^{3} \text{97 (91.0 mg, 0.30 mmol) dissolved in acetonitrile (5 ml)}
\end{align*}
\]
was added to the flask followed by methanol (40 μl, 0.90 mmol). The mixture was stirred for 2 h at room temperature, then diluted with diethyl ether. The white solid was filtered off and the solvent removed under reduced pressure. \(^1\)H NMR analysis of the resulting residue showed a mixture of 3-chloro-2-tridecanone\(^3\) 153; \(\delta_H\) (250 MHz, CDCl\(_3\)) 4.17 (1H, dd, 7.8, 6.2 Hz), 2.32 (3H, s), 1.90 (2H, m), 1.42-1.26 (16 H, m), 0.88 (3H, t, 6.4 Hz), 3-fluoro-2-tridecanone 154; \(\delta_H\) 4.55 (1H, ddd, 50.3, 7.5, 4.9 Hz), 2.09 (3H, d, 6.7 Hz), 1.63 (2H, m), 1.30 (2H, m), 1.11 (14H, m), 1.74 (3H, t, 6.8 Hz) and 3-methoxy-2-tridecanone 98; \(\delta_H\) 3.54 (1H, t, 6.2 Hz), 3.35 (3H, s), 2.15 (3H, s), 1.58 (2H, m), 1.36-1.25 (16H, m), 0.88 (3H, t, 6.3 Hz) and this data was found to be consistent with later experiments. The mixture was analysed by gas chromatography (25 m Cidex B column, 150°C) which gave the following relative yields: 3-chloro-2-tridecanone 153 (71%); 3-fluoro-2-tridecanone 154 (23%); 3-methoxy-2-tridecanone 98 (6%).

**General procedure A: Preparation of 1-(trimethylsilyl)acetylenes (161-165).**

![Chemical structure](image)

To the appropriate terminal acetylene 156-160 (45.0 mmol) dissolved in tetrahydrofuran (225 ml) at -78°C was added dropwise n-butyllithium (2.5 M in hexanes, 49.5 mmol). The mixture was stirred for 30 min and then chlorotrimethylsilane (14.7 g, 135 mmol) was added dropwise. After a further 20 min at -78°C the reaction was quenched with saturated NH\(_4\)Cl (5-10 ml) and allowed to warm to 0°C. The reaction mixture was poured into water (200 ml) and the layers were separated. The aqueous layer was extracted with diethyl ether (2 x 50 ml), the combined organic extracts were washed over MgSO\(_4\) and the solvent was removed under reduced pressure. The residue was purified by column chromatography in the appropriate solvent system or by distillation.

**1-(Trimethylsilyl)-1-dodecyne (161).**

Treatment of 1-dodecyne 156 (7.47 g, 45.0 mmol) with n-butyllithium (2.5 M in hexanes, 19.8 ml, 49.5 mmol) in tetrahydrofuran (225 ml) and then chlorotrimethylsilane (14.7 g, 135 mmol), as described in General Procedure A, and subsequent column chromatography (light petroleum) gave 1-(trimethylsilyl)-1-dodecyne 161 (10.3 g, 96%) as a colourless oil: \(v_{\text{max}}\) (film) 2958, 2855, 2176, 1466, 1249, 842 cm\(^{-1}\); \(\delta_H\) (250 MHz, CDCl\(_3\)) 2.21 (2H, t, 7.1 Hz),
1.50 (2H, m), 1.27 (14H, m), 0.89 (3H, t, 6.5 Hz), 0.15 (9H, s); δC (62.9 MHz, CDCl₃) 107.6 (s), 84.2 (s), 31.7 (t), 29.4 (t), 29.3 (t), 29.1 (t), 28.9 (t), 28.6 (t), 28.5 (t), 22.5 (t), 19.7 (t), 13.9 (q), 0.0 (q); m/z (E.I.) 238 (M⁺), 73, 58, 41; Observed (M⁺): 238.2107; C₁₅H₃₀Si requires: 238.2117.

1-(Tetrahydropyranloxy)-6-(trimethylsilyl)-5-hexyne (162).

Treatment of 6-(tetrahydropyranloxy)-1-hexyne 157 (11.43 g, 45.0 mmol) with n-butyllithium (1.6 M in hexanes, 30.9 ml, 49.5 mmol) in tetrahydrofuran (225 ml) and then chlorotrimethylsilane (14.7g, 135 mmol), as described in General Procedure A, and subsequent column chromatography (10% ethyl acetate/light petroleum) gave 1-(tetrahydropyranloxy)-6-(trimethylsilyl)-5-hexyne 162 (6.06 g, 53%) as a colourless oil:

vmax (CH₂Cl₂) 2944, 2170, 1249, 1120, 1035, 759 cm⁻¹; δH (250 MHz, CDCl₃) 4.44 (1H, t, 3.4 Hz), 3.66 (2H, m), 3.32 (2H, m), 2.12 (2H, t, 7.1 Hz), 1.76-1.30 (lOH, m), 0.10 (9H, s);
δC (62.9 MHz, CDCl₃) 107.1 (s), 98.6 (d), 84.6 (s), 66.8 (t), 62.1 (t), 30.6 (t), 28.7 (t), 25.34 (t), 25.31 (t), 19.53 (t), 19.49 (t), 0.0 (q); m/z (C.I.+, thermospray) 272 (MNH⁺), 255 (MH⁺), 102; Observed (MH⁺): 255.1783; CI₄H₂₇O₂Si requires: 255.1780.

1-(Trimethylsilyl)-7-hepten-1-yne (163).¹⁰⁹

Treatment of 1-hepten-6-yne 158 (2.63 g, 28.0 mmol) with n-butyllithium (2.5 M in hexanes, 12.3 ml, 30.1 mmol) in tetrahydrofuran (100 ml) and then chlorotrimethylsilane (9.12g, 84.0 mmol), as described in General Procedure A, and subsequent column chromatography (light petroleum) gave 1-(trimethylsilyl)-7-hepten-1-yne 163 (3.30 g, 71%) as a colourless oil (the spectroscopic data was consistent with the literature values)¹⁰⁹: vmax (film) 2175, 1640, 1245, 1020, 990, 912, 840, 755 cm⁻¹; δH (250 MHz, CDCl₃) 5.82 (1H, m), 5.15 (2H, m), 2.26-2.11 (4H, m), 1.93-1.51 (2H, m), 0.27 (9H, s).

1-Phenyl-2-(trimethylsilyl)ethyne (164).

Treatment of phenylacetylene 159 (4.60 g, 45.0 mmol) with n-butyllithium (1.6 M in hexanes, 30.9 ml, 49.5 mmol) in tetrahydrofuran (225 ml) and then chlorotrimethylsilane (14.7g, 135 mmol), as described in General Procedure A, and subsequent Kugelrohr distillation of the orange residue gave 1-phenyl-2-(trimethylsilyl)ethyne 164 (7.37 g, 94%) as a colourless oil (b.p. 150°C/15 mmHg); vmax (film) 3081, 2959, 2160, 1488, 1250 cm⁻¹; δH
(250 MHz, CDCl₃) 7.39 (2H, m), 7.23 (3H, m), 0.18 (9H, s); δC (62.9 MHz, CDCl₃) 131.9 (d), 128.5 (d), 128.2 (d), 123.3 (s), 105.4 (s), 94.2 (s), 0.0 (q); m/z (C.I.⁺, thermospray) 192 (MNH₄⁺), 135; Observed (MNH₄⁺): 192.1209, C₁₁H₁₉NSi requires: 192.1208.

3,3-Dimethyl-1-(trimethylsilyl)-1-butyne (165).⁸²

Treatment of 3,3-dimethyl-1-butyne 160 (5.00 g, 61.0 mmol) with n-butyllithium (2.5 M in hexanes, 26.8 ml, 67.1 mmol) in tetrahydrofuran (250 ml) and then chlorotrimethylsilane (19.8 g, 183.0 mmol), as described in General Procedure A, and subsequent Kugelrhors distillation of the crude residue gave 3,3-dimethyl-1-(trimethylsilyl)-1-butyne 165 (7.51 g, 80%) as a colourless oil (b.p. 80°C/15 mmHg, lit.⁸⁰ 80-81°C 15 mmHg), the spectroscopic data was consistent with the literature values; νmax (film) 2969, 2156, 1057, 760 cm⁻¹; δH (250 MHz, CDCl₃) 1.21 (9H, s), 0.13 (9H, s).

General procedure B: Preparation of (Z)-2-(trimethylsilyl)propen-3-ols (166-170).

The appropriate 1-(trimethylsilyl)acetylene 161-165 was dissolved in diethyl ether (100 ml/24.0 mmol) and cooled to 0°C. Di-iso-butylaluminium hydride (1.5 M in toluene, 1.5 eq) was added and the mixture was heated to reflux for 1 h. The mixture was cooled to 0°C and methylolithium (1.4 M in diethyl ether, 1.5 eq) was added gradually and the mixture was stirred for a further 30 min. Paraformaldehyde (15 eq) was cracked at 150-160°C and the gas was passed into the reaction mixture via a stream of nitrogen. When the paraformaldehyde had disappeared the reaction mixture was poured into a stirred solution of ethyl acetate (15 ml/1.0 mmol of di-iso-butylaluminium hydride) and water (1.5 ml/1.0 mmol of di-iso-butylaluminium hydride). An excess of anhydrous Na₂SO₄ was added and the mixture was stirred for 1-2 h and then filtered. The solvent was removed under reduced pressure and the residue was purified by column chromatography in the appropriate solvent system to give the product.
(Z)-2-(Trimethylsilyl)-2-tridecen-1-ol (166).

Treatment of 1-(trimethylsilyl)-1-dodecyn 161 (5.71 g, 24.0 mmol) in diethyl ether (100 ml) with di-iso-butylaluminium hydride (1.5 M in toluene, 24.0 ml, 36.0 mmol), methyllithium (1.4 M in diethyl ether, 26.0 ml, 36.0 mmol) and paraformaldehyde (10.8 g, 0.36 mol), as described in General Procedure B, and subsequent column chromatography (10% ethyl acetate/light petroleum) gave (Z)-2-(trimethylsilyl)-2-tridecen-1-ol 166 (4.21 g, 65%) as a colourless oil: v/T/£/X (film) 3468, 2956, 2855,1617,1466, 1373, 1246, 1047, 839 cm⁻¹; δH (250 MHz, CDCl₃) 6.21 (1H, t, 7.5 Hz), 3.94 (2H, m), 1.96 (2H, m), 1.22-1.09 (17H; m), 0.71 (3H, t, 6.2 Hz), 0.01 (9H, s); δC (62.9 MHz, CDCl₃) 144.8 (d), 138.8 (s), 69.1 (t), 31.9 (t), 31.8 (t), 29.8 (t), 29.6 (t), 29.4 (t), 29.3 (t), 22.6 (t), 14.1 (q), 0.0 (q) (two carbons in the alkyl chain were resolved); m/z (C.I.+ , thermospray) 270 (MNH₄⁺-H₂O); Observed (MNa⁺): 293.2281; C₁₆H₃₄OSiNa requires: 293.2277.

(E)-7-(Tetrahydropyranyloxy)-2-(trimethylsilyl)-2-hepten-1-ol (167).

Treatment of 1-(tetrahydropyranyloxy)-6-(trimethylsilyl)-5-hexyne 162 (5.33 g, 21.0 mmol) in diethyl ether (100 ml) with di-iso-butylaluminium hydride (1.5 M in toluene, 21.0 ml, 31.5 mmol), methyllithium (1.4 M in diethyl ether, 22.5 ml, 31.5 mmol) and paraformaldehyde (9.4 g, 0.31 mol), as described in General Procedure B, and subsequent column chromatography (20% ethyl acetate/light petroleum) gave (Z)-7-(tetrahydropyranyloxy)-2-(trimethylsilyl)-2-hepten-1-ol 167 (4.08 g, 68%) as a colourless oil: v/T/£/X (film) 3419, 2945, 2867, 1617, 1454, 1441, 1249, 1022, 839 cm⁻¹; δH (250MHz, CDCl₃) 6.19 (1H, t, 8.0 Hz), 4.58 (1H, t, 4.3 Hz), 4.12 (2H, s), 3.81 (2H, m), 3.44 (2H, m), 2.22 (1H, d, 7.2 Hz), 2.16 (1H, d, 7.2 Hz), 1.86-1.23 (11H, m), 0.18 (9H, s); δC (62.9 MHz, CDCl₃) 144.5 (d), 139.1 (s), 98.8 (d), 69.0 (t), 67.4 (t), 62.3 (t), 31.5 (t), 30.7 (t), 29.4 (t), 26.4 (t), 25.4 (t), 21.4 (t), 0.10 (q); m/z (C.I.+ , thermospray) 304 (MNH₄⁺), 271, 201, 169; Observed (MH⁺): 287.2047; C₁₅H₃₁O₃Si requires: 287.2042.

(Z)-2-(Trimethylsilyl)-2,7-octadien-1-ol (168).

Treatment of 1-(trimethylsilyl)-7-hepten-1-yne 163 (3.15 g, 19.0 mmol) in diethyl ether (80 ml) with di-iso-butylaluminium hydride (1.5 M in toluene, 19.0 ml, 28.5 mmol), methyllithium (1.4 M in diethyl ether, 20.3 ml, 28.5 mmol) and paraformaldehyde (8.7 g, 0.29 mol), as described in General Procedure B, and subsequent column chromatography
(10% ethyl acetate/light petroleum) gave (Z)-2-(trimethylsilyl)-2,7-octadien-1-ol 168 (1.96 g, 52%) as a colourless oil; \( \nu_{\text{max}} \) (film) 3340, 2952, 2926, 1641, 1617, 1249, 853 cm\(^{-1}\); \( \delta_H \) (250 MHz, CDCl\(_3\)) 6.19 (1H, t, 6.2 Hz), 5.81 (1H, m), 5.00 (2H, m), 4.13 (2H, m), 2.21-2.07 (4H, m), 0.92 (1H, broad, s), 0.17 (9H, s); \( \delta_C \) (62.9 MHz, CDCl\(_3\)) 1.44 (d), 139.4 (s), 138.5 (d), 114.7 (t), 69.2 (t), 33.4 (t), 31.2 (t), 29.0 (t), 0.18 (q); \( m/z \) (C.I.\(^+\), thermospray) 216 (MNH\(_4^+\)), 198 (MNH\(_4^+\)-H\(_2\)O), 109; Observed (MNH\(_4^+\)): 216.1784; C\(_{11}\)H\(_{26}\)NSiO requires: 216.1784.

(Z)-1-Phenyl-2-(trimethylsilyl)-1-propen-3-ol (169).

Treatment of 1-phenyl-2-(trimethylsilyl)-ethyne 164 (3.31 g, 19.0 mmol) in diethyl ether (80 ml) with di-iso-butylaluminium hydride (1.5 M in toluene, 19.0 ml, 28.5 mmol), methyllithium (1.4 M in diethyl ether, 20.3 ml, 28.5 mmol) and paraformaldehyde (8.7 g, 0.29 mol), as described in General Procedure B, and subsequent column chromatography (10% ethyl acetate/light petroleum) gave (Z)-3-phenyl-2-(trimethylsilyl)-2-propen-1-ol 169 (1.55 g, 40%) as a colourless oil; \( \nu_{\text{max}} \) (film) 3350, 3060, 3024, 2959, 2897, 1596, 1492, 1249, 839 cm\(^{-1}\); \( \delta_H \) (250 MHz, CDCl\(_3\)) 7.38 (1H, s), 7.26 (5H, m), 4.36 (2H, br s), 1.42 (1H, br, s), 0.01 (9H, s); \( \delta_C \) (62.9 MHz, CDCl\(_3\)) 143.5 (s), 141.6 (d), 139.6 (s), 129.0 (d), 128.6 (d), 127.0 (d), 68.8 (t), -0.26 (q); \( m/z \) (C.I.\(^+\), thermospray) 224 (MNH\(_4^+\)), 206 (MNH\(_4^+\)-H\(_2\)O), 189, 117; Observed (MNH\(_4^+\)): 224.1471, C\(_{12}\)H\(_{22}\)NSiO requires: 224.1471.

(Z)-4,4-Dimethyl-2-(trimethylsilyl)-2-penten-1-ol (170).

Treatment of 3,3-dimethyl-1-(trimethylsilyl)-1-butyne 165 (3.85 g, 25.0 mmol) in diethyl ether (100 ml) with di-iso-butylaluminium hydride (1.5 M in toluene, 25.0 ml, 37.5 mmol), methyllithium (1.4 M in diethyl ether, 26.8 ml, 37.5 mmol) and paraformaldehyde (11.2 g, 0.38 mol), as described in General Procedure B, and subsequent column chromatography (10% ethyl acetate/light petroleum) gave (Z)-4,4-dimethyl-2-(trimethylsilyl)-2-penten-1-ol 170 (2.29 g, 49%) as a colourless oil; \( \nu_{\text{max}} \) (film) 3386, 2869, 1596, 1463, 1203, 682 cm\(^{-1}\); \( \delta_H \) (250 MHz, CDCl\(_3\)) 6.33 (1H, t, 1.0 Hz), 4.12 (2H, br s), 1.12 (10H, s), 0.28 (9H, s); \( \delta_C \) (62.9 MHz, CDCl\(_3\)) 157.6 (d), 153.5 (s), 72.7 (t), 33.7 (s), 30.9 (q), 1.86 (q); \( m/z \) (C.I.\(^+\), thermospray) 204 (MNH\(_4^+\)), 186 (MNH\(_4^+\)-H\(_2\)O), 169; Observed (MNH\(_4^+\)): 204.1784; C\(_{10}\)H\(_{26}\)NSiO requires: 204.1784.
General procedure C: Preparation of \((2R^*,3\,S^*)\)-2,3-epoxy-2-(trimethylsilyl)propan-1-ols (171-175).\(^8\)

To stirred solution of the appropriate alkene 166-170 and vanadyl acetoacetonate (0.1 eq) in dichloromethane (5.0 ml/mmol) at 0°C was added dropwise tert-butyl hydroperoxide (2.0 eq) dissolved in dichloromethane (0.5 ml/mmol). The mixture was allowed to warm gradually to room temperature and was stirred for 2 h. The reaction mixture was poured into water (2 x volume of solvent used) and filtered into a separating funnel. The layers were separated and the aqueous layer was extracted with dichloromethane. The combined organic extracts were washed successively with 5% aqueous ferrous sulfate, water and brine then dried over anhydrous Na\(_2\)SO\(_4\). The solvent was removed under reduced pressure and the residue was purified by column chromatography in the appropriate solvent system to give the product.

\((2R^*,3\,S^*)\)-2,3-Epoxy-2-(trimethylsilyl)tridecan-1-ol (171).

Treatment of \((Z)\)-2-(trimethylsilyl)-2-tridecen-1-ol 166 (4.05g, 15.0 mmol) dissolved in dichloromethane (75 ml) with vanadyl acetoacetonate (397 mg, 1.50 mmol) and tert-butyl hydroperoxide (70% in water, 3.86 g, 30.0 mmol) in dichloromethane (30 ml), as described in General Procedure C, and subsequent column chromatography (20% ethyl acetate/light petroleum) gave \((2R^*,3\,S^*)\)-2,3-epoxy-2-(trimethylsilyl)tridecan-1-ol 171 (3.09 g, 72%) as a colourless oil; \(\nu_{\text{max}}\) (film) 3255, 2954, 2919, 2850, 1463, 1409, 1377, 1252, 1090, 844 cm\(^{-1}\); \(\delta_H\) (250 MHz, CDCl\(_3\)) 3.55 (1H, d, 12.2 Hz), 3.46 (1H, d, 12.3 Hz), 2.91 (1H, dd, 6.2, 4.7 Hz), 2.05 (1H, br s), 1.49-1.05 (18H, m), 0.73 (3H, t, 6.2 Hz), 0.00 (9H, s); \(\delta_C\) (CDCl\(_3\), 62.9 MHz) 66.1 (t), 62.4 (d), 59.1 (s), 33.5 (t), 31.9 (t), 31.2 (t), 31.5 (t), 31.1 (t), 30.9 (t), 30.7 (t), 28.8 (t), 24.3 (t), 15.7 (q), 0.0 (q); \(m/z\) (CI.\(^{+}\), thermospray) 304 (MNH\(_4^+\)), 270, 197; Observed (MNH\(_4^+\)): 304.2670; C\(_{16}\)H\(_{38}\)NO\(_2\)Si requires: 304.2672.
(2R*,3S*)-2,3-Epoxy-7-(tetrahydropyranloxy)-2-(trimethylsilyl)heptan-1-ol (172).

Treatment of (Z)-7-(tetrahydropyranloxy)-2-(trimethylsilyl)-2-hepten-1-ol 167 (3.43 g, 12.0 mmol) dissolved in dichloromethane (60 ml) with vanadyl acetoacetate (318 mg, 1.20 mmol) and tert-butyl hydroperoxide (3.0 M in 2,2,4-trimethylpentane, 8.0 ml, 24.0 mmol) in dichloromethane (24 ml), as described in General Procedure C, and subsequent column chromatography (25% ethyl acetate/light petroleum) gave (2R*,3S*)-2,3-epoxy-7-(tetrahydropyranloxy)-2-(trimethylsilyl)heptan-1-ol 172 (1.57 g, 43%) as a colourless oil; \( \nu_{\text{max}} \) (CH\(_2\)Cl\(_2\)) 3449, 2943, 2867, 1350, 1032, 842 cm\(^{-1}\); \( \delta_H \) (250 MHz, CDCl\(_3\)) 4.43 (1H, t, 3.4 Hz), 3.56 (4H, m), 3.29 (2H, m), 2.93 (1H, t, 4.6 Hz), 1.71-1.29 (13H, m), 0.10 (9H, s); \( \delta_C \) (62.9 MHz, CDCl\(_3\)) 98.8 (d), 67.2 (t), 64.3 (t), 62.3 (t), 60.6 (d), 60.0 (s), 30.7 (t), 30.2 (t), 29.6 (t), 25.4 (t), 24.0 (t), 19.2 (t), -1.6 (q); \( m/z \) (C.I.\(^+\), thermospray) 320 (MNH\(_4^+\)), 303 (MH\(^+\)), 201, 129; Observed (MH\(^+\)): 303.1995, C\(_{15}\)H\(_{31}\)O\(_4\)Si requires: 303.1992.

(2R*,3S*)-2,3-Epoxy-2-(trimethylsilyl)-7-octen-1-ol (173).

Treatment of (Z)-2-(trimethylsilyl)-2,7-octadien-1-ol 168 (1.68 g, 8.5 mmol) dissolved in dichloromethane (40 ml) with vanadyl acetoacetate (225 mg, 0.85 mmol) and tert-butyl hydroperoxide (70% in water, 2.18 g, 17.0 mmol) in dichloromethane (17 ml), as described in General Procedure C, and subsequent column chromatography (20% ethyl acetate/light petroleum) gave (2R*,3S*)-2,3-epoxy-2-(trimethylsilyl)-7-octen-1-ol 173 (1.08 g, 60%) as a yellow oil; \( \nu_{\text{max}} \) (film) 3448, 2931, 2860, 1641, 1414, 1251, 1079, 912 cm\(^{-1}\); \( \delta_H \) (250 MHz, CDCl\(_3\)) 5.79 (1H, m), 4.99 (2H, m), 3.69 (1H, d, 12.2 Hz), 3.59 (1H, d, 12.2 Hz), 3.05 (1H, dd, 7.1, 4.4 Hz), 2.08 (2H, m), 1.91 (1H, br s), 1.55 (4H, m), 0.14 (9H, s); \( \delta_C \) (62.9 MHz, CDCl\(_3\)) 139.8 (d), 116.5 (t), 66.1 (t), 62.2 (d), 58.7 (s), 35.0 (t), 31.4 (t), 28.1 (t), 0.0 (q); \( m/z \) (C.I.\(^+\)) 232 (MNH\(_4^+\)), 215 (MH\(^+\)), 176, 160, 136, 90; Observed (MH\(^+\)): 215.1467; C\(_{11}\)H\(_{23}\)O\(_2\)Si requires: 215.1467.

(1S*,2R*)-1,2-Epoxy-1-phenyl-2-(trimethylsilyl)propan-3-ol (174).

Treatment of (Z)-3-phenyl-2-(trimethylsilyl)-2-propen-1-ol 169 (1.55 g, 7.0 mmol) dissolved in dichloromethane (35 ml) with vanadyl acetoacetate (186 mg, 0.7 mmol) and tert-butyl hydroperoxide (70% in water, 1.80 g, 14.0 mmol) in dichloromethane (14 ml), as described in General Procedure C, and subsequent column chromatography (20% ethyl acetate/light petroleum) gave (1S*,2R*)-1,2-epoxy-1-phenyl-2-(trimethylsilyl)propan-3-ol 174 (1.12 g, 80%) as a yellow oil; \( \nu_{\text{max}} \) (CH\(_2\)Cl\(_2\)) 3444, 2931, 2860, 1641, 1414, 1251, 1079, 912 cm\(^{-1}\); \( \delta_H \) (250 MHz, CDCl\(_3\)) 5.94 (1H, m), 5.88 (2H, m), 3.77 (1H, d, 12.2 Hz), 3.69 (1H, d, 12.2 Hz), 3.05 (1H, dd, 7.1, 4.4 Hz), 2.08 (2H, m), 1.91 (1H, br s), 1.55 (4H, m), 0.14 (9H, s); \( \delta_C \) (62.9 MHz, CDCl\(_3\)) 139.8 (d), 116.5 (t), 66.1 (t), 62.2 (d), 58.7 (s), 35.0 (t), 31.4 (t), 28.1 (t), 0.0 (q); \( m/z \) (C.I.\(^+\)) 232 (MNH\(_4^+\)), 215 (MH\(^+\)), 176, 160, 136, 90; Observed (MH\(^+\)): 215.1467; C\(_{11}\)H\(_{23}\)O\(_2\)Si requires: 215.1467.
petroleum) gave (1S*,2R*)-1,2-epoxy-1-phenyl-2-(trimethylsilyl)-propan-3-ol 174 (847 mg, 55%) as a colourless oil; ν_{max} (film) 3429, 3063, 3031, 2956, 1449, 1399, 1250, 842 cm⁻¹; δ_H (250 MHz, CDCl₃) 7.29 (5H, m), 4.29 (1H, s), 3.93 (1H, dd, 12.5, 3.7 Hz), 3.79 (1H, dd, 12.5, 8.6 Hz), 1.80 (1H, dd, 8.8, 4.0 Hz), -0.17 (9H, s); δ_C (62.9 MHz, CDCl₃) 136.9 (s), 127.7 (d), 127.2 (d), 126.7 (d), 63.8 (t), 59.9 (s), 59.4 (d), -2.4 (q); m/z (CI⁺) 240 (MNH₄⁺), 150, 133, 90; Observed (MNH₄⁺): 240.1420; C₁₂H₂₂NO₂Si requires: 240.1419.

(2R*,3S*)-4,4-Dimethyl-2,3-epoxy-2-(trimethylsilyl)-pentan-1-ol (175).

Treatment of (Z)-4,4-dimethyl-2-(trimethylsilyl)-2-penten-1-ol 170 (2.05 g, 11.0 mmol) dissolved in dichloromethane (55 ml) with vanadyl acetoacetate (291 mg, 1.1 mmol) and tert-butyl hydroperoxide (70% in water, 2.83 g, 22.0 mmol) in dichloromethane (22 ml), as described in General Procedure C, and subsequent column chromatography (30% diethyl ether/light petroleum) gave (2R*,3S*)-4,4-dimethyl-2,3-epoxy-2-(trimethylsilyl)pentan-1-ol 175 (1.35 g, 61%) as a colourless oil; ν_{max} (film) 3440, 2906, 2870, 1465, 1386, 814 cm⁻¹; δ_H (250 MHz, CDCl₃) 3.66 (1H, dd, 11.6, 7.8 Hz), 3.53 (1H, dd, 11.6, 2.0 Hz), 2.89 (1H, s), 1.26 (1H, br s), 1.01 (9H, s), 0.24 (9H, s); δ_C (62.9 MHz, CDCl₃) 71.5 (d), 67.1 (t), 56.5 (s), 31.6 (s), 27.6 (q), 0.3 (q); m/z (CI⁺, thermospray) 220 (MNH₄⁺), 113; Observed (MNH₄⁺): 220.1733; C₁₀H₂₆NO₂Si requires: 220.1733.

General procedure D: Preparation of (2R*,3S*)-2,3-epoxy-1-(methanesulfonyloxy)-2-(trimethylsilyl)propanes (155, 176-179).

To a stirred solution of the appropriate (2R*,3S*)-2,3-epoxy-2-(trimethylsilyl)propan-1-ol 171-175 in dichloromethane (3.0 ml/mmol) containing triethylamine (1.5 eq) at 0°C was added methanesulfonyl chloride (1.1 eq) dissolved in dichloromethane (1 ml/mmol). The ice-bath was removed and the mixture stirred for 30 minutes then poured into ice/water (3 ml/mmol). The layers were separated and the aqueous layer extracted with dichloromethane. The combined organic extracts were washed successively with 2M hydrochloric acid, saturated aqueous NaHCO₃ and brine then dried over anhydrous Na₂SO₄. The solvent was removed under reduced pressure to give the product which was used without further
purification. In view of the instability of these compounds they were characterised by $^1$H NMR and I.R. only.

$(2R^*,3S^*)$-2,3-Epoxy-1-(methanesulfonyloxy)-2-(trimethylsilyl) tridecane (155).

\[
\begin{align*}
n-C_{10}H_{21} & \quad \begin{array}{c} \text{O} \\ \text{SiMe}_3 \\ \text{OH} \end{array} \quad \rightarrow \quad n-C_{10}H_{21} & \quad \begin{array}{c} \text{O} \\ \text{SiMe}_3 \\ \text{OMs} \end{array}
\end{align*}
\]

Treatment of $(2R^*,3S^*)$-2,3-epoxy-2-(trimethylsilyl)tridecan-1-ol 171 (429 mg, 1.5 mmol) dissolved in dichloromethane (4.5 ml) containing triethylamine (0.31 ml, 2.25 mmol) with methanesulfonyl chloride (0.13 ml, 1.65 mmol), as described in General Procedure D, gave $(2R^*,3S^*)$-2,3-epoxy-1-(methanesulfonyloxy)-2-(trimethylsilyl)tridecane 155 (455 mg, 83%) as a slightly yellow oil; $\nu_{\text{max}}$ (film) 2959, 2950, 2869, 1693, 1541, 1470, 1454, 1249, 1142 (S=O), 1109, 753 cm$^{-1}$; $\delta_H$ (250 MHz, CDCl$_3$) 4.18 (1H, d, 11.2 Hz), 4.17 (1H, d, 11.2 Hz), 3.02 (3H, s), 2.96 (1H, dd, 6.7, 4.5 Hz), 1.47-1.25 (18H, m), 0.87 (3H, t, 6.3 Hz), 0.19 (9H, s).

$(2R^*,3S^*)$-2,3-Epoxy-1-(methanesulfonyloxy)-7-(tetrahydropyranyloxy)-2-(trimethylsilyl)-heptane (176).

\[
\begin{align*}
\text{O} & \quad \begin{array}{c} \text{O} \\ \text{SiMe}_3 \\ \text{OH} \end{array} \quad \rightarrow \quad \text{O} & \quad \begin{array}{c} \text{O} \\ \text{SiMe}_3 \\ \text{OMs} \end{array}
\end{align*}
\]

Treatment of $(2R^*,3S^*)$-2,3-epoxy-7-(tetrahydropyranyloxy)-2-(trimethylsilyl)heptan-1-ol 172 (604 mg, 2.0 mmol) dissolved in dichloromethane (6 ml) containing triethylamine (0.42 ml, 3.0 mmol) with methanesulfonyl chloride (0.18 ml, 2.1 mmol), as described in General Procedure D, gave $(2R^*,3S^*)$-2,3-epoxy-1-(methanesulfonyloxy)-7-(tetrahydropyranyloxy)-2-(trimethylsilyl)heptane 176 (581 mg, 76%) as a yellow oil; $\delta_H$ (250 MHz, CDCl$_3$) 4.59 (1H, t, 3.4 Hz), 4.23 (1H, d, 11.4 Hz), 4.17 (1H, d, 11.4 Hz), 3.80 (2H, m), 3.44 (2H, m), 3.04 (3H, s), 2.99 (1H, t, 4.3 Hz), 1.89-1.39 (12H, m), 0.20 (9H, s).
(2R*,3S*)-2,3-Epoxy-1-(methanesulfonyloxy)-2-(trimethylsilyl)-7-octene (177).

Treatment of (2R*,3S*)-2,3-epoxy-2-(trimethylsilyl)-7-octen-1-ol 173 (321 mg, 1.5 mmol) dissolved in dichloromethane (4.5 ml) containing triethylamine (0.31 ml, 3.0 mmol) with methanesulfonyl chloride (0.13 ml, 1.65 mmol), as described in General Procedure D, gave (2R*,3S*)-2,3-epoxy-1-(methanesulfonyloxy)-2-(trimethylsilyl)-7-octene 177 (345 mg, 79%) as a yellow oil; δH (250 MHz, CDCl3) 5.79 (1H, m), 5.01 (2H, m), 4.23 (1H, d, 11.1 Hz), 4.17 (1H, d, 11.4 Hz), 3.03 (3H, s), 2.99 (1H, dd, 7.3, 4.1 Hz), 2.19 (2H, m), 1.56 (4H, m), 0.20 (9H, s).

(1S*,2R*)-1,2-Epoxy-3-(methanesulfonyloxy)-1-phenyl-2-(trimethylsilyl)propane (178).

Treatment of (1S*,2R*)-1,2-epoxy-1-phenyl-2-(trimethylsilyl)propan-3-ol 174 (333 mg, 1.5 mmol) dissolved in dichloromethane (4.5 ml) containing triethylamine (0.31 ml, 3.0 mmol) with methanesulfonyl chloride (0.13 ml, 1.65 mmol), as described in General Procedure D, gave (1S*,2R*)-1,2-epoxy-3-(methanesulfonyloxy)-1-phenyl-2-(trimethylsilyl)propane 178 (374 mg, 79%) as a yellow oil; δH (250 MHz, CDCl3) 7.43 (5H, m), 4.50 (2H, m), 4.32 (1H, s), 3.24 (3H, s), 0.00 (9H, s).
(2R*,3S*)-4,4-Dimethyl-2,3-epoxy-1-(methanesulfonyloxy)-2-(trimethylsilyl)pentane (179).

Treatment of (2R*,3S*)-4,4-dimethyl-2,3-epoxy-2-(trimethylsilyl)pentan-1-ol 175 (606 mg, 3.0 mmol) dissolved in dichloromethane (9 ml) containing triethylamine (0.63 ml, 4.5 mmol) with methanesulfonyl chloride (0.26 ml, 3.3 mmol), as described in General Procedure D, gave (2R*,3S*)-4,4-dimethyl-2,3-epoxy-1-(methanesulfonyloxy)-2-(trimethylsilyl)pentane 179 (737 mg, 87%) as a yellow oil; \( \delta_H \) (250 MHz, CDCl\(_3\)) 4.34 (1H, d, 10.6 Hz), 3.89 (1H, d, 10.5 Hz), 3.03 (3H, s), 2.79 (1H, s), 1.02 (9H, s), 0.20 (9H, s).

Reaction of (2R*,3S*)-2,3-epoxy-1-(methanesulfonyloxy)-2-(trimethylsilyl)-tridecane (155) with caesium fluoride and methanol.

Caesium fluoride (76.0 mg, 0.50 mmol) was weighed directly into an oven-dried round-bottomed flask which had been cooled to room temperature under an atmosphere of nitrogen. (2R*,3S*)-2,3-Epoxy-1-(methanesulfonyloxy)-2-(trimethylsilyl)tridecane 155 (183 mg, 0.50 mmol) dissolved in acetonitrile (5 ml) was added followed by methanol (240 \( \mu \)l, 6.00 mmol). The mixture was stirred for 24 h at room temperature during which a white precipitate formed. The mixture was diluted with diethyl ether (10 ml) and the solid was filtered off. The solvent was removed under reduced pressure and the residue was purified by column chromatography (30% diethyl ether/light petroleum) to give as the least polar fraction, 3-fluoro-2-tridecanone 154 (60.0 mg, 55%) as a colourless oil: \( \nu_{\text{max}} \) (film) 2955, 2926, 2855, 1727, 1467, 1420, 1358, 1124, 1084 cm\(^{-1}\); \( \delta_H \) (400 MHz, CDCl\(_3\)) 4.55 (1H, ddd, 50.3, 7.5, 1.01).
4.9 Hz), 2.09 (3H, d, 6.7 Hz), 1.63 (2H, m), 1.30 (2H, m), 1.11 (14H, m), 1.74 (3H, t, 6.8 Hz); δC (100 MHz, CDCl₃) 205.2 [s, (JCF = 26 Hz)], 92.8 [d, (JCF = 183 Hz)], 31.9 (t), 29.6 (t), 29.53 (t), 29.47 (t), 29.32 (t), 29.28 (t), 29.15 (t), 25.8 (q), 24.5 (t), 22.7 (t), 14.1 (q); δF (376 MHz, CDCl₃, referenced to TMS at 0.00 ppm) -189.65 to -189.98 (m); m/z (C.I.⁺, thermospray) 234 (MNH₄⁺), 154, 117; Observed (MNH₄⁺): 234.2233; C₁₃H₂₉FNO requires: 234.2233. Further elution gave 3-methoxy-2-tridecanone³ 98 (39.4 mg, 35%) as a colourless oil; νmax (film) 2926, 2855, 2826, 1716, 1466, 1354, 1129, 1109 cm⁻¹; δH (250 MHz, CDCl₃) 3.54 (lH, t, 6.2 Hz), 3.35 (3H, s), 2.15 (2H, m), 1.58 (2H, m), 1.36-1.25 (16H, m), 0.88 (3H, t, 6.3 Hz); δC (62.9 MHz, CDCl₃) 211.3 (s), 87.5 (d), 58.0 (q), 31.8 (t), 29.5 (t), 29.4 (t), 29.3 (t), 29.2 (t), 25.0 (t), 22.6 (q), 14.0 (q) (3 methylene carbons of the alkyl chain were not resolved); m/z (C.I.⁺, thermospray) 246 (MNH₄⁺), 229 (MH⁺); Observed (MH⁺): 229.2168; C₁₄H₂₉O₂ requires: 229.2168.

Reaction of (2R⁺,3S⁺)-2,3-epoxy-1-(methanesulfonyloxy)-2-(trimethylsilyl) tridecane 155 with caesium fluoride and sodium methoxide.

Caesium fluoride (90.0 mg, 0.60 mmol) and sodium hydride (15.0 mg, 0.60 mmol) were weighed directly into an oven-dried flask that had been cooled to room temperature under an atmosphere of nitrogen. Acetonitrile (6 ml) containing methanol (0.29 ml, 7.20 mmol) was added and the mixture was stirred for 5 min. (2S⁺,3R⁺)-2,3-Epoxy-1-(methanesulfonyloxy)-2-(trimethylsilyl)tridecane 155 (221 mg, 0.60 mmol) dissolved in acetonitrile (1 ml) was added and the solution was stirred for 24 h at room temperature during which a white precipitate formed. The mixture was diluted with diethyl ether (10 ml) and the white solid was filtered off. The solvent was removed under reduced pressure and the residue was purified by column chromatography (30% diethyl ether/light petroleum) to give 3-methoxy-2-tridecanone³ 98 (53.0 mg, 39%) as a colourless oil. The spectroscopic data was in accordance with that previously described.
General procedure E: Reaction of $\text{(2R}^*,\text{3S}^{*})\text{-2,3-epoxy-1-(methanesulfonyloxy)-2-(trimethylsilyl)propanes 155, 176-179 with sodium alkoxides.}$

![Chemical structure]

The appropriate alcohol $\text{R}^2\text{OH (3-10 eq) was added dropwise to sodium hydride (2.1 eq) stirred in tetrahydrofuran (5 ml/mmol) at 0°C. When gas evolution was complete the appropriate mesylate dissolved in tetrahydrofuran (2 ml/mmol) was added dropwise and the reaction mixture was gradually allowed to warm to room temperature. After the reaction was estimated to be complete, by TLC, the mixture was poured into water (7 ml/mmol), the layers were separated and the aqueous layer extracted with diethyl ether. The combined organic extracts were washed with brine and dried over MgSO$_4$. The solvent was removed under reduced pressure and the residue was purified by column chromatography in the appropriate solvent system.}

**Reaction of $\text{(2R}^*,\text{3S}^{*})\text{-2,3-epoxy-1-(methanesulfonyloxy)-2-(trimethylsilyl)tridecane (155) with sodium methoxide.}$**

![Chemical structure]

Treatment of $\text{(2R}^*,\text{3S}^{*})\text{-2,3-epoxy-1-(methanesulfonyloxy)-2-(trimethylsilyl)tridecane 155 (291 mg, 0.80 mmol) dissolved in tetrahydrofuran (2 ml) with a solution of sodium methoxide, prepared from methanol (0.24 ml, 8.00 mmol) added dropwise to sodium hydride (40.0 mg, 1.70 mmol) in tetrahydrofuran (4 ml) for 2.5 h, as described in General procedure E, and subsequent column chromatography (25% diethyl ether/light petroleum) gave 3-methoxy-2-tridecanone 98 (116 mg, 64%) as a colourless oil. The spectroscopic data in accordance with that previously described.}
Reaction of (2R*,3S*)-2,3-epoxy-1-(methanesulfonyloxy)-2-(trimethylsilyl) tridecane (155) with sodium benzyloxide.

Treatment of (2R*,3S*)-2,3-epoxy-1-(methanesulfonyloxy)-2-(trimethylsilyl)-tridecane 155 (437 mg, 1.20 mmol) dissolved in tetrahydrofuran (4 ml) with a solution of sodium benzyloxide, prepared from benzyl alcohol (0.37 ml, 3.6 mmol) and sodium hydride (60 mg, 2.50 mmol) in tetrahydrofuran (5 ml) for 2.0 h, as described in General Procedure E, and subsequent column chromatography (25% diethyl ether/light petroleum) gave 3-benzyloxy-2-tridecanone 181 (242 mg, 66%) as a yellow oil; $\nu_{\text{max}}$ (film) 3021, 2952, 2925, 2854, 1716, 1466, 1455, 1099, 734 cm$^{-1}$; $\delta_H$ (250 MHz, CDCl$_3$) 7.35 (5H, m), 4.58 (1H, d, 11.7 Hz), 4.42 (1H, d, 11.7 Hz), 3.75 (1H, dd, 7.5, 5.3 Hz), 2.18 (3H, s), 1.67 (2H, m), 1.36-1.26 (16H, m), 0.89 (3H, t, 6.2 Hz); $\delta_C$ (62.9 MHz, CDCl$_3$) 212.2 (s), 138.3 (s), 128.4 (d), 127.8 (d), 127.8 (d), 85.1 (d), 72.3 (t), 31.9 (t), 31.8 (t), 29.5 (t), 29.47 (t), 29.34 (t), 29.28 (t), 29.2 (t), 25.2 (q), 25.1 (t), 22.6 (t), 14.0 (q); $m/z$ (C.I.$^+$, thermospray) 322 (MNH$_4^+$), 170, 108; Observed (MNH$_4^+$): 322.2746; C$_{20}$H$_{36}$N$_2$O$_2$ requires: 322.2746.

Reaction of (2R*,3S*)-2,3-epoxy-1-(methanesulfonyloxy)-2-(trimethylsilyl) tridecane (155) with sodium iso-propoxide.

Treatment of (2R*,3S*)-2,3-epoxy-1-(methanesulfonyloxy)-2-(trimethylsilyl)-tridecane 155 (437 mg, 1.20 mmol) dissolved in tetrahydrofuran (2 ml) with a solution of sodium iso-propoxide, prepared from iso-propyl alcohol (0.28 ml, 3.6 mmol) and sodium hydride (60 mg, 2.50 mmol) in tetrahydrofuran (5 ml) for 2.5 h, as described in General Procedure E, and subsequent column chromatography (25% diethyl ether/light petroleum) gave 3-iso-propyloxy-2-tridecanone 182 (178 mg, 58%) as a colourless oil; $\nu_{\text{max}}$ (film) 2956, 2924, 2855, 1716, 1466, 1376, 1234, 1096 cm$^{-1}$; $\delta_H$ (250 MHz, CDCl$_3$) 3.68 (1H, dd, 7.4, 5.1 Hz), 104
3.51 (1H, m), 2.25 (3H, s), 1.47-1.21 (18H, m), 1.18 (3H, d, 6.2 Hz), 1.15 (3H, d, 6.0 Hz), 0.87 (3H, t, 6.1 Hz); δC (62.9 MHz, CDCl₃) 213.3 (s), 83.7 (d), 71.7 (d), 32.7 (t), 31.9 (t), 29.6 (t), 29.5 (t), 29.4 (t), 29.3 (t), 29.1 (t), 25.4 (t), 25.1 (q), 23.1 (q), 22.7 (t), 21.9 (q), 14.2 (q); m/z (C.I.⁺, thermospray) 274 (MNH₄⁺), 257 (MH⁺); Observed (MH⁺): 257.2481; C₁₆H₃₃O₂ requires: 257.2481.

Reaction of (2R⁺,3S⁺)-2,3-epoxy-1-(methanesulfonyloxy)-2-(trimethylsilyl) tridecane (155) with sodium 2-propen-1-oxide.

\[ \text{n-C}_{10}H_{21}O^+\text{SiMe}_3 \rightarrow \text{n-C}_{10}H_{21}O^-\text{Me} \]

Treatment of (2R⁺,3S⁺)-2,3-epoxy-1-(methanesulfonyloxy)-2-(trimethylsilyl)tridecane 155 (183 mg, 0.50 mmol) dissolved in tetrahydrofuran (1 ml) with a solution of sodium 2-propen-1-oxide, prepared from 2-propen-1-ol (0.17 ml, 2.5 mmol) and sodium hydride (25 mg, 1.05 mmol) in tetrahydrofuran (3 ml) for 2.5 h, as described in General Procedure E, and subsequent column chromatography (25% diethyl ether/light petroleum) gave 3-(2-propen-1-oxy)-2-tridecanone 183 (40.0 mg, 31%) as a yellow oil; νmax (film) 2952, 2926, 2854, 1718, 1640, 1129, 1097 cm⁻¹; δH (250 MHz, CDCl₃) 5.89 (1H, m), 5.29 (1H, m), 5.19 (1H, m), 4.02 (1H, m), 3.92 (1H, m), 3.69 (1H, dd, 7.3, 5.6 Hz), 2.16 (3H, s), 1.61 (2H, m), 1.32-1.21 (16H, m), 0.88 (3H, t, 6.3 Hz); δC (62.9 MHz, CDCl₃) 210.5 (s), 132.6 (d), 116.2 (t), 83.7 (d), 69.9 (t), 30.6 (t), 30.4 (t), 28.12 (t), 28.09 (t), 27.9 (t), 27.6 (t), 23.9 (t), 23.7 (q), 21.2 (t), 13.8 (q) (1 methylene carbon of the alkyl chain was not resolved); m/z (E.I.⁺) 255 (MH⁺), 211, 95, 81, 69, 57, 41; Observed (M⁺): 254.2245; C₁₆H₃₀O₂ requires: 254.2254.
Reaction of \((2R^*,3S^* )-2,3\text{-epoxy}-1\text{-}(\text{methanesulfonyloxy})-7\text{-}(\text{tetrahydropyranyloxy})-2\text{-}(\text{trimethylsilyl})\text{heptane} (176)\) with sodium methoxide.

\[
\begin{align*}
\text{OMs} & \quad \rightarrow \\
\text{OMe} &
\end{align*}
\]

Treatment of \((2R^*,3S^* )-2,3\text{-epoxy}-1\text{-}(\text{methanesulfonyloxy})-7\text{-}(\text{tetrahydropyranyloxy})-2\text{-}(\text{trimethylsilyl})\text{heptane} \text{ 176 (254 mg, 0.70 mmol)}\) dissolved in tetrahydrofuran (2 ml) with a solution of sodium methoxide, prepared from methanol (283 \(\mu l, 7.00 \text{ mmol}\)) and sodium hydride (36.0 mmg, 1.47 mmol) in tetrahydrofuran (5 ml) for 2.5 h, as described in General Procedure E, and subsequent column chromatography (25% diethyl ether/light petroleum) gave \(7\text{-}(\text{tetrahydropyranyloxy})\text{-3-methoxyheptan-2-one} \text{ 184 (105 mg, 61\%)}\) as a colourless oil; \(\nu_{\text{max}}\) (film) 2939, 2869, 1715, 1353, 1200, 1121, 1035 cm\(^{-1}\); \(\delta_H\) (250 MHz, CDCl\(_3\)) 4.56 (1H, t, 3.6 Hz), 3.80 (2H, m), 3.56 (1H, t, 6.8 Hz), 3.44 (2H, m), 3.36 (3H, s), 2.17 (3H, s), 1.84-1.36 (12H, m); \(\delta_C\) (62.9 MHz, CDCl\(_3\)) 211.5 (s), 98.9 (d), 87.4 (d), 67.2 (t), 62.4 (t), 58.1 (q), 31.7 (t), 30.8 (t), 29.5 (t), 25.5 (t), 25.1 (q), 22.0 (t), 19.7 (t); \(m/z\) (ClI\(^+\), thermospray) 245 (MH\(^+\)), 161, 142, 111; Observed (MNa\(^+\)): 267.1569; \(C_{13}H_{24}NaO_4\) requires: 267.1569.

Reaction of \((2R^*,3S^* )-2,3\text{-epoxy}-1\text{-}(\text{methanesulfonyloxy})-7\text{-}(\text{tetrahydropyranyloxy})-2\text{-}(\text{trimethylsilyl})\text{heptane} (176)\) with sodium benzyloxide.

\[
\begin{align*}
\text{OMs} & \quad \rightarrow \\
\text{OCH}_2\text{Ph} &
\end{align*}
\]

Treatment of \((2R^*,3S^* )-2,3\text{-epoxy}-1\text{-}(\text{methanesulfonyloxy})-7\text{-}(\text{tetrahydropyranyloxy})-2\text{-}(\text{trimethylsilyl})\text{heptane} \text{ 176 (176 mg, 0.48 mmol)}\) dissolved in tetrahydrofuran (1 ml) with a solution of sodium benzyloxide, prepared from benzyl alcohol (150 \(\mu l, 1.45 \text{ mmol}\)) and sodium hydride (24.0 mg, 1.00 mmol) in tetrahydrofuran (5 ml) for 2.5 h, as described in General Procedure E, and subsequent column chromatography (25% diethyl ether/light petroleum) gave \(7\text{-}(\text{tetrahydropyranyloxy})\text{-3-methoxyheptan-2-one} \text{ 185 (140 mg, 66\%)}\) as a colourless oil; \(\nu_{\text{max}}\) (film) 2939, 2869, 1715, 1353, 1200, 1121, 1035 cm\(^{-1}\); \(\delta_H\) (250 MHz, CDCl\(_3\)) 4.56 (1H, t, 3.6 Hz), 3.80 (2H, m), 3.56 (1H, t, 6.8 Hz), 3.44 (2H, m), 3.36 (3H, s), 2.17 (3H, s), 1.84-1.36 (12H, m); \(\delta_C\) (62.9 MHz, CDCl\(_3\)) 211.5 (s), 98.9 (d), 87.4 (d), 67.2 (t), 62.4 (t), 58.1 (q), 31.7 (t), 30.8 (t), 29.5 (t), 25.5 (t), 25.1 (q), 22.0 (t), 19.7 (t); \(m/z\) (ClI\(^+\), thermospray) 245 (MH\(^+\)), 161, 142, 111; Observed (MNa\(^+\)): 267.1569; \(C_{13}H_{24}NaO_4\) requires: 267.1569.
petroleum) gave 7-(tetrahydropyranlyoxy)-3-benzyloxyheptan-2-one 185 (93.0 mg, 60%) as a colourless oil; \( \nu_{\text{max}} \) (film) 3042, 2940, 2867, 1714, 1352, 1027 cm\(^{-1}\); \( \delta_H \) (250 MHz, CDCl\(_3\)) 7.24 (5H, m), 4.59 (1H, d, 12.9 Hz), 4.55 (1H, t, 2.8 Hz), 4.41 (1H, d, 12.9 Hz), 3.90-3.68 (3H, m), 3.48 (1H, m), 3.36 (1H, m), 2.18 (3H, s), 1.86-1.40 (12H, m); \( \delta_C \) (62.9 MHz, CDCl\(_3\)) 211.4 (s), 137.5 (s), 128.5 (d), 127.9 (d), 127.9 (d), 98.8 (d), 85.1 (d), 72.4 (t), 67.2 (t), 62.3 (t), 31.8 (t), 30.7 (t), 29.4 (t), 25.5 (t), 25.3 (q), 22.0 (t), 19.6 (t); \( m/z \) (C.I.\(^+\), thermospray) 321 (MH\(^+\)), 237, 228, 128; Observed (MNa\(^+\)): 343.1882; \( C_{19}H_{28}NaO_4 \) requires: 343.1885.

**Reaction of (2\( R^* \),3\( S^* \))-2,3-epoxy-1-(methanesulfonyloxy)-2-(trimethylsilyl)-7-octene (177) with sodium methoxide.**

Treatment of (2\( R^* \),3\( S^* \))-2,3-epoxy-1-(methanesulfonyloxy)-2-(trimethylsilyl)-7-octene 177 (321 mg, 1.10 mmol) dissolved in tetrahydrofuran (2 ml) with a solution of sodium methoxide, prepared from methanol (445 \( \mu \)l, 11.0 mmol) and sodium hydride (53.0 mmg, 2.20 mmol) in tetrahydrofuran (5 ml) for 2.5 h, as described in General Procedure E, and subsequent column chromatography (25% diethyl ether/light petroleum) gave 3-methoxy-7-octen-2-one 186 (94.6 mg, 55%) as a colourless oil; \( \nu_{\text{max}} \) (film) 2935, 2866, 2827, 1716, 1641, 1457 cm\(^{-1}\); \( \delta_H \) (250 MHz, CDCl\(_3\)) 5.66 (1H, m), 4.91 (2H, m), 3.44 (1H, t, 6.4 Hz), 3.24 (3H, s), 2.04 (3H, s), 1.94 (2H, m), 1.52 (2H, m), 1.37 (2H, m); \( \delta_C \) (62.9 MHz, CDCl\(_3\)) 211.7 (s), 138.5 (d), 115.3 (t), 87.7 (d), 58.4 (q), 33.7 (t), 31.5 (t), 25.4 (q), 24.8 (t); \( m/z \) (C.I.\(^+\), thermospray) 174 (MNH\(_4^+\)); Observed (MNH\(_4^+\)): 174.1494; \( C_{9}H_{20}NO_2 \) requires: 174.1494.
Reaction of (2R*, 3S*)-2,3-epoxy-1-(methanesulfonyloxy)-2-(trimethylsilyl)-7-octene (177) with sodium iso-propoxide.

Treatment of (2R*,3S*)-2,3-epoxy-1-(methanesulfonyloxy)-2-(trimethylsilyl)-7-octene 177 (146 mg, 0.50 mmol) dissolved in tetrahydrofuran (1 ml) with a solution of sodium iso-propoxide, prepared from iso-propyl alcohol (150 μl, 2.00 mmol) and sodium hydride (25.0 mmg, 1.05 mmol) in tetrahydrofuran (3 ml) for 2.5 h, as described in General Procedure E, and subsequent column chromatography (25% diethyl ether/light petroleum) gave 3-iso-propoxy-7-octen-2-one 187 (52.0 mg, 57%) as a colourless oil; v\text{max} (film) 3078, 2974, 2934, 1714, 1641, 1457, 1376, 1354, 1120, 913 cm\(^{-1}\); δ\textsubscript{H} (400 MHz, CDCl\(_3\)) 5.58 (1H, m), 4.77 (2H, m), 3.50 (1H, m), 3.33 (1H, m), 1.96 (3H, s), 1.87 (2H, m), 1.38-1.22 (4H, m), 0.99 (3H, d, 6.1 Hz), 0.95 (3H, d, 6.0 Hz); δ\textsubscript{C} (100 MHz, CDCl\(_3\)) 214.5 (s), 139.7 (d), 116.4 (t), 85.0 (d), 73.3 (d), 34.8 (t), 33.5 (t), 26.6 (q), 26.2 (t), 24.4 (q), 23.1 (q); m/z (C.I.\(^+\)) 202 (MNH\(_4^+\)); Observed (MNH\(_4^+\)): 202.1807; C\(_{11}\)H\(_{24}\)N\(_2\)O\(_2\) requires: 202.1807.

Reaction of (1S*, 2R*)-1,2-epoxy-3-(methanesulfonyloxy)-1-phenyl-2-(trimethylsilyl)-propane (178) with sodium methoxide.

Treatment of (1S*,2R*)-1,2-epoxy-3-(methanesulfonyloxy)-1-phenyl-2-(trimethylsilyl)-propane 178 (207 mg, 0.69 mmol) dissolved in tetrahydrofuran (2 ml) with a solution of sodium methoxide, prepared from methanol (279 μl, 6.90 mmol) and sodium hydride (35.0 mmg, 1.45 mmol) tetrahydrofuran (4 ml) for 2.0 h, as described in General Procedure E, and subsequent column chromatography (25% diethyl ether/light petroleum) gave as the least polar fraction methyl 3-phenylpropanoate 104 (20.0 mg, 18%) as a yellow pungent oil; v\text{max} (film) 3064, 3029, 2952, 1739, 1497, 1454, 1364, 1279, 1163, 735 cm\(^{-1}\); δ\textsubscript{H} (250 MHz, CDCl\(_3\)) 7.42 (3H, m), 7.35 (2H, m), 3.81 (3H, s), 3.10 (2H, t, 7.6 Hz), 2.78 (2H, t,
8.1 Hz; \( \delta_C \) (62.9 MHz, CDCl\(_3\)) 175.3 (s), 142.5 (s), 130.5 (d), 130.3 (d), 128.5 (d), 53.5 (q), 37.7 (t), 32.9 (t); \( m/z \) (C.I.\(^+\), thermospray) 182 (MNH\(_4^+\)); Observed (MNH\(_4^+\)): 182.1181; C\(_{10}\)H\(_{16}\)NO\(_2\) requires: 182.1181. Further elution gave 1-methoxy-1-phenylpropan-2-one 211 (31.0 mg, 27%) as a yellow oil;\(^{110} \nu_{\text{max}} \) (film) 3063, 3031, 2992, 2936, 1719, 1494, 1454, 1419, 1196, 1103, 735 cm\(^{-1}\); \( \delta_H \) (250 MHz, CDCl\(_3\)) 7.49 (5H, m), 4.78 (1H, s), 3.51 (3H, s), 2.24 (3H, s); \( \delta_C \) (62.9 MHz, CDCl\(_3\)) 207.0 (s), 136.3 (s), 129.2 (d), 128.9 (d), 127.3 (d), 89.8 (d), 57.6 (q), 25.4 (q); \( m/z \) (C.I.\(^+\), thermospray) 182 (MNH\(_4^+\)), 165; Observed (MNH\(_4^+\)): 182.1181; C\(_{10}\)H\(_{16}\)NO\(_2\) requires: 182.1181.

**Reaction of (2R\(^*\),3S\(^*\))-4,4-dimethyl-2,3-epoxy-1-(methanesulfonyloxy)-2-(trimethylsilyl)-pentane (179) with sodium benzyloxide.**

![Chemical structure of 179 and 188](image)

Treatment of (2R\(^*\),3S\(^*\))-4,4-dimethyl-2,3-epoxy-1-(methanesulfonyloxy)-2-(trimethylsilyl) pentane 179 (196 mg, 0.70 mmol) dissolved in tetrahydrofuran (2 ml) with a solution of sodium benzyloxide, prepared from benzyl alcohol (217 \( \mu \)l, 2.10 mmol) and sodium hydride (33.0 mmg, 1.41 mmol) in tetrahydrofuran (4 ml) for 2.0 h, as described in General Procedure E, and subsequent column chromatography (25% diethyl ether/light petroleum) gave a mixture of products (88.0 mg) that consisted predominantly of 4,4-dimethyl-3-benzyloxy-2-pentanone 188; \( \delta_H \) (250 MHz, CDCl\(_3\)) 7.35 (5H, m), 4.55 (1H, d, 11.6 Hz), 4.39 (1H, d, 11.7 Hz), 3.38 (1H, s), 2.18 (3H, s), 0.98 (9H, s).
Preparation of \((2S^*,3R^*,4S^*)-3,4\text{-}epoxy\text{-}3\text{-}(\text{trimethylsilyl})\text{tetradecan}\text{-2-ol}\) (192.).

To a stirred solution of \((2R^*,3S^*)\text{-}2,3\text{-}epoxy\text{-}2\text{-}(\text{trimethylsilyl})\text{tridecan}\text{-1-ol} 171\) (930 mg, 3.25 mmol), 4-methylmorpholine-N-oxide (571 mg, 4.87 mmol) and powdered 4 Å molecular sieves (1.60 g) stirred in dichloromethane (10 ml) at 0°C was added gradually tetrapropylammonium perruthenate (TPAP) (57.2 mg, 0.15 mmol). The mixture was stirred for 3 h and was allowed to gradually warm to room temperature. The mixture was filtered through a plug of flash silica and the solvent was removed under reduced pressure. The residue was purified by column chromatography (10% ethyl acetate/light petroleum) to give \((2S^*,3S^*)\text{-}2,3\text{-}epoxy\text{-}2\text{-}(\text{trimethylsilyl})\text{tridecan} 191\) (599 mg, δH (250 MHz, CDCl₃) 8.91 (1H, s), 3.07 (1H, dd, 6.8, 4.8 Hz), 1.76-1.23 (18H, m), 0.88 (3H, t, 6.3 Hz), 0.18 (9H, s).

This aldehyde (599 mg, 0.21 mmol) was dissolved in diethyl ether (3 ml) and treated with methylmagnesium iodide (3.0 M in diethyl ether, 0.84 ml, 2.52 mmol) at 0°C. The mixture was stirred for 1 h at 0°C after which the reaction was estimated to be complete by TLC. The mixture was poured into ice/water (10 ml) and diluted with diethyl ether (10 ml). The layers were separated and the aqueous layer was extracted with diethyl ether (2 x 5 ml). The combined organic extracts were washed with brine (10 ml) and dried over MgSO₄. The solvent was removed under reduced pressure and the residue was purified by column chromatography (10% ethyl acetate/light petroleum) to give \((2S^*,3R^*,4S^*)\text{-}3,4\text{-}epoxy\text{-}3\text{-}(\text{trimethylsilyl})\text{tetradecan} 192\) (184 mg, 19% over the two steps) as a yellow oil; νmax (film) 3458, 2956, 2925, 2855, 1466, 1408, 1386, 1135 cm⁻¹; δH (250 MHz, CDCl₃) 3.96 (1H, q, 6.3 Hz), 3.08 (1H, t, 6.4 Hz), 2.26 (1H, br s), 1.58-1.22 (18H, m), 1.23 (3H, d, 6.2 Hz), 0.88 (3H, t, 6.4 Hz), 0.17 (9H, s); δC (62.9 MHz, CDCl₃) 66.4 (d), 60.1 (s), 58.6 (d), 33.1 (t), 31.4 (t), 30.9 (t), 30.80 (t), 30.77 (t), 30.71 (t), 30.5 (t), 28.3 (t), 23.9 (t), 20.5 (q), 15.3 (q), 0.0 (q); m/z (E.I.⁺) 157, 130, 86, 76, 73, 41, 27; Observed (M⁺): 300.2483; C₁₇H₃₆O₂Si requires: 300.2484.
(2S*,3R*,4S*)-3,4-Epoxy-2-(methanesulfonyleoxy)-3-(trimethylsilyl)tetradecane (197).

Treatment of (2S*,3R*,4S*)-3,4-epoxy-2-(trimethylsilyl)tetradecan-2-ol 192 (180 mg, 0.60 mmol) in dichloromethane (1 ml) containing triethylamine (0.125 ml, 0.90 mmol) with methanesulfonyl chloride (54 µl, 0.66 mmol), as described in General Procedure D, gave (2S*,3R*,4S*)-3,4-epoxy-2-(methanesulfonyleoxy)-3-(trimethylsilyl)tetradecane 195 (185 mg, 82%) as a yellow oil; δH (250 MHz, CDCl3) 4.75 (1H, q, 6.5 Hz), 3.14 (1H, dd, 7.4, 4.8 Hz), 3.03 (3H, s), 1.44 (3H, d, 6.5 Hz), 1.61-1.22 (18H, m), 0.87 (3H, t, 6.2 Hz), 0.19 (9H, s).

Reaction of (2S*,3R*,4S*)-3,4-epoxy-2-(methanesulfonyleoxy)-3-(trimethylsilyl)tetradecane (195) with sodium methoxide.

Treatment of (2S*,3R*,4S*)-3,4-epoxy-2-(methanesulfonyleoxy)-3-(trimethylsilyl)tetradecane 195 (170 mg, 0.45 mmol) in tetrahydrofuran (1 ml) with a solution of sodium methoxide, prepared from methanol (182 µl, 4.50 mmol) and sodium hydride (23 mg, 0.94 mmol) in tetrahydrofuran (2 ml) for 16 h, as described in General Procedure E, and subsequent column chromatography (25% diethyl ether/light petroleum) gave 4-methoxy-3-tetradecanone 196 (63 mg, 58%) as a colourless oil; νmax (CH2Cl2) 2962, 1713, 1462, 1265, 1108, 746 cm⁻¹; δH (250 MHz, CDCl3) 3.59 (1H, t, 6.3 Hz), 3.34 (3H, s), 2.51 (2H, q, 7.4 Hz), 1.60 (2H, m), 1.35-1.25 (16H, m), 1.06 (3H, t, 7.3 Hz), 0.88 (3H, t, 6.5 Hz); δC (62.9 MHz, CDCl3) 213.8 (s), 87.3 (d), 58.1 (q), 32.1 (t), 31.9 (t), 30.7 (t), 29.5 (t), 29.4 (t), 29.3 (t), 28.8 (t), 25.1 (t), 22.7 (t), 22.3 (t), 14.1 (q), 7.3 (q); m/z (C.I.⁺, thermospray) 266 (MNH₄⁺), 244, 158, 141, 109, 95; Observed (MH⁺): 243.2323; C₁₅H₃₁O₂ requires: 243.2324.
Preparation of \((3S^*,4R^*,5S^*)-4,5\text{-epoxy-4-(trimethylsilyl)pentadecan-3-ol}\) (197).

\[
\begin{align*}
\text{n-C}_{10}H_{21} & \xrightarrow{\text{OH}} \text{n-C}_{10}H_{21} & \xrightarrow{\text{CHO}} \text{n-C}_{10}H_{21} \\
171 & \quad 191 & \quad 197
\end{align*}
\]

To a stirred solution of \((2R^*,3S^*)-2,3\text{-epoxy-2-(trimethylsilyl)tridecan-1-ol} 171\) (2.15 g, 7.50 mmol), 4-methylmorpholine-N-oxide (1.32 g, 11.3 mmol) and powdered 4 Å molecular sieves (3.75 g) stirred in dichloromethane (15 ml) at 0°C was added gradually tetrapropylammonium perruthenate (TPAP) (132 mg, 0.38 mmol). The mixture was stirred for 3 h and was allowed to gradually warm to room temperature. The mixture was then filtered through a plug of flash silica and the solvent was removed under reduced pressure. The residue was purified by column chromatography (10% ethyl acetate/light petroleum) to give \((2S^*,3S^*)-4,5\text{-epoxy-2-(trimethylsilyl)tridecanal} 191\) (1.29 g).

A portion of this aldehyde (1.14 g, 4.0 mmol) was dissolved in diethyl ether (12 ml) and treated with ethylmagnesium bromide (3.0 M in diethyl ether, 1.60 ml, 4.80 mmol) at 0°C. The mixture was stirred for 1 h at 0°C after which the reaction was estimated to be complete by TLC. The mixture was poured into ice/water (20 ml) and diluted with diethyl ether (20 ml). The layers were separated and the aqueous layer was extracted with diethyl ether (2 x 10 ml). The combined organic extracts were washed with brine (20 ml) and dried over MgSO₄. The solvent was removed under reduced pressure and the residue was purified by column chromatography (10% ethyl acetate/light petroleum) to give \((3S^*,4R^*,5S^*)-4,5\text{-epoxy-4-(trimethylsilyl)pentadecan-3-ol} 197\) (454 mg, 22% over the two steps) as a yellow oil; \(\nu_{\text{max}}\) (film) 3496, 2958, 2925, 2872, 1465, 1419, 1378, 1264, 1058, 755 cm⁻¹; \(\delta_H\) (250 MHz, CDCl₃) 3.76 (1H, dd, 8.4, 2.3 Hz), 3.09 (1H, t, 6.6 Hz), 2.20 (1H, s), 1.59-1.18 (20 H, m), 1.02 (3H, t, 7.3 Hz), 0.88 (3H, t, 5.5 Hz), 0.15 (9H, s); \(\delta_C\) (62.9 MHz, CDCl₃) 70.3 (d), 58.9 (s), 57.6 (d), 31.8 (t), 30.1 (t), 29.5 (t), 29.4 (t), 29.2 (t), 26.9 (t), 26.5 (t), 22.6 (t), 14.0 (q), 10.1 (q), -1.3 (q) (two carbons of the alkyl chain were not resolved); \(m/z\) (C.I.⁺, thermospray) 332 (MNH₄⁺), 297, 225; Observed (MNH₄⁺): 332.2985, C₁₈H₄₂NO₂Si requires: 332.2985.
Treatment of (3S*,4R*,5S*)-4,5-epoxy-4-(trimethylsilyl)pentadecan-3-ol 197 (439 mg, 1.40 mmol) in dichloromethane (3 ml) containing triethylamine (0.29 ml, 2.10 mmol) with methanesulfonyl chloride (0.12 ml, 1.54 mmol), as described in General Procedure D, gave (3S*,4R*,5S*)-4,5-epoxy-3-(methanesulfonyloxy)-4-(trimethylsilyl)pentadecane 198 (411 mg, 75%) as a yellow oil; δH (250 MHz, CDCl3) 4.62 (1H, dd, 7.1, 2.5 Hz), 3.14 (1H, dd, 4.7, 2.4 Hz), 3.05 (3H, s), 1.56 (2H, m), 1.63-1.26 (18H, m), 1.05 (3H, t, 7.3 Hz), 0.88 (3H, t, 6.2 Hz), 0.17 (9H, s).

Preparation of (1S*,2S*,3S*)-1-phenyl-2,3-epoxy-2-(trimethylsilyl)tridecan-1-ol (200).

To a stirred solution of (2R*,3S*)-2,3-epoxy-2-(trimethylsilyl)tridecan-1-ol 171 (2.86 g, 10.0 mmol), 4-methylmorpholine-N-oxide (1.76 g, 15.0 mmol) and powdered 4 Å molecular sieves (5.0 g) in dichloromethane (15 ml) at 0°C was added gradually tetrapropylammonium perruthenate (TPAP) (176 mg, 0.50 mmol). 84 The mixture was stirred for 3 h and was allowed to gradually warm to room temperature. The mixture was then filtered through a plug of flash silica and the solvent was removed under reduced pressure. The residue was purified by column chromatography (10% ethyl acetate/light petroleum) to give (2S*,3S*)-4,5-epoxy-2-(trimethylsilyl)tridecanal 191 (1.92 g).

A portion of this aldehyde (1.70 g, 6.00 mmol) was dissolved in diethyl ether (6 ml) and added to phenylmagnesium bromide (3.0 M in diethyl ether, 2.00 ml, 6.00 mmol) at 0°C. After 20 min the reaction was estimated to be complete, by TLC, and the mixture was poured into ice/water (20 ml) and diluted with diethyl ether (20 ml). The layers were separated and...
the aqueous layer was extracted with diethyl ether (2 x 10 ml). The combined organic extracts were washed with brine (20 ml) and dried over MgSO₄. The solvent was removed under reduced pressure and the residue was purified by column chromatography (20% diethyl ether/light petroleum) to give (1S*,2S*,3S*)-1-phenyl-2,3-epoxy-2-(trimethylsilyl)tridecan-1-ol 200 (444 mg, 20%) as a yellow oil; ν_max (film) 3459, 2923, 1465, 1250, 840, 699 cm⁻¹; δ_H (250 MHz, CDCl₃) 7.41 (5H, m), 4.89 (1H, s), 3.61 (1H, t, 4.6 Hz), 2.65 (1H, s), 1.62 (2H, m), 1.45-1.23 (16H, m), 0.93 (3H, t, 5.8 Hz), 0.00 (9H, s); δ_C (62.9 MHz, CDCl₃) 139.4 (s), 128.6 (d), 128.6 (d), 128.5 (d), 72.5 (d), 58.6 (s), 58.3 (d), 31.9 (t), 29.9 (t), 29.5 (t), 29.3 (t), 27.1 (t), 22.7 (t), 14.1 (q), -1.1 (q) (three carbons of the alkyl chain were not resolved); m/z (C.I.*, thermospray) 380 (MNH₄⁺), 362 (MNH₄⁺-H₂O), 290, 273; Observed (MNH₄⁺): 380.2985; C₂₂H₄₂N₀₂Si requires: 380.2985.

**Reaction of (2R*,3S*)-2,3-epoxy-1-(methanesulfonyloxy)-2-(trimethylsilyl)tridecane (155) with sodium phenoxide.**

A solution of sodium phenoxide was prepared by addition of phenol (141 mg, 1.50 mmol) dissolved in tetrahydrofuran (2 ml) to sodium hydride (25 mg, 1.05 mmol) at 0°C. (2R*,3S*)-2,3-epoxy-1-(methanesulfonyloxy)-2-(trimethylsilyl)tridecane 155 (182 mg, 0.5 mmol) dissolved in tetrahydrofuran (3 ml) was added dropwise to the stirred solution of sodium phenoxide solution at 0°C and then the mixture was allowed to gradually warm to room temperature. After 16 h the mixture was poured into water (10 ml) and diluted with diethyl ether (10 ml). The layers were separated and the aqueous layer extracted with dichloromethane (2 x 10 ml). The combined organic extracts were washed with brine (20 ml) and dried over Na₂SO₄. The solvent was removed under reduced pressure and the residue was analysed by ¹H NMR which showed a mixture of two compounds, one of which was unreacted starting material. The residue was purified by column chromatography (30% diethyl ether/light petroleum) to give as the least polar fraction (2R*,3S*)-2,3-epoxy-1-(phenyloxy)-2-(trimethylsilyl)tridecane 190 (56.0 mg, 31%) as a colourless oil; ν_max (film) 2925, 2855, 1600, 1497, 1248, 1039 cm⁻¹; δ_H (250 MHz, CDCl₃) 7.27 (2H, m), 6.87 (3H, m), 4.09 (1H, d, 9.6 Hz), 3.71 (1H, d, 9.7 Hz), 2.95 (1H, dd, 6.6, 4.7 Hz), 1.69-1.18 (18H, m), 0.88 (3H, t, 6.4 Hz), 0.19 (9H, s); δ_C (62.9 MHz, CDCl₃) 158.6 (s), 129.4 (d), 120.9 (d), 114
114.4 (d), 73.5 (t), 63.6 (d), 54.8 (s), 31.9 (t), 30.4 (t), 29.6 (t), 29.5 (t), 29.4 (t), 29.3 (t), 27.1 (t), 22.6 (t), 14.1 (q), -1.4 (q) (one carbon of the alkyl chain was not resolved); m/z (C.I.\textsuperscript{+}, thermospray) 380 (MNH\textsubscript{4}\textsuperscript{+}), 273; Observed (MNH\textsubscript{4}\textsuperscript{+}): 380.2985; C\textsubscript{22}H\textsubscript{42}NO\textsubscript{2}Si requires: 380.2985.

**Reaction of (2R\textsuperscript{*},3S\textsuperscript{*})-2,3-epoxy-1-(methanesulfonyloxy)-2-(trimethylsilyl)tridecane (155) with caesium fluoride and sodium azide in dimethylsulfoxide.**

\[
\begin{align*}
\text{Caesium fluoride (76.0 mg, 0.50 mmol) and sodium azide (97.0 mg, 1.50 mmol) were weighed directly into a round-bottomed flask that had been oven dried and cooled under an atmosphere of nitrogen. (2R\textsuperscript{*},3S\textsuperscript{*})-2,3-epoxy-1-(methanesulfonyloxy)-2-(trimethylsilyl)tridecane 155 (182 mg, 0.50 mmol) dissolved in dimethyl sulfoxide (5 ml) was added and the mixture was stirred at room temperature. After 16 h the reaction mixture was poured into water (10 ml) and the layers separated. The aqueous layer was extracted with dichloromethane (3 x 5 ml) and the combined organic extracts were washed with brine (2 x 10 ml) and dried over Na\textsubscript{2}SO\textsubscript{4}. The solvent was removed under reduced pressure and the residue was purified by column chromatography (20\% diethyl ether/light petroleum) to give as the least polar fraction (2R\textsuperscript{*},3S\textsuperscript{*})-1-azido-2,3-epoxy-2-(trimethylsilyl)tridecane 212 (72.0 mg, 46\%) as a colourless oil; \nu_{\text{max}} \text{ (film) 2962, 2855, 2096 (-N=N=-N), 1465, 1252, 842 cm}^{-1}; \delta_{\text{H}} \text{ (250 MHz, CDCl\textsubscript{3}) 3.35 (1H, d, 12.9 Hz), 3.17 (1H, d, 12.9 Hz), 2.94 (1H, dd, 6.6, 4.3 Hz), 1.64-1.17 (18H, m), 0.88 (3H, t, 6.3 Hz), 0.18 (9H, s); } \delta_{\text{C}} \text{ (62.9 MHz, CDCl\textsubscript{3}) 64.3 (d), 58.3 (t), 56.7 (s), 33.6 (t), 32.1 (t), 31.3 (t), 31.2 (t), 31.1 (t), 31.0 (t), 28.7 (t), 24.3 (t), 15.8 (q), 0.0 (q) (one carbon of the alkyl chain was not resolved); m/z (C.I.\textsuperscript{+}, thermospray) 329 (MNH\textsubscript{4}\textsuperscript{+}), 284, 244; Observed: (MNH\textsubscript{4}\textsuperscript{+}) 329.2737, C\textsubscript{16}H\textsubscript{37}ON\textsubscript{4}Si requires: 329.2736. Further elution gave unreacted (2R\textsuperscript{*},3S\textsuperscript{*})-2,3-epoxy-1-(methanesulfonyloxy)-2-(trimethylsilyl)tridecane 155 (76 mg, 42\%).
\end{align*}
\]
Reaction of $(2R^*,3S^*)$-2,3-epoxy-1-(methanesulfonyloxy)-2-(trimethylsilyl)tridecane (155) with caesium fluoride and sodium azide in acetonitrile.

Caesium fluoride (912 mg, 6.00 mmol) and sodium azide (117 mg, 1.80 mmol) were weighed directly into a flask that had been oven dried and cooled under an atmosphere of nitrogen. $(2R^*,3S^*)$-2,3-epoxy-1-(methanesulfonyloxy)-2-(trimethylsilyl)tridecane 155 (218 mg, 0.60 mmol) dissolved in acetonitrile (10 ml) was added and the heterogeneous mixture was stirred vigorously at room temperature. After 3 h the reaction mixture was diluted with diethyl ether (20 ml) and the white solids filtered off. The solvent was removed under reduced pressure and the residue was purified by column chromatography (20\% diethyl ether/light petroleum) to give as the least polar fraction 3-fluoro-2-tridecanone 154 (6.50 mg, 5\%). Further elution gave 3-azido-2-tridecanone 213 (48.0 mg, 33\%) as a colourless oil; $\nu_{\text{max}}$ (film) 2954, 2926, 2855, 2104 ($-N\equiv N\equiv N$), 1725, 668 cm$^{-1}$; $\delta_H$ (250 MHz, CDCl$_3$) 3.80 (1H, dd, 9.7, 5.0 Hz), 2.23 (3H, s), 1.74 (2H, m), 1.25 (16H, m), 0.87 (3H, t, 6.0 Hz); $m/z$ (C.I. $^+$, thermospray) 379 (MH$^+$), 269.

Reaction of $(2R^*,3S^*)$-2,3-epoxy-1-(methanesulfonyloxy)-2-(trimethylsilyl)tridecane (155) with lithium benzylamide.

To a stirred solution of benzylamine (0.20 ml, 1.80 mmol) in tetrahydrofuran (3 ml) at 0°C was added n-butyllithium (2.50 M in hexanes, 0.48 ml, 1.20 mmol). The solution was stirred for 5 min then $(2R^*,3S^*)$-2,3-epoxy-1-(methanesulfonyloxy)-2-(trimethylsilyl)tridecane 155 (226 mg, 0.60 mmol) dissolved in tetrahydrofuran (3 ml) was added dropwise and the reaction mixture was stirred at 0°C for 1.5 h. The reaction was quenched with saturated
NH₄Cl (3 ml) and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 x 5 ml) and the combined organic extracts were washed with brine (10 ml) and dried over Na₂SO₄. The solvent was removed under reduced pressure and the residue was purified by column chromatography (40% ethyl acetate/light petroleum) to give, as the least polar fraction, (2R*,3S*)-2,3-epoxy-2-(trimethylsilyl)tridecan-1-ol 171 (37.0 mg, 22%). Spectroscopic data for this material was in accordance with that previously described.

Further elution gave (2S*,3S*)-2,3-epoxytridecan-1-ol 214 (41.0 mg, 32%) as a colourless solid; νₘₐₓ (CHCl₃) 3257, 2953, 2921, 2869, 1245, 996, 902 cm⁻¹; δ_H (250 MHz, CDCl₃) 3.93 (1H, dd, 12.5, 2.5 Hz), 3.63 (1H, dd, 12.6, 4.4 Hz), 2.92 (2H, m), 2.16 (1H, br s), 1.55 (2H, m), 1.39 (2H, m), 1.26 (14H, m), 0.88 (3H, t, 6.8 Hz); δ_C (100 MHz, CDCl₃) 62.1 (t), 58.9 (d), 56.4 (d), 32.3 (t), 31.9 (t), 30.0 (t), 29.93 (t), 29.91 (t), 29.8 (t), 29.7 (t), 26.3 (t), 23.1 (t), 14.5 (q); m/z (C.I.⁺, thermospray) 232 (MNH₄⁺), 117; Observed (MNH₄⁺): 232.2277; C₁₃H₃₀N₂O₂ requires: 232.2276.

Reaction of (2R*,3S*)-2,3-epoxy-1-(methanesulfonyloxy)-2-(trimethylsilyl)tridecane (155) with sodium phenylthiolate.

A solution of sodium phenylthiolate was prepared by addition of thiophenol (0.18 ml, 1.80mmol) to sodium hydride (30 mg, 1.30 mmol) in tetrahydrofuran (4 ml) at 0°C. (2R*,3S*)-2,3-Epoxy-1-(methanesulfonyloxy)-2-(trimethylsilyl)tridecane 155 dissolved in tetrahydrofuran (2 ml) was added dropwise to the stirred solution of phenylthiolate and the mixture was allowed to warm to room temperature. The reaction was estimated to be complete, by TLC, after 2 h at which point the mixture was poured into water (10 ml) and diluted with diethyl ether (10 ml). The layers were separated and the aqueous layer extracted with diethyl ether (2 x 10 ml). The combined organic extracts were washed with brine (20 ml) and dried over MgSO₄. The solvent was removed under reduced pressure and the residue was purified by column chromatography (20% diethyl ether/light petroleum) to give (2S*,3S*)-2,3-epoxy-1-(phenylthio)-2-(trimethylsilyl)tridecane 215 (163 mg, 72%) as a colourless oil; νₘₐₓ (film) 3060, 2924, 2853, 1584, 1479, 1466, 1439, 1249, 841, 740 cm⁻¹; δ_H (250 MHz, CDCl₃) 7.36 (5H, m), 3.39 (1H, d, 12.8 Hz), 2.74 ( 1H, d, 12.9 Hz), 2.65 (1H, t, 6.1 Hz), 1.45-1.28 (18H, m), 0.95 (3H, t, 7.0 Hz), 0.27 (9H, s); δ_C (100 MHz, CDCl₃) 136.8
(s), 131.6 (d), 130.1 (d), 129.9 (d), 65.0 (d), 55.9 (s), 43.2 (t), 32.9 (t), 31.5 (t), 30.6 (t), 30.55 (t), 30.52 (t), 30.42 (t), 30.38 (t), 27.6 (t), 23.7 (t), 15.2 (q), 0.0 (q); \textit{m/z} (C.I.\textsuperscript{+}, thermospray) 379 (MH\textsuperscript{+}), 269; Observed (MH\textsuperscript{+}): 379.2491; C\textsubscript{22}H\textsubscript{39}OSSi requires: 379.2491.
5.3 Experimental for Chapter 3

General procedure F: Asymmetric epoxidation of (Z)-2-(trimethylsilyl) propen-1-ols (166-168).\textsuperscript{92}

\[
\begin{align*}
\text{R} \quad & \text{SiMe}_3 \\
166-168 & \rightarrow \\
\text{R}^1 \quad & \text{SiMe}_3 \\
217, 220, 221 & \text{OH}
\end{align*}
\]

To dichloromethane (1 ml/mmol) containing 4 Å molecular sieves (0.1 g/mmol) at -20°C was added titanium tetra-iso-propoxide (7.5 mol%) then L-(+)-diethyl tartrate (9.0 mol%) and the mixture was stirred for 5 min. Anhydrous tert-butyl hydroperoxide (5.0-6.0 M decane, 3 eq) was added dropwise and the mixture was stirred for 30 min. The appropriate (Z)-2-(trimethylsilyl)propen-1-ol 166-168 dissolved in dichloromethane (0.5 ml/mmol) was added to the mixture and the reaction mixture was stirred at -20°C. When the reaction was estimated to be complete, by TLC, the mixture was poured into a pre-cooled solution of ferrous sulfate (1.2 mmol/mmol) and citric acid (0.6 mmol/mmol) in water (1 ml/mmol) and stirred for 5 min. The layers were separated and the aqueous layer extracted with diethyl ether. The combined organic extracts were washed with brine and then poured into a 10% solution of NaOH in brine (10 ml/mmol) and stirred for 30 min. The layers were separated and the aqueous layer extracted with diethyl ether. The combined organic extracts were washed again with brine then dried over MgSO\textsubscript{4}. The solvent was removed under reduced pressure and the residue purified by column chromatography.

(2\textit{R},3\textit{S})-2,3-Epoxy-2-(trimethylsilyl)tridecan-1-ol (217).

Treatment of (Z)-2-(trimethylsilyl)-2-tridecen-1-ol 166 (3.78 g, 14.0 mmol) with titanium tetra-iso-propoxide (312 µl, 1.05 mmol), L-(+) diethyl tartrate (220 µl, 1.26 mmol) and tert-butyl hydroperoxide (5.0-6.0 M decane, 8.40 ml, 42.0 mmol) in dichloromethane (14 ml) containing 4 Å molecular sieves (1.4 g) at -20°C for 20 h, according to General Procedure F, and subsequent column chromatography (20% ethyl acetate/light petroleum) gave (2\textit{R},3\textit{S})-2,3-epoxy-2-(trimethylsilyl)tridecan-1-ol 217 (2.10 g, 53%, 84% ee) as a colourless oil; [\alpha]\textsubscript{D}\textsuperscript{20} = -10.7 (c 1.0, CHCl\textsubscript{3}). Other spectroscopic data is consistent with that reported for the racemic compound 171.
(2R,3S)-2,3-Epoxy-7-(tetrahydropyranloxy)-2-(trimethylsilyl)heptan-1-ol (220).

Treatment of (Z)-7-(tetrahydropyranloxy)-2-(trimethylsilyl)-2-hepten-1-ol 167 (610 mg, 2.10 mmol) with titanium tetra-iso-propoxide (47.0 µl, 0.15 mmol), L-(+)-diethyl tartrate (33.0 µl, 0.19 mmol) and tert-butyl hydroperoxide (5.0-6.0 M decane, 1.26 ml, 6.30 mmol) in dichloromethane (2.5 ml) containing 4Å molecular sieves (160 mg) at -20°C for 20 h, according to General Procedure F, and subsequent column chromatography (25% ethyl acetate/light petroleum) gave (2R,3S)-2,3-epoxy-7-(tetrahydropyranloxy)-2-(trimethylsilyl)heptan-1-ol 220 (356 mg, 56%, 83% ee) as a colourless oil; [α]D^20 = -9.6 (c 1.0, CHCl₃). Other spectroscopic data is consistent with that reported for the racemic compound 172.

(2R,3S)-2,3-Epoxy-2-(trimethylsilyl)-7-octen-1-ol (221).

Treatment of (Z)-2-(trimethylsilyl)-2,7-octadien-1-ol 168 (2.32 g, 11.7 mmol) with titanium tetra-iso-propoxide (262 µl, 0.84 mmol), L-(+)-diethyl tartrate (184 µl, 1.06 mmol) and tert-butyl hydroperoxide (5.0-6.0 M decane, 7.02 ml, 35.1 mmol) in dichloromethane (12 ml) containing 4Å molecular sieves (890 mg) at -20°C for 16 h, according to General Procedure F, and subsequent column chromatography (20% ethyl acetate/light petroleum) gave (2R,3S)-2,3-epoxy-2-(trimethylsilyl)-7-octen-1-ol 221 (1.04 g, 41%, 85% ee) as a yellow oil; [α]D^20 = -13.3 (c 1.0, CHCl₃). Other spectroscopic data is consistent with that reported for the racemic compound 173.

Determination of enantiomeric excess for the (2R,3S)-2,3-epoxy-2-(trimethylsilyl)propan-1-ols (217, 220, 221). 95

To a solution of N,N-dimethylaminopyridine (18.0 mg, 0.16 mmol) in dichloromethane (0.5 ml) containing triethylamine (100 µl, 0.70 mmol) was added (R)-(−)-α-methoxy-α-
(trifluoromethyl)phenylacetyl chloroide (30 µl, 0.16 mmol) followed immediately by the appropriate (2R,3S)-2,3-epoxy-2-(trimethylsilyl)propan-1-ol (0.15 mmol) dissolved in dichloromethane (0.5 ml). The mixture was stirred at room temperature until the reaction was estimated to be complete by TLC. 3-(N,N-Dimethylamino)propylamine (40-60 µl) was added and the solvent was removed under reduced pressure. The residue was passed through a short plug of flash silica (20% ethyl acetate/light petroleum) and the solvent removed under reduced pressure. Analysis by \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) showed two signals for proton H\textsubscript{a} (dd) corresponding to the two resulting diastereomeric esters. For example the \textsuperscript{1}H NMR of the MPTA ester of compound 220 showed two doublets; \( \delta \) 2.81 (0.91H, dd, 4.3, 2.9 Hz) (major), 2.74 (0.08H, dd, 4.3, 2.9 Hz) (minor) and from which the enantiomeric excess was determined to be 83% (Appendix 1).

**General procedure G: Reaction of (2R,3S)-2,3-epoxy-1-(methanesulfonyloxy)-2-(trimethylsilyl)propanes (150, 222, 223) with potassium alkoxides at low temperature.**

\[
\begin{align*}
\text{R}^1 & \quad \text{SiMe}_3 \\
\text{OMs} & \quad \text{KOR}^2 \\
\downarrow & \quad \text{18-crown-6} \\
\text{R}^1 & \quad \text{Me} \\
\text{OR}^2 & \quad \text{OMs}
\end{align*}
\]

The appropriate (2R,3S)-2,3-epoxy-1-(methanesulfonyloxy)-2-(trimethylsilyl)propane and 18-crown-6 (2.0 eq) were dissolved in tetrahydrofuran (2 ml/mmol) and cooled to -78°C. A 1.0 M solution of the potassium alkoxide in tetrahydrofuran was prepared from potassium hydride and the appropriate alcohol (R\textsuperscript{2}OH). The potassium alkoxide solution (2.0 eq) was added dropwise to the reaction mixture. The reaction mixture was stirred at -78°C until the reaction was estimated to be complete, by TLC, at which point it was quenched with diethyl ether containing 1% acetic acid (ca. 2 ml/mmol) and allowed to warm to 0°C. The mixture was poured into water (10 ml/mmol) and the layers separated. The aqueous layer was extracted with diethyl ether and the combined organic extracts washed with brine and dried over Na\textsubscript{2}SO\textsubscript{4}. The solvent was removed under reduced pressure and the residue purified by column chromatography.
Reaction of (2R,3S)-2,3-epoxy-1-(methanesulfonyloxy)-2-(trimethylsilyl)tridecane (150) with potassium methoxide.

\[
\text{\textit{n-C}_{10}\text{H}_{21}} \stackrel{\text{SiMe}_3}{\cdots} \stackrel{\text{OMs}}{\longrightarrow} \text{\textit{n-C}_{10}\text{H}_{21}} \stackrel{\text{Me}}{\cdots} \stackrel{\text{OMe}}{\longrightarrow}
\]

Treatment of (2R,3S)-2,3-epoxy-1-(methanesulfonyloxy)-2-(trimethylsilyl)tridecane 150 (145 mg, 0.4 mmol) dissolved in tetrahydrofuran (0.8 ml) containing 18-crown-6 (211 mg, 0.8 mmol) with potassium methoxide [1.0 M in tetrahydrofuran, 0.8 ml, 0.8 mmol, prepared from potassium hydride (80 mg, 2.0 mmol) and methanol (81 µl, 2.0 mmol) in tetrahydrofuran (2.0 ml)] for 2 h, according to General Procedure G, and subsequent column chromatography (25% diethyl ether/light petroleum) gave (3R)-3-methoxytridecan-2-one 218 (45 mg, 52%) as a colourless oil \([\alpha]_D^{20} = +59.7 \ (c \ 0.6, \ \text{CHCl}_3)\). Other spectroscopic data is consistent with that reported for the racemic compound 98. The enantiomeric excess was estimated to be 80% from the integration of the \(^1\)H NMR spectrum of the (+)-Eu-(hfch)_3 complex in which the methyl singlet 3.36 ppm is split into two resonances. This complex was prepared from (3R)-methoxytridecan-2-one (2.20 mg, 0.01 mmol) and (+)-Eu-(hfch)_3 (4.80 mg, 0.20 mmol) in CDCl_3 (1.0 ml).

Reaction of (2R,3S)-2,3-epoxy-1-(methanesulfonyloxy)-2-(trimethylsilyl)tridecane (150) with potassium 1-naphthalenemethoxide.

\[
\text{\textit{n-C}_{10}\text{H}_{21}} \stackrel{\text{SiMe}_3}{\cdots} \stackrel{\text{OMs}}{\longrightarrow} \text{\textit{n-C}_{10}\text{H}_{21}} \stackrel{Me}{\cdots} \stackrel{\text{OMe}}{\longrightarrow}
\]

Treatment of (2R,3S)-2,3-epoxy-1-(methanesulfonyloxy)-2-(trimethylsilyl)tridecane 150 (291 mg, 0.8 mmol) dissolved in tetrahydrofuran (1.6 ml) containing 18-crown-6 (422 mg, 1.60 mmol) with potassium methoxide [1.0 M in tetrahydrofuran, 1.6 ml, 1.60 mmol, prepared from potassium hydride (120 mg, 3.0 mmol) and 1-naphthalenemethanol (474 mg, 3.0 mmol) in tetrahydrofuran (3.0 ml)] for 2 h, according to General Procedure G, and subsequent
column chromatography (25% diethyl ether/light petroleum) gave (3R)-3-(1-
naphthylmenemethoxy)-tridecan-2-one 219 (161 mg, 57%, 79% ee) as a yellow oil; $v_{max}$ (film) 3049, 2925, 2854, 1715, 1599, 1512, 1466, 1353, 1168, 1098, 793 cm$^{-1}$; $\delta_H$ (400 MHz, CDC$_3$) 8.20 (2H, m), 7.75 (2H, m), 7.44-7.33 (3H, m), 4.95 (1H, d, 11.9 Hz), 4.76 (1H, d, 11.9 Hz), 3.73 (1H, dd, 8.0, 4.9 Hz), 2.05 (3H, s), 1.60-1.48 (2H, m), 1.23-1.06 (16H, m), 0.78 (3H, t, 6.7 Hz); $\delta_C$ (100 MHz, CDC$_3$) 213.6 (s), 135.8 (s), 135.0 (s), 133.7 (s), 130.9 (d), 130.6 (d), 128.8 (d), 128.2 (d), 127.9 (d), 127.1 (d), 126.0 (d), 86.8 (d), 72.8 (t), 34.0 (t), 33.9 (t), 31.5 (t), 31.3 (t), 31.2 (t), 27.4 (q), 27.1 (t), 24.7 (t), 16.1 (q); m/z (Cl.$^+$, thermospray) 372 (MNH$_4^+$); Observed (MNH$_4^+$) 372.2902; C$_{24}$H$_{38}$NO$_2$ requires 372.2903; $[\alpha]_D^{20} = +29.6$ (c 1.0, CHCl$_3$); The enantiomeric excess was determined to be 79% by HPLC using a Chiralcel OD HPLC column ($\lambda = 254$ nm, 0.3% iso-propanol/hexane, 0.6 ml/min): 31.90 min (minor), 34.12 min (major) (Appendix 2).

**Reaction of (2R,3S)-2,3-epoxy-1-(methanesulfonyloxy)-7-(tetrahydropyranloxy)-2-(trimethylsilyl)heptane (222) with potassium 1-naphthalenemethoxide.**

![Chemical structure](image)

Treatment of (2R,3S)-2,3-epoxy-1-(methanesulfonyloxy)-7-(tetrahydropyranloxy)-2-(trimethylsilyl)heptane 222 (280 mg, 0.77 mmol) dissolved in tetrahydrofuran (2.0 ml) containing 18-crown-6 (407 mg, 1.54 mmol) with potassium methoxide [1.0 M in tetrahydrofuran, 1.54 ml, 1.54 mmol, prepared from potassium hydride (80 mg, 2.0 mmol) and 1-naphthalenemethanol (316 mg, 2.0 mmol) in tetrahydrofuran (2.0 ml)] for 2 h, according General Procedure G and subsequent column chromatography (25% diethyl ether/light petroleum) gave (3R)-3-(1-naphthalenemethoxy)-7-(tetrahydropyranloxy)heptan-2-one 224 (143 mg, 53%, 83% ee) as a yellow oil; $v_{max}$ (film) 3048, 3007, 2942, 2868, 1713, 1598, 1511, 1453, 1440, 1353, 1137, 1033 cm$^{-1}$; $\delta_H$ (250 MHz, CDC$_3$) 8.13 (IH, m), 7.85 (2H, m), 7.55-7.43 (4H, m), 5.05 (1H, dd, 11.9, 2.1 Hz), 4.88 (1H, d, 11.9 Hz), 4.52 (1H, m),
3.85 (2H, m), 3.65 (1H, m), 3.48 (1H, m), 3.28 (1H, m), 2.15 (3H, s), 1.81-1.42 (12H, m); δC (62.9 MHz, CDCl₃) 211.3 (s), 133.7 (s), 132.9 (s), 131.6 (s), 128.9 (d), 128.4 (d), 126.6 (d), 126.2 (d), 125.8 (d), 125.2 (d), 123.9 (d), 98.7 (d), 84.6 (d), 70.7 (t), 67.0 (t), 62.2 (t), 31.7 (t), 30.1 (t), 29.3 (t), 25.4 (t), 25.4 (q), 21.9 (t), 19.5 (t); m/z (E.I.) 287, 243, 141 (100%), 85, 67, 55, 43, 27; Observed (M⁺): 370.2142; C₂₃H₃₀O₄ requires: 370.2144; [α]D 20 = +26.7 (c 0.95, CHCl₃); The enantiomeric excess was determined to be 83% by HPLC using a Chiralcel OD HPLC column (λ = 254 nm, 2.0% iso-propanol/hexane, 2.0 ml/min): 9.83 min (major), 11.21 min (minor).

Reaction of (2R,3S)-2,3-epoxy-1-(methanesulfonyloxy)-2-(trimethylsilyl)-7-octene (223) with potassium benzyloxyde.

Treatment of (2R,3S)-2,3-epoxy-1-(methanesulfonyloxy)-2-(trimethylsilyl)-7-octene 223 (292 mg, 1.0 mmol) dissolved in tetrahydrofuran (2.0 ml) containing 18-crown-6 (503 mg, 2.0 mmol) with potassium methoxide [1.0 M in tetrahydrofuran, 2.0 ml, 2.0 mmol, prepared from potassium hydride (120 mg, 3.0 mmol) and benzyl alcohol (310 µl, 3.0 mmol) in tetrahydrofuran (3.0 ml)] for 3 h, according to General Procedure G, and subsequent column chromatography (25% diethyl ether/light petroleum) gave (3R)-3-benzyloxy-7-octen-2-one 225 (120 mg, 52%, 82% ee) as a colourless oil; νmax (film) 3066, 3032, 2976, 2936, 2863, 1714, 1641, 1497, 1455, 1354, 1101, 912 cm⁻¹; δH (400 MHz, CDCl₃) 7.22-7.14 (5H, m), 5.59 (1H, m), 4.80 (2H, m), 4.42 (1H, d, 11.6 Hz), 4.26 (1H, d, 11.7 Hz), 3.60 (1H, dd, 7.7, 5.0 Hz), 2.01 (3H, s), 1.88 (2H, m), 1.53-1.30 (4H, m); δC (100 MHz, CDCl₃) 210.0 (s), 136.4 (d), 135.7 (s), 126.6 (d), 126.2 (d), 113.3 (t), 83.2 (d), 70.7 (t), 31.6 (t), 29.6 (t), 23.6 (q), 22.7 (t) (one of the aromatic carbon signals was not resolved); m/z (C.I.⁺, thermospray) 250 (MNH₄⁺); Observed (MNH₄⁺): 250.1807; C₁₅H₂₄NO₂ requires: 250.1807; [α]D 20 = +43.1 (c 1.0, CHCl₃). The enantiomeric excess was estimated to be 82% from the integration of the ¹H NMR spectrum of the (+)-Eu-(hfc)₃ complex in which the methyl singlet 2.82 ppm is split into two resonances. This complex was prepared from (3R)-benzoxy-7-octen-2-one (4.6 mg, 0.02 mmol) and Eu-(hfc)₃ (9.6 mg, 8 µmol) in CDCl₃ (1.0 ml).
Determination of the absolute configuration: Palladium catalysed hydrogenation of (3R)-benzyloxy-7-octen-2-one (225).

(3R)-3-benzyloxy-7-octen-2-one 225 (100 mg, 0.43 mmol) was dissolved in methanol (1 ml) and added to 10% palladium on activated carbon (52 mg) in methanol (2 ml). The flask was evacuated and filled with hydrogen gas via a balloon. The mixture was stirred under a positive pressure of hydrogen at room temperature and the reaction was followed by TLC. After 20 h, the starting material had been consumed and the catalyst was filtered off through a pad of Celite®. The solvent was removed under reduced pressure and the residue purified by column chromatography (20% ethyl acetate/light petroleum) to give as the most polar fraction (3R)-3-hydroxyoctan-2-one 226 (9.3 mg, 15%), \([\alpha]_D^{20} = -37.1\) (c 1.20, CHCl\(_3\)); \(\delta_H\) (250 MHz, CDCl\(_3\)) 4.18 (1H, m), 3.45 (1H, d, 4.7 Hz), 2.20 (3H, s), 1.62 (2H, m), 1.57-1.31 (6H, m), 0.89 (3H, t, 6.2 Hz); \(\delta_C\) (100 MHz, CDCl\(_3\)) 210.4 (s), 77.7 (d), 33.9 (t), 32.0 (t), 25.6 (q), 24.8 (t), 22.9 (t), 14.4 (q). The spectroscopic data are consistent with the literature values. The optical rotation of this material was measured on the J-line (mercury 578 nm) \([\alpha]_D^{25} = -40.0\) (c 0.03, CHCl\(_3\)) in order to compare it with (+)-(3S)-3-hydroxyoctan-2-one [lit.\(^{95}\) \([\alpha]_D^{25} = +91\) (c 0.03, CHCl\(_3\))].

Reaction of (2R,3S)-2,3-epoxy-1-(methanesulfonyloxy)-2-(trimethylsilyl)tridecane (150) with potassium methoxide and benzaldehyde.

(2R,3S)-2,3-epoxy-1-(methanesulfonyloxy)-2-(trimethylsilyl)tridecane 150 (158 mg, 0.43 mmol) and 18-crown-6 (227 mg, 0.86 mmol) were dissolved in tetrahydrofuran (1 ml) and cooled to -78°C. A 1.0 M solution of the potassium alkoxide in tetrahydrofuran (2 ml) was prepared from potassium hydride (80 mg, 2.0 mmol) and methanol (81 µl, 2.0 mmol). The
potassium alkoxide solution (0.86 ml, 0.80 mmol) was added dropwise to the reaction mixture and the reaction was followed by TLC. After 4 h, the starting material had been consumed and benzaldehyde (0.10 ml, 1.03 mmol) was added and the reaction mixture allowed to warm gradually (ca. 16 h) to 0°C. The reaction was quenched with saturated NaHCO₃ (2 ml) and the mixture poured into water (5 ml). The layers were separated and the aqueous layer was extracted with diethyl ether (3 x 5 ml). The combined organic extracts were washed with brine (20 ml) and dried over Na₂SO₄. The solvent was removed under reduced pressure and the residue purified by column chromatography (25% diethyl ether/light petroleum) to give (4R)-4-methoxy-1-phenyl-1-tetradecen-3-one 228 (68 mg, 50%) as a colourless oil; νₘₐₓ (film) 3082, 3062, 3028, 2925, 2825, 1689, 1608, 1576, 1496, 1450, 1330, 1202, 1108, 990 cm⁻¹; δH (400 MHz, CDCl₃) 7.58 (1H, d, 16.0 Hz), 7.43 (2H, m), 7.23 (3H, m), 6.94 (1H, d, 16.0 Hz), 3.58 (1H, dd, 7.6, 5.6 Hz), 3.20 (3H, s), 1.51 (2H, m), 1.25 (2H, m), 1.09 (14H, m), 0.69 (3H, t, 6.7 Hz); δC (100 MHz, CDCl₃) 202.2 (s), 144.4 (d), 135.0 (s), 131.1 (d), 130.0 (d), 129.3 (d), 120.8 (d), 87.5 (d), 58.5 (q), 32.9 (t), 32.3 (t), 30.0 (t), 29.9 (t), 29.85 (t), 29.8 (t), 29.7 (t), 25.6 (t), 23.1 (t), 14.5 (q); m/z (C.I.⁺, thermospray) 317 (MH⁺); Observed (MH⁺): 317.2481; C₂₁H₃₃O₂ requires: 317.2481; the enantiomeric excess was determined to be 35% by HPLC using a Chiralcel OD HPLC column (λ = 254 nm, 0.5% iso-propanol/hexanes, 1.0 ml/min): 8.21 (minor), 8.93 (major).
5.4 Experimental for Chapter 4

Preparation of 4,4-dimethyl-5-methylene-1,3,2-dioxathiolane-2-oxide (234).\textsuperscript{36}

![Reaction scheme]

To 3-hydroxy-3-methylbutan-2-one 233 (510 mg, 5.00 mmol) dissolved in dichloromethane (8 ml) containing triethylamine (1.39 ml, 10.0 mmol) at -78°C was added dropwise thionyl chloride (0.44 ml, 6.00 mmol) dissolved in dichloromethane (2 ml). The solution was stirred at -78°C for 2 h then saturated NaHCO\textsubscript{3} (5 ml) was added and the solution was allowed to warm to room temperature. The solution was poured into water and the layers separated. The aqueous layer was extracted with dichloromethane (2 x 10 ml) and the combined organic extracts washed with brine (20 ml) and dried over Na\textsubscript{2}SO\textsubscript{4}. The solvent was removed under reduced pressure and the residue purified by column chromatography (20% ethyl acetate/light petroleum) to give 3,3-dimethyl-4-methylene-1,3,2-dioxathiolane-2-oxide\textsuperscript{36} 234 (427 mg, 58%) as a colourless oil; \textit{v}\textsubscript{max} (film) 2989, 2934, 1700 (C=C), 1458, 1390, 1372, 1227, 1159, 955, 939, 837, 795 cm\textsuperscript{-1}; \delta\textsubscript{H} (360 MHz, CDCl\textsubscript{3}) 4.74 (1H, d, 3.2 Hz), 4.34 (1H, d, 3.4 Hz), 1.79 (3H, s), 1.56 (3H, s); \delta\textsubscript{C} (100 MHz, CDCl\textsubscript{3}) 160.7 (s), 89.1 (s), 85.8 (t), 30.6 (q), 28.8 (q). Numerous attempts to obtain good mass spectra and microanalytical data on this unstable compound were unsuccessful.

Preparation 5-methylene-4,4'-spirocyclohexyl-1,3,2-dioxathiolane-2-oxide (237).

![Reaction scheme]

To 1-acetylcyclohexan-1-ol 236 (426 mg, 3.00 mmol) dissolved in dichloromethane (6 ml) containing triethylamine (0.84 ml, 6.00 mmol) at -78°C was added thionyl chloride (0.24 ml,
3.30 mmol) dissolved in dichloromethane (1 ml) dropwise. The solution was stirred at -78°C for 2 h then saturated NaHCO₃ (3 ml) was added and the solution allowed to warm to room temperature. The solution was poured into water and the layers were separated. The aqueous layer was extracted with dichloromethane (2 x 5 ml) and the combined organic extracts were washed with brine (10 ml) and dried over Na₂SO₄. The solvent was removed under reduced pressure and the residue purified by column chromatography (20% ethyl acetate/light petroleum) to give 5-methylene-4,4'-spirocyclohexyl-1,3,2-dioxathiolane-2-oxide 237 (298 mg, 53%) as a colourless oil; v max (film) 2939, 2864, 1663 (C=C), 1449, 1217, 1065 cm⁻¹; δH (400 MHz, CDCl₃) 4.77 (1H, d, 3.4 Hz), 4.34 (1H, d, 3.2 Hz), 2.34 (1H, m), 1.93 (1H, m), 1.79-1.58 (8H, m); δC (100 MHz, CDCl₃) 159.4 (s), 90.0 (s), 85.7 (t), 38.0 (t), 36.5 (t), 23.3 (t), 23.1 (t), 20.8 (t). Numerous attempts to obtain good mass spectra and microanalytical data on this unstable compound were unsuccessful.

Preparation and decomposition of 4-methyl-5-methylene-4-phenyl-1,3,2-dioxathiolane-2-oxide (239).

To 2-hydroxy-2-phenylbutan-3-one 238 (246 mg, 1.50 mmol) dissolved in dichloromethane (3 ml) containing triethylamine (0.42 ml, 3.00 mmol) at -78°C was added dropwise thionyl chloride (0.12 ml, 1.60 mmol) in dichloromethane (1 ml). The solution was stirred at -78°C for 2 h then saturated NaHCO₃ (3 ml) was added and the solution allowed to warm to room temperature. The solution was poured into water and the layers separated. The aqueous layer was extracted with dichloromethane (2 x 5 ml) and the combined organic extracts washed with brine (10 ml) and dried over Na₂SO₄. The solvent was removed under reduced pressure and the residue purified by column chromatography (20% ethyl acetate/light petroleum) to give a yellow oil (105mg) which was found to be a 2:1 mixture of two compounds, the major component 4-methyl-5-methylene-4-phenyl-1,3,2-dioxathiolane-2-oxide 239 as a 50:50 mixture of diastereomers; δH (250 MHz, CDCl₃) 7.40-7.26 (5H, m), 4.89 (0.5H, d, 3.3 Hz), 4.85 (0.5H, d, 3.3 Hz), 4.43 (0.5H, d, 3.3 Hz), 4.34 (0.5H, d, 3.3 Hz), 2.08 (1.5H, s), 1.87 (1.5H, s) and the minor component 3-phenyl-3-buten-2-one 240; δH (250 MHz, CDCl₃)
7.40-7.26 (5H, m), 6.12 (1H, s), 5.91 (1H, s), 2.39 (3H, s). The $^1$H NMR data for compound 240 was consistent with the literature values.\textsuperscript{104}

Preparation of 2,2-dimethyl-4-[(2-nitrophenyl)selenomethyl]-1,3-dioxolane (241).

(2-Nitrophenyl)selenocyanate 147 (1.35 g, 6.00 mmol) and 2,2-dimethyl-4-hydroxymethyl-1,3-dioxolane (660 mg, 5.00 mmol) were dissolved in tetrahydrofuran (16 ml) and stirred at 0°C. Freshly distilled tri-n-butyl phosphine (1.46 ml, 6.00 mmol) was added dropwise and the mixture allowed to warm to room temperature. After 2 h the reaction was estimated, by TLC, to be complete and the solvent was removed under reduced pressure. The residue was purified by column chromatography (30% ethyl acetate/light petroleum) to give 2,2-dimethyl-4-[(2-nitrophenyl)selenomethyl]-1,3-dioxolane 241 (1.15 g, 72 %) as a yellow solid (m.p. 49-50°C); $\nu_{\text{max}}$ (CHCl$_3$) 3020, 3014, 2991, 2938, 2884, 1592, 1568, 1518, 1454, 1335, 1252, 1149, 1100, 792 cm$^{-1}$; $\delta_{H}$ (360 MHz, CDCl$_3$) 8.29 (1H, dd, 8.3, 1.3 Hz), 7.56 (2H, m), 7.34 (1H, m), 4.41 (1H, m), 4.16 (1H, dd, 8.5, 6.0 Hz), 3.82 (1H, dd, 8.5, 5.9 Hz), 3.24 (1H, dd, 12.4, 4.5 Hz), 3.00 (1H, dd, 12.4, 7.6 Hz), 1.47 (3H, s), 1.37 (3H, s); $\delta_{C}$ (100 MHz, CDCl$_3$) 146.9 (s), 133.7 (d), 132.3 (s), 129.0 (d), 126.5 (d), 125.8 (d), 110.0 (s), 74.2 (d), 69.4 (t), 29.0 (t), 27.0 (q), 25.5 (q); $m/z$ (Cl$^+$, thermospray) 335 (MNH$_4^+$), 260, 202, 139; Observed (MNH$_4^+$): 335.0510; C$_{12}$H$_9$N$_2$O$_4$Se requires: 335.0509.
Preparation of 1-[{(2-nitrophenyl)seleno]propan-2,3-diol (242).

2,2-Dimethyl-4-[(2-nitrophenyl)selenomethyl]-1,3-dioxolane 241 (1.15 g, 3.63 mmol) was dissolved in tetrahydrofuran (10 ml) and 2 M hydrochloric acid (10 ml) was added and the mixture heated to reflux for 1.5 h. The mixture was diluted with water (12 ml) and the layers separated. The aqueous layer was extracted with ethyl acetate (3 x 10 ml) and the combined organic extracts were dried over Na₂SO₄. The solvent was removed under reduced pressure to give a yellow solid. The solid was dissolved in a minimum quantity of ethyl acetate then light petroleum and was added dropwise precipitating pure 1-[{(2-nitrophenyl)seleno]propan-2,3-diol 242 (604 mg, 60%) as a yellow powder (m.p. 105-107°C); ν_max (CHCl₃) 3694, 3606, 3030, 2959, 2930, 1592, 1519, 1463, 1335, 1251, 1049 cm⁻¹; δ_H (400 MHz, CDCl₃) 8.22 (1H, m), 7.55 (1H, m), 7.48 (1H, m), 7.28 (1H, m), 3.95 (1H, dd, 11.1, 3.5 Hz), 3.62 (1H, dd, 11.1, 6.1 Hz), 3.03 (2H, m), 2.51 (1H, s), 1.90 (1H, s); δ_C (100 MHz, CDCl₃) 139.4 (s), 134.1 (d), 129.7 (d), 129.3 (s), 126.9 (d), 126.3 (d), 70.7 (d), 66.3 (t), 30.0 (t); m/z (Cl⁺, thermospray) 295 (MNH₄⁺); Observed (MNH₄⁺): 295.0196; C₉H₁₅O₄N₂Se requires: 295.0197.

Preparation of 4-[{(2-nitrophenyl)selenomethyl]-1,3,2-dioxathiolane-2-oxide (243).

Treatment of 1-[{(2-nitrophenyl)seleno]propan-2,3-diol 242 (359 mg, 1.30 mmol) in dichloromethane (5 ml) containing triethylamine (0.36 ml, 2.6 mmol) with thionyl chloride (0.12 ml, 1.6 mmol) in dichloromethane (1.5 ml) for 2 h, as described in General Procedure Y, (Vide Infra ) and subsequent column chromatography (20% ethyl acetate/light petroleum)
gave 4-[(2-nitrophenyl)selenomethyl]-1,3,2-dioxathiolane-2-oxide 243 (337 mg, 81%) as a yellow solid and as a 1:1 mixture of diastereomers (m.p. 51-53°C); $\nu_{\text{max}}$ (CHCl$_3$) 3027, 3020, 2901, 1592, 1569, 1521, 1335, 1305, 1253, 1195 cm$^{-1}$; $\delta$H (360 MHz, CDCl$_3$)
8.33 (1H, m), 7.59 (2H, m), 7.41 (1H, m), 5.18 (0.5H, m), 4.80 (1H, m), 4.67 (0.5H, dd, 8.9, 6.3 Hz), 4.59 (0.5H, t, 8.3 Hz), 4.33 (0.5H, dd, 8.4, 5.2 Hz), 3.64 (0.5H, dd, 13.0, 5.2 Hz), 3.37 (0.5H, dd, 13.2, 4.8 Hz), 3.26 (0.5H, dd, 12.9, 9.0 Hz), 3.00 (0.5H, dd, 13.2, 8.9 Hz); $\delta$C (100 Hz, CDCl$_3$) 147.6 (s), 134.5 (d), 130.7 (s), 130.6 (s), 129.4 (d), 129.2 (d), 127.1 (d), 126.9 (d), 81.7 (d), 78.9 (d), 71.8 (t), 71.7 (t), 28.7 (t), 27.3 (t) (not all of the aromatic carbons for the two diastereomers are resolved); $m/z$ (C.I.+, thermospray) 339 [MNH$_4^+$($^{78}$Se)]; Observed (MNH$_4^+$): 340.9710; C$_9$H$_{13}$N$_2$O$_5$S$_5$Se requires: 340.9710.

Preparation of \((E)-1\text{-phenyl-3-(phenylseleno)-1-propene (245)}\).\textsuperscript{111}

Diphenyl diselenide (2.50 g, 8.00 mmol) was dissolved in ethanol (80 ml) and cooled to 0°C. Sodium borohydride (608 mg, 16.0 mmol) was added gradually until the solution turned from yellow to colourless indicating that all of the diphenyl diselenide had been reduced. Cinnamyl chloride (2.07 g, 13.6 mmol) dissolved in ethanol (10 ml) was added and the solution was heated to reflux for 2 h. The solution was allowed to cool to room temperature and water (ca. 10 ml) was added dropwise. The layers were separated and the aqueous layer extracted with ethyl acetate (3 x 10 ml) then the combined organic extracts were washed with brine (30 ml) and the solvent removed under reduced pressure. The residue was purified by column chromatography (10% ethyl acetate/light petroleum) to give \((E)-1\text{-phenyl-3-(selenophenyl)propene 245}\) (3.08 g, 83%) as a yellow solid; m.p. 54-56°C [lit.,\textsuperscript{111} 54-55°C]; $\nu_{\text{max}}$ (CHCl$_3$) 3054, 2986, 1578, 1496, 1477, 1265 cm$^{-1}$; $\delta$H (250 MHz, CDCl$_3$) 7.54 (2H, m), 7.29-7.18 (8H, m), 6.32 (2H, m), 3.71 (2H, d, 7.6 Hz); $\delta$C (100 MHz, CDCl$_3$) 137.3 (s), 134.3 (d), 132.5 (d), 130.3 (s), 129.3 (d), 128.9 (d), 127.8 (d), 127.7 (d), 126.7 (d), 126.3 (d), 31.1 (t); $m/z$ (EI.+) 274 (M$^+$), 157, 117, 91, 77, 65, 51, 39; Observed (M$^+$) 274.0261; C$_{15}$H$_{14}$Se requires: 274.0260.
Preparation of 3-methyl-1-(phenylseleno)-2-butene (246).112

\[
\begin{align*}
\text{Me} & \text{Cl} \quad \text{Me} \quad \text{Me} \\
\text{Me} & \text{SePh} \\
\end{align*}
\]

Diphenyl diselenide (3.50 g, 8.00 mmol) was dissolved in ethanol (110 ml) and cooled to 0°C. Sodium borohydride (851 mg, 16.0 mmol) was added gradually until the solution turned from yellow to colourless indicating that all the diphenyl diselenide had been reduced. 1-Chloro-3-methyl-2-butene (1.99 g, 19.0 mmol) dissolved in ethanol (10 ml) was added and the solution was heated to reflux for 2 h. The solution was allowed to cool to room temperature and water (ca. 10 ml) was added dropwise. The layers were separated and the aqueous layer extracted with ethyl acetate (3 x 10 ml). The combined organic extracts were washed with brine (30 ml) and the solvent removed under reduced pressure. The residue was purified by column chromatography (10% ethyl acetate/light petroleum) to give 3-methyl-1-(phenylseleno)-2-butene 246 (2.08 g, 48%) as a yellow liquid;\textsuperscript{112} \nu \text{max} (\text{CHCl}_3) 3056, 2968, 2912, 2854, 1664, 1579, 1476, 1434, 1376, 1176, 1022, 841 \text{ cm}^{-1}; \delta_H (250 \text{ MHz, } \text{CDCl}_3) 7.52 (2H, m), 7.27 (3H, m), 5.40 (1H, m), 3.55 (2H, d, 3.2 Hz), 1.71 (3H, s), 1.50 (3H, s); \delta_C (62.9 \text{ MHz, } \text{CDCl}_3) 136.8 (s), 133.5 (d), 128.7 (d), 126.8 (d), 120.1 (d), 105.5 (s), 26.0 (t), 25.6 (q), 17.3 (q); m/z (C.I.\textsuperscript{+}, thermospray) 243 (MNH\textsubscript{4}\textsuperscript{+}), 225 (MNH\textsubscript{4}\textsuperscript{+}-H\textsubscript{2}O); Observed (MH\textsuperscript{+}): 227.0339; C\textsubscript{11}H\textsubscript{15}Se requires: 227.0338.

Preparation of (E)-1-phenyl-3-[2-nitrophenyl)seleno]-1-propene (247).

\[
\begin{align*}
\text{Ph} & \text{OH} \quad \text{Ph} \quad \text{Se} \quad \text{Ph} \\
\text{247} & \text{O}_2\text{N} \\
\end{align*}
\]

(2-Nitrophenyl)selenocyanate 147 (2.73 g, 12.0 mmol) and cinnamyl alcohol (1.34 g, 10.0 mmol) were dissolved in tetrahydrofuran (30 ml) and stirred at 0°C. Freshly distilled tri-n-butyl phosphine (2.92 ml, 12.0 mmol) was added dropwise and the mixture allowed to warm to room temperature. After 2 h the reaction was estimated, by TLC, to be complete and the solvent was removed under reduced pressure. The residue was purified by column chromatography (30% ethyl acetate/light petroleum) to give (E)-1-phenyl-3-[2-nitrophenyl)selenol]propene 247 (2.42 g, 76%) as a yellow solid (m.p. 87-89°C); \delta_H (400
MHz, CDCl3) 8.09 (1H, dd, 8.35, 1.4 Hz), 7.27 (2H, m), 7.17-7.04 (6H, m), 6.47 (1H, d, 15.7 Hz), 6.16 (1H, m), 3.61(2H, m); δC (100 MHz, CDCl3) 147.2 (s), 136.8 (s), 134.6 (d), 134.1 (d), 134.0 (s), 129.8 (d), 129.1 (d), 129.0 (d), 128.3 (d), 126.8 (d), 126.0 (d), 123.8 (d), 29.4 (t); m/z (C.I. +, thermospray) 337 (MNH4+); Observed (MNH4+) 327.0455; C13H17N2O2Se requires: 327.0455.

Preparation of 3-methyl-1-[(2-nitrophenyl)seleno]-2-butene (248).

(2-Nitrophenyl)selenocyanate (2.73 g, 12.0 mmol) and 3-methyl-2-buten-1-ol (860 mg, 10.0 mmol) were dissolved in tetrahydrofuran (30 ml) and stirred at 0°C. Freshly distilled tri-n-butyl phosphine (2.92 ml, 12.0 mmol) was added dropwise and the mixture allowed to warm to room temperature. After 2 h the reaction was estimated, by TLC, to be complete and the solvent was removed under reduced pressure. The residue was purified by column chromatography (30% ethyl acetate/light petroleum) to give 3-methyl-1-[(2-nitrophenyl)seleno]-2-butene 248 (2.25 g, 83%) as an orange oil; νmax (film) 3083, 3026, 2970, 2914, 2856, 1664, 1590, 1565, 1450, 1376, 1303, 1096, 1037 cm⁻¹; δH (250 MHz, CDCl3) 8.28 (1H, d, 9.6 Hz), 7.51 (2H, m), 7.31 (1H, m), 5.38 (1H, t, 7.9 Hz), 3.59 (2H, d, 8.0 Hz), 1.75 (6H, s); δC (100 MHz, CDCl3) 147.0 (s), 138.9 (s), 135.6 (s), 133.9 (d), 129.8 (d), 126.7 (d), 125.7 (d), 117.4 (d), 26.2 (q), 25.2 (t), 18.2 (q); m/z (E.I. +) 271 (M⁺), 302, 186, 156, 106, 69, 63, 53, 41, 27; Observed (M⁺): 271.0112; C11H13NO2Se requires: 271.0111.

133
General Procedure X: Asymmetric Dihydroxylation of Allylic Selenides (245-248).\textsuperscript{105,107}

The appropriate AD-mix (1.4 g/mmol) and methanesulfonamide (1 eq) were dissolved in a 1:1 mixture of tert-butanol and water (10 ml/mmol) and stirred vigorously while being cooled to 0°C. The appropriate allylic selenide 245-248 was added to the cold mixture as a neat liquid or dissolved in 1:1 tert-butanol/water (10-20 ml). The mixture was stirred at 0°C for approximately 8 h each day and kept in the refrigerator overnight (ca. 5°C). The reactions were followed by TLC and were generally complete within 4 days. Sodium metabisulfite Na\textsubscript{2}S\textsubscript{2}O\textsubscript{5} (1.0 g/mmol) was added to the mixture in small portions and the mixture stirred for 30 min while warming to room temperature. The layers were separated and the aqueous layer extracted with ethyl acetate. The combined organic extracts were washed with 1.0 M KOH, 5% HCl and brine then dried over MgSO\textsubscript{4}. The solvent was removed under reduced pressure and the residue purified by column chromatography in the appropriate solvent system to give the product.

\textcolor{red}{(1S,2R)-1,2-dihydroxy-3-(phenylseleno)-1-phenylpropane (249).}

Treatment of (E)-1-phenyl-3-(phenylseleno)-propene 244 (959 mg, 3.50 mmol) with AD-mix-\textalpha\ (4.90 g, 3.5 mmol) and methanesulfonamide (332 mg, 3.50 mmol) in 1:1 tert-butanol/water (35 ml) buffered with NaHCO\textsubscript{3} (882 mg, 10.5 mmol) for 7 days, according to General Procedure X, and subsequent column chromatography (50% ethyl acetate/light petroleum) gave (1S,2R)-1,2-dihydroxy-3-(phenylseleno)-1-phenyl-propane 249 (425 mg, 39%) as a colourless solid (m.p. 74-76°C); [\alpha]_D\textsuperscript{20} = -7.0 (c 1.0, CHCl\textsubscript{3}); \nu_{max} (CHCl\textsubscript{3}) 3386, 1578, 1495, 1478, 1437, 1047, 1021, 732 cm\textsuperscript{-1}; \delta_H (250 MHz, CDCl\textsubscript{3}) 7.42-7.20 (10H, m),
4.76 (1H, d, 6.4 Hz), 3.82 (1H, m), 2.95 (4H, m); \( \delta_C \) (100 MHz, CDCl\(_3\)) 140.8 (s), 133.0 (d), 129.6 (d), 129.0 (d), 128.8 (d), 128.6 (s), 127.6 (d), 127.3 (d), 77.1 (d), 74.9 (d), 32.4 (t); \textit{m/z} (C.I.\(^{+}\), thermospray) 326 (MNH\(_4{+}\)), 271; Observed (MNH\(_4{+}\)) 326.0659; \( C_{15}H_{20}NO_{2}Se \) requires: 326.0659.

(1\(R,2S\))-1,2-dihydroxy-3-(phenylseleno)-1-phenylpropane (250).

\[
\text{Ph} \rightleftharpoons \text{SePh}
\]

Treatment of (E)-1-phenyl-3-(selenophenyl)-propene 245 (959 mg, 3.50 mmol) with AD-mix-\(\beta\) (4.90 g, 3.5 mmol) and methanesulfonamide (332 mg, 3.50 mmol) in 1:1 tert-butanol/water (35 ml) buffered with NaHCO\(_3\) (882 mg, 10.5 mmol) for 7 days, according to General Procedure X, and subsequent column chromatography (50% ethyl acetate/light petroleum) gave (1\(R,2S\))-1,2-dihydroxy-3-(phenylseleno)-1-phenylpropane 250 (411 mg, 38%) as a colourless solid (m.p. 74-76°C); \([\alpha]_D^{20} = +5.0 \ (c \ 1.0, \ \text{CHCl}_3)\). Other spectroscopic data is reported for the (1\(S,2R\))-enantiomer 249.

(1\(R,2S\))-1,2-dihydroxy-3-[(2-nitrophenyl)seleno]-1-phenylpropane (251).

\[
\text{Ph} \rightleftharpoons \text{SePh}
\]

Treatment of (E)-1-phenyl-3-[(2-nitrophenyl)selenol]-1-propene 247 (1.02 g, 3.2 mmol) with AD-mix-\(\beta\) (4.48 g, ca. 3.2 mmol) and methanesulfonamide (304 mg, 3.2 mmol) in 1:1 tert-butanol/water (35 ml) for 4 days, according to General Procedure X, and subsequent column chromatography (50% ethyl acetate/light petroleum) gave (1\(R,2S\))-1,2-dihydroxy-3-[(2-nitrophenyl)seleno]-1-phenylpropane 251 (646 mg, 57%) as a yellow solid (m.p. 85-87°C); \([\alpha]_D^{20} = -16.3 \ (c \ 1.0, \ \text{CHCl}_3)\); \( \nu_{\text{max}} \) (CHCl\(_3\)) 3687, 3607, 3036, 3026, 2960, 2929, 2873, 1592, 1568, 1518, 1455, 1335 cm\(^{-1}\); \( \delta_H \) (400 MHz, CDCl\(_3\)) 8.03 (1H, dd, 8.3, 1.4 Hz), 7.20-7.14 (6H, m), 7.06 (1H, m), 6.98 (1H, m), 4.48 (1H, d, 6.9 Hz), 3.78 (1H, m), 2.80 (1H, dd,
13.0, 3.6 Hz), 2.66 (1H, dd, 12.9, 8.2 Hz) (signals for the hydroxyl protons were not observed); δC (100 MHz, CDCl3) 147.4 (s), 140.6 (s), 134.0 (d), 132.9 (s), 129.5 (d), 129.2 (d), 129.0 (d), 127.7 (d), 126.8 (d), 126.0 (d), 77.6 (d), 60.9 (d), 29.9 (t); m/z (E.I.*) 203, 186, 107, 79; Observed (M⁺): 353.0166; C15H15NO4Se requires: 353.0166.

(2R)-3-methyl-2,3-dihydroxy-1-(phenylseleno)-butane (252).

Treatment of 3-methyl-1-(phenylseleno)-2-butene 246 (1.81 g, 8.0 mmol) with AD-mix-α (11.2 g, 8.0 mmol) and methanesulfonamide (760 mg, 8.0 mmol) in 1:1 tert-butanol/water (80 ml) buffered with NaHCO₃ (3.02 mg, 24.0 mmol) for 6 days, according to General Procedure X, and subsequent column chromatography (50% ethyl acetate/light petroleum) gave (2R)-3-methyl-2,3-dihydroxy-1-(phenylseleno)butane 252 (238 mg, 12%) as a colourless oil; [α]D20 = -9.2 (c1.0, CHCl₃); νmax (CHCl₃) 3417, 3057, 2976, 1579, 1478, 1438, 1073 cm⁻¹; δH (400 MHz, CDCl₃) 7.53 (2H, m), 7.27 (3H, m), 3.45 (1H, dd, 10.6, 2.3 Hz), 3.21 (1H, dd, 12.8, 2.4 Hz), 2.89 (1H, dd, 11.8, 10.7 Hz), 1.22 (3H, s), 1.19 (3H, s) (signals for hydroxyl protons were not observed); δC (100 MHz, CDCl₃) 132.7 (d), 128.9 (d), 128.6 (s), 127.1 (d), 75.4 (d), 72.1 (s), 31.9 (t), 26.1 (q), 23.8 (q); m/z (C.I.+*, thermospray) 278 (MNH₄+), 276, 117; Observed (MNH₄+): 278.0659, C11H20NO2Se requires: 278.0659.

(2S)-3-methyl-2,3-dihydroxy-1-[(2-nitrophenyl)seleno]butane (253).

Treatment of (Z)-3-methyl-1-[(2-nitrophenyl)seleno]-2-butene 248 (1.54 g, 5.7 mmol) with AD-mix-β (7.98 g, 5.7 mmol) and methanesulfonamide (541 mg, 5.70 mmol) in 1:1 tert-butanol/water (55 ml) for 4 days, according to General Procedure X, and subsequent column chromatography (50% ethyl acetate/light petroleum) gave (2S)-3-methyl-2,3-dihydroxy-1-[(2-nitrophenyl)seleno]butane 253 (869 mg, 50%) as a yellow solid (m.p. 84-86°C); [α]D20 =
\(-30.8 \text{ (c 0.5, CHCl}_3\); } \nu_{\text{max}} \text{ (CHCl}_3\) 3695, 3605, 3066, 2983, 1593, 1517, 1422, 1335 \text{ cm}^{-1}; \delta_H \text{ (400 MHz, CDCl}_3\) 8.06 (1H, dd, 8.3, 1.4 Hz), 7.40 (1H, dd, 8.2, 1.3 Hz), 7.33 (1H, dt, 7.1, 1.4 Hz), 7.14 (1H, dt, 7.1, 1.4 Hz), 3.50 (1H, dd, 10.5, 2.4 Hz), 3.01 (1H, dd, 12.5, 2.4 Hz), 2.79 (1H, dd, 12.5, 10.5 Hz), 1.10 (3H, s), 1.06 (3H, s) (signals for the hydroxyl protons are very broad 2.7-1.8 ppm); \delta_C \text{ (100 MHz, CDCl}_3\) 147.6 (s), 135.2 (d), 134.1 (s), 129.8 (d), 126.8 (d), 126.2 (d), 77.6 (s), 73.4 (d), 30.1 (t), 26.7 (q), 23.0 (q); \text{m/z} \text{ (E.I.\+)} 203, 186, 106, 59, 43; \text{Observed (M\+)}: 303.0011; \text{C}_{11}\text{H}_{15}\text{NO}_4\text{Se requires: 303.0010.}

**General Procedure Y: Preparation of 5-[(arylselenomethyl]-1,3,2-dioxathiolane-2-oxides (254, 255, 258, 259).**

The appropriate arylselenodiol was dissolved in dichloromethane (4 ml/mmol) containing triethylamine (2 eq) and cooled to \(-78^\circ\text{C}\). Thionyl chloride (1.1 eq) dissolved in dichloromethane (1 ml/mmol) was added dropwise to the mixture. When the reactions was estimated, by TLC, to be complete it was quenched with saturated NH\(_4\)Cl (5 ml) and allowed to warm to room temperature. The mixture was poured into water (10 ml/mmol) and the layers separated. The aqueous layer was extracted with dichloromethane and the combined organic extracts were washed successively with 2 M HCl, saturated NaHCO\(_3\) and brine then dried over Na\(_2\)SO\(_4\). The residues was purified by column chromatography to give the product.

**(4S,5R)-4-Phenyl-5-(phenylselenomethyl]-1,3,2-dioxathiolane-2-oxide (254).**

Treatment of (1S,2R)-1,2-dihydroxy-3-(phenylseleno)-1-phenylpropane 249 (246 mg, 0.80 mmol) dissolved in dichloromethane (3 ml) containing triethylamine (0.22 ml, 1.60 mmol)
with thionyl chloride (70 μl, 0.96 mmol) dissolved in dichloromethane (0.5 ml) at -78°C for 1 h as, described in General Procedure Y, and subsequent column chromatography (25% ethyl acetate/light petroleum) gave (4S,5R)-4-phenyl-5-(phenylselenomethyl)-1,3,2-dioxathiolane-2-oxide 254 (207 mg, 73%) as a colourless gum and as a 1:1 mixture of diastereomers; \( \nu_{\text{max}} \) (CHCl\(_3\)) 3064, 3013, 2959, 2930, 2872, 1579, 1494, 1478, 1456, 1438, 1375, 1236, 949 cm\(^{-1}\); \( \delta_H \) (400 MHz, CDCl\(_3\)) 7.23-7.02 (10H, m), 5.59 (0.5H, d, 7.1 Hz), 5.03 (0.5H, d, 9.0 Hz), 4.80 (0.5H, m), 4.39 (0.5H, m), 3.24 (0.5H, dd, 13.0, 5.5 Hz), 3.15 (0.5H, dd, 13.1, 7.5 Hz), 3.10 (0.5H, dd, 13.5, 5.0 Hz), 3.01 (0.5H, dd, 13.5, 5.5 Hz); \( \delta_C \) (100 Hz, CDCl\(_3\)) 134.8 (s), 134.4 (s), 133.9 (d), 133.8 (d), 130.0 (d), 129.8 (d), 129.7 (d), 129.5 (d), 129.2 (d), 128.6 (s), 128.4 (s), 128.2 (d), 127.6 (d), 89.9 (d), 88.3 (d), 86.0 (d), 84.2 (d), 30.1 (t), 27.4 (t) (not all of the aromatic carbons for the two diastereomers were resolved); m/z (C.I.\(^{+}\), thermospray) 372 (MNH\(_4\)^+); Observed (MNH\(_4\)^+): 372.0172; C\(_{16}\)H\(_{18}\)NO\(_3\)Se requires: 372.1073.

(5 R)-4,4-dimethyl-5-(phenylselenomethyl)-1,3,2-dioxathiolane-2-oxide (255).

\[
\begin{align*}
&\text{Me} \quad \text{OH} \\
&\text{Me} \quad \text{SePh} \\
\text{OH} \\
&252 \\
\rightarrow \\
&\text{Me} \quad \text{OH} \\
&\text{Me} \quad \text{SePh} \\
\text{O} \\
&255 \\
\end{align*}
\]

Treatment of (2R)-3-methyl-2,3-dihydroxy-1-(phenylseleno)butane 252 (208 mg, 0.80 mmol) dissolved in dichloromethane (3 ml) containing triethylamine (0.22 ml, 1.60 mmol) with thionyl chloride (70 μl, 0.96 mmol) dissolved in dichloromethane (0.5 ml) for 2 h, as described in the General Procedure, and subsequent column chromatography (20% ethyl acetate/light petroleum) gave (5 R)-4,4-dimethyl-5-(phenylselenomethyl)-1,3,2-dioxathiolane-2-oxide 255 (150 mg, 61%) as a colourless oil and as a 1:1 mixture of diastereomers; \( \nu_{\text{max}} \) (film) 3058, 2983, 2934, 1579, 1478, 1438, 1375, 1212, 1073, 945, 736 cm\(^{-1}\); \( \delta_H \) (400 MHz, CDCl\(_3\)) 7.36 (2H, m), 7.11 (3H, m), 4.57 (0.5H, t, 6.9 Hz), 4.11 (0.5H, t, 6.6 Hz), 3.18 (0.5H, dd, 13.0, 7.6 Hz), 3.01 (0.5H, dd, 12.8, 7.3 Hz), 2.90 (0.5H, dd, 13.0, 6.5 Hz), 2.75 (0.5H, dd, 13.0, 6.6 Hz), 1.45 (1.5H, s), 1.43 (1.5H, s), 1.27 (1.5H, s), 1.07 (1.5H, s); \( \delta_C \) (100 Hz, CDCl\(_3\)) 134.1 (d), 133.8 (d), 129.9 (d), 129.8 (d), 129.1 (s), 128.8 (s), 128.5 (d), 128.3 (d), 91.1 (s), 89.5 (s), 88.9 (d), 83.7 (d), 27.6 (q), 27.5 (q), 27.4 (t), 25.3 (t), 24.0 (q), 22.7 (q); m/z (C.I.\(^{+}\), thermospray) 324 (MNH\(_4\)^+), 117; Observed (MNH\(_4\)^+): 324.0173; C\(_{11}\)H\(_{18}\)NO\(_3\)Se requires: 324.0172.
Treatment of (1R,2S)-1,2-dihydroxy-3-[(2-nitrophenyl)seleno]-1-phenylpropane 251 (529 mg, 1.50 mmol) dissolved in dichloromethane (6 ml) containing triethylamine (0.42 ml, 3.0 mmol) with thionyl chloride (0.12 ml, 1.6 mmol) dissolved in dichloromethane (1.5 ml) for 2 h, as described in General Procedure Y, and subsequent column chromatography (30% ethyl acetate/light petroleum) gave (4R,5S)-4-phenyl-5-[(2-nitrophenyl)selenomethyl]-1,3,2-dioxathiolane-2-oxide 258 (363 mg, 61%) as a yellow viscous oil and a 1:1 mixture of diastereomers; \( \nu_{\text{max}} \) (CHCl\(_3\)) 3063, 2956, 2928, 1576, 1517, 1489, 1476, 1365, 1240 cm\(^{-1}\); \( \delta_H \) (400 MHz, CDCl\(_3\)) 8.16 (1H, m), 7.41-7.25 (8H, m), 5.72 (0.5H, d, 7.8 Hz), 5.17 (0.5H, d, 9.2 Hz), 5.02 (0.5H, m), 4.58 (0.5H, m), 3.45 (0.5H, dd, 13.3, 6.9 Hz), 3.92-3.19 (1.5H, m); \( \delta_C \) (100 Hz, CDCl\(_3\)) 147.5 (s), 134.2 (d), 133.8 (s), 131.4 (s), 131.2 (s), 130.4 (d), 130.2 (d), 129.5 (d), 129.3 (d), 128.3 (d), 127.6 (d), 126.9 (d), 126.6 (d), 90.2 (d), 87.8 (d), 86.0 (d), 83.4 (d), 27.9 (t), 24.7 (t) (not all of the aromatic carbons for the two diastereomers were resolved); \( m/z \) (C.I.\(^+\), thermospray) 417 (MNH\(_4^+\)); Observed (MNH\(_4^+\)): 417.0023; 
C\(_{15}\)H\(_{17}\)N\(_2\)O\(_5\)Se requires: 417.0023.

Treatment of (2S)-3-methyl-2,3-dihydroxy-1-[(2-nitrophenyl)seleno]butane 253 (762 mg, 2.50 mmol) dissolved in dichloromethane (10 ml) containing triethylamine (0.70 ml, 5.0 mmol) with thionyl chloride (0.22 ml, 3.0 mmol) dissolved in dichloromethane (2.5 ml) for 2 h, as described in General Procedure Y, and subsequent column chromatography (50% ethyl acetate/light petroleum) gave (5S)-4,4-dimethyl-5-[(2-nitrophenyl)selenomethyl]-1,3,2-dioxathiolane-2-oxide 259 (647 mg, 61%) as a yellow oil; \( \nu_{\text{max}} \) (CHCl\(_3\)) 3063, 2985, 2941, 2869, 1586, 1518, 1488, 1479, 1367 cm\(^{-1}\); \( \delta_H \) (400 MHz, CDCl\(_3\)) 8.16 (1H, m), 7.41-7.25 (8H, m), 5.72 (0.5H, d, 7.8 Hz), 5.17 (0.5H, d, 9.2 Hz), 5.02 (0.5H, m), 4.58 (0.5H, m), 3.45 (0.5H, dd, 13.3, 6.9 Hz), 3.92-3.19 (1.5H, m); \( \delta_C \) (100 Hz, CDCl\(_3\)) 147.5 (s), 134.2 (d), 133.8 (s), 131.4 (s), 131.2 (s), 130.4 (d), 130.2 (d), 129.5 (d), 129.3 (d), 128.3 (d), 127.6 (d), 126.9 (d), 126.6 (d), 90.2 (d), 87.8 (d), 86.0 (d), 83.4 (d), 27.9 (t), 24.7 (t) (not all of the aromatic carbons for the two diastereomers were resolved); \( m/z \) (C.I.\(^+\), thermospray) 435 (MNH\(_4^+\)); Observed (MNH\(_4^+\)): 435.0023; 
C\(_{17}\)H\(_{21}\)N\(_2\)O\(_5\)Se requires: 435.0023.

\( (4R, 5S)-4\)-Phenyl-5-[(2-nitrophenyl)selenomethyl]-1,3,2-dioxathiolane-2-oxide (258).

\( (5S)-4,4\)-dimethyl-5-[(2-nitrophenyl)selenomethyl]-1,3,2-dioxathiolane-2-oxide (259).
acetate/light petroleum) gave (5S)-4,4-dimethyl-5-[(2-nitrophenyl)selenomethyl]-1,3,2-dioxathiolane-2-oxide 258 (813 mg, 93%) as a yellow solid and as a 1:1 mixture of diastereomers (m.p. 75-85°C); \( \nu_{\text{max}} \) (CHCl₃) 3049, 2980, 1593, 1568, 1335, 1304, 1159, 1067 cm⁻¹; \( \delta_H \) (400 MHz, CDCl₃) 8.12 (1H, m), 7.38 (2H, m), 7.20 (1H, m), 4.69 (0.5 H, dd, 7.8, 6.3 Hz), 4.25 (0.5 H, dd, 8.1, 5.6 Hz), 3.28 (0.5 H, dd, 12.7, 8.1 Hz), 3.10 (0.5 H, dd, 13.0, 7.8 Hz), 2.95 (0.5 H, dd, 12.7, 5.6 Hz), 2.84 (0.5 H, dd, 13.0, 6.1 Hz), 1.53 (1.5H, s), 1.49 (1.5H, s), 1.32 (1.5H, s), 1.18 (1.5H, s); \( \delta_C \) (100 Hz, CDCl₃) 147.3 (s), 134.5 (d), 132.0 (s), 131.6 (s), 129.4 (s), 129.1 (d), 127.1 (d), 127.0 (d), 126.7 (d), 126.6 (d), 91.4 (s), 89.9 (s), 88.2 (d), 82.9 (d), 27.5 (q), 27.2 (q), 26.0 (t), 24.1 (q), 23.4 (t), 22.9 (q) (not all aromatic carbons for the two diastereomers are resolved); m/z (C.I.⁺, thermospray) 369 (MNH₄⁺); Observed (MNH₄⁺): 369.0023; C₁₁H₁₇N₂O₅SSe requires: 369.0023.
Oxidation of (5S)-4,4-dimethyl-5-[(2-nitrophenyl)selenomethyl]-1,3,2-dioxathiolane-2-oxide (259).

To (5S)-4,4-dimethyl-5-[(2-nitrophenyl)selenomethyl]-1,3,2-dioxathiolane-2-oxide 259 (375 mg, 1.07 mmol) dissolved in tetrahydrofuran (6 ml) was added hydrogen peroxide (30% water, 1.80 ml, 21.4 mmol) and the mixture stirred at room temperature. After 2 h the reaction was estimated, by TLC, to be complete and the mixture was diluted with water (5 ml) and extracted with ethyl acetate (3 x 5 ml). The combined organic extracts were washed with 5% ferrous sulfate solution (20 ml) and brine (20 ml) then dried over Na₂SO₄ and the solvent removed under reduced pressure.

The residue was dissolved in CDCl₃ (3 ml) and heated to reflux. Samples were taken at 30 min intervals and analysed by TLC and ¹H NMR (250 MHz). After 4 h all of the selenoxide 261 had eliminated and the solvent was removed under reduced pressure. Purification by column chromatography (25% ethyl acetate/light petroleum) gave 4,4-dimethyl-5-methylene-1,3,2-dioxathiolane-2-oxide 234 (44.0 mg, 28%) as a pale yellow oil. The spectroscopic data for this material was consistent with the literature values and data for this compound prepared previously via a different method.
Oxidation of (4R,5S)-4-phenyl-5-[(2-nitrophenyl)selenomethyl]-1,3,2-dioxathiolane-2-oxide (258).

To (4R,5S)-4-phenyl-5-[(2-nitrophenyl)selenomethyl]-1,3,2-dioxathiolane-2-oxide 258 (205 mg, 0.5 mmol) dissolved in tetrahydrofuran (2 ml) was added hydrogen peroxide (30% water, 0.83 ml, 10 mmol) and the mixture stirred at room temperature. After 2 h the reaction was estimated, by TLC, to be complete and the mixture was diluted with water (5 ml) and extracted with ethyl acetate (3 x 5 ml). The combined organic extracts were washed with 5% ferrous sulfate solution (20 ml) and brine (20 ml) then dried over Na₂SO₄ and the solvent was removed under reduced pressure. The residue was dissolved in CDCl₃ (2 ml) and heated to reflux. Samples were taken at 30 min intervals and analysed by TLC and ¹H NMR (250 MHz). After 4 h all of the selenoxide 260 had eliminated and the solvent was removed under reduced pressure. Purified by column chromatography (25% ethyl acetate/light petroleum) gave (4R)-4-phenyl-5-methylene-1,3,2-dioxathiolane-2-oxide 262 (27.0 mg, 28%) as a yellow oil and a 9:1 mixture of diastereomers; νₘₐₓ (film) 3066, 3035, 2927, 2856, 1672, 1590, 1515, 1495, 1457, 1332, 1228, 1197, 958, 929 cm⁻¹; δₜ (400 MHz, CDCl₃) 7.50-7.39 (5H, m), 6.26 (0.9H, m), 5.95 (0.1H, m), 4.96 (0.1H, m), 4.86 (0.9H, m), 4.26 (0.1H, m), 4.13 (0.9H, m). Unfortunately this sample decomposed rapidly and could not be characterised further.
References


racemic material

enantiotomerically enriched material 83% ee

\[
\begin{align*}
\text{THPO} & \quad \text{SiMe}_3 \\
& \quad \text{Ph} \\
& \quad \text{CF}_3 \\
& \quad \text{OMe}
\end{align*}
\]
Appendix 2

HPLC traces for the enantiomeric excess determination of \((3R)-(1\text{-naphthalenemethoxy})\text{-tridecan-2-one.}\\

A. enantiomerically enriched material 79%ee

B. racemic material

C. spiked material; 1:1 mixture of A and B

Chiralcel OD HPLC column \((\lambda = 254 \text{ nm, 0.3\% 2-propanol/hexane, 0.6 ml min}^{-1})\)