APPROACHES TO THE
ASYMMETRIC SYNTHESIS OF
2-ARYLPROPANOIC ACIDS

A Thesis
Submitted Towards the
Degree of
Doctor of Philosophy

by

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CONTENTS

Acknowledgements -i-
Abstract -ii-
Statement -iii-
Publications -iv-
Introduction 1

Results and Discussion:

Chapter 1 - Asymmetric Synthesis of Ketoprofen 53
Chapter 2 - Asymmetric Synthesis of Ibuprofen 76
Chapter 3 - Asymmetric Synthesis of 2-Arylpropanoic Acids via Palladium Coupling Reactions 89
Chapter 4 - Asymmetric Synthesis of Ximoprofen 97
Chapter 5 - A Shorter Route for the Asymmetric Synthesis of Ketoprofen 117

Experimental:

General 145
Chapter 1 147
Chapter 2 160
Chapter 3 170
Chapter 4 181
Chapter 5 192
References 200
This thesis is dedicated to Ralph Massy-Westropp, who encouraged me to embark on this endeavour, and has been a constant source of assistance, patience and moral support throughout its entirety. He is also a great friend and I wish him all the best for his retirement.
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ABSTRACT

(S)-2-(3'-Benzoylphenyl)propanoic acid (ketoprofen) and (S)-2-[4'-(2''-methylpropyl)phenylpropanoic acid (ibuprofen) were synthesised in 96%+ e.e. Control of stereochemistry was achieved by a combination of Sharpless epoxidation followed by catalytic hydrogenolysis of the introduced benzylic epoxide oxygen bond.

The coupling of organic compounds in the presence of palladium with enantiopure 2-(3'-iodophenyl)propanoic and 2-(4'-iodophenyl)propanoic acids, prepared by the methodology above, was shown to be a general method for the synthesis of optically active arylpropanoic acids.

The four stereoisomers of the parent keto acid of the oximino drug 2-[4'-(3''-(hydroxyimino)cyclohexyl)phenyl]propanoic acid (ximoprofen) were prepared in high optical purity. The stereochemistry in the propanoic acid chain was established by the methodology above. The configuration of the centre in the cyclohexanone ring was controlled by the stereoselective conjugate addition of the arylpropanoic acid moiety to the enantiomers of 5-(trimethylsilyl)-2-cyclohexenone with subsequent removal of the trimethylsilyl group. Attempts to separate the (E) and (Z) isomers of the oxime derivative of one of the stereoisomers were unsuccessful.

An alternative method for the preparation of (S)-ketoprofen in high optical purity was developed. The stereochemistry was controlled by a combination of Sharpless asymmetric dihydroxylation followed by catalytic hydrogenolysis of the introduced benzylic hydroxyl group.
STATEMENT

This work contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text.

I give consent to this copy of my thesis, when deposited in the University Library, being available for loan and photocopying.

Josephine Newton
12th June, 1995.
PUBLICATIONS


INTRODUCTION

Many biological systems interact differently with the individual enantiomers of chiral compounds. For example, the terpene carvone exists naturally in both enantiomeric forms; (S)-carvone tastes of caraway whereas (R)-carvone tastes of spearmint.

![Chemical structures of (S)-carvone and (R)-carvone](image)

The implications of this biological selectivity can be much more serious, as illustrated by the following cases. Thalidomide was used in the 1960's as a sedative and hypnotic. Administered in its racemic form, its use by pregnant women resulted in a high incidence of foetal deaths and congenital malformations. It was subsequently found that the teratogenic effects were a property of only the (S) enantiomer, while the (R) enantiomer possessed the pharmacologically therapeutic activity.

![Chemical structures of (S)-thalidomide and (R)-thalidomide](image)
(R)-Penicillamine is efficacious in removing heavy metals from the body, and is used in the treatment of Wilson's disease and biliary cirrhosis, where serum and liver copper concentrations, respectively, are excessively high\textsuperscript{2}. It is also used as an antidote for lead, gold or mercury poisoning. This isomer rarely has severe side effects, whereas the (S) enantiomer causes optic atrophy and can lead to blindness.

\begin{center}
\begin{tikzpicture}
\node[draw,shape=circle] (A) {SH};
\node[draw,shape=circle,above of=A] (B) {$\text{NH}_2$};
\node[draw,shape=circle,right of=A] (C) {CO$_2$H};
\node[draw,shape=circle,above of=C] (D) {$\text{NH}_2$};
\node[draw,shape=circle,right of=C] (E) {CO$_2$H};
\node[draw,shape=circle,above of=E] (F) {SH};
\draw[<->] (A) -- (B);
\draw[<->] (B) -- (C);
\draw[<->] (C) -- (D);
\draw[<->] (D) -- (E);
\draw[<->] (E) -- (F);
\end{tikzpicture}
\end{center}

\begin{center}
(S)-penicillamine \hspace{2cm} (R)-penicillamine
\end{center}

These examples serve to highlight what is now a well established fact - that enantiomers of chiral drugs can differ enormously in their pharmacological activity. They may be absorbed, activated or degraded at different rates, one may be inactive, one may be toxic, or the two may have unequal degrees or different kinds of activities. For example the (S) enantiomer of ketoprofen has anti-inflammatory and analgesic properties whereas the (R) enantiomer shows activity against bone loss in periodontal disease, and has potential as a toothpaste ingredient\textsuperscript{5}. The chirality issue has been given much attention in recent years by pharmaceutical companies and regulatory bodies such as the United States Food and Drug Administration (FDA). There is a definite trend towards the development of drugs as single enantiomers, with the worldwide market for enantiopure drugs rising from $27.8$ billion in 1992 to $35.6$ billion in 1993 and having an estimated value of up to $60$ billion in 1997\textsuperscript{6}. One of the major factors influencing this trend is the position taken by the FDA, which was stated in May 1992 in a "Policy Statement for the Development of New Stereoisomeric Drugs". This statement addressed the chemistry,
pharmacology, toxicity and clinical aspects of stereoisomeric drug molecules\textsuperscript{1,4}. Although the FDA will continue to consider racemates as new drugs, guidelines for their approval are becoming more restrictive, with extensive testing of the individual enantiomers now required.

There is also a trend towards "racemic switches", single enantiomers redeveloped from chiral drugs originally marketed as racemates\textsuperscript{5}. Although there is no regulatory pressure for racemic switches, there are commercial advantages and these are being exploited by many pharmaceutical companies. Compounds belonging to the 2-arylpropanoic acid class of non-steroidal anti-inflammatory drugs (NSAIDs) are prime candidates for racemic switches. They are the largest single group of NSAIDs used as general analgesics and to treat rheumatoid arthritis\textsuperscript{1}. Currently there are at least fifteen 2-arylpropanoic acid drugs on the market, which include ibuprofen (1), naproxen (2), flurbiprofen (3) and ketoprofen (4).

\begin{align*}
\text{(1)} & & \begin{array}{c}
\text{CO}_2\text{H} \\
\text{\text{\text{-}}C-H}
\end{array} \\
\text{MeO}\text{C}_{\text{\text{-}}}
\text{(2)} & & \begin{array}{c}
\text{\text{\text{-}}C-H} \\
\text{CO}_2\text{H}
\end{array} \\
\text{(3)} & & \begin{array}{c}
\text{\text{\text{-}}C-H} \\
\text{F}
\end{array} \\
\text{(4)} & & \begin{array}{c}
\text{O} \\
\text{\text{\text{-}}C-H}
\end{array} \\
\text{CO}_2\text{H}
\end{align*}

The mode of action of these drugs is that by cyclooxygenase inhibition they stop the arachidonic acid cascade to prostaglandins and thromboxane A\textsubscript{2} which are
responsible for the inflammation mechanism\textsuperscript{7}. In all cases the desired pharmacological activity resides in the (S) enantiomer, however, with the exception of naproxen the drugs are marketed as racemates. The inactive (R) enantiomer, although innocuous, must be metabolised and excreted, which can place a burden on the kidneys. Further complications arise in the cases of ibuprofen, ketoprofen and flurbiprofen, as the (R) enantiomer undergoes a unidirectional inversion of configuration to produce the (S) enantiomer in vivo\textsuperscript{1} (figure 1). The (R)-profen forms the coenzyme A thioester and a racemase epimerises C2, producing (S)-profen-CoA which is subsequently hydrolysed to the (S)-profen.

\begin{center}
\begin{tikzpicture}
\node at (0,0) [rectangle,draw] {R-profen};
\node at (2,0) [rectangle,draw] {R-profen-CoA};
\node at (0,-2) [rectangle,draw] {S-profen};
\node at (2,-2) [rectangle,draw] {S-profen-CoA};
\node at (1,0) [circle,draw] {Acyl-CoA synthetase};
\node at (1,-2) [circle,draw] {Hydrolase};
\node at (1,1) [circle,draw] {Profen-CoA racemase};
\end{tikzpicture}
\end{center}

Figure 1

Although superficially this may seem desirable, the extent of the inversion varies between patients which leads to uncertainty in the effective dose. Furthermore, an acyl exchange mechanism with endogenous triacylglycerols competes with the hydrolysis of (S)-profen-CoA, and results in the
accumulation of (R)-profen residues in fatty tissues. Because the (S)-profen does not form the CoA thioester it cannot be incorporated into fatty tissue (hydrolysis of (S)-profen-CoA is rapid compared to racemisation). There is concern about the long term accumulation of (R)-profen residues in fatty tissues where there is unknown toxicity and the possibility of transport across the blood-brain barrier\(^1\).

For physiological as well as commercial reasons therefore, there is a great deal of interest in obtaining and marketing 2-arylpropanoic acids in enantiomerically pure form. Consequently there has been a multitude of publications\(^8\) over the past decade concerning methods for achieving this goal; approaches fall into two main categories: resolution of a racemate and asymmetric synthesis.

Although resolution methods are inherently inefficient (the maximum yield of the required enantiomer is 50\% unless the unwanted enantiomer can be recycled) there are several publications in this area. A classical resolution has been employed by Harrison et al\(^9\) to obtain optically pure (S)-naproxen (2b)* (figure 2). Treatment of racemic naproxen with (-)-cinchonidine afforded a mixture of diastereomeric salts. The lower solubility of the diastereomer of the (S)-acid was exploited and repeated crystallisation followed by acid treatment yielded the (S) enantiomer.

\* Throughout this thesis, the letter "a" following a compound number denotes the racemic form. Similarly, "b" and "c" denote the enantiomers.
Many of the more recent resolutions have been enzymatic. They may employ either stereoselective ester formation or hydrolysis\textsuperscript{10-13}. For example, Sheldon et al\textsuperscript{12} subjected the 2-chloroethyl ester of racemic ibuprofen to enzyme catalysed ammoniolysis (with the *Candida antarctica* lipase SP435) and stopped the reaction when 56\% of the substrate was consumed (figure 3). The remaining ester was predominantly the (S) enantiomer, with an e.e.*\textsuperscript{*} of 96\%, which could be hydrolysed without racemisation. These enzymatic resolutions are examples of kinetic resolution in which the diastereomeric transition state

*Throughout this thesis, the optical purity of a compound is expressed as an enantiomeric excess (e.e.). This is defined by equation 1, where $x$ is the major enantiomer and $y$ the minor enantiomer. The optical purity of a diastereomer is described by the analogous term, diastereomeric excess (d.e.).

\begin{equation}
\text{Equation 1: } \% \text{ e.e.} = \frac{x - y}{x + y} \times 100
\end{equation}
energies are sufficiently different to allow a substantial difference in rates of reaction.

\[
\begin{align*}
\text{H}_2\text{C} & \quad \text{H} \\
\text{H} & \quad \text{H} \\
\text{CO}_2\text{H} & \quad \text{CO}_2\text{H}
\end{align*}
\]

\[
\text{(RS)} \quad \text{NH}_4\text{OH, lipase SP435} \quad 56\% \text{ conversion}
\]

\[
\begin{align*}
\text{H}_2\text{C} & \quad \text{H} \\
\text{H} & \quad \text{H} \\
\text{CONNH}_2 & \quad \text{CO}_2\text{H}\text{CH}_2\text{CH}_2\text{Cl}
\end{align*}
\]

\[
\begin{align*}
\text{(R)} & \quad + \quad \text{(S)}
\end{align*}
\]

Figure 3

An advantage of asymmetric synthesis from achiral substrates over resolution methods is that the theoretical yield rises from 50% to 100%. Also, many of the procedures are applicable to a range of substrates, whereas successful resolutions tend to be specific for a particular compound. Many approaches to the asymmetric synthesis of 2-arylpropanoic acids have been explored; an examination of the stereogenic centre reveals the rationale behind many of these strategies. Of the four groups attached to the chiral centre, in principle, any one could be introduced in a stereoselective manner (figure 4):
a) The methyl group could be introduced into an arylacetic acid derivative, for example by alkylation.

b) The C-H bond could be formed by various reactions, for example by stereoselective protonation of a ketene or addition of hydrogen.

c) α-Methyl styrenes could be hydroformylated or hydrocarboxylated.

d) The aryl-C2 bond could be formed, for example by electrophilic substitution.

In fact, there are examples in the literature of each of these cases. A discussion of some representative methods follows.

Fuji et al.\(^4\) have stereoselectively methylated binaphthyl esters of arylacetic acids. The corresponding 2-arylpropanoic acids were then obtained by acid hydrolysis (figure 5).

![Figure 5](image-url)
Their results indicated that the phenolic hydroxyl group of 5 was necessary for reasonable diastereoselectivity. Thus, methylation of 5 afforded 7 in 35% yield with 72% e.e., whereas similar treatment of 6 afforded a 1:1 mixture of 8 and its epimer. The authors have proposed a mechanism to explain these results which relies on the exclusive formation of the enolate shown in figure 6a upon deprotonation of the ester with LDA in THF/HMPA. In this conformation the two naphthyl systems bisect each other at a torsional angle of about 90° for steric reasons, and electrostatic repulsion between the two negatively charged oxygens keeps them maximally apart.

Therefore, when (R)-binaphthol is used as a chiral auxiliary, the si-face of the nucleophilic carbon is shielded by the adjacent naphthyl ring and the re-face is more susceptible to alkylation. In the case of the methyl ether (6), the face discrimination is reduced due to the lesser electrostatic repulsion between the oxygen atoms, allowing rotation about the two carbon-oxygen bonds (fig 6b). The use of bulkier alkylating agents such as isopropyl and isobutyl iodide was explored and found to give greater stereoselectivity, although this is not relevant to 2-arylpropanoic acid synthesis.

As an example of the second class of reactions, Noyori et al\textsuperscript{15} have synthesised (S)-naproxen (2b) with 97% e.e. by homogeneous hydrogenation of the propenoic acid 9, using the chiral binaphthylphosphino ruthenium complex 10.
as catalyst (figure 7). It was proposed that a chelate complex in which the carboxylate and the olefinic double bond coordinate to the ruthenium metal is the reactive intermediate in this process. A variety of substrates were subjected to hydrogenation and it was found that the stereoselectivity was strongly affected by hydrogen pressure, but the effect was dependent on the substrate and was not straightforward.

![Figure 7](image)

Enantioselective protonation of a prochiral ketene intermediate as a route to these compounds has been explored by several groups. Larsen et al. have converted racemic 2-arylpropanoic acids to either their (S) or (R) enantiomers by tertiary amine mediated addition of chiral alcohols to aryl methyl ketenes, to give 2-arylpropanoic esters with d.e.s of 94-99%. Acid catalysed ester hydrolysis then liberated the acids. The chiral alcohols employed were the readily available, naturally occurring (S)-ethyl lactate (11), (R)-isobutyl lactate (12) and (R)-pantolactone (13) (figure 8).
A study of the structural effects of the alcohol was undertaken to determine the controlling feature of the chiral reagent. The most important feature was found to be the proximity of the hydroxyl group to a hydrogen bonding moiety, preferably a carbonyl, with a tertiary alkyl group adjacent to the stereogenic centre also being advantageous. Thus, \((R)\)-ibuprofen (1c) can be obtained with 99\%e.e. by the use of 13 (figure 8).

More recently Calmes et al.\textsuperscript{18} developed an asymmetric synthesis of ketoprofen based on this precedent and found that by varying the tertiary amine used for the ketene formation and as catalyst during addition, the ratio of diastereomeric esters could be strongly modified and even inverted. Under
optimal conditions (R)-ketoprofen was obtained, after saponification, in 98% e.e. The use of (S)-pantolactone (which is not commercially available) as the auxiliary gave (S)-ketoprofen with >99% e.e.

Hydroformylation\textsuperscript{19} and hydrocarboxylation\textsuperscript{20} of styrenes, examples of the third type, have been explored as key reactions in the asymmetric synthesis of 2-arylpropanoic acids. Alper and Hamel\textsuperscript{20} have synthesised (S)-ibuprofen (1b) and (S)-naproxen with 83% and 85% e.e., respectively, by the use of a binaphthyl based chiral ligand for the palladium chloride (PdCl\textsubscript{2}) catalysed hydrocarboxylation reaction (figure 9). The effect of the ratio of substrate : ligand : PdCl\textsubscript{2} was investigated and found to be a significant factor in the determination of enantioselectivity. Furthermore, there was a large variation in selectivity dependent on the ligand used; (-)-menthol, (R)-1,1′-binaphthene-2,2′-diol, (+)-diethyl tartrate and (S)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP) proved to be inefficient, affording acids of <70% optical purity, whereas (R)- and (S)-1,1′-binaphthyl-2,2′-diyl hydrogen phosphate (BNPPA) gave the optimal results quoted above.

\[
\begin{align*}
\text{O}_2, \text{THF}, \\
\text{BNPPA}, \\
PdCl_2, \text{CuCl}_2, \\
\text{HCl} \\
\rightarrow \\
\text{CO}_2 \text{H} \\
(1b) \\
\end{align*}
\]

\[\text{BNPPA} = \]

Figure 9
The fourth type of asymmetric synthesis, stereoselective formation of the aryl-C2 bond as a route to optically active 2-arylpropanoic acids, can be achieved by reaction of a nucleophilic aromatic moiety with an electrophilic alkyl moiety, or vice versa. An example of the former approach has been reported by Hiyama and Wakasa\textsuperscript{21}, who treated (E)-3-penten-2-yl pivalate with 6-methoxy-2-naphthylmagnesium bromide in the presence of the chiral catalyst NiCl\textsubscript{2}[(\textminus)-\(2S,3S\)-2,3-bis(diphenylphosphino)butane] (abbreviated as NiCl\textsubscript{2}[(S,S)-Chiraphos]. Naproxen (2b) was then generated by oxidative cleavage of the double bond, but only with 64\% e.e. (figure 10). The analogous palladium catalyst, PdCl\textsubscript{2}[(S,S)-Chiraphos] was found to be totally ineffective for the bond formation.

![Chemical structure](image)

Figure 10

Addition in the opposite sense has been demonstrated by Piccolo\textsuperscript{22}, who reported the alkylation of aromatic compounds such as benzene, toluene, chlorobenzene and naphthalene with optically active (S)-alkyl 2-(sulphonyloxy)propanoates in the presence of aluminium chloride to afford optically active (S)-alkyl 2-arylpropanoates in moderate to good chemical yields and optical yields of up to 99\% e.e. (figure 11).
The high stereospecificity of the reaction has been rationalised in terms of the formation of a rigid intermediate complex between the ester and aluminium chloride, followed by attack of the aromatic species on the stereogenic carbon from the back side, leading to inversion of configuration (figure 12). A limitation on the practical use of this method is the lack of regioselectivity; as with most Friedel-Crafts alkylations a mixture of ortho, meta and para substituted products is formed (only a minor amount of the meta isomer is usually formed). This was indeed the case when isobutylbenzene was alkylated, and extensive chromatography was required to separate the para substituted ester for hydrolysis to ibuprofen23.
As well as asymmetric syntheses based on formation of one of the four bonds to the chiral carbon, there are several publications concerning stereoselective rearrangement of acetals of the general type 14 where X is a leaving group, often a halogen. Treatment of the acetal with a Lewis acid facilitates the migration of the aryl group to the stereogenic carbon (figure 13). These reactions proceed with inversion of configuration.

The mechanism of this type of reaction is thought to be similar to that of the analogous electrophilic rearrangement of $\beta$-halo arylalkanes. The evidence supports a mechanism which proceeds via a cyclopropane-like intermediate (15) (figure 14).

Electron withdrawing groups decrease and electron donating groups increase the reaction rate, a fact which supports the hypothesis that the aryl group participates in the rearrangement. Molecular orbital calculations provide
additional support by estimating the bridged structure 15 to be 35-50 kcal/mol more stable than any possible conformations of the open chain species 16. When there is a carbonyl group in the benzylic position, the sp$^2$ nature of the carbonyl carbon inhibits the formation of the cyclic transition state, hence the non-occurrence of the acid-catalysed rearrangement in α-haloalkyl aryl ketones$^8$. However conversion of the carbonyl to an acetal not only restores the desired sp$^3$ geometry but also destabilises the first formed carbonium ion and thus facilitates aryl migration to give a highly stable oxonium ion. The most important attribute of this rearrangement in the context of asymmetric synthesis is its total stereospecificity. It proceeds with complete inversion of configuration at the carbon bearing the leaving group. The feature which limits the optically purity of the 2-arylpropanoic acids therefore, is the optical purity of the acetal substrate, as illustrated by the following example.

Piccolo et al$^{29}$ obtained optically active (S)-ibuprofen (1b) (82% e.e.) and (S)-naproxen (96% e.e.) by employing zinc chloride as a Lewis acid to catalyse the aryl migration of the corresponding optically active α-chloroacetals. The inferior optical purity of ibuprofen arises from the synthesis of the rearrangement substrate (figure 15). Optically pure (S)-2-chloropropanoic acid was prepared from (S)-alanine and converted to the acid chloride. This underwent a Friedel-Crafts reaction with isobutylbenzene to give 17, with a small amount of racemisation. Further racemisation occurred during the subsequent acetal formation, which gave 18 with 82% e.e. Rearrangement to 19 proceeded with no loss of optical activity and reasonable chemical yield (75%), as did the ester hydrolysis (65% chemical yield).

Similarly, Lewis acid rearrangement of the naproxen intermediates 20 (96% optically pure) and 21 (91 : 9 mixture of epimers at the migration terminus), gave naproxen with no loss of optical purity (figure 16).
Another approach is illustrated by the enantiodivergent synthesis of Takano et al\textsuperscript{33} of both the enantiomers of ibuprofen. It involves stereoselective substitution at the benzylic carbon of (2S,3S)-3-phenylglycidol (22b), which was obtained by Sharpless epoxidation\textsuperscript{34} of (E)-cinnamyl alcohol.
The epoxide could be regioselectively and stereospecifically opened by either AlMe₃ to afford (2R,3S)-1,2-glycol (23b) or the higher order organocuprate Me₂Cu(CN)Li₂ to afford (2R,3R)-1,2-glycol (24b). In each case the crude alkylation product was treated immediately with diethyl carbonate in the presence of potassium carbonate to yield the cyclic carbonates 25 and 26 in 59%
and 75% yield respectively. Incorporation of the isobutyl substituent by the use of Friedel-Crafts chemistry, followed by deprotection and oxidative cleavage of the diol furnished (S)- and (R)-ibuprofen (1b and 1c) with high optical purity (figure 17).

Chemistry developed by the Hamon - Massy-Westropp group, the subject of this thesis, also relies on the Sharpless epoxidation as a key step in the asymmetric synthesis of 2-arylpropanoic acids. Exploratory work in the group by Slobedman, Coghlan and Hecker\textsuperscript{35,36} is outlined in figure 18.

![Chemical reactions](image)

Figure 18

A Reformatsky reaction between acetophenone and ethyl bromoacetate yielded ethyl 3-hydroxy-3-phenylbutanoate 27, which was dehydrated with phosphorous oxychloride to give a mixture of alkenes. Fractional distillation furnished the (E)-ester 28 which was reduced with lithium aluminium hydride
to give the methylated analogue of (E)-cinnamyl alcohol 29. This underwent enantioselective epoxidation to 30b which could be regio and diastereoselectively ring opened by hydrogenolysis over a palladium catalyst to give, after chromatography, the diol 23b as a single diastereomer. Optically pure (S)-2-phenylpropanoic acid 31b was generated by oxidative cleavage of 23b with sodium metaperiodate and ruthenium trichloride hydrate.

This thesis discusses a range of chemical methods explored to synthesise the analogous halogen substituted intermediates 32b-35b and their conversion to various substituted 2-arylpropanoic acids.

\[
\begin{align*}
\text{(32b)} & \quad \text{(33b)} & \quad \text{(34b)} & \quad \text{(35b)} \\
\text{OH} & \quad \text{OH} & \quad \text{CO}_2\text{H} & \quad \text{CO}_2\text{H} \\
X & \quad X & \quad X & \quad X \quad \text{(halogen)}
\end{align*}
\]

The key, stereoselective reactions in this synthetic approach are the Sharpless epoxidation and hydrogenolysis of the resultant epoxide, and as such, they deserve further discussion.
Epoxides are extremely versatile and useful building blocks in organic synthesis as their reactivity in ring opening reactions provides a means for introduction of 1,2 bifunctionality into a molecule, often with excellent control of stereochemistry. With the current trend towards the synthesis of chiral compounds as single enantiomers, there have been hundreds of publications concerning the synthesis of chiral epoxides by chemical and biological methods, as surveyed in a recent review. Probably the most widely used of these methods is the Sharpless epoxidation, which uses allylic alcohols as substrates and gives epoxides of uniformly high optical purity throughout a range of substitution patterns in the substrate. Table 1 illustrates the versatility of the reaction.

<table>
<thead>
<tr>
<th>Allylic alcohol</th>
<th>Product</th>
<th>Yield %</th>
<th>e.e. %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph&lt;sup&gt;→&lt;/sup&gt;-OH</td>
<td>Ph&lt;sup&gt;→&lt;/sup&gt;-OH</td>
<td>89</td>
<td>&gt;98</td>
</tr>
<tr>
<td>C&lt;sub&gt;7&lt;/sub&gt;H&lt;sub&gt;15&lt;/sub&gt;-OH</td>
<td>C&lt;sub&gt;7&lt;/sub&gt;H&lt;sub&gt;15&lt;/sub&gt;-OH</td>
<td>74</td>
<td>86</td>
</tr>
<tr>
<td>C&lt;sub&gt;3&lt;/sub&gt;H&lt;sub&gt;7&lt;/sub&gt;-OH</td>
<td>C&lt;sub&gt;3&lt;/sub&gt;H&lt;sub&gt;7&lt;/sub&gt;-OH</td>
<td>88</td>
<td>95</td>
</tr>
<tr>
<td>Ph&lt;sup&gt;→&lt;/sup&gt;-OH</td>
<td>Ph&lt;sup&gt;→&lt;/sup&gt;-OH</td>
<td>79</td>
<td>&gt;98</td>
</tr>
<tr>
<td>=OH</td>
<td>=OH</td>
<td>65</td>
<td>90</td>
</tr>
</tbody>
</table>

Table 1
An advantageous feature of the reaction is that the absolute stereochemistry is predictable, according to a set of rules laid down by Sharpless; when the olefinic unit is in the plane of the drawing with the hydroxymethyl substituent on the lower right as shown in figure 19, the use of (+)-tartrate leads to addition of the epoxide oxygen from below the plane. Conversely, when (-)-tartrate is used, the epoxide oxygen is added from above the plane38.

![Diagram](image)

**Figure 19**

Another widely exploited feature of the reaction, although not relevant to the work discussed in this thesis, is its effectiveness in kinetic resolutions of secondary allylic alcohols34,39 (figure 20). The relative rates of reaction for the enantiomeric pairs of a variety of substrates studied by Sharpless range from about 15 : 1 to 140 : 1. Although the reactions were only carried out to approximately 55% completion, the observed optical purity of the recovered starting material was in many cases > 96% e.e., thus this method provides an excellent route to optically active allylic alcohols. If material of even higher optical purity is required, it can be obtained by allowing the reaction to run
further, thus the kinetic resolution of 2-methylhept-1-en-3-ol via epoxidation affords material of 96% e.e. at 55% conversion and 99.999999999% e.e. at 60% conversion (from theoretical calculations).

\[
R\begin{array}{c}
\text{Ti(O-iPr)}_4 \\
(+)-\text{DIPT} \\
\text{TBHP}
\end{array} \text{OH} \\
\text{R and R'} = \text{alkyl}
\]

Figure 20

The reaction requires four essential components: (+) or (-) diethyl tartrate (DET) (or diisopropyl tartrate (DIPT)), titanium tetraisopropoxide (Ti(Oi-Pr)_4), tert-butylhydroperoxide (TBHP) and an allylic alcohol. The presence of activated, crushed molecular sieves (zeolites) has been found to be crucial to the catalytic nature of the reaction, which suggests an extreme sensitivity to water. Furthermore, the procedure must be conducted at low temperature (-20°C) for optimal stereoselectivity. The structure of the active catalyst and the mechanism of the reaction are far from straightforward. Two detailed hypotheses have been put forward to account for the experimental observations, one by Sharpless^{40-42} and the other by Corey^{43}.

Sharpless proposes that upon mixing equimolar amounts of tartrate and Ti(Oi-Pr)_4, the equilibrium in figure 21a is soon established, due to the rapid exchange of titanium ligands in solution and the affinity of chelating diols (i.e., the tartrate) for titanium, which is higher than that of monodentate alcohols. After formation of the Ti(tartrate)(Oi-Pr)_2 complex, the two remaining alkoxide ligands are replaced in reversible exchange reactions by TBHP and the allylic alcohol to give the "loaded" catalyst Ti(tartrate)(TBHP)(allylic alcohol). Oxygen
is then transferred from the coordinated TBHP to the allylic alcohol to give the complex Ti(tartrate)(Oi-Bu)(epoxy alcohol) and the epoxy alcohol product is replaced by more TBHP and allylic alcohol to regenerate the "loaded" complex, which completes the catalytic cycle (figure 21b).

\[
\text{Ti(Oi-Pr)}_4 + \text{tartrate} \xrightarrow{\text{TBHP}} \text{Ti(Oi-Pr)}_2(\text{tartrate}) + 2 \text{i-PrOH}
\]

Figure 21a

![Diagram](image)

Although mechanistically figures 21a and 21b provide background to the reaction, the catalyst structure is more complex than indicated in these diagrams. Sharpless proposes a dimeric complex, Ti₂(tartrate)₂(OR)₄ (figure 22), which exists in fluxional equilibrium in solution. This species has not
been isolated due to the rapid exchange of ligands and the non-crystalline nature of the complex. The basis for the proposal is spectroscopic data and X-ray crystallographic structures obtained for several closely related compounds, which show very similar reactivity and enantiofacial selectivity. Examination of figure 22 reveals a tartrate-bridged, six coordinate structure with a $C_2$ axis of symmetry with the rotation axis perpendicular to the planar $Ti_2O_2$ ring.

The epoxidation probably occurs on a single titanium centre in the dimeric complex. The tartrate provides an asymmetric environment about each titanium atom, and the olefin and peroxide moieties must bind to the complex with a particular orientation with respect to one another. With regard to the replacement of the OR ligands, molecular modelling indicates that the bulky alkyl peroxide occupies the less sterically crowded equatorial position and the allylic alcohol the axial position. Theoretically, the peroxide O-O bond could be oriented in the equatorial plane, perpendicular to the plane, or at any angle in between these. However, the most favourable approach of the olefin to the coordinate peroxide is along the axis of the O-O bond being broken, and the conformation in which the O-O bond is nearly perpendicular to the equatorial
plane is most favoured for this to occur. Thus, figure 23 shows the most likely representation of the "loaded" catalyst at the time of oxygen transfer.40

In contrast, Corey's explanation of the Sharpless epoxidation involves an ion-pair like intermediate 36 (figure 24). One molecule of the tartrate ester is chelated to the titanium of the cationic moiety of 36, as is the hydroxyl group of the allylic alcohol. In this way hydrogen bonding to the carbonyl of the tartrate ester can occur. The peroxo group is chelated to the same titanium atom in such an orientation that steric interactions with the tert-butyl group are minimal. The specific arrangement of ligands about this titanium dictates that the absolute configuration of the titanium in the cationic moiety is determined by the tartrate ligand. As a consequence of these factors, intramolecular epoxidation at only one face of the double bond will be favoured if the olefin approaches the peroxo O-O bond with the C=C axis being approximately perpendicular to the O-O axis. As discussed in the Sharpless model, this is the most favourable arrangement for approach. Although Corey claims this hypothesis accounts for all known experimental data, including the observed kinetic resolution of racemic allylic alcohols, and is "more explicit and rational
than any of the mechanisms previously advanced", Sharpless rejects it on the grounds that it is inconsistent with the observed kinetic data.

Figure 24
In terms of synthetic application, reactions of the optically active epoxides from the Sharpless epoxidation must be highly stereoselective to ensure the optical purity is retained. Hydrogenolysis of benzylic C-O bonds has been shown to proceed stereoselectively, with varying degrees of control and with retention or inversion of configuration dependent on a number of factors including the catalyst used, solvent, leaving group ability of the oxygen, the amount of hydrogen on the catalyst, temperature, substrate structure and steric factors. Retention of configuration is usually observed over nickel, cobalt and copper catalysts, whereas palladium and platinum catalysts usually lead to inversion of configuration, often with excellent stereoselectivity\textsuperscript{44,45}. For example Esashi et al\textsuperscript{46} have shown that the reduction of ethyl atrolactate over a nickel catalyst proceeds with 99% retention of configuration and with a palladium catalyst 97.5% inversion of configuration (figure 25).

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {\text{ethyl atrolactate}};
\node (b) at (2,1) {\text{98\% e.e.}};
\node (c) at (2,-1) {\text{95\% e.e.}};
\draw [->] (a) -- (b);
\draw [<-] (a) -- (c);
\end{tikzpicture}
\end{center}

Figure 25

Several mechanisms have been proposed to account for these observations\textsuperscript{45}, with the most widely accepted being that of Esashi\textsuperscript{46}, which is based on the affinity of the metal for oxygen. He suggests initial π absorption of the phenyl group onto the catalyst surface followed by the nucleophilic attack of an electron from the surface of the catalyst on the adsorbed substrate. In the
resultant π benzylic complex, there is a tendency toward sp² hybridisation at the benzylic carbon, with the C-O bond becoming labile and finally breaking as the oxygen combines with hydrogen from the catalyst surface. Figure 26 illustrates the mechanism for the two possibilities of hydrogenolysis occurring with retention of configuration (route 1) and inversion (route 2).

Eshashi’s hypothesis is that the stereoselectivity is not determined by the adsorption of the substrate or by the decomposition of 40 and 40' with
hydrogen, but by the difference in free energy levels of the two transition states 39 and 39', since the activation energies for the cleavage of the C-O bond (38 to 40 and 38' to 40') is larger than those for the adsorption of the substrate (37 to 38 and 37 to 38') and decomposition of the carbon-metal bond of the $\pi$ benzylic complex to the adsorbed products (40 to 41 and 40' to 41'). In the case of palladium catalysis the free energy of transition state 39' is lower than that of 39, possibly due to the $S_N2$ nature of electron attack in route 2 being stereoelectronically advantageous over the $S_Ni$ type of displacement in route 1, in which the leaving group is ejected on the same side as electron attack. It follows that when nickel is the catalyst, the free energy level of 39 is lower than that of 39'. Nickel has a strong affinity for oxygen, thus it may adsorb the groups containing oxygen more strongly than palladium thereby decreasing the free energy level of 38 and the activation energy involved in the conversion of 38 to 40.

An important factor which influences the rate of hydrogenolysis, or whether the reaction proceeds at all, is the nature of the oxygen attached to the benzylic carbon. The greater the ability of the oxygen to bear a negative charge, the more easily it leaves, thus in the system PhCH$_2$OR, the rate increased in the order OH < O-alkyl < O-aryl < OH$^+$-alkyl < OH$_2^+$ < OAc < OCOCF$_3$. In cases where the oxygen is part of an epoxide ring, it can be considered an excellent leaving group due to the large release of ring strain upon cleavage of the C-O bond. Sugi et al$^{48}$ have successfully hydrogenolysed 1-phenyl-7-oxabicyclo[4.1.0.]heptane (42) and analogues under mild conditions, and Hamon et al$^{35}$, in preliminary work to this thesis, converted the epoxide 30b to the diol 23b as a single diastereomer, and established that the reaction had proceeded with inversion of configuration at the benzylic carbon (figure 27).
Conditions for the hydrogenolysis of benzylic C-O bonds may also effect cleavage of aryl-halogen bonds. The order of reactivity for the halogen loss is I > Br > Cl > F. This alternative mode of action of the reagents has the potential to compete with the cleavage of the benzylic C-O bond of epoxides 43 and 44, which is the desired process in the synthesis of the key intermediates 32b and 33b in the present study.
Several possibilities exist for the introduction of alkyl substituents into the aryl group of 32b or 33b (or the carboxylic acids 34b and 35b). Grignard formation and addition to a carbonyl moiety is an obvious approach; similarly other anionic forms of the aryl moiety could perform the addition. This method would require protection and subsequent deprotection of the hydroxyl groups and removal of the resultant hydroxyl at the addition site (unless it or a derivative is required). In principle 34b or 35b could be converted to the required dianion, but the likelihood of racemisation under the basic reaction conditions makes this approach less attractive.

Palladium catalysed coupling between aryl halides and organometallic reagents is now recognised as an extremely efficient method for C-C σ-bond formation, and could provide an alternative means of replacing the halogen of 32b, 33b, 34b or 35b (page 31) with a range of substituents. In 1972, Corriu and Kumada independently reported that the cross coupling of Grignard reagents with aryl halides was significantly catalysed by certain nickel-phosphine complexes. The synthetic utility of the reaction prompted further research into its scope and versatility, and today there is a multitude of publications concerning various catalysts, substrates and organometallic reagents. Palladium-phosphine complexes may be used interchangeably with their nickel analogues in many cases, and promote considerably greater chemoselectivity than the nickel catalysts. However they are not as reactive towards aryl halides and whereas nickel catalysed cross-couplings occur readily with aryl iodides and aryl bromides, palladium catalysed cross-couplings will not occur with aryl bromides unless they are activated by an electron withdrawing group (the order of reactivity of halogens in these reactions is I > Br > Cl).
Organometallics containing zinc, aluminium, tin and zirconium have also been utilised; as they are less electropositive than Grignard reagents they are more compatible with electrophilic functional groups such as esters, amides, nitriles and nitro compounds. Since Negishi et al.\textsuperscript{53} first reported the palladium catalysed cross-coupling of aryl zinc derivatives with aryl halides, methyl, alkenyl, benzyl and alkynyl zinc reagents have also been successfully employed\textsuperscript{54}. The mechanism involved in cross-couplings of this type is thought to proceed through an oxidative addition - transmetallation - reductive elimination cycle\textsuperscript{52}, as depicted in figure 28.

![Figure 28](image)

\begin{align*}
\text{PdLn} &= \text{palladium-phosphine complex} \\
\text{ArX} &= \text{aryl halide} \\
\text{R}_2\text{Zn} &= \text{methyl, alkenyl, benzyl or alkynylzinc}
\end{align*}

The above examples augured well for the current work and it was envisaged that the carboxylic acids 45b and 46b could be coupled to a variety of zinc reagents by use of the catalyst prepared from dichlorobis-
(triphenylphosphine)palladium(II) $[\text{Cl}_2\text{Pd(PPh}_3)_2]_2$ and two equivalents of diisobutylaluminium hydride (DIBALH), in accordance with the method of Negishi (figure 29).

![Figure 29](image)

(45b): *meta*  
(46b): *para*

There is precedent for palladium catalysed cross-coupling reactions occurring in the presence of a carboxylic acid moiety; Toyama Chemical Co. Ltd. prepared racemic 48 via the coupling of 46a with 47 in the presence of palladium chloride and zinc chloride (figure 30).

![Figure 30](image)

This approach would give access to a range of substituted arylpropanoic acids from a common precursor in each of the *meta* or *para* series (45b and 46b). Because the aryl substituent is introduced after the oxidation to the carboxylic acid, oxidation sensitive groups such as benzyl, alkenyl and alkynyl moieties could be incorporated.
The discussion so far has been concerned with the synthesis of 2-arylpropanoic acids with relatively simple aryl substituents. 2-[4'-{(3''-\{Hydroxyimino\}cyclohexyl)phenyl]propanoic acid (ximoprofen, 49) is a more complex target for asymmetric synthesis as it has two chiral centres and an oxime functionality which can exist in the (E) or (Z) configuration.

![Structural formula of ximoprofen](image)

Ximoprofen was reported in 1990\textsuperscript{56} to be a significantly more potent anti-inflammatory agent than ibuprofen (the most widely used drug of this class) with a lower incidence of gastro-intestinal side effects. Although several metabolic and pharmacokinetic studies have been published\textsuperscript{56-58}, no information has been reported regarding the pharmacological activity or synthesis of the individual stereoisomers of ximoprofen. This information is required by regulatory organisations before a new drug can be released for commercial use. Therefore development of a route to these stereoisomers could hasten the process of drug development.

From a retrosynthetic point of view, the oxime moiety can be formed from the corresponding carbonyl group, although whether there would be significant selectivity between the (E) and (Z) oximes is doubtful due to the similar nature of the two groups α to the carbonyl (they are both methylene groups). Chromatographic separation of the mixture would be necessary to obtain the individual oximes. The target molecule for the synthesis would therefore be
the corresponding keto acid 50, which can be considered to be made up of two portions, labelled subunit 1 (containing stereogenic centre 1) and subunit 2 (containing stereogenic centre 2) (figure 31).

![Subunit diagram](image)

(35b): $X = \text{halogen}$

Subunit 1 is analogous to the key intermediate carboxylic acid 35b, thus it was envisaged that the stereochemistry at centre 1 could be controlled by a Sharpless epoxidation of the precursor allylic alcohol and subsequent stereoselective hydrogenolysis to the diol as previously discussed. Oxidative cleavage of the diol would generate the carboxylic acid. Access to either configuration at centre 1 would be possible, by use of either (+)- or (-)-tartrate in the epoxidation reaction.

Control of stereochemistry at centre 2 could foreseeably be achieved by an asymmetric conjugate addition of subunit 1 in the form of a nucleophilic organocopper species to a chiral cyclohex-2-enone derivative, as outlined in figure 32. Removal of the $R^*$ group would yield subunit 2. Because the carboxylic acid moiety of subunit 1 would be incompatible with the nucleophilic environment of the reaction, it should be in a masked form, for example as the protected precursor diol 51b (figure 32).
There are examples in the literature of chiral cyclohex-2-enone derivatives which undergo asymmetric conjugate additions\(^{59,60}\). The mechanism of the addition reaction has not yet been elucidated, and probably varies depending on the substrate and the organocuprate used, however the basic principles are generally agreed upon. The initial step is thought to be co-ordination of the enone carbonyl with lithium or magnesium, followed by electron transfer from the organocuprate to the enone. The subsequent formation of the new C-C bond is not fully understood; it may occur via direct nucleophilic addition, it may involve a single electron transfer, or it may be preceded by co-ordination between copper and the \(\pi\) system\(^{61}\). A recent publication by Corey\(^{62}\) discusses the likely sequence of events for the addition of the homocuprate (Me\(_2\)CuLi)\(_2\) (52) to cyclohex-2-enone. The cuprate exists as a rectangular species with methyl groups at the corners and alternating lithium and copper atoms in the centre of each edge. Initial complexation between 52 and the enone leads to formation of a copper (III) \(\beta\)-adduct, possibly due to a \(d,\pi^*\)-complex such as 53 which involves copper as a \(d^{10}\) base and the carbonyl and olefinic carbons (\(\pi_3^*\)) as a \(\pi\)-acid. The \(d,\pi^*\) mechanistic pathway is outlined in figure 33.

\[
\text{Figure 32}
\]

\[
\text{\textit{OR}}
\]

\[
\text{\textit{R}} = a \text{ group which renders the molecule chiral}
\]

\[
\text{\textit{X}} = \text{halogen}
\]

\[
\text{\textit{R}} = a \text{ protecting group}
\]
Although the exact structure of the d,π*-complex is not known, Corey proposes 54 (R=H) as a more accurate geometrical representation of 53, which is consistent with experimental observations. If R=alkyl, the complex can exist in either the trans or cis geometry. Because the cis isomer will be less favourable due to repulsion between copper and the axial alkyl substituent (figure 34), the reaction pathway proceeds through trans-54 to give the observed trans addition products.

Corey’s explanation for the experimentally observed high diastereoselectivity in conjugate additions to 5-alkylated cyclohex-2-enones, in which trans-3,5-disubstituted cyclohexanones are formed is based on steric grounds. An
alternative rationalisation of the mechanism\textsuperscript{63-65} assumes that the kinetically controlled conjugate addition of an organometallic reagent to a conjugated cyclohexenone is subject to stereoelectronic control, as illustrated in figure 35 for a 5-alkyl-2-cyclohexenone. The figure illustrates the two modes of addition (approximately perpendicular to the plane of the double bond) to each of the conformers in which the R group is either axial or equatorial. Because the R group offers little hindrance in three of the four reaction paths it is considered that control of the addition depends on the relative energies of the transition states leading to the two boat and two chair-like intermediates. The pathways leading to the boat forms (B and C) would be energetically unfavourable. Of the two proceeding to the chair intermediates, one would be a higher energy pathway (D) in which severe steric interactions arise between the incoming group and R. The preferred pathway (A) is therefore that leading through the other chair intermediate to the observed trans-3,5-disubstituted-cyclohexanone.

![Figure 35](image-url)

**Figure 35**
One chiral cyclohexenone derivative which has been developed and studied by Asaoka et al\textsuperscript{66,67} is 5-trimethylsilyl-2-cyclohexenone, available as either enantiomer (55b or 55c) in optically pure form.

These workers designed the molecule specifically as a building block to aid in the synthesis of chiral natural products. Their reasoning behind the design was that the bulky trimethylsilyl (TMS) group would give rise to high diastereoselectivity upon approach of a nucleophile to the β-position of the enone. To test the stereoselectivity of the conjugate addition, several Grignard reagents (including phenyl, p-tolyl, methyl, tert-butyl and hexylmagnesium halide) were added to the racemic ketone 55a in the presence of copper bromide - dimethylsulphide complex (CuBr-SMe\textsubscript{2}), TMSCI and hexamethyl-phosphoric triamide (HMPA). The corresponding trans-3,5 adducts were obtained in high yields, with no trace of the cis isomer. Elimination of the TMS group from the products with cupric chloride in DMF gave the α,β-unsaturated ketone. The enone could be manipulated further as required.

Optically pure (S)- or (R)-ketone (55b or 55c) was obtained via a kinetic resolution of 55a by addition of 0.55 equivalents of p-toluenethiol in the presence of a catalytic amount of cinchonidine (figure 36).
The addition products 56b and 57b (only a small amount of 57b was produced) are crystalline and were readily separated from unreacted enone by filtration. Recrystallisation removed 57b and improved the optical purity of 56b from 57% to 100% e.e. Optically pure 55c was then generated by treatment of 56b with DBU. Distillation of the filtrate from the kinetic resolution afforded 55b (54% e.e.) which was converted to the crystalline trans-adduct by triethylamine catalysed addition of p-toluenethiol. Recrystallisation followed by treatment with DBU gave optically pure 55b. More recently, an alternative synthesis of optically pure 55b and 55c was developed by Takano et al\textsuperscript{68}, using an enzymatic reaction to introduce asymmetry into the molecule.

The above method relies on a substituent in the 5-position of the cyclohexenone ring for asymmetric induction. Posner et al\textsuperscript{63,64} have developed cyclohexenone and cyclopentenone derivatives with chiral sulphinyl moieties in the 2-position and shown that they undergo conjugate
addition reactions with a variety of nucleophiles to give 3-substituted cyclohexanones (and cyclopentanones) with good to excellent levels of optical purity. For example, addition of phenyllithium to (S)-2-(p-tolylsulphinyl)-2-cyclohexanone (58b) in 2,5-dimethyltetrahydrofuran (DMTHF) with chlorotitanium triisopropoxide, followed by in situ removal of the sulphinyl group with aluminium amalgam afforded 59b in 58% yield, with an e.e. of 93% (figure 37).

\[
\text{i) PhLi/(i-PrO)\text{TiCl} \\
\text{ii) Al-Hg}
\]

Figure 37

These authors proposed a mechanism in which the sulphonyl and the carbonyl chelate with chlorotitanium triisopropoxide to give the complex represented by structure 60 (figure 37a). As a result, the p-tolyl group is restrained in a position which shields one face of the olefin at the C-3 position, which allows nucleophiles to approach the more accessible face selectively.

\[
\text{Nu}
\]

Figure 37a
Posner has investigated factors which influence the stability of this complex, reasoning that the more stable the complex is, the greater the level of asymmetric induction should be. One variable he explored was the group attached to the aromatic ring. The expectation was that a more strongly electron donating group such as a methoxyl would increase the Lewis basicity of the sulphinyl oxygen, thereby strengthening the Ti-O bond and making a more conformationally rigid system. Indeed, comparison of 60 and 61 in conjugate additions with a variety of nucleophiles showed 61 to give a greater degree of stereoselectivity. Another variable considered was the solvent. Initial studies were performed with THF as solvent, however Posner reasoned that a reduction in the complexing ability of the solvent would allow more effective chelate formation between the Ti ion and the β-ketosulphoxide. DMTHF is known to have a lower complexing ability than THF and was chosen to test this hypothesis. p-Anisyl sulfoxides were not soluble in DMTHF, however comparison of stereoselectivity in conjugate additions of p-tolylsulphoxides showed DMTHF to be superior to THF. Optimal stereoselectivity was obtained using p-tolylsulphoxides in DMTHF.

Synthesis of 58b was achieved by Posner\textsuperscript{71} by the addition of the anion derived from bromo acetal 62 to (-)-menthyl p-toluenesulphinate 63 followed by acetal removal (figure 38). The sulphinate ester 63 is readily available from the reaction of p-toluenesulphinyl chloride with (-)-menthol. The mixture of diastereomeric menthyl p-toluenesulphinates 63 and 64 has been equilibrated and separated by selective crystallisation to enable the preparation of the pure diastereomer 63 (figure 38).
With respect to the asymmetric synthesis of ximoprofen, either 55b (or 55c) or 58b (or 58c) would be suitable substrates for the conjugate addition of the key intermediate 51 as discussed on pages 36-37.

The discussion to this point has dealt with the asymmetric syntheses of a variety of 2-arylpropanoic acids in which the stereochemistry at the 2 position is controlled by a Sharpless epoxidation and subsequent hydrogenolysis reaction. An alternative approach can be envisaged which makes use of a catalytic asymmetric dihydroxylation reaction to introduce chirality into the
molecule. This approach forms the basis of Chapter 5. The asymmetric dihydroxylation (AD) reaction has recently been developed by Sharpless et al.\textsuperscript{72,73} as a method for enantioselective formation of 1,2-diols from olefins. There is no requirement for a directing functional group in the substrate, unlike the Sharpless epoxidation reaction which only proceeds with allylic alcohols. The scope of the reaction therefore is much broader.

The procedure is an extension of the standard osmium tetroxide oxidation of olefins to cis-1,2-diols, which originally required a stoichiometric quantity of oxidant and was not enantioselective\textsuperscript{74}. The uneconomical nature of these conditions prompted the development of catalytic variants of the reaction which use inexpensive reagents to reoxidise the osmium \textit{in situ}. A range of co-oxidants has been used which includes hydrogen peroxide, sodium or potassium chlorate, \textit{tert}-butylhydroperoxide and N-methylmorpholine N-oxide. Potassium ferricyanide (K\textsubscript{3}Fe(CN)\textsubscript{6}) in the presence of potassium carbonate has recently been found to provide a powerful system for the osmium catalysed dihydroxylation of olefins\textsuperscript{72}. Tertiary amines have been found to accelerate the reaction by a phenomenon known as the ligand acceleration effect. This involves the formation of a monoamine complex between OsO\textsubscript{4} and the tertiary amine, with which the olefin reacts (see figure 39 for more detail of the mechanism).

Research by the Sharpless group addressed the matter of enantioselectivity in the osmylation, and it was found that the use of acetate esters of some cinchona alkaloids as chiral ligands in the reaction gave diols with moderate to good e.e.s. Various conditions and reagents were explored in an attempt to optimise the yield and optical purity of the products while maintaining efficient catalysis. Homogeneous reaction conditions allowed a second catalytic cycle to compete, which exhibited little or no enantioselectivity, resulting in product
diols with diminished e.e.s. Performing the reaction under two-phase conditions with K₃Fe(CN)₆ as co-oxidant virtually eliminated participation of the second catalytic cycle, as OsO₄ is the only oxidant in the organic layer where the osmylation takes place. The resultant osmium(VI) monoglycolate ester is hydrolysed at the aqueous/organic solvent interface and the diol and ligand are released into the organic layer. Meanwhile the reduced osmium VI is released into the aqueous phase where it is reoxidised to OsO₄ by K₃Fe(CN)₆ and then migrates back into the organic phase to restart the cycle (figure 39).

Another key discovery was that the rate of hydrolysis of the osmium(VI) glycolate product can be markedly increased by methyl sulphonamide (MeSO₂NH₂). This additive allows high catalytic turnovers even with sterically crowded substrates which include some tetrasubstituted olefins. This
"sulphonamide effect" enables most reactions to proceed at 0°C rather than room temperature, which usually improves the stereoselectivity (reactions of terminal olefins do not require addition of MeSO₂NH₂).

The use of different chiral ligands has also been investigated. Those with phthalazine and diphenylpyrimidine cores attached to a chiral heterocyclic spacer [dihydroquinidine (DHQD) or dihydroquinine (DHQ)] have been shown to be the most suitable in terms of stereochemical induction and the scope of the reaction (figure 40). In their role as chiral ligands, DHQD and DHQ function almost as if they were enantiomers, although they are in fact diastereomers.

![Phthalazine (PHAL) ligands](image1)

![Diphenylpyrimidine (PYR) ligands](image2)

*Alk = DHQD or DHQ

![DHQD](image3)

![DHQ](image4)

Figure 40
Several studies have been done to determine the mechanistic basis for enantioselectivity in the reaction\textsuperscript{73,75,76}. The most likely explanation has recently been put forward by Sharpless\textsuperscript{76}. He proposes that the osmaoxetane intermediate derived from styrene and (DHQD)\textsubscript{2}PHAL has the structure depicted in figure 41 (the structure is based on molecular mechanics calculations and NOE experiments). An important feature of the structure is the "enzyme-like binding pocket" in which the aromatic ring of the styrene resides. Excellent rates and enantioselectivities are obtained with phthalazine ligands and styrenes, due to especially good transition state stabilisation. This results from interactions between the aromatic substituent of the styrene and the phthalazine floor of the ligand, which occupy parallel planes. There are also favourable edge to edge interactions with the "bystander" methoxyquinoline ring.

![Diagram](image)

**Figure 41**

The cinchona alkaloid backbone contains other features which enhance ligand acceleration and enantioselectivity, some of which are listed below.

- the methoxyl group (see figure 40 or 41) increases binding to OsO\textsubscript{4} as well as increasing rates
- oxygenation at the benzylic position is essential to allow binding to OsO₄ (a carbon substituent is too bulky)
- the configuration at the benzylic carbon is important; only the erythro isomer allows high rates and binding.

An alternative mechanistic proposal by Corey⁶⁸ has fundamental problems associated with it and is not as well supported by experimental data⁶⁸a.

The scope of the Sharpless dihydroxylation reaction is broad. The substitution pattern of the olefinic substrate influences the outcome of the reaction, and some substitution classes give diols of higher e.e.s than others, however four out of the six possible substitution classes have representatives which can be hydroxylated with 94% e.e. or higher. Another advantageous feature of the reaction is that the absolute stereochemistry of product diols can be accurately predicted, by the use of a relatively simple mnemonic⁷³.

Either enantiomer of a particular diol is accessible, dependant on the choice of chiral ligand for the reaction. As mentioned in relation to figure 40, DHQ and DHQD are not strictly enantiomers, but the portions of the molecules involved in the chiral binding cleft of the catalyst are enantiomeric, therefore they lead to diols of opposite configuration. The reagents necessary for the reaction are commercially available as a premixed powder known as AD-mix. It is available in two forms; AD-mix-α contains potassium osmate (0.05%), (DHQ)₂-PHAL (5%), K₃FeCN₆ and K₂CO₃; AD-mix-β is identical except it contains (DHQD)₂-PHAL (5%) instead of (DHQ)₂-PHAL. The experimental procedure is simple and involves stirring the reagents in a t-butyl alcohol/water (1:1) mixture.

The Sharpless dihydroxylation reaction could provide an alternative to the Sharpless epoxidation reaction for the introduction of chirality in the asymmetric synthesis of 2-arylpropanoic acids. A suitable starting material
would be a substituted \( \alpha \)-methylstyrene derivative 65, which could be converted to the corresponding optically active diol 66b or 66c. Hydrogenolysis of the benzylid hydroxyl group with a palladium catalyst should then proceed with inversion of configuration to 67b or 67c, in an analogous manner to hydrogenolysis of the epoxide 30b (page 19-20). Oxidation of the resultant alcohol would afford the optically active 2-arylpropanoic acid. Good results in the dihydroxylation reaction have been obtained with model compounds. \( \alpha \)-Methylstyrene (65, R=H) has been treated with AD-mix-\( \beta \) to give 66c (R=H) with 94% e.e. and with AD-mix-\( \alpha \) to give 66b (R=H) with 93% e.e.

![Chemical diagram]

In any asymmetric synthesis it is important to be able to accurately evaluate the optical purity of products. Measurement of the optical rotation of a compound was once the most common method for the determination of its enantiomeric...
ratio, however values may be unreliable due to the sensitivity of the method to experimental conditions and the possibility of unsuspected impurities. Furthermore, relatively large sample sizes are required for polarimetric measurements and the maximum optical rotation of the compound in question must be known with certainty for the measurement to be meaningful. Many of the newer techniques allow more accurate analysis of enantiomeric composition and can be performed with less than one milligram of material.

These alternative methods include isotopic dilution, kinetic resolutions, enzymatic assays, gas and liquid chromatography with chiral stationary phases and various NMR techniques\(^\text{78}\). For the analysis of enantiomeric mixtures by NMR, the enantiomers must be converted to diastereomers or have diastereomeric interactions with their environment. Furthermore, some of the NMR signals due to the diastereomers (or diastereomeric complexes) must have non-equivalent chemical shift values. The relative intensities of the signals can then be measured and will reflect the enantiomeric ratio. Two methods are commonly used to discriminate between enantiomers by NMR. An enantiomeric mixture may be converted to a pair of diastereomers with an optically pure reagent, such as Mosher's acid (\(\alpha\)-methoxy-\(\alpha\)-trifluoromethylphenylacetic acid)\(^\text{68}\). It is important that the reaction proceeds quantitatively to avoid kinetic resolution. Mosher esters are particularly suitable derivatising agents as the singlets due to the methoxyl groups are often well resolved by \(^1\)H NMR and can be accurately integrated; the trifluoromethyl signals are also often well resolved by \(^19\)F NMR. The second method uses a chiral shift reagent. Many chiral shift reagents contain a rare earth metal (such as europium or praeseodymium) which provides a local magnetic field able to alter chemical shifts in spectra of organic molecules. The reagent also contains a chiral moiety (such as a camphor derivative), thus the interactions between the reagent and a chiral organic molecule are
diastereomeric. One commercially available chiral shift reagent, tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato] europium(III) derivative (69) is illustrated below.

![Chemical structure](image)

Diastereomeric ratios can also be accurately measured by HPLC if the isomers have different retention times. Thus, the diastereomeric mixture which arises from derivatisation of an enantiomeric mixture with an optically pure reagent such as 68 may be analysed by either NMR or HPLC. A suitable method for the determination of optical purity of 2-arylpropanoic acids has been developed by Hayball et al\textsuperscript{79}. These workers converted racemic ketoprofen (4a) to the (S)-1-phenylethylamides, via the acid chlorides, and found that the diastereomers separated by HPLC (figure 43). The above methods have been used for analysis of optically active compounds in the current work.

![Chemical structure](image)

Ar = 3-benzoylphenyl

Figure 43
RESULTS AND DISCUSSION

CHAPTER 1
ASYMMETRIC SYNTHESIS OF KETOPROFEN

(S)-Ketoprofen (4b) was chosen as the first synthetic target for the assessment of the feasibility of a general approach to the asymmetric synthesis of 2-arylpropanoic acids. One of the reasons for this choice was that ketoprofen is commercially a very important drug, currently marketed as a racemate but with the anti-inflammatory activity attributed to the (S) enantiomer. Also, it is one of the few meta substituted 2-arylpropanoic acid drugs, and it was considered desirable that the method be shown to be applicable to both meta and para systems.

A general overview of the planned synthesis is outlined in figure 44. It was envisaged that commercially available m-bromoacetophenone could be converted to the (E) bromo ester 70 which could then be reduced to the (E) allylic alcohol 71. The key steps for the control of stereochemistry in the synthesis would then be a Sharpless asymmetric epoxidation of 71, followed by stereoselective hydrogenolysis of the resultant optically active epoxide 72b, to the optically active diol 73b. It was proposed that the skeleton of the benzylic substituent then be introduced, possibly by protection of the diol portion of 73b as the acetonide 74b, metal-halogen exchange and addition of the resultant nucleophile to benzaldehyde. Hydrolysis of the acetal followed by oxidative cleavage would be expected to yield optically active ketoprofen.
The combination of Sharpless epoxidation and subsequent hydrogenolytic ring opening had been explored briefly by the Hamon - Massy-Westropp group\textsuperscript{35} in the analogous unsubstituted system 29 (figure 45). Epoxide 30 was obtained in 80% yield with 80-85% e.e. Recrystallisation of the \textit{p}-nitrobenzoate derivative,
followed by hydrolysis, gave optically pure 30. Hydrogenolysis of 30 gave the diol 31 as a single diastereomer, contaminated with a small amount of the rearrangement product 77, which was removed by chromatography.

![Chemical structure](image)

Figure 45

Although these results augured well for the brominated series, the possibility of hydrogenolysis of the bromine atom from the aromatic ring, as discussed on page 31, was kept in mind. Appropriate modifications to the synthetic strategy, should this alternative reaction occur, were considered.

The first step in the exploration of the proposed asymmetric synthesis of ketoprofen was conversion of $m$-bromoacetophenone to the bromo ester 70, by the use of the Wadsworth-Emmons reaction with triethyl phosphonoacetate (figure 46). Nicolas et al.\textsuperscript{80} have reported that optimal yields are obtained with THF as solvent and potassium tert-butoxide as base. Use of these conditions afforded a mixture of (E) and (Z) esters (70 and 78) in a ratio of approximately 7:1, determined by integration of the distinct olefinic and methyl signals in the $^1$H NMR spectrum. The olefinic proton of the thermodynamically more stable
(E) ester (70) resonates at δ 6.04 and that of the (Z) ester (78) at δ 5.90. The methyl protons resonate at δ 2.53 and δ 2.19 respectively. Both isomers exhibited long range coupling (approximately 1 Hz) between the olefinic and methyl protons. The triplets of the CH₂CH₃ protons of the two isomers overlap, as do the quartets due to the CH₂CH₃ protons. The isomers were separated by chromatography to give 70 in 65% yield. Distillation of a sample of 70 afforded analytically pure material.

Reduction of 70 to the allylic alcohol 71 was first attempted by the use of an excess of lithium aluminium hydride in ether at room temperature, however the product from this reaction was the saturated alcohol 79 (figure 47). The structure of this product was assigned on the basis of its ¹H NMR spectrum. There are no signals in the olefinic region and a complex set of overlapping multiplets between δ 0.9 and δ 4.0 which are consistent with the proposed structure. The reaction was repeated with THF as solvent and again 79 was the sole product. Double bond reduction was avoided when ether was used as the
solvent at -78°C. The required allylic alcohol 71 was obtained in 79% yield after chromatography, with no trace of 79. The 60 MHz, $^1$H NMR spectrum of 71 shows a 7 Hz triplet at δ 5.88 with further, unresolved small coupling to the methyl singlet at δ 2.00. A 7 Hz doublet due to the CH$_2$O protons resonates at δ 4.23.

![Diagram of reactions]

Figure 47

Although there is precedent for reduction of cinnamyl-like α,β-unsaturated systems to the saturated alcohols with lithium aluminium hydride$^6$, the reduction of the double bond of 70 under the initial reaction conditions was unexpected, as earlier work in the group had shown that reduction of the unbrominated analogue, 28, under the same conditions had proceeded smoothly to 29 (figure 48). It is likely that the electron withdrawing nature of the bromine in 70 renders the double bond more susceptible to reduction.
Although the aim of this synthesis was to obtain optically active ketoprofen, exploratory reactions were performed on racemic material, for two reasons. The first was that the preparation of racemic compounds is often less time consuming and uses more accessible reagents than that of optically active compounds, and the second was that for the determination of optical purity of any intermediates, an authentic racemic sample as a standard is essential. Therefore, allylic alcohol 71 was converted to the racemic epoxide 72a with m-chloroperbenzoic acid (figure 49). The product was obtained in 94% yield after chromatography, and distillation of a sample afforded analytically pure material. The $^1$H NMR spectrum of 72a shows a singlet at $\delta$ 1.67 due to the methyl group, a poorly resolved 5.2 Hz triplet at $\delta$ 2.21 due to the OH and a doublet of doublets at $\delta$ 3.05 due to the proton on the epoxide ring. Poorly resolved signals at $\delta$ 3.82 and $\delta$ 3.96 are revealed as two doublet of doublets upon D$_2$O exchange, each due to one of the methylene protons.
Hydrogenolysis of the racemic epoxide 72a was undertaken with a view to gain information on two crucial aspects of the synthesis. The first was to establish the relative reactivities of the bromine-aryl bond and the benzylic carbon-oxygen bond to hydrogenolysis, under various reaction conditions, with the aim of optimising the latter process. The second aspect was the stereoselectivity of the ring opening reaction. Whether the substrate epoxide is racemic or optically active, the product diols which arise from delivery of hydrogen with retention or inversion of configuration will be diastereomeric, and therefore likely to show differences in their NMR spectra. This is illustrated in figure 50. The optically active epoxide 72b can give rise to diols 73b and 80b, which are diastereomers. The ratio of the product diastereomeric diols is a consequence of the stereoselectivity of the hydrogenolysis reaction, and is independent of the optical purity of the starting epoxide.

Earlier work in the Hamon - Massy-Westropp group35 indicated that the optimal yield and stereoselectivity in hydrogenolysis of a benzylic epoxide were obtained by performing the reaction at low temperature with ethanol as solvent and a small amount of aqueous sodium hydroxide present. Thus, 10% palladium on carbon catalyst in ethanol and aqueous sodium hydroxide were
cooled to -45°C in a hydrogen atmosphere for 1.5 h to allow adsorption of hydrogen onto the catalyst surface. The racemic epoxide 72a was then added and progress of the reaction monitored by TLC. After 3.5 h no epoxide remained, and the product was isolated and purified by chromatography. $^1$H NMR clearly indicated that the epoxide had been converted to the diol consistent with the required product 73a (73a is a racemic mixture of 73b and 73c, figure 50). The methyl group appears at $\delta$ 1.27 as a 6.9 Hz doublet coupled to the benzylic proton, which appears as a 6.9 Hz quintet at $\delta$ 2.64. Two doublet of doublets at $\delta$ 3.16 and $\delta$ 3.27 are due to the methylene protons and a doublet of triplets at $\delta$ 3.58 is due to the adjacent CHOH proton. The coupling constants between these multiplets are consistent with their assignments. The aromatic region of the spectrum indicates that the bromine atom was lost during the reaction, and the product was the debrominated diol 81a (figure 51). Although integration of this complex region was not definitive, the relative narrowness and upfield shift of the signal compared to the brominated precursors ($\delta$ 7.08 - $\delta$ 7.24 for the product, $\delta$ 7.17 - $\delta$ 7.49 for the precursor bromo epoxide 72a) suggested the absence of an electronegative aryl substituent. Confirmation of the molecular formula of 81a was obtained by microanalysis of the diacetate 82a.

(81a): $R = H$
(82a): $R = Ac$

The possibility that epoxide ring opening occurs more readily than bromine loss in the hydrogenolysis reaction was considered, as this would mean the
required bromodiol 73a is an intermediate in the formation of 81a, and may possibly be isolated. However, cessation of the reaction when approximately half the starting epoxide 72a had been consumed yielded a mixture of only 72a and 81a.

As the hydrogenolysis reaction did not give the required product, the stereoselectivity of the ring opening was not closely examined. Instead, attention was focussed on circumventing the problem of halogen loss. As aryl-chlorine bonds are less susceptible to hydrogenolysis than aryl-bromine bonds47, it was considered that use of the analogous chloro series of compounds may be a more viable approach. However this was not pursued due to the foreseeable difficulties in the subsequent metal-halogen exchange to incorporate the benzylic substituent (chlorine is less reactive than bromine in these exchange reactions) and for other projected coupling reactions. An alternative approach was explored, which involved replacement of the bromine with a trimethylsilyl group, which was expected to survive the hydrogenolysis conditions. Various possibilities then existed for incorporation of the benzylic substituent, which will be discussed in due course.

Conversion of m-bromoacetophenone to m-(trimethylsilyl)acetophenone (85) was achieved by the route outlined in figure 52. The ketone was protected as the acetal 83 by reflux of a benzene solution with a catalytic amount of p-toluene sulphonphonic acid, with azeotropic removal of water. The Grignard reagent from 83 was formed and treated with an excess of chlorotrimethylsilane, to give the trimethylsilyl acetal 84 as a crystalline solid, which was recrystallised to analytical purity. Conversion to the trimethylsilyl ketone 85 was achieved by treatment of an aqueous methanolic solution of the acetal with a catalytic amount of HCl. The 1H NMR spectrum of 85 shows a sharp singlet at δ 0.29 due to the 9Hs of the trimethylsilyl group, a 3H singlet at
\( \delta 2.50 \) due to the CH\(_3\)CO protons and a complex set of aromatic signals between \( \delta 7.21 \) and \( \delta 8.14 \).

\[
\text{Br-} - \text{CH} = \text{O}
\]

\[
\text{HO} - \text{CH} = \text{O}
\]

\[
\text{Br} - \text{CH} = \text{O}
\]

\[
\text{Me}_3\text{SiClBr}
\]

\[
\text{Mg}
\]

\[
\text{Me}_3\text{SiCl}
\]

\[
(83)
\]

\[
(84)
\]

\[
(85)
\]

Figure 52

Under similar conditions to those used for the formation of the bromo ester 70 from \( m \)-bromoacetophenone (see page 56), the ketone 85 was converted to the trimethylsilyl ester 86 (figure 53). Again, a mixture of (E) and (Z) esters was formed, in a ratio of approximately 8:1, and was separated by chromatography. The \(^1\)H NMR spectrum of 86 is very similar to that of the bromo analogue 70, except for the presence of a 9H singlet at \( \delta 0.29 \) due to the trimethylsilyl group. In the same manner as the reduction of the bromo ester 70 to the allylic alcohol 71 (see page 57), 86 was reduced to 87. Again, the presence of a 9H singlet at \( \delta 0.28 \) is the only substantial difference between the \(^1\)H NMR spectra of the bromo compound 71 and the trimethylsilyl analogue 87. The allylic alcohol 87 was converted to racemic epoxide 88a by the use of \( m \)-chloroperbenzoic acid. Except for the presence of a 9H singlet at \( \delta 0.27 \), 88a has a very similar \(^1\)H NMR spectrum to the bromo epoxide 72a. Microanalytical data on intermediates 86
and 88a and high resolution mass spectrometric data on 87 were consistent with the assigned structures.

\[
\begin{align*}
\text{Me}_3\text{Si} & \quad \text{O} \\
\begin{array}{c}
\text{Me}_3\text{Si} \quad \text{Et} \quad \text{O} \\
(85)
\end{array} & \quad \xrightarrow{(\text{EtO})_2\text{POCH}_2\text{CO}_2\text{Et}, \\ t-\text{BuOK}} & \quad \text{Me}_3\text{Si} \quad \text{Et} \quad \text{CO}_2\text{Et} \\
(86)
\end{align*}
\]

\[\xrightarrow{\text{LiAlH}_4} \quad \begin{array}{c}
\text{Me}_3\text{Si} \quad \text{OH} \\
(87)
\end{array} \quad \xrightarrow{m-\text{CPBA}} \quad \text{Me}_3\text{Si} \quad \text{OH} \quad (88a)
\]

Figure 53

Hydrogenolysis of 88a was performed under similar reaction conditions to those used for the bromo epoxide 72a, except that the reaction temperature was maintained at \(-60^\circ\text{C}\) (figure 54).

\[
\begin{align*}
\text{Me}_3\text{Si} & \quad \text{O} \\
\begin{array}{c}
\text{Me}_3\text{Si} \quad \text{Et} \quad \text{OH} \\
(88a)
\end{array} & \quad \xrightarrow{\text{H}_2, \quad \text{Pd}/\text{C}} & \quad \text{Me}_3\text{Si} \quad \begin{array}{c}
\text{OH} \\
\text{OR}
\end{array} \quad (\pm)-(89a): R = H \\
(\pm)-(90a): R = \text{Ac}
\end{align*}
\]

Figure 54
TLC indicated that a reaction time of 6 h was required for complete consumption of starting material and at this time a single lower Rf spot was observed. Chromatography of the product as routine purification afforded the required diol 89a in 97% yield. The $^1$H NMR spectrum of 89a is similar to that of the debrominated diol 81a, discussed on page 60, except for the presence of a 9H singlet at $\delta$ 0.26 and a complex pattern in the aromatic region, which is similar to the trimethylsilyl substituted precursors and resonates at $\delta$ 7.16 - $\delta$ 7.40. Support for the assigned structure was obtained by microanalysis of the crystalline diacetate 90a.

The $^1$H NMR spectrum of diol 89a indicated that the product was a single diastereomer, however an authentic sample of the diastereomeric diol 91a was required to justify this claim. Hydrogenolysis of racemic epoxide 88a at room temperature gave a mixture of diastereomers 89a and 91a (figure 55).
The $^1$H NMR spectrum of the mixture shows a 7.0 Hz doublet at $\delta$ 1.35 due to the methyl group of 89a and a 7.1 Hz doublet at $\delta$ 1.27 due to the methyl group of 91a, in a ratio of approximately 10:1. The differences in the other signals in the spectrum are not as pronounced and are inadequate for analytical purposes. The methyl region however, provides a reliable standard for the analysis of a diastereomeric mixture of 89a and 91a. Thus, close examination of this region of the spectrum of the product from low temperature hydrogenolysis confirms that it is highly diastereomERICALLY pure. Expansion reveals a trace of doublet due to 91a. The peaks of this doublet are approximately the same height as the $^{13}$C-$^1$H satellite peaks from the major doublet, which are each 0.5% parent $^1$H-$^1$H doublet. Therefore the d.e. of 89a from the low temperature hydrogenolysis was approximately 99%.

Various possibilities were considered to incorporate the benzylic substituent of ketoprofen into the trimethylsilyl diol 89a. Eaborn et al. converted o-bis(trimethylsilyl)benzene (92) to o-trimethylsilylbenzophenone (93) by the use of Friedel-Crafts chemistry (figure 56).

![Chemical structures](image)

Figure 56
Under the same conditions, silyl diacetate 90a was treated with benzoyl chloride and aluminium chloride, however the sole product of the reaction was the desilylated diacetate 82a (figure 56), which had spectral data identical with those of the sample prepared earlier (see page 60).

As this approach did not appear promising, an alternative method for the incorporation of the benzylic substituent to 89a was explored. The trimethylsilyl group was replaced with a bromine atom to give 73a (figure 57), with the expectation that this would undergo metal-halogen exchange to form the aryllithium, which could then be added to benzaldehyde. The replacement was achieved by treating 89a with lithium bromide and N-chlorosuccinimide in methanol, in accordance with the method of Wilbur83. The required product 73a was isolated in 93% yield. The 1H NMR spectrum shows the characteristic pattern of multiplets due to the butane-1,2-diol portion of the molecule, which is common to all of the compounds containing this moiety and has been described previously. The absence of a singlet in the δ -0.5 - δ 0.5 region and altered pattern of the aromatic signal, consistent with the presence of an electronegative substituent, support the assigned structure.

The hydroxyl groups of 73a were incompatible with formation of the intermediate aryllithium reagent in the next step of the synthesis. Therefore they were protected as the acetonide 74a, by treatment of an acetone solution of 73a with a catalytic amount of p-toluenesulphonic acid (figure 58). The product
was isolated in 79% yield, and the structure confirmed by $^1$H NMR. The spectrum shows the benzylic methyl group as a 6.4 Hz doublet at δ 1.35 and the two methyl groups on the dioxolane ring as a singlets at δ 1.37 and δ 1.41. The benzylic proton appears as a quintet at δ 2.77, each of the protons of the methylene group as a doublet of doublets at δ 3.51 and δ 3.75 and the CHO proton as a complex multiplet at δ 4.14, due to splitting by the three non-equivalent adjacent protons. The aromatic region appears largely unchanged from that of the starting material.

For attachment of the benzylic substituent to 74a, the decision was made to utilise a lithium-halogen exchange reaction, followed by addition of benzaldehyde to the resultant aryllithium reagent (figure 59). This procedure was expected to be more efficient than the corresponding Grignard reaction. The exchange reaction of 74a employed two equivalents of tert-butyllithium at -78°C in ether and, after a period of 1.75 h at -78°C to allow complete formation of the aryllithium, an excess of benzaldehyde was added.
The reason two equivalents of tert-butyllithium were required is outlined in figure 60. The lithium-halogen exchange is reversible, and the second equivalent of tert-butyllithium serves to react with the tert-butyl bromide generated by the exchange, to promote elimination. Thus, the reverse exchange cannot occur and the equilibrium is forced to the right.

![Chemical equation]

After work up and chromatography, the product 75a was isolated in 76% yield. The signals in the $^1$H NMR spectrum due to the protected butane-1,2-diol portion (R) of the molecule (figure 60), have the same characteristic pattern as in the starting material. There is a broad doublet at $\delta$ 1.55 due to the OH, and a new doublet at $\delta$ 5.80 due to the benzylic CHOH. Upon D$_2$O exchange, the signal at $\delta$ 1.55 disappears and the one at $\delta$ 5.80 becomes a singlet. The aromatic region ($\delta$ 6.92 - $\delta$ 7.43) is complex and integrates for nine protons.

Conversion of the acetonide 75a to triol 76a was achieved by treatment of a methanolic solution of 75a with a catalytic amount of HCl (figure 61). The $\delta$ 1 -
δ 4 region of the $^1$H NMR spectrum upon D$_2$O exchange shows the characteristic pattern of all the precursor butane-1,2-diols. There is also a 1H singlet at δ 5.74 due to the benzylic CHOH and a complex, 9H set of signals in the aromatic region.

![Chemical structure](image)

Figure 61

The final step in this synthesis of ketoprofen (4a) was the oxidation of triol 76a. Sharpless et al.$^{84}$ have developed conditions for the efficient oxidative cleavage of 1,2-diols with sodium metaperiodate and a catalytic amount of ruthenium trichloride hydrate. These reagents generate the active oxidant, ruthenium tetraoxide, in situ. Sharpless observed some racemisation in oxidation of the model compound 81b to 2-phenylpropanoic acid (figure 62), but only such a small amount that it was not considered a threat to the viability of this approach.

![Chemical structure](image)

Figure 62
It was expected that treatment of 76a with an excess of oxidant would effect the oxidative cleavage of the diol and simultaneously oxidise the benzylic hydroxyl (figure 63). Indeed, the product obtained from this reaction, in 72% yield, was ketoprofen (4a). Although 4a has been reported to exist as a white crystalline solid, all attempts at crystallisation of the product, including chromatography and bulb to bulb distillation, failed. This failure was attributed to the small quantity of material available (37 mg). However, 1H NMR and IR data were identical with an authentic sample of ketoprofen. As the diol was racemic, no information could be obtained regarding possible racemisation in the optically active series.

![Figure 63](image)

The successful synthesis of racemic ketoprofen (4a) described above, confirmed the feasibility of this approach for the synthesis of the individual enantiomers of ketoprofen (4b and 4c). There was no reason to expect any differences in reactivity between the optically active and racemic intermediates, nor was racemisation anticipated during any of the reactions (except for a negligible amount in the final oxidation, as discussed). The excellent stereoselectivity of one of the key reactions, the hydrogenolysis of the epoxide, had been established. It remained, therefore, to procure a sample of optically active epoxide 88b and convert it to (S)-ketoprofen (4b).
Optically active epoxide 88b was obtained by Sharpless epoxidation of the allylic alcohol 87. The configuration of the epoxide and hence ketoprofen, is dependent on the configuration of the diisopropyl tartrate used in the reaction. As the synthetic target was (S)-ketoprofen and it was known from the literature\textsuperscript{44-46} that hydrogenolysis over a palladium catalyst occurs with inversion of configuration, the epoxide with the (S) configuration at the benzylic carbon was required (88b, figure 64). By application of the set of rules laid down by Sharpless for prediction of absolute stereochemistry (see page 22), it was determined that use of the (+)-tartrate was appropriate. Conversely, the use of the (-)-tartrate would lead to (R)-ketoprofen.

\[
\begin{align*}
\text{Me}_3\text{Si} & \quad \begin{array}{c} \text{Me}_3\text{Si} \end{array} \\
\begin{array}{c} \text{OH} \\
\end{array} & \quad \begin{array}{c} \text{OH} \\
\end{array} \\
\begin{array}{c} \text{(87)} \\
\end{array} & \quad \begin{array}{c} \text{(88b)} \\
\end{array} \\
\end{align*}
\]

\[
\begin{align*}
\text{3,5-DNBrCl,} & \quad \begin{array}{c} \text{Me}_3\text{Si} \end{array} \\
\text{pyridine} & \quad \begin{array}{c} \text{Me}_3\text{Si} \end{array} \\
\begin{array}{c} \text{H} \\
\end{array} & \quad \begin{array}{c} \text{H} \\
\end{array} \\
\begin{array}{c} \text{(94b)} \\
\end{array} & \quad \begin{array}{c} \text{(94b)} \\
\end{array} \\
\end{align*}
\]

![Figure 64](image)

Commercially available cinnamyl alcohol was used as a model compound in trial reactions, to optimise conditions and technique. Scrupulously anhydrous conditions and reagents are necessary for high yields. Thus, treatment of 87
with an excess of tert-butylhydroperoxide and catalytic quantities of (+)-diisopropyl tartrate and titanium tetraisopropoxide yielded the epoxide 88b in 94% yield after chromatography (figure 64). The optical purity of the epoxide was determined by the use of a chiral shift reagent, and estimated to be 90% e.e. The analysis is discussed in the next paragraph. The epoxide 88b, a colourless oil, was converted to the crystalline 3,5-dinitrobenzoate derivative (94b), which had a mp of 85.5-90.0°C. Two recrystallisations from ethanol afforded material with a mp of 90.0-92.0°C and $[\alpha]_D^{20} = -32.0^\circ$ (c=1.11, CCl$_4$). Hydrolysis of 94b then gave 88b of enhanced optical purity (98% e.e.), as determined by the analysis described below.

Analysis of the enantiomeric purity of 88b involved conversion to the acetate 95b (figure 65), and treatment of a deuterochloroform solution of this derivative with the chiral shift reagent tris[3-(heptafluoropropylhydroxy-methylene)-(+)-camphorato]europium(III) derivative (69) (analysis was attempted directly on the epoxy alcohol 88b, but was unsuccessful due to line broadening of the NMR signals).

![Figure 65](image)

Under these conditions, the two enantiomers of a racemic sample of acetate (95a) have different $^1H$ NMR spectra, due to the diastereomeric interactions
with optically pure 69. Of particular interest was the singlet due to the benzylic methyl group which resonates at δ 1.30 in the absence of shift reagent (figure 66a, page 74). To a racemic sample of acetate 95a, incremental addition of shift reagent to the NMR sample caused an increasing separation of this peak into two singlets; each one corresponds to one enantiomer of the racemate (figure 66b-f). An increasingly downfield shift of this signal with added shift reagent was also observed. There was an optimal ratio of shift reagent : acetate (figure 66e) above which baseline unevenness impeded analysis (figure 66f). At this ratio the two singlets were almost baseline resolved and provided a reliable standard for the analysis of the composition of the enantiomeric mixture. Figure 66g is a reproduction of the relevant methyl region of the 1H NMR spectrum of optically active epoxy acetate 95b, formed from a sample of epoxy alcohol 88b (from the Sharpless epoxidation) which had been recrystallised as the 3,5-dinitrobenzoate. The spectrum was run under the optimal conditions used for spectrum 66e, and it clearly showed the presence of a single enantiomer. Given the smooth baseline, it was assumed that even 1% of the other enantiomer would be apparent, thus optical purity of 98%+ was confidently claimed.
Figure 66
The remainder of the synthesis of (S)-ketoprofen was performed in the same manner as for the racemic series. Spectral data for all the intermediates were identical to those of the racemates. Finally, it remained to determine the optical purity of the product to establish whether or not racemisation had occurred. This involved derivatisation of ketoprofen with commercially available (S)-1-phenylethylamine (via the acid chloride) to form diastereomeric (S)-1-phenylethylamides, which were separable by HPLC. Integration of the HPLC peaks then gave the ratio of diastereomers and hence the ratio of enantiomers in the sample of ketoprofen. The analysis was kindly performed by P. J. Hayball, who developed the procedure\textsuperscript{79}.

By this method, the product of the asymmetric synthesis, (S)-ketoprofen (4b) was found to have an optical purity of 96% e.e. This value represents the minimum optical purity, as it is based on the assumption that the (S)-1-phenylethylamine used for derivitisation was 100% optically pure. The very slight loss of optical purity in comparison with epoxy alcohol \textit{88b} from the Sharpless reaction (98% e.e.) was consistent with Sharpless'\textsuperscript{84} observation that some racemisation occurred during the ruthenium tetraoxide oxidation.
CHAPTER 2

ASYMMETRIC SYNTHESIS OF IBUPROFEN

The asymmetric synthesis of (S)-ibuprofen (1b) was undertaken to demonstrate
that the route developed for the asymmetric synthesis of ketoprofen could be
applied to para substituted compounds. Ibuprofen is commercially extremely
important, as it is the most widely used of all the 2-arylpropanoic acid drugs.
Although it is marketed in racemic form, the (S) isomer is 160 times more
active than the (R) enantiomer. Complications can arise in the estimation of
dosages because of the (R) to (S) interconversion which occurs in vivo.
Therefore, ibuprofen is a prime candidate for a "racemic switch"5.

Because the loss of bromine occurred readily during hydrogenolysis of the meta
bromo epoxide 72a (figure 66), it was anticipated that the same unwanted
reaction would occur with the para substituted epoxide. It was later confirmed
by other work in these laboratories that this was indeed the case86.

Therefore, the planned synthesis of (S)-ibuprofen (an overview of which is
shown in figure 67) began with replacement of the bromine of commercially
available p-bromoacetophenone with a trimethylsilyl group. It was envisaged
that the resultant trimethylsilyl ketone 96 could then be converted to the (E)
ester 97, which on reduction would afford the (E) allylic alcohol 98.
Sharpless epoxidation

\[ (100b) \xrightarrow{\text{H}_2, \text{Pd/C}} (101b) \]

\[ (102b) \xrightarrow{} (103b) \]

\[ (104b) \xrightarrow{} (105b) \]

\[ (1b) \]

Figure 67
A Sharpless asymmetric epoxidation of 98 would generate the optically active epoxide 99b, which could then be opened by stereoselective hydrogenolysis, to give the optically active diol 100b. It was planned to replace the trimethylsilyl group of 100b with bromine, to give 101b, and protect the diol as the acetonide 102b. A metal-halogen exchange reaction, with addition of the resultant aryllithium to isobutyraldehyde, would give the alcohol 103b. Conversion of the acetal to the diol would afford 104b. Finally, removal of the benzylic hydroxyl group and oxidative cleavage of the diol would be expected to give optically active ibuprofen (1b).

The first intermediate in the synthesis, \( p \)-(trimethylsilyl)acetophenone (96), was formed by the route reported by Neville\(^8\), which is outlined in figure 68. \( p \)-Bromoacetophenone was protected as the acetal 106. The Grignard reagent from 106 was prepared and treated with an excess of chlorotrimethylsilane, to give the trimethylsilyl acetal 107 as a crystalline solid. Treatment of a methanolic solution of 107 with a catalytic amount of HCl then generated the required trimethylsilyl ketone 96.
The $^1$H NMR data of 96 were in agreement with those reported\cite{87}: a 9H singlet at $\delta$ 0.29 due to the trimethylsilyl protons, a 3H singlet at $\delta$ 2.60 from the benzylic methyl group and a symmetrical AA'BB' pattern in the aromatic region, due to the effect of the para substituent. Throughout this project, many of the para substituted aromatic intermediates show a similar characteristic AA'BB' pattern. It is often apparent as two doublets with a coupling constant of approximately 8 Hz, however the spectra of some intermediates also show a small coupling of approximately 1 Hz. In the spectrum of 96 the doublets resonate at $\delta$ 7.62 and $\delta$ 7.92.

An initial attempt to convert the ketone 96 to the (E) ethyl ester 97 with triethyl phosphonoacetate and potassium tert-butoxide as base (figure 69) gave a mixture of (E) and (Z) esters 97 and 108, in a ratio of approximately 8:1.

![Figure 69](image-url)
This was determined by integration of the well separated olefinic and methyl signals in the $^1$H NMR spectrum. The olefinic proton of 97 resonates at $\delta$ 6.15 and that of 108 at $\delta$ 5.88. The methyl protons resonate at $\delta$ 2.57 and $\delta$ 2.15 respectively. Both isomers exhibited long range coupling between the olefinic and methyl protons, with both signals apparent as 1.3 Hz doublets. The other signals of the two isomers in the spectrum overlap.

It has been observed recently$^{86}$ that in a similar system, use of lithium ethoxide as base and anhydrous ethanol as solvent affords a higher ratio of (E):(Z) isomers than the potassium tert-butoxide/THF combination. The reaction of 96 with triethyl phosphonoacetate was repeated under these conditions (figure 69). After 16 h at room temperature, an aliquot of the reaction mixture was removed and analysed by $^1$H NMR spectroscopy. A ratio of (E):(Z) isomers of approximately 8:1 was observed, however a further 4 h at reflux caused the ratio to improve to approximately 17:1. A longer reaction period did not alter this proportion. Thus, a 17:1 mixture of 97 and 108 was obtained in almost quantitative yield. This result suggested that the initial composition of the reaction product was the kinetic mixture of (E) and (Z) esters. Lithium ethoxide and ethanol, when heated, provided suitable conditions for the mixture to equilibrate to the thermodynamic product, probably by an addition/elimination mechanism. The equilibration did not occur with potassium tert-butoxide and THF, even when the mixture was heated.

The crude product of the previous step, a 17:1 mixture of esters 97 and 108, was reduced with lithium aluminium hydride at -78°C. The reaction was performed at low temperature to ensure that no reduction of the double bond occurred (figure 70). Fractional distillation of the product gave mainly the (E) allylic alcohol 98, which contained a trace (<5%) of the the (Z) isomer 109 from reduction of the (Z) ester 108. A sample was further purified for microanalysis
by flash chromatography to remove the (Z) isomer, however the bulk of the material was carried through to the next step without further purification. The $^1$H NMR spectrum of 98 shows a sharp singlet at $\delta$ 0.27 due to the 9Hs of the trimethylsilyl group. A slightly broadened 3H singlet at $\delta$ 2.07 is from the benzylic methyl group, which has a small long range coupling to the olefinic proton. This coupling also causes broadening of the triplet due to the olefinic proton at $\delta$ 5.99. A doublet at $\delta$ 4.35 is due to the CH$_2$O protons, and the aromatic region has the characteristic AA'BB' pattern of two 2H doublets, at $\delta$ 7.39 and $\delta$ 7.49, with further small coupling.

![Chemical structure](image)

Figure 70

At this point the synthesis diverged into a racemic and an optically active series of intermediates. Racemic epoxide 110a was obtained by treatment of allylic alcohol 98 with $m$-chloroperbenzoic acid, as a white crystalline solid in quantitative yield. The optically active epoxide 99b was derived from the same substrate by use of a Sharpless epoxidation reaction (figure 71). The remaining steps in the synthesis were performed under the same conditions for both the racemic and optically active series, therefore only the synthesis of optically active (S)-ibuprofen, the target molecule, will be discussed in detail.
The product of the Sharpless epoxidation 99b was obtained after chromatography as a white crystalline solid in 70% yield. The chromatography removed a trace of the epoxide derived from the small amount of (Z) allylic alcohol present. The $^1$H NMR spectrum of 99b shows a 9H singlet at $\delta$ 0.26 due to the trimethylsilyl group and a 3H singlet at $\delta$ 1.70 due to the benzylic methyl group. The proton on the epoxide ring appears as a doublet of doublets at $\delta$ 3.10, coupled to the methylene protons at $\delta$ 3.83 and $\delta$ 3.97 with coupling constants of 6 and 4 Hz respectively. Each of the methylene protons resonates as a doublet of doublets with a geminal coupling of 12 Hz. The aromatic protons appear as two 8 Hz doublets at $\delta$ 7.33 and $\delta$ 7.51. The optical purity of 99b was determined by analysis of the acetate derivative 111b with the chiral shift reagent tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium(III) derivative, in a similar manner to that used for the meta substituted epoxy acetate 95b, discussed on pages 72-74.
Figure 72a depicts the diagnostic methyl region of the $^1$H NMR spectrum of a sample of racemic epoxy acetate 111a in the presence of an optimal amount of shift reagent. The singlets at $\delta$ 1.89 and $\delta$ 1.93 correspond to the benzylic methyl groups of the enantiomers. Figure 72b shows the spectrum for a sample of optically active epoxy acetate 111b from the Sharpless epoxidation, under the same conditions. The optical purity was estimated to be 90% e.e. The alcohol 99b was recrystallised from pentane and a sample converted to the acetate 111b. Figure 72c shows the relevant section of this spectrum under the standard conditions. No peak is visible at $\delta$ 1.89, therefore optical purity of 98%+ was claimed (the chemical shift of the small peak just upfield of the main singlet does not correspond to that of the minor enantiomer).
Hydrogenolysis of epoxy alcohol 99b with palladium on charcoal catalyst at -60°C, proceeded with inversion of configuration to give the diol 100b as essentially a single diastereomer (99%+ d.e.) in quantitative yield (figure 73). The diastereomeric purity of 100b was determined by comparison of the 1H NMR spectrum with an authentic mixture of diastereomers, 100b and 112b, which was obtained from a similar reaction performed at room temperature.

![Chemical structure diagram](image)

**Figure 73**

The 1H NMR spectrum of 100b shows a 9H singlet at δ 0.25 due to the trimethylsilyl protons. The benzylic methyl group appears at δ 1.36 as a 7 Hz doublet coupled to the benzylic proton, which appears as a 7 Hz quintet at δ 2.79. Two doublet of doublets at δ 3.35 and δ 3.46 are due to the methylene protons, and are coupled to a doublet of triplets at δ 3.75, which is due to the adjacent CHOH proton. This pattern of multiplets was found to be characteristic of all the intermediates containing the butane-1,2-diol moiety, with negligible changes in chemical shifts due to different aryl substituents. The typical
AA'BB' pattern of two doublets was observed in the aromatic region, although they now resonate at δ 7.05 and δ 7.41.

The trimethylsilyl group of 100b was replaced with a bromine atom, by treatment with lithium bromide and N-chlorosuccinimide in methanol (figure 74). The required product 101b was obtained in 91% yield, and had very similar 1H NMR data to the starting diol, except for the absence of the singlet in the δ 0 region and a change in chemical shift of the aromatic doublets, to δ 7.05 and δ 7.41. Microanalytical data were consistent with the structure of 101b.

![Chemical structures](image)

Figure 74

The diol 101b was then protected as the acetonide 102b (figure 74), in preparation for the metal halogen exchange reaction. Treatment of an acetone solution of 101b with a catalytic amount of p-toluenesulphonic acid afforded the product in 73% yield. The 1H NMR spectrum of 102b shows the benzylic methyl group as a 7.0 Hz doublet at δ 1.35 and the other methyl groups as singlets at δ 1.39 and δ 1.41. The benzylic proton appears as a quintet at δ 2.77, each of the methylene protons as a doublet of doublets at δ 3.51 and δ 3.74 and
the CHO proton as a complex multiplet at δ 4.13. The changes in the aromatic region of the spectrum are negligible.

A metal halogen exchange reaction was employed to incorporate the isobutyl substituent. Thus, 102b was treated with two equivalents of tert-butyllithium at -78°C, followed by an excess of isobutyraldehyde (figure 75). The product 103b was obtained in 86% yield after chromatography. The signals in the 1H NMR spectrum due to the protected butane-1,2-diol portion of the molecule are very similar in pattern and chemical shift to those of the starting material. In addition, there are two doublets at δ 0.76 and δ 0.99 due to the methyl groups of the hydroxyisobutyl substituent, each with a coupling of approximately 7 Hz to the adjacent methine proton, which resonates as an octet at δ 1.92. The benzylic CHO proton appears as a 7 Hz doublet at δ 4.28. The doublets of the aromatic AA'BB' system resonate at δ 7.12 and δ 7.22.

Figure 75
The acetonide 103b was converted to the triol 104b in 85% yield, by treatment of a methanolic solution with a catalytic amount of HCl (figure 75). The 1H NMR spectrum of 104b shows the characteristic pattern of signals associated with the butane-1,2-diol moiety. The signals due to the hydroxyisobutyl substituent are very similar to those of the starting acetonide 103b, as are the aromatic signals.

The benzylic hydroxyl group was removed from 104b by hydrogenolysis over a palladium catalyst at room temperature and atmospheric pressure, to give 105b in 79% yield (figure 76). The 1H NMR spectrum of the product had changed significantly, except for the signals due to the butane-1,2-diol portion of the molecule. The two methyl signals of the isobutyl substituent are now coincident and appear as a 6H, 7 Hz doublet at δ 0.89. The adjacent methine proton has eight adjacent protons and although its signal appears to be a 7 Hz, seven line multiplet, it is almost certainly a nine line signal with the outer lines obscured by baseline noise. The benzylic methylene protons resonate at δ 2.44 as a 7 Hz doublet and the 4H aromatic signal is now a very narrow multiplet at δ 7.09, which appears almost as a singlet.
The final step in the asymmetric synthesis of (S)-ibuprofen (1b) was oxidative cleavage of the diol 105b to the carboxylic acid (figure 76). This was achieved with a catalytic amount of ruthenium trichloride hydrate and an excess of sodium metaperiodate, in accordance with the conditions developed by Sharpless. Thus, the required product was obtained in 90% yield as a colourless oil with spectral data identical with those of an authentic sample of ibuprofen. (S)-Ibuprofen has been reported to exist as a white crystalline solid, however attempts to induce crystallisation failed. This may be due to the small amount of material produced (27 mg). The optical purity of the product was determined by the same procedure as was used for the analysis of (S)-ketoprofen, that is, by HPLC analysis of the mixture of (S)-1-phenylethylamides (see page 75). (S)-Ibuprofen (1b) was found to have a minimum e.e. of 96% which is consistent with a very slight amount of racemisation during the oxidation.
CHAPTER 3

ASYMMETRIC SYNTHESIS OF 2-ARYLPROPANOIC ACIDS VIA PALLADIUM COUPLING REACTIONS

The asymmetric syntheses of ketoprofen and ibuprofen discussed in the previous two chapters demonstrated that the use of a Sharpless asymmetric epoxidation, followed by stereoselective hydrogenolysis of the resultant epoxide, was a practical method for the control of chirality in 2-arylpropanoic acids. The next goal of the project was to modify the synthesis to allow access to a range of 2-arylpropanoic acids. It was considered that such a modification may enable the synthesis of a large number of differently substituted 2-arylpropanoic acids from a common optically active precursor in each of the meta and para series. Such a route would be particularly useful should the preparation of new compounds for biological screening be required.

In the contemplation of the structure of suitable intermediates, it was considered desirable that the optically active propanoic acid moiety be in place, and the aryl ring be activated towards coupling reactions. This would mean that the aryl substituent could be introduced as the final step in the synthesis, thereby enabling oxidation sensitive side chains such as alkenyl groups to be incorporated. The only limitation on the suitability of substituents would be their compatibility with the coupling reaction used.

Palladium catalysed coupling reactions between aryl halides (particularly iodides) and organozinc reagents are known to occur readily in the presence of a wide range of functional groups\textsuperscript{51-53}. The compounds chosen as the key, common intermediates therefore were the optically active meta and para iodo
carboxylic acids 45b and 46b. An example of the coupling of the racemic para acid 46a had been reported. The iodo acids 45b and 46b were synthesised in two steps from the corresponding trimethylsilyl diols 89b (an intermediate in the (S)-ketoprofen synthesis) and 100b (an intermediate in the (S)-ibuprofen synthesis) (figure 78).

The trimethylsilyl diol 89b was converted to the iodo diol 113b in 82% yield, by treatment with an equimolar amount of iodine monochloride. The absence of a singlet in the $\delta -0.5$ - $\delta 0.5$ region of the $^1$H NMR spectrum of 113b confirms...
the loss of the trimethylsilyl group. The $\delta 1 - \delta 4$ region shows the characteristic pattern of multiplets common to all the intermediates containing the butane-1,2-diol moiety, which has been described previously. The aromatic region is complex and integrates for 4Hs. Similarly, 100b was converted to 114b. The $^1$H NMR spectrum of 114b is very similar to that of 113b except for the aromatic region, which shows the AA'BB' pattern common to many of the para substituted intermediates.

Treatment of the iododiols 113b and 114b with a catalytic amount of ruthenium trichloride and an excess of sodium metaperiodate, in accordance with the conditions of Sharpless$^{84}$, afforded the key intermediates, optically active carboxylic acids 45b and 46b (figure 78). The meta iodo acid 45b is a white crystalline solid with a mp of 49-52°C and $[\alpha]D^{20} = +43.4^\circ$. Its $^1$H NMR spectrum shows a 7 Hz doublet at $\delta 1.50$ due to the methyl group, a 7 Hz quartet at $\delta 3.67$ due to the benzylic proton and a complex, 4H aromatic signal at $\delta 7.04 - \delta 7.67$. The molecular formula was confirmed by microanalysis. The para iodo acid 46b is a white crystalline solid with a mp of 139-140°C and $[\alpha]D^{20} = +39.0^\circ$. Its $^1$H NMR spectrum shows a 7 Hz doublet at $\delta 1.49$, a 7 Hz quartet at $\delta 3.68$ and an AA'BB' pattern of two 8 Hz doublets at $\delta 7.07$ and $\delta 7.65$, due to the para substitution pattern of the aromatic ring. Its formula was also confirmed by microanalysis.

Samples of the racemic iodo acids 45a and 46a were obtained in a similar way, from racemic trimethylsilyl diols 89a and 100a (figure 78). The racemic meta iodo acid 45a is a white crystalline solid with a mp of 48.0-50.5°C with spectral data identical with those of the optically active analogue 45b. The racemic para iodo acid 46a is also a white crystalline solid with a mp of 100-102°C and with spectral data identical with those of 46b.
The coupling reactions were performed with both racemic and optically active iodo acids. Although the aim of this work was to establish a route which would provide ready access to a range of optically active coupled products, it was also necessary to obtain racemic samples to use as analytical standards for the determination of optical purity. In most cases, the racemic coupled products were obtained in a similar manner to the optically active analogues, therefore only the syntheses of the (S)-2-arylpropanoic acids will be reported in detail, with one exception, discussed below.

An exploratory palladium catalysed coupling reaction was performed on available racemic iodo diacetate 115a instead of the carboxylic acid (figure 79). A benzyl substituent was incorporated by the treatment of 115a with a large excess of benzylzinc reagent in the presence of bis(triphenylphosphine)palladium(0). The catalyst was generated by reduction of dichlorobis(triphenylphosphine)palladium(II) with two equivalents of diisobutylaluminium hydride. The benzylzinc reagent was prepared by addition of zinc chloride to an ethereal solution of benzylmagnesium chloride.

![Chemical Structures](image)

Figure 79
The coupled product 116a was isolated in 86% yield after chromatography. The
$^{1}$H NMR spectrum of 116a showed a 7 Hz doublet at $\delta$ 1.26 due to the benzylic
methyl group and two 3H singlets at $\delta$ 1.98 and $\delta$ 2.06 from the acetate methyl
groups. Other peaks which arise from the butane-1,2-diacetate moiety are a
multiplet at $\delta$ 2.98 from the benzylic methine proton, two doublet of doublets at
$\delta$ 3.77 and $\delta$ 4.11, each due to one of the CH$_2$OAc protons, and a multiplet at $\delta$
5.22 due to the CHOAc proton. The benzylic methylene protons appear as a
singlet at $\delta$ 3.96, and the aromatic protons as a complex, 9H signal at $\delta$ 7.04 - $\delta$
7.34. Microanalytical data were consistent with the structure of 116a. The
racemic, benzyl substituted acid, 118a, was obtained by hydrolysis of the
diacetate to the diol 117a with potassium carbonate and methanol, followed by
oxidative cleavage with ruthenium trichloride and sodium metaperiodate.

The remaining palladium catalysed coupling reactions were performed with
the *meta* and *para* iodo carboxylic acids 45b and 46b. Thus, the optically active
*meta* benzyl substituted acid 118b was prepared in 91% yield by the coupling of
45b with benzylzinc in the presence of bis(triphenylphosphine)palladium(0)
(figure 80).

![Figure 80](image)

With both a racemic and an optically active sample of the benzyl substituted
acid 118 in hand, it was possible to determine the enantiomeric purity of the
optically active sample. Racemic 118a was converted to the diastereomeric (S)-
phenylethylamides, which were found to be separable by HPLC. Optically active
118b was analysed under the same conditions and the ratio of diastereomers measured. It was found to have a minimum optical purity of 94% e.e.

To illustrate the generality of the procedure, the meta iodo acid 45b was also coupled with phenylzinc to give 119b in 74% yield, and with phenylethynylzinc to give 120b in 71% yield (figure 81). The \(^1\)H NMR spectrum of the phenyl substituted acid 119b shows the characteristic signals for the propanoic acid moiety, which are a 7 Hz doublet at approximately \(\delta 1.5\) and a 7 Hz quartet at approximately \(\delta 3.8\). It also shows a complex set of signals at \(\delta 7.25 - \delta 7.59\) due to the nine aromatic protons. These data are in agreement with those reported\(^89\). The optical purity of 119b was determined by HPLC analysis of the (S)-phenylethylamides and found to be 94% e.e. The \(^1\)H NMR spectrum of the phenylethynyl substituted acid 120b also shows the characteristic signals for the propanoic acid moiety, and a complex 9H signal at \(\delta 7.30 - \delta 7.55\) due to the aromatic protons. The structure was supported by microanalytical data. The optical purity of 120b was determined by the standard HPLC method and found to be 96% e.e.

![Figure 81](image-url)
In the para series, the optically active iodo acid 46b was coupled to a variety of organozinc reagents (figure 82). Coupling of 46b with phenylzinc gave 121b in 62% yield, as a white crystalline solid with a mp of 159-161°C. The $^1$H NMR spectrum of 121b shows the characteristic signals due to the propanoic acid protons and a 9H signal at δ 7.34 - δ 7.59, which are in agreement with the data reported for the racemate. The optical purity of 121b was determined by the standard method and found to be 94% e.e. The iodo acid 46b was also coupled with isobutylinzinc to give (S)-ibuprofen (1b) in 77% yield, which had mp and spectral data identical with those reported. The optical purity of 4b was 92% e.e.

As a final example to illustrate the versatility of palladium catalysed coupling reactions as a method for the synthesis of substituted 2-arylpropanoic acids, the para iodo acid 46b was coupled with isobutenylzinc, to give 122b in 90% yield.
(figure 82). As well as the usual methyl and methine signals from the propanoic acid moiety, the $^1$H NMR spectrum of 122b shows two 1 Hz, 3H doublets at $\delta$ 1.85 and $\delta$ 1.89, due to the methyl groups of the isobutenyl group which are long range coupled to the vinylic proton. The splitting is not as well resolved in the vinylic signal, and the peak appears as a broad singlet at $\delta$ 6.23. The aromatic AA'BB' protons resonate as two doublets at $\delta$ 7.18 and $\delta$ 7.26. The optical purity of 122b was determined by hydrogenation to ibuprofen (1b) followed by the standard HPLC analysis, and found to be 96% e.e.

To summarise, palladium catalysed coupling reactions between optically active meta and para iodophenylpropanoic acids 45b and 46b and organozinc reagents were shown to be effective for the asymmetric synthesis of 2-arylpropanoic acids. The generality of the approach was demonstrated by the incorporation of benzyl, phenyl, phenylethynyl, isobutyl and isobutenyl substituents. Because the stereochemistry of the iodo acids was established by a Sharpless epoxidation followed by hydrogenolysis, the enantiomeric (R) iodo acids could be easily prepared by the use of the opposite configuration tartrate in the epoxidation reaction.
There are eight possible stereoisomers of the experimental drug ximoprofen (49) (figure 83), as it contains two chiral centres and an oxime group, which can exist in either the \((E)\) or \((Z)\) configuration. As discussed on page 36 in the retrosynthetic analysis of ximoprofen, the oxime could be formed from the corresponding carbonyl compound, of which there are four possible stereoisomers, \(123b, 123c, 124b\) and \(124c\) (these were collectively labelled as compound 50 in the introduction for simplicity). Ximoprofen is known to be rapidly hydrolysed \emph{in vivo} to this parent keto acid\(^{56-58}\), however no information has been reported with regard to the preparation or pharmacological activity of the separate stereoisomers.

\[\text{(49)}\]

\[\text{(123b)}\]
\[\text{(123c) = enantiomer}\]

\[\text{(124b)}\]
\[\text{(124c) = enantiomer}\]

Figure 83
The aim of the work discussed in this chapter was to synthesise these four keto acid isomers (figure 83), and convert each of them to the oximes which may be separable by chromatography. The isomers could then be tested for pharmacological activity.

The synthesis of one of these isomers, \((2S,1''R)-2-(4'\,[-3''-oxocyclohexyl]-phenyl)propanoic\) acid (123b) will be discussed in detail. The stereogenic centre of the propanoic acid moiety will be referred to as the 2 position and the other as the 1'' position.

The approach investigated involved a stereoselective conjugate addition of the Grignard reagent from bromo acetonide 102b (an intermediate in the (S)-ibuprofen synthesis) to optically pure (R)-5-trimethylsilyl-2-cyclohexenone (55c), by the use of the conditions developed by Asaoka et al\(^6^7\) (figure 84). This gave the addition product 125b, which has the basic carbon skeleton of the required keto acid 123b.

The optically pure reagent 55c was formed according to the procedure of Asaoka\(^6^6,6^7\) (see page 40-41). As no spectral data were reported for the intermediates in the synthesis, they have been reported in the experimental section of this thesis. Optically pure 55c was obtained as a colourless oil with a bp similar to that reported. The \(^1\)H NMR spectrum shows a sharp, 9H singlet at \(\delta -0.01\) due to the trimethylsilyl group and a multiplet at \(\delta 1.40\) from the SiCH proton. The two methylene groups give rise to a complex 4H signal at \(\delta 2.09 - \delta 2.42\). The olefinic proton \(\alpha\) to the carbonyl group appears as a doublet of triplets at \(\delta 5.96\), with a 10 Hz coupling to the adjacent olefinic proton and a 1 Hz long range coupling. The \(\beta\) olefinic proton resonates at \(\delta 7.00\) as a multiplet.
The conjugate addition reaction\(^{67}\) (figure 84) was performed by addition of a THF solution of the Grignard reagent from 102b to 55c, in the presence of a catalytic amount of copper bromide-dimethylsulphide complex, HMPA and an excess of chlorotrimethylsilane. The reaction was worked up and without isolation the crude product (almost certainly the enol silyl ether) was dissolved in methanol and treated with potassium fluoride. The required product 125b was liberated and obtained in 44% yield after chromatography. The \(^1\)H NMR spectrum of 125b shows a 9H singlet at δ -0.06 due to the trimethylsilyl group and the SiCH proton appears as a multiplet at δ 1.13. The peaks due to the protected butane-1,2-diol portion of the molecule have not changed significantly from those of the starting material, bromo acetonide 102b, except that the signal from the benzylic proton now overlaps with that of one of the
cyclohexane protons. All of the protons on the cyclohexane ring, except for the SiCH proton, resonate between δ 1.95 and δ 2.75, and appear as a complex set of multiplets. An apparent singlet at δ 7.09 is due to the four aromatic protons. The structure of 125b was supported by microanalysis.

The chromatography of the conjugate addition product 125b removed a higher Rf component, which was found to be a mixture of starting enone 55c and the product 126b from cis addition of the Grignard reagent to the enone (figure 85).

![Figure 85](image)

Although the signals due to the protected butane-1,2-diol moiety in the 1H NMR spectrum of 126b are very similar to those of the required trans addition product 125b, there are significant differences in other regions of the spectrum. The 9H singlet due to the trimethylsilyl protons resonates at δ - 0.04 and the multiplet from the SiCH proton at δ 0.81. The complex set of signals from the cyclohexane protons resonates over a narrower range than that of 125b (δ 2.10 - δ 2.40) and the aromatic protons appear as a symmetrical pair of 2H doublets. The observation of the cis addition product 126b was unexpected because Asaoka\textsuperscript{67} had reported that the conjugate additions of model compounds were completely stereoselective. However as only a trace of 126b was produced and it was easily separable by chromatography, the imperfect selectivity of the reaction
did not affect the overall asymmetric synthesis. Since both the enone 55c and the bromo acetonide 102b were optically pure, removal of the cis product ensured that only one stereoisomer (125b) was present.

With the basic skeleton and required stereochemistry now in place, it remained to convert the trans addition product 125b to the target keto acid 123b. Elimination of the trimethylsilyl group was effected by the use of cupric chloride in anhydrous DMF, in accordance with the procedure of Asaoka (figure 86).

![Diagram](image)
TLC of the crude reaction product indicated that the major product was much more polar than the starting material 125b, and that there was a significant quantity of a higher Rf product. The products were separated by chromatography and $^1$H NMR spectroscopy confirmed that the major product was the diol 127b. As well as elimination of the trimethylsilyl group, the acetal had unexpectedly but fortuitously been converted to the diol under the reaction conditions.

The $^1$H NMR spectrum of 127b showed a 7 Hz doublet at $\delta$ 1.34 for the benzylic methyl group, which was coupled to a 7 Hz quintet at $\delta$ 2.78 due to the adjacent methine proton. Other peaks which arise from the butane-1,2-diol portion of the molecule are two doublet of doublets at $\delta$ 3.22 and $\delta$ 3.44 due to the methylene protons and a doublet of triplets at $\delta$ 3.73 from the CHOH proton. The four methylene protons and the benzylic proton of the cyclohexane ring appear as a complex set of multiplets which resonate between $\delta$ 2.46 and $\delta$ 2.71. The olefinic proton $\alpha$ to the carbonyl group resonates as a doublet of doublets at $\delta$ 6.12, with a 10 Hz coupling to the other olefinic proton and a 2 Hz long range coupling. The $\beta$ proton of the $\alpha,\beta$-enone system gives rise to a multiplet at $\delta$ 7.06, and the 4H aromatic signal is an apparent singlet at $\delta$ 7.17. Confirmation of the molecular formula of 127b was obtained by microanalysis.

The higher Rf component was also isolated and was analysed by $^1$H NMR spectroscopy. The spectrum indicated that it was a mixture of the two formate esters 161b and 162b, which may have arisen from reaction of the diol 127b with the solvent, DMF. Among the diagnostic features of the spectrum were two singlets at $\delta$ 8.11 and $\delta$ 8.24, each of which was assigned to the CHO proton of one of the esters. Twinning of the methyl doublet suggests the presence of two isomers (one doublet resonates at $\delta$ 1.32 and the other at $\delta$ 1.40). None of the other signals in the spectrum were diagnostic due to overlap.
This higher Rf component was treated with aqueous methanolic HCl, and the reaction monitored by TLC. After 3 h the starting material had been consumed, and a single, lower Rf compound had formed. The $^1$H NMR spectrum confirmed that the product was the diol 127b, which supported the structures assigned to the formate esters 161b and 162b, and suggested that the acidic conditions had caused them to hydrolyse. Thus, the work up conditions of the reaction of the trimethylsilyl acetonide 125b with cupric chloride/DMF were modified to include treatment of the crude product with aqueous methanolic HCl. The isolated yield of 127b improved to 54%.

The newly formed double bond from the elimination of the trimethylsilyl group was removed by hydrogenation over a palladium catalyst. Thus, 127b was converted to 128b in 62% yield (figure 87). Although the reaction was incomplete, unreacted starting material 127b was easily removed by chromatography and it was unnecessary to repeat this hydrogenation.

![Figure 87](image)

The signals in the $^1$H NMR spectrum of the product 128b which arise from the butane-1,2-diol portion of the molecule are very similar to those of the starting material. The cyclohexane protons are well enough resolved to be individually assigned; a complex 2H signal at $\delta$ 1.82 is due to the two axial protons on C4 and...
C5, the corresponding equatorial protons resonate at $\delta$ 2.11, the two C6 protons as a multiplet at $\delta$ 2.39, the two C2 protons as a multiplet at $\delta$ 2.55 and the axial, benzylic C3 proton as a triplet of triplets at $\delta$ 2.98. This signal has a 4.6 Hz axial-equatorial coupling to the signal at $\delta$ 2.11 and a 11.6 Hz axial-axial coupling to the signal at $\delta$ 1.82. The four aromatic protons are apparent as a singlet at $\delta$ 7.15.

The final step in the synthesis of the target keto acid 123b was the oxidative cleavage of the diol moiety of 128b to the carboxylic acid. This was achieved with sodium metaperiodate and a catalytic amount of ruthenium trichloride hydrate$^{84}$ (figure 88).

\[
\text{RuCl}_3 \cdot 3\text{H}_2\text{O}, \quad \text{NaIO}_4
\]

The product 123b was isolated in 82% yield as a white crystalline solid with a mp of 94.0-95.5°C and $[\alpha]_D^{20}= +52.2^\circ$. The signals of the $^1$H NMR spectrum of 123b were assigned with the help of a COSY experiment. A 7 Hz doublet at $\delta$ 1.50 is due to the methyl group of the propanoic acid chain and is coupled to the proton $\alpha$ to the carboxyl group, which appears as a 7 Hz quartet at $\delta$ 3.73. A complex 2H signal at $\delta$ 1.73 - $\delta$ 1.90 is due to the axial protons of C5 and C6 of the cyclohexane ring and a separate signal at $\delta$ 2.05 - $\delta$ 2.18 is due to the C5 and C6 equatorial protons. The two C4 protons resonate as a complex signal at $\delta$ 2.32 - $\delta$ 2.45 and those attached to C2 at $\delta$ 2.49 - $\delta$ 2.61. The axial C1 proton at $\delta$ 2.99 is
split into a triplet of triplets, with a 4.2 Hz axial-equatorial coupling and a 11.6 Hz axial-axial coupling. The aromatic protons have the characteristic pattern of \textit{para} substitution, which is a symmetrical pair of 8 Hz doublets at $\delta$ 7.18 and $\delta$ 7.28. The $^{13}$C spectrum of 123b is consistent with the proposed structure and with the presence of a single diastereomer. All of the peaks in the $^{13}$C spectrum were assigned with the help of a hetero COSY experiment, and are reported in the experimental section. The product 123b was found to have an optical rotation of $[\alpha]_{D}^{20} = +52^\circ$. Further support for the structure of the target molecule, keto acid 123b, was obtained by microanalysis.

The synthesis of the (2S, 1'R) isomer 123b showed that a practical route to the individual stereoisomers of the parent keto acid of ximoprofen had been developed. The next goal of the project was to make the other three stereoisomers. The synthesis of stereoisomer 123c, the enantiomer of 123b, required optically pure enone 55b and the Grignard reagent from optically pure bromo acetonide 102c (figure 89). However once these substrates were obtained, there was no reason to expect any differences between their transformation to keto acid 123c, and the transformation of their enantiomers to keto acid 123b, discussed above.

![Figure 89](image)
Optically pure enone 55b was obtained according to the method of Asaoka\textsuperscript{66}, and the purity was confirmed by an optical rotation measurement ([α]\textsubscript{D}\textsuperscript{20}= +35.7° ± 0.2°, lit\textsuperscript{66}: [α]\textsubscript{D}\textsuperscript{20}= +35.5°).

Optically pure bromo acetonide 102c was obtained similarly to its enantiomer 102b, discussed in chapter 2, except that (-)-diisopropyl tartrate was used in the Sharpless epoxidation reaction instead of the (+) isomer (figure 90).

Thus allylic alcohol 98 was converted to the optically active epoxide 99c which, after recrystallisation, was estimated to be 98%+ e.e. from NMR analysis of the acetate derivative with the optically active shift reagent, tris[3-(heptafluoropropylhydroxymethylene)-(+)camphorato]-europium(III) deriv-
ative. The epoxy alcohol 99c underwent a stereoselective hydrogenolysis with palladium on charcoal catalyst to give the optically active diol 100c. Treatment of 100c with lithium bromide and N-chlorosuccinimide gave the bromo diol 101c, which was converted to the required acetonide 102c with acetone and a catalytic amount of p-toluenesulphonic acid (figure 90). The spectral data of the intermediates 99c-102c were identical with those of the enantiomers, 99b-102b.

As expected, the conjugate addition of the bromoacetonide 102c to the enone 55b proceeded under the same conditions used for the enantiomers to give the
addition product 125c, which was treated with cupric chloride and anhydrous DMF to eliminate the trimethylsilyl group and convert the acetonide to the diol (figure 91). The modified work up conditions (treatment with aqueous methanolic HCl) were used to effect hydrolysis of any formate ester by-products, and the diol 127c was obtained. The double bond of 127c was reduced by hydrogenation to give the diol 128c, which was then converted to the required keto acid 123c by oxidative cleavage with ruthenium trichloride and sodium metaperiodate. Physical and spectral data of the intermediates 125c-128c were identical with those of their enantiomers 125b-128b. The only difference between the data of 123c and that of enantiomeric 123b was the optical rotation (123c: [α]D^20 = -53°, 123b: [α]D^20 = +52°). The numerical values of these optical rotations are equal within experimental error.

The remaining two stereoisomers of the keto acid to be synthesised, 124b and 124c, are diastereomeric with the two stereoisomers previously discussed (123b and 123c). The approach to their syntheses was the same as for the diastereomers, as no significant differences in the reactivity of the intermediates were envisaged (in principle there may be variation in reactivities, however these were expected to be minimal due to the distance between the stereogenic centres).

The synthesis of stereoisomer 124b was achieved in the same way as that of 123b, by the use of enone 55b and the Grignard reagent from bromo acetonide 102b (figure 92).
Thus the conjugate addition reaction of these optically active reagents under the standard conditions gave the trimethylsilyl ketone 130b. Although in principle the $^1$H NMR data of 130b may be different to the diastereomeric analogues 125b and 125c, in fact they are almost identical, probably because of the remoteness of the stereogenic centres. However 130b was obtained as a white crystalline solid with a mp of 73-74°C, whereas 125b and 125c were obtained as colourless oils. Microanalysis of 130b supported the assigned structure. Treatment of the addition product 130b with cupric chloride and
DMF effected elimination of the trimethylsilyl group and removal of the acetonide moiety to give the diol 131b. Hydrogenation of 131b afforded the diol 132b, which was converted to the required keto acid 124b by oxidative cleavage with ruthenium trichloride and sodium metaperiodate.

In the $^1$H NMR spectrum of 124b the benzylic methyl protons resonate as a 7 Hz doublet at $\delta$ 1.50 and the proton $\alpha$ to the carboxyl group as a 7 Hz quartet at $\delta$ 3.73. A complex 2H signal at $\delta$ 1.73 - $\delta$ 1.90 is due to the axial protons of C5 and C6 of the cyclohexane ring and a separate signal at $\delta$ 2.05 - $\delta$ 2.18 is seen for the C5 and C6 equatorial protons. The two C4 protons resonate as a complex signal at $\delta$ 2.32 - $\delta$ 2.45 and those attached to C2 at $\delta$ 2.49 - $\delta$ 2.61. The axial C1 proton at $\delta$ 2.99 is split into a triplet of triplets, with a 4.2 Hz axial-equatorial coupling and a 11.6 Hz axial-axial coupling. The aromatic AA'BB' protons appear as a symmetrical pair of 8 Hz doublets at $\delta$ 7.18 and $\delta$ 7.28. The $^{13}$C spectrum was also consistent with the assigned structure. Although these spectral data are virtually identical to those of the previously reported diastereomers 123b and 123c, the mp of 124b was found to be 132.0-133.5°C, which is significantly different from that of 123b and 123c (mp 94.0-95.5°C). The optical rotation was also at variance; 124b has $[\alpha]D^{20} = +48^\circ$, 123b has $[\alpha]D^{20} = +52^\circ$. Microanalysis provided support for the structure of the target molecule, keto acid 124b.

The fourth and final keto acid stereoisomer to be prepared was 124c, the enantiomer of 124b. The synthesis of 124c, outlined in figure 93, used the enone 55c and the Grignard reagent from bromo acetonide 102c for the conjugate addition reaction, to give 130c as a white crystalline solid with a mp of 73-74°C. The observation that both 124b and 124c were obtained as solids with the same mp, whereas 123b and 123c were both obtained as colourless oils, was consistent with the stereochemical relationship of the four isomers. Treatment of 130c with cupric chloride and DMF afforded 131c which was
reduced to 132c by hydrogenation. The keto acid 124c was obtained by oxidative cleavage of 132c with ruthenium trichloride and sodium metaperiodate. Physical and spectral data of the intermediates 130c-132c were identical with those of their enantiomers 130b-132b. Spectral and mp data of 124c were identical with those of enantiomeric 124b, and the optical rotation was of equal magnitude but opposite sign, as expected ([α]D20 of 124c = -48°).

Thus, all four stereoisomers of the target keto acid were obtained. It was known that this compound was one of the metabolites of the drug ximoprofen, although no information had been reported with regard to the pharmacological...
activity of the individual stereoisomers. Therefore the samples made by this route were valuable substrates for the elucidation of the relationship between stereochemical configuration and pharmacological activity. To this end, a colleague, P. J. Hayball, examined the activity of the individual stereoisomers of the keto acid by measuring their effect on human platelet cyclo-oxygenase \textit{in vitro} (NSAIDs act as competitive inhibitors of cyclo-oxygenase, an enzyme involved in the inflammation process). The amount of thromboxane B2 generated during the clotting of whole blood from four healthy volunteers was used as an index of cyclo-oxygenase activity. As expected, the (S) configuration at the centre \(\alpha\) to the carboxyl group was found to be essential for activity, but it was also found that the isomer possessing the (R) configuration in the cyclohexane moiety (that is, the \((2S,1''R)\) isomer 123b) was approximately an order of magnitude more active than the epimeric \((2S,1''S)\) diastereomer 124b.

Stereoisomer 123b was converted to a mixture of \((E)\) and \((Z)\) oximes 133b and 134b in the hope that the isomers could be separated chromatographically to provide a route for the preparation of the individual stereoisomers of ximoprofen. The mixture of oximes was formed by treatment of 123b with hydroxylamine hydrochloride in pyridine (figure 94).
The isomers \textbf{133b} and \textbf{134b} could not be separated by chromatography on silica because of the extreme polarity of the carboxyl group, which masked any differences in Rf due to the oxime functionality.

To circumvent this problem, the mixture of oximes was converted to the corresponding methyl esters \textbf{135b} and \textbf{136b}, which were much less polar than the carboxylic acids (figure 95). This was achieved by treatment of \textbf{133b} and \textbf{134b} with an ethereal solution of diazomethane.

![Figure 95](image)

The methyl esters \textbf{135b} and \textbf{136b} were separated by HPLC. The first eluting component was assigned as the (\textit{E}) isomer and the second eluting component as the (\textit{Z}) isomer. These assignments were based on findings by Duddeck et al\textsuperscript{91} during the study of cholestane derivatives (figure 96). They observed that the equatorial proton on the carbon \(\alpha\) to the oxime was shifted downfield when it was \textit{cis} to the oxime hydroxyl. Thus, derivative \textbf{137} shows the equatorial proton of C5 to resonate at \(\delta\) 3.45 and the equatorial proton of C7 at \(\delta\) 2.17, whereas derivative \textbf{138} shows peaks at \(\delta\) 2.33 due to the C5 equatorial proton and \(\delta\) 3.15 due to the C7 equatorial proton. These structures were confirmed by X-ray crystallography.
In the current work, the first eluting isomer gave rise to signals in its $^1$H NMR spectrum at $\delta$ 1.98 - $\delta$ 2.05 due to the two axial protons of C2 and C4 (figure 97), $\delta$ 2.57 for the equatorial proton of C2 and $\delta$ 3.37 for the equatorial proton of C4 (the resonances were assigned on the basis of chemical shift values and coupling to the distinctive benzylic proton as determined by a COSY experiment).
The $^1$H NMR spectrum of the second eluting isomer showed peaks at $\delta$ 1.94 and $\delta$ 2.11 respectively for the C2 and C4 axial protons, and $\delta$ 3.47 and $\delta$ 2.44 respectively for the C2 and C4 equatorial protons. By analogy with the spectral data of the cholestane derivatives in figure 96, the first eluting component was assigned as the (E) isomer 135b and the second eluting component as the (Z) isomer 136b.

It was expected that hydrolysis of the methyl ester 135b would give enantiomerically and diastereomerically pure carboxylic acid 133b (one of the eight possible stereoisomers of ximoprofen), however even under the mild conditions for ester hydrolysis reported by Evans et al$^{92}$ (lithium hydroxide in aqueous THF) the oxime isomerised.

![Figure 98](image)

Figure 98
Thus, hydrolysis of the pure (E) oxime ester 135b gave the carboxylic acids 133b and 134b as a 1:1 mixture (figure 98). It was also found that the pure (Z) oxime acid 134b isomerised to a mixture of 133b and 134b upon standing in deuterocloroform.

In summary, the four stereoisomers of the parent keto acid of the hydroxyoximino drug ximoprofen were prepared in high optical purity. The stereochemistry of the centre α to the carboxylic acid was established by the combination of a Sharpless asymmetric epoxidation (with either (+)- or (-)-diisopropyl tartrate) and stereoselective hydrogenolysis of the benzylic carbon-oxygen bond with inversion of configuration. The configuration of the centre in the cyclohexanone ring was controlled by the stereoselective conjugate addition of the arylpropanoic acid moiety to the enantiomers of 5-(trimethylsilyl)-2-cyclohexenone with subsequent removal of the trimethylsilyl group. The pharmacological activities of each of these four isomers were assessed by their in vitro inhibition of human platelet cyclo-oxygenase. As expected, the (S) configuration of the propanoic acid chain was essential for activity but it was also found that the stereochemistry in the cyclohexanone moiety was important. One of the keto acid stereoisomers was converted to a mixture of (E) and (Z) oximes, however attempts to separate the oxime isomers were unsuccessful.
CHAPTER 5

A SHORTER ROUTE FOR THE ASYMMETRIC SYNTHESIS OF KETOPROFEN

During the course of this work, several publications appeared in relation to the scope and synthetic usefulness of the Sharpless catalytic asymmetric dihydroxylation reaction\(^\text{72}\). A shorter route to the asymmetric synthesis of 2-arylpropanoic acids was envisaged which made use of this reaction for the control of chirality in the molecule. \((S)\)-Ketoprofen \((4b)\) was chosen as a representative target molecule for the exploration of the route because interest has been shown by a major pharmaceutical company in its commercial production\(^\text{93}\). However the principle behind the approach could be applied to the asymmetric synthesis of other \emph{meta} and \emph{para} substituted 2-arylpropanoic acids.

An overview of the proposed route is outlined in figure 99. The intention was to convert commercially available \(m\)-bromoacetophenone to the alkene \(139\) which could then be coupled to a benzyl group to give the intermediate \(140\). Although palladium catalysed coupling reactions occur more readily with aryl iodides than bromides, the reaction of the aryl bromide was explored first because of its availability (\(m\)-iodoacetophenone is not commercially available). A Sharpless asymmetric dihydroxylation reaction of the alkene \(140\) would give the optically active diol \(141b\). It was expected that a stereoselective hydrogenolysis of \(141b\) over a palladium catalyst would proceed with inversion of configuration to give the alcohol \(142b\) which could be oxidised to \((S)\)-ketoprofen \((4b)\).
A Wittig reaction was used to convert \textit{m}-bromoacetophenone to the alkene 139 (figure 100). Methyltriphenylphosphonium iodide was treated with an equimolar amount of potassium \textit{tert}-butoxide to generate the ylid, to which \textit{m}-bromoacetophenone was added. After work up and distillation the product 139 was obtained in 85\% yield.
The $^1$H NMR spectrum of 139 shows a 3H singlet at $\delta$ 2.12 due to the methyl group, two 1H singlets at $\delta$ 5.11 and $\delta$ 5.38 from the olefinic protons and a complex 4H aromatic signal at $\delta$ 7.15 - $\delta$ 7.60. These data were consistent with literature values.94

The next step in the synthesis was the treatment of bromo alkene 139 with an excess of benzylzinc in the presence of a catalytic amount of bis(triphenylphosphine)palladium(0), to give the coupled product 140 (figure 101). The catalyst was generated by reduction of dichlorobis(triphenylphosphine)palladium(II) with two equivalents of diisobutylaluminium hydride. Benzylzinc was prepared by addition of zinc chloride to an ethereal solution of benzylmagnesium chloride. The coupling proceeded smoothly to give the required product 140 in quantitative yield, however a significant amount of 1,2-diphenylethane was also present, and was inseparable from 140. The estimated yield was calculated from the total weight of the product and the percentage of 140 present in the mixture, as determined by $^1$H NMR. The 1,2-diphenylethane was almost certainly present in the benzylzinc reagent, and arose from the magnesium catalysed coupling of two molecules of benzyl chloride. Its presence clearly did not affect the yield of the palladium catalysed coupling reaction.

Figure 101
The crude product from the palladium catalysed coupling reaction was purified by chromatography. Both the required product 140 and 1,2-diphenylethane are unfunctionalised hydrocarbons of similar molecular weight, therefore it was not surprising that they were inseparable. The $^1$H NMR data of 1,2-diphenylethane have been reported$^{95}$ and are in agreement with those observed in a spectrum of the product mixture. The signals which arise from the product 140 are a 3H singlet at $\delta$ 2.13 from the methyl group, a 2H singlet at $\delta$ 3.99 for the benzylic methylene protons and two 1H singlets at $\delta$ 5.06 and $\delta$ 5.34 due to the olefinic protons. The $\delta$ 7.1 - $\delta$ 7.3 region of the spectrum is complex, as the signals from the nine aromatic protons of 140 and the ten aromatic protons of 1,2-diphenylethane overlap. Comparison of the integration value of the 2H methylene signal of 140 at $\delta$ 3.99 with that of the 4H methylene signal of 1,2-diphenylethane at $\delta$ 2.93 indicated that the components were present in a 61:39 ratio.

Sharpless has reported the conversion of $\alpha$-methylstyrene to the (S) diol 143b (figure 102) by the use of AD-mix-$\alpha$, a commercially available mixture of the reagents necessary for the catalytic asymmetric dihydroxylation reaction$^{77}$ (see page 49). The optical purity of 143b was reported to be 93% e.e.

$$\text{AD-mix-$\alpha$} \rightarrow \text{(143b)} \quad 93\% \text{ e.e.}$$

In the current work, the benzyl alkene 140 was treated with AD-mix-$\alpha$ in a similar manner to that reported for the treatment of $\alpha$-methylstyrene. The
presence of 1,2-diphenylethane in the sample of 140 was not expected to interfere with the reaction. The product of the reaction, obtained in 80% yield as a colourless oil, was the desired optically active diol 141b (figure 103). The 1,2-diphenylethane was easily removed by chromatography. The $^1$H NMR spectrum of 141b is consistent with the assigned structure. The methyl protons resonate as a singlet at $\delta$ 1.52 and the OH protons at $\delta$ 1.85 and $\delta$ 2.60, each as a broad singlet. Two doublets at $\delta$ 3.62 and $\delta$ 3.79 arise from the CH$_2$O protons which have a 10 Hz geminal coupling. A 2H singlet at $\delta$ 4.01 is due to the benzylic methylene group and a complex 9H signal between $\delta$ 7.22 and $\delta$ 7.34 belongs to the aromatic protons.

![Figure 103](image)

To determine the optical purity of the diol 141b, a sample of the racemate 141a was required as a standard. This was obtained by oxidation of 140 (containing 1,2-diphenylethane) with an excess of N-methylmorpholine oxide and a catalytic amount of osmium tetroxide, in accordance with the procedure of VanRheenen$^{96}$ (figure 104). The racemic diol 141a was obtained in quantitative yield and found to have $^1$H NMR data identical with those of the optically active analogue 141b. Microanalytical data supported the structure of 141a.
A sample of the racemic diol 141a was converted to the acetate 144a with an excess of acetic anhydride in pyridine (figure 105). No acetylation of the tertiary hydroxyl group was observed. The acetate 144a was analysed with the chiral shift reagent tris[3-(heptafluoropropylhydroxymethylene)-(+)camphorato]-europium(III) derivative. The analysis was performed on the acetate for two reasons. Firstly, past experience with this shift reagent had indicated that a free primary hydroxyl group in the substrate could give rise to line broadening in the $^1$H NMR spectrum, and secondly, the sharp singlet of the acetate methyl group had the potential to be a diagnostic peak.

The $^1$H NMR spectrum of the acetate 144a shows a sharp 3H singlet at $\delta$ 1.54 due to the benzylic methyl group and another at $\delta$ 2.01 due to the acetate methyl
The benzylic methylene protons appear as a singlet at δ 3.99 and the CH₂OAc protons as two 11 Hz doublets at δ 4.18 and δ 4.28. The aromatic protons resonate as a complex set of signals at δ 7.16 - δ 7.32. Upon addition of the chiral shift reagent to a deuterochloroform solution of the racemic acetate 144a, each of the methyl signals separated into two singlets. A downfield shift was also observed. In the presence of an optimal amount of shift reagent the singlet originally at δ 1.54 now appeared as two singlets at δ 2.55 and δ 2.58, due to the diastereomeric interactions of each enantiomer of the racemate with the optically active reagent. Similarly the singlet at δ 2.01 was now apparent as two singlets at δ 2.75 and δ 2.77 (figure 106a).

The analysis was repeated on a sample of the acetate 144a in deuterobenzene, in the hope that a change of solvent may improve the separation between the signals of the diastereomeric complexes. Unfortunately the degree of separation was less than with deuterochloroform as solvent. The analysis was repeated with carbon tetrachloride as the solvent and good separation of the signals was observed (figure 106b). The singlet which occurred at δ 1.54 in the spectrum of 144a without shift reagent now appeared as two singlets at δ 2.61.
and δ 2.67. Similarly, the singlet at δ 2.01 now appeared as two singlets at δ 2.81 and δ 2.88. The latter signal was considered to be the most diagnostic for the measurement of optical purity because there is almost baseline resolution between the two peaks.

A sample of the optically active diol 141b from the Sharpless asymmetric dihydroxylation reaction was converted to the acetate 144b. Under similar conditions to those used for the analysis of the racemate 144a, a carbon tetrachloride solution of 144b was treated with the chiral shift reagent. The relevant section of the resultant 1H NMR spectrum is reproduced in figure 107. Integration indicated that the enantiomers were present in a ratio of 94:6, or that the optical purity of the diol 141b was 88% e.e.
It was not possible to improve the optical purity of the diol 141b by recrystallisation because the compound existed as an oil. Attempts to induce crystallisation were unsuccessful. It was considered undesirable to convert the compound to a crystalline derivative as to do so would lengthen the synthesis, and one of the advantages of this approach is the relatively few steps involved. Therefore, material of 88% e.e. was carried through to the next step in the hope that one of the subsequent intermediates would be crystalline. If this were to be the case, there may be an opportunity to improve the optical purity by recrystallisation.

The next step in the synthesis was hydrogenolysis of the benzylic hydroxyl group of 141b with control of stereochemistry (figure 109). Earlier work had shown that benzylic epoxides were hydrogenolysed readily at low temperatures with excellent diastereoselectivity. For example, the racemic epoxy alcohol 88a was treated with palladium on carbon catalyst in a hydrogen atmosphere at -60°C to give the racemic diol 89a with 99% d.e. (figure 108) (see page 63).

However, when the diol 141b was treated with the same palladium catalyst under similar conditions no reaction occurred. The procedure was repeated at room temperature with various solvents (ethanol, dichloromethane and ethyl acetate) but only starting material was recovered. The explanation for the lower
reactivity of the diol 141b compared with the epoxide 88a involves the leaving group ability of the respective benzylic oxygens. In the case of the epoxide, the oxygen can be considered to be an excellent leaving group because of the large release of ring strain upon cleavage of the C-O bond. When the benzylic oxygen is not part of a cyclic system, the reactivity towards hydrogenolysis is proportional to the ability of the oxygen to bear a negative charge. Thus, in the system PhCH2OR, the rate of hydrogenolysis increased in the order OH < O-alkyl < O-aryl < OH⁺-alkyl < OH₂⁺ < OAc < OCOCF₃.

One possible way to improve the reactivity of the diol 141b towards hydrogenolysis was to increase the leaving group ability of the benzylic hydroxyl group. Another was to use a different catalyst and this approach was investigated first.

Raney nickel has been reported to catalyse hydrogenolysis reactions with a high degree of stereoselectivity; in some cases even higher than when palladium is used. However nickel catalysis leads to retention of configuration in the
products whereas palladium catalysis occurs with inversion. In the current work therefore, hydrogenolysis of 141b with Raney nickel would give the alcohol 142c which has the opposite configuration to that required (figure 109). Clearly, this problem could be circumvented by starting with the enantiomeric diol 141c, which could be easily prepared by the use of AD-mix-β instead of AD-mix-α in the Sharpless dihydroxylation reaction. Hydrogenolysis of 141c with Raney nickel would then give the required alcohol 142b (figure 109).

There was precedent for the hydrogenolysis of this type of diol with Raney nickel. Esashi et al46 reported that treatment of a very similar compound, 145b, with Raney nickel at 20°C and atmospheric pressure gave the alcohol 146b with 99% e.e. (figure 110). This example augured well for the current work.

![Figure 110](image)

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Exploratory reactions were performed on the available diol 141b with W4 Raney nickel under similar conditions to those used by Esashi for the model compound, 145b. After 40 h, TLC of the reaction mixture indicated that the starting material had been consumed and three products had formed (figure 111). These were separated by flash chromatography and their structures assigned on the basis of their 1H NMR spectra. The second eluting compound was the required product 142c, which made up approximately 42% of the total product. The first eluting component, which made up approximately 26% of
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the total product, was the alcohol 147b. Reduction of the less substituted aromatic ring had occurred as well as hydrogenolysis of the benzylic hydroxyl group. The third eluting component of the product mixture was the diol 148b, which arose from reduction of the less substituted aromatic ring of 141b without hydrogenolysis of the hydroxyl group.

The configuration of the three products was not confirmed. The stereochemical assignments illustrated in figure 111 are based on the assumption that the hydrogenolysis proceeded with retention of configuration. The $^1$H NMR spectrum of the required alcohol 142c contains a 7 Hz doublet at $\delta$ 1.26 due to the methyl group. This is coupled to a 7 Hz sextet at $\delta$ 2.92 which belongs to the benzylic methine proton. The CH$_2$OH protons appear as a 7 Hz doublet at $\delta$ 3.69 and the benzylic methylene protons as a
singlet at $\delta$ 3.99. The aromatic region integrates for nine protons and appears at $\delta$ 7.02 - $\delta$ 7.30 as a complex set of signals.

The $^1$H NMR spectrum of the by-product 147b shows similar signals for the benzylic methyl and methine protons, and the CH$_2$OH methylene protons in this case show coupling with the OH proton and appear as a 2H triplet at $\delta$ 3.72. One of the features of the spectrum which indicate that ring reduction had occurred is a complex set of signals in the $\delta$ 0.85 - $\delta$ 1.78 region which integrates for twelve protons and can be assigned to the cyclohexane protons and the OH. Another is the aromatic region which now integrates for four protons and resonates at $\delta$ 7.01 - $\delta$ 7.27. The benzylic methylene group appears as a 7 Hz doublet which indicates that it has an adjacent proton. This signal has a chemical shift value of $\delta$ 2.47 which suggests that it has only one adjacent aryl group (the same signal resonates as a singlet at $\delta$ 3.99 in the product 142c).

The other by-product of the Raney nickel catalysed hydrogenolysis reaction, 148b has a complex 13H set of signals between $\delta$ 0.85 and $\delta$ 1.85 in its $^1$H NMR spectrum, due to the cyclohexane and hydroxyl protons. The spectrum also shows a 3H singlet at $\delta$ 1.55 from the methyl group, a 7 Hz doublet at $\delta$ 2.51 from the benzylic methylene protons and two doublet of doublets at $\delta$ 3.65 and $\delta$ 3.82 due to the diastereotopic CH$_2$OH protons which are coupled to each other and to the adjacent OH. The aromatic protons resonate as a 4H signal at $\delta$ 7.03 - $\delta$ 7.31.

The significant quantities of ring reduced by-products 147b and 148b formed in the Raney nickel catalysed hydrogenolysis reaction detract from its usefulness. The reaction was repeated at 0°C instead of 20°C, in the hope that low temperature may inhibit ring reduction more than it inhibits hydrogenolysis of the benzylic C-O bond. Unfortunately the ratio of ring reduced products to
the required product was marginally higher than in the previous reaction. Further investigation of the use of Raney nickel as the catalyst for hydrogenolysis was not pursued.

An alternative approach to improve the reactivity of the diol 141b towards hydrogenolysis was to increase the leaving group ability of the benzylic hydroxyl group, as discussed on page 126. Addition of acid to a solution of 141b would effectively convert the relatively unreactive OH group to a more reactive OH$_2^+$ group, without adding further steps to the synthesis. It has been reported that a catalytic amount of perchloric acid greatly enhances the rate of hydrogenolysis of benzylic hydroxyl groups without causing racemisation$^{44,97}$. In light of these precedents, a solution of the diol 141b in ethyl acetate was treated with a palladium on carbon catalyst and a catalytic amount of aqueous perchloric acid in a hydrogen atmosphere (figure 112).

![Reaction Scheme](image)
The reaction did not proceed at 0°C, but upon warming to room temperature was complete within 12 h. By TLC the reaction product appeared as a single component, however the product 142b was isolated in only 34% yield after flash chromatography. Closer inspection of the earlier fractions from chromatography revealed that they contained a major amount of a compound that was not visible by UV light or any of the usual TLC development methods. 1H NMR spectroscopy of this compound indicated that it was the hydrocarbon 149. The by-product accounted for 66% of the total product by weight.

1H NMR data of the alcohol 142b were identical with those of the enantiomer 142c described previously. The 1H NMR spectrum of the hydrocarbon 149 shows the methyl groups as a 6H, 7 Hz doublet at δ 1.23, which is coupled to a 1H septet at δ 2.85. The benzylic methylene protons appear as a singlet at δ 3.97 and the aromatic protons as a 9H signal at δ 6.97 - δ 7.31. One possible mechanism for the formation of 149 is outlined in figure 113. It was considered possible that the hydrogenolysis product 142b dehydrated under the acidic conditions to give the alkene 140 which would undergo further reduction to 149.

To test this hypothesis, a sample of the hydrogenolysis product 142b was retreated under the same conditions. However only the starting material 142b was recovered which suggests that the by-product is not formed from the alcohol 142b. Another possible mechanism for the formation of 149 is outlined in figure 114. The starting diol 141b may dehydrate under the acidic reaction conditions to give the allylic alcohol 150. There is precedent for hydrogenolysis of allylic alcohols with a palladium catalyst98, and this may occur to give the alkene 140. Hydrogenation of the double bond would then give 149.
The hydrogenolysis reaction conditions were varied in an attempt to minimise the amount of 149 produced. Trifluoroacetic acid was used instead of perchloric acid in the hope that a weaker acid may be less likely to promote dehydration.
The rate of reaction at room temperature was found to be impractically slow. The reaction with perchloric acid was studied in other solvents; the use of dichloromethane gave the required product 142b in 69% yield and the use of ethanol gave 142b in 60% yield. Both of these results are substantial improvements on the 34% yield obtained with ethyl acetate. Therefore, on the basis of yield, the most suitable reaction conditions were the presence of a catalytic amount of perchloric acid with dichloromethane as solvent. However another important consideration was the optical purity of the product alcohol 142b.

The determination of the optical purity of the hydrogenolysis product 142b required a sample of the racemate 142a as a standard. This had been obtained earlier by hydrogenolysis of the racemic diol 141a with Raney nickel (figure 115).

![Figure 115](image_url)

Racemic alcohol 142a was converted to the acetate 151a (figure 115) for analysis with a chiral shift reagent. Treatment of solutions of 151a in various solvents
with the shift reagent tris[3-(heptafluoropropylhydroxymethylene)-(+)camphorato]europium(III) derivative failed to cause any significant peak separation in the $^1$H NMR spectra. Some separation of the methyl signals was observed, but it was insufficient for diagnostic purposes.

An alternative analysis was investigated which involved conversion of the racemic alcohol 142a to the diastereomeric Mosher esters 152b and 153b with optically active Mosher's acid 68 (figure 116). The esterification, which was performed in accordance with the procedure of Hassner\textsuperscript{99}, used an equimolar amount of N,N-dicyclohexylcarbodiimide and a catalytic amount of dimethylaminopyridine and proceeded in quantitative yield.

\[ \text{(142a)} \]

\[ \text{F}_3\text{C} \quad \text{OMe} \]
\[ \text{Ph} \quad \text{DCC, DMAP} \]

\[ \text{(68)} \]

\[ \text{(152b)} \]

\[ \text{Ph} \quad \text{MeO} \quad \text{CF}_3 \quad \text{Ph} \quad \text{MeO} \quad \text{CF}_3 \]

\[ \text{Ph} \]

\[ \text{(153b)} \]

\[ \text{Ph} \]

Figure 116

A $^1$H NMR spectrum of the 1:1 mixture of 152b and 153b showed that some signals of the diastereomers have significantly different chemical shift values.
The benzylic methyl peaks of the two isomers resonate as singlets at δ 1.26 and δ 1.28, but are not baseline resolved. The sextets from the benzylic methine protons at δ 3.14 overlap, as do the doublet of doublets at δ 4.31 and δ 4.47 due to the CH₂O protons. The benzylic methylene protons of 152b and 153b are coincident and appear as a singlet at δ 3.93, and the aromatic region is extremely complex. The most diagnostic signal in the spectrum is that of the methoxyl protons, which resonates at δ 3.36 for one diastereomer and δ 3.39 for the other (figure 117). Each of the signals shows a 1.3 Hz ¹H-¹⁹F long range coupling. These two signals are virtually baseline resolved and provide a reliable standard for the determination of the enantiomeric excess of a sample of optically active alcohol 142b.

![Figure 117](image)

Under similar conditions to those used for the analysis of the racemic alcohol 142a, the optical purity of the various samples of 142b were determined. Thus, the products of the hydrogenolysis reactions with ethyl acetate, dichloromethane and ethanol were each converted to the Mosher ester
derivatives. The relative integration values of the two methoxyl signals in each $^1$H NMR spectrum reflected the optical purity of the alcohols. For example, the Mosher ester of 142b from the hydrogenolysis of 141b in ethyl acetate was found to be a 90 : 10 mixture of diastereomers. Taking into account that the starting material 141b had an e.e. of 88%, this ratio indicated that the hydrogenolysis occurred with 96% inversion of configuration at the benzylic carbon and 4% retention. In a similar manner the hydrogenolysis in dichloromethane was found to have occurred with 88% inversion, and the reaction in ethanol with 93% inversion. The results of the hydrogenolysis of 141b in various solvents are summarised in table 2.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Yield of 142b/%</th>
<th>Inversion/%</th>
<th>Retention/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>EtOAc</td>
<td>33</td>
<td>96</td>
<td>4</td>
</tr>
<tr>
<td>CH₂Cl₂</td>
<td>69</td>
<td>88</td>
<td>12</td>
</tr>
<tr>
<td>EtOH</td>
<td>60</td>
<td>93</td>
<td>6</td>
</tr>
</tbody>
</table>

Table 2

The use of ethyl acetate as solvent gave the best stereoselectivity but the lowest yield, whereas dichloromethane gave the highest yield but the poorest stereoselectivity. The use of ethanol as solvent gave the best compromise between yield and degree of inversion of configuration, and was the solvent of choice for subsequent hydrogenolysis reactions of 141b.

The batch of optically active alcohol 142b which had been formed by hydrogenolysis of 141b in ethanol was used for the remainder of the synthesis of (S)-ketoprofen. The optical purity of the alcohol was 83% e.e. and it existed as a colourless oil. Attempts to induce crystallisation were unsuccessful, therefore
the enantiomeric excess could not be improved by recrystallisation, a procedure which is often effective. Two possibilities were considered to exploit this method for the preparation of (S)-ketoprofen (4b) of high optical purity from the precursor 142b of lesser optical purity. One was to oxidise 142b (83% e.e.) to 4b, which is reported to be a crystalline solid, and the other was to convert 142b (83% e.e.) to a crystalline derivative. Clearly, the derivative could then be converted back to the alcohol 142b for oxidation to 4b. The former possibility was explored first.

Oxidation of the carboxylic acid 154b to 4b with potassium permanganate in aqueous sodium hydroxide has been reported by Comisso et al. (figure 118). A significant amount (28%) of 3-benzoylaceto phenone (155) was formed as a by-product of the reaction.

\[
\begin{align*}
\text{Ph} & \text{CO}_2\text{H} & \text{Ph} & \text{CO}_2\text{H} \\
\text{KMnO}_4, \text{NaOH/H}_2\text{O} & & & + \\
(154b) & & & (155) \\
\end{align*}
\]

Figure 118

The alcohol 142b was treated under similar conditions, with the expectation that oxidation of the primary hydroxyl group would be effected as well as oxidation of the benzylic methylene group, to give 4b. The required product 4b
was obtained in 45% yield, together with the degradation by-products 155 and 156 (figure 119). The ketone 155 was separated by base extraction of a dichloromethane solution of the product mixture; the acidic components were soluble in the basic aqueous phase whereas the ketone remained in the organic phase. Attempts to separate the acidic by-product 156 from 4b by chromatography and crystallisation were unsuccessful.

![Figure 119](image-url)

Because this approach to the preparation of optically pure (S)-ketoprofen from 142b (83% e.e.) was complicated, the alternative approach (formation of a crystalline derivative) was investigated. The 3,5-dinitrobenzoate 157b was formed in 81% yield by treatment of 142b with 3,5-dinitrobenzoyl chloride in pyridine (figure 120). After purification by chromatography and storage at -20°C, 157b was obtained as a pale yellow crystalline solid. The benzylic methyl group appears as a 7 Hz doublet at δ 1.40 in the $^1$H NMR spectrum of 157b. The
benzylic methine proton gives rise to a 7 Hz sextet at δ 3.28, and the CH₂O protons to a 7 Hz doublet at δ 4.49. A 2H singlet at δ 3.97 is from the benzylic methylene group. The nine protons of the benzylphenyl system resonate between δ 7.07 and δ 7.31 and those of the dinitrophenyl ring as a 2H signal at δ 9.01 and a 1H signal at δ 9.18. Each of these downfield aromatic signals shows a 2 Hz meta coupling with the other.

The 3,5-dinitrobenzoate 157b was recrystallised twice from ether. The resultant white crystalline material had a mp of 65-66°C and [α]D²⁰ = -28°. The ester 157b was then hydrolysed to the alcohol 142b in 93% yield with potassium carbonate in aqueous methanol. The optical purity of the product 142b was determined by conversion to the Mosher ester derivative as discussed previously and found to be at least 99% e.e. Therefore, conversion of the alcohol 142b to the 3,5-dinitrobenzoate derivative followed by recrystallisation and hydrolysis was an extremely efficient method for the improvement of its optical purity.
The final step in the asymmetric synthesis of (S)-ketoprofen (4b) was the oxidation of the optically pure alcohol 142b. The use of potassium permanganate for this transformation had previously been shown to give an inseparable mixture of products (see figure 119, page 138).

In earlier work, the use of sodium metaperiodate and ruthenium trichloride hydrate had been successful for the oxidation of triol 76b to 4b (see pages 70 and 75) and had occurred with negligible racemisation (figure 121).

Treatment of the alcohol 142b under the same conditions afforded the carboxylic acid 158b in 59% yield after chromatography (figure 122). 1H NMR data of 158b were in agreement with those reported100.

Because the oxidation of 158b to (S)-ketoprofen had been reported100, it was considered unnecessary to perform the reaction. All that remained was to establish the optical purity of 158b to confirm that no racemisation had occurred
in the ruthenium tetraoxide oxidation. The optical rotation of \(158\text{b}\) was in agreement with the literature value for optically pure material\(^{100}\), however a more precise analysis was desired.

\[
\begin{align*}
\text{(158a)} & \quad \text{Ph} - \text{en} - \text{Ar} - \text{CO}_2\text{H} \\
\text{(159b)} & \quad \text{HO} - \text{C} - \text{H} - \text{N} - \text{+} - \text{HO} \\
\text{(160b)} & \quad \text{HO} - \text{C} - \text{H} - \text{N} - \text{+} - \text{HO} \\
\end{align*}
\]

\(\text{Ar} = 3\)-benzylphenyl

Figure 123

A suitable \(^1\text{H}\) NMR analysis was developed with the racemate \(158\text{a}\). Addition of an equimolar amount of optically pure cinchonidine to a deuterochloroform solution of the racemic acid \(158\text{a}\) afforded a 1:1 mixture of diastereomeric salts \(159\text{b}\) and \(160\text{b}\) (figure 123).
Some signals in the $^1$H NMR spectrum of the two isomers 159b and 160b are distinct. In particular, the benzylic methyl doublets at $\delta$ 1.44 and $\delta$ 1.47 partially overlap; the inner peak of each doublet is coincident but the outer peaks ($\delta$ 1.43 and $\delta$ 1.48) are well separated (figure 124a). The singlets due to the benzylic methylene groups are even more diagnostic; they resonate at $\delta$ 3.84 and $\delta$ 3.86 and are almost baseline resolved (figure 124a).

Under the same conditions as those used for analysis of the racemate, cinchonidine was added to a sample of optically active carboxylic acid 158b from
the ruthenium tetraoxide oxidation. Inspection of the $^1$H NMR spectrum of the resultant salt 159b showed it to have a d.e. of at least 99% (figure 124b). This reflects an optical purity of 99%+ e.e. for the acid 158b, and indicates that no racemisation occurred during the oxidation.

In summary, a method for the synthesis of (S)-ketoprofen of high optical purity was developed. The alkene 140, formed from readily available starting materials, underwent a Sharpless asymmetric dihydroxylation reaction to give the diol 141b with 88% e.e.

$$\text{(140)}$$

$$\text{(141b)}$$

$$\text{(142b)}$$

$$\text{(158b)}$$

$$\text{(4b)}$$

Stereoselective hydrogenolysis of the benzylic hydroxyl group of 141b with a palladium catalyst gave the alcohol 142b with 83% e.e. Conversion of this alcohol to the crystalline 3,5-dinitrobenzoate, recrystallisation and ester hydrolysis improved the optical purity to 99%+ e.e. Oxidation of 142b with ruthenium trichloride hydrate and sodium metaperiodate proceeded without
racemisation to give the ketoprofen precursor 15Bb with 99%+ e.e. Oxidation of 15Bb to (S)-ketoprofen (4b) has been demonstrated elsewhere\textsuperscript{100}. It is likely that further investigation of some of the steps would lead to higher yields, which would make this route to (S)-ketoprofen even more attractive.
EXPERIMENTAL

GENERAL

Melting points were determined using a Kofler hot stage apparatus under a Reichert microscope and are uncorrected.

Elemental analyses were carried out by the Canadian Microanalytical Service Ltd., New Westminster, Canada or Chemical and Micro Analytical Services Pty. Ltd., Victoria, Australia.

60 MHz $^1$H NMR spectra were recorded on a Varian T60 spectrometer; 200 MHz $^1$H NMR spectra were recorded on a Gemini 200 spectrometer and 300 MHz $^1$H NMR spectra were recorded on a Bruker CXP-300 or a Bruker ACP-300 spectrometer. $^{13}$C NMR spectra were recorded on a Bruker ACP-300 spectrometer. Chemical shift ($\delta$) values have been quoted in parts per million downfield from tetramethylsilane. Peak multiplicities have been abbreviated to s (singlet); d (doublet); t (triplet); q (quartet) and quint (quintet).

Mass spectra were recorded on an AEI MS-30 double focussing mass spectrometer.

Optical rotations were measured using a Perkin-Elmer 141MC Polarimeter. Specific rotations ([\alpha])$_D^{20}$ are reported in degrees per decimeter at 20°C and the concentration (c) is given in grams per 100 mL in the specified solvent.

Flash chromatography$^{101}$ was performed with Merck Kieselgel 60 (230-400 mesh ASTM). Thin layer chromatography (TLC) was performed with Merck DC-
Alufolien Kieselgel 60 F254 Art. 5554. TLC plates were visualized either with UV light or by immersion in ammonium molybdate dip [prepared by dissolving ammonium molybdate (20 g) in concentrated sulphuric acid (11.2 mL) and water (188 mL)] followed by heating.

All solvents were distilled before use. Anhydrous ether and THF were freshly distilled from sodium/benzophenone. Other anhydrous solvents and reagents were prepared according to standard laboratory procedures.

102.
EXPERIMENTAL
CHAPTER 1

Ethyl (E)- and (Z)-3-[3'-bromophenyl]-2-butenoate (70) and (78).

To potassium tert-butoxide (7.95 g, 71.0 mmol) in anhydrous THF (40 mL) at 0°C in a nitrogen atmosphere, was added triethyl phosphonoacetate (15.90 g, 71.0 mmol) in THF (40 mL). After stirring at room temperature for 30 min, 3-bromoacetophenone (14.1 g, 71.0 mmol) in THF (40 mL) was added and the reaction mixture stirred overnight at room temperature. Most of the THF was removed in vacuo and the residue dissolved in dichloromethane, washed with dilute HCl and dried with Na2SO4. The solvent was removed in vacuo and the residue subjected to chromatography with a gradient of hexane/dichloromethane as eluant to separate 70 (10.0 g, 42%) from 78. A sample of 70 was bulb-to-bulb distilled: 107°C/0.05 mm Hg (heated block); 1H NMR (300 MHz, CCl4) δ 1.27 (t, 3H, CH2CH3, J=7.0 Hz), 2.53 (d, 3H, H4, J=1.0 Hz), 4.14 (q, 2H, CH2CH3, J=7.0 Hz), 6.04 (q, 1H, H2, J=1.0 Hz), 7.17-7.57 (m, 4H, Ar-H). Anal. Found: C, 53.27; H, 4.89%. Calcd for C12H13O2Br: C, 53.55; H, 4.87%.

Data for 78: 1H NMR (60 MHz, CCl4) δ 1.10 (t, 3H, CH2CH3, J=7 Hz), 2.19 (d, 3H, H4, J=1 Hz), 3.95 (q, 2H, CH2CH3, J=7 Hz), 5.90 (q, 1H, H2, J=1 Hz), 7.10-7.60 (m, 4H, Ar-H). HRMS 268.00915, calcd for C12H13O2Br: 268.00916.

(E)-3-[3'-Bromophenyl]-2-buteno-1-ol (71).

To lithium aluminium hydride (1.83 g, 48.0 mmol) in anhydrous ether (45 mL) at -78°C was added 70 (12.9 g, 48.0 mmol), and the reaction was stirred at -78°C for 6 h. Ethyl acetate was added dropwise, the reaction allowed to warm to
room temperature, and 10% HCl added cautiously until two layers separated. The ethereal layer was decanted and the aqueous layer extracted with three portions of ether. The organic fractions were combined, dried with Na2SO4 and the solvent removed in vacuo. Chromatography of the residue with a gradient of ethyl acetate/hexane gave 71 as a colourless oil (8.6 g, 79%) which was unstable to distillation; 1H NMR (60 MHz, CCl4) 2.00 (s, 3H, CH3), 3.00 (br s, 1H, OH), 4.23 (d, 2H, CH2, J=7 Hz), 5.88 (t, 1H, H2, J=7 Hz), 6.95-7.60 (m, 4H, Ar-H).

(2RS,3RS)-3-Methyl-3-(3'-bromophenyl)oxiranemethanol (72a).

To (71) (200 mg, 0.88 mmol) in dichloromethane (4 mL) at 0°C was added m-chloroperbenzoic acid (80%, 0.21g, 0.97 mmol). After stirring at 0°C for 40 min the reaction mixture was added dropwise to a vigorously stirred excess of 10% NaOH/NaCl solution, which was prepared by dissolving NaCl (2 g) and NaOH (2 g) in water (18 mL). Sodium thiosulphate solution (0.1 M, 10 mL) was added. The organic layer was separated, dried with MgSO4 and the solvent removed in vacuo. Flash chromatography with dichloromethane/ethyl acetate (90/10, v/v) gave 72a as a colourless oil (202 mg, 94%) which was bulb to bulb distilled: 102°C/0.05 mm Hg (heated block); 1H NMR (300 MHz, CDCl3, D2O) δ 1.66 (s, 3H, CH3), 3.06 (dd, 1H, CHO, J=6.4 Hz and 4.3 Hz), 3.81 (dd, 1H, CH2O, J=6.4 Hz and 12.2 Hz), 3.95 (dd, 1H, CH2O, J= 4.3 Hz and 12.2 Hz), 7.17-7.49 (m, 4H, Ar-H). Anal. Found: C, 48.93; H, 4.52%. Calcd for C10H11O2Br: C, 49.40; H, 4.56%.

3-Phenylbutane-1,2-diol (81a).

Palladium on carbon (10%, 300 mg), ethanol (12 mL) and aqueous NaOH solution (1.0 M, 0.4 mL) were stirred in a hydrogen atmosphere for 1.5 h then cooled to -30°C. Epoxide 72a (189 mg, 0.78 mmol) in ethanol (4 mL) was added
and the reaction mixture was stirred at -30°C for 7 h. The hydrogen was cautiously replaced with air and the mixture filtered through Celite. Removal of the solvent in vacuo and flash chromatography with dichloromethane/ethyl acetate (90/10, v/v) as eluant gave 81a (116 mg, 90%): 1H NMR (300 MHz, CDCl3, D2O) δ 1.27 (d, 3H, CH3, J=6.9 Hz), 2.64 (quint, 1H, H3, J=6.9 Hz), 3.16 (dd, 1H, H1, J=7.7 Hz and 11.2 Hz), 3.27 (dd, 1H, H1, J=3.2 Hz and 11.2 Hz), 3.58 (dt, 1H, H2, J=3.2 Hz and 7.7 Hz) 7.08 - δ 7.24 (m, 5H, Ar-H).

3-Phenylbutane-1,2-diyl diacetate (82a).

To the diol 81a (approximately 100 mg) in pyridine (1.5 mL) was added acetic anhydride (1.0 mL). After 16 h at room temperature, dichloromethane was added to the mixture and it was washed with water, 5% HCl until acidic, 5% sodium bicarbonate solution and water. Removal of the solvent in vacuo and flash chromatography gave 82a: 1H NMR (60 MHz, CDCl3) δ 1.32 (d, 3H, CHCH3, J=7 Hz), 1.98 (s, 3H, COCH3), 2.02 (s, 3H, COCH3), 3.01 (m, 1H H3), 3.69 (dd, 1H, H1, J=6 Hz and 12 Hz), 4.15 (dd, 1H, H1, J=6 Hz and 12 Hz), 5.20 (m, 1H, H2), 7.14 - 7.28 (m, 5H, Ar-H); Anal. Found: C, 66.68; H, 7.22%. Calcd for C14H18O4: C, 67.20; H, 7.20%.

2-Methyl-2-(3'-bromophenyl)-1,3-dioxolane (83).

To 3-bromoacetophenone (25.6 g, 0.13 mol) in benzene (130 mL) were added ethylene glycol (9.3 g, 0.15 mol) and p-toluenesulphonic acid (0.1 g). The flask was fitted with a Dean- Stark water separator and the mixture refluxed for 20 h. The reaction mixture was cooled to room temperature, transferred to a separating funnel and washed with sodium carbonate solution, then water. The organic phase was dried with Na2SO4 and the solvent removed in vacuo. Distillation gave 83 as a colourless oil (31.1 g, 98%): bp 82°C/0.3 mm Hg (lit103
bp 128-130°C/12 mm Hg; \( ^1\)H NMR (60 MHz, CCl\(_4\)) \( \delta \) 1.58 (s, 3H, (CH\(_3\))\(_3\)), 3.50-4.18 (m, 4H, CH\(_2\)s), 6.99-7.60 (m, 4H, Ar-H).

**2-Methyl-2-(3'-(trimethylsilyl)phenyl)-1,3-dioxolane (84).**

A dry flask was charged with magnesium turnings (2.29 g, 94.1 mmol), anhydrous THF (110 mL) and a flake of iodine. The flask was heated to 60°C and 83 (22.2 g, 91.5 mmol) in THF (25 ml) was added over 2 h. After a further 4 h at 60°C, chlorotrimethylsilane (14.4 g, 133 mmol) was added and the reaction mixture stirred overnight. Most of the THF was removed *in vacuo*, and the residue dissolved in dichloromethane. The solution was washed with water, dried with Na\(_2\)SO\(_4\) and the solvent removed *in vacuo*, to give 84 as a white crystalline solid (19.42 g, 90%). Recrystallization from methanol gave pure material: mp 119-120°C. A sample was subjected to bulb to bulb distillation at 85-95°C/0.1 mm Hg (heated block); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 0.31 (s, 9H, (CH\(_3\))\(_3\)), 1.59 (s, 3H, CH\(_3\)), 3.50-4.17 (m, 4H, CH\(_2\)s), 7.17-7.60 (m, 4H, Ar-H). Anal. Found: C, 65.60; H, 8.27%. Calcd for C\(_{13}\)H\(_{20}\)O\(_2\)Si: C, 66.05; H, 8.53%.

**3-(Trimethylsilyl)acetophenone (85).**

The acetal 84 (6.2 g, 26.3 mmol) was dissolved in methanol (25 mL), water (5 mL), and 10% HCl (1.5 mL). After 1 h at room temperature the methanol was removed *in vacuo*, the residue dissolved in dichloromethane and washed with sodium bicarbonate solution. The organic phase was dried with Na\(_2\)SO\(_4\) and the solvent removed *in vacuo*. Distillation of the residue gave 85 as a colourless oil (4.9 g, 97%): bp 68°C/0.1 mm Hg; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 0.29 (s, 9H, (CH\(_3\))\(_3\)), 2.50 (s, 3H, CH\(_3\)), 7.21-8.14 (m, 4H, Ar-H) (lit\(^{104}\): no data reported).
Ethyl (E)-3-[3'-(trimethylsilyl)phenyl]-2-butenoate (86).

To potassium tert-butoxide (11.37 g, 101 mmol) in anhydrous THF (100 mL) at 0°C in a nitrogen atmosphere, was added triethyl phosphonoacetate (21.1 g, 90.5 mmol). After stirring at room temperature for 30 min, ketone 85 (17.38 g, 90.5 mmol) in THF (20 mL) was added and the reaction mixture stirred overnight at room temperature. Further triethyl phosphonoacetate (2.8 g, 14.5 mmol) was added and the reaction mixture stirred for 24 h. Most of the THF was removed in vacuo and the residue dissolved in dichloromethane, washed with dilute HCl and dried with Na2SO4. The solvent was removed in vacuo and the residue purified by chromatography with a gradient of hexane/dichloromethane as eluant to give 86 (10.0 g, 42%): bp 107°C/0.05 mm Hg; 1H NMR (300 MHz, CDCl3) δ 0.29 (s, 9H, (CH3)3, 1.32 (t, 3H, CH2CH3, J=7.1 Hz), 2.59 (d, 3H, H4, J=1.2 Hz), 4.22 (q, 2H, CH2CH3, J=7.1 Hz), 6.12 (q, 1H, H2, J=1.2 Hz), 7.25-7.59 (m, 4H, Ar-H). Anal. Found: C, 68.50; H, 8.43%. Calcd for C15H22O2Si: C, 68.66; H, 8.45%.

(E)-3-[3'-(Trimethylsilyl)phenyl]-2-butene-1-ol (87).

To lithium aluminium hydride (1.2 g, 31.6 mmol) in anhydrous ether (30 mL) at -78°C was added the ester 86 (7.4 g, 28.2 mmol), and the mixture stirred at -78°C for 6 h. Ethyl acetate was added dropwise, the reaction allowed to warm to room temperature, and 10% HCl added cautiously until two layers separated. The ethereal layer was decanted and the aqueous layer extracted with three portions of ether. The organic fractions were combined, dried with Na2SO4 and the solvent removed in vacuo. Residual starting material (2.6 g, 9.9 mmol) was removed by chromatography with a gradient of hexane/ethyl acetate as eluant to give 87 as a colourless oil (3.6 g, 58%): bp 130°C/0.1 mm Hg; 1H NMR (300 MHz, CDCl3) δ 0.28 (s, 9H, (CH3)3), 1.55 (br s, 1H, OH), 2.09 (d, 3H, CH3, J=1.3 Hz).
Hz), 4.37 (d, 2H, CH₂, J=6.9 Hz), 5.96 (dt, 1H, H₂, J= 1.3 Hz and 6.8 Hz), 7.25-7.55 (m, 4H, Ar-H). HRMS 222.06807, calculated for (C₁₃H₂₀O₂Si) 222.06808.

(2RS,3RS)-3-Methyl-3-[3’-(trimethylsilyl)phenyl]oxiranemethanol (88a).

To the alcohol 87 (1.00 g, 4.55 mmol) in dichloromethane (15 mL) at 0°C was added m-chloroperbenzoic acid (80%, 1.08 g, 5.00 mmol). After stirring at 0°C for 40 min the reaction mixture was added dropwise to a vigorously stirred excess of 10% NaOH/NaCl solution, which was prepared by dissolving NaCl (2 g) and NaOH (2 g) in water (18 mL). Sodium thiosulphate solution (0.1 M, 50 mL) was added. The organic layer was separated, dried with MgSO₄ and the solvent removed in vacuo. Flash chromatography with dichloromethane/ethyl acetate (95/5, v/v) as eluant gave 88a as a colourless oil (1.0 g, 93%): bp 102°C/0.05 mm Hg; ¹H NMR (300 MHz, CDCl₃, D₂O) δ 0.27 (s, 9H, (CH₃)₃), 1.71 (s, 3H, CH₃), 3.11 (dd, 1H, CHO, J=6.5 Hz and 4.2 Hz), 3.82 (dd, 1H, CH₂O, J=6.6 Hz and 12.2 Hz), 3.98 (dd, 1H, CH₂O, J=4.2 Hz and 12.2 Hz), 7.25-7.48 (m, 4H, Ar-H). Anal. Found: C, 65.38; H, 8.40%. Calcd for C₁₃H₂₀O₂Si: C, 66.06; H, 8.53%.

(2S,3S)-3-Methyl-3-[3’-(trimethylsilyl)phenyl]oxiranemethanol (88b).

Following the procedure of Sharpless34, a dry flask was flushed with nitrogen and charged with (L)-(+)diisopropyl tartrate (65 mg, 0.28 mmol) and anhydrous dichloromethane (35 mL). The flask was cooled to -20°C and activated, powdered 4A sieves (0.20 g) were added, followed by titanium(IV)isopropoxide (53 mg, 0.19 mmol) and tert-butylhydroperoxide solution (1.55 mL of a 4.8 M dichloromethane solution, 7.44 mmol). These reagents were stirred at -20°C in a nitrogen atmosphere for 1 h, then the allylic alcohol 87 (0.88 g, 4.0 mmol) in dichloromethane (2mL) was added over 10 min. After 3.5 h at -20°C, 10% aqueous NaCl/NaOH solution (0.32 mL) and ether (3.6 mL) were added and the
reaction mixture allowed to warm to 10°C and remain there for 10 min. MgSO4 (0.32 g) and Celite (0.04 g) were added and the reaction stirred for 15 min. Unreacted tert-butylhydroperoxide was removed from the filtered solution by azeotropic distillation with toluene. Flash chromatography with dichloromethane/ethyl acetate (95/5, v/v) as eluant gave 88b as a colourless oil (0.88 g, 94%): 1H NMR data are identical with those of racemic material.

\[(2S,3S)-3\text{-Methyl-3'-(trimethylsilyl)phenyl}\text{oxiranemethyl 3,5-dinitrobenzoate (94b).}\]

The epoxy alcohol 88b (0.68 g, 2.88 mmol) was dissolved in anhydrous dichloromethane (11 mL) in a nitrogen atmosphere and cooled to 0°C. 3,5-dinitrobenzoyl chloride (0.69 g, 2.97 mmol) and triethylamine (350 mg, 3.46 mmol) were added and the reaction stirred overnight at room temperature. 10% NaOH solution (10 mL) was added, the organic phase separated, washed with water and dried with Na2SO4. The solvent was removed in vacuo and the residue purified by flash chromatography with hexane/ethyl acetate (85/15, v/v) as eluant to give 94b as a white crystalline solid (0.97 g, 84%): mp 85.5-90°C. This was recrystallised twice from ethanol: mp 90-92°C; \([\alpha]D^{20} = -32.0^\circ\) (c=1.11, CCl4).

Hydrolysis of \((2S,3S)-3\text{-methyl-3'-(trimethylsilyl)phenyl}\text{oxiranemethyl 3,5-dinitrobenzoate (94b).}\)

To the ester 94b (1.66 g, 4.17 mmol) in methanol (25 mL) was added potassium carbonate (0.63 g, 4.59 mmol). After 2 h at room temperature, most of the methanol was removed from the deep purple solution and the residue dissolved in dichloromethane, washed with water and dried with MgSO4. Removal of the solvent in vacuo and flash chromatography with
dichloromethane/ethyl acetate (90/10, v/v) as eluant gave enantiomerically enriched epoxy alcohol 88b (0.73 g, 75%).

(2S,3S)-3-Methyl-3-[3'-(trimethylsilyl)phenyl]oxiranemethyl acetate (95b).

To the epoxy alcohol 88b (71 mg, 0.30 mmol) in pyridine (0.7 mL) was added acetic anhydride (0.4 mL), and the mixture was allowed to stand at room temperature overnight. Dichloromethane was added to the mixture and it was washed with water, 5% HCl until acidic, 5% sodium bicarbonate solution and water. Removal of the solvent in vacuo and flash chromatography with hexane/ethyl acetate (90/10, v/v) gave 95b as a colourless oil (70 mg, 82%): $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 0.25 (s, 9H, Si(CH$_3$)$_3$), 1.71 (s, 3H, CH$_3$), 2.10 (s, 3H, COCH$_3$), 3.09 (dd, 1H, H$_2$, J=4.3 Hz and 6.7 Hz), 4.18 (dd, 1H, H$_1$, J=6.7 Hz and 12.2 Hz), 4.45 (dd, 1H, H$_1$, J=4.3 Hz and 12.2 Hz), 7.35 (m, 4H, Ar-H).

(2RS,3RS)-3-Methyl-3-[3'-(trimethylsilyl)phenyl]oxiranemethyl acetate (95a).

The racemate 95a was obtained similarly to the optically active acetate 95b, from 88a. $^1$H NMR data of 95a are identical with those of 95b.

(2RS,3SR)-3-[3'-(Trimethylsilyl)phenyl]butane-1,2-diol (89a).

Palladium on carbon (10%, 0.77 g), ethanol (30 mL) and 1 M NaOH solution (1.0 mL) were stirred in a hydrogen atmosphere for 1.5 h, then cooled to -60°C. The epoxide 88a (0.58 g, 2.46 mmol) in ethanol (10 mL) was added over 10 min and the reaction stirred at -60°C for 6 h. The hydrogen was cautiously replaced with air and the mixture warmed to room temperature and filtered through Celite. Removal of the solvent in vacuo and flash chromatography with dichloromethane/ethyl acetate (90/10, v/v) as eluant gave 89a as a colourless
oil (0.56 g, 97%): $^1$H NMR (300 MHz, CDCl$_3$, D$_2$O) $\delta$ 0.26 (s, 9H, (CH$_3$)$_3$), 1.36 (d, 3H, CH$_3$, J=7.0 Hz), 2.78 (quint, 1H, H3, J=7.1 Hz), 3.35 (dd, 1H, H1, J=7.7 Hz and 11.2 Hz), 3.45 (dd, 1H, H1, J=3.1 Hz and 11.2 Hz), 3.76 (dt, 1H, H2, J=3.1 Hz and 7.7 Hz), 7.16-7.40 (m, 4H, Ar-H).

(2R,3S)-3-[3'-(Trimethylsilyl)phenyl]butane-1,2-diol (89b).

The optically active diol 89b was obtained similarly to the racemate 89a, from 88b. $^1$H NMR data of 89b are identical with those of the racemate 89a.

(2RS,3SR)-3-[3'-(Trimethylsilyl)phenyl]butane-1,2-diyl diacetate (90a).

The diol 89a (30 mg) was dissolved in pyridine (0.75 mL) and acetic anhydride (0.5 mL) and allowed to stand at room temperature overnight. Dichloromethane was added to the mixture and it was washed with water, 5% HCl until acidic, 5% sodium bicarbonate solution and water. Removal of the solvent in vacuo and flash chromatography with dichloromethane as eluant gave 90a (38 mg, 95%) which solidified upon bulb to bulb distillation: 120°-125°C/0.04 mm Hg (heated block); mp 52°-53°C; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 0.26 (s, 9H, (CH$_3$)$_3$), 1.30 (d, 3H, CHCH$_3$, J=6.9 Hz), 2.02 (s, 3H, COCH$_3$), 2.11 (s, 3H, COCH$_3$), 3.04 (quint, 1H, H3, J=7.0 Hz), 3.79 (dd, 1H, H1, J=6.4 Hz and 12.0 Hz), 4.12 (dd, 1H, H1, J=2.8 Hz and 12.0 Hz), 5.24 (m, 1H, H2), 7.19-7.40 (m, 4H, Ar-H). Anal. Found: C, 63.60; H, 8.13%. Calcd for C$_{17}$H$_{26}$O$_4$Si: C, 63.32; H, 8.13%.

Attempted Friedel-Crafts Acylation of Diacetate (90a)

According to the procedure of Eaborn$^{82}$, the diacetate 90a (42 mg, 0.13 mmol) in carbon disulphide (1 mL) was added to aluminium chloride (27 mg, 0.20 mmol)
in carbon disulphide (1 mL) in a nitrogen atmosphere. To the mixture was added benzoyl chloride (18.3 mg, 0.13 mmol) and the reaction was heated at reflux for 1 h. The reaction mixture was allowed to cool, added to water (2 mL) and extracted with dichloromethane. Removal of the solvent in vacuo and flash chromatography with hexane/ethyl acetate (85/15, v/v) gave the desilylated diacetate 82a: $^1$H NMR data identical with those reported for 82a earlier (see page 149).

(2RS,3SR)-3-(3'-Bromophenyl)butane-1,2-diol (73a).

Following the procedure of Wilbur$^83$, the silyldiol 89a (364 mg, 1.53 mmol) was dissolved in methanol (3 mL). Lithium bromide (160 mg, 1.84 mmol) and N-chlorosuccinimide (246 mg, 1.84 mmol) were added and the reaction stirred at room temperature for 1 h. The methanol was removed in vacuo, the residue dissolved in dichloromethane, washed with water and dried with MgSO$_4$. Flash chromatography with ethyl acetate/hexane (50/50, v/v) as eluant gave 73a as a colourless oil (334 mg, 89%): $^1$H NMR (300 MHz, CDCl$_3$, D$_2$O) $\delta$ 1.29 (d, 3H, CH$_3$, $J$=7.1 Hz), 2.71 (quint, 1H, H$_3$, $J$=7.3 Hz), 3.25 (dd, 1H, H$^1$, $J$=7.8 Hz and 11.3 Hz), 3.37 (dd, 1H, H$^1$, $J$=2.8 Hz and 11.3 Hz), 3.64 (dt, 1H, H$^2$, $J$=2.8 Hz and 7.8 Hz), 7.09-7.37 (m, 4H, Ar-H).

(2R,3S)-3-(3'-Bromophenyl)butane-1,2-diol (73b).

The optically active diol 73b was prepared similarly to the racemate 73a, from 89b. $^1$H NMR data of 73b are identical with those of 73a.
(4RS, 1'SR)-4-[1'-(3''-Bromophenyl)ethyl]-2,2-dimethyl-1,3-dioxolane (74a).

The diol 73a (420 mg, 1.71 mmol) in anhydrous acetone (18 mL) and p-toluenesulphonic acid (7 mg) were stirred at room temperature in a nitrogen atmosphere for 5 h. Saturated sodium bicarbonate solution was added and the acetone removed in vacuo. The residue was dissolved in dichloromethane, washed with water and dried with MgSO4. Removal of the solvent in vacuo, flash chromatography with hexane/ethyl acetate (90/10, v/v) as eluant and bulb to bulb distillation gave 74a (385 mg, 79%): 125°C/0.1 mm Hg (heated block); 1H NMR (300 MHz, CDCl3) δ 1.35 (d, 3H, CHCH3, J=6.4 Hz), 1.41 (s, 3H, CH3), 2.77 (quint, 1H, H1', J=7.0 Hz), 3.51 (dd, 1H, H5, J=6.9 Hz and 8.2 Hz), 3.57 (dd, 1H, H5, J=6.2 Hz and 8.3 Hz), 4.14 (m, 1H, H4), 7.11-7.37 (m, 4H, Ar-H). HRMS 284.04177, calcd for (C13H17BrO2) 284.04178.

(4&R, 1'S&1'R)-4-[1'-(3''-Bromophenyl)ethyl]-2,2-dimethyl-1,3-dioxolane (74b).

The optically active acetonide 74b was prepared similarly to the racemate 74a, from 73b. 1H NMR data of 74b are identical with those of 74a.

(4''RS,1''SR,1''RS) and (4''RS,1''SR,1''SR)-[3'-[1'-(2''',2''',3''-dioxolan-4''-yl)ethyl]phenyl]phenylmethanol (75a).

The bromoacetonide 74a (338 mg, 1.19 mmol) was dissolved in anhydrous ether and cooled to -78°C in a nitrogen atmosphere. Tert-butyllithium (1.42 mL of a 1.75 M hexane solution, 2.49 mmol) was added and these reagents were stirred at -78°C for 1.75 h before benzaldehyde (297 mg, 2.8 mmol) was added. After the reaction mixture had warmed to room temperature it was diluted with dichloromethane, washed with water and dried with MgSO4. Flash chromatography with hexane/ethylacetate (80/20, v/v) as eluant gave 75a as a
colourless oil (280 mg, 76%): $^1$H NMR (60 MHz, CDCl$_3$, D$_2$O) $\delta$ 1.30 (d, 3H, CHCH$_3$, $J$=7 Hz), 1.35 (s, 3H, CH$_3$), 1.40 (s, 3H, CH$_3$), 2.75 (quint, 1H, H1', $J$=7 Hz), 3.30-4.40 (complex, 3H, H4 and H5), 5.80 (s, 1H, CHO-H), 6.92-7.43 (m, 9H, Ar-H).

(4''R,1''S,1RS)-[3'-[1''-2''''-Dimethyl-1''',3'''-dioxolan-4'''-yl]ethyl]phenyl]phenylmethanol (75b).

The optically active compound 75b was obtained similarly to the racemate 75a, from 74b. $^1$H NMR data of 75b are identical with those of 75a.

(2RS,3SR,1''RS)- and (2RS,3SR,1''SR)-3-[3'-(Hydroxyphenylmethyl)-phenyl]butane-1,2-diol (76a).

The acetonide 75a (68 mg, 0.22 mmol) was dissolved in methanol (1 mL), water (0.2 mL) and 5% HCl (0.06 mL) and allowed to stand at room temperature for 8 h then at -20°C for 16 h. The methanol was removed in vacuo and the residue dissolved in dichloromethane, washed with water and dried with MgSO$_4$. Flash chromatography with ethyl acetate/hexane (75/25, v/v) as eluant gave 76a as a colourless oil (55 mg, 93%): $^1$H NMR (300 MHz, CDCl$_3$, D$_2$O) $\delta$ 1.28 (d, 3H, CH$_3$, $J$=7.0 Hz), 2.75 (quint, 1H, H3, $J$=6.9 Hz), 3.23 (dd, 1H, H1, $J$=7.5 Hz and 11.3 Hz), 3.37 (dd, 1H, H1, $J$=2.8 Hz and 11.3 Hz), 3.64 (dt, 1H, H2, $J$=2.5 Hz and 7.4 Hz), 5.74 (s, 1H, CHO-H), 7.03-7.32 (m, 9H, Ar-H).

(2R,3S,1''RS)-3-[3'-(Hydroxyphenylmethyl)phenyl]butane-1,2-diol (76b).

The optically active compound 76b was obtained similarly to the racemate 76a, from 75b. $^1$H NMR data of 76b are identical with those of 76a.
(RS)-2-(3'-Benzoylphenyl)propanoic acid (4a).

Following the procedure of Sharpless\textsuperscript{84}, the triol 76a (55 mg, 0.20 mmol) was dissolved in carbon tetrachloride (1.1 mL), acetonitrile (1.1 mL) and water (1.7 mL) and treated with ruthenium trichloride hydrate (1.1 mg) and sodium metaperiodate (225 mg, 1.0 mmol). The reaction mixture was stirred vigorously at room temperature for 1.25 h, then diluted with dichloromethane, washed with water and dried with MgSO\textsubscript{4}. Flash chromatography with ethyl acetate/hexane (70/30, v/v) as eluant gave 4a as a colourless oil (37 mg, 72%) which had spectral data identical with those of an authentic sample of ketoprofen.

(S)-2-(3'-Benzoylphenyl)propanoic acid (4b).

The optically active compound 4b was obtained similarly to the racemate 4a, from 76b. $^1$H NMR data of 4b are identical with those of 4a. [$\alpha$]$_D^{20}$=+54.4 (c=2.71, CH$_2$Cl$_2$) [lit\textsuperscript{105}: [$\alpha$]$_D^{20}$=+57.1 (c=0.76, CH$_2$Cl$_2$)].
EXPERIMENTAL
CHAPTER 2

2-(4'-Bromophenyl)-2-methyl-1,3-dioxolane (106).

A 500 mL flask was fitted with a Dean-Stark water separator and condenser and charged with 4-bromoacetophenone (51.2 g, 0.26 mol), benzene (250 mL), ethylene glycol (18.6 g, 0.30 mol) and p-toluenesulphonic acid (0.2 g). The mixture was refluxed until the evolution of water ceased (16 h). Most of the benzene was removed in vacuo, the residue dissolved in dichloromethane and washed with saturated sodium carbonate solution then water. The solution was dried with MgSO4 and the solvent removed in vacuo to give, after distillation, 106 as a colourless oil (61.0g, 97%) which still contained 5% ketone: bp 80-85°C/0.2 mm Hg (lit87 bp 175-180°C/20-30 mm Hg; mp 44-45°C; no NMR data reported); 1H NMR (60 MHz, CDCl3) δ 1.60 (s, 3H, CH3), 3.88 (m, 4H, CH2s), 7.50 (m, 4H, Ar-H).

2-Methyl-2-[4'-(trimethylsilyl)phenyl]-1,3-dioxolane (107).

A dry flask was fitted with a pressure equalizing dropping funnel and a condenser and charged with magnesium turnings (10.55g, 0.434 mol). Anhydrous THF (40 mL) and a flake of iodine were added to the flask, followed by 106 (52.7 g, 0.217 mol) in THF (140 mL) at a rate which maintained gentle reflux. After 1 h at reflux, chlorotrimethylsilane (26.1 g, 0.24 mol) was added and the reaction mixture stirred for 16 h at room temperature. THF and unreacted chlorotrimethylsilane were removed in vacuo and the residue dissolved in dichloromethane. The solution was washed with water, dried with MgSO4 and the solvent removed in vacuo. Distillation of the residue gave 107 as a white crystalline solid (38.4g, 75%): bp 85-90°C/0.22mm Hg; mp
57-59°C; \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \(\delta\) 0.26 (s, 9H, (CH\textsubscript{3})\textsubscript{3}), 1.65 (s, 3H, CH\textsubscript{3}), 3.77 (m, 2H, H4 and H5), 4.03 (m, 2H, H4 and H5), 7.48 (m, 4H, Ar-H) (lit\textsuperscript{87}: product not isolated).

4-(Trimethylsilyl)acetophenone (96).

The acetal 107 (72.0 g, 0.305 mol) in methanol (200 mL), water (40 mL) and 10% HCl (5.5 mL) was heated at 60°C for 1 h. The methanol was removed \textit{in vacuo} and the residue dissolved in dichloromethane, washed with sodium bicarbonate solution and dried with MgSO\textsubscript{4}. Removal of the solvent \textit{in vacuo} gave 96 as a colourless oil which was used without further purification (57.6g, 98%): (lit\textsuperscript{87}: mp 41°C); \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \(\delta\) 0.29 (s, 9H, (CH\textsubscript{3})\textsubscript{3}), 2.60 (s, 3H, CH\textsubscript{3}), 7.62 (d, 2H, Ar-H, J=8.2 Hz), 7.92 (d, 2H, Ar-H, J=8.2 Hz) (NMR data in agreement with lit\textsuperscript{87} values)

Ethyl (E)-3-[4'--(trimethylsilyl)phenyl]-2-butenoate (97).

To anhydrous ethanol (600 mL) was added lithium metal in small pieces (2.78 g, 0.402 mol). After the lithium had dissolved, triethyl phosphonoacetate (64.3 g, 0.287 mol) was added, and these reagents stirred at room temperature for 30 min. The ketone 96 (55.1 g, 0.287 mol) in ethanol (200 mL) was added and the reaction stirred at room temperature for 2 days, after which time further triethyl phosphonoacetate (12.9g, 57 mmol) was added. After stirring for 16 h at room temperature and 4 h at reflux the ethanol was removed \textit{in vacuo}. The residue was dissolved in dichloromethane, washed with water and dried with MgSO\textsubscript{4}. The solvent was removed \textit{in vacuo} to give 97 (80.0 g) which was used without further purification. A sample was purified for analysis by flash chromatography with hexane/ethyl acetate (97/3, v/v) as eluant and bulb to bulb distillation: 120°/0.07 mm Hg (heated block); \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \(\delta\)
0.27 (s, 9H, (CH₃)₃) 1.32 (t, 3H, CH₂CH₃, J=7.1 Hz), 2.57 (d, 3H, H₄, J=1.2 Hz), 4.21 (q, 2H, CH₂CH₃, J=7.1 Hz), 6.15 (d, 1H, H₂, J=1.3 Hz), 7.45 (d, 2H, Ar-H, J=8.2 Hz), 7.53 (d, 2H, Ar-H, J=8.2 Hz). Anal. Found: C, 68.66; H, 8.48%. Calcd for C₁₅H₂₂SiO₂: C, 68.73; H, 8.37%.

(E)-3-[4'-{(Trimethylsilyl)phenyl}]-2-buten-1-ol (98).

A dry flask was charged with lithium aluminium hydride (7.4 g, 0.195 mol) and anhydrous ether (450 mL). Crude 97 (66.5 g, 0.254 mol) in ether (350 mL) was added at a rate which maintained gentle reflux, and the reaction stirred for a further 40 min at room temperature. Ethyl acetate was cautiously added followed by dropwise addition of dilute HCl. The ethereal layer was decanted and the aqueous layer extracted with ether. The organic fractions were combined, dried with MgSO₄, and the solvent removed in vacuo. Fractional distillation gave 98 as a colourless oil (41.4 g, 74%). A sample was purified for analysis by flash chromatography with hexane/ethyl acetate (80/20, v/v) as eluant: bp 114-120°C/0.07 mm Hg; ¹H NMR (300 MHz, CDCl₃) δ 0.27 (s, 9H, (CH₃)₃), 2.07 (s, 3H, CH₃), 4.35 (d, 2H, CH₂, J=6.7 Hz), 5.99 (t, 1H, H₂, J=6.7 Hz), 7.39 (d, 2H, Ar-H, J=8.1 Hz), 7.49 (d, 2H, Ar-H, J=8.1 Hz). Anal. Found: C, 70.86; H, 9.15%. Calcd for C₁₃H₂₀SiO: C, 70.26; H, 8.95%.

(2S,3S)-3-Methyl-3-[4'-(trimethylsilyl)phenyl]oxiranemethanol (99b).

According to the method of Sharpless³⁴, a flask was charged with (L)-(+) diisopropyl tartrate (877 mg, 3.74 mmol) and anhydrous dichloromethane (480 mL), and cooled to -20°C. To the flask were added powdered, activated 4Å sieves (2.7 g), titanium tetraisopropoxide (731 mg, 2.58 mmol), tert-butylhydroperoxide (25.7 mL of a 3.95M dichloromethane solution, 102 mmol) and, after 1.25 h, 98 (12.0 g, 54.5 mmol) in dichloromethane (20 mL). After
stirring at -20°C for 3 h the reaction was quenched with 10% NaCl / NaOH solution (4.4 mL) and ether (49 mL). After the reaction mixture had warmed to 10°C and remained there for 10 min, MgSO₄ (4.9 g) and Celite (0.6 g) were added and the mixture stirred for 15 min. Unreacted tert-butyl hydroperoxide was removed from the filtered solution by azeotropic distillation with toluene. Flash chromatography of the residue with dichloromethane/ ethyl acetate (95/5, v/v) as eluant gave 99b as a white crystalline solid (9.0 g, 70%). Recrystallization from pentane gave enantiomerically enriched 99b (6.0 g): mp 41-43°C; ¹H NMR (300 MHz, CDCl₃) δ 0.26 (s, 9H, (CH₃)₃), 1.70 (s, 3H, CH₃), 3.10 (dd, 1H, H₂, J=4.2Hz and 6.5 Hz), 3.83 (dd, 1H, CH₂O, J=6.5 Hz and 12.2 Hz), 3.97 (dd, 1H, CH₂O, J=4.2 Hz and 12.2 Hz), 7.33 (d, 2H, Ar-H, J=8.1 Hz), 7.51 (d, 2H, Ar-H, J=8.1 Hz); Anal. Found: C, 65.67; H, 8.26%. Calcd for C₁₃H₂₉SiO₂: C, 66.06; H, 8.53; 98%+ e.e. (as determined by analysis of the acetate 111b with the chiral shift reagent tris[3-(heptafluoro-propylhydroxymethylene)-(+)-camphorato]europium(III) derivative).

(2RS,3RS)-3-Methyl-3-(4'-trimethylsilylphenyl)oxiranemethanol (99a).

To the allylic alcohol 98 (3.87 g, 17.6 mmol) in dichloromethane (60 mL) at 0°C was added m-chloroperbenzoic acid (80%, 4.2 g, 19.3 mmol). After stirring at 0°C for 20 minutes the reaction mixture was added dropwise to a vigorously stirred excess of 10% NaOH / NaCl solution, then 0.1 M sodium thiosulphate solution (200 mL) was added. The organic layer was separated, dried with MgSO₄, and the solvent removed in vacuo to give 99a as a white crystalline solid (4.15 g, 100%): mp 34-39°C; ¹H NMR data are identical with those of the optically active compound 99b.
(2R,3S)-3-Methyl-3-[4'-[(trimethylsilyl)phenyl]oxiranemethyl] acetate (111b).

To the alcohol 99b (50 mg) in pyridine (0.75 mL) was added acetic anhydride (0.5 mL). After 16 h at room temperature dichloromethane was added to the mixture and it was washed with water, 5% HCl until acidic, 5% sodium bicarbonate solution and water. Removal of the solvent in vacuo and flash chromatography with hexane/ethyl acetate (90/10, v/v) as eluant gave 111b: [α]D\textsuperscript{20} = -47.0° (c=1.33, CCl₄); \textsuperscript{1}H NMR (300 MHz, CDCl₃) δ 0.26 (s, 9H, (CH₃)₃), 1.71 (s, 3H, CH₃), 2.11 (s, 3H, COCH₃), 3.09 (dd, 1H, H₂, J=4.6 Hz and 6.4 Hz), 4.20 (dd, 1H, H₁, J=6.4 Hz and 12.1 Hz), 4.42 (dd, 1H, H₁, J=4.6 Hz and 12.1 Hz), 7.33 (d, 2H, Ar-H, J=8.1 Hz), 7.51 (d, 2H, Ar-H, J=8.1 Hz). The optical purity was determined by analysis with the chiral shift reagent tris[3-(heptafluoropropylhydroxymethylene)-(+-)-camphorato]europium(III) derivative and found to be 98%+ e.e.

(2R,3S)-3-Methyl-3-[4'-[(trimethylsilyl)phenyl]oxiranemethyl] acetate (111a).

The racemate 111a was obtained similarly to the optically active compound 111b, from 99a. \textsuperscript{1}H NMR data of 111a are identical with those of 111b.

(2R,3S)-3-[4'-[(Trimethylsilyl)phenyl]butane-1,2-diol (100b).

Palladium on carbon (10%, 2.5 g), ethanol (100 mL) and 1 M NaOH solution (5 mL) were stirred in a hydrogen atmosphere for 1.5 h, then cooled to -60°C. The epoxide 99b (2.9 g, 12.3 mmol) in ethanol (20 mL) was added over 10 min and the reaction was stirred at -60°C for 5 h. The hydrogen was cautiously replaced with air, the solution was filtered through Celite and the solvent removed in vacuo. The residue was purified by flash chromatography with hexane/ethyl acetate (50/50, v/v) as eluant to give 100b as a white crystalline solid (2.9 g,
100% which was recrystallized from pentane: mp 84.0-86.0°C; \(^{1}H\) NMR (300 MHz, CDCl\(_3\), D\(_2\)O) \(\delta\) 0.25 (s, 9H, (CH\(_3\))\(_3\)), 1.36 (d, 3H, CH\(_3\), J=7.0 Hz), 2.79 (quint, 1H, H\(_3\), J=7.2 Hz), 3.35 (dd, 1H, H\(_1\), J=7.7 Hz and 11.2 Hz), 3.46 (dd, 1H, H\(_3\), J=3.0 Hz and 11.2 Hz), 3.75 (dt, 1H, H\(_2\), J=3.0 Hz and 7.7 Hz), 7.18 (d, 2H, Ar-H, J=7.9 Hz), 7.45 (d, 2H, Ar-H, J=7.9 Hz). Anal. Found: C, 65.50; H, 9.30%. Calcd for C\(_{13}\)H\(_{22}\)O\(_2\)Si: C, 65.76; H, 9.00%.

(2RS,3SR)-3-[4'-(Trimethylsilyl)phenyl]butane-1,2-diol (100a).

The racemate 100a was obtained similarly to the optically active compound 100b, from 99a. \(^{1}H\) NMR data of 100a are identical with those of 100b.

Authentic mixture of (2R,3S) and (2R,3R)-3-[4'-(Trimethylsilyl)-phenyl]butane-1,2-diol (100b and 112b).

A mixture of diastereomers 100b and 112b were obtained similarly to pure 100b except the reaction was allowed to proceed at room temperature overnight: \(^{1}H\) NMR (300 MHz, CDCl\(_3\), D\(_2\)O) the signals of the two isomers overlap except for the methyl doublet: 100b: \(\delta\) 1.36 (d, 3H, J=7.0 Hz); 112b: \(\delta\) 1.25 (d, 3H, J=7.1 Hz).

(2R,3S)-3-(4'-Bromophenyl)butane-1,2-diol (101b).

According to the method of Wilbur\(^{83}\), the silyldiol 100b (3.86 g, 16.2 mmol), methanol (32 mL), lithium bromide (1.70 g, 20.5 mmol) and N-chlorosuccinimide (2.61 g, 19.6 mmol) were stirred at room temperature for 1.25 h. The methanol was removed \textit{in vacuo}, the residue dissolved in dichloromethane, washed with water and dried with MgSO\(_4\). Removal of the solvent and flash chromatography with hexane/ethyl acetate (50/50, v/v) as eluant gave 101b as a colourless oil (3.6 g, 91%): \(^{1}H\) NMR (300 MHz, CDCl\(_3\), D\(_2\)O) \(\delta\) 1.29 (d, 3H, CH\(_3\), J=7.1 Hz), 2.71 (quint, 1H, H\(_3\), J=7.3 Hz), 3.25 (dd, 1H, H\(_1\), J=7.0 Hz, J=7.3 Hz), 7.29 (d, 3H, J=7.0 Hz), 7.35 (d, 3H, J=7.3 Hz), 7.45 (d, 3H, J=7.3 Hz).
J=7.8 Hz and 11.3 Hz), 3.37 (dd, 1H, H1, J=2.8 Hz and 11.3 Hz), 3.64 (dt, 1H, H2, J=2.8 Hz and 7.8 Hz), 7.05 (d, 2H, Ar-H, J=8.3 Hz), 7.41 (d, 2H, Ar-H, J=8.3 Hz).

Anal. Found: C, 49.00; H, 5.35%. Calcd for C10H13BrO2: C, 48.88; H, 5.52%.

(2RS,3SR)-3-(4'-Bromophenyl)butane-1,2-diol (101a).

The racemate 101a was obtained similarly to the optically active compound 101b, from 100a. 1H NMR data of 101a are identical with those of 101b.

(4R,1'S)-4-[1'-(4''-Bromophenyl)ethyl]-2,2-dimethyl-1,3-dioxolane (102b).

The diol 101b (3.6 g, 14.7 mmol) in anhydrous acetone (146 mL) and p-toluene sulphonlic acid (40 mg) were stirred at room temperature in a nitrogen atmosphere for 5 h. Saturated sodium bicarbonate solution (3 mL) was added and the acetone removed in vacuo. The residue was dissolved in dichloromethane, washed with water, dried with MgSO4 and the solvent removed in vacuo. Flash chromatography with hexane/ethyl acetate (90/10, v/v) as eluant and bulb to bulb distillation gave 102b as a colourless oil (2.9 g, 73%): 120°C/0.05 mm Hg (heated block); [α]D²⁰=-7.4° (c=3.07, CDCl3); 1H NMR (300 MHz, CDCl3) δ 1.35 (d, 3H, CHCH3, J=7.0 Hz) 1.39 (s, 3H, CH3), 1.41 (s, 3H, CH3), 2.77 (quint, 1H, H1', J=6.9 Hz), 3.51 (dd, 1H, H5, J=6.8 Hz and 8.3 Hz), 3.74 (dd, 1H, H5, J=5.9 Hz and 8.3 Hz), 4.13 (dt, 1H, H4, J=6.5 Hz and 8.3 Hz), 7.08 (d, 2H, Ar-H, J=13.3 Hz), 7.42 (d, 2H, Ar-H, J=13.3 Hz). HRMS 284.0421, calcd for (C13H17BrO2) 284.0394.

(4RS, 1'SR)-4-[1'-(4''-Bromophenyl)ethyl]-2,2-dimethyl-1,3-dioxolane (102a).

The racemate 102a was obtained similarly to the optically active compound 102b, from 101a. 1H NMR data of 102a are identical with those of 102b.
In a dry flask, 102b (443 mg, 1.55 mmol) was dissolved in anhydrous ether (7 mL) and cooled to -78°C in a nitrogen atmosphere. Tert-butyllithium (1.86 mL of a 7.75 M hexane solution, 3.26 mmol) was added, these reagents were stirred at -78°C for 1.75 h and isobutyraldehyde (259 mg, 3.60 mmol) was added. The reaction mixture was allowed to warm to room temperature, the ether was removed in vacuo and the residue dissolved in dichloromethane and washed with water. The aqueous phase was extracted with dichloromethane and the organic fractions combined and dried with MgSO4. Removal of the solvent in vacuo and flash chromatography with hexane/ethyl acetate (80/20, v/v) gave 103b as a colourless oil (370 mg, 86%). \(^1\)H NMR (60 MHz, CDCl₃, D₂O) δ 0.69-1.60 (complex, 15H, CH₃s), 1.92 (m, 1H, CH(CH₃)₂), 2.79 (quint, 1H, CHCH₃, J=7 Hz), 3.30-4.20 (complex, 3H, H₄ and H₅), 4.26 (d, 1H, CHOH, J=7 Hz), 7.0-7.4 (m, 4H, Ar-H).

The racemate 103a was obtained similarly to the optically active compound 103b, from 102a. \(^1\)H NMR data of 103a are identical with those of 103b.

The acetonide 103a (370 mg, 1.33 mmol) was dissolved in methanol (7.5 mL), water (1.5 mL) and 5% HCl (0.6 mL), and allowed to stand overnight at room temperature. The methanol was removed in vacuo, the residue dissolved in
dichloromethane, washed with water and dried with MgSO₄. Flash chromatography with ethyl acetate/hexane (75/25, v/v) as eluant gave 104a as a colourless oil (270 mg, 85%): ¹H NMR (300 MHz, CDCl₃, D₂O) δ 0.76 (d, 3H, H3', J=6.8 Hz), 0.99 (d, 3H, C2'Me, J=6.7 Hz), 1.31 (d, 3H, H4, J=7.0 Hz), 1.92 (octet, 1H, H2', J=6.8 Hz), 2.74 (quint, 1H, H3, J=7.3 Hz), 3.23 (dd, 1H, H1, J=7.8 Hz and 11.3 Hz), 3.34 (dd, 1H, H1, J=2.8 Hz and 11.3 Hz), 3.64 (dt, 1H, H2, J=2.8 Hz and 7.8 Hz), 4.28 (d, 1H, H1', J=7.0 Hz), 7.12 (d, 2H, Ar-H, J=8.1 Hz), 7.22 (d, 2H, Ar-H, J=8.1 Hz).

(2R,3S,1"RS")-3-[4'-(1"-Hydroxy-2"-methylpropyl)phenyl]butane-1,2-diol (104b).

The optically active compound 104b was obtained similarly to the racemate 104a, from 103b. ¹H NMR data of 104b are identical with those of 104a.

(2RS,3SR)-3-[4'-(2"-Methylpropyl)phenyl]butane-1,2-diol (105a).

Palladium on carbon (10%, 55 mg) and dichloromethane (2 mL) were stirred at room temperature in a hydrogen atmosphere for 1 h, then the triol (47 mg, 0.2 mmol) in dichloromethane (2 mL) was added and the reaction mixture stirred in a hydrogen atmosphere overnight. The hydrogen was cautiously replaced with air, the solution filtered through Celite and the solvent removed in vacuo to give 105a as a colourless oil (35 mg, 79%): ¹H NMR (300 MHz, CDCl₃, D₂O) δ 0.89 (d, 6H, CH(CH₃)₂, J=6.7 Hz), 1.35 (d, 3H, H4, J=6.9 Hz), 1.84 (m, 1H, CH(CH₃)₂, J=6.8 Hz), 2.44 (d, 2H, H1', J=7.2 Hz), 2.78 (quint, 1H, H3, J=7.0 Hz), 3.36 (dd, 1H, H1, J=7.7 Hz and 11.2 Hz), 3.46 (dd, 1H, H1, J=3.0 Hz and 11.2 Hz), 3.74 (dt, 1H, H2, J=3.2 Hz and 7.7 Hz), 7.09 (m, Ar-H). Anal. Found: C, 75.33; H, 9.55% Calcd for C₁₄H₂₂O₂: C, 75.63; H, 9.97%.
(2R,3S)-3-[4'-(2''-Methylpropyl)phenyl]butane-1,2-diol (105b).

The optically active compound 105b was obtained similarly to the racemate 105a, from 104b. 105b was obtained as a white crystalline solid which was recrystallized from pentane: mp 62.0-65.5°C; $^1$H NMR data are identical with those of 105a.

(RS)-2-[4'-(2''-Methylpropyl)phenyl]propanoic acid (1a).

According to the procedure of Sharpless$^{84}$, the diol 105a (32 mg, 0.14 mmol) was dissolved in carbon tetrachloride (1.1 mL), acetonitrile (1.1 mL) and water (1.7 mL). Ruthenium trichloride hydrate (1.1 mg, 0.005 mmol) and sodium metaperiodate (180 mg, 0.84 mmol) were added and the reaction stirred vigorously at room temperature for 1.25 h. The reaction mixture was diluted with dichloromethane, washed with water and dried with MgSO$_4$. The solution was passed down a column of charcoal (2 cm) and the solvent removed in vacuo to give 1a as a colourless oil (27 mg, 90%) (lit$^{106}$ mp 75-77°C). Spectral data are identical with those of an authentic sample of ibuprofen: $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 0.89 (d, 6H, (CH$_3$)$_2$, J=6.7 Hz), 1.50 (d, 3H, H3, J=7.0 Hz), 1.84 (m, 1H, H2'', J=6.7 Hz), 2.44 (d, 2H, H1'', J=7.1 Hz), 3.70 (q, 1H, H2, J=7.0 Hz), 7.10 (d, 2H, Ar-H, J=7.8 Hz), 7.22 (d, 2H, Ar-H, J=7.8 Hz).

(S)-2-[4'-(2''-Methylpropyl)phenyl]propanoic acid (1b).

The optically active compound 1b was obtained similarly to the racemate 1a, from 105b. Bulb to bulb distillation and storage of the distillate in the freezer overnight facilitated crystallization of 1b: mp 49-51°C (lit$^{88}$: 50-52°C); $[\alpha]D^{20} = +57$ (c=2.33, EtOH), $[\alpha]D^{108} = +60$ (c=2.95, EtOH); $^1$H NMR data are identical with those of 1a.
EXPERIMENTAL
CHAPTER 3

(2R,3S)-3-(3'-Iodophenyl)butane-1,2-diol (113b).

To the silyldiol 89b (400 mg, 1.68 mmol) in dichloromethane (20 mL) was added iodine monochloride (273 mg, 1.68 mmol). After 1 h at room temperature the reaction mixture was diluted with dichloromethane and washed with 10% sodium thiosulphate solution until colourless. The aqueous phase was extracted with dichloromethane, the combined organic fractions dried with MgSO₄ and the solvent removed in vacuo. Flash chromatography with hexane/ethyl acetate (50/50, v/v) as eluant gave 113b as a colourless oil (400 mg, 82%) which was used without further purification. A sample was subjected to bulb to bulb distillation at 140°C/0.05 mm Hg (heated block); ¹H NMR (300 MHz, CDCl₃, D₂O) δ 1.30 (d, 3H, CH₃, J=7.0 Hz), 2.69 (quint, 1H, H3, J=7.0 Hz), 3.29 (dd, 1H, H1, J=7.7 Hz and 11.3 Hz), 3.42 (dd, 1H, H1, J=2.7 Hz and 11.3 Hz), 3.68 (dt, 1H, H2, J=2.7 Hz and 7.7 Hz), 7.00-7.56 (m, 4H, Ar-H).

(2R,3SR)-3-(3'-Iodophenyl)butane-1,2-diol (113a).

The racemate 113a was obtained similarly to the optically active compound 113b, from 89a. ¹H NMR data of 113a are identical with those of 113b.

(2R,3S)-3-(4'-Iodophenyl)butane-1,2-diol (114b).

To the silyldiol 100b (200 mg, 0.84 mmol) in dichloromethane (6 mL) was added iodine monochloride (142 mg, 0.87 mmol). After 30 min at room temperature the reaction mixture was diluted with dichloromethane and washed with 10% sodium thiosulphate solution until colourless. The aqueous phase was
extracted with dichloromethane, the combined organic fractions dried with MgSO₄ and the solvent removed *in vacuo*. Flash chromatography with hexane/ethyl acetate (50/50, v/v) as eluant gave 114b as a white crystalline solid (220 mg, 90%): mp 77.0-78.5°C; ¹H NMR (300 MHz, CDCl₃) δ 1.32 (d, 3H, CH₃, J=7.0 Hz), 1.85-2.70 (br, 2H, OH), 2.75 (quint, 1H, H3, J=7.2 Hz), 3.32 (dd, 1H, H1, J=7.5 Hz and 11.1 Hz), 3.45 (dd, 1H, H1, J=3.0 Hz and 11.1 Hz), 3.70 (dt, 1H, H2, J=3.0 Hz and 7.6 Hz), 6.95 (d, 2H, Ar-H, J=8.2 Hz), 7.66 (d, 2H, Ar-H, J=8.2 Hz).

(2RS,3SR)-3-(4'-Iodophenyl)butane-1,2-diol (114a).

The racemate 114a was obtained similarly to the optically active compound 114b, from 100a. ¹H NMR data of 114a are identical with those of 114b.

(S)-2-(3'-Iodophenyl)propanoic acid (45b).

According to the procedure of Sharples⁸⁴, the diol 113b (490 mg, 1.68 mmol) was dissolved in carbon tetrachloride (6 mL), acetonitrile (6 mL) and water (9 mL). Ruthenium trichloride hydrate (9.7 mg, 0.037 mmol) and sodium metaperiodate (1.51 g, 7.06 mmol) were added. The reaction mixture was stirred vigorously at room temperature for 1.25 h, diluted with dichloromethane and washed with water. The aqueous phase was extracted with dichloromethane, the organic fractions combined, dried with MgSO₄ and the solvent removed *in vacuo*. Flash chromatography with hexane/ethyl acetate (50/50, v/v) as eluant gave 45b as a white crystalline solid (320 mg, 69%) which was used without further purification. A sample was recrystallized from hexane: mp 49-52°C; [α]D²₀₊=+43.4° (c=1.20, CHCl₃); ¹H NMR (300 MHz, CDCl₃, D₂O) δ 1.50 (d, 3H, CH₃, J=7.2 Hz), 3.67 (q, 1H, H2, J=7.2 Hz), 7.04-7.67 (m, 4H, Ar-H). Found: C: 39.41%, H: 3.37%, C₉H₉I₂O₂ requires C: 39.15%, H: 3.29%.
(RS)-2-(3'-Iodophenyl)propanoic acid (45a).

The racemate 45a was obtained similarly to the optically active compound 45b, from 113a and was used without further purification. A sample was recrystallized from hexane: mp 48.0-50.5°C. ¹H NMR data of 45a are identical with those of 45b.

(S)-2-(4'-Iodophenyl)propanoic acid (46b).

According to the procedure of Sharpless²⁴, the diol 114b (220mg, 0.75 mmol) was dissolved in carbon tetrachloride (3.0 mL), acetonitrile (3.0 mL) and water (4.5 mL). Ruthenium trichloride hydrate (4.3 mg, 0.021 mmol) and sodium metaperiodate (674 mg, 3.2 mmol) were added. The mixture was stirred vigorously at room temperature for 1.25 h, diluted with dichloromethane and washed with water. The aqueous phase was extracted with dichloromethane, the organic fractions combined, dried with MgSO₄ and the solvent removed in vacuo. Flash chromatography with hexane/ethyl acetate (50/50, v/v) as eluant gave 46b as a white crystalline solid (157 mg, 75%) which was used without further purification. A sample was recrystallized from hexane: mp 139-140°C; [α]p²⁰=+39.0° (c=2.45, CHCl₃); ¹H NMR (300 MHz, CDCl₃ D₂O) δ 1.49 (d, 3H, CH₃, J=7.2 Hz), 3.68 (q, 1H, H2, J=7.2 Hz), 7.07 (d, 2H, Ar-H, J=8.3 Hz), 7.65 (d, 2H, Ar-H, J=8.3 Hz). Found: C: 39.15%, H: 3.17%, C₉H₉I₂O₂ requires C: 39.15%, H: 3.29%.

(RS)-2-(4'-Iodophenyl)propanoic acid (46a).

The racemate 46a was obtained similarly to the optically active compound 46b, from 114a and was used without further purification. A sample was recrystallized from hexane: mp 100-102°C. ¹H NMR data of 46a are identical
Palladium catalysed coupling reaction - General Procedure.

a) Formation of zinc alkyl or zinc aryl reagent. Grignard reagents were prepared from alkyl or aryl halides (redistilled) in either anhydrous THF or ether. The concentration of each Grignard reagent was determined by quenching an aliquot (0.5 mL) in HCl (10 mL of a 0.100 M solution) containing phenolphthalein (4 drops of a 1% ethanol solution) as indicator. The remaining acid was titrated with NaOH solution (concentration known to three decimal places, approximately 0.1 M) until the pink colour remained. The procedure was duplicated at least three times, and an average value used to determine the concentration of the Grignard reagent.

In a separate, flame dried flask, anhydrous zinc chloride (1.05 equivalents relative to the Grignard reagent) was dissolved in THF (0.15-0.20 g/mL) in a nitrogen atmosphere (exothermic). To this was added the Grignard reagent via syringe, and immediate formation of a white precipitate was observed. The mixture was stirred at room temperature for at least 10 min.

b) Coupling reaction. A flame dried, 2-necked flask was flushed with nitrogen and charged with dichlorobis(triphenylphosphine) palladium(II) (0.14 equiv), anhydrous THF (1 mL/50 mg iodoacid) and diisobutylaluminium hydride (0.28 equiv). The iodoacid (1.0 equiv) in THF (1 mL/50 mg) was added, followed by the zinc alkyl or zinc aryl reagent (5.0 equiv), including the precipitate and supernatant. The reaction mixture was stirred at room temperature in a nitrogen atmosphere for at least 1.5 h, the THF was removed in vacuo and the residue dissolved in dichloromethane. The solution was washed with 10% HCl and the aqueous layer extracted with dichloromethane. The organic
fractions were combined, washed with saturated sodium bicarbonate solution and the aqueous phase acidified by dropwise addition of concentrated HCl and extracted with dichloromethane. This fraction was dried with MgSO4 and the solvent removed in vacuo.

Determination of optical purity of products - General procedure.

The analysis of optical purity of the coupled products was kindly performed by P. J. Hayball, according to the reported procedure.79

(2RS,3SR)-3-(3'-Iodophenyl)butane-1,2-diy diacetate (115a).

To the silyldiol 89a (554 mg, 2.33 mmol) in pyridine (5 mL) was added acetic anhydride (3 mL), and the reaction mixture was allowed to stand at room temperature overnight. Dichloromethane was added to the mixture and it was washed with water, 5% HCl until acidic, 5% sodium bicarbonate solution and water. The solution was dried with MgSO4 and the solvent removed in vacuo. Flash chromatography with dichloromethane as eluant, followed by bulb to bulb distillation at 122°C/0.04 mm Hg (heated block) gave the intermediate (2RS,3SR)-3-[3'-(trimethylsilyl)phenyl]butane-1,2-diy diacetate as a white crystalline solid (710 mg, 95%): mp 52-53°C; 1H NMR (60 MHz, CDCl3) δ 0.35 (s, 9H, (CH3)3), 1.33 (d, 3H, H4, J=7 Hz), 2.03 (s, 3H, COCH3), 2.18 (s, 3H, COCH3), 3.00 (m, 1H, H3), 3.82 (dd, 1H, H1, J=6 Hz and 12 Hz), 4.21 (dd, 1H, H1, J=3 Hz and 12 Hz), 5.25 (m, 1H, H2), 7.18-7.50 (m, 9H, Ar-H).

In a similar manner to that used for the formation of 113b, (2RS,3SR)-3-[3'- (trimethylsilyl)phenyl]butane-1,2-diy diacetate (267 mg, 0.83 mmol) in dichloromethane (10 mL) was treated with iodine monochloride (135 mg, 0.83 mmol). TLC showed the reaction to be complete after 20 min, and work up
gave 115a as a colourless oil (304 mg, 97%): \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 1.27 (d, 3H, H4, J=7.0 Hz), 2.03 (s, 3H, COCH\(_3\)), 2.09 (s, 3H, COCH\(_3\)), 2.98 (m, 1H, H3), 3.79 (dd, 1H, H1, J=6.4 Hz and 12.0 Hz), 4.13 (dd, 1H, H1, J=3.0 Hz and 12.0 Hz), 5.20 (m, 1H, H2), 7.04-7.60 (m, 9H, Ar-H).

(2RS,3SR)-3-(3'-Benzylphenyl)butane-1,2-diol diacetate (116a).

The Grignard reagent from benzyl chloride in ether was prepared and found to be 0.954 M. It was converted to the corresponding zinc alkyl reagent, and coupled to 115a (128 mg, 0.34 mmol) by the general procedure to give 116a as a colourless oil (100 mg, 86%): \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 1.26 (d, 3H, H4, J=7.0 Hz), 1.98 (s, 3H, COCH\(_3\)), 2.06 (s, 3H, COCH\(_3\)), 2.98 (m, 1H, H3), 3.77 (dd, 1H, H1, J=6.4 Hz and 12.0 Hz), 3.96 (s, 2H, CH\(_2\)Ar), 4.11 (dd, 1H, H1, J=2.9 Hz and 12.0 Hz), 5.22 (m, 1H, H2), 7.04-7.34 (m, 9H, Ar-H). Found: C: 73.49%, H: 7.07%. C\(_{21}\)H\(_{24}\)O\(_4\) requires C: 74.09%, H: 7.11%.

(2RS,3SR)-3-(3'-Benzylphenyl)butane-1,2-diol (117a).

To 116a (80 mg) in methanol (1.5 mL) was added potassium carbonate (30 mg), and the reaction mixture was allowed to stand at room temperature for 2 h, at which time TLC showed the diacetate to have been consumed and a single product formed. The methanol was removed in vacuo, the residue dissolved in dichloromethane and washed with water. The aqueous phase was extracted with dichloromethane and the organic phase dried with MgSO\(_4\). Removal of the solvent in vacuo gave 117a as a colourless oil: \(^1\)H NMR (300 MHz, CDCl\(_3\), D\(_2\)O) \(\delta\) 1.31 (d, 3H, CH\(_3\), J=7.0 Hz), 2.68 (quint, 1H, H3, J=7.0 Hz), 3.29 (dd, 1H, H1, J=7.7 Hz and 11.2 Hz), 3.42 (dd, 1H, H1, J=2.7 Hz and 11.2 Hz), 3.68 (dt, 1H, H2, J=2.7 Hz and 7.7 Hz), 3.96 (s, 2H, CH\(_2\)Ar), 7.00-7.56 (m, 4H, Ar-H).
(RS)-2-(3'-Benzylphenyl)propanoic acid (118a).

By a similar procedure to that used for formation of the iodoacid 45b, 117a (45 mg, 0.18 mmol) in carbon tetrachloride (1.0 mL), acetonitrile (1.0 mL) and water (1.5 mL) was treated with ruthenium trichloride hydrate (1.0 mg, 0.004 mmol) and sodium metaperiodate (162 mg, 0.76 mmol). Work up gave 118a as a colourless oil (37 mg, 86%): $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 1.48 (d, 3H, H3, $J$=7.2 Hz), 3.69 (q, 1H, H2, $J$=7.2 Hz), 3.96 (s, 2H, CH$_2$Ar), 7.06-7.30 (m, 9H, Ar-H).

(S)-2-(3'-Benzylphenyl)propanoic acid (118b).

The Grignard reagent from benzyl chloride in ether was prepared and found to be 0.966 M. It was converted to the corresponding zinc alkyl reagent, and coupled to 45b (48 mg, 0.174 mmol) by the general procedure to give 118b as a colourless oil (38 mg, 91%). $^1$H NMR data are identical with those of the racemate 118a. The optical purity was determined by the general procedure and found to be 94% e.e.

(S)-2-(3'-Biphenylyl)propanoic acid (119b).

The Grignard reagent from bromobenzene in ether was prepared and found to be 1.53 M. It was converted to the corresponding zinc aryl reagent, and coupled to 45b (41 mg, 0.15 mmol) by the general procedure. 119b was obtained as a colourless oil (25 mg, 74%): $^1$H NMR (300 MHz, CDCl$_3$, D$_2$O) $\delta$ 1.56 (d, 3H, CH$_3$, $J$=7.2 Hz), 3.81 (q, 1H, H2, $J$=7.2 Hz), 7.25-7.59 (m, 4H, Ar-H) (NMR data are in agreement with literature values for the racemate). The optical purity was determined by the general procedure and found to be 96% e.e.
(RS)-2-(3’-Biphenyl)propanoic acid (119a).

The racemate 119a was obtained similarly to the optically active compound 119b, from 45a. 119a was obtained as a white crystalline solid in 83% yield: mp 64-68°C (lit89 mp 64 °C). After recrystallization from hexane: mp 49-51 °C; 1H NMR data are identical to those of 119b.

(S)-2-(3’-[Phenylethynyl]phenyl)propanoic acid (120b).

To a flame dried flask which had been flushed with nitrogen were added phenylacetylene (1.0 g, 9.79 mmol), anhydrous THF (5 mL) and n-butyllithium (4.20 mL of a 2.33 M hexane solution, 9.79 mmol). After stirring for 30 min at room temperature, anhydrous zinc chloride (1.40 g, 10.3 mmol) in THF (5mL) was added to the deep purple solution, whereupon the colour changed to bright orange. This zinc alkyl reagent was coupled to 45b (46 mg, 0.17 mmol) by the general procedure. Flash chromatography with hexane/ethyl acetate (70/30, v/v) as eluant gave 120b as a white crystalline solid (30 mg, 71%) which was recrystallized from hexane: mp 80-82°C; 1H NMR (300 MHz, CDCl3) δ 1.54 (d, 3H, CH3, J=7.2 Hz), 3.75 (q, 1H, H2, J=7.2 Hz), 7.30-7.55 (m, 9H, Ar-H). The optical purity was determined by the general procedure and found to be 96% e.e.

(RS)-2-(3’-[Phenylethynyl]phenyl)propanoic acid (120a).

The racemate 120a was obtained similarly to the optically active compound 120b, from 45a. 120a was obtained as a white crystalline solid in 77% yield: mp 72-75°C. Found C: 81.55%, H: 5.86%, C17H14O2 requires C: 81.58%, H: 5.64%. 1H NMR data are identical to those of 120b.
(S)-2-(4'-Biphenyl)propanoic acid (121b).

The Grignard reagent from bromobenzene in ether was prepared and found to be 0.76 M. It was converted to the corresponding zinc aryl reagent, and coupled to 46b (26 mg, 0.09 mmol) by the general procedure. 121b was obtained as a white crystalline solid (13 mg, 62%): mp 159-161°C; 1H NMR (300 MHz, CDCl3) δ 1.56 (d, 3H, CH3, J=7.2 Hz), 3.80 (q, 1H, H2, J=7.2 Hz), 7.34-7.59 (m, 9H, Ar-H) (NMR data are in agreement with literature values108). The optical purity was determined by the general procedure and found to be 94% e.e.

(RS)-2-(4'-Biphenyl)propanoic acid (121a).

The racemate 121a was obtained similarly to the optically active compound 121b, from 46a. 121a was obtained as a white crystalline solid in 67% yield: mp 147-149°C (lit90 mp 146 °C). 1H NMR data are identical to those of 121b.

(S)-2-(4'-(2''-Methyl-1''-propenyl)phenyl)propanoic acid (122b)

The Grignard reagent from 1-bromo-2-methyl-1-propene in THF was prepared and found to be 1.15 M. It was converted to the corresponding zinc alkyl reagent, and coupled to 46b (26 mg, 0.09 mmol) by the general procedure. 122b was obtained as a colourless oil (17 mg, 90%): 1H NMR (300 MHz, CDCl3) δ 1.51 (d, 3H, CH3, J=7.1 Hz), 1.85 (d, 3H, C2''CH3, J=1.1 Hz), 1.89 (d, 3H, H3'', J=1.2 Hz), 3.72 (q, 1H, H2, J=7.1 Hz), 6.23 (br s, 1H, H1''), 7.18 (d, 2H, Ar-H, J=8.2 Hz), 7.26 (d, 2H, Ar-H, J=8.2 Hz).
(S)-2-(4'-[2''-Methylpropyl]phenyl)propanoic acid (1b) via hydrogenation of 122b.

To 122b (9 mg, 0.04 mmol) in ethyl acetate (2.5 mL) was added palladium on carbon (10%, 10 mg) and the reaction mixture was stirred in a hydrogen atmosphere at room temperature for 1.5 h. The hydrogen was replaced with air and the catalyst removed by filtration through cotton wool. Flash chromatography with hexane/ethyl acetate (50/50, v/v) as eluant did not remove a lower Rf impurity. A dichloromethane solution of the residue was washed with sodium bicarbonate solution. The aqueous phase was acidified by dropwise addition of concentrated HCl and extracted with dichloromethane. The organic phase was dried with MgSO₄ and the solvent removed in vacuo to give 1b (6 mg, 69%). ¹H NMR data are identical with those reported earlier in this section. The optical purity was determined by the general procedure and found to be 96% e.e.

(±)-2-(4'-[2''-Methylpropyl]phenyl)propanoic acid (1b).

The Grignard reagent from 1-chloro-2-methylpropane in ether was prepared and found to be 1.60 M. It was converted to the corresponding zinc alkyl reagent and coupled to 46b (54 mg, 0.20 mmol) by the general procedure. 1b was obtained as a white crystalline solid (31 mg, 77%): mp 49-51°C. It was recrystallized from ethanol: mp 50-52°C (lit⁸⁸ mp 49-51°C, 95% optically pure); ¹H NMR data are identical with those reported earlier in this section. The optical purity was determined by the general procedure and found to be 92% e.e.
(RS)-2-(4'-[2''-Methylpropyl]phenyl)propanoic acid (1a).

The racemate 1a was obtained similarly to the optically active compound 1b, from 46a. 1a was obtained as a white crystalline solid in 75% yield: mp 76-77°C (lit mp 74 °C). 1H NMR data are identical with those reported earlier in this section.
EXPERIMENTAL
CHAPTER 4

(RS)-5-Trimethylsilyl-2-cyclohexen-1-one (55a).

According to the method of Asaoka\textsuperscript{66}, a 500 mL flask was fitted with a pressure equalizing dropping funnel and a thermometer and charged with lithium powder (20 g of 30% dispersion in oil, 0.88 mol) and anhydrous THF (160 mL). The mixture was cooled to -35° - -25°C using an ethylene glycol/dry ice bath and a mixture of anisole (42 g, 0.39 mol) and chlorotrimethylsilane (128 g, 1.18 mol) was added dropwise. The temperature of the reaction mixture was kept below -10°C during most of the addition, although it briefly rose to 10°C, due to a delay between addition and generation of heat. Another portion of THF (100 mL) was added to facilitate stirring, and the mixture was stirred at room temperature overnight. The mixture was filtered under nitrogen, the volatiles removed \textit{in vacuo} and the residue distilled to give 1-methoxy-3,6-bis(trimethylsilyl)cyclohexa-1,4-diene (80.5 g): bp 100-110°C/6 mm Hg (lit\textsuperscript{66} bp 95-105°C/6 mm Hg); \textsuperscript{1}H NMR (60 MHz, CDCl\textsubscript{3}) $\delta$ 0.0 (s, 18H, Si(CH\textsubscript{3})\textsubscript{3}), 2.68 (complex, 2H, SiCH), 3.85 (s, 3H, CH\textsubscript{3}O), 4.72 (br s, 1H, H2), 5.79 (m, 2H, H4 and H5) (lit\textsuperscript{66}: no NMR data reported). The intermediate contained 15% anisole and was used without further purification.

A 500 mL 3 necked flask was fitted with 3 condensers and charged with 1-methoxy-3,6-bis(trimethylsilyl)cyclohexa-1,4-diene (80.0 g, 0.40 mol) and ether (150 mL). 2M HCl (12 mL, 24 mmol) was added. After 40 min no sign of a reaction had been observed and the mixture was warmed to reflux. Concentrated HCl (2 mL) was added and an exothermic reaction caused the ether to reflux vigorously for 10 min. After stirring at room temperature for 1 h, the layers were separated and the aqueous phase extracted with ether. The
combined organic fractions were washed with sodium bicarbonate solution, dried with MgSO_4 and the solvent removed in vacuo to give crude 5-trimethylsilyl-3-cyclohexenone: 1H NMR (60 MHz, CDCl_3) δ 0.0 (s, 9H, Si(CH_3)_3), 1.80-2.90 (complex, 5H, H2, H5 and H6), 5.40-6.02 (m, 2H, H3 and H4) (lit^66: no NMR data reported). This intermediate contained residual anisole and was used without further purification.

To 5-trimethylsilyl-3-cyclohexenone (total product from previous step) in dichloromethane/ether (1:1, 250 mL) was added DBU (1.8 g), and the solution was allowed to stand at room temperature for 2 days. After washing with dilute HCl the solvent was removed in vacuo and the residue subjected to fractional distillation with a column (15 cm) of glass helices, to give 55a in 62% overall yield: bp 55.0-56.5°C/0.1 mm Hg (lit^66 bp 65.5-67.0°C/2 mm Hg); 1H NMR (300 MHz, CDCl_3) δ -0.01 (s, 9H, Si(CH_3)_3), 1.40 (m, 1H, SiCH), 2.09-2.42 (complex, 4H, H4 and H6), 5.96 (dt, 1H, H2, J=1.3 Hz and 10.1 Hz), 7.00 (m, 1H, H3) (no NMR data reported). The product contained residual anisole (10%) and was used without further purification.

(R)-5-Trimethylsilyl-2-cyclohexen-1-one (55c).

According to the method of Asaoka^66, 55a (38.0 g including 10% anisole, 0.20 mol) and p-toluenethiol (13.9 g, 0.11 mol) were added to a solution of cinchonidine (0.60 g, 2.0 mmol) in anhydrous toluene (1.1 L). The mixture was stirred at room temperature in a nitrogen atmosphere overnight and concentrated in vacuo to give a total volume of approximately 300 mL. The solution was washed with 2M HCl and dried with MgSO_4. The solvent was removed in vacuo and pentane (85 mL) was added to the white crystalline residue. The slurry was kept at -20°C overnight and the crystals collected by vacuum filtration (27.9 g). Two recrystallizations from hexane (10 mL/g) and
one from ethanol (10 mL/g) gave enantiomerically pure (3S,5S)-3-(4'-methylbenzenethio)-5-trimethylsilylcyclohexanone (11.0 g): mp 114-115°C (lit\textsuperscript{66}: no mp reported); [a]_D^20=+35.5° (c=1.00, CHCl\textsubscript{3}), lit\textsuperscript{66}: [a]_D^20=+35.5° (c=1.08, CHCl\textsubscript{3}). \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \(\delta\) 0.04 (s, 9H, Si(CH\textsubscript{3})\textsubscript{3}), 1.66 (m, 1H, SiCH), 1.81-2.68 (methylene envelope), 2.31 (s, 3H, CH\textsubscript{3}), 3.87 (m, 1H, SCH), 7.10 (d, 2H, Ar-H, J=8.0 Hz), 7.31 (d, 2H, Ar-H, J=8.0 Hz) (lit\textsuperscript{66}: no NMR data reported).

According to the method of Asaoka\textsuperscript{67}, (3S,5S)-3-(4'-methylbenzenethio)-5-trimethylsilylcyclohexanone (2.0 g, 6.85 mmol) was dissolved in dichloromethane (72 mL) and to this was added DBU (1.1 g, 7.3 mmol). The reaction mixture was stirred at room temperature overnight, washed with 2M HCl and dried with MgSO\textsubscript{4}. The solvent was removed \textit{in vacuo} and the residue purified by flash chromatography with hexane/ethyl acetate (92/8, v/v) as eluant, to give 55c as a colourless oil (1.2 g, 100%): \textsuperscript{1}H NMR data are identical with those of 55a.

(S)-5-(Trimethylsilyl)-2-cyclohexen-1-one (55b).

According to the method of Asaoka\textsuperscript{66}, the filtrate from the crystallization of (3S,5S)-3-(4'-methylbenzenethio)-5-trimethylsilylcyclohexanone was distilled to give a colourless oil (15 g) which contained 55b and anisole. Chromatography with a gradient of hexane/ethyl acetate as eluant removed the anisole to give 55b (5.1 g, 30.1 mmol) which was dissolved in anhydrous toluene (10 mL) and added to triethylamine (61 mg, 0.6 mmol). \textit{p}-Toluenethiol (3.91 g, 31.6 mmol) was added and the reaction mixture stirred at room temperature in a nitrogen atmosphere for 2 days. The solution was concentrated \textit{in vacuo} to approximately 100 mL, washed with 2 M HCl and dried with MgSO\textsubscript{4}. The solvent was removed \textit{in vacuo}, the residue (9.0 g) was dissolved in ethanol (32 mL) and kept at -20°C overnight. The resultant white crystals were separated by
filtration (4.3 g): \([\alpha]D^{20}=-26.7^\circ\) (c=1.16, CHCl_3) \[\text{lit}^{66}: [\alpha]D^{20}=-35.5^\circ\) (c=1.00, CHCl_3)]. Recrystallization from ethanol, then hexane, then ethanol gave enantiomerically pure \((3R,5R)-3-(4'-methylbenzenethio)-5\)-trimethylsilylcyclohexanone (2.0 g): mp 113-114.5°C (\[\text{lit}^{66}: \text{no mp reported}; [\alpha]D^{20}=-35.7^\circ\) (c=1.04, CHCl_3); \(^1^H\) NMR data are identical with those of the \((3S,5S)\) isomer. \(55b\) was obtained by treatment of the thioether with DBU as described for the enantiomer. \(^1^H\) NMR data are identical with those of \(55a\).

\((4S,1R)-4-[1'(4''-Bromophenyl)ethyl]-2,2\)-dimethyl-1,3-dioxolane (102c).

The bromoacetonide 102c was prepared by the sequence of reactions described for its enantiomer 102b except that (-)-diisopropyl tartrate was used in the Sharpless asymmetric epoxidation. The epoxy alcohol 99c was estimated to be 98%+ e.e. from NMR analysis of the acetate derivative with the optically active shift reagent tris-[3-(heptafluoropropylhydroxy-methylene)-(+)camphorato]-europium(III) derivative. Spectral data for the compounds 99c - 102c were identical with those reported for 99b - 102b.

\((3S,5R,1'S,4''R)-3-(4-[1''-2''-Dimethyl-1,3-dioxolan-4''-yl]ethyl)phenyl)-5-(trimethylsilyl)cyclohexanone (125b).

According to the procedure of Asaoka et al\(^{67}\), \(55c\) (574 mg, 3.42 mmol), anhydrous THF (55 mL), copper bromide-dimethyl sulphide complex (66 mg; prepared according to House\(^{110}\)), HMPA (1.25 g, 6.9 mmol) and chlorotrimethylsilane (1.07 g, 9.85 mmol) were cooled to -78°C and the Grignard reagent from 102b (5.13 mmol) in THF (6 mL) was added. The reaction mixture was allowed to warm to room temperature and hexane (170
mL) was added. The solution was washed with water then brine and the solvent removed in vacuo. The residue was dissolved in methanol (47 mL), potassium fluoride (1.3 g) was added and the reaction mixture allowed to stand for 15 min. Water (330 mL) was added and the aqueous mixture extracted thrice with dichloromethane. Flash chromatography with hexane/ether (75/25, v/v) gave 125b as a colourless oil (560 mg, 44%): $^1$H NMR (300 MHz, CDCl$_3$) δ -0.06 (s, 9H, Si(CH$_3$)$_3$), 1.13 (m, 1H, H5), 1.33 (d, CH$_3$CH, J=6.6 Hz), 1.33 and 1.37 (each s, 3H, C2''Me), 1.95-2.75 (complex, 8H, ring Hs and CH$_3$CH), 3.49 (dd, 1H, H5'', J=6.9 Hz and 8.3 Hz), 3.69 (dd, 1H, H5'', J=6.1 Hz and 8.3 Hz), 4.10 (dt, 1H, H4'', J=6.7 Hz and 8.1 Hz), 7.09 (apparent s, 4H, Ar-H). Anal. Found: C, 70.71; H, 8.98%. Calcd for C$_{22}$H$_{33}$SiO$_2$: C, 70.54; H, 9.15%.

(3$\mathcal{R}$,5$\mathcal{S}$,1$\mathcal{R}$, 4''$\mathcal{S}$)-3-(4-[1''-{2'',2''}-Dimethyl-1,3-dioxolan-4''-yl]ethyl)phenyl)-5-(trimethylsilyl)cyclohexanone (125c).

125c was obtained similarly to 125b as a colourless oil in 93% yield, by the use of 55b and 102c: $^1$H NMR data of 125c are identical with those of 125b.

(3$\mathcal{S}$,5$\mathcal{R}$,1$\mathcal{R}$, 4''$\mathcal{S}$)-3-(4-[1''-{2'',2''}-Dimethyl-1,3-dioxolan-4''-yl]ethyl)phenyl)-5-(trimethylsilyl)cyclohexanone (130c).

130c was obtained similarly to 125b as a white crystalline solid in 71% yield, by the use of 102c and 55c. A sample was recrystallized from ethanol: mp 73-74.5°C; $^1$H NMR (300 MHz, CDCl$_3$) δ -0.06 (s, 9H, Si(CH$_3$)$_3$), 1.13 (m, 1H, H5), 1.33 (d, CH$_3$CH, J=6.6 Hz), 1.33 and 1.37 (each s, 3H, C2''Me), 1.95-2.75 (complex, 8H, ring Hs and CH$_3$CH), 3.49 (dd, 1H, H5'', J=6.9 Hz and 8.3 Hz), 3.69 (dd, 1H, H5'', J=6.1 Hz and 8.3 Hz), 4.10 (dt, 1H, H4'', J=6.7 Hz and 8.1 Hz), 7.09 (apparent s, 4H, Ar-H). Anal. Found: C, 70.72; H, 8.93%. Calcd for C$_{22}$H$_{33}$SiO$_2$: C, 70.54; H, 9.15%.
(3R,5S,1'S, 4'R)-3-(4-[1''-2'',2''-Dimethyl-1,3-dioxolan-4''-yl]ethyl]phenyl)-5-(trimethylsilyl)cyclohexanone (130b).

130b was obtained similarly to 125b as a white crystalline solid in 51% yield, by the use of 102b and 55b. A sample was recrystallized from ethanol: mp 73-74°C; ¹H NMR data are identical with those of 130c.

(5R,1'S,2'S)-5-(4'-[2'',3''-Dihydroxy-1'-methylpropyl]phenyl)-2-cyclohexen-1-one (127b).

The silyl ketone 125b (550 mg, 1.47 mmol) and anhydrous copper (II) chloride (576 mg) in anhydrous DMF (5.9 mL) were stirred at 70°C in a nitrogen atmosphere for 30 min. The DMF was removed in vacuo and the residue was dissolved in methanol and 10% HCl (1mL). After 3 h at room temperature the methanol was removed, the residue dissolved in dichloromethane and washed with water. Flash chromatography with ethyl acetate/hexane (60/40, v/v) as eluant gave 127b as a white crystalline solid (205 mg, 54%). A sample was recrystallized from ethanol/hexane: mp 114-115°C; ¹H NMR (300 MHz, CDCl3) δ 1.34 (d, 3H, CH3, J=7.1 Hz), 2.46-2.71 (complex, 5H, H4, H5 and H6), 2.78 (apparent quint, 1H, CHCH3, J=7.1 Hz), 3.32 (dd, 1H, CH2OH, J=7.7 Hz and 17.2 Hz), 3.33 (m, 1H, H5), 3.74 (apparent sept, 1H, CH2OH, J=3.0 Hz and 7.7 Hz), 6.72 (dd, 1H, H2, J=2.2 Hz and 10.1 Hz), 7.06 (m, 1H, H3), 7.17 (s, 4H, Ar-H). Anal. Found: C, 73.82; H, 7.74%. Calcd for C16H20O3: C, 73.53; H, 7.58%.
(5S,1'R,2"R)-5-[(4'-[2",3"-Dihydroxy-1'-methylpropyl]phenyl)-2-cyclohexen-1-one (127c).

127c was obtained similarly to 127b as a colourless oil in 45% yield, from 125c. 

H NMR data of 127c are identical with those of 127b.

(5R,1'R,2"R)-5-[(4'-[2",3"-Dihydroxy-1'-methylpropyl]phenyl)-2-cyclohexen-1-one (131c).

131c was obtained similarly to 127b as a colourless oil in 53% yield, from 130c: 

H NMR (300 MHz, CDCl3) δ 1.34 (d, 3H, CH₃, J=7.1 Hz), 2.46-2.71 (complex, 4H, 
H₄, H₅ and H₆), 2.78 (apparent quint, 1H, CH₂CH₃, J=7.1 Hz), 3.32 (dd, 1H, 
CH₂OH, J=7.7 Hz and 11.2 Hz), 3.33 (m, 1H, H₅), 3.44 (dd, 1H, CH₂OH, J=3.0 Hz 
and 11.2 Hz), 3.73 (dt, 1H, CHOH, J=3.0 Hz and 7.7 Hz), 6.12 (dd, 1H, H₂, J=2.2 Hz 
and 10.1 Hz), 7.06 (m, 1H, H₃), 7.17 (s, 4H, Ar-H).

(5S,1'S,2"S)-5-(4'-[2",3"-Dihydroxy-1'-methylpropyl]phenyl)-2-cyclohexen-1-one (131b).

131b was obtained similarly to 127b as a colourless oil in 54% yield, from 130b. 

H NMR data of 131b are identical with those of 131c.

(3R,1'S,2"S)-3-[(4'-[2",3"-Dihydroxy-1'-methylpropyl]phenyl)cyclohexanone (128b).

Palladium on carbon (10%, 220 mg) and 127b (220 mg, 0.85 mmol) in ethyl 
acetate (29 mL) were stirred at room temperature in a hydrogen atmosphere for 
1.5 h. The hydrogen was cautiously replaced with air and the mixture filtered 
through Celite. Flash chromatography with ethyl acetate/hexane (70/30, v/v)
as eluant separated unreacted 127b from 128b, which was obtained as a white crystalline solid (136 mg, 62%): mp 93-96°C; ¹H NMR (300 MHz, CDCl₃) δ 1.34 (d, 3H, CH₃, J=7.0 Hz), 1.82 (complex, 2H, H₄ax and H₅ax), 1.95 (br s, 1H, OH), 2.11 (complex, 2H, H₄eq and H₅eq), 2.39 (m, 2H, H₆), 2.55 (m, 2H, H₂), 2.68 (br s, 1H, OH), 2.78 (apparent quint, 1H, CHCH₃, J=7.0 Hz), 2.98 (tt, 1H, H₃, J=4.6 Hz and 11.6 Hz), 3.33 (dd, 1H, CH₂OH, J=7.6 Hz and 11.2 Hz), 3.45 (dd, 1H, CH₂OH, J=3.0 Hz and 11.2 Hz), 3.73 (dt, 1H, CHOH, J= 3.0 Hz and 7.7 Hz), 7.15 (s, 4H, Ar-H).

(3S,1'R,2''R)-3-(4'-[2''',3'''-Dihydroxy-1'''-methylpropyl]phenyl)cyclohexanone (128c).

128c was obtained similarly to 128b as a white crystalline solid in 70% yield, from 127c: mp 93-96°C; ¹H NMR data of 128c are identical with those of 128b.

(3R,1'R,2''R)-3-(4'-[2''',3'''-Dihydroxy-1'''-methylpropyl]phenyl)cyclohexanone (132c).

132c was obtained similarly to 128b as a white crystalline solid in 94% yield, from 131c: mp 70-72°C; ¹H NMR (300 MHz, CDCl₃) δ 1.34 (d, 3H, CH₃, J=7.0 Hz), 1.82 (complex, 2H, H₄ax and H₅ax), 1.95 (br s, 1H, OH), 2.11 (complex, 2H, H₄eq and H₅eq), 2.39 (m, 2H, H₆), 2.55 (m, 2H, H₂), 2.68 (br s, 1H, OH), 2.78 (apparent quint, 1H, CHCH₃, J=7.0 Hz), (2.98, tt, 1H, H₃, J=4.6 Hz and 11.6 Hz), 3.33 (dd, 1H, CH₂OH, J=7.6 Hz and 11.2 Hz), 3.45 (dd, 1H, CH₂OH, J=3.0 Hz and 11.2 Hz), 3.73 (dt, 1H, CHO, J= 3.0 Hz and 7.7 Hz), 7.15 (s, 4H, Ar-H). Anal. Found: C, 72.96; H, 8.34. Calcd for C₁₆H₂₂O₃: C, 73.25; H, 8.45.
(3S,1"S,2"S)-3-(4'-[2",3"-Dihydroxy-1"-methylpropyl]phenyl)cyclohexanone (132b).

132b was obtained similarly to 132c as a white crystalline solid in 76% yield, from 131b: mp 70-72°C; ^H NMR data of 132b are identical with those of 132c.

(2S,1"R)-2-(4'-[3"-Oxocyclohexyl]phenyl)proanoic acid (123b).

According to the procedure of Sharpless, 128b (135 mg, 0.51 mmol) was dissolved in carbon tetrachloride (1.8 mL), acetonitrile (1.8 mL) and water (2.7 mL). Ruthenium trichloride hydrate (2.7 mg) and sodium metaperiodate (414 mg, 1.94 mmol) were added and the reaction mixture stirred vigorously at room temperature for 1.25 h. Dichloromethane and water were added, the organic phase washed with saturated sodium bicarbonate solution and the aqueous phase acidified and extracted with dichloromethane. The solvent was removed in vacuo to give 123b (104 mg, 82%). Recrystallization from ethanol/hexane (1:1) gave pure material: mp 94.0-95.5°C, [a]D^20=+52° (c=1.75, EtOH); v_max (CH_2Cl_2) 1225, 1710, 1720, 2950 cm^-1. ^H NMR (300 MHz, CDCl_3) δ 1.50 (d, 3H, CH_3, J=7.1Hz), 1.73-1.90 (complex, 2H, H_5 and H_6), 2.05-2.18 (complex, 2H, H_5 and H_6), 2.32-2.45 (m, 2H, H_4), 2.49-2.61 (m, 2H, H_2), 2.99 (tt, 1H, H_1, J=4.2 Hz and 11.6 Hz), 3.73 (q, 1H, CHCH_3, J=7.1 Hz), 7.18 (d, 2H, Ar-H, J=8.3 Hz), 7.28 (d, 2H, Ar-H, J=8.1 Hz). ^13C NMR (75.5 MHz, CDCl_3) δ 18.00 (C3), 25.38 (C5''), 32.53 (C6''), 41.00 (C4''), 44.20 (C1''), 44.81 (C2), 48.71 (C2''), 126.75 (C3' and C5''), 127.76 (C2' and C6''), 138.12 (C4'), 143.23 (C1'), 180.00 (C1), 211.56 (C3''). Anal. Found: C, 73.26; H, 7.37%. Calcd for C_{15}H_{18}O_3: C, 73.14; H, 7.37%. 
(2R,1'S)-2-(4'-[3''-Oxocyclohexyl]phenyl)propanoic acid (123c).

123c was obtained similarly to 123b as a white crystalline solid in 82% yield, from 128c. mp 92-94°C; [α]D20 = -53° (c=1.75, EtOH); 1H NMR data of 123c are identical with those of 123b.

(2S,1'S)-2-(4'-[3''-Oxocyclohexyl]phenyl)propanoic acid (124c).

124c was obtained similarly to 123b as a white crystalline solid in 83% yield, from 132c. 124c was recrystallized from ethanol/hexane: mp 132.0-133.5°C; [α]D20 = +48° (c=1.45, EtOH); 1H NMR data of 124c are identical with those of 124b.

(2R,1'R)-2-(4'-[3''-Oxocyclohexyl]phenyl)propanoic acid (124b).

124b was obtained similarly to 123b as a white crystalline solid in 79% yield, from 132b. It was recrystallized from ethanol/hexane: mp 132-133.5°C; [α]D20 = -48° (c=0.51, EtOH); 1H NMR data of 124b are identical with those of 124c.
(E,2S,1'R) and (Z,2S,1'R) Methyl 2-[4'-{(3''-[hydroxyimino)cyclohexyl]-phenyllpropanoate (135b) and (136b).

To 123b (34 mg, 0.13 mmol) in ether (1 mL) was added an ethereal solution of diazomethane until the yellow colour persisted. A drop of acetic acid was added and the solvent removed in vacuo. The crude keto ester (79 mg, 0.32 mmol) in pyridine (1.25 mL) was treated with hydroxylamine hydrochloride (112 mg, 1.61 mmol) for 16 h at room temperature in a nitrogen atmosphere. The pyridine was removed in vacuo, the residue dissolved in dichloromethane and washed with dilute HCl. The solvent was removed in vacuo to give 135b and 136b which were separated by HPLC.

Data for 135b: $^1$H NMR (300 MHz, CDCl$_3$) δ 1.49 (d, 3H, CH$_3$, J=7.2 Hz), 1.54-1.83 (complex, 4H, H5 and H6), 1.98-2.05 (complex, 2H, H$_{2ax}$ and H$_{4ax}$), 2.57 (d, complex small coupling, 1H, H$_{2eq}$, J=13.6 Hz), 2.75 (tt, 1H, H$_1$, J=11.9 Hz and 3.4 Hz), 3.37 (d, 1H, H$_{4eq}$, J=14.1 Hz), 3.67 (s, 3H, OCH$_3$), 3.71 (q, 1H, CHCH$_3$, J=7.2 Hz), 7.13-7.24 (m, 4H, Ar-H), 7.41 (br s, 1H, NOH).

Data for 136b: $^1$H NMR (300 MHz, CDCl$_3$) δ 1.49 (d, 3H, CH$_3$, J=7.1 Hz), 1.54-2.01 (complex, 4H, H5 and H6), 1.94 (dd, 1H, H$_{2ax}$, J=13.9 Hz and 12.5 Hz), 2.11 (d, 1H, H$_{4ax}$, J=13.6 Hz and 4.5 Hz), 2.44 (d, complex small coupling, 1H, H$_{4eq}$, J=13.5 Hz), 2.73 (tt, 1H, H$_1$, J=11.7 Hz and 3.5 Hz), 3.47 (d, complex small coupling, 1H, H$_{2eq}$, J=13.9 Hz), 3.67 (s, 3H, OCH$_3$), 3.71 (q, 1H, CHCH$_3$, J=7.1 Hz), 7.17-7.25 (m, 4H, Ar-H), 7.33 (br s, 1H, NOH).
2-(3'-Bromophenyl)propene (139).

A dry flask fitted with a pressure equalising dropping funnel and calcium chloride drying tube was charged with anhydrous potassium tert-butoxide (4.14 g, 37 mmol) and ether (100 mL). Methyltriphenylphosphonium iodide (14.95 g, 37 mmol) was added via a powder funnel over 2 min. To the bright yellow suspension was added 3-bromoacetophenone (6.77 g, 37 mmol) in ether (70 mL) over 1 h. The reaction mixture was stirred at room temperature overnight. Hexane (75 mL) was added and the solid material removed by filtration through a pad of Celite. The solvent was removed in vacuo and the residue purified by chromatography with hexane as eluant. Bulb to bulb distillation gave 139 as a colourless oil (5.22 g, 85%): 110-130°/0.5 mm Hg (heated block) (lit94: 217°C/atmospheric pressure); \[^1\text{H} \text{NMR (200 MHz, CDCl}_3\text{)}\] δ 2.12 (s, 3H, CH₃), 5.11 (s, 1H, CH₂), 5.38 (s, 1H, CH₂), 7.15-7.60 (m, 4H, Ar-H).

2-(3'-Benzyphenyl)propene (140).

A dry flask was charged with dichlorobis(triphenylphosphine)palladiumII (1.00 g, 1.42 mmol), THF (120mL) and DIBALH (405 mg, 2.85 mmol). The bromoalkene 139 (5.21 g, 26 mmol) in THF (20mL) was added, followed by benzyl zinc chloride (310 mL of a 0.42 M THF solution, 130 mmol, prepared according to the general procedure on page 173). The reaction mixture was stirred in a nitrogen atmosphere overnight. The solvent was removed in vacuo, the residue dissolved in dichloromethane and washed with water. The resultant emulsion was washed with brine and the organic layer separated. The interface region which remained as an emulsion was diluted with
dichloromethane and filtered through a pad of Celite. The combined organic fractions were dried with magnesium sulphate and the solvent removed \textit{in vacuo}. The residue was purified by chromatography with hexane as eluant to give a colourless oil (7.15 g) which was an inseparable mixture of 1,2-diphenylethane\textsuperscript{95} (1.74 g) and 140 (5.41 g, 100%): \textsuperscript{1}H NMR of 140 (200 MHz, CDCl\textsubscript{3}) \(\delta\) 2.13 (s, 3H, CH\textsubscript{3}), 3.99 (s, 2H, CH\textsubscript{2}), 5.06 (s, 1H, H1), 5.34 (s, 1H, H1), 7.18-7.29 (m, 9H, Ar-H).

(RS)-2-(3'-benzylphenyl)propane-1,2-diol (141a).

According to the method of VanRheenen\textsuperscript{96}, a dry flask was charged with N-methylmorpholine N-oxide (142 mg, 1.06 mmol), anhydrous acetone (0.2 mL) and osmium tetroxide (0.6 mL of a 1.75 M aqueous solution, 4.2 x 10\textsuperscript{-3} mmol). The alkene 140 (containing 1,2-diphenylethane) (196 mg total, 0.68 mmol alkene) in acetone (0.2 mL) was added and the reaction mixture was stirred vigorously in a nitrogen atmosphere overnight. A slurry of sodium hydrosulphite (20 mg) and florosil (68 mg) in water (0.6 mL) was added. The mixture was stirred for 10 min, filtered through a pad of Celite and the solvent removed \textit{in vacuo}. Flash chromatography with ethyl acetate/hexane (50/50, v/v) as eluant gave 141a as a colourless oil (165 mg, 100%) which was bulb to bulb distilled: 140-150\degree C/0.01 mm Hg (heated block); \textsuperscript{1}H NMR (200 MHz, CDCl\textsubscript{3}) \(\delta\) 1.52 (s, 3H, CH\textsubscript{3}), 1.85 (br s, 1H, OH), 2.60 (br s, 1H, OH), 3.62 (d, 1H, CH\textsubscript{2}O, J=10 Hz), 3.79 (d, 1H, CH\textsubscript{2}O, J=10 Hz), 4.01 (s, 2H, CH\textsubscript{2}), 7.22-7.34 (m, 9H, Ar-H).

Found: C 79.11%, H 7.45%, C\textsubscript{16}H\textsubscript{18}O\textsubscript{2} requires C 79.31%, H 7.49%.

(S)-2-(3'-benzylphenyl)propane-1,2-diol (141b).

According to the method of Sharpless\textsuperscript{77}, a mixture of water (127 mL), tert-butyl alcohol (127 mL) and AD-mix-\alpha (35.6 g) was cooled to 0\degree C. 2-(3'-
Benzyl)phenylpropene (containing 1,2-diphenylethane) (6.9 g total, 25.48 mmol alkene) was cooled to 0°C and added to the flask. The reaction mixture was stirred vigorously at 0°C for 10 h then allowed to warm to room temperature overnight. Sodium sulphite (38.2 g) was added and the mixture was stirred for 40 min. Dichloromethane (250 mL) was added, the layers separated and the aqueous phase extracted with dichloromethane (2 x 100 mL) (a third extraction contained no product). The organic fractions were combined, dried with magnesium sulphate and the solvent removed in vacuo to give a yellow oil which was purified by chromatography with a gradient of ethyl acetate/hexane as eluant. 141b was obtained as a colourless oil (4.96 g, 80%). A sample was bulb to bulb distilled: 170-180°C/0.02 mm Hg (heated block); [α]D²⁰ = +2.5° (c=2.35, EtOH); 1H NMR data are identical with those of the racemate 141a. The optical purity of 141b was determined by NMR analysis of the acetate derivative 144b with the optically active shift reagent tris[3-(heptafluoropropylhydroxymethylene)-(+)camphorato]europium(III) derivative and found to be 88%. e.e. (RS)-2-(3'-Benzy1phenyl)-2-hydroxypropyl acetate (144a).

To 141a (20 mg, 0.08 mmol) in pyridine (0.5 mL) was added acetic anhydride (50 μL) and the reaction mixture was stirred at room temperature for 1.5 h. Dichloromethane was added to the mixture and it was washed with water, 5% HCl until acidic, 5% sodium bicarbonate solution and water. Removal of the solvent in vacuo and flash chromatography with hexane/ethyl acetate (75/25, v/v) as eluant gave 144a as a colourless oil (23 mg, 100%): 1H NMR (300 MHz, CDCl₃) δ 1.54 (s, 3H, CH₃), 2.01 (s, 3H, COCH₃), 3.99 (s, 2H, ArCH₂), 4.18 (d, 1H, OCH₂, J=11.3 Hz), 4.28 (d, 1H, OCH₂, J= 11.3 Hz), 7.16-7.32 (m, 9H, Ar-H).
(S)-2-(3'-Benzylphenyl)-2-hydroxypropyl acetate (144b).

The optically active compound 144b was obtained similarly to the racemate 144a, from 141a. 1H NMR data of 144b are identical with those of 144a.

(S)-2-(3'-Benzylphenyl)propanol (142c).

To the diol 141b (39 mg, 0.16 mmol) in ethanol was added an excess of W4 Raney nickel. The reaction mixture was stirred at room temperature in a hydrogen atmosphere for 60 h. The hydrogen was cautiously replaced with air and the mixture filtered through a pad of Celite under a blanket of nitrogen. Removal of the solvent in vacuo and flash chromatography with hexane/ethyl acetate (70/30, v/v) afforded 142c (approximately 42%), (R)-2-[3'-(cyclohexylmethyl)-phenyl]propanol (147b, approximately 26%) and (S)-2-[3'-(cyclohexyl-methyl)phenyl]propane-1,2-diol (148b, approximately 32%). 1H NMR data of 142c are identical with those of 142a.

Data for 147b: 1H NMR (200 MHz, CDCl3) δ 0.85 - 1.78 (complex, 12H, ring Hs and OH) 1.26 (d, 3H, CH3, J=7.0 Hz), 2.47 (d, 2H, ArCH2, J=7.0 Hz) 2.92 (sextet, 1H, CHCH3, J=7.0 Hz), 3.72 (t, 2H, CH2O, J=6.9 Hz), 7.00 - 7.27 (m, 4H, Ar-H).

Data for 148b: 1H NMR (200 MHz, CDCl3) δ 0.85 - 1.85 (complex, 13H, ring Hs and OHs), 1.55 (s, 3H, CH3), 2.51 (d, 2H, ArCH2, J=7 Hz), 3.65 (dd, 1H, CH2OH, J=11 Hz and 7 Hz), 3.82 (dd, 1H, CH2OH, J=11 Hz and 4 Hz), 7.02 - 7.28 (m, 4H, Ar-H).
(RS)-2-(3'-Benzylphenyl)propanol (142a).

To 141a (1.00 g, 4.13 mmol) in ethanol (50 mL) was added palladium on carbon (10%, 1.00 g) and perchloric acid (0.75 mL of a 0.7 M aqueous solution, 0.5 mmol). The mixture was stirred in a hydrogen atmosphere for 20 h, the hydrogen was cautiously replaced with air and 5% sodium bicarbonate solution (1.5 mL) was added. The mixture was filtered through a pad of Celite and the solvent removed in vacuo to give a mixture of 142a and 2-(3'-benzyl)phenylpropane. Flash chromatography with hexane/ethyl acetate (70/30, v/v) as eluant gave 142a as a colourless oil (450 mg, 60%). \( ^1H \text{NMR (200 MHz, CDCl}_3 \):} \delta 1.26 (d, 3H, CH\textsubscript{3}, J=7.0 Hz), 1.58 (br s, 1H, OH), 2.92 (sextet, 1H, CHCH\textsubscript{3}, J=7.0 Hz), 3.69 (d, 2H, CH\textsubscript{2}O, J=6.9 Hz), 3.99 (s, 2H, CH\textsubscript{2}), 7.02-7.30 (m, 9H, Ar-H).

Found: C 85.17%, H 7.99%, C\textsubscript{16}H\textsubscript{18}O requires C 84.91%, H 8.02%.

(R)-2-(3'-Benzylphenyl)propanol (142b).

The optically active compound 142b was obtained similarly to the racemate 142a as a colourless oil, from 141b. \([\alpha]D\textsuperscript{20}= -5.7^\circ\text{ (c=0.88, EtOH)}\); \(^1H\text{ NMR data of 142b are identical with those of 142a. The optical purity of 142b was determined by NMR analysis of the Mosher esters 152b and 153b and found to be 83% e.e.}

(1S,2''R) - and (1R,2''R)-2-(3'-Benzylphenyl)propyl \(\alpha\)-methoxy \(\alpha\)-trifluoromethylphenylacetate (152b and 153b).

Following the procedure of Hassner\textsuperscript{99}, a flask was charged with 142a (52 mg, 0.23 mmol), dichloromethane (1.1 mL), dicyclohexylcarbodiimide (48 mg, 0.23 mmol), dimethylaminopyridine (5 mg, 0.02 mmol) and (R)-(+-)\(\alpha\)-methoxy-\(\alpha\)-(trifluoromethyl)phenylacetic acid (50 mg, 0.22 mmol). The reaction mixture was stirred in a nitrogen atmosphere overnight, diluted with dichloromethane
(5 mL), washed twice with water, twice with 5% acetic acid then twice with water. The solution was dried with magnesium sulphate and the solvent was removed *in vacuo*. Flash chromatography with hexane/ethyl acetate (95/5, v/v) as eluent gave a 1:1 mixture of 152b and 153b as a colourless oil (75 mg, 77%).

Data for 152b: $^1$H NMR (300 MHz, CDCl$_3$) δ 1.27 (d, 3H, CH$_3$), 3.15 (sextet, 1H, CHCH$_3$, J=6.9 Hz), 3.39 (m, 3H, OCH$_3$, J=1.0 Hz), 3.93 (s, 2H, ArCH$_2$), 4.29 (dd, 1H, OCH$_2$, J=7.3 Hz and 10.7 Hz), 4.48 (dd, 1H, OCH$_2$, J=6.8 Hz and 10.7 Hz), 7.03-7.37 (m, 9H, ArH).

Data for 153b: $^1$H NMR (300 MHz, CDCl$_3$) δ 1.27 (d, 3H, CH$_3$), 3.15 (sextet, 1H, CHCH$_3$, J=6.9 Hz), 3.36 (m, 3H, OCH$_3$, J=1.0 Hz), 3.93 (s, 2H, ArCH$_2$), 4.30 (dd, 1H, OCH$_2$, J=6.8 Hz and 10.7 Hz), 4.47 (dd, 1H, OCH$_2$, J=7.6 Hz and 10.7 Hz), 7.03-7.37 (m, 9H, ArH).

(R)-2-(3'-Benzylphenyl)propyl 3,5-dinitrobenzoate (157b).

To 142b (410 mg, 1.81 mmol) in dichloromethane (7 mL) was added pyridine (1 mL) and 3,5-dinitrobenzoyl chloride (475 mg, 2.06 mmol). The reaction mixture was stirred in a nitrogen atmosphere overnight then washed with water. The aqueous phase was extracted with dichloromethane, the organic fractions combined, dried with magnesium sulphate and the solvent removed *in vacuo*. Flash chromatography with hexane/ethyl acetate (90/10, v/v) as eluant gave 157b as a pale yellow oil (615 mg, 81%), which crystallised upon addition of ether (3 mL) and storage at -20°C overnight. Two recrystallisations from ether gave optically pure material (as determined by NMR analysis of the Mosher ester derivatives 152b and 153b) (428 mg): mp 65-66°C; $^1$H NMR (300 MHz, CDCl$_3$) δ 1.40 (d, 3H, CH$_3$), 3.28 (sextet, 1H, CHCH$_3$, J=7.0 Hz), 3.97 (s, 2H,
ArCH₂), 4.49 (d, 2H, OCH₂, J=7.3 Hz), 7.07-7.31 (m, 9H, ArH), 9.02 (m, 2H, ArNO₂, J=1.7 Hz), 9.18 (m, 1H, ArNO₂, J=1.9 Hz); \( \nu \text{max} (\text{CH}_2\text{Cl}_2) \) 1740, 1640, 1610, 1555, 1350 cm\(^{-1}\); \( [\alpha]_D^{20}= -28^\circ \) (c=1.70, CH₂Cl₂).

(R)-2-(3'-Benzylphenyl)propanol (142b) via hydrolysis of 3,5-dinitrobenzoate (157b).

To 157b (428 mg, 1.02 mmol) in dichloromethane (6 mL) and methanol (9 mL) was added potassium carbonate (400 mg) and the reaction mixture was stirred overnight. The solid was removed by filtration and the solvent removed \textit{in vacuo}. Flash chromatography with hexane/ethyl acetate (80/20, v/v) as eluant gave 142b (193 mg, 84%). The optical purity of 142b was determined by NMR analysis of the Mosher esters 152b and 153b and found to be 99%+ e.e.

(S)-2-(3'-Benzoylphenyl)propanoic acid (4b) via permanganate oxidation.

Following the procedure of Comisso\(^{100}\), sodium hydroxide (1.4 mL of a 1 M aqueous solution) and potassium permanganate (266 mg, 1.68 mmol) in water (7 mL) were added to 142b (71 mg, 0.31 mmol). The reaction mixture was stirred vigorously at room temperature for 6 h, cooled to 0°C and conc. sulphuric acid (0.27 mL) was added. Aqueous sodium sulphite was added until the purple colour disappeared and the aqueous phase was extracted five times with dichloromethane. The organic phase was extracted with 1 M sodium hydroxide solution then the aqueous phase acidified with conc. hydrochloric acid and extracted with dichloromethane. The solution was dried with magnesium sulphate and the solvent was removed \textit{in vacuo}, to give an inseparable mixture of 4b and 3-benzoylbenzoic acid (156).
(S)-2-(3'-Benzylphenyl)propanoic acid (158b).

According to the method of Sharpless\textsuperscript{84}, 142b was dissolved in carbon tetrachloride (5.6 mL), acetonitrile (5.6 mL) and water (8.4 mL). Ruthenium trichloride hydrate (20 mg) and sodium metaperiodate (916 mg, 4.3 mmol) were added and the mixture stirred vigorously at room temperature for 1.25 h. Dichloromethane and water were added then the organic phase was washed with saturated sodium bicarbonate solution. The aqueous phase was acidified with HCl and extracted with dichloromethane. Removal of the solvent \textit{in vacuo} and flash chromatography with ethyl acetate/hexane (50/50, v/v) as eluant gave 158b as a colourless oil (100 mg, 59\%): \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \(\delta\) 1.49 (d, 3\H, CH\textsubscript{3}, J=7.1 Hz), 3.69 (q, 1\H, CHCH\textsubscript{3}), 3.97 (s, 2\H, CH\textsubscript{2}Ar), 7.05 - 7.33 (m, 9\H, Ar-H) (NMR data is in agreement with lit.\textsuperscript{100} values).
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