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THE ASYMMETRIC SYNTHESIS OF (+)-GRANDISOL

A Thesis
Submitted Towards the
Degree of
Doctor of Philosophy

By

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B. Sc. (Hons)

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ABSTRACT

The pheromone, (+)-*cis*-2-isoprenyl-1-methylcyclobutene-ethanol **1**, commonly known as (+)-grandisol was synthesized in a 95±2% e.e. *via* an allylic alcohol, [(1S,5R)-5-methylbicyclo[3.2.0]hept-2-en-2-yl] methanol **38**, as the key intermediate. Optical activity was induced in the primary alcohol by a kinetic resolution reaction which involved the Sharpless asymmetric epoxidation reaction.

Two routes from (1SR,5SR)-5-methylbicyclo[3.2.0]heptan-2-one **12** to this key intermediate compound were explored. One was unsuccessful, the other allowed the synthesis of the allylic alcohol in four steps from commercially available sources.

Functional group interconversion of the allylic alcohol gives exclusively the *endo*cyclic alkene, (1S,5R)-2,5-dimethylbicyclo[3.2.0]hept-2-ene **10**. Conversion of the *endo*cyclic alkene to (+)-grandisol, by a combination of procedures previously established in the literature by two groups, was accomplished in four steps.

The requirements necessary for a highly selective kinetic resolution using the Sharpless asymmetric dihydroxylation reaction were investigated. Three different bicyclic alkenes were studied, (1S,5R)-2,5-dimethylbicyclo[3.2.0]hept-2-ene **10**, (1SR,5SR)-5-methyl-2-methylene bicyclo[3.2.0]heptane **9**, and (1RS,5SR)-5-methyl-2-phenylbicyclo[3.2.0]heptan-2-ene **125**. The Sharpless dihydroxylation reaction was diastereoselective in all cases, however high enantioselectivity was only achieved with the last alkene. This is consistent with substrate control in the asymmetric dihydroxylation reaction.

The pheromone, (1S)-1-methyl-2-cyclohexenol (MCL) **2** was synthesized in a 94±3% e.e. in three steps from 1-methylcyclohexene *via* a 'merged substitution-elimination reaction' involving phenylselenide anion. The stereochemistry was achieved by the Sharpless asymmetric dihydroxylation reaction.

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, 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.

Kellie Tuck
26th February 1999.

ABBREVIATIONS

Meta-Chloroperbenzoic acid	*m*CPBA
1,5-Diazabicyclo[4.3.0]non-5-ene	DBN
1,8-Diazabicyclo[5.4.0]undec-7-ene	DBU
Diethyl tartrate	DET
Diisopropyl tartrate	DIPT
Dimethylformamide	DMF
Dimethyl sulfoxide	DMSO
Dimethyl tartrate	DMT
Diastereomeric excess	d.e.
Enantiomeric excess	e.e.
Hexamethylphosphoramide	HMPA
Lithium diisopropylamide	LDA
2,6-Lutidine	Lu
1-Methylcyclohex-2-en-1-ol	MCL
N-Methyl morpholine *N*-oxide	NMO
Tetrahydrofuran	THF
N,N,N',N'-Tetramethylethylenediamine	TMEDA
Trimethyl silyl	TMS
Trimethylsilyl trifluoromethanesulfonate	TMSOTf

The term 'Correlated Spectroscopy' has been abbreviated to COSY. Similarly, the term 'Hetronuclear Shift Correlation' has been abbreviated to HETCOR.

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CHAPTER 1

INTRODUCTION

Section 1.1 General Introduction

For many years, the agricultural industry has relied upon chemical pesticides to control pest populations. These pesticides generally do not have a common resemblance with nature's compounds and consequently they are unselectively killing a wide range of insects, not just pests. These materials and their metabolites are permeating and contaminating our air, food, water, soil, and wildlife.[1] With concern over the environmental damage caused by the widespread use of pesticides, researchers are now investigating environmentally friendly alternatives. These include microbial pesticides, beneficial insects (predators and parasites), hormonal pesticides, naturally occurring insecticides and semiochemicals.[2]

Semiochemicals are chemicals involved in the communication of animals. They can be divided into two broad categories, interspecific action, between individuals of different species, or intraspecific action, between individual of the same species.[2] Pheromones are a subclass of semiochemicals and have intraspecific action. They are employed widely within the insect kingdom.[3] Pheromones are chemicals that are released by organisms into the environment either as odours or taste substances and they allow communication between members of the same species. For instance, they are used to increase the probability of successful mating or to indicate apprehension to members of the same species. Aggregation pheromones function in many different ways, including mate selection, defense against predators and the aggregation of members of the same species for feeding purposes.[3]

It is found that the response to such pheromones is often very structure dependent and involves not only chemical properties but also three-dimensional shape. Stereochemistry, in general, and chirality, in particular, are often of crucial importance. It has been observed with chiral pheromones that there can be a number of different responses by the insect to the compound presented. Mori has placed the type of response into eight categories.[4] They are, one enantiomer is active, and the corresponding enantiomer does not inhibit the action of the pheromone. One enantiomer is active but its enantiomer or diastereomer does inhibit the action of the pheromone. All stereoisomers are biologically active. In the same genus different species

use different enantiomers. Both enantiomers are required for bioactivity. One enantiomer is as active as the natural pheromone, but its activity can be enhanced by addition of the less active stereoisomer. Male insects use one enantiomer, the female uses the antipode, and lastly, only the meso-isomer is active.

The use of pheromones as alternatives to pesticides has numerous potential advantages. The compounds are naturally occurring, non-toxic and should not pollute the environment. Generally they are insect-specific and will not affect other ecosystems.[2]

There are a great number of different compounds which have evolved as pheromones, but in most cases, each insect generates and uses only minute quantities and so these compounds are not readily available from natural sources. For pheromones to be of any significant use in the agricultural industry they need to be obtained in much larger amounts. Chemical synthesis is the most obvious way to achieve this. The specific structure, the precise stereochemistry, the volatility, and often the requirement of optical purity presents the synthesis of many pheromones as a challenge to synthetic strategy and methodology. Such problems also present an educational experience for the synthetic organic chemists involved.

There are numerous methods for obtaining chiral compounds in non-racemic form. The most obvious way is transformation of naturally occurring chiral compounds to the desired compound by a series of chemical reactions. In this case no stereogenic centres required for the product are involved in the chemical transformations or if they are involved,the reactions are of known out-come, such as inversion of configuration.[5]

An alternative method for obtaining optically active precursors or products is the technique of resolution. This is the classical method of obtaining enantiomerically pure compounds from racemic mixtures. The third main area is asymmetric synthesis.[5]

Asymmetric synthesis can be defined as 'a synthesis in which an achiral unit in an ensemble of substrate molecules is converted to a chiral unit such that the possible stereoisomers are formed in unequal amounts'.[5] Asymmetric synthesis has been broadly divided into four major subclasses.

The first subclass is substrate controlled methods. This method introduces a new chiral centre into the molecule at a diastereotopic site controlled by a nearby stereogenic centre. For these reactions the starting material needs to be optically pure.[5]

The second subclass is auxiliary controlled methods. In these reactions, an enantiomerically pure directing group determines the absolute stereochemistry of the product. The directing group has deliberately been attached to an achiral substrate to control the relative stereochemistry and is removable. The auxiliary is often recycled after the reaction. The major difference from the first class is that an achiral substrate is converted to a chiral product.[5]

The third subclass is reagent controlled methods. In this technique, an achiral reagent is directly converted to a chiral product by the use of an intermolecular chiral reagent. This method is more effective than the auxiliary controlled method, which requires two extra steps to attach and remove the auxiliary.[5]

The fourth and final subclass is catalyst controlled methods. This method is superior to the other three methods, as it requires only a small amount of the catalyst. An achiral substrate is converted directly to a chiral product. This method is the technique of choice for introducing asymmetry into a molecule.[5] To date, few reactions successfully achieve this. However, two very successful examples of this method are the Sharpless asymmetric epoxidation reaction and the Sharpless asymmetric dihydroxylation reaction.

Two examples of aggregation pheromones addressed in this thesis are, grandisol **1** a component of the pheromonal secretion of *Anthomis grandis* and 1-methylcyclohex-2-enol (MCL*) **2**, a component of the pheromonal secretion of *Dendroctonus pseudotsugae*. The Douglas-fir beetle, *Dendroctonus pseudotsugae*, is a bark beetle which is a serious pest of the Douglas-fir tree, *Pseudotsuga menziesii*.

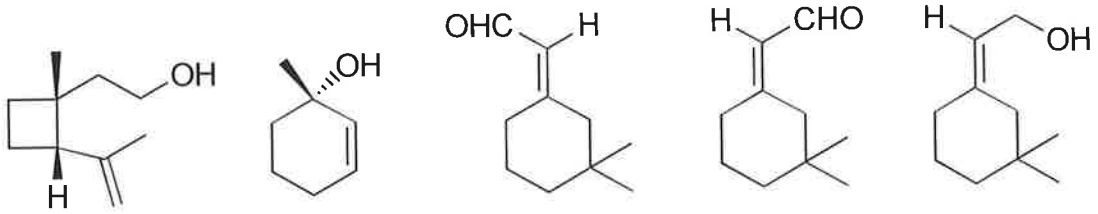
The cotton boll weevil, *Anthonomus grandis* Boheman, and the pink bollworm, *Pectinophora gossypiella*, are two serious pests of cotton crops in the United States and Central America.

* This abbreviation has been introduced for convenience.

Cotton is one of the most important vegetable fibers used to produce textiles. Annually billions of dollars are lost in production due to destruction of the crops by insects.

The cotton boll weevil was first detected in 1983 in Brazilian cotton fields and has spread rapidly since.[6] The cotton weevil and the pink bollworm have been difficult to eradicate and consequently both have caused huge crop losses. Many different insecticides have been used against the weevil, but because of unwanted side effects or because the weevil develops resistance, new insecticides constantly need to be found. The pink bollworm is a recent problem, its numbers have increased in the cotton fields because the pesticides used against the boll weevil have also killed the insects that were the bollworm's natural enemies.[7]

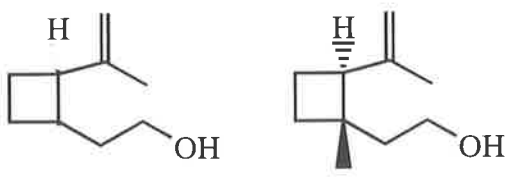
The male cotton weevil produces an aggregation pheromone mixture of four monoterpenes, the principal component is the terpene (+)-*cis*-2-isoprenyl-1-methylcyclobutene-ethanol **1**, commonly named (+)-grandisol. The other components of the aggregation mixture were identified as (E)-2-(3,3-dimethylcyclohexyliden)acetaldehyde **3**, its (Z)-isomer **4**, and (Z)-2-(3,3-dimethylcyclohexyliden)-1-ethanol **5**. (+)-Grandisol **1** is also found in the pheromonal secretion of several beetles.[11]



1 **2** **3** **4** **5**

Figure 1

The *cis*-fused cyclobutane ring found in (+)-grandisol **1**, is crucial for its bioactivity as an aggregation pheromone of the cotton boll weevil. The *trans* isomer fraganol **6**, a natural product isolated from the roots of *artemisia fragrens* Willd, was found to be 100 to 200 times less active than the *cis* compound **1** in a laboratory assay of the attractiveness to the weevils.[8]



1 **6**

Figure 2

Section 1.2 Previous Syntheses of Grandisol

Grandisol **1** has been a popular molecule to synthesize both as a synthetic challenge, or as a tool for investigating the properties of the naturally occurring compound. Hence, there have been numerous routes developed to both racemic and optically active grandisol **1r** and **1a**[*]. The previous syntheses which will be outlined in this thesis by no means represent a complete review and in this thesis the main emphasis is on asymmetric syntheses. The syntheses of grandisol from 1971-79[9] and 1979-89[10] are outlined in recent reviews.

There are numerous syntheses of optically active grandisol **1**, but if asymmetric syntheses are to become important for industrial preparations, it is necessary that the syntheses are short and from readily available materials. The development of new synthetic methods in organic chemistry also means that new synthetic strategies may be devised which may aid in this pursuit. For both these reasons a new asymmetric synthesis of grandisol **1** was investigated.

But first this work must be set in historical perspective. There are many syntheses, more recent or additional, of optically active grandisol **1** starting from optically active starting material, or achiral starting material, which are not covered by the previously mentioned review.[11, 12, 13, 14, 15, 16, *17*, 18] As they are of no immediate interest to the work described in this thesis they will not be discussed.

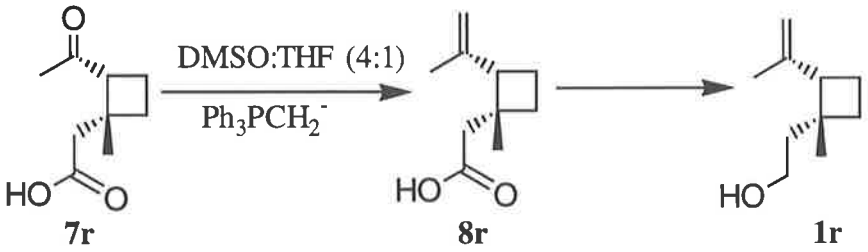
There are also other syntheses of racemic grandisol **1**, some more recent, which are not covered by the aforementioned reviews, however they have no relevance to this thesis and will not be discussed.[19, 20, 21, 22, 23, 24]

The syntheses of racemic grandisol of relevance to the route chosen in this thesis are outlined below.

Zurflüh and coworkers synthesized racemic grandisol **1r** for determination of the relative stereochemistry of the natural product.[25] The racemic compound was synthesized, in numerous

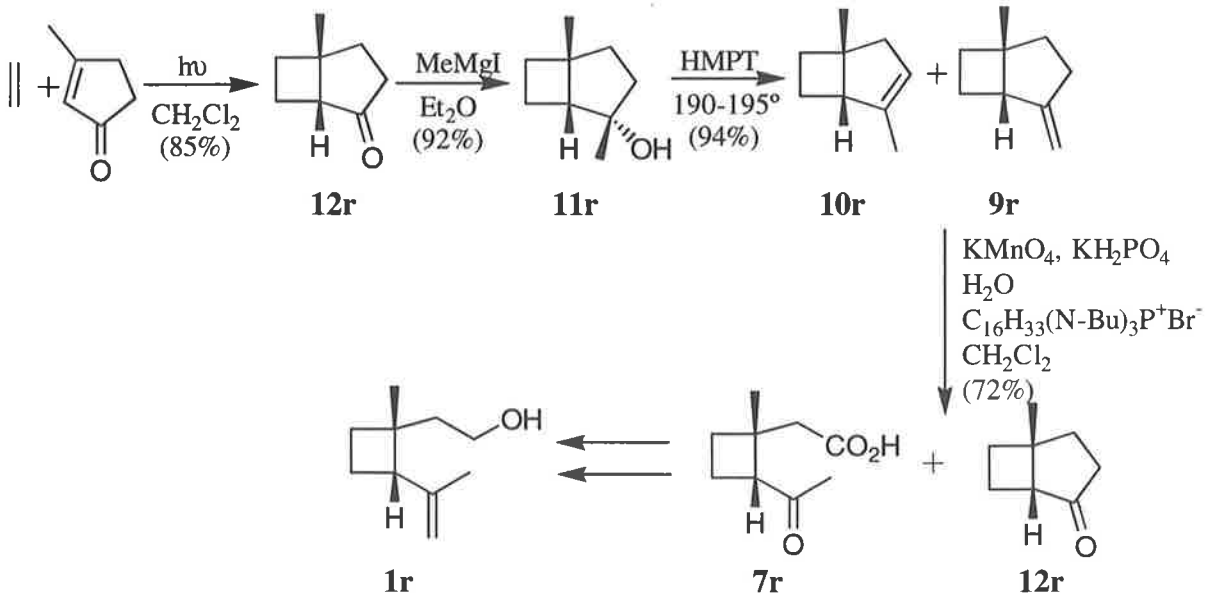
[*] Throughout this thesis, the letter 'r' following a compound number denotes the racemic form, but in schemes the symbol (±) has also been added as a reminder. Similarly 'a' and 'b' denote the enantiomers.

steps, *via* the keto-acid **7r** as the key intermediate. Wittig olefination gave the *cis*-olefinic acid **8r** in an 80% yield with only 3% isomerisation. Reduction of the olefinic acid **8r** with sodium dihydridobis(2-methoxyethoxy)aluminate in benzene-ether gave the racemic pheromone **1r**.



Scheme 1

Rosini recognized *cis*-(±)-2,5-dimethylbicyclo[3.2.0]hept-2-ene **10r** as an ideal intermediate for an efficient synthesis of (±)-grandisol **1r**. In 1979 his group synthesized the racemic keto-acid **7r** in four steps, (Scheme 2).[26] Conversion of this key keto acid **7r** to grandisol **1r** has been reported a number of times.[25,27,28]

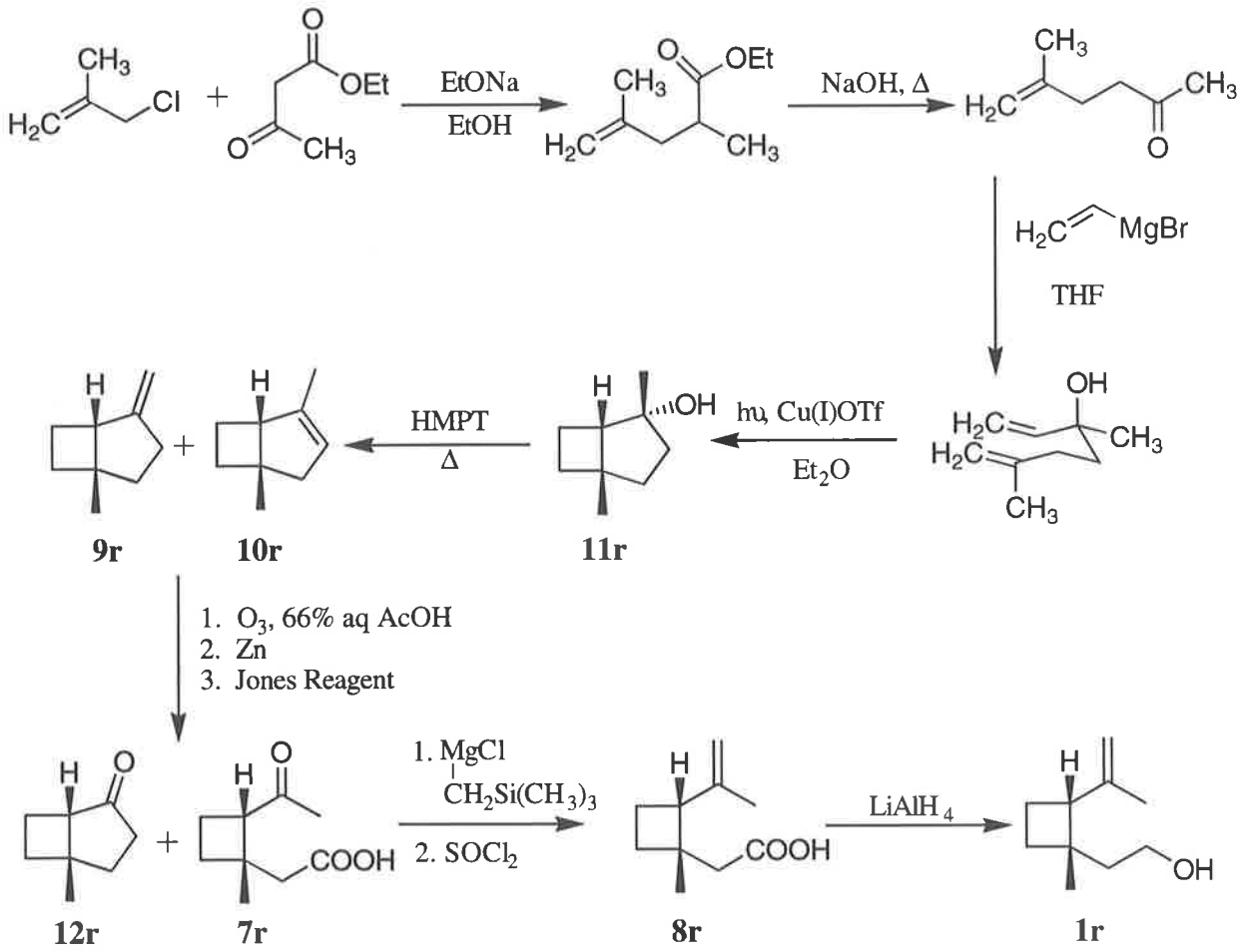


Scheme 2

The drawback in this synthetic sequence is the generation of the two alkenes **9r** and **10r** from the elimination of the tertiary hydroxyl **11r**. Reaction of the *exo*cyclic alkene **9r** with $KMnO_4$ produces the bicyclic ketone **12r** which can be recycled.

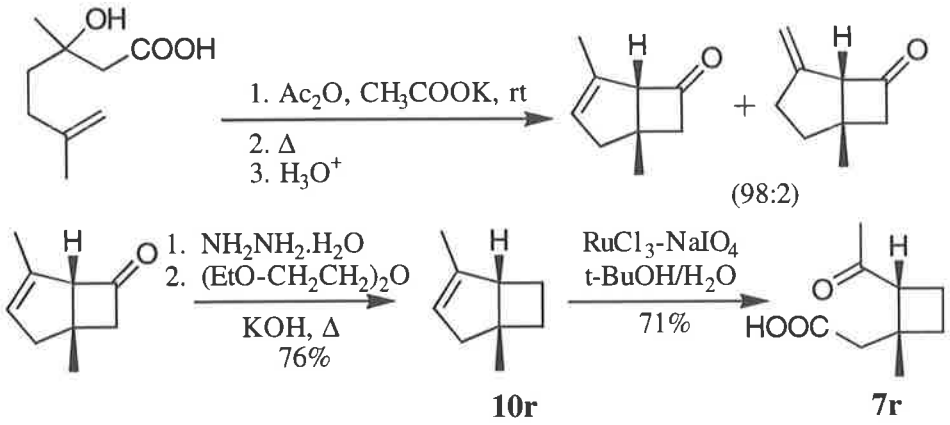
In 1985, *Rosini* improved his synthesis of (±)-grandisol **1r**, using alternative cheap and readily available starting materials.[29] Furthermore, after formation of the keto acid **7r** the synthesis

diverts from the procedure developed by *Zurflüh* and co-workers.[25] Methylenation was accomplished with trimethylsilylmethyl magnesium chloride and thionyl chloride, giving the acid **8r** without epimerisation occurring. A lithium aluminum hydride reduction in diethyl ether gives racemic grandisol **1r**. The synthesis is outlined in Scheme 3.[29]



Scheme 3

Rosini has developed a synthesis for the formation of *cis*-(±)-2,5-dimethylbicyclo[3.2.0]hept-2-ene **10r** without the contamination of the *exo*cyclic isomer **9r** (Scheme 4).Conversion of the *endo*cyclic isomer **10r** to the keto acid **7r** was accomplished with ruthenium chloride and sodium periodate. The keto acid **7r** was converted to grandisol **1r** by the same route as that shown in Scheme 2.[30]

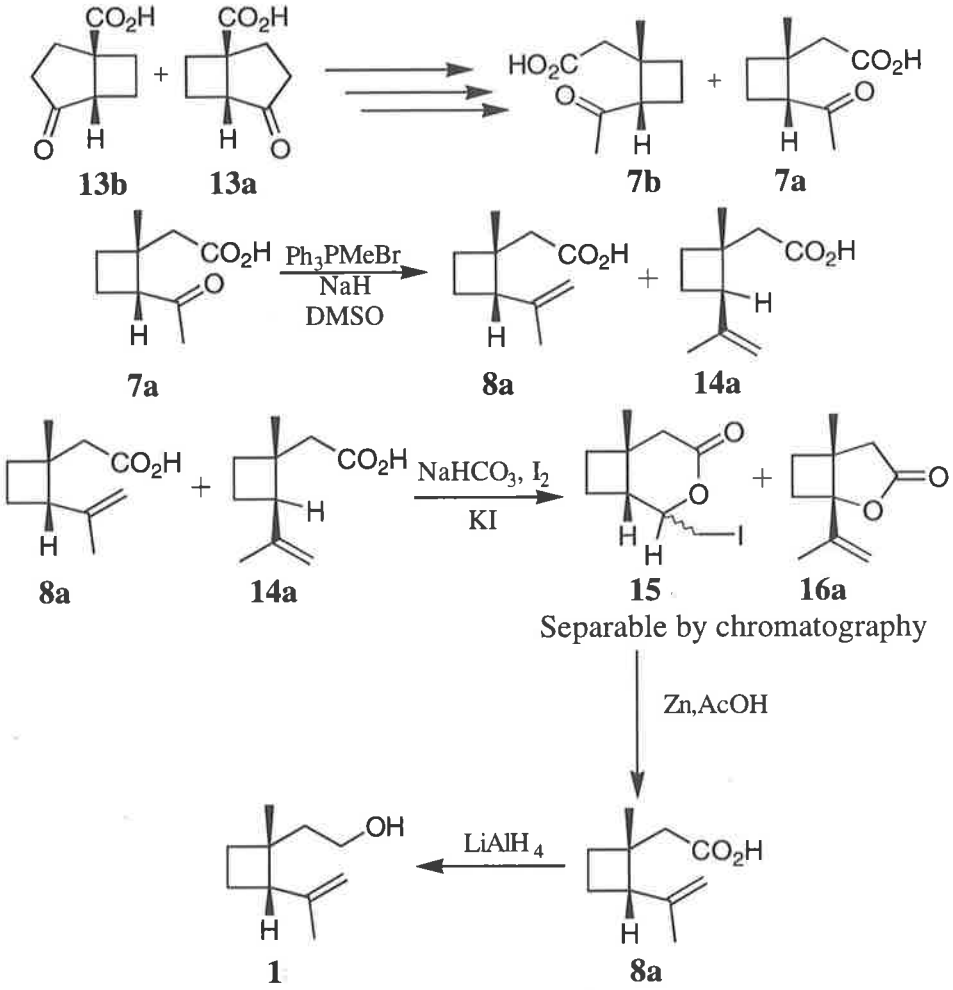


10r **7r**

Scheme 4

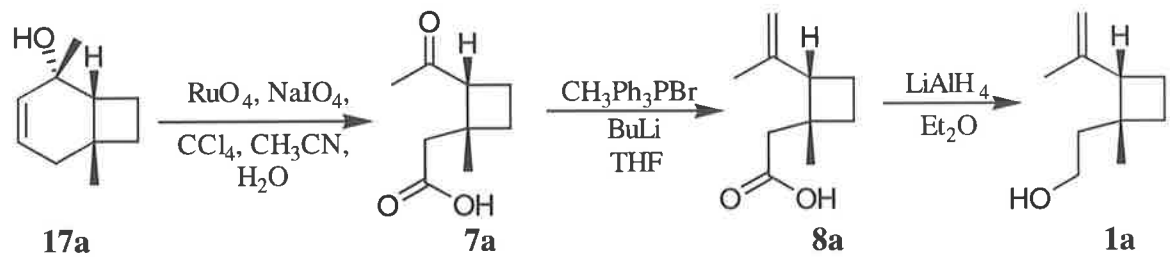
The syntheses of optically active grandisol of relevance to this work are outlined below.

Shortly after grandisol **1** was discovered as an aggregation pheromone of the cotton boll weevil, *Mori* synthesized both enantiomers of grandisol **1**. The route chosen is outlined in Scheme 5.[27] After a photochemical reaction and functional group transformation an acid **13** was obtained which could be resolved into the two enantiomers **13a** and **13b**. Separate conversion of these enantiomers to the keto-acids **7a** and **7b** was accomplished after several steps. A Wittig reaction on the keto-acid **7a** (DMSO, NaH, PPh_3CH_3Br) gave the required *cis*-olefinic acid **8a**, but it was contaminated with 10-20% of the *trans* isomer **14a**. The two isomers **8a** and **14a** were then converted, via an iodolactonization reaction, to compounds **15** and **16a** which could then be separated by chromatography. Reduction of the iodolactone **15** gave the pure *cis* isomer **8a**. A lithium aluminum hydride reduction then gave (+)-grandisol **1** . Repetition of this scheme with the other enantiomer of **7b** gives (-)-grandisol **1b**.[27] This synthesis gives useful spectroscopic data of the key intermediates **7**, **8** and **1**. Surprisingly, optical rotation and enantiomeric excess data is given only for the final product **1**.



Scheme 5

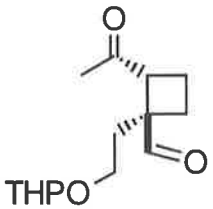
An alternative synthesis of the optically active key intermediate **7**, which also involved classical resolution has been accomplished by *Silverstein and Webster*.[31] After numerous steps pure enantiomers of the allylic alcohol **17** were obtained. The pure enantiomers **17a** and **17b** were then separately converted to optically pure grandisol **1**, via the keto-acid **7** (Scheme 6).



Scheme 6

A Wittig methylenation was used for construction of the isopropenyl group. This reaction has been reported many times, each with varying amounts of epimerisation.[25, 27] *Silverstein* and *Webster* deduced the factor in the isomerisation was the quantity of DMSO used in the Wittig

methylenation.[31] This was verified by *Stork and Cohen*, who methylenated a very similar compound **18** in pure THF and found no trace of isomerisation.[28]

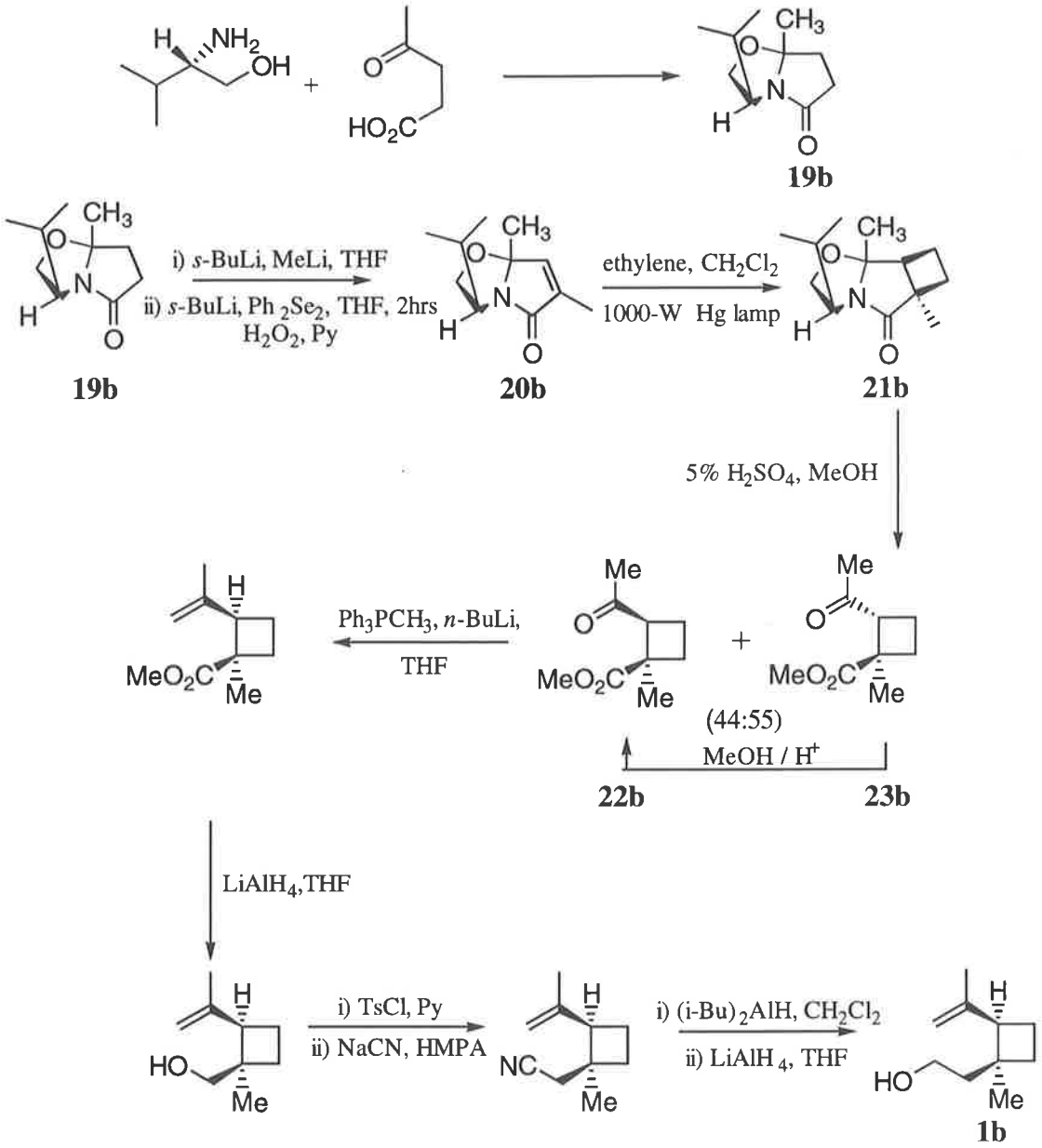


18

Figure 3

Hence, *Silverstein* and *Webster* used THF as a solvent for the Wittig reaction (THF, *n*-BuLi, PPh_3CH_3Br) and the *cis*-olefinic acid **8a** was obtained uncontaminated by the *trans*-isomer. The final step was the reduction of the carboxylic acid to the alcohol to give (+)-grandisol **1a** in a good yield. In the same manner the allylic alcohol **17b** was converted to (-)-grandisol **1b**. This procedure also only reports the optical rotation values for the final product.

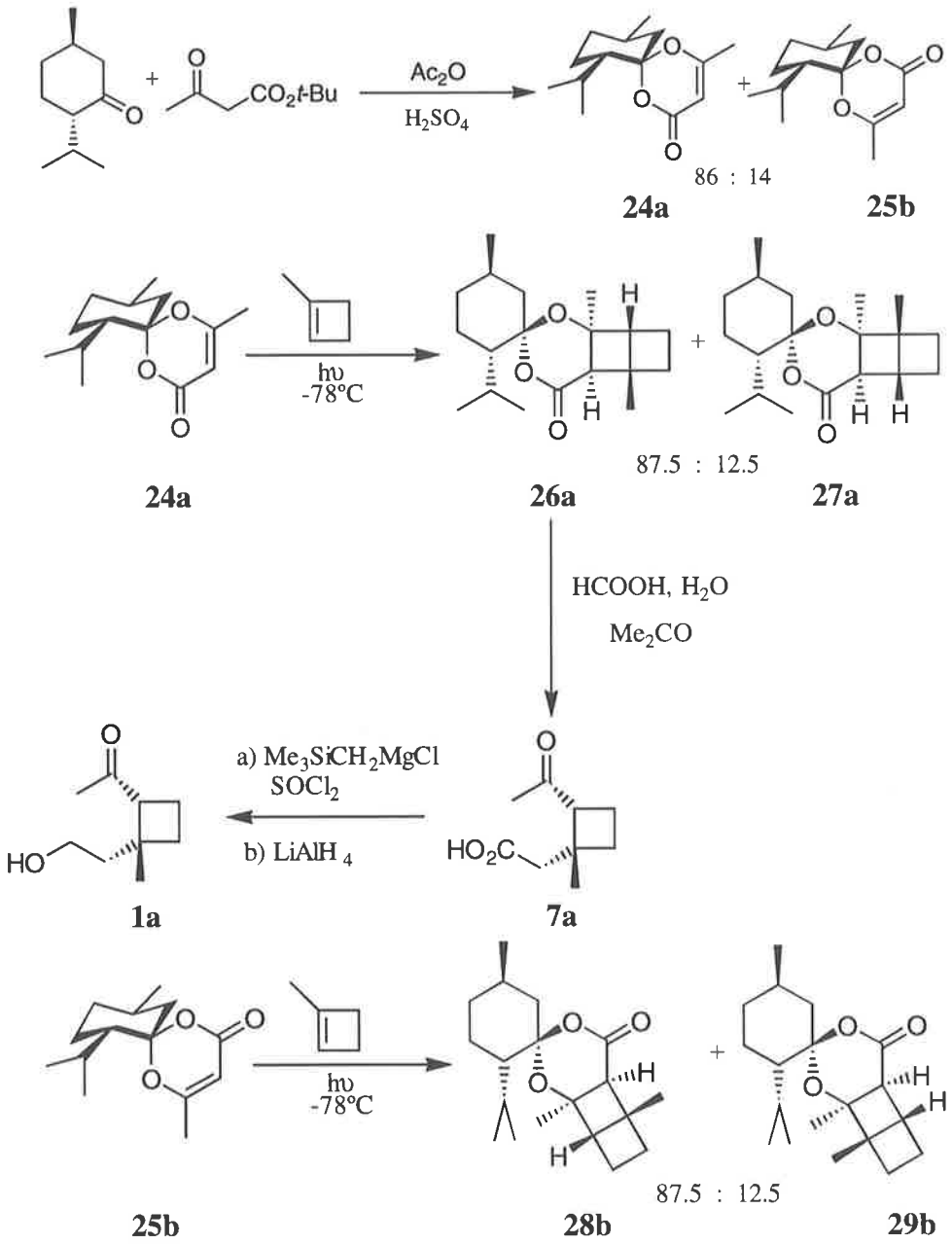
The next three syntheses of optically active grandisol **1** employ intramolecular photocycloaddition of alkenes to chiral α,β-unsaturated carbonyl compounds as the key steps. *Meyers and Fleming* have developed an asymmetric synthesis of (-)-grandisol utilizing a chiral auxiliary.[32] The α,β-unsaturated lactam **20b** was prepared from the lactam **19b**, which was prepared from (S)-valinol and levulinic acid. The key intermediate **21b** is formed from an asymmetric [2+2] cycloaddition of ethylene to α,β-unsaturated lactam **20b**. The photochemical product **21b** was contaminated with ca. 7-8% of its *endo*-cyclobutane-fused isomer, and as no separation of the *cis* and *trans*-cyclobutane isomers was attempted (-)-grandisol **1** was obtained in an 88% enantiomeric excess (Scheme 7). Another drawback of the reaction is that the acetyl group in **21b** epimerizes in the methanolic sulfuric solution to give the two isomers **22b** and **23b** which can be separated by chromatography. Fortunately, **23b** can be epimerized in a methanolic sulfuric solution to give a mixture of **22b** and **23b** (45:55). The pure isomer **22b** was then converted to (-)-grandisol **1b** by the route shown in Scheme 7.



Scheme 7

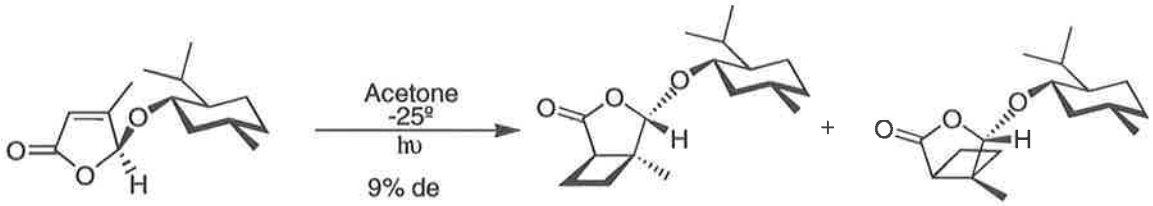
Demuth and coworkers have also synthesized both enantiomers of grandisol **1** by asymmetric synthesis [33] (Scheme 8). Condensation of (-)-menthone with *tert*-butyl acetoacetate gives an 86:14 ratio of the two isomers **24a** and **25b**, which could be separated by crystallization and chromatography. An asymmetric [2+2] cycloaddition reaction on the pure **24a** gave the two optically active photoproducts **26a** and **27a**. After separation of the two isomers **26a** and **27a** by chromatography, isomer **26a** was converted to the keto acid **7a**. The keto-acid **7a** was then converted to (+)-grandisol **1a** by the procedure of *Rosini* (Scheme 3).[29] An asymmetric [2+2] cycloaddition reaction on the pure **25b** gave the two optically active photoproducts **28b** and **29b**. After separation of **28b** and **29b** by chromatography, isomer **28b** was converted to (-)-grandisol **1b**. At the present this is the shortest enantioselective synthesis of the enantiomers of

grandisol in good yield. However, this synthesis does require extensive separation of diastereomers by chromatography.



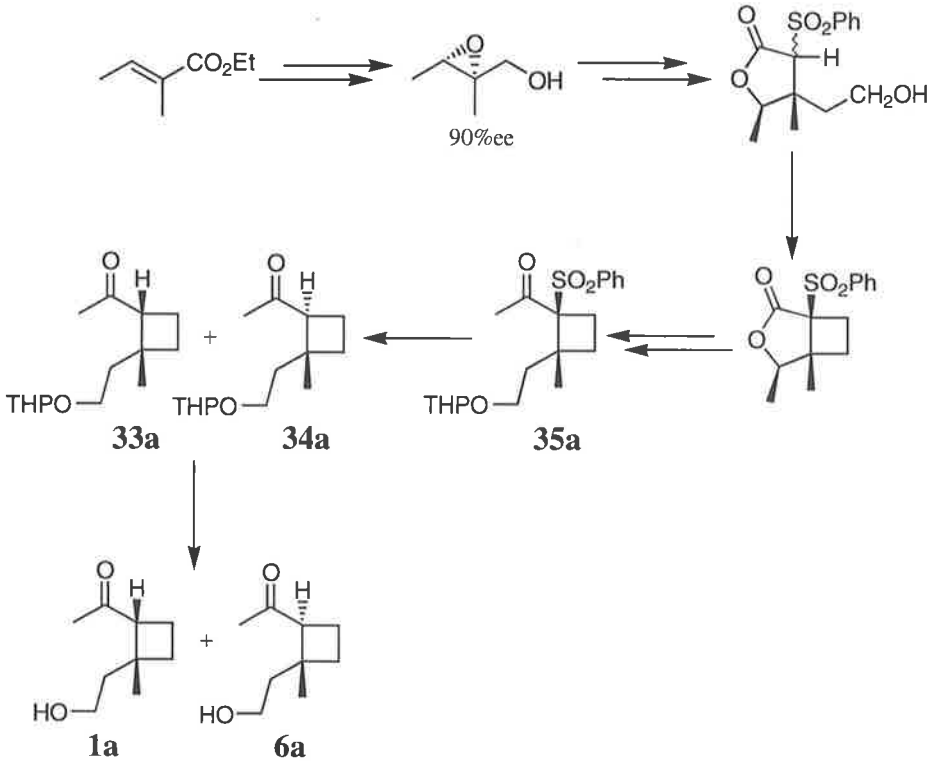
Scheme 8

Hoffman and Scharf have also used a [2+2] photocycloaddition to synthesize optically active grandisol **1**. Both enantiomers of grandisol are synthesized in an enantiomeric excess of greater than 90%, and diastereoselectively from the optically active furanone **30a** in six steps.[34] In the [2+2] photocycloaddition reaction, two diastereomeric cyclobutanes **31a** and **32a** are formed, which can be separated by chromatography (Scheme 9). The pure **31a** isomer is converted to (+)-grandisol **1a** and the pure **32a** isomer is converted to (-)-grandisol **1b**.[34]



Scheme 9

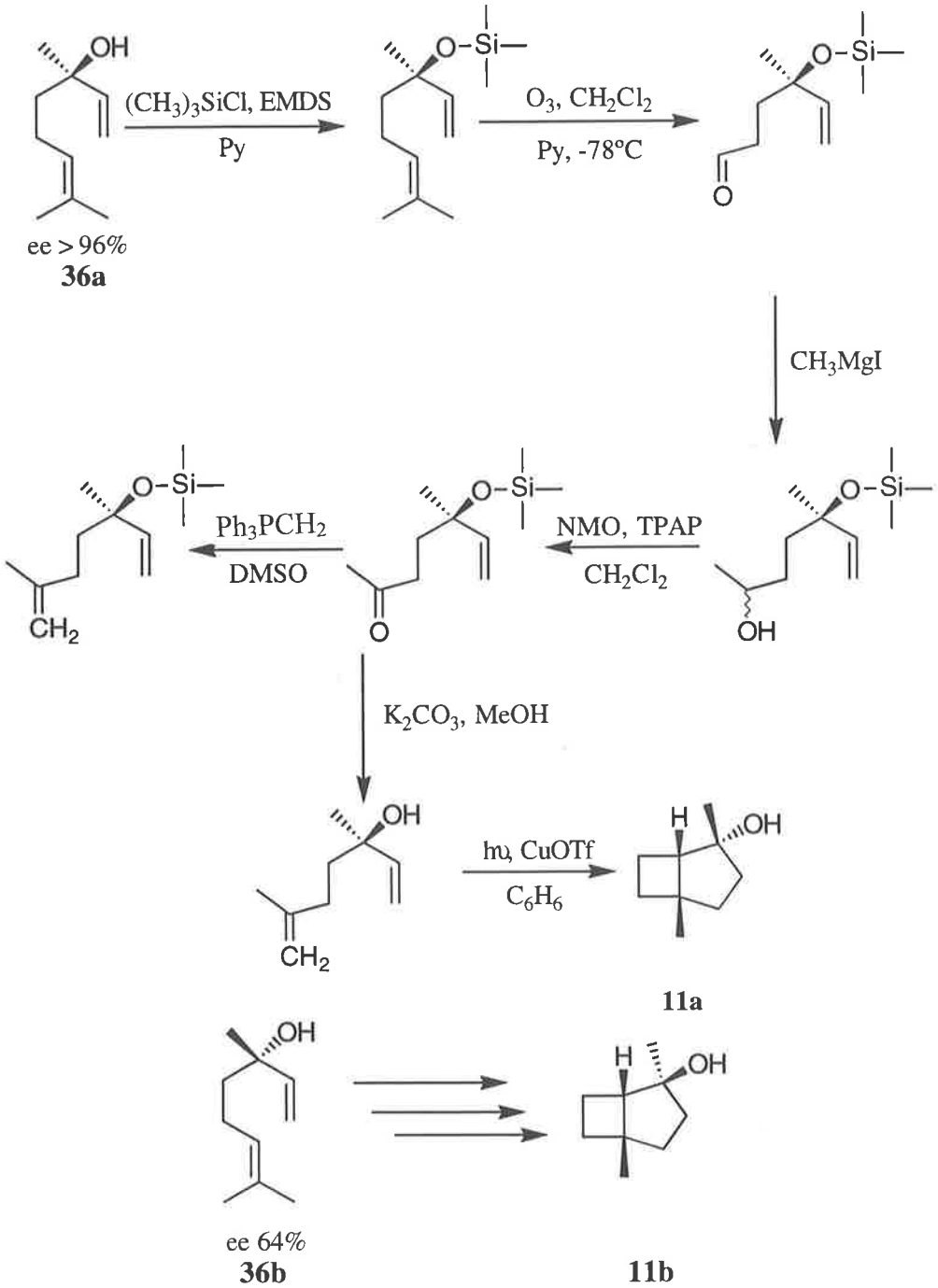
One synthesis of (+)-grandisol **1a** from achiral starting material uses the Sharpless asymmetric epoxidation reaction as the source of asymmetry.[8] The important intermediates of the synthesis are outlined in Scheme 10. Reductive cleavage of **35a** at ambient temperature gave a 1:10 epimeric mixture of **33a** and **34a**. When this reaction was performed at –40°C a 1:1 mixture of **33a** and **34a** was obtained. A Wittig reaction and cleavage of the protecting group gave (+)-grandisol **1a** and fraganol **6a** which were separated by chromatography. The synthesis is consists of 15 steps and in several steps unwanted isomers are formed which require chromatographic separation, consequently lowering the yield of the desired product.



Scheme 10

Rosini and coworkers have formed both enantiomers of the tertiary alcohol, 2,5-dimethylbicyclo[3.2.0]heptan-*endo*-2-ol **11**.[35, 36] There is potential for optically pure 2,5-dimethylbicyclo[3.2.0]heptan-*endo*-2-ol **11** to be converted to grandisol **1** by the procedure

previously used by *Rosini*.[29] In the earlier synthesis,[35] *Rosini's* group resolved the enantiomers of 2,5-dimethylbicyclo[3.2.0]heptan-*endo*-2-ol **11** by fractional crystallization, (1S)-(-)-camphanic acid chloride was used to from the diastereomeric esters. In the later synthesis[36] the enantiomers of key intermediate **11** are formed form optically active linalool **36**. (Scheme 11).



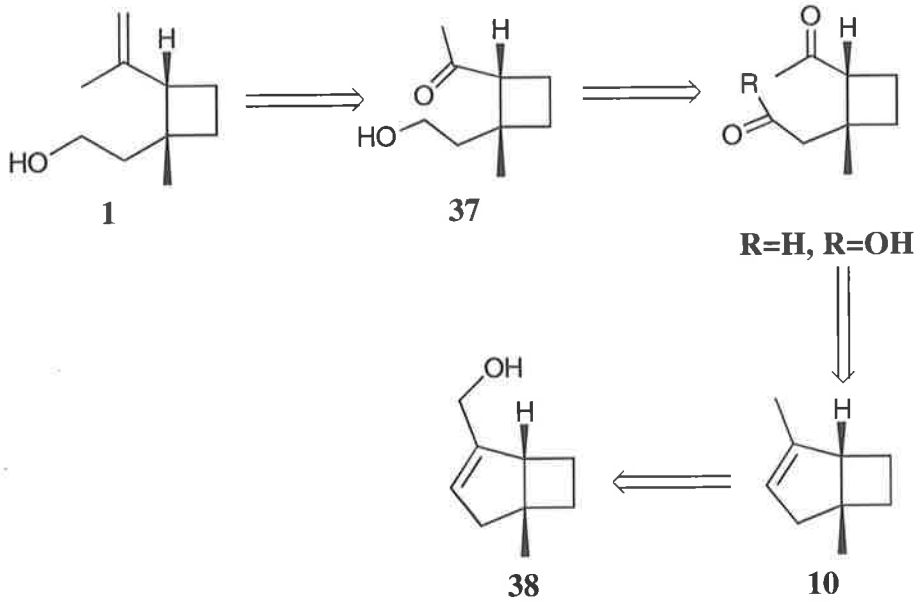
Scheme 11

These reactions require a stiochiometric amount of the chiral precursor linalool **36** and the enantiomeric excess of the products are limited by the optical purity of the starting material.

There is potential for optically active grandisol to be synthesized in a shorter number of steps by catalyst controlled methods (previously discussed on p. 3). The route to optically active grandisol proposed in this thesis will hopefully accomplish this goal.

Section 1.3 Proposed Synthesis of Grandisol

Outlined below is an overview of the proposed new asymmetric synthesis of (+)-grandisol **1a** (Scheme 12) Since the racemic alkene **10** can be converted efficiently to racemic grandisol **1r** it should be possible to convert the optically active alkene efficiently to optically active grandisol by the same route. Therefore, it is proposed to investigate potential new and efficient routes to this optically active alkene, which use catalytic means of asymmetric induction.



Scheme 12

It is proposed that the optically active alkene **10** can be prepared in two ways. It is possible that asymmetry can be introduced into the allylic alcohol **38** by a kinetic resolution upon asymmetric epoxidation with the Sharpless epoxidation reagent. The resolved allylic alcohol would then be converted to the optically active alkene. Alternatively, kinetic resolution of the racemic alkene **10** may be accomplished by use of the Sharpless asymmetric dihydroxylation reaction.

Section 1.3.1 Sharpless Epoxidation

The most versatile and widely used method for enantioselective epoxidation of allylic alcohol is the Sharpless epoxidation. It is also the reagent of choice in the kinetic resolution of allylic alcohols.[37] The reagents involved in this oxidation are *tert*-butyl hydroperoxide (an oxidant), titanium tetraisopropoxide (a Lewis acid), and a diester of (+)- or (-)-tartaric acid. The reaction is general for allylic alcohols; it is highly predictable and is often highly enantioselective. The reaction is chemoselective, such that the double bond oxidized is adjacent to a hydroxyl bearing carbon, and other double bonds present in the molecule are not oxidized. [37] There are several reviews dealing with the Sharpless epoxidation.[38, 39, 40, 41]

The absolute configuration of the epoxide produced by the Sharpless asymmetric epoxidation can be predicted using a simple model. If the substrate is drawn as shown (Figure 4), the oxygen is delivered from above the plane if a (-)-tartrate ester is used. If the enantiomeric tartrate is used delivery will be from below the plane.[37, 41]

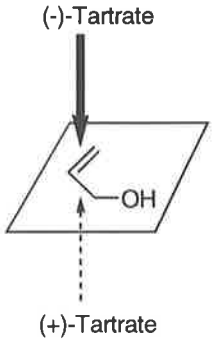


Figure 4

Sharpless proposes that when equimolar amounts of tartrate and Ti(O*i*-Pr)$_4$ are combined an equilibrium is immediately established (Figure 5).This is due to the rapid exchange of titanium ligands in solution and because the chelating diol (i.e., the tartrate) has a much higher binding constant for titanium than do monodentate alcohols. After formation of the Ti(O*i*-Pr)$_2$(tartrate) complex, the remaining two alkoxide ligands are replaced in reversible exchange reactions by the TBHP and the allylic alcohol to give the 'loaded' complex Ti(tartrate)(TBHP)(allylic alcohol). The complex Ti(tartrate)(*t*-OBu)(epoxy alcohol) is formed after oxygen is transferred from the coordinated hydroperoxide to the allylic alcohol. Both the epoxy alcohol and *t*-butoxide group are then replaced by TBHP and the allylic alcohol regenerating the 'loaded complex' which completes the catalytic cycle.[41] (Figure 6).

Figure 5

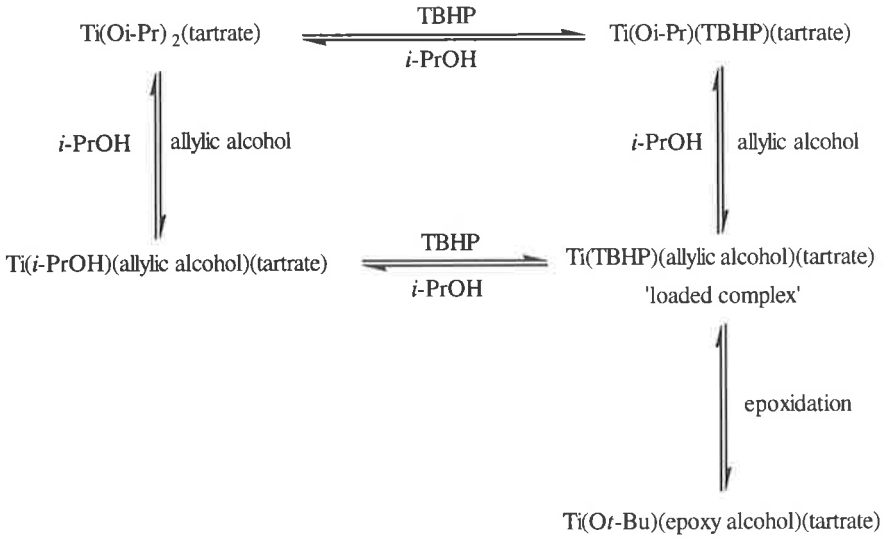


Figure 6

Spectroscopic measurements on the complex in solution strongly support that the major molecular species formed in solution is the dimeric composite, $Ti_2(tartrate)_2(OR)_4$. Efforts to isolate the complex formed, as a crystalline solid, have been unsuccessful. Assignment of the structure has been obtained for a closely related complex, $Ti_2(dibenzyltartramide)_2(OR)_4$. By this analogy the structure shown in Figure 7 has been proposed for the $Ti_2(tartrate)_2(OR)_4$ complex. To account for the similarity of all the tartrate ester groups in the ambient temperature NMR spectrum, an equilibrium between the two structurally degenerate complexes has been proposed.[37]

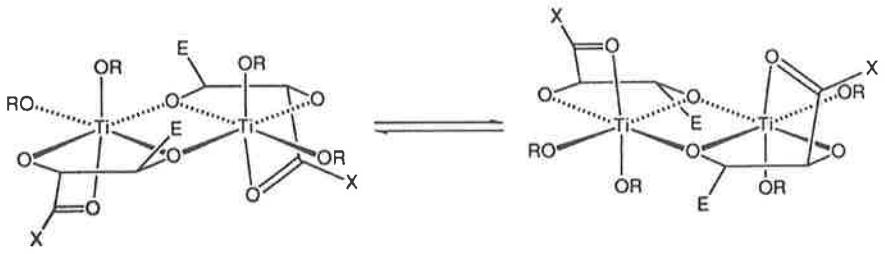


Figure 7

The kinetic resolution of allylic alcohols by the Sharpless epoxidation reaction is a useful procedure. This method can be illustrated simplistically with an allylic alcohol that has a substituent at C1 (Figure 8), but now both enantiofacial selectivity and diastereoselectivity must be considered. For a given tartrate, because of different diastereomeric interactions, one

of the enantiomers of the allylic alcohol will react more rapidly. Epoxidation of the enantiomer that has the R group orientated so it will not be in the direction of oxygen delivery proceeds normally. Epoxidation of the other enantiomer proceeds at a reduced rate because contact of between the C-1 substituent and the catalyst seriously hinders the required approach of olefin to oxidant. If there is only enough oxidant to consume all of the faster reacting enantiomer, and the rate difference is sufficiently high (~25:1), then the reaction will effectively stop after one enantiomer has reacted. This would leave the slower reacting enantiomer of the allylic alcohol unreacted.[37, 41]

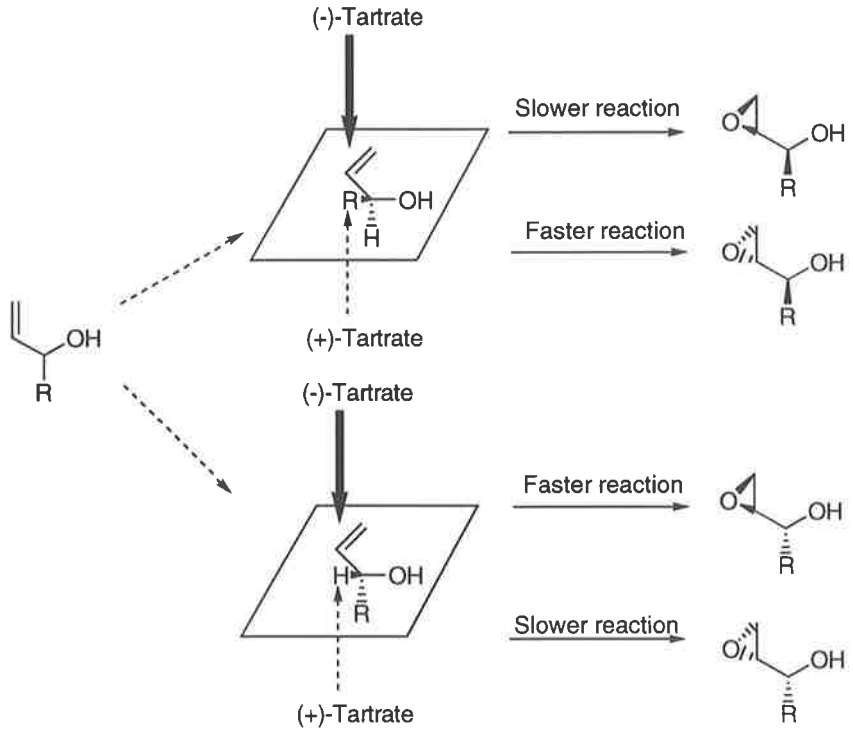
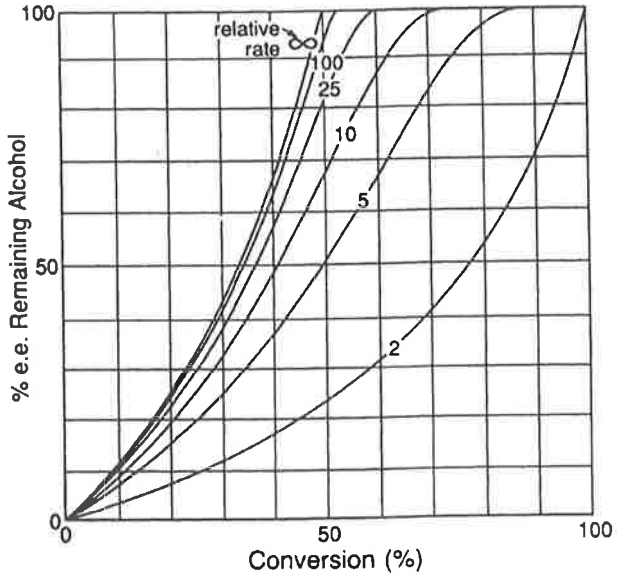


Figure 8

Although kinetic resolution is most frequently encountered and applied to chiral C-1 substituted allylic alcohols the rationale is also applicable to allylic alcohols with chiral substituents at other positions.

Sharpless has defined the ratio of the rates of epoxidation of the two enantiomers, k_{fast}/k_{slow} as the relative rate (k_{rel}), where k_{rel} is related to the percent conversion of the allylic alcohol and the enantiomeric purity of the remaining allylic alcohol.

Kagan has derived a mathematical relationship for the kinetics of kinetic resolutions. The relationship can be represented graphically.[42]



The mathematical equation used was:

$$\frac{K_A}{K_B} = \frac{\ln(A / Ao)}{\ln(B / Bo)} = \frac{\ln(1-C)(1-ee)}{\ln(1-C)(1+ee)}$$

Equation 1

Where C is the fraction of consumption of the racemate, e.e. is the % e.e./100, and A and B refer to the concentration of the fast and slow reacting enantiomers respectively.

It is interesting to note, from the graph, that a relative rate difference of 100 is nearly as effective as a relative rate difference of infinity. Even if there is a small relative rate difference substances with high enantiomeric purity can be obtained, if some sacrifice of yield is acceptable.

An interesting experimental observation in the Sharpless asymmetric epoxidation is lower reaction temperatures and larger tartrate groups are factors, which increase the magnitude of k_{rel} and consequently improve the efficiency of the kinetic resolution process.[41]

Although there are numerous examples in the literature of kinetic resolutions of secondary allylic alcohols, there are few reported for kinetic resolution on primary allylic alcohols. The known kinetic resolutions of primary allylic alcohols are illustrated in Table 1.[43]

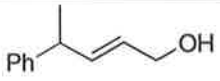
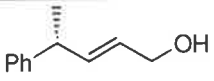
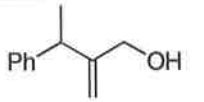
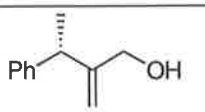
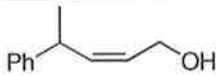
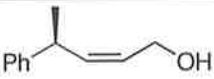
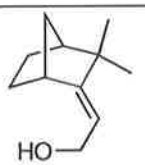
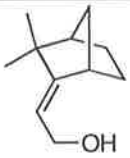
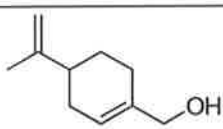
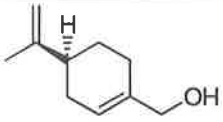
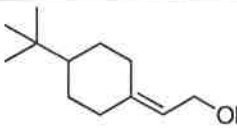
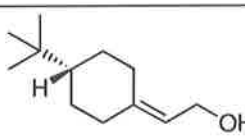
Racemic Substrate	% e.e. of recovered substrate	Recovered substrate configuration*
	6	
	80	
	95	
 + enantiomer	85	
	48	
	70	

Table 1

* (+)-DIPT was employed in all cases. Most reactions were run to about 60% conversion at –20°C.

In the proposed synthesis of (+)-grandisol **1a**, it is of interest if the Sharpless asymmetric epoxidation reaction can be successfully used for a kinetic resolution in a molecule where the chiral centre is remote from the hydroxyl.

Below are shown the enantiomers of the allylic alcohol **38** drawn so the mnemonic of Sharpless can be used. It is assumed from this mnemonic that when D-(-)-DIPT is used attack of the complex will come preferentially from the top face in one enantiomers **38a** and from the bottom face in **38b**. Whereas L-(+)-DIPT will come from the bottom face in the enantiomer **38a** and from the top face in **38b** (Figure 9).The active complex in the Sharpless epoxidation reaction is bulky and it is presumed due to the convex/concave face of the allylic alcohol **38** that the convex face will be most open to attack by this reagent, whereas the concave face will be effectively closed to attack. Thus when L-(+)-DIPT is used, there should be a higher rate of attack on the right hand side enantiomer **38b**, whereas the enantiomer on the left hand side **38a**

will be slower. This could result in an effective kinetic resolution, and the optically enriched allylic alcohol could then be obtained after the reaction (Figure 9).

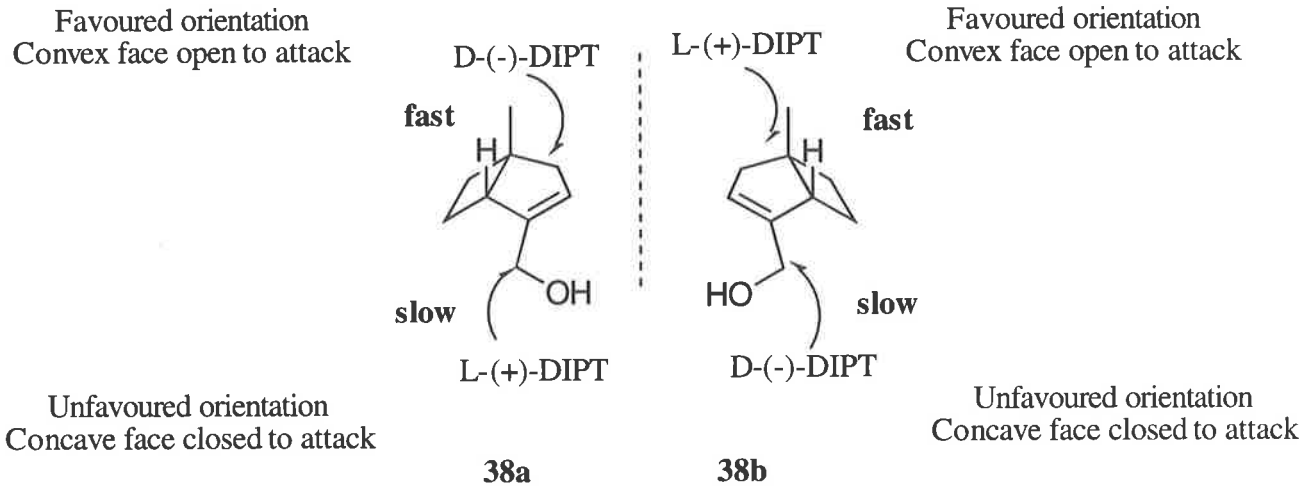


Figure 9

Section 1.3.2 Sharpless Asymmetric Dihydroxylation Reaction

The osmium catalyzed asymmetric dihydroxylation (AD) is a more general reaction than the titanium-mediated asymmetric epoxidation. Whereas the epoxidation reaction requires coordination of the reagent to the hydroxyl group and therefore only applies to allylic alcohols. The hydroxylation reaction works with alkenes, and therefore a wider range of substrates is available. The reaction is easy to perform; it takes place in the presence of water and is insensitive to oxygen. The reaction consists of four main components, potassium ferricyanide (an oxidant), potassium carbonate (a base, to help in the hydrolysis of the osmate ester) and potassium osmate(VI) dihydrate and the chiral ligand (which together form the chiral catalyst). It has also been found that the addition of methane-sulfonamide further accelerates the hydrolysis of the osmium(VI) glycolate product and is a useful addition to certain reactions. In particular, this allows high catalytic turnovers, even with sterically hindered substrates. Because of the 'sulfonamide effect', most AD reactions can be carried out at 0°C, which has a beneficial influence on selectivity.

The two chiral ligands are diastereomers and not enantiomers due to the presence of the ethyl group at C3 (Figure 10).However, because of the remote location of this group, they operate like enantiomers in the AD reaction and have been called

'pseudoenantiomers' for this reason. The use of the ligands derived from these two 'pseudoenantiomeric' alkaloids lead to diols of opposite configuration but since they are not enantiomers the e.e.'s obtained, although usually similar, are not identical.

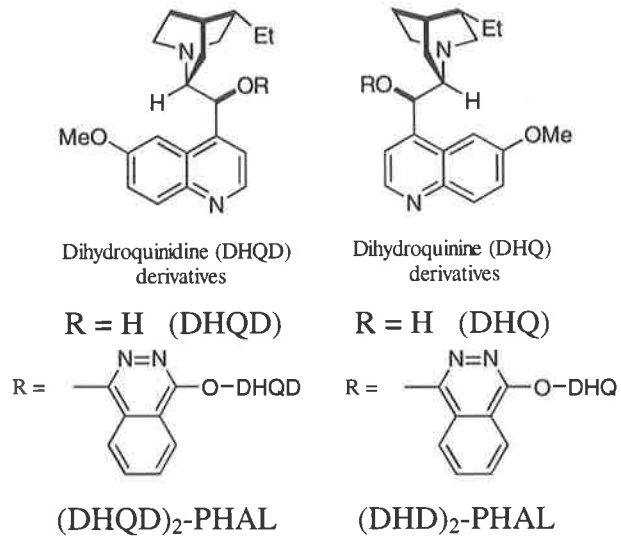
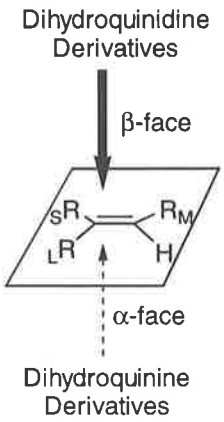


Figure 10

In a similar manner to the Sharpless asymmetric epoxidation reaction, the dihydroxylation reaction also has a mnemonic. The asymmetric complex formed by osmium tetroxide, the chiral ligand, and the olefinic substrate delivers preferentially two oxygen atoms to one face of the olefin, dependent on which antipode of the chiral auxiliary is used. The oxygens will be delivered from the upper or β-face if a dihydroquinidine (DHQD) derived chiral auxiliary is used, and from the lower or α-face if a dihydroquinine (DHQ) derived auxiliary is used when the alkene is viewed as shown in Figure 11.[44]



R_L = largest substituent

R_s = smallest substituent other than hydrogen.

R_M = medium-sized substituent

Figure 11

There have been several applications of the Sharpless asymmetric dihydroxylation reaction for the kinetic resolution of chiral racemic olefins, however with few exceptions the AD reaction has proven to be ineffective for kinetic resolutions.[45] The reasons for this are not understood. Investigations by *Sharpless* and coworkers have revealed some racemic olefins that are suitable, these results are summarized in Table 2.[46]

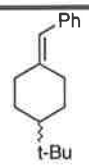
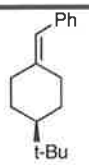
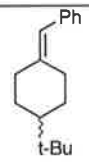
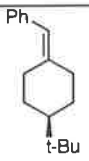
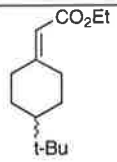
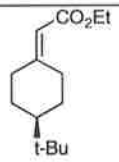
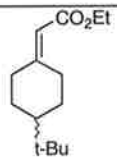
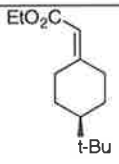
Olefin	Ligand	k_{rel}	Recovered olefin
	$(DHQD)_2$-PHAL	9.7	
	$(DHQ)_2$-PHAL	5	
	$(DHQD)_2$-PHAL	32.0	
	$(DHQ)_2$-PHAL	26.5	

Table 2

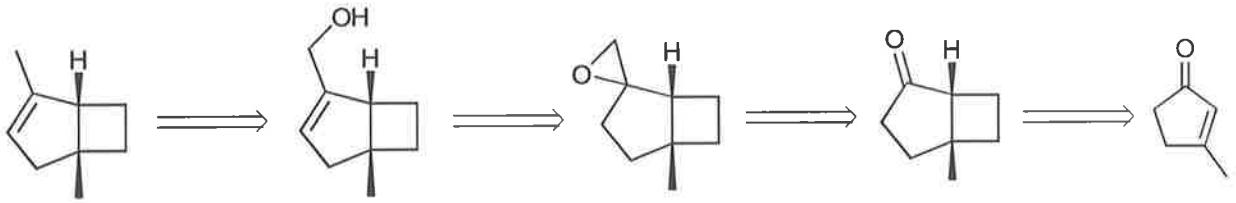
Since the features that define what makes a good substrate have not been delineated and since one of the intermediates in our proposed scheme is an alkene, it is proposed to investigate whether or not it also constitutes a good substrate for kinetic resolution.

Section 1.4 Proposed Synthesis of the Key Intermediate Required for Kinetic Resolution

A kinetic resolution is not the best method of synthesizing optically active compounds. In a kinetic resolution the desired product is formed in a yield of 50%, at best, if there is no way of incorporating the side product into the reaction scheme. If kinetic resolution is to be used as a method of inducing optical activity it is best it is used as soon as possible in the reaction sequence rather than to waste half the hard-earned product at a later stage of the synthesis.

Therefore, it is important that the synthesis of key intermediates **10** and **38** is accomplished in a short number of steps. For this synthesis it is proposed that the key intermediate **38** could be formed in only three steps from readily available material.

Allylic alcohols can be prepared in a number of ways. One of the most direct ways involves the elimination of epoxides,[47] therefore it is proposed that the allylic alcohol **38** can be synthesized from 3-methyl-2-cyclopentenone in three steps. The retrosynthetic pathway is outlined in Scheme 13.



10 **38** **12**

Scheme 13

It is known the bicyclic ketone **12** is available in high yield via a [2+2] photocycloaddition on 3-methyl-2-cyclopentenone. Addition of either of Corey's ylids[48] on the ketone **12** should give the epoxide. Treatment of this epoxide with a non-nucleophilic amide base might give the required racemic allylic alcohol **38**.

Section 1.4.1 Corey's Epoxidation Reaction

Mechanistic studies have been carried out using dimethyl-sulfonium methylide [$(CH_3)_2S^+ CH_2^-$] and dimethyl sulfoxonium methylide [$(CH_3)S^+{=}O\ CH_2^-$].[49] Johnson *et al* discovered reaction of the stabilized ylid, dimethyl sulfoxonium methylide, was reversible, whereas the addition of the non-stabilized ylid, dimethyl sulfonium methylide, was irreversible.[49]

Due to the convex, concave nature of the faces of the carbonyl group in the bicyclic ketone it is expected the ylid will preferentially attack from the convex face. Approach of a reagent to the concave face is subject to a greater steric hindrance than that to the convex face (Figure 12), but in principle, two epoxides could form **40** and **41**.

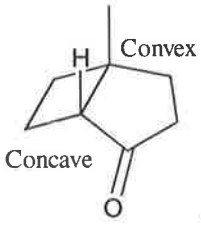
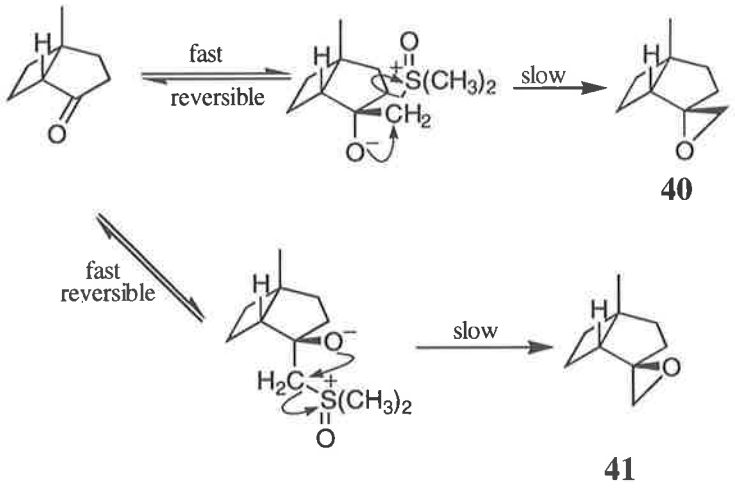


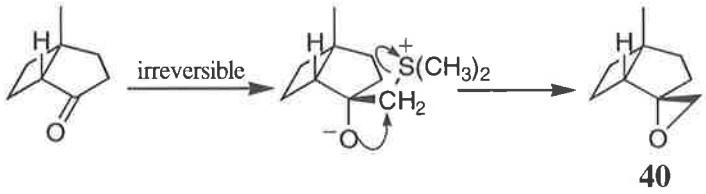
Figure 12

Attack of the stabilized ylid, (reversible addition), on the bicyclic ketone may give the two epoxides **40** and **41** in a different ratio to that obtained from the non-stabilized ylid. In this case the ratio of the epoxides formed is not dependent on the preferred side of attack, but on the relative energies of the transition states from the betaine intermediates to the products. As the first step in the reaction is fast and reversible, it is the relative rates of the second step which is product determining. Hence, it is not easy to predict the preferred product (Scheme 14).



Scheme 14

Attack of the non-stabilized ylid (irreversible addition), on the bicyclic ketone should give only a ratio of epoxides which reflects only the ease of approach of the reagent and this reaction should favour the epoxide shown (Scheme 15).

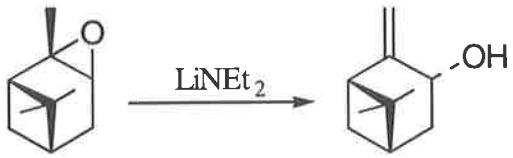


Scheme 15

Section 1.4.2 Base Induced Eliminations

There are a number of methods in the literature for conversion of epoxides to allylic alcohols; the most common is the base-promoted reaction of epoxides. A review in Organic Reactions discussed the effect of strong nucleophilic bases on epoxides.[47]

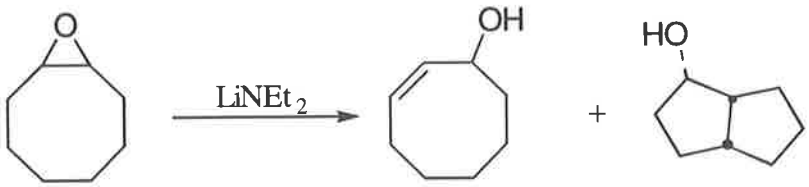
Several isomeric products are formed on treatment of epoxides with strong bases. This reaction can occur with remarkable selectivity. Reaction of α-pinene oxide with lithium diethylamide selectively converts the epoxide to an allylic alcohol with positional and stereochemical control (Scheme 16).[50]



(90-95%)

Scheme 16

The allylic alcohol is not always the major product. *Cis*-cyclooctene oxide is converted to *endo*-2-bicyclo[3.3.0]octanol with the allylic alcohol as the minor product, but presumably in this case the propensity to transannular reactions predominates (Scheme 17). Occasionally an isomeric carbonyl compound is produced [47] (Scheme 18).



(16%) (70%)

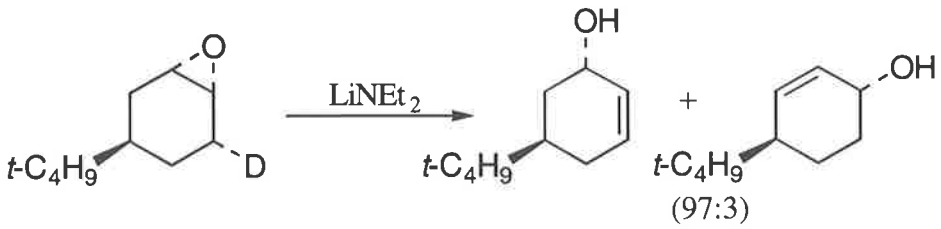
Scheme 17

(46%)

Scheme 18

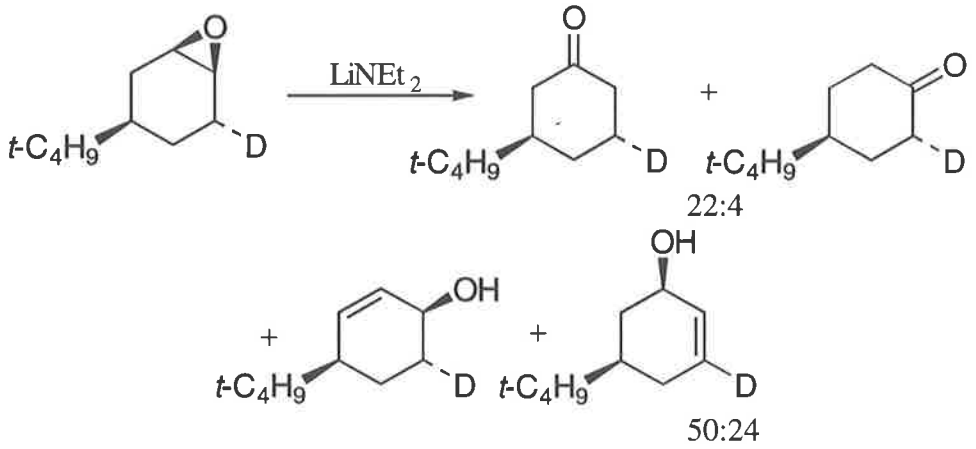
It has been observed that isomerisations of *cis*- and *trans*-4-*tert*-butylepoxycyclohexanes with lithium diethylamide proceed by *syn* elimination. The *trans* isomer reacts more readily and only the allylic alcohol products shown are observed (Scheme 19). Deuterium-labeling

experiments (Scheme 19) show that the epoxide is transformed to the predominant allylic alcohol by loss of the adjacent *cis* deuterium atom.[47]



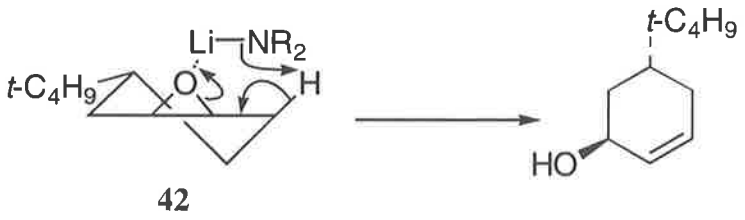
Scheme 19

The *cis*-epoxide reacts more slowly and yields two cyclohexanone products as well as the two diastereomeric corresponding allylic alcohols, as produced in the *trans*-elimination. The deuterium labelled epoxide gives the allylic alcohol with retention of the deuterium label, *via* a *syn* elimination (Scheme 20).



Scheme 20

It is believed there is coordination of an oxygen lone pair with an electron-deficient lithium centre as represented by the complex **42** in Scheme 21 (the lithium amide reagent is depicted as monomeric for simplicity). Decomposition of complex **42** in a cyclic, concerted manner provides a route to allylic alcohol products, *via* removal of a *syn* hydrogen (Scheme 21).



42

Scheme 21

Ketone formation occurs when neither β-elimination or transannular insertion processes are possible, or from further isomerisation of allylic alcohols under the reaction condition. There are two postulated pathways to give enolate anions. The first is an α-elimination, followed by a hydrogen migration from the adjacent ring carbon, pathway a. The alternative is an electrocyclic ring opening, sometimes called a β-elimination, pathway b (Figure 13).

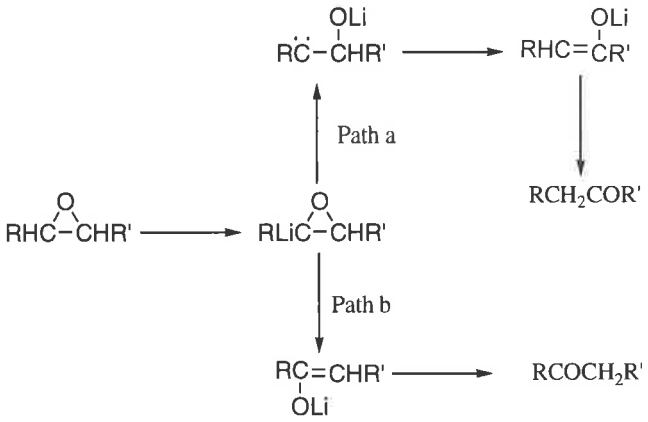
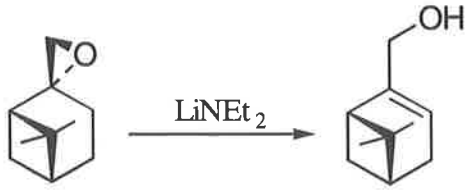


Figure 13

When the β–elimination process is slow a competing cyclization process, as in *cis*-cyclooctene oxide, the bicyclic alcohol is observed (Scheme 17). Experimental evidence suggests this occurs *via* a carbenoid mechanism, the initial step involves metalation of the epoxide ring. The metalated epoxide is thought to undergo an α-elimination then insertion of the carbenoid centre into a neighbouring C-H bond.[47]

Lithium diethylamide is the base of choice in isomerisations of epoxides to alcohols; it generally favors allylic alcohol formation even for epoxycycloalkanes, which undergo epoxide metalation. Nucleophilic addition of the base to the epoxide is often a problem; this can normally be solved with the use of bulkier lithium amides. However, an increase in steric hindrance of the reagent can result in an increase of metalation with epoxycycloalkanes, leading to ketone formation or transannular insertion.

All the experimental observations, discussed above, are on non-terminal epoxides; there are only a few examples of the formation of allylic alcohols from terminal epoxides. One example is β–Pinene oxide which undergoes isomerisation with lithium diethylamide to give the corresponding allylic alcohol in an 81% yield (Scheme 22).[51]

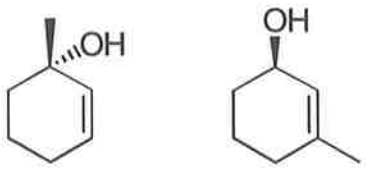


Scheme 22

Section 1.5 Previous Syntheses of MCL

Another pheromone of interest to this thesis is 1-Methyl-2-cyclohexen-1-ol (MCL) **2**, a pheromone produced by the Douglas-fir beetle. The Douglas-fir beetle, *Dendroctonus pseudotsugae*, is a bark beetle, which is a serious pest of the Douglas-fir tree, *Pseudotsuga menziesii*. In the past control measures have consisted of application of orthodichlorobenzene, trichlorobenzene, dichloroethylether or ethylene dibromide in either diesel oil or water emulsion.[52] One approach to safely control the Douglas-fir beetle has been to use semiochemicals either to induce attack and contain infestations around certain trees,[53] or to repel beetles from trees by treatment with pheromone components.[54]

The female Douglas-fir beetle releases a complex mixture of pheromones.[55,56] The compound 1-Methyl-2-cyclohexen-1-ol (MCL) **2** has been identified as a component of the aggregation pheromone of the female Douglas-fir beetle (Figure 14).

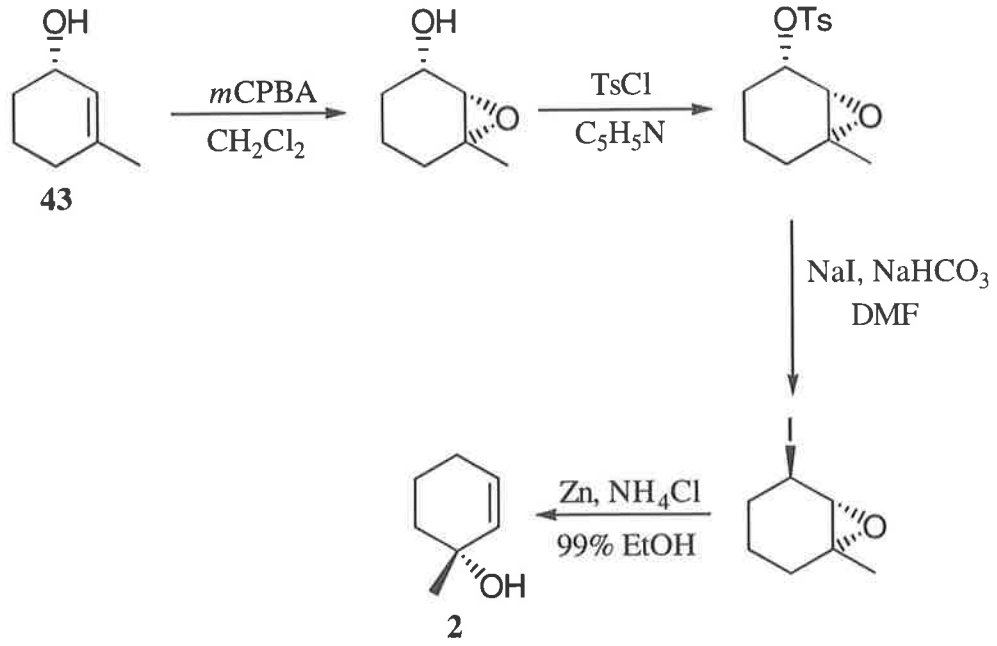


2 **43**

Figure 14

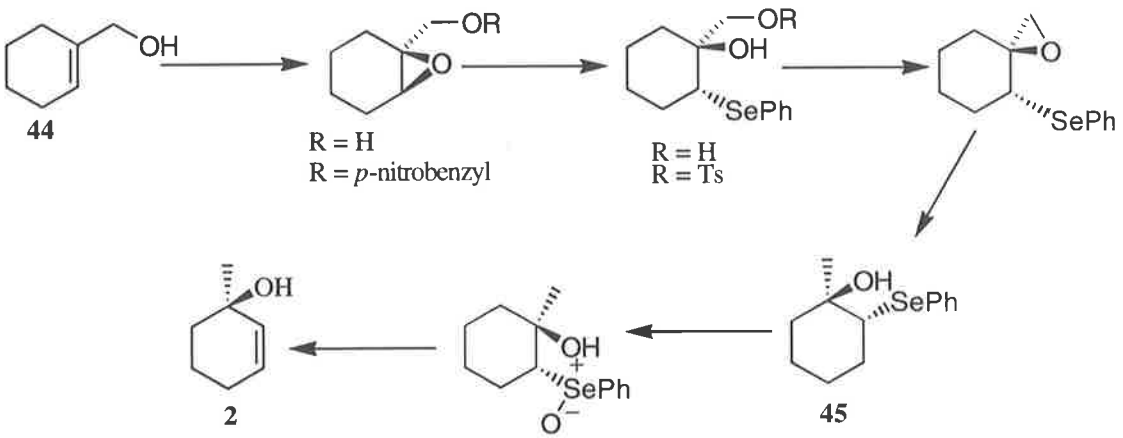
1-Methyl-2-cyclohexen-1-ol (MCL) **2** has been made by several different methods. Although the structure is simple, difficulty has been encountered synthesizing pure enantiomers due to the allylic and tertiary nature of the hydroxyl group. Pure enantiomers have been prepared by rearrangements of optically active seudenol (3-methyl-2-cyclohexen-1-ol) **43**, which is a chiral pool compound obtained by enzymatic means.[57,58,59]

One of the most direct syntheses for formation of MCL **2** is outlined in Scheme 23.[57]



Scheme 23

Optically active 1-methyl-2-cyclohexen-1-ol **2** has been prepared, by a previous worker in these laboratories, by asymmetric synthesis as outlined in Scheme 24.[60] Asymmetry was introduced with the Sharpless asymmetric epoxidation of cyclohex-1-enylmethanol **44**.[60] Subsequent functional group manipulation, as outlined, allowed conversion of this material with excellent control of the stereochemistry, to the desired product. Unfortunately synthesis of the allylic alcohol **44** took a number of steps and the overall synthesis was not efficient.



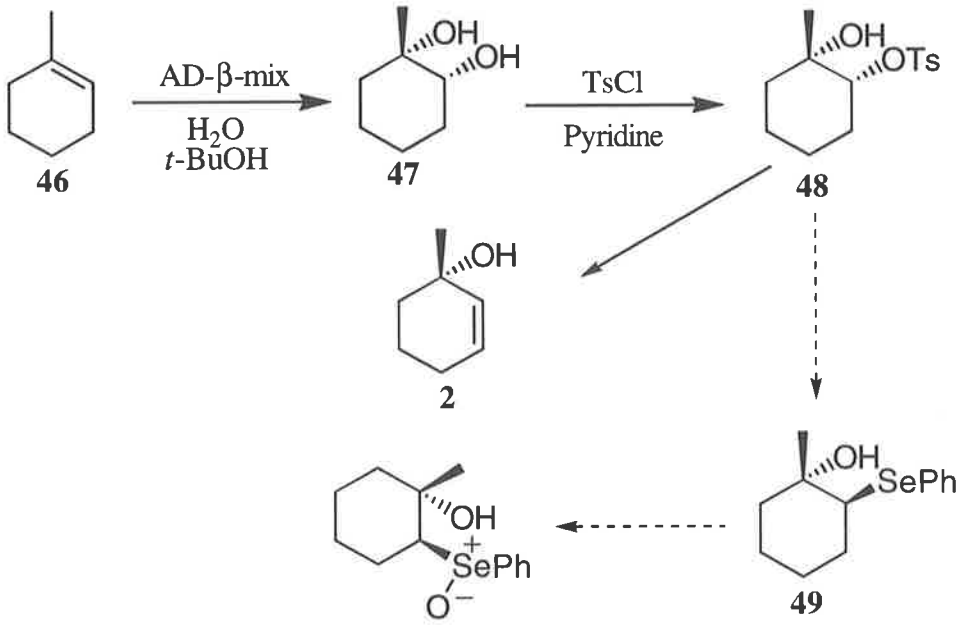
Scheme 24

An alternative, shorter route to optically active MCL **2** was discovered in the author's Honours year.[61] The synthetic pheromone, MCL **2**, was synthesized optically active in three steps from 1-methyl-1-cyclohexene **46** (Scheme 25). A Sharpless asymmetric dihydroxylation reaction on 1-methyl-1-cyclohexene **46** gave the optically active diol **47** in an enantiomeric excess of 52%.

Due to the volatility and water solubility of the diol **47** a modification of the standard work-up procedure was required. The enantiomeric excess was determined by chiral shift NMR experiments on the corresponding secondary mono acetate.

Conversion of the diol to the mono secondary tosylate **48** gave material that, as expected was only ca. 75% of the major enantiomer. The optical purity of the tosylate was determined by chiral shift NMR experiments. Recrystallization from diethyl ether and hexane gave material with an enantiomeric excess of 78%, i.e. 89% of the major enantiomer. Inconveniently, the racemic tosylate is less soluble than the optically active compound and, of course, yield needs to be sacrificed to improve the enantiomeric excess.

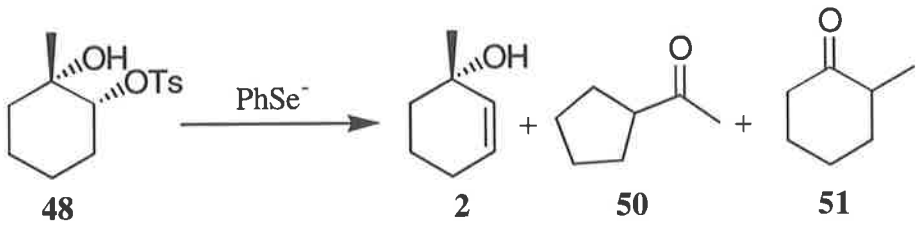
It was envisaged the tosylate in the presence of phenyl selenide anion might give the corresponding selenium compound **49**. Oxidation would give the selenoxide, which is the enantiomer of the selenoxide prepared previously in Scheme 24.



Scheme 25

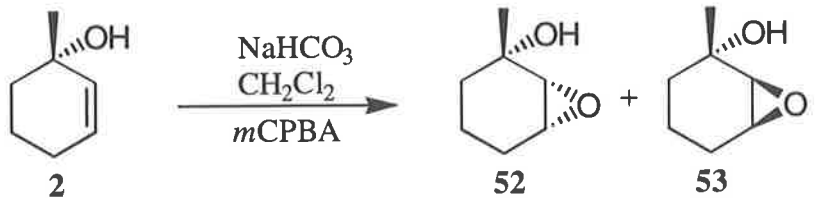
Treatment of the tosylate **48** with phenyl selenide anion, formed by addition of sodium borohydride to diphenyl diselenide, proceeded directly to the pheromone **2** (Scheme 26).The initial reaction gave a mixture of the alcohol **2** and the ketones **50** and **51**. A base treatment of the tosylate, *t*-BuOK, gave the ketones **50** and **51** by a negative ion pinacol rearrangement.[62] It was concluded the ketones were artifacts formed from adventitious sources of base. A wash of

the glassware with ammonium chloride solution before reaction of tosylate **48** with phenyl selenide anion obviates the formation of these ketones **50** and **51**. However, the optically active pheromone **2** was formed in only a 23% yield from the optically active tosylate **48** with inseparable impurities present.



Scheme 26

The enantiomeric purity of the tertiary allylic alcohol **2** could not be determined directly by chiral shift experiments. Conversion of the alcohol **2** to the epoxide **52** with a buffered solution of *m*CPBA (*meta*-chloroperbenzoic acid) gave two diastereomers. The *cis* and *trans* isomers **52** and **53** were obtained in a ration of 93:7 (Scheme 27).



Scheme 27

Chiral shift NMR analysis on the racemic epoxide **52** showed partial separation of the epoxy protons. Unfortunately, due to the contamination of the *cis*-epoxide **52** with its *trans* isomer **53** baseline separation was not achieved. The exact enantiomeric excess of the optically active epoxide could not be determined and it was unknown if the optical purity of the tertiary alcohol was maintained in the elimination of the tosyl group.

To complete this synthesis several aspects need to be investigated. It needs to be determined if the optically active tosylate **48** can be recrystallized to a higher enantiomeric excess and if the optical purity of the tosylate **48** is maintained in the elimination reaction. In addition, it would be of interest to investigate further the mechanism of the unusual elimination reaction initiated by phenyl selenide ion. The asymmetric synthesis of MCL **2** is discussed in Chapter 5 of this thesis.

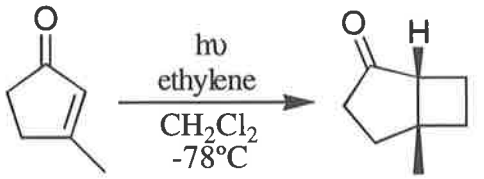
CHAPTER 2

RESULTS AND DISCUSSION

FORMATION OF A KEY INTERMEDIATE

Section 2.1 Formation of the Bicyclic Ketone

The initial step of the synthesis was the formation of the bicyclic ketone **12r**, *via* a [2+2] cycloaddition reaction (Scheme 28).



54 **(±)-12r**

Scheme 28

This reaction has been done before, however, the non-availability of the required apparatus meant modification to the procedure was required. Therefore, a discussion of the main feature of the reaction is pertinent. The bicyclic ketone **12r** has been synthesized on two different scales by the same research group in the literature.[63,64] In both references the bicyclic ketone **12r** is synthesized from the corresponding unsaturated ketone **54** *via* a [2+2] photocycloaddition reaction. The first example irradiates a 20 gram solution of 3-methyl-2-cyclopentenone **54** with a 450-W mercury arc at -70°C for 48 hours, to give the bicyclic ketone **12r** in an 85% yield.[63] The second approach uses a 1000-W street lamp at -75°C on a 25-gram scale of ketone **54**, to yield the bicyclic ketone **12r** after 12 hours in a 90% yield.[64] Both procedures recommend the reaction being performed in a triple walled Dewar vessel constructed of Pyrex (Figure 15). The inner vessel consists of a water and vacuum jacket, permitting safe use of circulating tap water as a lamp coolant when irradiations are performed at -78°C. The outer jacket is a cylindrical vessel of suitable volume, fitted with a coarse fritted disc, for gas dispersion. Three layers of Pyrex constitute an effective filter for the light in the 280-300nm region and secondary photolysis products are rarely observed.

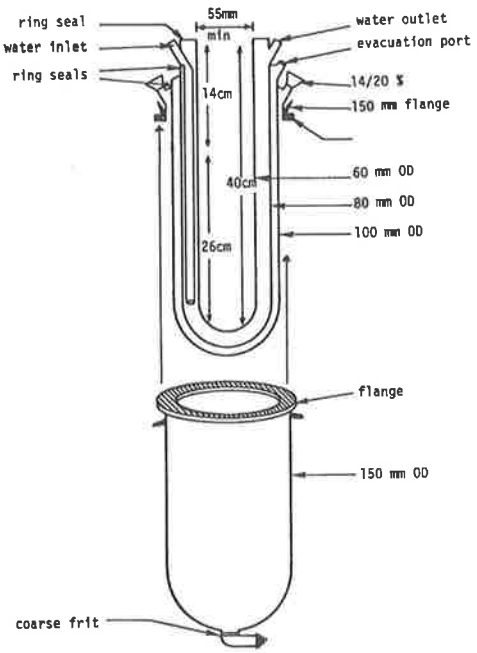
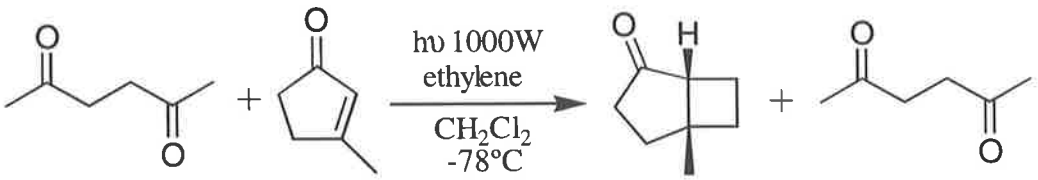


Figure 15

Because this is the start of a synthesis, the larger scale higher yielding procedure was desirable. The exact apparatus described above was unavailable in these laboratories, due to limitation in the glassblowing facilities available, and could not be made as described. A suitably modified apparatus was built. It is similar to the apparatus described above, except that a stainless steel metal pot and nylon seal form the outer jacket, which constrains the reagent. A sintered glass filter is required so ethylene can be bubbled though the system, acting as a reagent and a stirrer. This was led through the side of the metal pot. The dimensions of the inner jacket are nearly identical to the recommended apparatus above.

Complications arose in the formation of the bicyclic ketone **12r** as commercially available 3-methylcyclopentenone **54** was contaminated with up to five percent acetonylacetone **55** (as determined by ^{1}H and ^{13}C NMR[65]). Initially the bicyclic compound was synthesized, with the diketone **55** contamination present, with the above described large scale reactor (Scheme 29). The diketone impurity **55** remained unchanged after the reaction.*

* The experimental details for the synthesis of the bicyclic ketone **12r**, with the diketone **55** contamination present, have not been included.



55 **54** **(±)-12r** **55**

Scheme 29

The boiling points of the two ketones (**12r** and **55**) differ by 2-3°C at 65mm/Hg and attempts at purification of the product by spinning band distillation were moderately successful. The diketone **55** could not be removed completely and recovery of the pure bicyclic ketone **12r** was poor. Although separation of the two ketones **12r** and **55** by chromatography was possible on a small scale, this was impractical on a large scale.

Girard T reagent **56** can be used to separate the ketonic material from non-ketonic material. There is an example in the literature for separation of a saturated and unsaturated cyclic material (Figure 16) with the Girard T reagent.[66]

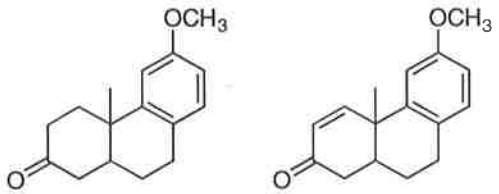
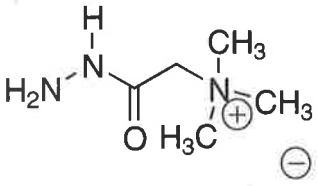


Figure 16

Girard T reagent **56** is a water soluble amine which forms water soluble hydrazones with ketones under acidic conditions (Figure 17).



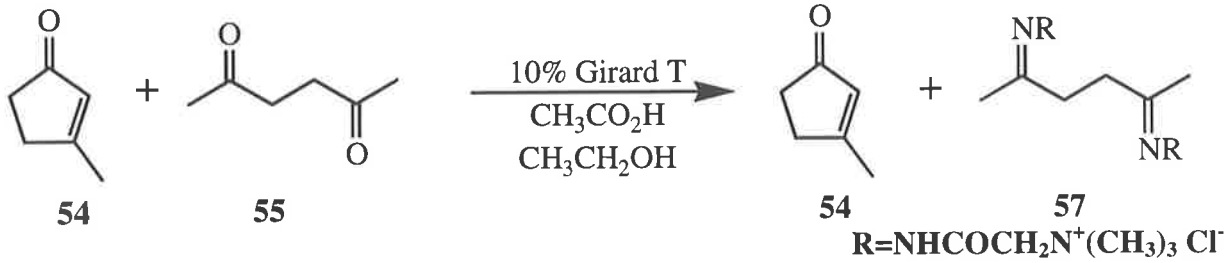
56

Figure 17

α, β-

Since saturated ketones react considerably faster than unsaturated ketones with nucleophilic reagents it was considered that the diketone **55** should react with Girard T reagent in preference to 3-methyl-2-cyclopentenone **54**, even through the latter is in a greater amount. The commercial ketone mixture in the presence of a 10% solution of Girard T should result in

reaction of the saturated diketone to form the water-soluble hydrazone **57** whereas most of the cyclic ketone **54** should then be recovered unchanged. Extraction of the saturated derivative **57** with water would then leave the 3-methyl-2-cyclopentenone **54** in the organic solvent. Application of this procedure to the commercial ketone followed by a distillation gave the pure ketone **54** in a 77% yield of recovered material (Scheme 30). However, this was a rather tedious procedure.

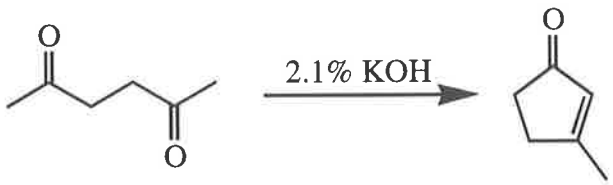


54 **55** **54** **57**

R=NHCOCH$_2$N$^+$(CH$_3$)$_3$ Cl$^-$

Scheme 30

To avoid the need for purification of the commercially available 3-methyl-2-cyclopentenone **54**, the desired ketone **54** was synthesized by a method that assures total reaction of all the starting material.[67,68] Reaction of acetonylacetone **55** with aqueous potassium hydroxide gave 3-methyl-2-cyclopentenone **54** in a 45% yield, after purification by distillation from polymeric material (Scheme 31). The ketone was >99% pure by GC analysis.

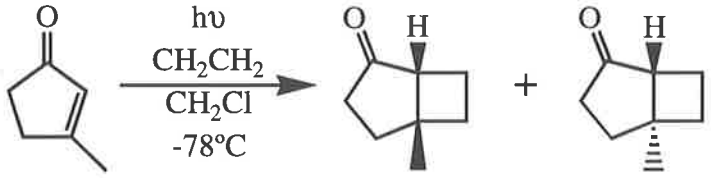


55 **54**

Scheme 31

Repetition of the photochemical reaction on a larger scale with the ketone **54**, containing no impurities, gave after distillation of the solvent the required bicyclic ketone **12r** in a 77% yield (Scheme 32). A careful distillation is required when solvent is removed because the product is volatile and otherwise a considerable amount of the volatile product can be lost. It was found that the position of the ^{1}H NMR signals for this product correspond to the literature values run at a lower field strength,[63] but due to the greater complexity of the signals at 300 MHz it was not clear if the product was really the desired *cis*-isomer **12c**. The literature values in carbon tetrachloride consist of a 3H singlet at δ1.30 and a 9H multiplet in the region 1.55-

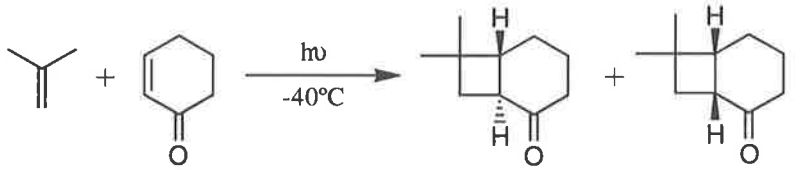
2.6.[26,29,63,69,70] Previous syntheses of this bicyclic ketone from the photochemical reaction have assumed the product is *cis*, however the ^{1}H NMR signals are not well resolved.[63,64]



54 **12c** **12t**

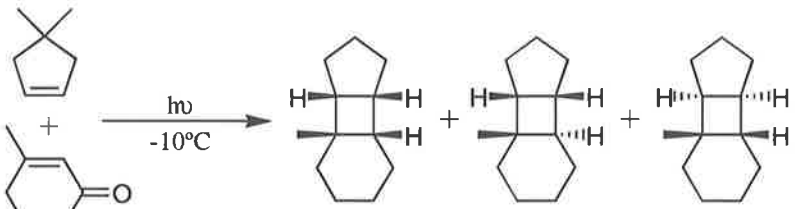
Scheme 32

From the Woodward and Hoffman rules,[71] a concerted [2+2]‡ cycloaddition can only proceed *via* a suprafacial attack. This results in *cis* stereochemistry of the product, unless a radical reaction occurs. Corey, in his caryophyllene synthesis noted both the *cis* and *trans* isomers were formed during a [2+2] cycloaddition, this was reasoned by an 'orientated π–complex' intermediate in triplet state photoannelations of cyclohexanones.[72] Surprisingly the *trans* isomer was the isomer formed in a higher yield.[72] (Scheme 33).Corey's caryophyllene alcohol synthesis also gave *cis* and *trans* isomers [73] (Scheme 34).



trans/*cis* 4:1

Scheme 33

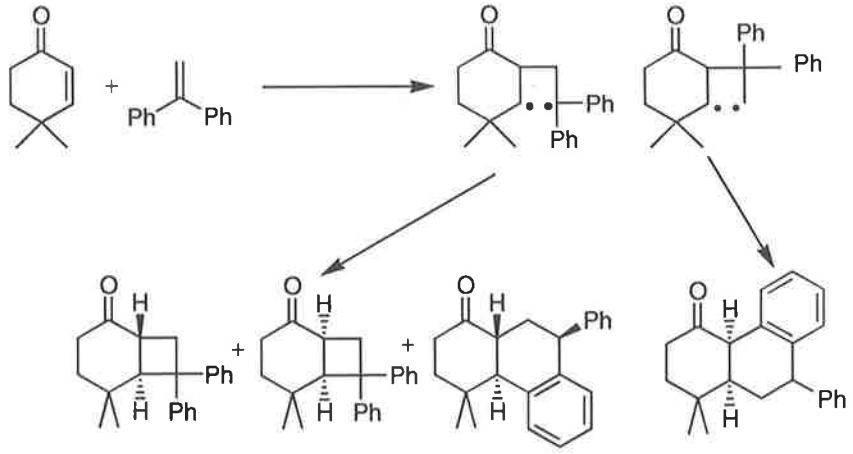


12% 14% 74%

Scheme 34

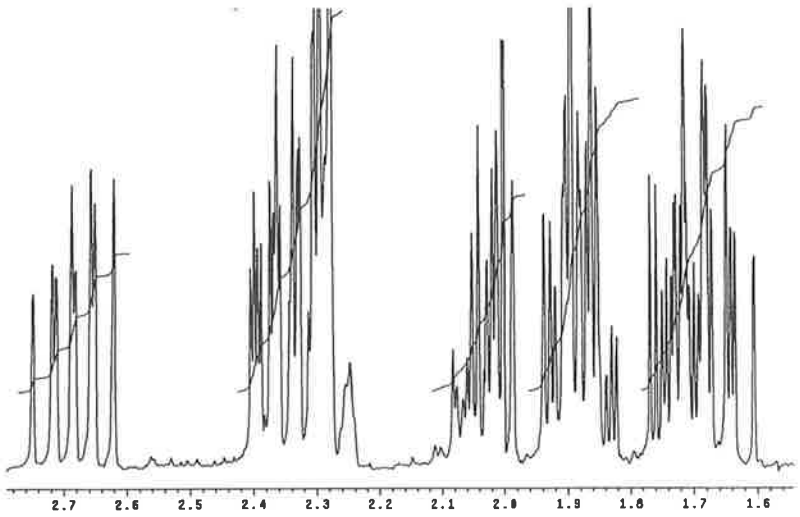
There is also a recent mention in the literature of a 'triplet exciplex intermediate' in a [2+2] cycloaddition.[74] Irradiation of 1,1-diphenylethylene with 4,4-dimethylcyclohexenone in cyclohexane gives four major products. Two of the products are the expected head to tail cyclobutanes. The other two products arise from an α-ortho ring closure followed by a 1,3-hydrogen shift, previously observed in alkene triplet state photoadditions [74] (Scheme 35).

‡ [2+2] has been used as an abbreviation for [π2+π2]. The stereochemistry of the orbital interactions has been omitted.



Scheme 35

The ^{1}H NMR spectrum obtained for the product of the photochemical reaction **12r** showed a sharp singlet resonance at δ1.23, due to the methyl group. The remainder of the spectrum is difficult to interpret at first sight and does not correspond with that naively expected for the compound. A complex pattern, consisting of 5H, occurs in the region δ1.5-2.1 and an unresolved multiplet of 3H is present in the region δ2.2-2.4. A resonance at δ2.70, integrating for 1H, is complex and it was not immediately obvious if this resonance was a doublet of doublets of doublet or two doublets of doublets (Figure 18).



The 600 MHz ^{1}H NMR spectrum of the bicyclic ketone **12**.

Figure 18

In the bicyclic ketone **12r** the proton which was expected to be furthest downfield is H1 (Figure 19). This methine proton should only couple with its vicinal neighbours and therefore would exhibit a doublet of doublets resonance with coupling constants of approximately 9-13

Hz.[75] For the ^{1}H NMR signals (Figure 18) to be consistent with this coupling, perhaps *cis* and *trans* isomers of the ketone are present from the photochemical reaction. Each proton would exhibit a doublet of doublets. Hence, the resonance at δ2.70 would result from two overlapping doublet of doublets occurring in a 1:1: ratio.

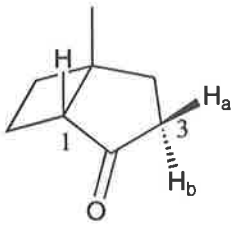
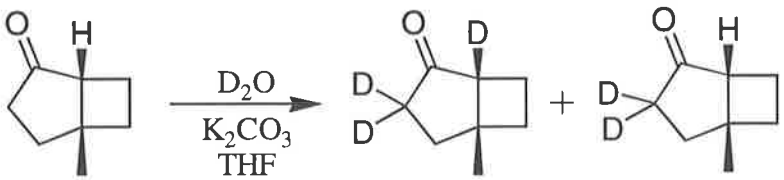


Figure 19

Consequently, from this interpretation of the ^{1}H NMR data it is possible both the *cis* and *trans* isomers of the bicyclic ketone could have formed in a :1:1 ratio. However, the ^{13}C NMR showed only eight resonances and from this and the fact that there is only one sharp signal for the methyl group in the ^{1}H NMR, it is presumed only one isomer of the bicyclic ketone has formed.

This means the ^{1}H NMR spectrum was in need of a different interpretation and some expenditure of effort was needed to clarify the situation. The signal at δ2.70 was clearly a doublet of doublet of doublets with coupling constants of 9, 11, and 18 Hz. The coupling constant of 18 Hz suggests geminal coupling to an adjacent neighbour. Therefore, it is more likely that this resonance is due to the *endo* or *exo* proton of the methylene group (H3) on the other side of the carbonyl and not the methine proton (H1), as first presumed.

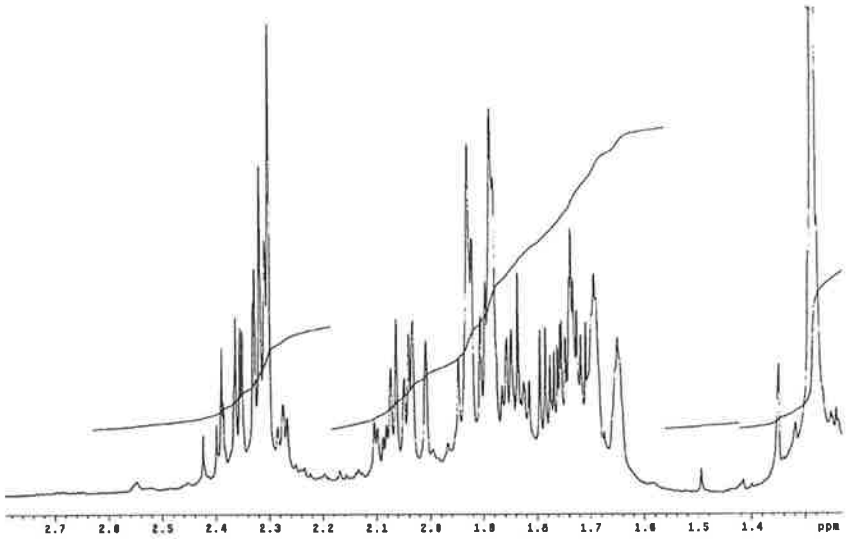
Exchange of the acidic protons in the bicyclic ketone **12r** with deuterium oxide-potassium carbonate confirmed which protons were adjacent to the carbonyl group in the ^{1}H NMR [72] (Scheme 36).



(±)-12r **(±)-58r** **(±)-59r**

Scheme 36

The ^{1}H NMR of the product formed from refluxing the ketone **12r** in THF with potassium carbonate and deuterium oxide lacked the doublet of doublet of doublets at δ2.7 and the complex signal at δ2.23-2.35 now integrated to 1½ H, rather than 3H. (Figure 20) The two methylene protons at the C3 position are expected to exchange more rapidly than the proton at C1, mainly due to the difficulty of enolate double bond formation *exo* to a four membered ring. The mass spectrum revealed the mono, di (**59r**) and tri (**58r**) deuterated ketones were present in a ratio of 3.5:24:3.8, this could be determined from expansion and integration of the peaks at 125, 126 and 127 in the mass spectrum.

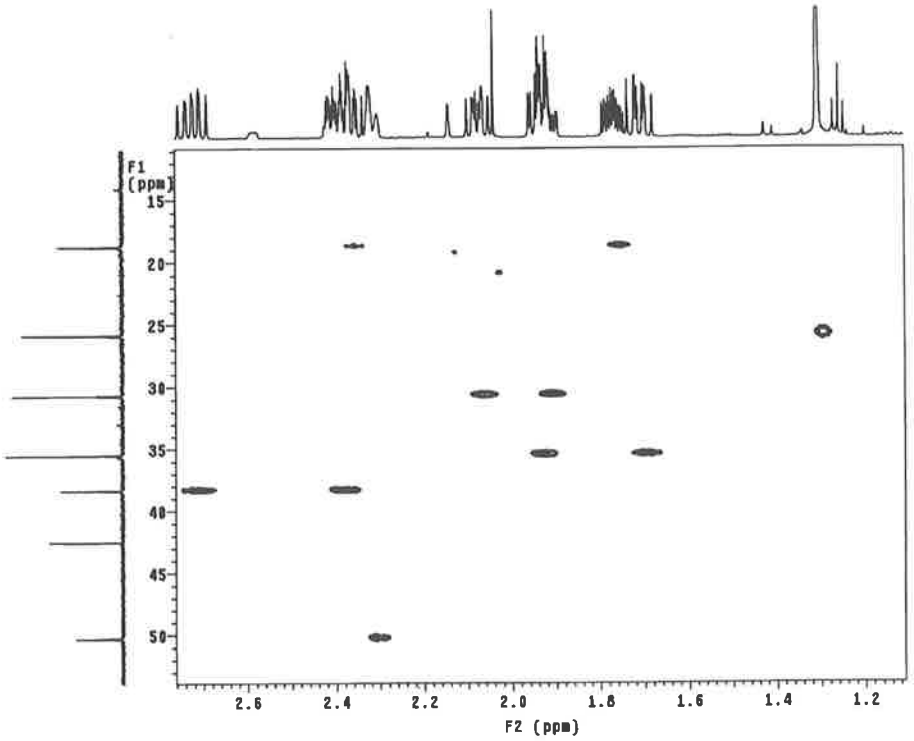


The 300MHz ^{1}H NMR spectrum of the deuterated ketones **58r** and **59r**.

Figure 20

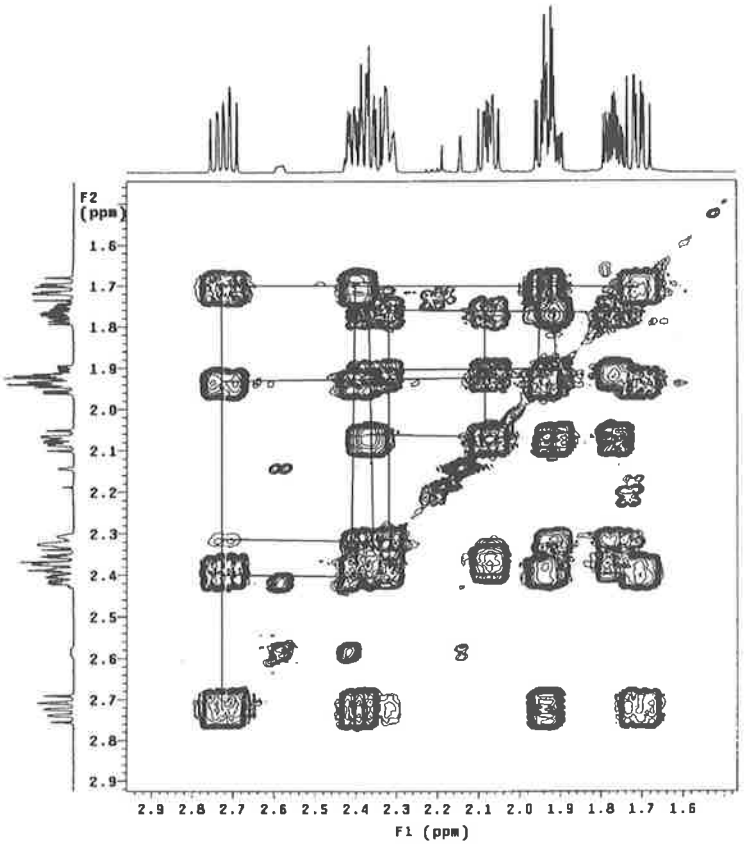
From the simplification of the complex in the region δ2.23-2.4 it is presumed the resonance for the other proton at C3, which is expected to be a doublet of doublet of doublets, occurs at approximately δ2.4. The proton at C1, which is partially exchanged, also occurs in the region δ2.3-2.4 (Figure 20).

From this, it is confirmed that one of the protons at the C3 position is responsible for the doublet of doublet of doublets at δ2.7. It appears as if the two protons at C3 are in different chemical and magnetic environments and therefore exhibit different chemical shifts. Confirmation of this can be seen from the HETCOR spectrum (Figure 21). With the use of HETCOR and COSY experiments all the protons in the bicyclic ketone **12r** can be assigned. (The COSY spectrum is reproduced in Figure 22).



The HETCOR spectrum of the bicyclic ketone **12**.

Figure 21



The 600 MHz COSY spectrum of the bicyclic ketone **12**.

Figure 22

The ^{1}H NMR of the *cis* bicyclic ketone **12r** shows a sharp 3H singlet as δ1.26 due to the resonance of the methyl group. A 2H complex in the region of δ1.55-1.80 is due to one proton at C4 and one proton at C6, the 2H complex at δ1.81-1.95 is due to one proton at C7 and one proton at C4. The other proton at C7 exhibits a 1H multiplet at δ2.0-2.1. The 3H complex at δ2.25-2.42 is due to the proton at C1, one proton at C3 and one proton at C6. The other proton at C3 exhibits a doublet of doublet of doublets with a geminal coupling constant of 18 Hz and two vicinal coupling constants of 9 and 11 Hz.

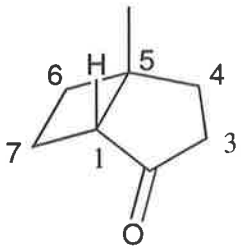


Figure 23

It was of interest if the doublet of doublet of doublets at δ2.7 was due to $H3_a$ or $H3_b$. (Figure 24) A NOE difference experiment, on the resonance at δ2.7, shows no enhancement of the methyl resonance at δ1.2. There is enhancement of the resonances at δ2.4, 1.9 and 1.7. It is presumed that the enhancements result from interaction of the proton at C3 with its geminal and vicinal (C4) neighbours. A NOESY experiment on the bicyclic ketone **12r** shows a large number of cross peaks and no useful information about the position of H_a or H_b could be obtained. The NOESY spectrum is reproduced in the appendix. In conclusion, it could not be determined by NOE or NOESY experiments if the doublet of doublet of doublets at δ2.7 was due to the *exo* or *endo* proton at C3.

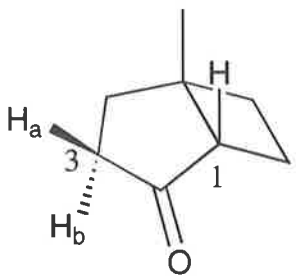


Figure 24

In the literature, the bicyclic ketone **12r** has been used in the syntheses of numerous compounds, hence it must initially have been the *cis* ketone. Our concern was that the products of the previous photochemical reactions could have been both the *trans* and *cis* isomers that

then rapidly equilibrated to solely the *cis* product. However, the ^{1}H NMR of the product of the photochemical reaction gives only one compound. The fact that it does not equilibrate to a new structure proves that it was *cis* product.

After confirmation that the product from the photochemical reaction was the desired *cis* bicyclic ketone **12**, the next step of the synthesis was formation of the corresponding epoxide. Corey's sulfoxonium salt **60** was the reagent initially used, this salt **60** is easier to synthesize, and reaction conditions are not as complicated as for the sulfonium salt **61**.

Section 2.2 Reaction with Corey's ylids

The geometrical optimized structure of the bicyclic ketone **12r** is shown in Figure 25[f], this confirms that the bicyclic ketone has a concave/convex structure. The top convex face is open to attack, whereas attack from the bottom concave face is not favoured. From the optimized structure, it is proposed that a nucleophile will preferentially attack the top open face.

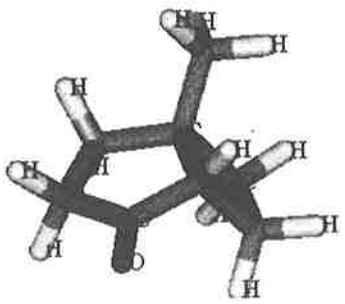
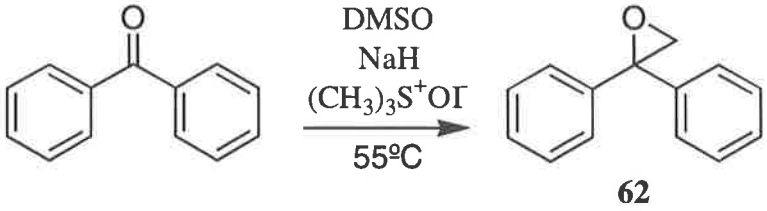


Figure 25

To ensure that the correct procedure was employed the stabilized ylid epoxidation reaction was tried initially on benzophenone, a compound for which the reaction is reported in the literature.[48] It was found for the reaction to proceed cleanly and in good yields extremely dry conditions were required. The ylid ($(CH_3)_2O{=}S^+{-}CH_2$) was formed by addition of $(CH_3)_3S^+OI^-$ **60**, at ambient temperature, to a suspension of sodium hydride in DMSO. Addition of benzophenone to this solution and heating of the reaction mixture to 55°C gave the corresponding epoxide **62** in a 76% yield after work up and removal of the solvent (Scheme 37).

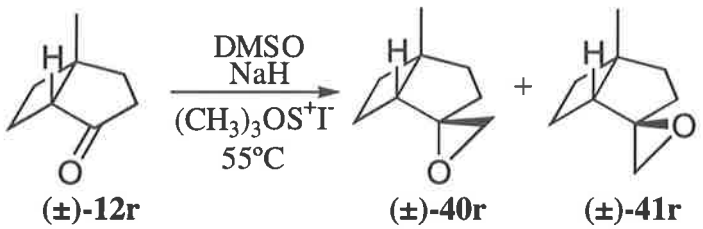
[f] The geometry optimization was calculated using the molecular modeling program SPARTAN™. An AM1 basis set was used. The energy calculated was –168.653 KJ/mol.



62

Scheme 37

Reaction of dimethyl sulfoxonium methylide with the bicyclic ketone **12r** gave two epoxides **40r** and **41r**, it was hoped only one isomer would form (Scheme 38). Initially the epoxides **40r** and **41r** were obtained in a low yield, due to the volatility of the products. If the solvent was carefully removed by distillation the two epoxides **40r** and **41r** were obtained in a good yield of 75%, after purification by a short path distillation.



(±)-12r **(±)-40r** **(±)-41r**

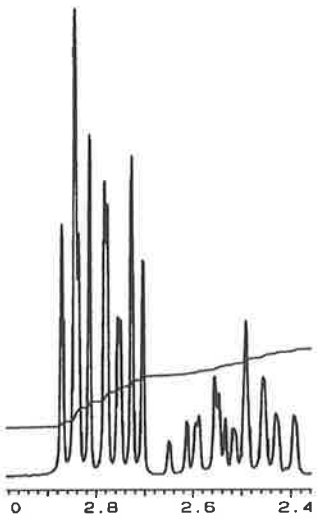
Scheme 38

For simplicity, throughout this thesis the epoxide with the oxygen *cis* to the methyl group **41r** is defined as the *exo*-epoxide. Similarly, the epoxide with the oxygen *trans* to the methyl group **40r** is defined as the *endo*-epoxide.

The ^{1}H NMR spectrum at 200 MHz the two epoxides **40r** and **41r** was initially difficult to interpret due to the complexity of the resonances. A thorough interpretation of the NMR was necessary to determine which resonances belonged to the same epoxide. The acquisition of a ^{1}H NMR at 600 MHz eventually clarified the situation somewhat.

The 600 MHz ^{1}H NMR spectrum shows two sharp 3H singlets at δ1.20 and 1.26, each presumably due to the resonances of the methyl groups of the respective epoxides. The two methylene protons at H1' are diastereotopic and exhibit an AB quartet at 200 MHz. However, at 600 MHz the resonance disperses and each epoxide now exhibits two doublets, each due to a methylene proton. The two doublets at δ2.70 and δ2.79, are from protons of the same epoxide formed in a higher yield, they have a geminal coupling constant of 4.5 Hz. The two doublets at

δ2.73 and δ2.82 belong to the other epoxide and have a geminal coupling constant of 5.3 Hz. The peak at δ2.73 displays a long range W-coupling of 0.8 Hz at 200 and 300 MHz. (Figure 26). It could not be determined which epoxide has the correct geometry to exhibit a W-coupling. Normally geminal coupling constants are large in the order of 9-15 Hz.[75] The geminal coupling constants observed for the two epoxides **40r** and **41r** are 4.5 and 5.3 Hz, smaller than expected. However, the geminal coupling constant of a proton on a cyclopropane ring is 3-9 Hz. Adjacent electronegative elements also donate electrons into the antibonding σ*-orbital of the proton and this results in a smaller coupling constant,[75] these two factors could both explain the size of the geminal coupling constants observed for the epoxides **40r** and **41r**.



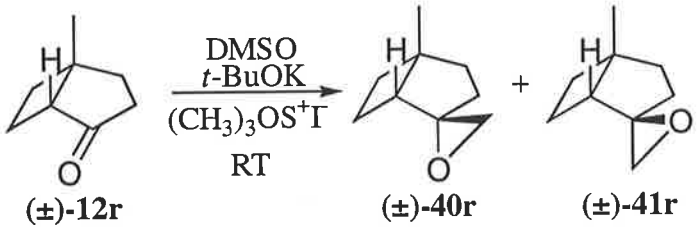
A section of the 200MHz ^{1}H NMR spectrum of the two epoxides **40** and **41**.

Figure 26

A large undefined complex signal in the region of δ1.45-2.20 is due to eight of the ring protons from each epoxide. One of the methylene protons adjacent to the epoxide group ($H3_a$) from the lesser formed epoxide resonates as a triplet of doublets at δ2.45, with a geminal coupling of 13 Hz and a 7 Hz vicinal coupling. One of the protons at C3 of the major epoxide resonates as a triplet of doublets at δ2.45, with a geminal coupling of 14 Hz and an 8 Hz vicinal coupling. The position of the protons at C3 in the ^{1}H NMR spectrum was determined by COSY and HETCOR experiments on the pure *endo*-epoxide **40r**. Formation of this epoxide will be discussed later in 'Chapter 2, Results and Discussion'.

From integration of the methyl resonances it is found that the two epoxide isomers **40r** and **41r** are formed in a ratio of 4.3:5.7 (Figure 26). However, the structure for the major and minor epoxides could not be assigned solely from their ^{1}H NMR chemical shifts. It was determined later after several experiments that the major product was the isomer **41r** with the oxygen *cis* to the methyl group.

An extensive literature search of reactions with the stabilized ylid revealed adaptations of Corey's procedures. As sodium hydride is hazardous on large, industrial scales, an alternative less reactive base, potassium tert-butoxide, was used to form the ylid.[76] Trimethylsulfoxonium iodide and potassium *tert*-butoxide in DMSO produces the corresponding ylid, which reacts with aldehydes and ketones at ambient temperature to produce the corresponding epoxides.[76] Use of this procedure on the bicyclic ketone **12r** gave the two epoxides **40r** and **41r** in a 67% yield after purification by chromatography (Scheme 39).



Scheme 39

Interestingly, the two epoxides **40r** and **41r** formed in a 5.7:4.3 ratio. That is the major epoxide now formed was the minor epoxide formed when sodium hydride was used as the base and the reaction temperature was 55°C. The region from δ2.4-2.9 of the ^{1}H NMR spectrum is reproduced in Figure 27.

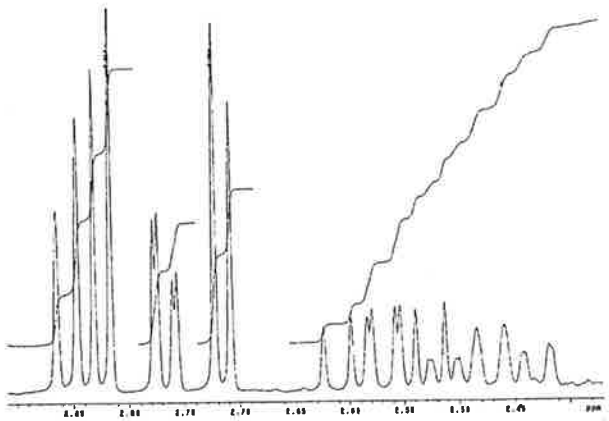
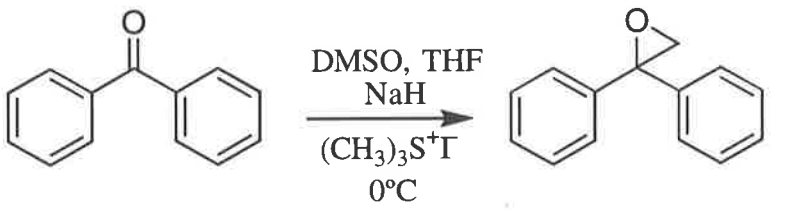


Figure 27

It was of interest to see what occurred when Corey's non-stabilized ylid reacted with the bicyclic ketone. As previously discussed in the introduction it was expected that a different ratio of isomers would form and it was hoped that the two epoxides (above) could then be correctly identified.

Again, to ensure the correct procedure was employed the reaction was tested on benzophenone. Dimethyl sulfonium methylide was formed by initially heating a solution of DMSO and sodium hydride to 70°C, to form the corresponding anion, the solution was then diluted with THF and cooled to 0°C whereupon trimethylsulfonium iodide is added. The ketone is subsequently added at 0°C and the reaction mixture was then stirred at ambient temperature.

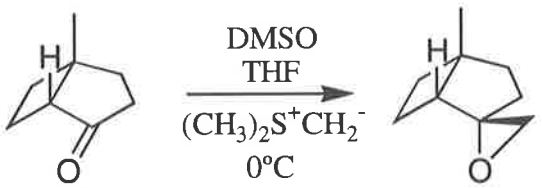
Under strictly anhydrous conditions, the corresponding epoxide **62** was obtained in a 70% yield (Scheme 40).



62

Scheme 40

Under identical conditions, as above, addition of dimethyl sulfonium methylide, to the ketone at 0°C gave in a 68% yield after purification by distillation, only one epoxide (Scheme 41).

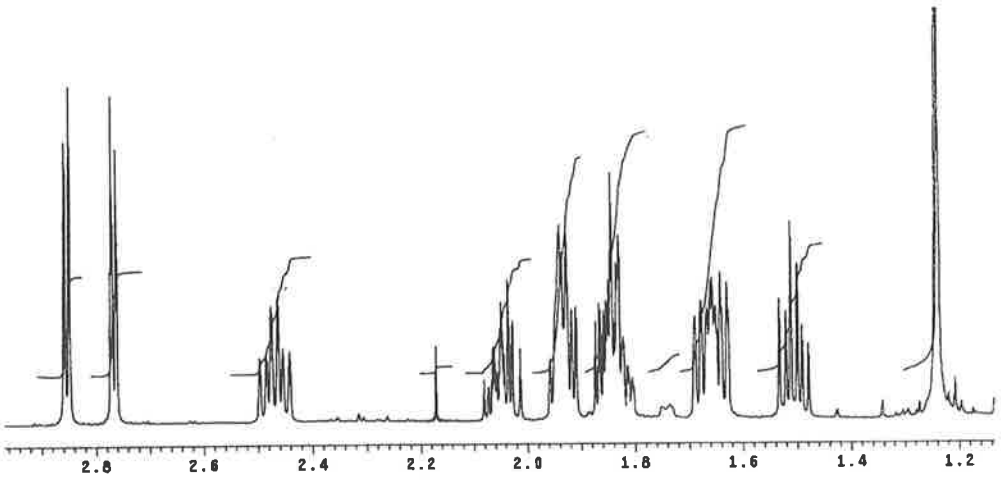


(±)-12r **(±)-40r**

Scheme 41

It was presumed that the epoxide from the reaction was the *endo*-epoxide **40r**. This rationale is based on the argument presented in the introduction, that the top of the bicyclic ketone being more hindered than the bottom side for attack by a nucleophile. Further support for this conclusion is presented later.

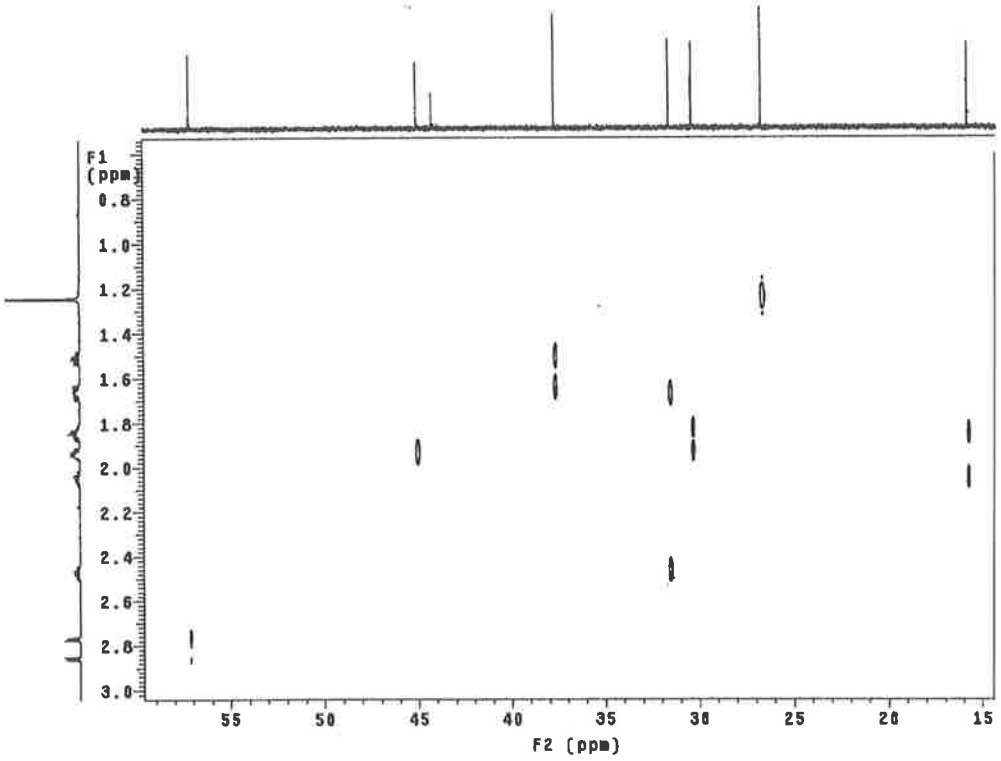
The ^{1}H NMR spectrum at 600 MHz showed a sharp singlet at δ1.26, for the methyl group. The resonance at δ1.50 is a 1H triplet of doublets due to one of the protons at H4. The 2H complex at δ1.67 is due to one proton at C3 and the other proton of C4. The 2H complex is due to a proton at C6 and the methine proton at C1. The 1H multiplet at δ2.06 is due to one proton at H7. The other proton at C3 resonates as a triplet of doublets at δ2.45, with a geminal coupling of 13 Hz and a 7 Hz vicinal coupling. The epoxide protons at C1' appear as two doublets at δ2.73 and δ2.82 and have a geminal coupling constant of 5.3 Hz. The region of δ2.2-2.9 of the ^{1}H NMR spectrum is reproduced below (Figure 28).This spectrum clearly corresponded to that of the minor epoxide present in the mixture of epoxides prepared previously.



The ^{1}H NMR spectrum at 600MHz of the epoxide **40**.

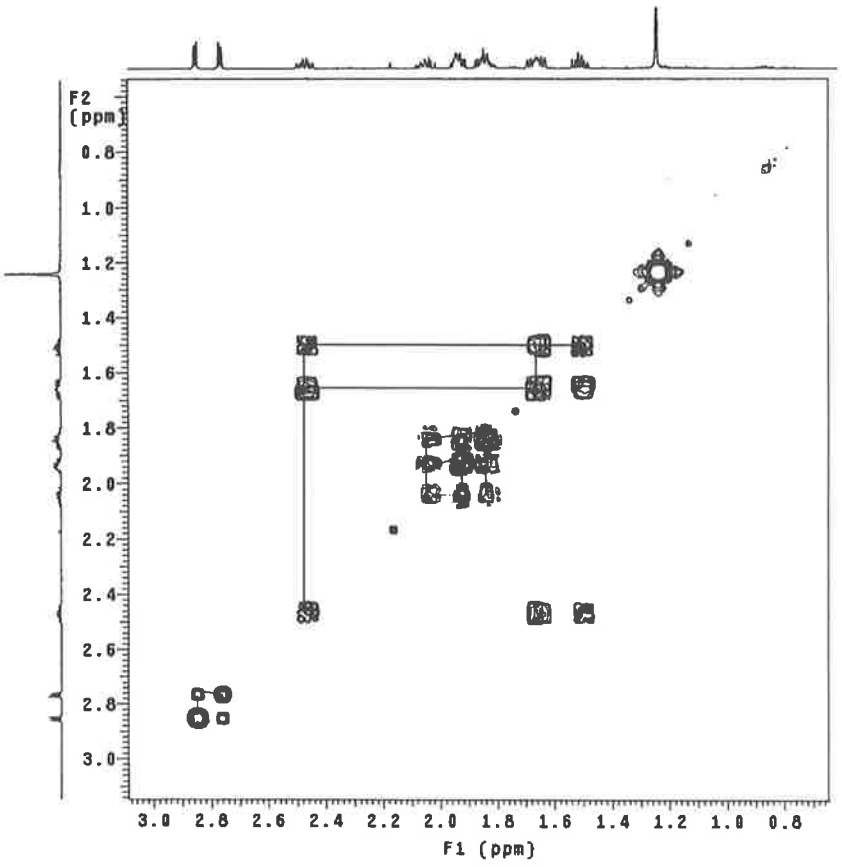
Figure 28

The protons at C3 were identified by interpretation of the HETCOR and COSY spectrum (Figure 29 and Figure 30).



The HETCOR spectrum of the epoxide **40**.

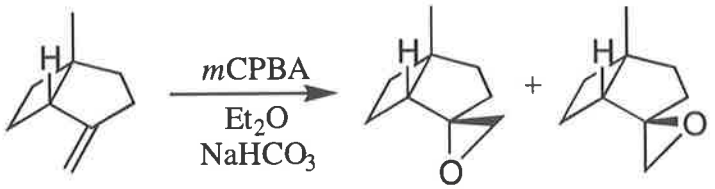
Figure 29



The COSY spectrum at 600MHz of the epoxide **40**.

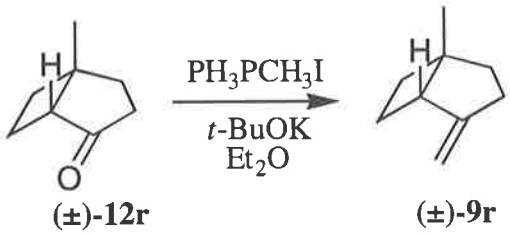
Figure 30

In an attempt to confirm the stereochemistry of the epoxides from the ylid reactions the epoxides were formed *via* a different route. It is expected one face of the bicyclic alkene **9r** will be more hindered to approach than the other. Epoxidation of the alkene **9r**, with *m*CPBA should give the *exo*-epoxide **41r** as the major product (Scheme 42).



Scheme 42

A Wittig reaction on the bicyclic ketone **12r** gave the desired alkene **9r** (Scheme 43). The product was very difficult to handle due to its volatility and the alkene was obtained in a yield of only 40%. The ^{1}H NMR spectrum showed a sharp singlet at δ1.20, for the methyl group. The δ1.5-2.3 region of the spectrum is complex as signals from seven of the ring protons overlap. The doublet of multiplets at δ2.42 has a coupling constant of 17 Hz, it is presumed this resonance is due to one of the protons at H3 which coupling to its geminal neighbour. The other proton at C3 resonates as a multiplet at δ2.75. The alkene protons appear as two broad singlets at δ4.66 and δ4.76.



Scheme 43

Conversion of the alkene **9r** to the epoxides **40r** and **41r** was performed by addition of *m*CPBA to the alkene **9r** dissolved in the co-solvent system of diethyl ether and aqueous sodium bicarbonate, at two different temperatures. At -5°C two epoxides resulted in a 2:8 ratio, the major isomer formed was same as the minor product formed in the non-stabilized ylid reaction. At a lower temperature, -12°C, the reaction was more selective and a :1:9 ratio of the two epoxides resulted. This is consistent with the major epoxide, formed from reaction of *m*CPBA with the alkene **9r**, having the structure **41r** since attack from the convex side of the molecule

is expected to be favoured (Scheme 42). Figure 31 shows epoxide proton region of the ^1H NMR at 300 MHz for reaction at –5 and –12°C.

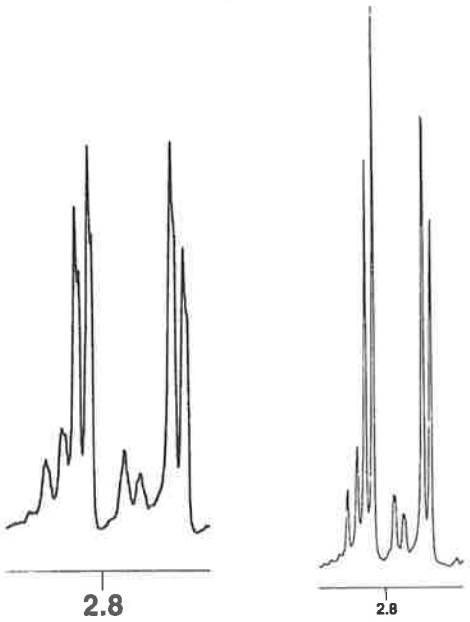
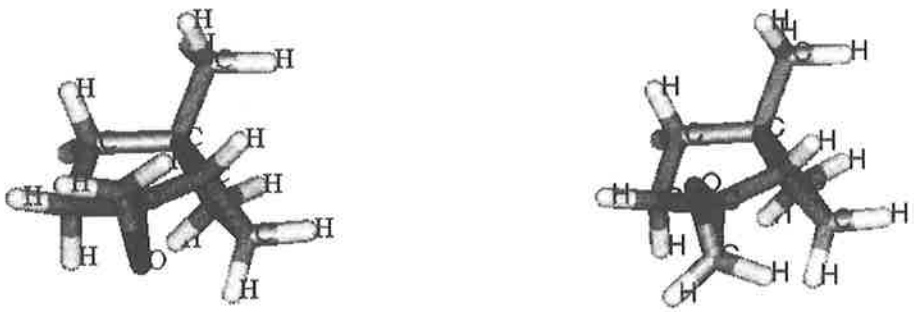


Figure 31

In order to correlate the reactions of the bicyclic ketone **12r** with Corey's ylids, a few more varyied reaction conditions using these ylids were required. Also, in the hope to understand the ratio of the epoxides **40r** and **41r** obtained when this reaction was first run molecular modeling calculations were performed on the epoxide products.

Shown below are the geometrical optimized structure[‡] of the two epoxide isomers **40r** and **41r** (Figure 32).



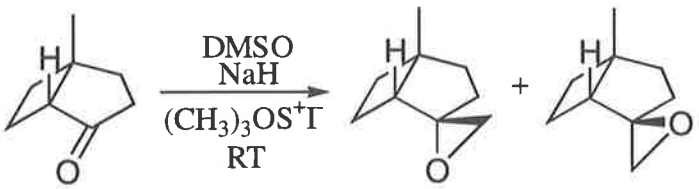
(±)-40r **(±)-41r**

Figure 32

[‡] The geometrical optimizations were calculated using the molecular modeling program SPARTAN™. An AM1 basis set was used.

The energy calculated for the geometrical optimized structure of **40r** was –43.939966 KJ/mol. The energy calculated for the geometrical optimized structure of **41r** was –44.834451 KJ/mol. The valuable information obtained from these calculations is that the isomer with the epoxide *cis* to the methyl group **41r** is slightly more stable, and it can be postulated that this isomer is the thermodynamic product from the stabilized epoxidation reaction. However, it it is worth noting that these calculations are performed in the gas phase and also that due to the authors inexperience in molecular calculations they may not be entirely soundly based. From the molecular modeling results, it is expected the ratio of the two epoxides **40r** and **41r** would be approximately 1:1. Experimental results do not reflect this ratio and under different reaction conditions the formation of one isomer of the epoxide is always preferred.

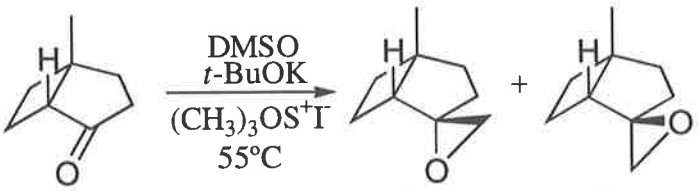
Reaction of the bicyclic ketone **12r** with dimethyl sulfoxonium methylide, formed by reaction of sulfoxonium salt **60** with the anion of DMSO, at ambient temperature gave a ratio of 4.3:5.7 of the *endo*-epoxide **40r** and the *exo*-epoxide **41r** respectively (Scheme 44). That is the same ratio as previously obtained when the reaction was performed at 55°C.



(±)-12r **(±)-40r** **(±)-41r**

Scheme 44

Reaction of the bicyclic ketone **12r** with dimethyl sulfoxonium methylide, formed by reaction of sulfoxonium salt **60** with potassium *t*-butoxide in DMSO, was attempted at 55°C (Scheme 45). After the solution was worked-up the ^{1}H NMR spectrum of the crude product revealed that the epoxides **40r** and **41r** had formed in a ratio of 5.5:4.5 (*endo*-epoxide **40r** : *exo*-epoxide **41r**), as determined by computer integration of the methyl resonances in the ^{1}H NMR spectrum. That is the ratio of epoxides is almost identical to the ratio obtained when the reaction was performed at ambient temperature with potassium *t*-butoxide. The ^{1}H NMR spectrum of the crude product was not as clean as when the reaction is performed at ambient temperature, this is presumably due to the prolonged heating of the DMSO. It appears that the ratio of the epoxides formed is dependent on the base used and not the temperature of the reaction.



(±)-12r **(±)-40r** **(±)-41r**

Scheme 45

The results from all the reactions for formation of the epoxide isomers **40r** and **41r** are correlated in Table 3.

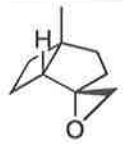
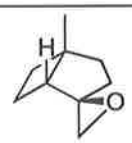
	Stabilized ylid				Non-stabilized ylid	*m*CPBA	
	NaH, 55°C	NaH, ambient temp.	*t*-BuOK, ambient temp.	*t*-BuOK,. 55°C	NaH, DMSO 0°C	-5°C	-12°C
 **40r**	4.3	4.3	5.7	5.5	1	2	1
 **41r**	5.7	5.7	4.3	4.5	0	8	9

Table 3

The formation of the epoxide **41r** as the major product from the *m*CPBA reaction can be rationalized by consideration of the convex/concave geometry of the ketone. Attack by a nucleophile from the top face is favoured in comparison to that from the bottom face, hence the predominant isomer of the kinetic product, is the epoxide with the oxygen *cis* to the methyl group **41r**. The same argument can be used for the non-stabilized epoxidation reaction, the sole product arises from the face of initial attack and is the isomer **40r**.

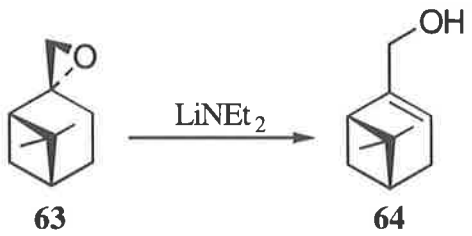
Epoxidation reactions from the use of Corey's stabilized ylid are more difficult to explain. Both the stabilized and non-stabilized ylid reactions form a betaine intermediate and the reaction is a two step process. As previously discussed in the 'Introduction' the first reaction in the stabilized ylid reaction is reversible and the ratio of the epoxides formed is not dependent on the preferred side of attack, but on the relative energies of the transition states from the

betaine intermediates to the products. From the experimental results obtained the base used has an unusual effect on the ratio of the epoxide isomers formed in the stabilized ylid reaction. The calculated thermodynamic product (**41r**) is the major product when sodium hydride is used as the base, however is the minor product with potassium *t*-butoxide. The base must have some effect on the relative energies of the transition states of the betaine intermediates, but in order to explain this result more research will need to be done.

After the preparation of desired epoxide **40r** and **41r**, the next step in the synthetic sequence was the formation of the allylic alcohol **38**, the key intermediate. Initially, this was attempted *via* a base-induced isomerisation. However, as will become obvious later in the 'Results and Discussion' this was not a simple task.

Section 2.3 Base-induced isomerisation

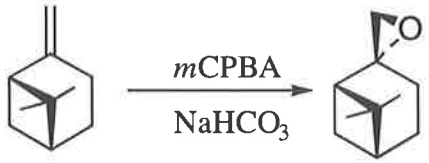
In the literature, there is an example of a base-induced elimination reaction on β-pinene oxide **63** with lithium diethylamide in diethyl ether. The corresponding allylic alcohol **64** is obtained in an 81% yield.[51] The reaction is slow and required two days at reflux to go to completion (Scheme 46).



63 **64**

Scheme 46

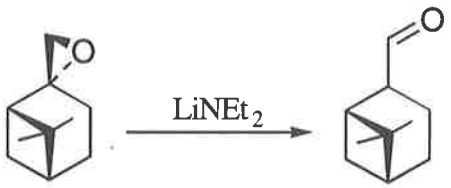
To ensure the correct procedure was employed the base-induced isomerisation reaction was initially tried on β-Pinene oxide **63**. Pure β-pinene was obtained by a spinning band distillation of commercially available β-pinene, to remove any α-pinene contamination. The epoxide **63** was then formed from the alkene by reaction with *m*CPBA, in the presence of sodium carbonate as a buffer.[51] The desired product was isolated in a 57% yield as a colourless oil (Scheme 47).



63

Scheme 47

The reaction of β-pinene oxide **63** with two and a half equivalents of lithium diethylamide, in diethyl ether, formed from diethylamine and *n*-BuLi, did not give the allylic alcohol **64** after a 48 hour reflux. The only product identified was presumed to be the aldehyde **65**, because there was a characteristic signal in the NMR at δ9.4 (Scheme 48).

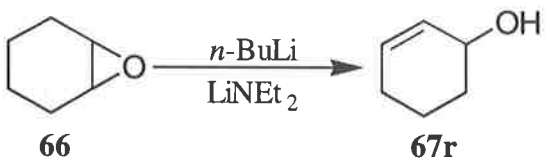


63 **65**

Scheme 48

Reaction of β-pinene oxide **63** with two and a half equivalents of lithium diethylamide, formed from diethylamine and MeLi (literature conditions)[51] also gave the aldehyde **65** as the only recognizable product. In both cases the aldehyde **65** could not be isolated in a respectable yield. The aldehyde was unstable and did not survive chromatographic purification.

Due to the lack of success, in our hands, of the base-induced isomerisation reaction on β-pinene oxide **63**, a rearrangement reaction was attempted on cyclohexene oxide **66** (Scheme 49).There are numerous examples in the literature of base-induced isomerisations on molecules with a similar structure to cyclohexene oxide **66**.[47, 77]

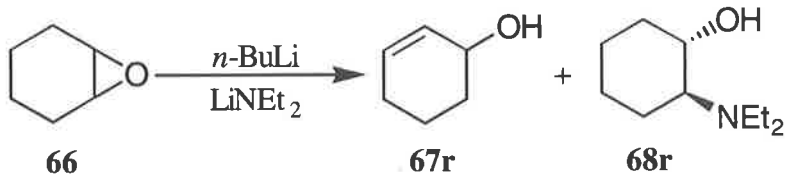


66 **67r**

Scheme 49

Following the literature method of *Crandall* and *Chang*,[77] reaction of cyclohexene oxide **66** was performed with one and a half equivalents of lithium diethylamide (formed from *n*BuLi and lithium diethylamine). The corresponding allylic alcohol **67r** was obtained in a near

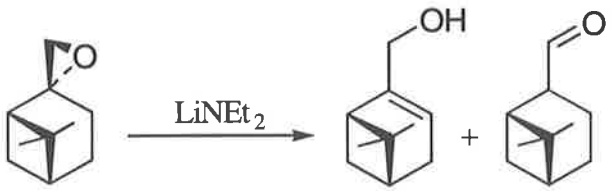
quantitative yield after a two days reflux along with a small amount of *trans*-2-(diethylamino)cyclohexanol **68r** (6%) [78] (Scheme 50).As Cyclohexene oxide is a non-terminal epoxide it does not have the problems associated with terminal epoxides.[47]



66 **67r** **68r**

Scheme 50

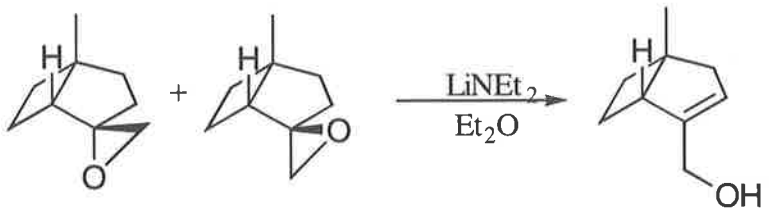
Due to the success of this reaction, the base-induced isomerisation was reattempted on β-pinene oxide **63** under identical conditions to those used above. The desired allylic alcohol **64** was obtained after purification by chromatography in a 21% yield. The other isolated product of the reaction was presumed to be the aldehyde **65**. (Scheme 51). Even though the allylic alcohol **64** was finally obtained, the yield of 21% did not compare to the literature yield of 81%.[51]



63 **64** **65**

Scheme 51

The conditions of the base-induced elimination of β-pinene oxide were employed with the, bicyclic epoxides **40r** and **41r** (Scheme 52).



(±)-40r **(±)-41r** **(±)-38r**

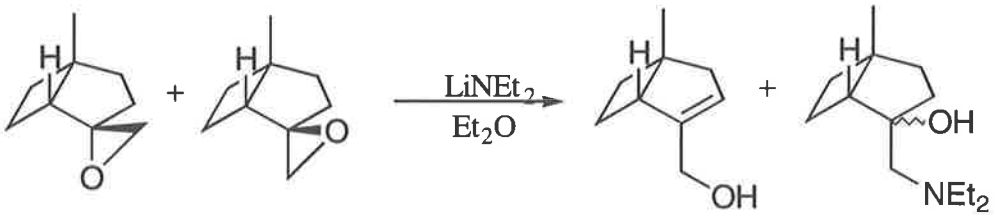
Scheme 52

It was recognized that both isomers of the epoxides **40r** and **41r** had the correct geometry, to react with the non-nucleophilic base. An accessible proton *syn* to the oxygen is required in

these elimination reactions.[47] The reaction was attempted on the mixture first, as this was the material available at the time.

Reaction of the epoxides **40r** and **41r** with one and a half equivalents of lithium diethylamide gave no recognizable material after refluxing for 15 hours. For this reason, the reaction was repeated using two and a half equivalents of lithium diethylamide. In this case, a product that could be the allylic alcohol **38r** was obtained but only in a 2% yield. The ^{1}H NMR spectrum of the product shows a 3H singlet at δ1.27 due to the methyl group. The methylene ring protons resonate as a 7H complex between δ1.35-2.75. The protons adjacent to the hydroxyl group resonate as an AB quartet at δ4.20. The broad singlet at δ5.62 is due to the olefinic proton. This was subsequently confirmed to be the desired allylic alcohol **38r**, see later in 'Results and Discussion, Chapter 2'.

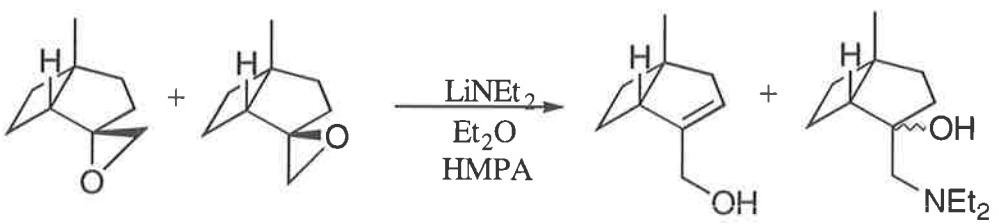
It was presumed the major product of the reaction was the substituted product **69r** as shown by the quartet at δ2.63 and the triplet at δ1.03 in the ^{1}H NMR spectrum of the crude product (Scheme 53).



(±)-40r **(±)-41r** **(±)-38r** **69r**

Scheme 53

It is known that there is a pronounced effect of hexamethylphosphoramide (HMPA) on epoxide rearrangements promoted by lithium amides that strongly favours formation of allylic alcohols.[47] For this reason, the reaction was repeated in the presence of hexamethylphosphoramide (HMPA) (Scheme 54).

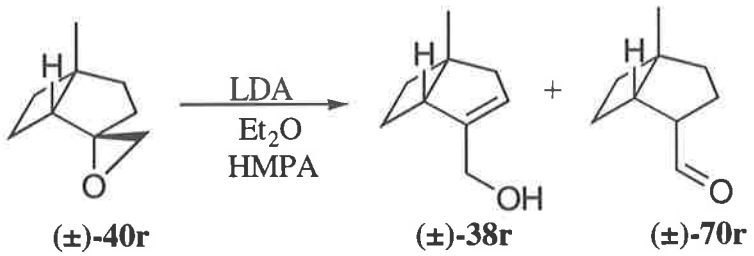


(±)-40r **(±)-41r** **(±)-38r** **69r**

Scheme 54

Reaction of the two epoxides **40r** and **41r** with lithium diethylamide in the solvent system of diethyl ether and HMPA gave the allylic alcohol **38r** in a 1% yield after purification by chromatography. Again, it was possible that the substituted product **69r** was the favoured product from this reaction. Hence, the reaction was repeated with lithium diisopropylamide (LDA). The bulkier amide base should discourage the nucleophilic reaction from occurring.

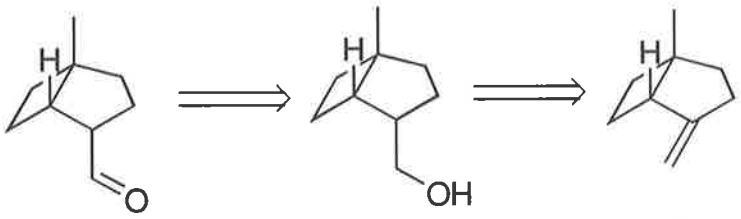
Reaction of one isomer of the epoxide **40r** with two and a half equivalents of LDA, gave only a trace (~0.5%) of the desired allylic alcohol **38r** as shown by the ^{1}H NMR spectrum of the crude product. The major product from the reaction was obtained in a 24% yield after purification by chromatography. The characteristic peak at δ9.77 in the ^{1}H NMR spectrum suggested that it was the aldehyde **70r**.



(±)-40r **(±)-38r** **(±)-70r**

Scheme 55

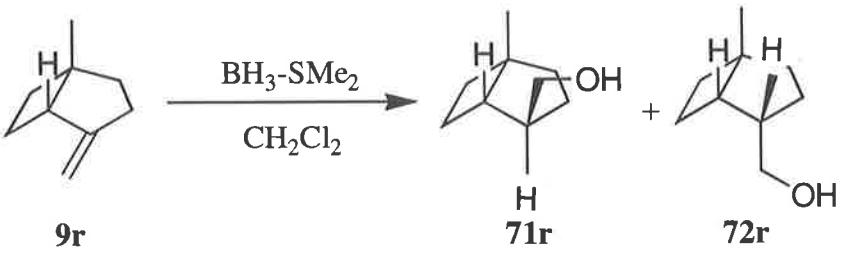
This was verified by the synthesis of the aldehyde **70r** by an alternative method as outlined by the retrosynthetic scheme (Scheme 56).



70 **9**

Scheme 56

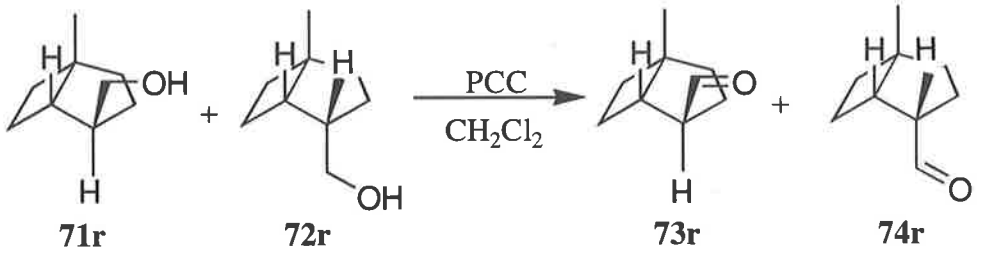
Reaction of alkene **9r** with borane-methyl sulfide complex[79] (no active 9-BBN was available in these laboratories) gave the corresponding alcohols **71r** and **72r** in a 30% yield (Scheme 57) The low yield is presumably due to the small scale and the moderate volatility of the products. From integration of the resonances due to the protons adjacent to the hydroxyl group, it was found that the two alcohol isomers **72r** and **71r** are formed in a ratio of 8.3:1.7. It is presumed attack of the reagent will preferentially occur from the top face to give the hydroxyl ~~cis~~ trans to the methyl group, that is the isomer **72r** as the major product



9r **71r** **72r**

Scheme 57

Oxidation with pyridinium chlorochromate[80] on a mixture of the two alcohols **71r** and **72r** gave the corresponding aldehydes **73r** and **74r** in a 90% yield. (Scheme 58). From integration of the aldehyde resonances, it was found that the two aldehyde isomers **74r** and **73r** are formed in a ratio of 7.5:2.5, and again the major isomer is the isomer with the aldehyde group *cis* to the methyl group. The ^{1}H NMR spectrum of the major product **74r** corresponded to that of the aldehyde **70r** formed *via* a base-induced isomerisation of the epoxide **40r**.

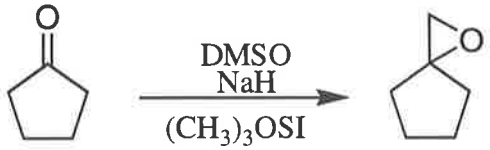


71r **72r** **73r** **74r**

Scheme 58

Due to the unsuccessful base-induced isomerisation reaction on the bicyclic epoxides **40r** and **41r**, a series of different reaction conditions were attempted on the corresponding five-membered ring epoxide **75r**. This compound was chosen for the following reasons; So as not to waste the hard-earned, valuable epoxides **40r** and **41r**; The five-membered ring epoxide can be easily synthesized in gram quantities from the corresponding carbonyl using ylid chemistry.[48] Since the five–membered ring epoxide **75r** is a terminal epoxide, its chemistry should be similar to the bicyclic epoxides **40r** and **41r** and it should make a good model compound.

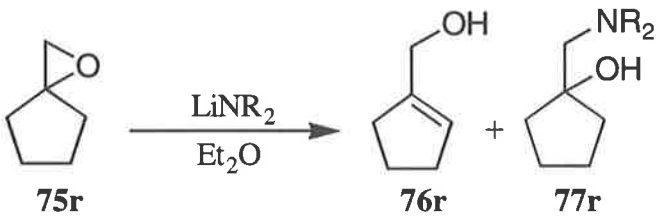
The epoxide model **75r** was formed from cyclopentanone using Corey's stabilized ylid. After purification by chromatography, the epoxide **75r** was obtained in a 68% yield. The ^{1}H NMR spectrum of **75r** shows a singlet at δ2.86 due to the protons on the epoxide group. The ring protons produce a complex pattern in the region of δ1.5-2.1.



75r

Scheme 59

Initially, base-induced isomerisation was attempted using a non-nucleophilic amide base. This was attempted for two reasons. Firstly, it was of interest to see if the allylic alcohol **76r** would form under these conditions, and in addition, this would provide a starting point for comparison to the reactions on the bicyclic epoxides **40r** and **41r**. Separate reaction of the model epoxide **75r** with lithium diethyl amide and LDA gave the allylic alcohol **76r** in ~30% yield. The yield was determined by the ^{1}H NMR spectrum of the crude product with the presence of an internal standard. The other identifiable product in the ^{1}H NMR of the crude product was presumed to be the substituted product **77r**. In the case of the lithium diethyl amide reaction, there was a characteristic quartet in the NMR at δ2.6, presumably due to the protons on the amine chain. Likewise, the ^{1}H NMR of the crude product from the LDA reaction showed a multiplet at δ2.41 (Scheme 60).



75r **76r** **77r**

Scheme 60

The reaction and the conditions used are summarized in Table 4.

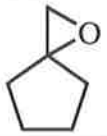
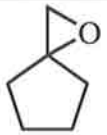
Epoxide	Concentration	Reagents	Conditions	Products
	0.15 M	$LiNEt_2$ (1.5 eq) Et_2O	Reflux, 6 hrs RT, 40 hrs	~30% allylic alcohol + Subs. Prod.
	0.15 M	LDA (1.5 eq) Et_2O HMPA	Reflux, 15 hrs	~30% allylic alcohol + Subs. Prod.

Table 4

The results summarised in the above table are not included in the experimental section. The reaction conditions are identical to the reaction conditions for the bicyclic epoxides **40r** and **41r**

Reaction of the five-membered ring epoxide **75r** with several alternative bases was attempted. In no case was the allylic alcohol **76r** formed and except for entry 4, no products could be even tentatively identified. Hence, none of the conditions used will be discussed in detail and they are summarized in Table 5, and the experimental details for these reactions are not reported.

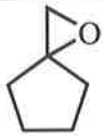
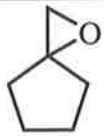
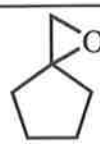
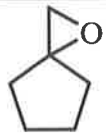
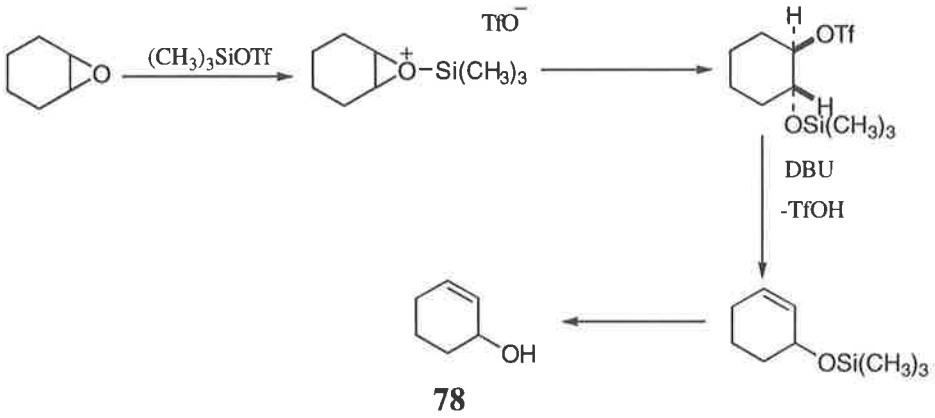
	Epoxide	Concentration	Reagents	Conditions	Products
1		0.32 M	*n*BuLi (1.5 eq) Et_2O	1hr -40°C 8 hrs RT	No starting material and no identifiable products
2		0.5 M	DBU (2 eq) DMSO	70°C 5 days	No starting material and no identifiable products
3		0.32 M	*t*BuOK (1.1 eq) DMSO	15 hrs RT	No starting material and no identifiable products
4		0.37 M	*t*BuOK (0.8eq) LDA (0.8eq) THF[81]	0°C 2 hrs RT 24 hrs	Aldehyde product (~20%)

Table 5

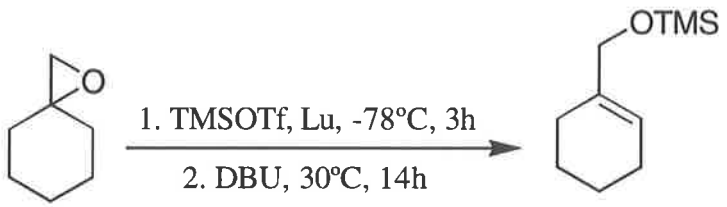
After a through literature search an alternative method for the rearrangement of epoxide to allylic alcohols was found. Trimethylsilyl trifluoromethanesulfonate (TMSOTf) is a powerful silylating agent. Exposure of an epoxide with equimolar equivalents of TMSOTf and 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) (or a 1:1 mixture of TMSOTf, 2,6-lutidine and then DBU) gives the isomeric allyl silyl ether. Deprotection with dilute hydrochloric acid or methanolic KF affords the allylic alcohol (Scheme 61).[82, 83] The six membered TMS protected alcohol **78** was formed in a yield of 87%.[82]



78

Scheme 61

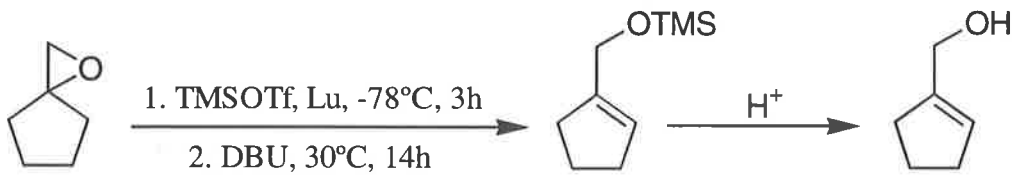
This reaction has been performed on a large number of epoxides. More importantly, there is an example on a terminal epoxide. Reaction of the epoxide **79** under the conditions of *Noyori*[82,83] gives the corresponding protected TMS ether **80** in a 72% yield (Scheme 62)



79 **80**

Scheme 62

Initially the reaction conditions were tried on the model epoxide **75r**, so as not to waste the hard-earned bicyclic epoxides **40r** and **41r** (Scheme 63)

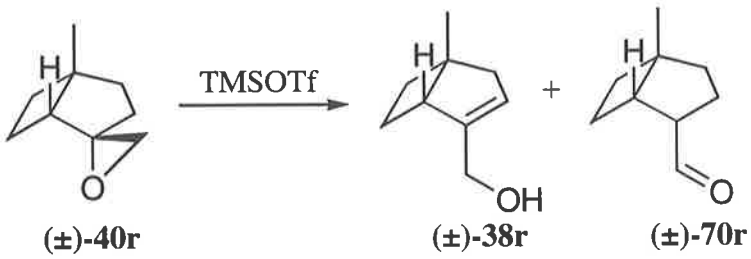


75r **78** **76r**

Scheme 63

The reaction was performed following the reaction conditions of *Noyori*.[82] After an acid work-up, to hydrolyze the protected trimethyl silyl ether, the corresponding allylic alcohol **76r** was obtained in a 44% yield. No evidence for the trimethyl silyl protected alcohol **78** was detected in the ^{1}H NMR spectrum.

Following the success of the trimethyl silyl triflate reaction on the five-membered ring epoxide **75r**, the reaction was attempted on the epoxide with the oxygen *trans* to the methyl group **40r** (Scheme 64).



(±)-40r **(±)-38r** **(±)-70r**

Scheme 64

Reaction with trimethyl silyl triflate on the bicyclic epoxide gave varying results. These are summarized in Table 6.

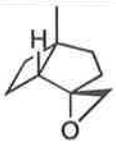
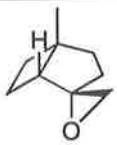
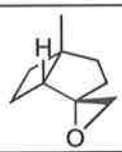
	Epoxide	Concentration	Reagents, Conditions	Products
1		0.39	TMSOTf, 2,6-lutidine, Toluene, -78°C, 3 hr DBU, RT 16 hrs	No starting material and no identifiable products
2		0.30	TMSOTf, benzene, DBU, RT 15 hrs	Trace of allylic alcohol **38r** and trace of aldehyde **70r** formed.
3		0.42	TMSOTf, CH_2Cl_2, DBU, RT 15 hrs	Allylic alcohol **38r**, 27% yield.

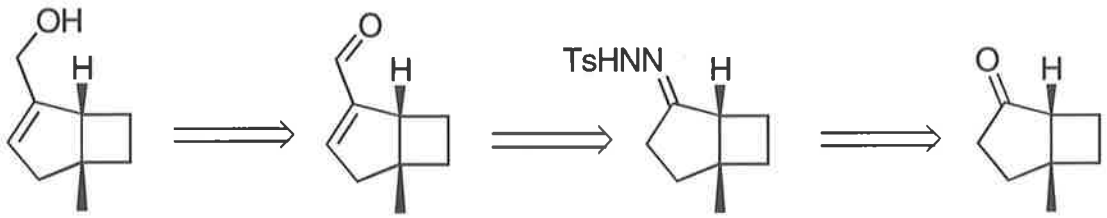
Table 6

Although the last entry did give the allylic alcohol **38r** in a 27% yield, this yield was not sufficiently high for a key intermediate in a multi-step synthesis. Improvement of the yield of this reaction proved difficult and consequently an alternative route was investigated.

Section 2.4 Shapiro reaction

An alternative route which, at least on paper should allow easy formation of the key intermediate, the allylic alcohol **38r**, from the bicyclic ketone was investigated. Bearing in

mind that it is desirable that the route to the key intermediate **38r** is short, it was proposed that the allylic alcohol **38r** could be formed in two or three steps from the bicyclic ketone **12** as indicated in the retrosynthetic scheme (Scheme 65). A Shapiro reaction on the tosylhydrazone **81** could give the allylic alcohol **38** directly, if formaldehyde is used as the electrophile or the α,β–unsaturated aldehyde **82**, if DMF is used as the electrophile. Reduction of the aldehyde **82** would the give the key intermediate **38** in a two-step synthesis from the hydrazone **81**. The tosylhydrazone **81** could be formed in one step from the bicyclic ketone **12**.



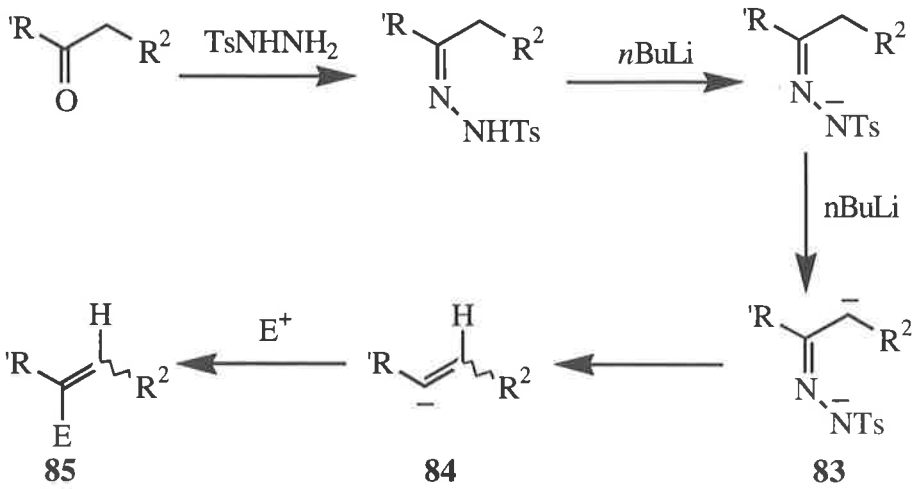
38 **82** **81** **12**

Scheme 65

The Shapiro reaction is an important reaction in the proposed synthesis and as a result the mechanism and the known examples should be discussed in detail.

Shapiro Reaction

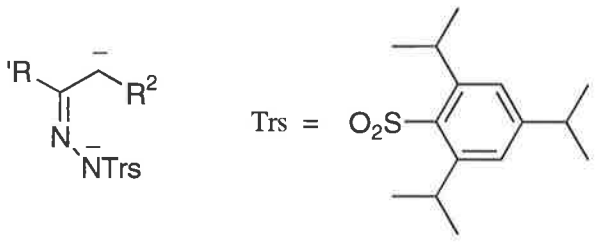
Until 1975, the Shapiro reaction was used only for the preparation of simple alkenes.[84] The reasons for this is that fragmentation of **83** to **84** is so slow, that partial protonation of **84** by the solvent takes place. This prior protonation does not make any difference in the preparation of the alkene, **85** where E=H, but is highly undesirable when E≠H. Hence, when E≠H the yields of **85** are low, and byproducts are formed. Another problem is the ortho-protons on the 4-tosylsulfonyl ring are significantly acidic and can be a proton source for the anion **84** [85] (Scheme 66).



Scheme 66

By overcoming these disadvantages, hydrazones can be converted with excess *n*-BuLi into vinyl carbanions **84** in good yields. This has been achieved by two modifications. The use of excess *n*-BuLi removes an ortho proton in the aromatic ring, and obviates the competitive ortho-metalation in the aromatic ring. The rate of fragmentation of **83** to **84** is rapid when TMEDA is used as a solvent, and **84** is notcompetitivelyprotonated by the solvent. This solvent acts by complexing the Li ion and effectively breaking the covalent nature of the bond by separation of the tight ion pairs.[85] An interesting feature of the Shapiro reaction is that the double bond of the resulting alkene is always at the least substituted carbon in the starting hydrazone.

Alternative (2,4,6-triisopropylphenysulfonyl)hydrazones, can also be used. These hydrazones are converted in high yields into **84**, in the solvent system of TMEDA or a 10% solution of hexane in TMEDA. Orthometalation is impossible and **86** fragments very rapidly to **84** at 0°C [85,86] (Figure 33).



86

Figure 33

Trapping of the vinyl carbanion intermediate has been achieved with numerous electrophiles,[87,88] some of which are illustrated in Figure 34.

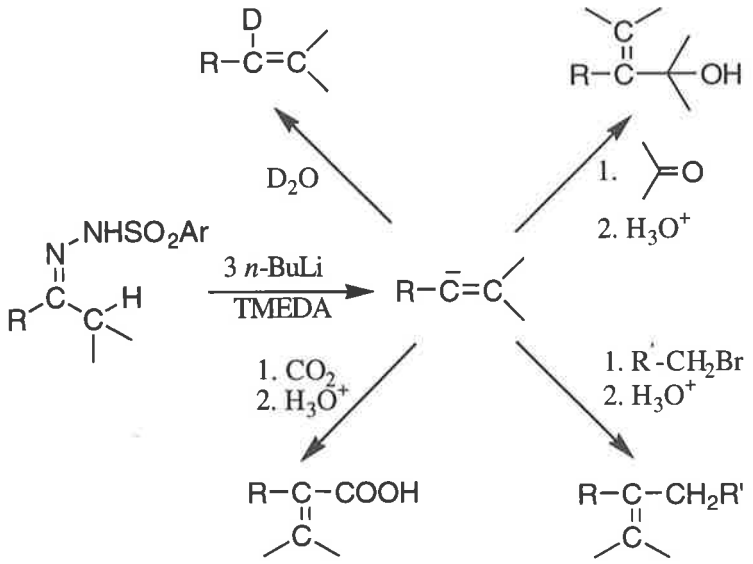
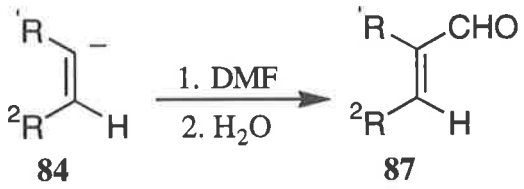


Figure 34

Also of particular interest to this project is the addition of DMF to the vinyl carbanion intermediate **84** to give the corresponding aldehyde **87**, after hydrolysis (Scheme 67). This has been successfully attempted on a number of substrates, illustrated in Table 7.[89]



84 **87**

Scheme 67

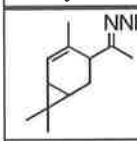
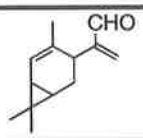
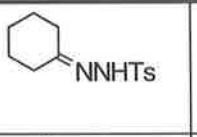
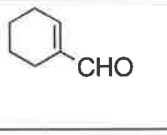
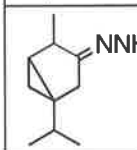
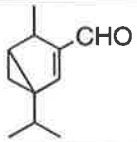
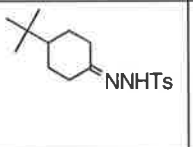
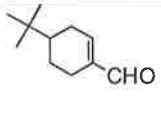
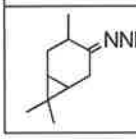
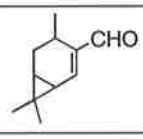
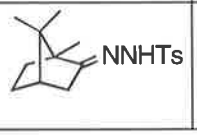
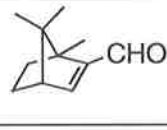
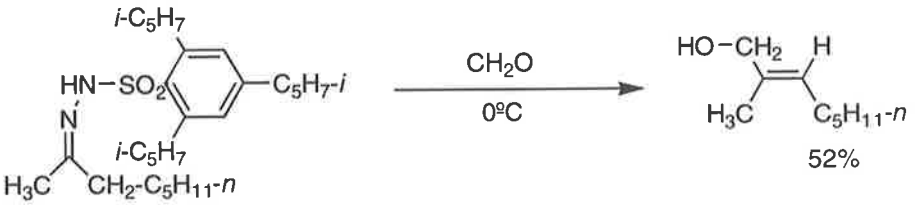
Hydrazone	Products	Yield	Hydrazone	Products	Yield
		60			54
		55			57
		60			10

Table 7

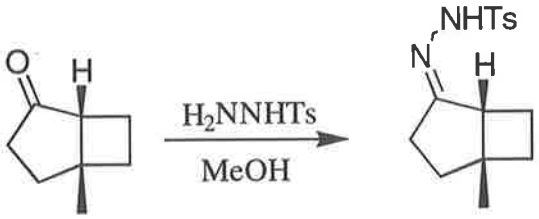
The reaction of the tosylhydrazone of camphor gives only a 10% yield and this is considered to be due to the steric hindrance in the approach of the dimethylformamide. The sterically less demanding electrophilie D_2O offers no problems and is incorporated quantitatively.[89]

There is an example in the literature of the vinyl carbanion intermediate **84** being trapped with formaldehyde, to give the corresponding allylic alcohol.[86] This reaction was performed on the trisylalkylhydrazone (Scheme 68).



Scheme 68

Reaction of the bicyclic ketone **12r** with tosylhydrazine gave the desired tosylhydrazone in a 89% yield (Scheme 69).

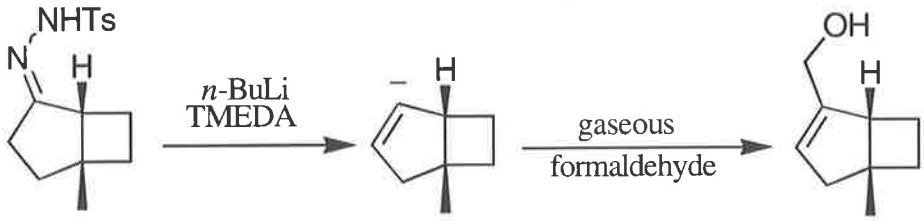


(±)-12r **(±)-81r**

Scheme 69

The ^{1}H NMR spectrum shows two sharp singlets, in the ratio of 1:1, at δ1.21 and δ1.23, for the angular methyl group, due to the presence of *syn* and *anti* isomers of the derivative. The methyl groups on the aromatic ring for both isomers resonate as a broad singlet at δ2.42. The bicyclic ring protons appear as a complex of resonances in the region of δ1.35-2.9, a 2H broad singlet at δ4.06 is due to the NH proton of each isomer. The aromatic protons resonate as a 4H doublet of multiplets at δ7.30 and a 4H doublet at δ7.82. Microanalysis was consistent with the assigned structure.

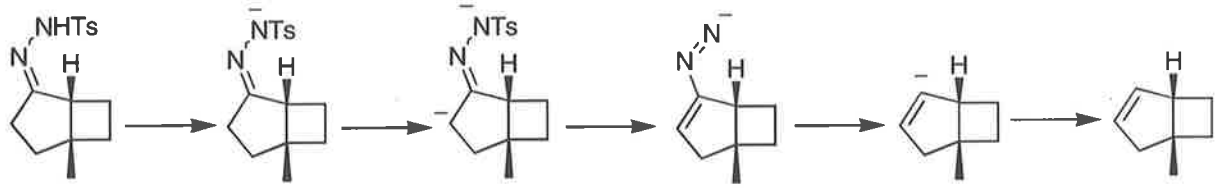
The next step was an attempt to do the modified Shapiro reaction on the tosylhydrazone **81r** to give the desired allylic alcohol **38r** directly (Scheme 70).



(±)-81r **(±)-82** **(±)-38**

Scheme 70

Cooling of the suspension of the tosylhydrazone **81r** in TMEDA to –78°C resulted in the solution freezing. As three equivalents of *n*-BuLi was added to the reaction vessel, the frozen suspension began to melt and eventually the solution became a dark red homogeneous solution. On allowing the solution to warm to ambient temperature the colour changed from initially dark red, to a deeper red colour, and finally to a brown-red colour. Gas evolution within the solution was also observed, and this was presumed to be due to the nitrogen from fragmentation of the tosylhydrazone **81r** (Scheme 71). It was assumed that after evolution of nitrogen gas from the reaction vessel has ceased the required anion **82r** had completely formed. To completely quench the anion **82r** only one equivalent of water is required. Consequently, it seemed desirable to leave the anion **82r** unquenched in solution for a short a period as possible so as to avoid the formation of the unwanted bicyclic alkene **89r**.



Scheme 71[λ]

Hence, the reaction mixture was only stirred at ambient temperature for 20 minutes, until it was assumed nitrogen evolution from the reaction mixture had ceased. The reaction mixture was then cooled to 0°C and gaseous formaldehyde was bubbled into the solution. It was hoped that the anion **82r** would react with the gaseous formaldehyde to give, after work-up, the allylic alcohol **38r**. The ^{1}H NMR spectrum of the crude material showed a trace of a product that appeared to be the allylic alcohol **38r**, (confirmed later), but the main component was the starting hydrazone **81r**. This was unusual as no starting hydrazone **81r** should remain if three equivalents of *n*-BuLi were used in the reaction.[78]

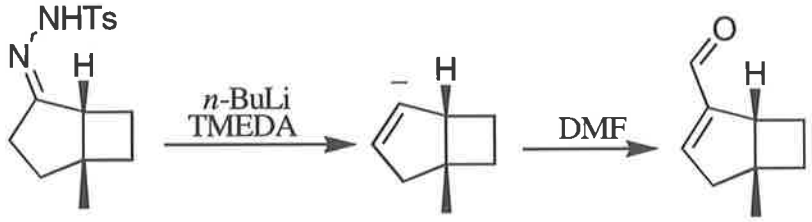
After several repeat reactions gave similar results, it was reasoned that the anion **82r** may only form slowly from the dianion. It was impractical to measure the evolution of nitrogen and therefore instead the reaction was repeated and the solution was stirred at 35°C for four hours.

[λ] For simplicity, the anion on the tosyl group is not shown.

After this time, the reaction mixture changed to a brown-yellow colour that may indicate that only the anion **82r** remained. The ^{1}H NMR spectrum of the crude material, after work-up, showed the presence of a product that was later confirmed to be the allylic alcohol **38r**, but numerous impurities were also present, which could not be even tentatively identified. Isolation of the allylic alcohol **38r** was achieved in a poor yield of only about 5% after purification by chromatography, however, it was still contaminated by impurities.

It was considered that the meagre yield of the allylic alcohol **38r** from the tosylhydrazone reaction could be due to the re-polymerization of the gaseous formaldehyde in the delivery tube of the reaction vessel before it reached the reaction mixture. Addition of solid *p*-formaldehyde directly to the reaction vessel, after formation of the anion, did not improve the yield of the reaction.

As reactions of the anion **82r** with formaldehyde did not give the desired allylic alcohol **38r** in usable yields, formation of the α,β-unsaturated aldehyde **88r** was then attempted (Scheme 72). Reaction of the anion **82r** with DMF should give, upon hydrolytic work-up, the corresponding α,β-unsaturated aldehyde **88r**.[87]



(±)-81r **(±)-82** **(±)-88r**

Scheme 72

The anion **82** was formed using three equivalents of *n*-BuLi in the solvent system of TMEDA. After addition of *n*-BuLi to the reaction mixture the solution was stirred at ambient temperature for 4 hours, to allow sufficient time for formation of the desired anion **82**. The anion **82** was then quenched with DMF.

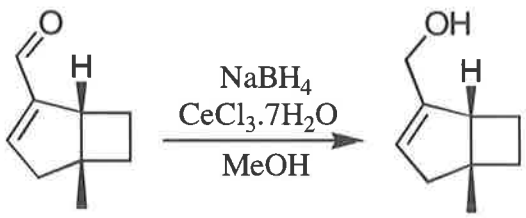
The ^{1}H NMR spectrum of the crude material revealed that a very clean reaction had taken place. It was presumed that this was the desired aldehyde because there was a characteristic signal in the ^{1}H NMR spectrum at δ9.78. There were no signals for the starting tosylhydrazone

81r but there were resonances for unreacted DMF. Due to the instability of the aldehyde **88r**, it was normally converted without purification to the allylic alcohol **38r**. A small portion of the aldehyde **88r** was subjected to chromatography so an analytical sample could be obtained.

The ^{1}H NMR spectrum of the aldehyde **88r** shows a 3H singlet at δ1.27 due to the methyl group. The methylene ring protons resonate as a 3H complex between δ1.6-2.1 and a 3H complex between δ2.2-2.6. An allylic proton resonates as a broad doublet at δ3.02, with a coupling constant of 8 Hz, from similarities to the ^{1}H NMR spectrum of the allylic alcohol **38r**, see later, this resonance is presumably due to the methine proton. A broad singlet at δ6.87 is due to the olefinic proton. The aldehyde proton resonates as a sharp singlet at δ9.78.

Optimization for the yield of the aldehyde **88r** was only found after numerous reactions. It is essential that the TMEDA is purified to remove primary and secondary amines and then freshly dried immediately prior to the reaction.[90] At least three equivalents of *n*-BuLi are required and sufficient time allowed to ensure complete formation of the anion **82**. The DMF must be anhydrous and the hydrolytic work-up procedure must be conducted with care. The best conditions found for the reaction are carefully recorded in the experimental section and it is advisable to adhere to them closely.

The aldehyde **88r** was cleanly reduced to the allylic alcohol **38r** with sodium borohydride in the presence of ceric chloride. Ceric chloride was added as a precautionary measure, to alleviate the possibility of the double bond also being reduced.[91]



(±)-88r **(±)-38r**

Scheme 73

After work-up of the reaction mixture, the ^{1}H NMR spectrum of the crude material showed that the reaction was very clean. The only resonances in the ^{1}H NMR spectrum appeared to be due to the allylic alcohol **38r**. However, after work-up the allylic alcohol was obtained as an orange

oil. Since TLC showed only one spot, other than the colour on the base-line, the product was purified by squat chromatography. After purification, the allylic alcohol was obtained in a 83% yield over the two steps. These reactions were repeated numerous times and initially the yield of the reaction ranged from 30-50% over the two steps. However, when the reaction conditions and the technique were perfected a yield of over 70%, for the two steps, could be obtained consistently for the allylic alcohol **38r**.

The region for the ring protons in the ^{1}H NMR spectrum of the allylic alcohol **38r** is complex, and a 600 MHz NMR spectrum was required so the situation could be clarified. Both COSY and HETCOR experiments were required so all the protons in the ^{1}H NMR spectrum could be assigned. These spectra have been reproduced in Figure 36, Figure 37 and Figure 38.

The ^{1}H NMR spectrum can therefore be described as follows. A sharp singlet at δ1.27 is assigned to the methyl group. The resonance at δ1.69 is a 1H multiplet due to one of the protons at C7. The 1H complex at δ1.79 is due to of the one proton at C6, the other proton at C6 resonates as a multiplet at δ1.94. The region of δ2.1-2.3 is a 3H complex due to two protons at C4 and one proton at C7. The methine proton resonates as a doublet at δ2.74, with a coupling constant of 8 Hz. The protons adjacent to the hydroxyl group resonate as an AB quartet at δ4.16. The broad 1H multiplet at δ5.62 is due to the olefinic proton (Figure 36). Microanalysis also supported the assigned structure.

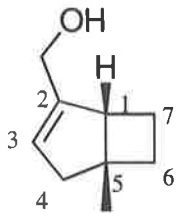
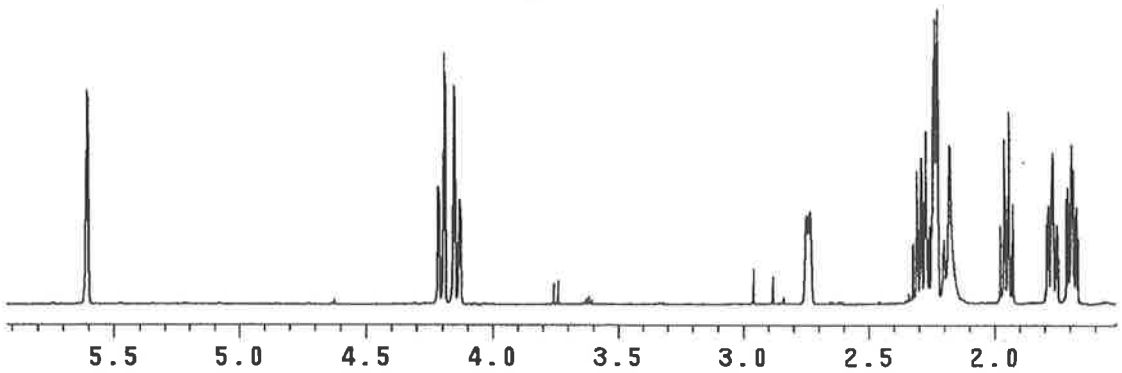
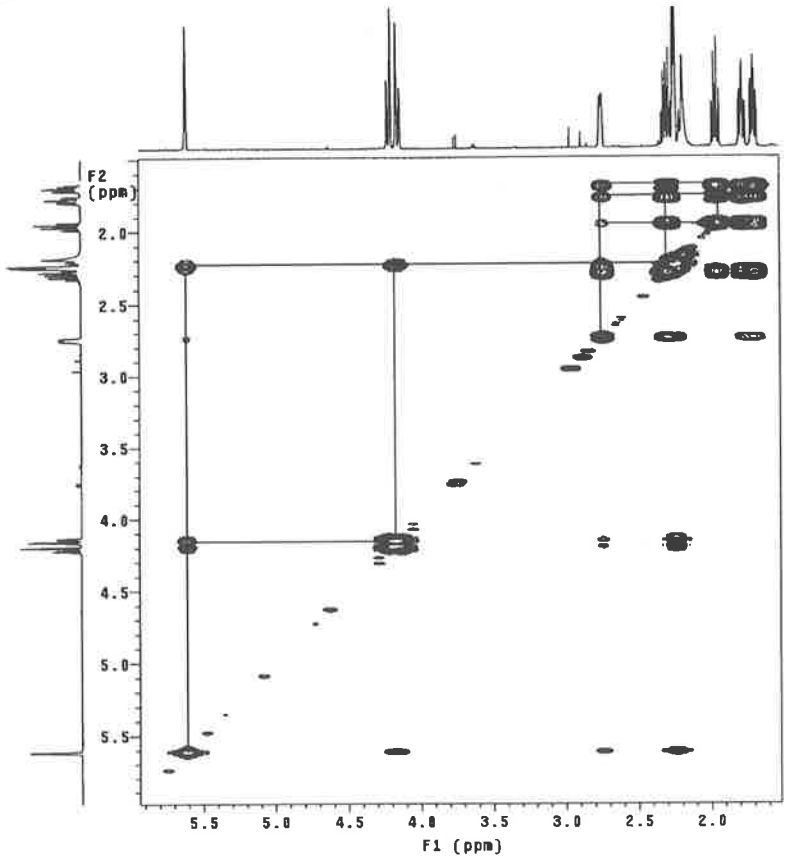


Figure 35



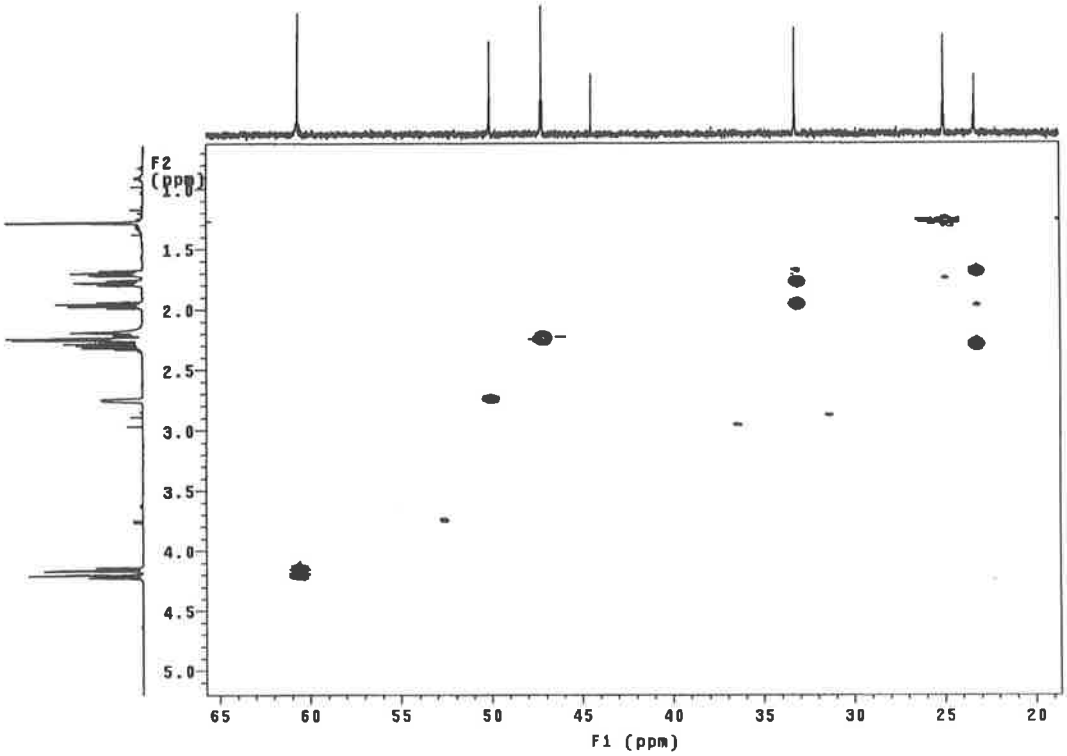
A portion of the 600MHz ^{1}H NMR spectrum of the allylic alcohol **38**.

Figure 36



The COSY spectrum at 600 MHz of the allylic alcohol **38**.

Figure 37



The HETCOR spectrum of the allylic alcohol **38**.

Figure 38

In conclusion, a four-step synthesis of the key intermediate **38r** from commercially available materials has been accomplished. These reactions can be performed on multi-gram scales and the key allylic alcohol can be prepared in a 57% yield overall from 3-methylcyclopenten-1-one. Now that the key intermediate **38r** had been successfully synthesized, the kinetic resolution of the primary allylic alcohol **38r** could be attempted. This will be discussed in 'Chapter 3, Results and Discussion'.

CHAPTER 3

RESULTS AND DISCUSSION

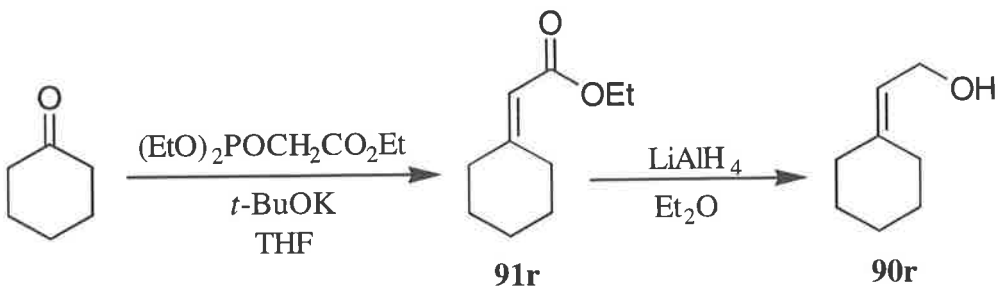
A KINETIC RESOLUTION OF A KEY INTERMEDIATE AND THE SYNTHESIS OF OPTICALLY ACTIVE GRANDISOL

Section 3.1 Sharpless Asymmetric Epoxidation Reaction

From previous experience within the group, it is known that the Sharpless asymmetric epoxidation reaction is not a simple reaction to perform and some practice is required before the skills required are learnt.[95] Sharpless has reported extensive experimental details for the epoxidation reaction and one point that he stresses is the reaction's susceptibility to water.[39] It is desirable that kinetic resolution reactions are run to about a 60% conversion, and that the progress of the reaction is monitored. Clearly, it is important that when taking aliquots for this monitoring, that the reaction vessel is not inadvertently contaminated with water. With these problems in mind, the reaction conditions and a method for monitoring the progress of the reaction were determined on a more readily available compound, the six-membered ring allylic alcohol **90**.

Section 3.1.1 Six-membered Ring Trial Compound

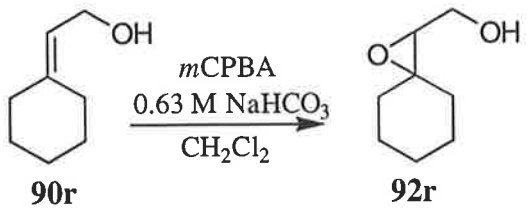
The six-membered ring allylic alcohol **90r** was formed in two steps from cyclohexanone. A Wittig - Horner reaction[92] on cyclohexanone gave the corresponding α,β-unsaturated ester **91r**. Reduction of the α,β-unsaturated ester **91r** with lithium aluminum hydride, using a general procedure,[93] gave the desired allylic alcohol **90r** (Scheme 74).



91r **90r**

Scheme 74

The racemic epoxy alcohol **92r** was formed so its resonances in the ^{1}H NMR spectrum could be assigned. Reaction of the allylic alcohol **90r** with *m*CPBA, in the presence of sodium bicarbonate, gave the epoxy alcohol **92r** in an 80% yield after purification by chromatography. (Scheme 75).



90r **92r**

Scheme 75

The ^{1}H NMR spectrum shows a complex in the region δ1.5-1.8 due to the methylene protons. The hydroxyl group exhibits a broad 1H singlet at δ2.2. The multiplet at δ2.95 is due to the proton at C2, it is at least a four line pattern and is the X portion of the ABX system. The protons adjacent to the hydroxyl group exhibits two multiplet centered at δ3.69 and δ3.85, it is at least an 8 line pattern and is the AB portion of the ABX system (Figure 39).

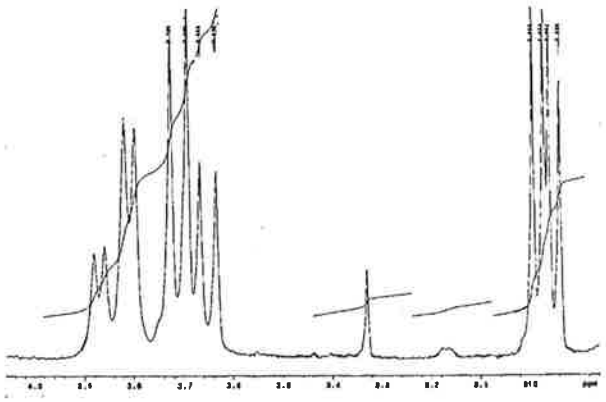
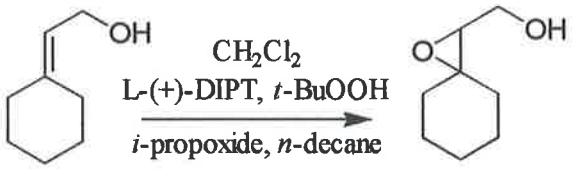


Figure 39

The conditions used to follow the reaction were those recommended by Sharpless for kinetic resolutions of secondary allylic alcohols and are as follows.[40] It is recommended that *n*-decane is the internal standard, one equivalent of *tert*-butyl hydroperoxide, and catalytic amounts of titanium tetraisopropoxide and L-(+)-DIPT (or D-(-)-DIPT) are used. Aliquots from the reaction mixture are taken at desired intervals, diluted with 100 μL of diethyl ether and then quenched with an aqueous solution of $FeSO_4$ and citric acid, GLC (Gas Liquid Chromatography) is then used to monitor the progress of the reaction.

As the six-membered ring alcohol **90r** is achiral, a kinetic resolution can not occur, and the rate of the reaction is dependent only on the concentration of *tert*-butyl hydroperoxide. For this reason, a graphical plot of time vs. the concentration of the allylic alcohol is expected to give a straight line.

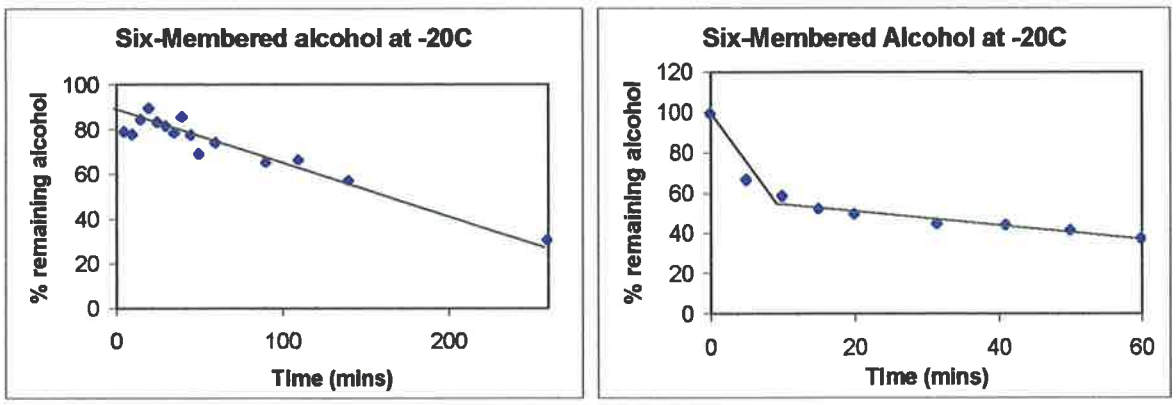
Initially, the reaction was attempted with the standard conditions of Sharpless, discussed above [40] (Scheme 76).



90r **92a**

Scheme 76

Aliquots from the reaction mixture were quenched following the procedure of Sharpless,[40] with diethyl ether as the extraction solvent. The GLC results obtained are shown graphically in Figure 40(a). From the experimental results, the extraction procedure does not give consistent results of the amount of allylic alcohol remaining in solution. This result could be due to the water solubility of the extraction solvent, and the allylic alcohol inconsistently remains in the aqueous layer. This problem could be avoided if the extraction solvent was dichloromethane. However, a line of best fit can be drawn and it appears that the graph follows a general trend, which indicates that the reaction is zero-order.



(a) **(b)**

Figure 40

Repetition of the reaction with dichloromethane as the extraction solvent gave consistent results for the amount of remaining allylic alcohol. However, when time vs. the amount of remaining allylic alcohol were plotted two lines of varying slope were obtained, as seen in Figure 40(b). The slope of the line should give the rate of reaction, this therefore implies that the reaction has two different rates, which can not be true. Consequently, the reaction vessel must have been contaminated with water at the ten-minute mark, which slowed the reaction. The presence of water also has a disastrous consequence on the enantiomeric excess of the product.[40] Two lines with different slopes are expected in the kinetic resolution of the key intermediate **38**, hence this problem of water contamination has to be excluded if the reaction of the key intermediate **38** is to be successfully followed by GLC.

The reaction was repeated with extreme care taken so water was not introduced into the reaction vessel. Each aliquot was taken with a different syringe that had been oven dried for at least 24 hours. Also the temperature was decreased to –40°C, in an effort to slow the reaction down since the first part of the reaction in Figure 40(a) suggests that the 50% mark is reached in less than 10 mins. The results are shown in Figure 41. It can be seen that all point lie within close proximity to the line of best fit.

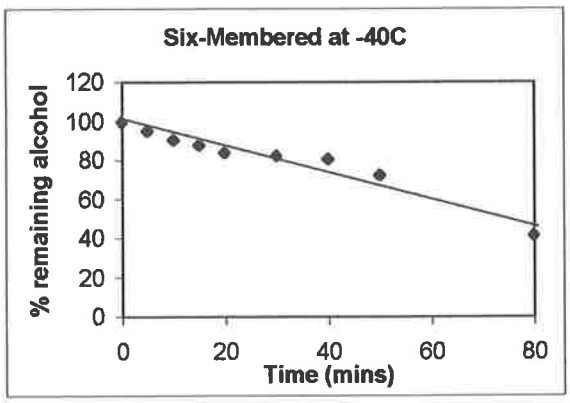


Figure 41

After the GLC results had been obtained a solution of $FeSO_4$ and citric acid were added to the reaction vessel to quench any remaining *tert*-butyl hydroperoxide. As a matter of convenience the mixture was left at ambient temperature for 15 hours and then worked-up. The ^1H NMR spectrum of the product obtained was different to that of the racemic epoxide **92r**. The ^1H NMR spectrum of the purified product showed a 4H complex at δ1.5, and another 4H complex at δ1.8. The AB portion of the ABX system exhibits at least a 12 line pattern at δ3.46 and the

other at δ3.59. The X portion resonates as at least a four line pattern centered at δ4.01. A broad singlet at δ5.66 is due to one proton. The region from δ3.5-5.8 in the ^{1}H NMR spectrum is shown in Figure 42.

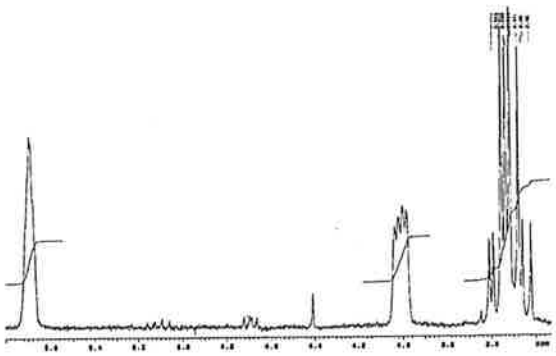
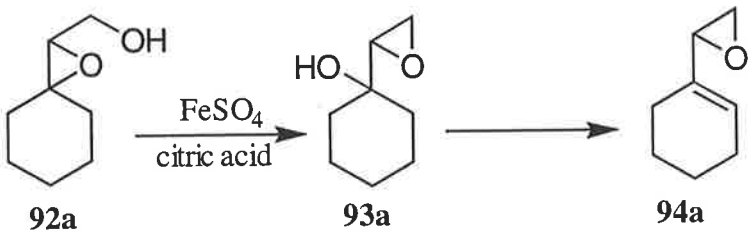


Figure 42

The ^{13}C NMR had eight resonances, and GC-MS revealed a molecular weight of 124. This product was thought to be the rearrangement product epoxide **94a**, which fitted the above evidence (Scheme 77). Due to the instability of the product, a microanalysis was not attempted.



92a **93a** **94a**

Scheme 77

After a series of experiments on the racemic epoxide **92r**, it was found that only the presence of $FeSO_4$ was required for rearrangement of this epoxide **92r** (Table 8). It was presumed that $FeSO_4$ was acting as a Lewis acid, which resulted in a 'Payne-type'[94] rearrangement to give the epoxy-alcohol **93a**.[§] Elimination of the tertiary hydroxyl would then give the olefin **94a**.

Conditions	Products
$FeSO_4$ / Citric acid, 2 days, ambient temperature.	Olefin **94r**
Citric acid, 2 days, ambient temperature.	Starting material **92r**
$FeSO_4$, 2 days, ambient temperature.	Olefin **94r**

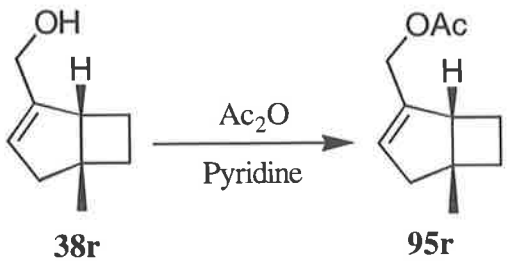
Table 8

[§] Literature examples of acid catalyzed Payne rearrangements could not be found. Payne rearrangements are base catalyzed.

It was found that this reaction was slow and if the Sharpless epoxidation reaction was worked-up quickly, formation of this product was minimal and the optically active epoxy alcohol **92a** was obtained in a 45% yield. The racemic epoxide **92r**, in the presence of chiral shift reagent, tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium (III) derivative, gave baseline separation of the multiplet initially at δ2.95 in the ^{1}H NMR spectrum. However, other peaks also occurred in this area and consequently the optical purity of the epoxide **92a** from the Sharpless asymmetric epoxidation reaction could only be estimated to be >90%.

Section 3.1.2 Determination of Optical Purity of the Key Intermediate

Before a kinetic resolution on the key intermediate **38** could be attempted, a method for the determination of optical purity of the resolved substrate **38** was required. From previous experience within the group it has been shown that the optical purity of many alcohols is most effectively determined as the acetate derivative, by 200 or 300 MHz spectroscopy in the presence of the chiral shift reagent tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium (III) derivative.[95,96] The primary alcohol in the presence of chiral shift reagents often lead to unacceptable line broadening in the ^{1}H NMR spectrum. In addition, it has also been found that the sharp methyl singlet of the acetate derivative can normally be used to determine the optical purity. For these reasons, the racemic allylic alcohol **38r** was acetylated with acetic anhydride in pyridine to give the acetylated product **95r** (Scheme 78). The ^{1}H NMR spectrum of the acetate is similar to that of the allylic alcohol **38r** with an additional singlet methyl peak at δ2.06 and the absence of the OH peak. In addition, the AB quartet that resonated at δ4.16 in the allylic alcohol **38** now appears as a broad singlet at δ4.63.



38r **95r**

Scheme 78

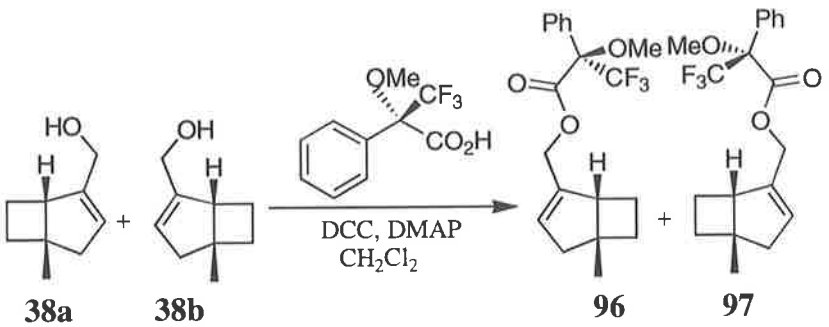
It is known that chiral shift analysis gives the best separation when the ^{1}H NMR experiment is performed in a solution of carbon tetrachloride, with a small quantity of d_6-benzene added so the spectrometer can be easily locked to this resonance.[61] Analysis of the acetate **95r** with the

chiral shift reagent tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium (III) derivative gave only broadening of peaks from which no useful information could be obtained. Consequently, chiral shift analysis was attempted on the free allylic alcohol **38r**. Partial separation of the olefinic resonance did occur, but as the separation was not baseline, this method could not be used to accurately determine the optical purity of the allylic alcohol **38r**. Chiral GC [SGE Cydex-B column (25m × 0.22mm)] did achieve some, but incomplete, separation of the enantiomers of the racemic allylic alcohol **38r**.[97]

No separation was observed for the diastereomeric urethanes derived from (S)-(-)-α-methylbenzyl isocyanate,[98] either in the NMR spectrum or by chromatography.

Alternatively, alcohols can be acylated with α-Methoxy-α-(trifluoromethyl)phenylacetic acid to give diastereomers.[99] The methoxyl or other resonances of the alcohol portion in the ^{1}H NMR spectrum of the derivative mixture are often of sufficiently different chemical shift to allow integration. Sometimes, the ^{19}F NMR spectrum can also be used to determine the diastereomeric ratio.

Reaction of the racemic allylic alcohol **38r** with (+)-α-Methoxy-α-(trifluoromethyl)phenyl-acetyl chloride gave the corresponding MTPAA esters (Mosher esters) **96** and **97** (Scheme 79).



38a **38b** **96** **97**

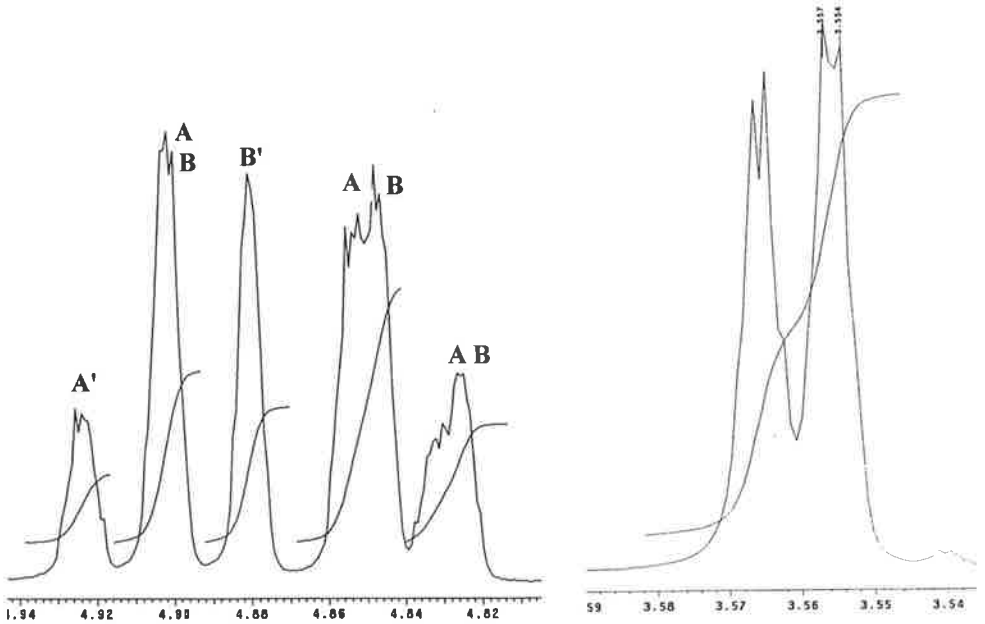
Scheme 79

The ^{1}H NMR spectrum of these MTPAA esters (Mosher esters) **96** and **97** at 200MHz shows the appearance of two diastereomers and can be described as follows. Two sharp singlets occur near δ1.23 due to one of the methyl groups on the bicyclic ring from each diastereomer. The methyl resonances do not give baseline separation and thus can not be used

for determination of optical purity. The ring protons from both diastereomers resonate as a complex in the region δ1.3-2.1. For both diastereomers, one of the allylic protons at C4 resonates as a multiplet at δ2.62. The methoxyl group from both diastereomers appears as two singlets, one diastereomer resonances at δ3.55, and the other at δ3.56. However, the separation is not baseline. The protons adjacent to the methoxyl group, for both diastereomers, appear as a distorted AB quartet centred at δ4.85. The olefinic proton, in both diastereomers, resonates as a broad singlet at δ5.7. The aromatic protons appear as a complex at δ7.35-7.55. A ^{19}F NMR spectrum of the racemic Mosher esters **96** and **97** also gave no useful separation of resonances.

The resonance, at δ4.85 in the 200 MHz ^{1}H NMR spectrum which is due to the diastereotopic protons of the methylene group bearing oxygen, does partially separate into two separate patterns at 600 MHz. Almost complete separation of the methoxyl signals was also observed but, because this region could be contaminated with reagent signals, it was only safe to use for confirmation of the enantiomeric excess (Figure 43). From an optically enriched sample of the Mosher esters it was later confirmed that the resonances at δ4.85 were due to two overlapping AB quartets. One AB quartet occurs at δ4.83, 4.85, 4.91 and 4.93 (**A**). The other AB quartet occurs at δ4.83, 4.85, 4.88 and 4.91 (**B**).

Figure 43 shows the ^{1}H NMR spectrum of the AB quartet region and methoxyl region of the racemic Mosher esters **96** and **97** at 600MHz.



The two AB quartets of the Mosher ester

The methoxyl region of the Mosher Ester

Figure 43

It can be seen that one peak of the AB quartet of each diastereomer is distinct from the other. **A'** in the case of one diastereomer, and **B'** in the case of the other. With the help of Equation 2,[75] an estimate for the enantiomeric excess of optically active allylic alcohol can be made.

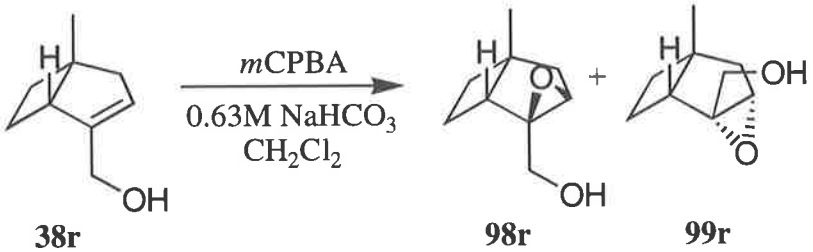
$$I_3/I_4 = I_2/I_1 = (\nu_4 - \nu_1)/(\nu_3-\nu_2)$$

I = relative intensity of the lines
ν = chemical shift of the lines

Equation 2

Section 3.1.3 Kinetic Resolution of the Key Intermediate

Initially, formation of the racemic epoxide from the allylic alcohol **38r** was attempted. It was of interest whether the reagent would approach solely from the top face. (Scheme 80). Reaction of the allylic alcohol with *m*CPBA at –40°C* gave predominately one epoxide, presumed to be the *exo*-epoxide, with the oxygen *cis* to the methyl group **98r**. The ratio of the *exo*-epoxide to the *endo*-epoxide **99r**, (with the oxygen *trans* to the methyl group) was 4.3:1. Separation of the two diastereomers could be achieved by careful chromatography. The *exo*-epoxide **98r** was isolated in a yield of 44% and the *endo*-epoxide **99r** in a yield of 7%.



38r **98r** **99r**

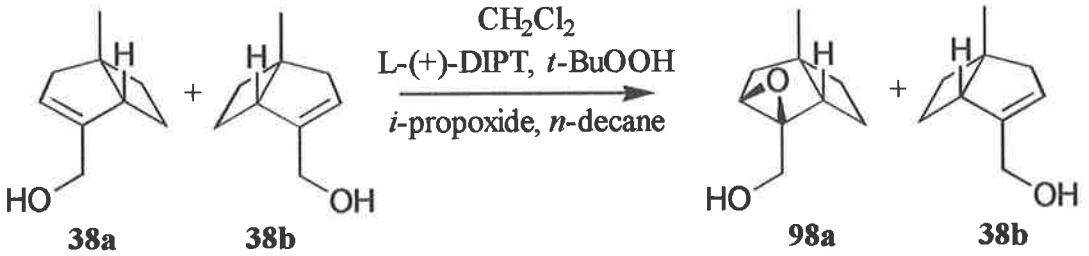
Scheme 80

The ^{1}H NMR spectrum of the *exo*-epoxide **98r** shows a 3H singlet at δ1.12 due to the methyl group. The ring protons resonate as a 7H complex between δ1.7-2.1. The resonances for the methine proton adjacent to the epoxide group exhibits a doublet of doublets at δ2.44 with coupling constants of 5 and 8.5 Hz. A broad singlet at δ3.60 is due to the hydroxyl group. The methylene protons adjacent to the hydroxyl group are diastereotopic and resonate as an AB

* The temperature of –40°C was chosen so comparisons could be made with the Sharpless asymmetric epoxidation reaction.

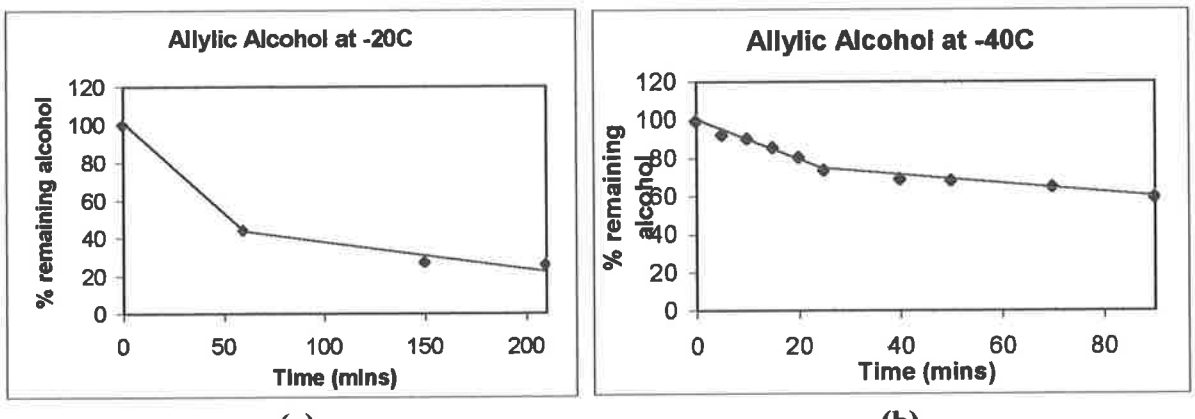
quartet at δ3.74 and δ3.94. The ^{1}H NMR spectrum of the *endo*-epoxide **99r** shows a 3H singlet at δ1.19 due to the methyl group. The ring protons resonate as a 3H complex at δ1.6 and a 5H complex between δ1.8-2.2. The methylene protons adjacent to the hydroxyl group are diastereotopic and resonate as an AB quartet at δ3.76 and δ3.90.

A kinetic resolution of the allylic alcohol **38** under identical conditions to that used for the six-membered ring allylic alcohol **90** at –20°C gave the graph illustrated in Figure 44(a) (Scheme 81).



Scheme 81

It was hoped that one enantiomer would react faster than the other would, giving a graph with two different sloped lines. The initial reaction went faster than expected and not enough aliquots were taken, however, this trend was observed. Repetition of the reaction at –40°C gave a much slower reaction and better defined two different sloped lines are observed (Figure 44(b)).



(a) **(b)**

Figure 44

In both cases, the reaction was worked-up at the % conversion shown and the enantiomeric excess of the starting alcohol was determined from the corresponding Mosher derivative **96**. The enantiomeric excess determination will be discussed later in 'Results and Discussion,

Chapter 3'. The enantiomeric excesses for the allylic alcohol **38** from these two reactions are correlated in Table 9.

Temperature	% Conversion	% e.e. of allylic alcohol
-20°C	70	74%
-40°C	60	>95%

Table 9

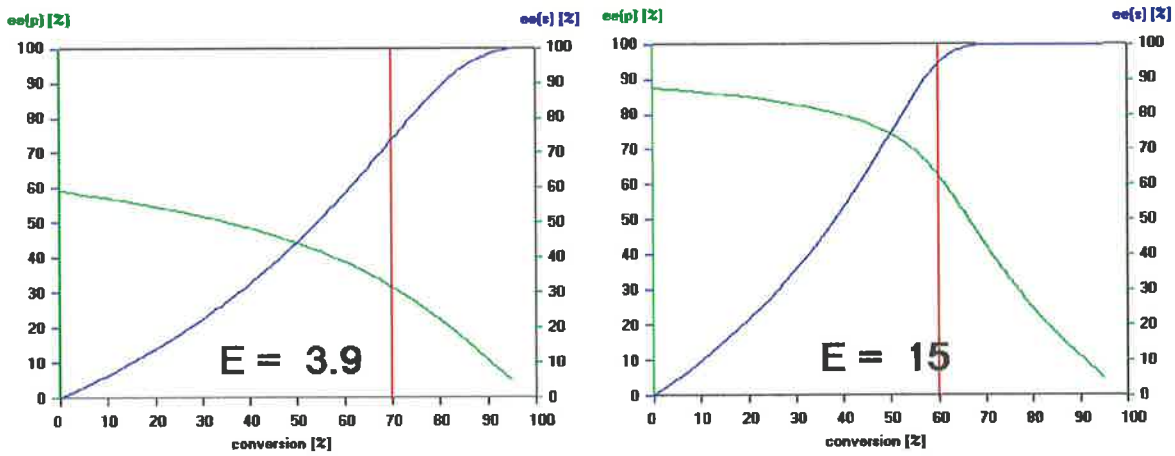
By use of Equation 1, previously discussed in the introduction p. 19, the selectivity of the Sharpless asymmetric epoxidation reaction can be expressed graphically.[δ] The graphical program needs two of three possible parameters. These are; the enantiomeric excess of the resolved substrate, the enantiomeric excess of the product and the percentage conversion of the reaction. If two parameters are known, the third can be calculated. Using these three parameters, the reaction can be expressed graphically. However it must be realised that a small difference in the enantiomeric excess or % conversion used in the calculation program, can have a large difference on the appearance of the graph obtained, and consequently the value of the 'Enantiomeric Ratio, E' obtained is not very meaningful.

$$\frac{K_A}{K_B} = \frac{\ln(A/Ao)}{\ln(B/Bo)} = \frac{\ln(1-C)(1-ee)}{\ln(1-C)(1+ee)}$$

Equation 1

The results from the reaction at –20°C are shown in Figure 45(a). The reaction was 70% complete and the enantiomeric excess of the starting substrate was 74%. The red line represents the data used in the calculation program.

[δ] The graphical representations were performed with 'Enantiomeric Ratio', a freeware program, available at http:// www-orgc.tu-graz.ac.at/. The theory is based on Equation 1.



-20°C (a) -40°C (b)

Figure 45[ζ]

The graphical representation of the reaction at –40°C is shown in Figure 45(b), the selectivity of the reaction is superior to the reaction run at –20°C. It was hoped that decreasing the temperature even further to –60°C, the selectivity would also increase. By decreasing the temperature the chance of contaminating the reaction with water when taking aliquots increases, hence, it was reasoned that it was better to limit the amount of *tert*-butyl hydroperoxide rather than follow the reaction by GLC.[§] Reaction at –60°C, with *tert*-butyl hydroperoxide as the limiting reagent, again improved the selectivity of the reaction.

From the results of the kinetic resolution at –40°C and –60°C it was difficult to determine why the reaction at –20°C gave such a poor enantiomeric excess of the substrate. For this reason, the reaction was repeated under identical conditionsto the reaction at –60°C, with no aliquots taken during the reaction. The results from the reaction at –60°C and –20°C are correlated in Table 10.

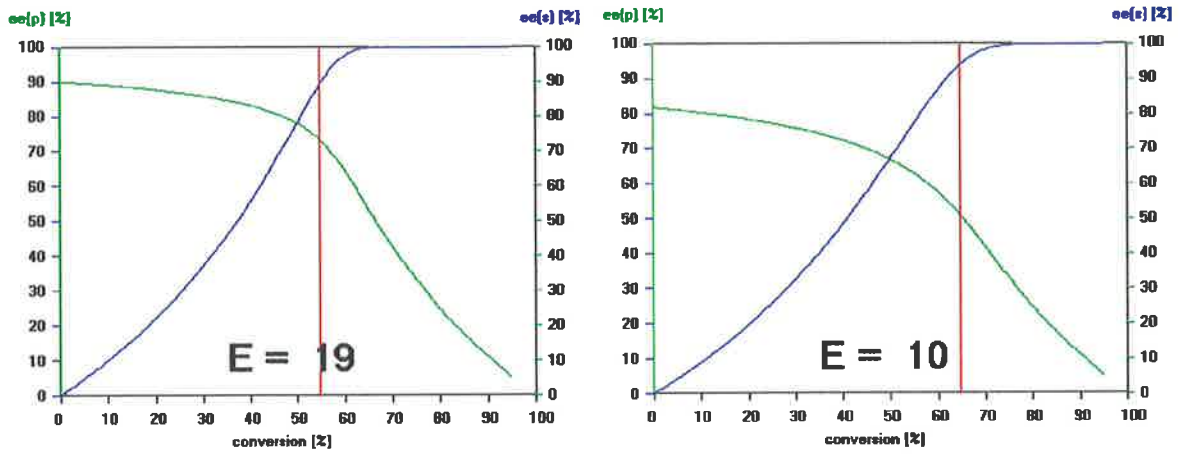
Temperature	% Conversion	% e.e. of allylic alcohol
-60°C	55	90%
-20°C	65	>95%

Table 10

[ζ] E is the Enantiomeric Ratio of the reaction.

[§] T_o and T_{final} samples were taken to determine the % conversion of the reaction.

The graphical representation for both reactions is shown in Figure 46. It can be seen from the graphs that the selectivity of the kinetic resolution at –60°C is superior to the reaction at –20°C and –40°C. However, as stated previously, a small change in the enantiomeric excess used in the calculation program has a large effect on the value of the 'Enantiomeric Ratio, E' obtained. For this reason, it was concluded that the two graphs in Figure 46 are nearly identical, in both cases the reaction only need to be run to ~60% completion to obtain an enantiomeric excess of >95% for the starting substrate.



-60°C (a) **-20°C (b)**

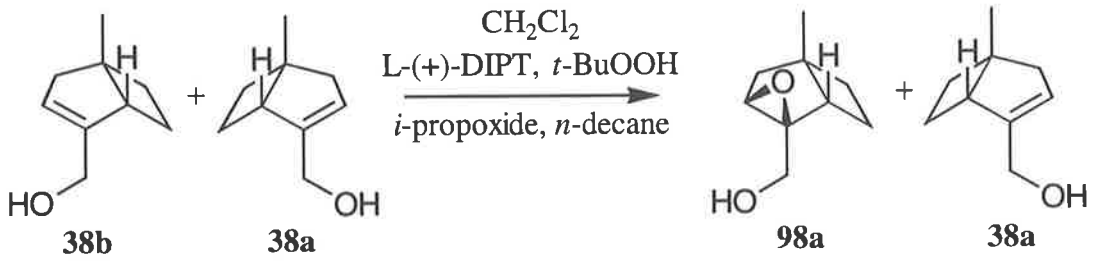
Figure 46

An increase in selectivity as the temperature is lowered is expected. Lowering the temperature decreases the rate of the reaction and increases its selectivity.[44] The two different results for the reaction run at –20°C are probably due to contamination by water in the first experiment. As such, they show that water has a extensive influence on the enantiomeric excess of the reaction and how crucial it is that the reaction technique is perfected.

The optimum conditions for the kinetic resolution reaction are as follows. It is essential that the dichloromethane is freshly dried, otherwise the optical purity of the substrate and the product will be reduced. The dichloromethane solution of the alcohol and *n*-decane must be dried over activated 3Å sieves for at least 30 minutes prior to addition. The *tert*-butyl hydroperoxide solution also needs to be dried over activated 3Å sieves for at least 15 minutes. The solution of titanium *i*-propoxide, the tartrate, *tert*-butyl hydroperoxide and 4Å sieves needs to be aged at –20°C for at least one hour, the reaction mixture is then cooled to the desired temperature and the solution of *n*-decane and allylic alcohol is then added. Best results are achieved when the

amount of *tert*-butyl hydroperoxide is limited to ~0.6 mol % and the reaction is not followed by GC, eliminating the possibility of water contamination. The best conditions found for the reaction are carefully recorded in the experimental section and it is recommended they are followed.

It is presumed in the kinetic resolution reaction that attack will preferentially come from the top face, hence, the configuration of the optically enriched allylic alcohol is that shown, i.e. represented by **38a**. (Scheme 82).



38b **38a** **98a** **38a**

Scheme 82

The optically active allylic alcohol used in the complete synthesis of grandisol had an estimated enantiomeric excess of greater than 95% and an optical rotation of $[\alpha]_D^{20}$= -1.77 ± 0.2[¢] (c= 1.5 CH_2Cl_2).

Section 3.1.4 Enantiomeric Purity Determination

As previously discussed in this chapter, formation of the MTPAA esters (Mosher esters) could be used for estimation of optical purity.

The ^{1}H NMR spectrum of the racemic and optically active Mosher esters from the kinetic resolution reaction at –20°C and –40°C are reproduced in Figure 47. Figure 47(a) shows the AB quartet region of the ^{1}H NMR spectrum. It can be seen from Figure 47(a) that the resonance of the racemic Mosher esters is two overlapping AB quartets. The diastereomeric excess of the optically active Mosher esters was determined by cutting and weighing peak A' and peak B'. From Equation 1, p. 19, it was found that peak A' needed to be multiplied by a

[¢] The error in the optical rotation value was calculated from the deviation in the values obtained from the polarimeter.

scaling factor of 1.98. An estimate of the diastereomeric excess could then be made by use of Equation 3. When peak A' could not be detected the enantiomeric excess was estimated to be >95%.

$$EE\% = \left[\frac{B'}{1.98A' + B'} + \frac{1.98A'}{1.98A' + B'}\right] \times 100$$

Equation 3

As separation of the methoxyl resonances is not baseline they are only used as a confirmation of the enantiomeric excess calculated, and it appears to correspond with the enantiomeric excess determined from the AB quartet resonance. (Figure 47(b)) However, it should be noted that the enantiomeric excess of the allylic alcohol **38** determined by this method is only an estimate. It is hoped that later in the synthesis an accurate method to determine the optical purity of one of the intermediates will be found.

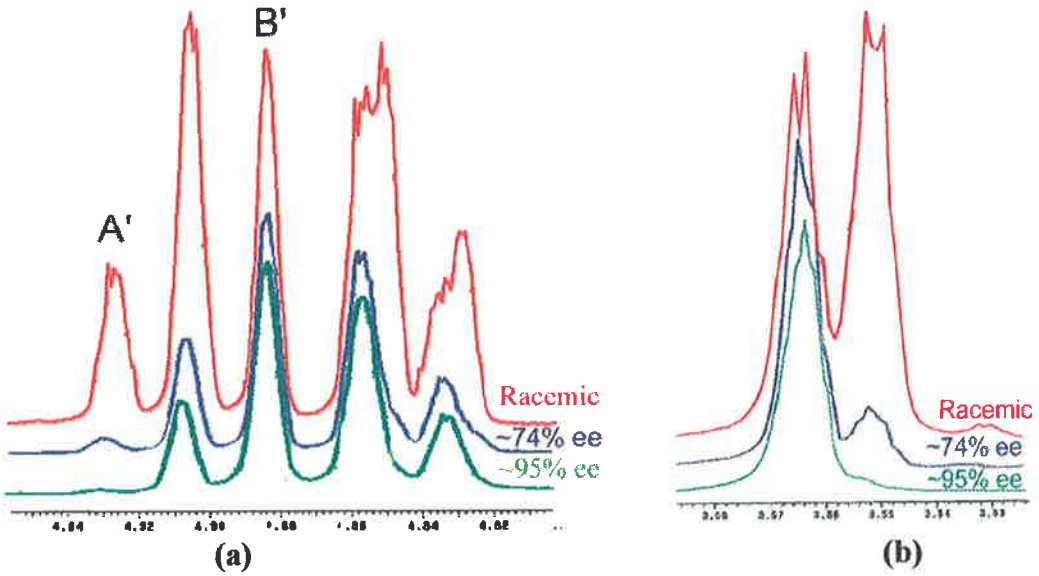
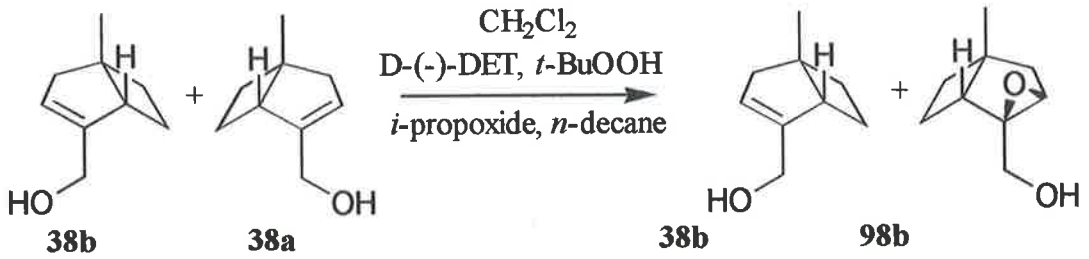


Figure 47[ξ]

The determination of optical purity of the allylic alcohol **38**, by integration of the AB quartets of the diastereotopic Mosher ester derivatives, relied on the fact that the diastereomeric resonances were indeed AB quartets. By Figure 47(a) this appears to be the case, but our initial interpretation may be incorrect, it should be proven beyond doubt.

[ξ] The enantiomeric excess referred to are those of the allylic alcohol **38**.

Hence, the kinetic resolution reaction was repeated with D-(-)-DET, (no D-(-)-DIPT was avaliable in these laboratories) the tartrate has the opposite configuration to that previously used (Scheme 83). The Mosher esters of the optically enriched allylic alcohol from the kinetic resolution reaction with D-(-)-DET should have the opposite configuration to the Mosher ester obtained previously.



Scheme 83

The kinetic resolution reaction with D-(-)-DET was taken to 85% completion and the enantiomeric excess of the resolved substrate was 94%. The ^{1}H NMR spectrum of the racemic Mosher ester and the optically active Mosher esters from the kinetic resolution reaction with L-(+)-DIPT and D-(-)-DET are reproduced in Figure 48. It is concluded that the resonances due to the diastereotopic protons of the methylene group bearing the oxygen are both AB quartets, and our method for determination of the enantiomeric excess of the allylic alcohol is valid.

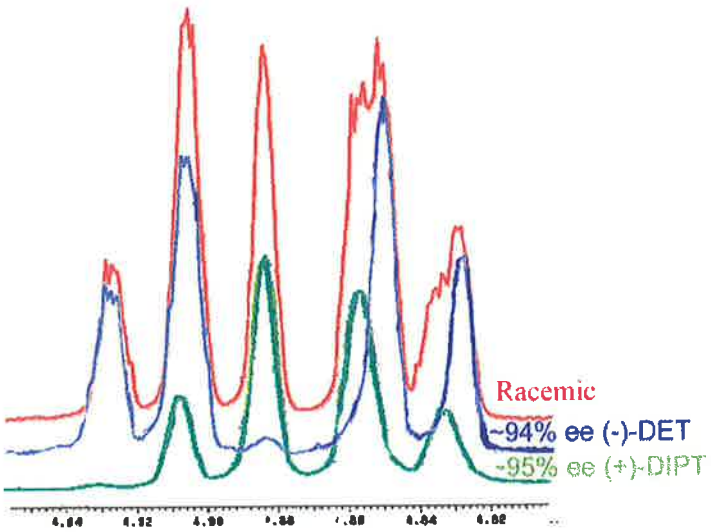
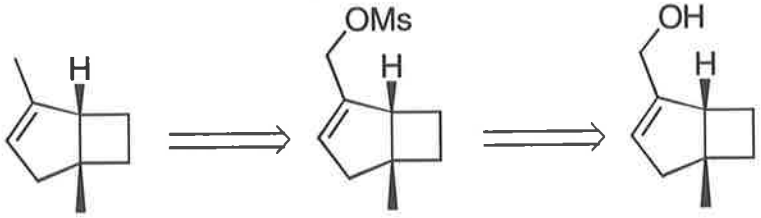


Figure 48

Section 3.2 Formation of the Bicyclic Alkene

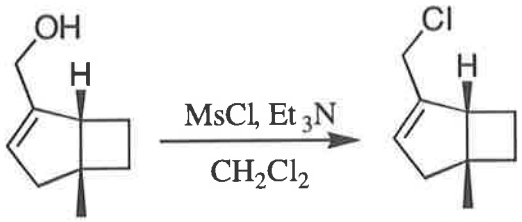
The next step in the synthesis was conversion of the optically active allylic alcohol **38** to the corresponding bicyclic alkene **10**. It was proposed that reduction of the mesylate **100** would give the bicyclic alkene **10** in good yield (Scheme 84).



10 **100** **38**

Scheme 84

Reaction of the racemic allylic alcohol **38r** with methanesulfonyl chloride gave the chloride **101r** in a 20% yield after purification by chromatography (Scheme 85).



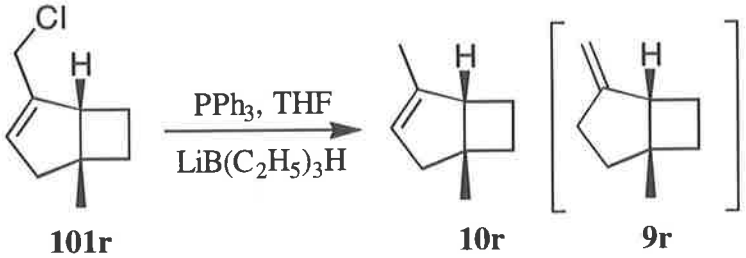
38r **101**

Scheme 85

The ^{1}H NMR spectrum of the product shows a 3H singlet at δ1.29 due to the methyl group. The methylene ring protons resonate as a 4H complex between δ1.5-2.1 and a 2H complex between δ2.2-2.6. An allylic proton resonates as a broad doublet at δ2.88, with a coupling constant of 8 Hz. A 2H AB quartet resonates at δ4.17 and there is a broad 1H multiplet at δ5.78. The product **101r** was unstable and decomposed at ambient temperature after a few hours.

Reduction of the racemic allylic chloride **101r** was attempted with lithium triethylborohydride in the presence of triphenylphospine [100] (Scheme 86). The ^{1}H NMR spectrum of the crude product showed the presence of triphenylphosphine and numerous solvent impurities. However, there was an olefinic peak at δ5.28 that corresponds to the literature value for the olefinic resonance of the *endo*cyclic alkene **10r**.[26] No resonance could be seen for the *exo*cyclic

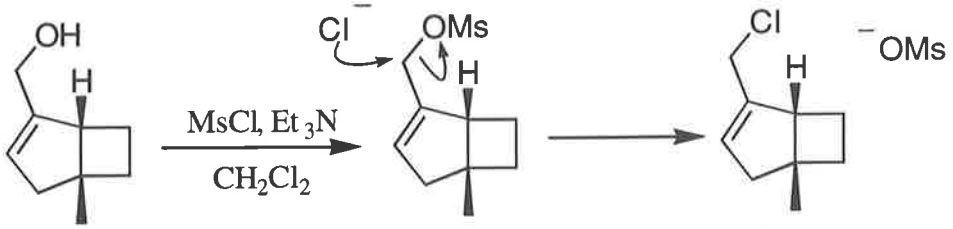
alkene **9r**. Due to its volatility, the *endo*cyclic alkene was not be isolated from this small scale reaction.



101r **10r** **9r**

Scheme 86

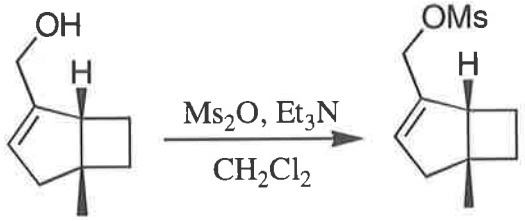
It is presumed the allylic chloride **101** is formed by a nucleophilic substitution by the chloride anion on the mesylate **41r** [101] (Scheme 87). This problem can be avoided if methanesulfonic anhydride is used as the reagent, instead of methanesulfonyl chloride.



38r **100r** **101r**

Scheme 87

Reaction of the racemic allylic alcohol **38r** with methanesulfonic anhydride gave the desired mesylate **100r** in a yield of 78% after purification by chromatography (Scheme 88).



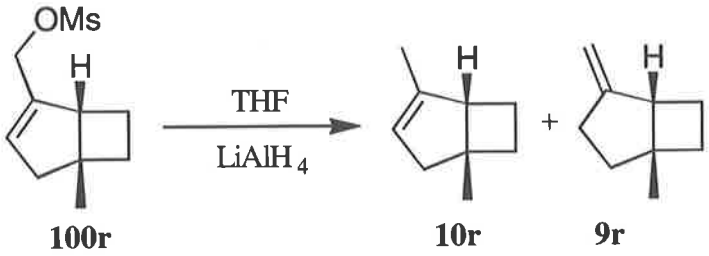
38r **100r**

Scheme 88

The ^{1}H NMR spectrum of the mesylate **100r** shows a 3H singlet at δ1.29 due to the methyl group on the bicyclic ring. The methylene ring protons resonate as a 3H complex between δ1.4-2.0 and a 3H complex at δ2.33 and a 1H multiplet at δ2.78. The sharp 3H singlet at δ3.00 is due to the methyl group of the mesylate. The protons adjacent to the mesylate group do not

show their diastereotopic nature as they exhibit a 2H singlet at δ4.79. The olefinic proton resonates as a broad singlet at δ5.85.

The mesylate **100r** was reduced to the *endo*cyclic alkene **10r** with lithium aluminum hydride in THF. (Scheme 89).

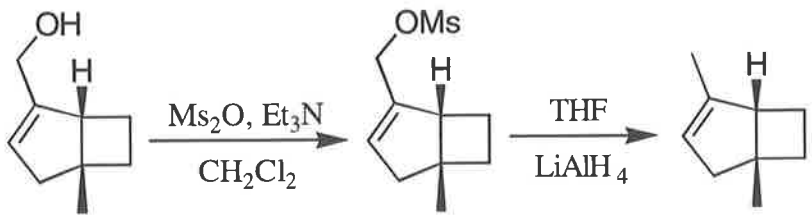


100r **10r** **9r**

Scheme 89

When the mesylate **100r** was purified, the ^{1}H NMR spectrum of the crude material revealed that a very clean reaction had taken place. However, if the crude mesylate is used numerous by-products are formed. The ^{1}H NMR spectrum was identical to that reported for the *endo*cyclic alkene **10r**.[26,30] GLC analysis of the product from the clean reaction 'spiked' with a pure sample of the *exo*cyclic alkene **9r** (previously formed as described in 'Chapter 2, Results and Discussion') gave only one broad peak, other than the solvent peak. However, the ^{1}H NMR spectrum did not show the *exo*cyclic alkene, diagnostic by the presence of two signals at δ4.55 and δ4.67. Hence, the *endo*cyclic alkene **10r** was the only product of the reaction. This is important because if all of the solvent was removed and the *endo*cyclic alkene was purified a yield of only ~20% was obtained. This low yield was presumably due to the volatility of the *endo*cyclic alkene **10r**. For this reason, the *endo*cyclic alkene **10r** was used with dichloromethane present and without purification in the next reaction.

Repetition of the above two reactions on the optically active allylic alcohol **38a** gave the optically active alkene **10a**. (Scheme 90).



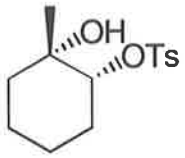
38a **100a** **10a**

Scheme 90

The optically active mesylate **100a** was formed in a yield of 78% after purification by chromatography. The optically active *endo*cyclic alkene **10a** was not isolated and used with solvent impurity in the next step.

Section 3.2.1 Optical Purity of the Bicyclic Alkene

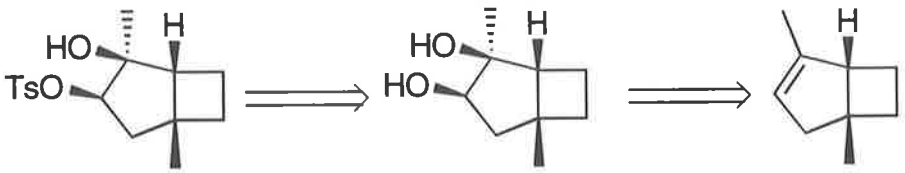
Although it is unlikely that racemisation could occur during either of these steps it is still of interest to see if the optical purity of the allylic alcohol **38a** had been maintained in the *endo*cyclic alkene **10a**, and to confirm the earlier estimate. From previous experience,[61] it is known that the enantiomeric excess of the tosylate **48** can be determined by chiral shift NMR experiments ('Chapter 5, Results and Discussion'). (Figure 49).



48

Figure 49

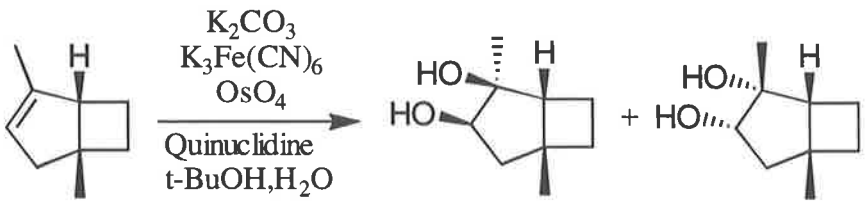
This could also possibly apply to the bicyclic tosylate **102**, which could be formed from the *endo*cyclic alkene **10** via the bicyclic diol **103** (Scheme 91).



102 **103** **10**

Scheme 91

A Sharpless dihydroxylation reaction on the racemic *endo*cyclic alkene **10r**, with quinuclidine,[46] an achiral ligand gave the required racemic diol **103r** in a 60% yield after chromatography (Scheme 92). It is presumed attack of the osmate ester will preferentially come from the top face, to give the isomer with the hydroxyl groups *cis* to the methyl **103r** as the major product. The ^{1}H NMR spectrum showed only one diastereomer, presumed to be the diol **103r**.

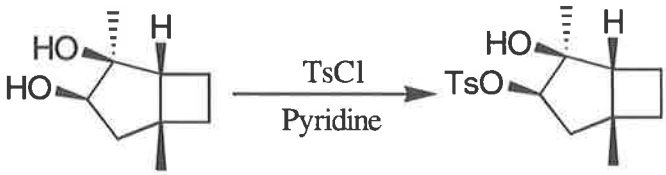


10r **103r** **104r**

Scheme 92

The ^{1}H NMR spectrum of the diol **103r** shows a two 3H singlets due to the methyl groups, one at δ1.20 and the other at δ1.22. A 7H complex between δ1.4-2.2 is due to the methylene protons. The methine proton adjacent to the hydroxyl group resonates as a doublet of doublet at δ4.19, with coupling constants of 7 and 10.5 Hz.

Reaction of the diol **103r** with tosyl chloride[102] gave the corresponding tosylate in an 85% yield (Scheme 93).The ^{1}H NMR spectrum shows three sharp 3H singlets, at δ1.12 and δ1.19 due to the methyl groups on the bicyclic ring and at δ2.45 due to the methyl of the tosylate group. The methylene envelope occurs as a 4H complex at δ1.6-1.8 and a 2H complex at 1.9-2.2. The methine proton adjacent to the hydroxyl group exhibits a 1H doublet of doublets at δ4.85, with coupling constants of 7 and 10.5 Hz. The aromatic AA' BB' signals appear as two 2H doublets at δ7.35 and δ7.81, which couple to each other with a coupling constant of 8 Hz.

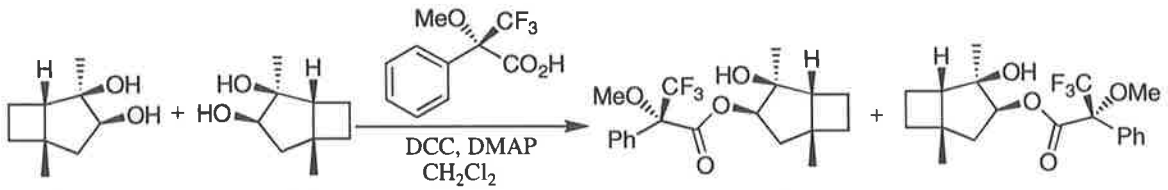


103r **102r**

Scheme 93

Separate chiral shift ^{1}H NMR experiments with tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium (III) derivative on both the racemic tosylate **102r** and the racemic free diol **103r** gave no useful separation of resonances.

Hence, reaction of the racemic diol **103r** with (+)-α-Methoxy-α-(trifluoromethyl)phenylacetic acid to give the corresponding racemic MTPAA esters (Mosher esters) **105** and **106** was attempted (Scheme 94).



Scheme 94

The ^{1}H NMR spectrum of these Mosher esters **105** and **106** at 600MHz shows the appearance of two diastereomers, in a 1:1 ratio, and can be described as follows. Two sharp singlets occur at δ1.10 and 1.20 due to one of the methyl groups, the other methyl group resonates at δ1.25 for one diastereomer and δ1.27 for the other diastereomer. The separation of all four methyl resonances is baseline, however resonances for the ring protons also occur in this region. The ring protons of both diastereomers resonate as a complex from δ1.1-2.2. For both diastereomers, one of the allylic protons resonates as a multiplet at δ2.62. The methoxyl group from each diastereomer appears as a broad singlet, for one diastereomer it resonates at δ3.55 and the other at δ3.57. The separation is baseline, but because this region could be contaminated with reagent signals, it was only used for confirmation of the enantiomeric excess. The proton adjacent to the secondary hydroxyl group appears as a doublet of doublet. In one diastereomer this is at δ5.38, with coupling constants of 7 and 11 Hz and the in the other at δ5.44, with coupling constants of 6.5 and 11 Hz. At 600 MHz the separation of these resonances is clearly baseline, as can be seen in Figure 51, and this can be used for the determination of optical purity. The aromatic protons appear as a complex at δ7.35-7.55.

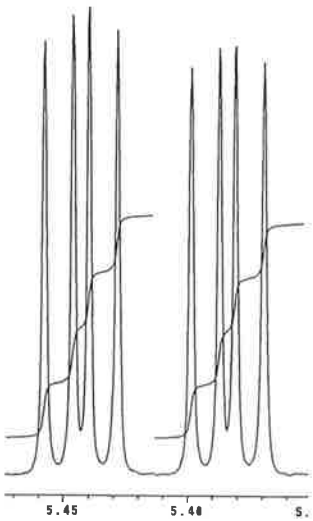
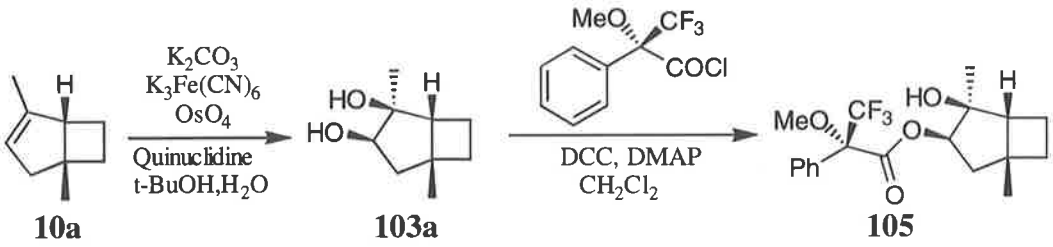


Figure 51

Repetition of the above two reactions on a sample of the optically active alkene **10a** obtained from the allylic alcohol **38a** with an enantiomeric excess of ~85%, as estimated by the method described earlier gave the corresponding optically active Mosher ester **105** (Scheme 95).



10a **103a** **105**

Scheme 95

The optically active diol **103a** was formed in a yield of 60% after purification by chromatography and the optically active Mosher ester **105** was formed in a yield of 63%. The ^{1}H NMR spectrum of the optically active Mosher ester **105** showed that the optically purity of the allylic alcohol had been maintained. Figure 52 shows two doublet of doublets, due the protons adjacent to the secondary hydroxyl group, for each diastereomer. From the inte-gration for these two areas an enantiomeric excess of 86% is obtained. This confirms that the earlier estimates of the optical purity of the allylic alcohols is reliable and that this level of optical purity has been retained.

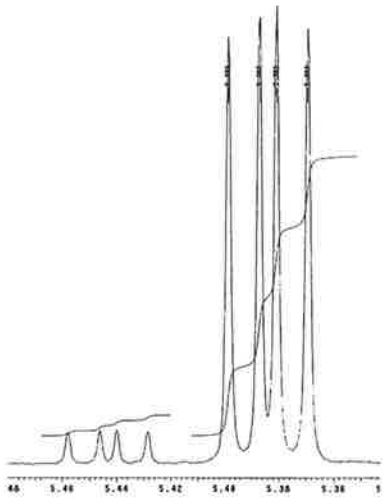
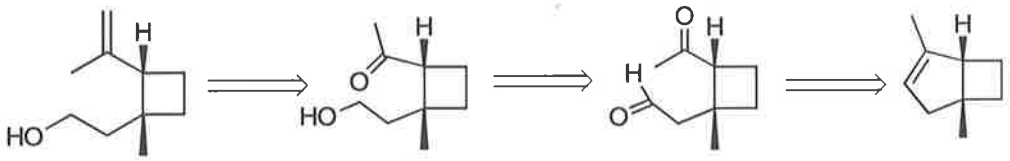


Figure 52

With a viable route for the formation of the optically active bicyclic alkene **10a** the formation of grandisol **1** was thus attempted.

Section 3.3 Attempted Formation of Grandisol via the Ketal

Initially the formation of grandisol **1** was attempted via the ketal **107** (Scheme 96). Reductive cleavage of the bicyclic alkene **10** should give the ketal **107** in one step. Selective reduction of the aldehyde in preference to the ketone, possibly at low temperature, would then give the ketol **108**. A Wittig reaction on the ketol should then give grandisol **1**.

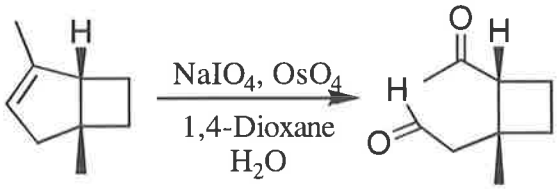


1 **108** **107** **10**

Scheme 96

The racemic ketal **107r** has been made previously by *Rosini*.[29] A reductive ozonolysis reaction on a mixture of the racemic *endo*cyclic alkene **10r** and the *exo*cyclic alkene **9r** gave the racemic ketal **107r** and the racemic bicyclic ketone **12r**. However, due to the non-availability of an ozonolysis machine in these laboratories the required procedure needed to be modified.

Reductive cleavage of the racemic bicyclic alkene **10r** was attempted by modification of a literature procedure.[103] Reaction of the bicyclic alkene **10r** with sodium periodate and osmium tetroxide gave the desired ketal **107r** (Scheme 97), identified by comparison of the ^{1}H NMR spectrum of the crude product and literature values. However, numerous unidentifiable products were also formed and the yield of the ketal **107r** was low. Varied concentrations did not change the outcome of this reaction, and due to the lack of time and success, this reaction was discarded.

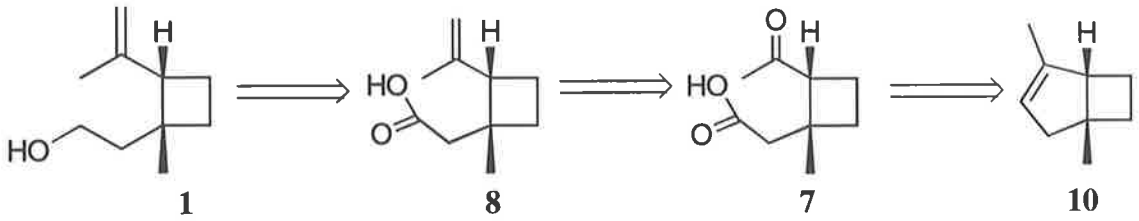


10r **107r**

Scheme 97

Section 3.4 Formation of Grandisol via the Keto-Acid

Formation of optically active grandisol **1** was then attempted via the keto-acid **7** with use of the procedures reported by *Rosini*[30] and *Webster* and *Silverstein.*[31] Grandisol **1** can be formed in three steps from the bicyclic alkene **10** (Scheme 98).

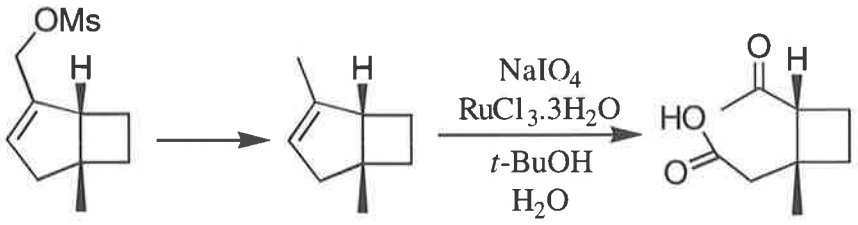


1 **8** **7** **10**

Scheme 98

Initially the reaction conditions were attempted with the racemic compound so as not to waste the valuable optically active alkene **10a**.

Reaction of the racemic bicyclic alkene **10r** (with some solvent impurity present) with sodium periodate and ruthenium chloride gave the keto acid **7r** in a 50% yield from the mesylate **100r**, two steps (Scheme 99). However, the reported procedure of *Rosini*[30] needed to be slightly modified. After the reaction was stirred at ambient temperature for 30 min, the ^{1}H NMR of the crude product showed the presence of the keto acid **7r**, but also the presence of the ketal **107r**, identified by the resonance at δ9.69. When the reaction was heated at 40°C for 15 hours no aldehyde product was observed. The small impurities present could not be removed by chromatography, but fortutiously they did not affect the next step of the reaction. Except for small impurity peaks the ^{1}H NMR spectrum of the keto acid **7r** corresponded to that previously reported in the literature.[30,31]



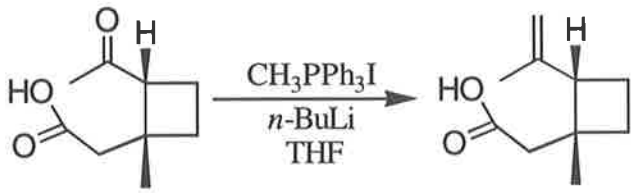
100r **10r** **7r**

Scheme 99

Purification of the keto acid **7r** was attempted *via* a base extraction, however some epimerisation adjacent to the keto group occurred. This was identified by the appearance of a

methyl peak at δ1.13, and a triplet at δ3.21 in the ^{1}H NMR spectrum of the product. This method of purification of the keto acid **7r** may be usable if extreme care was taken so the pH of the mixture did not exceed 11-12. This conclusion is based on the fact that no epermisation of the keto acid 7 occurs during a Wittig reaction with the ylid $Ph_3PCH_2^-$.

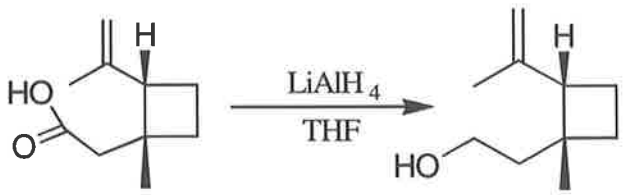
A Wittig reaction of the racemic keto acid **7r** using the procedure of *Webster* and *Silverstein*[31] gave, in a 76% yield (lit.[31] 68%), the corresponding racemic acid **8r** without epimerisation. (Scheme 101). After purification by chromatography a white solid was obtained with a melting point of 46-47°C. The ^{1}H NMR spectrum corresponded to that of the acid **8r** previously reported in the literature.[30,31]



7r **8r**

Scheme 100

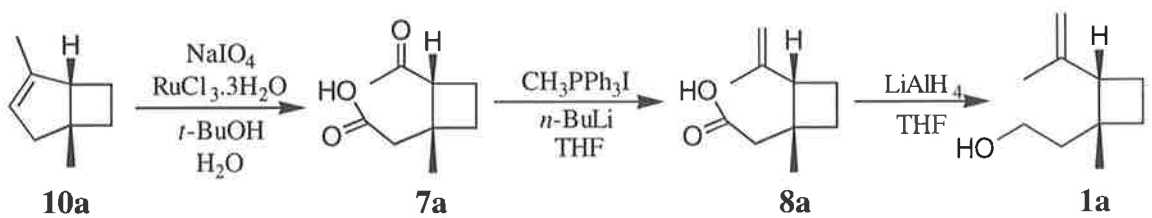
Following the conditions of *Webster* and *Silverstein*,[31] reduction of the acid **8r** with lithium aluminum hydride gave, in a 70% yield (lit.[31] 70%), racemic grandisol **1r**. The ^{1}H NMR spectrum corresponded to that previously reported in the literature.[30,31]



8r **1r**

Scheme 101

After the best conditions for the above reactions were determined, the optically active alkene **10a** was converted to optically active grandisol **1a**. (Scheme 102).



10a **7a** **8a** **1a**

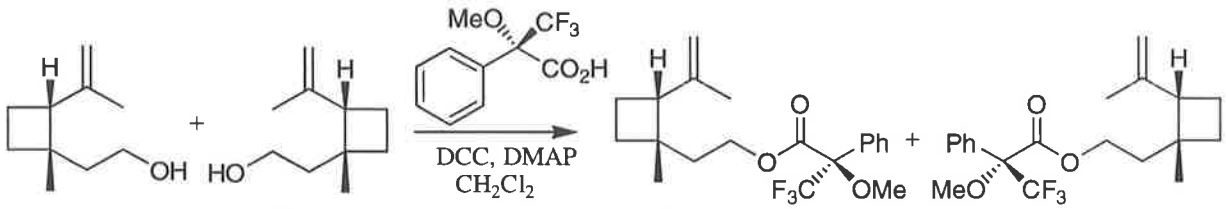
Scheme 102

Reaction of the solution of the optically active alkene **10a** in dichloromethane with sodium periodate and ruthenium trichloride gave the corresponding keto acid **7a** in a 54% yield over the two steps, from the mesylate **100a**. Purification of the acid by chromatography was incomplete. Small impurities remained in the light brown oil. This oil had a an optical rotation of $[\alpha]_D^{20}$= -28.0 ± 2[ø] (c= 2.58 CH_2Cl_2) [Lit. $[\alpha]_D^{20}$= -41.0 (c= 8.446 EtOAc)].[6]

A Wittig reaction on the optically active keto acid **7a** gave, in a 62% yield after purification by chromatography, the acid **8a**. The ^{1}H NMR spectrum of the optically active compound was identical to the racemic compound and is reproduced in the 'Appendix'. The white crystalline solid had an optical rotation of $[\alpha]_D^{20}$= +94.6 ± 2[ø] (c= 1.08 CH_2Cl_2).

Reduction of the acid **8a** gave optically active grandisol **1a** in a 95% yield. The ^{1}H NMR spectrum of the optically active compound was identical to the racemic compound and is reproduced in the 'Appendix'. The colourless oil had an optical rotation of $[\alpha]_D^{20}$= +20.4 ± 2[ø] (c= 1.2 *n*-hexane) [Lit. $[\alpha]_D^{20}$= +18.4 (c= 1.1, *n*-hexane)[31], $[\alpha]_D^{24.2}$= +20.5 (c= 0.585, *n*-hexane)[104]]. The optical rotation of this synthetic grandisol **1a** formed corresponds with that of the natural product. Consequently, it can be said without doubt that attack in the Sharpless epoxidation reaction does preferentially come from the top face and the products from the allylic alcohol **38** have configuration shown.

The Mosher ester of grandisol **1** was formed to determine the optical purity of the final product. This is the method used by *Mori*.[104] Reaction of both racemic grandisol **1r** and optically active grandisol **1a** with (+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid gave the corresponding MTPAA esters (Mosher ester) **109** and **110** (Scheme 103).



1a **1b** **109** **110**

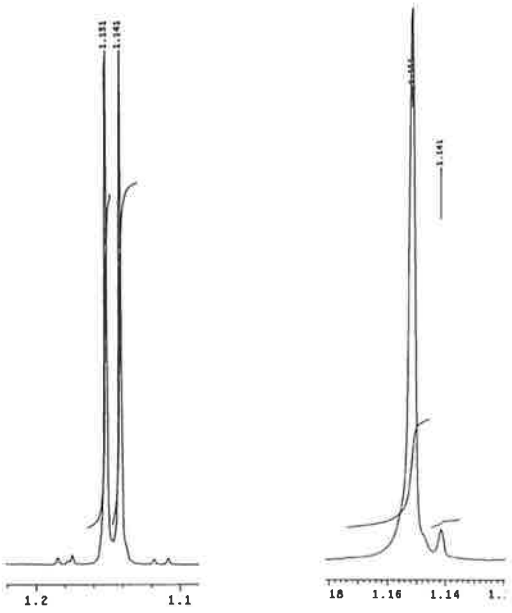
Scheme 103

[ø] The error in the optical rotation value was calculated from the deviation in the values obtained from the polarimeter.

The ^{1}H NMR spectrum of the racemic Mosher esters **109** and **110** at 600MHz shows the appearance of two diastereomers, in a 1:1 ratio, and can be described as follows. Two sharp singlets occur at δ1.14 and δ1.15 due to the methyl groups of the bicyclic ring, the separation is baseline as can be seen in Figure 52a, and provides a method for analysis of optical purity. The allylic methyl group resonates at δ1.64 for one diastereomer and δ1.65 for the other. The separation of both methyl resonances is baseline, however resonances for the ring protons also occur in this region. The ring protons of both diastereomers resonate as a complex from δ1.4-2.0. For both diastereomers, the methine proton resonates as a triplet at 2.58, the methoxyl group from both diastereomers appears as a singlet at δ3.55. The protons adjacent to the ester moiety appear as a complex, from which no useful information can be obtained. The olefinic protons resonate as two broad doublets at δ4.37 and δ4.64. The aromatic protons appear as a complex at δ7.35-7.55.

The 600 MHz ^{1}H NMR spectrum of the racemic Mosher ester is reproduced in the 'Appendix'. The enantiomeric excess of optically active grandisol **1a** was determined to be 94±2%, by cutting and weighing the methyl resonances (Figure 52b). This was prepared from optically active allylic alcohol **38** of an estimated enantiomeric excess of 95%.

Figure 52a shows the methyl region at ~δ1.15 of the racemic Mosher ester of grandisol **1r**. Figure 52b shows the methyl region at ~δ1.15 of the optically active Mosher ester of grandisol **1a**.



a) b)

Figure 52

Consequently, a new asymmetric synthesis of optically active grandisol **1a** has been accomplished which uses catalyst-controlled methods. The key intermediate **38r** can be formed in four steps and in a 57% yield from commercially purified material. A kinetic resolution of the key intermediate **38r** gives material which could, in principle, have an enantiomeric excess as high as almost 100%, if one is willing to sacrifice yield. However, it has been shown that the allylic alcohol **38a** can be formed in greater than 95% enantiomeric excess when the kinetic resolution is taken to 60% conversion. A route for formation of the optically active bicyclic alkene **10a**, exclusive of the *exo* isomer, has been found. Conversion of the bicyclic alkene **10a**, by the procedures of *Rosini*[30] and *Webster* and *Silverstein*[31], gives (+)-grandisol in good yield.

This synthesis gave the naturally occurring enantiomer (+)-grandisol **1a** in 10 steps from commercially available achiral starting materials.

CHAPTER 4

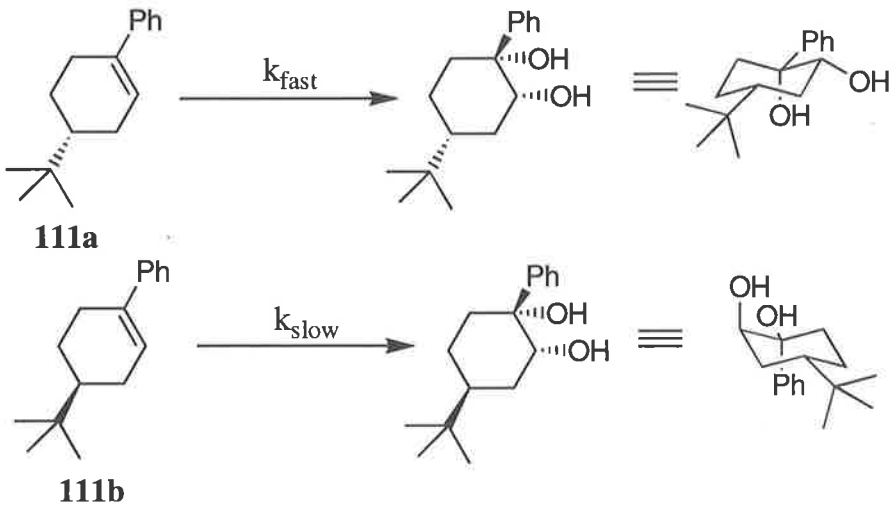
RESULTS AND DISCUSSION

KINETIC RESOLUTIONS WITH THE SHARPLESS DIHYDROXYLATION REACTION

Section 4.1 Previous Work

During the time this work was in progress, three important results concerning kinetic resolutions by the Sharpless asymmetric dihydroxylation reaction were discovered.

In an attempt to synthesize a new chiral auxiliary, *Hamon* and *Christie* attempted a kinetic resolution on substrate **111**.[105] It was reasoned, due to the high enantioselectivity shown by 1-phenylcyclohexene in the asymmetric dihydroxylation reaction, that alkene **111** might also react enantioselectively with the reagent. If the reagent were AD-mix-β, by Sharpless' mnemonic,[45] both alkenes would be dihydroxylated from below, to give the corresponding diols (Scheme 104). Due to the tertiary butyl substituent one of the diols has an equatorial phenyl group while the other has this group axial. It was proposed that if the transition state for the rate determining step was product like then the rate at which the two enantiomers react might be significantly different and a kinetic resolution could result.[105]



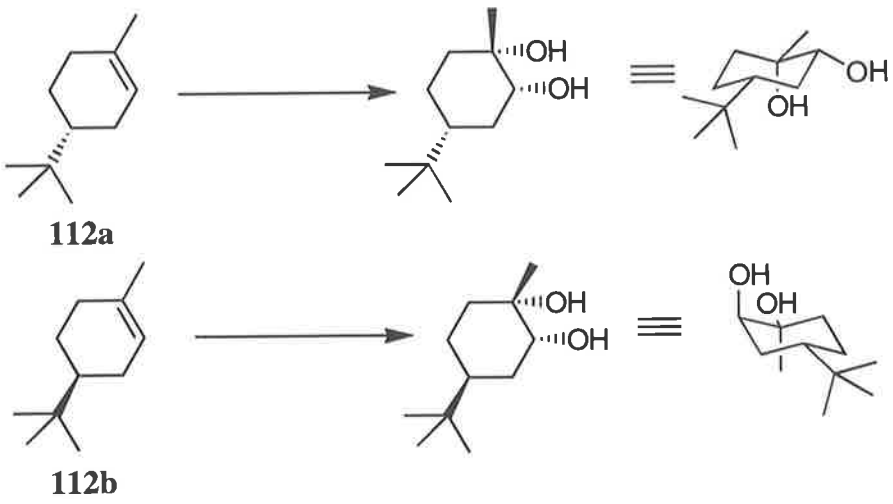
AD-mix-β

Scheme 104

However, it was found that the relative rates of reaction of the enantiomeric alkenes were of the order of $k_{fast}/k_{slow} = 2$. Although, when an excess of oxidant is used the two diols form in a

one to one ratio and the enantiomeric excess of both is very high. An early rather than a late transition state appeared to be consistent with the result.[105]

The same reaction was applied by *Hamon, Christie* and *Kennedy* to the asymmetric dihydroxylation of the alkene **112**.[106] Reaction of the alkene **112** with excess oxidant gave the corresponding diols in high enantiomeric excess (>90% e.e.) (Scheme 105). 1-Methylcyclohexene shows a relatively poor enantioselectivity in the asymmetric dihydroxylation reaction (~52% e.e.),[45, 61] and it is surprising therefore that the two diols from the reaction of alkene **112** are formed in high enantioselectivity.



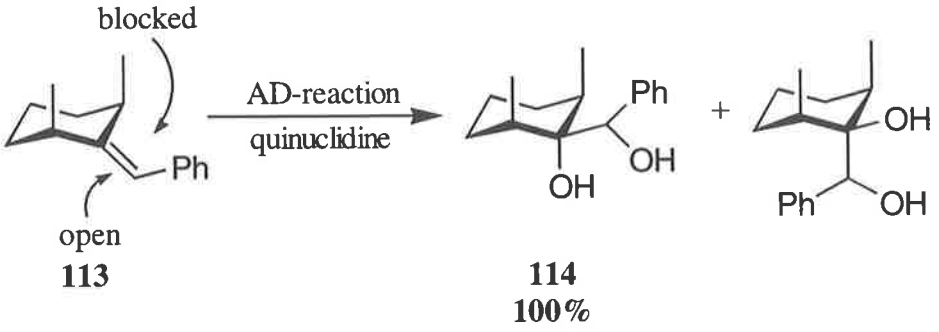
112a

112b

AD-mix-β

Scheme 105

An effective kinetic resolution, with an early transition state reaction, would require some other condition to favour reaction of one enantiomer in preference to the other. This could be achieved if the starting alkene had a steric barrier, which would direct attack of the reagent to only one face. *Gardiner et al.* discovered that reaction of the alkene **113** with quinuclidine (used in place of the enantiomerically pure chiral ligand in the AD reaction) gave exclusively attack from the bottom face, *trans* to the methyl groups, resulting in only one diastereomer forming **114** [107] (Scheme 106).



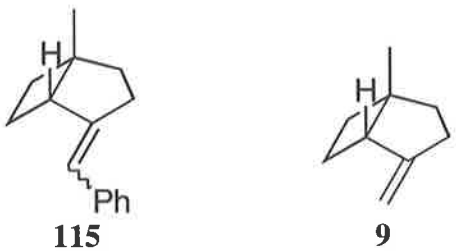
113 **114** **100%**

Scheme 106

Reaction with $(DHQD)_2$-PHAL as the chiral ligand gave the diol **114** in an optimum enantiomeric excess of 86%, with only a 40% conversion. Its enantiomer was obtained in ≥ 95% enantiomeric excess when $(DHQ)_2$-PHAL was the chiral ligand. Based on the diastereomeric outcome it was rationalized that the results are consistent with substrate control of the dihydroxylation *anti* to the two-diaxial methyl groups, but matched with catalyst facial selectivities based on Sharpless's mnemonic.

Section 4.2 Proposed Alkene's

The bicyclic alkenes **115** and **9** might shed some insight to the requirements required for a highly selective kinetic resolution (Figure 53).The product from cleavage of the double bond in either alkene could then be used to synthesize optically active grandisol **1**. From previous experiments ('Chapter 2 and Chapter 3'), it has been shown that the top face of the bicyclic ring system is relatively open to attack whereas the bottom face is essentially closed. The E or Z isomer of the alkene **115** is similar to the substrate of *Gardiner*[107] and may result in a highly selective kinetic resolution.

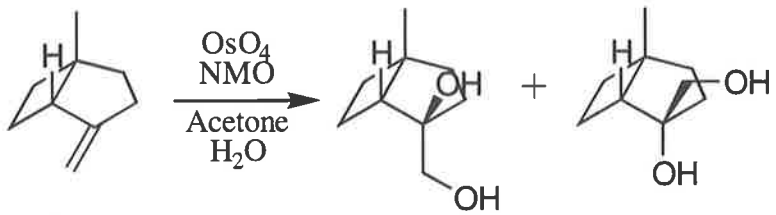


115 **9**

Figure 53

Section 4.2.1 Dihydroxylation Conditions on the Di-Substituted Alkene

The alkene **9** has been previously synthesized as described in 'Chapter 2, Results and Discussion'. Initially the racemic diol was formed by modification of *VanRheenen's* general procedure.[108] In theory, two possible diastereomers could form. Reaction of the alkene **9r** with osmium tetroxide and *N*-methyl morpholine *N*-oxide (NMO) gave one diol preferentially in a yield of 38%, and it is assumed to result from top face attack and is the isomer **116r** (Scheme 107).

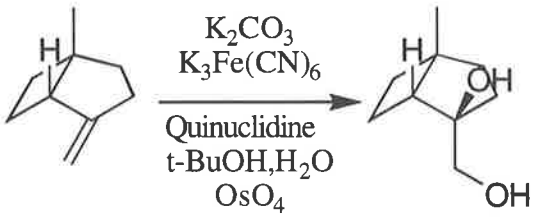


(±)-9r **(±)-116r** **(±)-117r**

Scheme 107

The ^{1}H NMR spectrum of the diol shows a singlet at δ1.26 due to the methyl group, the ring protons appear as an unresolved complex in the region of δ1.3-2.2. A poorly resolved signal at δ3.61 is revealed to be an AB quartet, upon a D_2O exchange, due to the methylene protons adjacent to the hydroxyl group. There is a small AB quartet at δ3.35, presumed to be due to the methylene protons adjacent to the hydroxyl group of the minor isomer **117r** (Figure 54a).

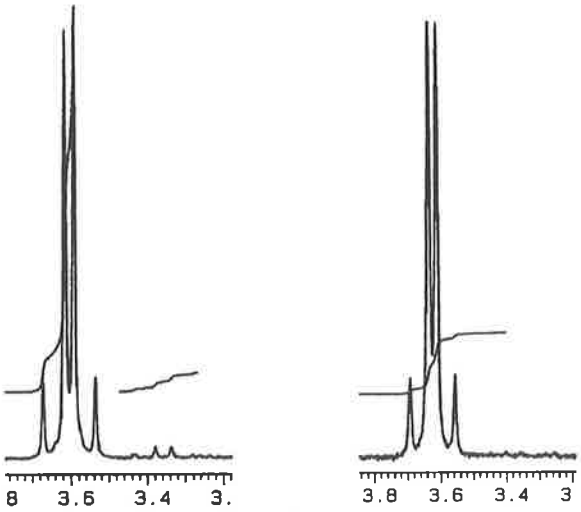
Reaction of the alkene **9r** with quinuclidine (used in place of the enantiomerically pure chiral ligand in the AD reaction) gave exclusively attack from the top face to give the diol **116r** in a 31% yield (Scheme 108) The ^{1}H NMR spectrum was identical to that of the major diol formed by *VanRheenen's* method and no minor isomer could be observed (Figure 54b).



(±)-9r **(±)-116r**

Scheme 108

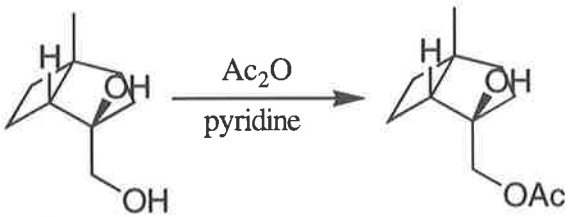
Figure 54 shows the resonances in the ^{1}H NMR spectrum due to the protons adjacent to the primary hydroxyl group. Figure 54a shows the presence of diastereomers.



a) Diol from reaction with OsO_4 b) Diol from reaction with Quinuclidine

Figure 54

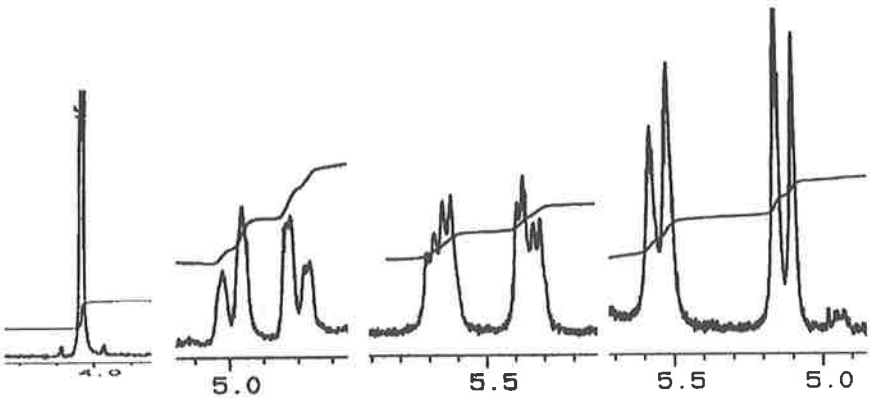
In order to test eventually the optical purity of the diol **116a** formed by the use of a chiral ligand, the corresponding mono acetate **118r** was formed (Scheme 109). The ^1H NMR spectrum of the acetate is similar to that of the diol **116r** with an additional singlet methyl peak at δ2.08 and the absence of the OH peak. In addition, the AB quartet that resonated at δ3.61 in the diol **116r** now appears as a very distorted AB system centred at δ4.15.



(±)-116r **(±)- 118r**

Scheme 109

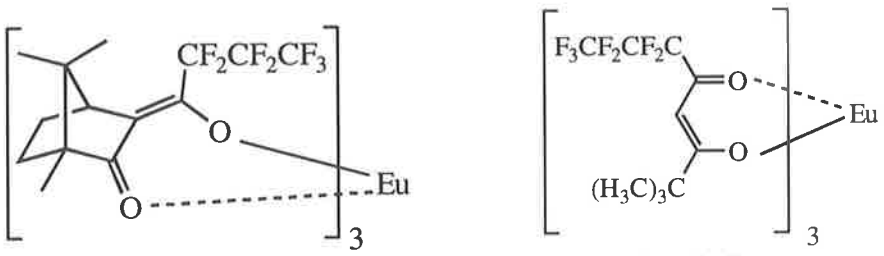
Chiral shift ^1H NMR experiments, with tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium(III), [Eu(hfc)$_3$], on the racemic acetate **118r** gave no useful separation of the acetate or ring methyl. However, it was observed, as shown in Figure 55 a, b, and c, that as the concentration of the chiral shift reagent was increased, the very distorted AB quartet initially at δ4.15 (a), became a distorted AB quartet (b), and eventually two overlapping AB quartets (c).



a) $Eu(hfc)_3$ b) $Eu(hfc)_3$ c) $Eu(hfc)_3$ d) $Eu(fod)_3$

Figure 55

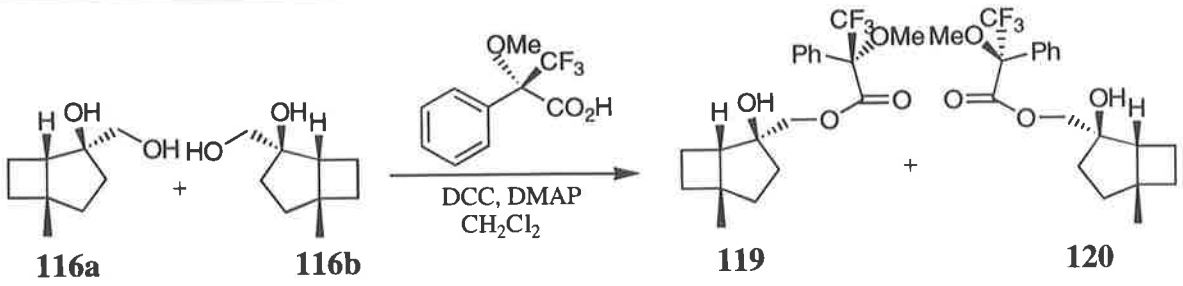
It appears that Figure 55c shows two overlapping AB quartets, but it was possible the resonance could be a doublet of doublets each due to one enantiomer. To confirm this chiral shift experiments were performed with an achiral shift reagent, $Eu(fod)_3$. Addition of the achiral shift reagent, $Eu(fod)_3$, to the racemic acetate **118r** gave one AB quartet, Figure 55d, confirming that the resonances seen in Figure 55c were two overlapping AB quartets, one from each enantiomer. The achiral shift reagent, $Eu(fod)_3$, enhances the diastereotopic differences in the molecule but will not differentiate enantiomers. Whereas, the chiral shift reagent, $Eu(hfc)_3$, differentiate the enantiomers but not to a sufficient extent to be useful to determine the optical purity of the acetate **118r**.



[Eu(hfc)$_3$] **Eu(fod)$_3$**

Figure 56

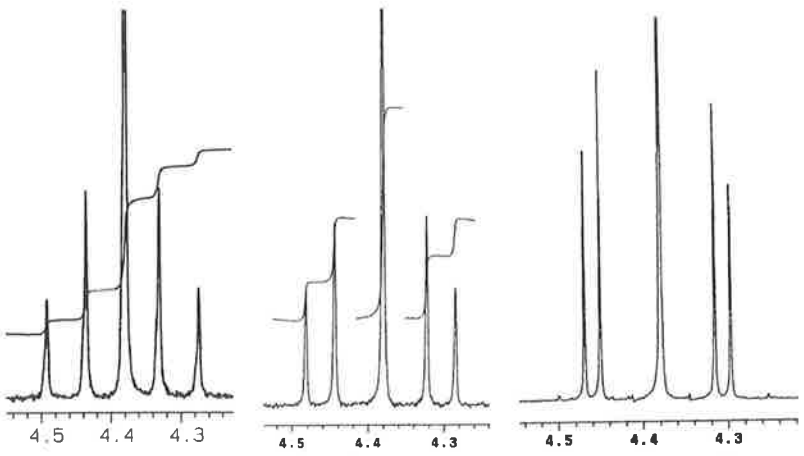
Alternatively, the racemic diol **116r** was acylated with α-methoxy-α-(trifluoromethyl)phenyl-acetic acid to give the corresponding Mosher esters **119** and **120**. (Scheme 110).



116a **116b** **119** **120**

Scheme 110

The 200 MHz ^{1}H NMR spectrum of the racemic Mosher esters **119** and **120** shows the presence of two diastereomers and can be described as follows. The two finely separated singlets at δ1.23 and δ1.25 are due to the methyl group of each diastereomer. For both diastereomers, the ring protons resonate as a complex in the region δ1.3-2.1. The methoxyl protons are coincident and appear as a broad singlet, at δ3.55, and the aromatic protons appear as a complex at δ7.35-7.55. The most useful signal in the ^{1}H NMR spectrum is the complex signal at δ4.37, as can be seen in Figure 57a. Initially it was postulated that each diastereomer resonated as an AB quartet, and the overlap of two AB quartets resulted in the complex observed. By increasing the field strength to 300 and 600 MHz, it became obvious that the methylene group of one diastereomer exhibits a very distorted AB quartet (nearly a singlet), while the other diastereomer exhibits an AB quartet (Figure 57b and Figure 57c). These resonances could be used to determine the optical purity of the diol **116**. The two methyl singlets give baseline separation at 600 MHz and could be used to confirm the optical purity of the diol **116**.

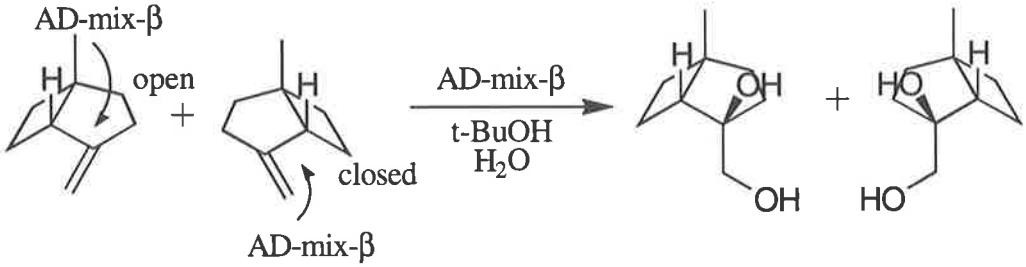


a) 200 MHz **b) 300 MHz** **c) 600 MHz**

Figure 57

It has been shown with quinuclidine that the bottom face of the alkene **9** is essentially blocked. If the alkene **9** is drawn as shown in Scheme 111, it is hoped that in the case of the alkene **9a**,

that the chiral oxidant will attack preferentially from the top face. Whereas it is hoped that in its enantiomer **9b** attack will occur from the bottom face. Although it was unlikely that the chiral reagent will be enantioselective, it was still of interest to see if the chiral reagent was diastereoselective.



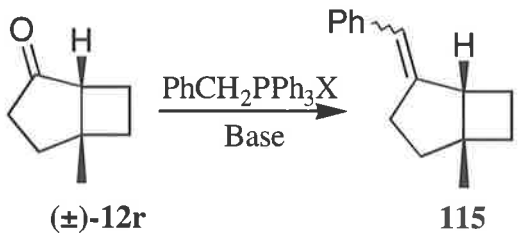
Scheme 111

Aliquot's of the reaction mixture were taken at 1, 2, 3, 5, 6 and 24-hours. All aliquots showed only one isomer, **116**, in the ^{1}H NMR spectrum of the crude product. The alkene **9** was not observed in the ^{1}H NMR spectrum due to its volatility.

Analysis of the one and 24-hour aliquots revealed that in both cases the diol isomers **116a** and **116b** had formed in a 1:1 ratio, from interpretation of the ^{1}H NMR spectrum of the Mosher ester. As expected the Sharpless dihydroxylation reaction on the bicyclic alkene **9** is not enantioselective, however, it was diastereoselective.

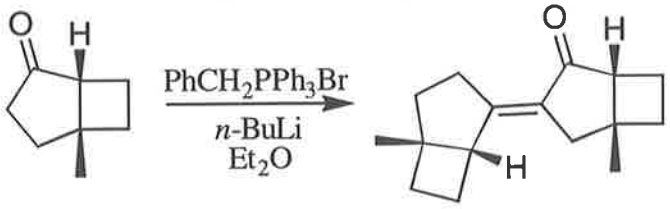
Section 4.3 Formation of the Phenyl Alkene

Using the observations of *Gardiner*,[107] the alkene **115** should be a better substrate to undergo a kinetic resolution with the Sharpless dihydroxylation reaction. The phenyl alkene **115** might be formed from the bicyclic ketone **12r** *via* a Wittig reaction, however formation of E and Z isomers would be expected but it was hoped that these diastereomers could be separated (Scheme 112).



Scheme 112

The ketone group in the bicyclic ketone appears to be more hindered than was expected and somewhat surprisingly, a Wittig reaction with the phosphorane, $Ph_3Ph^-CH_2Ph$, under various conditions did not occur. It appeared that the bicyclic ketone **12r** was too hindered and in most cases only starting material remained. Interestingly, when *n*-BuLi was used as the base, in a slight excess, the aldol product **121r** resulted (Scheme 113).The conditions used are outlined in the experimental section p. 171. Cyclopentanones are relatively acidic ketones and perhaps just an acid-base reaction was occurring in the attempted Wittig reaction.

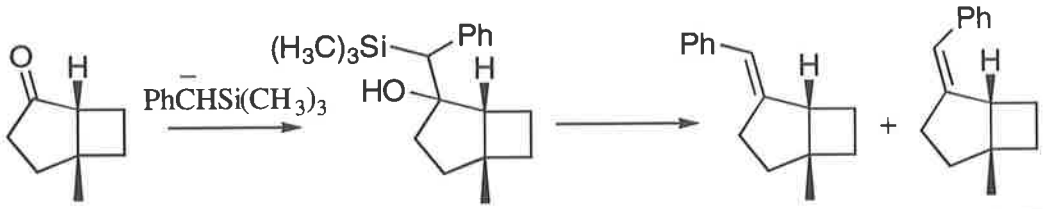


12r **121r**

Scheme 113

Section 4.3.1 Peterson Olefination Reaction

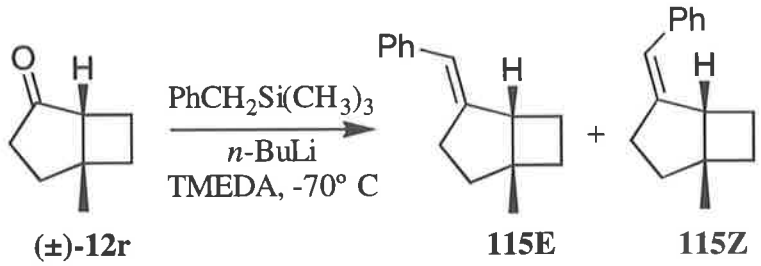
An alternative to a Wittig reaction is the Peterson olefination reaction. The Peterson olefination has been found to convert carbonyl compounds, that have enolizable hydrogens, into alkenes.[109,110] Reaction of benzylmethylidinetrimethylsilane with the bicyclic ketone **12r** should give the β-hydroxylsilane **118**, which should then give the alkene **115** after elimination (Scheme 114).



(±)-12r **118** **115E** **115Z**

Scheme 114

Reaction of the bicyclic ketone **12r** with benzylmethylidinetrimethylsilane in the solvent system of TMEDA did give the required alkenes **115** (**E** and **Z**) but only in a yield of 8% (Scheme 115).The ^1H NMR spectrum showed the presence of E and Z isomers, formed in a relative ratio of 1:1.3. Due to the low yield obtained and because the alkene was mixture of isomers, which were inseparable by normal chromatography, an alternative method for formation of the alkene **115** was sought.

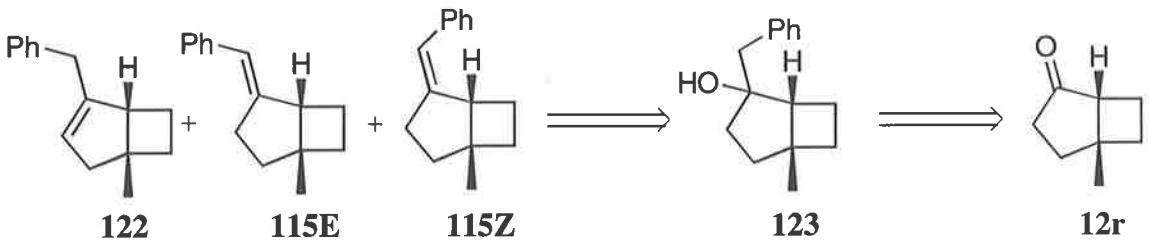


(±)-12r **115E** **115Z**

Scheme 115

Section 4.3.2 Formation of the Alkene via an Elimination Reaction

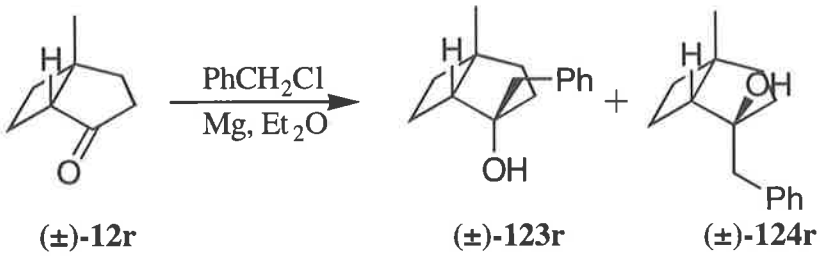
A Grignard reaction on the bicyclic ketone **12r** should give the alcohol **123**. A mixture of the alkenes **115E**, **115Z** and presumable the *endo* isomer **122** might form after an elimination reaction but in better yield so that separation could be attempted (Scheme 116).



122 **115E** **115Z** **123** **12r**

Scheme 116

A Grignard reaction on the bicyclic ketone **12r** gave the desired tertiary alcohol **123** as a white solid in a yield of 94% (Scheme 117).

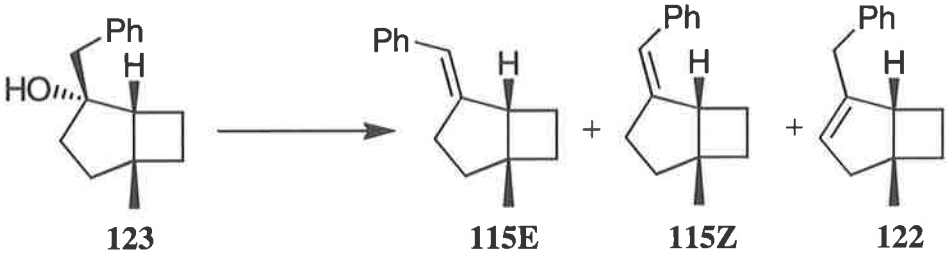


(±)-12r **(±)-123r** **(±)-124r**

Scheme 117

The ^{1}H NMR spectrum shows only one diastereomer, presumed to be the isomer **123r**, and can be explained as follows. A 3H singlet at δ1.28 is due to the methyl group on the bicyclic ring. The 10H complex between δ1.5-2.2 is due to the methylene ring protons and the hydroxyl group. The benzylic protons exhibit an AB quartet at δ2.65 and δ2.71 and the aromatic protons appear as a 5H complex at δ7.3. Microanalysis supported the assigned structure. The 600 MHz ^{1}H NMR, COSY and HETCOR spectra are reproduced in the 'Appendix'.

Elimination of the tertiary hydroxyl could give three products, the E and Z isomers of the desired alkene **115** and the unwanted *endo*cyclic alkene **122** but the proportion of these might be dependent on their mode of formation (Scheme 118).



123 **115E** **115Z** **122**

Scheme 118

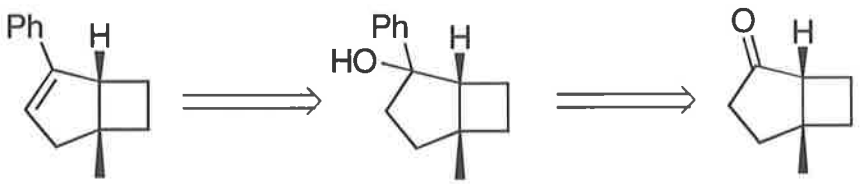
Several reaction conditions were attempted; however, a mixture of alkenes that proved to be inseparable was always obtained. The olefinic protons resonate at different chemical shifts, in the ^{1}H NMR spectrum, for each of the isomers. The broad singlet at δ5.25 is due to the olefinic proton of the *endo*cyclic alkene **122**. The olefinic proton of the alkenes **115E** and **115Z** resonates as broad singlets at δ6.20 for one isomer and at δ6.30 for the other, but the E and Z isomers could not be differentiated by their ^{1}H NMR spectrum. The results are summarized in Table 11. Unfortunately, different reactions conditions do not significantly change the ratio of alkenes formed, and it appears that there is a 50% probability that the double bond will be *exo* or *endo*. Attempts to isomerize the alkenes were unsuccessful, no change in the relative ratio was observed when the mixture of alkenes in *d*-chloroform was refluxed in the presence of iodine.[111] Reverse phase TLC plates showed no separation of the isomers and minimal separation, not enough to be useful, occurred on normal TLC plates impregnated with silver nitrate. This route did not prove to be viable as the *exo*cyclic alkene **115** could not be obtained without contamination of significant quantities of the *endo*cyclic alkene **122**. Consequently, formation of this substrate was abandoned.

Concentration	Reagents	Conditions	Products‡
0.06 M	*p*-Toluene sulfonic acid (catalytic), $CDCl_3$	Ambient temp, 24 hrs	Starting material
0.06 M	DMSO	160°C, 24 hrs	Alkene 2 : 1 : 3 (**115** : **115** : **122**)
0.03 M	$SOCl_2$, Py, CH_2Cl_2	Ambient temp, 15 hrs	Alkene 1.8 : 1 : 2.8 (**115** : **115** : **122**)
0.03 M	$SOCl_2$, Py, CH_2Cl_2	-78°C, 2 hrs	Alkene 2 : 1 : 3 (**115** : **115** : **122**)
0.05	MsCl, Et_3N, CH_2Cl_2	Ambient temp, 2 hrs	Alkene 2.1 : 1 : 3.2 (**115** : **115** : **122**)

Table 11

Section 4.4 Alternative Alkenes

The new alkene **125** should also satisfy the requirements for a highly selective kinetic resolution. The alkene **125** might be formed exclusively from the alcohol **126** *via* an elimination reaction. In this case, it is not possible for E and Z isomers to form and because of the strain that would be introduced, it is unlikely that the double bond will form *exo* to the cyclobutane ring. The required alcohol **126** could be formed from the bicyclic ketone **12r** *via* a Grignard reaction. Cleavage of the double bond in the alkene **125** will not give the optically active bicyclic ketone **12r**, and it can-not be used in the synthesis of grandisol but it might give some insight into features affecting kinetic resolution by the Sharpless asymmetric dihydroxylation reaction.



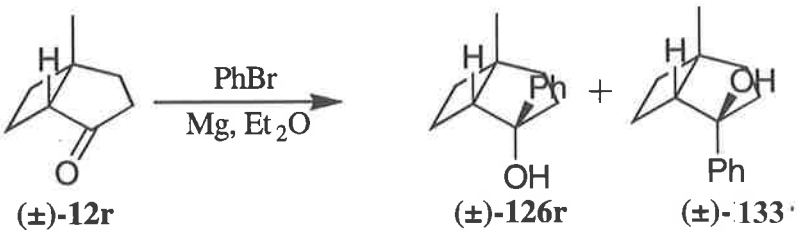
125 **126** **12r**

Scheme 119

A Grignard reaction on the bicyclic ketone **12r** gave the desired tertiary alcohol **126r** in a yield of 88% as a colourless liquid, which crystallized in part on standing. Again, only signals for

‡ The E and Z isomers could not be differentiated in the ^1H NMR spectrum.

one diastereomer were observed in the ^{1}H NMR spectrum and it is assumed to be the alcohol **126r** in which the hydroxyl group is *trans* to the methyl group. (Scheme 120).

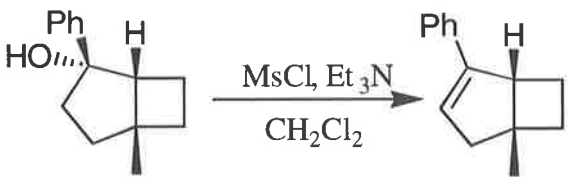


(±)-12r **(±)-126r** **(±)-133**

Scheme 120

The 600 MHz ^{1}H NMR spectrum of the alcohol **126r** shows a 3H singlet at δ1.22 due to the methyl group on the bicyclic ring. One of the protons at C4 resonates as a doublet of triplets at δ1.29, with coupling constants of 6.5 and 13 Hz. The other proton at C4 resonates as a doublet of doublet of doublets at δ1.50, with coupling constants of 2, 6 and 13 Hz. The protons at C6 resonate as a 2H multiplet at δ1.90. The protons of C7 and one proton of C3 resonate as a 3H complex at δ2.0-2.1, the other proton at C3 resonates as a doublet of triplets at δ2.43, with coupling constants of 6.5 and 13 Hz. The methine proton appears as a doublet of doublets at δ2.60, with coupling constants of 5.5 and 9.5 Hz, and the aromatic protons resonate as a complex between δ7.2-7.4. The 600 MHz ^{1}H NMR, COSY and HETCOR spectra are reproduced in the 'Appendix'.

The tertiary alcohol **126r** was easily dehydrated to give the required alkene **125r**.[112] Initially yields of only 50% were obtained after purification of the alcohol **126r** by chromatography. It was noticed if the alkene **125r** was left at ambient temperature for 24 hours that the ^{1}H NMR spectrum had changed considerably and no longer resembled the alkene **125r**. The addition of a small amount of 2,6-di-*tert*-butyl-*p*-cresol, acting as a radical inhibitor, during the work-up excluded this problem and the alkene could then consistently be obtained in yields of ~80%.



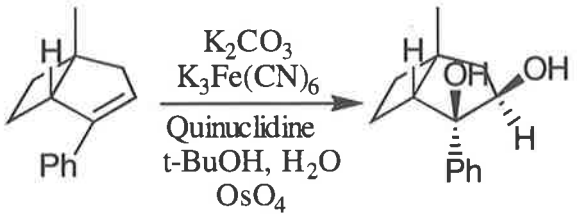
126r **125r**

Scheme 121

The ^{1}H NMR spectrum of the alkene **125r** shows a 3H singlet at δ1.20 due to the methyl group. The ring protons exhibit a 3H complex in the region δ1.6-2.0, another 3H complex at δ2.1-2.4 and an allylic proton resonates as a broad singlet at δ3.05. The olefinic proton appears as a broad singlet at δ6.05 and the aromatic protons exhibit a 5H multiplet in the region δ7.0-7.3. Due to the instability of the alkene **125r**, a microanalysis was not attempted.

Section 4.4.1 Kinetic Resolution of the New Alkene

Reaction of the alkene **125r** with quinuclidine (used in place of the enantiomerically pure chiral ligand in the AD reaction) gave exclusively attack from one side, assumed to be the top face, to give the diol **127r** as a white solid in a 50% yield, mp 116-118°C. (Scheme 122).

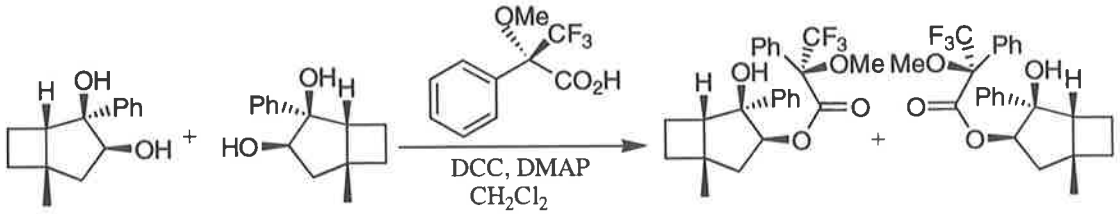


125r **127r**

Scheme 122

The ^{1}H NMR spectrum of the diol **127r** shows a 3H singlet at δ1.29 due to the methyl group. The ring protons exhibit a 5H complex in the region δ1.6-1.9, a 1H multiplet at δ2.0 and another 1H multiplet δ2.45. The methine proton adjacent to the hydroxyl group appears as a doublet of doublets at δ4.95, with coupling constants of 7 and 10.5 Hz. The aromatic protons resonate as a complex in the region δ7.2-7.5. A microanalysis of the diol **127r** was attempted with two different samples, and in duplicate with one sample, however in all cases they did not correspond to the structure **127r**. The values required for the diol **127r** are C, 77.03; H, 8.31. The values found were C, 75.95; H, 8.39; C, 75.99; H, 8.38 and C, 75.96; H, 8.28. The microanalyses values could correspond to 1/6th of a molecule of water being incorporated into the crystal structure.

The racemic diol **127r** was acylated with α-Methoxy-α-(trifluoromethyl)phenylacetic acid to give the corresponding Mosher esters **128** and **129** (Scheme 123).



127a **127b** **128** **129**

Scheme 123

The 300 MHz ^{1}H NMR spectrum of the racemic Mosher esters **128** and **129** shows the presence of two diastereomers and can be described as follows. The two finely separated singlets at δ1.33 and δ1.35 are due to the methyl group of each diastereomer. For both diastereomers, the ring protons resonate as a complex in the region δ1.3-2.5. The tertiary hydroxyl of each diastereomer also comes in the region δ1.3-2.5. The methoxyl protons both appear as a broad singlet at δ3.37 and δ3.53 and give baseline separation (Figure 58). The methine proton adjacent to the ester moiety, of both diastereomers, resonates as a multiplet at δ6.26, and the aromatic protons appear as a complex at δ7.35-7.55.

Figure 58 shows the ^{1}H NMR spectrum of the methoxyl region of the Mosher esters **128** and **129**.

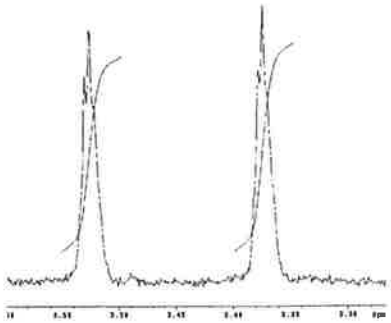
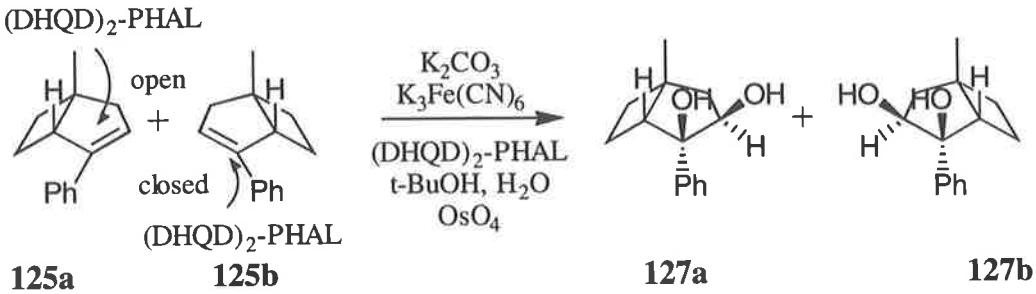


Figure 58

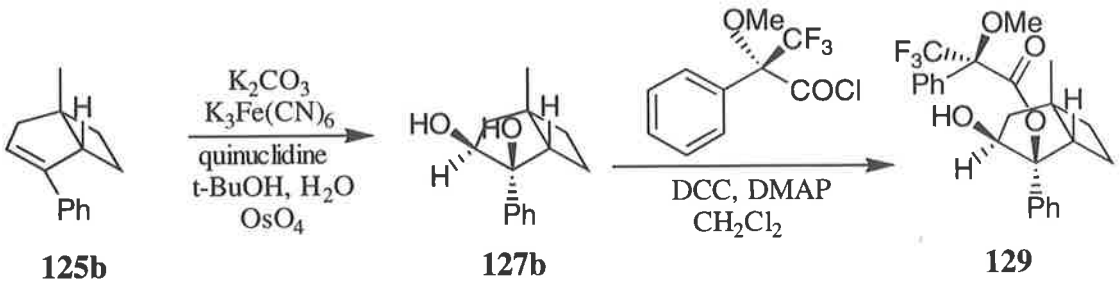
Using Sharpless' mnemonic,[113] when the alkene **125** is drawn as shown in Scheme 124, the alkene **125a** should be dihydroxylated from the top face whereas its enantiomer **125b** will be dihydroxylated from below. As the bottom face is essentially closed to attack it is hoped that enantiomer **125a** will react in preference to enantiomer **125b**, resulting in a kinetic resolution.



125a **125b** **127a** **127b**

Scheme 124

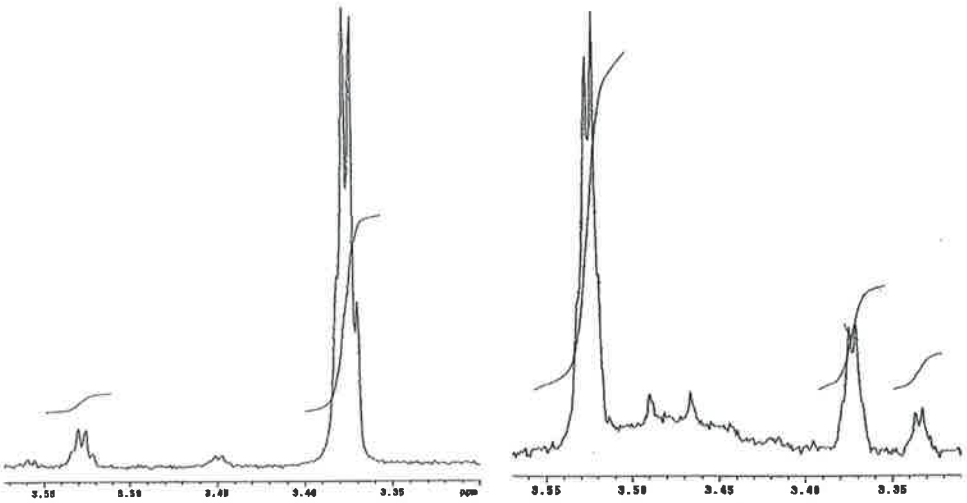
Instead of using the commercial AD-mix, the components were separately combined in solution so that the amount of oxidant (potassium ferricyanide) could be limited. The chiral ligand used was $(DHQD)_2$-PHAL, which will approach from the β–face. Initially, the oxidant was limited to 26% (2 molar equilvalents of potassium ferricyanide are required) and after work-up the ^1H NMR of the crude product indicated that the reaction had gone to 40% completion. Separation of the starting alkene **125b** and diol **127a** was achieved by chromatography. The diol **127a** from the reaction was converted to the corresponding Mosher ester and the enantiomeric excess was determined to be 88%. The starting alkene **125b** was converted to its corresponding diol with quinuclidine, an achiral reagent and then to the corresponding Mosher ester (Scheme 125). The enantiomeric excess of the starting alkene **125b** was 52% (Figure 59).



125b **127b** **129**

Scheme 125

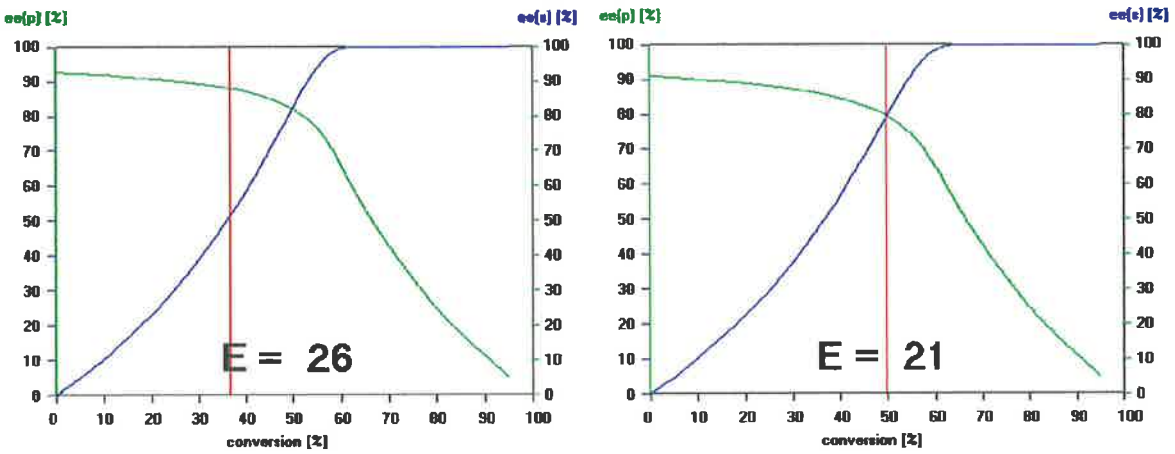
Figure 59a shows the methoxyl region for the Mosher esters prepared from the diol **127a**, the diol from the Sharpless asymmetric dihydroxylation. Figure 59b shows the methoxyl region for the Mosher esters prepared from the diol **127b** of the recovered alkene **125b**. The diol **127b** was formed from the alkene **125b** with quinuclidine as the achiral reagent.



a) b)

Figure 59

The relative rates of the two enantiomers as determined with the selectivity program (previously discussed in 'Chapter 3, Results and Discussion') are shown in Figure 60a, in this case the enantiomeric excesses from the product and substrate were used to plot the graph. From the graph, by running the reaction to 60% the enantiomeric excess of the recovered alkene would be >95%, resulting in highly selective kinetic resolution.



a) b)

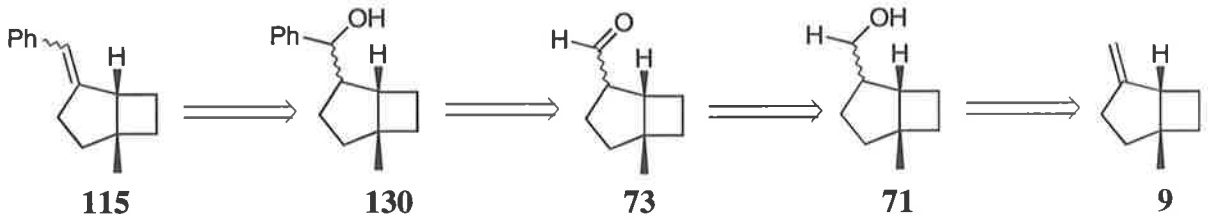
Figure 60

When the reaction was run to ~70% conversion (determined from the ^{1}H NMR spectrum of the crude product, only enough oxidant was added for a 50% conversion) the enantiomeric excess of the recovered substrate and product were both found to be 80%. The graph shown in Figure 60b was obtained from the selectivity program when the enantiomeric excesses from the recovered substrate and product were used. It can be seen that the graph predicts the reaction has gone only 50%, the conversion expected. This inconsistency could be due to some of the

alkene decomposing during the reaction and hence the ^{1}H NMR spectrum of the crude product is not entirely accurate. In the future, precautions will need to be taken so that the percentage conversion is correctly determined. However, this graph gives a very similar result to the graph in Figure 60a. By limiting the oxidant and by running the reaction to 60% the enantiomeric excess of the recovered alkene would be >95%.

The alkene **125** appears to be the ideal substrate to control a highly selective kinetic resolution and an early rather than a late transition state is consistent with the result.

In light of this observation, it is perhaps worth persevering with the formation of the alkene **115**. An alternative method for its formation is outlined in Scheme 126. An elimination reaction on the alcohol **130** should give the alkene **115**, two possible isomers could form and of course, it would be necessary to find a method to separate them. The alcohol **130** could be formed from the aldehyde **73** with a Grignard reaction. The aldehyde **73** has been previously formed from the bicyclic alkene **9** ('Chapter 2, Results and Discussion'). However, due to insufficient time this synthesis was not attempted.



115 **130** **73** **71** **9**

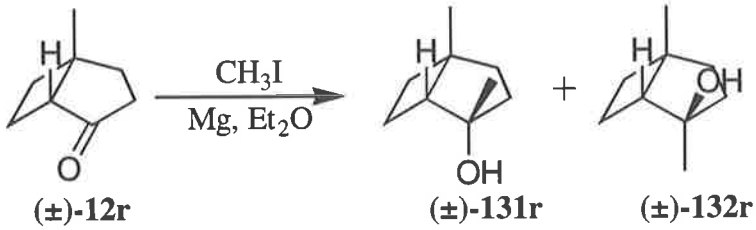
Scheme 126

Section 4.4.2 Kinetic Resolution of the Methyl Alkene

The last substrate chosen to study the kinetic resolution was the methyl alkene **10**, this alkene is of interest as it can be used in the synthesis of (+)-grandisol. However, if this substrate is to be used in the synthesis of (+)-grandisol it is desirable that it is formed in a short number of steps.

A Grignard reaction on the bicyclic ketone **12r** gave the methyl alcohol **131r** in a yield of 66% after purification by chromatography (Scheme 127). Resonances for only one diastereomer were observed in the ^{1}H NMR spectrum and it is assumed that the isomer is **131r**. The ^{13}C NMR spectrum corresponded very closely with that reported in the literature. The ^{1}H NMR

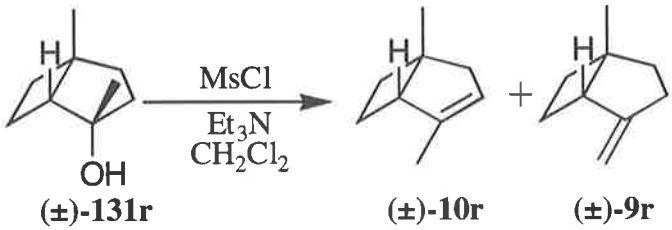
spectrum of the product is nearly identical to that reported in the literature, except for the methyl resonances.[26,29] The literature reports the methyl groups occur at δ1.35 and δ1.85, however they were found at δ1.16 and δ1.20. The difference could be a misprint or simply because the ^{1}H NMR spectrum reported in the literature was performed in a carbon tetrachloride solution using a 60 MHz or 100 MHz spectrometer.



(±)-12r **(±)-131r** **(±)-132r**

Scheme 127

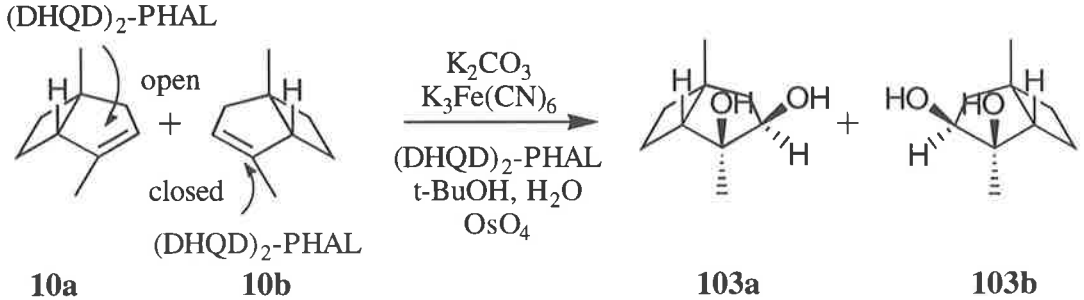
In the literature, it is reported that elimination of the alcohol **131r** by heating in HMPA gives a 7:3 ratio of the *endo*cyclic **10r** and *exo*cyclic **9r** alkenes. However, elimination with methane sulfonyl chloride increased the preference of the *endo*cyclic alkene **10r** (9:1 *endo*:*exo*) (Scheme 128). This reaction was performed several times, with varying scales and different concentrations. When the elimination was done on a large scale the *exo*cyclic alkene **9r** could not be detected in the ^{1}H NMR spectrum. The yield of the isolated product was only 55% and this is probably due to the volatility of the alkenes.



(±)-131r **(±)-10r** **(±)-9r**

Scheme 128

By the same reasoning discussed previously for the benzyl alkene **125**, it is hoped that enantiomer **10a** will react in preference to enantiomer **10b** (Scheme 129).

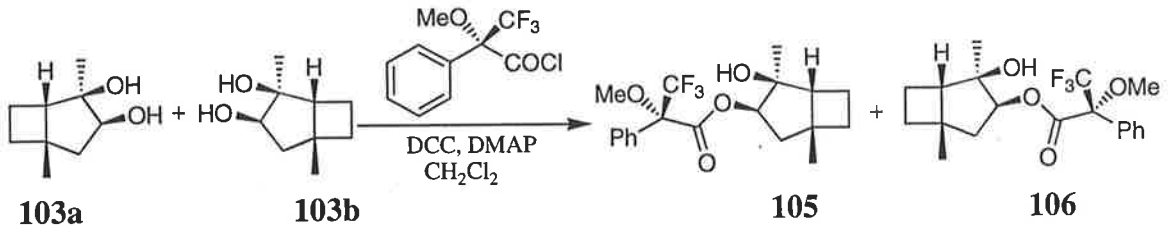


10a **10b** **103a** **103b**

Scheme 129

The racemic diol **103r** has been formed previously and it is known that the optical purity of the diol **103a** can be determined from the corresponding Mosher ester (see 'Chapter 3, Results and Discussion').

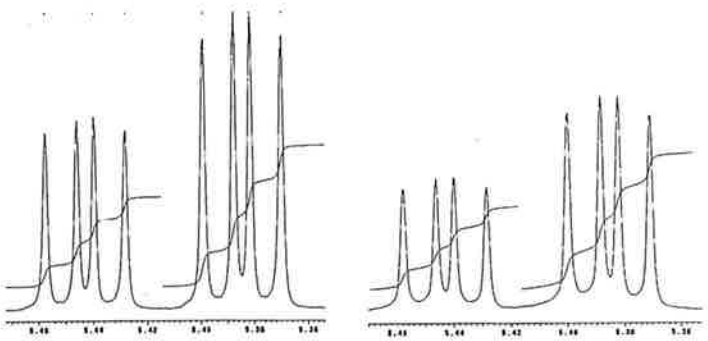
The Sharpless dihydroxylation reaction was performed at 0°C using a limited amount of oxidant and $(DHQD)_2$-PHAL as the chiral ligand. Initially, the alkene was not isolated. If this kinetic resolution proved to be viable, a procedure for isolation of the alkene would be determined. By limiting the oxidant, the reaction had gone to a 26% completion and the enantiomeric excess of the product, found by conversion to the Mosher esters **105** and **106**, was 23% (Scheme 130 and Figure 61a). The enantiomeric ratio for this reaction was 1.8.



103a **103b** **105** **106**

Scheme 130

Repetition of this reaction at ambient temperature gave a very similar result, when the reaction was taken to 26% conversion (determined by the amount of oxidant added) the enantiomeric excess of the product was found to be 24% (Figure 61b). The outcome for this reaction is similar to that for the *exo*cyclic alkene **9r** attempted previously. The reaction is very diastereoselective but is only slightly enantioselective.

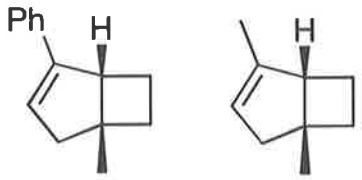


a) 0°C b) Ambient temperature

Figure 61

The rate at which the enantiomers react is substantially different in the alkenes **125** but not in the alkene **10**. From the experimental evidence, attack from the top face is favoured in both

cases. The difference between the two results is based on the catalyst facial selectivities in the Sharpless asymmetric dihydroxylation reaction. The enantiomeric excess of 1-phenylcyclohexene is >97%, and 1-phenylcyclopentene is 97%, when $(DHQD)_2$-PHAL is used as the chiral ligand, whereas 1-methylcyclohexene is only 52% and that for methylcyclopentene has not been reported. However, what controls these facial selectivities is not always immediately obvious since it has been found that for 1-methyl-4-*tert*-butylcyclohexene **112** that the corresponding diols form in high enantioselectivity (see 'Chapter 4, Results and Discussion' p. 104).



125 **10**

Figure 62

In conclusion, a substrate has been found that undergoes a highly selective kinetic resolution. However, in order to determine what precisely is required for a highly selective kinetic resolution with the Sharpless asymmetric dihydroxylation reaction, more research will need to be done.

CHAPTER 5

RESULTS AND DISCUSSION

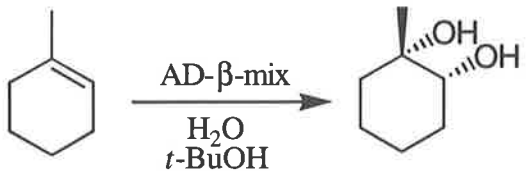
ASYMMETRIC SYNTHESIS OF

1-METHYL-2-CYCLOHEXEN-1-OL

Section 5.1 Formation of 1-Methyl-2-Cyclohexen-1-ol

As previously discussed in the introduction, several aspects of the asymmetric synthesis of MCL **2** needed to be investigated. The synthesis of the pheromone needed to be accomplished on a multigram scale, so problems with the volatility and handling of the pheromone would be overcome.

A Sharpless asymmetric dihydroxylation reaction on 1-methylcyclohexene gave the optically active diol **47a** (Scheme 131) in an 85% yield with a 52±3% e.e., after a modified work up.

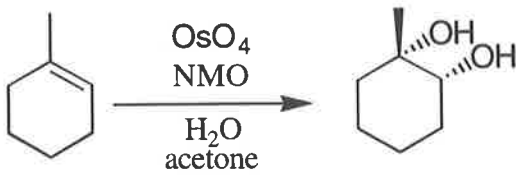


47a

Scheme 131

Due to the water solubility of the diol, the standard work up procedure[45] needed to be modified. Hence, the KOH solution which is normally used to remove methanesulfonamide was omitted and no extra water was added in the work up procedure. Due to the considerable volatility of the diol, solvent was removed by fraction distillation at each stage of the purification. After chromatography and then sublimation (50°C/0.5mm) the diol was obtained in an 85% yield.
The enantiomeric excess was determined by chiral shift NMR experiments with tris-[3-(heptafluoropropy-hydroxymethylene)-*d*-camphorato] europium (III) derivative on the corresponding secondary mono acetate. (See 'Introduction') The enantiomeric excess was unaffected by scaling and found to be the same as obtained earlier.[61]

The racemic diol **47r** was formed by reaction of 1-methylcyclohexene and osmium tetroxide in the presence of NMO in a 65% yield. (Scheme 132),

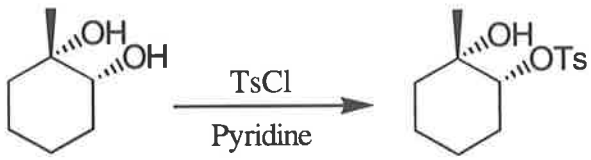


(±)-47r

Scheme 132

The ^{1}H NMR data of the racemic diol was identical with that of the optically active diol and with the literature values reported for the (1R, 2S) enantiomer.[114]

The optically active diol **47a** was converted to the optically active tosylate **48a** by modification of a procedure outlined in Reagents for Organic Synthesis.[102] Purification by chromatography gave the optically active tosylate **48a** in an 83% yield, with a 55±3% e.e.. (Scheme 133).



47 **48**

Scheme 133

Repetition of this reaction, on a larger scale, with the racemic diol **47r** gave the racemic tosylate **48r** in a 94% yield.

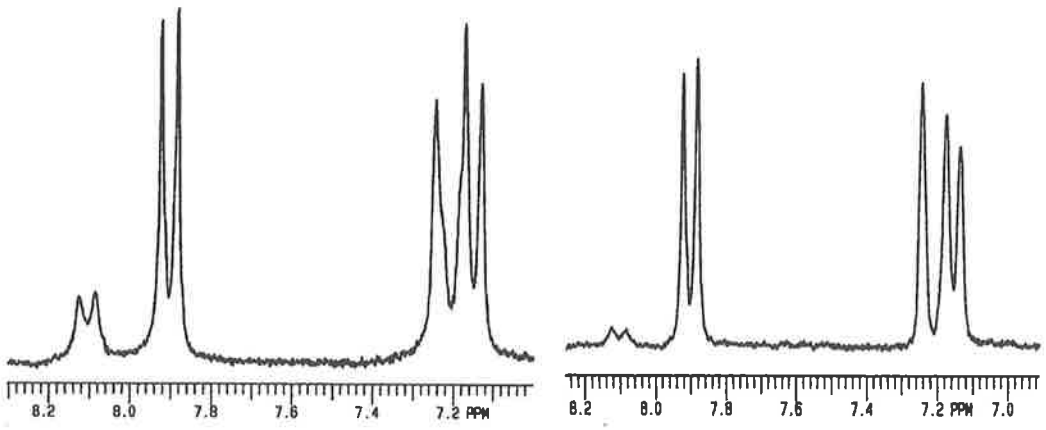
The ^{1}H NMR spectrum shows two sharp 3H singlets, at δ1.14 due to the methyl group and at δ2.45 due to the tosylate methyl. The hydroxyl group exhibits a broad 1H singlet at δ1.59. The methylene envelope occurs in the region δ1.2-1.6, (this unresolved pattern is due to each proton coupling to its vicinal and geminal neighbouring protons). The signal at δ4.36 is a 1H doublet of doublets with an axial-equatorial coupling constant of 4 Hz and a axial-axial coupling constant of 10 Hz, due to the proton at C2. The aromatic AA' BB' signals appear as two 2H doublets at δ7.34 and δ7.80, which couple to each other with a coupling constant of 8 Hz.

As previously discussed in the 'Introduction', the enantiomeric excess was determined by chiral shift NMR experiments on the tosylates **48** with tris-[3-(heptafluoropropy-hydroxymethylene)-*d*-camphorato] europium (III) derivative.

Also previously discussed in the 'Introduction', the optical purity of the optically active tosylate **48a** could be improved by recrystallization from diethyl ether and hexane. After one recrystallization, the tosylate **48a** was obtained with an enantiomeric excess of 78±3%.

Repeated recrystallization of the large-scale optically active tosylate **48a** gave material that had an enantiomeric excess of 94±3%, after four recrystallizations. The optically active tosylate **48** was obtained in a recovery yield of 37% after four recrystallizations.

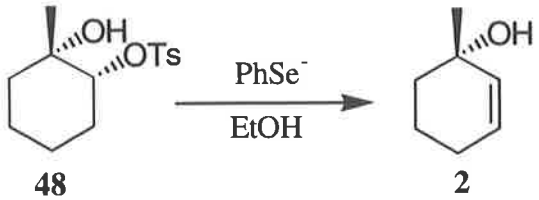
The enantiomeric excess was determined by chiral shift NMR experiments of the tosylate **48** in the presence of tris-[3-(heptafluoropropyl-hydroxymethylene)-d-camphorato)] europium (III) derivative. The ortho aromatic protons of the racemate, originally at δ7.80, gave baseline separation in the presence of the chiral shift reagent. The aromatic region of the ^{1}H NMR spectra of the enantiomerically enriched samples is reproduced in Figure 63. Integration of the optically enriched tosylate indicates the enantiomers were present in a ratio of 97:3, a result that was verified by the method of cutting and weighing the peaks of the reproduced spectra (Figure 63b).



a) 52% e.e. b) 94% e.e.

Figure 63

Both the racemic and optically active tosylates **48r** and **48a** were separately converted to the allylic alcohol **2r** and **2a** by reaction with phenyl selenide anion (Scheme 134).



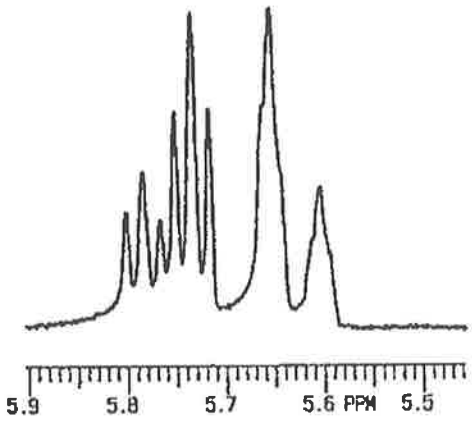
48 **2**

Scheme 134

Reaction of the optically active tosylate **48** with phenyl selenide anion followed by removal of the solvent by fractional distillation followed by a short path distillation gave in a 78% yield, the optically active allylic alcohol **2a**.

Repetition of the above reaction with the racemic tosylate **48r**, gave the racemic allylic alcohol **2r** in a 55% yield.

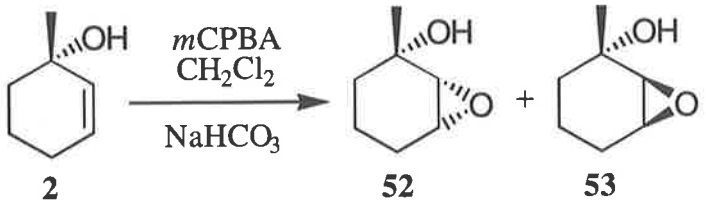
The ^{1}H NMR spectrum is consistent with that expected for the structure of **2**. There is a 3H singlet at δ1.29 due to the methyl group, a 2H multiplet at δ2.10 due to the allylic protons and the methylene envelope occurs in the region δ1.5-1.8. The olefinic protons give a 1H multiplet of doublet at δ5.65 with a coupling constant of 10 Hz and a 1H doublet of triplet with a coupling constant of 4 and 10 Hz at δ5.75 (Figure 64). The literature values for **2** are a 1H singlet at δ1.29, a multiplet at δ1.45-2.05 consisting of 7H and signals due to the olefinic protons as a multiplet at δ5.55-5.90.[115]



A 200MHz ^{1}H NMR spectrum of the olefinic region of the allylic alcohol **2**.

Figure 64

As the optical purity of the allylic alcohol **2** could not be determined directly, it was converted to the epoxides (Scheme 135).As discussed in the 'Introduction', both the *cis* **52** and the *trans* **53** epoxides were formed from this reaction, initially in a ratio of 93:7.



2 **52** **53**

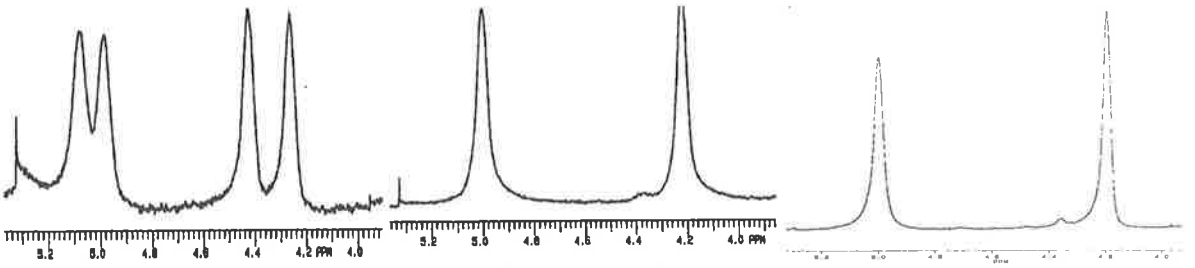
Scheme 135

Consequently, due to the impurity of the *trans* epoxide **53**, baseline separation of the resonances due to the epoxide protons in the ^{1}H NMR did not occur in the presence of chiral shift reagent. To achieve baseline separation, it was necessary to exclude the formation of the *trans* epoxide **53**. It is known that *m*CPBA coordinates to the hydroxyl group and therefore can deliver the oxidant from the same face as the hydroxyl.[116] If the *m*CPBA is added slowly to the reaction mixture, so there is time for it to coordinate to the hydroxyl, then hopefully only the *cis* epoxide **52** should form. Hence, formation of the racemic epoxide was performed at –5°C, with *m*CPBA added portionwise over five minutes. The *cis* epoxide **52** was formed in an 84% yield and no *trans* epoxide **53** could be detected in the ^{1}H NMR spectrum.

Chiral shift NMR experiments of the pure racemic *cis* epoxide **52r**, with tris-[3-(heptafluoropropyl-hydroxymethylene)-d-camphorato)] europium (III) derivative, then gave baseline separation of the epoxy protons in the ^{1}H NMR spectrum.

Formation of the optically active epoxide at –5°C gave the *cis* epoxide **52a** isolated in a 55% yield. Again, no *trans* epoxide **53a** was detected in the ^{1}H NMR spectrum. Chiral shift NMR experiments of the pure optically active *cis* epoxide **52a**, with tris-[3-(heptafluoropropyl-hydroxymethylene)-d-camphorato)] europium (III) derivative confirmed that the enantiomeric purity from the tosylate **48a** had been maintained.

The epoxy-proton region of the resultant ^{1}H NMR spectrum is reproduced in Figure 65.



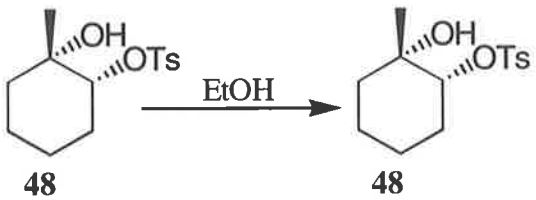
Racemic Optically active 200 MHz Optically active 300 MHz

Figure 65

Hence, a three-step synthesis of optically active 1-methylcyclohex-2-enol (MCL) has been accomplished from achiral materials.

Section 5.2 Merged-Substitution Elimination Reaction

The mechanism for the fortuitous elimination reaction which was discovered during this synthesis is interesting and needs to be explained. That the reaction of the tosylate **48** with phenyl selenide anion in ethanol is not an E_1 mechanism can be deduced from the observation that the half life for the reaction is concentration dependent, and no products from the pinacol rearrangement are observed when care is taken to remove adventitious base. Furthermore, it is found that the tosylate **48** is recovered unchanged in refluxing ethanol. (Scheme 136).



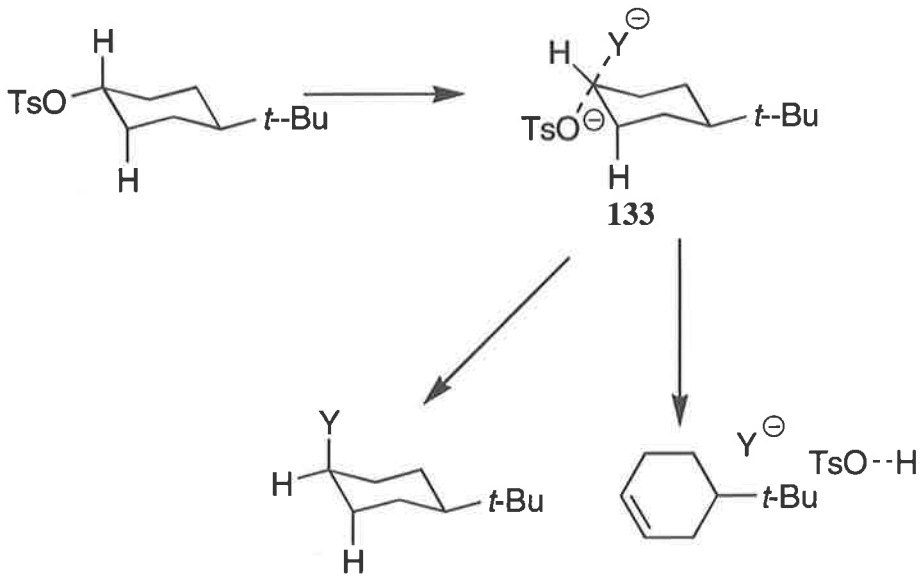
48 **48**

Scheme 136

It is curious why phenyl selenide anion, a powerful nucleophile to carbon but non-nucleophilic to a hydrogen attached to oxygen of an alcohol would become nucleophilic to a hydrogen attached to carbon. The relative pK_a of an alcohol proton (ROH) is approximately 15. The pK_a of a selenium proton (H_2Se) is approximately four.

To consider the reasons for this observation in more detail the research of *Winstein* and *Parker* needs to be introduced.[117] *Winstein* and *Parker* studied elimination accompanied bimolecular nucleophilic substitution reactions (S_N2) of *p*-toluenesulfonates. *Trans*-4-*t*-butylcyclohexyl *p*-toluenesulfonate, which has the toluenesulfonyloxy group constrained to an equatorial position,

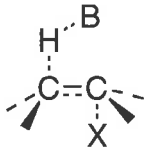
undergoes a partial substitution and partial elimination reaction with LiBr in acetone at 75°C (Scheme 137).



Scheme 137

An E2 mechanism was precluded by stereoelectronic considerations. An S_N2 reaction followed by an E2 reaction did not account for the observed elimination, as the intermediate bromide is too unreactive. An E1 elimination mechanism was discounted due to the substantial rate factor difference when lithium bromide and lithium perchlorate were used as the nucleophile. *Winstein* and *Parker* concluded that the mechanism could be described as a merged substitution-elimination reaction. That is where the mechanism of this reaction retains the S_N2 characteristics **133** where there is mainly a partly covalent S_N2-like linkage between the base and the α-carbon.[117]

Since *Winstein* and *Parker* drew attention to the dichotomy of weak bases but good nucleophiles which promote elimination reactions there has been considerable debate as to the verity of his suggestion. It was later posulated that the transition state is best represented by **134**, where the base exerts some electrostatic repulsion on the leaving group [118, 119] (Figure 66).

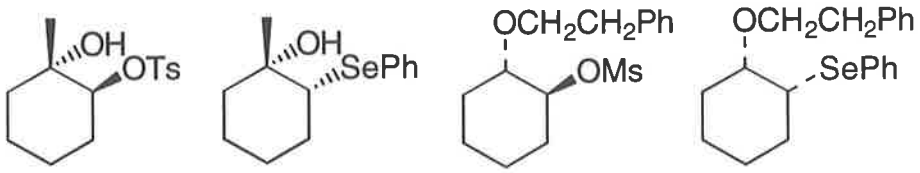


134

Figure 66

However, it appears that no clear explanation has been given for what is actually happening in these reactions. The formation of the allylic alcohol **2** is an extreme example of this phenonomenon, and it is hoped that this observation will stimulate debate on the subject.

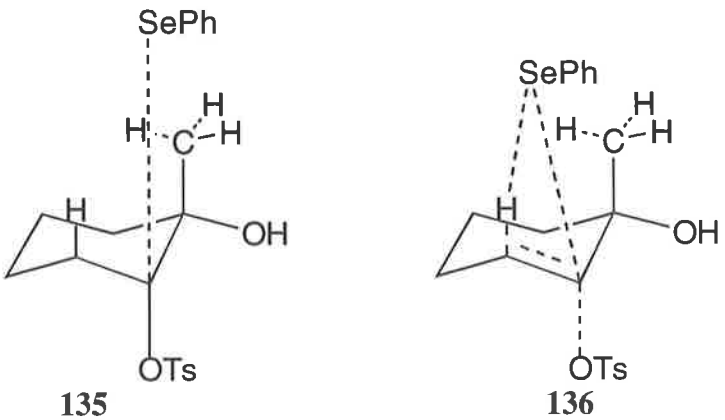
Under the same conditions, with NaSePh, as when the tosylate **48** gives only the elimination product both the racemic isomeric *trans*-tosylate **137**[120] and the racemic mesylate **139**[61] undergo clean substitution reactions to give the *cis*-selenide derivatives **138** and **140** respectively (Figure 67).



137 **138** **139** **140**

Figure 67

From a study of models it can be seen that when the leaving group is axial, rear-side attack is less hindered. Also, the nucleophile, the reaction centre and the leaving group can stay co-linear throughout the reaction. Hence, it is likely that the selenide ion initially follows a trajectory co-incident with the dipole axis of the molecule **135**. However, the methyl group hinders the approach of the nucleophile to the backside of the tosyl group. The deflected nucleophile could then encounter the hydrogen atom, which is held in an antiperiplaner arrangement to the leaving group, with sufficient energy to overcome the barrier to elimination, and thus this becomes the low energy process. The transition state could be similar to the model proposed in **136**. (Figure 68).



135 **136**

Figure 68

In both cases of the tosylate **137** and the mesylate **139**, the selenide anion's ability for carbon nucleophilicity is not hindered by steric barriers which would obstruct its approach. Presumably, the trajectory of the selenide anions is co-linear and an S_N2 substitution reaction results (Figure 69).

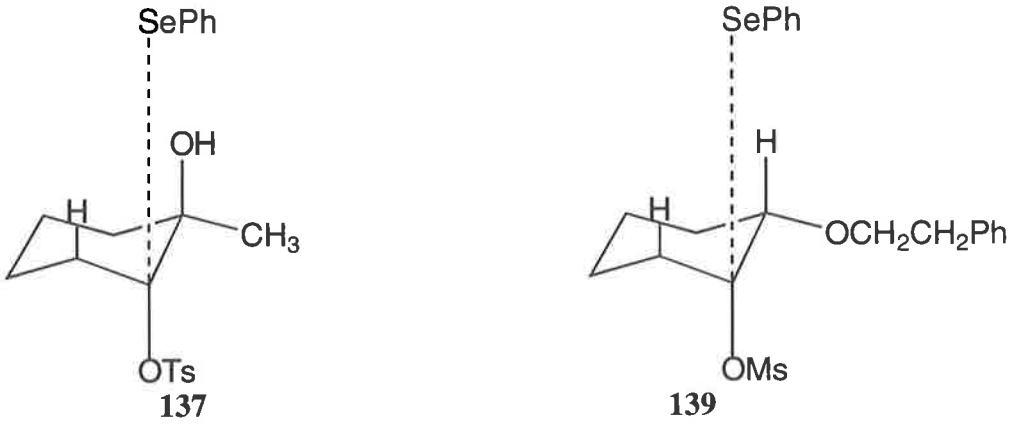
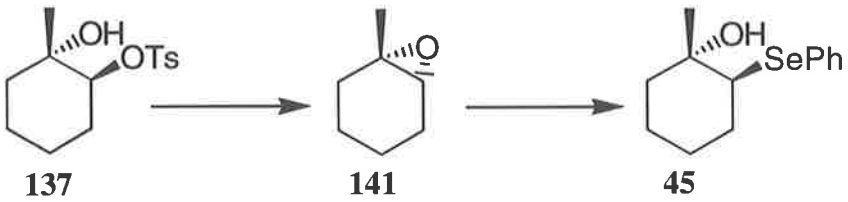


Figure 69

It could be postulated that the selenide formed from the *trans*-tosylate occurred via the epoxide **141** to give, in fact, the *trans*-selenide **45** (Scheme 138). However, the *trans*-selenide **45** has been formed previously,[60] and the spectral data obtained for the new selenide (*cis*-selenide **138**) is not consistent with the data for the *trans*-selenide **45**.



Scheme 138

In conclusion, a three-step synthesis of optically active 1-methylcyclohex-2-enol (MCL) has been accomplished from achiral materials. The route is far more efficient than any syntheses to date. If there are further developments to the Sharpless asymmetric dihydroxylation reaction which allow a more enantioselective preparation of the diol **47** the route will be extremely efficient. Furthermore, this synthesis has revealed an interesting elimination reaction that will hopefully help to solve the ambiguities originating from the mechanism of weak-base elimination reactions.

The synthesis of MCL outlined in this chapter has recently been published[121] and a copy of the paper is included in the Appendix.

GENERAL EXPERIMENTAL

Melting points were determined using a Reichert hot stage apparatus, and are uncorrected. NMR spectra were measured with Varian spectrometers, with operating frequencies of 200 MHz ^{1}H and 50 MHz ^{13}C, or 300MHz ^{1}H and 75 MHz ^{13}C, or 600 MHz ^{1}H and 150 MHz ^{13}C. $CDCl_3$ was used as the solvent, unless otherwise indicated. ^{1}H resonances are quoted in parts per million downfield from the ^{1}H resonance of tetramethylsilane (TMS). ^{13}C resonances were referenced using the $CDCl_3$ resonance (which falls δ77.0ppm downfield from the TMS resonance). The multiplicities of signals are reported as being: s, singlet; d, doublet; t, triplet; q, quartet; m, an unassignable multiplicity or overlapping signals; dd, doublet of doublets; dt, doublet of triplets; ddd, doublet of doublet of doublets; br, broadened signal. Geminal protons with different chemical shifts are denoted H_a and H_b. All coupling constants are quoted in Hertz (Hz) with no sign given. Chiral shift NMR experiments were measured using tris-[3-(heptafluoropropyl-hydroxymethylene)-d-camphorato]-europium(III) in a solvent system of CCl_4 (0.5 mL) and C_6D_6 (0.1 mL).

Infra-red spectra were recorded on a Jasco A-102 spectrometer or a ATI Mattson Genisis series FTIR™ spectrometer as either nujol mulls or liquid films (neat) on sodium chloride plates or as KBr pellets in solution cells (were indicated). GLC analyses were carried out on a DANI 8510 Gas Chromatograph with a SGE S.C.O.T. 50m OV101 column. All mass spectra are electron impact (EI) mass spectra, measured with a VG ZAB 2HF mass spectrometer operating at an ionization energy of 70 eV or if indicated GC-MS measured on a Finnigan MAT GCQ spectrometer operating at an ionisation energy of 70 eV. Accurate mass determinations using liquid secondary ion mass spectroscopy (LI-MIS) were made by the Organic Mass Spectrometry Facility at the University of Tasmania. Microanalyses were performed by the University of Otago, Department of Chemistry, Dunedin, New Zealand

Optical rotations were measured using a Steeg and Reuter SR 100 Digital 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[122] was performed with Merck Kieselgel 60 (230-400 mesh ASTM). TLC was performed with Merck aluminum backed silica gel 60 F_{254} sheets. Visualization of the developed plates was achieved with 254 nm light and by staining with ammonium molybdate dip [prepared by dissolving ammonium molybdate (20 g) in concentrated sulfuric 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. Anhydrous dichloromethane was freshly distilled from phosphorus pentachloride. Other anhydrous solvents and reagents were prepared according to standard laboratory procedures.[90] All organic extracts were dried over anhydrous sodium sulfate, unless otherwise stated.

Mineral oil was removed from NaH 60% suspension by washing with hexane several times under a nitrogen atmosphere.

The naming program ACD/Name, version 2.51 was used for the nomenclature of the majority of compounds. With the exceptions of the alkene **9**, the epoxides **40** and **41** and the hydroxy epoxides **98** and **99**.

CHAPTER 6

Experimental

Section 2.1 Formation of the bicyclic ketone

Purification of 3-methyl-2-cyclopentenone **54** by Girard T

Girard T reagent (3.9 g, 23.7 mmols) was added to a mixture of the commercial ketones, 3-methyl-2-cyclopentenone and 2,5-hexanedione (25.0 g, 260 mmols), dissolved in ethanol (100 mL) and acetic acid (1.8 mL). The reaction mixture was refluxed under nitrogen for 3 hours. Dichloromethane (100 mL) was added to the cooled solution and the solution washed with water (3×30 mL) and saturated brine solution (1×20 mL). The organic layer was dried and solvent was removed at atmospheric pressure by distillation. Purification of the product by distillation (85°C/26mm Hg) gave the *title compound* as a colourless liquid (19.3 g, 77% recovery). The ^{1}H NMR spectrum showed no 2,5-hexanedione [signals expected at δ_H: 2.10 (s, 6H), 2.63 (s, 4H)]. δ_H (200 MHz): 2.16 (3H, br s, CH_3), 2.45 (2H, m, H4), 2.58 (2H, m, H5), 5.96 (1H, br s, H2).

3-methyl-2-cyclopentenone **54** CAS [1120-73-6]

According to the literature procedure,[67] 2,5-Hexanedione **55** (10 mL, 85.0 mmols) was added dropwise to a boiling solution of 2.1% (w/v) of aqueous KOH (55 mL) so that the mixture remained at reflux (~10 min). The resulting solution was refluxed for a further 45 min then rapidly cooled to ambient temperature by immersion of the reaction flask into an ice-water bath. $NaCl_{(s)}$ was added to the solution until saturation was reached, the solution was then extracted with dichloromethane (5×20 mL). The combined organic extracts were washed with brine (20 mL) and dried ($MgSO_4$). The solution was concentrated by rotary evaporation under reduced pressure (40°C/110mm Hg). Distillation of the residue, bp 72°C/14mm Hg, gave 3-methyl-2-cyclopentenone as a colourless liquid (3.64 g, 45%), lit[67] 53% bp 66.5°C/9mm Hg. GLC analysis (120°C) showed the material to be >99% pure. δ_H (200 MHz): 2.16 (3H, br s, CH_3), 2.45 (2H, m, H4), 2.58 (2H, m, H5), 5.96 (1H, br s, H2).

(1SR,5SR)-5-Methylbicyclo[3.2.0]heptan-2-one **12r** CAS [5049-35-3]

A solution of 3-methyl-2-cyclopenteneone **54** (18.9 g, 197 mmols) in dichloromethane (2 L), under a constant flow of ethylene, in a specially devised apparatus (see 'Chapter 2, Results and Discussion'), was cooled to -78°C, with the aid of a 'dry-ice' acetone bath. Once the solution was saturated with ethylene, irradiation was commenced with a 1000-W mercury vapour lamp. [CAUTION: It is an important fire safety requirement to ensure that an atmosphere of CO2 blankets the whole apparatus whenever this powerful lamp is turned on. This can be achieved by building walls high enough around the 'dry-ice' acetone bath to ensure the escaping CO_2 from this blanket thereby excluding air.] The temperature of the solution was maintained at -78°C and a constant pressure of ethylene was bubbled through the reaction mixture, to stir the mixture. Reaction progress was monitored by GLC and after 16 hours, the reaction was 99% complete. The reaction vessel was allowed to warm to ambient temperature, so that excess ethylene could escape. Removal of the solvent by distillation at atmospheric pressure and distillation, 98°C /56mm Hg, gave *the title compound* as a colourless liquid (19.0 g, 77%). δ_H (600 MHz)[¶]: 1.26 (3H, s, CH_3), 1.55-1.80 (2H, complex, $H4_a$, $H6_a$), 1.82-1.95 (2H, complex, $H4_b$, $H7_a$), 2.0-2.1 (1H, multiplet, $H7_b$), 2.25-2.42 (3H, complex, H1, $H3_a$, $H6_b$), 2.68 (dt, 1H, $H3_b$, J= 9.0, 11.0, 18.5 Hz). δ_c and DEPT (50 MHz): 18.7 (CH_2), 25.8 (CH_3), 30.6 (CH_2), 35.4 (CH_2), 38.3 (CH_2), 42.5 (q), 50.2 (CH), 222.5 (CO). υ_{max}(neat): 3000(s), 1731(s), 1454(s), 1411(s), 1376(s), 1276(s), 1243(s), 1164(s), 1097(s), 933(s) cm^{-1}. M/z: 124($M^{+\cdot}$,33%), 109(18), 96(100), 81(67), 67(55), 55(94). Lit δ_H (CCl_4)[‡][123] δ 1.25 (s, 3H, CH_3). δ_c (75 MHz)[124] 18.5, 25.6, 30.5, 35.3, 38.1, 42.3, 50.0, 222.0. The spectra are reproduced in 'Chapter 2 Results and Discussion' on p. 38, and 41.

3,3-Dideuterated (1SR,5SR)-5-Methylbicyclo[3.2.0]heptan-2-one **59r** and 1,3,3-trideuterated (1SR,5SR)-5-Methylbicyclo[3.2.0]heptan-2-one **58r**

A solution of (1SR,5SR)-5-methylbicyclo[3.2.0]heptan-2-one **12r** (121 mg, 0.98 mmols), anhydrous potassium carbonate (738 mg, 5.34 mmols) and deuterium oxide (5 mL, 273 mmols) in anhydrous THF (13 mL) were refluxed for 15 hours under nitrogen. Diethyl ether

[¶] COSY and HETCOR experiments were used to assign the resonances.

[‡] The field strength is not quoted

(40 mL) was added to the cooled solution and the reaction was washed with water (50 mL). The organic phase was dried (Na_2SO_4) and solvent removed *in vacuuo* to give a mixture of the mono, di **59r** and tri-deuterio **58r** species as a colourless liquid (105 mg, 85%). δ_H (300 MHz): 1.29 (3H, s, CH_3), 1.55-2.0 (5H, complex, H4, $H6_a$, H7), 2.23-2.35 (1½H, complex, ½H1 and $H6_b$). δ_c (50 MHz): 18.7, 25.8, 30.6, 35.4, 38.3 (t), 42.5, 50.2, 222.5. M/z :127 ($M^{+\cdot}$, 3%), 126(22), 125(3), 124(1), 98(70), 55(100). By expansion of a region of the MS the ratio of 127 : 126 : 125 : 124 is 3.8 : 24 : 3.5 : 1.

Section 2.2 Reaction with Corey's ylids

Trimethylsulfonium Iodide **61** CAS [2181-42-2]

According to the procedure of Emeleus and Heal,[63] methyl iodide (3.05 mL, 49.0 mmols) and dimethylsulfide (3.6 mL, 49.0 mmols) [CAUTION: Stench] were mixed and allowed to stand at ambient temperature, under a nitrogen atmosphere, overnight. The resulting solid white cake was crushed and recrystallized from 95% ethanol to give the *title compound* as white crystals (6.35 g, 64%). [CAUTION: The reaction was performed in the fumehood, as a precaution against volatile sulfur compounds. All disregarded solutions were carefully quenched with sodium hypochlorite solution.]

Trimethylsulfoxonium Iodide **60** CAS [1774-47-6]

According to the procedure of Corey's[48], methyl iodide (15 mL, 240 mmols) and dimethyl sulfoxide (36 mL, 507 mmols) were combined and solution refluxed, under a nitrogen atmosphere, for 48 hours. The crystals were filtered, washed with chloroform giving white crystals (28.6 mg, 54%). Recrystallisation from water, then drying of the white crystals (P_2O_5) gave the *title compound* (21.3 g, 40%).

1,1-Diphenylethyleneoxirane **62** CAS [882-59-1]

a) Method Using Trimethylsulfoxonium Iodide **60**

To establish the conditions needed for the reactions the following model compound was made according to the method of *Corey* and *Chaykovsky*[48] with benzophenone (456 mg, 2.50 mmols). The title compound was obtained as a white solid (373 mg, 76%). δ_H (300 MHz): 3.20

(2H, s, CH_2), 7.26 (10H, m, Ar-H). δ_c (50 MHz): 56.6, 61.6, 127.3, 127.8, 128.2, 129.9, 132.2, 139.5. Lit.δ 3.18 (2H), 7.36 (10H) [48]

b) Method Using Trimethylsulfonium Iodide **61**

To establish the conditions needed for the reactions the following model compound was made according to the method of *Corey* and *Chaykovsky*[48] with benzophenone (456 mg, 2.50 mmols). The title compound was obtained as a white solid (366 mg, 69%) with some starting material present.

(1SR,2RS,5SR)-5-Methyl-2-methylene oxide bicyclo[3.2.0]heptane **40r** and (1SR,2SR,5SR)-5-Methyl-2-methylene oxide bicyclo[3.2.0]heptane **41r**

a) Method Using Trimethylsulfoxonium Iodide **60** and NaH

i) Reaction at 55°C

To anhydrous, degassed DMSO (7 mL) was added sodium hydride (dispersion, oil removed) (123 mg, 5.11 mmols). The flask, under a nitrogen atmosphere, was fitted with a gooch tube containing trimethylsulfoxonium iodide **60** (1.21 g, 5.51 mmols). Sulfoxonium iodide **60** was added portionwise over 10 minutes. After the reaction mixture had stirred at ambient temperature for 30 minutes (1SR,5SR)-5-methylbicyclo[3.2.0]heptan-2-one **12r** (502 mg, 4.04 mmols) was added dropwise over 5 minutes. The reaction mixture stirred at ambient temperature for 15 min then heated at 55°C for 2 hours. After cooling to ambient temperature the reaction mixture was poured into cold water (20 mL), then extracted with diethyl ether (3×30 mL). The combined organic phases were washed with water (5×20 mL) and saturated brine solution (20 mL). The organic phases were dried and solvent was removed by distillation at atmospheric pressure. An evaporative distillation (kugelrohr), 70°C/760mm Hg gave the *title compounds* as a colourless liquid (421 mg, 75%). ^{1}H NMR showed the presence of the two epoxides in a 43:57 ratio (*endo* **40r** : *exo* **41r**)

Data for *endo* **40r** : δ_H (600 MHz): 1.26 (s, 3H, CH_3), 1.5-2.2 (complex, 8H, H1, $H3_a$, H4, H6, H7), 2.45 (td, 1H, $H3_b$, J=7.2, 13.2 Hz), 2.73 (1H, dd, H1', J= 0.82 and 5.4 Hz), 2.82 (1H, d, H1', J=5.4 Hz). δ_c (50 MHz) : 15.7, 26.6, 30.3, 31.6, 37.7, 44.3, 45.1, 57.0, 67.2.

Data for *exo* **41r**: δ_H (600 MHz): 1.20 (s, 3H, CH_3), 1.5-2.2 (complex, 8H, H1, $H3_a$, H4, H6, H7), 2.56 (td, 1H, $H3_b$, J=7.8, 13.8 Hz), 2.70 (1H, d, J= 4.5 Hz, H1'), 2.79 (1H, d, J= 4.5 Hz, H1'). δ_c (50 MHz) : 17.5, 26.4, 29.6, 32.7, 38.9, 45.3, 47.9, 48.5, 69.4.

Data for *endo* **40r** and *exo* **41r** : υ_{max}: 3000(s), 2250(m), 1468(m), 1455(m), 1249(w) cm^{-1}. M/z: 138($M^{+\cdot}$,4%), 123(30), 57(97), 56(85), 43(100), 41(83). Accurate Mass Spectrum: (MH^+) Expect 139.11228 Obtained 139.11201.

ii) Reaction at ambient temperature

The above reaction was repeated at ambient temperature with the following quantities; DMSO (2.5 mL), sodium hydride (dispersion, oil removed) (21 mg, 0.88 mmols), trimethylsulfoxonium iodide **60** (251 g, 1.14 mmols) and (1SR,5SR)-5-methylbicyclo[3.2.0]heptan-2-one **12r** (0.05 mL, 0.40 mmols). After work-up the ^1H NMR of the crude product showed the presence of the two epoxides in a 43:57 ratio (*endo* **40r** : *exo* **41r**)

b) Method Using Trimethylsulfoxonium Iodide **60** and *t*-BuOK

i) Reaction at ambient temperature

Trimethylsulfoxonium iodide **60** (300 mg, 1.36 mmols), (1SR,5SR)-5-methylbicyclo [3.2.0]heptan-2-one **12r** (111 mg, 0.89 mmols) and anhydrous, degassed DMSO (3 mL) were combined under a nitrogen atmosphere. A solution of potassium *t*-butoxide (138 mg, 0.88 mmols) in DMSO (3 mL) was then added portionwise. After stirring at ambient temperature for 5 hours the solution was diluted with water and extracted with dichloromethane (2×). The combined organic phases were washed with water (4×), dried and solvent carefully removed *in vacuo*. Purification by flash chromatography with ethyl acetate/hexane (5/95 v/v) gave the *title compounds* as a colourless liquid (81 mg, 67%). The ^1H NMR spectrum showed the presence of the two epoxides in a 57:43 ratio (*endo* **40r**: *exo* **41r**), from integration of the methyl resonances.

Data for *endo* **40r**: δ_H (600 MHz): 1.26 (s, 3H, CH_3), 1.5-2.2 (complex, 8H, H1, $H3_a$, H4, H6, H7), 2.45 (td, 1H, $H3_b$, J=7.2, 13.2 Hz), 2.73 (1H, dd, H1', J= 0.82 and 5.4 Hz), 2.82 (1H, d, H1', J=5.4 Hz). δ_c (50 MHz) : 15.67, 26.58, 30.30, 31.56, 37.65, 44.25, 45.11, 57.00, 67.19.

Data for *exo* **41r**: δ_H (600 MHz): 1.20 (s, 3H, CH_3), 1.5-2.2 (complex, 8H, H1, $H3_a$, H4, H6, H7), 2.56 (td, 1H, $H3_b$, J=7.8, 13.8 Hz), 2.70 (1H, d, J= 4.5 Hz, H1'), 2.79 (1H, d, J= 4.5 Hz, H1'). δ_c (50 MHz) : 17.5, 26.4, 29.6, 32.7, 38.9, 45.3, 47.9, 48.5, 69.4.

ii) Reaction at 60°C

The above reaction was repeated at ambient temperature with the following quantities; trimethylsulfoxonium iodide **60** (313 mg, 1.42 mmols), (1SR,5SR)-5-methylbicyclo

[3.2.0]heptan-2-one **12r** (0.1 mL, 0.80 mmols), DMSO (3 mL) and a solution of potassium *t*-butoxide (138 mg, 0.88 mmols) in DMSO (3 mL). After work-up the ^{1}H NMR of the crude product showed the presence of the two epoxides in a 55:45 ratio (*endo* **40r**: *exo* **41r**).

c) Method Employing Trimethylsulfonium Iodide **61** and NaH

Sodium hydride (dispersion, oil removed) (323 mg, 13.4 mmols) was added to anhydrous DMSO (4 mL) under a nitrogen atmosphere. The reaction mixture heated to 72°C, whereupon hydrogen was given off. THF (8 mL) was added and the solution subsequently cooled to 0°C. Trimethylsulfonium iodide **61** (1.66 g, 6.31 mmols) dissolved in DMSO (10 mL) was added over 3 minutes then stirred for a further minute and (1SR,5SR)-5-methylbicyclo[3.2.0]heptan-2-one **12r** (610 mg, 4.92 mmols) was added dropwise. After stirring for 10 minutes at 0°C the ice bath was removed and solution stirred at ambient temperature for 2 1/2 hours. The reaction mixture was then diluted with water (100 mL), and extracted with dichloromethane (3×50 mL). The combined organic extracts were washed with water (5×40 mL), dried and solvent removed *in vacuuo*. An evaporative distillation (kugelrohr) (150°C/ 880 mm Hg) gave the *endo* epoxide **40r** as a colourless liquid (466 mg, 68%). δ_H (600 MHz)[¶]: 1.26 (s, 3H, CH_3), 1.50 (td, 1H, $H4_a$, J=7.2, 12.6 Hz), 1.67 (complex, 2H, $H4_b$ and $H3_a$), 1.82 (complex, 2H, $H6_a$ and $H7_a$), 1.94 (complex, 2H, H1 and $H6_b$), 2.06 (m, 1H, $H7_b$), 2.45 (td, 1H, $H3_b$, J=7.2, 13.2 Hz), 2.73 (1H, dd, H1', J= 0.82 and 5.4 Hz), 2.82 (1H, d, H1', J=5.4 Hz). δ_c[†] (50 MHz): 15.7 (CH_2, C7), 26.6 (CH_3), 30.3 (CH_2, C6), 31.6 (CH_2, C3), 37.7 (CH_2, C4), 44.3 (q), 45.1 (CH, C1), 57.0 (CH_2, C1'), 67.2 (q). υ_{max}: 3000(s), 2250(m), 1468(m), 1455(m), 1265(s) cm^{-1}. M/z: 138($M^{+\cdot}$,30%), 123(30), 81(81), 69(87), 57(35), 55(100), 43(67), 41(74). The spectra are reproduced in 'Chapter 2 Results and Discussion' on p. 48, and 49.

[¶] COSY and HETCOR experiments were used to assign the resonances.

[†] DEPT and HETCOR experiments were used to assign the resonances.

(1SR,5SR)-5-Methyl-2-methylene bicyclo[3.2.0]heptane* **9r** CAS [73416-66-1]

This compound has been previously prepared by *Rosini*, by an alternative procedure.[26]

To a solution of methyltriphenylphosphonium iodide (4.23 g, 10.5 mmols) in diethyl ether (25 mL), under a nitrogen atmosphere, was added potassium *t*-butoxide (1.62 g, 14.5 mmols) over 5 minutes. After stirring of the reaction mixture at ambient temperature for 20 minutes, the yellow reaction mixture was cooled to 0°C and (1SR,5SR)-5-methylbicyclo[3.2.0]heptan-2-one (1.10 g, 8.94 mmols) was added dropwise. After stirring for 15 hours at ambient temperature, the still yellow solution was filtered through celite and solvent was removed at atmospheric pressure. An evaporative distillation (kugelrohr) 760mm/60°C gave the *title compound* as a colourless liquid (436 mg, 40%). δ_H (200 MHz): 1.20 (3H, s, CH_3), 1.2-2.0 (5H, complex, ring protons), 2.30 (2H, complex, ring protons), 2.42 (1H, dm, 16.6 Hz, ring proton), 2.75 (1H, m, ring proton), 4.66 (1H, br s, alkene proton), 4.76 (1H. br s, alkene proton). δ_c (50 MHz) : 22.0, 26.4, 30.2, 33.2, 40.2, 45.8, 48.7, 104.3, 158.5. υ_{max} : 3000(s), 2900(m), 1620(w), 1455(w) cm^{-1}. M/z: 122($M^{+\cdot}$,29%), 107(44), 93(72), 79(100), 59(95), 43(19). Anal Calcd for C_9H_{14} : C, 88.53; H, 11.47. Found: The analyst claimed that the sample is too volatile.

(1SR,2RS,5SR)-5-Methyl-2-methylene oxide bicyclo[3.2.0]heptane **40r** and (1SR,2SR,5SR)-5-Methyl-2-methylene oxide bicyclo[3.2.0]heptane **41r**

a) Method employing *m*CPBA at -5°C

The alkene (30 mg, 0.25 mmols) **9r** was added to the two phase solution of ether (3 mL) and 0.68M aqueous sodium bicarbonate solution (3 mL). After cooling of the reaction to 0°C *m*CPBA (71 mg of 90% *m*CPBA, purified from Aldrich 60% *m*CPBA,[125] 0.37 mmols) was added portionwise over 15 minutes. The reaction mixture was then left to stir at ambient temperature for 15 hours. Dichloromethane (20 mL) and water (10 mL) were added and the organic phase separated. The organic phase was successively washed with 1M sodium hydroxide (2×10 mL) and water (10 mL). The organic phase was dried and solvent was removed *in vacuuo* to give the *title compound* (21 mg, 60%).^{1}H NMR showed the presence of the two epoxides in a 20:80 ratio (*endo* **40r** : *exo* **41r**) Data for *endo* **40r**: δ_H (300 MHz): 1.26

* The naming program names the alkene **9** as (1SR,5SR)-1-methyl-4-methylene bicyclo[3.2.0]heptane, however for consistency the above name is used, which is the nomenclature used by *Rosini*.

(s, 3H, CH_3), 1.5-2.2 (complex, 8H, ring protons), 2.45 (td, 1H, H3', J=7.2, 13.2 Hz), 2.73 (1H, dd, H1', J= 0.82 and 5.4 Hz), 2.82 (1H, d, H1', J=5.4 Hz). Data for *exo* **41r**: δ_H (300 MHz): 1.20 (s, 3H, CH_3), 1.5-2.2 (complex, 8H, ring protons), 2.56 (td, 1H, H3', J=7.8, 13.8 Hz), 2.70 (1H, d, J= 4.5 Hz, H1'), 2.79 (1H, d, J= 4.5 Hz, H1').

b) Method employing *m*CPBA at -12°C

The above procedure was repeated with the following quantities; alkene **9r** (48 mg, 0.39 mmols), dichloromethane (4 mL), 0.63M sodium bicarbonate (2 mL) and *m*CPBA (76 mg of 90% *m*CPBA, purified from Aldrich 60%, 0.39 mmols). The reaction mixture was cooled to -12°C and *m*CPBA was added over 10 minutes. The *title compound* was obtained as a colourless liquid (35 mg, 64%). The ^{1}H NMR spectrum showed the presence of the two epoxides in a 10:90 ratio (*endo* **40r**: *exo* **41r**), by integration of the methyl resonances.

Section 2.3 Based-induced Isomerisations

β-Pinene oxide **63** CAS [23516-38-3]

β-Pinene was initially distilled with a spinning band column, to separate the α-pinene isomer. β-Pinene oxide **63** was prepared according to the literature,[77] with β-pinene (2.00 g, 14.7 mmols), sodium bicarbonate (4.47 g), dichloromethane (60 mL) and *m*CPBA (3.74 g, 65% Aldrich, 21.7 mmols). The *title compound* was obtained as a colourless liquid (1.26 g, 57%). δ_H (200 MHz): 0.93 (s, 3H, CH_3), 1.25 (s, 3H, CH_3), 1.2-2.6 (complex, 8H, ring protons), 2.60 (1H, AB quartet, H1', J= 5.4 Hz), 2.77 (1H, AB quartet, H1', J=5.4 Hz).

(6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)methanol **64** CAS[515-00-4]

Attempt 1[126]

Under a nitrogen atmosphere, *n*BuLi (1.4 mL, 3.22 mmols, 2.3 M solution in hexane) was added to a solution of diethylamine (0.34 mL, 3.25 mmols) in diethyl ether (1.5 mL), cooled to 0°C. After 10 min β-pinene oxide (199 mg, 1.31 mmols) in diethyl ether (2.5 mL) was added and the solution refluxed for 2 days. The reaction mixture was cooled and poured into water (100 mL), dichloromethane (30 mL) was added and the organic layer separated. The aqueous layer was extracted with dichloromethane (30 mL) and the combined organic layers were washed with 15% aqueous hydrochloric acid, saturated sodium bicarbonate solution and water. The organic layer was dried and solvent removed *in vacuo*. Flash chromatography with hexane/ ethyl acetate (97/3 v/v) as an eluant gave one major fraction which was identified to be

6,6-dimethylbicyclo[3.1.1]hept-en-2-carbaldehyde **65** (15%). δ_H (200 MHz) : 0.90 (s, 3H, CH_3), 0.94 (s, 3H, CH_3), 1.0-2.5 (m, 9H), 9.76 (s, 1H). υ_{max} (neat): 2700(w), 1716(s) cm^{-1}

Attempt 2[126]

Under a nitrogen atmosphere, *n*MeLi (3.0 mL, 3.33 mmols, 1.1 M solution in diethyl ether), formed from MeI and Li, was added to a solution of diethylamine (0.35 mL, 3.35 mmols) in diethyl ether (1.0 mL), cooled to 0°C. After 10 min β-pinene oxide (201 mg, 1.32 mmols) in diethyl ether (0.7 mL) was added and the solution refluxed for 2 days. The reaction mixture was cooled and poured into water (100 mL). Dichloromethane (30 mL) was added and the organic layer separated. The aqueous layer was extracted with dichloromethane (30 mL) and the combined organic layers were washed with water. The organic layer was dried and solvent removed *in vacuuo*, 6,6-dimethylbicyclo[3.1.1]hept-en-2-carbaldehyde **65** was the only product identified (10%). δ_H (200 MHz): 0.85 (s), 0.89(s), 1.0-2.8 (m), 3.45(d), 9.43(s). 9.61(s), 9.75(s).

Attempt 3[126]

Under a nitrogen atmosphere, *n*BuLi (3.0 mL, 6.0 mmols, 2.0 M solution in hexane) was added to a solution of diethylamine (0.47 mL, 4.5 mmols) in diethyl ether (5.0 mL), cooled to 0°C. After 10 min β-pinene oxide (395 mg, 2.59 mmols) in diethyl ether (12.0 mL) was added and the solution refluxed for 2 days. The reaction mixture was cooled and poured into water (100 mL). Dichloromethane (30 mL) was added and the organic layer separated. The aqueous layer was extracted with dichloromethane (30 mL) and the combined organic layers were washed with 7.5% hydrochloric acid, saturated sodium bicarbonate, and water. The organic layer was dried and solvent removed *in vacuuo*. Flash chromatography with hexane/ethyl acetate (95/5 v/v) as an eluant gave the *title compound* **64**, as a colourless liquid (89 mg, 21%) with the aldehyde **65** as the other product (6%).

Alcohol **64**: δ_H ($CDCl_3$, D_2O, 200 MHz): 0.85 (s, 3H, CH_3), 1.16 (d, 1H, J=8.7 Hz, ring protons), 1.31 (s, 3H, CH_3) 2.0-2.58 (m, 5H, ring protons), 3.99 (br s, 2H, H1'), 5.47 (br s, 1H, H2).

Aldehyde **65**: δ_H (200 MHz): 0.70 (s, 3H, CH_3), 1.31 (s, 3H, CH_3) 1.8-2.58 (m, 9H), 9.76 (s, 1H).

2-Cyclohexen-1-ol **67r** CAS [822-67-3]

According to the literature procedure,[47] *n*BuLi (3.1 mL, 6.2 mmols, 2.0M solution in hexane), diethylamine (0.47 mL, 4.5 mmols) in diethyl ether (5.0 mL), cyclohexene oxide **66** (0.25 mL, 2.47 mmols) in diethyl ether (12.0 mL) were combined and the solution refluxed for 24 hours. After work-up the *title product* was obtained with *trans*-2-(diethylamino)cyclohexanol **68r** (6%) present.[78] No purification was attempted. The peaks for the major component in the ^{1}H NMR spectrum were the same as those found for the commercial product.[65] Alcohol **67r**: δ_H ($CDCl_3$, D_2O, 300 MHz): 1.6-2.1 (complex, 6H, methylene protons), 4.20 (br s, 1H, 1H), 5.7-5.9 (complex, 2H, H2 and H3).

Attempted formation of [(1RS, 5SR)-5-methylbicyclo[3.2.0]hept-2-en-2-yl]methanol **38r**

Attempt 1

Under a nitrogen atmosphere, *n*BuLi (1.8 mL, 3.6 mmols, 2.0 M solution in hexane) was added to a solution of diethylamine (0.38 mL, 3.64 mmols) in diethyl ether (3.0 mL), cooled to 0°C. After 10 min a solution of the *exo* and *endo* epoxides **40r** and **41r** (206 mg, 1.49 mmols) in diethyl ether (7.0 mL) was added and the solution refluxed for 15 hours. The solution was cooled to ambient temperature and poured into water. Dichloromethane was added and the organic layer extracted, the aqueous layer was then re-extracted with dichloromethane. The combined organic extracts were dried and solvent was removed *in vacuo*. The ^{1}H NMR spectrum of the crude product showed the peaks detailed below and also peaks at; δ1.03 (t) and δ2.63 (q). Flash chromatography with ethyl acetate/hexane (3/97 v/v) as an eluant initially gave material that was unidentifiable, further elution with ethyl acetate/hexane (3/97 v/v) gave the *title compound* as a colourless liquid (4 mg, 2%). δ_H (300 MHz): 1.27 (s, 3H, CH_3), 1.35-2.5 (m, 6H, ring protons), 2.75 (br d, J=5.6 Hz, 1H, H4), 4.20 (AB quartet, 2H, H1'), 5.62 (br s, 1H, H3).

Attempt 2

Under a nitrogen atmosphere, *n*BuLi (0.9 mL, 1.8 mmols, 2.0 M solution in hexane) was added to a solution of diethylamine (0.18 mL, 1.82 mmols) in diethyl ether (1.5 mL), cooled to 0°C. Hexamethylphosphoramide (0.6 mL) was added and after 10 min a solution of the *exo* and *endo* epoxides **40r** and **41r** (95 mg, 0.69 mmols) in diethyl ether (3.5 mL) was added and the

solution refluxed for 15 hours. The solution was cooled to ambient temperature and poured into water. Dichloromethane was added and the organic layer extracted, the aqueous layer was then re-extracted with dichloromethane. The combined organic extracts were dried and solvent was removed at atmospheric pressure by distillation. The ^{1}H NMR spectrum of the crude product showed the peaks detailed below and also peaks at; δ1.03 (t) and δ2.63 (q). Flash chromatography with ethyl acetate/hexane (3/97 v/v) as an eluant initially gave material that was unidentifiable, further elution with ethyl acetate/hexane (3/97 v/v) gave the *title compound* as a colourless liquid (1.0 mg, 1%). δ_H (300 MHz): 1.27 (s, 3H, CH_3), 1.35-2.5 (m, 6H, ring protons), 2.75 (br d, J=5.6 Hz, 1H, H4), 4.20 (AB quartet, 2H, H1'), 5.62 (br s, 1H, H3).

Attempt 3

Under a nitrogen atmosphere, *n*BuLi (0.9 mL, 1.8 mmols, 2.0 M solution in hexane) was added to a solution of diisopropylamine (0.24 mL, 1.71 mmols) in diethyl ether (1.5 mL), cooled to 0°C. After 10 min a solution of the *endo*-epoxide **40r** (99 mg, 0.72 mmols) in diethyl ether (4 mL) and HMPA (0.1 mL) were added and the solution refluxed for 15 hours. The solution was cooled to ambient temperature and poured into water. Dichloromethane was added and the organic layer extracted, the aqueous layer was then re-extracted with dichloromethane. The combined organic extracts were dried and solvent was removed *in vacuo*. Flash chromatography with ethyl acetate/hexane (10/90 v/v) as an eluant gave what was presumed to be the aldehyde **70r** as the major product (24 mg, 24%). δ_H (200 MHz): 1.27 (s, 3H, CH_3), 1.0-2.5 (m, 10H, ring protons), 9.77 (s, 1H).

[(1RS,2RS,5SR)-5-Methylbicyclo[3.2.0]hept-2-yl]methanol **71r** and [(1RS,2SR,5SR)-5-methylbicyclo[3.2.0]hept-2-yl]methanol **72r**

The alkene **9r** (105 mg, 0.86 mmols) in diethyl ether (2 mL) was cooled to 0°C and a solution of borane-methyl sulfide complex (0.1 mL, 1 mmols, 10.0 M solution in diethyl ether) was added dropwise. After being allowed to stir at ambient temperature for 15 hrs, ethanol (0.1 mL) and 3N sodium hydroxide (0.4 mL) were added and the solution was cooled to 0°C. Hydrogen peroxide (0.4 mL, 30% solution in water) was added and the solution refluxed for 2 hrs. After cooling to ambient temperature the solution was diluted with water and extracted with diethyl ether. The aqueous phase was successively washed with water (2×) then saturated sodium chloride solution (1×). The organic extract was dried and solvent was removed *in vacuo*. Flash

chromatography with ethyl acetate/hexane (10/90 v/v) as an eluant gave the *title compounds* as a colourless oil (36 mg, 30%). The ^{1}H NMR spectrum showed the presence of two isomers in a ratio of 8.3:1.7. $\upsilon_{max}(CDCl_3)$: 3459(br), 3000(s), 1077(m) cm^{-1}

δ_H (200 MHz): 1.20 (6H, s, CH_3), 1.2-2.25 (20H, complex, ring protons + OH), 2.35 (2H, m, H2), 3.35 (2H, d, H1', J = 7.4 Hz, **72r**), 3.65 (2H, d, H1', J = 7.4 Hz, **71r**). δ_c (50 MHz): 13.60, 27.07, 28.76, 31.03, 40.26, 42.56, 44.90, 46.05, 63.07.

(1RS,2RS,5SR)-5-Methylbicyclo[3.2.0]hept-2-carbaldehyde **73r** and (1RS,2SR, 5SR)-5-methylbicyclo[3.2.0]hept-2-carbaldehyde **74r**

To a solution of pyridinium chlorochromate (78 mg, 0.36 mmols) in dichloromethane (1 mL), under a nitrogen atmosphere, was added a mixture of the alcohols **71r** and **72r** (26 mg, 0.18 mmols) in dichloromethane (0.5 mL). After being allowed to stir for 15 hours the solution was diluted with diethyl ether (10 mL). The solution was decanted from the precipitate and the residue was washed with diethyl ether (10 mL). The organic solution was filtered through fluorisil. Removal of the solvent *in vacuo* gave the *title compound* as a slightly brown oil (22 mg, 90%). The ^{1}H NMR spectrum showed the presence of two isomers in a ratio of 7.5:2.5

δ_H (200 MHz): 1.30 (6H, s, CH_3), 1.2-2.25 (18H, complex, ring protons), 2.65 (1H, m, H2, **74r**), 2.75 (1H, m, H2, **73r**), 9.59 (1H, s, aldehyde, **74r**), 9.77 (1H, s, aldehyde, **73r**)

1-oxaspiro[2.4]heptane **75r**

To anhydrous, degassed DMSO (25 mL) was added sodium hydride (730 mg, 30.42 mmols), (dispersion, oil removed). The flask was fitted with a gooch tube containing trimethylsulfoxonium iodide **60** (7.17 g, 30.6 mmols) and put under a nitrogen atmosphere. The sulfoxonium iodide **60** was added portionwise over 10 minutes. After the reaction mixture had stirred at ambient temperature for 30 minutes, cyclopentanone (2.3 mL, 26.0 mmols) was then added over 5 minutes. The reaction mixture was stirred at ambient temperature for 15 min then heated at 60°C for 2 hours. After cooling to ambient temperature, the reaction mixture was poured into water (80 mL), then extracted with dichloromethane (2×40 mL). The combined organic phases were washed with water (3×60 mL) and saturated brine solution (60 mL). The organic phases were dried and solvent was removed by distillation at atmospheric pressure. Flash chromatography with ethyl acetate/hexane (10/90 v/v) as an eluant gave the *title*

compound as a colourless liquid (2.43 g, 68%). δ_H (200 MHz): 1.5-2.1 (complex, 8H, methylene protons), 2.86 (s, 2H, H1').

Reaction of 1-oxaspiro[2.4]heptane **75r** with Trimethylsilyl Triflate (TMSOTf)

This experiment is based on the general procedure of *Noyori et al.*[82,83] A solution of toluene (3.5 mL), 2,6-lutidine (0.25 mL) and trimethylsilyl triflate (0.40 mL, 2.0 mmols), under a nitrogen atmosphere, was cooled to –78°C. The epoxide **75r** (222 mg, 2.23 mmols) was added dropwise and the solution stirred at –78°C for 3 hours. The reaction mixture was allowed to warm to ambient temperature and DBU (0.3 mL) was added. After stirring at ambient temperature for 16 hours, the solution was poured into water. Dichloromethane was added and the aqueous phase was separated, the aqueous phase was then extracted with dichloromethane (2×). The combined organic phases were washed with 15% hydrochloric acid, dried and solvent was removed *in vacuuo*. Cyclopentenylmethanol **76r** was obtained as a colourless liquid (96 mg, 44%). δ_H (300 MHz): 1.0-2.1 (m, 6H, ring protons), 4.20 (AB quartet, 2H, H1'), 5.62 (br s, 1H, H2).

Attempted formation of [(1RS,5SR)-5-methylbicyclo[3.2.0]hept-2-en-2-yl]methanol **38r** with TMSOTf

Attempt 1

A solution of toluene (3.5 mL), 2,6-lutidine (0.25 mL) and trimethylsilyl triflate (0.40 mL, 2.0 mmols), under a nitrogen atmosphere, was cooled to –78°C. The *endo* epoxide **40r** (203 mg, 1.47 mmols) was added dropwise and the solution stirred at –78°C for 3 hours. The reaction mixture was allowed to warm to ambient temperature and DBU (0.25 mL) was added. After stirring at ambient temperature for 16 hours, the solution was poured into water. Dichloromethane was added and the aqueous phase separated. The aqueous phase was extracted with dichloromethane (2×). The combined organic phases were washed with 15% hydrochloric acid, dried and solvent was removed *in vacuuo*. The ^{1}H NMR showed no identifiable products.

Attempt 2

A solution of benzene (1.4 mL), DBU (0.1 mL) and *endo*-epoxide **40r** (63 mg, 0.46 mmols) were combined, under a nitrogen atmosphere at ambient temperature. Trimethylsilyl triflate (0.08 mL, 0.40 mmol) was added and the solution stirred for 15 hours. The solution was poured into 15% hydrochloric acid and dichloromethane added and the aqueous phase separated. The Aqueous phase was re-extracted with dichloromethane (2×) The combined organic phases were washed with brine, dried and solvent removed *in vacuuo*. The crude ^{1}H NMR showed a minimal amount of the allylic alcohol **38** (~5%) and aldehyde **70r** present (~2%) **70r**.

Aldehyde **70r**: δ_H (200 MHz): 1.27 (s, 3H, CH_3), 1.0-2.5 (m, 10H, ring protons), 9.77 (s, 1H).

Alcohol **38**: δ_H (200 MHz): 1.27 (s, 3H, CH_3), 1.35-2.5 (m, 6H, ring protons), 2.75 (br d, J=5.6 Hz, 1H, allylic proton), 4.20 (AB quartet, 2H, H1'), 5.62 (br s, 1H, H3).

Attempt 3

A solution of dichloromethane (1.5 mL), DBU (0.2 mL) and *endo*-epoxide **40r** (99 mg, 0.72 mmols) were combined, under a nitrogen atmosphere at ambient temperature. Trimethylsilyl triflate (0.23 mL) was added and the solution stirred for 15 hours. The solution was poured into 15% hydrochloric acid and dichloromethane added and the aqueous layer separated. The aqueous phase was re-extracted with dichloromethane (2×) The combined organic phases were washed with brine, dried and solvent was removed *in vacuuo*. Purification by flash chromatography with dichloromethane/hexane (15/85 v/v) gave the *title compound* as a colourless liquid (27.3 mg, 27%). δ_H (200 MHz): 1.27 (s, 3H, CH_3), 1.35-2.5 (m, 6H, ring protons), 2.75 (br d, J=5.6 Hz, 1H, H4), 4.20 (AB quartet, 2H, H1'), 5.62 (br s, 1H, H3).

Section 2.4 Formation of allylic alcohol via tosylhydrazone.

A Mixture of E and Z isomers of *N*'-1-[(1SR, 5SR)-5-methylbicyclo[3.2.0]hep-2-yliden]-4-methyl-1-benzene sulfono-hydrazide **81r**

Tosylhydrazine (3.53 g, 18.9 mmols) was added to 60% aqueous methanol (46.7 mL) heated to 60°C. (1SR,5SR)-Methylbicyclo[3.2.0]heptan-2-one **12r** (2.33 g, 18.8 mmols) was then added dropwise to the clear solution. The reaction mixture was immediately stored at 5°C for 15 hours. The resultant white crystals were filtered, washed with 60% aqueous methanol, and air-

dried for 10 minutes. The *title compound* was yielded as white crystals (4.91 g, 89%), mp 174-176°C. Attempts to recrystallize the *title compound* from both methanol and 60% aqueous methanol were unsuccessful. ^{1}H NMR revealed a 1:1 mixture of isomers. δ_H (200 MHz): 1.21 (s, 3H, CH_3), 1.23 (s, 3H, CH_3), 2.42 (br s, 6H, Ar-CH_3), 1.35-2.9 (m, 18H, ring protons), 4.06 (br s, 2H, NH), 7.30 (dm, J= 8.0 Hz, 4H, Ar,), 7.82 (d, J= 8.0 Hz, 4H, Ar). δ_c (50 MHz): 18.6, 21.4, 21.5, 25.3, 25.5, 27.9, 29.8, 30.0, 33.2, 36.7, 37.3, 42.1, 44.1, 45.9, 48.0, 127.9, 129.5, 135.6, 143.58, 171.4, 172.3. υ_{max}: 3297, 3220 (2 peaks, NH), 2954(s), 2863(s), 1598(w), 1494(w), 1452(w), 1384 (m), 1166(s), 673(m) cm^{-1}. M/z: 293($M^{+\cdot}$,100%), 137(94), 109(38), 93(59). Anal Calcd for $C_{15}H_{20}O_2SN$: C, 61.61; H, 6.89. Found: C, 61.48; H, 7.03.

Attempted formation of [(1RS,5SR)-5-methylbicyclo[3.2.0]hept-2-en-2-yl] methanol **38r** directly from the hydrazone **81r**

Caution: Nitrogen is produced in this reaction and allowance must be made for its escape. Do not use a sealed system.

The reaction was carried out in a 3-necked flask. A nitrogen line was fitted to one neck, a septum in another, and the last neck had an apparatus attached so gaseous formaldehyde could be bubbled through.

A suspension of the tosylhydrazone **81r** (1.40 g, 4.82 mmols) and TMEDA (15 mL) was cooled to -78°C, under a nitrogen atmosphere. The suspension froze to give a white solid after 10 minutes. *n*-BuLi (2.5 M, 8.1 mL, 20.25 mmols) was added dropwise over a 10 minute period, the frozen mixture melted as the *n*-BuLi was added. The resulting light orange solution was allowed to warm to ambient temperature, the solution initially turned a dark red, and then changed to a yellow-brown colour on reaching ambient temperature. The solution was stirred for a further 4 hours, then cooled to 0°C. A vessel, directly attached by a short path, containing paraformaldehyde (1.03 g, 34.32 mmols) was heated to 180°C, and gaseous formaldehyde was bubbled through the solution. The reaction mixture was then allowed to warm to ambient temperature. After being allowed to stir for 15 hours, the reaction mixture was poured in water and extracted with dichloromethane (3×). The combined organic phases were washed with 15% HCl (2×) then saturated sodium bicarbonate solution, dried and solvent was removed at atmospheric pressure by distillation. Flash chromatography with dichloromethane as an eluant gave the *title compound* as a light orange oil (33 mg, 5%). δ_H (300 MHz): 1.27 (s, 3H, CH_3), 1.35-2.5 (m, 6H, ring protons), 2.75 (br d, J=8.0 Hz, 1H, allylic), 4.20 (AB quartet, 2H, H1'),

5.62 (br s, 1H, H3). δ_c (75 MHz) : 23.3, 25.0, 33.2, 44.5, 47.2, 50.1, 60.9, 125.5, 147.1. υ_{max}: 3613(s), 3039(w), 2894(s), 2861(s), 1452(m), 1375(w), 1027(s), 979(s), 817(w) cm^{-1}. M/z: 138($M^{+\cdot}$,17%), 110(51), 105(43), 95(100), 79(90), 67(37), 49(67), 39(55), 31(38).

(1RS,5SR)-5-methylbicyclo[3.2.0]hept-2-ene-2-carbaldehyde **88r**

Caution: Nitrogen is produced in this reaction and allowance must be made for its escape. Do not use a sealed system.

A suspension of the tosylhydrazone **81r** (1.04 g, 3.59 mmols) and TMEDA (15 mL) was cooled to -78°C, under a nitrogen atmosphere. After 10 min *n*-BuLi (2.3 M, 4.6 mL, 10.58 mmols) was added dropwise to the frozen suspension. After addition was complete, the solution was kept at -78°C for 15 min, then allowed to warm to ambient temperature, where the solution turned a dark red. After the solution was stirred for a further 5 hours it was cooled to 0°C and DMF (0.4 mL, 5.18 mmols) was added, and the solution stirred at ambient temperature overnight. The reaction mixture was poured into 7.5% HCl (60 mL) and extracted with dichloromethane (4×40 mL). The combined organic phases were washed with brine (40 mL), dried and solvent removed *in vacuuo*. The crude material was used directly in the next reaction. A small portion was chromatographed with dichloromethane to give a pure sample for analytical methods. δ_H (300 MHz): 1.30 (s, 3H, CH_3), 1.6-2.1 (m, 3H, ring protons), 2.2-2.6 (m, 3H, ring protons), 3.02 (br d, J=8.2 Hz, 1H, allylic), 6.87 (br s, 1H, H3), 9.78 (s, 1H, H-C=O). δ_c (75 MHz) : 23.4, 24.6, 33.0, 44.4, 46.9, 47.9, 150.8, 152.6, 190.1. υ_{max}(neat): 3051(s), 2864(s), 2824(s), 2723(m), 1680(s), 1451(s), 1265(s), 1174(m) cm^{-1}. M/z: 136($M^{+\cdot}$,11%), 121(41), 108(57), 84(84), 79(100), 65(16), 39(34).

[(1RS,5SR)-5-methylbicyclo[3.2.0]hept-2-en-2-yl] methanol **38r** from the aldehyde **88r**

The crude aldehyde **88r** (max. 3.59 mmols) was dissolved in methanol (15 mL) and ceric chloride (0.1 mL) was added. To the reaction mixture, under a nitrogen atmosphere, was added portion wise sodium borohydride (201 mg, 5.32 mmols). After being allowed to stir at ambient temperature for 4 hours the solution was diluted with dichloromethane (40 mL), washed with 7.5% HCl (30 mL). The aqueous phase was further extracted with dichloromethane (2×20 mL). The combined organic extracts were washed with brine (10 mL), dried and solvent removed *in vacuuo*. Flash chromatography with dichloromethane as an eluant gave the *title compound* (477

mg, 83%, over two steps). δ_H (600 MHz)[¶]: 1.27 (s, 3H, CH_3), 1.69 (m, 1H, $H7_a$), 1.79 (m, 1H, $H6_a$), 1.94 (m, 1H, $H6_b$), 2.1-2.3 (complex, 3H, H4, $H7_b$), 2.74 (d, 1H, J=7.8 Hz, H1), 4.12 (AB quartet, 1H, J=15.5 Hz, $H1_a$'), 4.20 (AB quartet, 1H, J=15.5 Hz, $H1_b$'), 5.62 (s, 1H, H3). δ_c and DEPT (75 MHz) : 23.2 (CH_2), 25.0 (CH), 33.2 (CH_2), 44.4 (q), 47.2 (CH_2), 50.1 (CH_3), 60.5 (CH_2), 125.0 (CH), 146.9 (q). υ_{max}(neat): 3338 (br, s, OH), 3051(s), 2864(s), 1450(s), 1035(s), 995(m) cm^{-1}. M/z: 138($M^{+\cdot}$,15%), 123(8), 110(42), 95(100), 79(90), 49(65). Accurate Mass Spectrum: (MH^+) Expect 139.11228 Obtained 139.11195. Anal Calcd for $C_9H_{14}O$: C, 78.21; H, 10.20 Found: C, 78.19; H, 9.96.

Section 3.1.1 Six-membered Ring Trial Compound

Ethyl 2-cyclohexylidenacetate **91r** CAS [1552-92-7]

This experiment is based on the general procedure of *Wadsworth* and *Emmons*.[127] To a suspension of potassium *t*-butoxide (9.98 g, 88.9 mmols) in anhydrous THF (50 mL), cooled to 0°C, was added dropwise a solution of triethylphosphonoacetate (17.5 mL, 19.77 g, 88.2 mmols) in anhydrous THF (50 mL) and let stir at ambient temperature for 30 minutes. Then cyclohexanone (8.9 mL, 8.42 g, 88.5 mmols) in anhydrous THF (50 mL) was added dropwise. Upon work-up and removal of solvent by distillation at atmospheric pressure, the *title compound* was obtained as a colourless liquid (8.36 g, 56%). The ester was used without purification in the next step. δ_H (300 MHz): 1.27 (3H, t, CH_3, J=7.1Hz) 1.6 (6H, m, methylene ring protons), 2.17 (2H, m, H2), 2.80 (2H, m, H6), 4.13 (2H, q, $C\underline{H_2}CH_3$, J=7.1Hz), 5.6 (1H, m, olefinic proton). δ_C (75MHz): 14.1, 26.1, 27.6, 28.4, 29.6, 37.8, 59.2, 113.0, 163.4, 166.8. υ_{max}(neat): 2879(s), 2856(s), 1716(s), 1648(s), 1448(s), 1378(s)cm^{-1}. M/z: 168(M^+ ,100%), 140(45), 123(70).

2-Cyclohexyliden-1-ethanol **90r** CAS [932-89-9]

The *title compound* was prepared by a general literature procedure.[93] To a suspension of lithium aluminum hydride (729.9 mg, 19.2 mmols) in diethyl ether (22 mL) cooled to -78°C was added ethyl 2-cyclohexylidenacetate **91r** (2.89 g, 17.2 mmols). After stirring at -78°C for 4 hours then ambient temperature for 2hr the reaction was carefully quenched with 15% $HCl_{(aq)}$. After work-up the solvent was removed *in vacuuo* to yield a colourless liquid (2.16 g, 89%). The alcohol was used without purification. δ_H (300 MHz): 1.57 (6H, m, H3, H4, H5) 2.17 (4H, m, H2, H6), 4.13 (2H, d, CH_2OH, J=6.9Hz), 5.36 (1H, td, olefinic proton, J= 6.9, 2.4Hz). δ_C (75MHz): 26.5, 27.7, 28.3, 28.7, 36.9, 58.4, 120.4, 144.5. υ_{max}(neat): 3332(broad), 2925(s), 1447(s), 1240(s)cm^{-1}. M/z: 126(M^+ ,22%), 108(100), 93(60).

(±)-1-Oxaspiro[2.5]oct-2-ylmethanol **92r**

To a solution of 2-cyclohexyliden-1-ethanol **90r** (202 mg, 1.60 mmols) in dichloromethane (2 mL) was added 0.63M aqueous sodium bicarbonate (2 mL). After the solution was cooled to 0°C, *mCPBA* (358 mg of 80% *m*CPBA, purified from Aldrich 60% *m*CPBA,[125] 1.76 mmols) was added portionwise over 5 minutes. After stirring at 0°C for 1 hour the reaction was stirred at ambient temperature overnight. Dichloromethane was added and the reaction mixture was

washed with 6N NaOH (1×) and $NaHCO_3$ (1×). The organic phase was dried and the solvent was removed *in vacuuo*. Flash chromatography with hexane/ethyl acetate (70/30 v/v) as an eluant gave the *title compound* as a colourless liquid (180 mg, 80%). δ_H (300MHz): 1.5-1.8 (10H, complex, methylene envelope), 2.2 (1H, br s, OH), 2.97 (1H, X portion of ABX system, at least 4 lines, H2), [AB of ABX system, at least 8 lines, centred at 3.69 (1H, H1'$_a$) and centred at 3.85 (1H, H1'$_b$)]. δ_C (75MHz): 24.7, 25.4, 35.3, 60.9, 63.4, 64.1. M/z: 143(MH^+ ,5%), 88(100).

Tris-[3-(heptafluoropropyl-hydroxymethylene)-d-camphorato]-europium(III) (11 mg) added to the epoxide **92r** (9 mg) in CCl_4 (0.5 mL) and C_6D_6 (0.1 mL) gave useful separation of the peak initially at δ3.69 in the ^1H NMR spectrum (200 MHz).

Attempted preparation of optically active 1-Oxaspiro[2.5]oct-2-ylmethanol **92a** from Sharpless asymmetric epoxidation reaction

Following the procedure of Sharpless,[40] an anhydrous flask was flushed with nitrogen and charged with *n*-decane (40 μL), (L)-(+)-diisopropyl tartrate (27 mg, 0.12 mmols), activated, powdered 4 Å sieves (38 mg), and a solution of the alcohol (100 mg, 0.80 mmols) in anhydrous dichloromethane (2 mL), previously dried over 3Å sieves for 1hr. The flask was cooled to –20°C and titanium(IV)isopropoxide (0.35 mL, 0.08 mmols) were added and the solution stirred at –20°C for 1 hour. The flask was then cooled to –40°C and *tert*-butyl hydroperoxide solution (0.15 mL of a 4.2 M dichloromethane solution, 0.63 mmol), previously dried[40] and then freshly dried over freshly activated 3Å sieves for 15 min. At timed intervals, aliquots (0.1 mL) of the reaction mixture were taken (with an oven dried syringe), quenched with 0.1 mL of a solution of $FeSO_4$ (1.6 g/5 mL) and citric acid (0.5 g/5 mL), dichloromethane (0.1 mL) was added and the organic layer separated. The organic layer was then analyzed by GLC (150°C) for the remaining allylic alcohol relative to the internal standard *n*-decane. After the reaction was complete it was quenched with 5 mL of a solution of $FeSO_4$ (1.6 g/5 mL) and citric acid (0.5 g/5 mL) then left for 15 hours (convenience). The reaction mixture was diluted with dichloromethane and the organic layer was separated and the aqueous layer was re-extracted with dichloromethane (2×). The combined organic phases were washed with saturated sodium chloride solution (1×), dried and solvent removed *in vacuuo*. Flash chromatography with hexane/ethyl acetate (70/30 v/v) did not give the expected product but a colourless liquid identified as 2-(1-Cyclohexenyl)oxirane **94a** (47%). δ_H (200MHz): 1.5 (4H,

complex, methylene envelope), 1.8 (4H, complex, methylene envelope), [AB of ABX system at least 8 lines, one centred at 3.46 (1H, H3') and the other centred at 3.59 (1H, H3'$_b$)], 4.01 (1H, X portion of ABX system, at least 4 lines, H2'), 5.66 (1H, br s, H2). δ_C (150MHz): 22.4, 22.5, 24.8, 24.9, 65.4, 76.2, 123.9, 136.7. GC/MS: 124 (M^+ ,65%), 109(17), 96(82), 95(100), 80(75).

Successful preparation of optically active 1-Oxaspiro[2.5]oct-2-ylmethanol **92a** from Sharpless asymmetric epoxidation reaction

The above procedure was repeated with the following quantities; *n*-decane (40 μL), (L)-(+)-diisopropyl tartrate (24 mg, 0.10 mmols), activated, powdered 4 Å sieves (33 mg), a solution of the alcohol (102 mg, 0.81 mmols) in anhydrous dichloromethane (2 mL), titanium(IV)isopropoxide (0.35 mL, 0.08 mmols) and and *tert*-butyl hydroperoxide solution (0.16 mL of a 3.8 M dichloromethane solution, 0.61 mmol). At timed intervals, aliquots (0.1 mL) of the reaction mixture were taken (with an oven dried syringe), quenched with 0.1 mL of a solution of $FeSO_4$ (1.6 g/5 mL) and citric acid (0.5 g/5 mL), dichloromethane (0.1 mL) was added and the organic layer separated. After the reaction was complete it was quenched with sodium thiosulfate (5 mL) and then left for two days (for comparison with the $FeSO_4$ solution). Upon work-up and chromatography, (same as the above reaction), the *title compound* was obtained as a colourless oil (52 mg, 45%) with no rearranged epoxide **94a** present in the ^{1}H NMR spectum. δ_H (300MHz): 1.5-1.8 (10H, complex, methylene envelope), 2.2 (1H, br s, OH), 2.97 (1H, X portion of ABX system, at least 4 lines, H2), [AB of ABX system, at least 8 lines, one centred at 3.69 (1H, H1'$_a$) and the other centred at 3.85 (1H, H1'$_b$)].

Tris-[3-(heptafluoropropyl-hydroxymethylene)-d-camphorato]-europium(III) (11 mg) added to the epoxide **92a** (9 mg) in CCl_4 (0.5 mL) and C_6D_6 (0.1 mL) gave separation of the peaks initially at δ3.69 in the ^{1}H NMR spectrum (200 MHz) and the enantiomeric excess was be estimated to be at least 90%.

2-(1-Cyclohexenyl)oxirane **94r**

To a solution of the racemic 1-oxaspiro[2.5]oct-2-ylmethanol **92r** (410 mg, 2.88 mmols) in dichloromethane (8 mL) and water (5 mL) was added iron(II) sulfate heptahydrate (1.68 g, 6.04 mmols). After stirring at ambient temperature for 6 days the dichloromethane (30 mL) was added to the solution and the aqueous phase separated. The aqueous phase was re-

extracted with dichloromethane (2×) and the combined organic layers were dried and solvent was removed *in vacuuo*. Flash chromatography with hexane/ethyl acetate (70/30 v/v) as an eluant gave the *title compound* as a colourless liquid (271 mg, 76%). δ_H (200MHz): 1.5 (4H, complex, methylene envelope), 1.8 (4H, complex, methylene envelope), [AB of ABX system at least 8 lines, one centred at 3.46 (1H, H3') and the other centred at 3.59 (1H, H3'$_b$)], 4.01 (1H, X portion of ABX system, at least 4 lines, H2'), 5.66 (1H, br s, H2).

Section 3.1.2 Determination of Optical Purity of the Key Intermediate

[(1SR,5SR)-5-Methylbicyclo[3.2.0]hept-2-ene-2-yl]methyl acetate **95**

To the alcohol **38**, (18 mg, 0.13 mmols) dissolved in pyridine (0.3 mL) was added acetic anhydride (0.05 mL, 0.49 mmols) and the reaction mixture was stirred at ambient temperature, under a nitrogen atmosphere, for 10 hours. A few drops of water were then added, to hydrolyze the excess acetic anhydride. Dichloromethane (20 mL) and water (10 mL) were added to the mixture and it was washed with 15% hydrochloric acid solution (2×20 mL), saturated sodium bicarbonate solution (10 mL), dried and solvent removed *in vacuuo*. The *title compound* was obtained as a white solid* (20 mg, 86%). δ_H (200 MHz): 1.26 (s, 3H, CH_3), δ 1.3-2.4 (6H, complex, ring protons), 2.06 (s, 3H, $COCH_3$), 2.72 (br d, J=7.8 Hz, 1H, H4), 4.63 (br s, 2H, H1'), 5.66 (br s, 1H, H3). δ_c (50 MHz): 20.9, 23.2, 25.0, 33.1, 44.5, 47.3, 50.5, 62.1, 128.7, 141.8, 170.9. υ_{max}: 2947(s), 2839(s), 1732(s), 1452(m), 1378(m), 1254(s), 897(m) cm^{-1}. M/z: 180($M^{+\cdot}$,3%), 179(17), 138(10), 121(100), 120(67), 105(45), 92(81), 43(15).

Tris-[3-(heptafluoropropyl-hydroxymethylene)-d-camphorato]-europium(III) (16 mg) added to the acetate **95** (6 mg) in CCl_4 (0.5 mL) and C_6D_6 (0.1 mL) gave no significant separation of peaks in the ^{1}H NMR spectrum at 200 MHz.

[(1RS, 5SR)-5-Methylbicyclo[3.2.0]hept-2-en-2-yl] methanol **38**

Tris-[3-(heptafluoropropyl-hydroxymethylene)-d-camphorato]-europium(III) (17 mg) added to the alcohol **38** (6 mg) in CCl_4 (0.5 mL) and C_6D_6 (0.1 mL) gave no significant separation of peaks in the ^{1}H NMR spectrum at 200 MHz.

* In the preparation of many derivatives for optical purity measurements, no purification was attempted so as to avoid possible fractionation of diastereomers.

GC analysis of the allylic alcohol **38** with an SGE Cydex-B, 25m × 0.22mm, [110°C for 11 min, then ramped to 200°C at 50°C/min, then held for 2 min] gave partial separation, but not enough to be useful.[97]

Mosher ester of the racemic allylic alcohol **38r**: [(1SR,2RS,5SR)-5-Methylbicyclo[3.2.0]-hep-2-en-yl]methyl (2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate **96** and **97**

According to the procedure of Hassner,[99] a solution of the (R)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (26 mg, 0.11 mmols), N,N-dicyclohexylcarbodiimide (DCC) (19 mg, 0.090m mmols), the racemic alcohol **38r** (14 mg, 0.102 mmols), dimethyl-aminopyridine (2 mg, 0.019 mmols) in dichloromethane (0.7 mL) were allowed to stand at ambient temperature until esterification was complete. The N,N-dicyclohexyl urea was filtered and the filtrate washed with water (3×5 mL), 5% citric acid solution (3×5 mL) and again with water (3×5 mL), dried and the solvent evaporated *in vacuuo*. Flash chromatography with hexane/ethyl acetate* (95/5, v/v) as an eluant gave the corresponding Mosher ester as a colourless oil (15 mg, 55%). The ^{1}H NMR spectrum at 200 MHz showed the presence of only one diastereomer except for the two sharp methyl singlets near δ1.23. From the ^{1}H NMR spectrum of the products from the racemic and optically active samples it was possible to assign the following data.

Data for **96:** δ_H (600 MHz): 1.24 (s, 3H, CH_3), 1.3-2.0 (6H, complex, ring protons), 2.24 (m, 3H, ring protons), 2.62 (m, 1H, H4), 3.55 (br s, 3H, OCH_3), [AB quartet, one centred at 4.84 (1H, H1'$_a$) and the other at 4.91 (1H, H1'$_b$)], 5.69 (br s, 1H, H3), 7.35-7.55 (m, 5H, ArH).

Data for **97:** δ_H (600 MHz): 1.24 (s, 3H, CH_3), 1.3-2.0 (6H, complex, ring protons), 2.24 (m, 3H, ring protons), 2.62 (m, 1H, H4), 3.56 (br s, 3H, OCH_3), [AB quartet, one centred at 4.84 (1H, H1'$_a$) and the other at 4.89 (1H, H1'$_b$)], 5.70 (br s, 1H, H3), 7.35-7.55 (m, 5H, ArH). The AB quartet region of the ^{1}H NMR spectrum is reproduced in 'Chapter 2, Results and Discussion' p. 81.

* In the preparation of Mosher esters for optical purity measurements, purification by chromatography was performed with a short column and care was taken so as to avoid possible fractionation of diastereomers

Mosher ester of the optically active allylic alcohol **38a** : [(1SR,2RS,5SR)-5-Methylbicyclo[3.2.0]-hep-2-en-yl]methyl (2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate **96** and **97**

The above procedure was repeated with numerous optically active allylic alcohols **38a**. By separation of resonances for the diastereotopic methylene group of the diastereomers in the ^{1}H NMR spectrum the enantiomeric excess could be estimated, as previously discussed in 'Chapter 3, Results and Discussion'

Section 3.1.3 Kinetic Resolution of the Key Intermediate

[(1RS,2RS,5RS,7RS)-8-oxatricycl[5.1.0.0^{2,5}]octyl]methanol **98r** and [(1SR,2RS,5RS,7SR)-8-oxatricycl[5.1.0.0^{2,5}]octyl]methanol **99r**[§]

A solution of the allylic alcohol **38** (33 mg, 0.24 mmols) in dichloromethane (2 mL) was cooled to –40°C and *mCPBA* (104 mg of 80% *m*CPBA, purified from Aldrich 60% *m*CPBA, 0.49 mmols) was added portionwise over 5 minutes and let stir at -40°C overnight. Then dichloromethane was added and the reaction mixture was washed with $Na_2S_2O_3$ (1×) and 3N $NaOH_{(aq)}$ (1×). The organic phase was dried and the solvent was removed *in vacuo*. The ^{1}H NMR spectrum of the crude product showed the ratio of *exo* to *endo* epoxide was 4.3:1. Flash chromatography with hexane/ethyl acetate (70/30 v/v) as an eluant gave two epoxides as a colourless oil. *Exo*-epoxide **98r** (16 mg, 44%), *Endo*-epoxide **99r** (2 mg, 7%)

Exo-epoxide **98** δ_H (300MHz, $CDCl_3/D_2O$): 1.12 (s, 3H, CH_3), 1.7-2.1 (complex, 7H, ring protons), 2.44 (dd, 1H, C<u>H</u>-O, J = 5, 8.5 Hz), 3.74 and 3.94 (AB quartet, 2H, H1', J = 12.5 Hz). δ_c (50 MHz): 16.9, 28.6, 32.9, 42.6, 44.5, 46.2, 59.1, 64.4, 73.4. υ_{max}(neat): 3432 (br, s, OH), 2861(s), 1272(s), 1184(s), 1041(s) cm^{-1}. M/z: 155(MH^+,10%), 125(30), 105(35), 95(100), 79(1990), 43(80).

Endo-epoxide **99** δ_H (300MHz, $CDCl_3/D_2O$): 1.19 (s, 3H, CH_3), 1.6 (complex, 3H, ring protons), 1.8-2.2 (complex, 5H, ring protons), 3.76 and 3.90 (AB quartet, 2H, H1', J = 13 Hz). δ_c (50 MHz): 17.0, 27.1, 34.0, 41.7, 44.3, 46.5, 60.6, 67.3, 72.4.

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§ The naming program names the epoxides as [(1a<u>RS</u>, 1b<u>RS</u>, 3<u>RS</u>, 4<u>RS</u>)-3a-methylperhydrocyclobuta[3,4]cyclopenta[*b*] oxiren-1-yl]methanol **98r** and [(1a<u>SR</u>, 1b<u>RS</u>, 3<u>RS</u>, 4<u>RS</u>)-3a-methylperhydrocyclobuta[3,4]cyclopenta[*b*] oxiren-1-yl]methanol. However as these names bear no resemblance to the structures the above names have been used.

Kinetic Resolution of [(1RS,5SR)-5-methylbicyclo[3.2.0]hept-2-en-2-yl] methanol **38**

In general, these reactions were run as follows although the scale, number of aliquots and the time of quenching were varied throughout the studies. This procedure is the one used in the synthesis of (+)-grandisol **1a**.

A solution of L-(+)-diisopropyl tartrate (295 mg, 1.26 mmols), titanium *i*-propoxide (196 mg, 0.69 mmols), freshly activated powdered 4Å sieves (337 mg) and freshly distilled anhydrous dichloromethane (4 mL) were combined, put under a small pressure of dry nitrogen, cooled to –15°C. *tert*-Butyl hydroperoxide (1.1 mL, 5.9 M, 6.4 mmols), previously dried[40] and then freshly dried over freshly activated 3Å sieves for 15 min, was added and the solution was then cooled to –40°C and aged at –40°C for 2 hours. Then a solution of *n*-decane (0.4 mL) and the allylic alcohol **38** (1.63 g, 11.8 mmols) in dichloromethane (5 mL), which had been drying over freshly activated 3Å sieves for 15 min, were added, the sieves were washed with additional dichloromethane (2 mL) and the washings were also added to the reaction mixture. [A T_o GLC sample had been taken from the *n*-decane and allylic alcohol solution before it was added to the reaction mixture.] After the reaction had stirred at –40°C for 15 hours, an aliquot (0.1 mL) was removed (with an oven dried syringe) and quenched with 0.1 mL of a solution of $FeSO_4$ (1.6 g/5 mL) and citric acid (0.5 g/5 mL), dichloromethane (0.1 mL) was added and the organic layer separated. GLC showed that the reaction had gone to 59% completion. $Na_2S_2O_3$ (3 mL) was added and the reaction mixture was allowed to warm to ambient temperature. Dichloromethane (20 mL) was added and the organic phase was separated. The aqueous phase was re-extracted with dichloromethane (3×20 mL). The combined organic phases were washed with saturated NaCl (10 mL), dried and solvent was removed *in vacuuo*. Flash chromatography with hexane/ethyl acetate (85/15 v/v) as an eluant gave the allylic alcohol as a colourless oil (490 mg, 31% recovery). δ_H (300 MHz): 1.27 (s, 3H, CH_3), 1.35-2.5 (m, 6H, ring protons), 2.75 (br d, J=5.6 Hz, 1H, H4), 4.20 (AB quartet, 2H, H1'), 5.62 (br s, 1H, H3). $[\alpha]_D^{20}$=-1.77 ± 0.2 (c= 1.5 CH_2Cl_2).

Section 3.1.4 Enantiomeric Purity Determination

Mosher ester of the optically active allylic alcohol **38a**: [(1S,2R,5S)-5-methylbicyclo[3.2.0]hep-2-en-yl]methyl (2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate **96**

The general procedure for Mosher ester formation, p.[157], was repeated with the following reagents. Allylic alcohol **38** (7 mg, 0.05 mmols), DMAP (5 mg, 0.02 mmols), DCC (20 mg, 0.09 mmols), R-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (20 mg, 0.08 mmols) and dichloromethane (0.5 mL). The corresponding Mosher ester was obtained as a colourless oil (15 mg, 80%)

By separation of resonances for the diastereotopic methylene group of the diastereomers in the ^{1}H NMR spectrum the enantiomeric excess was estimated to be >95%. (diagram p. 88)

Section 3.2 Formation of the Bicyclic Alkene

(1SR,5SR)-2-(Chloromethyl)-5-methylbicyclo[3.2.0]hept-2-ene **101r**

To a solution of the alcohol **38** (214 mg, 1.54 mmols) in dichloromethane (3 mL) and triethylamine (0.15 mL), cooled to 0°C, was added methanesulfonyl chloride (0.1 mL, 1.29 mmol). The reaction was then stirred at ambient temperature for 15 hours. Water and dichloromethane were added to the reaction mixture. The organic layer was separated, washed with 7.5% hydrochloric acid (3×10 mL), saturated sodium bicarbonate solution (10 mL), dried and solvent removed *in vacuo*. Purification by chromatography with ethyl acetate/hexane (5/95 v/v) gave the allylic chloride as the major fraction (48 mg, 20%). δ_H (200 MHz): 1.29 (s, 3H, CH_3), 1.5-2.1 (complex, 4H, ring protons), 2.2-2.5 (complex, 2H,ring protons), 2.88 (br d, 1H, J= 8.4 Hz), 4.17 (AB quartet, 2H, H1'), 5.78 (m, 1H, olefinic proton). M/z: 156(M^+,25%), 105(72), 93(100), 55(95).

[(1RS,5SR)-5-methylbicyclo[3.2.0]hept-2-en-2-yl]methyl methanesulfonate **100r**

Methanesulfonic anhydride[128] (846 mg, 4.85 mmols) was added portionwise to a solution of the allylic alcohol **38** (438 mg, 3.17 mmols) and triethylamine (1 mL) in dichloromethane (4 mL), cooled to 0°C. After stirring at ambient temperature for 2 ½ hours the solution was diluted with dichloromethane and the mixture was washed with 15% $HCl_{(aq)}$. The aqueous phase was re-extracted with dichloromethane (2×). The combined organic layers were washed with saturated NaCl, dried and solvent was removed *in vacuo*. Purification by

chromatography with hexane/ethyl acetate (75/15 v/v) gave the *title compound* as a colourless oil (543 mg, 78%). δ_H (300 MHz): 1.29 (s, 3H, CH_3), 1.4-2.0 (m, 3H, ring protons), 2.33 (m, 3H, ring protons), 2.78 (m, 1H, allylic proton), 3.00 (s, 3H, O_2S-CH_3), 4.79 (s, 2H, H1'), 5.85 (br s, 1H, H3). δ_c (75 MHz): 23.2, 25.0, 33.1, 37.8, 44.6, 47.4, 50.2, 67.5, 132.2, 140.2. υ_{max}(neat): 3020(s), 2869(s), 1425(s), 1253(s), 1176(s), 970(s), 767(s) cm^{-1}. M/z: 217(MH^+,6%), 167(5), 138(18), 121(42), 95(83), 79(100).

[(1R,5S)-5-methylbicyclo[3.2.0]hept-2-en-2-yl]methyl methanesulfonate **100a**

The above procedure was repeated with methanesulfonic anhydride[128] (629 mg, 3.60 mmols), the allylic alcohol **38** (471 mg, 3.40 mmols), triethylamine (0.5 mL) and dichloromethane (4 mL). After purification, the *title* compound was obtained as a colourless oil (583 mg, 78%). ^{1}H NMR data of **100a** are identical with those of **100r**.

(1RS,5SR)-2,5-dimethylbicyclo[3.2.0]hept-2-ene CAS [73416-59-8] **10r**

From the allylic chloride **101**

The allylic chloride **101** (41 mg, 0.26 mmols) and triphenylphosphine (92 mg, 0.35 mmols) were combined and dissolved in THF (8 mL). To the stirred solution, under a nitrogen atmosphere, was added lithium triethylborohydride (0.8 mL, 1 M, 0.8 mmols). After the reaction mixture was stirred at ambient temperature overnight 10% $NaOH_{(aq)}$ and saturated NaCl were added. Hexane was added and the aqueous layer was separated. The aqueous layer was then re-extracted with hexane (3×). The combined organic layers were washed successively with 10% $NaOH_{(aq)}$ and saturated NaCl. The organic layer was dried and solvent was removed *in vacuo*. The ^{1}H NMR spectrum of the crude product showed resonances which corresponded to the literature values for the alkene, however numerous impurities were also present. Lit[26] δ_H (100 MHz): 1.25 (s, 3H, CH_3), 1.71 (br s, 3H, $C\underline{H}_3$-C=CH-), 5.28 (m, 1H, olefinic).

From the mesylate

A suspension of $LiAlH_4$ (122 mg, 3.21 mmols) and THF (3 mL), under a nitrogen atmosphere, was cooled to 0°C. A solution of the mesylate **100r** (350 mg, 1.60 mmols) in THF (3 mL) was cautiously added and the solution was stirred at ambient temperature for 15 hours. The solution was carefully quenched with water and then poured into water (150 mL). The solution was extracted with dichloromethane (3×20 mL). The combined organic layers were washed with

water (6×100 mL) and saturated NaCl (1×100 mL), then dried and solvent was removed by distillation at atmospheric pressure. The *title compound* was obtained as a clear oil, with some solvent impurity (450 mg). It was used crude in the next reaction. δ_H (300 MHz): 1.25 (s, 3H, CH_3), 1.4-2.0 (m, 3H, ring protons), 1.71 (br s, 3H, $\underline{C}H_3$-C=CH), 2.10 (m, 3H, ring protons), 2.55 (m, 1H, allylic proton), 5.28 (br s, 1H, H3). δ_c (75 MHz): 14.5, 22.9, 25.1, 33.2, 44.4, 47.6, 53.6, 124.2, 143.1, THF and CH_2Cl_2 resonances were also present. GC-Ms: 123(MH^+,32%), 122(28), 107(22), 94(45), 79(100). ^{1}H NMR and ^{13}C data corresponded with the literature values.[26, 30]

(1S,5R)-2,5-dimethylbicyclo[3.2.0]hept-2-ene **10a** CAS [73416-59-8]

The above procedure was repeated with $LiAlH_4$ (146 mg, 3.84 mmols), THF (4 mL), and the mesylate **100a** (583 mg, 2.66 mmols) in THF (3 mL). After solvent was removed by distillation at atmospheric pressure, the *title compound* was obtained as a clear oil, with some solvent impurity. It was used crude in the next reaction. The ^{1}H NMR data of **10a** are identical with those of **10r**.

Section 3.2.1 Optical Purity of the Bicyclic Alkene

(1RS,2SR,3RS,5RS)-2,5-Dimethylbicyclo[3.2.0]heptan-2,3-diol **103r**

General Procedure for diol formation with Quinuclidine

Following the procedure of Sharpless,[46,129] a 25-mL roundbottom flask was charged with *t*-butyl alcohol (1.5 mL) and water (1.5 mL). Potassium carbonate (134 mg, 0.97 mmols), potassium ferricyanide (369 mg, 1.12 mmols), quinuclidine hydrochloride (1 mg, 0.01 mmols), an aqueous solution of 4% osmium tetroxide (0.02 mL, 0.8 mg, 0.003 mmols), and methane sulfonamide (30 mg, 0.31 mL), only required if the olefin is trisubstituted, were then added. To the well-stirred solution was added the desired alkene **10r** (35 mg, 0.29 mmols). Once the reaction was complete (15 hours), solid sodium sulfite (430 mg, 3.41 mmols) was added and the solution stirred at ambient temperature for 30 min. Dichloromethane (10 mL) was added to the reaction mixture, and after separation of the layers, the aqueous phase was further extracted with dichloromethane (3×5 mL). The combined organic extracts were dried and concentrated to give the diol **103r** and the ligand. The crude product is purified by flash chromatography (Ethyl acetate/hexane(30/70 v/v)) to afford the 1,2-diol **103r** as white crystals (15 mg, 60%). Mp 66-67°C. δ_H (300 MHz): 1.20 (s, 3H, H_3C-C-OH), 1.22 (s, 3H, CH_3), 1.4-2.2 (m, 7H, ring

protons), 4.19 (dd, 1H, J=7, 10.5 Hz, H1). δ_c (75 MHz): 16.5, 20.1, 28.2, 30.9, 40.4, 46.5, 52.8, 77.9, 80.6. $\upsilon_{max}(CDCl_3)$: 3608(b, OH), 3432(b, OH), 2869(s), 1405(s), cm^{-1}. M/z: 156(MH^+,1%), 67(25), 43(100).

(1R,2S,3R,5R)-2,5-Dimethylbicyclo[3.2.0]heptan-2,3-diol **103a**

The same general procedure, (above) was repeated with potassium carbonate (124 mg, 0.89 mmols), potassium ferricyanide (303 mg, 0.92 mmols), quinuclidine hydrochloride (2.3 mg, 0.03 mmols), *t*-butyl alcohol (2 mL), water (2 mL), an aqueous solution of 4% osmium tetroxide (0.05 mL, 2.0 mg, 0.007 mmols) and (1SR,5RS)-2,5-dimethylbicyclo[3.2.0]hept-2-ene **10a** (20 mg, 0.16 mmols). The ^{1}H NMR data of **103a**, after purification, are identical with those of **103r**.

The racemic monotosylate derivative **102r** of (1RS,2SR,3RS,5RS)-2,5-dimethylbicyclo[3.2.0]heptan-2,3-diol **103r**

To a solution of the racemic diol **103r** (10 mg, 0.068 mmols) in pyridine (0.5 mL), cooled to 0°C, was added *p*-toluene sulfonyl chloride (23 mg, 0.01 mmols). After standing the reaction mixture at 5°C for 15 hours a drop of water was added to hydrolyze any excess *p*-toluene sulfonyl chloride. Dichloromethane and 15% $HCl_{(aq)}$ were added and the organic layer separated. The aqueous phase was re-extracted with dichloromethane (2×). The combined organic phases were washed with water (1×) then dried. Removal of solvent *in vacuo* gave the *title compound* as a colourless oil (18 mg, 85%). δ_H (300 MHz, $CDCl_3/D_2O$): 1.12 (s, 3H, CH_3), 1.17 (s, 3H, CH_3), 1.38 (m, 1H, ring proton), 1.6-1.8 (complex, 4H, ring protons), 1.9-2.2 (complex, 2H, ring protons), 2.45 (s, 3H, CH_3), 4.85 (dd, 1H, J=7, 10.5 Hz, H3), 7.35 (d, 2H, J= 8 Hz, Ar), 7.81 (d, 2H, J= 8 Hz, Ar). δ_C (75 MHz): 16.2, 20.0, 21.6, 27.7, 30.6, 40.8, 42.7, 50.9, 80.4, 86.6, 127.8, 129.8, 141.8, 144.8. M/z: 310($M^{+\cdot}$, 4%), 267(35), 71(100).

Tris-[3-(heptafluoropropyl-hydroxymethylene)-d-camphorato]-europium(III) (14 mg) added to the tosylate (9 mg) in CCl_4 (0.5 mL) and C_6D_6 (0.1 mL) gave no significant separation of peaks in the ^{1}H NMR spectrum at 200 MHz.

Mosher Ester of the racemic diol **103r**: (1SR,3SR,4RS,5SR)-4-Hydroxy-1,4-dimethylbicyclo[3.2.0]hep-3-yl (2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate **105** and **106**

The general procedure for Mosher ester formation, p.157, was repeated with the following reagents. Diol **103r** (8 mg, 0.05 mmols), DMAP (2 mg, 0.01 mmols), DCC (23 mg, 0.11 mmols), R-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (23 mg, 0.10 mmols) and dichloromethane (0.5 mL). The corresponding Mosher ester was obtained as a colourless oil (16 mg, 85%). The peaks from which the optical purity was measured are show in detail in 'Chapter 3, Results and Discussion' p. 95. From the ^{1}H NMR spectrum of the products from the racemic and optically active samples it was possible to assign the following data.

Data for **106:** δ_H (600 MHz): 1.20 (s, 3H, CH_3), 1.27 (s, 3H, CH_3), 1.1-2.2 (7H, complex, ring protons), 2.62 (m, 1H, H4), 3.55 (br s, 3H, OCH_3), 5.38 (dd, 1H, J= 7, 11 Hz, H3), 7.35-7.55 (m, 5H, ArH).

Data for **105:** δ_H (600 MHz): 1.10 (s, 3H, CH_3), 1.25 (s, 3H, CH_3) 1.1-2.2 (7H, complex, ring protons), 3.57 (br s, 3H, OCH_3), 5.44 (dd, 1H, J= 6.5, 11 Hz, H3), 7.35-7.55 (m, 5H, ArH).

Mosher Ester of the optically active diol **103r**: (1R,3R,4S,5R)-4-Hydroxy-1,4-dimethylbicyclo[3.2.0]hep-3-yl (2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate **106**

The general procedure for Mosher formation, p. 157, was repeated with the following reagents. Diol **103a** (5 mg, 0.03 mmols), DMAP (2 mg, 0.02 mmols), DCC (13 mg, 0.06 mmols), R-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (13 mg, 0.06 mmols) and dichloromethane (0.5 mL). The corresponding Mosher ester was obtained as a colourless oil (8 mg, 63%) The peaks from which the optical purity was measured are show in detail in 'Chapter 3, Results and Discussion' p. 96

Section 3.3 Attempted Formation of Grandisol via the Ketal

Attempted formation of 2-[(1RS,2RS)-2-acetyl-1-methylcyclobutyl] acetaldehyde

The alkene **10r** (50mg, 0.41 mmols), 4% osmium tetroxide (0.05 mL, 2 mg, 0.008 mmols), 1,4-dioxane (1 mL) and water (0.5 mL) were combined. To a rapidly stirred solution was added sodium periodate (211 mg, 0.98 mmols). After being left to stir at ambient temperature for 24

hours the solution was diluted with water (2 mL) and diethyl ether (10 mL). The aqueous layer was separated and re-extracted with diethyl ether (2×). The combined organic extracts were dried and solvent was removed *in vacuo*. Purification by chromatography with hexane/ethyl acetate (90/10 v/v) gave a brown oil (10 mg, 16%). The ^{1}H NMR spectrum showed numerous products. The peaks for the major component were the same as those found in the literature for the *title compound*. Lit δ_H (90 MHz): 1.4 (s, 3H, CH_3), 2.5-1.5 (m, 4H), 2.08 (s, 3H, $COCH_3$), 2.55 (d, 2H, J=1.8 Hz), 3.09 (t, 1H, J=7.2 Hz), 9.7 (t, 1H, 1.8Hz).

Section 3.4 Formation of Grandisol via the Keto-Acid

(1RS,2SR)-2-Acetyl-1-methylcyclobutaneacetic acid **7r**

By the adapted procedure of *Rosini*,[30] to a well stirred mixture of 2,5-dimethylbicyclo[3.2.0]hept-2-ene **10r** (, maximum 1.60 mmols, contains solvent) in *t*-butyl alcohol (1.5 mL) and water (3 mL), at ambient temperature, was added $NaIO_4$ (1.51 g, 7.07 mmols) then $RuCl_3.3H_2O$ (11 mg, 0.05 mmols). The solution was then heated at 40°C for 15 hours. After cooling to ambient temperature, the mixture was filtered and the filtrate was extracted with ethyl acetate. The extract was washed with saturated $NaCl_{(aq)}$, dried and solvent removed *in vacuuo* to give a brown oil. Purification by flash chromatography with a gradient of ethyl acetate/hexane (30/70 v/v) as an eluant gave the *title compound* as a light brown oil (135 mg, 50% over two steps). The ^{1}H NMR spectrum also showed impurities that could not be identified. The major peaks gave the following resonances; δ_H (300 MHz, $CDCl_3/D_2O$): 1.42 (s, 3H, CH_3), 2.13 (s, 3H, $COCH_3$), 1.7-2.3 (complex, 4H, ring protons), 2.52 (AB quartet, 2H, H2'), 3.11 (t, 1H, J= 7.0 Hz, H2). δ_C (75 MHz): 17.5, 27.7, 30.5, 30.8, 39.7, 41.2, 55.0, 178.1, 210.0. M/z: 171(MH^+, 91%), 153(89), 43(100). The major peaks of ^{1}H NMR spectrum correspond to those of the literature.[30,31]

(1R,2S)-2-Acetyl-1-methylcyclobutaneacetic acid **7a**

The above procedure was repeated with the following quantities; 2,5-dimethylbicyclo[3.2.0]hept-2-ene **10a** (maximum 2.66 mmols, contains solvent), *t*-butyl alcohol (1.5 mL) and water (3 mL), at ambient temperature, was added $NaIO_4$ (2.07 g, 9.68 mmols) then $RuCl_3.3H_2O$ (12 mg, 0.06 mmols). Purification by flash chromatography with a gradient of ethyl acetate/hexane (50/50 v/v) as an eluant gave the *title compound* as a light

brown oil (244 mg, 54% over two steps). $[\alpha]_D^{20}$=-28.0 ± 2 (c= 2.58 CH_2Cl_2). Lit. $[\alpha]_D^{20}$=-41.0 ± 2 (c= 8.446 EtOAc).[6] The ^{1}H NMR spectrum of the major peaks correspond with those of **7r**.

(1RS,2SR)-2-Isopropenyl-1-methylcyclobutaneacetic acid **107r**

Following the procedure of *Webster* and *Silverstein*,[31] A suspension of methyltriphenyl-phosphonium iodide (445 mg, 1.03 mmols) in THF (6 mL) was cooled to 0°C. *n*BuLi (0.35 mL, 0.87 mmols, 2.5 M solution in hexane) was added dropwise over a period of 5 min. The ylide solution was stirred for 1 hr. The keto-acid **7r** (73 mg, 0.43 mmols) in THF (2 mL) was added over a 5 min period at 0°C. After stirring for 15 hours at ambient temperature the solution was poured into water (20 mL) and extracted with diethyl ether (3×20 mL). The organic layer was discarded and the aqueous layer was acidified to pH=1 with 15% $HCl_{(aq)}$, then extracted with dichloromethane (3×30 mL) The combined organic extracts were washed with saturated $NaCl_{(aq)}$ solution, dried and solvent removed *in vacuuo*. Purification by flash chromatography with a gradient of ethyl acetate/hexane (20/80 v/v) as an eluant gave the *title compound* as a colourless oil, which crystallized on standing (55 mg, 76%). Mp. 46-47°C. δ_H (300 MHz, $CDCl_3$, D_2O): 1.32 (s, 3H, CH_3), 1.66 (s, 3H, =C(CH$_3$)), 1.6-2.1 (complex, 5H, ring protons + $H2_a$'), 2.54 (d, 1H, J= 15 Hz, $H2_b$'), 2.63 (t, 1H, J= 8 Hz, methine proton), 4.66 (br s, 1H, alkene proton), 4.85 (br s, 1H, alkene proton). δ_C (75 MHz): 18.9, 23.0, 28.0, 29.2, 38.6, 41.3, 52.1, 110.5, 144.5, 178.9. M/z: 168(M^+, 18%), 108(95), 80(75), 70(100). The ^{1}H NMR spectral data corresponded to that of the literature.[30,31]

(1S,2R)-2-Isopropenyl-1-methylcyclobutaneacetic acid **8a**

The above procedure was repeated with the following quantities; methyltriphenyl-phosphonium iodide (1.64 g, 3.81 mmols) in THF (20 mL), *n*BuLi (1.45 mL, 3.62 mmols, 2.5 M solution in hexane) and the keto-acid **7a** (245 mg, 1.43 mmols) in THF (2 mL). Purification by flash chromatography with a gradient of ethyl acetate/hexane (20/80 v/v) as an eluant gave the *title compound* as a colourless oil, which crystallized on standing (149 mg, 62%). $[\alpha]_D^{20}$=+94.6 ± 2 (c= 1.08 CH_2Cl_2). The ^{1}H NMR data of **8a** are identical with those of **8r**. The ^{1}H NMR spectrum is reproduced in the 'Appendix'.

(1RS,2SR)-Isopropenyl-1-methylcyclobutaneethanol [(±)-Grandisol] **1r**

To a suspension of lithium aluminum hydride (40 mg, 1.06 mmols) in THF (1 mL), cooled to 0°C was added the acid **8r** (61 mg, 0.36 mmols) in THF (1.5 mL). After stirring at ambient temperature for 3 hours the solution was carefully quenched with water. The solution was diluted with dichloromethane and washed with 15% $HCl_{(aq)}$. After separation of the organic layer, the aqueous layer was re-extracted with dichloromethane (2×). The combined organic extracts were dried and solvent was removed *in vacuuo* to give a colourless oil (39 mg, 70%) δ_H (300 MHz): 1.17 (s, 3H, CH_3), 1.67 (s, 3H, $=C(CH_3)$), 1.3-2.1 (complex, 7H, ring protons + H2' + OH), 2.55 (t, 1H, J= 9 Hz, methine proton), 3.68 (m, 2H, CH_2OH), 4.64 (br s, 1H, alkene proton), 4.84 (br s, 1H, alkene proton). δ_C (75 MHz): 19.2, 23.2, 28.4, 29.4, 37.0, 41.3, 52.5, 60.0, 109.7, 145.2. GC-MS: (MH^+, 15%), 137(50), 109(55), 81(50), 67(100). The spectral data corresponded to that of the literature.[30,31]

(1R,2S)-Isopropenyl-1-methylcyclobutaneethanol [(+)-Grandisol] **1a**

The above procedure was repeated with the following quantities; lithium aluminum hydride (64 mg, 1.73 mmols) in THF (2 mL), and the acid **8a** (64 mg, 0.38 mmols) in THF (2 mL). After removal of solvent *in vacuuo* a colourless oil was obtained (56 mg, 95%). $[\alpha]_D^{20}$=+20.4 ± 2 (c= 1.2 *n*-hexane). Lit. $[\alpha]_D^{20}$=+18.4 (c= 1.1, *n*-hexane).[31] ^{1}H NMR data of **1a** are identical with those of **1r**. The ^{1}H NMR spectrum is reproduced in the 'Appendix'.

Mosher ester of racemic grandisol **1r**: 1-[(1SR)-2-{2-[1RS,2SR)-2-isopropenyl-1-methylcyclobutyl]ethoxy}-1-methoxy-1-(trifluoromethyl)-2-propenyl]benzene **109** and **110**

The general procedure for Mosher formation, p.157, was repeated with the following reagents. Grandisol **1r** (8 mg, 0.05 mmols), DMAP (1 mg, 0.01 mmols), DCC (14 mg, 0.07 mmols), R-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (18 mg, 0.08 mmols) and dichloromethane (0.5 mL). The corresponding Mosher ester was obtained as a colourless oil (12 mg, ~65%). From the ^{1}H NMR spectrum of the products from the racemic and optically active samples it was possible to assign the following data. The peaks from which the optical purity was measured are shown in detail in 'Chapter 3, Results and Discussion' p. 101.

Data for **109:** δ_H (600 MHz): 1.14 (s, 3H, CH_3), 1.64 (s, 3H, CH_3), 1.45-1.65 (complex, 3H), 1.75-2.0 (complex, 3H), 2.58 (t, 1H, J= 9 Hz, methine proton), 3.55 (br s, 3H, OCH_3), 4.37 (m,

2H, CH_2OH), 4.64 (br s, 1H, alkene proton), 4.84 (br s, 1H, alkene proton), 7.35-7.55 (m, 5H, ArH).

Data for **110:** δ_H (600 MHz): 1.15 (s, 3H, CH_3), 1.65 (s, 3H, CH_3) 1.45-1.65 (complex, 3H), 1.75-2.0 (complex, 3H), 2.58 (t, 1H, J= 9 Hz, methine proton), 3.55 (br s, 3H, OCH_3), 4.37 (m, 2H, CH_2OH), 4.64 (br s, 1H, alkene proton), 4.84 (br s, 1H, alkene proton), 7.35-7.55 (m, 5H, ArH).

Mosher ester of optically active grandisol **1a**: 1-[(1R)-2-{2-[1R,2S)-2-isopropenyl-1-methylcyclobutyl]ethoxy}-1-methoxy-1-(trifluoromethyl)-2-propenyl]benzene **109** and **110**

The general procedure for Mosher formation, p. 157, was repeated with the following reagents. Grandisol **1a** (7 mg, 0.04 mmols), DMAP (5 mg, 0.04 mmols), DCC (20 mg, 0.10 mmols), R-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (20 mg, 0.09 mmols) and dichloromethane (0.5 mL). The corresponding Mosher ester was obtained as a colourless oil (11 mg, ~70%). The spectrum was mainly the same as that reported above for the racemic Mosher esters. The peaks from which the optical purity was measured are shown in detail in 'Chapter 3, Results and Discussion' p. 101.

Section 4.2.1 Dihydroxylation Conditions on the Di-substituted Alkene

(1SR,5SR)-2-(Hydroxymethyl)-5-methylbicyclo[3.2.0]heptan-2-ol **116r** and **117r**

With Osmium Tetroxide

N-Methylmorpholine *N*-oxide (346 mg, 2.95 mmols) was added to the co-solvent system of water (1 mL) and acetone (5 mL). The alkene **10r** (163 mg, 1.33 mmols) and an aqueous solution of 4% osmium tetroxide (0.170 mL, 6.8 mg, 0.03 mmols) were added and the reaction mixture stirred vigorously for 48 hours. A slurry of fluorisil (164.4 mg) and sodium hydrosulphite (40.0 mg) in water (2 mL) was added, the mixture stirred for 1 hour then filtered through a pad of celite. The solvent was removed by distillation and the residue was transferred to a separating funnel with water (10 mL). The aqueous solution was extracted with dichloromethane (2×), the combined organic extracts dried and the solvent removed by distillation. Flash chromatography with ethyl acetate/hexane (40/60 v/v) gave the *title compound* as a white solid (80 mg, 38%). Recrystallization from ether and hexane produced white crystals, mp 84-85°C δ_H (200 MHz, $CDCl_3$, D_2O): 1.26 (s, 3H, CH_3), 1.3-2.2 (m, 10H, ring protons), 3.35 (AB quartet, minor isomer, 2%), 3.61 (AB quartet, 2H, H1'). δ_c (50 MHz) : Major isomer **116r**: 16.3, 27.8, 30.3, 35.0, 38.2, 44.9, 52.0, 65.7, 85.3. Minor isomer **117r**: 13.7, 26.5, 31.1, 34.1, 37.5, 43.3, 47.7, 67.8, 82.4. υ_{max}: 3583(br, s, OH), 3413(br, s, OH), 2946(s), 2859(s), 1452(m), 1373(w), 1016(s)cm^{-1}. M/z: 157($M^{+\cdot}$,1%), 139(37), 126(82), 122(98), 109(36), 100(100), 83(35), 55(40). Anal Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 69.14; H, 10.58.

With Quinuclidine

The general procedure, p. 162 was repeated with potassium carbonate (433 mg, 3.13 mmols), potassium ferricyanide (973 mg, 2.95 mmols), quinuclidine (2 mg, 0.02 mmols), *t*-butyl alcohol (5 mL), water (5 mL), an aqueous solution of 4% osmium tetroxide (0.03 mL, 1.2 mg, 0.005 mmols) and the alkene **10r** (164 mg, 1.34 mmols). After stirring (mechanical stirrer (500 rpm)) at ambient temperature for 24 hours the reaction was quenched with sodium sulfite (1.5 g, 11.9 mmols). Purification by flash chromatography with a gradient of ethyl acetate/hexane (40/60 v/v) as an eluant gave the isomer **116r** as white crystals (65 mg, 31%). δ_H (200 MHz, $CDCl_3$, D_2O): 1.26 (s, 3H, CH_3), 1.3-2.2 (m, 10H, ring protons), 3.61 (AB quartet, 2H, H1'). The other diastereomer was not detected.

[(1SR,2RS,5SR)-2-Hydroxy-5-methylbicyclo[3.2.0]hept-2-yl]methyl acetate **118r**

To the diol **116r** (13 mg, 0.08 mmols) dissolved in pyridine (0.5 mL) was added acetic anhydride (0.05 mL, 0.49 mmols) and the reaction mixture was stirred at ambient temperature for 10 hours. A few drops of water were then added to hydrolyze the excess acetic anhydride. Dichloromethane (20 mL) and water (10 mL) were added to the mixture and it was washed with 7.5% hydrochloric acid solution (2×20 mL), saturated sodium bicarbonate solution (10 mL), dried and solvent removed *in vacuuo*. The *title compound* was obtained as a white solid (15 mg, 96%). δ_H (200 MHz): 1.27 (s, 3H, CH_3), 1.3-2.2 (9H, complex, ring protons), 2.08 (s, 3H, $COCH_3$), 4.15 (very distorted AB system, 2H, H1'). δ_c (50 MHz): 16.6, 20.8, 27.8, 30.3, 35.3, 38.2, 45.0, 52.5, 68.1, 83.4, 171.2. υ_{max} : 3596(m), 3484(w), 2948(s), 2861(m), 1731(s), 1247(s), 1037(m) cm^{-1}. Chiral shift analysis with tris-[3-(heptafluoropropyl-hydroxymethylene)-d-camphorato]-europium(III) (16 mg) added to the acetate (12 mg) in CCl_4 (0.5 mL) and C_6D_6 (0.1 mL) separated the very distorted AB system at δ4.15 into two overlapping AB quartet, one resonance centred at δ5.74 and the other resonance at δ6.10 (200 MHz). The acetate (15 mg) in CCl_4 (0.5 mL) and C_6D_6 (0.1 mL) in the presence of the achiral shift reagent Eu(fod)$_3$ (11 mg) at 200 MHz gives only one AB quartet at δ5.73 and the other resonance at δ6.38 (J=11.6 Hz) (200 MHz). The ^{1}H NMR spectra for both chiral shift reagents are reproduced in 'Chapter 4, Results and Discussion p. 108'.

Mosher esters of the racemic diol **116r**: [(1SR,2RS,5SR)-2-Hydroxy-5-methylbicyclo[3.2.0]hep-2-yl]methyl (2R)-3,3,3-trifluoro-2-methoxy-2-phenyl-propanoate **119** and **120**

According to the procedure of Hassner, p. 157, a flask was charged successively with the diol **10r** (15 mg, 0.098 mmols), dichloromethane (0.7 mL), dicyclohexylcarbodiimide (16 mg, 0.079m mmols), dimethylaminopyridine (2 mg, 0.007 mmols) and (R)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (20 mg, 0.087 mmols). Flash chromatography with hexane/ethyl acetate (90/10 v/v) as an eluant gave a 1:1 mixture of the *title compound* as a colourless liquid (16 mg, 45%). The ^{1}H NMR at 200 MHz was identical for both diastereomers, except the methyl resonance was at δ1.23 for one diastereomer and at δ1.25 for the other diastereomer. The optical purity could be determined from intergration of the AB quartet at δ4.30 and δ4.46 for one diastereomer, and the very distorted AB quartet at δ4.37 for

the other diastereomer. The peaks from which the optical purity was measured are show in detail in 'Chapter 4, Results and Discussion' p. 109.

Data for **119** and **120:** δ_H (600 MHz): 1.23 (s, 3H, CH_3), 1.25 (s, 3H, CH_3), 1.3-2.1 (18H, complex, ring protons), 3.55 (br s, 6H, OCH_3), 4.30 and 4.46 (AB quartet, 2H, H1', J = 11.4 Hz), 4.37 (very distorted AB quartet (almost singlet), 2H, H1'), 7.35-7.55 (m, 10H, ArH).

Attempted kinetic Resolution of (1SR,5RS)-1-methyl-4-methylenebicyclo[3.2.0]-heptane **9r** with AD-mix-β

A mixture of AD-mix-β (1.44 g, 1mmol equivalent), t-butyl alcohol (5 mL), water (5 mL) were cooled to 0°C, where upon some of the dissolved salts precipitated. The alkene **9r** (131 mg, 1.07 mmols) was added and the reaction mixture stirred with a mechanical stirrer (500rpm) at 0°C. Aliquot's were taken after 1,2,3,5 and 6 hours. Each aliquot (0.2 mL) was diluted with ethyl acetate (0.5 mL), and an aqueous solution of 1.5g/5 mL sodium sulfite (0.5 mL) was added. The aqueous phase was further extracted with ethyl acetate (2×0.5 mL). The combined organic phases were dried ($MgSO_4$) and solvent removed *in vacuuo*. After 24 hours, the reaction was worked-up under Sharpless conditions. Sodium sulfite (1.5 g, 11.9 mmols) was added and the mixture allowed to warm to ambient temperature. Ethyl acetate (10 mL) was then added and the aqueous phase further extracted with ethyl acetate (3×5 mL). The combined organic phases were dried ($MgSO_4$) and solvent removed *in vacuuo*. Squat column chromatography with hexane/ethyl acetate (70/30 v/v) as an eluant gave the diol as a white solid. The ^1H NMR spectrum of the aliquots taken at 1,2,3,5,6, and 24 hours all showed only the presence of one diastereomer, **116**. δ_H (300 MHz): 1.26 (s, 3H, CH_3), 1.3-2.2 (complex, 10H, ring protons), 3.61 (AB quartet, 2H, H1').

The 1 and 24 hour aliquots were converted to the Mosher esters by the procedure described earlier (p. 157). In both cases the optical purity was determined to be 0% e.e..

Section 4.3 Formation of the Phenyl Alkene

Attempted formation of a mixture of E and Z isomers of (1SR,5RS)-1-methyl-4-[1-phenylmethylidene] bicyclo[3.2.0]heptane **115r**

a) Method Employing Potassium *t*-Butoxide

Potassium *t*-butoxide (202 mg, 1.79 mmols) was added portionwise over 5 minutes to a solution of benzyltriphenylphosphonium bromide (760 mg, 1.76 mmols) in diethyl ether (8

mL) to give a deep yellow solution. After 1hour, the bicyclic ketone **12r** (195 mg, 1.57 mmols) was added dropwise. The pale yellow mixture was then stirred at ambient temperature for 24 hours, after which TLC revealed starting material present. After 3 days of stirring the mixture at ambient temperature, TLC revealed starting material still remained. Filtration of the solution through celite and removal of the solvent *in vacuuo* showed only starting material in the ^{1}H NMR spectrum.

b) Method Employing *n*-BuLi

Dropwise addition of 1.6M n-BuLi (0.7 mL, 1.12 mmols) to a stirred solution benzyltriphenylphosphonium bromide (407 mg, 0.94 mmols) in THF (1 mL) gave a deep orange solution, which was stirred for 30 minutes. The bicyclic ketone **12r** (110 mg, 0.884mmol) was added dropwise and the pale yellow solution stirred at ambient temperature for 5 hours. TLC revealed starting material present. After stirring of the reaction at ambient temperature for 24 hours, starting material remained. Filtration through celite and removal of the solvent *in vacuuo* gave the crude product. Flash chromatography with a gradient of ethyl acetate/hexane (5/95 v/v) as an eluant gave starting material and an unknown compound, later identified to be the aldol product **121r** (10%). δ_H (300 MHz): 1.25 (s, 3H, CH_3), 1.30 (s, 3H, CH_3) 1.35-2.0 (m, 9H, ring protons), 2.1-2.8 (m, 6H, ring protons), 3.42 (m, 1H, ring proton). δ_c (75 MHz): 20.8, 23.0, 25.7, 29.8, 32.9, 34.7, 38.0, 39.3, 43.0, 43.5, 46.5, 48.2, 52.8, 129.3, 164.7. υ_{max}(liq $CDCl_3$): 3450(br, s, OH), 3084(s), 3029(s), 1760(w), 1675(s), 1600(s), 1395(s), 1050(s), 875(s) cm^{-1}. M/z: 230($M^{+\cdot}$, 56%), 202(100), 174(43), 147(28), 91(53), 55(55), 41(56).

c) Method Employing NaH

DMSO (3 mL) and sodium hydride (36 mg, 1.51 mmols), oil removed, were combined and heated to 70°C. Benzyltriphenylphosphonium bromide (864 mg, 2.00 mmols) was added portion wise and the solution stirred for 10 minutes. The bicyclic ketone **12r** (98 mg, 0.79 mmols) was added slowly over 10 minutes. The reaction mixture was then stirred overnight for 2 days, poured into water, extracted with dichloromethane (3×). The combined organic extracts were washed with water (5×), dried and the solvent removed *in vacuuo*. The ^{1}H NMR spectrum revealed only starting material.

d) Method Employing 50% NaOH[129]

Dichloromethane (1.5 mL), benzyltriphenylphosphonium bromide (374 mg, 1.16 mmols) and the bicyclic ketone **12r** (101 mg, 0.81 mmols) were combined. A 50% aqueous NaOH solution (1.5 mL) was added and the solution stirred overnight. The solution was poured into water and

extracted with dichloromethane (3×), combined organic extracts dried, and solvent removed *in vacuuo*. The ^{1}H NMR spectrum revealed starting material.

e) Method Employing *t*-Amylate[130]

Sodium *t*-amylate was formed by addition of 2-methyl-2-butanol (0.25 mL, 2.28 mmols) to a solution of sodium hydride (56 mg, 2.32 mmols), oil removed, in xylene (5 mL). The solution was then stirred for 20 minutes.

To benzyltriphenylphosphonium bromide (279 mg, 0.65 mmols) in xylene (2 mL) was added sodium *t*-amylate (1 mL), formed above. The bicyclic ketone **12r** (61 mg, 0.48 mmols) was added dropwise and the solution refluxed for 30 minutes. The reaction mixture was dissolved in hexane, filtered through celite and solvent removed *in vacuuo*. ^{1}H NMR showed starting material with small olefinic peaks at δ 6.2 and 6.3. Flash chromatography with a gradient of hexane gave a trace of the *title compound* (<1%). δ_H (200 MHz): 1.22 (s, 6H, CH_3), 1.00-2.0 (m, 18H, ring protons), 6.20 (m, 1H, methylene), 6.30 (m, 1H, methylene), 7.15 (m, 10H, Ar).

Section 4.3.1 Peterson Olefination

Formation of a mixture of E and Z isomers of (1SR,5RS)-1-methyl-4-[1-phenylmethylidene] bicyclo[3.2.0]heptane **115E** and **115Z**

n-BuLi (0.3 mL, 2.5 M solution, 0.75 mmol) was added to a solution of benzyltrimethylsilane (0.15 mL, 0.79 mmols) and TMEDA (1 mL), cooled to 0°C. After stirring at ambient temperature for 2 hours the solution was cooled to -70°C and the bicyclic ketone **12r** (80 mg, 0.65 mmols) was added dropwise. After stirring at –70°C the reaction was allowed to warm to ambient temperature, and stirred for a further 15 hours. The solution was quenched with water (0.2 mL), dichloromethane was added and the mixture washed with 4% $HCl_{(aq)}$, dried and solvent removed *in vacuuo*. Flash chromatography with ethyl acetate/hexane (5/95 v/v) gave the *title compounds* as a colourless liquid (10 mg, 8%). The ^{1}H NMR spectrum revealed the presence of olefinic stereoisomers. δ_H (200 MHz): **Isomer a**: 1.65 (s, 3H, CH_3), 1.8-2.4 (complex, 5H, ring protons), 2.7-3.4 (complex, 4H, ring protons), 6.64 (br s, 1H, H1'), 7.5-7.8 (m, 5H, Ar). **Isomer b**: δ 1.66 (s, 3H, CH_3), 1.8-2.4 (complex, 5H, ring protons), 2.7-3.4 (complex, 4H, ring protons), 6.74 (br s., 1H), 7.5-7.8 (m, 5H, Ar). Integration of the olefinic resonances showed they had formed in a 1.3:1 ratio (Isomer a:Isomer b). The stereoisomers were unable to be distinguished in the ^{1}H NMR spectrum.

Section 4.3.2 Formation of the Alkene via an Elimination Reaction

(1SR,2RS,5SR)-2-Benzyl-5-methylbicyclo[3.2.0]heptan-2-ol **123r**

Dry diethyl ether (6 mL), magnesium turnings (332 mg, 13.64 mmols) and 1 crystal of iodine were combined in a nitrogen atmosphere. A solution of benzyl chloride (1.4 mL, 11.77 mmols) in dry diethyl ether (6 mL) was added dropwise cautiously to the reaction mixture. After addition was complete, the reaction mixture was further refluxed for 1hr. To the bicyclic ketone **12r** (0.5 mL, 4.03 mmols) in diethyl ether (8 mL) cooled to 0°C was added dropwise the above Grignard reagent. After being stirred at ambient temperature for 15 hours, the reaction mixture was transferred to a separating funnel with dichloromethane, washed successively with aqueous saturated ammonium chloride solution, saturated sodium chloride, dried and solvent removed *in vacuuo*. Recrystallization of the product from hexane gave cubic white crystals (820 mg, 94%), mp 91-93°C. δ_H (600 MHz)[¶]: 1.28 (s, 3H, CH_3), 1.5 (complex, 2H, $H3_a$ and $H4_a$), 1.8 (complex, 5H, H6, H7 and $H(3or4)_b$), 2.0-2.1 (complex, 2H, H1 and $H(3or4)_b$), 2.65 and 2.71 (AB quartet, 2H, J= 13.5 Hz, H1'), 7.30 (m, 5H, Ar). δ_c (50 MHz) and DEPT: 14.3 (CH_2), 27.8 (CH_3), 31.2 (CH_2), 36.7 (CH_2), 38.0 (CH_2), 43.3 (q), 45.8 (CH_2), 50.6 (CH), 81.4 (q), 126.2 (CH_3), 128.2 (CH_3), 130.6 (CH_3), 137.6 (q). υ_{max} : 3585(br, s, OH), 3446(br, s, OH), 3084(s), 3029(s), 1602(s), 1494(s), 1359(s), 774(s) cm^{-1}. M/z: 216($M^{+\cdot}$,4%), 125(53), 97(30), 91(100), 65(24), 55(53). Anal Calcd for $C_{15}H_{20}O$: C, 83.28; H, 9.32. Found: C, 83.26; H, 9.14. The spectra are reproduced in the 'Appendix'.

Elimination of (1SR,2RS,5SR)-2-benzyl-5-methylbicyclo[3.2.0]heptan-2-ol **123r**

a) Acid Catalysed

To a solution of (1SR,2RS,5SR)-2-benzyl-5-methylbicyclo[3.2.0]heptan-2-ol **123r** (10 mg, 0.04 mmols) in $CDCl_3$ (0.7 mL) was added a catalytic amount of *p*-toluene sulfonic acid (3 crystals). After 24 hours, at ambient temperature, only starting material was present by ^1H NMR.

b) Method Employing DMSO

A solution of the alcohol **123r** (10 mg, 0.04 mmols) in DMSO (0.7 mL) was heated to 130°C for 24 hours. No change was observed in the ^1H NMR spectrum. The same solution was heated

[¶] COSY and HETCOR experiments were used to assign the resonances.

at 160°C for 24 hours. Three olefins, inseparable by normal chromatography, were obtained.δ_H (300 MHz): 1.24 (s, CH_3), 1.2-3.0 (m, ring protons), 3.35 (AB quartet, CH_2-Ph), 5.25 (br s, olefinic **122**), 6.20 (br s, olefinic **115**), 6.30 (br s, olefinic **115**), 7.1-7.33 (m, 15H, Ar-H). Integration of the vinylic resonances showed the olefins had formed in a ratio of 2 : 1 : 3 (**115** : **115** : **122**).

c) Method Employing Thionyl Chloride

i) At Ambient Temperature

To a solution of the alcohol **123r** (23 mg, 0.11 mmols), dichloromethane (3 mL) and pyridine (0.3 mL), in a nitrogen atmosphere, was added thionyl chloride (0.1 mL, 163 mg, 1.37 mmols). The resulting solution was stirred at ambient temperature for 15 hours. The solution was diluted with dichloromethane, washed with 15% hydrochloric acid (1×), dried and solvent removed *in vacuuo*. Flash chromatography of the combined fractions with hexane (100 v/v) as an eluant gave a mixture of the alkenes (15 mg, 70%). The ratio obtained was 1.8 : 1.0 : 2.8 (**115** : **115** : **122**) as measured from the vinylic resonances.

ii) At –78°C

To a solution of the alcohol **123r** (19 mg, 0.087 mmols), dichloromethane (3 mL) and pyridine (0.3 mL), in a nitrogen atmosphere at -78°C, was added thionyl chloride (0.1 mL, 163 mg, 1.37 mmols). The resulting solution was stirred at -78°C for 2 hours, then allowed to warm to ambient temperature. The solution was diluted with dichloromethane, washed successively with 15% hydrochloric acid (2×), saturated sodium bicarbonate, saturated sodium chloride solution, dried and solvent removed *in vacuuo* (15 mg, 85%). The three olefins were obtained in a ratio of 2 : 1 : 3 (**115** : **115** : **122**) as measured from the vinylic resonances.

d) Method Employing Methane Sulfonyl Chloride

To a solution of the alcohol **123r** (23 mg, 0.10 mmols), dichloromethane (2 mL) and triethylamine (0.05 mL), cooled to 0°C, was added methane sulfonyl chloride (0.02 mL, 0.26 mmols). The resulting solution was stirred at ambient temperature for 2 hours. The solution was diluted with dichloromethane, washed with 15% hydrochloric acid (2×). The aqueous phase was re-extracted with dichloromethane (2×). The combined organic extracts were washed with water, dried and solvent removed *in vacuuo* (18 mg, 91%). The three olefins were obtained in a ratio of 2.1 : 1.0 : 3.2 (**115** : **115** : **122**) as measured from the vinylic resonances. No change in the relative ratio was observed when the mixture of alkenes in *d*-chloroform was refluxed in the presence of iodine. Reverse phase TLC plates showed no separation of the

isomers and minimal separation, not enough to be useful, occurred on normal TLC plates impregnated with silver nitrate.

Section 4.4 Alternative Alkenes

(1SR, 2SR, 5SR)-5-methyl-2-phenylbicyclo[3.2.0]heptan-2-ol **126r**

Dry diethyl ether (6 mL), magnesium turnings (339 mg, 13.95 mmols) and a crystal of iodine were combined in a nitrogen atmosphere. Bromobenzene (1.4 mL, 13.24 mmols) added dropwise to the reaction mixture. After addition was complete, the reaction mixture was further refluxed for 1hr. To the Grignard reagent, cooled to 0°C, was added a solution of the bicyclic ketone **12r** (0.5 mL, 4.03 mmols) in diethyl ether (3 mL). After being stirred at ambient temperature for 15 hours, the reaction mixture was transferred to a separating funnel with dichloromethane. The reaction mixture was successively washed with aqueous saturated ammonium chloride solution, saturated sodium chloride, dried and solvent removed *in vacuo*. Flash chromatography with hexane/ethyl acetate (70/30 v/v) as an eluant gave the *title compound* as a colourless liquid, which crystallized in part on standing (719 mg, 88%). Mp 56-58°C δ_H (600 MHz)[¶]: 1.22 (s, 3H, CH_3), 1.29 (dt, 1H, J=6.5, 13.2 Hz, $H4_a$), 1.50 (ddd, 1H, J= 1.8, 6.0, 13.2 Hz, $H4_b$), 1.90 (m, 2H, H6), 2.0-2.1 (complex, 3H, $H3_a$, H7), 2.43 (dt, 1H, J= 6.5 Hz, 13.2 Hz, $H3_b$), 2.60 (dd, 1H, J=5.4, 9.5 Hz, H1), 7.22 (d, 1H, J=7.5 Hz, H4'), 7.31 (dd, 2H, J=7.5, 8.4 Hz, H3'), 7.42 (d, 2H, J=8.4 Hz, H2'). δ_C (150 MHz): 14.7(CH_2), 26.5(CH_3), 31.3(CH_2), 37.8(CH_2), 40.3(CH_2), 44.4(q), 51.5(CH), 82.9(q), 125.6(CH), 126.8(CH), 128.0(CH), 147.9(q). υ_{max}(neat): 3369(br s), 3000(s), 1594(s), 1494(s), 1234(s), 1056(s), 764(s), 700(s)cm^{-1}. M/z: 200(M^+ ,10%), 183(15), 128(47), 115(57), 105(82), 77(100). The diagnostic regions of the spectra are reproduced in the 'Appendix'.

(1RS,5SR)-5-methyl-2-phenylbicyclo[3.2.0]heptan-2-ene **125r**

To a solution of (1SR, 2SR, 5SR)-5-methyl-2-phenylbicyclo[3.2.0]heptan-2-ol **126r** (688 mg, 3.4 mmols) in dichloromethane (5 mL) was added triethylamine (0.4 mL). The solution was cooled to 0°C and methane sulfonyl chloride (0.4 mL, 6.46 mmols) was added dropwise and the mixture stirred at ambient temperature for 4 hours. Then 2,6-di-*tert*-butyl-*p*-cresol was added as a radical inhibitor and the reaction mixture was washed with 15% $HCl_{(aq)}$. The

[¶] COSY and HETCOR experiments were used to assign the resonances.

aqueous layer was extracted with dichloromethane (2×), the combined organic layers were washed with brine (1×), dried and solvent was removed *in vacμuo*. Flash chromatography with hexane as an eluant gave the *title compound* as a colourless liquid (507 mg, 81%). If the alkene **125r** was not being used immediately more 2,6-di-*tert*-butyl-*p*-cresol was added and the alkene **125r** was stored in the refrigerator. δ_H (300 MHz): 1.20 (s, 3H, CH_3), 1.6-2.0 (complex, 3H, ring protons), 2.1-2.4 (complex, 3H, ring protons), 3.05 (br s, 1H, ring proton), 6.05 (br s, 1H, olefinic), 7.0-7.3 (m, 5H, aromatic protons). δ_C (75 MHz): 24.0, 25.5, 33.2, 43.6, 48.2, 50.8, 125.4, 125.7, 126.7, 128.1, 135.7, 145.2. υ_{max}(neat): 3000(s), 1594(m), 1494(s), 1446(s), 754(s), 690(s)cm^{-1}. M/z: 184(M^+,30%), 156(100), 115(45).

Section 4.5 Kinetic Resolution of the New Alkene

(1SR,2SR,3SR,5SR)-5-Methyl-2-phenylbicyclo[3.2.0]heptan-2,3-diol **127r**

The general procedure for achiral dihydroxylation, p. 162, was repeated with potassium carbonate (165 mg, 1.19 mmols), potassium ferricyanide (761 mg, 2.31 mmols), methane sulfonamide (67 mg, 0.71 mL), quinuclidine (2.9 mg, 0.03 mmols), *t*-butyl alcohol (3 mL), water (3 mL), an aqueous solution of 4% osmium tetroxide (0.05 mL, 2.0 mg, 0.01 mmols) and (1RS, 5SR)-5-methyl-2-phenylbicyclo[3.2.0]heptan-2-ene **125r** (164 mg, 1.34 mmols). After stirring at ambient temperature for 24 hours the reaction mixture was quenched with sodium sulfite (734 mg, 5.8 mmols) Purification by flash chromatography with ethyl acetate/hexane (30/70 v/v) as an eluant gave the *title compound* as white crystals (146 mg, 50%), mp 116-118°C. δ_H (300 MHz): 1.29 (s, 3H, CH_3), 1.65-1.9 (complex, 5H, ring protons), 2.0 (m, 1H, ring proton), 2.45 (m, 1H, ring proton), 4.95 (dd, 1H, J= 6.9 and 10.5 Hz, H3), 7.2-7.5 (m, 5H, aromatic protons). δ_C (75 MHz): 16.2, 28.0, 29.6, 30.6, 40.1, 46.2, 53.0, 74.9, 83.6, 126.9, 127.3, 128.2, 142.0. υ_{max}(neat): 3490(br, s, OH), 3295(br, s, OH), 2800(s), 1500(w), 1270(m), 1150(m), 1100(s), 750(s), 700(s)cm^{-1}. M/z: 218(M^+ ,25%), 189(55), 180(65), 149(75), 122(100). An analytical sample was recrystallized from hexane. Anal Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 75.95; H, 8.39, C, 75.99; H, 8.38, and C, 75.96; H, 8.28. from 2 different preparations (one was analyzed in duplicate)

(1R,2R,3R,5R)-5-Methyl-2-phenylbicyclo[3.2.0]heptan-2,3-diol **127a**

In a similar manner; the optically active alkene **125b** (from the kinetic resolution, 40% conversion, below) was dihydroxylated with the following reagents. Potassium carbonate (116

mg, 0.84 mmols), potassium ferricyanide (303 mg, 0.92 mmols), methane sulfonamide (67 mg, 0.71 mL), quinuclidine (2.9 mg, 0.03 mmols), *t*-butyl alcohol (3 mL), water (3 mL), an aqueous solution of 4% osmium tetroxide (0.05 mL, 2.0 mg, 0.01 mmols) and the optically active alkene **125b** (52 mg, 0.28 mmols). Upon work-up and purification the *title compound* was obtained as white crystals (45 mg, 74%).

Kinetic resolution of (1SR,2SR,3SR,5SR)-5-Methyl-2-phenylbicyclo[3.2.0]-heptan-2,3-diol **127r**:

Kinetic Resolution taken to 40% conversion

A mixture of potassium carbonate (73 mg, 0.53 mmols), potassium ferricyanide (118 mg, 0.36 mmols), methane sulfonamide (37 mg, 0.38 mmols), $(DHQD)_2$-PHAL (2 mg, 0.01 mmols), *t*-butyl alcohol (3 mL), water (3 mL), an aqueous solution of 4% osmium tetroxide (0.05 mL, 2.0 mg, 0.01 mmols) were combined and cooled to 0°C. The mixture was stirred with the aid of a mechanical stirrer (350 rpm). Once the reaction mixture had reached 0°C, the stirring was stopped and (1RS, 5SR)-5-methyl-2-phenylbicyclo[3.2.0]heptan-2-ene **125r** (125 mg, 0.68 mmols) was added. After stirring at 0°C for 3 hours the reaction was quenched with sodium sulfite solution (4 mL, 0.5 g/mL). The solution was then worked-up according to the general procedure on p. 162. The ^{1}H NMR spectrum of the crude product showed the reaction was 40% complete (however, only enough oxidant to be 26% complete). Purification by flash chromatography with a gradient of ethyl acetate/hexane (20/80 v/v) as an eluant gave the *title compound* **127a** as white crystals (30 mg, 23%) and the alkene **125b** (52 mg, 41%). The enantiomeric excess of the optically active diol **127a** was determined by direct conversion to the Mosher esters (detailed below) and found to be 88%. The optical purity of the active alkene **125b** was determined by initially converting the alkene **125b** to the optically active diol **127b**, and then to the corresponding Mosher esters (the enantiomeric excess was found to be 52%).

Kinetic Resolution taken to 75% conversion

The above procedure was repeated with potassium carbonate (84 mg, 0.61 mmols), potassium ferricyanide (189 mg, 0.57 mmols), methane sulfonamide (44 mg, 0.46 mmols), $(DHQD)_2$-PHAL (2 mg, 0.01 mmols), *t*-butyl alcohol (3 mL), water (3 mL), an aqueous solution of 4% osmium tetroxide (0.05 mL, 2.0 mg, 0.01 mmols) and (1RS, 5SR)-5-methyl-2-phenylbicyclo[3.2.0]heptan-2-ene **125r** (108 mg, 0.58 mmols). The ^{1}H NMR spectrum of the crude product showed the reaction was 70% complete (however, only enough oxidant for 50%

completion). Upon work-up and purification the diol **127a** was obtained as white crystals (68 mg, 53%) and the alkene **125b** as a colourless oil (32 mg, 30%). The enantiomeric excess of the optically active diol **127a** was determined by direct conversion to the Mosher esters (detailed below) and found to be 80%. The optical purity of the active alkene **125b** was determined by initially converting the alkene **125b** to the optically active diol **127b**, and then to the corresponding Mosher esters (the enantiomeric excess was also found to be 80%).

Formation of the racemic Moshers esters of the phenyl diol: (1RS, 3RS, 4RS, 5RS)-4-Hydroxy-1-methyl-4-phenylbicyclo[3.2.0]hept-3-yl (2R)-3,3,3-trifluoro-2-methoxy-2-phenylprop-anoate **128** and **129**

According to the procedure of Hassner, p. 157 a flask charged successively with the diol **127r** (7 mg, 0.03 mmols), dichloromethane (0.5 mL), dicyclohexylcarbodiimide (22 mg, 0.11 mmols), dimethylaminopyridine (5 mg, 0.04 mmols) and (R)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (23 mg, 0.10 mmols). Flash chromatography with hexane/ethyl acetate (95/5 v/v) as an eluant gave a 1:1 mixture of the *title compound* as a colourless liquid (9 mg, 63%). The peaks from which the optical purity was measured are show in detail in 'Chapter 4, Results and Discussion' p. 117. From the ^{1}H NMR spectrum of the products from the racemic and optically active samples it was possible to assign the following data.

Data for **128:** δ_H (300 MHz): 1.33 (s, 3H, CH_3), 1.3-2.5 (9H, complex, ring protons, + OH), 3.37 (br s, 3H, OCH_3), 6.26 (dd, 1H, H3), 7.35-7.55 (m, 5H, ArH).

Data for **129:** δ_H (300 MHz): 1.35 (s, 3H, CH_3), 1.3-2.5 (9H, complex, ring protons, + OH), 3.53 (br s, 3H, OCH_3), 6.28 (dd, 1H, H3), 7.35-7.55 (m, 5H, ArH).

Formation of the optically active Moshers esters of (1R,2R,3R,5R)-5-Methyl-2-phenylbicyclo[3.2.0]heptan-2,3-diol **127a** and (1S,2S,3S,5S)-5-Methyl-2-phenylbicyclo[3.2.0]heptan-2,3-diol **127b**

Diols from Kinetic Resolution taken to 40% conversion

The above procedure was separately repeated with the optically active diols **127a** and **127b**. The enantiomeric excess determined by cutting and weighing of the methoxyl resonances was determined to be 88% for the optically active diol **127a** and 52% for the optically active diol **127b**.

Diols from Kinetic Resolution taken to 75% conversion

The above procedure was separately repeated with the optically active diols **127a** and **127b**. The enantiomeric excess determined by cutting and weighing of the methoxyl resonances was determined to be 80% for the optically active diol **127a** and 80% for the optically active diol **127b**.

Section 4.6 Kinetic Resolution of the Methyl Alkene

(1RS,2RS,5RS)-2,5-Dimethylbicyclo[3.2.0]heptan-2-ol **131r**

Dry diethyl ether (10 mL), magnesium turnings (589 mg, 24.23 mmols) and a crystal of iodine were combined in a nitrogen atmosphere. Iodomethane (1.0 mL, 15.95 mmols) added dropwise to the reaction mixture. After addition was complete, the reaction mixture was further refluxed for 1hr. To the Grignard reagent, cooled to 0°C, was added the bicyclic ketone **12r** (1.0 mL, 8.18 mmols). After stirring the reaction mixture at ambient temperature for 15 hours, the reaction mixture was quenched with aqueous saturated ammonium chloride solution, then transferred to a separating funnel with diethyl ether. The aqueous layer was re-extracted with diethyl ether (3×), and the combined organic layers washed with saturated sodium chloride solution, dried and solvent removed *in vacuuo*. Sublimation (70°C / 0.5 mm Hg) gave the *title compound* as a white solid (757 mg, 66%). Mp 55-56°C. δ_H (300 MHz, $CDCl_3/D_2O$): 1.16 (s, 3H, CH_3), 1.20 (s, 3H, CH_3), 1.3-1.5 (3H, complex), 1.7-2.0 (5H, complex), 2.12 (td, 1H, J=7.5, 13.05Hz, $H3_a$). δ_C (75 MHz): 14.4(CH_2), 27.7(CH_3), 28.2(CH_3), 30.1(CH_2), 38.1 (CH_2) 39.1(CH_2), 43.3(q), 52.1(CH), 79.2(q). υ_{max}(neat): 3332 (br. s), 3000(s), 1164(s), 10.31 (s), 7221(m) cm^{-1}. M/z: 140(M^+, 4%), 123(25), 128(47), 97(100). The spectral data corresponds closely with that in the literature, except for the chemical shift for the methyl groups. [26,29]

(1SR,5RS)-2,5-dimethylbicyclo[3.2.0]hept-2-ene **10r**

To a solution of (1RS,2RS,5RS)-2,5-dimethylbicyclo[3.2.0]heptan-2-ol **131r** (579 mg, 4.12 mmols) in dichloromethane (16 mL) was added triethylamine (1 mL) and dimethylaminopyridine (40.0 mg, 0.33 mmols). The solution was cooled to 0°C and methane sulfonyl chloride (0.5 mL, 6.46 mmols) was added dropwise. After stirring at ambient temperature for 15 hours the reaction mixture was diluted with dichloromethane and washed with 15% $HCl_{(aq)}$. The aqueous layer was extracted with dichloromethane (2×), the combined organic layers were washed with brine (1×), dried and solvent was removed *in vacuuo*. The

title compound was obtained as a colourless liquid (280 mg, 85%). δ_H (300 MHz): 1.25 (s, 3H, CH_3), 1.4-2.0 (m, 3H, ring protons), 1.71 (br s, 3H, CH_3-C=CH), 2.10 (m, 3H, ring protons), 2.55 (m, 1H, allylic proton), 5.28 (br s, 1H, H3). In a reaction done on a smaller scale the ^{1}H NMR spectrum of the crude product indicated the presence of some of the *exo*cyclic alkene **9r**. None was detected from this larger scale reaction.

Attempted Kinetic Resolution of (1SR,5RS)-2,5-dimethylbicyclo[3.2.0]hept-2-ene **10r**

Reaction at 0°C

A mixture of potassium carbonate (96 mg, 0.69 mmols), potassium ferricyanide (179 mg, 0.54 mmols), methane sulfonamide (41 mg, 0.43 mmols), $(DHQD)_2$-PHAL (2 mg, 0.01 mmols), *t*-butyl alcohol (4 mL), water (4 mL), an aqueous solution of 4% osmium tetroxide (0.05 mL, 2.0 mg, 0.01 mmols) were combined and cooled to 0°C. The mixture was stirred with the aid of a mechanical stirrer (350rpm). Once the reaction mixture had reached 0°C, the stirring was stopped to add (1SR,5RS)-2,5-dimethylbicyclo[3.2.0]hept-2-ene **10r** (128 mg, 1.05 mmols). The reaction mixture was stirred at 0°C for 5 hours and then quenched with sodium sulfite solution (4 mL, 0.5 g/mL). The solution was then worked-up according to the general procedure on p. 162. Purification by flash chromatography with a gradient of ethyl acetate/hexane (30/70 v/v) as an eluant gave the *title compound* **103a** as white crystals (21 mg, 13%). The remaining alkene **10** was not recovered due to its volatility. The ^{1}H NMR data of **103a** are identical with those of **103r**. The optical purity was determined as described earlier on p. 164. It was found to be 23% e.e. after the reaction had gone to a 26% completion.

Reaction at Ambient Temperature

The above reaction was repeated at ambient temperature with the following quantities; potassium carbonate (96 mg, 0.69 mmols), potassium ferricyanide (187 mg, 0.57 mmols), methane sulfonamide (48 mg, 0.50 mmols), $(DHQD)_2$-PHAL (3 mg, 0.01 mmols), *t*-butyl alcohol (4 mL), water (4 mL), an aqueous solution of 4% osmium tetroxide (0.05 mL, 2.0 mg, 0.01 mmols) and (1SR,5RS)-2,5-dimethylbicyclo[3.2.0]hept-2-ene **10r** (125 mg, 1.02 mmols). Upon work-up and purification, the *title compound* **103a** was obtained as white crystals (22 mg, 13%). The optical purity was determined as described earlier on p. 164. It was found to be 24% e.e. after the reaction had gone to a 26% completion.

Section 5.1 Formation of 1-Methyl-2-Cyclohexen-1-ol

(1S,2R)-1-Methyl-cyclohexan-1,2-diol CAS [108392-44-5] **47a**

A mixture of AD-mix-β (35.8 g), t-butyl alcohol (125 mL), water (125 mL), and methane sulphonamide (2.45 g, 25.7 mmols) was cooled to 0°C, where upon some of the dissolved salts precipitated. 1-Methyl-1-cyclohexene (3.0 mL, 23.4 mmols) was added and the reaction mixture stirred with a mechanical stirrer (500rpm) for 48 hours at 0°C. Sodium sulphite (37.9 g, 300 mmols) was added and the mixture allowed to warm to ambient temperature, and then stirred for a further 30 minutes. Dichloromethane (50 mL) was then added and the aqueous phase re-extracted with dichloromethane (3×50 mL). The combined organic fractions were dried and solvent removed by distillation through a column packed with glass helices to give a yellow oil. Purification by flash chromatography with a gradient of ethyl acetate/hexane (10/90 v/v) as an eluant gave the *title compound* as yellow crystals. Further purification by sublimation at 60°C/0.5T gave white crystals (1.9 g, 85%), mp 67-68°C. δ_H (200 MHz): 1.24 (s, 3H, Me), 1.2-1.6 (complex, methylene envelope, 8H), 1.9 (br s, 1H, -OH), 1.8 (br s, 1H, -OH), 3.4 (dd, J= 3.9, 8.9 Hz, 1H, H2). δ_c: 21.5, 23.1, 26.5, 30.3, 36.8, 71.6, 74.8. υ_{max}: 3550(m, 2 peaks), 3475(w), 2975(s), 1040(m) cm^{-1}. M/z: 130($M^{+\cdot}$,14%), 112(29), 71(100). Lit[131] : δ_H : δ 1.25 (s, 3H), 1.0-1.9 (m, 8H), 3.38 (m, 1H).

(1SR,2RS) 1-Methyl-cyclohexan-1,2-diol **47r**

N-methylmorpholine *N*-oxide (3.71 g, 31.6 mmols) was added to the co-solvent system of water (2 mL) and acetone (12 mL). 1-Methyl-1-cyclohexene (2.5 mL, 21.2 mmols) and an aqueous solution of 40.85 mg/ mL Osmium tetroxide (0.7 mL, 28.6 mg, 0.11 mmols) and were added and the reaction mixture stirred vigorously overnight. A slurry of fluorisil (1.75 g) and sodium hydrosulfite (0.59 g) were added, the mixture stirred for 30 minutes at ambient temperature then filtered through a pad of celite. Solvent was removed by distillation through a short fractionating column packed with glass helices. The residual mixture was extracted with dichloromethane (3×10 mL), the combined organic extracts were dried and solvent was removed by distillation. Flash chromatography with ethyl acetate/hexane (30/70 v/v) gave the *title compound* (2.06 g, 75%). Further purification by sublimation at 50°C/0.5T gave white crystals (1.75 g, 63%). The spectral data corresponded with the data for the (1S,2R) enriched isomer.

(1R,2S)-(2-Methyl-2-hydroxy)cyclohexyl *p*-toluenesulphonate **48a**

A solution of the optically enriched diol **47a** (2.59 g, 19.9 mmols) dissolved in pyridine (45 mL) was cooled to 0°C. To this was added *p*-toluene sulfonyl chloride (5.38 g, 28.2 mmols) and the reaction mixture was then kept at 5°C for 15 hours. The resulting solution was poured over a slurry of ice, then extracted with dichloromethane (3×). The organic phases were washed successively with 7.5% hydrochloric acid (3×) and saturated sodium bicarbonate solution, dried and solvent removed *in vacuuo*. Purification by chromatography with ethyl acetate/hexane (20/85 v/v) yielded the *title compound* as white crystals (4.61 g, 82%), mp 80-81°C. δ_H (200 MHz): 1.14 (s, 3H, CH_3), 1.2-1.8 (8H, complex, methylene envelope), 1.59 (s, 1H, HO), 2.45 (s, 3H, Ar-CH_3), 4.36 (dd, 1H, H1, J =9.94, 4.04 Hz), 7.34 (d, J = 8.22 Hz, 2H, Ar), 7.80 (d, J = 8.22 Hz, 2H, Ar). δ_c (50 MHz): 20.66, 21.58, 23.48, 26.87, 28.02, 37.52, 70.58, 86.99, 127.65, 129.75, 134.39, 144.64. υ_{max} : 3600(s), 2850(s), 1600(s), 1500(m), 1260(m), 1180(w)cm^{-1}. M/z: 285($M^{+\cdot}$,5%), 267(10), 155(18), 129(45), 113(100). Anal Calcd for $C_{14}H_{20}O_4S$: C, 59.13; H, 7.03. Found: C, 58.94; H, 6.98.

Chiral shift analysis of the tosylate (12 mg) with tris-[3-(heptafluoropropyl-hydroxymethylene)-*d*-camphorato] europium(III) (12 mg) derivative in CCl_4 (0.5 mL) and C_6D_6 (0.08 mL) gave separation with broadening of the two aromatic peaks initially at δ7.34 and δ7.80 in the ^1H NMR spectrum (200 MHz), with baseline separation occurring to give two broad doublets at δ7.91 and δ8.12 for the resonance originally at δ7.80. Cutting and weighing of the broad doublet resonances at δ7.91 and δ8.12 gave an enantiomeric excess of 55±3%. Recrystallization from hexane-diethyl ether gave the optically active tosylate in a 37% recovery yield. With a 94% e.e. after 4 recrystallizations, the racemate is less soluble. The peaks from which the optical purity was measured are show in detail in 'Chapter 5, Results and Discussion' p. 126.

(1RS,2SR)-(2-Methyl-2-hydroxy)cyclohexyl *p*-toluenesulphonate **48r**

The above procedure was repeated with the diol **47r** (1.56 g, 12.01 mmols), pyridine (20 mL) and *p*-toluene sulfonyl chloride (3.10 g, 1.36 mmols). Purification by chromatography with ethyl acetate/hexane (30/70 v/v) yielded the *title compound* as white crystals (3.21 g, 94%), mp 80-81°C The spectral data corresponded with the data for the (1S,2R) isomer.

Chiral shift analysis of **48r** (23.6 mg) with tris-[3-(heptafluoropropyl-hydroxymethylene)-*d*-camphorato] europium(III) (20.4 mg) in CCl_4 (0.5 mL) and C_6D_6 (0.08 mL) gave separation

of the two aromatic peaks initially at δ7.34 and δ7.80 in a 1:1 ratio in the ^{1}H NMR spectrum at 200 MHz, with baseline separation occurring with the peak originally at δ7.80.

(1S)-1-Methyl-2-cyclohexenol CAS [112837-29-3] **2a**

Dry ethanol (14 mL) was added to diphenyl diselenide (1.39 g, 4.48 mmols) in a dried roundbottom flask, initially washed with saturated ammonium chloride and water. Sodium borohydride (557.2 mg, 14.73 mmols) was added at a rate to keep the reaction mixture below reflux. The tosylate **48a** (2.07 g, 7.29 mmols) was added to the clear solution and the reaction mixture was refluxed for 3 hours under a nitrogen atmosphere, then stirred for 12 hours. Removal of ethanol by distillation at atmospheric pressure through a vacuum-jacketed column gave a yellow solution. The residue was evaporatively distilled (kugelrohr) 120°/35mm Hg to give the *title compound* as a colourless liquid (636.2 mg, 78%). δ_H (200 MHz): 1.29 (s, 3H, CH_3), 1.5-1.8 (methylene envelope + OH, 5H), 2.1 (m, 2H, H4), 5.60 (dm, J = 10 Hz, 1H, H3), 5.75 (td, J= 4 and 10 Hz, 1H, H2). Decoupling at δ 2.1 reveals the peaks at δ 5.75, 5.60 as an AB quartet. δ_c (50 MHz): 19.55, 25.09, 29.32, 37.90, 67.89, 129.11, 133.74. M/z: 112($M^{+\cdot}$,5%), 97(100), 95(24), 84(44), 79(29), 69(88), 54(36), 48(23).

(1SR)-1-Methyl-2-cyclohexenol **2r**

The above procedure was repeated with dry ethanol (15 mL), diphenyl diselenide (1.54 g, 4.94 mmols), sodium borohydride (613.2 mg, 16.20 mmols) and the tosylate **48r** (2.19 g, 7.72 mmols). After an evaporative distillation (kugelrohr) 120°/35mm Hg the *title compound* was obtained as a colourless liquid in an overall yield of 55%. The spectral data corresponded with the data for the (1S) isomer.

(1SR,2RS,3RS)-2,3-Epoxy-1-methyl-cyclohexanol **52r**

0.63M Sodium bicarbonate solution (2 mL) was added to the synthetic racemic pheromone **2r** (149 mg, 1.32 mmols) dissolved in ether (2 mL) and the solution was cooled to -5°C. *m*CPBA (377.4 mg of 85% *m*CPBA, Aldrich 60% purified, 1.86 mmols) was added portionwise over 5 minutes and the biphasic solution was then stirred at ambient temperature for 3 hours. Dichloromethane (20 mL) was added to the mixture, it was washed with 1M aqueous sodium hydroxide solution (20 mL), water (20 mL), dried, and solvent removed *in vacuo*. Purification by chromatography with ethyl acetate/hexane (30/70 v/v) yielded the *title compound* as a

colourless liquid (145 mg, 84%). δ_H (300 MHz): 1.2-2.1 (methylene envelope, 6H), 1.33 (s, 3H, CH_3), 2.40 (br s, 1H, OH), 3.10 (d, J= 4 Hz, H2), 3.36 (m, 1H, H3). δ_c (75 MHz): 16.48, 23.83, 26.02, 36.04, 56.10, 59.20, 68.79. Chiral shift analysis of the epoxide (11 mg) with tris-[3-(heptafluoropropyl-hydroxymethylene)-*d*-camphorato] europium(III) (7 mg) in CCl_4 (0.5 mL) and C_6D_6 (0.08 mL) gave good separation of the epoxy protons at δ2.40 and δ3.10. The peaks from which the optical purity was measured are show in detail in 'Chapter 5, Results and Discussion' p. 129.

(1S,2R,3R)-2,3-Epoxy-1-methyl-cyclohexanol **52a**

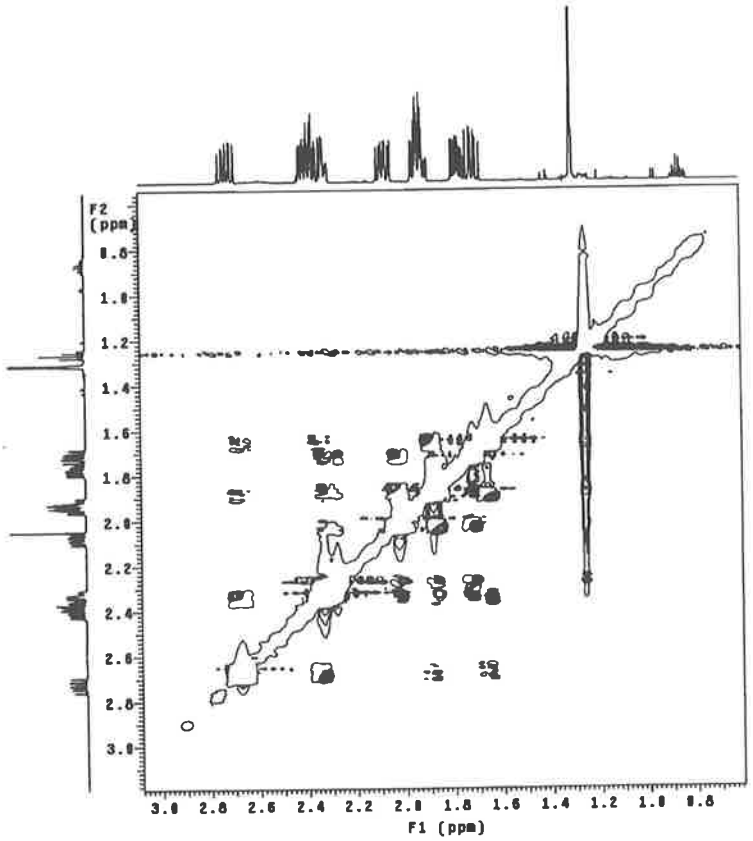
The above procedure was repeated with 0.63M Sodium bicarbonate solution (2 mL), the enantioriched synthetic pheromone **2a** (101 mg, 0.89 mmols), ether (3 mL), 85% mixture of *m*CPBA (201 mg of the 85% *m*CPBA, 0.99 mmols) at -5°C. Purification by chromatography with ethyl acetate/hexane (30/70 v/v) yielded the *title compound* as a colourless liquid (63 mg, 55%). Chiral shift analysis of the epoxide (4 mg) with tris-[3-(heptafluoropropyl-hydroxymethylene)-*d*-camphorato] europium(III) (3 mg) in CCl_4 (0.5 mL) and C_6D_6 (0.08 mL) gave good separation of the epoxy protons at δ2.40 and δ3.10. The enantiomeric excess (94±2% e.e.) was the same as obtained for the optically enriched tosylate sample employed (94±2% e.e.). The peaks from which the optical purity was measured are show in detail in 'Chapter 5, Results and Discussion' p. 128.

Section 5.2 Merged-Substitution Elimination Reaction

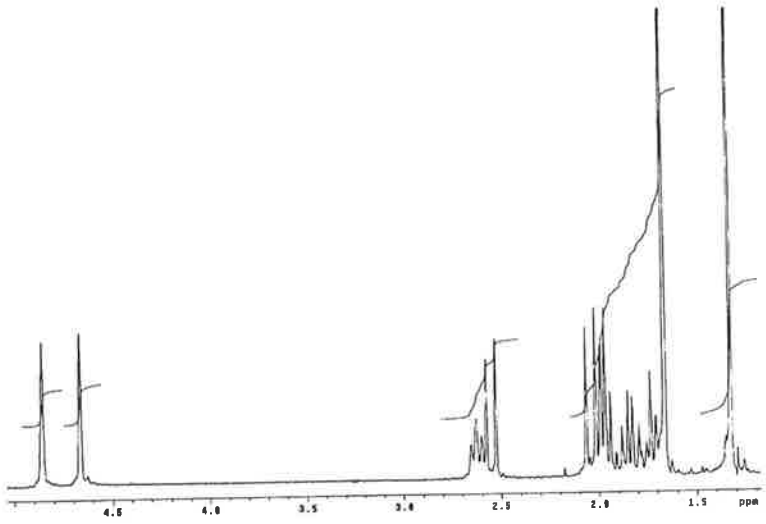
Attempted formation of (1S)-1-Methyl-2-cyclohexenol **2r** by Solvolysis

The racemic tosylate **48r** (153 mg, 0.53 mmols) in dry ethanol (4 mL) in a dried roundbottom flask, initially washed with saturated ammonium chloride and water, was refluxed for 4 hours under a nitrogen atmosphere. Dichloromethane (50 mL) was added to the reaction mixture, the reaction mixture washed with water (2×40 mL), the organic extract dried and solvent removed at atmospheric pressure by distillation (103 mg). The ^{1}H NMR showed no traces of the alkene, only the tosylate is present.

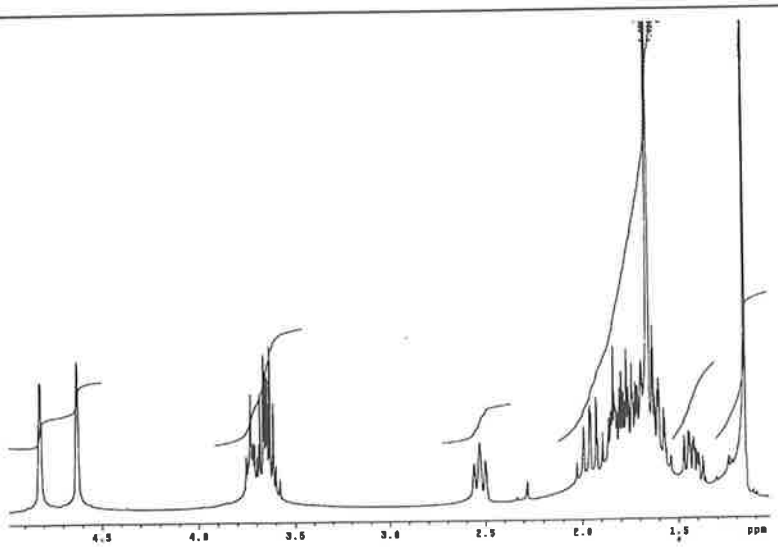
APPENDIX



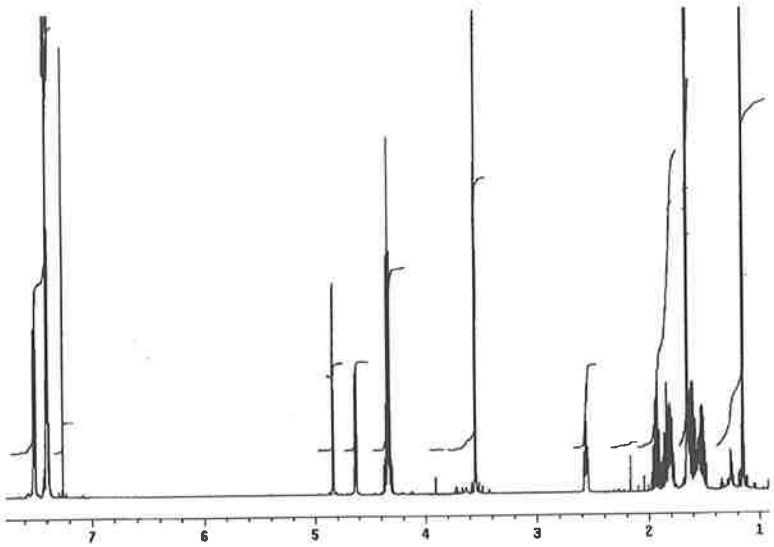
The NOESY spectrum at 600 MHz of the bicyclic ketone **12r**.



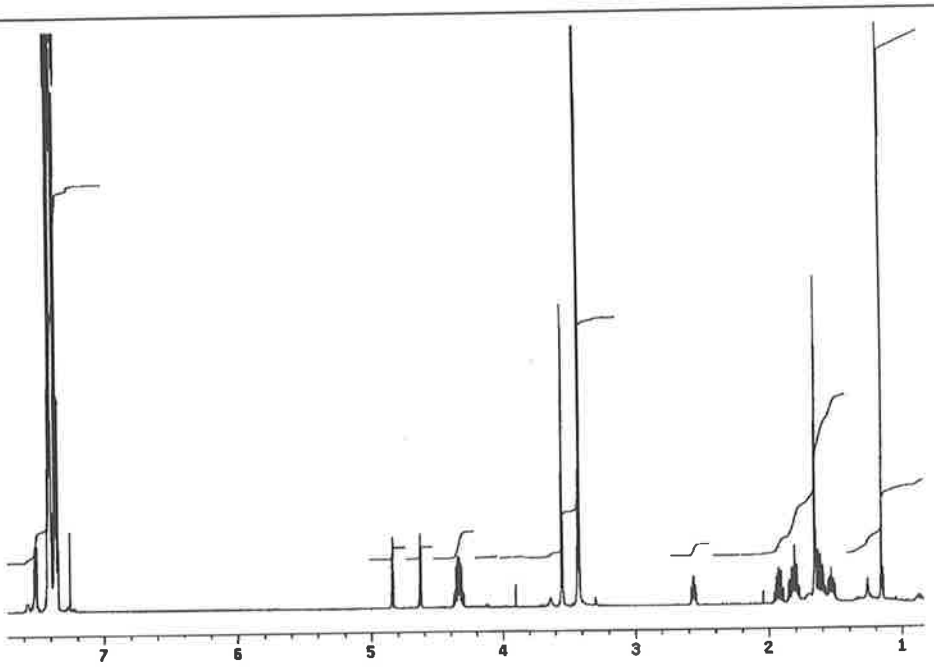
The ^{1}H NMR spectrum at 300 MHz of the optically active alkene acid **8a**.



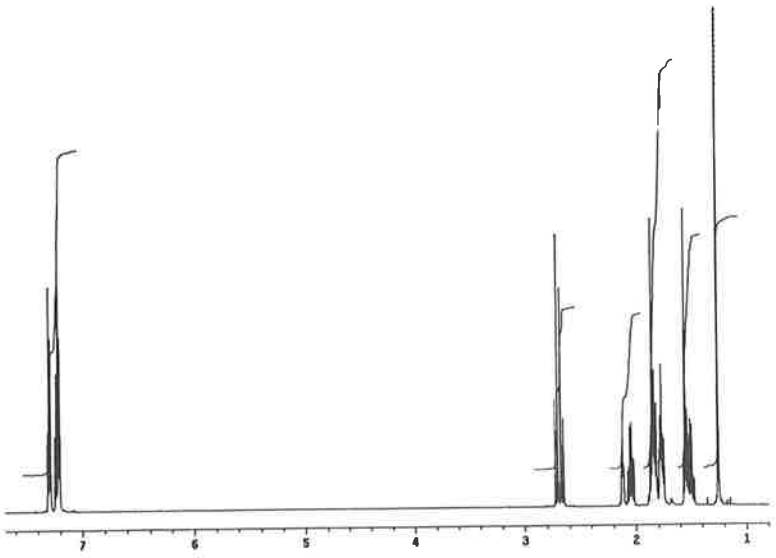
The ^{1}H NMR spectrum at 300 MHz of optically active grandisol **1a**.



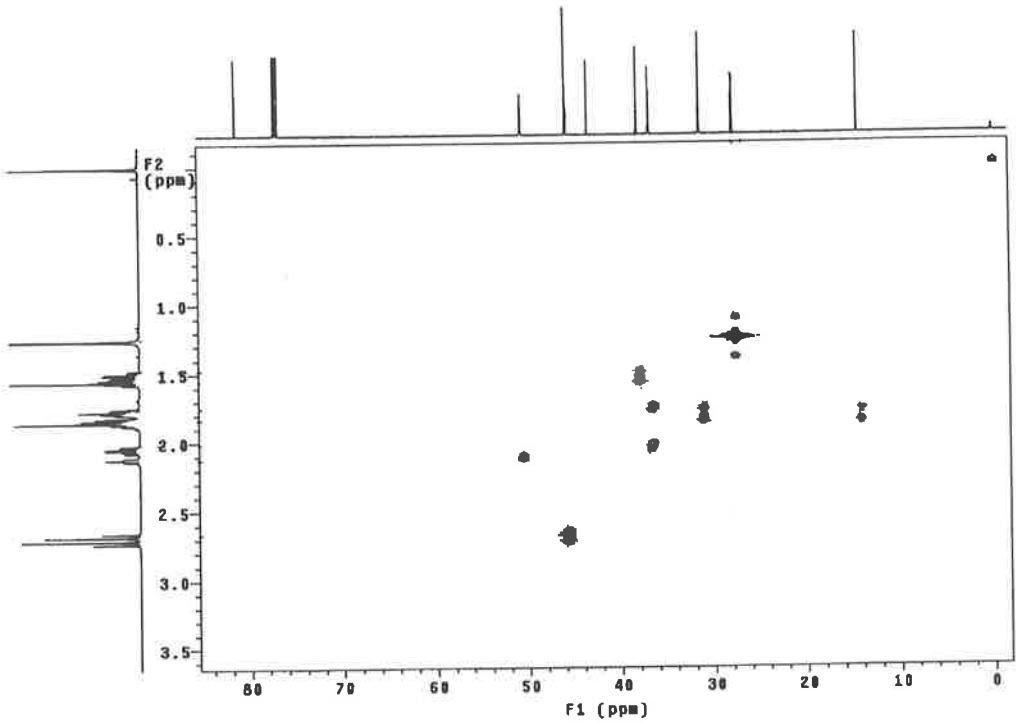
The ^{1}H NMR spectrum at 600 MHz of the racemic Mosher esters of grandisol **1**.



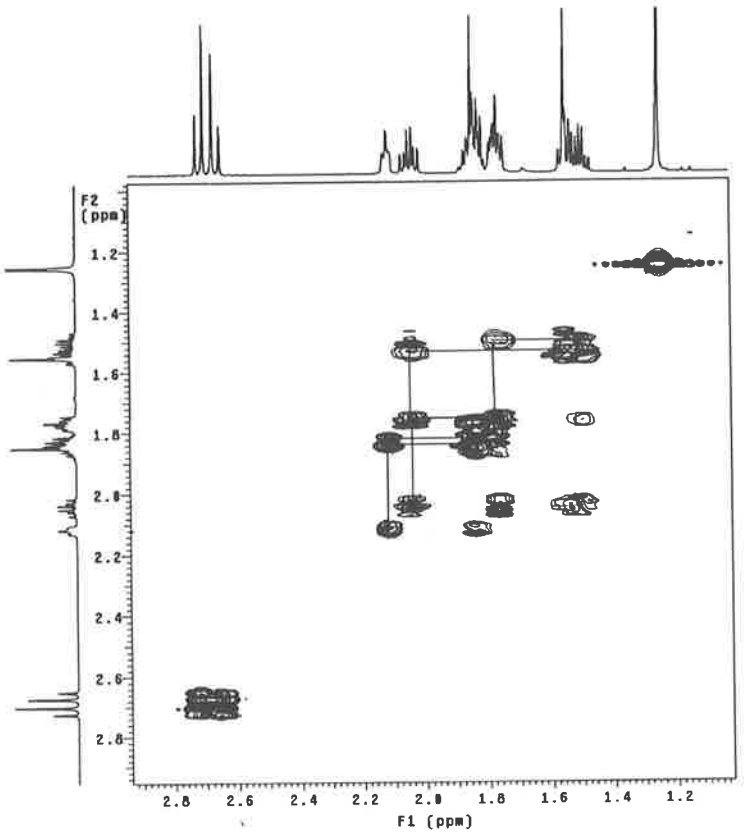
The ^{1}H NMR spectrum at 600 MHz of the optically active Mosher esters of grandisol **1**.



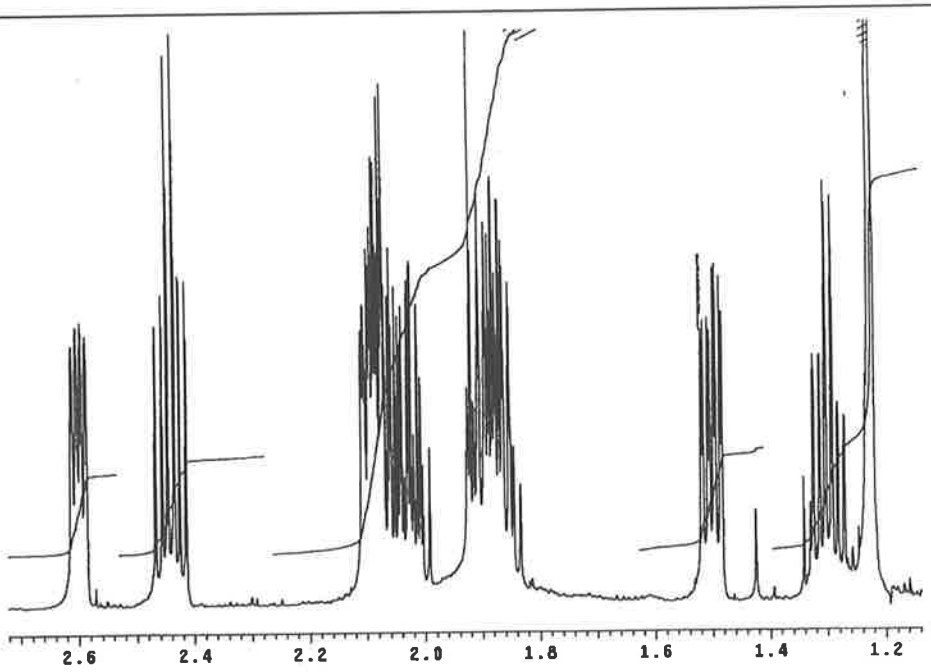
The 600 MHz ^{1}H NMR spectrum of (1SR,2RS,5SR)-2-Benzyl-5-methylbicyclo[3.2.0]heptan-2-ol **123r**



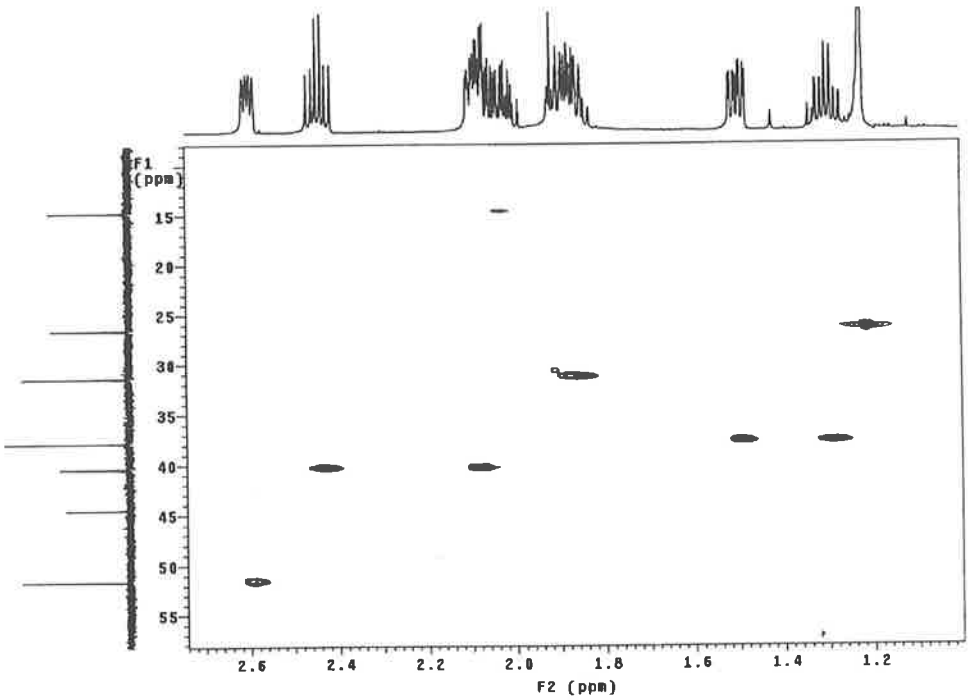
The HETCOR spectrum of (1SR,2RS,5SR)-2-Benzyl-5-methylbicyclo[3.2.0]heptan-2-ol **123r**.



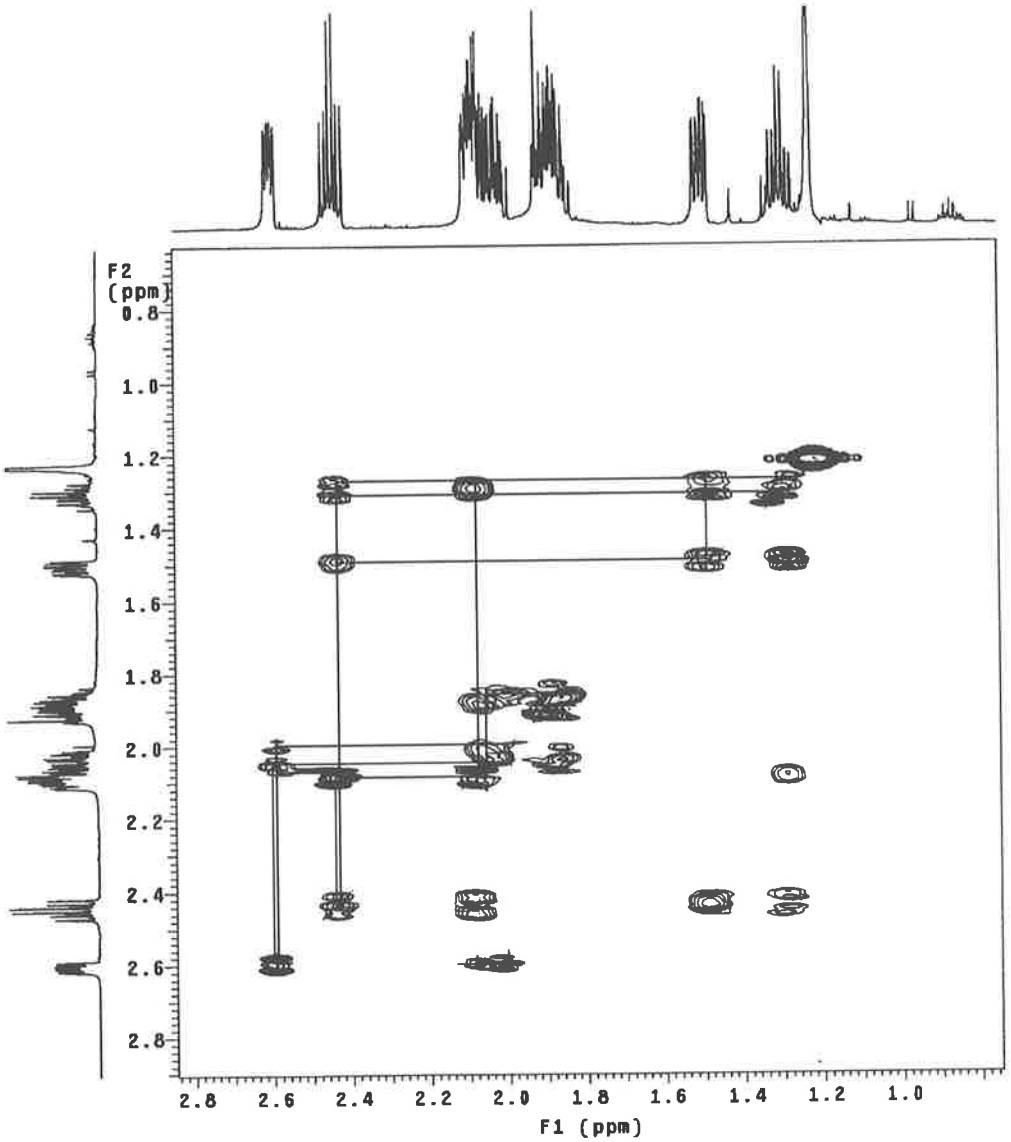
The COSY spectrum at 600 MHz of (1SR,2RS,5SR)-2-Benzyl-5-methylbicyclo[3.2.0]heptan-2-ol **123r**.



The region δ1.2-2.7 of the 600 MHz ^{1}H NMR spectrum of (1SR, 2SR, 5SR)-5-methyl-2-phenylbicyclo[3.2.0]heptan-2-ol **126r**.



The HETCOR spectrum of (1SR, 2SR, 5SR)-5-methyl-2-phenylbicyclo[3.2.0]heptan-2-ol **126r**.



The COSY spectrum at 600 MHz of (1SR, 2SR, 5SR)-5-methyl-2-phenylbicyclo[3.2.0]heptan-2-ol **126r**.

A concise asymmetric synthesis of the pheromone 1-methylcyclohex-2-enol *via* a 'merged substitution-elimination reaction'

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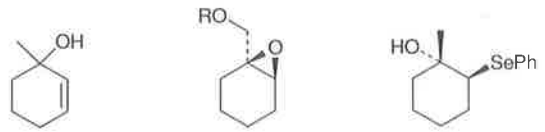
The title compound is prepared (> 94% ee) by a three step synthesis from 1-methylcyclohexene *via* a 'merged substitution-elimination reaction' involving a phenylselenide ion.

One of the constituents of the pheromone system of the beetle *Dendroctonus pseudotsugae Hopkins*, an economically important pest of the Douglas fir tree, is the aggregation pheromone 1-methylcyclohex-2-enol **1**. Previous syntheses of the optically active pheromone **1** have involved the conversion of optically active intermediates, prepared by classical resolution,[1] enzymically,[2,3] from the chiral pool,[4] or by multistep asymmetric syntheses.[5,6]



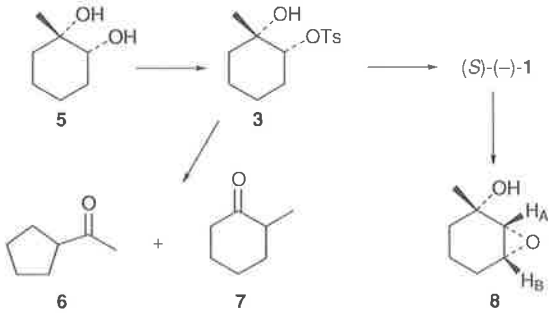
1 **2** **4**

If asymmetric syntheses are to become important for industrial preparations it is necessary to illustrate that they can be made simple and short. However, this is not necessarily a trivial exercise. With this pedagogical principle in mind, we sought to modify our earlier route[5] in the hope that the separate enantiomers might be more readily prepared. Serendipity has played an important role in providing a simple solution to this problem and we disclose a three step asymmetric synthesis of this pheromone which is applicable to the synthesis of either enantiomer, and which gives the constituent in an enantiomeric purity exceeding 94% ee. Ironically the aggregation pheromone found naturally is only 10% ee[7] but the challenge of the asymmetric synthesis has been pedagogically both useful and exciting. A key step in our earlier synthesis[5] of this pheromone involved nucleophilic substitution of the epoxide **2**. Although both the leaving groups in the epoxide **2** and the tosylate **3** are in a *pseudo* neopentyl location, a study of models suggests that tosylate **3** is considerably more hindered to nucleophilic attack than the epoxide **2**. However, it was considered that with the powerful nucleophile NaSePh, tosylate **3** might also, like epoxide **2**, react to give in this case the selenide **4**. Thermal elimination of the selenoxides[5] derived from **4** would give the pheromone **1**. Asymmetric dihydroxylation of 1-methylcyclohexene should give the optically active diol **5** from which the tosylate **3** could be prepared.

After this work had commenced, Sharpless reported,[9] as a footnote, the ee (52%, by chiral HPLC) for the asymmetric dihydroxylation (AD β mix) of 1-methylcyclohexene to the diol **5**, but no experimental details for the preparation were provided. Owing to the water solubility and considerable volatility of the diol **5**, we have found it necessary to modify, somewhat, the standard work-up procedures for this reaction by removal of the KOH wash normally used to remove methanesulfonamide. The product is then isolated, in 85% yield, by fractional distillation of all solvents, chromatography and sublimation (50 °C/0.5 Torr). Conversion of the diol **5** to the mono secondary tosylate **3** (85% yield, 94% yield for the racemate on a larger scale) gives material which, although it is initially only 75% of the major enantiomer,‡ can nevertheless be fractionally recrystallised to high enantiomeric purity (94% ee after four recrystallisations from diethyl ether–hexane, 37% yield, the racemate is less soluble).

Treatment of the tosylate **3** with NaSePh (PhSeSePh, $NaBH_4$, EtOH[10]), in boiling EtOH, did not give the sought after substitution reaction. Rather surprisingly an elimination reaction occurred instead. The initial reaction gave a mixture of the alcohol **1** and the ketones **6** and **7**. It had been assumed from the outset that base treatment of the tosylate **3** would give the ketones **6** and **7**, by a negative-ion pinacol rearrangement,[11] and this was confirmed by treatment of the tosylate with $KOBu^t$ (in THF at room temperature, **6** : **7** = 8 : 1, 90%). Selenide ion is too weak a base to abstract a proton from an alcohol and it was likely that ketones **6** and **7** were artifacts formed from adventitious sources of base. A wash of the glassware with NH_4Cl solution prior to the reaction of tosylate **3** with NaSePh, obviates the formation of these ketones and the volatile alcohol (*S*)-(−)-**1**§ is isolated, in 78% yield, by fractional distillation. The enantiomeric purity of the tertiary allylic alcohol **1** could not be obtained directly by chiral shift NMR experiments and we did not have access to complexation GC.[1] Conversion of the alcohol to the epoxide **8** (with slow addition of MCPBA to alcohol **1**, $NaHCO_3$, Et_2O, 0 °C, 70%, the diastereomer is not formed) and chiral shift NMR experiments‡ on this (94% ee) confirmed that the enantiomeric purity from the tosylate had been maintained.

The mechanism for the elimination reaction observed is intriguing. The reaction of the tosylate **3** with NaSePh in EtOH is not an E_1 mechanism since the qualitative observation is that the half-life for the reaction is concentration dependent; because no products from pinacol rearrangement are observed when care is taken to remove adventitious base; and because the tosylate is recovered unchanged after reflux in EtOH. The question arises, therefore, as to why selenide anion, a powerful nucleophile to carbon but non-nucleophilic to hydrogen attached to the oxygen of an alcohol, should suddenly change allegiance and become a nucleophile to hydrogen attached to carbon. Winstein, in a paper published in 1956,[8] first drew attention to the dichotomy of weak bases but good nucleophiles which promote elimination reactions when he wrote about merged substitution-elimination reactions. Since then there has been considerable debate[12,13] as to the veracity of his suggestion but, in our opinion, no clear

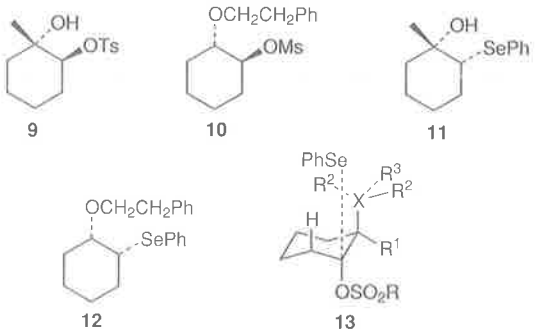


5 **3** **6** **7** **8**

Scheme 1

explanation has been given for what is actually occurring in these reactions. Since our example appears to be one of the more extreme examples of this phenomenon, we would like to present our observations in the hope that they will rekindle debate on this subject.

Under the same conditions, with NaSePh, as when the tosylate **3** gives only the elimination product **1**, both the racemic isomeric *trans*-tosylate **9** and the racemic mesylate **10** undergo clean substitution reactions to give the selenide derivatives **11**¶[14] and **12** respectively. It has been shown[15] that for the



4-*tert*-butylcyclohexyl derivatives the axial tosylate reacts faster than the equatorial tosylate in S_N2 reactions. Conformational mobility is clearly demonstrated for the tosylate **3**, even at room temperature, since it is likely that the compounds **6** and **7** come from two different chair conformers. From a study of models it is seen that when the leaving group is axial not only is the rear-side attack less hindered but, the nucleophile, the reaction centre and the leaving group can stay co-linear throughout the reaction.‖ Perhaps herein lies an explanation for our observations. It is likely that the selenide ion follows a trajectory co-incident with the dipole axis of the molecule and that in both the compounds **9** and **10** the propensity for carbon nucleophilicity is not thwarted by steric barriers since only lone pairs (see **13**) would hinder the approach. In the case of the tosylate **3**, however, the methyl group would clearly present an obstacle to rear-side attack and the deflected nucleophile might then encounter the hydrogen atom, held in an antiperiplanar relationship to the leaving group, with sufficient energy to overcome the barrier to elimination and this then becomes the lower energy process.

In conclusion, therefore, we have developed a three step asymmetric synthesis of the pheromone, from achiral starting materials. The route is probably far more efficient than any to date and will be extremely efficient if further developments to the Sharpless procedure allows a more enantioselective preparation of the diol **5**. Furthermore the synthesis has revealed an intriguing elimination reaction which may help to unravel the paradoxes arising in the mechanism of weak-base elimination reactions.

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Footnotes

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‡ All chiral shift NMR experiments were run in 15% C_6D_6 in CCl_4 with Eu(hfc)$_3$. Racemic tosylate **6**. δ_H (200 MHz, $CDCl_3$) 1.14 (s, 3 H, CH_3), 1.2–1.8 (complex, 8 H, methylene envelope), 1.59 (s, 1 H, OH), 2.45 (s, 1 H, Ar-CH_3), 4.36 (dd, 1 H, *J* 4.04, 9.94 Hz, H1), 7.34 (d, 2 H, *J* 8.22 Hz, Ar-H), 7.80 (d, 2 H, *J* 8.22 Hz, Ar-H). The doublet originally at δ 7.80 separates, to baseline, into two doublets with the shift reagent. Racemic epoxide **8**. δ_H (200 MHz, $CDCl_3$) 1.2–2.1 (complex, 6 H, methylene envelope), 1.33 (s, 3 H, CH_3), 2.40 (br s, 1 H, OH), 3.10 (d, 1 H, *J* 4.0 Hz, H2), 3.36 (m, 1 H, H3). The multiplet originally at δ 3.36 separates, to baseline, into two broadened singlets with the shift reagent.

§ Pheromone **1**. δ_H (200 MHz, $CDCl_3$) 1.29 (s, 3 H, CH_3), 1.5–1.8 (complex, 4 H, methylene envelope), 2.0 (m, 2 H, H4), 5.60 (br d, 1 H, *J* 10.0 Hz, H2), 5.75 (td, 1 H, *J* 4.0, 10.0 Hz, H3). δ_C (75.5 MHz, $CDCl_3$) 19.5, 25.0, 29.3, 37.8, 67.9, 128.9, 133.7.

¶ A referee has suggested that this compound might have the structure **4** if it arose through double inversion *via* the epoxide. However, optically active compound **4** is already known[5] and the spectral data are different.

‖ A study of a model (axial leaving group down) shows that the reacting centre can move up smoothly towards the nucleophile as overlap of the orbitals takes place. This would give the product in the boat conformation. No such smooth pathway exists for the equatorial leaving group. We believe that this requirement would also account for the known *trans*-diaxial opening of cyclic epoxides.

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