ASYMMETRIC SYNTHESIS USING CHIRAL VINYL ETHERS

A Thesis submitted for the Degree of
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STATEMENT

The accompanying thesis submitted for the degree of Ph.D. entitled "Asymmetric Synthesis using Chiral Vinyl Ethers" is based on work conducted by the author in the Department of Chemistry of the University of Leicester mainly during the period between October 1989 and September 1992.

All the work recorded in this thesis is original unless otherwise acknowledged in the text or by references.

None of the work has been submitted for another degree in this or any other University.

Signed: ........................................... Date: 12/12/92

Part of this work has been published as a communication;

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by

DAVID ANTHONY DAWKINS

ABSTRACT

Using chiral alcohol precursors, a number of chiral vinyl ethers were prepared by mercuric acetate-catalysed transetherification with butyl vinyl ether. α-Lithiation of (1R)-menthyl vinyl ether was unsuccessful under a variety of conditions. (1S)-(Menthylthio)ethene was prepared from (1S)-menthanethiol but deprotonation was not possible as the thioether was found to decompose rapidly at room temperature. The deprotonation of (R)-phenethyl vinyl ether, (S)-1-(2-naphthyl)-1-ethyl vinyl ether and (S)-1-phenyl-1-butyl vinyl ether and attempted reaction with benzaldehyde yielded none of the α-alkylated adduct but a Wittig rearrangement reaction was seen.

The cycloaddition reaction of benzonitrile oxide with a range of chiral vinyl ethers was investigated. The isoxazoline product was isolated as a mixture of two diastereoisomers after flash column chromatography. In most cases the diastereoisomer ratio neared 1:1, but (S)-1-(2-naphthyl)-1-ethyl vinyl ether and 1-phenyl-1-butyl vinyl ether gave a single diastereoisomer of the isoxazoline product, after chromatography, with a variety of nitrile oxides. Conditions have been developed for the removal of the chiral auxiliary but as yet only achiral isoxazolines have been obtained by this method. Attempts at ring deprotonation/allylation and also the addition of a nucleophile or radical to the isoxazoline C=N bond were hindered by the instability of the isoxazoline adducts. A chiral vinyl pyrrolidinone was also prepared and found to undergo an asymmetric cycloaddition reaction with benzonitrile oxide to yield a single diastereoisomer of the isoxazoline product. The equivalent acrylamide was synthesised and, although this gave a 1:1 mixture of diastereoisomers with both benzonitrile oxide and 2,2-dimethylpropanenitrile oxide, these diastereoisomers could be separated. Removal of the chiral auxiliary yielded hydroxyisoxazolines with an enantiomeric excess of 90-94%. Attempts to investigate the extent of any asymmetric induction in the cycloaddition of nitrile oxides to chiral vinyl sulphoxides were hampered by the instability of the isoxazoline product, which underwent an immediate syn-elimination.

In an effort to determine the potential of chloromethyl-(1R)-menthyl ether as a chiral OH protecting group, a series of (1R)-menthoxyethyl ethers were prepared from a variety of racemic and homochiral alcohols. Conditions for deprotection were developed which did not lead to the racemisation of homochiral alcohols. The usefulness of the (1R)-menthoxyethyl ether group as a simple means of measuring enantiomeric excess was demonstrated in a silicon-directed diene synthesis.
ACKNOWLEDGEMENTS

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ABBREVIATIONS

AIBN - 2,2'-azobisisobutyronitrile
aq. - aqueous
b.p. - boiling point
d.e. - diastereoisomeric excess
D.E.P.T. - Distortionless Enhancement by Polarisation Transfer
DIBAL-H - diisobutylaluminium hydride
DMSO - dimethylsulphoxide
e.e. - enantiomeric excess
g.c. - gas chromatography
h.p.l.c. - high performance liquid chromatography
LDA - lithium diisopropylamide
L-Selectride - lithium tri-sec-butyl borohydride
m.p. - melting point
MEM - 2-methoxyethoxymethyl
NCS - N-chlorosuccinimide
n.m.r. - nuclear magnetic resonance
PCC - pyridinium chlorochromate
TBAF - tert-butyl ammonium fluoride
THF - tetrahydrofuran
T.l.c. - thin layer chromatography
TMEDA - N,N,N',N'-tetramethylethlenediamine
Ts - p-toluenesulphonyl

(1R)-Menthy in the text and men. in the reaction schemes refer to derivatives of
(1R,2S,5R)-(−)-2-isopropyl-5-methylcyclohexan-1-ol.
CHAPTER 1

Deprotonation of Chiral Vinyl Ethers
1.1.1 ASYMMETRIC SYNTHESIS

When a new chiral centre is created in a chemical reaction, the two possible configurations need not be formed in equal amounts if there is any asymmetry in the substrate. Such syntheses are known as asymmetric or stereoselective syntheses and are of great synthetic value to the organic chemist. Asymmetric carbon-carbon bond forming reactions, in particular, have been important in the synthesis of a wide range of optically active compounds.\(^1\)\(^2\)

If a new chiral centre is created in a molecule that is already optically active, the two diastereoisomers of the product may be formed in unequal amounts by two reaction pathways which are diastereoisomeric and therefore have different activation energies. This is known as asymmetric induction. Usually, from a synthetic point of view, the more unequal the ratio of products formed, then the more useful is the reaction. Such asymmetric reactions can normally be rationalised in terms of the steric and electronic interactions which stereochemically control the course of the reaction. For certain additions to the carbonyl group of ketones containing an asymmetric α-carbon, Cram's rule predicts which diastereoisomer will predominate.\(^3\)

The two faces of the carbonyl group in aldehydes and ketones with an α-chiral centre are diastereotopic, hence nucleophilic addition to such compounds can lead to two diastereoisomeric products. Although there is free rotation about the single bond between the carbonyl group and the α-carbon atom, studies by Cram predict which conformation will lead to the formation of the major product. In a more recent investigation of this topic, Felkin\(^4\) and Ahn\(^5\) proposed that, when the α-carbon has three groups which may be classified as small (S), medium (M) and large (L), then conformation (1) will lead to the major product. Here the groups are staggered so that
the carbonyl oxygen is between the large and medium groups. The incoming nucleophile preferentially attacks on the side of the plane containing the small group to give the major product diastereoisomer (2). The other face of the carbonyl is attacked in a more hindered, staggered conformation (3) in which the carbonyl oxygen lies between the large and small groups. This leads to the formation of the minor diastereoisomer (4), Figure 1.

![Figure 1](image)

A specific example is shown in Figure 2 where the most important steric interactions in both conformations are those of the R group, which prefers to lie between the large and small groups, as in conformation (5), rather than between the large and medium groups, as in conformation (6).
Attack on a different conformation is preferred when one of the substituents on the α-carbon has a lone pair (e.g. OH, OMe, NMe2, SMe) which may coordinate to an organometallic reagent. Here the carbonyl group and the coordinating substituent are held syn-periplanar by a 5-membered chelate ring. Attack by the nucleophile then occurs preferentially from the less hindered side of the intermediate (7) to give the major product (8), Figure 3.
1.1.2 KETONE SYNTHESIS

Alddehydes and ketones are important functional groups in organic synthesis. The synthesis of a ketone (9) may be summarised in the following retrosynthetic analysis.\(^6\)
The ethyl cation synthon (11) has a convenient synthetic equivalent in ethyl iodide. The usefulness of this disconnection depends therefore on the development of synthetic equivalents of the acyl anion (10).

1.1.3 ACYL ANION EQUIVALENTS

Acylic anions have been prepared by the addition of an alkyl lithium to carbon monoxide but the high reactivity of acyl anions often leads to side reactions. Other methods have been based on the addition of an alkyl halide to carbon monoxide by use of a transition metal catalyst (12).10

\[
\text{Li[PhFe(CO)_4]} + \text{C}_6\text{H}_5\text{CH}_2\text{Br} \xrightarrow{\text{CO}} \text{C}_6\text{H}_5\text{COCH}_2\text{C}_6\text{H}_5
\]

There are several classes of acyl anion equivalent. Three of the most well established equivalents of these important species are produced by deprotonation of 1,3-dithianes, protected cyanohydrins and vinyl ethers.

2-Substituted-1,3-dithianes (13) are readily deprotonated to give the 2-lithio-1,3-dithiane (14). Condensation with aldehydes and ketones followed by hydrolysis leads to \(\alpha\)-hydroxycarbonyl compounds (15), Scheme 1.11
Protected cyanohydrins have found widespread use as acyl anion equivalents. Lithiated O-silylcyanohydrins (16), in particular, have been used in a similar fashion to dithianes, Scheme 2.\textsuperscript{12}

\textbf{Scheme 2}

Lithiated vinyl ethers (17) may also be alkylated and then hydrolysed to the respective carbonyl compound (18), Scheme 3.\textsuperscript{13,14}
In our studies we will concentrate on developing new acyl anion equivalents based on lithiated vinyl ethers. In addition to the alkylation reaction already mentioned, these acyl anion equivalents also react with carbonyl compounds.

\[ \text{MeO} \text{Li} \quad \text{PhCHO} \quad \text{MeO} \quad \text{Ph} \]

(17) \quad (19)

A new chiral centre is created in the adduct (19) and so it is possible that asymmetric induction can be developed in this reaction if we start from a chiral lithiated vinyl ether (20).

\[ \text{R}^* \text{O} \text{Li} \quad \text{PhCHO} \quad \text{R}^* \text{O} \quad \text{Ph} \]

(20)

1.1.4 α-HETEROATOMIC STABILISED CARBANIONS

The acidity of a specific proton in a molecule is directly related to the stability of the carbanion formed after deprotonation. One factor that affects the stability of the carbanion is the hybridisation of the carbon atom bearing the negative charge. This is illustrated by simple hydrocarbons, where acetylenic protons are more acidic than vinylic protons which, in turn, are more acidic than alkyl protons.
The higher the s-character at the carbanion centre (sp > sp² > sp³), the closer the electrons are to the positive charge of the nucleus, which leads to a more stable carbanion. Although alkynes, alkenes and alkanes are all relatively weak acids with pKa values of ca. 25, 36 and 50 respectively (cf. RCOOH, pKa 4-5), the relative kinetic and thermodynamic acidities of alkenes and alkanes can be enhanced by the introduction of a heteroatom α to the respective proton. This is due to an increase in the stability of the resulting carbanion by the inductive effect and, in the case of sulphur and phosphorous, a stabilising effect which has been attributed to either πn-δπ bonding or the polarisability of the atom.

The effect of different heteroatoms on the kinetic acidity of α-protons is illustrated in Table 1, where f is the ratio of the deuterium exchange rate for a given C-D bond in the compound (21) compared with that for the C-D bond in deuterated benzene (22) (i.e. the rate of deuterium of the compound with a deuterium atom previously introduced was determined).  

\[
\text{C}_6\text{H}_5\text{XCD}_3 \xrightarrow{\text{KNH}_2, \text{NH}_3} \text{C}_6\text{H}_2\text{XCD}_2
\]

(21)

\[
\text{C}_6\text{D}_6 \xrightarrow{\text{KNH}_2, \text{NH}_3} \text{C}_6\text{D}_5
\]

(22)
The extent to which the carbanion is stabilized by the \( \alpha \)-heteroatom depends on the position of the heteroatom in the Periodic Table. Stabilisation is usually greatest when the heteroatom is further to the right of a row and is in the third rather than the second or fourth rows. Therefore the presence of these heteroatoms significantly increases the acidity of \( \alpha \)-protons.

In addition, a number of modifications of the heteroatom lead to stabilisation of the resulting carbanion. These include attachment of an electron-withdrawing group to the heteroatom; the presence of a charge-dipole interaction, (23); the ability to delocalise the negative charge, (24); the heteroatom being partially or fully charged, (25), e.g. phosphonyl, sulphinyl, Figure 4.

<table>
<thead>
<tr>
<th>SUBSTITUENT</th>
<th>( f )</th>
<th>( f_{\text{ref}} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{C}_2\text{H}_3\text{SCH}_3 )</td>
<td>( 1 \times 10^4 )</td>
<td>( 2 \times 10^4 )</td>
</tr>
<tr>
<td>( \text{C}_2\text{H}_3\text{SeCH}_3 )</td>
<td>( 1 \times 10^4 )</td>
<td>( 2 \times 10^4 )</td>
</tr>
<tr>
<td>( \text{C}_2\text{H}_3\text{OCH}_3 )</td>
<td>0.22</td>
<td>40</td>
</tr>
<tr>
<td>( \text{C}_2\text{H}_3\text{P(CH}_3)_2 )</td>
<td>140</td>
<td>( 3 \times 10^4 )</td>
</tr>
<tr>
<td>( \text{C}_2\text{H}_3\text{N(CH}_3)_2 )</td>
<td>0.005</td>
<td>1</td>
</tr>
</tbody>
</table>

**TABLE 1:** The effect of heteroatom substitution on the kinetic acidity of \( \alpha \)-protons.
The presence of alkyl groups attached to the carbanionic centre lowers the stabilisation whilst the attachment of electron-withdrawing groups or a second heteroatom enhances the stabilisation of the carbanion.

Although the relative inductive stabilising effect of heteroatoms on carbanions is not in doubt, the controversy between the pπ-dπ orbital theory and polarisation theory in explaining the difference in carbanion stabilisation by heteroatoms lying in the same column of the Periodic Table has not yet been resolved. The "d-orbital" theory explains the higher acidity of compounds bearing heteroatoms possessing unoccupied 3d or 4d orbitals by stabilisation of the carbanion by delocalisation of the charge in
the relatively low-lying orbitals. This allows carbanion 2p\textsubscript{z}-heteroatom d\pi overlap, which should be better with 3d than with 4d orbitals, Figure 5.

![Figure 5](image)

The "polarisation theory" is mainly related to the results of theoretical calculations which stress the unimportance of d\pi-p\pi overlap to explain the higher stabilisation of carbanions bearing a heteroatom belonging to the second or third rows of the Periodic Table. All theoretical results are explained in terms of the polarisability of the heteroatom, a property which is related to the electronegativity of the heteroatom. Analogous to the d\pi-p\pi orbital theory, the polarisation theory also explains the greater acidity of compounds in which the heteroatom belongs to the third row of the Periodic Table.

1.1.5 METHOXYVINYLLITHIUM AND ITS ANALOGUES

The use of methoxyvinylithium (17) as a synthetic equivalent of the acyl carbanion (10) was reported by Baldwin et al.\textsuperscript{13} Reaction of the acyl anion equivalent (17) with electrophiles and subsequent acid hydrolysis of the product gave the corresponding carbonyl compounds (26) in high yield, Scheme 4.
Reaction with aldehydes and ketones gave \( \alpha \)-ketois (27) after hydrolysis.

Ethyl vinyl ether has been employed in a manner analogous to that described for methyl vinyl ether. Attempts to deprotonate phenyl vinyl ether (28) resulted in ortho-metallation of the benzene ring but the vinyl anion was formed by a second deprotonation.

Similarly, the analogous thio- (29) and seleno-ethers (30) also act as masked acyl anion equivalents, Scheme 5. Deprotonation is achieved with n-butyllithium instead of t-butyllithium, which is necessary for the deprotonation of vinyl ethers. Although sulphur and selenium are less electronegative than oxygen as they are below oxygen.
in Group VI of the Periodic Table, ππ-dπ bonding stabilises the anions formed. Hence the α-proton is more acidic than in the equivalent vinyl ether and may be removed using a weaker base.

Larson et al. have recently prepared a chiral silicon analogue (31) of the acyl anion (17) and reacted with a range of aldehydes. The selectivity of the addition was poor, ca. 1:1, although the resulting diastereoisomers (32a) and (32b) could be separated and the silicon moiety removed by protodesilylation, Scheme 6.
1.1.6 LITHIOMETHOXYALLENE AND ITS ANALOGUES

The preparation of methoxyallene (33) and its α-lithio-derivative (34) was first reported by Hoff et al.\textsuperscript{19}
1-Lithio-1-methoxyallene (34) can be alkylated\textsuperscript{19} or reacted with aldehydes and ketones.\textsuperscript{20} Acid hydrolysis gives the substituted carbonyl compound (35) or (36), Scheme 7.

In these cases the lithiated allene (34) acts as an \(\alpha,\beta\)-unsaturated acyl anion equivalent (37).

Reich et al.\textsuperscript{21} used the ethoxyethyl allenyl ether (38) in a similar manner to prepare a variety of vinyl, ethynyl and acyl silyl ketones, Scheme 8.
Braun et al.\textsuperscript{22} reported the highly stereoselective addition of a crotonaldehyde synthons (39) to benzaldehyde, with a diastereoisomeric excess of 92\%, Scheme 9.
Work was undertaken in this department in an effort to develop a chiral α-lithiated α-alkoxyallene (40) as an analogous synthon. This would provide the potential for similar methodology, Scheme 10.
The chiral allenyl ethers (41)-(44) were prepared from the respective propargyl ethers by adaptation of a method used by Wilson and Cram.24

The allenyl ethers (41) and (42) proved to be unstable but compound (43) could be lithiated and reacted with benzaldehyde to give a 1:1 mixture of the required diastereoisomers (45a) and (45b).
The allene (44) was found to be reasonably stable but attempted lithiation gave only decomposition products.

1.1.7 CHIRAL ACYL ANION EQUIVALENTS

A wide variety of chiral acyl anion equivalents have been developed. One class of compounds that have been extensively studied are α-aminonitriles. Reactions of deprotonated, racemic aminonitriles with aldehydes and ketones have been used in the preparation of α-hydroxyketones, α-aminoalcohols and α-aminoketones. Similarly, Enders et al. have used chiral α-aminonitriles such as compound (46) in the enantioselective synthesis of α-hydroxyketones (47), with an enantiomeric excess of up to 97%.

As 1,3-dithiane and substituted dithianes are well known acyl anion equivalents,
Aggarwal et al. prepared the chiral acyl anion equivalent (48) by stereoselective oxidation of dithiane. Deprotonation and reaction with aldehydes gave diastereoisomeric products such as compounds (49a) and (49b) in ratios of between 50:50 and 87:13.

The chiral sulphoxide (50) has been found to give a single diastereoisomer of the adduct (51) on lithiation and reaction with benzaldehyde.

A further sulphur-containing chiral acyl anion equivalent is (+)-(S)-p-tolyl p-tolythiomethyl sulphoxide (52). The anion prepared from the homochiral sulphoxide (52) was reacted with aldehydes to give the adduct (53). Protection of the hydroxyl group and then removal of the chiral auxiliary gave the methoxyaldehyde.
(56) with an enantiomeric excess of 46-70%, Scheme 11. Reduction of the chiral sulphoxide (54) to the sulphide (55) has the disadvantage that the chiral auxiliary is lost in this reaction sequence.

Scheme 11
Recently, work in this department was undertaken to develop a chiral α-
sulphinylvinyl carbanion which gave asymmetric induction on reaction with
aldehydes. It was found that deprotonation of (+)-(E)-2-phenyl-1-[(1R)-p-
tolysulphinylethylene (57) and condensation with aldehydes gave diastereoselectivities
of up to 85:15 for the formation of the adducts (58a) and (58b). Development of
desulphurisation conditions would provide access to hydroxycarbonyl compounds and
thus to a new acyl anion equivalent.

\[
\begin{align*}
\text{(57)} & \quad \text{LLDA} \quad \text{2. PhCHO} \\
\text{(58a)} & \quad \text{Ph} \\
\text{(58b)} & \quad \text{Ph}
\end{align*}
\]

1.2 RESULTS AND DISCUSSION

Previous reports on the deprotonation chemistry of vinyl ethers had been limited to
the use of simple achiral examples. However, during the course of our studies,
McDougall et al. described the lithiation of chiral vinyl ethers derived from simple
chiral permethylated carbohydrates at a meeting of the American Chemical Society,
although only brief details were given. Vinyl ethers (59) and (61), prepared from
carbohydrates such as D-glucose, D-mannose and L-rhamnose, were found to give the
chiral alcohols (60) and (62) with a diastereoisomeric excess of 10-90%.
\[ \text{R}^\prime \text{OH} \xrightarrow{1. \text{s-BuLi, THF, -78}} \text{R}^\prime \text{CHO} \]

(59)

\[ \text{R}^\prime \text{OH} \xrightarrow{1. \text{s-BuLi, THF, -78}} \text{R}^\prime \text{CHO} \]

(61)

\[ \text{R}^\prime = \text{Sugar} \]

\[ \text{R}^\prime \text{OH} \xrightarrow{2. \text{RCHO}} \]

(60)

(62)

\( \alpha \)-Lithiation of the vinyl ether (59) and then reaction with aldehydes gave adducts with a higher diastereoisomeric excess than was observed for adducts formed via \( \beta \)-lithiation of the vinyl ether (62), as would be expected. It was also found that cuprates derived from these \( \alpha \)-lithiated vinyl ethers undergo conjugate addition reactions, with the diastereoisomeric excess ranging from 60-90%.

We set out to prepare a variety of enantiomerically pure vinyl ether anions and aimed to measure the diastereoselectivity of their reaction with aldehydes. Chiral vinyl ethers may be easily synthesised by the literature mercuric acetate-catalysed transetherification reaction of chiral alcohols with butyl vinyl ether. Initially our studies centred on (1R)-menthyl vinyl ether (63), which was prepared from (1R)-menthol (a cheap, homochiral alcohol) by the literature method.
In our efforts to deprotonate (1R)-menthyl vinyl ether we first applied the conditions used for the lithiation of methyl vinyl ether. Use of t-butyllithium in THF at -78°C and then addition of benzaldehyde to trap any anion formed resulted in the production of a small amount of benzyl alcohol due to reduction of the aldehyde by t-butyllithium but none of the desired product was formed. The reaction was repeated using TMEDA in place of THF, according to the procedure for the deprotonation of ethyl vinyl ether, but no reaction was observed. We then carried out a systematic study on the effect of different conditions on the reaction between secondary and tertiary-butyllithium and (1R)-menthyl vinyl ether. The results are shown in Table 2. No conditions for effective deprotonation were found and, in each case, all of the menthyl vinyl ether was isolated unchanged.
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<tr>
<td>t-BuLi</td>
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<td>THF</td>
<td>-78</td>
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<tr>
<td>t-BuLi</td>
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<td>THF</td>
<td>0</td>
</tr>
<tr>
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<td>1.0</td>
<td>THF</td>
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<tr>
<td>t-BuLi</td>
<td>2.0</td>
<td>THF</td>
<td>r.t</td>
</tr>
<tr>
<td>t-BuLi</td>
<td>4.0</td>
<td>THF</td>
<td>-78</td>
</tr>
<tr>
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<td>THF</td>
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<tr>
<td>t-BuLi</td>
<td>1.0</td>
<td>TMEDA</td>
<td>-55</td>
</tr>
<tr>
<td>t-BuLi</td>
<td>1.0</td>
<td>1:1 THF/DME</td>
<td>-78</td>
</tr>
<tr>
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<td>1:1 THF/DME</td>
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<tr>
<td>t-BuLi</td>
<td>2.0</td>
<td>1:1 THF/DMEDA</td>
<td>-55</td>
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<td>t-BuLi</td>
<td>2.0</td>
<td>1:1 THF/DMEDA</td>
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<td>t-BuLi</td>
<td>4.0</td>
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<td>r.t</td>
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<tr>
<td>t-BuLi</td>
<td>4.0</td>
<td>1:1 THF/DMEDA</td>
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<tr>
<td>t-BuLi</td>
<td>4.0</td>
<td>1:1 THF/DMEDA</td>
<td>r.t</td>
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<tr>
<td>s-BuLi</td>
<td>1.0</td>
<td>THF</td>
<td>-78</td>
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<td>s-BuLi</td>
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<td>s-BuLi</td>
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<td>s-BuLi</td>
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<td>s-BuLi</td>
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<tr>
<td>s-BuLi</td>
<td>2.0</td>
<td>THF</td>
<td>r.t</td>
</tr>
</tbody>
</table>

Table 2: Attempted deprotonation conditions for (1R)-menthyl vinyl ether.
We attempted to rationalise our inability to deprotonate (1R)-menthyl vinyl ether so that we might find a suitable alternative substrate. If we consider (1R)-menthyl vinyl ether, the preferred conformation of the cyclohexane ring is where the ring substituents all occupy equatorial positions. In this conformation the ring substituents are in fixed positions but there may be rotation about the bond between the vinyl group and the oxygen atom, Figure 6.

Within the vinyl moiety, the CH₃ group is obviously larger than the H₂ atom and therefore the CH₃ group will occupy a less sterically hindered position than the H₂ atom. For example conformation (64) is less favourable than conformation (65) as there is greater steric hindrance between the CH₃ group and the axial hydrogen atoms in conformation (64). However, if there is bond rotation to conformation (65), some of this steric hindrance is alleviated as the smaller H₂ atom will not interact to the same extent. Hence the vinyl proton, H₃, is in a more sterically hindered position in the more favourable conformation (65). To remove this vinyl proton in achiral vinyl ethers a strong base such as t-butyllithium or s-butyllithium is necessary. The steric strain involved in removal of the sterically hindered proton, H₃, with these bulky
hindered bases must be so great that this deprotonation is prohibited.

However, if we consider the equivalent thioether (66), this steric interaction may be reduced.

This is because the S-C bonds are longer than the O-C bonds in the vinyl ether (63). The bond between an sp\(^\dagger\) carbon atom and an oxygen atom is typically 1.41 Å in length,\(^{37}\) whereas the equivalent C-S bond is typically 1.81 Å long.\(^{38}\) In the case of an sp\(^\dagger\) carbon atom, the C-O bond length\(^{39}\) of 1.34 Å compares with 1.75 Å for the equivalent C-S bond.\(^{40}\) As the two C-S bonds that link the vinyl group with the cyclohexane ring will be significantly longer than the two C-O bonds in the vinyl ether (63), the vinyl group will be further from the axial hydrogen atoms on the ring. As a result the vinyl proton, H\(^\circ\), will be in a less sterically hindered position in the thioether (66) than in the vinyl ether (63). Deprotonation with a hindered base should therefore be easier. Also the presence of sulphur in place of oxygen should increase the acidity of the vinyl proton, H\(^\circ\), as discussed earlier (p.7). This effect is illustrated by comparison of 1,3-dioxane (67) with 1,3-dithiane (68).
Lithiation of dithiane (68) proceeds using n-butyllithium but this is not a strong enough base to deprotonate dioxane (67).^8

We therefore decided that it would be worthwhile to switch our attention to the thioether (66). Deprotonation of the vinyl thioether (66) would produce a homochiral vinyl anion. In the literature^45 1-(alkylthio)vinylolithiums have been found to behave in an analogous manner to the 1-(alkoxy)vinylolithiums formed by the deprotonation of vinyl ethers. Therefore, if conditions for the deprotonation of the thioether (66) could be found, the same synthetic methodology would be possible as for lithiated vinyl ethers.

We believed that we would be able to prepare the thioether (66) from (1R)-menthanethiol so it was first necessary to synthesise the thiol in optically pure form. A literature survey revealed that the synthetic approaches to optically pure thiols are relatively few in number and for the most part their applicability is limited.^41 This is due to moderate or low chemical yields and also the absence of any proof of optical
purity. However, Mikolajczyk et al.\cite{Mikolajczyk} report an efficient and highly stereoselective conversion of (1R)-menthol into (1S)-menthanethiol, with an enantiomeric excess of at least 95%, Scheme 12.

![Scheme 12](image)

**Scheme 12**

Following the literature procedure,\cite{Procedure} (1R)-menthol was first reacted with p-toluenesulphonyl chloride to give (1R)-menthyl tosylate (69). Treatment of the tosylate (69) with potassium thioacetate in DMSO gave (1S)-menthyl thioacetate (70). Inversion of configuration occurs as this is a typical $S_N2$ reaction. Reduction of the thioacetate (70) with lithium aluminium hydride gave (1S)-menthanethiol (71).

We aimed to synthesise the (1S)-thioether by first converting the thiol (71) to the disulphide. Cleavage of the S-S bond in the
disulphide with vinyl Grignard should then yield the (1R)-thioether. This approach seemed reasonable as the oxidation of thiols to disulphides is a well documented literature reaction\(^{43}\) and there are several examples of the nucleophilic addition of Grignard reagents to disulphides.\(^{44}\)

Oxidation of the thiol (71) proceeded smoothly using PCC in dichloromethane to yield the disulphide (72) as a white solid.

\[
\begin{align*}
\text{(71)} & \quad \xrightarrow{\text{PCC}} \quad \text{(72)}
\end{align*}
\]

The presence of the disulphide was confirmed by mass spectrometry, where a molecular ion peak was seen at \(m/z=342\). The preparation of (1R)-dimethyl disulphide has previously been reported by Suga and coworkers.\(^{45}\)

However, no reaction was seen with the disulphide (72) and vinyl Grignard in THF, even after heating to reflux for several hours. In an alternative approach, vinyllithium was generated by the literature reaction of phenyllithium with tetravinyltin\(^{46}\) and heated to reflux, in ether, with the disulphide (72). The thioether (73) could be isolated as a colourless oil after flash column chromatography but, within an hour at room temperature, virtually complete decomposition back to the disulphide (72) had occurred, Scheme 13.
A 90 MHz ¹H n.m.r. spectrum of the vinyl thioether, run immediately after the product was isolated, confirmed that the desired product had been formed by analogy with the spectrum of menthyl vinyl ether. The vinyl proton adjacent to sulphur in the vinyl thioether and the equivalent proton in the vinyl ether both gave doublets of doublets at $\delta_n 6.3$.

Presumably this decomposition is initially due to hydrolysis of the thioether (73) by atmospheric moisture to give the thiol (71), Scheme 14.
Aerial oxidation of thiols to disulphides is known and so it seems possible that the thiol (71) is oxidised to the disulphide (72) on standing. This oxidation is thought to proceed by the mechanism shown, Scheme 15.

\[
\begin{align*}
\text{MenS}^- + \text{O}_2 & \rightarrow \text{RS}^- + \text{O}_2^- \\
\text{MenS}^- + \cdot\text{O}_2^- & \rightarrow \text{RS}^- + \cdot\text{O}_2^- \\
2\text{MenS}^- & \rightarrow \text{MenSSMen}
\end{align*}
\]

Scheme 15  \hspace{1cm} \text{Men} = \text{Neomenthyl}

The synthesis and isolation of the thioether (73) proved impossible to repeat due to the instability of the product. As a result we were unable to investigate the deprotonation chemistry of this chiral vinyl thioether.

We next prepared a vinyl ether (74) from (R)-phenethyl alcohol by the standard reaction with butyl vinyl ether and mercuric acetate. Deprotonation is possible here at the vinyl carbon or at the benzylic position.
When the vinyl ether (74) was treated with t-butyllithium, followed by addition of benzaldehyde, a new product was obtained. The product was isolated as a colourless oil and the infra-red spectrum showed the presence of a hydroxyl group resonance at 3040 cm⁻¹, which suggested that the alcohol (75) had been formed.

However, n.m.r. revealed that the product had an identical number of protons and carbon atoms to the starting material (74) and so the adduct (75) could not have been formed. The ¹H n.m.r. spectrum showed that the vinyl moiety was intact but that the CH proton was now at higher field (δ₆ 6.13 in the product as opposed to δ₆ 6.29 in the vinyl ether). Also, the signal due to the CH at the chiral centre, which had been observed at δₓ 77.30 in the ¹³C n.m.r. spectrum of the vinyl ether (74), was absent from the ¹³C n.m.r. spectrum of the product. The carbon n.m.r. spectrum of the product contained a new signal due to a quaternary carbon atom at δₓ 74.69. Therefore it seemed likely that the product formed by deprotonation of the vinyl ether (74) was the alcohol (76).
To confirm the structure of the product, the alcohol (76) was treated with glacial acetic acid to give the isomeric form (77).

The $^1$H and $^{13}$C n.m.r. spectra of this compound were identical to those of an authentic sample of 3-phenyl-2-buten-1-ol prepared from acetophenone by the literature method. Scheme 16.49
Reaction of acetophenone with the Reformatsky reagent from ethyl bromoacetate gave the β-hydroxyester (78). Dehydration with phosphorous oxychloride and then reduction with sodium borohydride gave the alcohol (77).

The formation of the rearrangement product (76) seemed a little curious at first but this reaction has been reported in the literature for several allyl and benzyl vinyl ethers and it is known as the Wittig rearrangement. The mechanism of this rearrangement has been extensively studied and it is thought to involve a radical-pair mechanism and a [1,2] migration of the vinyl substituent, Scheme 17.

Scheme 17

The Wittig rearrangement gave the chiral alcohol (76) in racemic form as the first stage of the reaction involves deprotonation at the chiral centre and therefore epimerisation.
The chiral vinyl ethers (79) and (81) were also synthesised by mercuric acetate-catalysed transesterification of the parent alcohols with butyl vinyl ether. On treatment with t-butyllithium, followed by addition of benzaldehyde, the vinyl ethers (79) and (81) gave the Wittig rearrangement products (80) and (82) respectively.

![Chemical diagrams](image)

Both alcohols, (80) and (82), were found to be racemic. In both cases, the doublet of doublets in the 'H n.m.r. spectrum due to the CH of the vinyl moiety appears at higher field in the rearrangement product than in the original vinyl ether. In the vinyl ether (79) this signal appears at $\delta^H 6.29$, whereas it is found at $\delta^H 6.17$ for the alcohol (80). Similarly, this signal is observed at $\delta^H 6.34$ for the vinyl ether (81) as opposed to $\delta^H 6.16$ for the rearrangement product (82).

As would be expected, all of these Wittig rearrangements proceeded equally well in the absence of benzaldehyde to give the alcohols (76), (80) and (82) with virtually identical yields.
CHAPTER 2

Addition of Nitrile Oxides to Chiral Vinyl Ethers
2.1.1 ISOXAZOLINES (DIHYDROISOXAZOLEs)

Three isoxazoline structures are possible but only 2-isoxazolines are well known.\textsuperscript{31} Isomeric forms with the double bond between carbon atoms 3 and 4, or between carbon atoms 4 and 5 find expression as carbonyl or thiocarbonyl derivatives.

The value of isoxazolines in organic synthesis is in the access they give to acyclic compounds via cleavage of the ring. They provide a valuable stereocontrolled route to a variety of compounds, including $\beta,\gamma$-hydroxyketones (83) and $\gamma$-aminoalcohols (84), Scheme 18.

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {\text{HCl, H}_2\text{O}};
\node (b) at (2,0) {\text{LiAlH}_4};
\node (c) at (2.5,1.5) {\text{OH}};
\node (d) at (2.5,-1.5) {\text{NH}_2};
\node (e) at (1.5,0) {}; \node (f) at (3.5,0) {};
\node (g) at (1.5,1.5) {}; \node (h) at (3.5,1.5) {};
\node (i) at (1.5,-1.5) {}; \node (j) at (3.5,-1.5) {};
\draw (a) -- (c) -- (e); \draw (a) -- (d) -- (f); \draw (b) -- (g) -- (i); \draw (b) -- (h) -- (j);
\end{tikzpicture}
\end{center}

\textbf{Scheme 18}

Isoxazolines can be prepared from the oximes of $\alpha,\beta$-unsaturated ketones (85) or $\beta$-halogeno-ketones (86).\textsuperscript{31,32}
Our studies have concentrated on a further method: the 1,3-dipolar addition of nitrile oxides to alkenes, which is discussed below.

2.1.2 NITRILE OXIDES

Nitrile oxides are usually prepared in situ and not isolated, although stable isolable examples have been obtained. They are generally formed from oximes by reaction with N-chlorosuccinimide to form the hydroximoyl chloride (87), which then undergoes elimination with triethylamine to give the nitrile oxide (88).

\[
\begin{align*}
\text{PhC} = \text{NOH} & \xrightarrow{\text{NCS}} \text{PhC} = \text{NOH} \xrightarrow{\text{NET}_3} \text{PhC} \equiv \ddot{\text{N}} - \ddot{\text{O}} \\
\text{H} & \quad \text{Cl}
\end{align*}
\]

Other synthetic methods include the dehydration of primary nitro compounds with an aryl isocyanate and oxidation of oximes.

Nitrile oxides are categorised along with azides, nitrones, ozone and ylids as 1,3
dipoles. They undergo [3+2] cycloadditions with alkenes, a reaction that can be classified as a concerted $\pi_m+\pi_m$ process involving 6π electrons, analogous to a thermal Diels-Alder reaction. With monosubstituted olefins, reaction gives exclusively or predominantly the 5-substituted isoxazoline, whatever the nature of the substituent on the dipolarophile, Scheme 19.

![Scheme 19](image)

Frontier Molecular Orbital Theory of Cycloaddition Reactions\(^\text{26}\) may be used to explain qualitatively the relative reactivity of different dipole-alkene combinations and the regioselectivity of the observed reactions. In the cycloaddition reaction the two possible orbital interactions are between the LUMO of the nitrile oxide and the HOMO of the alkene or between the HOMO of the nitrile oxide and the LUMO of the alkene. Which of the two possible interactions occurs depends on the relative difference in energy between the participating orbitals. The predominating interaction has the smallest energy difference between the interacting orbitals. In most cases of nitrile oxide cycloaddition the main interaction is between the LUMO of the nitrile oxide and the HOMO of the alkene. This is true for a wide variety of alkenes, Fig. 7.
Figure 7: Frontier orbital energy levels for benzonitrile oxide and various alkenes. The predominant interaction is shown.

The regioselectivity of the reaction is dependent on the orbital coefficients of each atom in the alkene HOMO and nitrile oxide LUMO. The end of the 1,3 dipole with the largest orbital coefficient will combine with the end of the dipolarophile possessing the largest orbital coefficient, Figure 8.
The largest orbital coefficient in both the HOMO and LUMO of the alkene is always found on the unsubstituted end. In the nitrile oxide LUMO it is on the carbon atom and in the HOMO it is on the oxygen. As the predominant interaction is between the HOMO of the alkene and the LUMO of the nitrile oxide then this large-large/small-small interaction results in the regioselective formation of a 5-substituted 2-isoxazoline (92).

From Figure 7 it can be seen that for electron-rich and conjugated alkenes, (89) and (90) respectively, the LUMO of the 1,3 dipole participates in the controlling interaction and only the 5-substituted isomer is formed. Consequently, electron-releasing groups on the dipolarophile (91) accelerate the rate of reaction. Electron-deficient dipolarophiles also react rapidly because both the HOMO and LUMO of the 1,3 dipole now interact and the regioselectivity of the reaction is lowered. For example, the reaction between methyl acrylate and benzonitrile oxide leads to the formation of 3.6% of the 4-substituted isomer. Electron-releasing substituents on the nitrile oxide also cause a substantial increase in the amount of the 4-substituted
product (93). When highly electron-deficient alkenes are used, such as 1,1-dicyanoethylene, the 4-substituted isomer is the major product\(^{40}\) and with acrylic acid it is the only isomer obtained.\(^{51}\)

A free radical mechanism was proposed for the cycloaddition of nitrile oxides to double bonds\(^{44}\) but this has been rejected by Huisgen.\(^{55}\)

2.1.3 ASYMMETRIC NITRILE OXIDE CYCLOADDITIONS

In contrast to the well-documented asymmetric Diels-Alder reactions\(^1\), some of which proceed with near perfect diastereoselectivity, asymmetric nitrile oxide cycloadditions have only recently been explored. Kozikowski et al. have examined the diastereofacial selection in nitrile oxide additions to an allylic asymmetric centre\(^{62}\) and also the effect of chiral nitrile oxides.\(^{63}\) These attempts to achieve enantioselective synthesis of isoxazolines using optically active nitrile oxides have so far only met with limited success. The nitrile oxide (95), derived from the optically active nitro compound (94), formed cycloadducts with several olefins with diastereoselectivities of only 1.5:3:1, Scheme 20. The major product (96) of the reaction of the nitrile oxide (95) with cis-but-2-ene was converted into the optically pure \(\beta\)-hydroxycarboxylic acid (97). The sequence provides a useful route to optically active compounds of this class.
Kanemasa et al. have studied the stereoselective\textsuperscript{64} and regioselective\textsuperscript{65} addition of nitrile oxides to allyl alcohols. Highly diastereoselective chelation-controlled nitrile
Oxide additions to allyl alcohol derivatives (98) were reported with product ratios of up to 98:2.

\[
\text{Me PhCNO} \xrightarrow{\text{MeMgl}} \text{OMgI} \xrightarrow{\text{MeMgl}} \text{Ph Me Ph à Me} (98) 98:2
\]

Le Gall and coworkers\(^6\) have examined facial selectivity during the cycloaddition of nitrile oxides with iron-complexed trienes (99), observing product ratios of c.a. 90:10 in the formation of the optically active complexed isoxazolines (100a) and (100b).

\[
\text{99\%}
\]

Also the diastereofacial selectivity in 1,3-dipolar cycloaddition of nitrile oxides to racemic methylphenylvinylphosphine oxide (101) has been studied by Brandi et al.\(^7\). The phosphinylisoxazolines (102a) and (102b) were formed with only moderate selectivity (c.a. 2:1).
Many of the chiral auxiliaries that have been developed for use in the asymmetric Diels-Alder reaction have been surveyed for their effectiveness in nitrile oxide cycloadditions. Chiral acrylates, crotonates and acrylimides have all been the subject of numerous studies. Curran et al. found that the acrylate (103) gave substituted isoxazolines (104) with diastereoselectivities of up to 78:22.

Addition of Lewis acid catalysts such as EtAlCl, EtAlCl, and TiCl resulted in significant decreases in both the rate of cycloaddition and the isolated yield of the products, without noticeably changing the diastereoisomer ratio. This is probably because nitrile oxides are excellent Lewis bases and complexation with these Lewis acids effectively inhibits the reaction.

Olsson and coworkers studied substituted bornyl acrylates and reported diastereoselectivities of up to 84:16 with the naphthylacrylate (105). Olsson et al.
have also observed diastereoselectivities of up to 90:10 with the equivalent crotonate (106). During studies on chiral acrylimides, Curran et al.\textsuperscript{71} discovered that product ratios of 95:5 could be obtained using the acrylimide (107).

Curran et al.\textsuperscript{72} have reported diastereoselectivities of up to 95:5 in the cycloaddition reactions of Oppolzer's chiral sultam (108)\textsuperscript{72}, Scheme 21. In all cases a single diastereoisomer of the substituted isoxazoline was isolated after chromatography.

\textbf{Scheme 21}
The scope of asymmetric nitrile oxide cycloadditions using this auxiliary has been illustrated in the total syntheses of (+)-hepialone (109), (-)-(1R,3R,5S)-1,3-dimethyl-2,9-dioxabicyclo[3.3.1]nonane (110) and (-)-7,7-dimethyl-6,8-dioxabicyclo[3.2.1]octane (111). In all three syntheses cycloadditions of nitrile oxides to the acryloyl sultam (108) with high diastereoselectivities (85:15 to 92:8) were used to give, after chromatography, a single diastereoisomer of the respective substituted isoxazoline. Ring opening followed by further functional group interconversions (including removal of the chiral auxiliary) yielded the natural products in optically pure form. For example, formation of the nitrile oxide from the oxime (112) and then cycloaddition to the chiral acryloyl sultam (108) gave the cycloadduct (113) as a 92:8 mixture of diastereoisomers, Scheme 22 (the major product is shown). After deprotection and tosylation, hydrogenation of the tosylate (114) gave a single enantiomer of the β-hydroxyketone (115). Further reaction gave optically pure (-)-7,7-dimethyl-6,8-dioxabicyclo[3.2.1]octane (111).
Oppolzer et al.\textsuperscript{75} have prepared both enantiomers of a second chiral sultam ((116a) and (116b)), from saccharine, which appears to be the most efficient chiral auxiliary to date. Diastereoselectivities of between 95:5 and 98:2 were reported for the addition of nitrile oxides to this sultam and again the minor product could be removed by chromatography, Scheme 23. Using both enantiomers of the sultam, both enantiomers of the isoxazoline product may be synthesised.
High diastereoselectivity in intramolecular nitrile oxide cycloadditions has been utilised in the total synthesis of a number of natural products. Kozikowski and coworkers have synthesised several natural products using this method, including (+)-palliclavin (117). The key step in this particular synthesis is a stereoselective intramolecular nitrile oxide cycloaddition, Scheme 24.

Scheme 23
2.1.4 CYCLOADDITION REACTIONS OF VINYL ETHERS

Vinyl ethers undergo a variety of cycloaddition reactions. The reactivity of the double bond has been utilised in the preparation of a range of polymers from vinyl ethers by cationic homopolymerisation and cationic or free radical copolymerisation.\textsuperscript{76}

The reaction of vinyl ethers with tetrafluoroethylene produces 3-alkoxy-1,1,2,2-tetrafluorocyclobutanes (118).\textsuperscript{79}
In a similar way, vinyl ethers react with N-carbonylsulphonamides (119) to give N-substituted 4-alkoxy-2-azetidinones (120).\textsuperscript{40}

\[
\text{EtO} \quad \text{CH}_3\text{C}_6\text{H}_4\text{SO}_2\quad \text{N}=\text{C}=\text{O} \quad \rightarrow \quad \text{EtO} \quad \text{CH}_3\text{C}_6\text{H}_4\text{SO}_2 \quad \text{N}=\text{C}=\text{O}
\]

(119) (120)

Diphenylketene reacts with vinyl ethers to produce 3-alkoxy-2,2-diphenylcyclobutanones (121).\textsuperscript{41}

\[
\text{EtO} \quad \text{O}=\text{C}=\text{CPh}_2 \quad \rightarrow \quad \text{EtO} \quad \text{Ph} \quad \text{Ph}
\]

(121)

Nitrones undergo 1,3-dipolar cycloadditions with vinyl ethers to give exclusively 5-substituted 2-isoxazolidines (122).\textsuperscript{42}
The addition of 2,3,4,5-tetrahydropyridine N-oxide (123) to (R)-2,2-dimethyl-1-phenylpropyl vinyl ether (124) has been used to synthesise 2-(N-benzylpiperidin-2-yl)ethanol (125) with an enantiomeric excess of 95%, Scheme 25.\textsuperscript{83}

Similarly the 1,3-dipolar addition of nitrile oxides to a series of achiral vinyl ethers has been reported.\textsuperscript{86} The reaction gives exclusively 5-substituted 2-isoxazolines (126).
This dipolar addition of nitrile oxides to vinyl ethers has been utilised in the synthesis of C-linked polysaccharides. Reaction of the ribose-derived nitrile oxide (127) with the exo-methylene sugar (128) gave a single diastereoisomer of the isoxazoline (129).
The use of a chiral vinyl ether in a tandem [4+2]/[3+2] cycloaddition also has been reported.\textsuperscript{86} The nitroalkene (130) undergoes highly selective tandem cycloaddition with the vinyl ether (131), Scheme 26. Hydrogenation of the resulting nitroso acetal (132) gave the α-hydroxy lactam (133) with an enantiomeric excess of up to 99%.

\[
\text{Me} \quad \text{O} \quad \text{Me} \quad \text{CO}_3\text{Me} \quad + \quad \text{OCH}_2\text{t-Bu}
\]

(130) \quad (131)

\[
\text{MeO}_2\text{C} \quad \text{O} \quad \text{N} \quad \text{O} \quad \text{OR} \quad \text{H}_2 \quad \text{H} \quad \text{OR} \quad \text{H}
\]

(132) \quad \text{H}_2 \quad \text{H} \quad \text{H} \quad \text{Me}

(133)

Scheme 26

Vinyl ethers have electron-rich double bonds as the alkoxy group is electron-donating. As a result, vinyl ethers react with dienes bearing electron-withdrawing substituents and with other electron-deficient dienes such as α,β-unsaturated carbonyl compounds.

The reaction of α,β-unsaturated carbonyl compounds with vinyl ethers is an effective synthesis of 3,4-dihydro-2H-pyrans (134).\textsuperscript{87}
The most important cycloaddition reaction of vinyl ethers is their Diels-Alder reaction with dienes bearing electron-withdrawing substituents. Recently efforts have been made to develop asymmetric Diels-Alder reactions using chiral vinyl ethers. Posner et al. studied the reaction of the dienyl sulphone (135) with a series of chiral vinyl ethers. The vinyl ether (136) gave the bicyclic lactone (137) with a diastereoisomeric excess of 84%, Scheme 27, and the adduct (137) was then used in a total synthesis of (-)-methyl triacetyl-4-epishikimate (138).

Similarly, Thornton et al. investigated the Diels-Alder reaction of the pyrone (139) with a variety of chiral vinyl ethers. The adduct (140) was formed with diastereoisomeric ratios of up to 88:12.
High diastereoselectivity was observed in the previous literature example\textsuperscript{43} of the addition of a nitrile oxide to a chiral vinyl ether and also in the Diels-Alder reactions of chiral vinyl ethers\textsuperscript{59,60,61} and their reaction with 2,3,4,5-tetrahydropyridine N-oxide.\textsuperscript{62} Given this encouraging literature precedent, we hoped to observe some asymmetric induction in the cycloaddition reactions of nitrile oxides with a series of chiral vinyl ethers.

\section*{2.2 RESULTS AND DISCUSSION}

In the literature the regioselective addition of nitrile oxides to simple achiral vinyl ethers has been reported.\textsuperscript{74} We wished to investigate the extent of any asymmetric induction in the cycloaddition reaction of nitrile oxides with chiral vinyl ethers. To develop the necessary conditions for this reaction, the reaction between butyl vinyl ether and 2-hydroxybenzaldehyde oxime was first attempted under the same conditions used by Torssell et al.\textsuperscript{92} Scheme 28.
The 'H n.m.r. spectrum of the product (141) contains a doublet of doublets at $\delta_u$ 5.63 due to the acetal proton, H-5. The chemical shift of this proton and the extensive molecular orbital calculations (p.40) that have been used to study nitrile oxide cycloaddition reactions of this type, show that exclusively the 5-substituted 2-isoxazoline (141) was formed. This is in accord with the literature precedent for this regioselective cycloaddition reaction. Clearly, if the 4-substituted 2-isoxazoline (142) was formed, the H-4 proton would appear at significantly higher field. The H-5 proton of the product (141) couples with the H-4 protons of the ring to give a classic ABX system at $\delta_u$ 3.29 and 3.42.
Having found suitable conditions for this reaction we now wished to extend the reaction to chiral vinyl ethers. Following the literature procedure, a series of homochiral vinyl ethers ((63) and (143)-(145)) was prepared from the respective optically pure alcohols. The reaction of each vinyl ether with benzonitrile oxide was then carried out and the adducts (146)-(149) were isolated as mixtures of diastereoisomers, as determined from the $^1$H n.m.r. spectra, Table 3. In each case, the two diastereoisomers gave well separated doublets of doublets for the H-5 proton and so the product ratio could be measured from the relative integrals of these signals.

![Chemical structures](image.png)

**TABLE 3:** Results of benzonitrile oxide cycloaddition to chiral vinyl ethers.

<table>
<thead>
<tr>
<th>VINYL ETHER</th>
<th>ADDUCT</th>
<th>PRODUCT RATIO WITH PhCNO</th>
<th>YIELD (%)</th>
<th>CHEMICAL SHIFT OF H-5 (δ)</th>
</tr>
</thead>
<tbody>
<tr>
<td>63</td>
<td>146</td>
<td>58:42</td>
<td>41</td>
<td>5.73, 5.81</td>
</tr>
<tr>
<td>143</td>
<td>147</td>
<td>66:34</td>
<td>51</td>
<td>5.38, 5.74</td>
</tr>
<tr>
<td>144</td>
<td>148</td>
<td>57:43</td>
<td>45</td>
<td>5.42, 5.43</td>
</tr>
<tr>
<td>145</td>
<td>149</td>
<td>52:48</td>
<td>59</td>
<td>5.58, 5.93</td>
</tr>
</tbody>
</table>

It can be seen that the asymmetric induction observed is quite disappointing, with (1R)-8-phenylmenthyl vinyl ether (143) giving the best result. In an effort to improve
on these results, the vinyl ethers (79) and (81) were prepared.

![Chemical structures](79) (81)

The results obtained by these chiral vinyl ethers with a series of nitrile oxides, 

RCNO, are detailed in Table 4.

<table>
<thead>
<tr>
<th>R</th>
<th>PRODUCT RATIO</th>
<th>VINYL ETHER (79)</th>
<th>VINYL ETHER (81)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CRUDE</td>
<td>ISOLATED (% YIELD)</td>
<td>CRUDE</td>
</tr>
<tr>
<td>Ph</td>
<td>3:1</td>
<td>1 (43)</td>
<td>2:1</td>
</tr>
<tr>
<td>2-OH-Ph</td>
<td>1</td>
<td>1 (36)</td>
<td>-</td>
</tr>
<tr>
<td>CH&lt;sub&gt;3&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;Ph</td>
<td>3:1</td>
<td>1 (28)</td>
<td>4:1</td>
</tr>
<tr>
<td>4-NO&lt;sub&gt;2&lt;/sub&gt;-Ph</td>
<td>1</td>
<td>1 (26)</td>
<td>1:1</td>
</tr>
<tr>
<td>C(CH&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>3:1</td>
<td>1 (53)</td>
<td>4:1</td>
</tr>
<tr>
<td>CH&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>4:1</td>
<td>1 (37)</td>
<td>3:1</td>
</tr>
<tr>
<td>CH&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>3:1</td>
<td>1 (40)</td>
<td>1</td>
</tr>
<tr>
<td>CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>3:1</td>
<td>2:1&lt;sup&gt;2&lt;/sup&gt; (37)</td>
<td>4:1</td>
</tr>
</tbody>
</table>

Table 4: Results of nitrile oxide cycloaddition to the vinyl ethers (79) and (81).

Notes

1. Measured from the <sup>13</sup>C n.m.r. spectra of the crude reaction mixtures.
2. Measured from the integral of the H-5 signal in the 'H n.m.r. spectrum of the isolated product after flash column chromatography.
3. The product seemed to be too unstable to allow measurement of the crude or isolated product ratios.
In almost every case the vinyl ethers (79) and (81) gave a single diastereoisomer of the isoxazoline product after flash column chromatography. The crude ratios are merely rough estimates calculated from the relative peak intensities in the $^{13}$C n.m.r. spectrum, as the $^1$H n.m.r. spectra were too congested to allow any accurate measurement. Capillary g.c. and h.p.l.c. would give a more reliable measurement but, as only a single signal was seen for the product using both techniques, we were dependent on $^{13}$C n.m.r. to measure the diastereoisomer ratio.

Although the $^{13}$C n.m.r. spectra were complex, measurement of the product ratio was possible as both diastereoisomers of the product usually gave separate signals for the carbon atoms of the isoxazoline ring. These appeared at characteristic chemical shifts, Table 5.
<table>
<thead>
<tr>
<th>VINYL ETHER</th>
<th>R</th>
<th>ADDUCT</th>
<th>$^{13}$C N.M.R. SHIFT (δ)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>C-3</td>
</tr>
<tr>
<td>79</td>
<td>Ph</td>
<td>150</td>
<td>156.92</td>
</tr>
<tr>
<td>79</td>
<td>2-OH-Ph</td>
<td>151</td>
<td>157.34</td>
</tr>
<tr>
<td>79</td>
<td>CH$_2$CH$_2$Ph</td>
<td>152</td>
<td>158.53</td>
</tr>
<tr>
<td>79</td>
<td>4-NO$_2$-Ph</td>
<td>153</td>
<td>155.44</td>
</tr>
<tr>
<td>79</td>
<td>C(CH$_3$)$_3$</td>
<td>154</td>
<td>158.71</td>
</tr>
<tr>
<td>79</td>
<td>CH$_3$CH$_2$CH$_3$</td>
<td>155</td>
<td>159.18</td>
</tr>
<tr>
<td>79</td>
<td>CH$_3$CH$_2$</td>
<td>156</td>
<td>160.31</td>
</tr>
<tr>
<td>79</td>
<td>CH$_3$</td>
<td>157</td>
<td>155.79</td>
</tr>
<tr>
<td>81</td>
<td>Ph</td>
<td>158</td>
<td>156.93</td>
</tr>
<tr>
<td>81</td>
<td>CH$_2$CH$_2$Ph</td>
<td>159</td>
<td>158.65</td>
</tr>
<tr>
<td>81</td>
<td>4-NO$_2$-Ph</td>
<td>160</td>
<td>155.42</td>
</tr>
<tr>
<td>81</td>
<td>C(CH$_3$)$_3$</td>
<td>161</td>
<td>166.31</td>
</tr>
<tr>
<td>81</td>
<td>CH$_3$CH$_2$CH$_3$</td>
<td>162</td>
<td>159.10</td>
</tr>
<tr>
<td>81</td>
<td>CH$_3$CH$_2$</td>
<td>163</td>
<td>160.35</td>
</tr>
<tr>
<td>81</td>
<td>CH$_3$</td>
<td>164</td>
<td>155.70</td>
</tr>
</tbody>
</table>

**TABLE 5: $^{13}$C n.m.r. shifts of the carbon atoms of the isoxazoline ring.**

The ratios measured from the crude $^{13}$C n.m.r. spectra should not necessarily be regarded as an accurate measure of the relative amount of each diastereoisomer present because of the probability of differences in relaxation time. However, these crude spectra clearly show the presence of a significant amount of the minor diastereoisomer, which is not isolated after flash column chromatography. One possible explanation would be that the two diastereoisomers are separated during chromatography. This can be discounted as the same amount of material was collected from the flash column as was loaded on to it and only one component was
collected from the flash column as was loaded on to it and only one component was found to be an isoxazoline product. None of the isolated components showed the $^1$H n.m.r. peaks observed for the minor isomer. Therefore it does not appear that any separation is taking place. However, a significant amount of either (S)-1-(2-naphthyl)ethan-1-ol or (S)-1-phenylbutan-1-ol is also collected during flash column chromatography. This suggests that some degree of decomposition of the minor product occurs as, if the acetal linkage were to be cleaved, then the parent alcohol would be produced. This decomposition theory is supported by the fact that the yield of the isolated product is typically around 40% but virtually no unreacted vinyl ether is isolated. Attempts to test this theory by simply stirring a solution of the crude reaction mixture, obtained from the addition of benzonitrile oxide to the vinyl ether (79), with silica gel were unsuccessful in that no decomposition was observed under these conditions. The same ratio of the two diastereoisomeric products was observed after stirring with silica gel. One other explanation for the disappearance of the minor product is that some equilibration of the diastereoisomeric products takes place during chromatography. The fact that there was no change in the product ratio on stirring with silica gel shows that this is unlikely. However, in an effort to test whether this was possible, the isoxazoline product (150) was stirred in dichloromethane with (1R)-menthol and a trace of p-toluenesulphonic acid.
The equilibration product (146) was not observed by t.l.c. of the reaction mixture against a sample of the isoxazoline (146) prepared in the earlier reaction of (1R)-menthyl vinyl ether with benzonitrile oxide (p.60). Only decomposition of the isoxazoline to naphthylethanol and a mixture of polar byproducts was seen. Therefore the decomposition of the minor diastereoisomer during chromatography does seem the most plausible explanation of the results we have obtained.

Further work has since shown that, if a standard aqueous work-up is employed after the reaction of benzonitrile oxide with the vinyl ether (79), careful flash column chromatography allows the separation and isolation of both the major and minor products in the ratio 3:1. Crude \(^1\)H and \(^13\)C n.m.r. spectra indicate that the products are formed in this ratio, which is in agreement with the crude \(^13\)C n.m.r. ratio shown in Table 4 (p.59).

In the case of the isolated product (150) of the reaction between the vinyl ether (79) and benzonitrile oxide, an X-ray crystal structure determination was performed to establish the configuration at the new chiral centre, Figure 9 [see also Appendix].
Figure 9: X-ray Crystal Structure of (5R)-5-[(S)-1-(2-Naphthyl)-1-ethoxy]-3-phenyl-2-isoxazoline (150).
The x-ray crystal structure shows that the isoxazoline (150) has the (R)-configuration at the new asymmetric centre.

![Chemical structure of isoxazoline (150)](image)

The selectivity of the reaction is dependant on the preferred reactive conformation of the vinyl ether (79). Six possible conformations (165)-(170) of the vinyl ether are shown in Figure 10.

![Possible conformations of vinyl ether](image)
*Ab initio* molecular orbital calculations were undertaken\(^9\) using Gaussian 90\(^\text{\textregistered}\) in order to determine the energy of each conformation after the geometries were fully optimised. The lowest calculated energy was taken to be zero and the other energies calculated relative to this. The relative energies are shown above.

If we consider the vinyl ether, the oxygen lone pairs may point away from the double bond, as in conformation (171), or towards the double bond, as in conformation (172).

\[
\begin{array}{c}
\text{(171)} \\
\text{(172)}
\end{array}
\]

However, it has been predicted by previous studies\(^{55}\) on vinyl ethers that the preferred reactive vinyl ether conformation is one where both of the oxygen lone pairs are directed away from the double bond, as in conformation (171).

Conformation (167) is one conformation which gives rise to the observed product.

\[
\begin{array}{c}
\text{H} \\
\text{H} \\
\text{O} \\
\text{Naph} \\
\text{C}_2 \text{C} \text{Me} \text{H} \\
\text{H}
\end{array}
\]

Here the oxygen lone pairs and the naphthyl group point away from the double bond. The naphthyl group is in the least hindered position, coplanar to the double bond. The two carbon atoms of the double bond, the oxygen atom and the attached
carbon atom define a plane. In the cycloaddition reaction the nitrile oxide can approach from above or below this plane, giving rise to the two possible configurations at the new chiral centre formed at C. In conformation (167) the naphthalene group points outwards and the CH₃ and H groups at C are above and below the plane of the double bond. The correct configuration of the product is obtained when the nitrile oxide approaches from below the plane, on the same face as the hydrogen atom of C. The nitrile oxide therefore attacks the least hindered face of the double bond, Figure 11.

It therefore seems likely that conformation (167) is the preferred reactive conformation of the vinyl ether (79), although it is not the lowest energy conformation. However, this is not the only possible conformation that can be used to explain the product formed. The conformations (168)-(170) may be discounted as the oxygen lone pairs are no longer in the favoured position pointing away from the double bond. However the conformation (166) would also give the correct configuration at the chiral centre formed when attacked by the nitrile oxide from the least hindered face. In this case the hydrogen atom attached to C is in the plane of
the double bond, with the naphthyl and methyl groups above and below the plane.

The nitrile oxide should approach the double bond from the lower face, on the same face as the methyl group, as this is again the least hindered face, Figure 12.

Figure 12

Although some crystalline adducts were formed by the vinyl ether (81), unfortunately none of these gave crystals that were suitable for an x-ray crystal structure determination. Therefore we can not be certain of the configuration at the new chiral centre in the products. However it seems likely that the (S)-vinyl ether (81) will also give a product with the (R)-configuration at the new chiral centre as the vinyl ethers (79) and (81) are similar in structure.

The results obtained with the vinyl ethers (79) and (81) show that the asymmetric addition of nitrile oxides to chiral vinyl ethers provides an effective method for the synthesis of gram quantities of enantiomerically pure 5-substituted 2-isoxazolines.

In order to increase the synthetic utility of this method, work was undertaken to develop conditions under which the chiral moiety derived from the vinyl ether could be removed to yield a single enantiomer of a chiral product.

68
A variety of reductive methods are known for the cleavage of the N-O bond in 2-isoxazolines to leave stable aminoalcohols. Therefore the isoxazoline (150) was treated with a variety of reducing agents in an attempt to effect this transformation, Table 6.

<table>
<thead>
<tr>
<th>REAGENT(S)</th>
<th>ISOLABLE PRODUCT(S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NaBH₄</td>
<td>(S)-1-(2-Naphthyl)ethan-1-ol</td>
</tr>
<tr>
<td>LiAlH₄</td>
<td>(S)-1-(2-Naphthyl)ethan-1-ol</td>
</tr>
<tr>
<td>DIBAL-H</td>
<td>(S)-1-(2-Naphthyl)ethan-1-ol</td>
</tr>
<tr>
<td>H₂, Pd/C</td>
<td>(S)-1-(2-Naphthyl)ethan-1-ol</td>
</tr>
<tr>
<td>H₂, Raney Ni</td>
<td>(S)-1-(2-Naphthyl)ethan-1-ol + Polymer (approx. C₆)</td>
</tr>
<tr>
<td>L-Selectride</td>
<td>(S)-1-(2-Naphthyl)ethan-1-ol</td>
</tr>
</tbody>
</table>

TABLE 6: Effect of reductive conditions on the isoxazoline (150).

It can be seen that most methods of reductive cleavage bring about N-O bond cleavage to give (S)-1-(2-Naphthyl)ethan-1-ol but no other isolable fragment. The production of this naphthyl alcohol but no other stable product is almost certainly due to the instability of the acetal linkage in the substituted isoxazoline as this is a well documented reaction of isoxazolines.

L-Selectride left the N-O bond intact but yielded an achiral product, 3-phenyl-2-isoxazoline, along with the naphthyl alcohol. The reaction must presumably go by a mechanism similar to that shown in Scheme 29.
The identity of this achiral product was confirmed by the synthesis of an authentic sample of 3-phenyl-2-isoxazoline by the literature reaction of benzonitrile oxide with ethene. The authentic sample showed identical $^1$H and $^{13}$C n.m.r. spectra.

The instability of the acetal linkage in the isoxazoline product seems to prevent the removal of the chiral auxiliary to give a chiral product. However, as it is possible to remove this chiral unit using L-Selectride whilst leaving the isoxazoline ring intact, a way around this problem would be to introduce another chiral centre into the ring before removal of the chiral unit. One way to do this would be via nucleophilic addition to the C=N bond of the isoxazoline ring.
Although numerous examples of nucleophilic addition to oxime ethers are known, there are only a few reported examples of the addition of nucleophiles to isoxazolines. In the literature, nucleophilic addition to 3-nitro- and 3-phenylsulphonyl-2-isoxazolines has been reported. The 3-substituents were displaced by a variety of nucleophiles in an addition-elimination reaction.

![Reaction diagram](image)

Boron trifluoride etherate mediated nucleophilic addition of the acetylide (174) to the isoxazoline (173) has also been reported. The adduct (150) was treated with a range of organometallic reagents in an effort to observe nucleophilic addition, Table 7.
TABLE 7: Attempted nucleophilic addition to the isoxazoline ring.

Unfortunately, none of the nucleophiles investigated gave any of the desired addition product, even after heating to reflux for several hours. Sodium acetylide gave a small amount of (S)-1-(2-naphthyl)ethan-1-ol but no other isolable fragment.

In an effort to promote nucleophilic addition, methods of N-methylation were investigated. Mindful of the need to preserve the acid-sensitive acetal linkage, mild conditions using methyl iodide and dimethyl sulphate and trimethyloxonium tetrafluoroborate were investigated but without any success.

In this department, the intramolecular reactions of aryl and vinyl radicals with oxime ethers have been investigated. A typical example of this is the intramolecular radical cyclisation reaction of the oxime ether (175).

 Attempts were made in this department to achieve the addition of a radical to a number of 5-substituted 2-isoxazolines. As with

\[
\begin{array}{c}
\text{Bu}_3\text{SnH} \\
\text{AIBN, C}_2\text{H}_4
\end{array}
\]
nucleophilic addition, this reaction would lead to the formation of a new chiral centre. Both intermolecular and intramolecular reactions were attempted under the conditions developed for oxime ethers but unfortunately no radical addition was observed.

A further method of creating a new chiral centre in the isoxazoline ring would be to deprotonate and then alkylate the ring at the 4-position.

This has been reported for 3-phenyl-2-isoxazolines and used to synthesise a number of 4-substituted 2-isoxazolines. However, our attempts at deprotonation/alkylation of the isoxazoline (150) were unsuccessful, Table 8.
REAGENT(S) | ISOLABLE PRODUCT(S)
---|---
1. n-BuLi, -78°C
2. MeI | No reaction
1. n-BuLi, 0°C
2. MeI | (S)-1-(2-Naphthyl)ethan-1-ol
1. LDA, -78°C
2. MeI | No reaction
1. LDA, 0°C
2. MeI | No reaction

**TABLE 8: Attempted deprotonation/alkylation of the isoxazoline ring.**

In most cases no reaction was seen but, using n-butyllithium at 0°C, (S)-1-(2-naphthyl)ethan-1-ol was isolated along with 8% of the ester (176). The ester (176) seems to be formed by a small amount of deprotonation of the acetal proton, H-5, followed by elimination of benzonitrile as shown in the proposed mechanism.

The structure of the ester (176) was confirmed by the preparation of an authentic sample from the reaction of (S)-1-(2-naphthyl)ethan-1-ol with n-butyllithium and then
acetyl chloride. The authentic sample gave identical $^1$H and $^{13}$C n.m.r. data.

Therefore, the acetal linkage of the isoxazoline (150) does not appear to be stable to either nucleophilic addition to the carbon-nitrogen double bond or deprotonation of the isoxazoline ring. As the vinyl ethers derived from both (S)-1-(2-naphthyl)ethan-1-ol and (S)-1-phenylbutan-1-ol were so successful in the asymmetric synthesis of substituted 2-isoxazolines, it was decided to investigate whether the equivalent acrylates underwent cycloaddition with nitrile oxides with anywhere near the same degree of asymmetric induction. The chiral auxiliary could then be removed using L-Selectride, as reported in the literature for analogous acrylate adducts.

The acrylates (177) and (178) were prepared from the respective alcohols by deprotonation with n-butyllithium and reaction with acryloyl chloride.
Surprisingly, the acrylates (177) and (178) were both novel compounds. They showed characteristic carbonyl absorptions at 1715 cm\(^{-1}\) and 1725 cm\(^{-1}\) respectively in their infra-red spectra. Reaction of the acrylates with benzonitrile oxide was possible under the usual conditions to give the 5-substituted 2-isoxazolines (179) and (180).

![Chemical Structures](image)

Both reactions followed the literature precedent\(^{48, 60}\) for the regioselective addition of nitrile oxides to acrylates as only the 5-substituted 2-isoxazolines were formed. This is indicated by the fact that the signals in the \(^1\)H n.m.r. spectra due to the H-5 protons appear at \(\delta\)\(_n\) 5.1-5.2, compared to \(\delta\)\(_n\) 5.2-5.8 for the vinyl ether adducts. The extensive molecular orbital calculations (p.40) that have been carried out on the reaction of nitrile oxides with acrylates confirm this observation.

Although the \(^1\)H n.m.r. signals due to the H-5 proton were not as well separated as for previous examples, the relative intensities showed that both adducts were formed as an approximate 1:1 mixture of diastereoisomers. This might have been expected.
as the chiral centre in the acrylate is one atom further away from the new chiral centre than was the case with the equivalent vinyl ether. Consequently 1,4-asymmetric induction is now required, as opposed to 1,3-asymmetric induction in the case of the vinyl ethers.

The asymmetric induction observed in the reaction of nitrile oxides with chiral vinyl ethers prompted us to investigate whether this stereoselectivity was also exhibited by N-vinyl pyrrolidinones.

N-Vinyl compounds are used for the synthesis of a number of important polymers, such as poly(vinylpyrrolidinone), but we could find no examples of the reaction of nitrile oxides with vinyl pyrrolidinones. Initially we studied the reaction of benzonitrile oxide with 1-ethenyl-2-pyrrolidinone (181), which, although it is achiral, is commercially available. Under the usual conditions, regioselective addition was again observed and only the 5-substituted 2-isoxazoline (182) was isolated.

The regiochemistry of this addition would be expected to follow the usual pattern (p.40) and the \(^1\text{H}\) n.m.r. shift of the proton at the 5-position on the isoxazoline ring confirms that the 5-substituted 2-isoxazoline is formed. A characteristic doublet of doublets at \(\delta_\text{H} 6.63\) was seen due to the H-5 proton, which compares with a chemical shift of \(\delta_\text{H} 5.2-5.8\) for the equivalent adduct derived from vinyl ethers.
Having established that the cycloaddition reaction proceeded under the same conditions and with the same regioselectivity as with vinyl ethers, the next requirement was to investigate whether asymmetric induction was possible with a chiral vinyl pyrrolidinone.

Koga et al.\textsuperscript{105} report the synthesis of a single enantiomer of the pyrrolidinone (183).

\[
\begin{align*}
\text{(183)}
\end{align*}
\]

This has proved to be an extremely effective chiral auxiliary when applied to asymmetric conjugate addition\textsuperscript{105} and Diels-Alder\textsuperscript{106} reactions. It therefore seemed possible that this auxiliary might be equally successful when applied to nitrile oxide cycloadditions.

Following the literature procedure\textsuperscript{105} the pyrrolidinone (183) was prepared in 3 steps from the commercially available acid (184), Scheme 30.
Esterification with methanol and a catalytic amount of concentrated sulphuric acid, followed by reduction of the ester (185) with sodium borohydride, gave the alcohol (186) in virtually quantitative yield. Protection with triphenylmethyl chloride yielded the auxiliary (183).

In the literature several methods for the synthesis of N-vinyl compounds are reported. The reaction of imides and lactams with acetylene at high temperature was reported by Reppe but unfortunately the high temperatures and pressures involved lead to the formation of byproducts. Also the elimination of the parent alcohol from N-(1-alkoxyethyl) derivatives is another possible method but these starting materials are accessible only by a multi-step synthesis. Transvinylation of nitrogen-containing heterocycles with vinyl acetate in the presence of mercury salts has been described, but in this method the addition of oleum is essential. Attempts by Hopff and coworkers to synthesise N-vinylimides by transvinylation with vinyl acetate at room temperature and at 72°C were unsuccessful. However, N-vinyl pyrrolidinones have been synthesised by Bayer et al. by the reaction of pyrrolidinones with vinyl acetate and a catalytic amount of sodium tetrachloropalladate. Following this procedure, the chiral vinyl pyrrolidinone (187) was synthesised as colourless crystals from the pyrrolidinone (183).

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{\text{NH}} & \quad \text{\text{PdCl}}_2 \\
\text{OCPh}_3 & \quad \text{OCPh}_3
\end{align*}
\]

(183)  (187)
Despite ensuring that the catalyst and vinyl acetate used were dried carefully and that moisture was excluded from the apparatus, low yields (17% at best) were obtained using this method. The remaining material isolated was the unreacted pyrrolidinone (183), which could be recycled. The vinyl protons of the product (187) displayed the characteristic pattern in the $^1$H n.m.r. spectrum seen for vinyl ethers but these signals appeared at lower field e.g. a doublet of doublets was observed for the NCH proton at $\delta_n$ 7.0 as opposed to $\delta_n$ 6.1-6.4 for the OCH proton in vinyl ethers.

Reaction of the chiral vinyl pyrrolidinone (187) with benzonitrile oxide gave a single diastereoisomer of the 5-substituted 2-isoxazoline (188) according to both the $^1$H and $^{13}$C n.m.r. spectra.

\[ \text{PhCNO} \rightarrow \begin{array}{c}
\text{(187)} \\
\text{PhCPh}_3 \\
\text{N} \\
\text{OCPh}_3 \\
\text{Ph} \\
\end{array} \]

\[ \begin{array}{c}
\text{(188)} \\
\text{H}_5 \\
\text{O} \\
\text{OCPh}_3 \\
\text{Ph} \\
\end{array} \]

The exclusive formation of this 5-substituted isoxazoline was predicted by molecular orbital arguments given on p.40. In the $^1$H n.m.r. spectrum of the isoxazoline (188) a single doublet of doublets was seen at $\delta_n$ 6.49 due to the H-5 proton. This compares with a chemical shift of $\delta_n$ 5.2-5.8 for the same signal in the $^1$H n.m.r. spectra of vinyl ether adducts. Unfortunately, although the adduct (188) was isolated as colourless crystals, our x-ray crystallographer was unable to determine the x-ray crystal structure of the product. Therefore we can not be certain of the configuration at the chiral centre formed in the reaction. However, we
have tentatively assigned the (S)-configuration to this centre. This is because the double bond would be expected to be coplanar with the pyrrolidinone ring by analogy with vinyl ethers. Also, the double bond should be orientated away from the bulky trityl group in a more sterically favoured position. The nitrile oxide would then be expected to attack the double bond from the less hindered lower face, away from the trityl group. This would lead to the formation of the product (188), where the new chiral centre has the (S)-configuration.

Because of our inability to obtain an x-ray crystal structure of the product (174) we were unable to confirm this theory. For this reason, and also because of the difficulties we found in synthesising the vinyl pyrrolidinone (187) in good yield, it was decided to investigate the reaction of the equivalent acrylamide with nitrile oxides. Deprotonation of the pyrrolidinone (183) with n-butyllithium at -78°C and reaction with acryloyl chloride yielded the acrylamide (189), with a characteristic carbonyl absorption at 1725 cm⁻¹ in the infra-red spectrum.
Reaction of the acrylamide (189) with benzonitrile oxide, under the usual conditions, proceeded in noticeably higher yield than was found for vinyl ethers (71% as opposed to around 40%). The 'H n.m.r. spectrum revealed that the two diastereoisomeric products (190a) and (190b) were formed as a 1:1 mixture.

The regiochemistry of this addition would be expected to follow the usual pattern (p.40) and the 'H n.m.r. shift of the proton at the 5-position on the isoxazoline ring...
indicates that exclusively the 5-substituted 2-isoxazoline was formed. The H-5 proton gave a doublet of doublets at $\delta$ 6.03 for the adduct (190a) and $\delta$ 6.07 for the adduct (190b). These two diastereoisomers could be separated by flash column chromatography and recrystallised. At this stage the $^1$H and $^{13}$C n.m.r. spectra of both diastereoisomers indicated that none of the other opposite diastereoisomer was present. Following the same procedure as that used by Oppolzer et al., each diastereoisomer was treated with L-Selectride to yield the enantiomers (191a) and (191b) and regenerate the chiral auxiliary (183).
As both enantiomers are known compounds,\textsuperscript{72} their optical purity was calculated by comparison of their optical rotations with the literature values. This revealed that the (R)-enantiomer (191a) was formed with an enantiomeric excess of 91\% and the (S)-enantiomer (191b) with an enantiomeric excess of 92\%. The formation of a Mosher ester\textsuperscript{11} with Mosher’s acid chloride was attempted to provide another measure of the enantiomeric excess but unfortunately neither enantiomer was stable to this reaction and only decomposition of the isoxazolines was observed.

Similarly the adducts (192a) and (192b) were formed as a 1:1 mixture by reaction of the acrylimide (189) with 2,2-dimethylpropanenitrile oxide.
Again these two diastereoisomers could be separated by flash column chromatography and the $^1$H and $^{13}$C n.m.r. shifts were sufficiently different for the two diastereoisomers that it was possible to confirm that there was no detectable amount of the opposite diastereoisomer present. In this case the characteristic doublet of doublets seen for the H-5 proton in the $^1$H n.m.r. spectrum was found at $\delta = 5.85$ for the isoxazoline (192a) and $\delta = 5.90$ for the isoxazoline (192b). Treatment of the adducts (192a) and (192b) with L-Selectride yielded both enantiomers of the isoxazoline, (193a) and (193b), along with the chiral auxiliary (183).
Measurement of the optical rotations and comparison with the literature values showed that the hydroxyisoxazolines (193a) and (193b) were formed with enantiomeric excesses of 90% and 94% respectively. Again only decomposition of these isoxazolines was observed when Mosher ester formation was attempted by reaction with Mosher's acid chloride. Therefore, although no asymmetric induction
was observed in the addition of nitrile oxides to the chiral acrylamide (189), the two
diastereoisomers formed could be separated by flash column chromatography.
Treatment with L-Selectride regenerates the chiral auxiliary and yields the respective
chiral hydroxyisoxazoline with an enantiomeric excess of 90-94%.

One further class of compound it was felt merited investigation were chiral vinyl
sulphoxides. These compounds have been used extensively in asymmetric Diels-Alder
reactions but we could find no examples of their reaction with nitrile oxides.

Chiral vinyl sulphoxides are readily accessible from (1R)-menthyl (S)-p-
toluenesulphinate (194). This was prepared according to the literature procedure, Scheme 31.

\[
\begin{align*}
\text{ether, pyridine} & \quad \text{OH} \\
\text{ether, pyridine} & \quad \text{O}^- \\
\text{recrystallisation acetone / HCl} & \quad \text{OMen} \\
\end{align*}
\]

\[ (194) \]

**Scheme 31**

The yield of the (S)-sulphinate (194) was optimised by redissolving the crude
mixture in acetone containing a few drops of concentrated hydrochloric acid to bring
about epimerisation at sulphur, Scheme 32. As only the (S)-enantiomer is crystalline
it may be easily separated.

\[
\text{Cl} \quad \text{Cl} \\
\text{p-Tol} \quad \text{OMen} \\

\text{HCl} \quad \text{H}_2\text{O} \\
\text{OMen} \quad \text{OMen} \\
\text{crystallisation} \quad \text{acetone} / \text{HCl} \\
\text{OMen} \quad \text{OMen} \\
\text{p-Tol} \quad \text{p-Tol} \\
\text{(S)-(194)} \quad \text{(R)-(194)}
\]

Scheme 32

Treatment of the sulphotide (194) with vinyl magnesium bromide gave the vinyl sulphotide (195).

\[
\begin{align*}
\text{p-Tol} & \quad \text{OMen} \\
\text{THF} & \quad \text{THF} \\
\text{(194)} & \quad \text{(195)}
\end{align*}
\]

Reaction of the vinyl sulphotide (195) with benzonitrile oxide under the usual conditions gave none of the desired product (196) but only the isoxazole (197) was isolated, Scheme 33.
Scheme 33

The structure of the product was confirmed by the synthesis of an authentic sample of 3-phenylisoxazole by the literature reaction of benzonitrile oxide with vinyl bromide. The authentic sample gave identical $^1$H and $^1$C n.m.r. spectra.

In the reaction of the sulfoxide (195) with benzonitrile oxide, the desired product (196) must be formed but there is an immediate elimination reaction, Scheme 34. Indeed, this has been reported for some simple achiral vinyl sulfoxides and a syn-elimination process was found to be involved.
Clearly this elimination reaction could be prevented by simply blocking the syn-position by carrying out the cycloaddition with the (Z)-isomer of the vinyl sulphone.

This method has been used successfully in the literature, where Caramella et al. have reported the regioselective synthesis of racemic 2-isoxazolines with the sulphone substituent at the 5-position and have rationalised their results using the molecular orbital arguments described earlier (p. 40). Synthesis of the (Z)-isomer of a vinyl sulphone is not straightforward as our method relies on the addition of Grignard reagents to (1R)-menthyl (S)-p-toluene sulphone. A problem associated with this method is the unavailability of pure (E) or (Z)-vinyl halides from which to prepare the Grignard reagent. Most commercially available vinyl halides are supplied as mixtures of the two geometrical isomers, the (E)-isomer being the major component. However, according to the literature, when the corresponding Grignard reagent prepared from β-bromostyrene is reacted with (1R)-menthyl (S)-p-toluene sulphone (194), the (E) and (Z)-isomers of the sulphone formed are easily separable by flash column chromatography. Therefore this reaction was carried out according to the literature procedure to give a 3:1 mixture of the (E) and (Z)-
We aimed to carry out the reaction of both isomers with benzonitrile oxide, expecting the (Z)-isomer to give the desired cycloaddition product (199) and the (E)-isomer to form this product initially but then to undergo elimination to the isoxazole (200).

Unfortunately, no reaction with benzonitrile oxide was observed with either isomer, even after heating to reflux for several hours.

To summarise, in this work the asymmetric addition of nitrile oxides to chiral vinyl ethers has been used to synthesise a range of enantiomerically pure 5-substituted 2-isoxazolines. Conditions have been developed for the removal of the chiral auxiliary but as yet we have only been able to obtain achiral isoxazolines by this method. The instability of the acetal linkage in the isoxazoline products seems to prevent deprotonation/alkylation of the isoxazoline ring or the addition of a nucleophile or a
radical to the C=N bond of the ring. A chiral vinyl pyrrolidinone has also been prepared and found to undergo an asymmetric cycloaddition reaction with benzonitrile oxide to give a single diastereoisomer of the isoxazoline product. The equivalent acrylamide has also been synthesised. Although this gave a 1:1 mixture of diastereoisomers with both benzonitrile oxide and 2,2-dimethylpropanenitrile oxide, these diastereoisomers could be separated by flash column chromatography and the chiral auxiliary removed to give hydroxyisoxazolines with an enantiomeric excess of 90-94%. Attempts to investigate the extent of any asymmetric induction in the addition of nitrile oxides to chiral vinyl sulfoxides were hampered by the instability of the isoxazoline product, which underwent an immediate syn-elimination.
CHAPTER 3

(1R)-Menthoxymethyl ether, a Chiral OH Protecting Group and its use in the Measurement of Enantiomeric Excess
3.1.1 PROTECTING GROUPS IN ORGANIC SYNTHESIS

When a chemical reaction is to be carried out selectively at one reactive site in a multifunctional compound other reactive sites must be temporarily blocked. Many protecting groups have been developed for this purpose. They must fulfil a variety of requirements. The protecting group must react selectively in good yield to give a protected substrate that is stable to further reactions. Ideally it should give crystalline derivatives (without the generation of new chiral centres) that may be easily separated from side products associated with its formation or cleavage. Also it is important that the protecting group has a minimum of additional functionality to avoid further sites of reaction. The protecting group must be selectively removed in good yield by readily available reagents that will not attack the regenerated functional group.

With the need to synthesise more complicated structures, chemists have had to develop new protecting groups and more effective conditions for the formation and cleavage of protected compounds. For example, the development of carbohydrate chemistry required extensive protection of carbonyl and hydroxyl groups. As a result, a large number of mutually complementary protecting groups are now available.

3.1.2 PROTECTION OF ALCOHOLS USING THE ETHER LINKAGE

Generally an alcohol can be converted to an ether by reaction with an alkylating agent in the presence of a base. Formation of a simple methyl ether (201) is not a good method for protection as the methyl group can not easily be removed. However, protection by the formation of a methoxy ether (202) is a useful method as the acetal linkage can usually be hydrolysed to the parent alcohol.
Some of the most common ethers used for the protection of OH groups are methoxymethyl (MOM) ether, 2-methoxyethoxymethyl (MEM) ether, benzyl ether, benzyloxymethyl ether and tetrahydropyranyl (THP) ether.

MOM ethers such as compound (203) are usually formed by reaction of the respective alcohol with chloromethyl methyl ether in the presence of an amine base. Diisopropylethylamine is not a strong enough base to deprotonate the alcohol but its overall effect is to absorb the HCl produced in the reaction to form i-PrN^EtHCl.
The protecting group can be removed by methanolation under acidic conditions, as the acetal linkage is acid-labile.\textsuperscript{118}

\[
\begin{align*}
  &\text{MeOH} \\
  &\text{Conc. HCl}
\end{align*}
\]

MEM ethers, for example compound (204), were designed to protect primary, secondary or tertiary alcohols with formation and cleavage under aprotic conditions.\textsuperscript{119} They can be formed using 2-methoxyethoxymethyl chloride under basic conditions and are stable to mild acid hydrolysis but can be cleaved by zinc bromide or titanium tetrachloride.\textsuperscript{119}

\[
\begin{align*}
  &\text{MeOH} \\
  &\text{Conc. HCl}
\end{align*}
\]

Benzyl ethers (205) are one of the most common protecting groups. Alcohols can be protected with benzyl chloride or bromide in the presence of sodium hydride.\textsuperscript{120} Under these conditions the alcohol is completely deprotonated before reaction with the benzyl halide.
Cleavage is usually possible by hydrogenation.  

Benzylxymethyl ethers can be formed from the chloroether with an amine present, as shown for the formation of the ether (206).
Deprotection is achieved on treatment with sodium in ammonia.\textsuperscript{122}

Protection with dihydropyran in the presence of acid leads to THP ethers such as compound (207).\textsuperscript{123}
One disadvantage of using this protecting group is that, since a new chiral centre is created when a THP ether is formed, the product may contain a mixture of diastereoisomers.

Cleavage is usually carried out using acidic conditions.¹³⁴
3.1.3 MEASUREMENT OF ENANTIOMERIC EXCESS

The enantiomeric excess (optical purity) of a reaction where two enantiomeric products are formed can be defined as the percentage excess of one enantiomer over the other.\(^{125}\)

\[
\text{Enantiomeric excess} = \frac{[R] - [S]}{[R] + [S]} \times 100\% = \%R - \%S
\]

The importance of asymmetric organic synthesis means that efficient methods for the accurate measurement of enantiomeric excess are essential. The earliest method used was to compare the optical rotation of the synthesised compound \((\alpha)_{\text{obs}}\) with the known rotation for the optically pure compound \((\alpha)_{\text{max}}\), assuming that there is a linear relationship between optical rotation and concentration.

\[
\text{Enantiomeric excess} = \frac{\alpha_{\text{obs}}}{\alpha_{\text{max}}} \times 100\%
\]

Recently other more widely applicable methods have been developed.

2.1.4 MOSHER ESTERS

Mosher’s studies on the asymmetric reduction of allyl phenyl ketones by optically active Grignard reagents\(^{126}\) led him to devise a new method\(^{111,127}\) for the measurement of the enantiomeric purity of optically active alcohols which avoided the limitations of polarimetry. As polarimetry involves comparison of the optical rotation with the known rotation for the optically pure compound, the product must be a known compound and also the literature value must be assumed to be reliable. If the optical
purity of a new compound is to be measured then chemical degradation to a known compound is necessary.

Mosher's method relies on the n.m.r. non-equivalence of diastereotopic groups and does not require the measurement to be compared with data from known homochiral compounds. The method involves reaction with (S)-(-)-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA) (208) of an alcohol of unknown enantiomeric excess to form the corresponding diastereoisomeric esters, (209a) and (209b).

\[
\text{Enantiomeric excess} = \frac{I(1) - I(2)}{I(1) + I(2)} \times 100\%
\]

The CF₃ group in each diastereoisomer ((209a) and (209b)) usually gives a separate signal in the fluorine n.m.r. spectrum. Their relative intensities are directly proportional to the amounts of each enantiomer of the optically active alcohol. Therefore, if we consider two signals with intensities I(1) and I(2), the enantiomeric excess may be calculated.
In addition to the enantiomeric excess it is important to know the absolute configuration of an alcohol under investigation. An empirically derived correlation of configuration and n.m.r. chemical shifts for diastereotopic MTPA esters has been developed and rationalised in terms of the models Mosher gives for (R)-MTPA and (S)-MTPA derivatives, Figure 13.177a

In this simple example the shielding effect of the aromatic ring leads to the n.m.r. non-equivalence of the two diastereoisomers. The same group (L or L) is shielded in one diastereoisomer (and therefore upfield) and much less shielded in the opposite diastereoisomer. These models have been successfully applied to numerous examples.
The reliability of this method of determining enantiomeric purity requires that there be neither racemisation nor kinetic resolution in the synthesis of the diastereoisomers. The reaction must be quantitative with respect to the alcohol in order for the diastereoisomer ratio to reflect exactly the enantiomer ratio.

The major advantages of this method are that the presence of the CF₃ group permits the use of fluorine n.m.r. so that spectra are usually very simple and also the method is very versatile i.e. it may be used for determination of the enantiomeric composition of primary and secondary amines as well as alcohols. As a result, the preparation of a Mosher ester is a well established method of measuring enantiomeric excess.

3.1.5 OTHER METHODS OF DETERMINING ENANTIOMERIC PURITY

Many other chiral derivatising reagents are commercially available for determining the enantiomeric purity of a variety of compounds. (R)-(−)-α-Methoxyphenylacetic acid (212) has been used in the n.m.r. analysis of the configuration of the bis-nor-Wieland-Miescher ketone (210) (5-methylbicyclo[3.3.0]oct-1-en-3,6-dione) after the stereo- and regio-selective reduction of the ketone to the alcohol (211).
(+)-10-Camphorsulphonyl chloride (213) has been used to determine the enantiomeric purity of a range of chiral amines.²ₓ⁰

(4R,5R)-(+)−2-Chloro-4,5-dimethyl-1,3,2-dioxaphospholane-2-oxide (214) has proved a useful derivatising agent for the enantiomeric assay of alcohols and amines by ³¹P n.m.r.²ₓ¹
Also, suitable derivatives of these chiral reagents often find preparative utility via chromatographic resolution.

Our aim was to develop a protecting group that, whilst fulfilling all the necessary requirements of a protecting group, was also chiral. If a mixture of two enantiomers of a chiral alcohol were protected with this reagent then the ratio of the diastereoisomers produced could be measured from the $^1$H n.m.r. integrals due to the n.m.r. non-equivalence of diastereotopic groups. Therefore, if this protecting group was introduced at an early stage in a reaction scheme where diastereoisomers were produced at each stage, the diastereoisomer ratio could be measured at each stage. As long as the protecting group was not influencing the stereochemistry of the reaction, this measurement would monitor the stereochemical integrity of each compound in the sequence. There would therefore be no need to prepare a Mosher ester at each stage.

3.2 RESULTS AND DISCUSSION

One approach to finding a chiral OH protecting group is to prepare homochiral chloroethers and to use them in an analogous way to other ether protecting groups. Chloromethyl-(1R)-menthyl ether (215) is a known compound$^{132}$ and it has been used for the resolution of an oxime,$^{133}$ an allylic alcohol$^{134}$ and an iron acyl complex$^{135}$.  

104
The chloroether (215) was prepared by the literature reaction of (1R)-menthol and paraformaldehyde in a stream of dry HCl gas. Because of its toxic nature, no further purification of the chloroether (215) was attempted and it was used crude in reaction with chiral alcohols. Protection of alcohols was possible under mild basic conditions at room temperature to yield the respective (1R)-menthoxymethyl ether.
Using this procedure, a series of (1R)-menthoxymethyl ethers (216)-(222) were prepared from racemic and homochiral alcohols, Table 9.

<table>
<thead>
<tr>
<th>Alcohol</th>
<th>Product</th>
<th>Yield</th>
<th>Yield for protection of racemic methyl mandelate</th>
</tr>
</thead>
<tbody>
<tr>
<td>MeMeHO</td>
<td>MM CO₂Et</td>
<td>85%</td>
<td></td>
</tr>
<tr>
<td>PhMeHO</td>
<td>MMO CO₂Me</td>
<td>79%</td>
<td>Yield (217)</td>
</tr>
<tr>
<td>MeHO</td>
<td>MMO CO₂Me</td>
<td>77%</td>
<td></td>
</tr>
<tr>
<td>PhMeHO</td>
<td>MMO Me</td>
<td>89%</td>
<td></td>
</tr>
<tr>
<td>OMePhOH</td>
<td>OMMO</td>
<td>65%</td>
<td></td>
</tr>
</tbody>
</table>

MM = (1R)-menthoxymethyl ether

**Table 9**: Alcohols protected with chloromethyl-(1R)-menthyl ether
In each case the ratio of diastereoisomers formed could be measured from the $^1$H n.m.r. spectrum using the integral of the signal for the acetal protons. These protons gave a characteristic AB system, typically at $\delta$ 4.4-5.0, in which the peaks were well separated so that integration of the diastereotopic signals was possible to give a measure of the ratio of the diastereoisomers. In some cases measurement was also possible using the signal due to the H-1 proton of the (1R)-menthyl group. This was observed as a triplet of doublets at $\delta$ 3.3-3.5.

The $^1$H n.m.r. spectra of the (1R)-menthoxymethyl ethers of (S)-methyl mandelate and racemic methyl mandelate clearly illustrate how the signal for the acetal protons may be used to determine the diastereoisomer ratio, Figure 14.
Figure 14
To test the accuracy of this measurement, both enantiomers of methyl mandelate were protected with chloromethyl-(1R)-menthyl ether and three different mixtures of diastereoisomers were prepared. The diastereoisomer ratio was then determined using the n.m.r. method, Table 10.

<table>
<thead>
<tr>
<th>Diastereoisomer ratio by weight</th>
<th>Diastereoisomer ratio by n.m.r.</th>
</tr>
</thead>
<tbody>
<tr>
<td>75 : 25</td>
<td>74 : 26</td>
</tr>
<tr>
<td>50 : 50</td>
<td>51 : 49</td>
</tr>
<tr>
<td>25 : 75</td>
<td>24 : 76</td>
</tr>
</tbody>
</table>

**TABLE 10**: Measurement of the diastereoisomer ratio of synthetic mixtures of protected methyl mandelate.

Table 10 shows that this is a reliable method for determination of the ratio of diastereoisomers. These results suggest that the measurement is accurate to within 1% but a more realistic error is probably around 5%.

In a further effort to assess the accuracy of these results, various protected racemic alcohols were investigated by both capillary g.c. and h.p.l.c. Unfortunately separate peaks for the two diastereoisomers were not seen with any of the alcohols used. Therefore we were unable to make any measurement of the diastereoisomer ratio using these techniques.

Deprotection of (1R)-menthoxymethyl ethers is possible using zinc bromide in dichloromethane at room temperature. Deprotection of the acetal (217) under these conditions yielded (S)-methyl mandelate with the normal optical rotation, showing that
no racemisation occurred during the protection or deprotection processes.

During recent studies in this department on the synthesis of homochiral dienes, the diene \((227)\) was prepared from (S)-ethyl lactate, Scheme 35.
Reagents: (i) PhCH₂OCH₂Cl, i-Pr₂EtN
(ii) LiAlH₄
(iii) CrO₃, pyridine
(iv) Me₃SiCH₂MgCl
(v) BrMgCHCH₂
(vi) EtCO₂H, EtCO₂Na

Scheme 35
In this synthesis, measurement of the enantiomeric excess of each intermediate in the reaction scheme was necessary. Attempts to prepare Mosher esters from the alcohols formed during the reaction sequence met with little success as only the alcohol (223) was stable to this reaction and the Mosher ester formed (along with that derived from racemic ethyl lactate) gave no peaks in the $^1$H n.m.r. spectrum that were suitably resolved. The optical purity of the aldehyde (224) was calculated as 86% by comparison with the known optical rotation. Addition of trimethylsilylmethylmagnesium chloride to the aldehyde (224) gave a single diastereoisomer by n.m.r. of the alcohol (225) and the configuration was assigned by application of Cram's rule. Oxidation of the alcohol (225) and then addition of vinylmagnesium bromide yielded the alcohol (226) as a 2:1 mixture of diastereoisomers. Peterson elimination gave the chiral diene (227), but the optical purity of this compound could only be assumed to be high given that the alcohol (225) was isolated as a single diastereoisomer. Therefore some form of measurement was needed to support this assumption.

In the above reaction sequence, a benzyloxymethyl ether is used as a protecting group. However it occurred to us that, if a chiral protecting group could be introduced at an early stage, then diastereoisomers would be produced at each stage. The diastereoisomer ratio could be measured for each intermediate and, as long as the protecting group did not influence the stereochemistry of the reaction, this measurement would monitor the stereochemical integrity of each compound in the sequence.

Therefore, in order to illustrate the use of the (IR)-menthoxymethyl ether protecting group, the chiral diene (232) was synthesised from (S)-ethyl lactate, Scheme 36.
(S)-Ethyl lactate was protected as the (1R)-menthoxymethyl ether (216), which was a single diastereoisomer from both the ¹H and ¹³C n.m.r. spectra. We are confident that we would have been able to detect the other diastereoisomer from the following control experiment: the ether (216) was treated with LDA and then reprotonated by...
addition of water, giving a 56:44 mixture of diastereoisomers. This was measured from the acetal proton signals in the $^1$H n.m.r. spectrum.

Reduction of the ester (216) with lithium aluminium hydride produced the alcohol (228) as a 90:10 mixture of diastereoisomers, which was again measured from the $^1$H n.m.r. spectrum. Oxidation was carried out under basic Swern conditions as acidic conditions would almost certainly have cleaved the acetal linkage. Swern oxidation of the alcohol (228) led to the aldehyde (229), which the signal for the aldehyde proton in the $^1$H n.m.r. spectrum showed to be a 90:10 mixture of diastereoisomers. Addition of trimethylsilylmethylmagnesium chloride to the aldehyde (229) gave the alcohol (230) as one diastereoisomer at the adjacent chiral centres 2 and 3 according to the $^1$H and $^{13}$C n.m.r. spectra. The configuration at the chiral centre formed has been assigned by analogy with the equivalent alcohol (225). The $^1$H n.m.r. signals were not sufficiently well resolved to allow an accurate measurement of the diastereoisomeric excess at this stage. Swern oxidation of the alcohol (230) followed by addition of vinyl Grignard reagent led to the alcohol (231) as a 2:1 mixture of diastereoisomers at the adjacent chiral centres 2 and 3. In this case the acetal protons did not give clearly separate signals but the signals for H-3, OH and CH=CH$_2$ all allowed measurement of the diastereoisomer ratio. The stereochemical assignment of these two diastereoisomeric alcohols was of little importance here as one of the chiral centres is destroyed in forming the final diene product (232). Peterson elimination of the adduct (231) was carried out under basic conditions in order to preserve the acid-labile acetal linkage. Treatment with potassium hydride yielded the diene (232) as an 88:12 mixture of diastereoisomers. This final measurement was possible by using the signal for the acetal protons in the $^1$H n.m.r. spectrum.
Therefore the presence of the chiral protecting group enables measurement of the optical purity of the intermediates (216), (228) and (229). More importantly, it allows us to be certain of the optical purity of the final diene product (232). Also the diastereoselectivity of the sequence (216)-(231) was the same as when the benzyloxymethyl ether was used as the protecting group, hence the (1R)-menthoxymethyl ether group does not lead to asymmetric induction in these reactions.

Asymmetric induction might not have been expected as the new chiral centre is created five atoms away from the chiral centre at the 1-position on the menthyl ring.
EXPERIMENTAL
EXPERIMENTAL

All 90 MHz 'H n.m.r. spectra were recorded on a Varian EM-390 spectrometer. High field 'H n.m.r. (300 MHz) and 13C n.m.r. (75 MHz) spectra were recorded on a Bruker AM-300 spectrometer at the University of Leicester. 13C n.m.r. spectra were recorded using D.E.P.T.

All coupling constants for AB systems have been corrected using the standard formula.14

Accurate mass measurements were made at the SERC mass spectrometry centre, University College of Swansea using ammonia chemical ionisation conditions and standard mass spectra were recorded on a Micromass 16B spectrometer. Elemental analysis was carried out by Butterworth Laboratories, Teddington, Middlesex. Optical rotations were recorded on a Perkin-Elmer 141 polarimeter and infra-red spectra on a Perkin-Elmer 298 spectrometer. Melting points were determined on a Kofler hot-stage and are uncorrected.

Rash column chromatography was carried out according to the method of Still et al.13 using Kiesel 60, 230-400 mesh (ASTM) silica gel manufactured by Merck & Co. T.l.c was conducted on precoated aluminium sheets (60F-254) with a 0.2 mm layer thickness, manufactured by Merck & Co.

H.p.l.c. was carried out on a Shimadzu LC-4A liquid chromatograph and capillary g.c. on a Pye Unicam PU 4500 capillary chromatograph, using a BP 10 ID 0.22 25 mm column.

n-Butyllithium was obtained as a 1.6M solution in hexanes, s-butyllithium as a 1.3M solution in cyclohexane and t-butyllithium as a 1.7M solution in pentane. L-Selectride and vinylmagnesium bromide were both obtained as 1.0M solutions in THF.
Petroleum ether refers to the 40-60°C fraction and all petroleum ether, petroleum ether 60-80°C and TMEDA was distilled prior to use. THF and toluene were distilled from sodium metal in the presence of benzophenone. Ether refers to diethyl ether and this was dried by distillation from lithium aluminium hydride. Dichloromethane was distilled from powdered calcium hydride.

The standard aqueous work-up described involved pouring the reaction mixture into water and extracting three times with dichloromethane. The organic phase was then dried with anhydrous magnesium sulphate, filtered and the solvent removed under reduced pressure.
A solution of (IR)-menthol (5.0 g, 32.1 mmol) and a catalytic amount of mercuric acetate in butyl vinyl ether (50 ml) was heated under reflux for 6 h. Excess butyl vinyl ether was then removed under reduced pressure to give (IR)-menthyl vinyl ether (63) as a colourless liquid (2.88 g, 49%) after flash column chromatography (10:1 petroleum ether-ether).

δ<sub>n</sub> (300 MHz; CDCl<sub>3</sub>) 0.77-1.70 (16H, m), 2.03-2.15 (2H, m), 3.52 (1H, td, J<sub>trans</sub>=10.7, 4.2 Hz, H-1), 3.92 (1H, dd, J<sub>trans</sub>=6.5, 1.4 Hz, OCH<sub>trans</sub>=CH<sub>trans</sub>, 4.26 (1H, dd, J<sub>trans</sub>=14.1, 1.4 Hz, OCH<sub>trans</sub>=CH<sub>trans</sub>, 6.30 (1H, dd, J<sub>trans</sub>=14.1 Hz, J<sub>gauche</sub>=6.5 Hz, OCH<sub>gauche</sub>=CH<sub>gauche</sub>);

δ<sub>e</sub> (300 MHz; CDCl<sub>3</sub>) 16.36 (CH<sub>3</sub>), 20.69 (CH<sub>3</sub>), 22.09 (CH<sub>3</sub>), 23.62 (CH<sub>3</sub>), 25.89 (CH<sub>3</sub>), 31.54 (CH<sub>3</sub>), 34.49 (CH<sub>3</sub>), 40.89 (CH<sub>3</sub>), 47.85 (CH<sub>3</sub>), 79.61 (CH<sub>3</sub>), 87.42 (CH<sub>3</sub>), 151.13 (CH).

(1R)-Menthyl p-toluenesulphonate (69)\textsuperscript{49}

A solution of (1R)-menthol (7.0 g, 44.9 mmol) and p-toluenesulphonyl chloride (12.83 g, 67.3 mmol) in pyridine (75 ml) was stirred, at 0°C, for 16 h. The reaction mixture was then poured into ice-water to give (1R)-menthyl p-toluenesulphonate (69) as white crystals (13.31 g, 95%), which were filtered, washed with water and dried.
in a dessicator.

(1S)-Menthyl thioacetate (70)

To a stirred suspension of potassium thioacetate (17.5 g, 154 mmol) in DMSO (80 ml) was added (1R)-menthyl p-toluenesulphonate (69) (13.30 g, 42.6 mmol). The reaction was stirred, under nitrogen, at 45°C for 24h. Standard aqueous work-up yielded (1S)-menthyl thioacetate (70) as a colourless oil (4.83 g, 53%) after flash column chromatography (10:1 petroleum ether-ether).

δ (300 MHz; CDCl₃) 0.78-1.17 (12H, m), 1.28-1.49 (2H, m), 1.56-1.88 (4H, m), 2.32 (3H, s, O=CCH₃), 4.08 (1H, dt, J=5.2, 3.2 Hz, H-1);

δ (75 MHz; CDCl₃) 20.72 (CH₃), 20.93 (CH₃), 22.13 (CH₃), 27.79 (CH₃), 28.14 (CH), 30.52 (CH), 31.06 (CH₃), 35.09 (CH₃), 42.02 (CH₃), 45.25 (CH), 47.67 (CH), 195.09 (C).
To a stirred suspension of lithium aluminium hydride (836 mg, 22.0 mmol) in dry ether (10 ml), under nitrogen, at room temperature was added a solution of (1S)-menthyl thioacetate (70) (4.70 g, 22.0 mmol) in dry ether (10 ml). The reaction mixture was heated to reflux for 2h, cooled to room temperature and carefully treated with water to destroy unreacted lithium aluminium hydride. The gelatinous precipitate was dissolved in 10% aqueous sulphuric acid (20 ml), the organic layer separated and the aqueous layer extracted with ether. The combined organic extracts were dried (MgSO₄) and the solvent removed under reduced pressure. (1S)-Menthanethiol (71) was obtained as a colourless oil (2.29 g, 61%) after flash column chromatography (6:1 petroleum ether-ether).

δₙ (300 MHz; CDCl₃) 0.79-1.07 (11H, m), 1.20-1.53 (4H, m), 1.65-1.90 (4H, m), 3.47-3.51 (1H, m, H-1);

δₐ (75 MHz; CDCl₃) 20.38 (CH₃), 20.87 (CH₃), 22.16 (CH₃), 24.20 (CH₃), 25.94 (CH), 30.32 (CH), 35.33 (CH₃), 40.15 (CH), 44.09 (CH₃), 48.28 (CH).
(1S)-Dimethyl disulphide (72)

To a stirred suspension of pyridinium chlorochromate (3.10 g, 14.4 mmol) in dichloromethane (25 ml), under nitrogen, was added a solution of (1S)-menthanethiol (71) (1.65 g, 9.59 mmol) in dichloromethane (20 ml). The mixture was stirred at room temperature for 3h. Standard aqueous work-up gave (1S)-dimethyl disulphide (72) as a white solid (915 mg, 56%) after flash column chromatography (petroleum ether).

\[ \delta_{\text{H}} \text{ (300 MHz; } \text{CDCl}_3) \text{ 0.81-1.26} \text{ (24H, m), 1.62-1.97} \text{ (10H, m), 2.31} \text{ (2H, ddd, } J=13.6, 5.5, 3.2 \text{ Hz, H-2)}, \text{ 3.22} \text{ (2H, brd, } J=3.0 \text{ Hz, H-1}); \]

\[ \delta_{\text{C}} \text{ (75 MHz; } \text{CDCl}_3) \text{ 20.65} \text{ (CH₃), 21.22} \text{ (CH₃), 22.22} \text{ (CH₂), 25.90} \text{ (CH₃), 26.21} \text{ (CH), 29.96} \text{ (CH), 35.52} \text{ (CH₂), 39.83} \text{ (CH₂), 48.81} \text{ (CH), 52.61} \text{ (CH);} \]

M/Z 342 (M⁺, 8), 139 (63), 97 (16), 95 (16), 83 (100), 81 (21), 69 (33), 57 (29), 55 (35), 43 (17), 41 (26).
To phenyllithium (1.8M solution in cyclohexane-ether, 0.57 ml, 1.02 mmol), under nitrogen, at room temperature was added rapidly tetravinyltin (0.87 mg, 0.38 mmol). After 40 min at room temperature, a solution of (1R)-dimenthyl disulphide (72) (350 mg, 1.02 mmol) in dry ether (5 ml) was added and the reaction mixture heated to reflux for 1 h. Standard aqueous work-up and flash column chromatography (petroleum ether) gave (1S)-(menthylthio)ethene (73) as a colourless oil (120 mg, 34%). Immediate 'H n.m.r confirmed that the desired product had been formed (by analogy with the 'H n.m.r. spectrum of (1R)-menthyl vinyl ether) but, within an hour at room temperature, virtually complete decomposition to (1S)-dimenthyl disulphide had occurred.

\[ \delta_c \ (90 \text{ MHz; CDCl}_3) \ 0.6-2.5 \ (18 \text{H, m}), \ 3.2-3.5 \ (1 \text{H, m, H-1}), \ 5.2 \ (1 \text{H, d, } J=10 \text{ Hz, SCH=CH}_2), \ 5.4 \ (1 \text{H, dd, SCH=CH}_{\text{trans}}), \ 6.3 \ (1 \text{H, dd, } J_{\text{trans}}=18 \text{ Hz, } J_{\text{cis}}=10 \text{ Hz, SCH=CH}_2). \]
(R)-Phenethyl vinyl ether (74)^63

\[
\begin{align*}
\text{H} & \quad \text{Ph} & \quad \text{O} \\
& \quad \text{Me}
\end{align*}
\]

(74)

Following the same procedure as for the preparation of compound (63), (R)-phenethyl alcohol (1.0 g, 8.20 mmol), butyl vinyl ether (30 ml) and a catalytic amount of mercuric acetate gave (R)-phenethyl vinyl ether (74) as a colourless liquid (456 mg, 38%) after flash column chromatography (10:1 petroleum ether-ether).

\[\delta_c (300 \text{ MHz; } \text{CDCl}_3) 1.49 (3\text{H}, \text{ d}, J=6.5 \text{ Hz}, \text{ CH}_3), 3.96 (1\text{H}, \text{ dd}, J=6.6, 1.7 \text{ Hz}, \text{ OCH=CH}_2), 4.24 (1\text{H}, \text{ dd}, J=14.2, 1.7 \text{ Hz}, \text{ OCH=CH}_2), 4.86 (1\text{H}, \text{ q}, J=6.5 \text{ Hz}, \text{ PhCHO}), 6.29 (1\text{H}, \text{ dd}, J=14.2 \text{ Hz}, J_{\text{ax}}=6.5 \text{ Hz}, \text{ OCH=CH}_2), 7.20-7.45 (5\text{H}, \text{ m, aromatic});\]

\[\delta_c (75 \text{ MHz; } \text{CDCl}_3) 23.61 (\text{CH}_3), 77.30 (\text{CH}), 89.20 (\text{CH}), 125.71 (\text{CH}), 127.48 (\text{CH}), 128.45 (\text{CH}), 142.89 (\text{C}), 150.48 (\text{CH}).\]

(2RS)-2-Phenyl-3-buten-2-ol (76)^158

\[
\begin{align*}
\text{HO} & \quad \text{Ph} \\
& \quad \text{Me}
\end{align*}
\]

(76)

To a stirred solution of (R)-phenethyl vinyl ether (74) (500 mg, 3.38 mmol) in THF (2 ml) and TMEDA (2 ml), under nitrogen, at -60°C was added dropwise t-butyllithium (2.19 ml, 3.72 mmol). After 2h benzaldehyde (394 mg, 3.38 mmol) was
added dropwise and the reaction stirred for a further 2 h before warming to room temperature. The reaction was then quenched by careful addition of saturated aqueous ammonium chloride solution. Standard aqueous work-up yielded (2RS)-2-phenyl-3-buten-2-ol (76) as a colourless oil (115 mg, 23%) after flash column chromatography (5:1 petroleum ether-ether).

\[ \delta_\text{H} (300 \text{ MHz}; \text{CDCl}_3) 1.61 \text{ (3H, s, CH)}_2, 2.23 \text{ (1H, brs, OH)}, 5.10 \text{ (1H, dd, } J=10.5, 1.1 \text{ Hz, CCH=CH}_2), 5.26 \text{ (1H, dd, } J=17.3, 1.1 \text{ Hz, CCH=CH}_2) \text{), 6.13 \text{ (1H, dd, } J_{\text{trans}}=17.3 \text{ Hz, } J_{\text{cis}}=10.5 \text{ Hz, CCH=CH}_2) \text{, 7.18-7.45 (5H, m, aromatic)}; \delta_\text{C} (75 \text{ MHz}; \text{CDCl}_3) 29.22 \text{ (CH)}_2, 74.69 \text{ (C), 112.23 (CH), 125.12 (CH), 126.86 (CH), 128.11 (CH), 144.78 (CH), 146.37 (C). I.R. data is detailed on page 209.}

3-Phenyl-2-buten-1-ol (77)

To a stirred solution of (2RS)-2-phenyl-3-buten-2-ol (76) (90 mg, 0.61 mmol) in THF (5 ml) was added glacial acetic acid (5 ml). The reaction mixture was then heated to reflux for 1 h. Standard aqueous work-up gave 3-phenyl-2-buten-1-ol (77) as a colourless oil (31 mg, 34%) after flash column chromatography (1:1 petroleum ether-ether).

\[ \delta_\text{H} (300 \text{ MHz}; \text{CDCl}_3) 1.98 \text{ (3H, s, CH)}_2, 3.18 \text{ (1H, brs, OH), 4.28 (2H, dd, } J=6.5, 0.7 \text{ Hz, CCH(OH)), 5.91-5.95 (1H, m, C=CH), 7.16-7.36 (5H, m, aromatic)}; \delta_\text{C} (75 \text{ MHz}; \text{CDCl}_3) 15.86 \text{ (CH)}_2, 59.58 \text{ (CH)}, 125.65 \text{ (CH), 126.64 (CH), 127.08 (CH).} \]
The spectra were identical to those obtained from an authentic sample of 3-phenyl-2-buten-1-ol, which was synthesised from acetophenone by the literature method.

(S)-1-(2-Naphthyl)-1-ethyl vinyl ether (79)

Following the same procedure as for the preparation of compound (63), (S)-1-(2-naphthyl)ethan-1-ol (5.0 g, 29.1 mmol), butyl vinyl ether (50 ml) and a catalytic amount of mercuric acetate gave (S)-1-(2-naphthyl)-1-ethyl vinyl ether (79) as a colourless liquid (4.65 g, 81%) after flash column chromatography (10:1 petroleum ether-ether).

Rf 0.71 (10:1 petroleum ether-ether);

$\nu_{max}$ (film) 3060w, 2980m, 2960m, 2930m, 2870w, 1630m, 1610m, 1375w, 1315m, 1265w, 1190s, 1170s, 1125m, 1110w, 1080m, 1020w, 970w, 950m, 910s, 860m, 820s, 735s, 705w, 650w;

$\delta_{H}$ (300 MHz; CDCl$_3$) 1.56 (3H, d, J=6.5 Hz, CH$_3$), 3.94 (1H, dd, J=6.7, 1.7 Hz, OCH$_3$), 4.30 (1H, dd, J=14.2, 1.7 Hz, OCH$_3$), 4.99 (1H, q, J=6.5 Hz, NaphCHO), 6.34 (1H, dd, J=14.2 Hz, J=6.7 Hz, OCH$_3$), 7.37-7.45 (3H, m,
aromatic), 7.70-7.79 (4H, m, aromatic);

\( \delta_c \) (75 MHz; CDCl\(_3\)) 23.53 (CH\(_3\)), 77.40 (CH), 89.36 (CH\(_2\)), 123.72 (CH), 124.56 (CH), 125.79 (CH), 126.08 (CH), 127.63 (CH), 127.84 (CH), 128.37 (CH), 132.90 (C), 133.21 (C), 140.26 (CH), 150.44 (CH);

M/Z 198 (M\(^+\), 3), 169 (2), 155 (100), 141 (3), 128 (13), 115 (7), 101 (1), 91 (1), 63 (1), 57 (6), 49 (4), 43 (16), 39 (6);

C\(_{16}\)H\(_{16}\)O [M\(^+\)] requires 198.1045

found 198.1045.

**Attempted lithiation of (S)-1-(2-naphthyl)-1-ethyl vinyl ether (79)**

Following the same procedure as for the preparation of compound (76), (S)-1-(2-naphthyl)-1-ethyl vinyl ether (79) (500 mg, 2.53 mmol), t-butyllithium (1.63 ml, 2.78 mmol) and benzaldehyde (295 mg, 2.78 mmol) gave no reaction. T.l.c. showed that only starting material was present.

**(2RS)-2-(2-Naphthyl)-3-buten-2-ol (80)**

\[ \text{HO} \]
\[ \text{Me} \]

\( \text{(80)} \)

A solution of (S)-1-(2-naphthyl)-1-ethyl vinyl ether (79) (870 mg, 4.39 mmol) in TMEDA (2 ml) and 60-80 petroleum ether (2 ml) was stirred, under nitrogen, at room
temperature. n-Butyllithium (5.16 ml, 8.78 mmol) was added dropwise and the reaction mixture stirred for 17h before quenching with saturated aqueous ammonium chloride solution. Standard aqueous work-up gave (2RS)-2-(2-naphtyl)-3-buten-2-ol (80) as a colourless oil (615 mg, 71%) after flash column chromatography (2:1 petroleum ether-ether).

Rf 0.11 (2:1 petroleum ether-ether);

$\nu_{\text{max}}$ (film) 3400 brs (OH), 3080 w, 3060 s, 3020 w, 2980 s, 2930 w, 2870 w, 1630 w, 1600 m, 1500 m, 1450 w, 1435 w, 1410 m, 1370 s, 1270 m, 1250 m, 1210 w, 1185 s, 1145 m, 1130 s, 1060 m, 1020 m, 995 s, 950 m, 925 s, 905 s, 860 s, 820 w, 770 w, 735 s, 665 m, 620 m, 610 m;

$\delta$ (300 MHz; CDCl$_3$) 1.66 (3H, s, CH$_3$), 2.41 (1H, brs, OH), 5.10 (1H, dd, J=10.6, 1.1 Hz, CCH=CH$_2$), 5.27 (1H, dd, J=17.3, 1.1 Hz, CCH=CH$_2$), 6.16 (1H, dd, $J_{\text{trans}}$=17.3 Hz, J$_{\text{cis}}$=10.6 Hz, CCH=CH$_2$), 7.36-7.51 (3H, m, aromatic), 7.70-7.87 (4H, m, aromatic);

$\delta$ (75 MHz; CDCl$_3$) 29.10 (CH$_3$), 74.82 (C), 112.59 (CH$_2$), 123.31 (CH), 124.04 (CH$_2$), 125.71 (CH), 125.92 (CH), 127.37 (CH), 127.77 (CH), 128.08 (CH), 132.33 (C), 133.03 (C), 143.67 (C), 144.59 (CH);

M/Z 198 (M$^+$, 61), 183 (33), 165 (29), 155 (91), 141 (35), 128 (36), 115 (11), 101 (6), 77 (12), 71 (6), 63 (7), 55 (100), 51 (10), 43 (88), 39 (7);

C$_7$H$_9$O [M$^+$] requires 198.1045
found 198.1045.
Following the same procedure as for the preparation of compound (63), (S)-1-phenylbutan-1-ol (5.5 g, 36.7 mmol), butyl vinyl ether (50 ml) and a catalytic amount of mercuric acetate gave (S)-1-phenyl-1-butyl vinyl ether (81) as a colourless liquid (4.86 g, 75%) after flash column chromatography (5:1 petroleum ether-ether).
(3RS)-3-Phenvl-1-hexen-3-ol (82)

Following the same procedure as for the preparation of compound (76), (S)-1-phenyl-1-butyl vinyl ether (390 mg, 2.22 mmol), t-butyllithium (1.40 ml, 2.44 mmol) and benzaldehyde (259 mg, 2.44 mmol) gave (3RS)-3-phenyl-1-hexen-3-ol (82) as a colourless oil (110 mg, 28%) after flash column chromatography (5:1 petroleum ether-ether).

R<sub>f</sub> 0.48 (2:1 petroleum ether-ether);

ν<sub>max</sub> (film) 3450brw (OH), 3090m, 3060m, 3020m, 2970s, 2940s, 2970s, 2940s, 2870s, 2850w, 1640w, 1600w, 1490m, 1465m, 1410m, 1375m, 1310m, 1265m, 1235m, 1165m, 1130m, 1110m, 1070m, 1050m, 1030m, 1015m, 990s, 925s, 900w, 885w, 860m, 770s, 740s, 705s, 690s, 610m;

δ<sub>e</sub> (300 MHz; CDCl<sub>3</sub>) 0.86 (3H, t, J<sub>6,7</sub>=7.4 Hz, CH<sub>3</sub>), 1.14-1.39 (2H, m, CH<sub>2</sub>CH<sub>2</sub>), 1.84 (2H, quintet of doublets, J<sub>6,8</sub>=11.3, 5.5 Hz, CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 2.06 (1H, brs, OH), 5.11 (1H, dd, J<sub>1,2</sub>=10.7 Hz, CCH=CH<sub>2</sub>), 6.17 (1H, dd, J<sub>3,4</sub>=17.3 Hz, CH=CH<sub>2</sub>), 7.17-7.43 (5H, m, aromatic);

δ<sub>c</sub> (75 MHz; CDCl<sub>3</sub>) 14.35 (CH<sub>3</sub>), 16.88 (CH<sub>2</sub>), 44.36 (CH<sub>2</sub>), 76.98 (C), 112.35 (CH<sub>2</sub>), 125.34 (CH), 126.64 (CH), 128.05 (CH), 144.32 (CH), 145.68 (C);

M/Z 176 (2), 159 (2), 149 (2), 133 (100), 128 (3), 115 (9), 105 (12), 91 (4), 77 (6), 55 (34), 51 (7), 43 (12), 39 (6);
\[ \text{C}_{16}\text{H}_{14}\text{O} \quad \text{requires} \quad 176.1201 \]
\[ \text{found} \quad 176.1201. \]

\textit{(5RS)-5-Butoxy-3-(2-hydroxyphenyl)-2-isoxazoline (141)}

\begin{center}
\begin{tikzpicture}
  \node (a) at (0,0) {\textbf{OH}};
  \node (b) at (0.5,0) {\textbf{O}};
  \node (c) at (1,0) {\textbf{Bu}};
  \node (d) at (0,-0.5) {\textbf{N}};
  \node (e) at (0.5,-1) {\textbf{O}};
\end{tikzpicture}
\end{center}

(141)

A solution of 2-hydroxybenzaldehyde oxime (1.12 g, 8.2 mmol), N-chlorosuccinimide (1.36 g, 9.0 mmol) and pyridine (2 drops) in chloroform (30 ml) was heated under reflux for 20 min. The solution was then cooled to room temperature and butyl vinyl ether (820 mg, 8.2 mmol) and a solution of triethylamine (911 mg, 9.0 mmol) in chloroform (5 ml) added dropwise. The mixture was heated under reflux for 1 h and then evaporated under reduced pressure. Flash column chromatography (10:1 petroleum ether-ether) yielded \textit{(5RS)-5-butoxy-3-(2-hydroxyphenyl)-2-isoxazoline (141)} as a colourless oil (687 mg, 36%).

\[ R_f \quad 0.27 \quad (10:1 \text{ petroleum ether-ether}); \]

\[ \nu_{\text{max}} \quad (\text{film}) \quad 3180 \text{brm (OH)}, \quad 3050\text{w}, \quad 3010\text{w}, \quad 2960\text{s}, \quad 2930\text{s}, \quad 2910\text{s}, \quad 2870\text{s}, \quad 1615\text{m}, \]
\[ 1595\text{s}, \quad 1560\text{w}, \quad 1485\text{s}, \quad 1465\text{s}, \quad 1410\text{s}, \quad 1360\text{s}, \quad 1310\text{s}, \quad 1260\text{s}, \quad 1220\text{s}, \quad 1190\text{s}, \quad 1155\text{m}, \]
\[ 1100\text{s}, \quad 1040\text{m}, \quad 1030\text{m}, \quad 1010\text{w}, \quad 995\text{w}, \quad 970\text{w}, \quad 925\text{s}, \quad 890\text{w}, \quad 850\text{s}, \quad 820\text{s}, \quad 795\text{s}, \quad 765\text{s}, \]
\[ 755\text{s}, \quad 705\text{m}, \quad 660\text{s}, \quad 655\text{s}, \quad 645\text{s}; \]

\[ \delta_{\text{H}} \quad (300 \text{ MHz; CDCl}_3) \quad 0.85-0.93 \quad (3\text{H}, \text{ m, CH}_3), \quad 1.29-1.42 \quad (2\text{H}, \text{ m, CH}_2\text{CH}_3), \quad 1.49- \]
\[ 1.61 \quad (2\text{H}, \text{ m, CH}_2\text{CH}_2\text{CH}_2), \quad 3.29 \text{ and } 3.42 \quad (2\text{H}, \text{ B and A of ABX system, } J_{\text{AB}}=17.3 \text{ Hz,}} \]

130
$J_{ax}=6.4\text{ Hz}, J_{ax}=1.8\text{ Hz}, H-4$, 3.55 (1H, dt, $J=9.5, 6.5\text{ Hz}, CH_3CH_2CHO$), 3.85 (1H, dt, $J=9.5, 6.6\text{ Hz}, CH_2CH_2CHO$), 5.63 (1H, dd, $X$ of ABX system, $J_{ax}=6.4\text{ Hz}, J_{ax}=1.8\text{ Hz}$, H-5), 6.87-7.33 (4H, m, aromatic), 9.79 (1H, brs, OH);

$\delta_c$ (75 MHz; CDCl$_3$) 13.78 (CH$_3$), 19.17 (CH$_2$), 31.50 (CH$_2$), 41.60 (CH)$_2$, 68.42 (CH$_3$), 102.13 (CH), 113.69 (C), 116.95 (CH), 119.47 (CH), 128.55 (CH), 131.81 (CH), 157.36 (C), 158.90 (C);

M/Z 235 (M$^+$, 10), 161 (100), 133 (32), 119 (9), 101 (30), 91 (32), 85 (4), 78 (13), 71 (2), 65 (24), 57 (76), 51 (8), 41 (82);

C$_{22}$H$_{20}$NO, [M$^+$] requires 235.1208
found 235.1217.

(5RS)-5-[(1R)-Menthoxy]-3-phenyl-2-isoxazoline (146)

Following the same procedure as for the preparation of compound (141), reaction of benzaldehyde oxime (665 mg, 5.49 mmol), N-chlorosuccinimide (807 mg, 6.04 mmol), pyridine (2 drops), (1R)-menthyl vinyl ether (63) (1.0 g, 5.49 mmol) and triethylamine (610 mg, 6.04 mmol) gave (5RS)-5-[(1R)-menthoxy]-3-phenyl-2-isoxazoline (146) (677 mg, 41%) as an oily 1:1.38 mixture of diastereoisomers after flash column chromatography (petroleum ether).
R<sub>a</sub> 0.37 (10:1 petroleum ether-ether);

[α]<sup>19</sup> = -52.5° (C=4, CH<sub>2</sub>Cl<sub>2</sub>);

λ<sub>max</sub> (film) 3050w, 3010w, 2960s, 2870s, 1445m, 1415w, 1380m, 1355s, 1330m,
1295w, 1250w, 1240m, 1215w, 1185m, 1155w, 1085s, 1055w, 1040m, 1010m, 990m,
975m, 930s, 915s, 885s, 840s, 830s, 805m, 755s, 690s, 670s, 665w;

δ<sub>δ</sub> (300 MHz; CD<sub>3</sub>Cl) 0.63-1.68 (16H, m), 2.03-2.16 (2H, m) 3.11-3.49 (2H, m,
2H-4 and 0.4H-1'), 3.62 (0.6H, td, J=10.6, 6.2 Hz, H-1'), 5.73 (0.4H, dd, J=6.7, 1.8
Hz, H-5), 5.81 (0.6H, dd, J=6.5, 1.6 Hz, H-5), 7.34-7.45 (2H, aromatic), 7.59-7.69
(3H, m, aromatic);

δ<sub>δ</sub> (75 MHz; CDCl<sub>3</sub>) 15.89 (CH<sub>3</sub>), 16.32 (CH<sub>3</sub>), 20.87 (CH<sub>3</sub>), 21.03 (CH<sub>3</sub>), 22.17
(CH<sub>3</sub>), 22.31 (CH<sub>3</sub>), 23.26 (CH<sub>3</sub>), 23.29 (CH<sub>3</sub>), 25.34 (CH), 25.71 (CH), 31.36 (CH),
31.64 (CH), 34.25 (CH), 34.43 (CH), 40.08 (CH), 41.56 (CH), 41.70 (CH), 43.09
(CH), 47.88 (CH), 48.31 (CH), 75.59 (CH), 80.65 (CH), 99.49 (CH), 104.75 (CH),
126.77 (CH), 128.59 (CH), 129.31 (C), 129.43 (C), 130.04 (CH), 156.66 (C), 156.76
(C);

M/Z 302 ([MH]<sup>+</sup>, 100), 276 (13), 232 (26), 233 (6), 183 (2), 162 (8), 148 (19), 136
(9), 120 (8), 101 (2), 95 (2), 81 (2), 58 (3), 44 (5);

C<sub>19</sub>H<sub>20</sub>NO<sub>3</sub> [MH]<sup>+</sup> requires 302.2120
found 302.2120.
(1S)-endo-Bornyl vinyl ether (144)*

Following the same procedure as for the preparation of compound (63), (1S)-endo-borneneol (5.0 g, 32.5 mmol), n-butyl vinyl ether (50 ml) and a catalytic amount of mercuric acetate gave (1S)-endo-bornyl vinyl ether (144) as a colourless liquid (3.99 g, 68%) after flash column chromatography (10:1 petroleum ether-ether).

δ (300 MHz; CDCl3) 0.83-0.97 (9H, m), 1.07 (1H, dd, J=13.4, 3.4 Hz), 1.18-1.32 (2H, m), 1.65-1.76 (2H, m), 1.96-2.06 (1H, m), 2.16-2.26 (1H, m), 3.92 (1H, dd, J=6.7, 1.6 Hz, OCH=CHbre), 4.01 (1H, ddd, J=9.5, 3.3, 2.0 Hz, H-1), 4.10 (1H, dd, J=14.4, 1.6 Hz, OCH=CHbre), 6.38 (1H, dd, J=14.4 Hz, J=6.7 Hz, OCH=OCHbre);

δ (75 MHz; CDCl3) 13.69 (CH3), 18.86 (CH3), 19.73 (CH3), 26.73 (CH3), 27.96 (CH3), 36.39 (CH3), 45.01 (CH), 47.73 (C), 49.18 (C), 83.75 (CH), 86.90 (CH), 151.76 (CH).
Following the same procedure as for the preparation of compound (141), benzaldehyde oxime (669 mg, 5.52 mmol), N-chlorosuccinimide (811 mg, 6.07 mmol), pyridine (2 drops), (1S)-endo-bornyl vinyl ether (144) (1.0 g, 5.52 mmol) and triethylamine (613 mg, 6.07 mmol) gave (5RS)-5-(1S)-endo-bornyl-3-phenyl-2-isoxazoline (148) (741 mg, 45%) as an oily 1:1.31 mixture of diastereoisomers after flash column chromatography (petroleum ether).

Rf 0.61 (10:1 petroleum ether-ether);

[α]D = -21.9° (C=8, CHCl3);

νmax (film) 3060w, 2980s, 2950s, 2980s, 1630w, 1590s, 1565m, 1590m, 1475m, 1445m, 1385s, 1375s, 1380m, 1305w, 1260s, 1230m, 1205m, 1185m, 1135s, 1110s, 1075s, 1045s, 1035s, 1020m, 960s, 920s, 910s, 885s, 850s, 820m, 790w, 745s, 730m, 695s, 685s, 665w, 650m, 615w;

δH (300 MHz; CDCl3) 0.79-1.29 (12H, m), 1.46-1.76 (4H, m), 1.97-1.26 (2H, m), 3.91-4.01 (0.6H, m, H-1'), 4.08-4.16 (0.4H, m, H-1'), 5.42 (0.6H, dd, J=10.8, 5.4 Hz, H-5), 5.43 (0.4H, dd, J=10.7, 5.4 Hz, H-5), 7.33-7.42 (3H, m, aromatic), 7.81-7.90
\( \delta \) (75 MHz; CDCl\(_3\)) 13.32 (CH\(_3\)), 13.69 (CH\(_3\)), 18.81 (CH\(_3\)), 18.84 (CH\(_3\)), 19.74 (CH\(_3\)), 20.13 (CH\(_3\)), 20.46 (CH\(_3\)), 26.52 (CH\(_2\)), 26.65 (CH\(_2\)), 28.08 (CH\(_2\)), 28.27 (CH\(_2\)), 36.12 (CH\(_2\)), 37.54 (CH\(_2\)), 45.01 (CH), 47.23 (C), 47.54 (C), 48.86 (C), 49.37 (C), 81.48 (CH), 85.27 (CH), 103.07 (CH), 106.29 (CH), 127.03 (CH), 127.06 (CH), 128.30 (CH), 128.32 (CH), 132.80 (C), 132.86 (C), 137.34 (C);

\( \text{M/Z} \) 300 ([MH]\(^+\),100), 200 (5), 170 (5), 146 (83), 137 (87), 120 (71), 103 (29), 85 (52), 83 (22), 64 (7), 39 (6);

\( \text{C}_{14} \text{H}_{18} \text{NO}_{3} \) [MH]\(^+\) requires \( 300.1964 \)
found \( 300.1964. \)

\((2RS,5R)-5\text{-Methyl-2-}(1\text{-methyl-1-phenylethyl})\text{cyclohexanone}^{39} \)

Bromobenzene (7.85 g, 50 mmol) was added in one portion to a mixture of magnesium turnings (11.0 g, 0.45 mol) and ether (50 ml) under nitrogen. The mixture was then heated to reflux without stirring. When the reaction had started, bromobenzene (70.65 g, 0.45 mol) in ether (100 ml) was added with stirring so as to maintain a gentle reflux. After addition was complete, the reaction was heated to reflux for an additional 1h. The solution was then cooled to room temperature and added, via a cannula, to a vigorously stirred suspension of copper (I) bromide (4.4 g,
31 mmol) in ether (70 ml), under nitrogen, at -20°C. The reaction was stirred at -20°C for 30 min. A solution of (R)-pulegone (40 g, 0.26 mol) in ether (50 ml) was added, with stirring, over 2 h and the reaction kept at -20°C overnight. The reaction mixture was then added to ice-cold 2M hydrochloric acid (300 ml) with vigorous stirring. The organic layer was separated and the aqueous layer saturated with ammonium chloride and extracted with ether. The combined organic phases were washed with saturated aqueous sodium hydrogen carbonate solution and the solvent removed under reduced pressure. A solution of the resulting crude oil and potassium hydroxide (70.0 g, 1.2 mol) in ethanol (600 ml) and water (80 ml) was heated to reflux for 3 h to bring about equilibration of the product. The solution was concentrated under reduced pressure to a volume of about 200 ml and water (500 ml) added. The aqueous solution was saturated with sodium chloride and extracted with ether. The organic layers were combined, dried (MgSO₄) and the solvent removed under reduced pressure. Distillation (135-144°C at 0.5 mm) (lit. b.p 100-110°C at 0.05 mm) afforded (2RS,5R)-5-methyl-2-(1-methyl-1-phenylethyl)cyclohexanone as a pale yellow oil (48.7 g, 80%). The product was assumed to exist as an 87:13 mixture of diastereoisomers as reported.¹¹⁹

\[
\text{(2RS,5R)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexanone}^{119}
\]

A mixture of sodium (14.2 g, 61.7 mmol) and toluene (200 ml) was heated to reflux
with the exclusion of moisture. By vigorous stirring a fine suspension of sodium was obtained. A solution of equilibrated (2RS,5R)-5-methyl-2-(1-methyl-1-phenylethyl) cyclohexanone (48.3 g, 0.21 mol) in 2-propanol (36.2 g, 0.60 mol) was added to this stirred solution so as to maintain a controlled reflux. After addition was complete, the reaction mixture was heated to reflux for an additional 8 h and then cooled to 0°C. The mixture was diluted with ether (200 ml) and carefully poured into ice-water (250 ml). The organic phase was separated and the aqueous phase saturated with sodium chloride and extracted with ether. The combined organic layers were washed with saturated aqueous sodium chloride solution, dried (MgSO₄) and the solvent removed under reduced pressure. Distillation (140-146°C at 0.5 mm) (lit. b.p 103-107°C at 0.01 mm) yielded (1RS,2SR,5R)-5-methyl-2-(1-methyl-1-phenylethyl)cyclohexanol as a pale yellow oil (33.17 g, 68%). The product was assumed to exist as an 87:13 mixture of diastereoisomers as reported.

(1R,2S,5R)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl chloroacetate

A solution of (1RS,2SR,5R)-5-methyl-2-(1-methyl-1-phenylethyl)cyclohexanol (33.17 g, 14.3 mmol) and N,N-dimethylaniline (17.3 g, 143 mmol) in ether (50 ml) was stirred at 0°C with the exclusion of water. Chloroacetyl chloride (17.8 g, 157 mmol) in ether (50 ml) was added at such a rate that this temperature was maintained.
The reaction was stirred for an additional 1h and then allowed to warm to room temperature. Reaction was completed by heating to reflux for 3h. After standard aqueous work-up, a viscous oil (46.1 g) was obtained which yielded white crystals on addition of ethanol (50 ml). The crystals were filtered with suction and twice recrystallised from ethanol to give (1R,2S,5R)-5-methyl-2-(1-methyl-1-phenylethyl)cyclohexyl chloroacetate (14.39 g, 33%).

(1R)-8-Phenylmenthol

A solution of (1R,2S,5R)-5-methyl-2-(1-methyl-1-phenylethyl)cyclohexyl chloroacetate (14.19 g, 46.0 mmol) and potassium hydroxide (5.15 g, 92.0 mmol) in ethanol (300 ml) and water (40 ml) was heated under reflux for 2h. The solution was then concentrated under reduced pressure to a volume of about 50 ml and water (200 ml) and ether (100 ml) added. After the organic phase was separated, the aqueous phase was saturated with sodium chloride and extracted with ether. The combined organic layers were dried (MgSO₄) and the solvent removed under reduced pressure. Distillation (147-149°C at 3 mm) (lit. b.p 105-115°C at 0.01 mm) yielded (1R)-8-phenylmenthol as a colourless liquid (8.97 g, 84%).

[α]₀ = -26.0° (C=1.97, EtOH) (lit. [α]₀ = -26.4° ± 0.1).
Following the same procedure as for the preparation of compound (63), (1R)-8-phenylmenthol (3.0 g, 12.9 mmol), butyl vinyl ether (40 ml) and a catalytic amount of mercuric acetate gave (1R)-8-phenylmenthyl vinyl ether (143) as a colourless liquid (770 mg, 23%) after flash column chromatography (10:1 petroleum ether-ether).

$\delta$ (300 MHz; CDCl$_3$) 0.66-1.04 (6H, m), 1.18-1.60 (9H, m), 1.79 (1H, ddd, $J=11.7$, 10.1, 3.5 Hz), 2.00 (1H, ddd, $J=12.4$, 5.9, 3.8 Hz), 3.55 (1H, td, $J=9.9$, 4.2 Hz, H-1), 3.93 (1H, dd, $J=6.6$, 1.3 Hz, OCH=CH$_2$), 4.17 (1H, dd, $J=14.1$, 1.3 Hz, CH=CH$_2$), 6.14 (1H, dd, $J_{trans}=14.1$ Hz, $J_{cis}=6.6$ Hz, OCH=CH$_2$), 7.10-7.30 (5H, m, aromatic);

$\delta$ (75 MHz; CDCl$_3$) 21.84 (CH$_3$), 24.93 (CH$_3$), 27.05 (CH$_3$), 29.17 (CH$_3$), 31.63 (CH), 34.64 (CH$_3$), 40.38 (C), 41.49 (CH$_3$), 51.51 (CH), 80.66 (CH), 87.67 (CH$_3$), 125.03 (CH), 125.86 (CH), 127.67 (CH), 150.12 (CH), 150.48 (C).
Following the same procedure as for the preparation of compound (141), reaction of benzaldehyde oxime (310 mg, 2.56 mmol), N-chlorosuccinimide (376 mg, 2.81 mmol), pyridine (2 drops), (1R)-8-phenylmenthyl vinyl ether (143) (660 mg, 2.56 mmol) and triethylamine (284 mg, 2.81 mmol) gave (5RS)-3-phenyl-5-(1R)-8-phenylmenthoxyl-2-isoxazoline (147) (495 mg, 51%) as a waxy white solid and a 1:1.94 mixture of diastereoisomers after flash column chromatography (10:1 petroleum ether-ether).

R f 0.21 (6:1 petroleum ether-ether);

[α]D = -44.4° (C=10, CHCl3);

νmax (CHCl3) 3125w, 3065s, 3030s, 2975m, 1600w, 1495m, 1460m, 1370w, 1360s, 1340w, 1240w, 1215w, 1190s, 1130w, 1095s, 1080s, 1055w, 1035w, 1020w, 1005w, 975w, 930m, 910w, 890m, 875m, 840s, 810m, 760w, 735m, 710w, 680s;

δH (300 MHz; CDCl3) 0.76-1.54 (13H, m), 1.56-1.74 (2H, m), 1.81-1.94 (1H, m), 2.15-2.38 (1.3H, m), 2.43 and 3.10 (1.4H, B and A of ABX system, Jα=17.1 Hz, Jβ=6.8 Hz, Jγ=1.7 Hz, H-4), 2.93 (0.3 H, B of partially masked ABX system, Jα=17.5 Hz, Jβ=6.8 Hz, H-4), 3.48 (0.3H, td, J=10.3, 4.3 Hz, H-1’), 3.86 (0.7H, td, J=10.6, 3.6 Hz, H-1’), 5.38 (0.3H, X of partially masked ABX system, dd, Jα=6.8 Hz,
J_{\text{ax}}=1.8 \text{ Hz}, H-5), 5.74 (0.7H, X of ABX system, dd, J_{ax}=6.8 \text{ Hz}, J_{ax}=1.7 \text{ Hz}, H-5), 6.89-6.93 (2H, m, aromatic), 7.10-7.69 (8H, m, aromatic);

$\delta$ (75 MHz; CDCl$_3$) 21.97 (CH$_3$), 22.13 (CH$_3$), 24.49 (CH$_3$), 25.26 (CH$_3$), 26.66 (CH$_3$), 27.64 (CH$_3$), 29.18 (CH$_2$), 31.25 (CH), 31.53 (CH), 34.64 (CH$_2$), 34.94 (CH$_2$), 39.25 (CH$_3$), 39.66(CH), 39.76 (C), 41.42 (CH$_2$), 41.52 (CH$_2$), 43.88 (CH$_2$), 51.51 (CH), 75.38 (CH), 81.67 (CH), 97.59 (CH), 104.66 (CH), 124.04 (CH), 124.67 (CH), 125.27 (CH), 125.37 (CH), 126.68 (CH), 126.76 (CH), 126.84 (CH), 127.37 (CH), 127.73 (CH), 128.48 (CH), 128.57 (CH), 128.60 (CH), 129.27 (C), 129.48 (C), 129.95 (CH), 130.08 (CH), 152.06 (C), 153.05 (C), 156.83 (C), 157.10 (C);

M/Z 378 ([MH]+, 100), 276 (73), 248 (6), 227 (6), 215 (10), 163 (8), 146 (34), 119 (29), 105 (7), 91 (4);

C$_{25}$H$_{24}$NO$_5$ [MH]$^+$ requires 378.2433
found 378.2400.

Methyl (R)-1-ethenloxy-1-phenylacetate (145)$^{99}$

\[
\begin{align*}
\text{O} & \quad \text{CO}_2\text{Me} \\
\text{H} & \quad \text{Pb} \\
\end{align*}
\]

(145)

Following the same procedure as for the preparation of compound (63), (R)-methyl mandelate (4.5 g, 27.1 mmol), butyl vinyl ether (50 ml) and a catalytic amount of mercuric acetate gave methyl (R)-1-ethenloxy-1-phenylacetate (145) as a colourless liquid (703 mg, 14%) after flash column chromatography (5:1 petroleum ether-ether)
and Kugelröhr distillation (160°C at 1mm).

(5RS)-5-[Methyl (R)-1-phenylacetate-1-oxyl-3-phenyl-2-isoxazoline (149)

\[
\begin{align*}
\text{O} & \text{N} \text{Ph} \\
\text{O} & \text{H} \text{CO}_2\text{Me} \\
\text{Ph} & 
\end{align*}
\]

Following the same procedure as for the preparation of compound (141), benzaldehyde oxime (252 mg, 2.08 mmol), N-chlorosuccinimide (306 mg, 2.29 mmol), pyridine (2 drops), methyl (R)-1-ethenyloxy-1-phenylacetate (145) (400 mg, 2.08 mmol) and triethylamine (231 mg, 2.29 mmol) gave (5RS)-5-[methyl (R)-1-phenylacetate-1-oxyl-3-phenyl-2-isoxazoline (149) as a white solid (383 mg, 59%) and a 1:1.08 mixture of diastereoisomers after flash column chromatography (2:1 petroleum ether-ether). The product was recrystallised from petroleum ether as a white solid, m.p 117.5-119.5°C.

\[ R, 0.23 \text{ (1:1 petroleum ether-ether)}; \]
\[ [\alpha]_D = -28.0^\circ \text{ (C=10, CH}_2\text{Cl}_2); \]
\[ \text{C}_{16}\text{H}_{14}\text{NO}, \text{ requires C 69.44%, H 5.51%, N 4.50%}; \]
\[ \text{found C 69.13%, H 5.53%, N 4.50%}. \]
\[ \nu_{\text{max}} \text{ (CH}_2\text{Cl}_2) \text{ 3080w, 3050w, 2980w, 1775s (C=O), 1490w, 1480w, 1450w, 1440m, 1415w, 1370s, 1335w, 1220s, 1185s, 1105s, 1080s, 1040m, 980w, 940s, 880m, 860s, 820w, 690m, 680m}; \]
δ (300 MHz; CDCl₃) 3.30-3.47 (2H, m, H-4), 3.65 (1.5H, s, OCH₃), 3.72 (1.5H, s, OCH₃), 5.39 (0.5H, s, OCHPh), 5.49 (0.5H, s, OCHPh), 5.58 (0.5H, dd, J=6.0, 1.5 Hz, H-5), 5.93 (0.5H, dd, J=5.4, 2.3 Hz, H-5), 7.24-7.51 (8H, m, aromatic), 7.62-7.69 (2H, m, aromatic);

δ (75 MHz; CDCl₃) 41.83 (CH₃), 42.21 (CH₃), 52.28 (CH₃), 52.34 (CH₃), 76.21 (CH), 77.00 (CH), 100.10 (CH), 101.14 (CH), 126.87 (CH), 126.92 (CH), 127.28 (CH), 127.77 (CH), 128.48 (CH), 128.66 (CH), 128.73 (CH), 128.79 (CH), 129.07 (CH), 130.42 (CH), 134.97 (C), 135.67 (C), 157.32 (C), 170.21 (C), 170.99 (C);

M/Z 312 ([M]+, 2), 149 (41), 147 (17), 146 (100), 145 (14), 144 (13), 121 (48), 118 (19), 107 (56), 105 (31), 104 (12), 103 (23), 91 (20), 79 (42), 77 (89), 51 (37), 28 (75).

(5R)-5-((S)-1-(2-Naphthyl)-1-ethoxy)-3-phenyl-2-isoxazoline (150)

Following the same procedure as for the preparation of compound (141), benzaldehyde oxime (1.22 g, 10.1 mmol), N-chlorosuccinimide (1.48 g, 11.1 mmol), pyridine (2 drops), (S)-1-(2-naphthyl)-1-ethyl vinyl ether (79) (2.0 g, 10.1 mmol) and triethylamine (1.12 g, 11.1 mmol) gave (5R)-5-((S)-1-(2-naphthyl)-1-ethoxy)-3-phenyl-2-isoxazoline.
2-isoxazoline (150) as a white solid (1.39 g, 43%) after flash column chromatography (10:1 petroleum ether-ether). The product was recrystallised from petroleum ether as a white solid, m.p 128-130°C.

$R_f$ 0.15 (10:1 petroleum ether-ether);

$[\alpha]_D = -67.9^\circ$ (C=8, CHCl$_3$);

C$_7$H$_{11}$NO$_3$ requires C 79.47%, H 6.03%, N 4.41%,

found C 79.52%, H 6.07%, N 4.40%.

$\nu_{\text{max}}$ (CH$_2$Cl$_2$) 3030w, 2970w, 2930m, 1355m, 1305w, 1190m, 1170m, 1125w, 1075s, 1020w, 955w, 935s, 925s, 880m, 870m, 845s, 820s, 800m, 670w;

$\delta$ (300 MHz; CDCl$_3$) 1.52 (3H, d, J=6.5 Hz, CH$_3$), 3.13-3.27 (2H, m, H-4), 5.14 (1H, q, J=6.5 Hz, NaphCHO), 5.49 (1H, dd, J=5.4, 2.9 Hz, H-5), 7.30-7.49 (6H, m, aromatic), 7.63-7.69 (2H, m, aromatic), 7.78-7.85 (4H, m, aromatic);

$\delta$ (75 MHz; CDCl$_3$) 23.85 (CH$_3$), 41.54 (CH$_3$), 74.88 (CH), 100.22 (CH), 124.17 (CH), 125.90 (CH), 125.96 (CH), 126.22 (CH), 126.76 (CH), 127.62 (CH), 127.82 (CH), 128.53 (CH), 128.59 (CH), 129.11 (CH), 130.15 (CH), 133.04 (C), 133.11 (C), 139.54 (C), 156.92 (C);

M/Z 318 ([MH]$^+$, 17), 155 (100), 128 (6), 103 (3), 77(4).
(5R)-3-(2-Hydroxyphenyl)-5-[(S)-1-(2-naphthyl)-1-ethoxyl-2-isoxazoline (151)

In the same way, 2-hydroxybenzaldehyde oxime (346 mg, 2.53 mmol), N-chlorosuccinimide (371 mg, 2.78 mmol), pyridine (2 drops), (S)-1-(2-naphthyl)-1-ethyl vinyl ether (79) (500 mg, 2.53 mmol) and triethylamine (281 mg, 2.78 mmol) gave (5R)-3-(2-hydroxyphenyl)-5-[(S)-1-(2-naphthyl)-1-ethoxyl-2-isoxazoline (151) as a waxy white solid (286 mg, 36%) after flash column chromatography (5:1 petroleum ether-ether).

Rf 0.28 (5:1 petroleum ether-ether);

[α]D = -60.6° (C=8, CH2Cl2);

νmax (CH2Cl2) 3180brw (OH), 2950s, 2920s, 2860s, 1615m, 1590m, 1490m, 1460m, 1360s, 1305m, 1220m, 1185s, 1170m, 1155m, 1125s, 1085s, 1040m, 1025m, 1000m, 975w, 920w, 850s, 820s, 795s, 660m;

δH (300 MHz, CDCl3) 1.53 (3H, d, J=6.5 Hz, CH3), 3.25 and 3.34 (2H, B and A of ABX system, JAB=17.3 Hz, JAA=6.0 Hz, JAB=2.2 Hz, H-4), 5.13 (1H, q, J=6.5 Hz, NaphCHO), 5.48 (1H, X of ABX system, JAX=6.0 Hz, JAX=2.2 Hz, H-5), 6.86-6.91 (1H, m, aromatic), 7.01-7.05 (1H, m, aromatic), 7.15 (1H, dd, J=7.7, 1.6 Hz, aromatic),
7.26-7.32 (1H, m, aromatic), 7.43-7.52 (3H, m, aromatic), 7.78-7.87 (4H, m, aromatic), 9.84 (1H, brs, OH);

δ (75 MHz; CDCl,) 23.74 (CH,), 41.68 (CH), 75.27 (CH), 99.04 (CH), 113.64 (C), 116.93 (CH), 119.42 (CH), 124.05 (CH), 125.97 (CH), 126.05 (CH), 126.29 (CH), 127.63 (CH), 127.80 (CH), 128.50 (CH), 128.64 (CH), 131.80 (CH), 133.09 (C), 139.12 (C), 157.34 (C), 158.93 (C);

M/Z 334 ([MH]+, 40), 287 (4), 180 (8), 155 (100), 136 (7);

C₆H₆NO₂ [MH]+ requires       334.1443
                         found       334.1443.

1-Phenylpropionaldehyde oxime

A solution of 1-phenylpropionaldehyde (2.0 g, 14.9 mmol) and hydroxylamine hydrochloride (4.14 g, 59.6 mmol) in pyridine (50 ml) was stirred at room temperature for 19h and the solvent then removed under reduced pressure. Standard aqueous work-up and flash column chromatography (2:1 petroleum ether-ether) gave 1-phenylpropionaldehyde oxime as a white solid (1.22 g, 55%). The structure of the product was confirmed by 90 MHz ¹H n.m.r.
Following the same procedure as for the preparation of compound (141), 1-phenylpropanaldehyde oxime (377 mg, 2.53 mmol), N-chlorosuccinimide (371 mg, 2.78 mmol), pyridine (2 drops), (S)-1-(2-naphthyl)-1-ethyl vinyl ether (79) (500 mg, 2.53 mmol) and triethylamine (281 mg, 2.78 mmol) gave (5R)-5-[(S)-1-(2-naphthyl)-1-ethyl vinyl ether-3-phenethyl-2-isoxazoline (152) as a white solid (247 mg, 28%) after flash column chromatography (10:1 petroleum ether-ether). The product was recrystallised from petroleum ether as a white solid, m.p 123.5-125°C.

\[ R_f \text{ 0.15 (10:1 petroleum ether-ether);} \]

\[ [\alpha]_D = -71.8^\circ \text{ (C=10, CHCl);} \]

\[ C_{16}H_{12}O_2 \text{ requires C 79.97%, H 6.71%, N 4.06%;} \]

\[ \text{found C 80.17%, H 6.68%, N 4.23%;} \]

\[ \nu_{\text{max}} \text{ (CHCl) 3020w, 2920m, 2860w, 1595w, 1490w, 1435w, 1360m, 1300m, 1265w, 1160m, 1125w, 1070s, 1025w, 1000w, 930m, 860s, 820s;} \]

\[ \delta (300 \text{ MHz; CDCl)} 1.50 (3H, d, J=6.5 Hz, CH3), 2.51-2.69 (4H, m, CH2CH2Ph), 2.83-2.88 (2H, m, H-4), 5.07 (1H, q, J=6.5 Hz, NaphCHO), 5.27 (1H, dd, J=5.0, 3.2 Hz, H-5), 7.09-7.26 (5H, m, aromatic), 7.36-7.45 (3H, m, aromatic), 7.52-7.80 (4H,
m, aromatic);

δ (75 MHz; CDCl₃) 23.83 (CH₃), 29.29 (CH₃), 32.38 (CH₃), 43.76 (CH₃), 74.42
(CH), 99.23 (CH), 124.13 (CH), 125.76 (CH), 125.86 (CH), 126.12 (CH), 126.16
(CH), 127.55 (CH), 127.74 (CH), 128.16 (CH), 128.36 (CH), 128.41 (CH), 132.94 (C),
133.05 (C), 139.63 (C), 140.32 (C), 158.53 (C);

M/Z 345 (M⁺, 2), 155 (100), 127 (6), 115 (3), 104 (1), 91 (12), 77 (4), 65 (4), 49
(3).

(5R)-5-(S)-1-(2-Naphthyl)-1-ethoxy-3-(4-nitrophenvl)-2-isoxazoline (153)

In the same way, 4-nitrobenzaldehyde oxime (587 mg, 3.54 mmol), N-
chlorosuccinimide (519 mg, 3.89 mmol), pyridine (2 drops), (S)-1-(2-naphthyl)-1-ethyl
vinyl ether (79) (700 mg, 3.54 mmol) and triethylamine (393 mg, 3.89 mmol) gave
(5R)-5-(S)-1-(2-naphthyl)-1-ethoxy-3-(4-nitrophenvl)-2-isoxazoline (153) as a white
solid (333 mg, 26%) m.p 167.5-169.5°C after flash column chromatography (10:1

148
petroleum ether-ether).  

Rf 0.17 (4:1 petroleum ether-ether);  

$\alpha_{b} = -9.0^\circ$ (C=1, CH$_2$Cl$_2$);  

$\nu_{\text{max}}$ (CH$_2$Cl$_2$) 2920 w, 1765 w, 1705 w, 1600 w, 1570 w, 1520 s, 1340 s, 1315 m, 1230 w, 1190 m, 1125 w, 1110 m, 1075 m, 1010 w, 980 w, 935 m, 920 m, 895 m, 850 s, 835 s, 820 s, 795 m;  

$\delta_{c}$ (300 MHz; CDCl$_3$) 1.55 (3H, d, J=6.5 Hz, CH$_3$), 3.24-3.36 (2H, m, H-4), 5.16 (1H, q, J=6.5 Hz, NaphCHO), 5.62 (1H, dd, J=5.0, 3.5 Hz, H-5), 7.40-8.37 (11H, m, aromatic);  

$\delta_{c}$ (75 MHz; CDCl$_3$) 23.74 (CH$_3$), 40.91 (CH$_3$), 73.37 (CH), 101.09 (CH), 123.69 (CH), 123.78 (CH), 124.02 (CH), 124.05 (CH), 125.88 (CH), 126.03 (CH), 126.27 (CH), 127.35 (CH), 127.43 (CH), 127.60 (CH), 127.77 (CH), 128.58 (CH), 129.17 (CH), 130.26 (CH), 131.07 (CH), 133.02 (C), 135.14 (C), 139.12 (C), 148.33 (C), 155.44 (C), 190.20 (C);  

M/Z 362 (M$^+$, 1), 191 (3), 172 (1), 155 (100), 128 (11), 115 (5), 102 (7), 89 (4), 76 (6), 63 (4), 50 (6), 42 (4);  

C$_8$H$_5$N$_2$O. [M$^+$] requires 362.1267  
found 362.1270.  

2,2-Dimethylpropionaldehyde oxime$^{44}$  

Following the same procedure as for the preparation of 1-phenylpropionaldehyde oxime, 2,2-dimethylpropionaldehyde (4.0 g, 46.5 mmol) and hydroxylamine hydrochloride (12.93 g, 190 mmol) gave 2,2-dimethylpropionaldehyde oxime as colourless crystals (2.27 g, 48%) after flash column chromatography (1:1 petroleum
ether-ether). The structure of the product was confirmed by 90 MHz \(^1\)H n.m.r.

(5R)-3-(2,2-Dimethylpropyl)-5-[(S)-1-(2-naphthyl)-1-ethoxy]-2-isoxazoline (154)

Following the same procedure as for the same preparation of compound (141), 2,2-dimethylpropionaldehyde oxime (200 mg, 1.98 mmol), N-chlorosuccinimide (291 mg, 2.18 mmol), pyridine (2 drops), (S)-1-(2-naphthyl)-1-ethyl vinyl ether (79) (392 mg, 1.98 mmol) and triethylamine (220 mg, 2.18 mmol) gave (5R)-3-(2,2-dimethylpropyl)-5-[(S)-1-(2-naphthyl)-1-ethoxy]-2-isoxazoline (154) as a white solid (311 mg, 53%) after flash column chromatography (5:1 petroleum ether-ether). The product was recrystallised from petroleum ether as a white solid, m.p 81-83°C.

\( R_f 0.10 \) (5:1 petroleum ether-ether);

\([\alpha]_D = -81.3^\circ (C=10, \text{CHCl}_3)\);

\( \text{C}_{19}\text{H}_{18}\text{NO}_4 \) requires

- C 76.73%, H 7.79%, N 4.71%

found

- C 76.44%, H 7.89%, N 4.67%.

\( \nu_{\text{max}} \) (\( \text{CHCl}_3 \)) 2960m, 2920m, 2900w, 2860w, 1475w, 1455w, 1360m, 1510w, 1185m, 1170w, 1120m, 1075s, 1010w, 935s, 850s, 820m, 790m;

\( \delta_c \) (300 MHz, \( \text{CDCl}_3 \)) 1.20 (9H, s, C(CH\(_3\))\(_3\)), 1.49 (3H, d, J=6.6 Hz, CH\(_3\)), 2.80 (2H,
d, J=4.0 Hz, H-4), 5.07 (1H, q, J=6.6 Hz, NaphCHO), 5.30 (1H, t, J=4.0 Hz, H-5),
7.38-7.47 (3H, m, aromatic), 7.73-7.82 (4H, m, aromatic);

δc (75 MHz; CDCl₃) 23.88 (CH₃), 27.44 (CH₃), 28.05 (CH₃), 29.33 (CH₂), 32.92 (C),
40.99 (CH₂), 74.34 (CH), 99.50 (CH), 124.22 (CH), 125.78 (CH), 125.86 (CH), 126.13
(CH), 127.59 (CH), 127.79 (CH), 128.42 (CH), 133.01 (C), 133.14 (C), 139.83 (C),
158.71 (CH), 166.18 (C);

M/Z 298 ([M]+, 100), 172 (4), 155 (43), 144 (19), 126 (7), 116 (3), 100 (5), 58
(2), 44 (2).

Butyraldehyde oxime⁴²

Following the same procedure as for the preparation of 1-phenylpropionaldehyde
oxime, butyraldehyde (4.0 g, 55.6 mmol) and hydroxylamine hydrochloride (15.4 g,
220 mmol) gave butyraldehyde oxime as a colourless liquid (3.53 g, 73%) after flash
column chromatography (2:1 petroleum ether-ether). The structure of the product was
confirmed by 90 MHz ¹H n.m.r.

(5R)-5-(S)-1-(2-Naphthyl)-1-ethoxy-3-propyl-2-isoxazoline (155)

Following the same procedure as for the preparation of compound (141),
butyraldehyde oxime (220 mg, 2.53 mmol), N-chlorosuccinimide (371 mg, 2.78 mmol), pyridine (2 drops), (S)-1-(2-naphthyl)-1-ethyl vinyl ether (79) (500 mg, 2.53 mmol) and triethylamine (281 mg, 2.78 mmol) gave (5R)-5-[(S)-1-(2-naphthyl)-1-ethoxyl]-3-propyl-2-isoxazoline (155) as a colourless oil (250 mg, 37%) after flash column chromatography (3:1 petroleum ether-ether).

\[ \alpha \text{D} = -173.6^\circ \quad (C=10, \text{CHCl}_3) \]

\( R_f 0.10 \) (3:1 petroleum ether-ether);

\( \lambda_{\text{max}} \) (film): 3055m, 2960s, 2930s, 2860m, 1720w, 1630w, 1600m, 1510m, 1455m, 1415m, 1365m, 1305m, 1300m, 1275w, 1170s, 1135m, 1080s, 1015m, 940s, 865s, 825s, 785m, 750s, 715w, 695w, 670w, 630w;

\( \delta_\text{H} \) (300 MHz; CDCl\(_3\)) 1.04 (3H, t, \( J=7.3 \) Hz, CH\(_3\)CH\(_2\)CH\(_3\)), 1.58-1.75 (5H, m, Naph\( \text{CH}\)), and 2.44 (2H, t, \( J=7.5 \) Hz, CH\(_3\)CH\(_2\)CH\(_3\)), 2.83 and 2.93 (2H, B and A of ABX system, \( J_{\text{ABX}}=17.5 \) Hz, \( J_{\text{ABX}}=6.2 \) Hz, \( J_{\text{ABX}}=1.7 \) Hz, H-4), 5.17 (1H, q, \( J=6.5 \) Hz, Naph\( \text{CHO} \)), 5.40 (1H, X of ABX system, dd, \( J_{\text{AX}}=6.2 \) Hz, \( J_{\text{AX}}=1.7 \) Hz, H-5), 7.49-7.58 (3H, m, aromatic), 7.83-7.92 (4H, m, aromatic);

\( \delta_\text{C} \) (75 MHz; CDCl\(_3\)) 13.54 (CH\(_3\)), 19.61 (CH\(_3\)), 23.77 (CH\(_3\)), 29.32 (CH\(_3\)), 43.50 (CH\(_3\)), 74.32 (CH), 99.05 (CH), 124.12 (CH), 125.72 (CH), 125.79 (CH), 126.06 (CH), 127.50 (CH), 127.70 (CH), 128.34 (CH), 132.90 (C), 133.01 (C), 139.65 (C), 159.18 (C);

M/Z 284 ([MH]+, 100), 240 (2), 172 (3), 155 (71), 130 (24), 112 (8), 86 (8), 58 (2);

\( C_{16}H_{23}NO_3 \) [MH]* requires 284.1650

found 284.1651.

152
Propionaldehyde oxime

Following the same procedure as for the preparation of 1-phenylpropionaldehyde oxime, propionaldehyde (3.0 g, 51.7 mmol) and hydroxylamine hydrochloride (14.38 g, 207 mmol) gave propionaldehyde oxime as a colourless liquid (2.11 g, 56%) after flash column chromatography (2:1 petroleum ether-ether). The structure of the product was confirmed by 90 MHz 'H n.m.r.

(5R)-3-Ethyl-5-(S)-1-(2-naphthyl)-1-ethoxyl-2-isoxazoline (156)

Following the same procedure as for the preparation of compound (141), propionaldehyde oxime (184 mg, 2.53 mmol), N-chlorosuccinimide (371 mg, 2.78 mmol), pyridine (2 drops), (S)-1-(2-naphthyl)-1-ethyl vinyl ether (79) (500 mg, 2.53 mmol) and triethylamine (281 mg, 2.78 mmol) gave (5R)-3-ethyl-5-(S)-1-(2-naphthyl)-1-ethoxyl-2-isoxazoline (156) as a white solid (248 mg, 40%) after flash column chromatography (3:1 petroleum ether-ether). The product was recrystallised from petroleum ether as a white solid, m.p 70.5-72°C.

R, 0.11 (3:1 petroleum ether-ether);
[α]D = -209.3° (C=10, CHCl₃);
C\textsubscript{8}H\textsubscript{8}NO\textsubscript{2} requires C 75.81\%, H 7.11\%, N 5.20\%.

found C 75.89\%, H 7.24\%, N 5.38\%.

\( \nu \) (CH\textsubscript{2}Cl\textsubscript{2}) 3100s, 3145m, 3090w, 1590m, 1505w, 1465m, 1420w, 1380m, 1370m, 1330w, 1320m, 1310m, 1225w, 1195m, 1185m, 1140w, 1100s, 1015w, 960w, 955s, 870s, 860s, 840s, 815w, 740m;

\( \delta \) (300 MHz; CDCl\textsubscript{3}) 1.16 (3H, t, J=7.5 Hz, CH\textsubscript{2}CH\textsubscript{3}), 1.51 (3H, d, J=6.5 Hz, Naph\textsubscript{CH\textsubscript{2}}CHO), 2.34-2.48 (2H, m, CH\textsubscript{2}CH\textsubscript{3}), 2.75 and 2.86 (2H, B and A of ABX system, I\textsubscript{ax}=17.5 Hz, I\textsubscript{ab}=6.3 Hz, I\textsubscript{bx}=1.8 Hz, H-4), 5.08 (1H, q, J=6.5 Hz, NaphCHO), 5.32 (1H, X of ABX system, dd, I\textsubscript{ax}=6.3 Hz, I\textsubscript{bx}=1.8 Hz, H-5), 7.30-7.58 (3H, m, aromatic), 7.83-7.92 (4H, m, aromatic);

\( \delta \) (75 MHz; CDCl\textsubscript{3}) 10.77 (CH\textsubscript{3}), 21.21 (CH\textsubscript{2}), 23.90 (CH\textsubscript{2}), 43.56 (CH\textsubscript{2}), 43.56 (CH), 99.31 (CH), 124.22 (CH), 125.82 (CH), 125.91 (CH), 126.18 (CH), 127.62 (CH), 127.81 (CH), 128.47 (CH), 133.02 (C), 133.13 (C), 139.78 (C), 160.31 (C);

M/Z 269 (M\textsuperscript{+}, 4), 172 (16), 157 (19), 156 (16), 155 (100), 154 (46), 153 (21), 152 (15), 129 (44), 128 (23), 127 (26), 29 (56), 19 (31).
In the same way, acetaldehyde oxime (145 mg, 2.53 mmol), N-chlorosuccinimide (371 mg, 2.78 mmol), pyridine (2 drops), (S)-1-[(2-naphthyl)-1-ethyl vinyl ether (79) (500 mg, 2.53 mmol) and triethylamine (281 mg, 2.78 mmol) gave (5RS)-5-[(S)-(2-naphthyl)-1-ethoxy]-3-methyl-2-isoxazoline (157) as a 2:1 mixture of diastereoisomers and a white solid (237 mg, 37%) after flash column chromatography (2:1 petroleum ether-ether). The product was recrystallised from petroleum ether as a white solid, m.p 92-95°C.

Rf 0.12 (2:1 petroleum ether-ether);

[α]D = -143.4° (C=8, CHCl₃);

C₂₀H₁₃NO₅ requires C 75.27%, H 6.71%, N 5.49%,
found C 75.33%, H 6.76%, N 5.48%.

υmax (CHCl₃) 3050m, 2960s, 2930s, 2870s, 1600w, 1505w, 1535s, 1515w, 1415s, 1380s, 1370s, 1270m, 1260w, 1245w, 1225w, 1215w, 1175s, 1125s, 1070s, 1020s, 1000s, 975m, 950m, 925s, 835s, 750s, 715w, 665m, 640m, 620w;

δH (300 MHz; CDCl₃) 1.49 (2H, d, J=6.5 Hz, NaphCH₂CHO), 1.53 (1H, d, J=6.5 Hz, NaphCH₂CHO), 1.97 (3H, s, N=CCH₃), 2.71 (1H, dd, J=17.6, 1.1 Hz, H-4), 2.82 (1H, ddd, J=17.6, 6.2, 1.1 Hz, H-4), 5.00 (0.3H, q, J=6.5 Hz, NaphCHO), 5.06 (0.7H, q,
J=6.5 Hz, NaphCHO), 5.29 (1H, dd, J=6.2, 1.8 Hz, H-5), 7.37-7.48 (3H, m, aromatic),
7.72-7.82 (4H, m, aromatic);

δ (75 MHz; CDCl3) 12.94 (CH3), 13.87 (CH3), 23.85 (CH3), 25.23 (CH3), 43.99
(CH3), 45.05 (CH3), 70.01 (CH), 74.55 (CH), 99.50 (CH), 100.73 (CH), 123.66 (CH),
123.90 (CH), 124.10 (CH), 124.17 (CH), 125.53 (CH), 125.81 (CH), 125.91 (CH),
126.17 (CH), 127.47 (CH), 127.54 (CH), 127.60 (CH), 127.80 (CH), 128.00 (CH),
128.47 (CH), 132.72 (C), 133.01 (C), 133.10 (C), 133.24 (C), 139.66 (C), 143.56 (C),
155.79 (C);

M/Z 255 (M+, 3), 180 (1), 155 (100), 127 (10), 115 (4), 84 (3), 77 (3), 62 (2), 56
(4), 41 (2).

3-Phenyl-5-[(S)-1-phenyl-1-butoxy]-2-isoxazoline (158)

Following the same procedure as for the preparation of compound (141),
benzaldehyde oxime (138 mg, 1.14 mmol), N-chlorosuccinimide (167 mg, 1.25 mmol),
pyridine (2 drops), (S)-1-phenyl-1-butyl vinyl ether (81) (200 mg, 1.14 mmol) and
triethylamine (126 mg, 1.25 mmol) gave a single diastereoisomer of 3-phenyl-5-[(S)-1-
phenyl-1-butoxy]-2-isoxazoline (158) as a waxy white solid (111 mg, 33%) after flash
column chromatography (10:1 petroleum ether-ether).

Rf 0.43 (3:1 petroleum ether-ether);
[α]$_D$ = -135.2$^\circ$ (C=5, CH$_2$Cl$_2$); 

$\nu_{max}$ (CH$_2$Cl$_2$) 3030w, 2960m, 2930m, 2870w, 1490w, 1445w, 1360m, 1185m, 1080s, 1030w, 1000w, 975w, 930s, 880m, 845s, 675w, 630w;

$\delta$(300 MHz; CDCl$_3$) 0.87 (3H, t, J=7.3 Hz, CH$_3$), 1.21-1.43 (2H, m, CH$_2$CH$_3$), 1.55-1.66 (1H, m, CH$_3$CH$_2$CH$_3$), 1.74-1.86 (1H, m, CH$_3$CH$_2$CH$_3$), 3.17-3.32 (2H, m, H-4), 4.81 (1H, dd, J=7.5, 6.2 Hz, PhCHO), 5.48 (1H, dd, J=5.2, 3.0 Hz, H-5), 7.26-7.50 (2H, m, aromatic), 7.61-7.71 (8H, m, aromatic);

$\delta$(75 MHz; CDCl$_3$) 13.81 (CH$_3$), 18.82 (CH$_3$), 39.95 (CH$_3$), 41.53 (CH$_3$), 78.47 (CH), 100.04 (CH), 126.81 (CH), 127.08 (CH), 127.73 (CH), 128.42 (CH), 128.63 (CH), 129.24 (C), 130.16 (CH), 141.46 (C), 156.93 (C);

M/Z 296 ([MH]+, 46), 276 (6), 164 (15), 146 (23), 133 (25), 118 (6), 83 (41), 64 (16), 49 (100);

C$_9$H$_{18}$NO$_3$ [MH]$^+$ requires 296.1650
found 296.1651.

5-[(S)-1-Phenyl-1-butoxyl-3-phenylethyl-2-isoxazoline (159)

\[
\begin{array}{c}
\text{Ph} \\
\text{Pr} \\
\text{H} \\
\text{O} \\
\text{N} \\
\text{CH$_2$CH$_2$Ph}
\end{array}
\]

(159)

In the same way, 1-phenylpropionaldehyde oxime (677 mg, 4.55 mmol), N-chlorosuccinimidide (668 mg, 5.0 mmol), pyridine (2 drops), (S)-1-phenyl-1-butyl vinyl ether (81) (800 mg, 4.55 mmol) and triethylamine (505 mg, 5.0 mmol) gave a single
diastereoisomer of 5-[(S)-1-phenyl-1-butoxy]-3-phenylethyl]-2-isoxazoline (159) as a colourless oil (645 mg, 44%) after flash column chromatography (5:1 petroleum ether-ether).

Rf 0.20 (3:1 petroleum ether-ether);

$[\alpha]_D = -121.7^\circ \ (C=10, \text{CH}_2\text{Cl}_2)$;

$\nu_{\text{max}} \ (\text{film}) \ 3050\text{m}, 3020\text{s}, 2960\text{s}, 2860\text{s}, 1595\text{m}, 1490\text{m}, 1445\text{s}, 1415\text{w}, 1335\text{m}, 1155\text{s}, 1060\text{s}, 1025\text{s}, 970\text{s}, 915\text{s}, 865\text{s}, 830\text{s}, 750\text{s}, 695\text{s}, 620\text{m};$

$\delta_r \ (300 \text{ MHz; CDCl}_3) \ 0.88 \ (3\text{H, t, } J=7.3 \text{ Hz, } \text{CH}_3\text{CH}_2\text{CH}_3), 1.17-1.42 \ (2\text{H, m, CH}_3\text{CH}_2\text{CH}_3), 1.52-1.64 \ (1\text{H, m, CH}_3\text{CH}_2\text{CH}_3), 1.72-1.84 \ (1\text{H, m, CH}_3\text{CH}_2\text{CH}_3), 2.66-2.96 \ (6\text{H, m, CH}_3\text{CH}_2\text{Ph and H-4}), 4.74 \ (1\text{H, dd, } J=7.5, 6.1 \text{ Hz, PhCH}O), 5.26 \ (1\text{H, dd, } J=6.2, 1.7 \text{ Hz, H-5}), 7.02-7.34 \ (10\text{H, m, aromatic});$

$\delta_c \ (75 \text{ MHz; CDCl}_3) \ 13.84 \ (\text{CH}_3), 18.81 \ (\text{CH}_3), 29.38 \ (\text{CH}_3), 32.58 \ (\text{CH}_3), 39.97 \ (\text{CH}_3), 43.77 \ (\text{CH}_3), 78.03 \ (\text{CH}), 99.08 \ (\text{CH}), 126.24 \ (\text{CH}), 127.01 \ (\text{CH}), 127.62 \ (\text{CH}), 128.19 \ (\text{CH}), 128.23 \ (\text{CH}), 128.35 \ (\text{CH}), 128.44 \ (\text{CH}), 140.39 \ (\text{C}), 141.56 \ (\text{C}), 158.65 \ (\text{C});$

M/Z 323 ($M^+$, 6), 183 (15), 133 (20), 132 (21), 131 (100), 120 (18), 107 (35), 105 (34), 104 (20), 103 (18);

C$_{36}$H$_{32}$NO$_2$ [$M^+$] requires 323.1885
found 323.1885.
3-(4-Nitrophenyl)-5-((S)-1-phenyl-1-butoxy-1-2-isoxazoline (160)

In the same way, 4-nitrobenzaldehyde oxime (943 mg, 5.68 mmol), N-chlorosuccinimide (843 mg, 6.25 mmol), pyridine (2 drops), (S)-1-phenyl-1-butyl vinyl ether (81) (1.0 g, 5.68 mmol) and triethylamine (631 mg, 6.25 mmol) gave a single diastereoisomer of 3-(4-nitrophenyl)-5-((S)-1-phenyl-1-butoxy-1-2-isoxazoline (160) as a white solid (433 mg, 23%) after flash column chromatography (4:1 petroleum ether-ether). The product was recrystallised from methanol as a white solid, m.p 105-107°C.

Rf 0.10 (4:1 petroleum ether);

[α] D = -63.1° (C=10, CH₂Cl₂);

C₆H₅N₂O₃ requires C 67.04%, H 5.92%, N 8.23%,
found C 67.17%, H 6.12%, N 8.16%.

ν max (CH₂Cl₂) 2970 w, 2940 w, 2880 w, 1605 m, 1580 w, 1535 s, 1525 s, 1490 w, 1385 w, 1350 s, 1315 w, 1295 w, 1195 m, 1115 m, 1085 s, 1020 w, 925 m, 905 w, 895 w, 860 s, 840 s, 805 m, 715 w;

δ (300 MHz; CDCl₃) 0.89 (3H, t, J=7.3 Hz, CH₃CH₂CH₂), 1.23-1.44 (2H, m, CH₂CH₂CH₂), 1.58-1.70 (1H, m, CH₂CH₂CH₂), 1.76-1.88 (1H, m, CH₂CH₂CH₂), 3.29 and
3.37 (2H, B and A of ABX system, \( J_{AB} = 17.4 \, \text{Hz}, J_{AX} = 6.1 \, \text{Hz}, J_{AX} = 2.3 \, \text{Hz}, H-4 \)), 4.84 (1H, dd, \( J = 10.3, 6.4 \, \text{Hz}, \text{PhCHO} \)), 5.61 (1H, X of ABX system, dd, \( J = 6.1 \, \text{Hz}, J_{AX} = 2.3 \, \text{Hz}, H-5 \)), 7.30-7.43 (4H, m, aromatic), 7.87-7.94 (3H, m, aromatic), 8.23-8.46 (2H, m, aromatic);

\[ \delta_c (75 \, \text{MHz; CDCl}_3) 13.68 (\text{CH}_3), 18.69 (\text{CH}_3), 39.76 (\text{CH}_3), 40.82 (\text{CH}_3), 78.86 (\text{CH}), 100.87 (\text{CH}), 123.80 (\text{CH}), 124.11 (\text{CH}), 126.95 (\text{CH}), 127.44 (\text{CH}), 127.80 (\text{CH}), 128.41 (\text{CH}), 133.36 (\text{CH}), 135.23 (\text{C}), 140.97 (\text{C}), 148.34 (\text{C}), 155.42 (\text{C}); \]

\[ M/Z 192 ([\text{M}+\text{H}^+]^\text{+}-\text{OCH}_2\text{PrPh}, 81), 164 (30), 149 (20), 146 (13), 135 (89), 134 (100), 133 (23), 132 (10), 119 (18), 118 (100), 117 (22), 116 (25), 108 (59), 107 (23), 106 (66), 105 (49), 104 (52), 103 (51). \]

3-(2,2-Dimethylpropyl)-5-((S)-1-phenyl-1-butoxy)-2-isoxazoline (161)

In the same way, 2,2-dimethylpropionaldehyde oxime (459 mg, 4.55 mmol), N-chlorosuccinimide (668 mg, 5.0 mmol), pyridine (2 drops), (S)-1-phenyl-1-butyl vinyl ether (81) (800 mg, 4.55 mmol) and triethylamine (505 mg, 5.0 mmol) gave a single diastereoisomer of 3-(2,2-dimethylpropyl)-5-((S)-1-phenyl-1-butoxy)-2-isoxazoline (161) as a colourless oil (590 mg, 47%) after flash column chromatography (10:1 petroleum ether-ether).

\[ R_f 0.10 \ (10:1 \text{ petroleum ether-ether}); \]
\[ \alpha \text{L} = -197.4^\circ \text{ (C}=10, \text{CH}_2\text{Cl}) ; \]

\( \nu_{\text{max}} \text{ (film)} \) \ 3020s, 2940s, 2860s, 1550w, 1450s, 1415w, 1395w, 1360s, 1335m, 1255m, 1175s, 1120m, 1105s, 1070s, 1030m, 970m, 930s, 900w, 845s, 795s, 755s, 700s, 630w;

\( \delta \text{ (300 MHz; CDCl}_3 \) \ 0.88 (3H, t, J=7.3 Hz, \text{CH} \text{CH}_2 \text{CH}_3), 1.16-1.63 (12H, m, C(\text{CH})_3 \text{ and CH} \text{CH} \text{CH}), 1.71-1.88 (1H, m, CH \text{CH}_2 \text{CH}) \), \( J \approx 1.72 \text{ Hz}, J_\text{ax}=5.8 \text{ Hz}, J_\text{ax}=2.0 \text{ Hz, H-4}, 4.75 (1H, dd, J=7.8, 6.0 \text{ Hz, PhCHO}), 5.27 (1H, X of ABX system, dd, J=5.8 Hz, J_\text{ax}=2.0 \text{ Hz, H-5}), 7.21-7.36 (5H, m, aromatic);

\( \delta \text{ (75 MHz; CDCl}_3 \) \ 13.84 (\text{CH}), 18.87 (\text{CH}), 28.11 (\text{CH}), 32.98 (\text{C}), 40.02 (\text{CH}), 41.04 (\text{CH}), 77.62 (\text{CH}), 99.11 (\text{CH}), 127.03 (\text{CH}), 127.56 (\text{CH}), 128.33 (\text{CH}), 141.75 (\text{C}), 166.31 (\text{C});

\( M/Z \) \ 275 (M\text{+}, 3), 232 (17), 150 (22), 134 (35), 133 (100), 132 (83), 131 (16), 127 (12), 126 (83), 125 (16), 118 (13), 117 (100), 116 (13), 115 (32), 110 (56);

\( C_{\text{a}H_{\text{b}}\text{NO}_{\text{c}}} \text{ [M+]} \) \ requires 275.1885

\( \text{found} \) \ 275.1885.

5-(S)-1-Phenyl-1-butoxy-3-propyl-2-isoxazoline (162)

\[
\begin{align*}
\text{H} &\quad \text{Pr} \\
\text{Ph} &\quad \text{O} \\
& \quad \text{N} \\
& \quad \text{CH}_2\text{CH}_2\text{CH}_3
\end{align*}
\]

(162)

In the same way, butyraldehyde oxime (247 mg, 2.84 mmol), N-chlorosuccinimide

161
(417 mg, 3.13 mmol), pyridine (2 drops), (S)-1-phenyl-1-butyl vinyl ether (81) (500 mg, 2.84 mmol) and triethylamine (316 mg, 3.13 mmol) gave a single diastereoisomer of 5-((S)-1-phenyl-1-butoxy-1-propyl-2-isoxazoline (162) as a colourless oil (289 mg, 39%) after flash column chromatography (5:1 petroleum ether-ether).

$R_f$ 0.33 (2:1 petroleum ether-ether);

$[\alpha]_D = -210.4^\circ$ (C=5, CH$_2$Cl$_2$);

$\nu_{\text{max}}$ (film) 3065w, 3045w, 2960s, 2925s, 2880s, 1485w, 1455s, 1415m, 1375m, 1355m, 1290m, 1265w, 1175s, 1065s, 1020m, 965s, 940m, 890s, 870s, 825s, 780m, 765s, 700s, 620w;

δ$_c$ (300 MHz; CDCl$_3$) 0.85 (3H, t, $J$=7.4 Hz, CH$_3$CH$_2$CPh), 0.94 (3H, t, $J$=7.4 Hz, N=CCH$_3$CH$_2$CPh), 1.17-1.38 (2H, m, CH$_3$CH$_2$CPh), 1.49-1.65 (3H, m, NCCCH$_3$CH$_2$CPh and CH$_3$CH$_2$CPh), 1.69-1.80 (1H, m, CH$_3$CH$_2$CPh), 2.30-2.37 (2H, m, N=CCH$_3$CH$_2$CPh), 2.70 and 2.84 (2H, B and A of ABX system, $J_{\alpha\beta}$=17.4 Hz, $J_{\alpha\gamma}$=6.2 Hz, $J_{\beta\gamma}$=1.5 Hz, H-4), 4.73 (1H, dd, $J$=7.8, 5.9 Hz, PhCHO), 5.24 (1H, X of ABX system, dd, $J_{\alpha\beta}$=6.2 Hz, $J_{\alpha\gamma}$=1.5 Hz, H-5), 7.20-7.33 (5H, m, aromatic);

δ$_c$ (75 MHz; CDCl$_3$) 13.43 (CH$_3$), 13.66 (CH$_3$), 18.71 (CH$_3$), 19.67 (CH$_3$), 29.25 (CH$_3$), 39.90 (CH$_3$), 43.33 (CH$_3$), 77.68 (CH), 98.77 (CH), 126.87 (CH), 127.46 (CH), 128.22 (CH), 141.44 (C), 159.10 (C);

M/Z 262 ([MH]+, 100), 242 (13), 188 (6), 150 (13), 130 (27), 112 (20), 91 (14), 86 (25), 74 (13), 58 (10), 44 (13);

C$_9$H$_{16}$NO$_3$ [MH]$^+$ requires 262.1807

found 262.1810.
3-Ethyl-5-[(S)-1-phenyl-1-butoxyl]-2-isoxazoline (163)

In the same way, propionaldehyde oxime (207 mg, 2.84 mmol), N-chlorosuccinimide (417 mg, 3.13 mmol), pyridine (2 drops), (S)-1-phenyl-1-butoxyl vinyl ether (81) (500 mg, 2.84 mmol) and triethylamine (316 mg, 3.13 mmol) gave a single diastereoisomer of 3-ethyl-5-[(S)-1-phenyl-1-butoxyl]-2-isoxazoline (163) as a colourless oil (246 mg, 35%) after flash column chromatography (5:1 petroleum ether-ether).

R<sub>f</sub> 0.26 (2:1 petroleum ether-ether);
[α]<sub>β</sub> = -265.4° (C=10, CH<sub>2</sub>C)<sub>2</sub>;
ν<sub>max</sub> (film) 3080w, 3050w, 2955s, 2860s, 1605m, 1595w, 1460s, 1425m, 1370m, 1350m, 1300m, 1175s, 1090s, 1015m, 975m, 935s, 845s, 760s, 705s, 640w;
δ<sub>h</sub> (300 MHz; CDCl<sub>3</sub>) 0.88 (3H, t, J=7.3 Hz, CH<sub>3</sub>CHCH)<sub>2</sub>, 1.07-1.42 (5H, m, CH<sub>2</sub>CHCH<sub>2</sub> and CH<sub>2</sub>CHCH<sub>2</sub>), 1.53-1.64 (1H, m, CH<sub>2</sub>CHCH<sub>2</sub>), 1.72-1.84 (1H, m, CH<sub>2</sub>CHCH<sub>2</sub>);

δ<sub>c</sub> (75 MHz; CDCl<sub>3</sub>) 10.90 (CH<sub>3</sub>), 13.84 (CH<sub>3</sub>), 18.86 (CH<sub>3</sub>), 21.23 (CH<sub>3</sub>), 40.03 (CH<sub>3</sub>), 43.46 (CH<sub>3</sub>), 78.42 (CH<sub>3</sub>), 99.08 (CH<sub>3</sub>), 127.04 (CH<sub>3</sub>), 127.63 (CH<sub>3</sub>), 128.37 (CH<sub>3</sub>),
141.67 (C), 160.35 (C);

\[ M/Z \ 248 \ (\text{MH}^+ \text{, 100}), \ 228 \ (10), \ 205 \ (4), \ 150 \ (6), \ 133 \ (10), \ 116 \ (17), \ 108 \ (8), \ 98 \ (14), \ 91 \ (15), \ 72 \ (8); \]

\[ \text{C}_{10}\text{H}_{13}\text{NO}, \text{[MH]}^+ \text{ requires 248.1651}; \]

\[ \text{found 248.1650.} \]

3-Methyl-5-((S)-1-phenyl-1-butoxy)-2-isoxazoline (164)

In the same way, acetaldehyde oxime (335 mg, 5.68 mmol), N-chlorosuccinimide (834 mg, 6.25 mmol), pyridine (2 drops), (S)-1-phenyl-1-butyl vinyl ether (81) (1.0 g, 5.68 mmol) and triethylamine (631 mg, 6.25 mmol) gave a single diastereoisomer of 3-methyl-5-((S)-1-phenyl-1-butoxy)-2-isoxazoline (164) as a colourless oil (696 mg, 53%) after flash column chromatography (3:1 petroleum ether-ether).

Rf 0.12 (3:1 petroleum ether-ether);

\[ [\alpha]_D = -241.3^\circ \text{ (C=10, CHCl}_3); \]

\[ \nu_{\max} \text{ (film) 3020w, 2920s, 2860s, 1415m, 1380m, 1325s, 1305m, 1170s, 1025s, 970m, 920s, 865s, 840s, 755s, 700s, 645w, 625m;} \]

\[ \delta_{\text{H}} \text{ (300 MHz; CDCl}_3) \text{ 0.87 (3H, t, J=7.3 Hz, CH}_3\text{CH}_2\text{CH}_3), \text{ 1.15-1.41 (2H, m, CH}_2\text{CH}_2\text{CH}_3), \text{ 1.52-1.64 (1H, m, CH}_2\text{CH}_2\text{CH}_3), \text{ 1.72-1.84 (1H, m, CH}_2\text{CH}_2\text{CH}_3), \text{ 2.02 (3H, s, CH}_3\text{CN), 2.72 (1H, d, J=17.6 Hz, H-4), 2.89 (1H, ddd, J=17.6, 6.4, 1.1 Hz, H-} \]
4.75 (1H, dd, J=7.5, 6.2 Hz, PhCHO), 5.28 (1H, dd, J=6.4, 1.4 Hz, H-5), 7.23-7.36 (5H, m, aromatic);

δc (75 MHz; CDCl₃) 13.03 (CH₃), 13.82 (CH₃), 18.83 (CH₃), 40.00 (CH₃), 45.05 (CH₃), 78.09 (CH), 99.32 (CH), 127.02 (CH), 127.64 (CH), 128.38 (CH), 141.58 (C), 155.70 (O);

M/Z 234 (M⁺, 4), 190 (15), 150 (11), 134 (13), 133 (100), 132 (47), 131 (11), 117 (87), 107 (69), 105 (17);

C₆H₇NO₂ [M⁺] requires 233.1416
found 233.1420.

(S)-1-(2-Naphthyl)ethyl-1-(2-propenoate) (177)

A solution of (S)-1-(2-naphthyl)ethan-1-ol (1.0 g, 5.81 mmol) in THF (8 ml) was stirred, under nitrogen, at 0°C and n-butyllithium (3.82 ml, 6.10 mmol) added dropwise. After 1h, acryloyl chloride (579 mg, 6.40 mmol) was added dropwise and the reaction mixture stirred for 30 min. Quenching with saturated aqueous sodium hydrogen carbonate solution followed by standard aqueous work-up yielded (S)-1-(2-naphthyl)ethyl-1-(2-propenoate) (177) as a waxy white solid (1.23 g, 94%) after flash column chromatography (10:1 petroleum ether-ether).
$\beta$ 0.17 (10:1 petroleum ether-ether);

$[\alpha]_D$ -92.5° (C=20, CH₂Cl₂);

$\nu_{\text{max}} (\text{CHCl}_3)$ 3050 w, 3020 w, 2980 s, 2920 m, 2860 w, 1715 s (C=O), 1630 m, 1615 m, 1600 m, 1505 m, 1445 m, 1400 s, 1370 m, 1320 s, 1265 s, 1250 m, 1105 m, 1060 s, 1040 s, 1015 s, 980 s, 965 m, 920 m, 890 m, 855 s, 815 s, 805 s, 745 s, 720 w, 660 m, 615 m;

$\delta$ (300 MHz; CDCl₃) 1.63 (3H, d, $J=6.6$ Hz, CH₃), 5.75 (1H, dd, $J=10.3, 1.5$ Hz, OCCH=CH₂), 6.12 (1H, q, $J=6.6$ Hz, NaphCHO), 6.15 (1H, dd, $J=17.3, 10.3$ Hz, OCCH=CH₂), 6.42 (1H, dd, $J=17.3$ Hz, 1.5 Hz, OCCH=CH₂), 7.37-7.47 (3H, m, aromatic), 7.73-7.79 (4H, m, aromatic);

$\delta$ (75 MHz; CDCl₃) 22.12 (CH₂), 72.50 (CH), 123.95 (CH), 124.92 (CH), 125.97 (CH), 126.03 (CH), 126.06 (CH), 126.12 (CH), 127.56 (CH), 127.93 (CH), 128.29 (CH), 128.62 (CH), 130.69 (CH₂), 132.94 (C), 133.08 (C), 138.81 (C), 165.29 (C).

M/Z 226 (M⁺, 100), 181 (4), 172 (41), 155 (100), 141 (3), 127 (17), 115 (7), 102 (3), 89 (1), 77 (3), 63 (3), 55 (42), 30 (2), 43 (15);

C₆H₄O₂ [M⁺] requires 226.0994
found 226.0994.
Following the same procedure as for the preparation of compound (141), benzaldehyde oxime (268 mg, 2.21 mmol), N-chlorosuccinimide (325 mg, 2.43 mmol), pyridine (2 drops), (S)-1-(2-naphthyl)ethyl-1-(2-propenoate) (177) (500 mg, 2.21 mmol) and triethylamine (245 mg, 2.43 mmol) gave (5RS)-5-[(S)-1-(2-naphthyl)-1-ethoxycarbonyl]-3-phenyl-2-isoxazoline (179) as an approximate 1:1 mixture of diastereoisomers and a white solid (511 mg, 67%) after flash column chromatography (10:1 petroleum ether-ether). The product was recrystallised from methanol as a white solid, m.p 112-114°C.

Rf 0.36 (1:1 petroleum ether-ether);

\([\alpha]_D = +21.0^\circ \) (C=1, CH₂Cl₂);

C₀H₉NO₂ requires  C 76.50%, H 5.54%, N 4.06%,

found  C 76.54%, H 5.70%, N 4.01%.

\(u_{\text{exc}}\) (CH₂Cl₂) 3030w, 2970w, 2920w, 1730s (C=O), 1600w, 1495w, 1440w, 1350s,
1325m, 1305m, 1200s, 1170s, 1125m, 1060s, 1000s, 950w, 915w, 880s, 855s, 815s,
665w;

\(\delta_h\) (300 MHz; CDCl₃) 1.61 (3H, d, J=6.6 Hz, CH₃), 3.33-3.54 (2H, m, H-4), 5.05-
5.15 (1H, m, H-5), 6.08 (1H, q, J=6.6 Hz, NaphCH₂), 7.23-7.78 (12H, m, aromatic);
\( \delta_c \) (75 MHz; CDCl\(_3\)) 21.94 (CH\(_3\)), 22.05 (CH\(_4\)), 38.49 (CH\(_3\)), 38.72 (CH\(_2\)), 73.91 (CH), 74.10 (CH), 78.11 (CH), 78.14 (CH), 123.65 (CH), 123.82 (CH), 124.79 (CH), 125.19 (CH), 126.04 (CH), 126.15 (CH), 126.24 (CH), 126.75 (CH), 127.52 (CH), 127.56 (CH), 127.94 (CH), 128.27 (CH), 128.43 (CH), 130.26 (CH), 132.91 (C), 138.04 (C), 138.12 (C), 155.86 (C), 169.21 (C), 169.30 (C);

M/Z 345 (M', 8), 155 (100), 118 (6), 103 (1), 91 (1), 77 (6), 51 (2).

(S)-1-Phenylbutyl-1-(2-propenoate) (178)

\[
\begin{align*}
\text{Ph} & \quad \text{O} \\
\text{Pr} & \quad \text{O} \\
\text{H} & \quad \text{O}
\end{align*}
\]

Following the same procedure as for the preparation of compound (177), (S)-(S)-1-phenylbutyl-1-ol (1.0 g, 6.67 mmol), n-butyllithium (4.16 ml, 7.0 mmol) and acryloyl chloride (664 mg, 7.33 mmol) gave (S)-1-phenylbutyl-1-(2-propenoate) (178) as a colourless liquid (754 mg, 55%) after flash column chromatography (10:1 petroleum ether-ether).

R\(_f\) 0.17 (10:1 petroleum ether-ether);

\([\alpha]_D = -106.8^\circ \quad (C=5, \text{CH}_2\text{Cl}_2)\); 

\(v_{\text{max}} \) (film) 3065w, 3030m, 2960s, 2870m, 1725s (C=O), 1635m, 1620m, 1495w, 1455m, 1405s, 1380w, 1270s, 1190s,1105m, 1045s, 985m, 965m, 915w, 845w, 810m, 760s, 700s, 670w;

\(\delta_c \) (300 MHz; CDCl\(_3\)) 0.91 (3H, t, J=7.3 Hz, CH\(_3\)), 1.23-1.42 (2H, m, CH\(_2\)CH\(_3\)), 1.72-1.84 (1H, m, CH\(_2\)CH\(_3\)), 1.88-1.99 (1H, m, CH\(_2\)CH\(_3\)), 5.78 (1H, dd, J=10.3,
1.5 Hz, OCCH=CH), 5.81 (1H, dd, J=7.7, 1.5 Hz, PhCHO), 6.13 (1H, dd, J=17.3 Hz, J=10.3 Hz, OCCH=CH), 6.40 (1H, dd, J=17.3, 1.5 Hz, OCCH=CH), 7.22-7.94 (5H, m, aromatic);

δ (75 MHz; CDCl₃) 13.80 (CH₃), 18.78 (CH₃), 38.48 (CH₃), 76.01 (CH), 126.43 (CH), 127.78 (CH), 128.35 (CH), 128.70 (CH), 130.57 (CH₂), 140.72 (C), 165.42 (C).

M/Z 204 (M⁺, 7), 161 (18), 149 (7), 133 (100), 117 (35), 105 (10), 91 (38), 77 (10), 71 (15), 55 (65);

C₁₈H₂₉O₂ [M⁺] requires 204.1150
found 204.1150.

(5RS)-3-Phenyl-5-[1-phenyl-1-butoxycarbonyl]-2-isoxazoline (180)

Following the same procedure as for the preparation of compound (179), benzaldehyde oxime (297 mg, 2.45 mmol), N-chlorosuccinimide (360 mg, 2.70 mmol), pyridine (2 drops), (S)-1-phenylbutyl-1-(2-propenoate) (178) (500 mg, 2.45 mmol) and triethylamine (273 mg, 2.70 mmol) gave (5RS)-3-phenyl-5-[1-phenyl-1-butoxycarbonyl]-2-isoxazoline (180) (271 mg, 34%) as an oily approximate 1:1 mixture of diastereoisomers after flash column chromatography (3:1 petroleum ether-ether).

Rₛ 0.15 (3:1 petroleum ether-ether);
\[ \alpha_l = -33.9^\circ \] (C=10, CH<sub>3</sub>Cl);

\[ \nu_{max} \] (film) 3060w, 3030m, 2960s, 2870m, 1735s (C=O), 1600w, 1495w, 1450m,
1355s, 1275w, 1210s, 1105w, 1075w, 1055w, 1005m, 940m, 890s, 760s;

\[ \delta \] (300 MHz; CDCl<sub>3</sub>) 0.90 (1.5H, t, J=7.3 Hz, CH<sub>3</sub>), 0.92 (1.5H, t, J=7.4 Hz, CH<sub>3</sub>),
1.22-1.45 (2H, m, CH<sub>2</sub>), 1.72-2.02 (2H, m, CH<sub>2</sub>CH<sub>2</sub>), 3.52-3.65 (2H, m, H-4),
5.11-5.19 (1H, m, H-5), 5.81 (1H, dd, J=7.8, 6.2 Hz, PhCHO), 7.14-7.43 (8H, m, aromatic), 7.62-7.67 (2H, m, aromatic);

\[ \delta \] (75 MHz; CDCl<sub>3</sub>) 13.66 (CH<sub>3</sub>), 18.68 (CH<sub>2</sub>), 38.17 (CH<sub>3</sub>), 32.28 (CH<sub>2</sub>), 38.58
(CH<sub>2</sub>), 38.79 (CH<sub>3</sub>), 77.51 (CH), 77.60 (CH), 78.16 (CH), 126.22 (CH), 126.47 (CH),
126.78 (CH), 127.92 (CH), 128.05 (CH), 128.41 (CH), 128.64 (CH), 139.89 (C),
155.83 (C), 169.27 (C);

M/Z 324 ([MH]+, 100), 248 (8), 209 (8), 192 (32), 174 (6), 146 (26), 133 (17), 108
(14), 91 (26);

C<sub>9</sub>H<sub>13</sub>NO, [MH]+ requires 324.1600
found 324.1600.
Following the same procedure as for the preparation of compound (141), benzaldehyde oxime (545 mg, 4.50 mmol), N-chlorosuccinimide (661 mg, 4.95 mmol), pyridine (2 drops), 1-ethenyl-2-pyrrolidinone (500 mg, 4.50 mmol) and triethylamine (500 mg, 4.95 mmol) gave (5RS)-3-phenyl-5-[1-(2-pyrrolidinyl)]-2-isoxazoline (182) as a white solid (522 mg, 50%) m.p 133-135°C after flash column chromatography (4:1 petroleum ether-ether) and recrystallisation (methanol).

\[
\text{R, } 0.10 \text{ (4:1 petroleum ether-ether);}
\]

\[\text{C}_{15}\text{H}_{13}\text{N}_{2}\text{O} \text{ requires } C 67.81\%, \text{ H } 6.13\%, \text{ N } 12.17\%,
\]

\[\text{found } C 68.08\%, \text{ H } 6.18\%, \text{ N } 12.26\%.
\]

\[\nu_{\text{max}} \text{ (CHCl}_3\text{) 3010w, 2950w, 2880w, 1690s (C=O), 1485m, 1460m, 1405s, 1355s, 1310m, 1260m, 1215m, 1075w, 1020w, 990w, 950w, 885s, 830s, 800m, 670m, 625w;}
\]

\[\delta_\text{H} \text{ (300 MHz; CDCl}_3\text{) 1.91-2.10 (2H, m, H-4'), 2.39 (2H, t, J=8.3 Hz, H-3'), 3.13-3.36 (3H, m, 2H-5' and H-4), 3.54 (1H, dd, J=17.7, 9.9 Hz, H-4), 6.63 (1H, dd, J=9.9, 3.5 Hz, H-5), 7.38-7.47 (3H, m, aromatic), 7.65-7.71 (2H, m, aromatic);}
\]

\[\delta_\text{C} \text{ (75 MHz; CDCl}_3\text{) 17.69 (CH), 31.00 (CH), 37.03 (CH), 41.50 (CH), 81.93 (CH), 126.68 (CH), 128.60 (C), 128.82 (CH), 130.48 (CH), 155.43 (C), 175.28 (C);}
\]

\[M/Z 230 (M^+, 19), 213 (11), 172 (35), 147 (15), 146 (76), 145 (83), 144 (40), 117
\]
Methyl (S)-2-pyrrolidinone-5-carboxylate

A solution of (S)-2-pyrrolidinone-5-carboxylic acid (5.5 g, 42.6 mmol) and concentrated sulphuric acid (0.5 ml) in methanol (100 ml) was heated under reflux for 1h. The solvent was removed under reduced pressure to give methyl (S)-2-pyrrolidinone-5-carboxylate as a white solid (5.91 g, 97%) after flash column chromatography (4:1 chloroform-methanol). The structure of the product was confirmed by ¹H n.m.r.

(S)-5-Hydroxymethyl-2-pyrrolidinone

A solution of methyl (S)-2-pyrrolidinone-5-carboxylate (5.91 g, 41.3 mmol) in methanol (100 ml) was stirred at room temperature and sodium borohydride (1.57 g, 41.3 mmol) added slowly. After addition was complete, the solvent was removed under reduced pressure to give (S)-5-hydroxymethyl-2-pyrrolidinone as a white solid (4.65 g, 98%) after flash column chromatography (5:1 chloroform-methanol). The structure of the product was confirmed by ¹H n.m.r.

(S)-5-[(Triphenylmethoxy)methyl]-2-pyrrolidinone (183)

A solution of (S)-5-hydroxymethyl-2-pyrrolidinone (4.1 g, 35.7 mmol), triphenylmethyl chloride, 4-dimethylaminopyridine (436 mg, 3.6 mmol) and triethylamine (10 ml) in dichloromethane (100 ml) was stirred at room temperature for
16h. Standard aqueous work-up yielded (S)-5-[(triphenylmethoxy)methyl]-2-pyrrolidinone (183) as a white solid (7.80 g, 61%) m.p 163-165°C (lit. m.p 165.5-166°C) after flash column chromatography (1:1 ethyl acetate-petroleum ether) and crystallisation from dichloromethane by dropwise addition of petroleum ether.

δₙ (300 MHz; CDCl₃) 1.51-1.63 (1H, m, H-4), 1.91-2.03 (1H, m, H-4), 2.18-2.30 (2H, m, H-3), 3.11 and 3.01 (2H, B and A of ABX system, J_B=9.1 Hz, J_AB=7.4 Hz, J_AB'=4.4 Hz, OCH₃), 3.71-3.79 (1H, m, H-5), 7.11-7.43 (16H, m, aromatic and NH);

δ_c (75 MHz; CDCl₃) 23.23 (CH₂), 29.77 (CH₂), 54.01 (CH), 66.77 (CH₃), 86.58 (C), 126.93 (CH), 127.70 (CH), 128.46 (CH), 143.56 (C), 178.42 (C).

(S)-1-Ethenvl-5-r(triphenvlmethoxv)methyll-2-pvrrolidinone (187)

O

\[ \text{O} \]

\[ \text{OCPB₃} \]

(187)

To a stirred solution of (S)-5-[(triphenylmethoxy)methyl]-2-pyrrolidinone (183) (7.90g, 18.8 mmol) in vinyl acetate (80 ml) was added sodium tetrachloropalladate (50 mg) and the mixture was heated under reflux for 18h, with the exclusion of moisture. After cooling to room temperature, activated charcoal (200 mg) was added and the mixture was shaken for 10 min, filtered and the solvent removed under reduced pressure. The same quantities of catalyst and vinyl acetate were then added again and the procedure repeated. (S)-1-Ethenvl-5-[(triphenylmethoxv)methyl]-2-pvrrolidinone (187) was obtained as colourless crystals (1.48 g, 17%) m.p 181-184°C after flash
column chromatography (1:1 petroleum ether–ether) and recrystallisation (methanol).

R<sub>f</sub> 0.26 (1:1 petroleum ether–ether);

[α]<sub>D</sub> = -327.5° (C=0.4, CH<sub>2</sub>Cl<sub>2</sub>);

C<sub>8</sub>H<sub>6</sub>NO<sub>2</sub> requires C 81.43%, H 6.57%, N 3.65%,

found C 81.07%, H 6.60%, N 3.57%.

ν<sub>max</sub> (CH<sub>2</sub>Cl<sub>2</sub>) 3020w, 1685w, 1630s (C=O), 1485w, 1435w, 1380m, 1210s,
1150w, 1080m, 1030m, 1000w, 975w, 910s, 855w, 740m, 665m, 645m, 630m;

δ<sub>α</sub> (300 MHz; CDCl<sub>3</sub>) 1.94-2.12 (2H, m, H-4), 2.33 (1H, ddd, J=17.3, 9.2, 2.4 Hz,
H-3), 2.71 (1H, dt, J=17.3, 10.2 Hz, H-3), 3.09 and 3.48 (2H, B and A of ABX
system, J<sub>AB</sub>=9.7 Hz, J<sub>AB</sub>=4.8 Hz, J<sub>AB</sub>=2.7 Hz, OCH<sub>3</sub>), 3.96-4.00 (1H, m, H-5), 4.23 (1H,
d, J=16.4 Hz, NCH=CH<sub>2</sub>), 4.35 (1H, d, J=9.1 Hz, NCH=CH<sub>2</sub>), 7.00 (1H, dd,
J<sub>trans</sub>=16.4 Hz, J<sub>cis</sub>=9.1 Hz, NCH=CH<sub>2</sub>), 7.17-7.40 (15H, m, aromatic);

δ<sub>α</sub> (75 MHz; CDCl<sub>3</sub>) 22.11 (CH<sub>3</sub>), 30.68 (CH<sub>2</sub>), 55.85 (CH), 61.67 (CH<sub>2</sub>), 86.87 (C),
94.40 (CH<sub>2</sub>), 127.02 (CH), 127.80 (CH), 128.10 (CH), 128.44 (CH), 143.55 (C),
173.77 (C);

M/Z 384 ([M]+, 34), 243 (100), 165 (3), 142 (12), 110 (9), 44 (2);

C<sub>8</sub>H<sub>6</sub>NO<sub>2</sub> [MH]+ requires 384.1964

found 384.1964.
3-Phenyl-5-((S))-5-((triphenylmethoxy)methyl)-2-pyrrolidinonyl-2-isoxazoline (188)

Following the same procedure as for the preparation of compound (141), benzaldehyde oxime (95 mg, 0.78 mmol), N-chlorosuccinimide (115 mg, 0.86 mmol), pyridine (2 drops), (S)-1-ethenyl-5-((triphenylmethoxy)methyl)-2-pyrrolidinone (187) (300 mg, 0.78 mmol) and triethylamine (87 mg, 0.86 mmol) gave a single diastereoisomer of 3-phenyl-5-((S))-5-((triphenylmethoxy)methyl)-2-pyrrolidinonyl-2-isoxazoline (188) as a white solid after flash column chromatography (2:1 ether-petroleum ether). Recrystallisation (methanol) gave colourless crystals (108 mg, 27%) m.p 191-194°C.

Rf 0.16 (2:1 petroleum ether-ether);

$[\alpha]_D = +29.5\,^\circ$ (C=10, CHCl$_3$);

C$_8$H$_8$N$_2$O$_2$ requires C 78.86%, H 6.02%, N 5.58%,

found C 78.87%, H 6.08%, N 5.61%.

$n$ (300 MHz; CDCl$_3$) 1.82-1.89 (1H, m, H-4'), 2.06-2.40 (2H, m, H-3' and H-4'), 2.57 (0.5H, t, J=9.7 Hz, H-3'), 2.62 (0.5H, t, J=6.8 Hz, H-3'), 3.00-3.09 (2H, m, H-4

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and CHOCPH₃, 3.20 (1H, dd, J=9.9, 3.2 Hz, H-4), 3.40 (1H, dd, J=17.7, 10.4 Hz, CHOCPH₃), 3.87-3.92 (1H, m, H-5'), 6.49 (1H, dd, J=10.4, 3.9 Hz, H-5), 7.06-7.67 (20H, m, aromatic); δ, (75 MHz; CDCl₃) 23.36 (CH₃), 30.69 (CH₂), 39.07 (CH₂), 55.82 (CH), 64.79 (CH₂), 83.60 (CH), 86.92 (C), 126.74 (CH), 127.16 (CH), 127.80 (CH), 127.92 (CH), 128.49 (CH), 128.68 (CH), 130.28 (CH), 143.27 (C), 156.19 (C), 176.55 (C); M/Z 243 (CPh₃, 100), 193 (3), 161 (4), 148 (24), 133 (11), 116 (63), 101 (3), 80 (13), 58 (4), 44 (17).

(S)-1-(2-Propenoyl)-5-(triphenylmethoxy)methyl-2-pyrrolidinone (189)

Following the same procedure as for the preparation of compound (177), reaction of (S)-5-[(triphenylmethoxy)methyl]-2-pyrrolidinone (183) (5.0 g, 14.0 mmol), n-butyllithium (9.19 ml, 14.7 mmol) and acryloyl chloride (1.39 g, 15.4 mmol) at -78°C gave (S)-1-(2-propenoyl)-5-[(triphenylmethoxy)methyl]-2-pyrrolidinone (189) as a white solid (3.90 g, 68%) m.p 137.5-139°C after flash column chromatography (4:1 petroleum ether-ether) and recrystallisation (methanol).

Rₜ 0.07 (4:1 petroleum ether-ether);

[α]₀ = -107.2° (C=10, CH₃Cl);
C_{9}H_{12}NO, requires C 78.81%, H 6.12%, N 3.40%.
found C 79.19%, H 6.22%, N 3.45%.

\textit{\textbf{\nu}_{\text{max}} (CHCl_{3}) 3020w, 1725s (C=O), 1670s, 1615w, 1445w, 1400m, 1460m, 1435m, 1410m, 1220s, 1195s, 1150w, 1085m, 1070m, 1050w, 1030m, 1000w, 980w, 970w, 810w, 795w, 730w, 630m;}

\begin{align*}
\delta_{\text{H}} (300 \text{ MHz; CDCl}_{3}) & 1.91-2.12 (2H, m, H-4), 2.47 (1H, ddd, J=20.0, 9.5, 2.2 Hz, H-3), 2.96-3.06 (1H, m, H-3), 3.14 and 3.59 (2H, B and A of ABX system, J_{\alpha}=9.8 Hz, J_{\beta}=3.8 Hz, J_{\gamma}=2.6 Hz, \text{CH}OCH_{3}), 4.48-4.51 (1H, m, H-5), 5.83 (1H, dd, J=10.4, 2.0 Hz, OCCH=CH_{2}), 6.45 (1H, dd, J=17.0, 2.0 Hz, OCCH=CH_{2}), 7.08-7.46 (15H, m, aromatic), 7.54 (1H, dd, J_{\text{trans}}=17.0 Hz, J_{\text{cis}}=10.4 Hz, OCCH=CH_{2}); \\
\delta_{\text{C}} (75 \text{ MHz; CDCl}_{3}) & 21.09 (\text{CH}_3), 33.16 (\text{CH}_2), 56.67 (\text{CH}), 63.95 (\text{CH}_2), 86.97 (C), 127.05 (CH), 127.81 (CH), 128.43 (CH), 129.48 (CH), 130.55 (CH), 143.54 (C), 165.52 (C), 176.34 (C).
\end{align*}

M/Z 412 ([M+H]^+, 1), 243 (100), 170 (34), 152 (3), 116 (10), 98 (6), 84 (8), 55 (7), 44 (1).
(5R)- and (5S)-3-Phenyl-5-(S)-5-(triphenylmethoxy)methyl-2-pyrrolidinonyl-1-carbonyl-2-isoxazoline (190a) and (190b)

Following the same procedure as for the preparation of compound (141), benzaldehyde oxime (589 mg, 4.87 mmol), N-chlorosuccinimide (715 mg, 5.35 mmol), pyridine (2 drops), (S)-1-(2-propenoyl)-5-[(triphenylmethoxy)methyl]-2-pyrrolidinone (189) (2.0 g, 4.87 mmol) and triethylamine (541 mg, 5.35 mmol) gave (5R)-3-phenyl-5-(S)-5-(triphenylmethoxy)methyl-2-pyrrolidinonyl-1-carbonyl-2-isoxazoline (190a) (566 mg, 22%) m.p 150-152°C and (5S)-3-phenyl-5-(S)-5-(triphenylmethoxy)methyl-2-pyrrolidinonyl-1-carbonyl-2-isoxazoline (190b) (1.26 g, 49%) m.p 58-61°C after flash column chromatography (1:1 petroleum ether-ether) and recrystallisation (methanol).

(190a)

\[ R_f 0.09 \]

\[ [\alpha]_D = -53.6^\circ \text{ (C}=10, \text{CH}_2\text{Cl}_2); \]

\[ C_{26}H_{28}N_2O_4 \text{ requires} \quad \text{C} 76.96\%, \text{H} 5.70\%, \text{N} 5.28\%, \]

\[ \text{found} \quad \text{C} 76.65\%, \text{H} 5.69\%, \text{N} 5.37\%. \]

\[ \nu_{max} \text{ (CH}_2\text{Cl}_2) 3490\text{w}, 3200\text{w}, 3050\text{w}, 2940\text{w}, 1770\text{s} \text{ (C=O)}, 1715\text{s} \text{ (C=O)}, 1445\text{w}, 1430\text{w}, 1345s, 1270m, 1230m, 1175s, 1160s, 1085w, 1025w, 1015w, 1000w, 915w, \]
δ₀ (300 MHz; CDCl₃) 1.99-2.19 (2H, m, H-4'), 2.49 (1H, ddd, J=17.8, 9.2, 2.0 Hz, H-3'), 2.94-3.07 (1H, m, H-3'), 3.25 and 3.59 (2H, B and A of ABX system, Jₓₓ=10.0 Hz, Jₓₓ=3.8 Hz, Jₓₓ=2.6 Hz, CH₂OCPh), 3.40 and 3.81 (2H, B and A of ABX system, Jₓₓ=17.2 Hz, Jₓₓ=11.8 Hz, Jₓₓ=6.5 Hz, H-4), 4.41-4.44 (1H, m, H-5'), 6.03 (1H, X of H-4 ABX system, dd, Jₓₓ=11.8 Hz, Jₓₓ=6.5 Hz), 7.05-7.66 (20H, m, aromatic);

δ₁ (75 MHz; CDCl₃) 21.56 (CH₃), 32.84 (CH₃), 39.43 (CH₃), 56.73 (CH), 63.34 (CH₂), 79.40 (CH), 87.14 (C), 126.76 (CH), 127.17 (CH), 127.93 (CH), 128.41 (CH), 128.60 (CH), 130.17 (CH), 143.44 (C), 155.33 (C), 169.73 (C), 176.52 (C);

M/Z 280 (28), 245 (11), 244 (11), 183 (11), 167 (18), 165 (15), 149 (100), 121 (11), 113 (25), 105 (46), 104 (16), 103 (30).

(190b)

Rₐ 0.05 (1:1 petroleum ether-ether);

[α]₀ = -29.0° (C=10, CH₂Cl₂);

δ₀ (300 MHz; CDCl₃) 1.97-2.05 (1H, m, H-4'), 2.15-2.29 (1H, m, H-4'), 2.54-2.70 (1H, m, H-3'), 2.96-3.09 (1H, m, H-3'), 3.19 (1H, brd, J=8.3 Hz, H-4), 3.42-3.54 (2H, m, CH₂OCPh), 3.80 (1H, dd, J=17.3, 5.9 Hz, H-4), 4.45 (1H, brd, J=8.5 Hz, H-5'), 6.07 (1H, dd, J=11.7, 5.9 Hz, H-5), 7.18-7.54 (20H, m, aromatic);

δ₁ (75 MHz; CDCl₃) 22.06 (CH₃), 32.76 (CH₃), 39.21 (CH₃), 56.69 (CH), 63.61 (CH₂), 79.14 (CH), 86.95 (C), 126.77 (CH), 127.16 (CH), 127.87 (CH), 128.30 (CH), 128.61 (CH), 130.17 (CH), 143.37 (C), 155.49 (C), 169.49 (C), 176.64 (C).
A solution of (5R)-3-phenyl-5-[(S)-5-(triphenylmethoxy)methyl-2-pyrrolidinonyl]-1-carbonyl]-2-isoxazoline (190a) (307 mg, 0.58 mmol) in THF (5 ml) was stirred, under nitrogen, at room temperature. L-Selectride (2.32 ml, 2.32 mmol) was added dropwise and the reaction stirred for 18h. Standard aqueous work-up yielded (5R)-3-phenyl-2-isoxazoline-5-methanol (191a) as a colourless oil (74 mg, 72%) after flash column chromatography (2:1 petroleum ether). The 90 MHz 'H n.m.r. spectrum of the product was consistent with the literature data.

\[ [\alpha]_D = -154.3^\circ \text{ (C=1, CHCl}_3 \text{) (lit. } [\alpha]_D = -169.5^\circ). \]

(5S)-3-Phenyl-2-isoxazoline-5-methanol (191b)

In the same way, (5S)-3-phenyl-5-[(S)-5-(triphenylmethoxy)methyl-2-pyrrolidinonyl]-1-carbonyl]-2-isoxazoline (190b) (330 mg, 0.62 mmol) and L-Selectride (2.49 ml, 2.49 mmol) gave (5S)-3-phenyl-2-isoxazoline-5-methanol (191b) as a colourless oil (86 mg, 78%). The 90 MHz 'H n.m.r. spectrum of the product was consistent with the literature data.

\[ [\alpha]_D = +156.1^\circ \text{ (C=1, CHCl}_3 \text{) (lit. } [\alpha]_D = +169.5^\circ). \]
(5R)- and (5S)-3-(2,2-Dimethylpropyl)-5-(S)-5-(triphenylmethoxy)methyl-2-pyrrolidinyl-1-carbonyl-2-isoxazoline (192a) and (192b)

Following the same procedure as for the preparation of compounds (190a) and (190b), 2,2-dimethylpropanaldehyde oxime (491 mg, 4.87 mmol), N-chlorosuccinimide (715 mg, 5.35 mmol), pyridine (2 drops), (S)-1-(2-propenoyl)-5-[(triphenylmethoxy)methyl]-2-pyrrolidinone (2.0 g, 4.87 mmol) (189) and triethylamine (540 mg, 5.35 mmol) gave (5R)-3-(2,2-dimethylpropyl)-5-(S)-5-(triphenylmethoxy)methyl-2-pyrrolidinyl-1-carbonyl-2-isoxazoline (192a') (649 mg, 26%) and (5S)-3-(2,2-dimethylpropyl)-5-(S)-5-(triphenylmethoxy)methyl-2-pyrrolidinyl-1-carbonyl-2-isoxazoline (192b) (1.72 g, 69%) as waxy white solids after flash column chromatography (1:1 petroleum ether-ether).

(192a)

Rf 0.09 (1:1 petroleum ether-ether);

$[\alpha]_D = -81.3^\circ$ (C=10, CH$_2$Cl$_2$);

$\nu_{max}$ (CH$_2$Cl$_2$) 3050 w, 3020 m, 2960 s, 2920 m, 2900 m, 2860 m, 1730 s (C=O), 1695 s, 1590 w, 1475 m, 1445 m, 1360 s, 1220 s, 1195 s, 1150 s, 1085 s, 1060 m, 1030 s, 1000 m, 970 m, 940 w, 925 w, 900 w, 870 s, 855 s, 810 m, 730 w, 660 w, 645 m, 630 s, 615 w;

$\delta$ (300 MHz; CDCl$_3$) 1.19 (9H, s, C(CH$_3$)$_3$), 2.14-1.97 (2H, m, H-4'), 2.41-2.50
(1H, m, H-3'), 2.90-3.06 (2H, m, H-3' and H-4), 3.23 and 3.56 (2H, B and A of ABX system, J^=9.9 Hz, J^=4.0 Hz, J^=2.6 Hz, CHOCPh), 3.44 (1H, dd, J=17.3, 11.6 Hz, H-4), 4.43-4.46 (1H, m, H-5'), 5.85 (1H, dd, J=11.6, 6.8 Hz, H-5), 7.38-7.19 (15H, m, aromatic);

δ (75 MHz; CDCl₃) 21.48 (CH₃), 28.09 (CH₃), 32.83 (CH₃), 32.92 (C), 38.87 (CH₃), 56.62 (CH), 63.29 (CH₃), 78.58 (CH), 87.09 (C), 127.14 (CH), 127.91 (CH), 128.40 (C), 143.43 (C), 164.40 (C), 170.26 (C), 176.37 (C);

M/Z 243 (CPh⁺, 100), 228 (3), 215 (1), 184 (3), 165 (26), 152 (4), 126 (13), 105 (6), 84 (10), 68 (3), 57 (18), 41 (10);

C₁₁H₁₀NO requires 126.0919
found 126.0920.

Note

No molecular ion was seen but the C₁₁H₁₀NO fragment corresponds to

![Chemical structure](image)

(192b)

R₉ 0.05 (1:1 petroleum ether-ether);

[α]D  = -20.1° (C=10, CH₂Cl₂);

δ (300 MHz; CDCl₃) 1.16 (9H, s, C(CH₃)₃), 1.85-1.92 (1H, m, H-4'), 2.04-2.18 (1H, m, H-4'), 2.49 (1H, dd, J=18.0, 9.7 Hz, H-3'), 2.83-2.96 (1H, m, H-3'), 3.12-3.24 (2H, m, CHOCPh, and H-4), 3.38 (1H, dd, J=17.1, 11.3 Hz, H-4), 3.60-3.64 (1H, m, OCH₂CPh), 4.40 (1H, brd, J=5.1 Hz, H-5'), 5.90 (1H, dd, J=11.1, 6.6 Hz, H-5), 7.21-
7.35 (15H, m, aromatic);

δc (75 MHz; CDCl₃) 21.74 (CH₃), 28.02 (CH₃), 32.63 (CH₃), 32.90 (C), 37.83 (CH₂),
56.79 (CH), 63.73 (CH₃), 78.12 (CH), 87.00 (C), 124.14 (C), 127.83 (CH), 128.40
(CH), 143.44 (C), 164.96 (C), 169.72 (C), 176.28 (C).

(5R)-3-(2,2-Dimethylpropyl)-2-isoxazoline-5-methanol (193a)

Following the same procedure as for the preparation of compounds (191a) and
(191b), (5R)-3-(2,2-dimethylpropyl)-5-[(S)-5-(triphenylmethoxy)methyl-2-
pyrrolidinonyl-1-carbonyl]-2-isoxazoline (192a) (1.0 g, 1.96 mmol) and L-Selectride
(7.84 ml, 7.84 mmol) gave (5R)-3-(2,2-dimethylpropyl)-2-isoxazoline-5-methanol
(193a) as a colourless oil (256 mg, 83%) after flash column chromatography (2:1
petroleum ether-ether). The 90 MHz 'H n.m.r. spectrum of the product was consistent
with the literature data.68

[α]₀ = +117.0° (C=1, CHCl₃) (lit. [α]₀ = +130.5°).

(5S)-3-(2,2-Dimethylpropyl)-2-isoxazoline-5-methanol (193b)

In the same way, (5S)-3-(2,2-dimethylpropyl)-5-[(S)-5-(triphenylmethoxy)methyl-2-
pyrrolidinonyl-l-carboxyl]-2-isoxazoline (192b) (500 mg, 0.98 mmol) and L-Selectride (3.92 ml, 3.92 mmol) gave (5S)-3-(2,2-dimethylpropyl)-2-isoxazoline-5-methanol (193b) as a colourless oil (70 mg, 45%) after flash column chromatography (2:1 petroleum ether-ether).

\[ [\alpha]_D = -122.6^\circ \ (C=1, \ CHCl_3) \  \text{lit. } [\alpha]_D = -130.5^\circ \]

**p-Tolylsulphinyl chloride**

Thionyl chloride (65 ml, 0.90 mmol) was dissolved in an equal volume of dry ether and the sodium salt of p-toluenesulphinic acid (25 g, 0.14 mmol) added portionwise under a nitrogen atmosphere. After addition was complete, the reaction was warmed gently for 2h, with stirring. Excess thionyl chloride and solvent were then removed under reduced pressure and the residue redissolved in dry ether then filtered to remove any inorganic solids. The solvent was removed under reduced pressure to give p-tolylsulphinyl chloride as a yellow oil (18.6 g, 76%), which was used crude in the next stage.

**Methyl (S)-p-toluenesulphinate (194)**

A solution of p-tolylsulphinyl chloride (18.6 g, 107 mmol) in dry ether (50 ml) was added dropwise to a stirred solution of (1R)-menthol (12.5 g, 80 mmol) and pyridine (13.0 ml, 160 mmol) in ether (100 ml), under nitrogen, at 0°C. Once the addition was
complete, the mixture was allowed to warm to room temperature and stirred for a further 18 h. Standard aqueous work-up gave a solid which was recrystallised from hot acetone as colourless crystals. The mother liquor was concentrated, redissolved in hot acetone with 3 drops of concentrated hydrochloric acid and cooled again to afford additional crystals. The process was repeated twice and the combined crystals were recrystallised from acetone to give (1R)-menthyl (S)-p-toluenesulphinate (194) as colourless needles (13.45 g, 43%).

(R)-p-Tolylsulphinylethylene (195)\(^{46}\)

\[
\begin{align*}
\text{O} & \\
\text{p-Tol}^- & \\
\text{S}^+ & \\
\hline
(195)
\end{align*}
\]

A solution of (1R)-menthyl (S)-p-toluenesulphinate (194) (4.8 g, 16.3 mmol) in THF (25 ml) was stirred, under nitrogen, at room temperature. Vinyl magnesium bromide (18.0 ml, 18.0 mmol) was added dropwise and the reaction mixture then heated to reflux for 4 h. Standard aqueous work-up yielded (R)-p-tolylsulphinylethylene (195) as a pale yellow liquid (1.59 g, 59%) after flash column chromatography (1:1 petroleum ether-ether).

\[\delta (300 \text{ MHz; CDCl}_3) 2.37 (3\text{H, s, CH}_3), 5.85 (1\text{H, d, J}=9.5 \text{ Hz, OSCH=CH}_3\text{, CH}_3), 6.16 (1\text{H, d, J}=16.4 \text{ Hz, OSCH=CH}_3\text{, CH}_3), 6.58 (1\text{H, dd, J}_\text{trans}=16.4 \text{ Hz, J}_\text{cis}=9.5 \text{ Hz, OSCH=CH}_3), 7.27-7.30 (2\text{H, m, aromatic}), 7.47-7.51 (2\text{H, m, aromatic});\]

\[\delta (75 \text{ MHz; CDCl}_3) 21.34 (\text{CH}_3), 120.08 (\text{CH}_3), 124.71 (\text{CH}), 130.02 (\text{CH}), 140.00 (\text{C}), 141.67 (\text{C}), 143.01 (\text{CH}).\]
Following the same procedure as for the preparation of compound (141), benzaldehyde oxime (728 mg, 6.02 mmol), N-chlorosuccinimide (885 mg, 6.63 mmol), pyridine (2 drops), (R)-p-tolylsulphinylethylene (195) (1.0 g, 6.02 mmol) and triethylamine (669 mg, 6.63 mmol) gave 3-phenylisoxazole (197) as a colourless oil (484 mg, 56%) after flash column chromatography (10:1 petroleum ether-ether).

\[ \delta_\mathrm{H} (300 \text{ MHz}; \text{CDCl}_3) 6.55 (1\text{H}, \text{d}, J=1.7 \text{ Hz}, \text{H}-4), 7.31-7.40 (3\text{H}, \text{m}, \text{aromatic}), 7.25-7.81 (2\text{H}, \text{m}, \text{aromatic}), 8.33 (1\text{H}, \text{d}, J=1.7 \text{ Hz}, \text{H}-5); \]

\[ \delta_\mathrm{C} (75 \text{ MHz}; \text{CDCl}_3) 102.46 (\text{CH}), 126.81 (\text{CH}), 128.76 (\text{C}), 128.91 (\text{CH}), 129.99 (\text{CH}), 159.00 (\text{CH}), 161.40 (\text{C}). \]

**Note**

The spectra were identical to those obtained from an authentic sample of 3-phenylisoxazole, which was synthesised by the literature reaction of vinyl bromide with benzonitrile oxide.\(^6\)
Magnesium turnings (570 mg, 23.8 mmol) and a crystal of iodine were covered by the minimum amount of THF, under nitrogen. β-Bromostyrene (0.80 ml, 6.30 mmol) was added dropwise and an immediate reaction was evident. The remainder of the halide (2.04 ml, 15.9 mmol) was added in THF (10 ml) so as to maintain a gentle reflux. The reaction mixture was heated under reflux for a further 3 h. After allowing to cool, the Grignard reagent was added dropwise to a solution of (1R)-menthyl (S)-p-toluenesulphinate (194) (5.2 g, 17.7 mmol) in benzene (30 ml), under nitrogen. The reaction was stirred at room temperature for 2 h and then quenched with saturated aqueous ammonium chloride solution. Standard aqueous work-up, flash column chromatography (2:1 ether-petroleum ether) and then recrystallisation (petroleum ether) gave (+)-(E)-2-phenyl-1-[{(R)-p-tolylsulphinyl}ethylene (198a) as a white solid (1.81 g, 42%) and (-)-(Z)-2-phenyl-1-[{(R)-p-tolylsulphinyl}ethylene (198b) as a pale yellow solid (608 mg, 14%).

(198a)

\[ \begin{align*}
\text{O} & \\
\text{p-Tol} & \text{S}^+ & \text{Ph} \\
\end{align*} \]

(198a)

(198b)

\[ \begin{align*}
\text{O} & \\
\text{p-Tol} & \text{S}^+ & \text{Ph} \\
\end{align*} \]

(198b)

δ\(_{\text{H}}\) (300 MHz; CDCl\(_3\)) 2.36 (3H, s, CH\(_3\)), 6.80 (1H, d, \(J_{\text{H-H}}=15.5\) Hz, H-1), 7.42-7.26 (8H, m, aromatic), 7.54-7.57 (2H, m, aromatic and H-2);

δ\(_{\text{C}}\) (75 MHz; CDCl\(_3\)) 21.36 (CH\(_3\)), 124.77 (CH), 127.63 (CH), 128.77 (CH), 129.64 (CH), 130.04 (CH), 132.98 (CH), 133.65 (C), 135.74 (CH), 140.58 (C), 141.60 (C).
\[ \delta_\text{H} (300 \text{ MHz}; \text{CDCl}_3) 2.38 (3\text{H}, \text{s, CH}_3), 6.42 (1\text{H}, \text{d, } J_{\text{CH}}=10.6 \text{ Hz, H-1}), 7.05 (1\text{H, d, } J_{\text{CH}}=10.6 \text{ Hz, H-2}), 7.53-7.56 (9\text{H, m, aromatic}); \]

\[ \delta_\text{C} (75 \text{ MHz}; \text{CDCl}_3) 21.34 (\text{CH}_3), 124.26 (\text{CH}), 128.56 (\text{CH}), 129.40 (\text{CH}), 129.68 (\text{CH}), 130.01 (\text{CH}), 133.71 (\text{C}), 136.81 (\text{CH}), 138.40 (\text{CH}), 141.25 (\text{C}), 141.32 (\text{C}). \]

**Attempted reaction of (+)-(E)-2-phenyl-1-[(R)-p-tolylsulphinyl]ethylene (198a) with benzonitrile oxide**

Following the same procedure as for the preparation of compound (141), benzaldehyde oxime (250 mg, 2.07 mmol), N-chlorosuccinimide (304 mg, 2.28 mmol), pyridine (2 drops), (+)-(E)-2-phenyl-1-[(R)-p-tolylsulphinyl]ethylene (198a) (500 mg, 2.07 mmol) and triethylamine (230 mg, 2.28 mmol) gave no reaction, even after heating to reflux for 3h. T.l.c. and \(^1\text{H n.m.r.} \) showed that only starting material was present.

**Attempted reaction of (-)-(Z)-2-phenyl-1-[(1R)-p-tolylsulphinyl]ethylene (198b) with benzoaldehyde oxime**

The reaction was carried out in the same way and with the same quantities as described above but using (-)-(Z)-2-phenyl-1-[(1R)-p-tolylsulphinyl]ethylene (198b). Again t.l.c. and \(^1\text{H n.m.r.} \) showed that only starting material was present.
(1R)-Menthol (15.6 g, 100 mmol) and paraformaldehyde (9.0 g, 100 mmol) were mixed and a stream of dry hydrogen chloride gas passed over the stirred mixture for 4h at 0°C. The viscous liquid formed was separated from the unreacted solids by centrifugation. Chloromethyl-(1R)-menthyl ether (215) was obtained as a colourless liquid (18.29 g, 89%) and was used crude in the following reactions.

(2S)-Ethyl-2-(1R)-menthoxymethyl lactate (216)

A solution of ethyl (S)-(-)-lactate (150 mg, 1.22 mmol) and N,N-diisopropylethylamine (630 mg, 4.88 mmol) in dichloromethane (5 ml) was stirred under nitrogen. Chloromethyl-(1R)-menthyl ether (215) (750 mg, 3.66 mmol) was
added dropwise and the mixture left to stir at room temperature for 20h. Standard aqueous work-up gave (2S)-ethyl-1-((1R)-menthoxymethyl)lactate (216) as a colourless oil (310 mg, 85%) after flash column chromatography (10:1 petroleum ether-ether).

Rf 0.55 (3:1 petroleum ether-ether);

\[ \alpha_{D} = -142.0^\circ \] (C=4, CH\textsubscript{2}Cl\textsubscript{2});

\[ \nu_{max} \text{ (film) 2950m, 2920m, 2870w, 1735m, 1710s (C=O), 1430w, 1360w, 1250m, 1220m, 1185w, 1170w, 1150m, 1115m, 1075w, 1040w, 1015m, 890w, 720s; \]

\[ \delta_{C} \text{ (300 MHz; CDCl}\textsubscript{3}) 0.73-1.19 \text{ (14H, m)}, 1.28 \text{ (3H, t, } J=7.1 \text{ Hz, CO}_{2}\text{CH}_{2}\text{CH}_{2}), 1.41 \text{ (3H, d, } J=6.9 \text{ Hz, OCH(O)}; 1.61-1.68 \text{ (2H, m), 2.06-2.25 \ (2H, m), 3.42 \ (1H, td, } J=10.4, 4.2 \text{ Hz, H-1}), 4.20 \text{ (2H, q, } J=7.1 \text{ Hz, CO}_{2}\text{CH}_{2}), 4.37 \text{ (1H, q, } J=6.9 \text{ Hz, H-2), 4.65 \text{ and 4.91 \ (2H, AB system, } J_{ab}=7.5 \text{ Hz, OCH(O); } \]

\[ \delta_{C} \text{ (75 MHz; CDCl}_{3} \text{) 14.17 \text{ (CH}_3), 15.86 \text{ (CH}_3), 18.37 \text{ (CH}_3), 21.12 \text{ (CH}_3), 22.23 \text{ (CH}_3), 22.95 \text{ (CH}_3), 25.32 \text{ (CH), 31.38 \text{ (CH), 34.35 \text{ (CH), 40.50 \text{ (CH), 48.21 \text{ (CH), 60.77 \text{ (CH), 70.50 \text{ (CH), 76.27\text{(CH), 90.96 \text{ (CH), 173.00 \text{ (C; } \]

M/Z 287 ([MH]+, 63), 249 (7), 186 (29), 169 (39), 156 (11), 131 (100), 119 (17), 95 (6), 81 (57), 47 (17);

C\textsubscript{16}H\textsubscript{22}O\textsubscript{3}, [MH]+ requires 287.2222
found 287.2222.
In the same way, (S)-methyl mandelate (200 mg, 1.22 mmol), N,N-diisopropylethylamine (630 mg, 4.88 mmol) and chloromethyl-(1R)-menthyl ether (215) (750 mg, 3.66 mmol) gave (2S)-methvl-2-l(1R)-menthoxvmethvllmandelate (217) as a colourless oil (320 mg, 79%) after flash column chromatography (10:1 petroleum ether-ether).

\[ \alpha_p = +4.1^\circ \ (c=4, \ CHC_2Cl_2); \]
\[ R_f 0.50 \ (3:1 \ petroleum \ ether-ether); \]
\[ \nu_{max} \ (film) \ 2960s, 2920s, 2860s, 1750s \ (C=O), \ 1450m, \ 1430w, \ 1365w, \ 1340w, \]
\[ 1265w, \ 1255w, \ 1205m, \ 1170s, \ 1145m, \ 1130m, \ 1110s, \ 1075m, \ 1055m, \ 1040s, \]
\[ 1035w, \ 1025s, \ 1005s, \ 990s, \ 980m, \ 950m, \ 910m, \ 840w, \ 730s, \ 695w, \ 640w; \]
\[ \delta_\nu \ (300 \ MHz; CDCl_3) \ 0.76-1.03 \ (12H, m), \ 1.19-1.38 \ (2H, m), \ 1.61-1.65 \ (2H, m), \]
\[ 2.00 \ (1H, brd, J=11.4 \ Hz), \ 2.23 \ (1H, quintet of doublets, J=7.0, 2.5 \ Hz, H-2'), \ 3.47 \ (1H, td, J=10.6, 4.3 \ Hz, H-1'), \ 3.69 \ (3H, s, OCH_3), \ 4.60 \ and \ 4.90 \ (2H, AB system, \]
\[ J_{\alpha}=7.4 \ Hz, \ OCH_3O, \ 5.31 \ (1H, s, H-2), \ 7.27-7.47 \ (5H, m, aromatic); \]
\[ \delta_c \ (75 \ MHz; CDCl_3) \ 15.81 \ (CH_3), \ 22.18 \ (CH_3), \ 22.93 \ (CH_3), \ 23.02 \ (CH_3), \ 25.30 \ (CH), \ 31.38 \ (CH), \ 34.24 \ (CH_3), \ 41.41 \ (CH_3), \ 48.32 \ (CH), \ 52.07 \ (CH_3), \ 56.12 \ (CH), \]
\[ 77.96 \ (CH), \ 91.64 \ (CH_3), \ 127.35 \ (CH), \ 128.39 \ (CH), \ 128.49 \ (CH), \ 136.01 \ (C), \ 171.07 \]
(C);

\[ \text{M/Z} 335 ([MHT]^+, 65), 184 (100), 169 (50), 149 (25), 139 (14), 121 (24), 95 (8), 81 (8), 47 (22); \]

\[ \text{C}_{19}\text{H}_{18}\text{O}_{4}, [\text{MHT}]^+ \text{ requires 335.2222} \]
\[ \text{found 335.2222.} \]

(2RS)-Methyl-2-(1R)-menthoxymethyl]mandelate (233)

\[ \text{Ph} \]
\[ \text{O} \]
\[ \text{O} \]
\[ \text{CO}_2\text{Me} \]

\[(233)\]

In the same way, (RS)-methyl mandelate (200 mg, 4.88 mmol), \( \text{N,N-diisopropylethylamine} \) (630 mg, 19.5 mmol) and chloromethyl-(1R)-menthyl ether (215 g, 14.6 mmol) gave (2RS)-methyl-2-(1R)-menthoxymethyl]mandelate (233) as a colourless oil (370 mg, 90%) after flash column chromatography (10:1 petroleum ether-ether).

\[ \alpha_\text{D} = -106.3^\circ \text{ (C=4, CH}_2\text{Cl}_2); \]

\[ \delta_\text{H} (300 \text{ MHz; CDCl}_3) 0.59-1.03 (12H, m), 1.17-1.36 (2H, m), 1.57-1.65 (2H, m), 1.98-2.29 (2H, m), 3.38 (0.5H, td, \text{J}=10.6, 4.3 \text{ Hz, H-1'}), 3.47 (0.5H, td, \text{J}=10.6, 4.2 \text{ Hz, H-1'}), 3.68 (1.5H, s, OCH_3), 3.69 (1.5H, s, OCH_3), 4.60 \text{ and 4.90 (1H, AB system, J}_{ab}=7.4 \text{ Hz, OCHO}), 4.76 \text{ and 4.85 (1H, AB system, J}_{ab}=7.4 \text{ Hz, OCHO}), 5.31 (1H, s, H-2), 7.27-7.47 (5H, m, aromatic); \]

192
\( \delta_c (75 \text{ MHz; } CDCl_3) \): 15.69 (CH\(_3\)), 15.93 (CH\(_3\)), 21.18 (CH\(_3\)), 21.22 (CH\(_3\)), 22.23 (CH\(_3\)), 22.30 (CH\(_3\)), 23.02 (CH\(_3\)), 23.05 (CH\(_3\)), 25.43 (CH), 25.57 (CH), 31.45 (CH), 31.52 (CH), 34.40 (CH), 41.09 (CH), 41.55 (CH), 48.42 (CH), 48.46 (CH), 52.22 (CH), 76.04 (CH), 76.24 (CH), 77.10 (CH), 78.12 (CH), 90.55 (CH), 91.78 (CH), 127.49 (CH), 127.78 (CH), 128.53 (CH), 128.64 (CH), 128.79 (CH), 136.01 (C), 136.13 (C), 171.02 (C), 171.23 (C);

(2RS)-Methyl-2-[(1R)-menthoxymethyl]lactate (218)

\begin{center}
\includegraphics[width=0.2\textwidth]{image}
\end{center}

In the same way, methyl (RS)-lactate (150 mg, 1.54 mmol), N,N-diisopropylethylamine (795 mg, 6.16 mmol) and chloromethyl-(1R)-menthyl ether (215) (945 mg, 4.62 mmol) gave (2RS)-methyl-2-[(1R)-menthoxymethyl]lactate (218) as a colourless oil (300 mg, 77%) after flash column chromatography (10:1 petroleum ether-ether).

\( R_f 0.39 \) (5:1 petroleum ether-ether);

\( [\alpha]_D = -5.7^\circ \) (C=4, CH\(_2\)Cl\(_2\));

\( \nu_{\text{max}} \) (film) 2950s, 2920s, 2870s, 1745s (C=O), 1445m, 1370w, 1265w, 1240w, 1205m, 1170s, 1150m, 1115s, 1075s, 1040s, 1015s, 980w, 965w, 955w, 910w, 840w;

\( \delta_c (300 \text{ MHz; } CDCl_3) \): 0.73-1.27 (14H, m), 1.41 (1.5H, d, J=6.9 Hz, OCH\(_2\)CH), 1.42
(1.5H, d, J=6.9 Hz, OCHCH3), 1.60-1.69 (2H, m), 2.04-2.25 (2H, m), 3.33 (0.5H, td, 
J=10.5, 4.3 Hz, H-1'), 3.41 (0.5H, td, J=10.5, 4.2 Hz, H-1'), 3.728 (1.5H, s, OCH3), 
3.734 (1.5H, s, OCH3), 4.39 (0.5H, q, J=6.9 Hz, H-2), 4.41 (0.5H, q, J=6.9 Hz, H-2), 
4.65 and 4.90 (1H, AB system, J,^=7.5 Hz, OCHO), 4.76 and 4.83 (1H, AB system, 
J,ab=7.3 Hz, OCHO);

δc (75 MHz; CDCl3) 15.71 (CH3), 18.02 (CH3), 18.20 (CH3), 20.95 (CH3), 22.09 
(CH3), 22.82 (CH3), 22.90 (CH3), 25.17 (CH), 25.21 (CH), 31.23 (CH), 31.35 (CH), 
34.16 (CH3), 34.22 (CH3), 40.36 (CH3), 42.11 (CH3), 48.06 (CH), 48.38 (CH), 51.57 
(CH3), 69.96 (CH), 70.32 (CH), 76.15 (CH3), 78.72 (CH3), 90.88 (CH3), 93.05 (CH3), 
173.05 (C), 173.17 (C);

M/Z 290 ([M+NH+]+, 49), 273 (31), 186 (51), 169 (47), 156 (28), 139 (8), 122 
(100), 95 (7), 81 (8), 58 (10), 47 (54);

C28H42NO4 ([M+NH+]+) requires 290.2331
found 290.2331.

Note
The compound was detected as the [M+NH+] ion under ammonia chemical 
ionisation conditions.
In the same way, (1RS)-1-phenylethanol (150 mg, 1.22 mmol), N,N-diisopropylethylamine (630 mg, 4.88 mmol) and chloromethyl-(1R)-menthyl ether (215) (750 mg, 3.66 mmol) gave (1RS)-1-((1R)-menthoxymethoxy)-1-phenylethane (219) as a colourless oil (315 mg, 89%) after flash column chromatography (20:1 petroleum ether-ether).

RF 0.57 (12:1 petroleum ether-ether);

\[ [\alpha]_D = -52.5^\circ \] (C=4, CHCl₃);

\[ \nu_{max} (\text{CHCl}_3) 3020 \text{m}, 2910 \text{s}, 2800 \text{w}, 1490 \text{w}, 1450 \text{s}, 1370 \text{s}, 1345 \text{m}, 1300 \text{w}, 1210 \text{m}, 1170 \text{s}, 1150 \text{s}, 1100 \text{s}, 1060 \text{s}, 1020 \text{s}, 990 \text{s}, 980 \text{s}, 960 \text{s}, 910 \text{s}, 860 \text{w}, 840 \text{m}; \]

\[ \delta_\text{h} (300 \text{MHz; CDCl}_3) 0.67-1.09 (14H, m), 1.45 (3H, d, J=6.6 \text{ Hz}, H-2), 1.58-1.69 (2H, m), 1.98-2.22 (1.5H, m), 2.33 (0.5H, quintet of doublets, J=9.2, 2.5 \text{ Hz}, H-2'), 3.29 (0.5H, td, J=10.5, 4.3 \text{ Hz}, H-1'), 3.46 (0.5H, td, J=10.6, 4.2 \text{ Hz}, H-1'), 4.42 and 4.76 (1H, AB system, J_{ab}=7.4 \text{ Hz}, \text{OCHO}), 4.61 and 4.67 (1H, AB system, J_{ab}=7.1 \text{ Hz}, \text{OCHO}), 4.79-4.88 (1H, m, H-2), 7.21-7.32 (5H, m, aromatic);

\[ \delta_\text{e} (75 \text{ MHz; CDCl}_3) 15.96 (\text{CH}_3), 15.99 (\text{CH}_3), 21.11 (\text{CH}_3), 22.24 (\text{CH}_3), 22.31 (\text{CH}_3), 23.04 (\text{CH}_3), 23.11 (\text{CH}_3), 23.69 (\text{CH}_3), 25.31 (\text{CH}), 25.39 (\text{CH}), 31.40 (\text{CH}), 31.60 (\text{CH}), 34.36 (\text{CH}_3), 34.45 (\text{CH}_3), 40.41 (\text{CH}_3), 42.81 (\text{CH}_3), 48.27 (\text{CH}), 73.30 \]
(CH), 73.60 (CH), 75.45 (CH), 78.99 (CH), 89.18 (CH$_3$), 92.61 (CH$_3$), 126.35 (CH), 126.54 (CH), 127.32 (CH), 127.43 (CH), 128.27 (CH), 128.29 (CH), 143.17 (C), 143.35 (C);

M/Z 308 ([M+NH$_4^+$]*, 40), 261 (26), 186 (25), 174 (19), 152 (15), 140 (28), 122 (93), 105 (100), 95 (11), 81 (14), 47 (53);

C$_{10}$H$_{12}$NO$_2$ [M+NH$_4^+$] * requires 308.2590
found 308.2589.

Note
The [M+NH$_4^+$] * ion was observed under ammonia chemical ionisation conditions.

(2RS)-1-(1R)-Menthoxy methoxyl-2-methoxy-2-phenylethane (220)

![Chemical structure diagram]

In the same way, (1RS)-2-methoxy-2-phenylethanol-1-ol (500 mg, 3.29 mmol), N,N-diisopropylethylamine (1.70 g, 13.2 mmol) and chloromethyl-(1R)-menthyl ether (215) (2.02 g, 9.87 mmol) gave (2RS)-1-(1R)-menthoxy methoxy-2-methoxy-2-phenylethane (220) as a colourless oil (682 mg, 65%) after flash column chromatography (10:1 petroleum ether-ether).

R$_f$ 0.11 (10:1 petroleum ether-ether);

[α]$_D$ = -72.3° (C=10, CH$_2$Cl$_2$);
δ (300 MHz; CDCl₃) 0.74-1.04 (12H, m), 1.15-1.42 (2H, m), 1.58-1.65 (2H, m),
2.04-2.22 (2H, m), 3.27-3.42 (4H, m, OCH₂ and H-1'), 3.63-3.76 (2H, m, H-1), 4.35-
4.39 (1H, m, H-2), 4.64 and 4.89 (1H, AB system, Jₓₓ=7.1 Hz, OCHO), 4.69 and 4.83
(1H, AB system, Jₓₓ=7.0 Hz, OCHO), 7.25-7.37 (5H, m, aromatic);

δ (75 MHz; CDCl₃) 15.88 (CH₃), 21.16 (CH₃), 22.31 (CH₃), 23.00 (CH₃), 23.04
(CH₃), 25.25 (CH), 31.46 (CH), 34.38 (CH₃), 40.96 (CH₃), 41.66 (CH₃), 48.28 (CH),
48.44 (CH), 56.84 (CH₃), 56.87 (CH₃), 72.13 (CH₃), 72.29 (CH₃), 76.44 (CH), 77.47
(CH), 83.05 (CH), 83.10 (CH), 93.49 (CH₃), 94.49 (CH₃), 126.90 (CH), 126.95 (CH),
127.95 (CH), 128.38 (CH), 138.74 (C), 138.88 (C);

M/Z 290 ([MH⁺]-OCH₃), 9, 139 (49), 138 (21), 135 (14), 134 (15), 133 (17), 123
(19), 122 (53), 121 (100), 120 (14), 119 (12), 105 (27), 104 (36), 103 (26);

C₈H₁₀O, [MH⁺]⁺ requires 321.2430
found 321.2430.

(3RS)-3,7-Dimethyl-3-[(1R)-Menthoxymethoxy]oct-6-en-1-yne (221)

In the same way, (3RS)-3,7-dimethyloct-6-en-1-yne (190 mg, 1.22 mmol), N,N-
diisopropylethylamine (630 mg, 4.88 mmol) and chloromethyl-(1R)-menthyl ether
(215) (750 mg, 3.66 mmol) gave (3RS)-3,7-dimethyl-3-[(1R)-menthoxymethoxy]oct-6-
en-1-vne (221) as a colourless oil (380 mg, 96%) after flash column chromatography (10:1 petroleum ether-ether).

Rf 0.89 (4:1 petroleum ether-ether);

[α]D = -68.8° (C=4, CHCl3);

νmax (film) 3010w, 2960s, 2920s, 2890m, 2870m, 2850m, 1450w, 1385w, 1375w, 1215m, 1180w, 1165w, 1145w, 1130w, 1110m, 1075w, 1020s, 990m, 980m, 970w, 960w, 910m, 840w, 760s, 735s, 670m, 660w, 630m, 605m;

δH (300 MHz; CDCl3) 0.75-1.05 (14H, m), 1.16-1.81 (14H, m), 2.06-2.30 (4H, m), 3.25-3.42 (1H, m, H-1'), 4.87 and 5.10 (1H, AB system, J=8.8 Hz, OCHO), 4.95 and 5.00 (1H, AB system, J=6.9 Hz, OCHO), 5.09-5.14 (1H, m, HC=C);

δC (75 MHz; CDCl3) 15.73 (CH3), 15.95 (CH3), 16.06 (CH3), 17.61 (CH3), 21.09 (CH3), 21.13 (CH3), 22.28 (CH3), 22.35 (CH3), 23.10 (CH3), 23.19 (CH3), 25.36 (CH), 25.63 (CH), 27.39 (CH3), 27.68 (CH3), 31.54 (CH), 31.60 (CH), 34.46 (CH), 34.51 (CH3), 41.00 (CH3), 41.17 (CH3), 42.20 (CH3), 42.53 (CH3), 48.30 (CH), 48.47 (CH), 73.06 (C), 73.29 (C), 76.57 (CH), 76.91 (CH), 76.99 (C), 77.42 (C), 78.41 (CH), 89.10 (CH), 89.42 (CH3), 90.92 (CH3), 123.80 (CH), 131.74 (C);

M/Z 325 ([MH]+, 9), 169 (35), 139 (100), 119 (42), 95 (37), 83 (92), 69 (53), 55 (45), 41 (42);

C36H46O3 [MH]+ requires 325.3107
found 325.3107.
In the same way, (1RS)-(2-naphthyl)ethan-1-ol (210 mg, 1.22 mmol), N,N-diisopropylethylamine (630 mg, 4.88 mmol) and chloromethyl-(1R)-menthyl ether (215) (750 mg, 3.66 mmol) gave (1RS)-1-(1R)-menthoxymethoxy-1-(2-naphthyl)ethane (222) as a colourless oil (390 mg, 94%) after flash column chromatography (20:1 petroleum ether-ether).

\[ R, 0.70 \text{ (9:1 petroleum ether-ether)}; \]
\[ [\alpha]_D = -41.5^\circ \text{ (C=4, CHCl}_3); \]
\[ \delta_6 (300 \text{ MHz; CDCl}_3) 0.66-1.42 (14H, m), 1.49-1.56 (5H, m), 1.98-2.25 (1.5H, m), 2.39 (0.5H, quintet of doublets, J=6.9, 2.4 Hz, H-2'), 3.30 (0.5H, td, J=10.5, 4.5 Hz, H-1'), 3.48 (0.5H, td, J=10.5, 4.2 Hz, H-1'), 4.47 and 4.78 (1H, AB system, J=7.3 Hz, OCHO), 4.64 and 4.70 (1H, AB system, J=7.0 Hz, OCHO), 4.99 (0.5H, q, J=7.0 Hz, NaphCHO), 5.01 (0.5H, q, J=7.0 Hz, NaphCHO), 7.18-7.48 (3H, m, aromatic), 7.74-7.80 (4H, m, aromatic); \]
\[ \delta_6 (75 \text{ MHz; CDCl}_3) 15.99 \text{ (CH}_3), 16.02 \text{ (CH}_3), 21.06 \text{ (CH}_3), 21.11 \text{ (CH}_3), 21.21 \text{ (CH}_3), 22.22(\text{CH}_3), 22.32 \text{ (CH}_3), 23.02 \text{ (CH}_3), 23.10 \text{ (CH}_3), 23.62 \text{ (CH}_3), 25.31 \text{ (CH}_3), 25.42 \text{ (CH)}, 31.37 \text{ (CH)}, 31.59 \text{ (CH)}, 34.36 \text{ (CH}_3), 34.43 \text{ (CH}_3), 40.40 \text{ (CH}_3), 42.84 \text{ (CH}_3), 48.24 \text{ (CH)}, 48.62 \text{ (CH), 73.38 (CH), 73.74 (CH), 75.47 (CH), 79.05 (CH),} \]
89.18 (CH₂), 92.64 (CH₃), 124.24 (CH), 124.28 (CH), 125.39 (CH), 125.60 (CH), 125.64 (CH), 125.67 (CH), 125.93 (CH), 127.56 (CH), 127.75 (CH), 128.20 (CH), 128.86 (CH), 132.95 (C), 133.01 (C), 133.18 (C), 140.48 (C), 140.64 (C);

\[
\text{M/Z 358 ([M+NH₄]^+, 5), 184 (7), 172 (24), 155 (100), 47 (6);} \\
\text{C₉H₆NO₃ [M+NH₄]^+ requires 358.2746} \\
\text{found 358.2746.}
\]

**Note**

The \([M+NH₄]^+\) ion was observed under ammonia chemical ionisation conditions.

**Deprotection of (2S)-methyl-2-[(1R)-menthoxymethyl]mandelate (217)**

A solution of (2S)-methyl-2-[(1R)-menthoxymethyl]mandelate (217) (300 mg, 0.90 mmol) in dichloromethane (5 ml) was stirred at room temperature. Zinc bromide (1.0 g, 4.44 mmol) was added and the mixture stirred, under nitrogen, for 2h. The reaction mixture was poured into water and extracted with ether. The organic phase was washed with saturated aqueous sodium hydrogen carbonate solution and saturated aqueous sodium chloride solution, dried (MgSO₄) and the solvent removed under reduced pressure. (S)-Methyl mandelate was obtained as a white solid (106 mg, 71%) with an identical \(^1H\) n.m.r. spectrum and optical rotation ([α]_D = +144° (C=1, methanol)) to the optically pure compound.

**Epimerisation of (2S)-ethyl-2-[(1R)-menthoxymethyl]lactate (216)**

To a stirred solution of diisopropylamine (152 mg, 1.50 mmol) in THF (5 ml), under nitrogen, at 0°C was added n-butyllithium (0.94 ml, 1.50 mmol) dropwise. After 30 min, the LDA solution was cooled to -78°C and a solution of (2S)-ethyl-2-[(1R)-....
menthoxymethyl]lactate (216) (200 mg, 0.70 mmol) in THF (5 ml) added dropwise. The reaction was stirred at this temperature for 1 h and then allowed to warm to room temperature before quenching with water. Standard aqueous work-up yielded (2RS)-ethyl-2-[(1R)-menthoxymethyl]lactate (189 mg, 95%) as an oily 1:1.24 mixture of diastereoisomers after filter flash column chromatography (5:1 petroleum ether-ether).

δ (300 MHz; CDCl₃) 0.73-1.51 (20H, m), 1.58-1.68 (2H, m), 2.06-2.33 (2H, m), 3.34 (0.5H, td, J=10.5, 4.1 Hz, H-1'), 3.42 (0.5H, td, J=10.5, 4.3 Hz, H-1'), 4.19 (1H, q, J=7.1 Hz, CO₂CH), 4.20 (1H, q, J=7.1 Hz, CO₂CH), 4.37 (0.5H, q, J=6.9 Hz, H-2), 4.39 (0.5H, q, J=6.9 Hz, H-2), 4.65 and 4.91 (1H, AB system, J=7.5 Hz, OCHO), 4.77 and 4.83 (1H, AB system, J=7.3 Hz, OCHO);

δc (75 MHz; CDCl₃) 14.17 (CH₃), 14.23 (CH₃), 15.97 (CH₃), 16.08 (CH₃), 18.25 (CH₃), 18.43 (CH₃), 21.13 (CH₃), 21.18 (CH₃), 22.32 (CH₃), 23.04 (CH₃), 23.13 (CH₃), 25.34 (CH₃), 25.40 (CH₃), 31.47 (CH₃), 31.59 (CH₃), 34.39 (CH₃), 34.45 (CH₃), 42.07 (CH₃), 42.37 (CH₃), 48.30 (CH₃), 48.63 (CH₃), 60.81 (CH₃), 70.18 (CH₃), 70.58 (CH₃), 76.35 (CH₃), 76.68 (CH₃), 91.04 (CH₃), 93.28 (CH₃), 172.91 (C), 173.04 (C).

(2S)-2-[(1R)-Menthoxymethoxy]propan-1-ol (228)

To a stirred suspension of lithium aluminium hydride (2.33 g, 61.2 mmol) in dry
ether (20 ml), under nitrogen, was added dropwise a solution of (2S)-ethyl-2-[(1R)-menthoxyethyl]lactate (216) (17.5 g, 61.2 mmol) in dry ether (30 ml). The reaction mixture was then heated to reflux for 1 h. After cooling to room temperature, the excess lithium aluminium hydride was destroyed by careful addition of 15% aqueous sodium hydroxide solution. Standard aqueous work-up gave (2S)-2-[(1R)-menthoxyethyl]propan-1-ol (228) (12.1 g, 81%) as an oily 9:1 mixture of diastereoisomers after flash column chromatography (3:1 petroleum ether-ether).

Rf 0.10 (3:1 petroleum ether-ether);

$\alpha_L = -83.8^\circ$ (C=4, CHC13);

$\nu_{max}$ (film) 3590brw (OH), 3430w, 3020w, 2960s, 2920s, 2870s, 2810w, 1450m, 1375m, 1345w, 1215m, 1165m, 1140m, 1100m, 1050s, 1025s, 980s, 955m, 910m, 840w, 795w, 740w, 665w, 610w;

$\delta_c$ (300 MHz; CDC13) 0.73-1.06 (12H, m), 1.11-1.25 (4H, m), 1.29-1.42 (1H, m), 1.57-1.64 (2H, m), 2.05-2.18 (2H, m), 3.26-3.36 (2H, m, H-1' and OH), 3.45 and 3.52 (2H, AB system, $J_{AB}=11.9$ Hz, $J_{AB}=6.8$ Hz, $J_{AB}=3.2$ Hz, H-1), 3.69-3.79 (IH, m, H-2), 4.73 and 4.87 (0.2H, AB system, $J_{AB}=6.8$ Hz, OCHO), 4.78 and 4.83 (1.8H, AB system, $J_{AB}=7.4$ Hz, OCH4O);

$\delta_c$ (75 MHz; CDCl3) 15.75 (CH3), 15.89 (CH3), 16.53 (CH3), 16.91 (CH3), 20.86 (CH3), 20.93 (CH3), 22.04 (CH3), 22.84 (CH3), 22.93 (CH3), 25.19 (CH), 31.33 (CH), 32.40 (CH), 34.05 (CH3), 34.12 (CH3), 41.21 (CH3), 40.20 (CH3), 48.06 (CH), 48.22 (CH), 66.39 (CH3), 66.49 (CH3), 75.34 (CH), 77.09 (CH), 79.54 (CH), 92.37 (CH3), 94.67 (CH);

M/Z 245 ([MH]+, 100), 227 (10), 186 (22), 174 (18), 156 (46), 139 (12), 94 (12), 87 (10), 81 (7), 58 (6), 52 (6), 47 (7);
A solution of oxalyl chloride (9.44 g, 74.4 mmol) in dichloromethane (20 ml) was stirred, under nitrogen, at -78°C. DMSO (7.74 g, 99.2 mmol) in dichloromethane (20 ml) was then added dropwise and the reaction stirred for 3 min. A solution of (2S)-2-[(lR)-menthoxy]propan-1-ol (228) (12.1 g, 49.6 mmol) in dichloromethane (20 ml) was added and the reaction stirred for a further 15 min. Triethylamine (10.02 g, 99.2 mmol) was then added and, after 10 min at -78°C, the reaction was allowed to warm to room temperature. After 1h at room temperature, the reaction mixture was poured into water. Standard aqueous work-up yielded (2S)-2-[(1R)-menthoxy]propan-1-ol (229) (6.35 g, 53%) as an oily 9:1 mixture of diastereoisomers after flash column chromatography (5:1 petroleum ether-ether).

Rf 0.17 (2:1 petroleum ether-ether);

[α]D = -84.7° (C=4, CH2Cl2);

νmax (film) 2940s, 2900s, 2870s, 2850s, 2810m, 2720w, 1735s (C=O), 1450m, 1370m, 1345w, 1290w, 1240w, 1185m, 1170m, 1150m, 1105s, 1060s, 1030s, 980m,
960m, 910m, 840w;

$\delta_0$ (300 MHz; CDCl$_3$) 0.69-1.40 (17H, m), 1.57-1.64 (2H, m), 2.02-2.17 (2H, m), 3.34 (1H, td, $J$=13.6, 4.3 Hz, H-1'), 4.13 (1H, qd, $J$=5.4, 1.6 Hz, H-2), 4.70 and 4.88 (2H, AB system, $J_{ab}$=7.3 Hz, OCH$_2$O), 9.60 (0.1H, d, $J$=1.3 Hz, O=CH), 9.62 (0.9H, d, $J$=1.3 Hz, O=CH);

$\delta_c$ (75 MHz; CDO,) 14.71 (CH$_3$), 14.86 (CH$_3$), 15.74 (CH$_3$), 15.80 (CH$_3$), 20.89 (CH$_3$), 22.05 (CH$_3$), 22.77 (CH$_3$), 24.97 (CH), 25.12 (CH), 31.20 (CH), 31.27 (CH), 34.08 (CH$_3$), 41.15 (CH$_3$), 41.27 (CH$_3$), 48.06 (CH), 48.18 (CH), 76.55 (CH), 76.92 (CH), 77.73 (CH), 92.04 (CH$_3$), 92.44 (CH$_3$), 202.42 (C), 202.53 (C);

M/Z 260 ([M+NH$_4^+$], 100), 243 (16), 186 (12), 169 (10), 156 (9);

C$_{19}$H$_{26}$NO$_3$ [M+NH$_4^+$] requires 260.2226
found 260.2226.

Note
The compound was detected as the [M+NH$_4^+$] ion under ammonia chemical ionisation conditions.

(3S,2R)-3-[(1R)-Menthoxymethoxybutan-2-ol]trimethylsilane (230)

![Diagram of (3S,2R)-3-[(1R)-Menthoxymethoxybutan-2-ol]trimethylsilane (230)]

Magnesium turnings (1.18 g, 51.2 mmol) and a crystal of iodine were covered by
the minimum amount of dry ether, under nitrogen. A solution of chloromethyltrimethylsilane (6.28 g, 51.2 mmol) in dry ether (15 ml) was then added and the reaction mixture heated to reflux to initiate Grignard formation. After heating to reflux for a further 1h, the mixture was cooled to room temperature and then added to a solution of (2S)-2-[(1R)-menthoxymethoxy]propan-1-ol (229) (6.20 g, 25.6 mmol) in dry ether (30 ml), under nitrogen, at -78°C. The reaction was stirred at -78°C for 2h and then allowed to warm to room temperature before quenching with water. Standard aqueous work-up gave (3S,2R)-3-[(1R)-menthoxymethoxybutan-2-ol]trimethylsilane (230) as a colourless oil (3.58 g, 42%) after flash column chromatography (5:1 petroleum ether-ether).

\[ \text{R, 0.26 (5:1 petroleum ether-ether);} \]
\[ \left[ \alpha \right]_D = -40.5° (C=4, \text{CHCl}_3); \]
\[ \nu_{\text{max}} \text{ (film) 3580w, 3440brw (OH), 2930s, 2870s, 1450m, 1410w, 1375m, 1345w, 1270w, 1240m, 1200w, 1180w, 1160w, 1145m, 1075s, 1030s, 980m, 960w, 910w, 865s, 840s;} \]
\[ \delta_\nu (300 \text{ MHz; CDCl}_3) 0.07 (9H, s, \text{Si(CH}_3)_3), 0.59-1.43 (19H, m), 1.61-1.68 (2H, m), 2.08-2.22 (2H, m), 2.39 (1H, brs, OH), 3.33 (1H, td, J=10.5, 4.2 Hz, H-1'), 3.70 (1H, qd, J=6.3, 2.5 Hz, H-3), 3.89 (1H, ddd, J=10.0, 4.7, 2.5 Hz, H-2), 4.77 and 4.86 (2H, AB system, J=7.2 Hz, OCH_2O); \]
\[ \delta_\delta (75 \text{ MHz; CDCl}_3) 0.83 (\text{CH}_3), 13.42 (\text{CH}_2), 16.09 (\text{CH}_2), 19.67 (\text{CH}_2), 21.08 (\text{CH}_2), 22.24 (\text{CH}_2), 23.06 (\text{CH}_2), 25.33 (\text{CH}), 31.52 (\text{CH}), 34.27 (\text{CH}_2), 42.06 (\text{CH}_2), 48.41 (\text{CH}), 70.86 (\text{CH}), 77.99 (\text{CH}), 78.66 (\text{CH}), 92.98 (\text{CH}); \]
\[ M/Z 331 ([\text{M}^+], 55), 313 (6), 241 (7), 186 (34), 169 (74), 156 (41), 139 (17), 90 (100); \]

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A solution of oxalyl chloride (635 mg, 5.00 mmol) in dichloromethane (5 ml) was stirred, under nitrogen, at -78°C. DMSO (520 mg, 6.67 mmol) in dichloromethane (5 ml) was added dropwise and the reaction stirred for 3 min. A solution of (3S,2R)-3-[(1R)-menthoxymethoxybutan-2-ol]trimethylsilane (230) (1.1 g, 3.33 mmol) in dichloromethane (10 ml) was added and the reaction stirred for a further 15 min. Triethylamine (674 mg, 6.67 mmol) was then added and, after 10 min at -78°C, the reaction mixture was allowed to warm to room temperature. After 1h at room temperature the reaction mixture was poured into water. Standard aqueous work-up gave the crude silylketone as a colourless oil, which was dissolved in THF (10 ml) and cooled, under nitrogen, to -78°C. Vinyl Grignard (6.66 ml, 6.66 mmol) was added and the reaction stirred at -78°C for 1h, then allowed to warm to room temperature and quenched by careful addition of water. Standard aqueous work-up yielded (2RS,3S)-2-ethenyl-3-[(1R)-menthoxymethoxybutan-2-ol]trimethylsilane (231) (449 mg, 38%) as an oily 2:1 mixture of diastereoisomers at centres 2 and 3 after flash column
chromatography (10:1 petroleum ether-ether).

Rf 0.48 (5:1 petroleum ether-ether);

[α]D = -58.4° (C=4, CH3Cl);

νmax (film) 3420brw (OH), 3010w, 2920s, 2870s, 1450m, 1375m, 1345w, 1240w, 1215m, 1140m, 1105m, 1075m, 1025s, 980m, 925m, 910m, 860s, 845s, 730w;

δ (300 MHz; CDCl3) 0.00 (9H, s, Si(CH3)3), 0.72-1.39 (19H, m), 1.57-1.63 (2H, m), 2.09-2.21 (2H, m), 2.86 (0.3H, brs, OH), 2.97 (0.7H, brs, OH), 3.21-3.31 (1H, m, H-1'), 3.38 (0.7H, q, J=6.4 Hz, H-3), 3.51 (0.3H, q, J=6.4 Hz, H-3), 4.74 and 4.82 (1.4H, AB system, JAB=6.9 Hz, OCHO), 4.81 (0.6H, A of partially masked AB system, JAB=6.7 Hz, OCHO), 5.07 (0.7H, dd, J=10.7, 1.8 Hz, CCH=CCH), 5.10 (0.3H, dd, J=10.7, 1.8 Hz, CCH=CCH), 5.24 (0.3H, dd, J=17.2, 1.8 Hz, CCH=CCH), 5.32 (0.7H, dd, J=17.2, 1.8 Hz, CCH=CCH), 5.75 (0.7H, dd, J=17.2, 1.8 Hz, CCH=CCH), 5.84 (0.3H, dd, J=17.2, 1.8 Hz, CCH=CCH);

δ (75 MHz; CDCl3) 0.54 (CH2), 15.19 (CH2), 15.52 (CH2), 15.92 (CH2), 20.93 (CH2), 22.07 (CH2), 22.10 (CH2), 22.91 (CH2), 23.08 (CH2), 25.12 (CH2), 31.44 (CH2), 34.16 (CH2), 42.00 (CH2), 48.13 (CH2), 48.26 (CH2), 76.44 (C), 76.99 (C), 79.01 (CH2), 79.36 (CH2), 82.99 (CH2), 83.54 (CH2), 94.45 (CH2), 94.98 (CH2), 113.32 (CH2), 113.57 (CH2), 141.35 (CH), 142.88 (CH);

M/Z ([MH]+-H2O, 85), 273 (9), 243 (16), 227 (7), 215 (23), 201 (41), 183 (13), 169 (29), 155 (20), 139 (28), 111 (100), 81 (16), 73 (7);

C2 H10 O2 Si [MH]+-H2O requires 339.2719
found 339.2719.
To a stirred suspension of excess potassium hydride (obtained as a 35% dispersion in mineral oil) in THF (5 ml), under nitrogen, at room temperature was added a solution of (2RS,3S)-2-ethenyl-3-[(1R)-menthoxymethoxybutan-2-ol]trimethylsilane (231) (200 mg, 0.56 mmol) in THF (5 ml). After stirring for 1h, the reaction was quenched by careful addition of water. Standard aqueous work-up gave (4S)-3-methylene-4-[(1R)-menthoxymethoxy]pent-1-ene (232) as an oily 88:12 mixture of diastereoisomers after flash column chromatography (20:1 petroleum ether-ether).

\[ \text{[a]_D^\text{CHCl}_3 = -1.6'} \]

\[ \nu_{\text{max}} (\text{CHCl}_3) 2950 \text{v}, 2920 \text{v}, 2870 \text{w}, 1450 \text{w}, 1370 \text{m}, 1170 \text{w}, 1150 \text{w}, 1115 \text{m}, 1100 \text{m}, 1080 \text{w}, 1025 \text{w}, 980 \text{w}, 960 \text{w}, 910 \text{v}, 840 \text{w}; \]

\[ \delta (300 \text{ MHz; CDCl}_3) 0.73-1.43 (17 \text{H, m}), 1.59-1.67 (2 \text{H, m}), 2.09-2.64 (2 \text{H, m}), 3.30 (1 \text{H, td, } J=10.4, 4.4 \text{ Hz, H-1'}), 4.51-4.59 (1.1 \text{H, m, H-4 and 0.1OCHO}), 4.67 \text{ and 4.71 (1.8H, AB system, } J_{\text{H,H}}=7.0 \text{ Hz, OCH}_2\text{O}), 4.79 (0.1 \text{H, A of partially masked AB system, } J_{\text{H,H}}=7.3 \text{ Hz, OCHO}), 5.08 (1 \text{H, d, } J=11.2 \text{ Hz, CH=CH=CCH}_3\text{a)}, 5.16 (2 \text{H, d, } J=9.0 \text{ Hz, OCH=CCH}_3\text{a}), 5.36 (0.9 \text{H, d, } J=17.9 \text{ Hz, CH=CCH}_3\text{a)}, 5.38 (0.1 \text{H, d, } J=17.9 \text{ Hz, CH=CCH}_3\text{a)}, 6.31 (1 \text{H, dd, J}_{\text{trans}}=17.9 \text{ Hz, J}_{\text{eq}}=11.2 \text{ Hz, H-2}); \]
\[ \delta_c \ (75 \text{ MHz}; \text{CDCl}_3) \quad 16.09 \ (\text{CH}_3), 21.18 \ (\text{CH}_3), 21.40 \ (\text{CH}_3), 22.34 \ (\text{CH}_3), 22.70 \ (\text{CH}_3), 23.16 \ (\text{CH}_3), 25.38 \ (\text{CH}), 31.46 \ (\text{CH}), 31.65 \ (\text{CH}), 34.41 \ (\text{CH}_2), 34.51 \ (\text{CH}_2), 40.40 \ (\text{CH}_2), 42.82 \ (\text{CH}_2), 48.29 \ (\text{CH}), 48.70 \ (\text{CH}), 71.47 \ (\text{CH}), 71.82 \ (\text{CH}), 78.94 \ (\text{CH}), 89.03 \ (\text{CH}_2), 95.59 \ (\text{CH}_2), 114.48 \ (\text{CH}_2), 114.68 \ (\text{CH}_2), 135.83 \ (\text{CH}), 147.50 \ (\text{C}); \]

M/Z 284 ([M+NH₄]⁺, 88), 267 (7), 249 (15), 237 (13), 219 (18), 186 (34), 169 (28), 156 (28), 137 (20), 111 (100), 95 (18), 90 (12), 81 (48), 47 (54);

\[ \text{C}_9\text{H}_{16}\text{NO}_3 \ [\text{M+NH}_4]^+ \quad \text{requires} \quad 284.2590 \]

\[ \text{found} \quad 284.2589. \]

Note

The compound was detected as the [M+NH₄]⁺ ion under ammonia chemical ionisation conditions.

Correction

I.R. data for compound (77);

\[ \nu_{\text{IR}}(\text{film}) \quad 3040\text{brs} \ (\text{OH}), 3080\text{m}, 3020\text{w}, 2980\text{s}, 2930\text{m}, 2870\text{w}, 1490\text{m}, 1445\text{m}, 1410\text{m}, 1370\text{m}, 1285\text{w}, 1265\text{w}, 1220\text{m}, 1175\text{m}, 1120\text{m}, 1100\text{m}, 1060\text{m}, 1025\text{s}, 990\text{m}, 925\text{s}, 875\text{w}, 770\text{s}, 740\text{m}, 720\text{m}, 700\text{s}, 685\text{m}; \]
APPENDIX

X-RAY CRYSTAL STRUCTURE DATA FOR COMPOUND (150)

All crystals examined were composed of more than one component. The crystal used for data collection was split into two fragments of approximately equal intensity. Photographic data indicated sufficient resolution of the components to allow data collection without overlap.

Crystal data: C$_{n}$H$_{m}$NO$_{z}$, M=317.4, monoclinic, space group P2$_{1}$, $a = 18.570(26)$, $b = 5.829(2)$, $c = 7.945(11)$ Å, $\beta = 90.41(1)^{\circ}$, $\mu = 860(2)$ Å$^{-1}$, $z = 2$, $D_{r} = 1.23$ g cm$^{-3}$, $\mu(MoK\alpha) = 0.44$ cm$^{-1}$, crystal dimensions 0.80 x 0.48 x 0.14 mm.

This data was collected at 298 K, using Mo-K\(\alpha\) x-radiation of wavelength 0.7107 Å, on a Stoe STADI-2 Weissenberg diffractometer. The structure was solved using the TREF direct methods option of SHELXS 86. All subsequent calculations were carried out using the program SHELX. Full matrix least squares refinement of 217 parameters gave the indices $R = 0.0584$ and $R_{w} = 0.059$ for 1154 independent reflections ($I > 3\sigma(I)$) in the range $7 < 2\theta < 54^\circ$. The final residual Fourier map was featureless ($0.15 e\AA^{-3}$).

Atomic coordinates, bond lengths and angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.

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* G.M. Sheldrick SHELXS 84. Program for the solution of crystal structures. University of Göttingen, Germany.

**Figure 9:** X-ray Crystal Structure of (5R)-5-[(S)-1-(2-Naphthyl)-1-ethoxy]-3-phenyl-2-isoxazoline (150).
TABLE 1: Bond lengths (Å) for compound (150), C₅H₆NO₂

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<th>Bond</th>
<th>Length (Å)</th>
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<td>C(23)-C(14)</td>
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<td>C(17)-C(16)</td>
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<td>N(2)-O(1)</td>
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<td>C(18)-C(17)-H(17)</td>
<td>112.9(5)</td>
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</tbody>
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