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

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"-{hydoxyimino}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.

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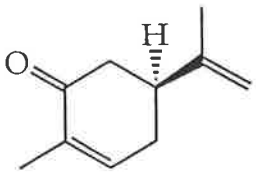
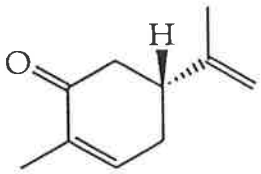
7. Enantioselective Syntheses of 2-Arylpropanoic Acid Non-steroidal Anti-inflammatory Drugs and Related Compounds, D.P.G. Hamon, R.A. Massy-Westropp and J.L. Newton, full paper submitted, April 1995.

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[1].

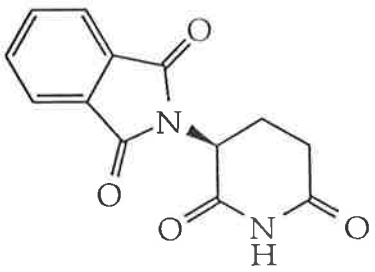


(S)-carvone

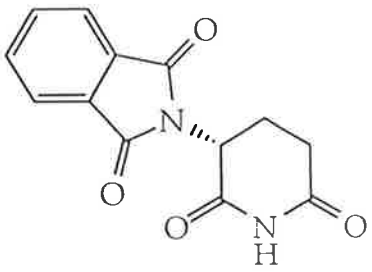


(R)-carvone

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[2]. 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[3].

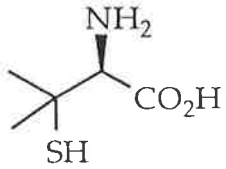


(S)-thalidomide

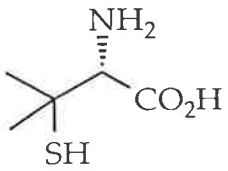


(R)-thalidomide

(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[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.



(S)-penicillamine

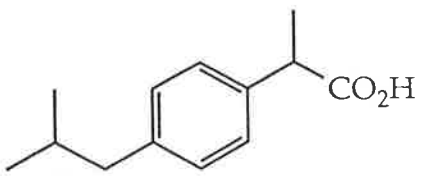


(R)-penicillamine

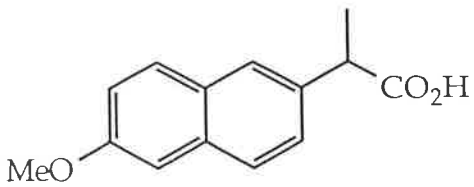
These examples serve to highlight what is now a well established fact - that enantiomers of chiral drugs can differ enormously in their pharmacological activity. They may be absorbed, activated or degraded at different rates, one may be inactive, one may be toxic, or the two may have unequal degrees 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[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[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[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.

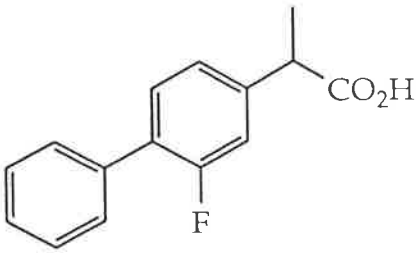
There is also a trend towards "racemic switches", single enantiomers redeveloped from chiral drugs originally marketed as racemates[5]. Although there is no regulatory pressure for racemic switches, there are commercial advantages and these are being exploited by many pharmaceutical companies. Compounds 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[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).



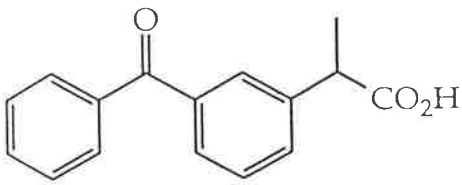
(1)



(2)



(3)



(4)

The mode of action of these drugs is that by cyclooxygenase inhibition they stop the arachidonic acid cascade to prostaglandins and thromboxane A2 which are

responsible for the inflammation mechanism[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*[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.

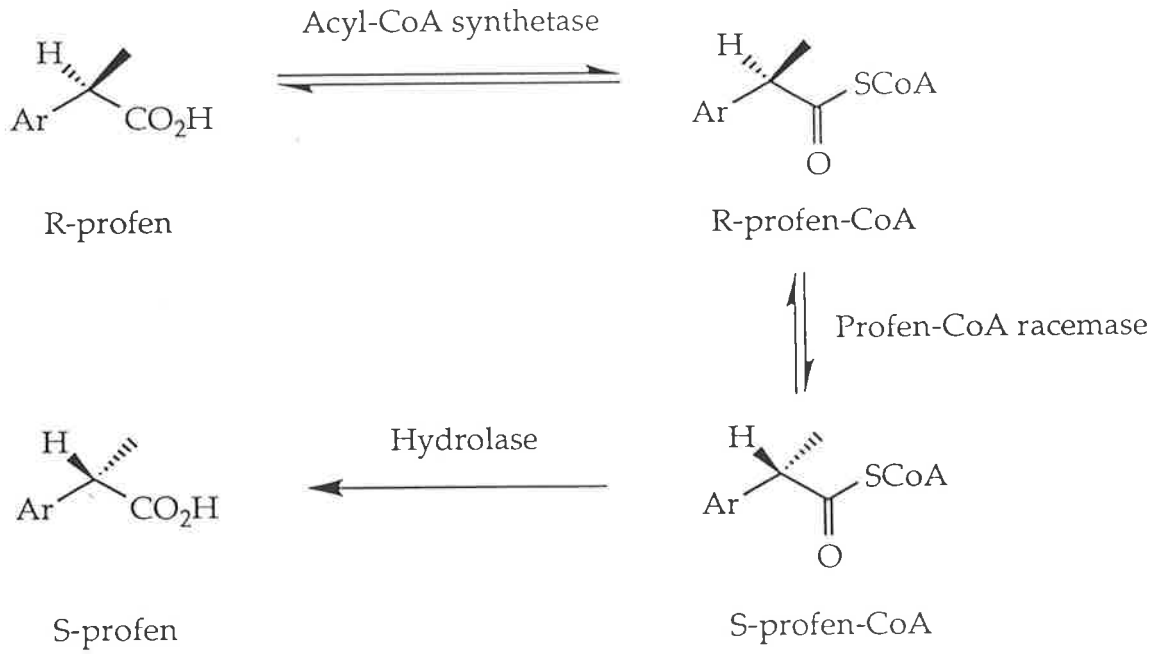


Figure 1

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.

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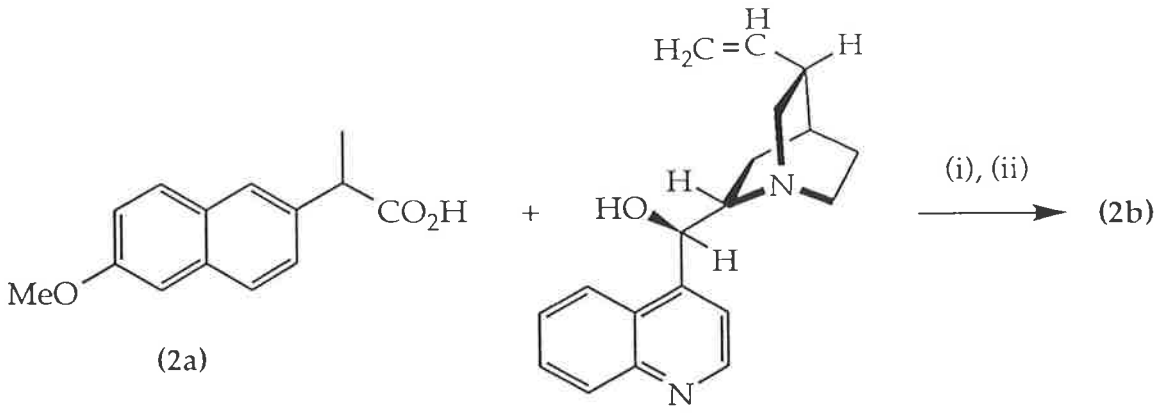
* Throughout this thesis, the letter "**a**" following a compound number denotes the racemic form. Similarly, "**b**" and "**c**" denote the enantiomers.



(i) recrystallisation
(ii) HCl

Figure 2

Many of the more recent resolutions have been enzymatic. They may employ either stereoselective ester formation or hydrolysis[10-13]. For example, Sheldon et al[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.* of 96%, which could be hydrolysed without racemisation. These enzymatic resolutions are examples of kinetic resolution in which the diastereomeric transition state

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* 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.).

Equation **1**: $$\% \text{ e.e.} = \frac{x - y}{x + y} \times 100$$

energies are sufficiently different to allow a substantial difference in rates of reaction.

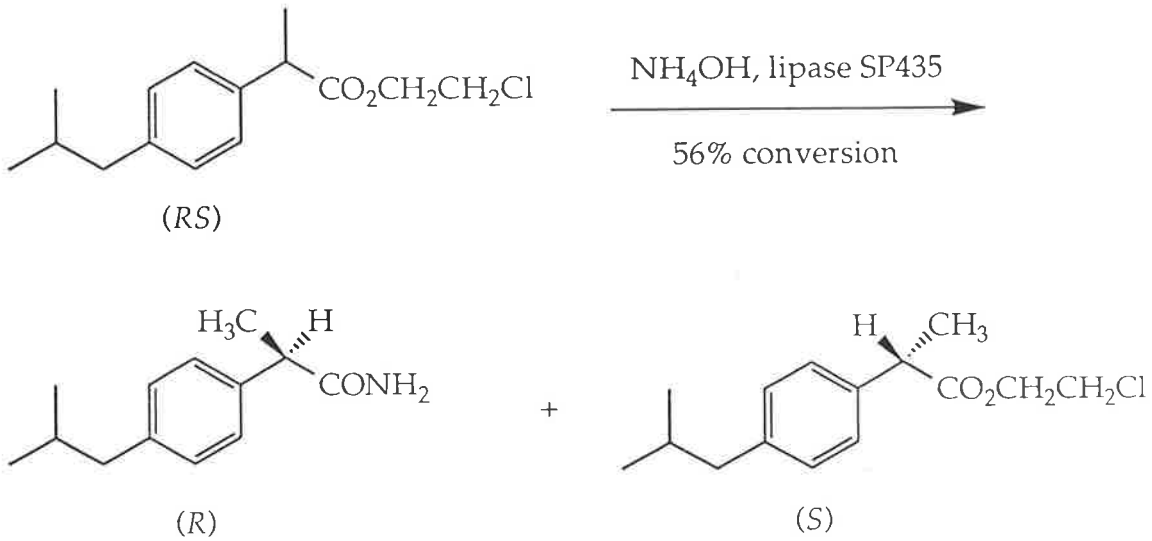


Figure 3

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):

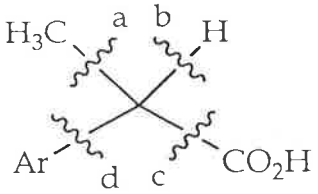


Figure 4

a) The methyl group could be introduced into an arylacetic acid derivative, for example by alkylation

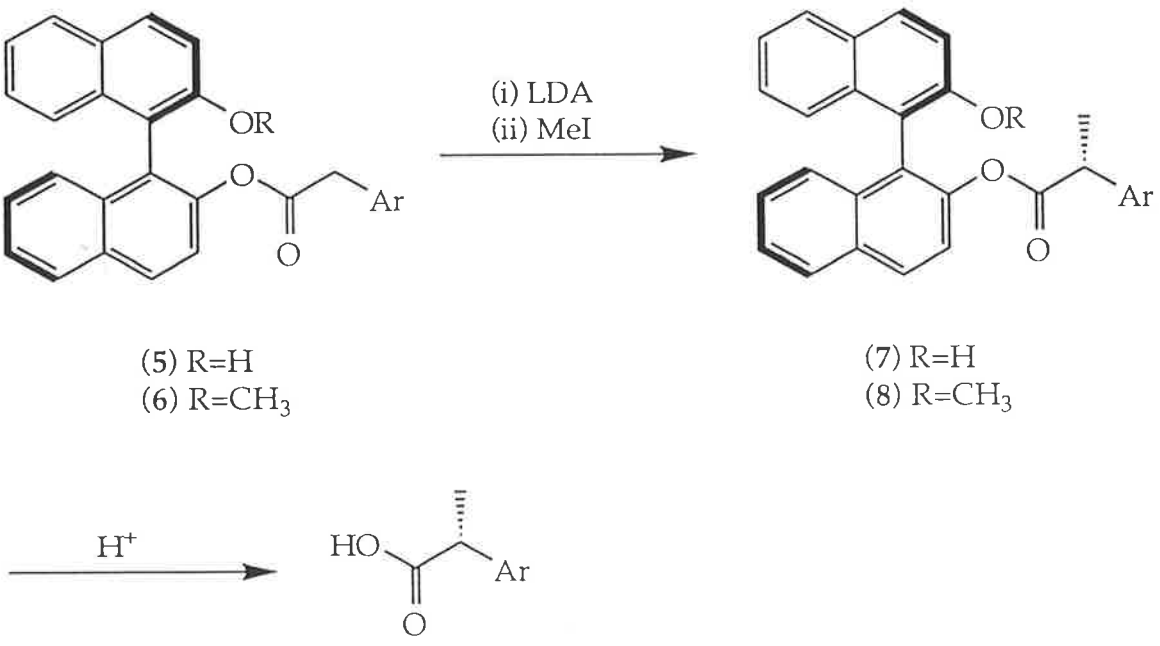
b) The C-H bond could be formed by various reactions, for example by stereoselective protonation of a ketene or addition of hydrogen

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[14] have stereoselectively methylated binaphthyl esters of arylacetic acids. The corresponding 2-arylpropanoic acids were then obtained by acid hydrolysis (figure 5).



(5) R=H
(6) R=CH_3

(7) R=H
(8) R=CH_3

Figure 5

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.

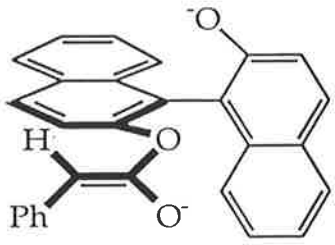


Figure 6a

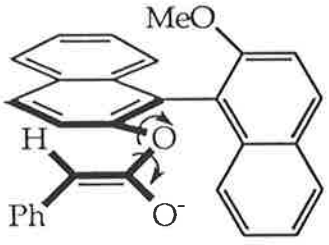
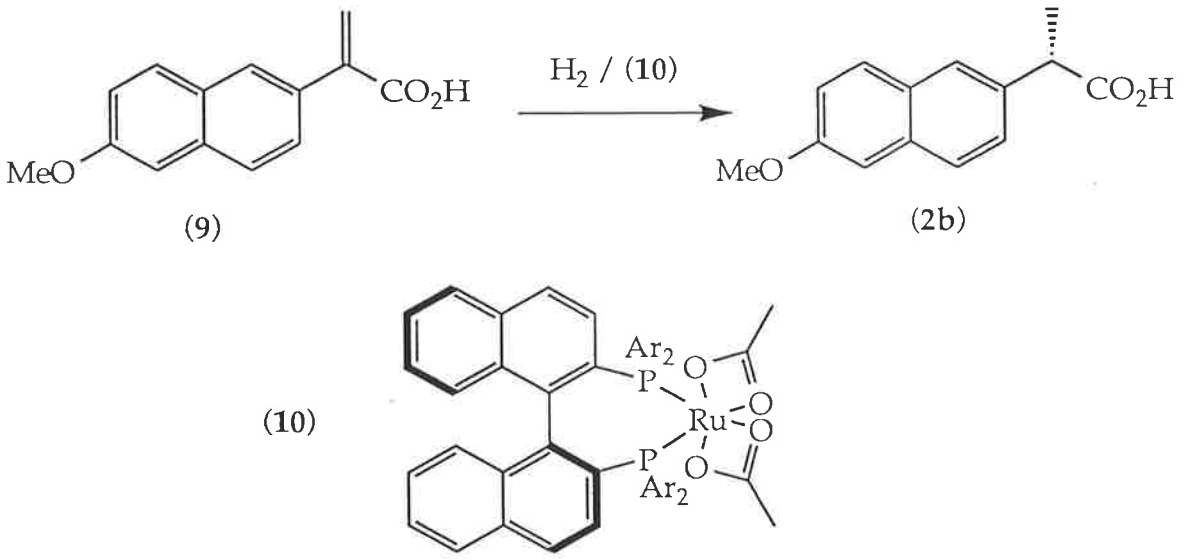


Figure 6b

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[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[8]. 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.



(9) (2b)

(10)

Figure 7

Enantioselective protonation of a prochiral ketene intermediate as a route to these compounds has been explored by several groups[16-18]. Larsen et al[16] 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).

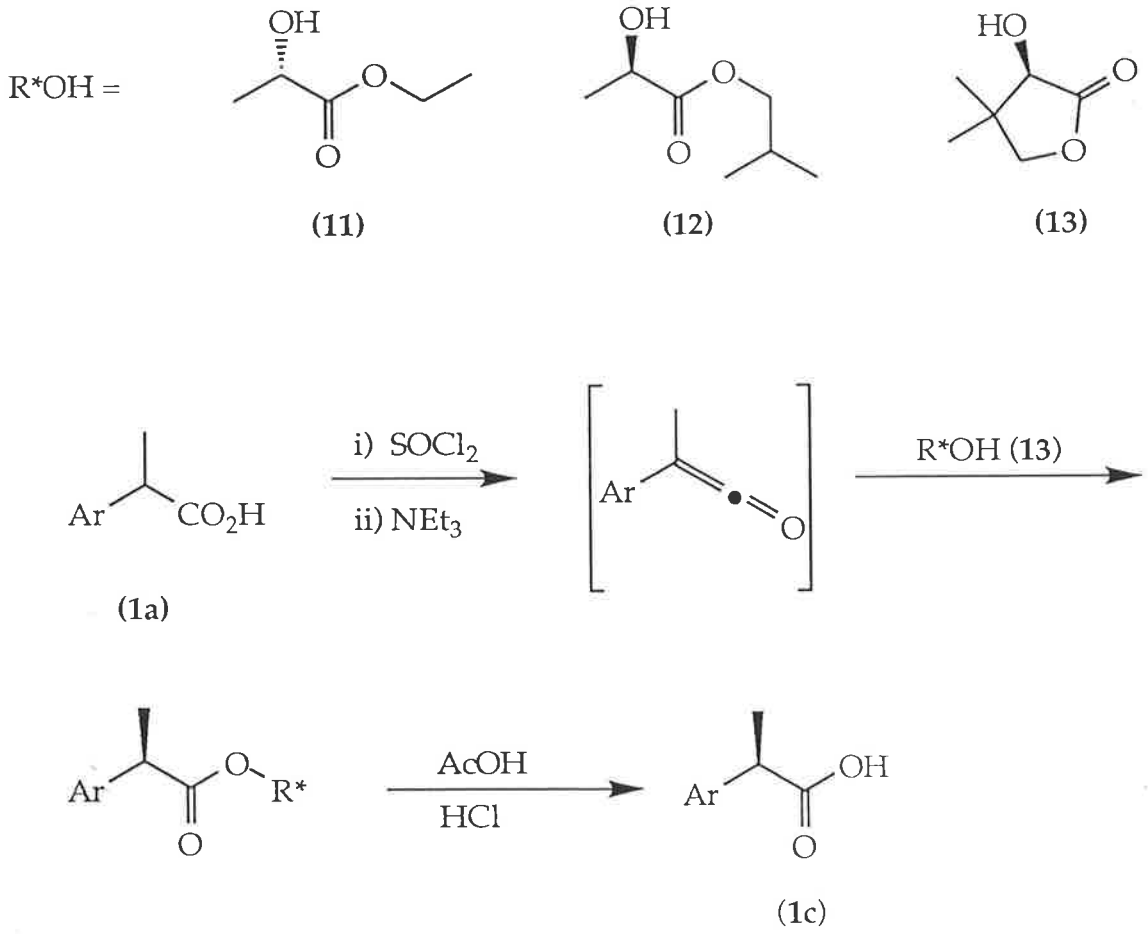


Figure 8

More recently Calmes et al[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[19] and hydrocarboxylation[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[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 ($PdCl_2$) catalysed hydrocarboxylation reaction (figure 9). The effect of the ratio of substrate : ligand : $PdCl_2$ 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 <10% optical purity, whereas *(R)*- and *(S)*-1,1'-binaphthyl-2,2'-diyl hydrogen phosphate (BNPPA) gave the optimal results quoted above.

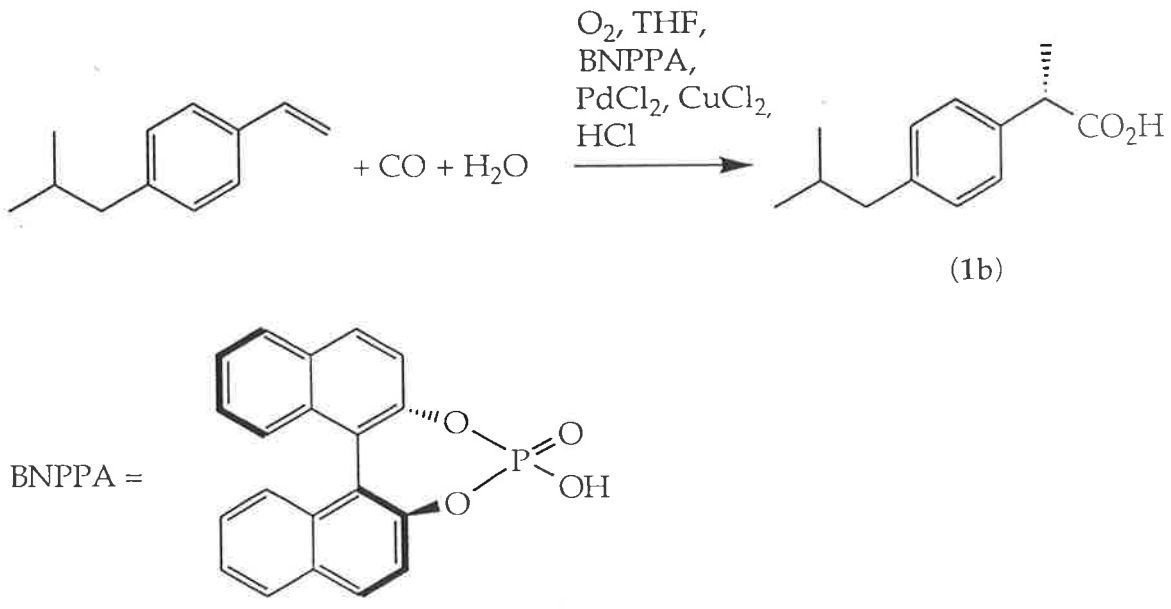


Figure 9

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[21], who treated *(E)*-3-penten-2-yl pivalate with 6-methoxy-2-naphthylmagnesium bromide in the presence of the chiral catalyst $NiCl_2$[(-)-(2*S*,3*S*)-2,3-bis(diphenylphosphino)butane] (abbreviated as $NiCl_2$[(*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, $PdCl_2$[(*S*,*S*)-Chiraphos] was found to be totally ineffective for the bond formation.

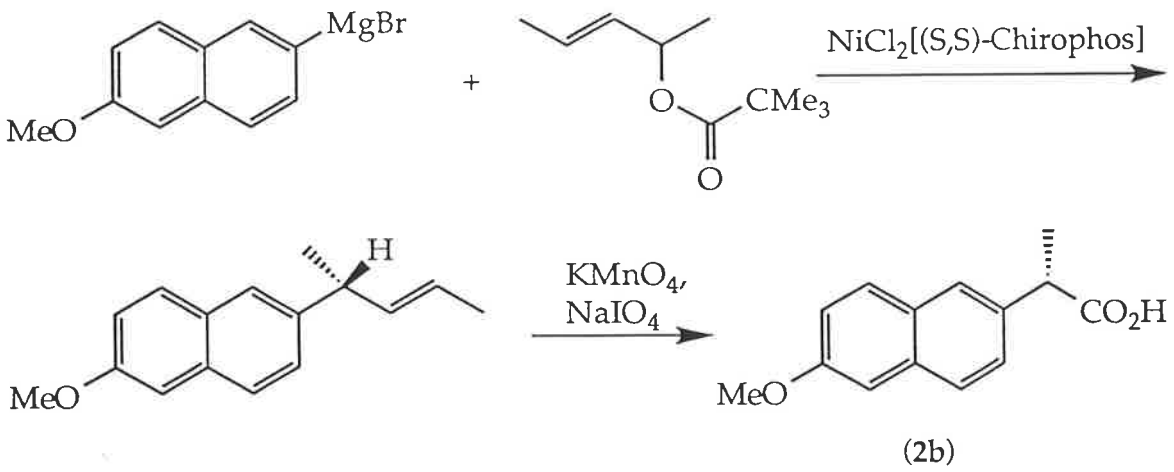
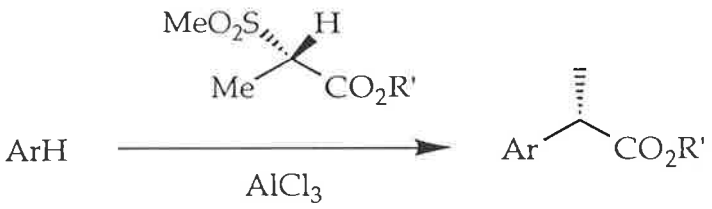


Figure 10

Addition in the opposite sense has been demonstrated by Piccolo[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).



R' = Me or Et
Ar = Ph, $PhCH_3$, PhCl or naphthyl

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 ibuprofen[23].

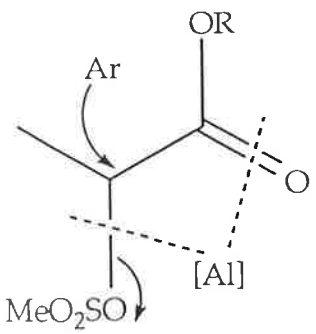
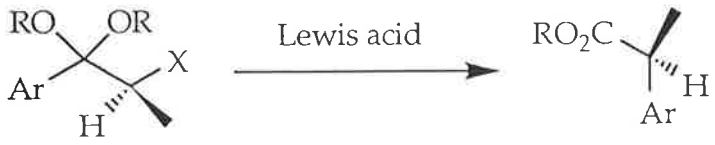


Figure 12

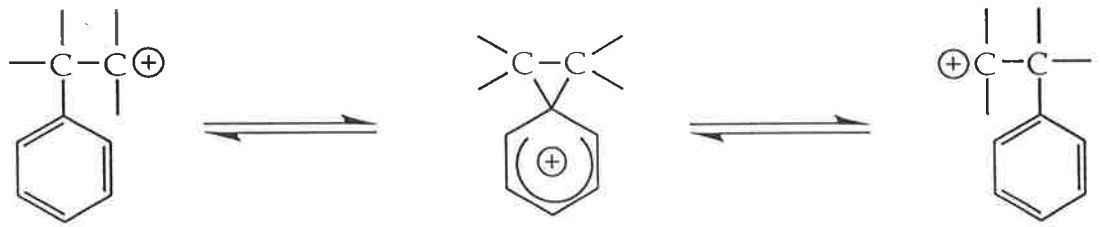
As well as asymmetric syntheses based on formation of one of the four bonds to the chiral carbon, there are several publications[24-32] concerning stereoselective rearrangement of acetals of the general type **14** where X is a leaving group, often a halogen. Treatment of the acetal with a Lewis acid facilitates the migration of the aryl group to the stereogenic carbon (figure 13). These reactions proceed with inversion of configuration.



14

Figure 13

The mechanism of this type of reaction is thought to be similar to that of the analogous electrophilic rearrangement of β-halo arylalkanes. The evidence supports a mechanism which proceeds via a cyclopropane-like intermediate[24] (15) (figure 14).



(15) **(16)**

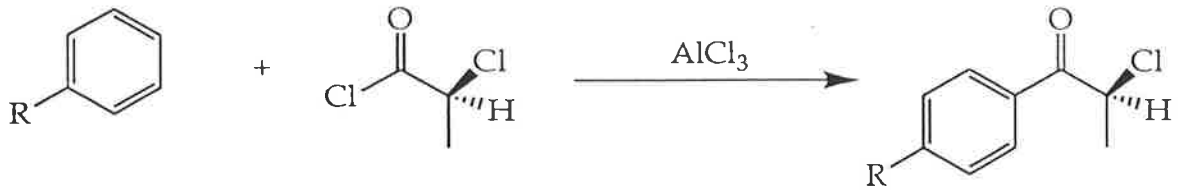
Figure 14

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

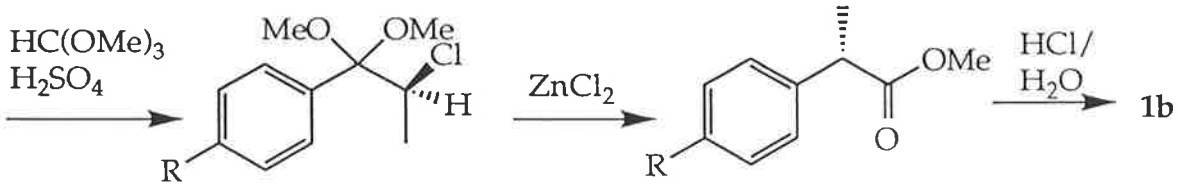
additional support by estimating the bridged structure **15** to be 35-50 kcal/mol more stable than any possible conformations of the open chain species **16**. When there is a carbonyl group in the benzylic position, the sp^2 nature of the carbonyl carbon inhibits the formation of the cyclic transition state, hence the non-occurence 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).



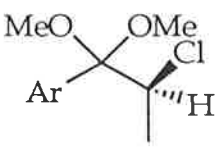
(17)

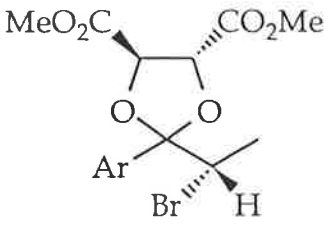


(18) (19)

R = isobutyl

Figure 15





(20) (21)

Ar = 6-methoxy-2-naphthyl

Figure 16

Another approach is illustrated by the enantiodivergent synthesis of Takano et al[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[34] of *(E)*-cinnamyl alcohol.

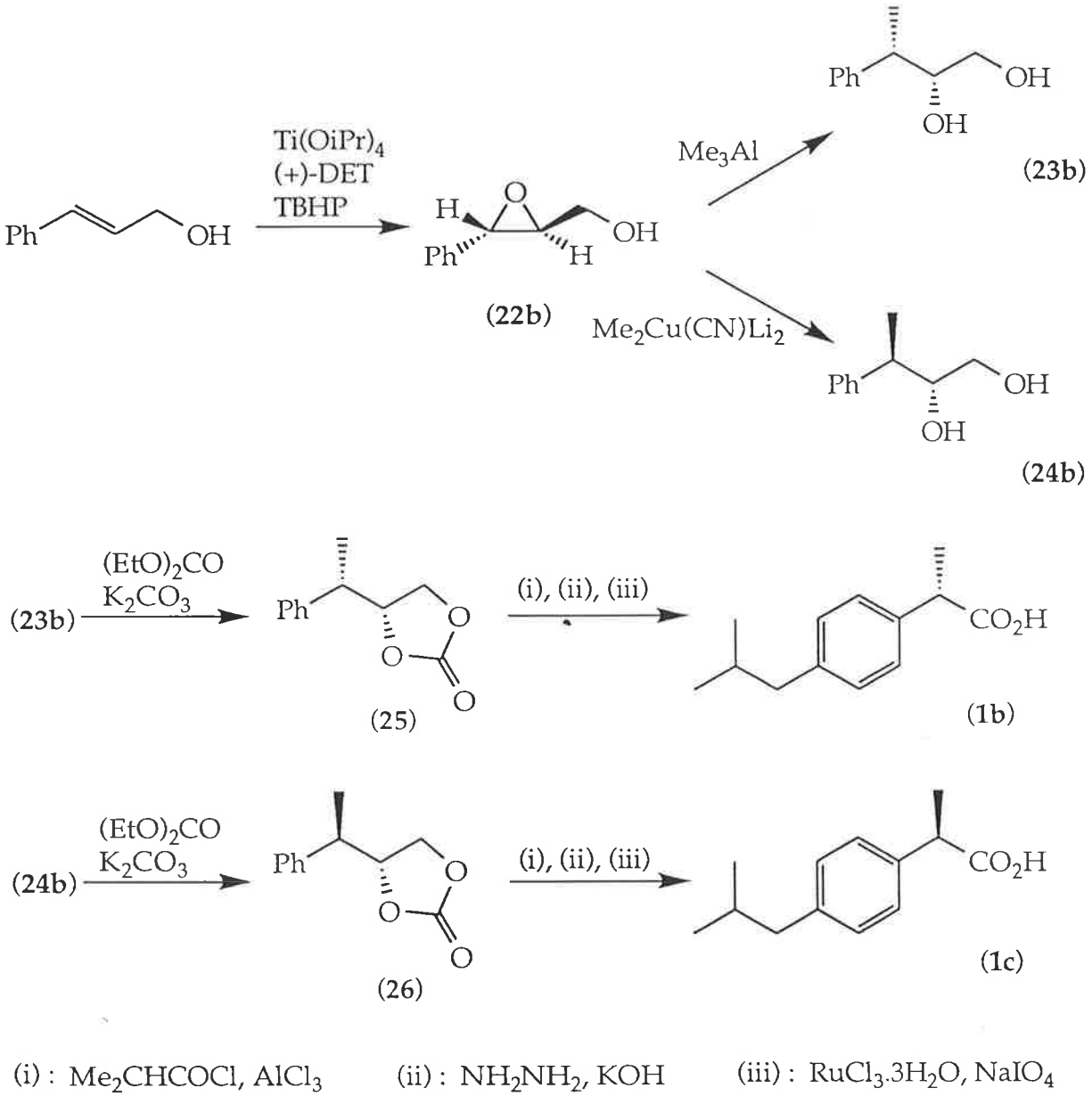


Figure 17

The epoxide could be regioselectively and stereospecifically opened by either AlMe3 to afford (2*R*,3*S*)-1,2-glycol (**23b**) or the higher order organocuprate Me2Cu(CN)Li2 to afford (2*R*,3*R*)-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[35,36] is outlined in figure 18.

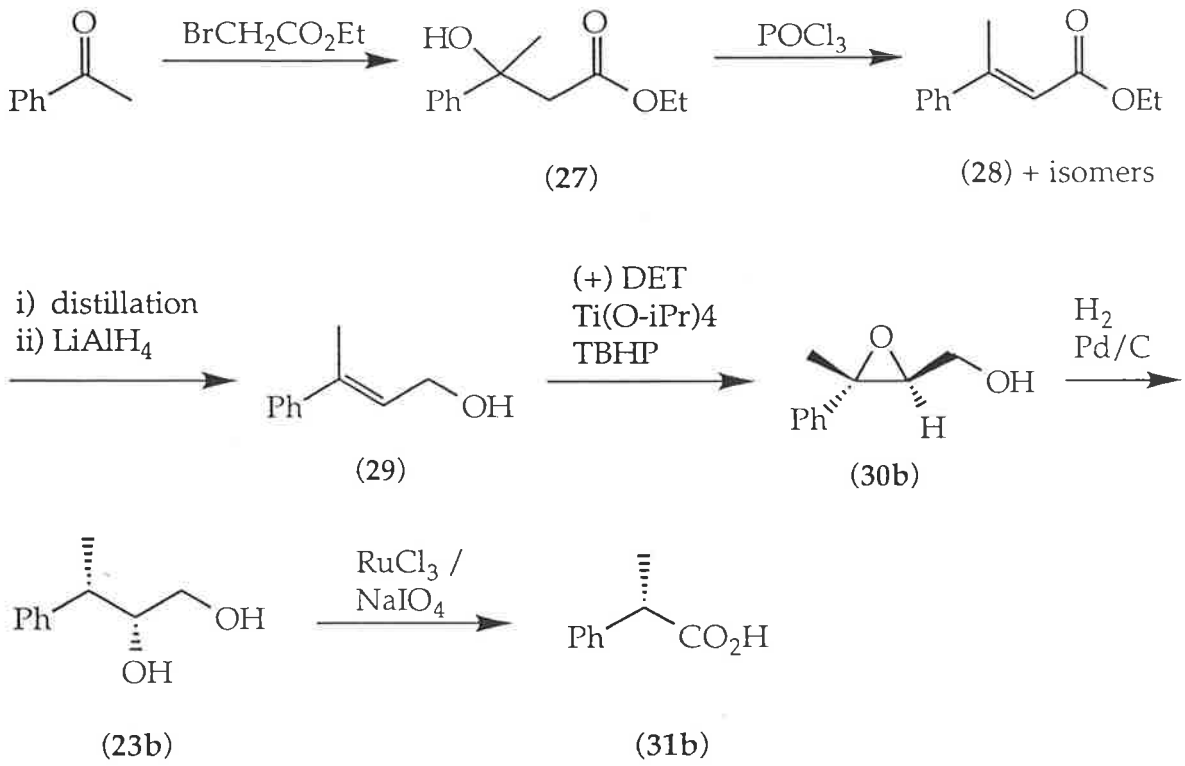
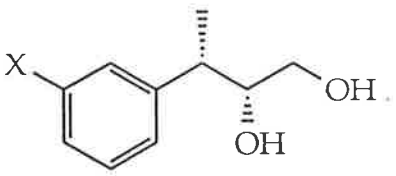


Figure 18

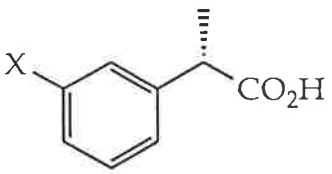
A Reformatsky reaction between acetophenone and ethyl bromoacetate yielded ethyl 3-hydroxy-3-phenylbutanoate **27**, which was dehydrated with phosphorous oxychloride to give a mixture of alkenes. Fractional distillation furnished the *(E)*-ester 28 which was reduced with lithium aluminium hydride

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.

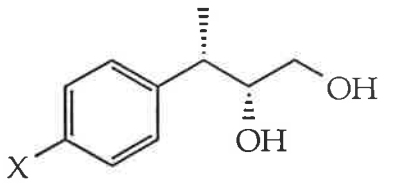
This thesis discusses a range of chemical methods explored to synthesise the analogous halogen substituted intermediates **32b-35b** and their conversion to various substituted 2-arylpropanoic acids.



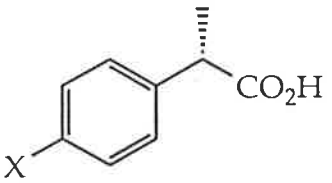
(32b)



(34b)



(33b)



(35b)

X = halogen

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[37]. Probably the most widely used of these methods is the Sharpless epoxidation[34,38], 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.

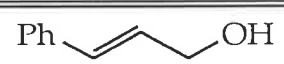
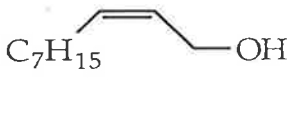
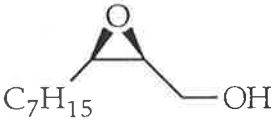
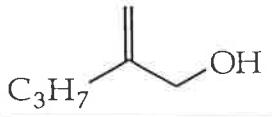
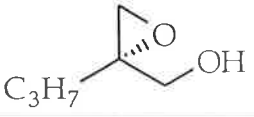
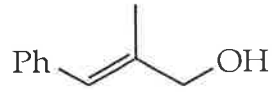
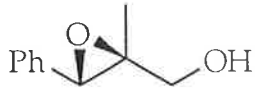
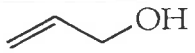
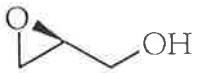
Allylic alcohol	Product	Yield %	e.e. %
		89	>98
		74	86
		88	95
		79	>98
		65	90

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 plane[38].

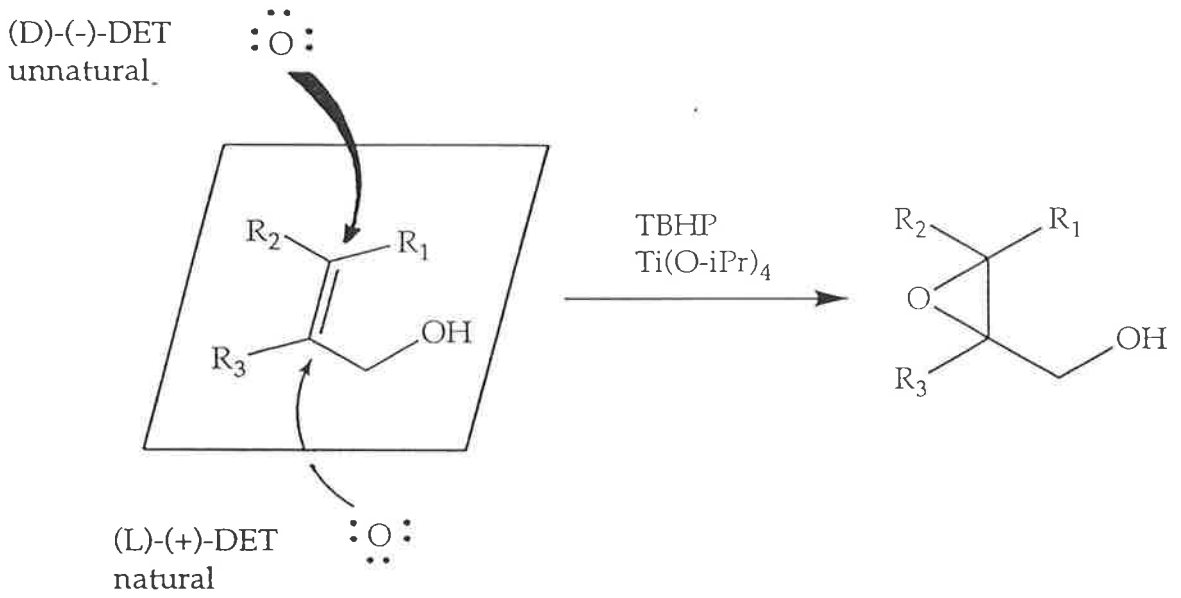
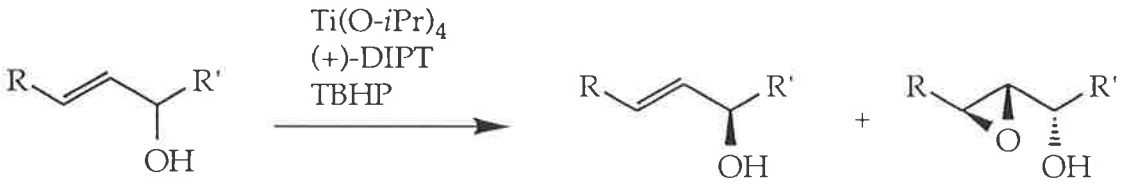


Figure 19

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 alcohols[34,39] (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 and R' = alkyl

Figure 20

The reaction requires four essential components: (+) or (-) diethyl tartrate (DET) (or diisopropyl tartrate (DIPT)), titanium tetraisopropoxide (Ti(O*i*-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(O*i*-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)(O*i*-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)(O*t*-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).

Figure 21a

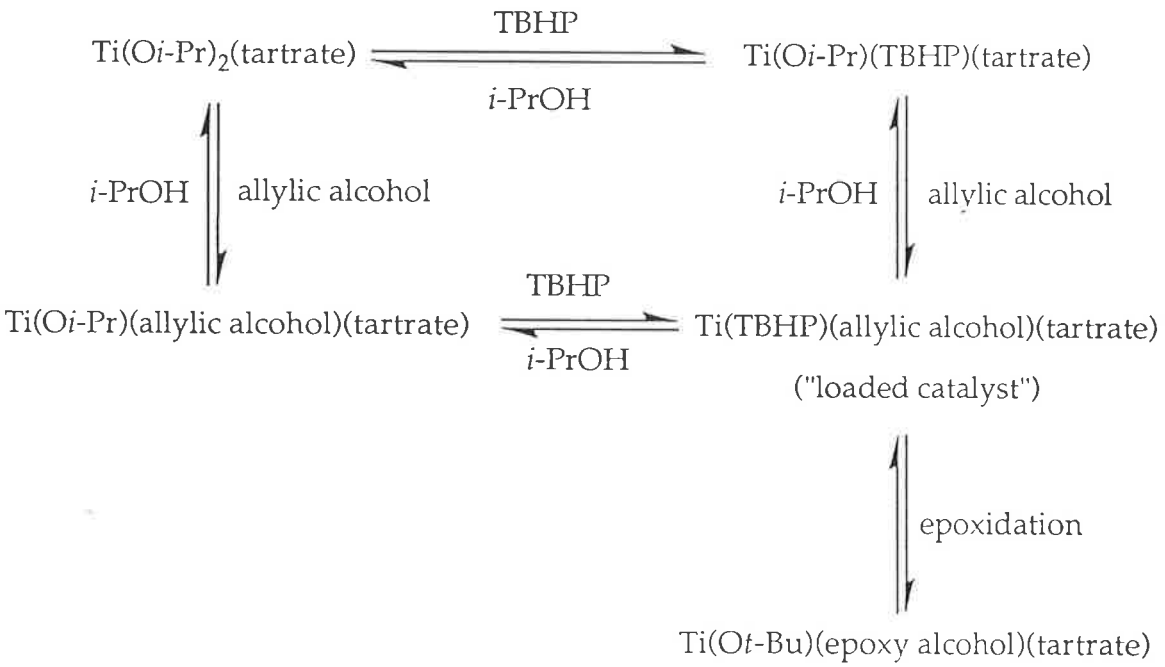


Figure 21b

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, $Ti_2(tartrate)_2(OR)_4$ (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.

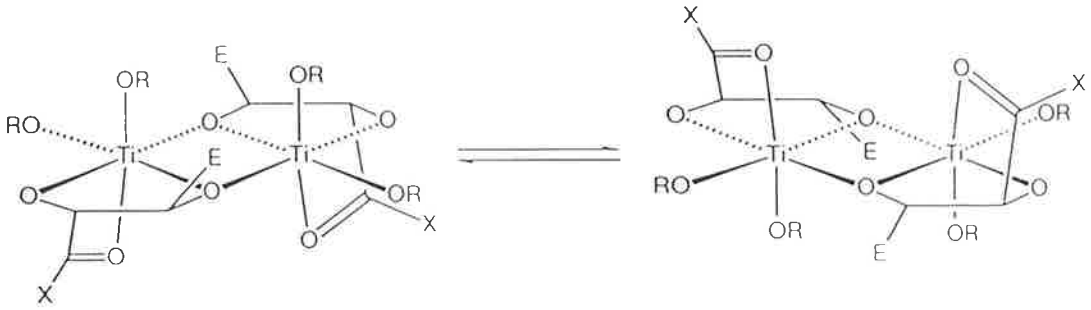


Fig 22

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].

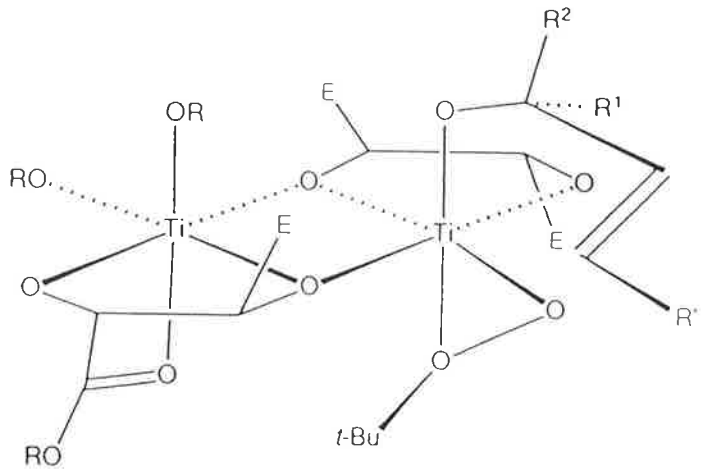
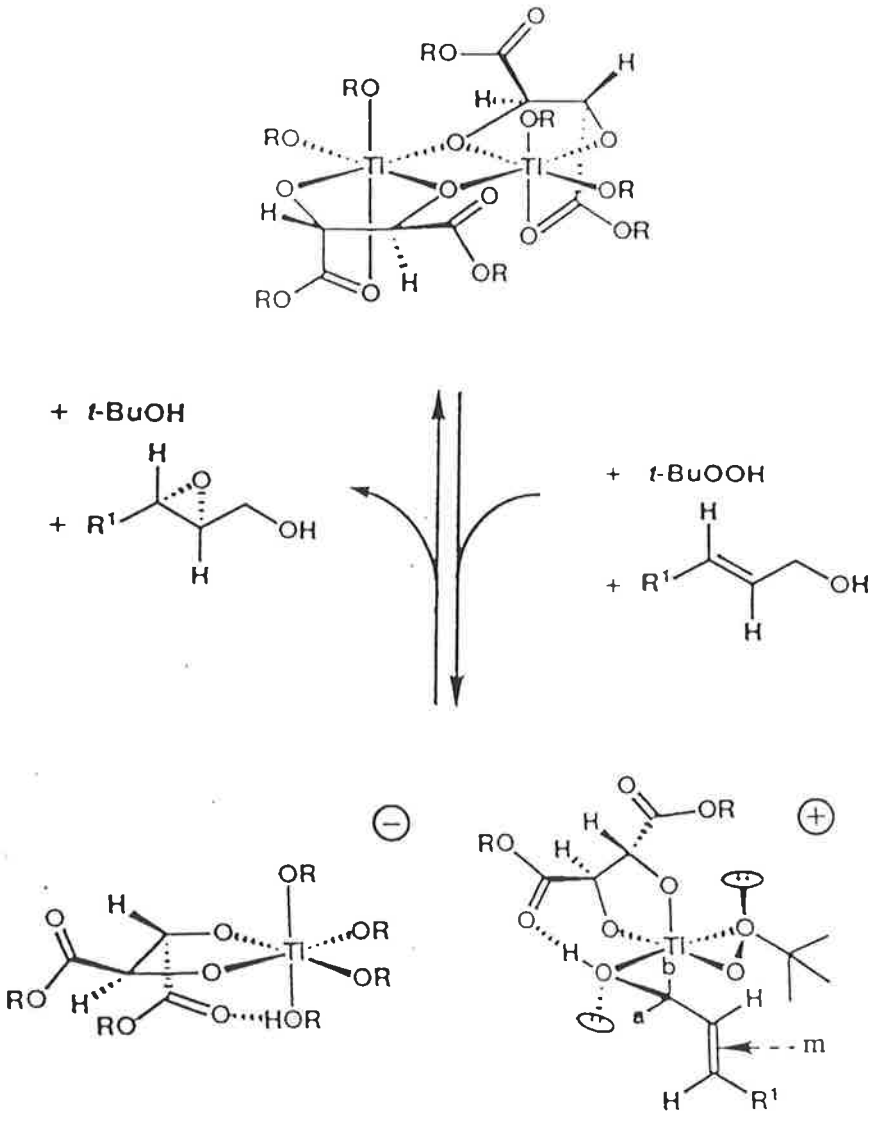


Fig 23

In contrast, Corey's[43] 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 peroxy 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 peroxy 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.



(36)

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[44,45]. For example Esashi et al[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) .

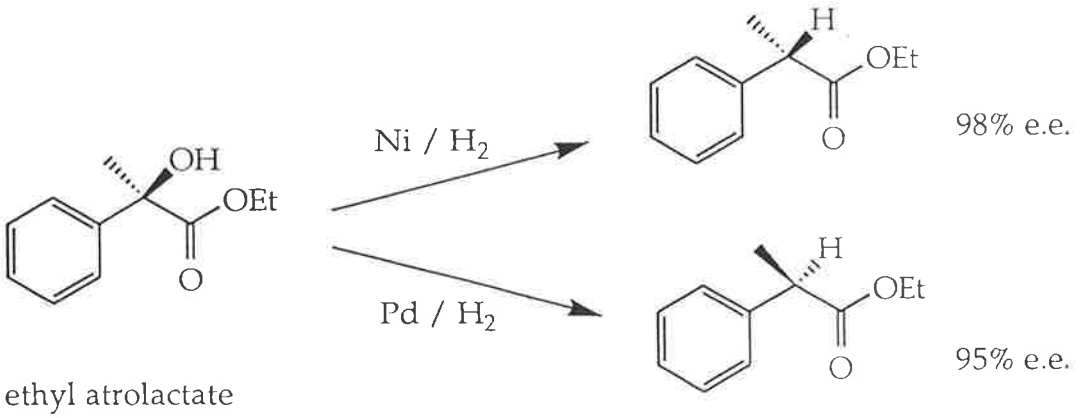


Figure 25

Several mechanisms have been proposed to account for these observations[45], with the most widely accepted being that of Esashi[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 sp^2 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).

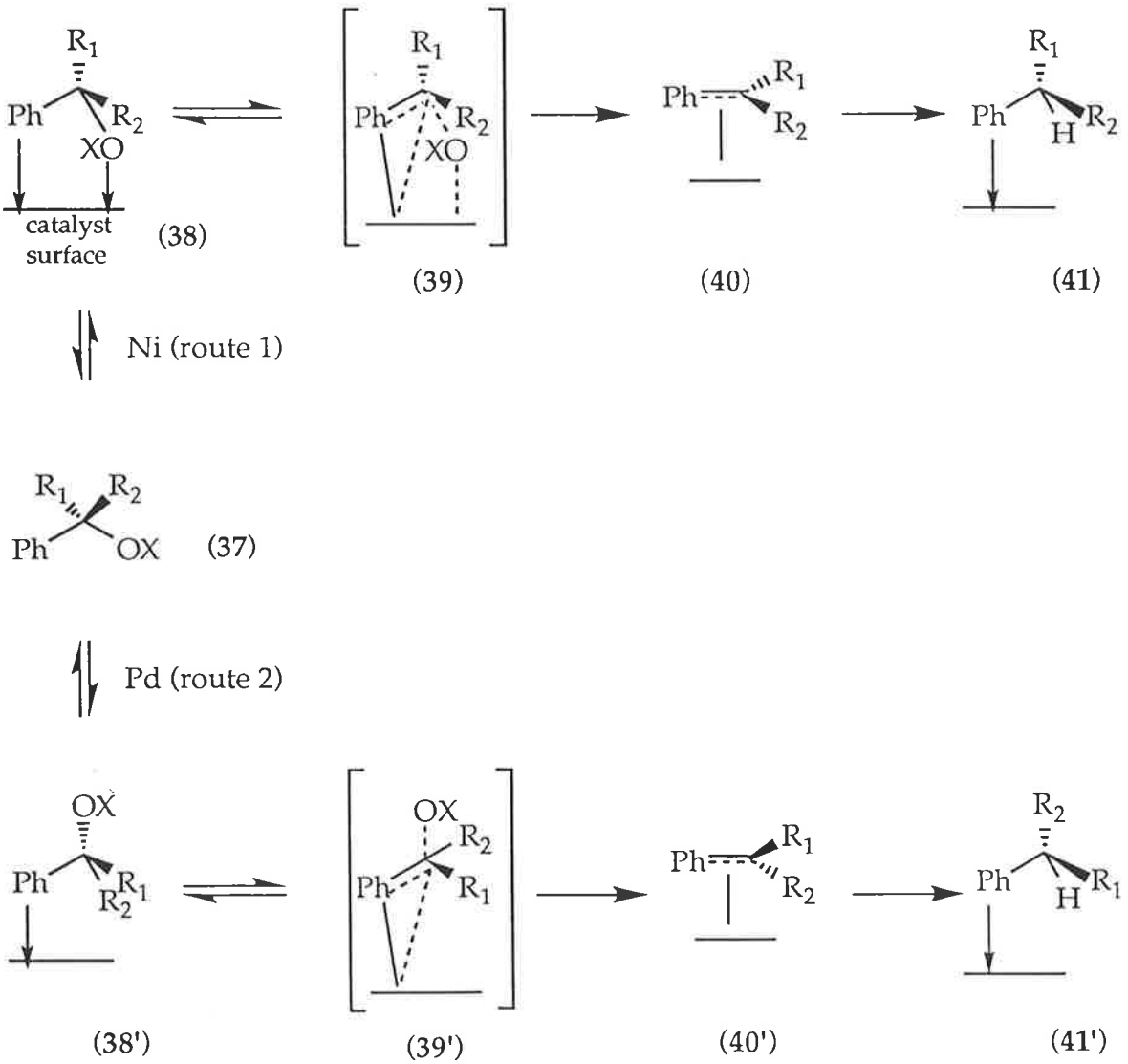


Figure 26

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 π 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 $PhCH_2OR$, the rate increased in the order $OH < O\text{-alkyl} < O\text{-aryl} < OH^+\text{-alkyl} < OH_2^+ < OAc < OCOCF_3$[44]. 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[48]. 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).

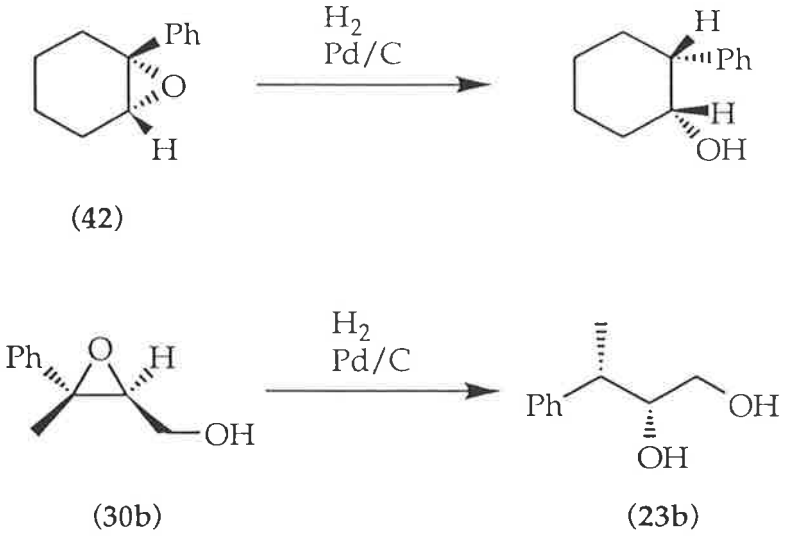
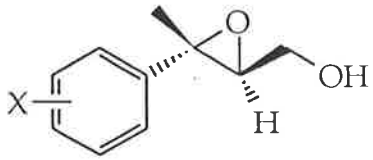
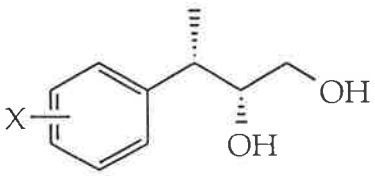


Figure 27

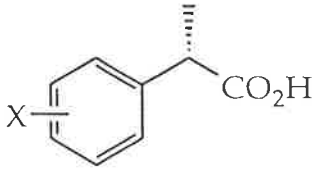
Conditions for the hydrogenolysis of benzylic C-O bonds may also effect cleavage of aryl-halogen bonds[47]. The order of reactivity for the halogen loss is I > Br > Cl > F. This alternative mode of action of the reagents has the potential to compete with the cleavage of the benzylic C-O bond of epoxides **43** and **44**, which is the desired process in the synthesis of the key intermediates **32b** and **33b** in the present study.



(**43**): X = *meta* halogen
(**44**): X = *para* halogen



(**32b**): X = *meta* halogen
(**33b**): X = *para* halogen

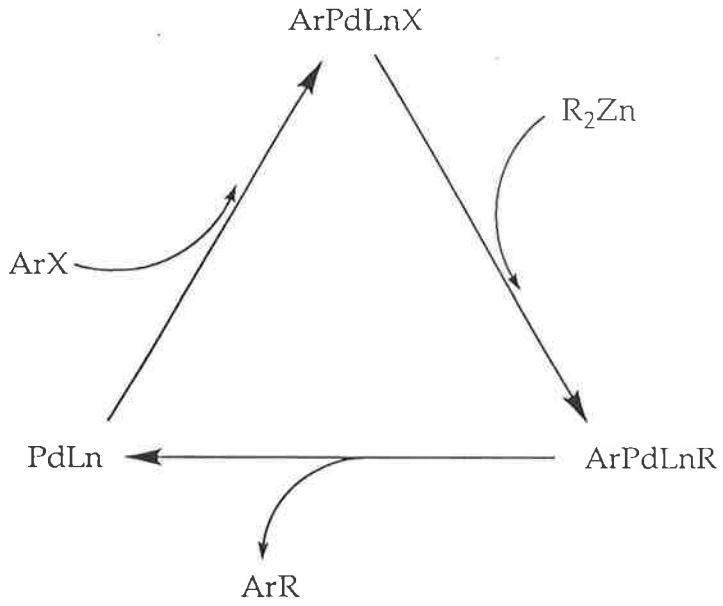


(**34b**): X = *meta* halogen
(**35b**): X = *para* halogen

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[49] and Kumada[50] 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[51,52]. 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[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[54]. The mechanism involved in cross-couplings of this type is thought to proceed through an oxidative addition - transmetallation - reductive elimination cycle[52], as depicted in figure 28.

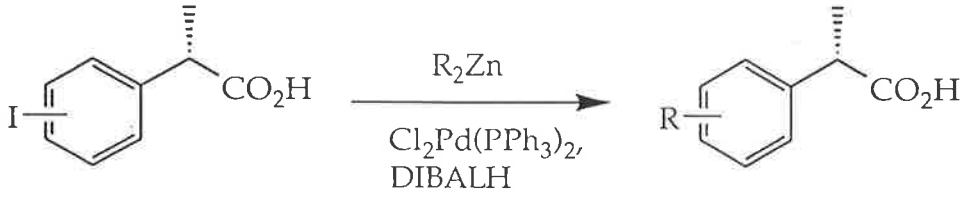


PdLn = palladium-phosphine complex
ArX = aryl halide
R_2Zn = methyl, alkenyl, benzyl or alkynylzinc

Figure 28

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-

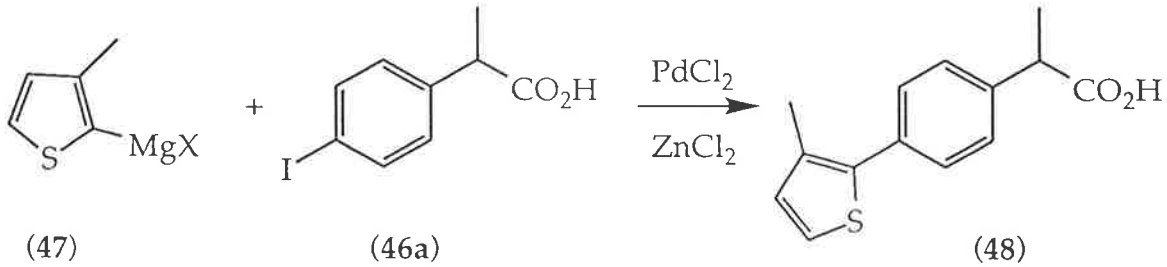
(triphenylphosphine)palladiumII [$Cl_2Pd(PPh_3)_2$] and two equivalents of diisobutylaluminium hydride (DIBALH), in accordance with the method of Negishi (figure 29).



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

Figure 29

There is precedent for palladium catalysed cross-coupling reactions occurring in the presence of a carboxylic acid moiety; Toyama Chemical Co. Ltd.[55] prepared racemic **48** via the coupling of **46a** with **47** in the presence of palladium chloride and zinc chloride (figure 30).

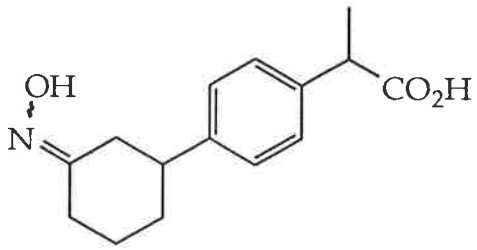


(47) **(46a)** **(48)**

Figure 30

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.

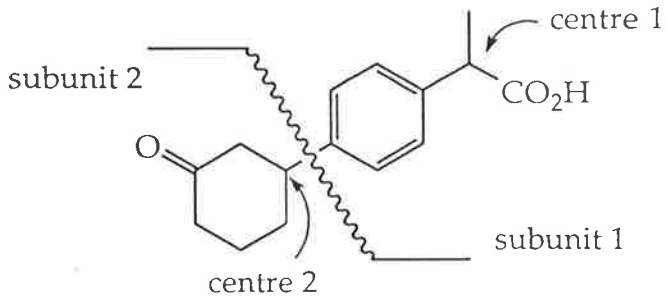


(49)

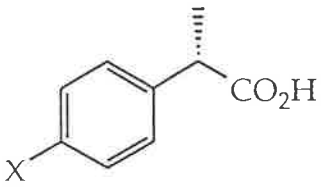
Ximoprofen was reported in 1990[56] to be a significantly more potent anti-inflammatory agent than ibuprofen (the most widely used drug of this class) with a lower incidence of gastro-intestinal side effects. Although several metabolic and pharmacokinetic studies have been published[56-58], no information 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).



(50)



(35b): X = halogen

Figure 31

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).

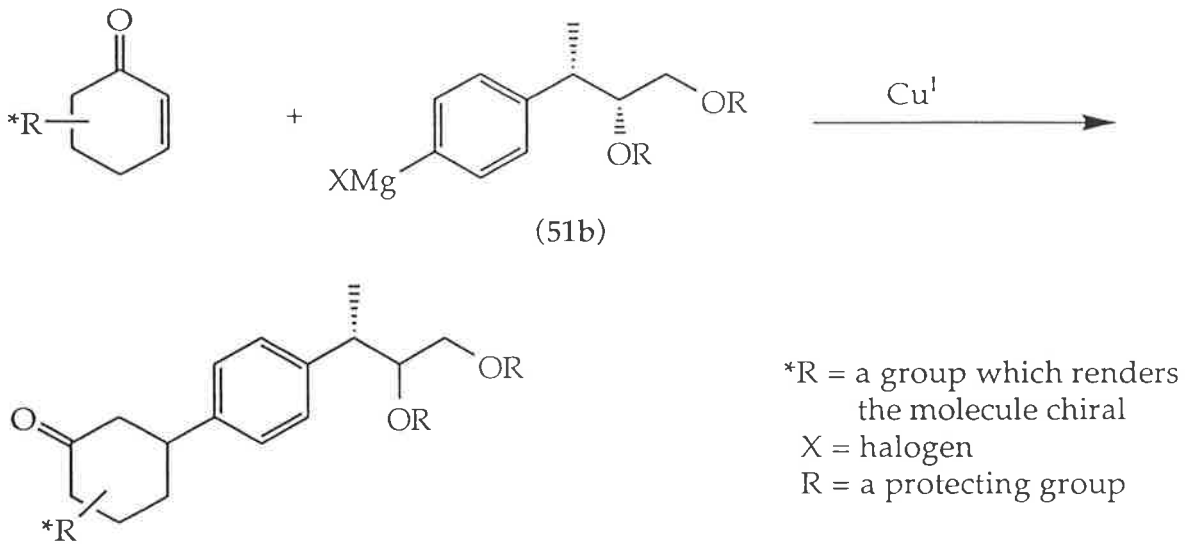


Figure 32

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 π system[61]. A recent publication by Corey[62] discusses the likely sequence of events for the addition of the homocuprate $(Me_2CuLi)_2$ **(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) β-adduct, possibly due to a d,π*-complex such as **53** which involves copper as a d^{10} base and the carbonyl and olefinic carbons (π_3*) as a π-acid. The d,π* mechanistic pathway is outlined in figure 33.

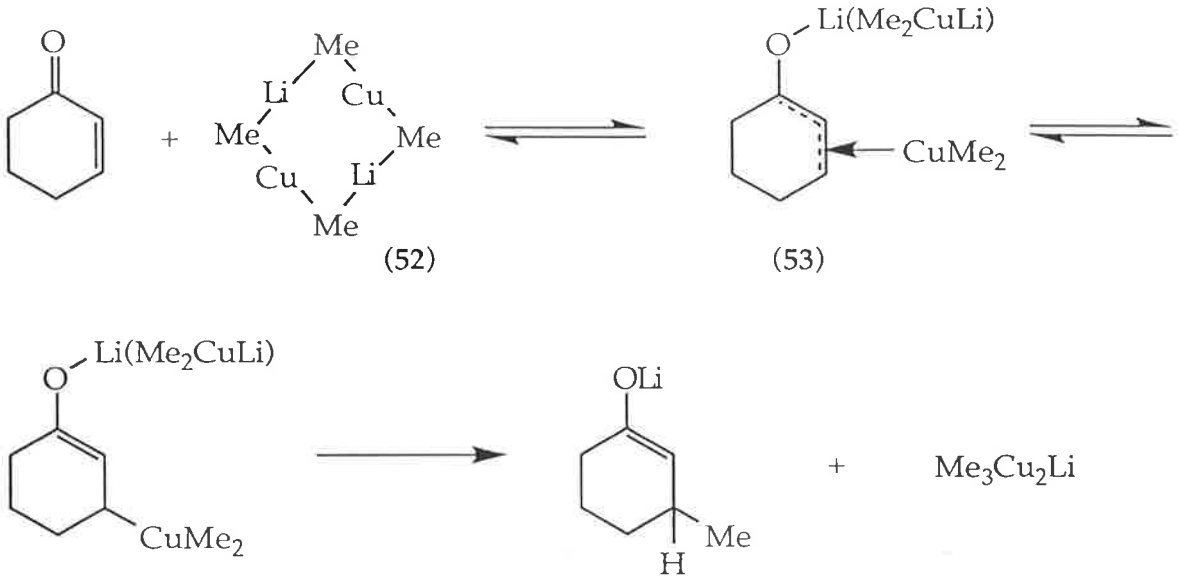
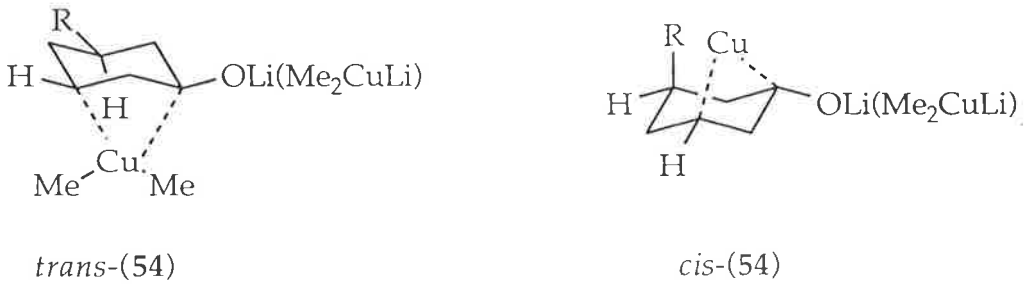


Figure 33

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.



trans-(**54**) *cis*-(54)

Figure 34

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[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.

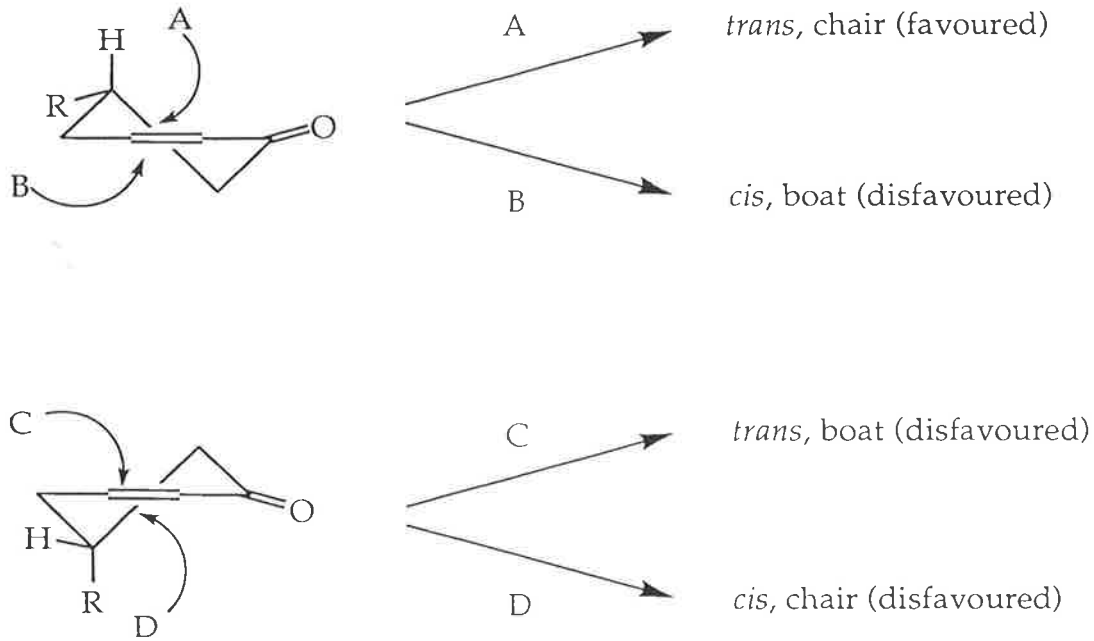
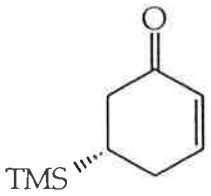
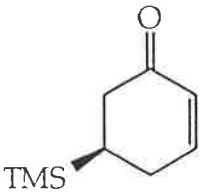


Figure 35

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



(55b)



(55c)

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_2), TMSCl 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).

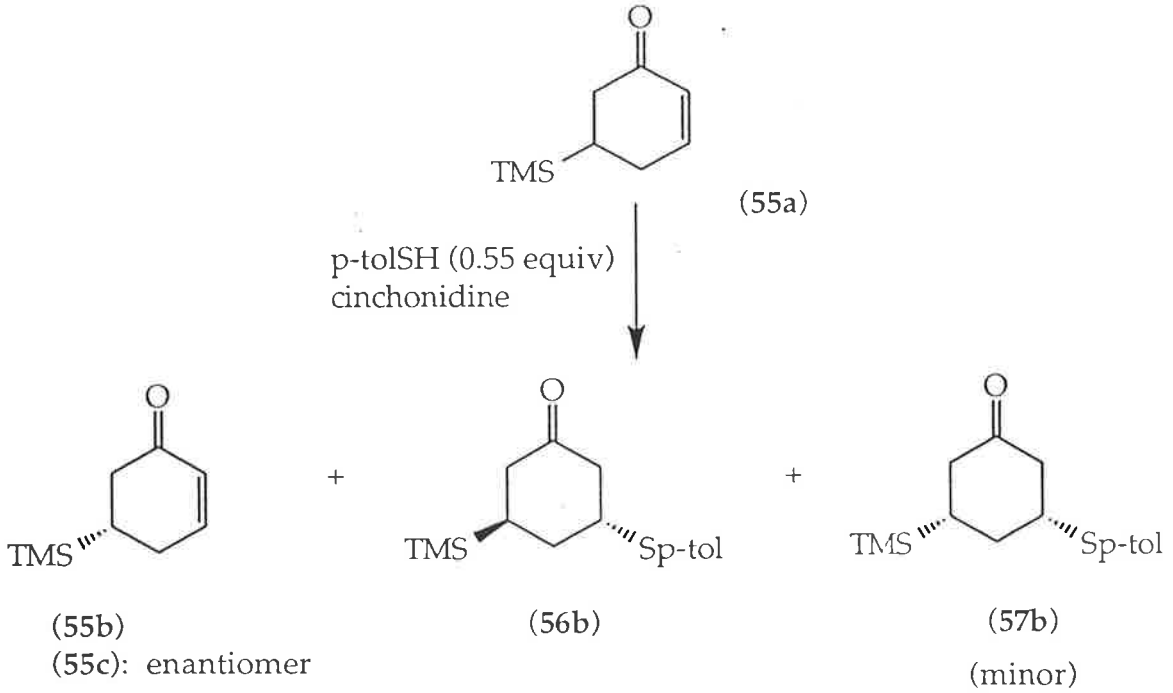
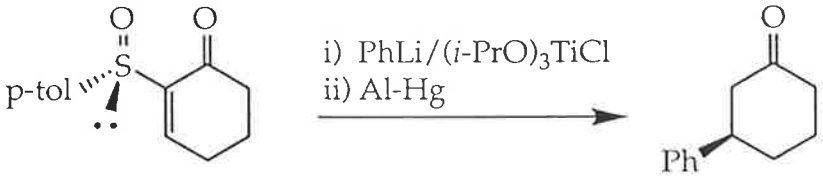


Figure 36

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[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[63,64] have developed cyclohexenone and cyclopentenone derivatives with chiral sulphinyl moieties in the 2-position and shown that they undergo conjugate

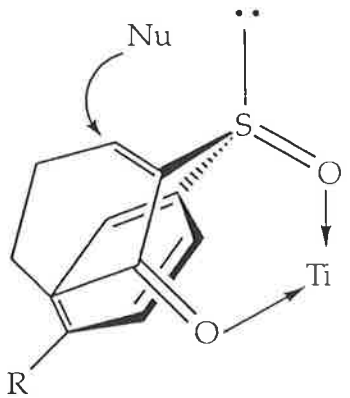
addition reactions with a variety of nucleophiles to give 3-substituted cyclohexanones (and cyclopentanones) with good to excellent levels of optical purity. For example, addition of phenyllithium to *(S)*-2-(*p*-tolylsulphinyl)-2-cyclohexenone (**58b**) in 2,5-dimethyltetrahydrofuran (DMTHF) with chlorotitanium 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).



(58b) (59b)

Figure 37

These authors proposed a mechanism in which the sulphoxide 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.



(**60**) R = Me
(**61**) R = OMe

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 sulphoxides 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[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).

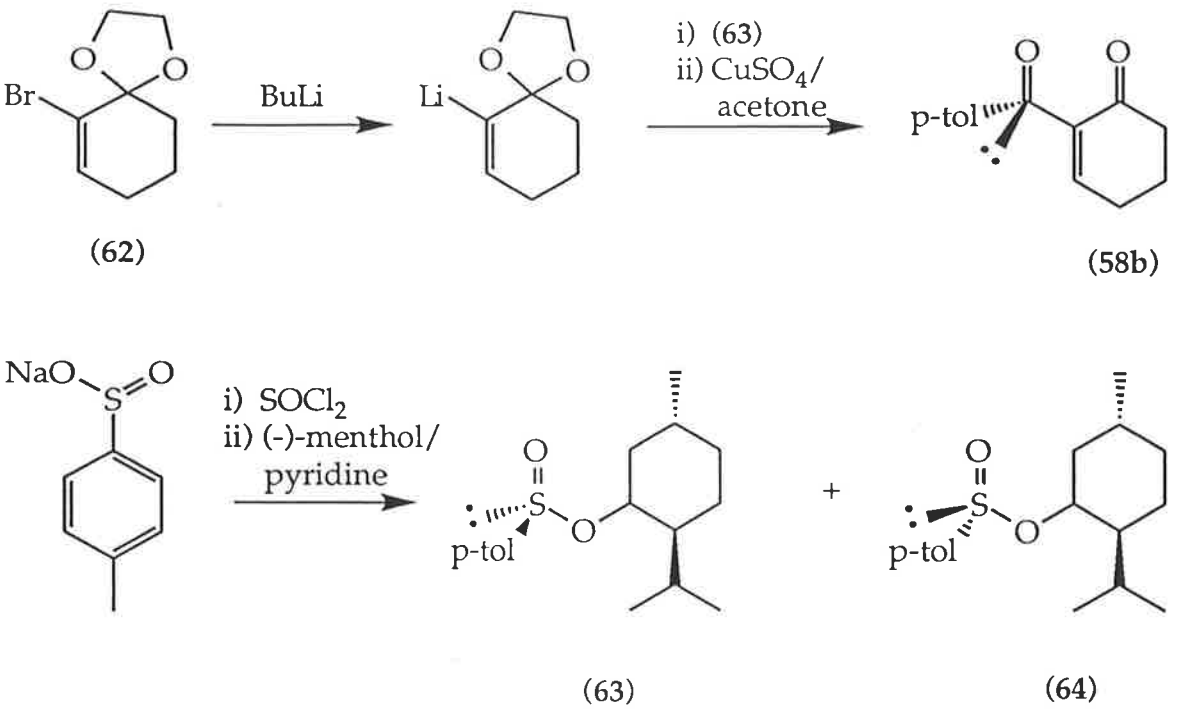
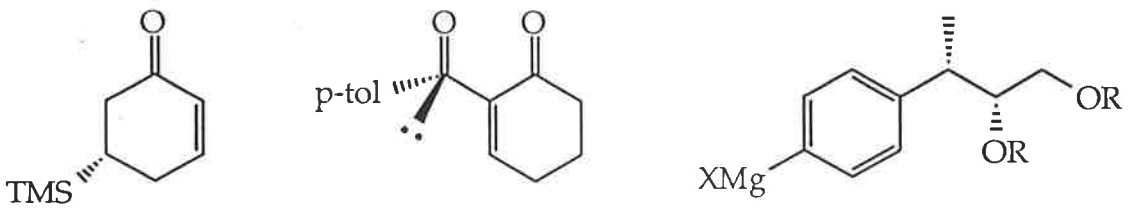


Figure 38

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.



(55b)
(55c): enantiomer

(58b)
(58c): enantiomer

(51b)
(51c): enantiomer

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[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[74]. The uneconomical nature of these conditions prompted the development of catalytic variants of the reaction which use inexpensive reagents to reoxidise the osmium *in situ*. A range of co-oxidants has been used which includes hydrogen peroxide, sodium or potassium chlorate, *tert*-butylhydroperoxide and N-methylmorpholine N-oxide. Potassium ferricyanide ($K_3Fe(CN)_6$) in the presence of potassium carbonate has recently been found to provide a powerful system for the osmium catalysed dihydroxylation of olefins[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_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 $K_3Fe(CN)_6$ as co-oxidant virtually eliminated participation of the second catalytic cycle, as OsO_4 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 OsO_4 by $K_3Fe(CN)_6$ and then migrates back into the organic phase to restart the cycle (figure 39).

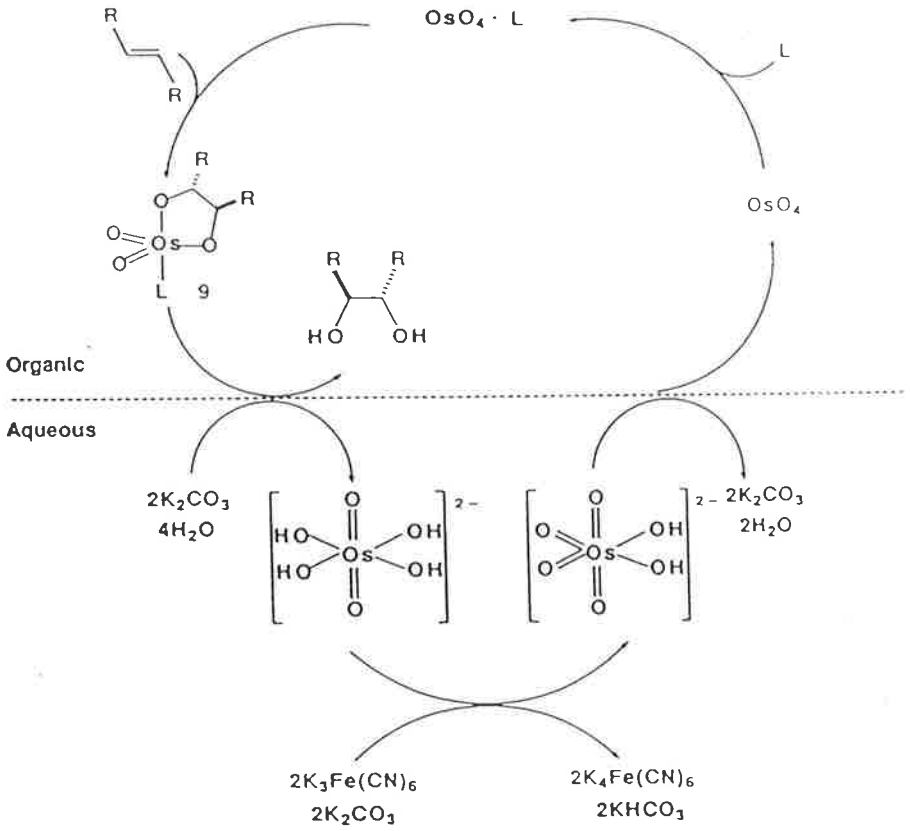
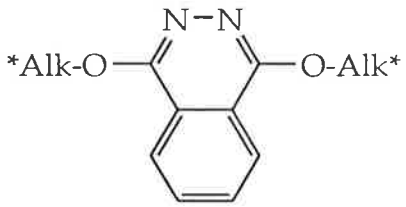


Figure 39

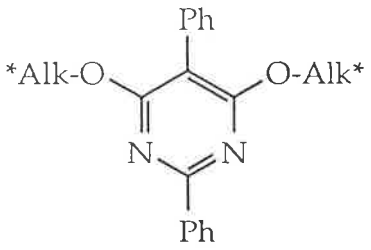
Another key discovery was that the rate of hydrolysis of the osmium(VI) glycolate product can be markedly increased by methyl sulphonamide ($MeSO_2NH_2$). This additive allows high catalytic turnovers even with sterically crowded substrates which include some tetrasubstituted olefins. This

"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 $MeSO_2NH_2$).

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.

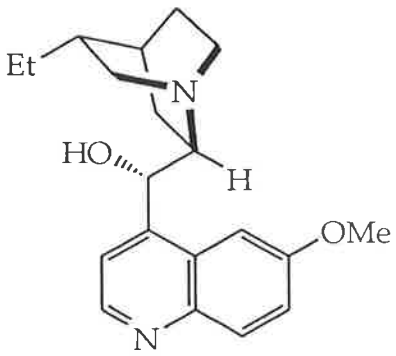


Phthalazine (PHAL) ligands

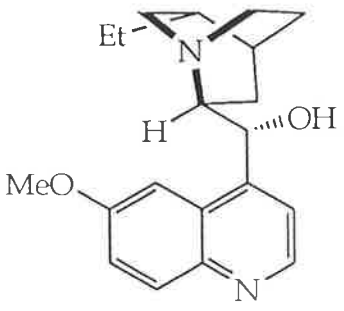


Diphenylpyrimidine (PYR) ligands

*Alk = DHQD or DHQ



DHQD



DHQ

Figure 40

Several studies have been done to determine the mechanistic basis for enantioselectivity in the reaction[73,75,76]. The most likely explanation has recently been put forward by Sharpless[76]. He proposes that the osmaoxetane intermediate derived from styrene and $(DHQD)_2PHAL$ 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.

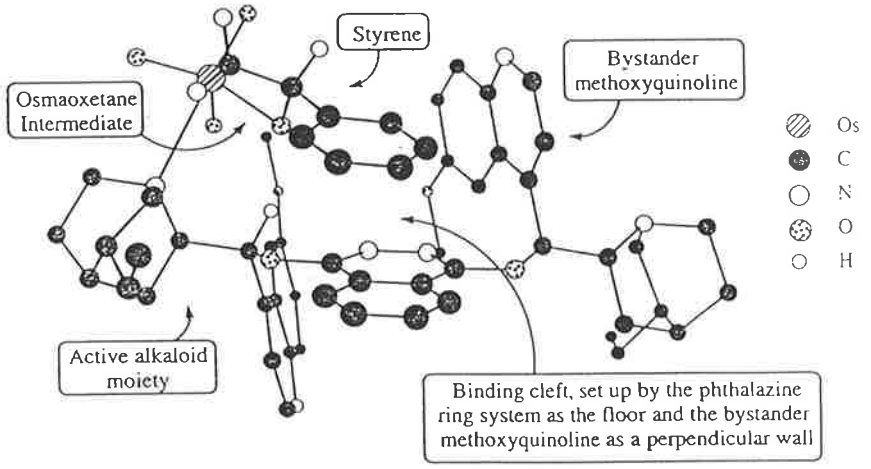


Figure 41

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_4 as well as increasing rates

- oxygenation at the benzylic position is essential to allow binding to OsO_4 (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 Corey[68] has fundamental problems associated with it and is not as well supported by experimental data[68a].

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 mnemonic[73].

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%), K_3FeCN_6 and K_2CO_3; 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 α-methylstyrene derivative **65**, which could be converted to the corresponding optically active diol **66b** or **66c**. Hydrogenolysis of the benzylic hydroxyl group with a palladium catalyst should then proceed with inversion of configuration to **67b** or **67c**, in an analagous 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. α-Methylstyrene (**65**, R=H) has been treated with AD-mix-β to give **66c** (R=H) with 94% e.e. and with AD-mix-α to give **66b** (R=H) with 93% e.e.[77]

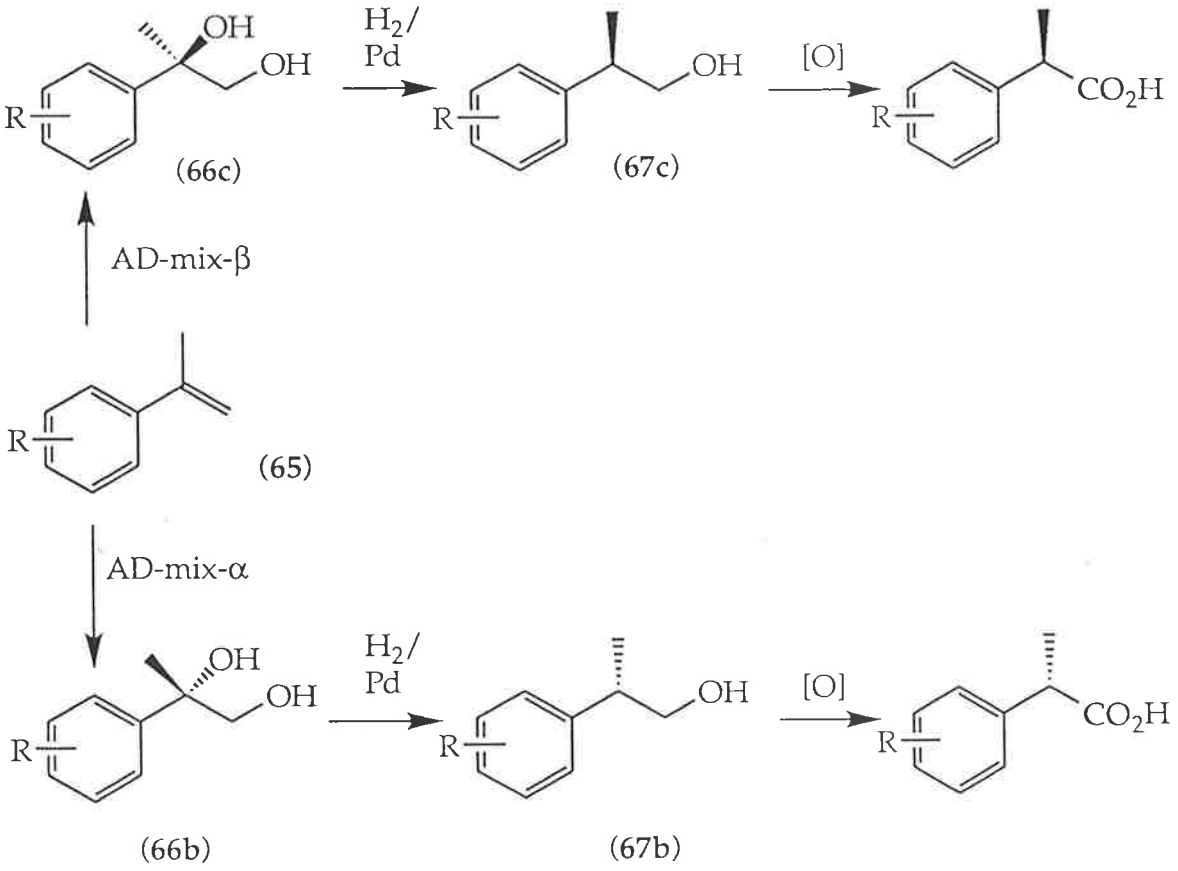


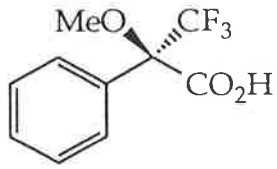
Figure 42

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

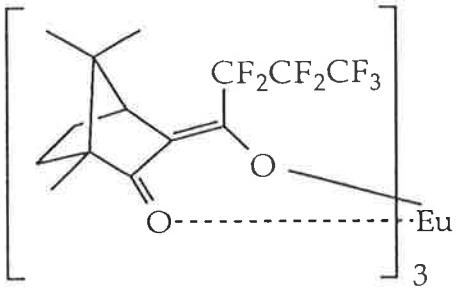
ratio, however values may be unreliable due to the sensitivity of the method to experimental conditions and the possibility of unsuspected impurities. Furthermore, relatively large sample sizes are required for polarimetric measurements and the maximum optical rotation of the compound in question must 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[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 diasteromers with an optically pure reagent, such as Mosher's acid (α-methoxy-α-trifluoromethylphenylacetic acid) (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.

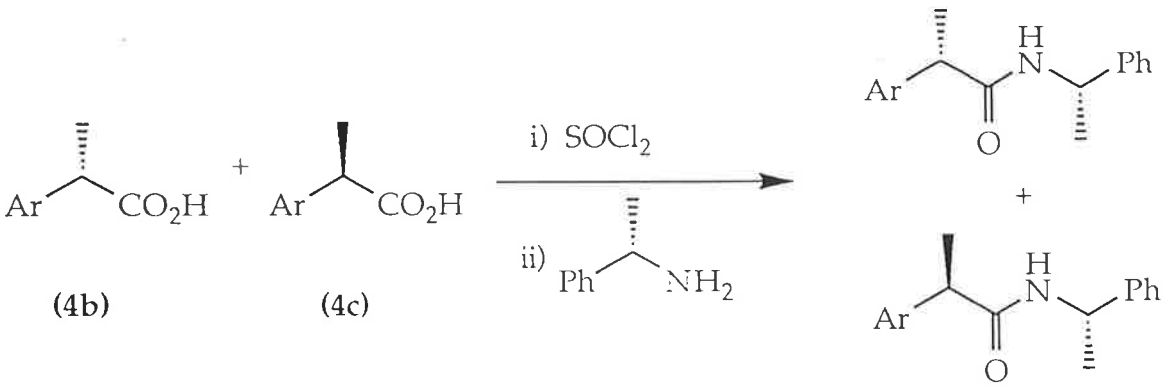


(68)



(69)

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[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.



(4b) (4c)

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-infammatory 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.

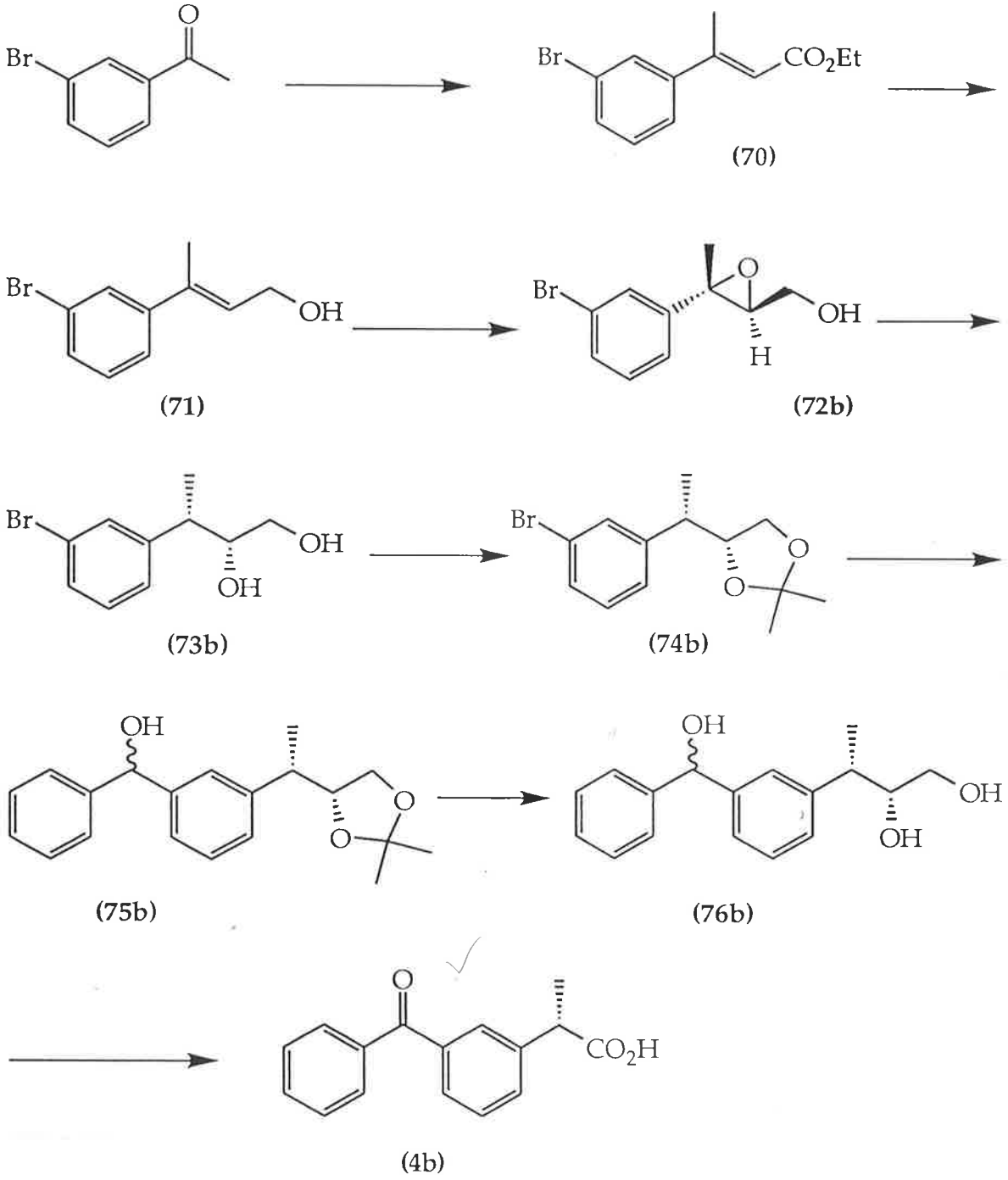


Figure 44

The combination of Sharpless epoxidation and subsequent hydrogenolytic ring opening had been explored briefly by the Hamon - Massy-Westropp group[35] in the analogous unsubstituted system **29** (figure 45). Epoxide **30** was obtained in 80% yield with 80-85% e.e. Recrystallisation of the *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.

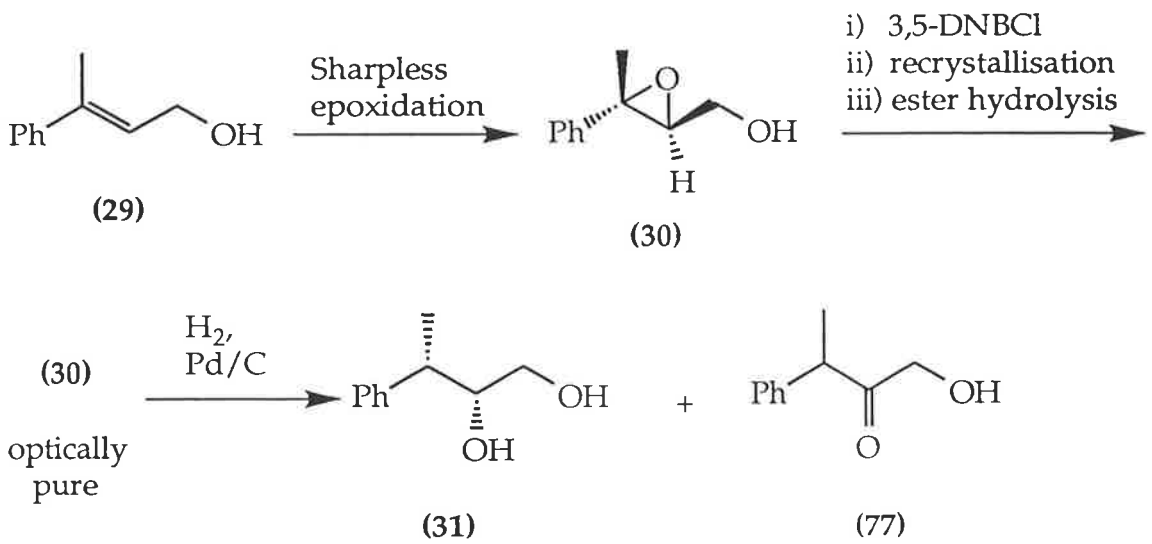


Figure 45

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[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 CH_2CH_3 protons of the two isomers overlap, as do the quartets due to the CH_2CH_3 protons. The isomers were separated by chromatography to give **70** in 65% yield. Distillation of a sample of **70** afforded analytically pure material.

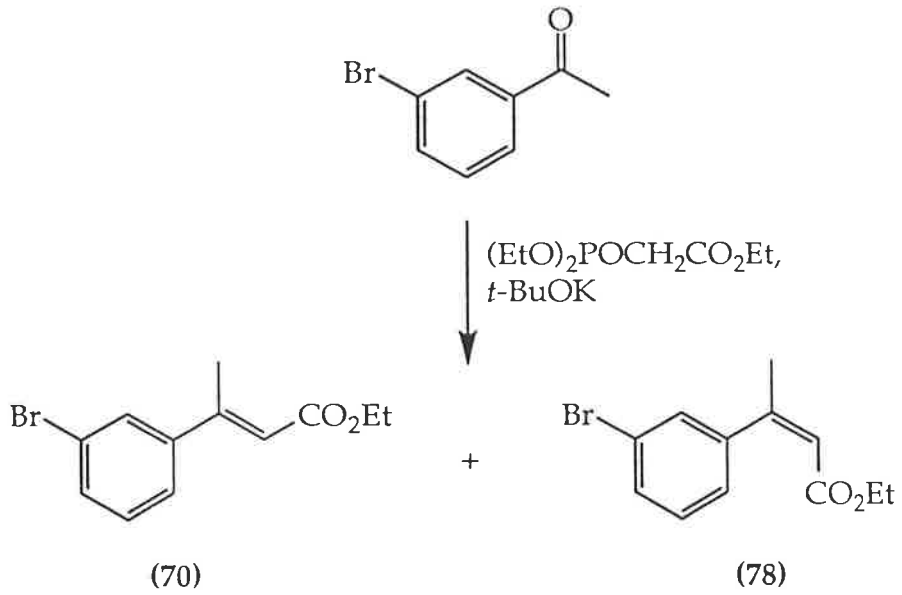


Figure 46

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, ^1H 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_2O protons resonates at δ 4.23.

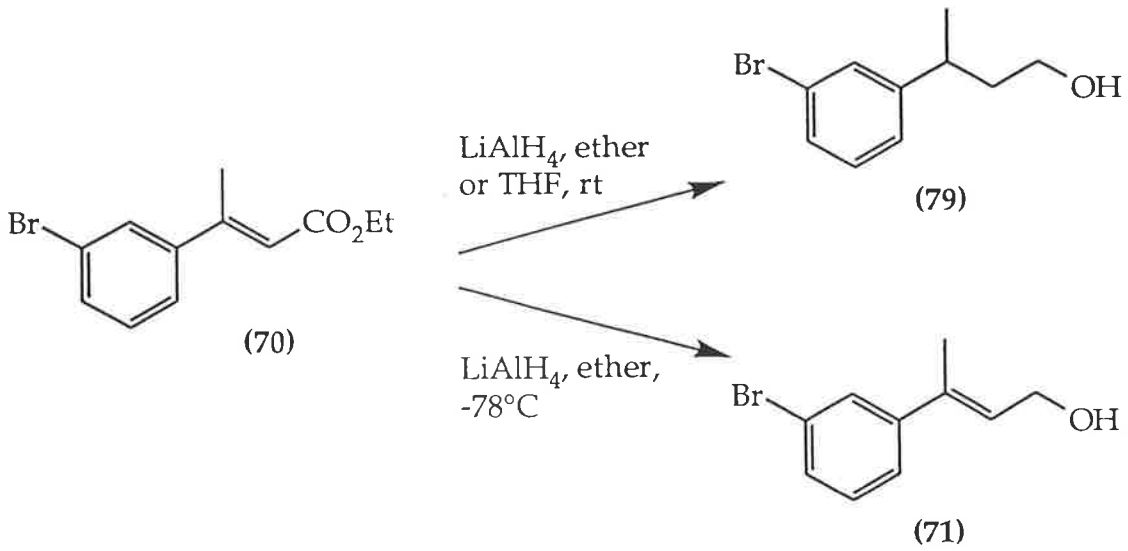
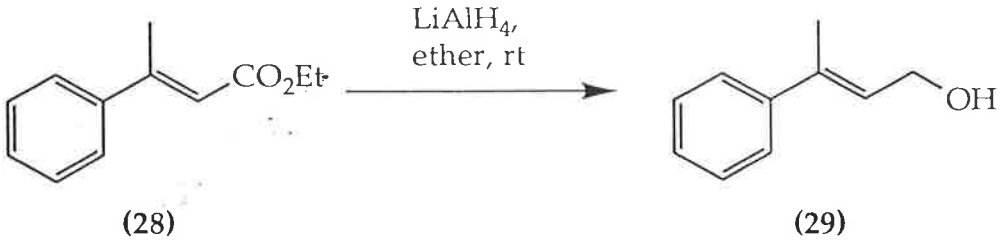


Figure 47

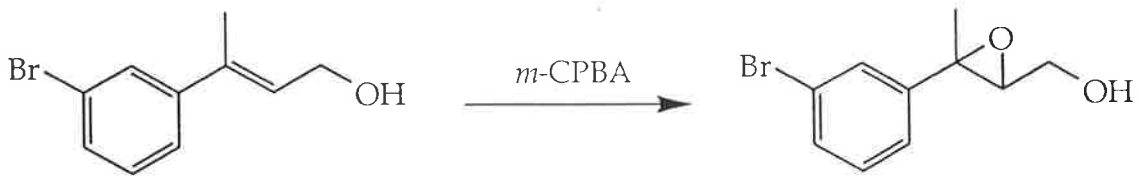
Although there is precedent for reduction of cinnamyl-like α,β-unsaturated systems to the saturated alcohols with lithium aluminium hydride[6], the reduction of the double bond of **70** under the initial reaction conditions was unexpected, as earlier work in the group had shown that reduction of the 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.



(28) (29)

Figure 48

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 δ 1.67 due to the methyl group, a poorly resolved 5.2 Hz triplet at δ 2.21 due to the OH and a doublet of doublets at δ 3.05 due to the proton on the epoxide ring. Poorly resolved signals at δ 3.82 and δ 3.96 are revealed as two doublet of doublets upon D_2O exchange, each due to one of the methylene protons.



(71) (72a)

Figure 49

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 diasteromeric diols is a consequence of the stereoselectivity of the hydrogenolysis reaction, and is independent of the optical purity of the starting epoxide.

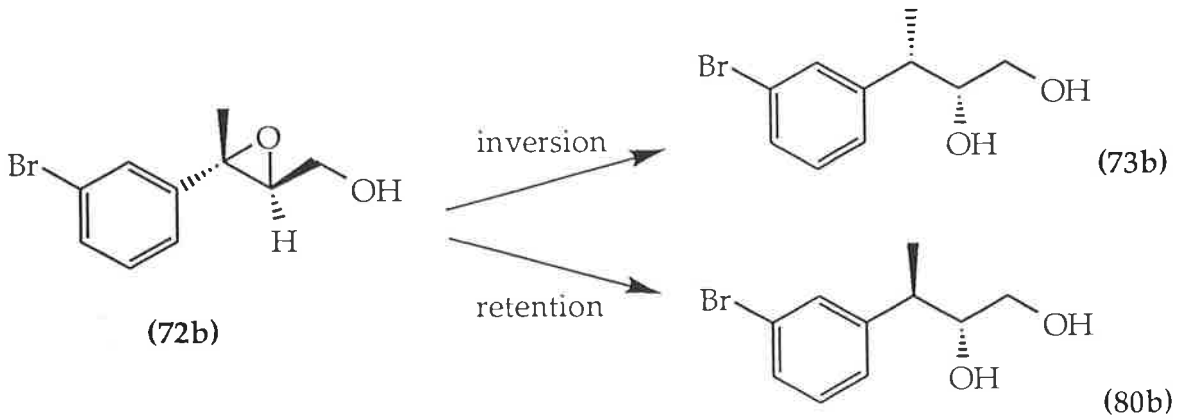
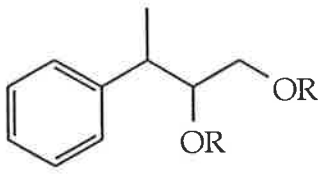


Figure 50

Earlier work in the Hamon - Massy-Westropp group[35] 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. ^1H 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 δ 1.27 as a 6.9 Hz doublet coupled to the benzylic proton, which appears as a 6.9 Hz quintet at δ 2.64. Two doublet of doublets at δ 3.16 and δ 3.27 are due to the methylene protons and a doublet of triplets at δ 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 (δ 7.08 - δ 7.24 for the product, δ 7.17 - δ 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

Figure 51

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 bonds[47], 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*-toluenesulphonic 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 ^{1}H NMR spectrum of **85** shows a sharp singlet at δ 0.29 due to the 9Hs of the trimethylsilyl group, a 3H singlet at

δ 2.50 due to the CH_3CO protons and a complex set of aromatic signals between δ 7.21 and δ 8.14.

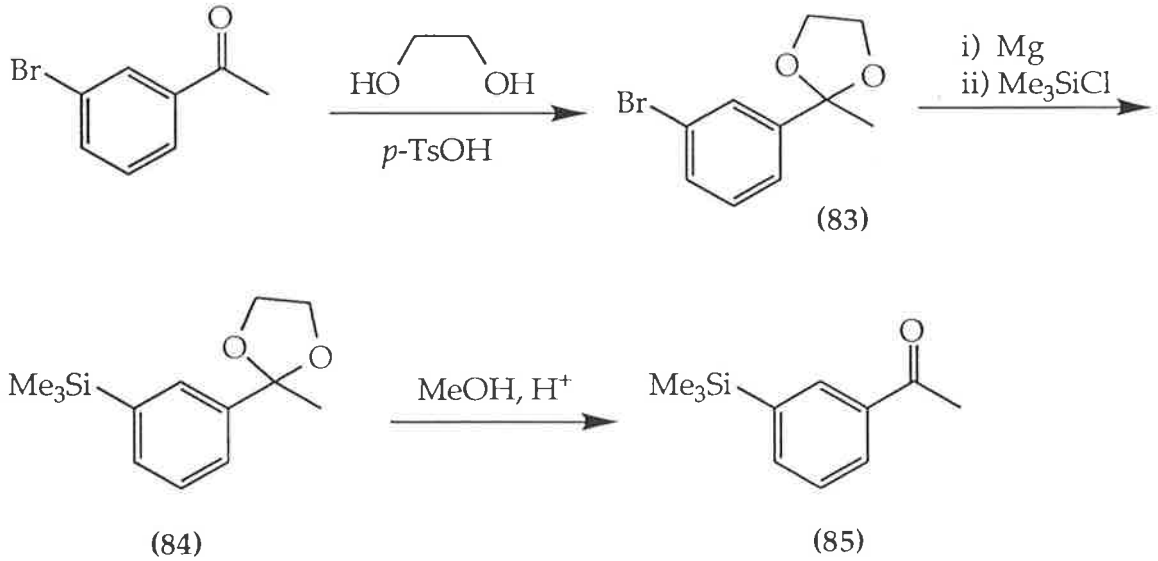


Figure 52

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 ^1H NMR spectrum of **86** is very similar to that of the bromo analogue **70**, except for the presence of a 9H singlet at δ 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 δ 0.28 is the only substantial difference between the ^1H 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 δ 0.27, **88a** has a very similar ^1H 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.

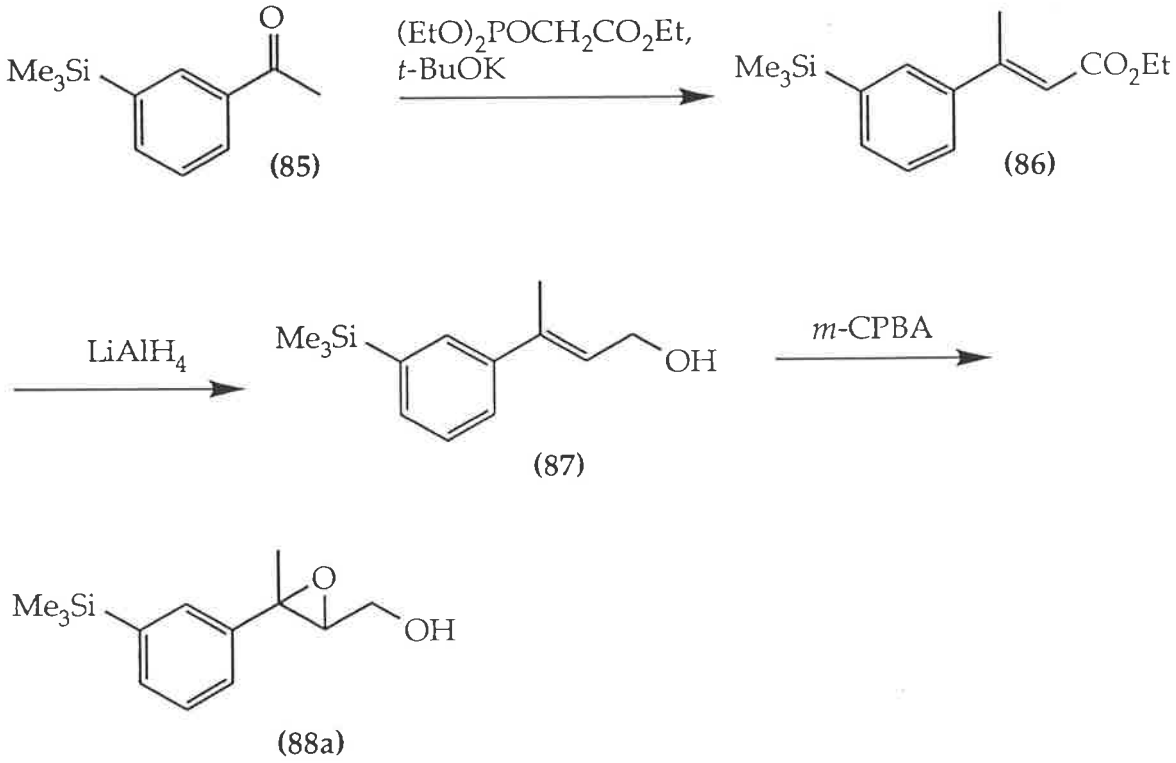


Figure 53

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°C (figure 54).

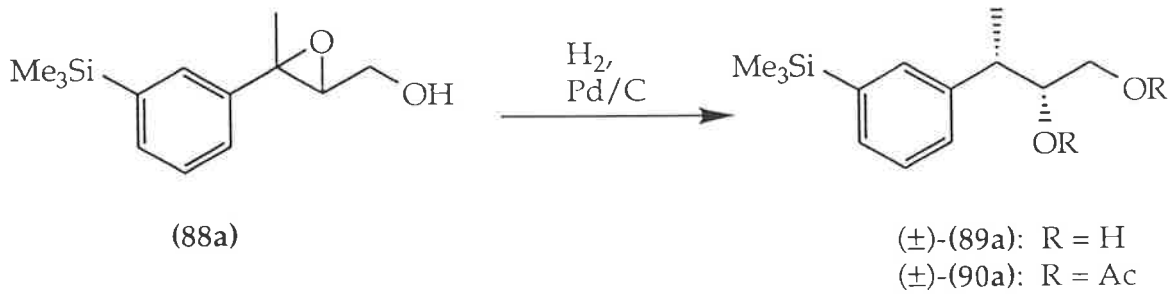


Figure 54

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 δ 0.26 and a complex pattern in the the aromatic region, which is similar to the trimethylsilyl substituted precursors and resonates at δ 7.16 - δ 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).

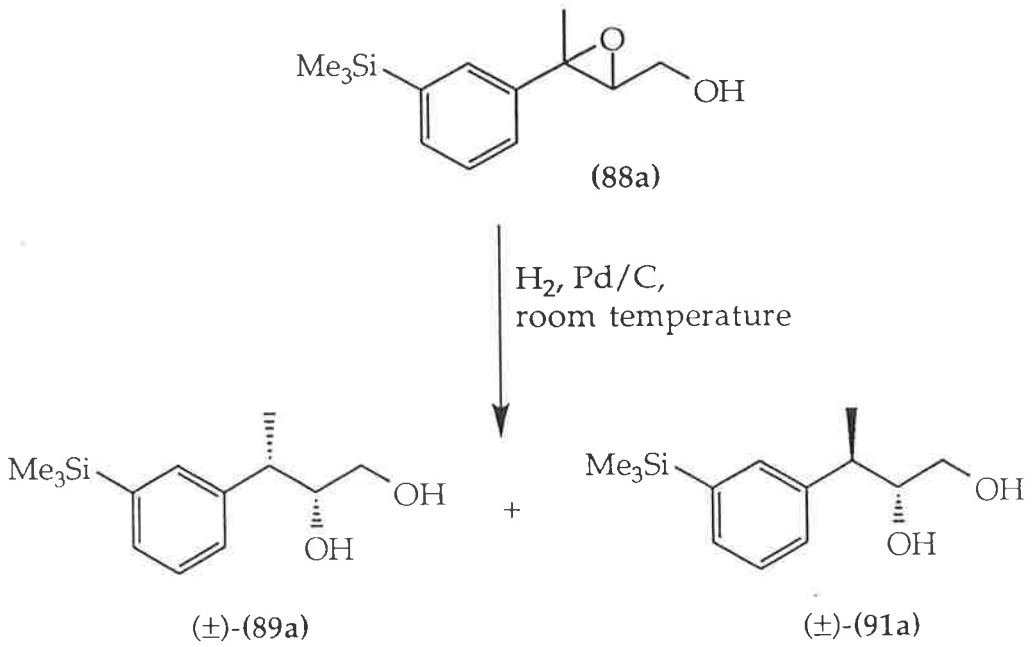


Figure 55

The ^1H NMR spectrum of the mixture shows a 7.0 Hz doublet at δ 1.35 due to the methyl group of **89a** and a 7.1 Hz doublet at δ 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-^1H satellite peaks from the major doublet, which are each 0.5% parent ^1H-^1H 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[82] converted *o*-bis(trimethylsilyl)benzene (**92**) to *o*-trimethylsilylbenzophenone (**93**) by the use of Friedel-Crafts chemistry (figure 56).

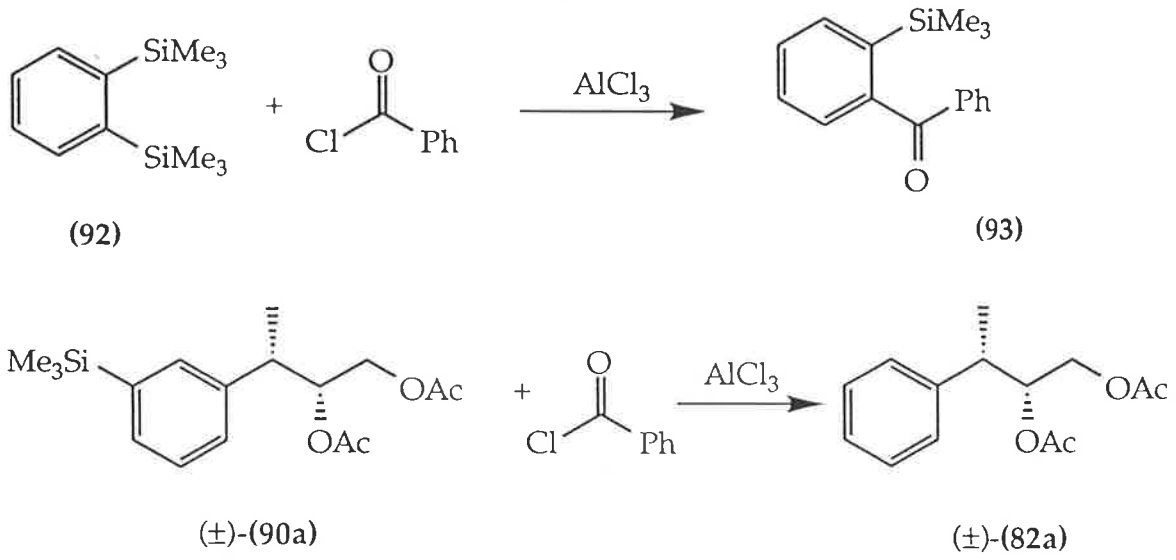


Figure 56

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).

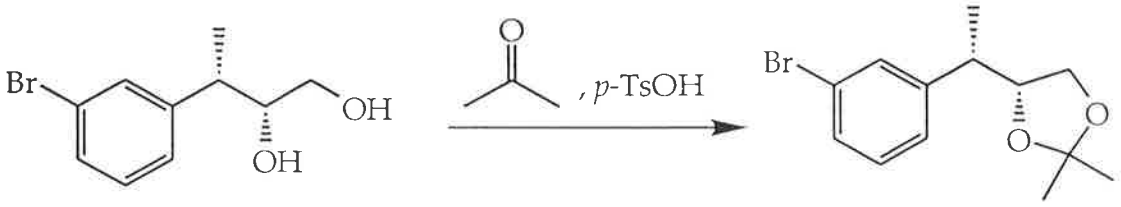
As this approach did not appear promising, an alternative method for the incorporation of the benzylic substituent to **89a** was explored. The trimethylsilyl group was replaced with a bromine atom to give **73a** (figure 57), with the expectation that this would undergo metal-halogen exchange to form 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 Wilbur[83]. The required product **73a** was isolated in 93% yield. The ^{1}H 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.

(±)-(89a) (±)-(73a)

Figure 57

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

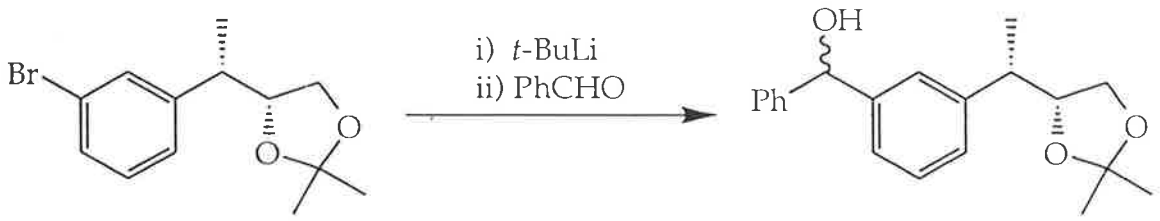
was isolated in 79% yield, and the structure confirmed by ^{1}H NMR. The spectrum shows the benzylic methyl group as a 6.4 Hz doublet at δ 1.35 and the two methyl groups on the dioxolane ring as a singlets at δ 1.37 and δ 1.41. The benzylic proton appears as a quintet at δ 2.77, each of the protons of 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.



(±)-(73a) (±)-(74a)

Figure 58

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.



(±)-(74a) (±)-(75a)

Figure 59

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.

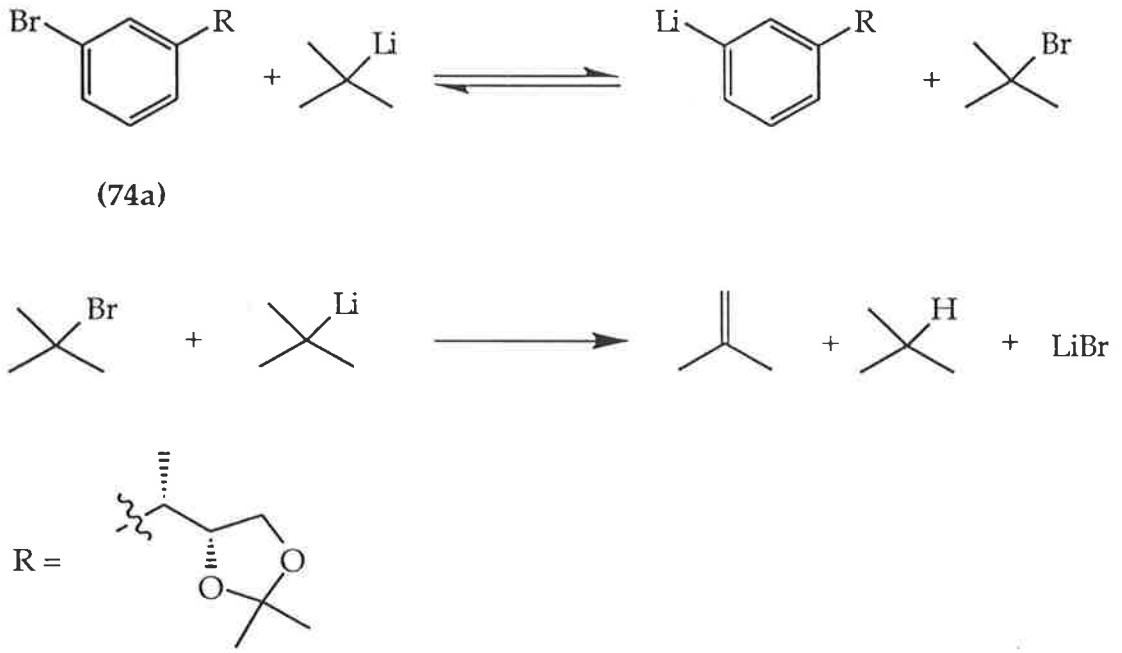
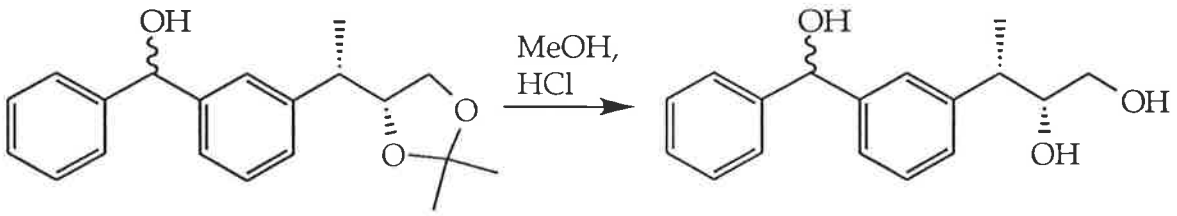


Figure 60

After work up and chromatography, the product **75a** was isolated in 76% yield. The signals in the ^1H 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 δ 1.55 due to the OH, and a new doublet at δ 5.80 due to the benzylic CHOH. Upon D_2O exchange, the signal at δ 1.55 disappears and the one at δ 5.80 becomes a singlet. The aromatic region (δ 6.92 - δ 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 δ 1 -

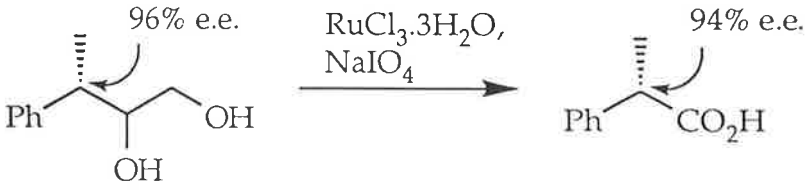
δ 4 region of the ^1H NMR spectrum upon D_2O exchange shows the characteristic pattern of all the precursor butane-1,2-diols. There is also a 1H singlet at δ 5.74 due to the benzylic CHOH and a complex, 9H set of signals in the aromatic region.



(±)-(75a) **(±)-(76a)**

Figure 61

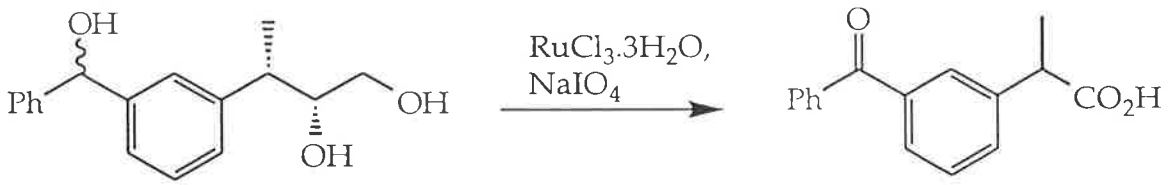
The final step in this synthesis of ketoprofen (**4a**) was the oxidation of triol **76a**. Sharpless et al[84] have developed conditions for the efficient oxidative cleavage of 1,2-diols with sodium metaperiodate and a catalytic amount of ruthenium trichloride hydrate. These reagents generate the active 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.



(81b)

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[85], 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.



(±)-(76a) **(4a)**

Figure 63

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[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.

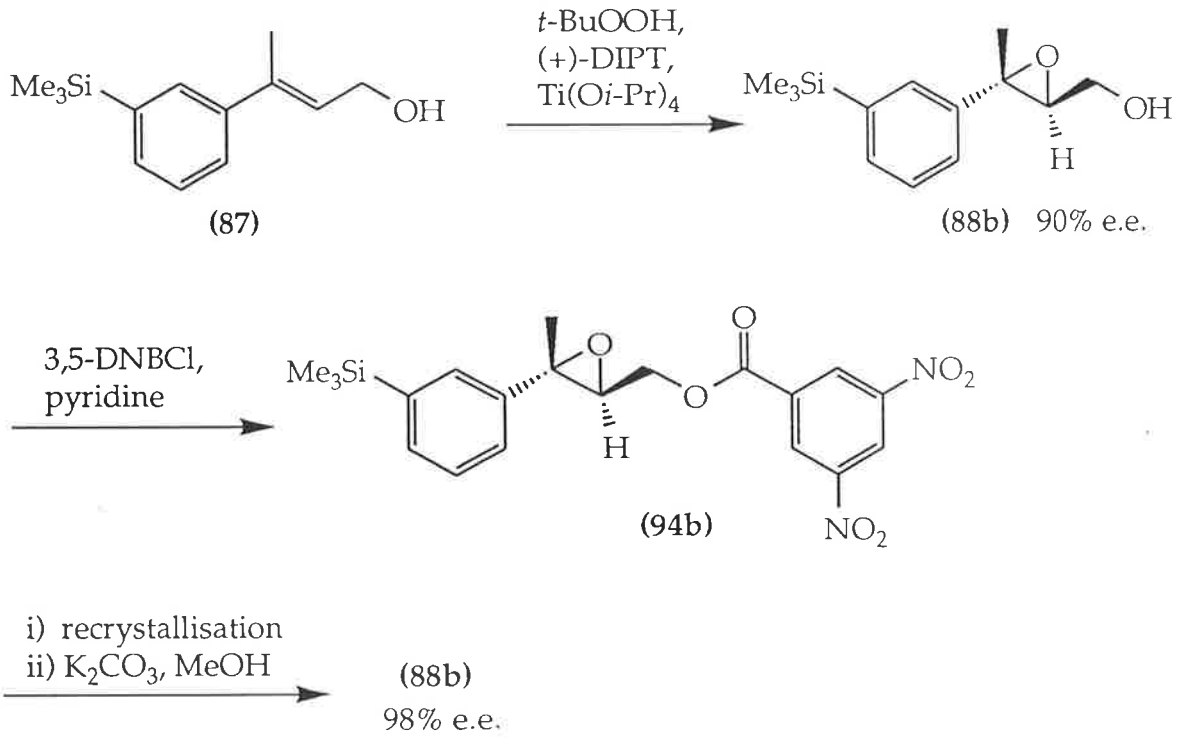
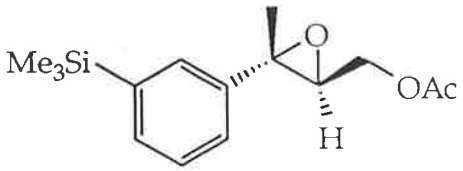


Figure 64

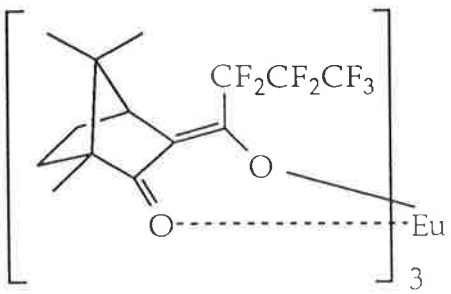
Commercially available cinnamyl alcohol was used as a model compound in trial reactions, to optimise conditions and technique. Scrupulously anhydrous conditions and reagents are necessary for high yields. Thus, treatment of **87**

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° (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).



(95b)
(95a) = racemate



(69)

Figure 65

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 ^{1}H 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.

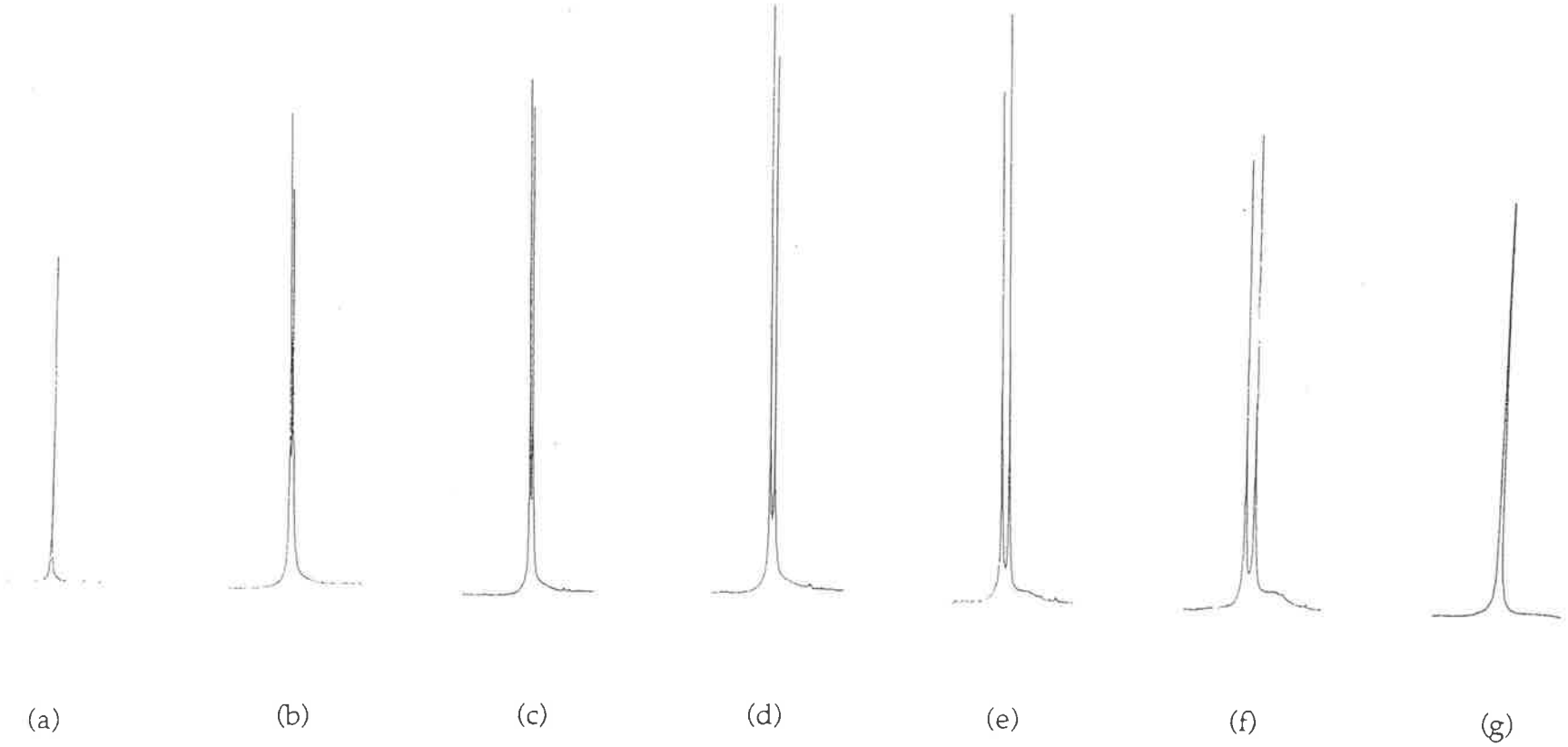


Figure 66

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[79].

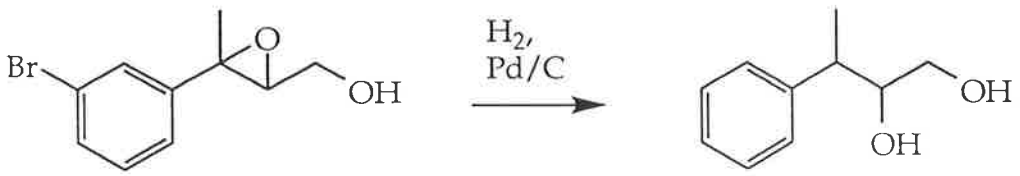
By this method, the product of the asymmetric synthesis, *(S)*-ketoprofen (**4b**) was found to have an optical purity of 96% e.e. This value represents the minimum optical purity, as it is based on the assumption that the *(S)*-1-phenylethylamine used for derivitisation was 100% optically pure. The very slight loss of optical purity in comparison with epoxy alcohol **88b** from the Sharpless reaction (98% e.e.) was consistent with Sharpless's[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 canditate 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 case[86].



(72a) **(81a)**

Figure 66

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**.

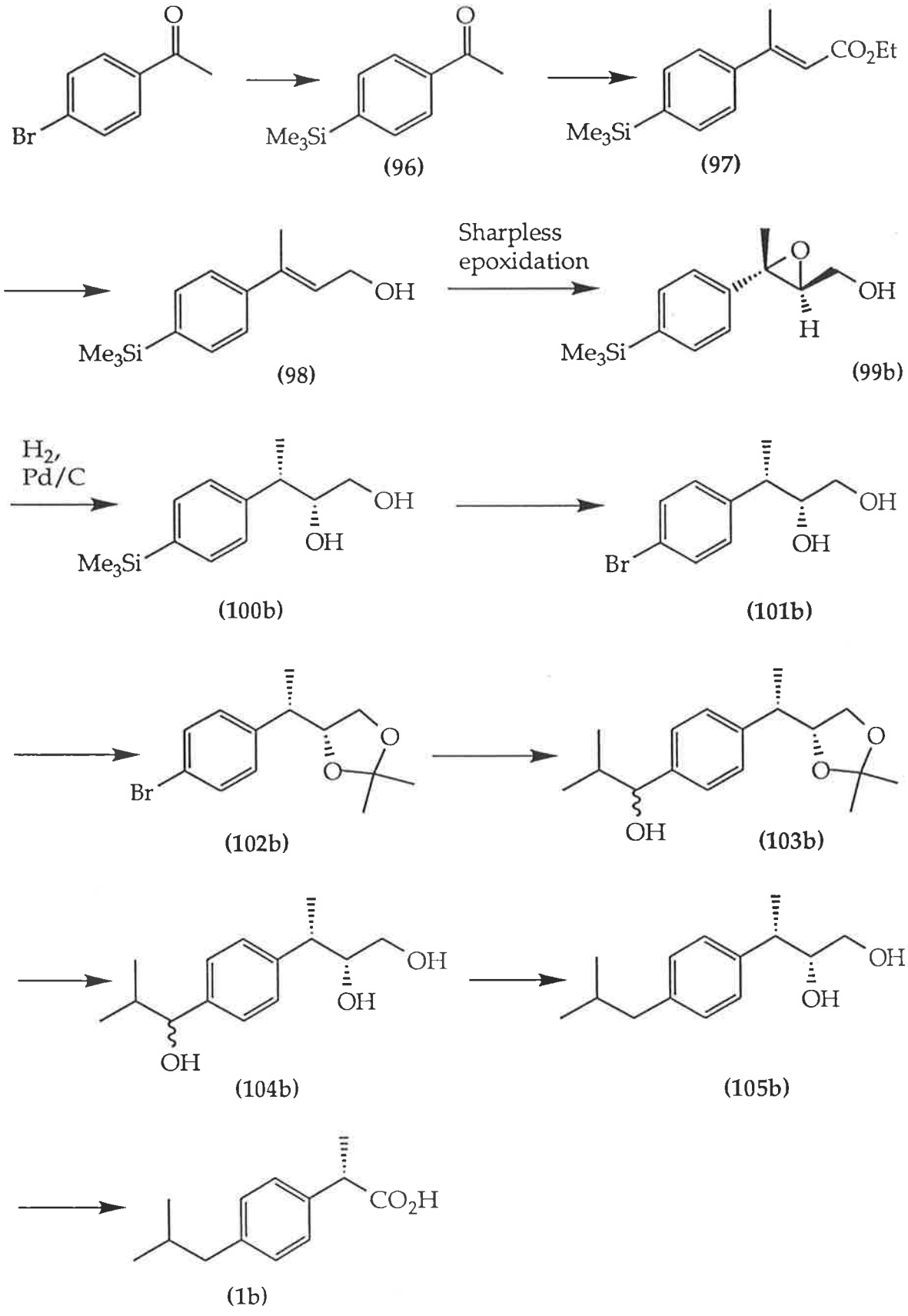

Br
Me3Si
(96)
CO2Et
Me3Si
(97)
OH
Me3Si
(98)
Sharpless
epoxidation
O
OH
H
Me3Si
(99b)
H2,
Pd/C
OH
OH
Me3Si
(100b)
OH
OH
Br
(101b)
Br
O
O
(102b)
O
O
OH
(103b)
OH
OH
OH
(104b)
OH
OH
(105b)
CO2H
(1b)

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[87], 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**.

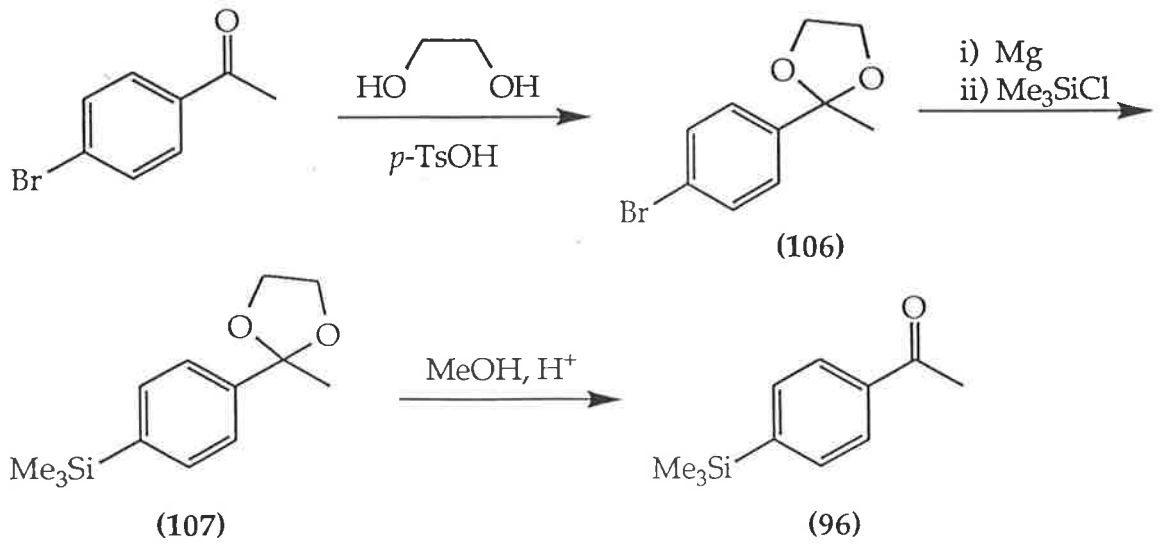


Figure 68

The ^1H NMR data of **96** were in agreement with those reported[87]: a 9H singlet at δ 0.29 due to the trimethylsilyl protons, a 3H singlet at δ 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 δ 7.62 and δ 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.

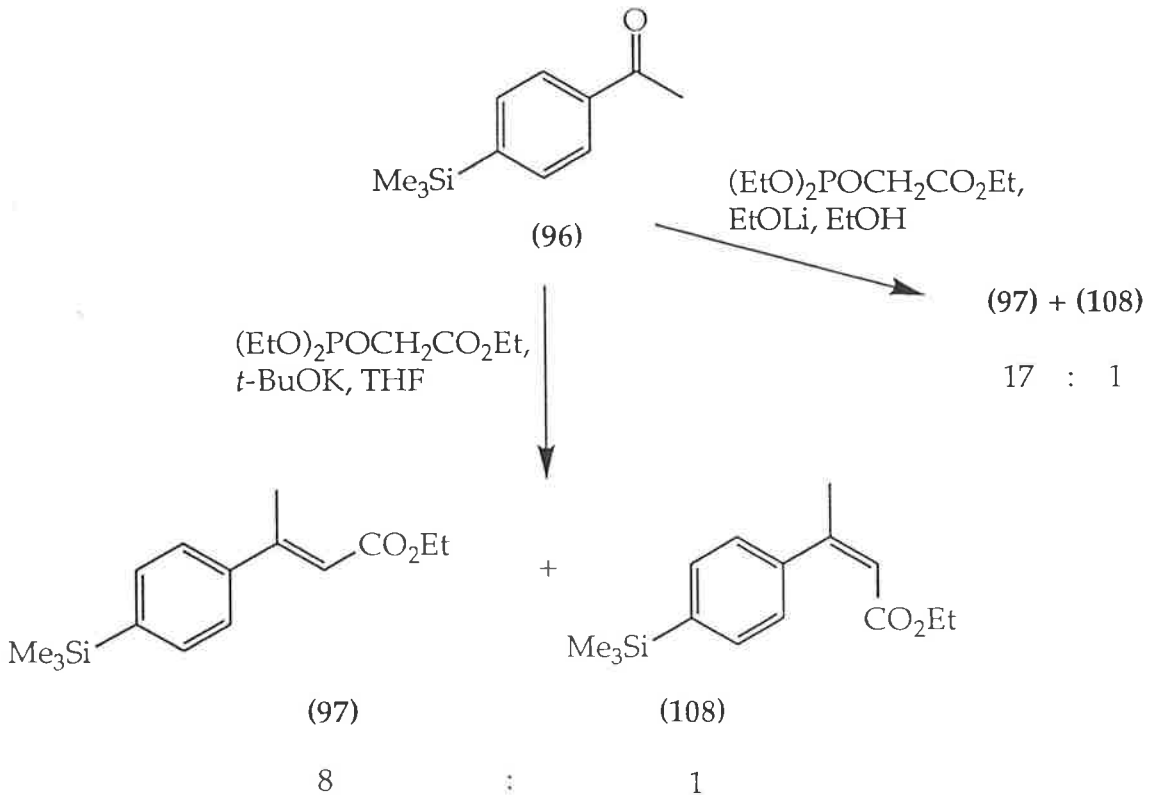


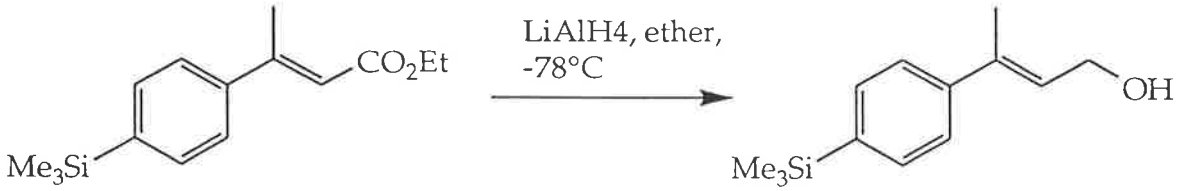
Figure 69

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 δ 6.15 and that of **108** at δ 5.88. The methyl protons resonate at δ 2.57 and δ 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 ^1H NMR spectrum of **98** shows a sharp singlet at δ 0.27 due to the 9Hs of the trimethylsilyl group. A slightly broadened 3H singlet at δ 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 δ 5.99. A doublet at δ 4.35 is due to the CH_2O protons, and the aromatic region has the characteristic AA'BB' pattern of two 2H doublets, at δ 7.39 and δ 7.49, with further small coupling.



(97) (98)

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.

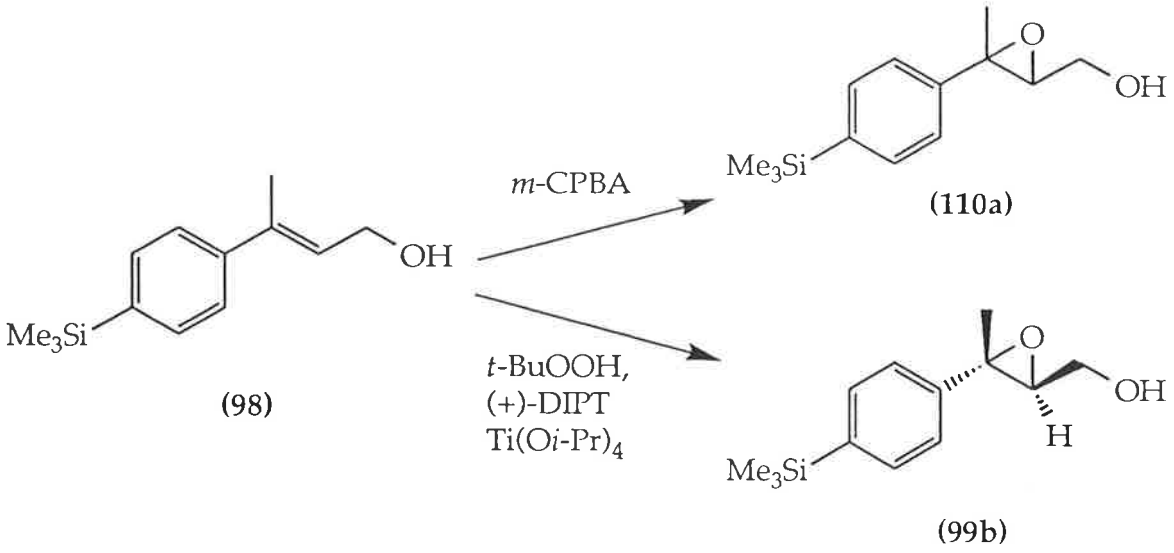
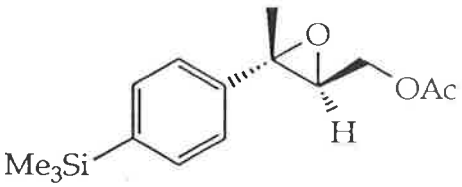
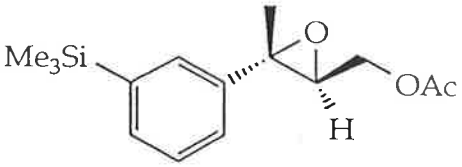


Figure 71

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 δ 0.26 due to the trimethylsilyl group and a 3H singlet at δ 1.70 due to the benzylic methyl group. The proton on the epoxide ring appears as a doublet of doublets at δ 3.10, coupled to the methylene protons at δ 3.83 and δ 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 δ 7.33 and δ 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.



(111b)
(111a) = racemate



(95b)
(95a) = racemate

Figure 72a depicts the diagnostic methyl region of the ^1H NMR spectrum of a sample of racemic epoxy acetate **111a** in the presence of an optimal amount of shift reagent. The singlets at δ 1.89 and δ 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 δ 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).

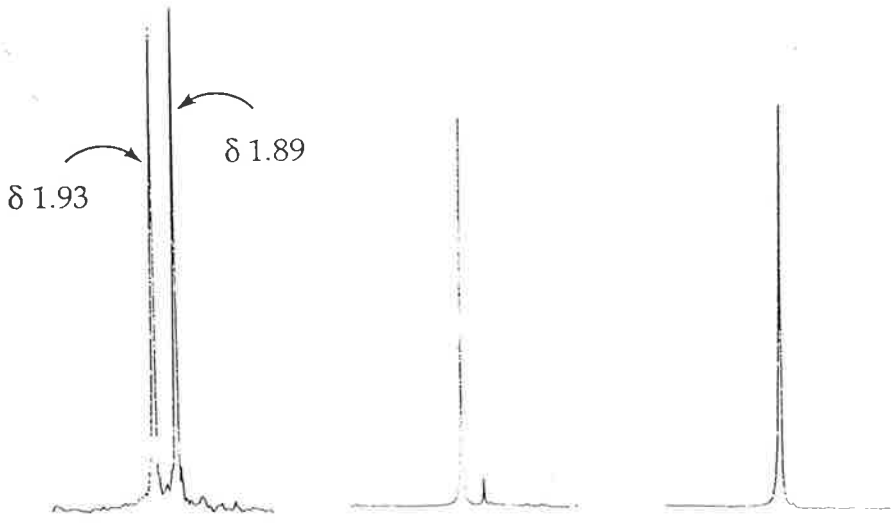


Figure 72

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.

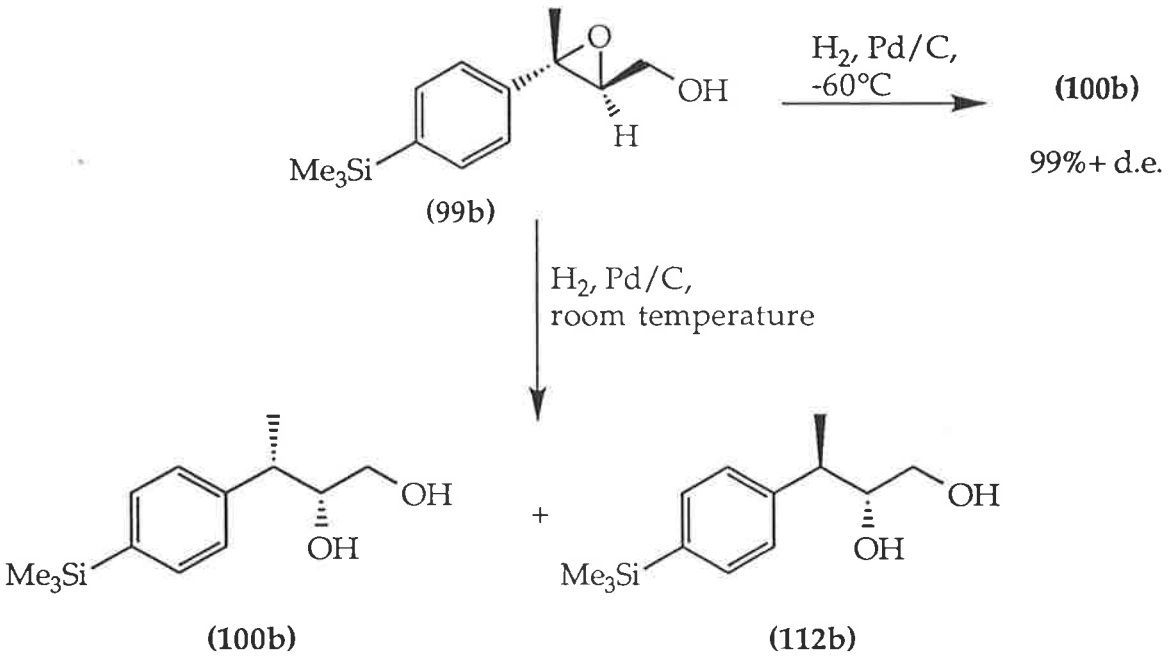


Figure 73

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 ^{1}H 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**.

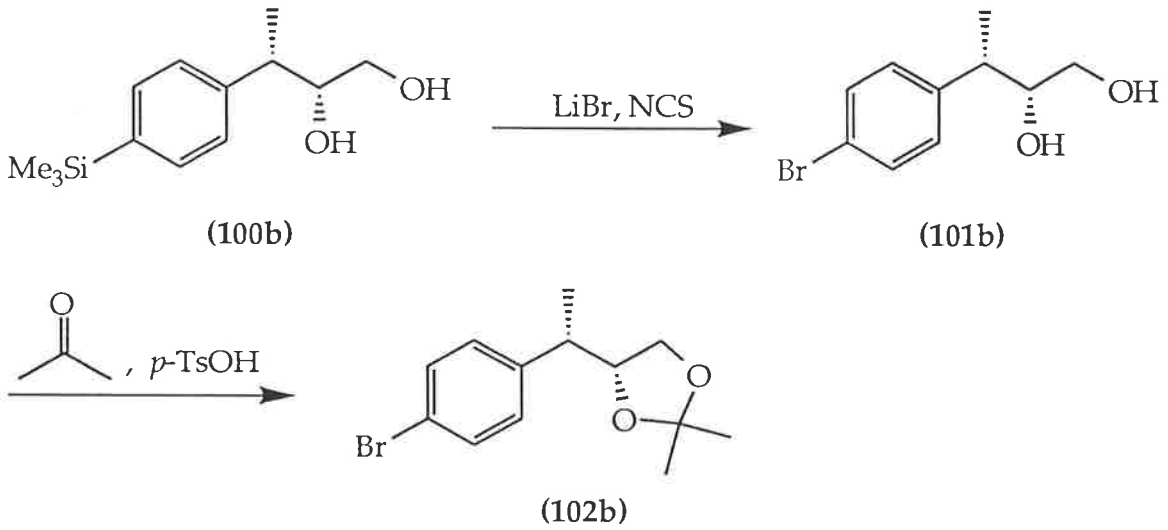


Figure 74

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 ^{1}H 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 ^{1}H 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.

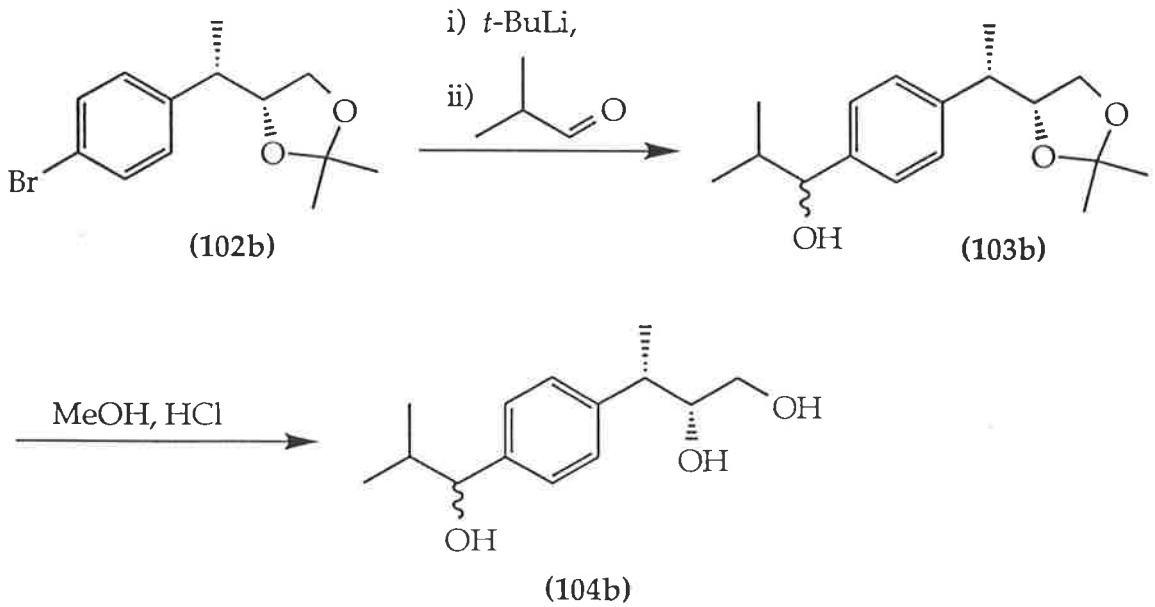
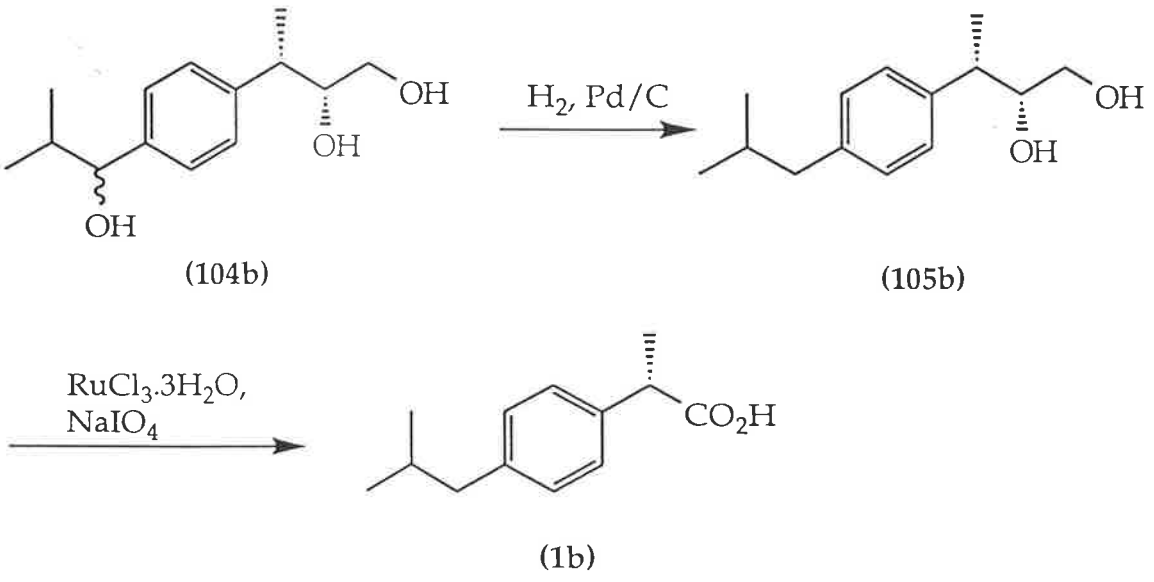


Figure 75

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.



(104b) (105b)

(1b)

Figure 76

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[84]. 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[84].

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 subsituent 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[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[55]. 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).

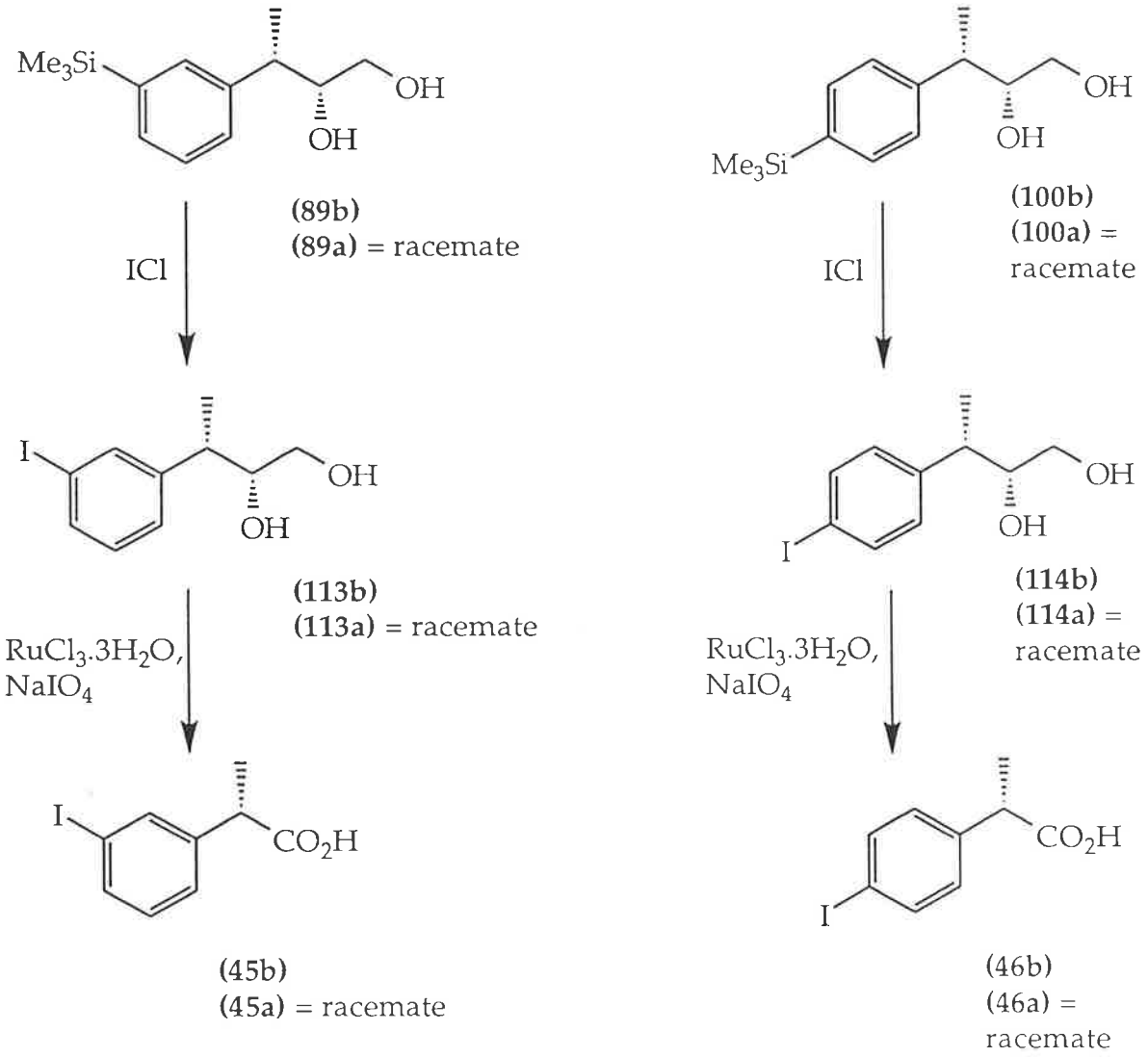


Figure 78

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 δ -0.5 - δ 0.5 region of the ^{1}H NMR spectrum of **113b** confirms

the loss of the trimethylsilyl group. The δ 1 - δ 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°. Its ^{1}H NMR spectrum shows a 7 Hz doublet at δ 1.50 due to the methyl group, a 7 Hz quartet at δ 3.67 due to the benzylic proton and a complex, 4H aromatic signal at δ 7.04 - δ 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°. Its ^{1}H NMR spectrum shows a 7 Hz doublet at δ 1.49, a 7 Hz quartet at δ 3.68 and an AA'BB' pattern of two 8 Hz doublets at δ 7.07 and δ 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(triphenyl-phosphine)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 .

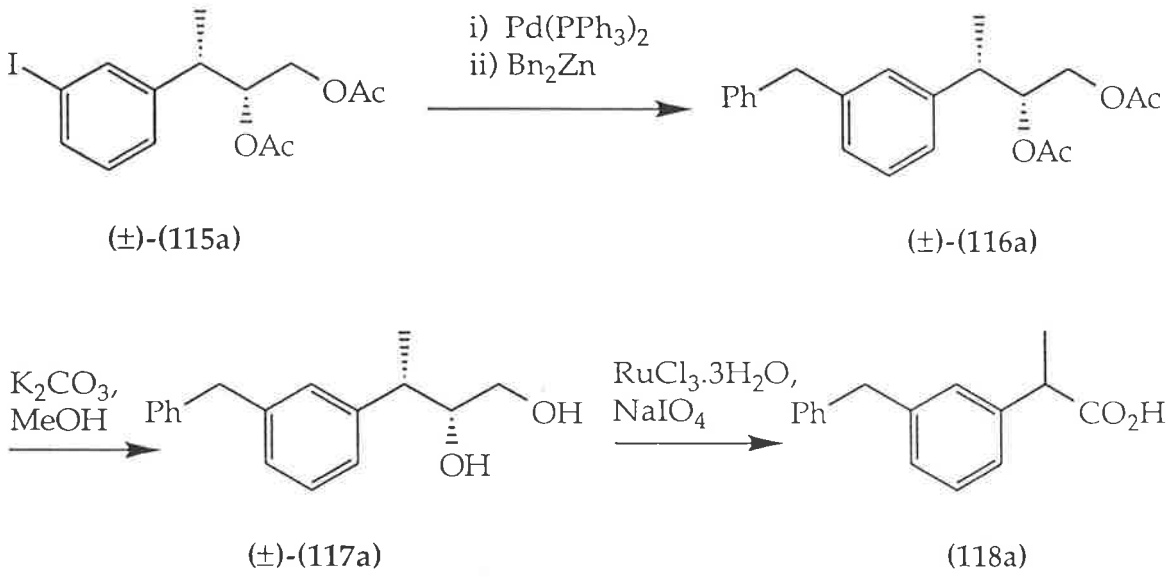
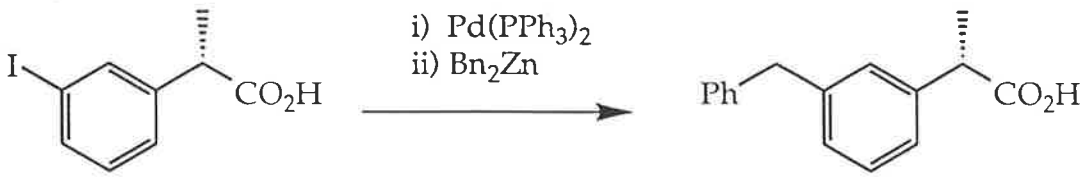


Figure 79

The coupled product **116a** was isolated in 86% yield after chromatography. The ^1H NMR spectrum of **116a** showed a 7 Hz doublet at δ 1.26 due to the benzylic methyl group and two 3H singlets at δ 1.98 and δ 2.06 from the acetate methyl groups. Other peaks which arise from the butane-1,2-diacetate moiety are a multiplet at δ 2.98 from the benzylic methine proton, two doublet of doublets at δ 3.77 and δ 4.11, each due to one of the CH_2OAc protons, and a multiplet at δ 5.22 due to the CHOAc proton. The benzylic methylene protons appear as a singlet at δ 3.96, and the aromatic protons as as a complex, 9H signal at δ 7.04 - δ 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).



(45b) **(118b)**

Figure 80

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 δ 1.5 and a 7 Hz quartet at approximately δ 3.8. It also shows a complex set of signals at δ 7.25 - δ 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 δ 7.30 - δ 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.

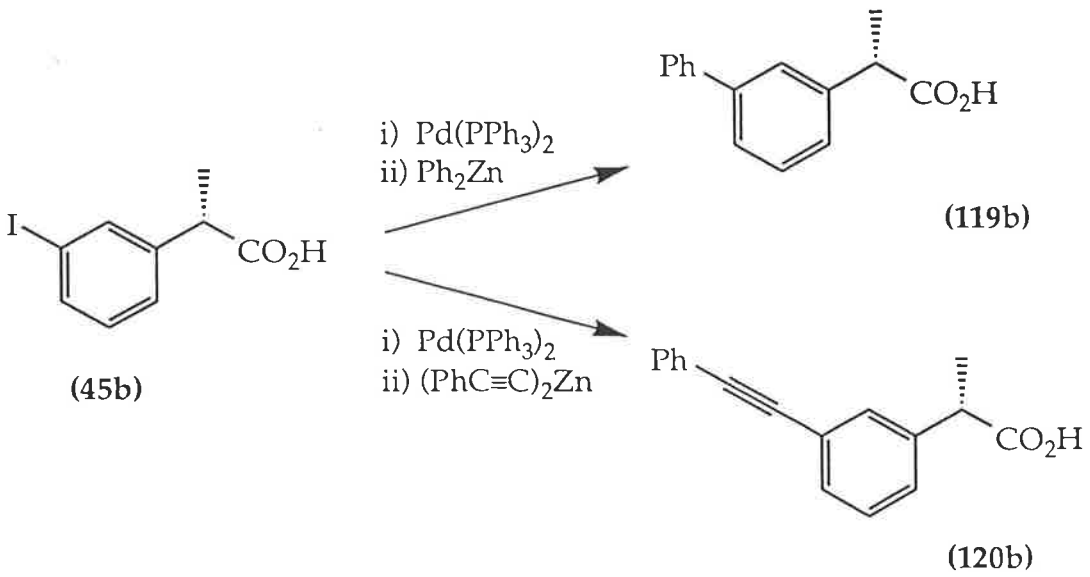


Figure 81

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 ^1H 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[90]. 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 isobutylzinc to give *(S)*-ibuprofen (**1b**) in 77% yield, which had mp and spectral data identical with those reported[88]. The optical purity of **4b** was 92% e.e.

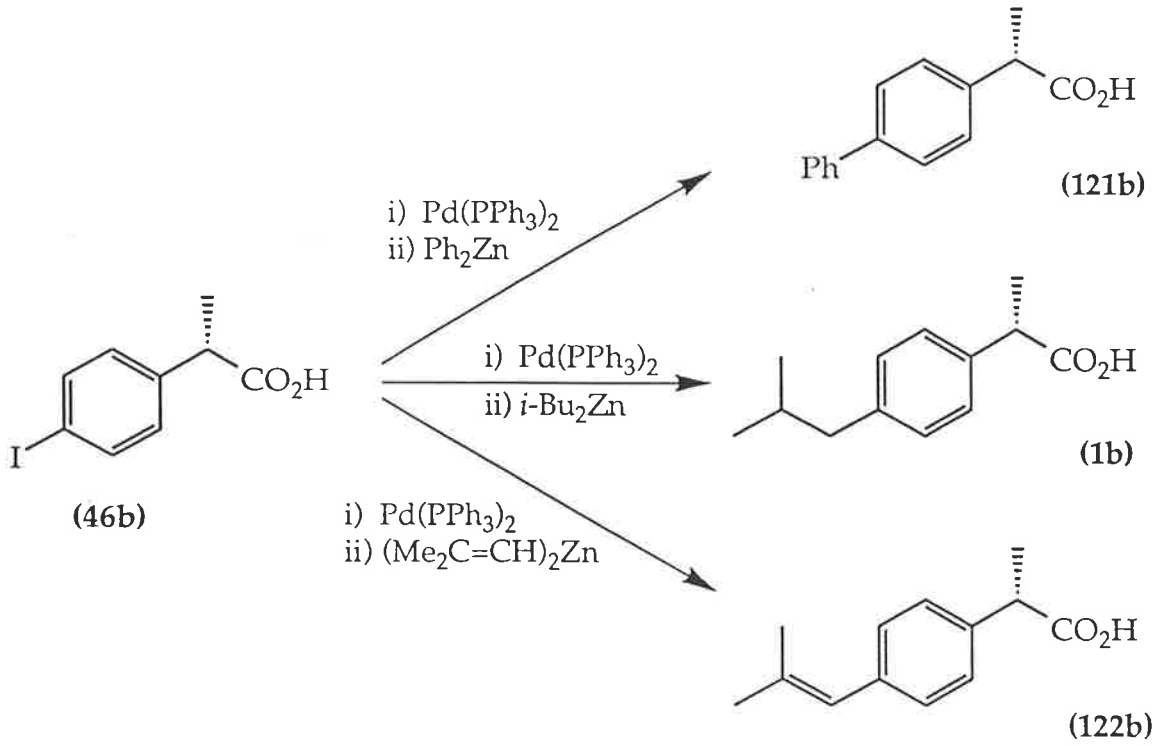


Figure 82

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

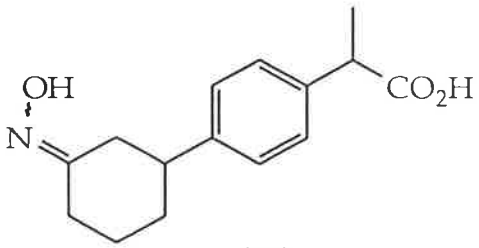
(figure 82). As well as the usual methyl and methine signals from the propanoic acid moiety, the ^{1}H NMR spectrum of **122b** shows two 1 Hz, 3H doublets at δ 1.85 and δ 1.89, due to the methyl groups of the isobutenyl group which are long range coupled to the vinylic proton. The splitting is not as well resolved in the vinylic signal, and the peak appears as a broad singlet at δ 6.23. The aromatic AA'BB' protons resonate as two doublets at δ 7.18 and δ 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.

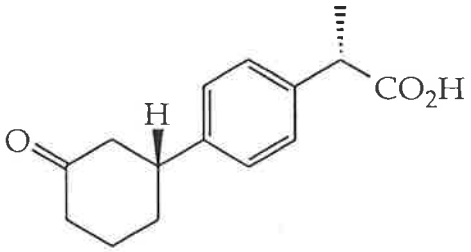
CHAPTER 4

ASYMMETRIC SYNTHESIS OF XIMOPROFEN

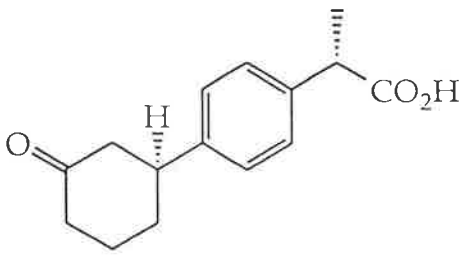
There are eight possible stereoisomers of the experimental drug ximoprofen (**49**) (figure 83), as it contains two chiral centres and an oxime group, which can exist in either the (*E*) or (*Z*) configuration. As discussed on page 36 in the retrosynthetic analysis of ximoprofen, the oxime could be formed 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 *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.



(49)



(123b)
(123c) = enantiomer



(124b)
(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, (2*S*,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[67] (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[66,67] (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 δ -0.01 due to the trimethylsilyl group and a multiplet at δ 1.40 from the SiC**H** proton. The two methylene groups give rise to a complex 4H signal at δ 2.09 - δ 2.42. The olefinic proton α to the carbonyl group appears as a doublet of triplets at δ 5.96, with a 10 Hz coupling to the adjacent olefinic proton and a 1 Hz long range coupling. The β olefinic proton resonates at δ 7.00 as a multiplet.

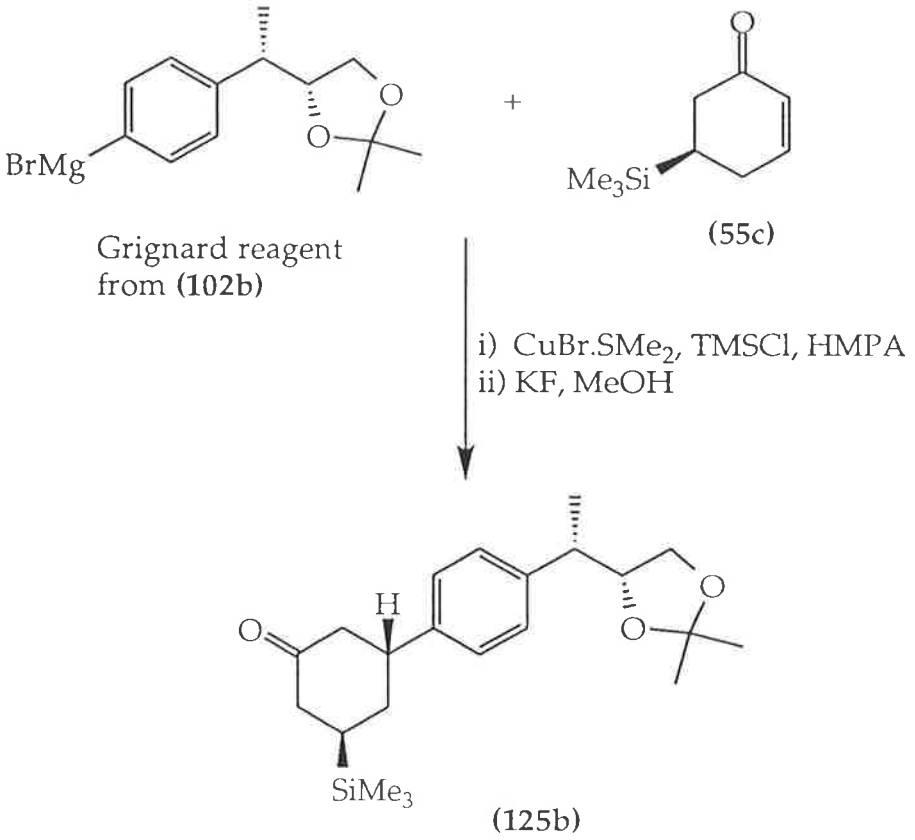
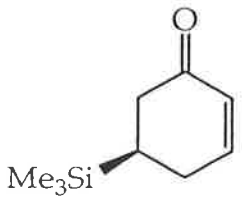


Figure 84

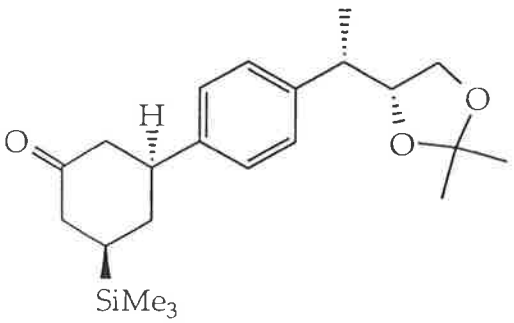
The conjugate addition reaction[67] (figure 84) was performed by addition of a THF solution of the Grignard reagent from **102b** to **55c**, in the presence of a catalytic amount of copper bromide-dimethylsulphide complex, HMPA and an excess of chlorotrimethylsilane. The reaction was worked up and without 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).



(55c)



(126b)

Figure 85

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[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[67] (figure 86).

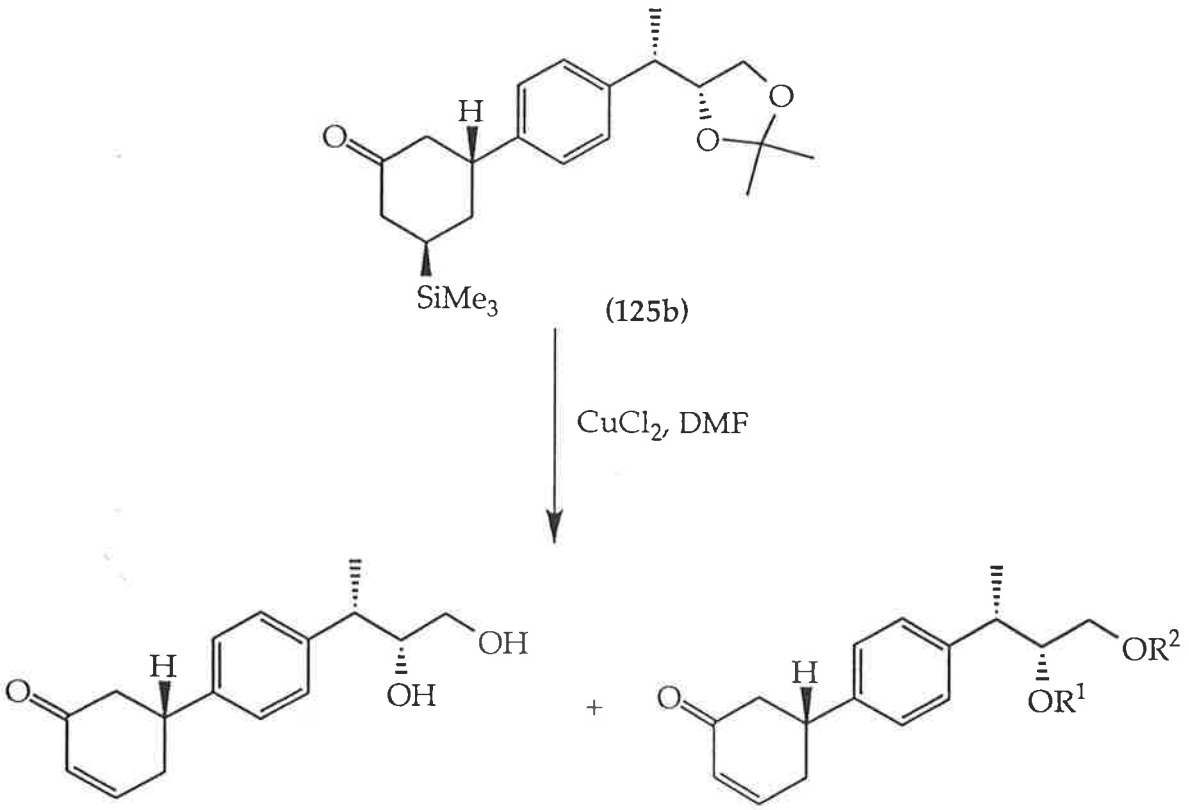


Figure 86

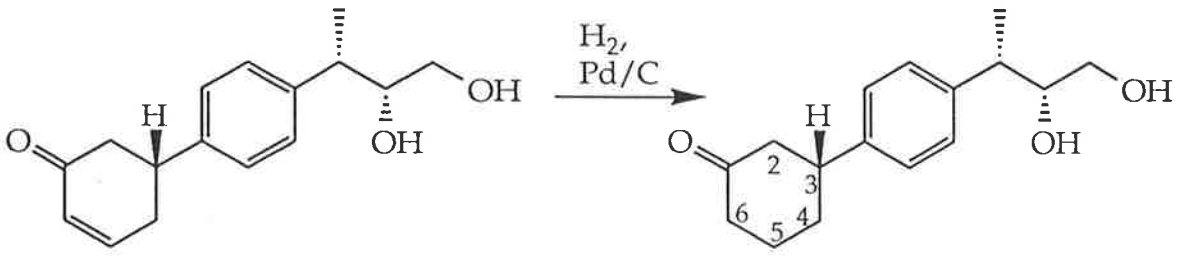
TLC of the crude reaction product indicated that the major product was much more polar than the starting material **125b**, and that there was a significant quantity of a higher Rf product. The products were separated by chromatography and ^{1}H NMR spectroscopy confirmed that the major product was the 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 δ 1.34 for the benzylic methyl group, which was coupled to a 7 Hz quintet at δ 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 δ 3.22 and δ 3.44 due to the methylene protons and a doublet of triplets at δ 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 δ 2.46 and δ 2.71. The olefinic proton α to the carbonyl group resonates as a doublet of doublets at δ 6.12, with a 10 Hz coupling to the other olefinic proton and a 2 Hz long range coupling. The β proton of the α,β-enone system gives rise to a multiplet at δ 7.06, and the 4H aromatic signal is an apparent singlet at δ 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 δ 8.11 and δ 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 δ 1.32 and the other at δ 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 monitered 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.



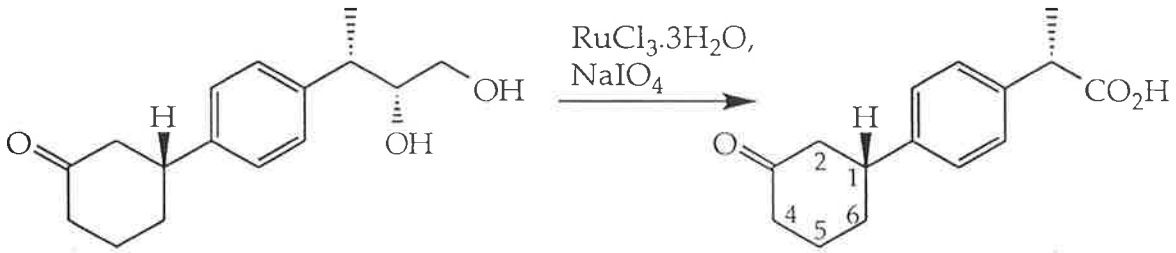
(127b) (128b)

Figure 87

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 δ 1.82 is due to the two axial protons on C4 and

C5, the corresponding equatorial protons resonate at δ 2.11, the two C6 protons as a multiplet at δ 2.39, the two C2 protons as a multiplet at δ 2.55 and the axial, benzylic C3 proton as a triplet of triplets at δ 2.98. This signal has a 4.6 Hz axial-equatorial coupling to the signal at δ 2.11 and a 11.6 Hz axial-axial coupling to the signal at δ 1.82. The four aromatic protons are apparent as a singlet at δ 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).



(128b) **(123b)**

Figure 88

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°. The signals of the the ^1H NMR spectrum of **123b** were assigned with the help of a COSY experiment. A 7 Hz doublet at δ 1.50 is due to the methyl group of the propanoic acid chain and is coupled to the proton α to the carboxyl group, which appears as a 7 Hz quartet at δ 3.73. A complex 2H signal at δ 1.73 - δ 1.90 is due to the axial protons of C5 and C6 of the cyclohexane ring and a separate signal at δ 2.05 - δ 2.18 is due to the C5 and C6 equatorial protons. The two C4 protons resonate as a complex signal at δ 2.32 - δ 2.45 and those attached to C2 at δ 2.49 - δ 2.61. The axial C1 proton at δ 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 *para* substitution, which is a symmetrical pair of 8 Hz doublets at δ 7.18 and δ 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 $[a]_D^{20}$= +52°. Further support for the structure of the target molecule, keto acid **123b**, was obtained by microanalysis.

The synthesis of the (2*S*, 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.

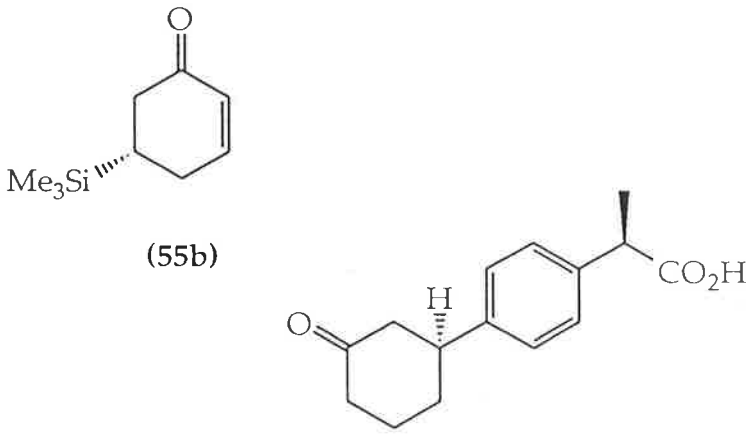


Figure 89

Optically pure enone **55b** was obtained according to the method of Asaoka[66], and the purity was confirmed by an optical rotation measurement ($[\alpha]_D^{20}$= +35.7° ± 0.2°, lit[66]: $[\alpha]_D^{20}$= +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).

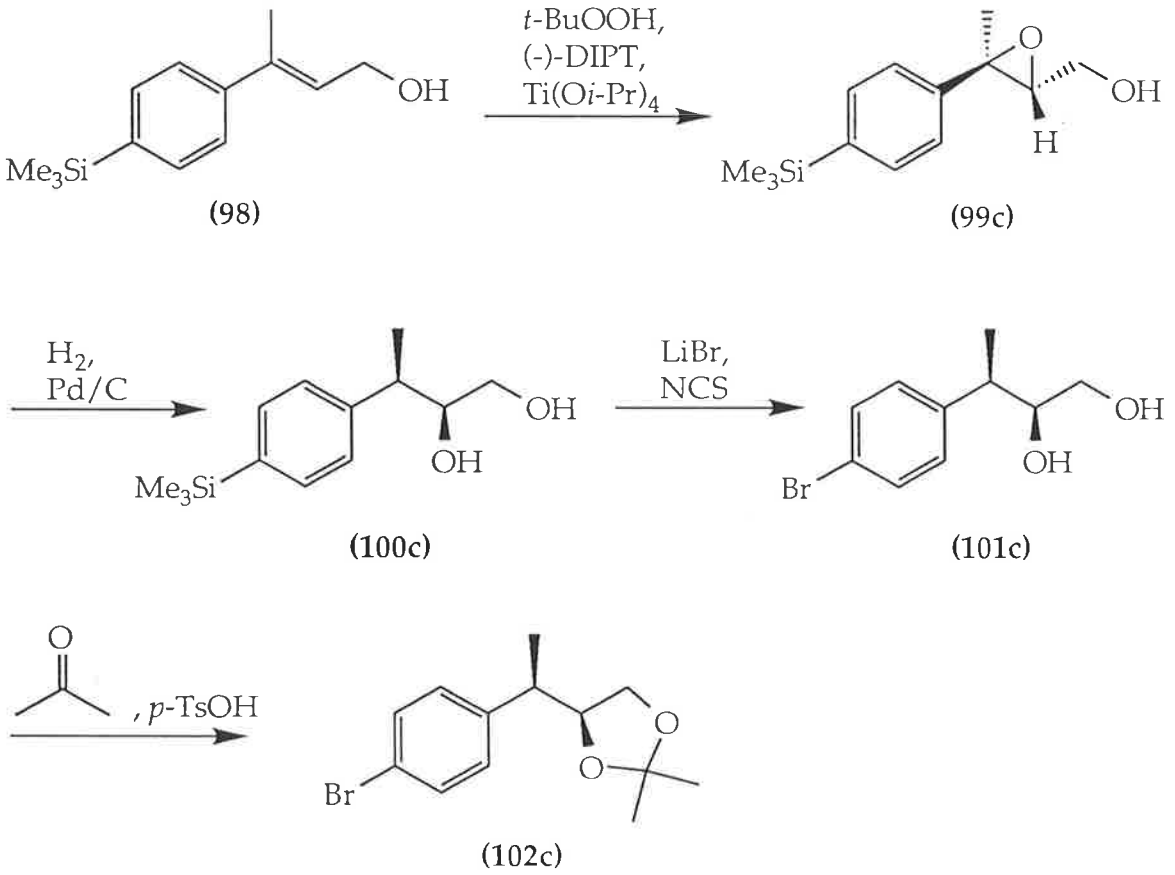


Figure 90

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**.

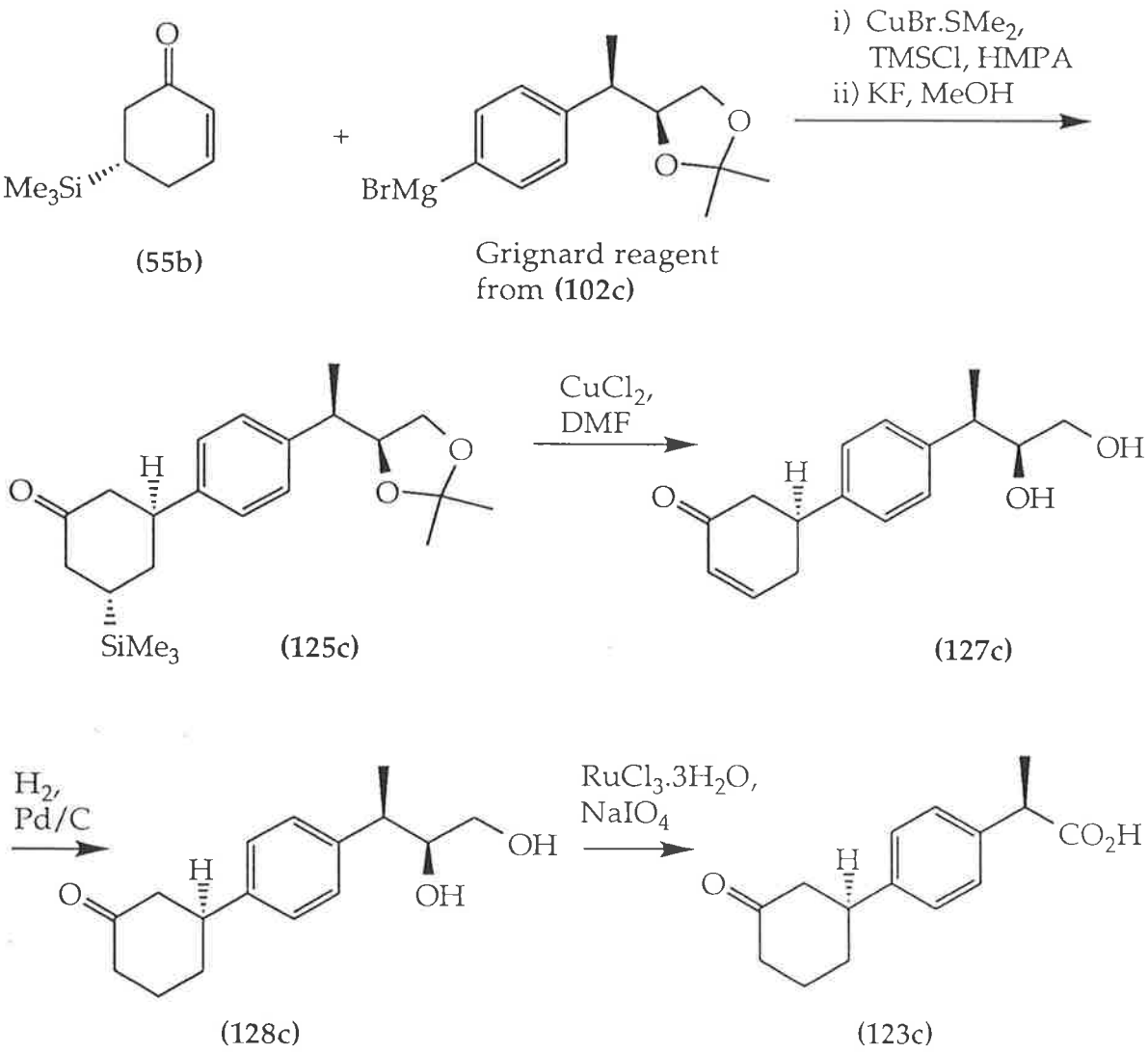


Figure 91

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**: $[\alpha]_D^{20}$= -53°, **123b**: $[\alpha]_D^{20}$= +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).

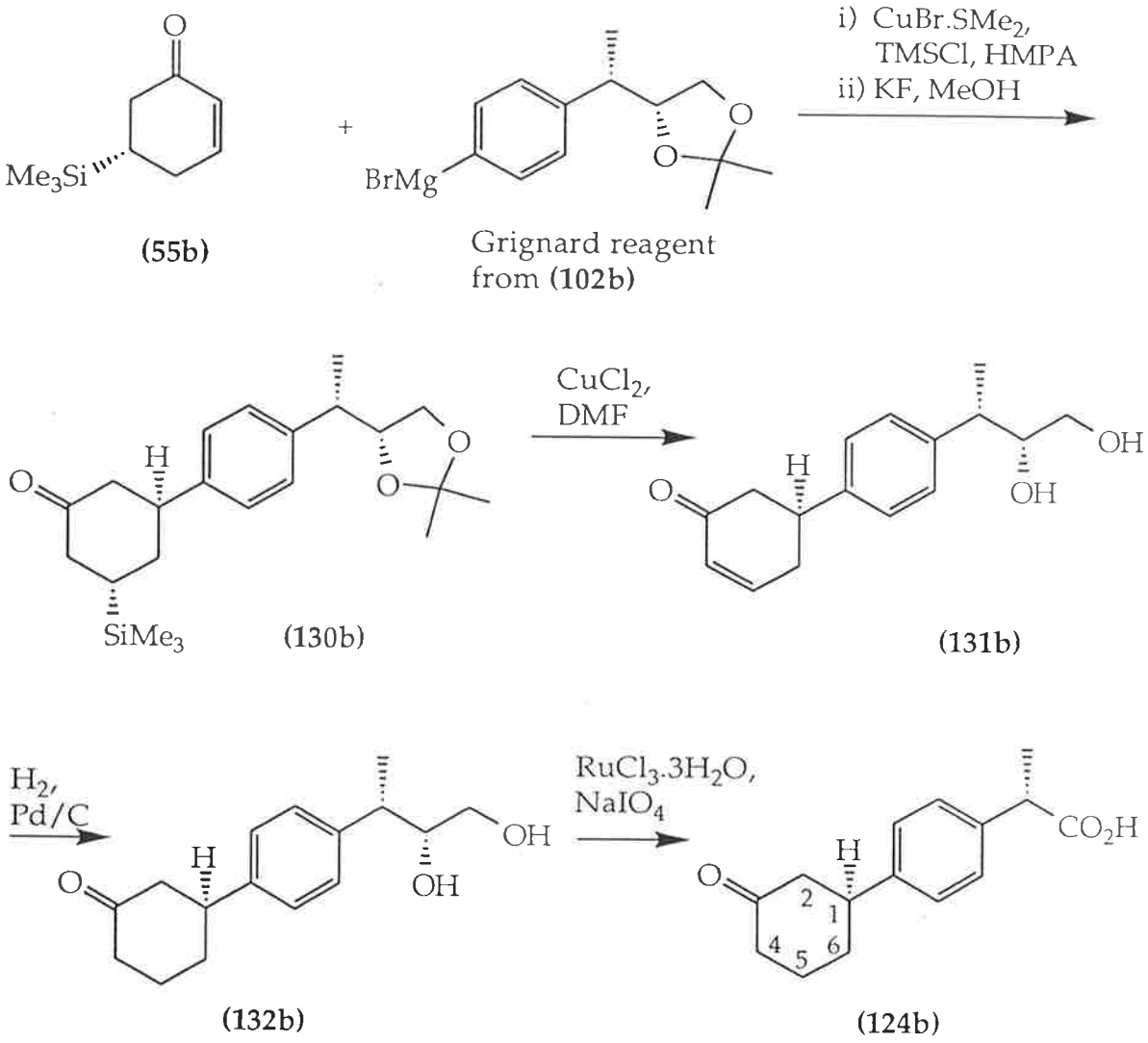


Figure 92

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 δ 1.50 and the proton α to the carboxyl group as a 7 Hz quartet at δ 3.73. A complex 2H signal at δ 1.73 - δ 1.90 is due to the axial protons of C5 and C6 of the cyclohexane ring and a separate signal at δ 2.05 - δ 2.18 is seen for the C5 and C6 equatorial protons. The two C4 protons resonate as a complex signal at δ 2.32 - δ 2.45 and those attached to C2 at δ 2.49 - δ 2.61. The axial C1 proton at δ 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 δ 7.18 and δ 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°, **123b** has $[\alpha]_D^{20}$= +52°. 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 ($[\alpha]_D^{20}$ of **124c** =-48°).

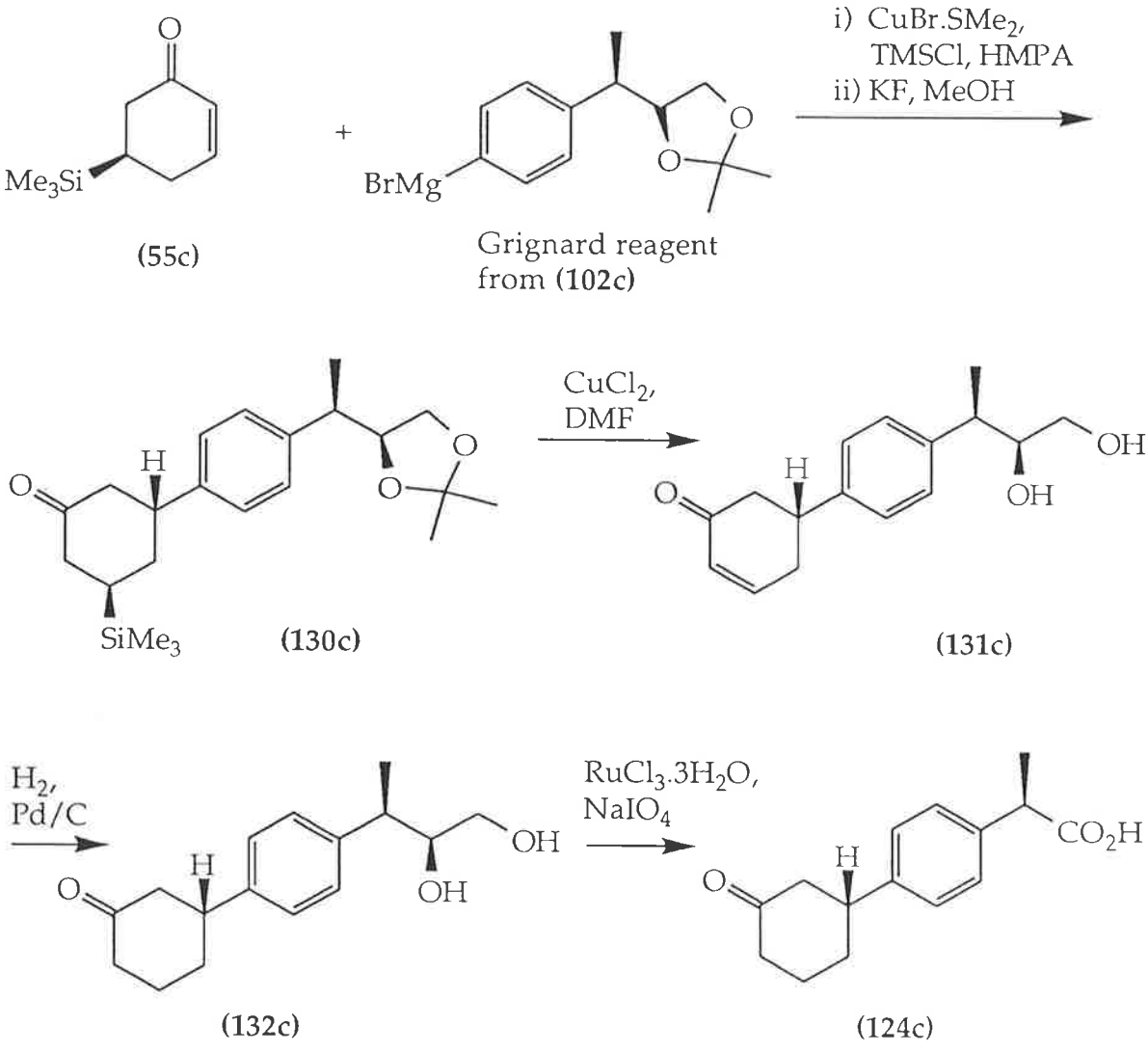
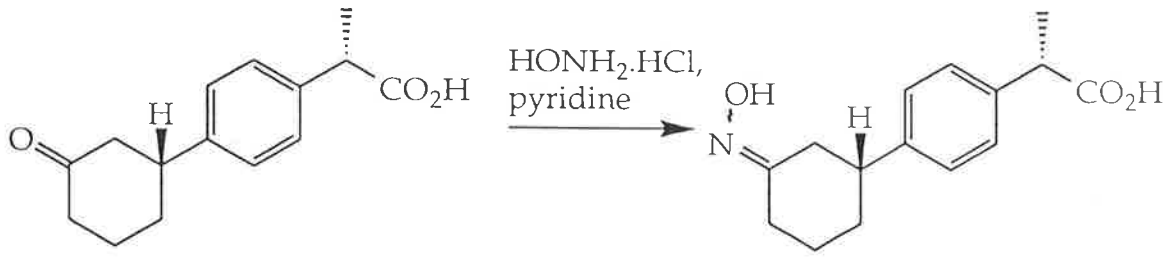


Figure 93

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 *in vitro* (NSAIDs act as competitive inhibitors of cyclo-oxygenase, an enzyme involved in the inflammation process). The amount of thromboxane B_2 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 α 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 (2*S*,1''*R*) isomer **123b**) was approximately an order of magnitude more active than the epimeric (2*S*,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).



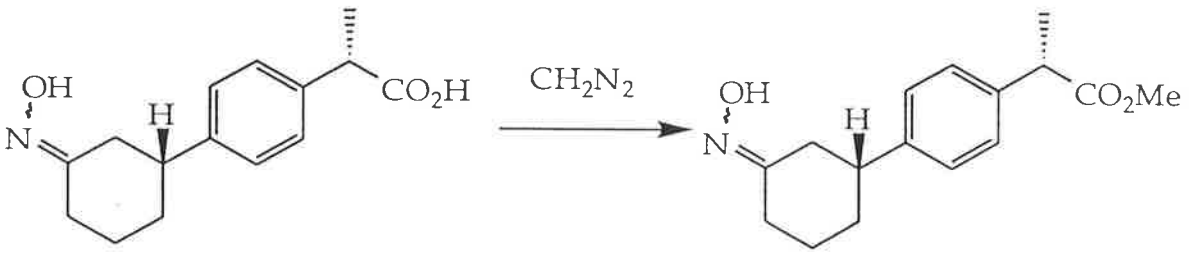
(123b)

(E): **(133b)**
(Z): **(134b)**

Figure 94

The isomers **133b** and **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 **135b** and **136b**, which were much less polar than the carboxylic acids (figure 95). This was achieved by treatment of **133b** and **134b** with an ethereal solution of diazomethane.

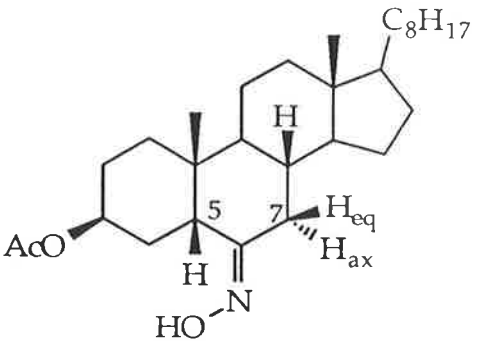


(*E*): **(133b)**
(*Z*): **(134b)**

(*E*): **(135b)**
(*Z*): **(136b)**

Figure 95

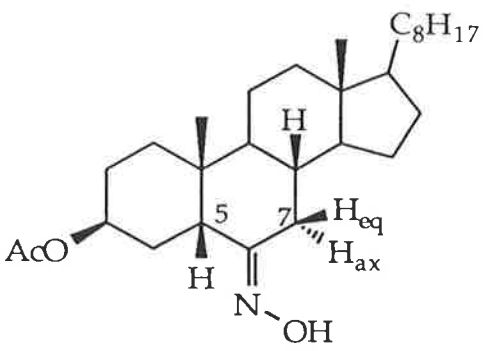
The methyl esters **135b** and **136b** were separated by HPLC. The first eluting component was assigned as the (*E*) isomer and the second eluting component as the (Z) isomer. These assignments were based on findings by Duddeck et al[91] during the study of cholestane derivatives (figure 96). They observed that the equatorial proton on the carbon α to the oxime was shifted downfield when it was *cis* to the oxime hydroxyl. Thus, derivative **137** shows the equatorial proton of C5 to resonate at δ 3.45 and the equatorial proton of C7 at δ 2.17, whereas derivative **138** shows peaks at δ 2.33 due to the C5 equatorial proton and δ 3.15 due to the C7 equatorial proton. These structures were confirmed by X-ray crystallography.



(137)

C5 H_{eq}: δ 3.45

C7 H_{eq}: δ 2.17



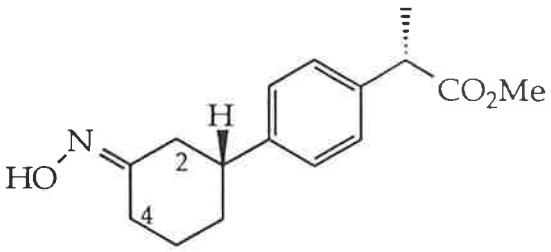
(138)

C5 H_{eq}: δ 2.33

C7 H_{eq}: δ 3.15

Figure 96

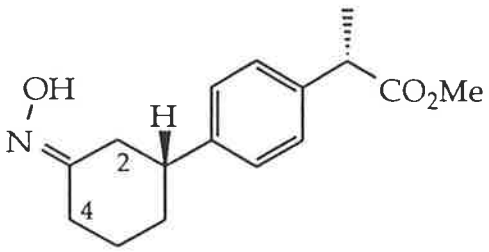
In the current work, the first eluting isomer gave rise to signals in its ^1H NMR spectrum at δ 1.98 - δ 2.05 due to the two axial protons of C2 and C4 (figure 97), δ 2.57 for the equatorial proton of C2 and δ 3.37 for the equatorial proton of C4 (the resonances were assigned on the basis of chemical shift values and coupling to the distinctive benzylic proton as determined by a COSY experiment).



(135b)

C4 H_{eq}: δ 3.37

C2 H_{eq}: δ 2.57



(136b)

C4 H_{eq}: δ 2.44

C2 H_{eq}: δ 3.47

Figure 97

The ^1H NMR spectrum of the second eluting isomer showed peaks at δ 1.94 and δ 2.11 respectively for the C2 and C4 axial protons, and δ 3.47 and δ 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.

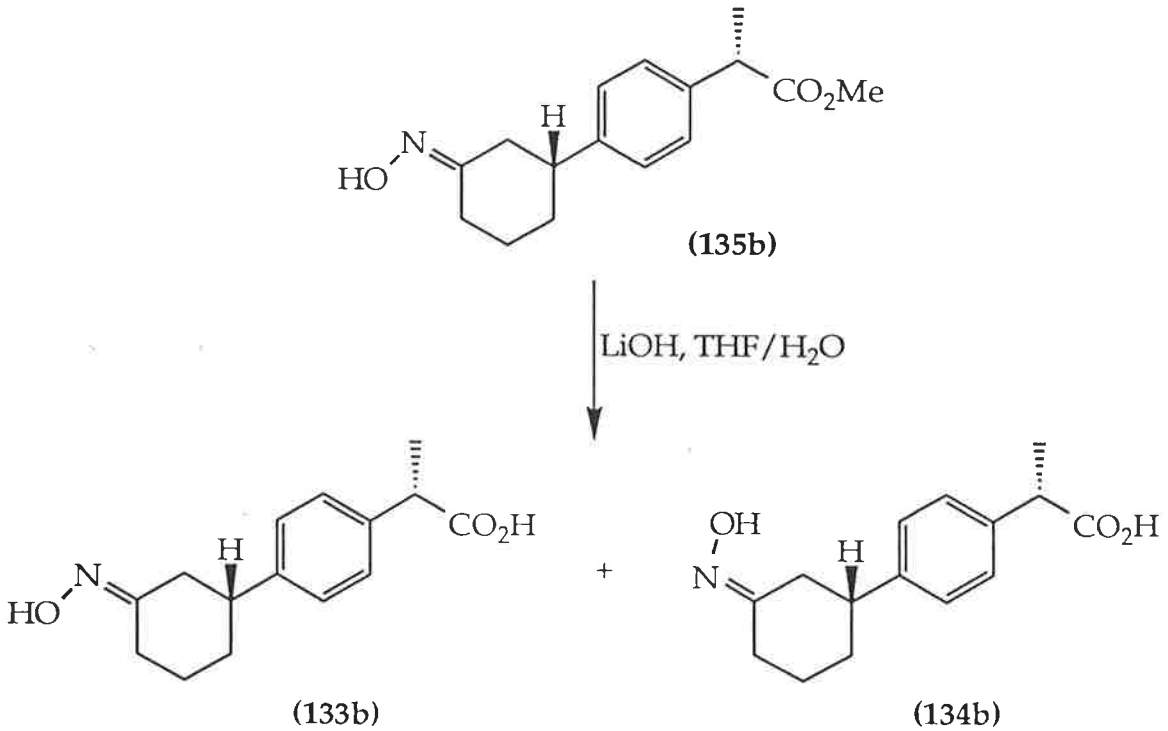


Figure 98

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 deuterochloroform.

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[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[93]. However the principle behind the approach could be applied to the asymmetric synthesis of other *meta* and *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**).

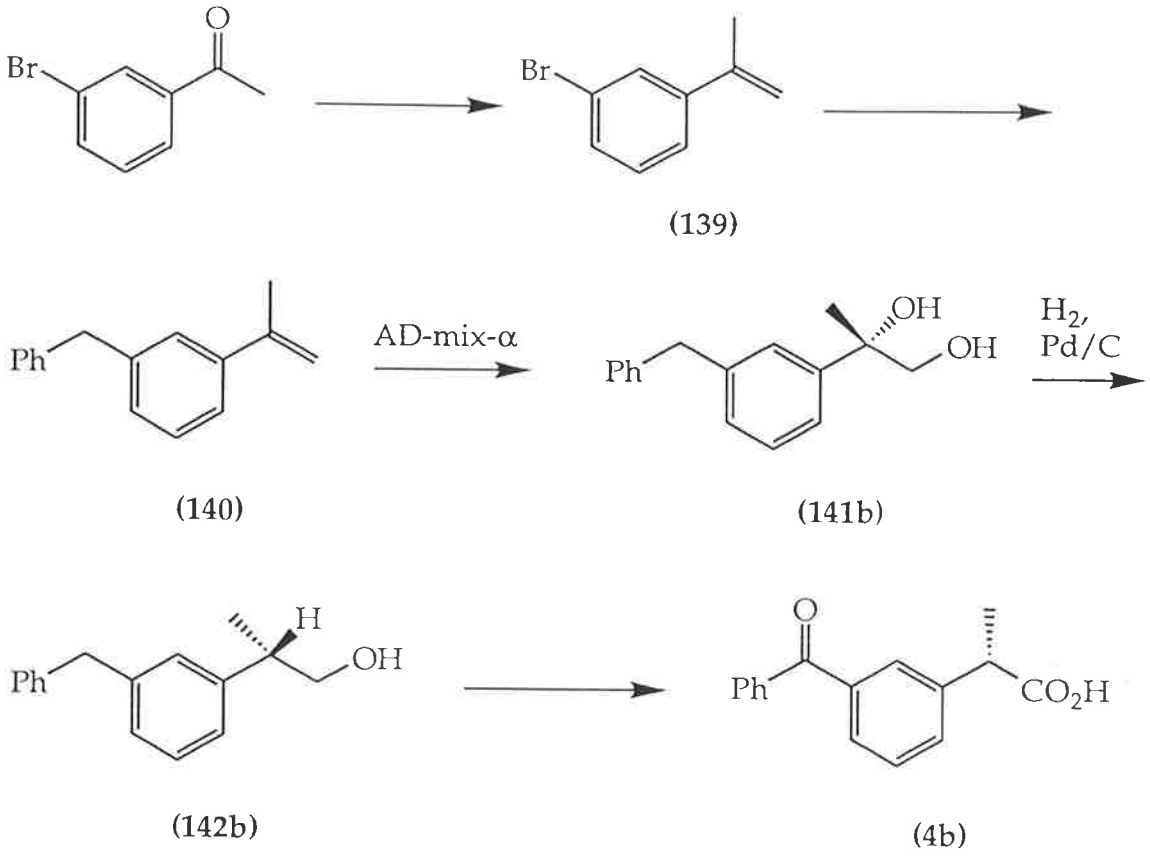


Figure 99

A Wittig reaction was used to convert *m*-bromoacetophenone to the alkene **139** (figure 100). Methyltriphenylphosphonium iodide was treated with an equimolar amount of potassium *tert*-butoxide to generate the ylid, to which *m*-bromoacetophenone was added. After work up and distillation the product **139** was obtained in 85% yield.

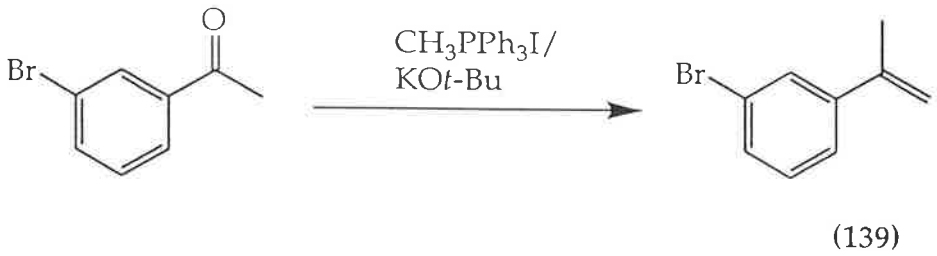
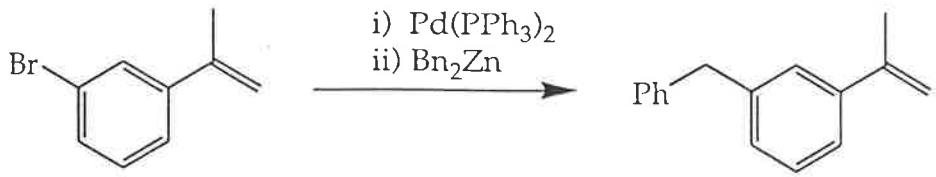


Figure 100

The ^1H NMR spectrum of **139** shows a 3H singlet at δ 2.12 due to the methyl group, two 1H singlets at δ 5.11 and δ 5.38 from the olefinic protons and a complex 4H aromatic signal at δ 7.15 - δ 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 diisobutyl-aluminium 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 ^1H 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.

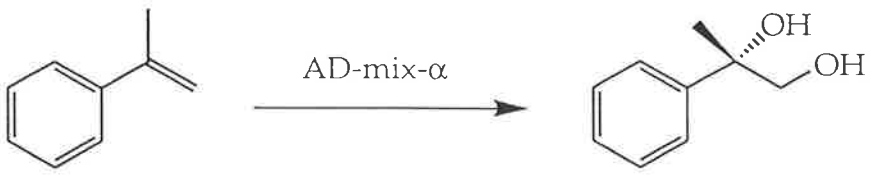


(139) (140)

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 ^1H 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 δ 2.13 from the methyl group, a 2H singlet at δ 3.99 for the benzylic methylene protons and two 1H singlets at δ 5.06 and δ 5.34 due to the olefinic protons. The δ 7.1 - δ 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 δ 3.99 with that of the 4H methylene signal of 1,2-diphenylethane at δ 2.93 indicated that the components were present in a 61:39 ratio.

Sharpless has reported the conversion of α-methylstyrene to the *(S)* diol **143b** (figure 102) by the use of AD-mix-α, 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.



(143b) 93% e.e.

Figure 102

In the current work, the benzyl alkene **140** was treated with AD-mix-α in a similar manner to that reported for the treatment of α-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 ^1H NMR spectrum of **141b** is consistent with the assigned structure. The methyl protons resonate as a singlet at δ 1.52 and the OH protons at δ 1.85 and δ 2.60, each as a broad singlet. Two doublets at δ 3.62 and δ 3.79 arise from the CH_2O protons which have a 10 Hz geminal coupling. A 2H singlet at δ 4.01 is due to the benzylic methylene group and a complex 9H signal between δ 7.22 and δ 7.34 belongs to the aromatic protons.

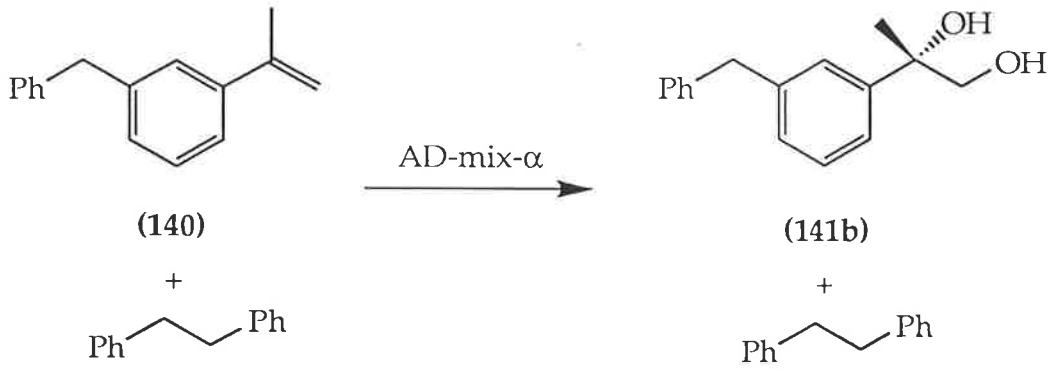


Figure 103

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 ^1H NMR data identical with those of the optically active analogue **141b**. Microanalytical data supported the structure of **141a**.

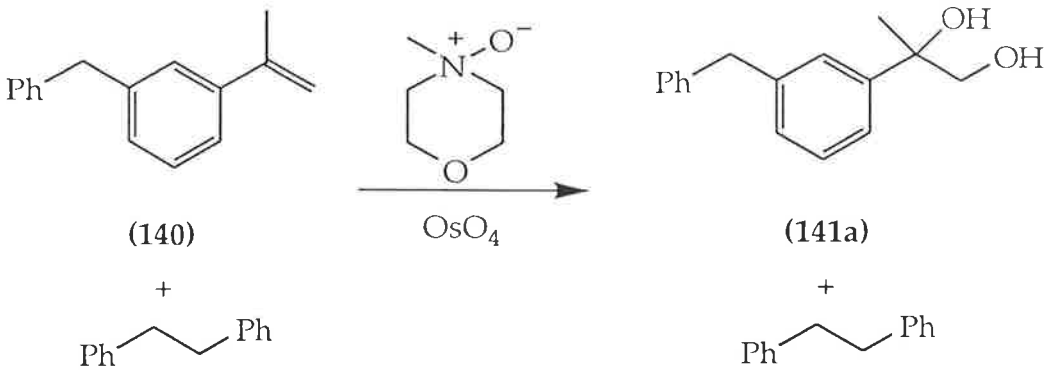


Figure 104

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.

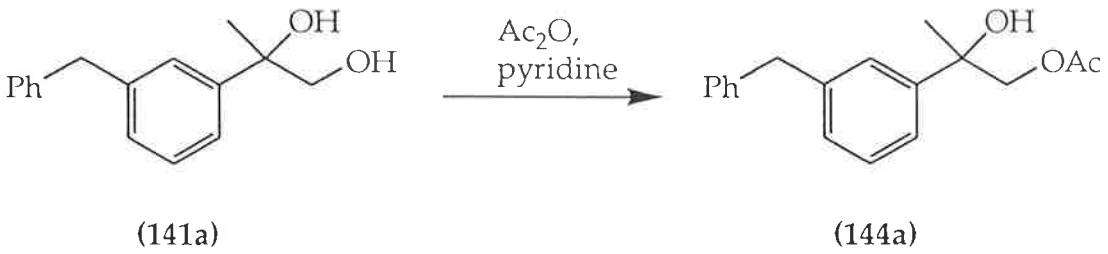


Figure 105

The ^{1}H NMR spectrum of the acetate **144a** shows a sharp 3H singlet at δ 1.54 due to the benzylic methyl group and another at δ 2.01 due to the acetate methyl

group. The benzylic methylene protons appear as a singlet at δ 3.99 and the CH_2OAc 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).

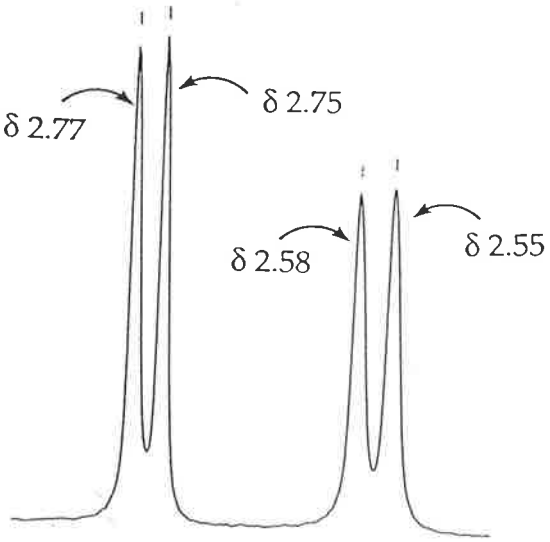


Figure 106a

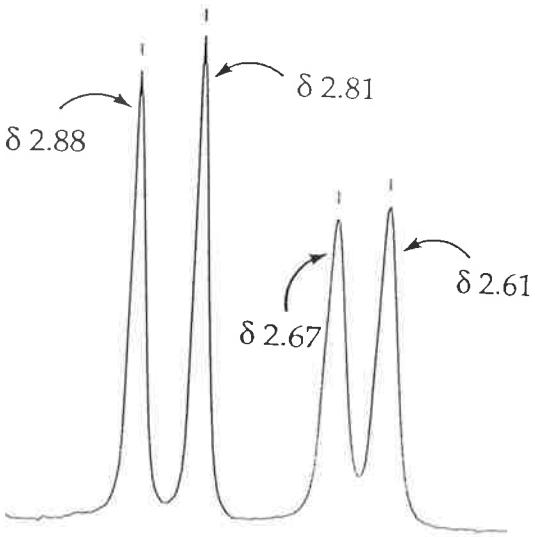
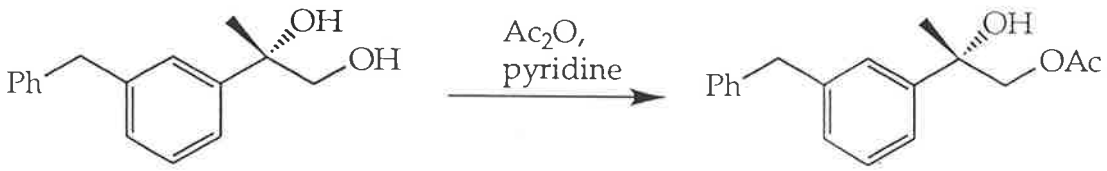


Figure 106b

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.



(141b) **(144b)**

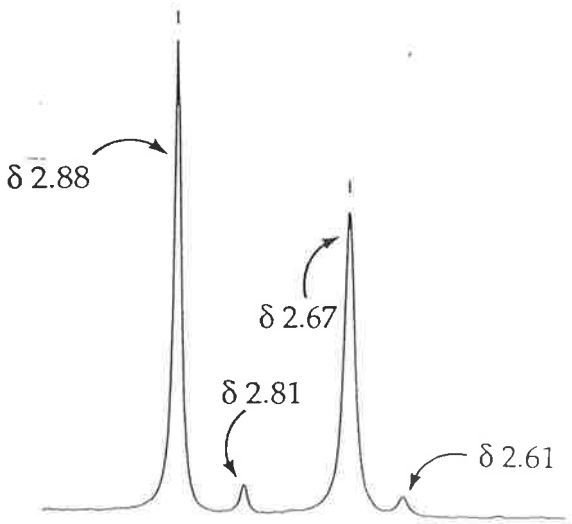
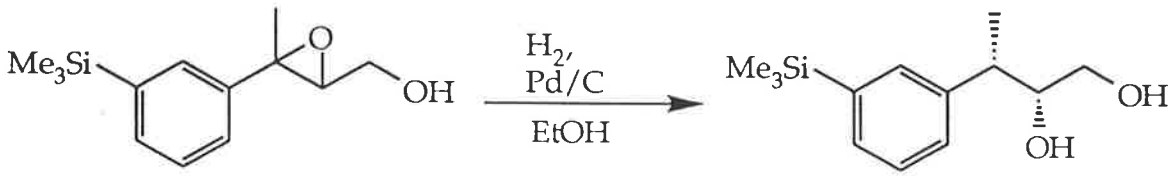


Figure 107

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).



(88a)

(±)-(89a)
99% d.e.

Figure 108

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[48]. 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 $PhCH_2OR$, the rate of hydrogenolysis increased in the order OH < O-alkyl < O-aryl < OH^+-alkyl < OH_2^+ < OAc < $OCOCF_3$[44].

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.

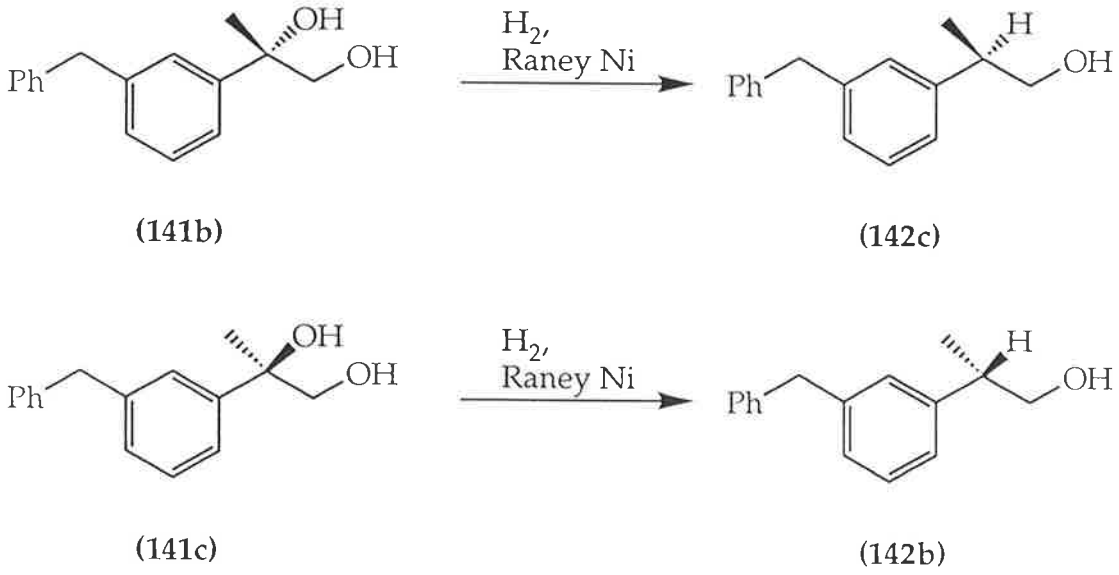
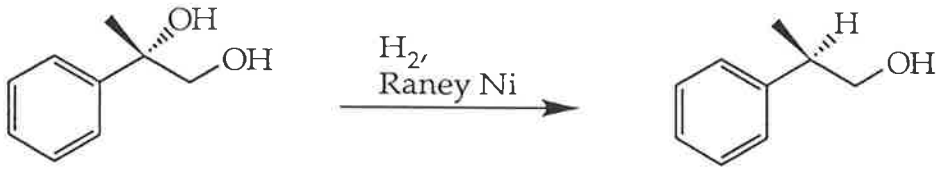


Figure 109

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[46]. 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 al[46] 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.



(145b) **(146b)**
99% e.e.

Figure 110

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

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.

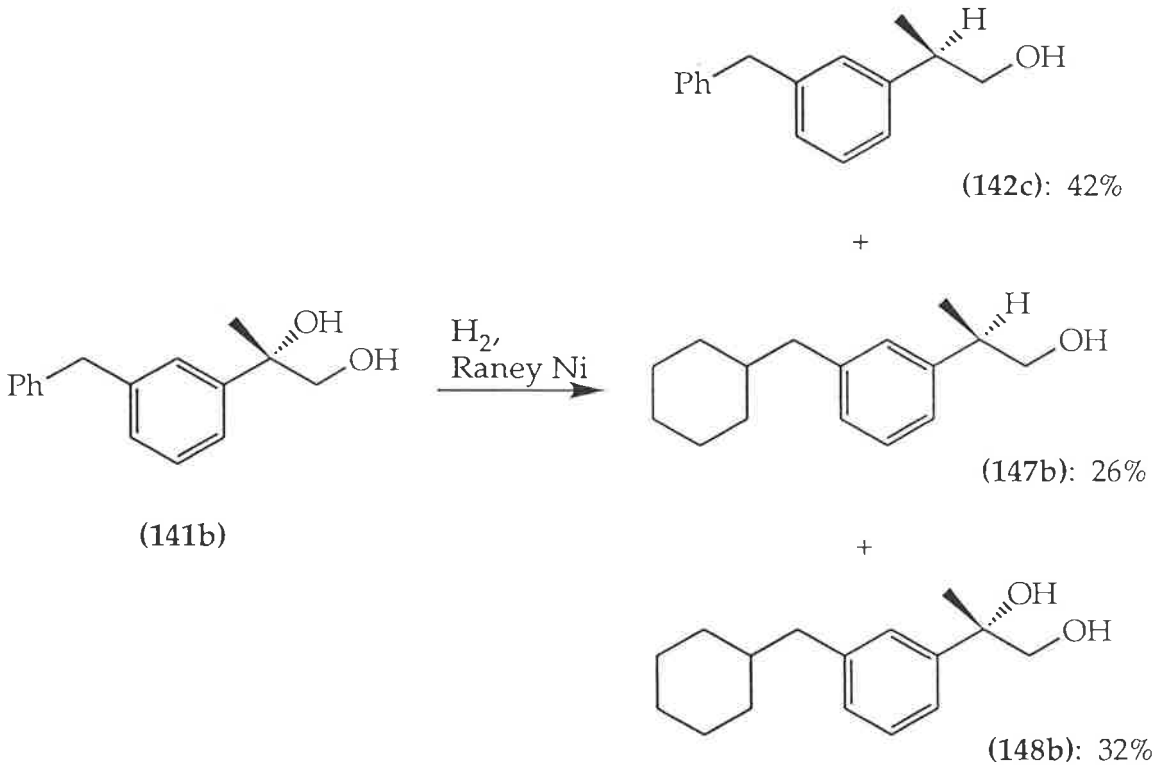


Figure 111

The configuration of the three products was not confirmed. The stereochemical assignments illustrated in figure 111 are based on the assumption that the hydrogenonolysis proceeded with retention of configuration. The ^1H NMR spectrum of the required alcohol **142c** contains a 7 Hz doublet at δ 1.26 due to the methyl group. This is coupled to a 7 Hz sextet at δ 2.92 which belongs to the benzylic methine proton. The CH_2OH protons appear as a 7 Hz doublet at δ 3.69 and the benzylic methylene protons as a

singlet at δ 3.99. The aromatic region integrates for nine protons and appears at δ 7.02 - δ 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_2OH methylene protons in this case show coupling with the OH proton and appear as a 2H triplet at δ 3.72. One of the features of the spectrum which indicate that ring reduction had occurred is a complex set of signals in the δ 0.85 - δ 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 δ 7.01 - δ 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 δ 2.47 which suggests that it has only one adjacent aryl group (the same signal resonates as a singlet at δ 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 δ 0.85 and δ 1.85 in its ^{1}H NMR spectrum, due to the cyclohexane and hydroxyl protons. The spectrum also shows a 3H singlet at δ 1.55 from the methyl group, a 7 Hz doublet at δ 2.51 from the benzylic methylene protons and two doublet of doublets at δ 3.65 and δ 3.82 due to the diastereotopic CH_2OH protons which are coupled to each other and to the adjacent OH. The aromatic protons resonate as a 4H signal at δ 7.03 - δ 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).

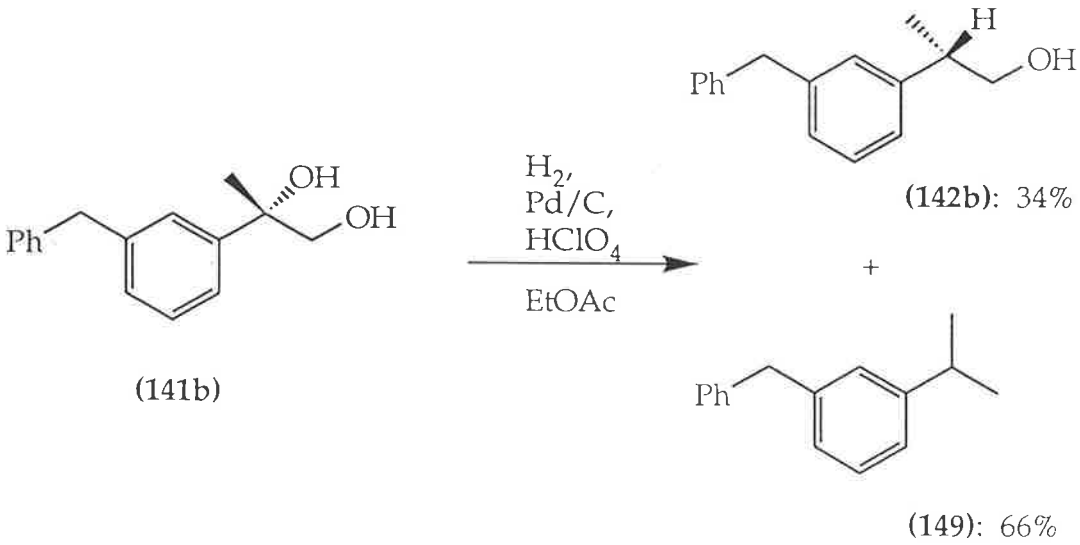
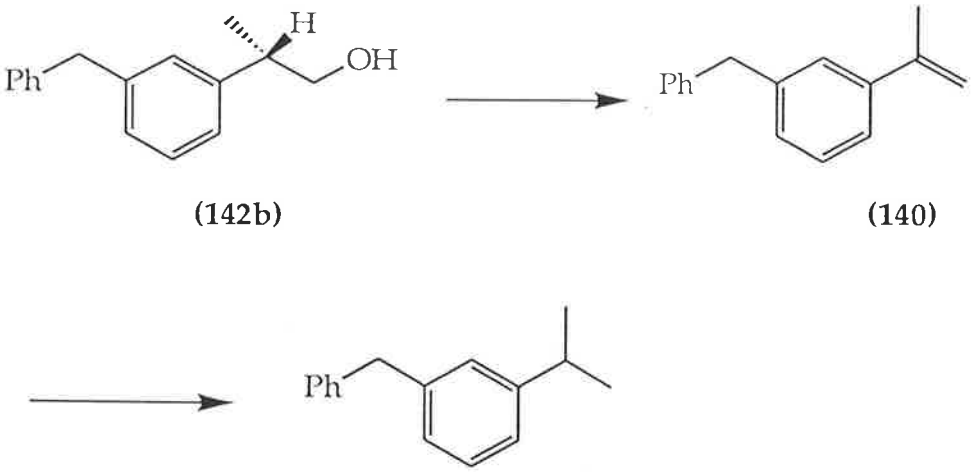


Figure 112

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. ^{1}H NMR spectroscopy of this compound indicated that it was the hydrocarbon **149**. The by-product accounted for 66% of the total product by weight.

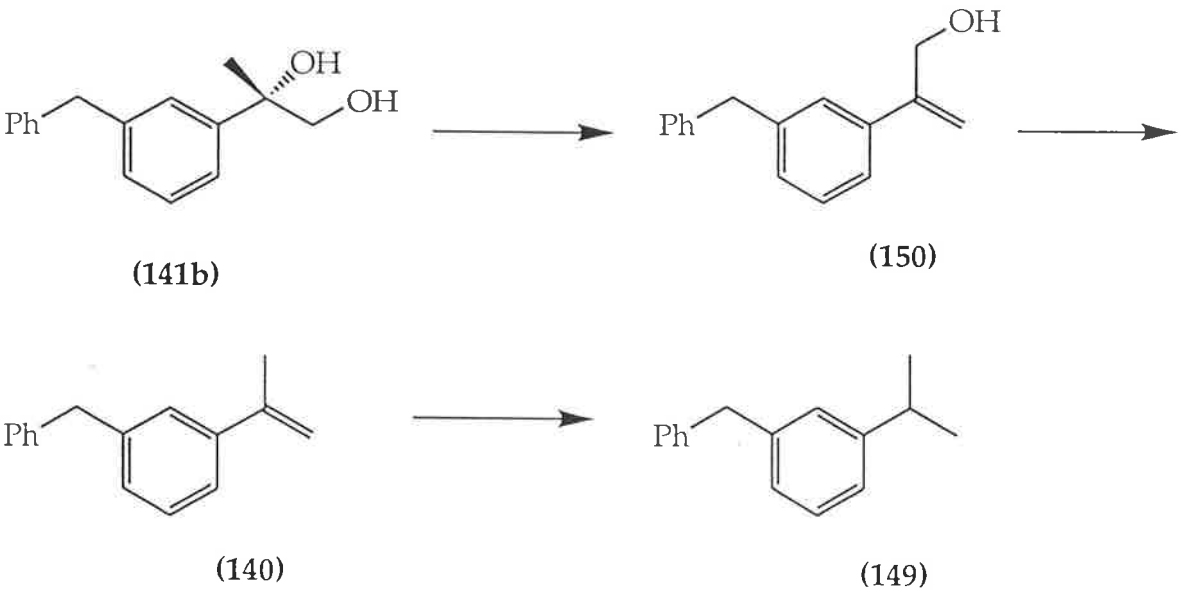
^{1}H NMR data of the alcohol **142b** were identical with those of the enantiomer **142c** described previously. The ^{1}H NMR spectrum of the hydrocarbon **149** shows the methyl groups as a 6H, 7 Hz doublet at δ 1.23, which is coupled to a 1H septet at δ 2.85. The benzylic methylene protons appear 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 catalyst[98], and this may occur to give the alkene **140**. Hydrogenation of the double bond would then give **149**.



(142b) **(140)** **(149)**

Figure 113



(141b) **(150)** **(140)** **(149)**

Figure 114

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 impracticably 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).

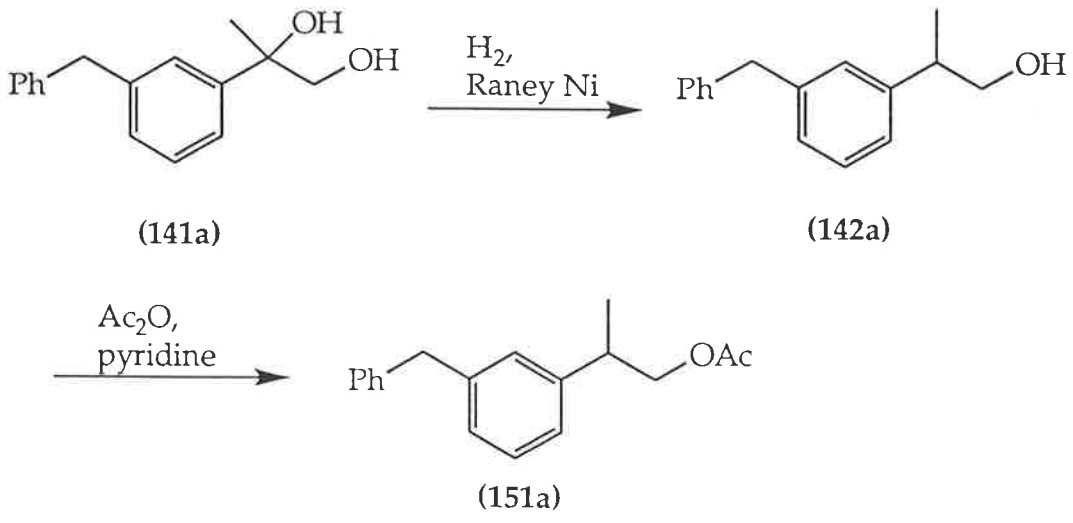


Figure 115

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 ^1H 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[99], used an equimolar amount of N,N-dicyclohexylcarbodiimide and a catalytic amount of dimethylaminopyridine and proceeded in quantitative yield.

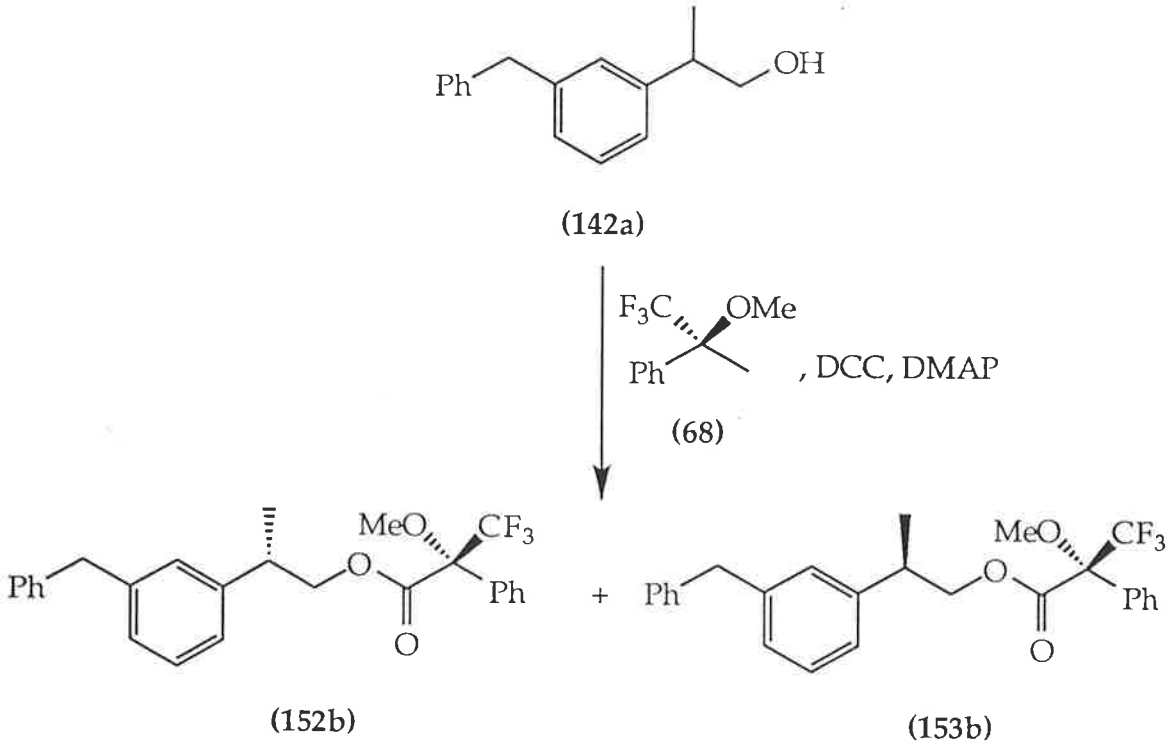


Figure 116

A ^1H 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 CH_2O 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 ^{1}H-^{19}F 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**.

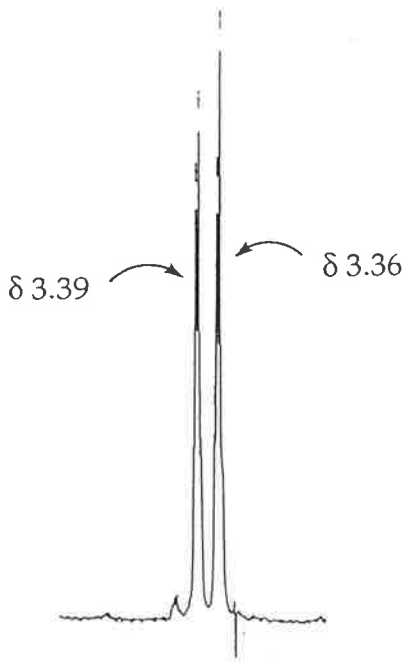


Figure 117

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 ^1H 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.

Solvent	Yield of 142b/%	Inversion/%	Retention/%
EtOAc	33	96	4
CH_2Cl_2	69	88	12
EtOH	60	93	6

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[100], 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[100] (figure 118). A significant amount (28%) of 3-benzoylacetophenone (**155**) was formed as a by-product of the reaction.

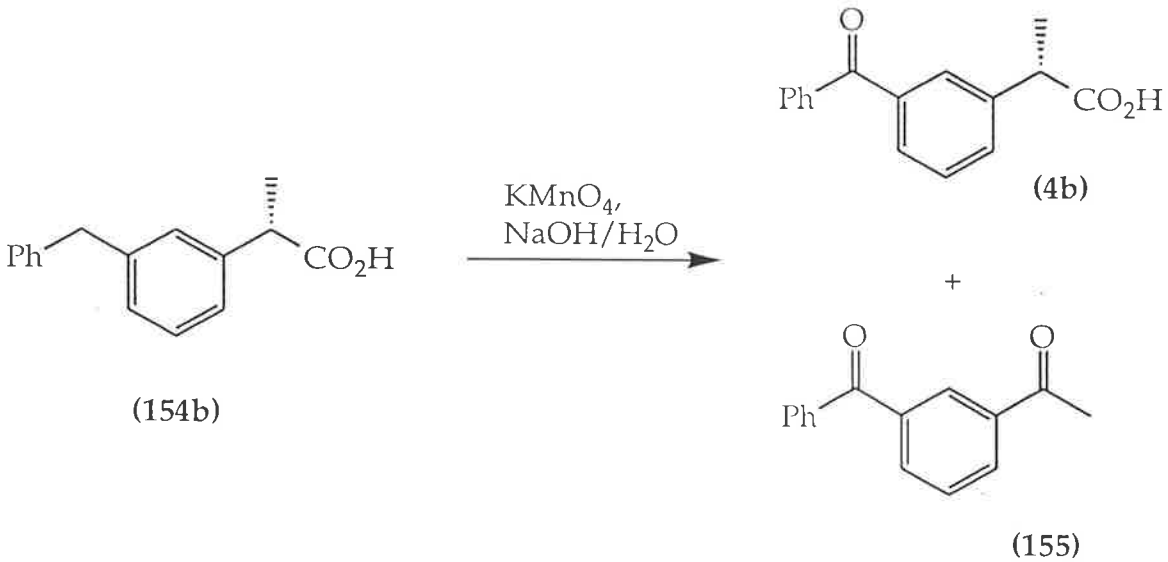


Figure 118

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.

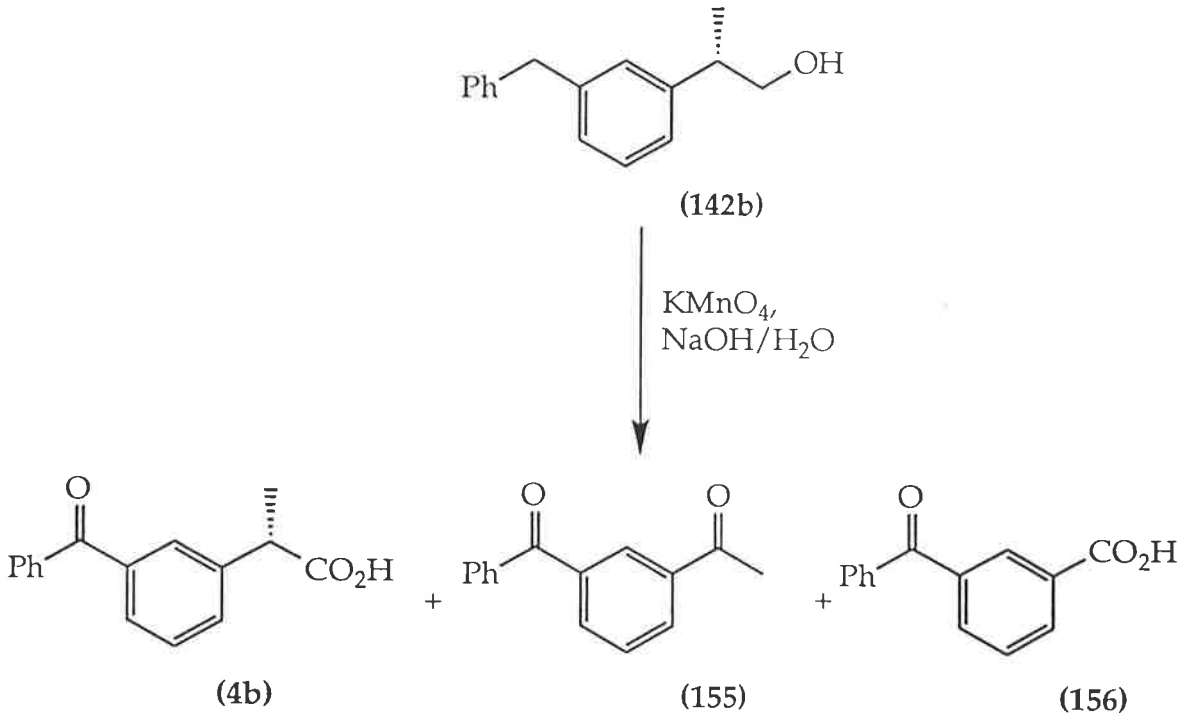


Figure 119

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 CH_2O 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.

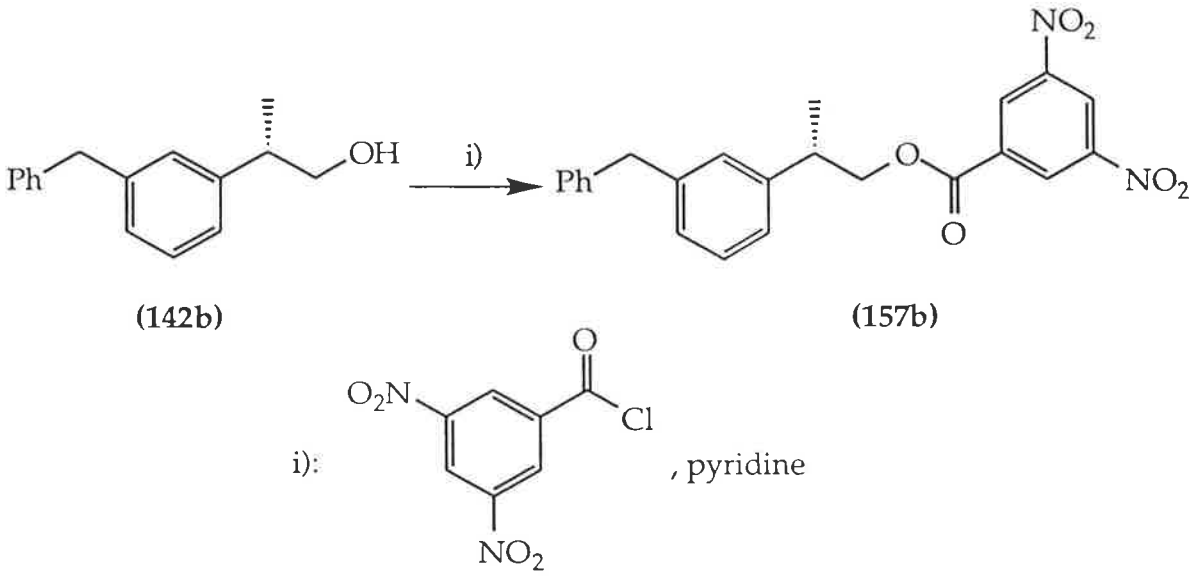
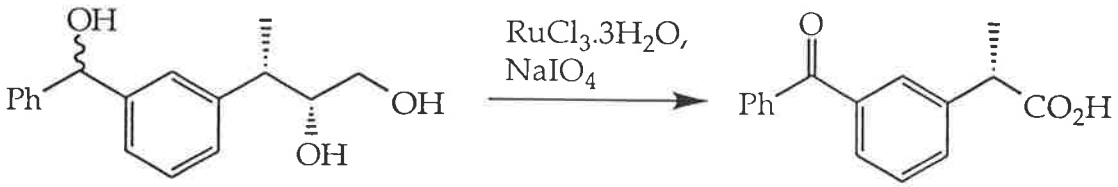


Figure 120

The 3,5-dinitrobenzoate **157b** was recrystallised twice from ether. The resultant white crystalline material had a mp of 65-66°C and $[\alpha]_D^{20}$= -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).

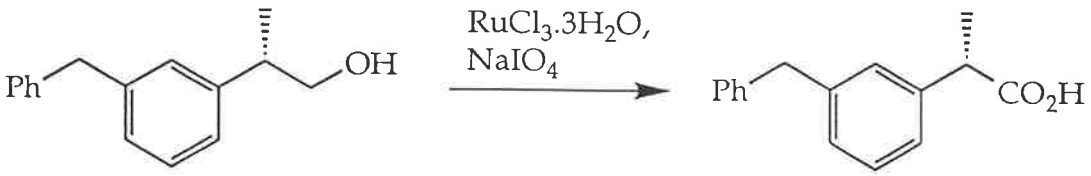
In earlier work, the use of sodium metaperiodate and ruthenium trichloride hydrate had been successful for the oxidation of triol **76b** to **4b** (see pages 70 and 75) and had occurred with negligible racemisation (figure 121).



(76b) (4b)

Figure 121

Treatment of the alcohol **142b** under the same conditions afforded the carboxylic acid **158b** in 59% yield after chromatography (figure 122). ^{1}H NMR data of **158b** were in agreement with those reported[100].



(142b) (158b)

Figure 122

Because the oxidation of **158b** to *(S)*-ketoprofen had been reported[100], 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 **158b** was in agreement with the literature value for optically pure material[100], however a more precise analysis was desired.

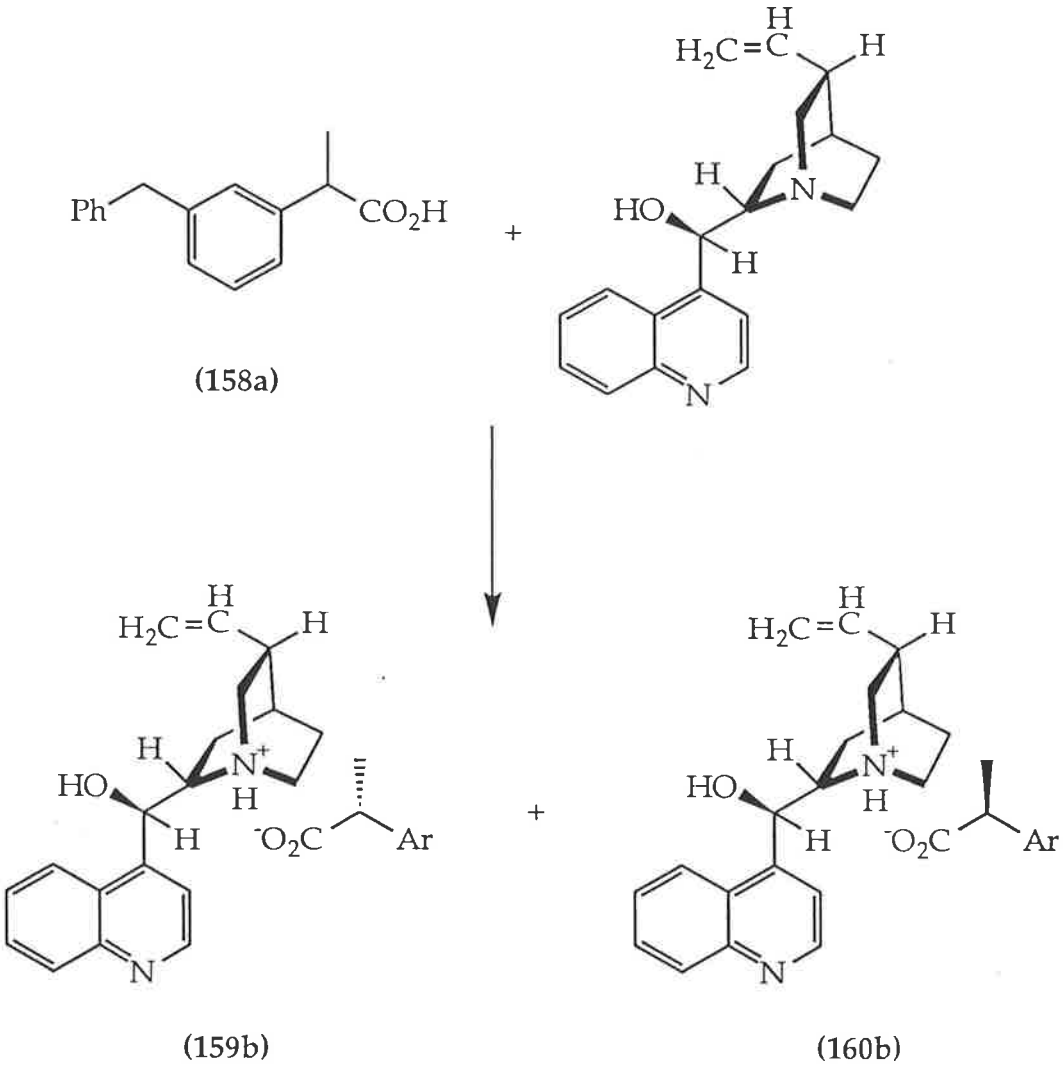


Figure 123

A suitable ^1H NMR analysis was developed with the racemate **158a**. Addition of an equimolar amount of optically pure cinchonidine to a deuterochloroform solution of the racemic acid **158a** afforded a 1:1 mixture of diastereomeric salts **159b** and **160b** (figure 123).

Some signals in the ^1H NMR spectrum of the two isomers **159b** and **160b** are distinct. In particular, the benzylic methyl doublets at δ 1.44 and δ 1.47 partially overlap; the inner peak of each doublet is coincident but the outer peaks (δ 1.43 and δ 1.48) are well separated (figure 124a). The singlets due to the benzylic methylene groups are even more diagnostic; they resonate at δ 3.84 and δ 3.86 and are almost baseline resolved (figure 124a).

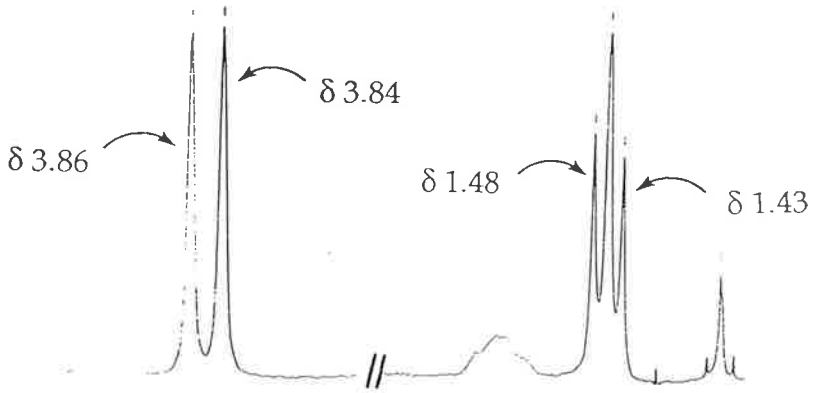


Figure 124a

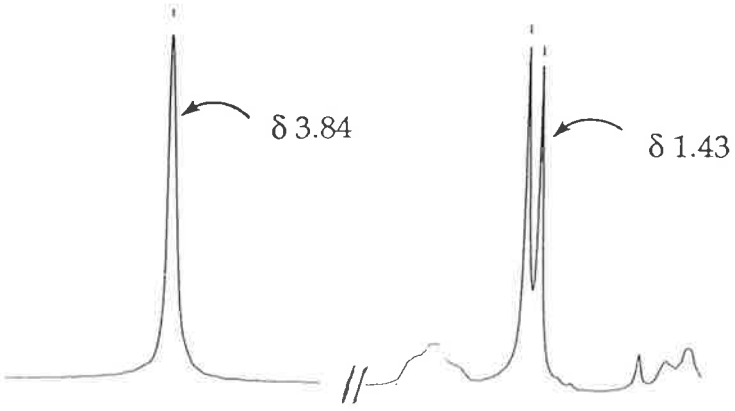
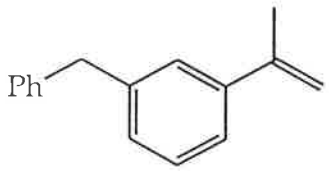


Figure 124b

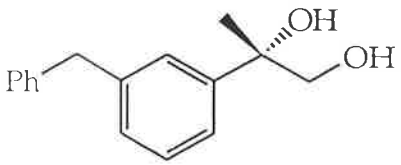
Under the same conditions as those used for analysis of the racemate, cinchonidine was added to a sample of optically active carboxylic acid **158b** from

the ruthenium tetraoxide oxidation. Inspection of the ^1H 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.

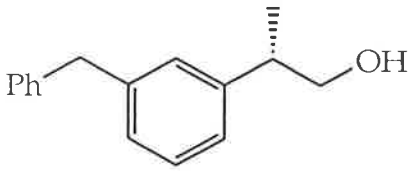
In summary, a method for the synthesis of *(S)*-ketoprofen of high optical purity was developed. The alkene **140**, formed from readily available starting materials, underwent a Sharpless asymmetric dihydroxylation reaction to give the diol **141b** with 88% e.e.



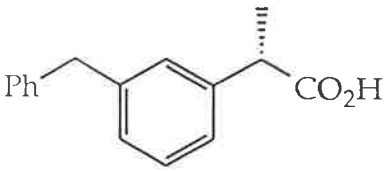
(140)



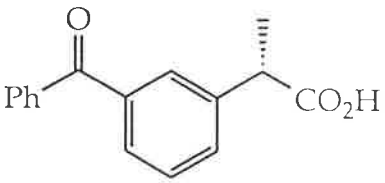
(141b)



(142b)



(158b)



(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 **158b** with 99%+ e.e. Oxidation of **158b** to *(S)*-ketoprofen (**4b**) has been demonstrated elsewhere[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 (δ) values have been quoted in parts per million downfield from tetramethylsilane. Peak multiplicities have been abreviated 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 F_{254} 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 concentated 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 (14.1g, 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 Na_2SO_4. 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); ^{1}H NMR (300 MHz, CCl_4) δ 1.27 (t, 3H, CH_2CH_3, J=7.0 Hz), 2.53 (d, 3H, H4, J=1.0 Hz), 4.14 (q, 2H, CH_2CH_3, 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 $C_{12}H_{13}O_2Br$: C, 53.55; H, 4.87%.

Data for **78**: ^{1}H NMR (60 MHz, CCl_4) δ 1.10 (t, 3H, CH_2CH_3, J=7 Hz), 2.19 (d, 3H, H4, J=1 Hz), 3.95 (q, 2H, CH_2CH_3, J=7 Hz), 5.90 (q, 1H, H2, J=1 Hz), 7.10-7.60 (m, 4H, Ar-H). HRMS 268.00915, calcd for $C_{12}H_{13}O_2Br$: 268.00916.

(*E*)-3-[3'-Bromophenyl]-2-buten-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 Na_2SO_4 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; ^{1}H NMR (60 MHz, CCl_4) , 2.00 (s, 3H, CH_3), 3.00 (br s, 1H, OH), 4.23 (d, 2H, CH_2, 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 $MgSO_4$ 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); ^{1}H NMR (300 MHz, $CDCl_3$, D_2O) δ 1.66 (s, 3H, CH_3), 3.06 (dd, 1H, CHO, J=6.4 Hz and 4.3 Hz), 3.81 (dd, 1H, CH_2O, J=6.4 Hz and 12.2 Hz), 3.95 (dd, 1H, CH_2O, 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 $C_{10}H_{11}O_2Br$: 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%): ^{1}H NMR (300 MHz, $CDCl_3$, D_2O) 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**: ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.32 (d, 3H, CHCH3, J=7 Hz), 1.98 (s, 3H, $COCH_3$), 2.02 (s, 3H, $COCH_3$), 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 $C_{14}H_{18}O_4$: 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 Na_2SO_4 and the solvent removed *in vacuo*. Distillation gave **83** as a colourless oil (31.1 g, 98%): bp 82°C/0.3 mm Hg (lit[103]

bp 128-130°C/12 mm Hg); ^{1}H NMR (60 MHz, CCl_4) δ 1.58 (s, 3H, $(CH_3)_3$), 3.50-4.18 (m, 4H, CH_2s), 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_2SO_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, $CDCl_3$) δ 0.31 (s, 9H, $(CH_3)_3$), 1.59 (s, 3H, CH_3), 3.50-4.17 (m, 4H, CH_2s), 7.17-7.60 (m, 4H, Ar-H). Anal. Found: C, 65.60; H, 8.27%. Calcd for $C_{13}H_{20}O_2Si$: 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_2SO_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, $CDCl_3$) δ 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 Na_2SO_4. 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, $CDCl_3$) δ 0.29 (s, 9H, $(CH_3)_3$), 1.32 (t, 3H, CH_2CH_3, J=7.1 Hz), 2.59 (d, 3H, H4, J=1.2 Hz), 4.22 (q, 2H, CH_2CH_3, 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 $C_{15}H_{22}O_2Si$: C, 68.66; H, 8.45%.

(*E*)-3-[3'-(Trimethylsilyl)phenyl]-2-buten-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 Na_2SO_4 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, $CDCl_3$) δ 0.28 (s, 9H, $(CH_3)_3$), 1.55 (br s, 1H, OH), 2.09 (d, 3H, CH_3, J=1.3

Hz), 4.37 (d, 2H, CH_2, 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 ($C_{13}H_{20}OSi$) 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%, 1.08g, 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 $MgSO_4$ 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, $CDCl_3$, D_2O) δ 0.27 (s, 9H, $(CH_3)_3$), 1.71 (s, 3H, CH_3), 3.11 (dd, 1H, CHO, J=6.5 Hz and 4.2 Hz), 3.82 (dd, 1H, CH_2O, J=6.6 Hz and 12.2 Hz), 3.98 (dd, 1H, CH_2O, 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 $C_{13}H_{20}O_2Si$: C, 66.06; H, 8.53%.

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

Following the procedure of Sharpless[34], 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. $MgSO_4$ (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-Methyl-3-[3'-(trimethylsilyl)phenyl]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 Na_2SO_4. 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° (c=1.11, CCl_4).

Hydrolysis of (2S,3S)-3-methyl-3-[3'-(trimethylsilyl)phenyl]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 $MgSO_4$. 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, $CDCl_3$) δ 0.25 (s, 9H, $Si(CH_3)_3$), 1.71 (s, 3H, CH_3), 2.10 (s, 3H, $COCH_3$), 3.09 (dd, 1H, H2, J=4.3 Hz and 6.7 Hz), 4.18 (dd, 1H, H1, J=6.7 Hz and 12.2 Hz), 4.45 (dd, 1H, H1, 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_2O) δ 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, $CDCl_3$) δ 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 $C_{17}H_{26}O_4Si$: 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_2O) δ 1.29 (d, 3H, CH_3, J=7.1 Hz), 2.71 (quint, 1H, H3, J=7.3 Hz), 3.25 (dd, 1H, H1, 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), 7.09-7.37 (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 $MgSO_4$. 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** (385mg, 79%): 125°C/0.1 mm Hg (heated block); ^1H NMR (300 MHz, $CDCl_3$) δ 1.35 (d, 3H, $CHCH_3$, J=6.4 Hz), 1.37 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 2.77 (quint, 1H, H1', J=7.0 Hz), 3.51 (dd, 1H, H5, J=6.9Hz and 8.2 Hz), 3.75 (dd, 1H, H5, J=6.2Hz and 8.3 Hz), 4.14 (m, 1H, H4), 7.11-7.37 (m, 4H, Ar-H). HRMS 284.04177, calcd for ($C_{13}H_{17}BrO_2$) 284.04178.

(4R, 1'S)-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,1RS)- and (4'''RS,1''SR,1SR)-[3'-[1''-(2''',2'''-Dimethyl-1''',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 $MgSO_4$. 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_2O) δ 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, CHOH), 6.92-7.43 (m, 9H, Ar-H).

(4'''R,1''S,1RS)-[3'-[1''-(2''',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_2O) δ 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, CHOH), 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[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 $MgSO_4$. 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**. ^1H NMR data of **4b** are identical with those of **4a**. $[\alpha]_D^{20}=+54.4$ (c=2.71, CH_2Cl_2) [lit[105]: $[\alpha]_D^{20}=+57.1$ (c=0.76, CH_2Cl_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 $MgSO_4$ 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 (lit[87] bp 175-180°C/20-30 mm Hg; mp 44-45°C; no NMR data reported); ^1H NMR (60 MHz, $CDCl_3$) δ 1.60 (s, 3H, CH_3), 3.88 (m, 4H, CH_2s), 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 $MgSO_4$ 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; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.26 (s, 9H, $(CH_3)_3$), 1.65 (s, 3H, CH_3), 3.77 (m, 2H, H4 and H5), 4.03 (m, 2H, H4 and H5), 7.48 (m, 4H, Ar-H) (lit[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 *in vacuo* and the residue dissolved in dichloromethane, washed with sodium bicarbonate solution and dried with $MgSO_4$. Removal of the solvent *in vacuo* gave **96** as a colourless oil which was used without further purification (57.6g, 98%): (lit[87]: mp 41°C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.29 (s, 9H, $(CH_3)_3$), 2.60 (s, 3H, CH_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[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 *in vacuo*. The residue was dissolved in dichloromethane, washed with water and dried with $MgSO_4$. The solvent was removed *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); ^{1}H NMR (300 MHz, $CDCl_3$) δ

0.27 (s, 9H, $(CH_3)_3$) 1.32 (t, 3H, CH_2CH_3, J=7.1Hz), 2.57 (d, 3H, H4, J=1.2 Hz), 4.21 (q, 2H, CH_2CH_3, 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 $C_{15}H_{22}SiO_2$: C, 68.73; H, 8.31%.

(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 $MgSO_4$, 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; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.27 (s, 9H, $(CH_3)_3$), 2.07 (s, 3H, CH_3), 4.35 (d, 2H, CH_2, 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 $C_{13}H_{20}SiO$: C, 70.26; H, 8.95%.

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

According to the method of Sharpless[34], 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 4A 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, $MgSO_4$ (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, $CDCl_3$) δ 0.26 (s, 9H, $(CH_3)_3$), 1.70 (s, 3H, CH_3), 3.10 (dd, 1H, H2, J=4.2Hz and 6.5 Hz), 3.83 (dd, 1H, CH_2O, J=6.5 Hz and 12.2 Hz), 3.97 (dd, 1H, CH_2O, 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 $C_{13}H_{20}SiO_2$: 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**: $[\alpha]_D^{20}$= -47.0° (c=1.33, CCl_4); ^1H NMR (300 MHz, $CDCl_3$) δ 0.26 (s, 9H, $(CH_3)_3$), 1.71 (s, 3H, CH_3), 2.11 (s, 3H, $COCH_3$), 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-(heptafluoro-propylhydroxymethylene)-(+)-camphorato]-europium(III) derivative and found to be 98%+ e.e.

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

The racemate **111a** was obtained similarly to the optically active compound **111b**, from **99a**. ^1H 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_2O) δ 0.25 (s, 9H, $(CH_3)_3$), 1.36 (d, 3H, CH_3, J=7.0 Hz), 2.79 (quint, 1H, H3, J=7.2 Hz), 3.35 (dd, 1H, H1, J=7.7 Hz and 11.2 Hz), 3.46 (dd, 1H, H1, J=3.0 Hz and 11.2 Hz), 3.75 (dt, 1H, H2, 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 $C_{13}H_{22}O_2Si$: 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_2O) the signals of the two isomers overlap except for the methyl doublet: **100b**: δ 1.36 (d, 3H, J=7.0 Hz); **112b**: δ 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 *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_2O) δ 1.29 (d, 3H, CH_3, J=7.1 Hz), 2.71 (quint, 1H, H3, J=7.3 Hz), 3.25 (dd, 1H, H1,

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 $C_{10}H_{13}BrO_2$: 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*-toluenesulphonic 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 $MgSO_4$ 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); $[\alpha]_D^{20}$= -7.4° (c=3.07, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.35 (d, 3H, $CHCH_3$, J=7.0 Hz) 1.39 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 2.77 (quint, 1H, H1', J=6.9 Hz), 3.51 (dd, 1H, H5, J=6.8Hz and 8.3 Hz), 3.74 (dd, 1H, H5, J=5.9Hz 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 ($C_{13}H_{17}BrO_2$) 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**.

(4'''R,1''S,1RS)-1-{4-[1''-(2''',2'''-Dimethyl-1''',3'''-dioxolan-4'''-yl)ethyl]phenyl}-2-methyl-1-propanol (103b)

In a dry flask, **102b** (443 mg, 1.55 mmol) was dissolved in anhydrous ether (7mL) and cooled to -78°C in a nitrogen atmosphere. *Tert*-butyllithium (1.86 mL of a 1.75 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 $MgSO_4$. 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, $CDCl_3$, D_2O) δ 0.69-1.60 (complex, 15H, CH_3s), 1.92 (m, 1H, $CH(CH_3)_2$), 2.79 (quint, 1H, $CHCH_3$, 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).

(4'''RS,1''SR,1RS)- and (4'''RS,1''SR,1SR)-1-{4-[1''-(2''',2'''-Dimethyl-1''',3'''-dioxolan-4'''-yl)ethyl]phenyl}-2-methyl-1-propanol (103a).

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**.

(2RS,3SR,1''RS)- and (2RS,3SR,1''SR)-3-[4'-(1''-Hydroxy-2''-methylpropyl)-phenyl]butane-1,2-diol (104a).

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 $MgSO_4$. 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, $CDCl_3$, D_2O) 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, $CDCl_3$, D_2O) δ 0.89 (d, 6H, $CH(CH_3)_2$, J=6.7 Hz), 1.35 (d, 3H, H4, J=6.9 Hz), 1.84 (m, 1H, $CH(CH_3)_2$, 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 $C_{14}H_{22}O_2$: 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, $CDCl_3$) δ 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), [lit[108]: $[\alpha]_D^{20}$=+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 $MgSO_4$ 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, $CDCl_3$, D_2O) δ 1.30 (d, 3H, CH_3, 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).

(2RS,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 $MgSO_4$ 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, $CDCl_3$) δ 1.32 (d, 3H, CH_3, 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 Sharpless[84], 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 $MgSO_4$ 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; $[\alpha]_D^{20}$=+43.4° (c=1.20, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, D_2O) δ 1.50 (d, 3H, CH_3, 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%, $C_9H_9IO_2$ 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. ^{1}H NMR data of **45a** are identical with those of **45b**.

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

According to the procedure of Sharpless[84], 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 $MgSO_4$ 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; $[\alpha]_D^{20}$=+39.0° (c=2.45, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$ D_2O) δ 1.49 (d, 3H, CH_3, 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%, $C_9H_9IO_2$ 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. ^{1}H NMR data of **46a** are identical

with those of **46b**.

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 $MgSO_4$ 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-diyl 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 $MgSO_4$ 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-diyl diacetate as a white crystalline solid (710 mg, 95%): mp 52-53°C; ^{1}H NMR (60 MHz, $CDCl_3$) δ 0.35 (s, 9H, $(CH_3)_3$), 1.33 (d, 3H, H4, J=7 Hz), 2.03 (s, 3H, $COCH_3$), 2.18 (s, 3H, $COCH_3$), 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-diyl 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, $CDCl_3$) δ 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-diyl 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, $CDCl_3$) δ 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_2Ar), 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_2O) δ 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_2Ar), 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, $CDCl_3$) δ 1.48 (d, 3H, H3, J=7.2 Hz), 3.69 (q, 1H, H2, J=7.2 Hz), 3.96 (s, 2H, CH_2Ar), 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_2O) δ 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[89]). The optical purity was determined by the general procedure and found to be 96% e.e.

(RS)-2-(3'-Biphenylyl)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 (lit[89] mp 64 °C). After recrystallization from hexane: mp 49-51 °C; ^{1}H 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; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.54 (d, 3H, CH_3, 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%, $C_{17}H_{14}O_2$ requires C: 81.58%, H: 5.64%. ^{1}H NMR data are identical to those of **120b**.

(S)-2-(4'-Biphenylyl)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; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.56 (d, 3H, CH_3, 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 values[108]). The optical purity was determined by the general procedure and found to be 94% e.e.

(RS)-2-(4'-Biphenylyl)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 (lit[90] mp 146 °C). ^{1}H 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%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.51 (d, 3H, CH_3, J=7.1 Hz), 1.85 (d, 3H, C2''CH_3, 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** (9mg, 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 $MgSO_4$ 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.

(S)-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 (lit[88] 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[109] mp 74 °C); ^{1}H 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[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 *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[66] bp 95-105°C/6 mm Hg); ^{1}H NMR (60 MHz, $CDCl_3$) δ 0.0 (s, 18H, $Si(CH_3)_3$), 2.68 (complex, 2H, SiCH), 3.85 (s, 3H, CH_3O), 4.72 (br s, 1H, H2), 5.79 (m, 2H, H4 and H5) (lit[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[66]: no mp reported); $[\alpha]_D^{20}$=+35.5° (c=1.00, $CHCl_3$), lit[66]: $[\alpha]_D^{20}$=+35.5° (c=1.08, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ -0.04 (s, 9H, $Si(CH_3)_3$), 1.66 (m, 1H, SiCH), 1.81-2.68 (methylene envelope), 2.31 (s, 3H, CH_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[66]: no NMR data reported).

According to the method of Asaoka[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 $MgSO_4$. The solvent was removed *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%): ^1H NMR data are identical with those of **55a**.

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

According to the method of Asaoka[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). *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 *in vacuo* to approximately 100 mL, washed with 2 M HCl and dried with $MgSO_4$. The solvent was removed *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° (c=1.16, $CHCl_3$) [lit[66]: $[\alpha]_D^{20}$=-35.5° (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 (lit[66]: no mp reported); $[\alpha]_D^{20}$=-35.7° (c=1.04, $CHCl_3$); ^1H 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. ^1H 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",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_3CH, J=6.6 Hz), 1.33 and 1.37 (each s, 3H, C2''Me), 1.95-2.75 (complex, 8H, ring Hs and CH_3CH), 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%.

(3R,5S,1'R, 4''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**.

(3S,5R,1'R, 4''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_3CH, J=6.6 Hz), 1.33 and 1.37 (each s, 3H, C2''Me), 1.95-2.75 (complex, 8H, ring Hs and CH_3CH), 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; ^{1}H 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; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.34 (d, 3H, CH_3, J=7.1 Hz), 2.46-2.71 (complex, 5H, H4, H5 and H6)), 2.78 (apparent quint, 1H, $CHCH_3$, J=7.1 Hz), 3.32 (dd, 1H, CH_2OH, J=7.7 Hz and 11.2 Hz), 3.33 (m, 1H, H5), 3.44 (dd, 1H, CH_2OH, 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). Anal. Found: C, 73.82; H, 7.74%. Calcd for $C_{16}H_{20}O_3$: 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**. ^{1}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**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.34 (d, 3H, CH_3, J=7.1 Hz), 2.46-2.71 (complex, 4H, H4, H5 and H6), 2.78 (apparent quint, 1H, $CHCH_3$, J=7.1 Hz), 3.32 (dd, 1H, CH_2OH, J=7.7 Hz and 11.2 Hz), 3.33 (m, 1H, H5), 3.44 (dd, 1H, CH_2OH, 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**. ^{1}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; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.34 (d, 3H, CH_3, J=7.0 Hz), 1.82 (complex, 2H, $H4_{ax}$ and $H5_{ax}$), 1.95 (br s, 1H, OH), 2.11 (complex, 2H, $H4_{eq}$ and $H5_{eq}$), 2.39 (m, 2H, H6), 2.55 (m, 2H, H2), 2.68 (br s, 1H, OH), 2.78 (apparent quint, 1H, $CHCH_3$, J=7.0 Hz), 2.98 (tt, 1H, H3, J=4.6 Hz and 11.6 Hz), 3.33 (dd, 1H, CH_2OH, J=7.6 Hz and 11.2 Hz), 3.45 (dd, 1H, CH_2OH, 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; ^{1}H 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; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.34 (d, 3H, CH_3, J=7.0 Hz), 1.82 (complex, 2H, $H4_{ax}$ and $H5_{ax}$), 1.95 (br s, 1H, OH), 2.11 (complex, 2H, $H4_{eq}$ and $H5_{eq}$), 2.39 (m, 2H, H6), 2.55 (m, 2H, H2), 2.68 (br s, 1H, OH), 2.78 (apparent quint, 1H, $CHCH_3$, J=7.0 Hz), (2.98, tt, 1H, H3, J=4.6 Hz and 11.6 Hz), 3.33 (dd, 1H, CH_2OH, J=7.6 Hz and 11.2 Hz), 3.45 (dd, 1H, CH_2OH, 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). Anal. Found: C, 72.96; H, 8.34. Calcd for $C_{16}H_{22}O_3$: 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; ^{1}H NMR data of **132b** are identical with those of **132c**.

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

According to the procedure of Sharpless[84], **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, $[\alpha]_D^{20}$=+52° (c=1.75, EtOH); υ_{max} (CH_2Cl_2) 1225, 1710, 1720, 2950 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.50 (d, 3H, CH_3, J=7.1Hz), 1.73-1.90 (complex, 2H, H5 and H6), 2.05-2.18 (complex, 2H, H5 and H6), 2.32-2.45 (m, 2H, H4), 2.49-2.61 (m, 2H, H2), 2.99 (tt, 1H, H1, 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). ^{13}C 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; $[\alpha]_D^{20}$=-53° (c=1.75, EtOH); ^{1}H 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; $[\alpha]_D^{20}$= +48° (c=1.45, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.50 (d, 3H, CH_3, J=7.1Hz), 1.73-1.90 (complex, 2H, H5 and H6), 2.05-2.18 (complex, 2H, H5 and H6), 2.32-2.45 (m, 2H, H4), 2.49-2.61 (m, 2H, H2), 2.99 (tt, 1H, H1, 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); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 18.02 (C3), 25.38 (C5''), 32.53 (C6''), 40.99 (C4''), 44.20 (C1''), 44.80 (C2), 48.71 (C2''), 126.77 (C3' and C5'), 127.78 (C2' and C6'), 138.12 (C4'), 143.23 (C1'), 180.00 (C1), 211.54 (C3''). Anal. Found: C, 72.81; H, 7.37. Calcd for $C_{15}H_{18}O_3$: C, 73.14; H, 7.37.

(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; $[\alpha]_D^{20}$= -48° (c=0.51, EtOH); ^{1}H 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)-phenyl]propanoate (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, $H2_{ax}$ and $H4_{ax}$), 2.57 (d, complex small coupling, 1H, $H2_{eq}$, J=13.6 Hz), 2.75 (tt, 1H, H1, J=11.9 Hz and 3.4 Hz), 3.37 (d, 1H, $H4_{eq}$, 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, $H2_{ax}$, J=13.9 Hz and 12.5 Hz), 2.11 (d, 1H, $H4_{ax}$, J=13.6 Hz and 4.5 Hz), 2.44 (d, complex small coupling, 1H, $H4_{eq}$, J=13.5 Hz), 2.73 (tt, 1H, H1, J=11.7 Hz and 3.5 Hz), 3.47 (d, complex small coupling, 1H, $H2_{eq}$, 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).

EXPERIMENTAL
CHAPTER 5

2-(3′-Bromophenyl)propene (139).

A dry flask fitted with a pressure equalising dropping funnel and calcium choride 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 (6.17 g, 31 mmol) in ether (70 mL) over 1h. 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) (lit[94]: 217°C/atmospheric pressure); ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.12 (s, 3H, CH_3), 5.11 (s, 1H, CH_2), 5.38 (s, 1H, CH_2), 7.15-7.60 (m, 4H, Ar-H).

2-(3′-Benzylphenyl)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 *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[95] (1.74 g) and **140** (5.41 g, 100%): ^{1}H NMR of **140** (200 MHz, $CDCl_3$) δ 2.13 (s, 3H, CH_3), 3.99 (s, 2H, CH_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[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, 4.2×10^{-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 *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°/0.01 mm Hg (heated block); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.52 (s, 3H, CH_3), 1.85 (br s, 1H, OH), 2.60 (br s, 1H, OH), 3.62 (d, 1H, CH_2O, J=10 Hz), 3.79 (d, 1H, CH_2O, J=10 Hz), 4.01 (s, 2H, CH_2), 7.22-7.34 (m, 9H, Ar-H). Found: C 79.11%, H 7.45%, $C_{16}H_{18}O_2$ requires C 79.31%, H 7.49%.

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

According to the method of Sharpless[77], a mixture of water (127 mL), *tert*-butyl alcohol (127 mL) and AD-mix-α (35.6 g) was cooled to 0°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); $[\alpha]_D^{20}$= +2.5° (c=2.35, EtOH); ^{1}H 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-(heptafluoropropylhydroxy-methylene)-(+)-camphorato]-europium(III) derivative and found to be 88%. e.e.

(RS)-2-(3'-Benzylphenyl)-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%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.54 (s, 3H, CH_3), 2.01 (s, 3H, $COCH_3$), 3.99 (s, 2H, $ArCH_2$), 4.18 (d, 1H, OCH_2, J=11.3 Hz), 4.28 (d, 1H, OCH_2, 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**. ^{1}H 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%). ^{1}H NMR data of **142c** are identical with those of **142a**.

Data for **147b**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.85 - 1.78 (complex, 12H, ring Hs and OH) 1.26 (d, 3H, CH_3, J=7.0 Hz), 2.47 (d, 2H, $ArCH_2$, J=7.0 Hz) 2.92 (sextet, 1H, $CHCH_3$, J=7.0 Hz), 3.72 (t, 2H, CH_2O, J=6.9 Hz), 7.00 - 7.27 (m, 4H, Ar-H).

Data for **148b**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.85 - 1.85 (complex, 13H, ring Hs and OHs), 1.55 (s, 3H, CH_3), 2.51 (d, 2H, $ArCH_2$, J=7 Hz), 3.65 (dd, 1H, CH_2OH, J=11 Hz and 7 Hz), 3.82 (dd, 1H, CH_2OH, 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%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.26 (d, 3H, CH_3, J=7.0 Hz), 1.58 (br s, 1H, OH), 2.92 (sextet, 1H, $CHCH_3$, J=7.0 Hz), 3.69 (d, 2H, CH_2O, J=6.9 Hz), 3.99 (s, 2H, CH_2), 7.02-7.30 (m, 9H, Ar-H). Found: C 85.17%, H 7.99%, $C_{16}H_{18}O$ 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**. $[\alpha]_D^{20}$= -5.7° (c=0.88, EtOH); ^{1}H 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 α-methoxy α-trifluoromethylphenylacetate (152b and 153b).

Following the procedure of Hassner[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)-(+)-α-methoxy-α-(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 eluant 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), 3.13 (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,

$ArCH_2$), 4.49 (d, 2H, OCH_2, J=7.3 Hz), 7.07-7.31 (m, 9H, ArH), 9.02 (m, 2H, $ArNO_2$, J=1.7 Hz), 9.18 (m, 1H, $ArNO_2$, J=1.9 Hz); υ_{max} (CH_2Cl_2) 1740, 1640, 1610, 1555, 1350 cm^{-1}; $[\alpha]_D^{20}$=-28° (c=1.70, CH_2Cl_2).

(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 *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 *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[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 *in vacuo* and flash chromatography with ethyl acetate/hexane (50/50, v/v) as eluant gave **158b** as a colourless oil (100 mg, 59%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.49 (d, 3H, CH_3, J=7.1 Hz), 3.69 (q, 1H, $CHCH_3$), 3.97 (s, 2H, CH_2Ar), 7.05 - 7.33 (m, 9H, Ar-H) (NMR data is in agreement with lit.[100] values).

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