Synthesis and Evaluation of Some New Terpene-Based Chiral Auxiliaries and Catalysts

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Declaration

I declare that this thesis is my own composition, that the work of which it is a record has been carried out but myself, and that it has not been submitted in any previous application for a higher degree.

The thesis describes the results of research carried out in the Department of Chemistry of The University of Edinburgh, under the supervision of Dr. I. Gosney since 1st October 1992, the date of my admission as a research student.

Allan A. Doyle

For my mum and dad and my wife Alison

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Courses Attended

The following is a statement of the courses attended during the period of research:-

1. Merck, Sharp and Dohme, Medicinal Chemistry Lectures, Prof. R. Baker and Dr. P. Leeson, Department of Chemistry, University of Edinburgh, 1993, 1994 and 1995.
2. NMR of Biological Molecules, Dr. J. Parkinson and Dr. I. Sadler, Department of Chemistry, University of Edinburgh, 1993.
3. Chemical Development in the Pharmaceutical Industry, Smith-Kline Beecham, various speakers, Department of Chemistry, University of Edinburgh, 1993.
4. Industrial Fine Organic Chemistry, Prof. A. McKillop (University of East Anglia), Department of Chemistry, University of Edinburgh, 1993.
5. Hydrogen Peroxide and its Derivatives in Industry, Solvay Interox, various speakers, Department of Chemistry, University of Edinburgh, 1994.
6. Industrial Biocatalysts, Smith-Kline Beecham, various speakers, Department of Chemistry, University of Edinburgh, 1994.
7. Industrial Chemistry, Zeneca Grangemouth, various speakers, Department of Chemistry, University of Edinburgh, 1995.
8. Organic Research Seminars, various speakers, Department of Chemistry, University of Edinburgh, 3 years attendance.
9. Current Topics in Organic Chemistry, various speakers, Department of Chemistry, University of Edinburgh, 3 years attendance.

10. Royal Society of Chemistry, Perkin Division (Scottish Section), annual meetings, various speakers, 3 years attendance.

Abstract

The work described in this thesis has been primarily concerned with the synthesis of a number of different and novel chiral auxiliaries. All of the chosen synthetic routes to the desired auxiliaries utilised cheap and readily available terpenes from the "chiral pool".

The utility of the successfully synthesised auxiliaries was evaluated in a range of asymmetric transformations: Lewis-acid catalysed Diels-Alder cycloadditions, 1,4-conjugate additions, boron enolate mediated aldol reactions and acylation reactions.

The most successful auxiliaries were found to be two homologous camphor-based oxazolidin-2-one auxiliaries both of which were shown to impart excellent levels of asymmetric induction in all of the aforementioned reactions.

In addition to chiral auxiliaries, some investigations were carried out on the development of camphor-derived chiral catalysts. The utility of these oxazaborolidine catalysts in asymmetric Diels-Alder cycloadditions and asymmetric ketone reduction reactions was then evaluated. It was found that neither catalyst imparted any stereoselectivity in the Diels-Alder reactions and only very low levels were observed in ketone reductions.

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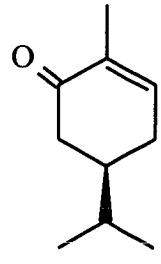
Introduction

1. The Need for Optical Purity

During the past 15 to 20 years industrial and academic institutions alike have shown a great deal of interest in the field of asymmetric synthesis. This intense research has been carried out because the importance of obtaining enantiomerically pure compounds is now well established. The chirality of a molecule can often determine its properties in unexpected ways. This phenomena is particularly important in the food, pharmaceutical and agrochemicals industries. For example, the (*R*)-isomer of carvone **1** tastes of spearmint whereas the (*S*)-isomer **2** tastes of caraway (Figure 1). The artificial sweetener aspartame **3** has four possible stereoisomers, but only the one shown in Figure 1 is sweet, the other three tasting bitter.



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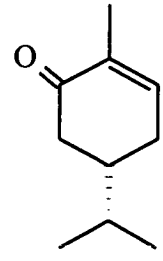

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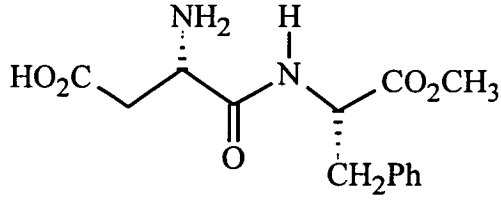

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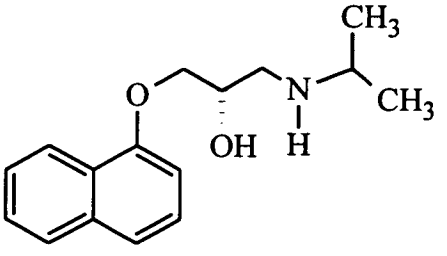
Figure 1

The need for optical purity is especially important in the pharmaceutical industry. A recent survey[1] has shown that of the 1850 drugs on the market, 570 are sold as

single stereoisomers. As the biological environment of our bodies is chiral so different enantiomers of a drug may react in differing ways. For example, with the commonly prescribed drug propanolol, used in the treatment of high blood pressure, only the (*S*)-isomer **4** is an effective β-blocker. On the other hand, the (*R*)-isomer **5** acts as a contraceptive (Figure 2). Likewise, the (*S*)-conformer of penicillamine **6** is



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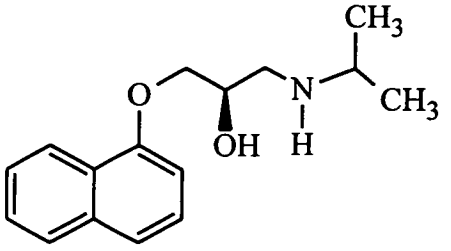

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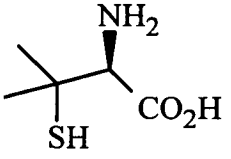

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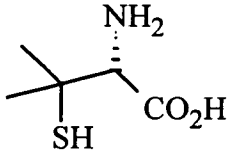

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Figure 2

an effective chelating agent for the removal of heavy metals from the body whereas its (*R*)-isomer **7** causes blindness.

As well as being a potential health hazard, the marketing of optically impure products may also have environmental implications. This is especially true in the agrochemicals industry; in the case of the pyrethrin insecticide deltamethrin **8** (Figure 3) only the stereoisomer shown is active, with the other seven all being inactive. Consequently, if sold impure over 87% of the product sprayed on crops is just acting as a pollutant.

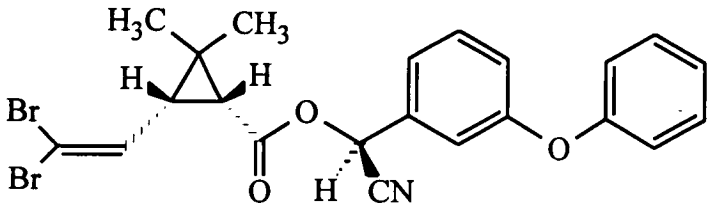

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Figure 3

The methods used for obtaining enantiomerically pure compounds can be broadly classified into three main groups: (a) asymmetric synthesis, (b) chiral pool approach and (c) resolution.

2. Asymmetric Synthesis

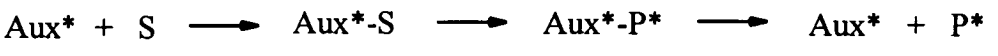
The term asymmetric synthesis covers a wide spectrum of work that can be conveniently sub-divided into three further groups: (i) the use of chiral auxiliaries, (ii) the use of chiral catalysts and (iii) the use of chiral reagents.

These three areas will be discussed subsequently in this introduction, though most emphasis will be placed on the use of chiral auxiliaries since this is the area that this research project is primarily concerned with.

2.1 Use of Chiral Auxiliaries

In recent years there has been considerable interest shown in the use of chiral auxiliaries. Indeed it is difficult to open a journal on asymmetric synthesis without finding yet more new auxiliaries. A chiral auxiliary is defined as an optically pure compound (Aux*) to which is attached a prochiral substrate (S) (Scheme 1). A reaction is then performed on the substrate, during which the auxiliary directs its

course, resulting in the formation of a chiral product (P*). After the reaction is complete the product is cleaved off and the auxiliary hopefully recycled.



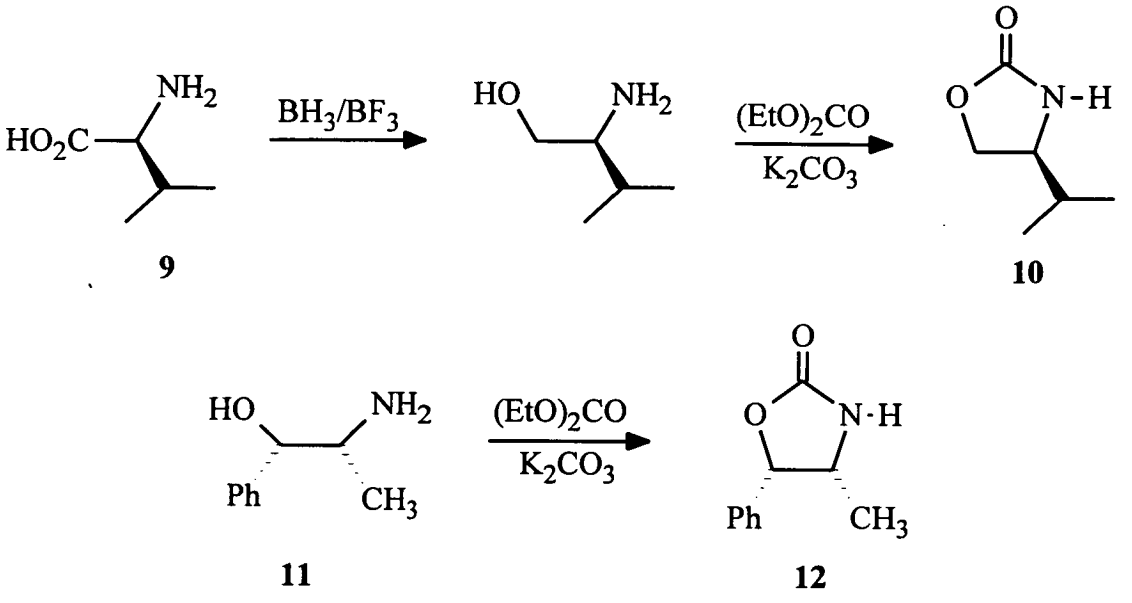
Scheme 1

The main requirements placed on an auxiliary are: (a) it must be available in an enantiomerically pure form, preferably with both enantiomers being accessible, (b) it must be easily attached to prochiral substrates, (c) it must be able to transfer its chirality effectively in order to impart high levels of diastereoselectivity and (d) it must be easily removed and preferably recycled.

In this introduction an account will be given of some of the most commonly used and most efficient chiral auxiliaries.

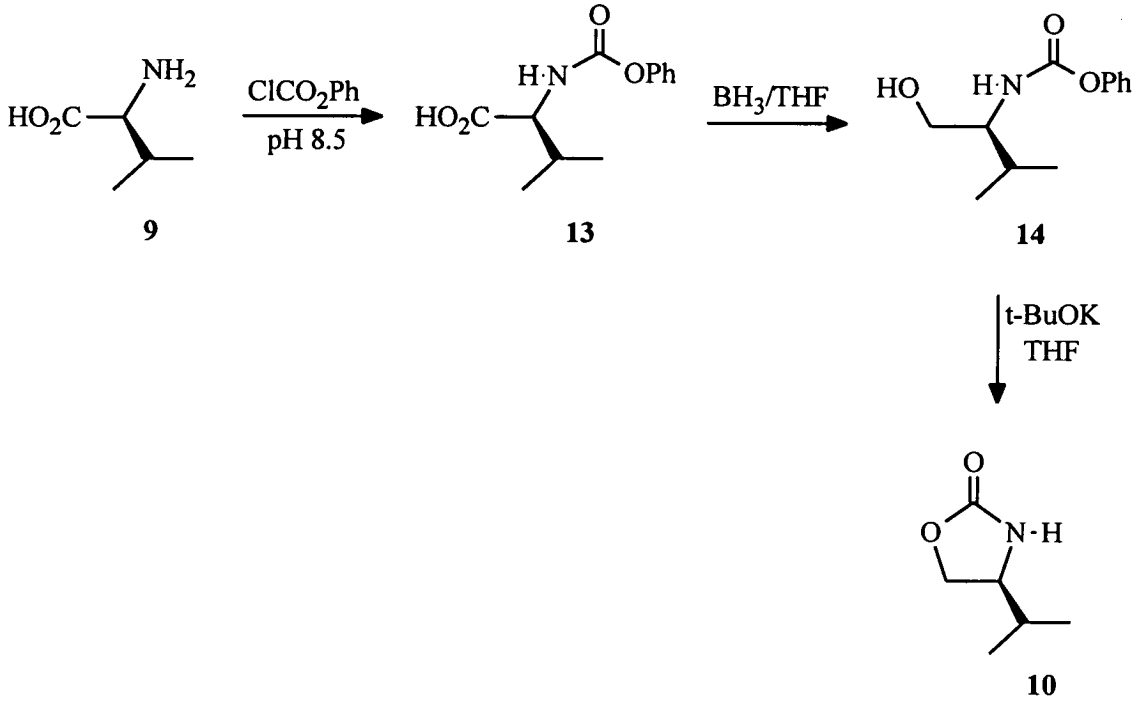
2.1.1 Evans' Oxazolidin-2-ones

Perhaps two of the most widely known and versatile chiral auxiliaries that have been developed hitherto are the oxazolidin-2-ones **10** and **12.** Evans[2] synthesised both compounds from the naturally occurring compounds (*S*)-valine **9** and (1*S*, 2*R*)-norephedrine **11,** respectively (Scheme 2). More recent work carried out by Wuts[3]



Scheme 2

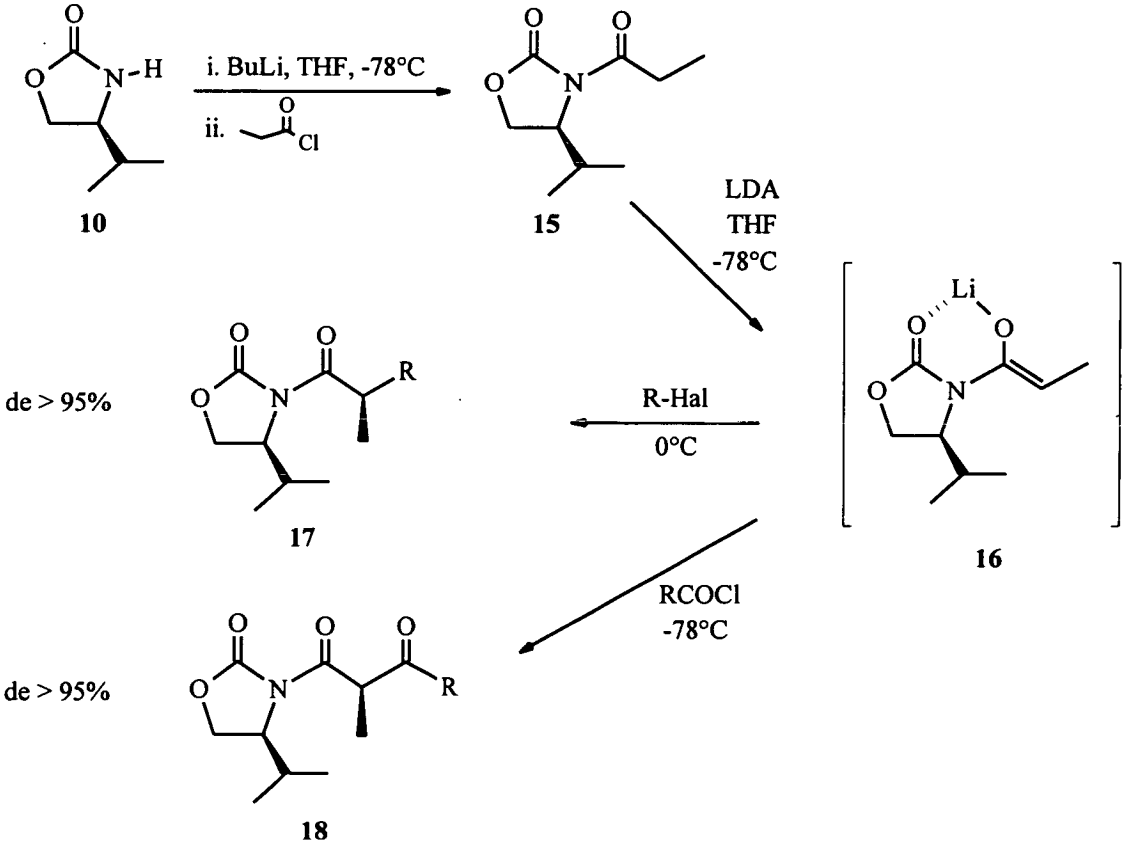
has led to an improved synthesis of **10** that is adaptable to large scale preparations (Scheme 3). The procedure starts with a Schotten-Baumann acylation of (*S*)-valine **9**



Scheme 3

using phenyl chloroformate in aqueous sodium hydrogen carbonate. Reduction of the resultant acid **13** with borane yields alcohol **14**, which when treated with a catalytic amount of potassium *tert*-butoxide gives the auxiliary **10**, in 43% overall yield.

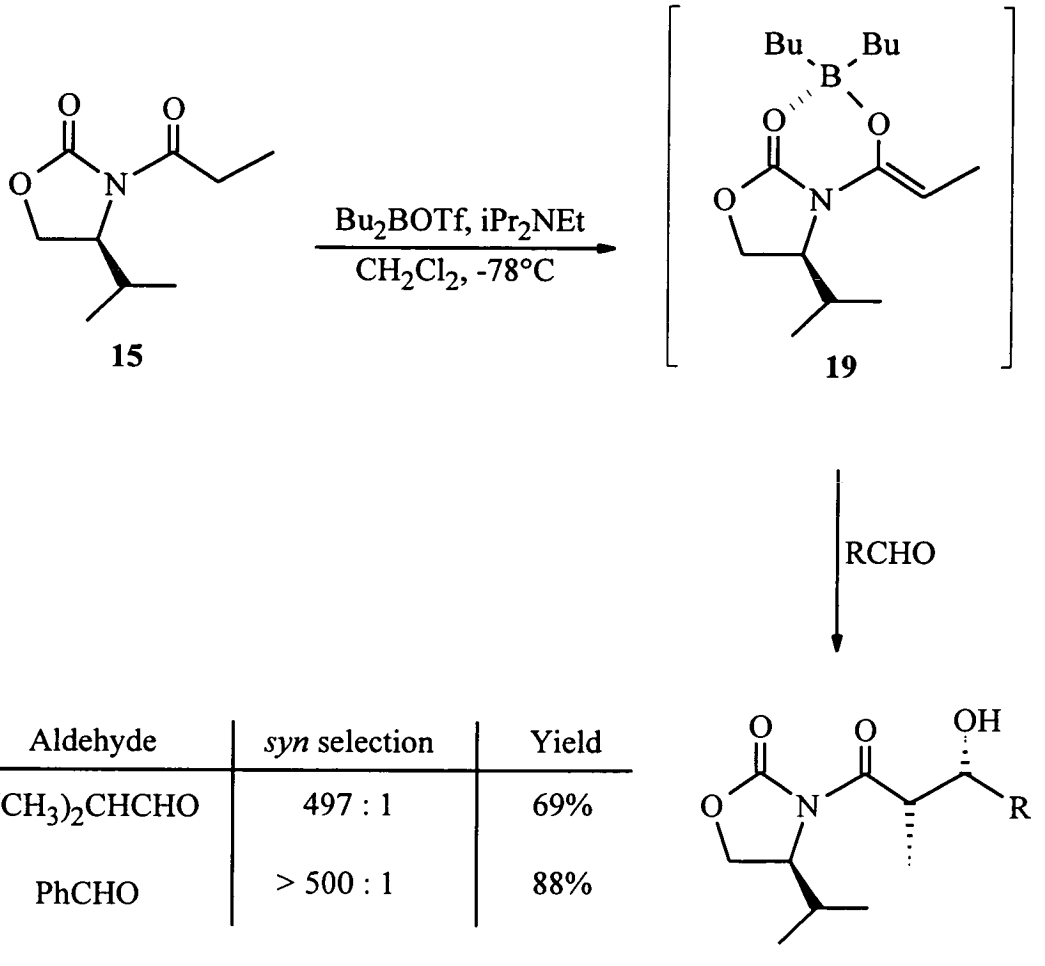
The (*S*)-valine derived auxiliary **10** is readily functionalised by treatment with *n*-butyllithium and propionyl chloride to form the imide **15** (Scheme 4). Treatment of propionate **15** with LDA affords the *Z*-enolate **16,** which can then be either alkylated[4] to form the alkylation product **17** or acylated[5] to furnish the acylated compound **18** (Scheme 4). Both of these reactions proceed with excellent levels of diastereoselectivity.



Scheme 4

The excellent levels of asymmetric induction observed in these reactions is due to the fact that essentially only the *Z*-enolate is formed[4], and that the electrophile approaches the face of the enolate which is away from the bulky isopropyl group.

In contrast to the foregoing successful asymmetric transformations, aldol reactions using the lithium enolate **16** exhibited only very poor levels of diastereoselectivity. However, when the boron enolate **19** is employed, very high levels of asymmetric induction are observed (Scheme 5)[6]. An explanation for this enhanced performance is presented later in the discussion (section 2.6).

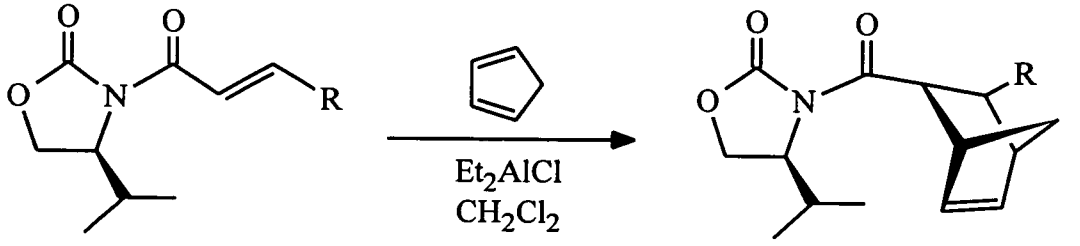


15 **19**

Aldehyde	*syn* selection	Yield
$(CH_3)_2CHCHO$	497 : 1	69%
PhCHO	> 500 : 1	88%

Scheme 5

As well as the enolate reactions mentioned above, such auxiliaries have also been used in Lewis-acid catalysed asymmetric Diels-Alder reactions with cyclopentadiene[7] (Scheme 6). Evans reported excellent *endo/exo* selectivity, together with very high diastereomeric excesses for the *endo* isomers.

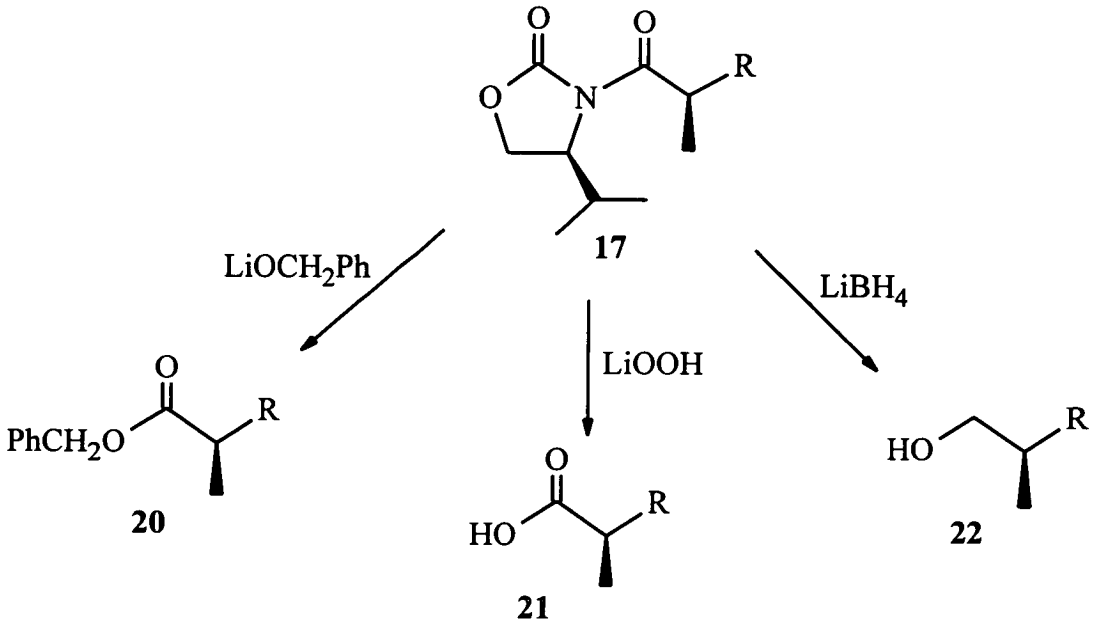


R = H, Me, Ph

Yields = 81 - 83%
de (*endo*) = 86 - 90%

Scheme 6

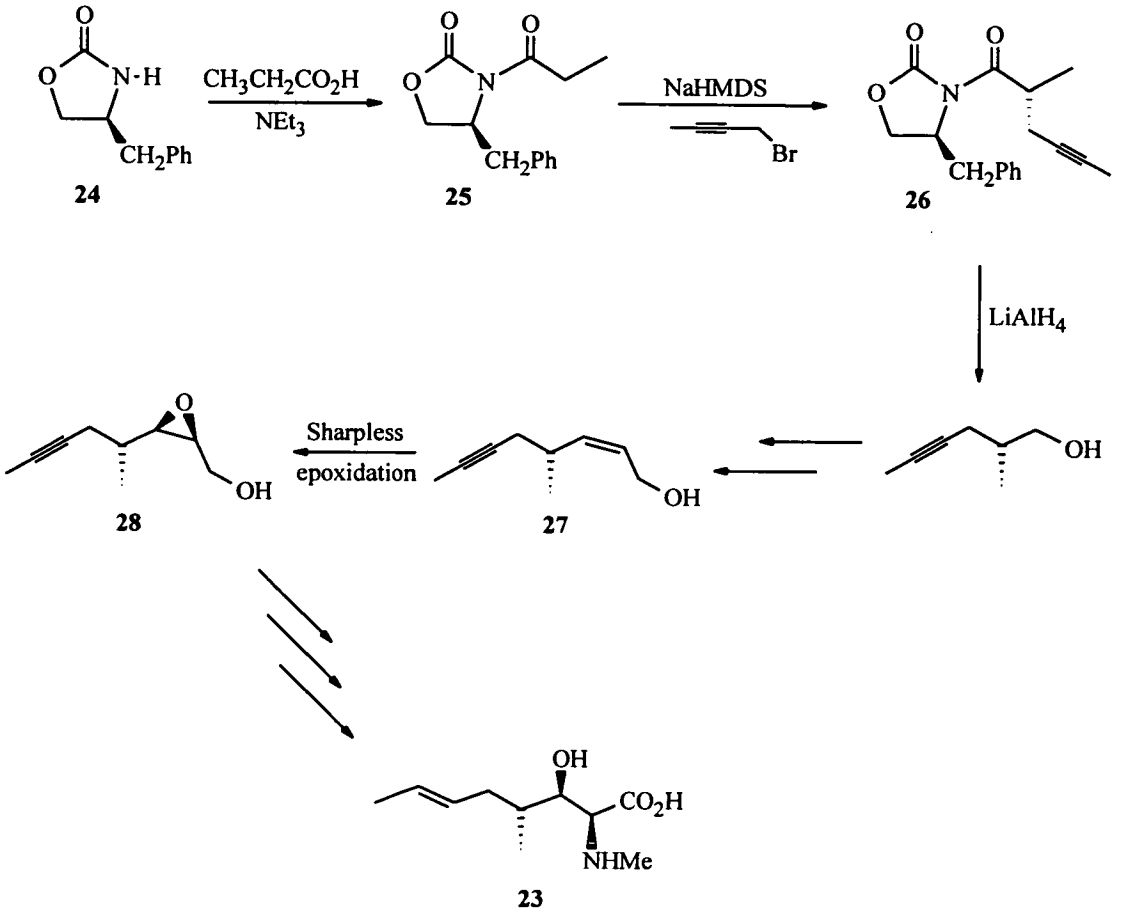
As mentioned previously the auxiliary must be easily cleaved, and consequently a number of different conditions have been developed to achieve this, depending on the functional group that is required in the product (Scheme 7). Cleavage with lithium benzyloxide[4] affords the benzyl ester **20**, whilst cleavage with lithium hydroperoxide[8] furnishes the acid **21**, and cleavage with lithium borohydride[9] gives the primary alcohol **22**.



Scheme 7

Evans' auxiliaries have been widely used in a number of natural product syntheses[10-12]. One recent example is Savignac's synthesis of the β-hydroxy-α-amino acid (2*S*, 3*R*, 4*R*)-2-methylamino-3-hydroxy-4-methyloct-6-enoic acid **23**[13]. Amino acids of this type are found in nature both as natural products and as components of more complex natural products such as cyclic polypeptides.

The key step in the synthesis of **23** is the introduction of the (*R*)-stereochemistry at the 4-position *via* alkylation of the propionate **25**, derived from the auxiliary **24**, to afford **26** (Scheme 8). The other two stereo-centres were set-up by Sharpless epoxidation (see section 2.2.2) of the allylic alcohol **27** to give the enantiomerically pure epoxide **28**, in 50% yield.

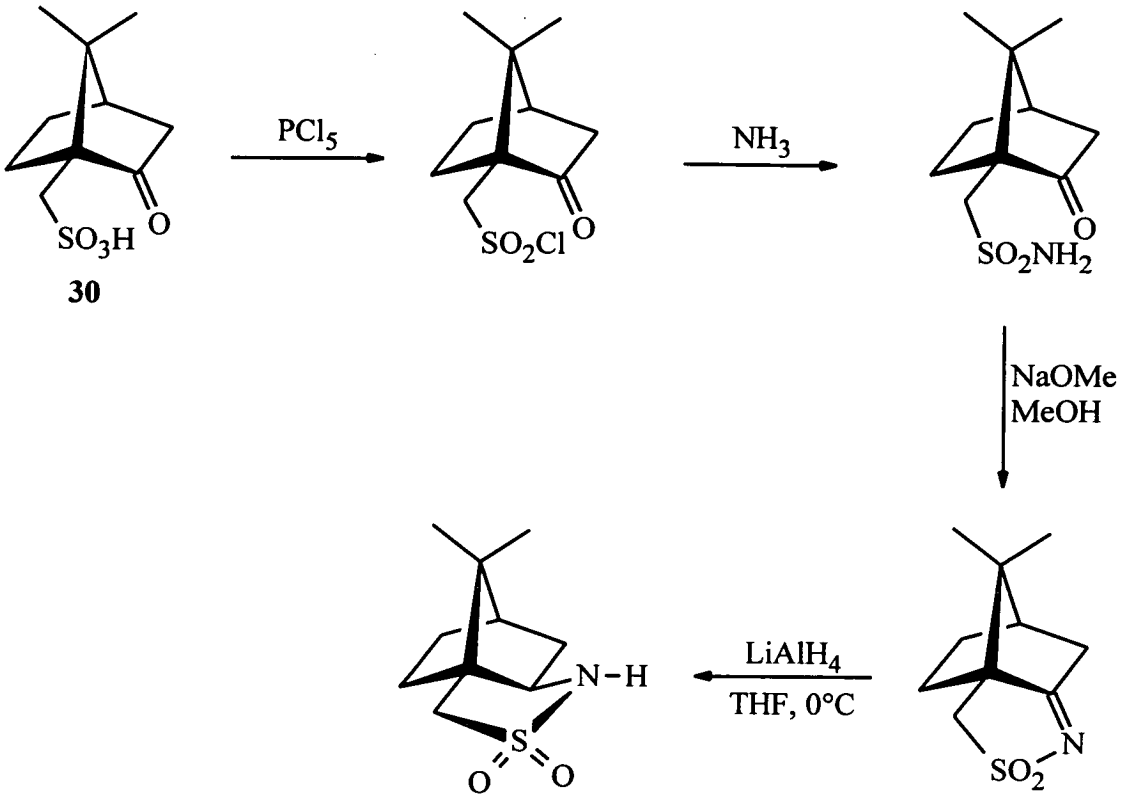


24 25 26 28 27 23

Scheme 8

2.1.2 Oppolzer's Chiral Sultam

One of the most widely used and recognised chiral auxiliaries is undoubtedly Oppolzer's chiral sultam **29**, which is synthesised in four steps from (1*S*)-(+)-10-camphorsulphonic acid **30,** as shown in Scheme 9, in very good yield (63%)[14]. This



30

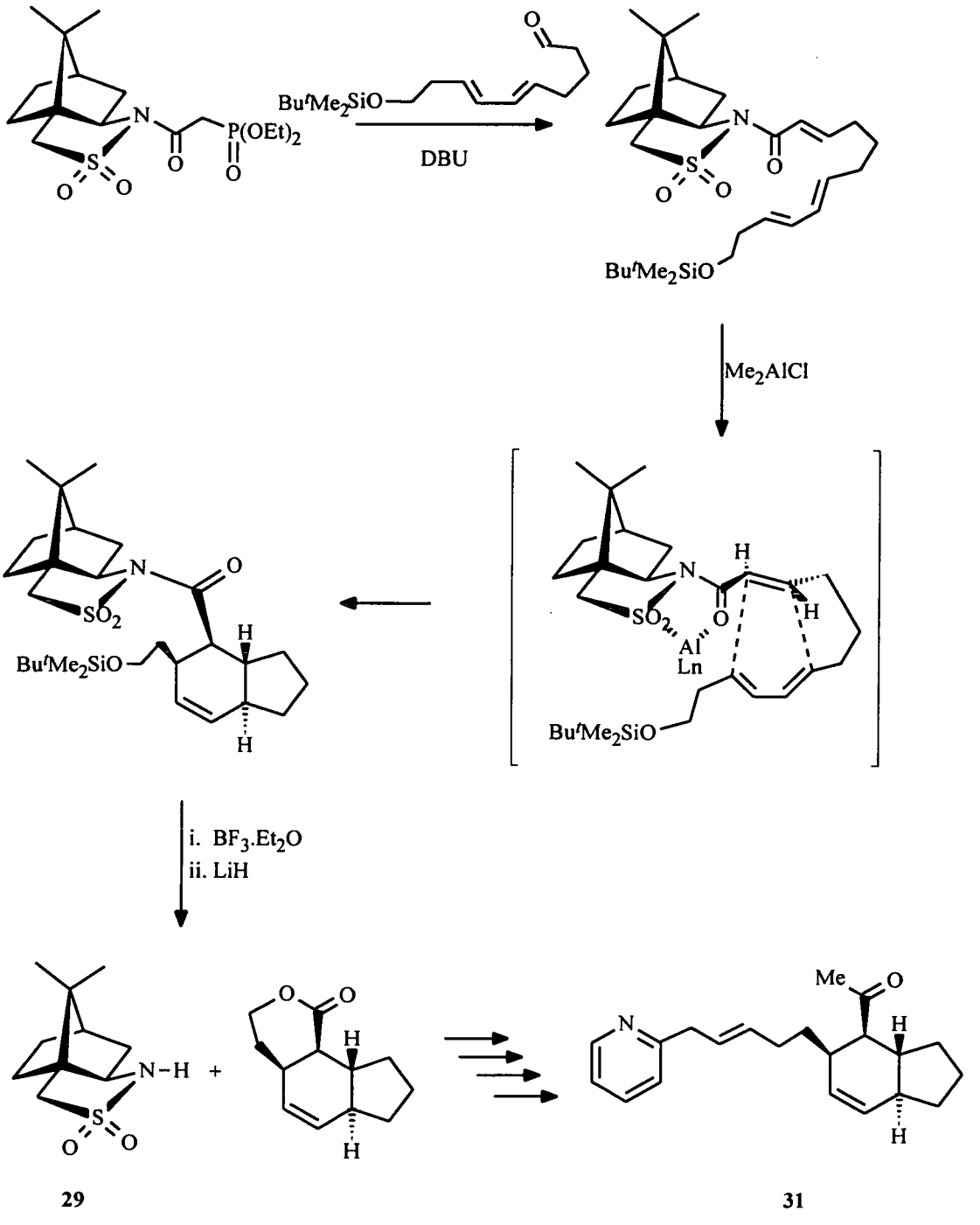
29

Scheme 9

auxiliary has the advantage that as (1*R*)-(-)-10-camphorsulphonic acid is also commercially available, its enantiomer can also be used.

As with the Evans oxazolidinones, sultam **29** is easily functionalised with either saturated or unsaturated acid chlorides. The synthetic utility of **29** parallels that of Evans' auxiliaries and has been shown to impart excellent levels of diastereoselectivity in alkylations[15], aldol reactions[16] and in Diels-Alder reactions[17]. The high levels of selectivity observed in these reactions arises from the attacking species approaching from the least hindered bottom face of any enolate or dienophile, *i.e.* away from the bulk of the bornane ring. In order to illustrate this selective approach Oppolzer's synthesis of the natural product pulo'upone **31**[18] is given in

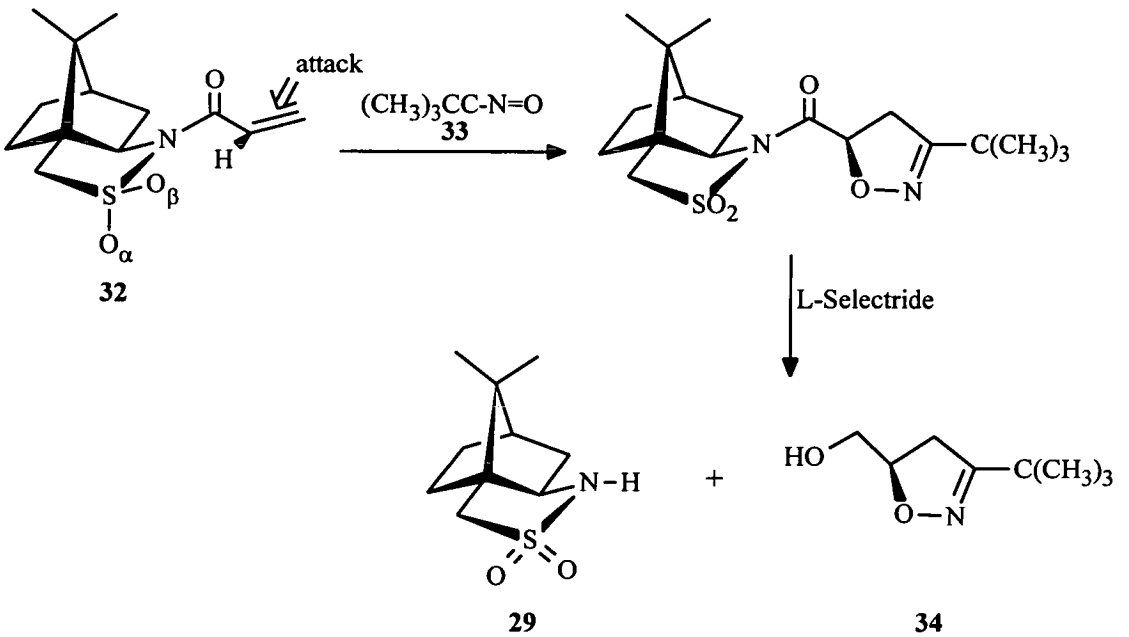
Scheme 10. The four stereocentres in **31** were all formed in the correct orientation by means of an intramolecular Diels-Alder. It is worth noting that in the chelated



Scheme 10

transition state assembly the bulk of the bornane skeleton shields the top face of the dienophile; consequently the diene portion is forced to react on the lower C_α-*re* face.

As has been mentioned, all of the previous reactions rely on the bulk of the auxiliary shielding the upper face of the addending enolate or dienophile, but surprisingly there is an exception to this rule. In the case of 1,3-dipolar cycloaddition reactions, the dipole attacks the top face (C_α-*re*) of the dienophile and still exhibits excellent levels of diastereoselectivity. This phenomena of C_α-*re* face attack can be explained by considering the reaction between the acrylate **32** and 2,2-dimethylpropane nitrile oxide **33**, to give the isoxazoline **34** (Scheme 11). Curran[19]



Scheme 11

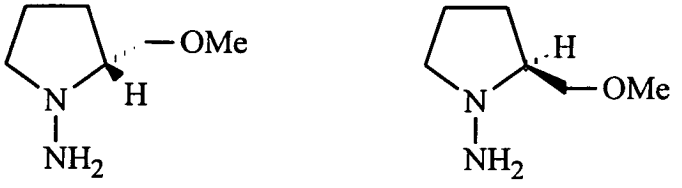
suggests that this reversal in facial selectivity is due to the S-O_α bond providing either a steric or electronic encumbrance to attack on the lower (C_α-*si*) face.

After the asymmetric transformations are complete, cleavage and recovery of Oppolzer's auxiliary can be brought about by employing conditions similar to those used for the Evans auxiliaries.

The one major drawback with the sultam auxiliary **29** is that since the CH_2 group adjacent to the SO_2 function is acidic, there is the possibility of side reactions being encountered during enolate reactions.

2.1.3 Enders' SAMP and RAMP Auxiliaries

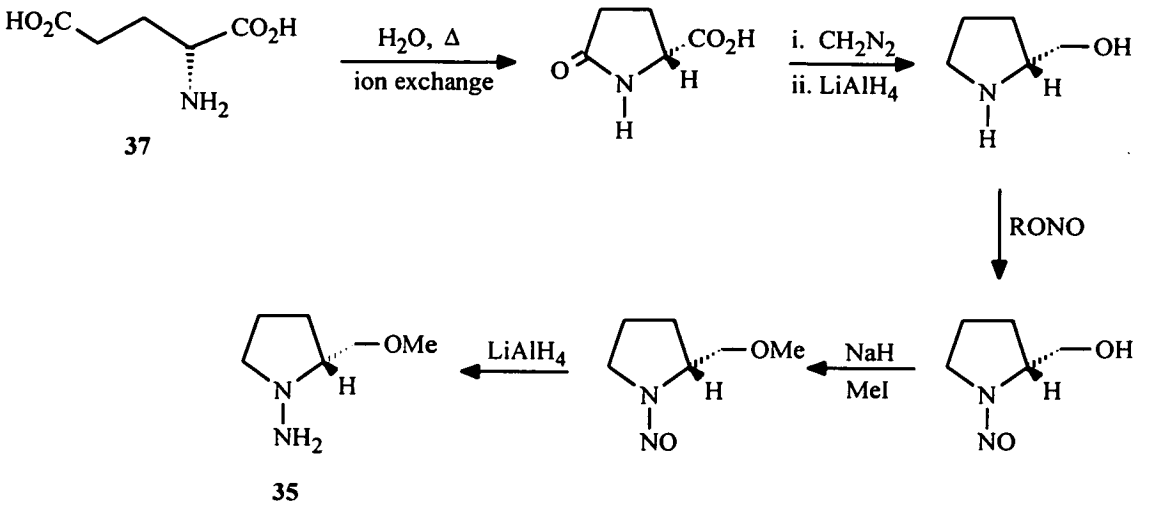
The two chiral hydrazines (*R*) and (*S*)-1-amino-2-methoxymethylpyrrolidine (RAMP **35** and SAMP **36**) (Figure 4) have been shown by Enders to function as



RAMP **35** SAMP **36**

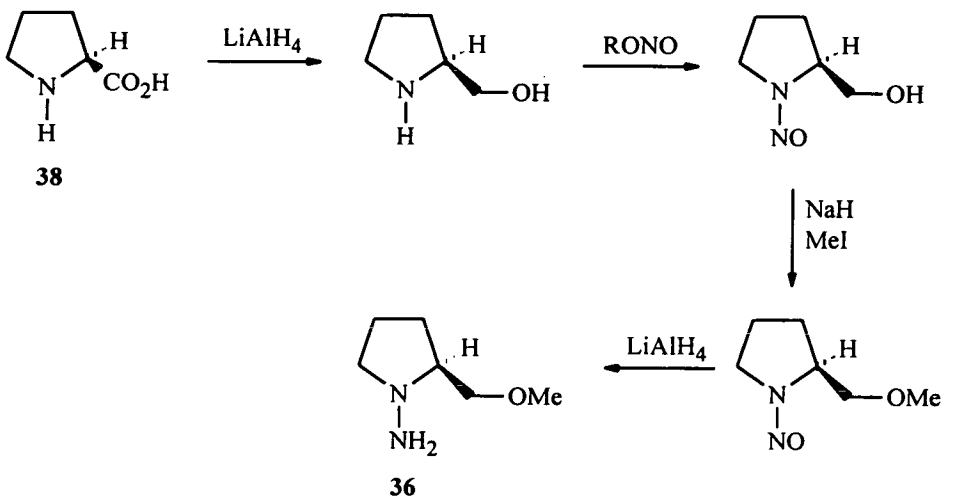
Figure 4

efficient chiral auxiliaries[20]. RAMP **35** is derived from (*R*)-glutamic acid **37** in an overall yield of 35% (Scheme 12).



Scheme 12

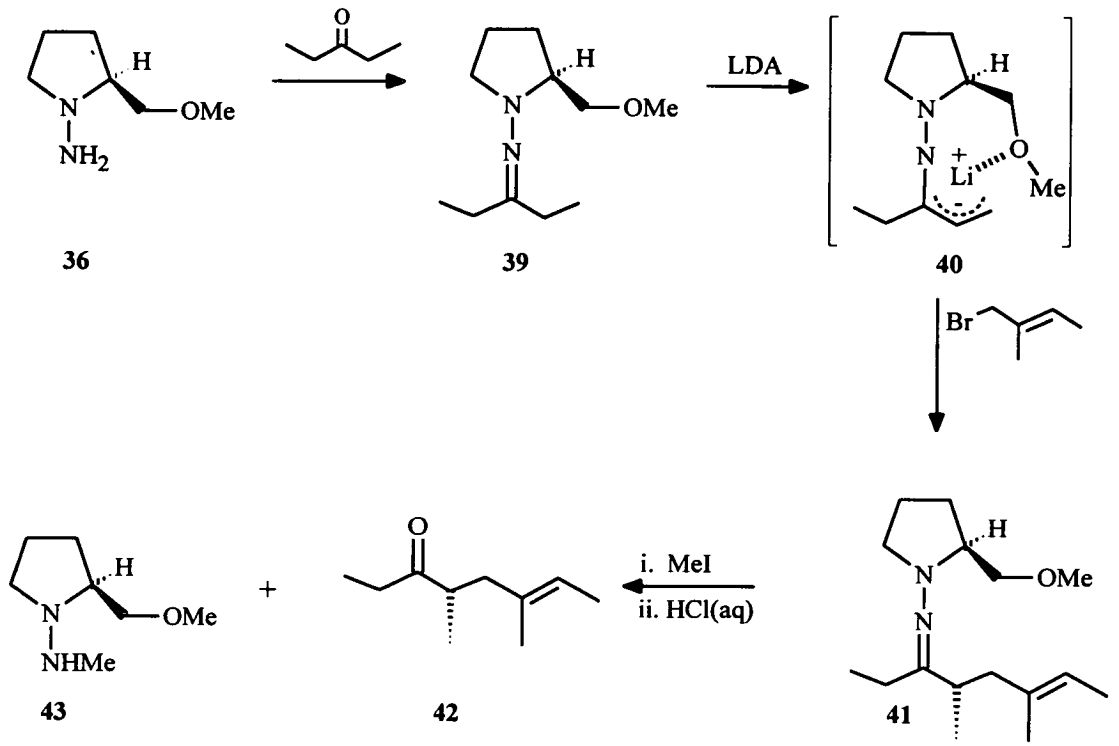
The other enantiomer SAMP **36** is obtained from the amino acid (*S*)-proline **38** in four synthetic steps in an overall yield of 50% (Scheme 13).



Scheme 13

SAMP and RAMP were developed primarily for the asymmetric alkylation of aldehydes and ketones[21, 22]. Enders' synthesis of the defence secretion of the "daddy long-legs" spider, *Leiobunum vittatium*[23], is just one example of such an alkylation process (Scheme 14). Essentially pentan-3-one was reacted with SAMP **36** to form the imine **39**, which was subsequently deprotonated with LDA to form enolate **40**,

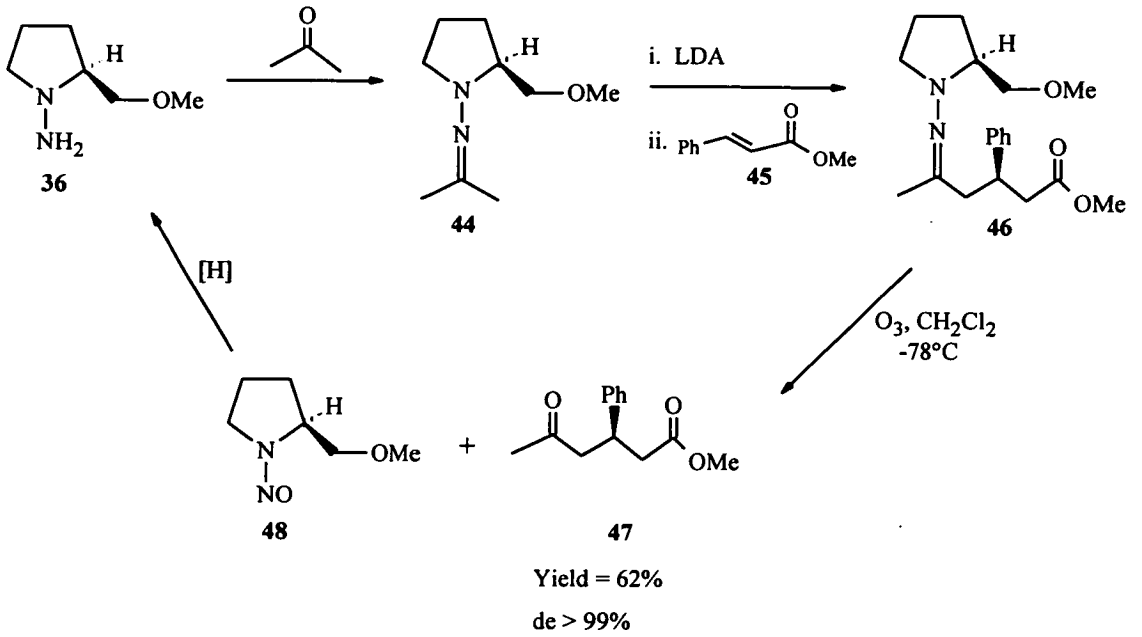
and then reacted with *E*-1-bromo-2-methylbut-2-ene to yield **41**. In the final step, quaternisation with methyliodide followed by acid hydrolysis yielded the defence compound **42** and the *N*-methylated species **43** which unfortunately is not recyclable.



Scheme 14

The reasons for the stereochemical outcome of the reactions are not fully understood, but it is thought that the enolate **40** has a rigid chelated structure that makes the C_α-*re* and C_α-*si* faces non-equivalent.

As well as for alkylations, Enders has used his auxiliaries in asymmetric 1,4-conjugate reactions to furnish β-substituted δ-ketoesters[24] (Scheme 15). As with the

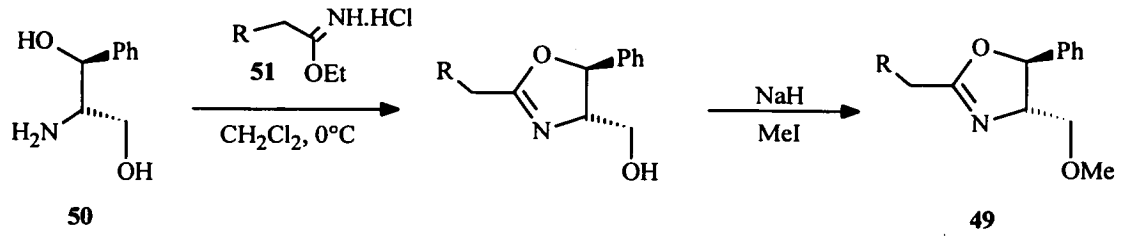


Scheme 15

preceding alkylation reaction, Michael addition relies on forming the lithium enolate of **44** which is reacted with the α,β-unsaturated ester **45** to furnish **46**. Cleavage of the auxiliary by ozonolysis (the alternative to MeI/acid hydrolysis) afforded the desired β-substituted δ-ketoester **47** and the nitrosamine **48**, which upon reduction gives the recycled SAMP **36**.

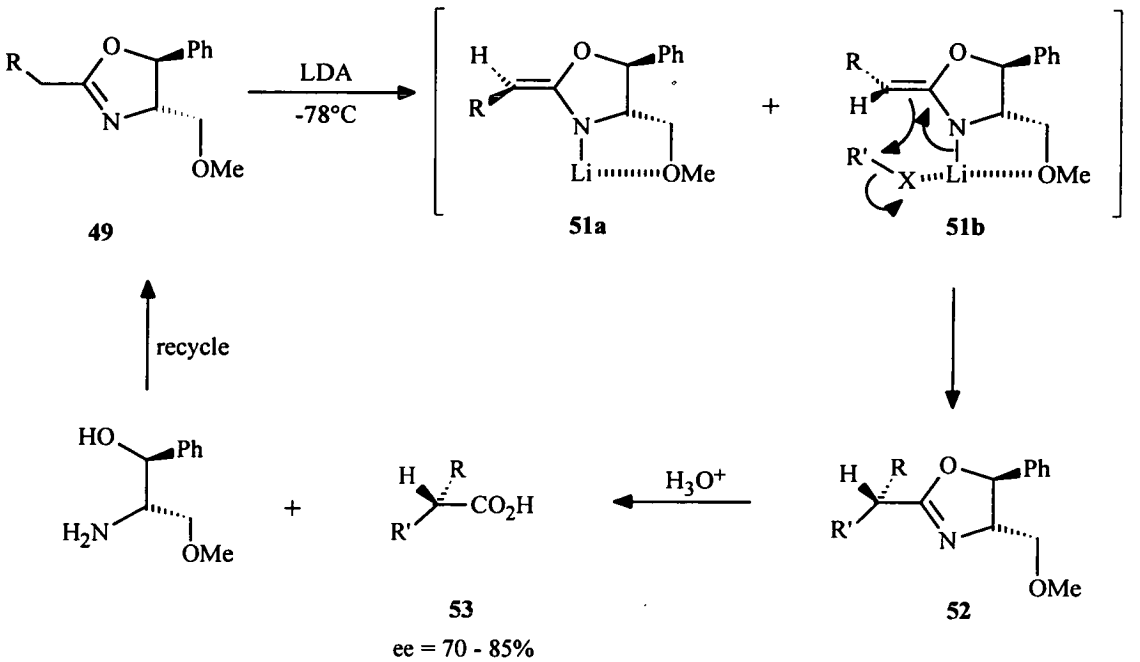
2.1.4 Meyers' Chiral Oxazolines

Another very versatile chiral auxiliary is oxazoline **49** developed by Meyers[25, 26], and formed by the reaction of commercially available (1*S*, 2*S*)-(+)-2-amino-1-phenyl-1,3-propanediol **50** with the imino-ether **51** (Scheme 16). The most well known use



Scheme 16

of the auxiliary **49** is in the synthesis of C_α-disubstituted carboxylic acids (Scheme 17)[27]. Thus the auxiliary is first metallated with LDA to form the two lithiated



Scheme 17

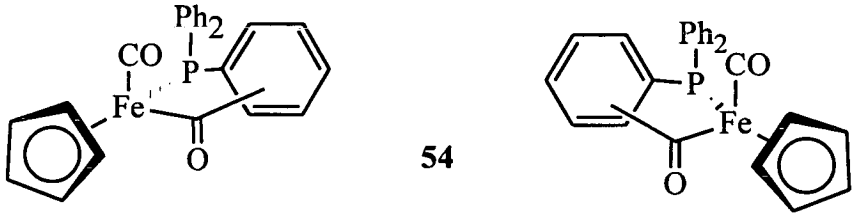
species **51(a)** and **51(b)** in a ratio of approximately 1:9 respectively, however it is only the *Z*-azaenolate **51(b)** however that undergoes alkylation to furnish the alkylated oxazoline **52**, by attack from the lower face owing to complexation with the lithium. Upon mild hydrolysis of **52**, the desired disubstituted acid **53** is afforded with predominantly the (*S*)-configuration (*i.e.* R' > R) and with very good levels of

enantioselectivity. It is worth noting that the stereochemistry of the acid **53** can be reversed if the alkyl groups are introduced into the synthesis in reverse order.

The good degree of asymmetric induction imparted by the auxiliary **49** relies primarily on two key points. Firstly, the large phenyl group on the top face must play an important role since if it is replaced by a methyl group or a hydrogen, the level of stereoselectivity observed falls dramatically. In addition, if the methoxy function is replaced by a methyl group, there is also a loss of asymmetric induction. This implies that the methoxy group is required to chelate to lithium and help to create the rigid complex **51(b)**. It is this rigidity that is responsible for the high levels of asymmetric induction imparted by the oxazoline **49**.

2.1.5 Davies' Iron Acetyl Auxiliary

One of the most unusual chiral auxiliaries that have been developed is Davies' iron acetyl auxiliary **54**[28] which is shown in Figure 5 in both enantiomeric forms.



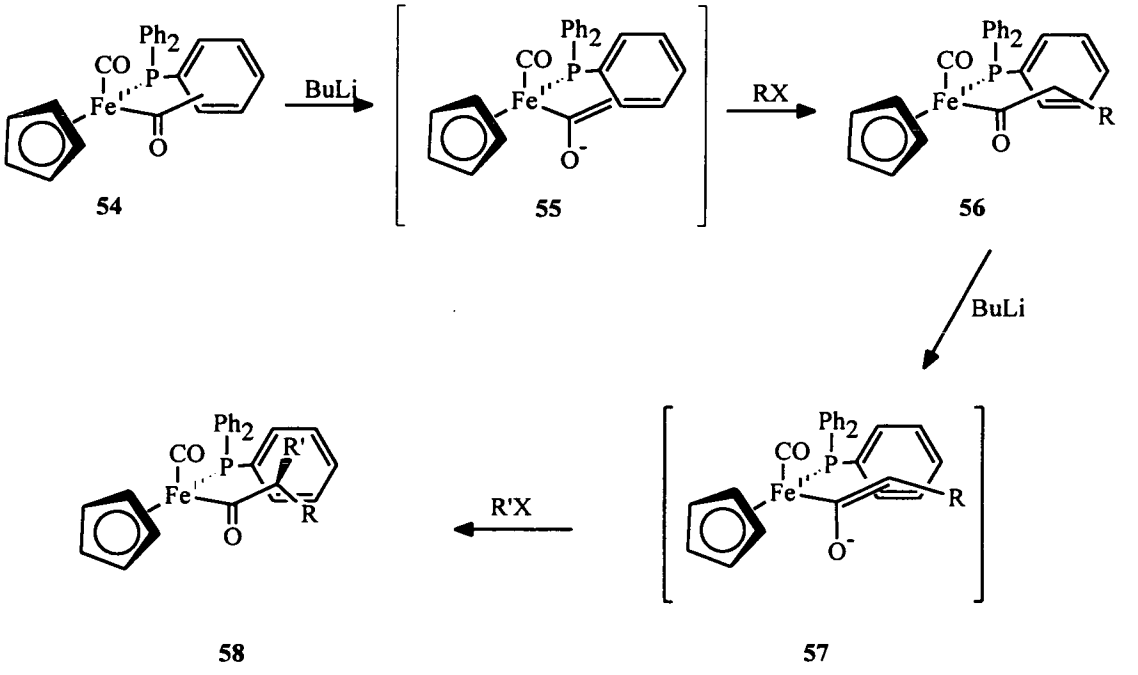
R(-) *S*(+)

Figure 5

The complex **54** has been shown to have an octahedral arrangement with the carbon monoxide, triphenylphosphine and acetyl ligands each occupying one orthogonal site with the other three being taken up by the cyclopentadiene. The acetyl ligand always orientates itself *anti* to the carbon monoxide, and one of the

phenyl groups from the triphenylphosphine ligand always resides below the acetyl group, and hence blocks one face from attack during any reaction.

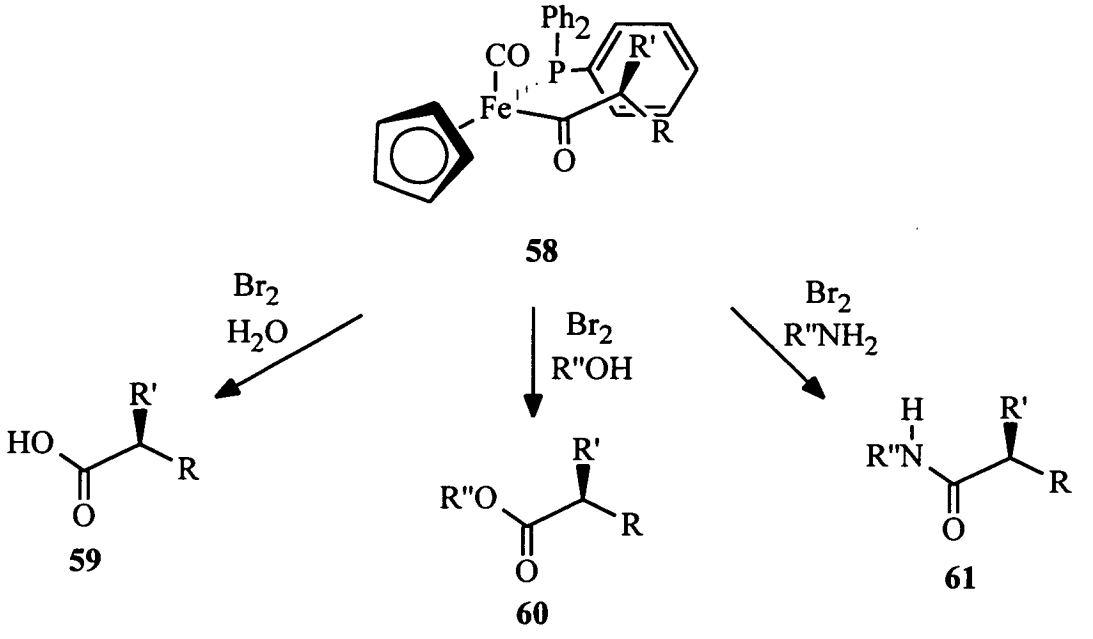
The auxiliary has been shown to be effective in alkylation reactions where treatment of the complex **54** with butyllithium forms the enolate **55**, which is then treated with an appropriate alkyl halide to give **56**. Further treatment with butyllithium leads to the formation of the *E*-enolate **57** selectively (for steric reasons the acyl ligand is unable to adopt the conformation for the *Z*-enolate). Alkylation of enolate **57** from the unhindered face generates the new chiral product **58** with almost complete stereo-control (Scheme 18). Since both enantiomers of **54** are available, albeit by chiral resolution, both product enantiomers are accessible by this route.



54 **55** **56** **58** **57**

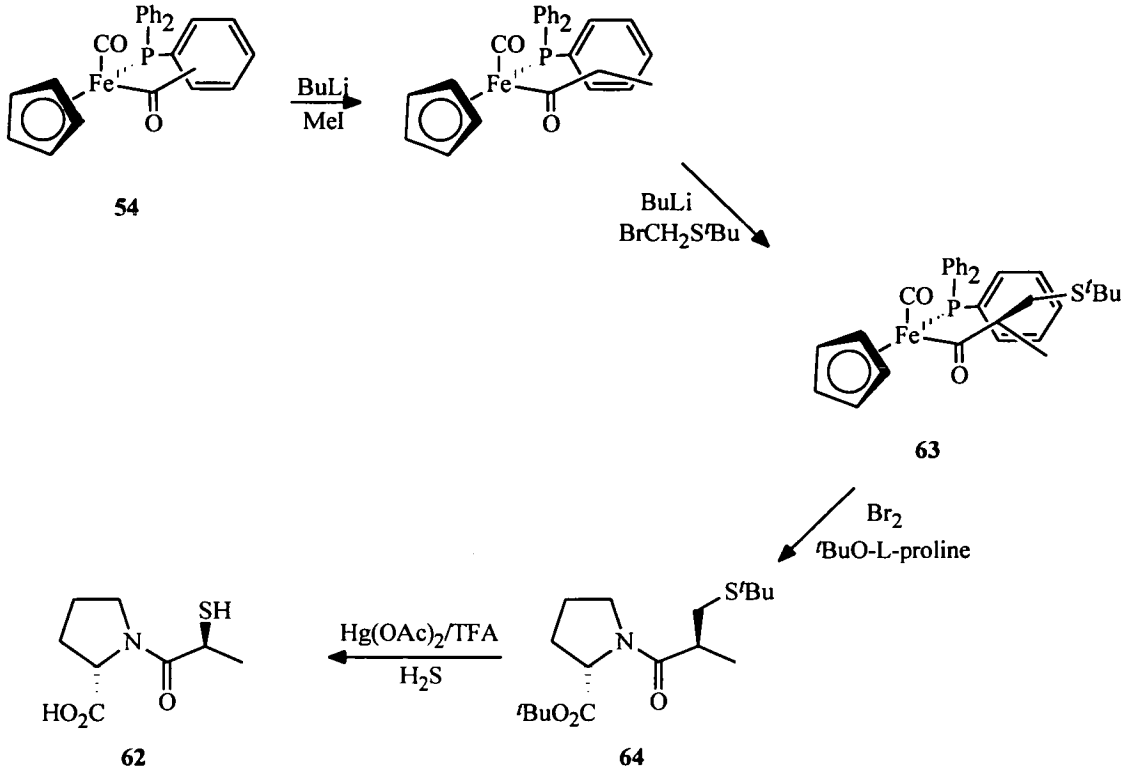
Scheme 18

In the final step, the addend is cleaved using bromine in the presence of water, alcohol or amine to give the corresponding acid **59**, ester **60** or amide **61**, respectively (Scheme 19).



Scheme 19

Davies' auxiliary **54** has been used successfully in the synthesis of the antihypertensive drug (-)-captopril **62**[29] (Scheme 20), but it does unfortunately suffer



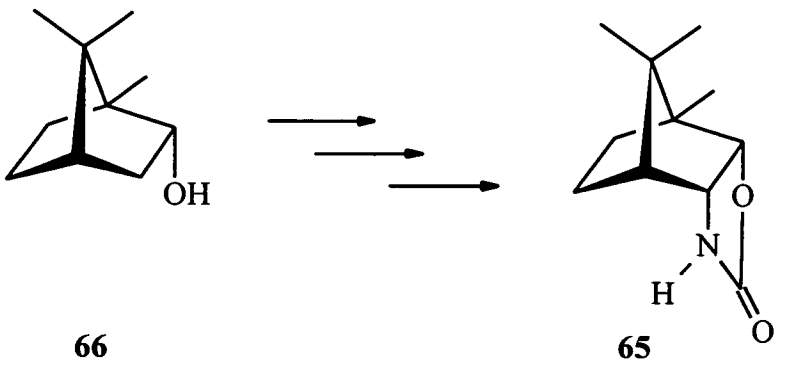
Scheme 20

from two major draw-backs, *viz* high molecular weight (mw = 453) such that large amounts of auxiliary are required for stoichiometric reactions. Also upon cleavage the auxiliary is destroyed which means it has to be regenerated since the enantiomers are separated by resolution, these problems combine to make the use of **54** very uneconomical.

2.1.6 Edinburgh's Chiral Oxazolidin-2-one Auxiliaries

In recent years, our group here in Edinburgh has developed a number of novel oxazolidin-2-one chiral auxiliaries from cheap readily available terpenes and carbohydrates. Previous routes to oxazolidinones have employed the direct cyclocarbamation of expensive optically pure β-amino alcohols, or involved tedious separation of racemic analogues[30, 31]. The Edinburgh approach uses a nitrene-mediated route whereupon an alcohol is converted into a nitrenoformate (*via* the corresponding chloroformate and azidoformate) which then inserts stereospecifically into a C-H bond to form the desired oxazolidinone (the reader is directed to the discussion section 5.1 for a full account of this process).

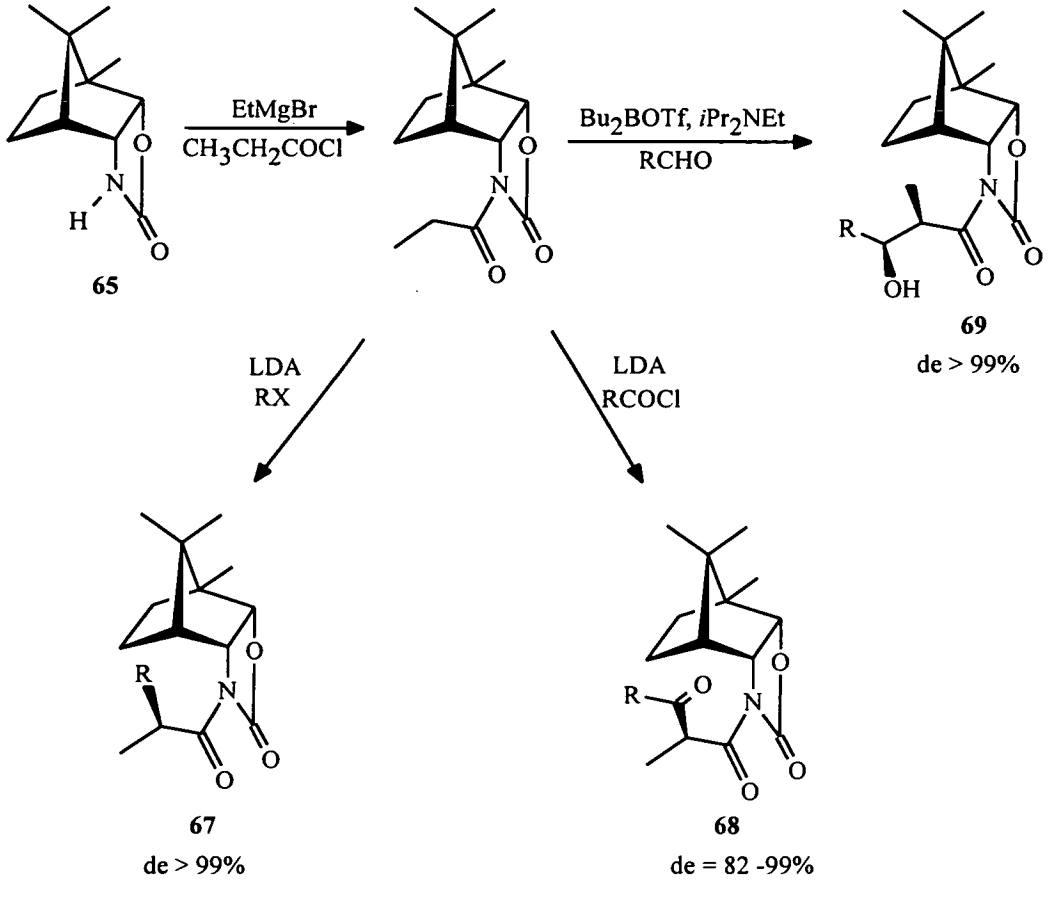
The first oxazolidin-2-one auxiliary developed by this approach was Chirabornox **65**[32], which is furnished in three steps and 43% overall yield from the cheap commercially available terpene *endo*-(1*S*)-(-)-borneol **66** (Scheme 21). Compound **65**



66 65

Scheme 21

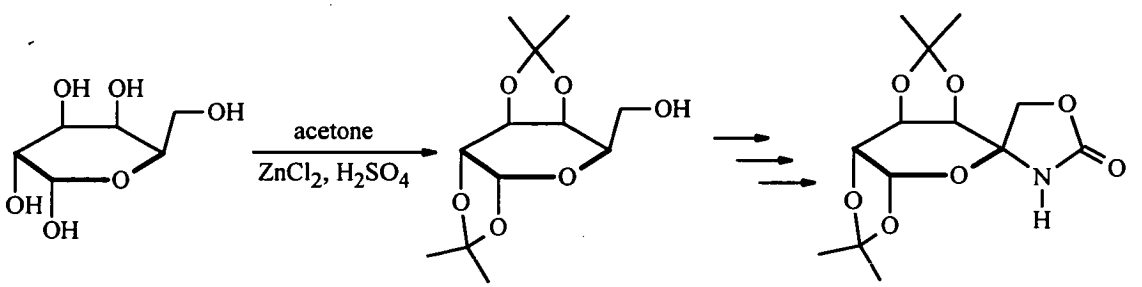
is easily functionalised by treatment with ethylmagnesium bromide, followed by reaction with an acid chloride (Scheme 22). Chirabornox has been shown to impart excellent levels of diastereoselectivity in alkylation, acylation and aldol reactions (Scheme 22), to give products **67**, **68** and **69** respectively. These chiral adducts can



Scheme 22

be cleaved readily using the conditions developed for the Evans auxiliaries (section 2.1.1), allowing recovery of the parent auxiliary **65** in very high yields. Unfortunately, Chirabornox performed rather poorly in asymmetric Diels-Alder and conjugate addition reactions, this lack of diastereoselectivity arising from poor topological bias on the front face of the bornane ring (a full explanation is given in the discussion, Chapter 1).

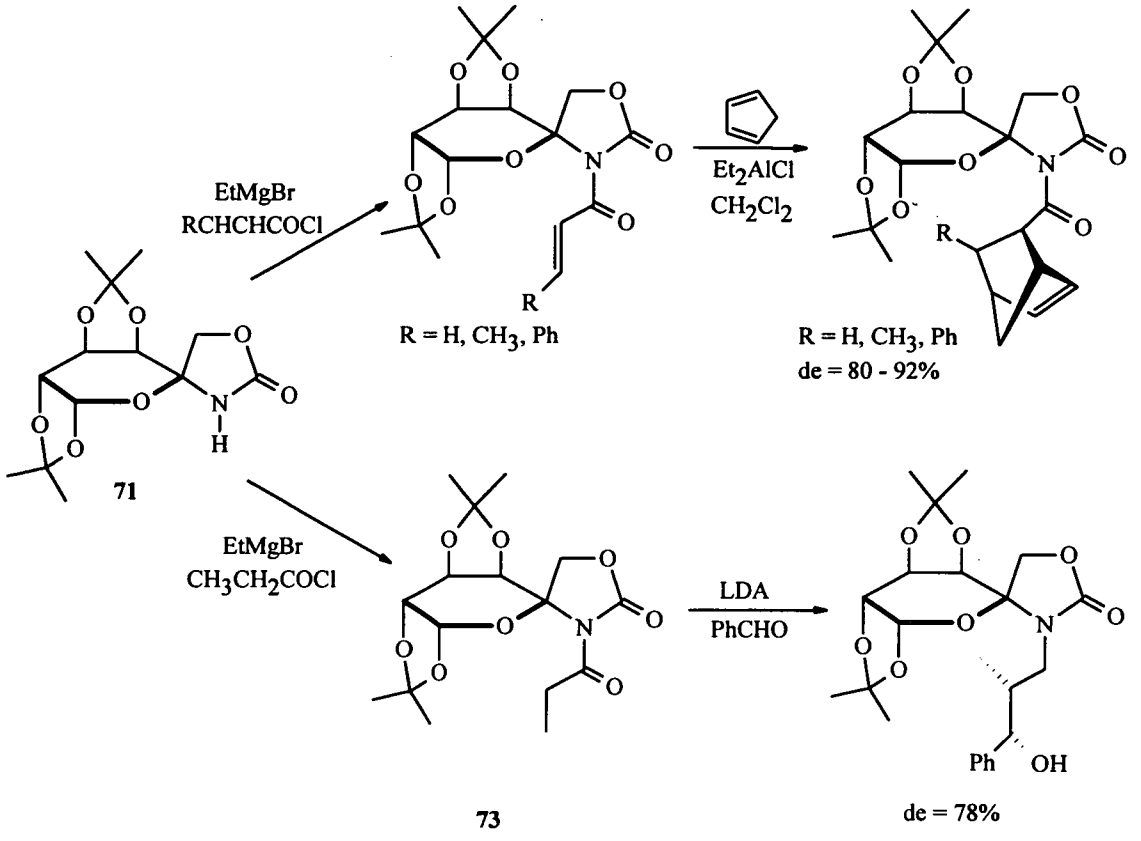
In seeking better stereocontrol attention was turned to carbohydrate systems. These studies led to the development of the spiro-oxazolidin-2-one Chiragalox **71**[33], which is obtained in four steps and overall yield of 53% from D-(+)-galactose **70** *via* the protected alcohol **72** followed by the nitrene insertion route previously mentioned (Scheme 23).



70 **72** **71**

Scheme 23

Chiragalox **71** was shown to impart excellent diastereoselectivity in a number of reactions, but most notably in Diels-Alder and aldol reactions (Scheme 24). It is

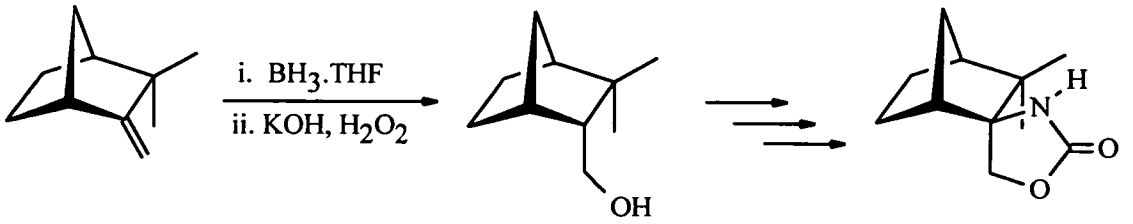


Scheme 24

interesting to note that the aldol reaction between the propionate **73** and bezaldehdye was mediated *via* the lithium enolate. As was mentioned previously, it has been shown by a number of workers[6, 16, 34] that lithium enolate aldol reactions, in general, produce very low levels of asymmetry in the products, but Chiragalox **71** was seen to confound this generalisation. Gaur[35] noted that when the reaction was attempted with the boron enolate an intractable tar was produced. However, Chiragalox **71** does suffer one draw back in that epimerisation can occur about the spiro-centre on cleavage, resulting in the recovered auxiliary being racemic.

The most successful auxiliary developed here in Edinburgh is undoubtedly the camphene-derived auxiliary, Chiracamphox **75**[36], which is now commercially available. Hydroboration of camphene **74** to give *endo*-camphenol **76** followed by

the nitrene insertion methodology afforded the spiro-oxazolidin-2-one **75** in very good yield (70%) (Scheme 25). An added benefit to this auxiliary is that both



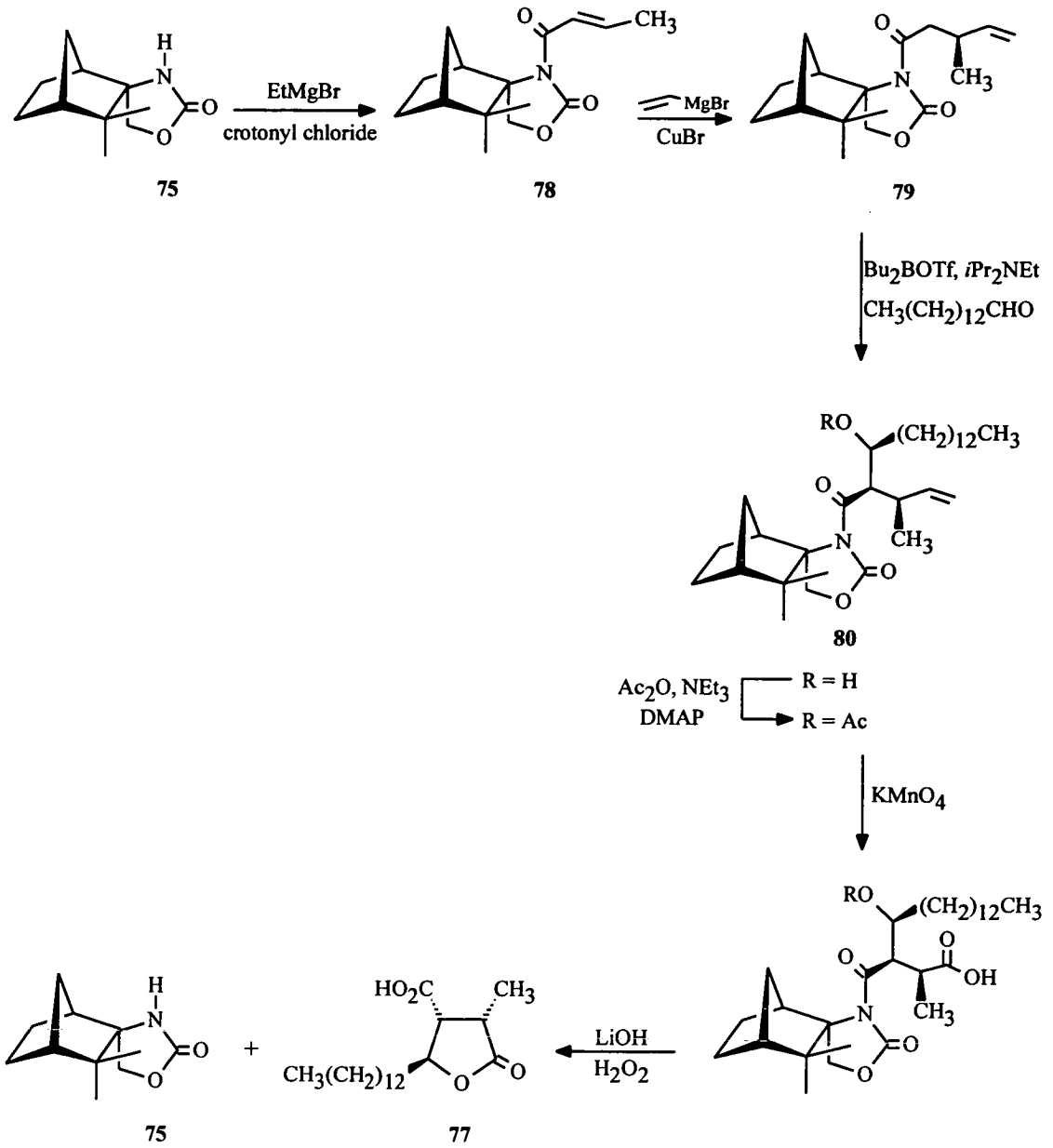
74 **76** **75**

Scheme 25

enantiomers of camphene **74** can be easily synthesised, and consequently both enantiomers of **75** are obtainable.

Functionalisation of Chiracamphox occurs readily upon treatment of its magnesium salt with an appropriate acid chloride. In each case, the adducts perform excellently in lithium enolate mediated alkylation and acylation reactions, boron enolate aldol reactions, Lewis-acid catalysed Diels-Alder reactions and in 1,4-conjugate additions with diastereomeric excesses between 85 and 99% in all these reactions.

(-)-Chiracamphox has also been used in an elegant synthesis of the tri-substituted γ-lactone (-)-dihydroprotolichesterinic acid **77** (Scheme 26)[37]. The key steps involved



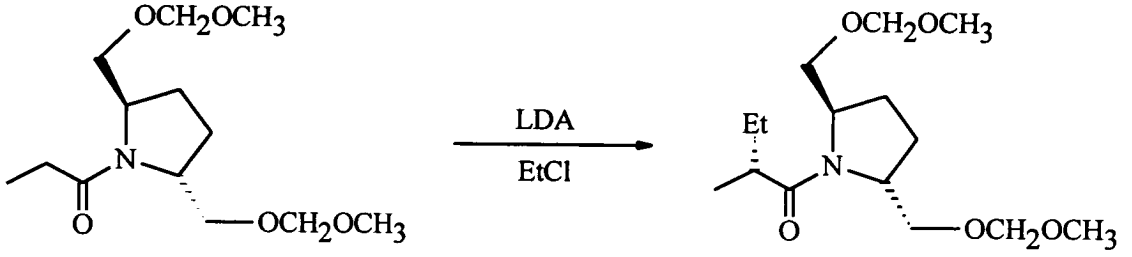
Scheme 26

a conjugate addition reaction between the crotonate **78** and vinylmagnesium bromide to furnish **79**, followed by a boron enolate aldol reaction between **79** and tetradecanal to afford compound **80** with all the desired stereocentres in place. A further three steps yielded chirally-pure **77** in 57% overall yield. This is a considersble improvement on the previous synthesis of **77** by Mulzer[38] which was 14 steps long and led to **77** in only 0.4% overall yield.

2.1.7 Chiral Auxiliaries with C_2-Symmetry

The final class of chiral auxiliaries to be mentioned in this brief overview of the field are those that possess a C_2 axis of symmetry. The presence of the C_2 axis reduces the number of possible diastereomeric transition states that can be adopted during an asymmetric transformation. A good review of this field of research has been written by Whitsell[39].

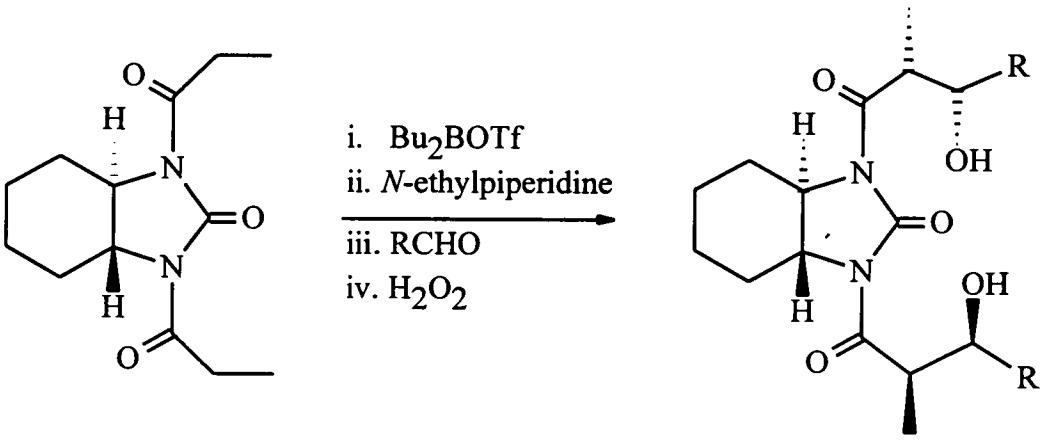
Katsuki has developed the chiral pyrrolidine **81,** which has been used in alkylation[40] (Scheme 27) and acylation reactions[41] with a great deal of success.



81 de = 95%

Scheme 27

Davies has also employed his bis-functionalised imidazolidinone-based auxiliary **82** in asymmetric boron enolate mediated aldol reactions with excellent levels of diastereoselectivity[42] (Scheme 28).



82

Scheme 28

2.2 The Use of Chiral Catalysts

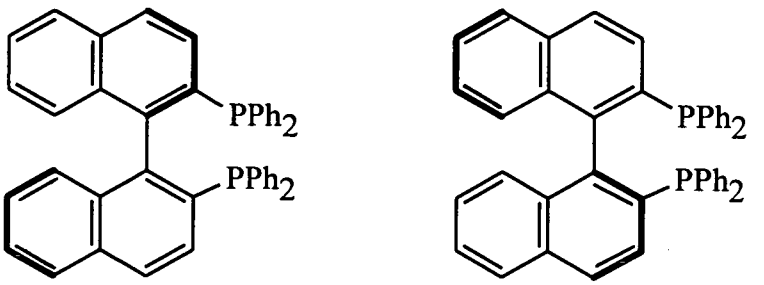
As illustrated in the previous sections, chiral auxiliaries are an excellent tool for imparting stereochemistry into a desired product, but the approach does suffer from two main disadvantages: (a) as stoichiometric amounts of auxiliary are required, and consequently their use is expensive in large scale reactions, and (b) the use of chiral auxiliaries results in two extra synthetic manipulations in a route, *i.e.* the introduction and cleavage of auxiliary.

In order to overcome these problems, a great deal of research has been devoted to the development of chiral catalysts for use in asymmetric transformations. In this section, a small selection of such catalysts is described, but it must be noted that this is a very large and ever expanding field of research.

2.2.1 Chiral Hydrogenation Catalysts

Catalytic hydrogenation is probably the most developed process compared to other asymmetric transformations, and from an industrial viewpoint, homogeneous hydrogenation catalysts are the most widely used[43].

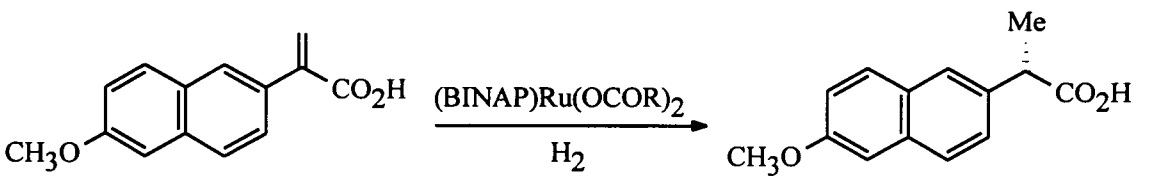
Some of the most versatile catalysts are those derived from (*R*) and (*S*)-BINAP[44] (2,2'-bis(diphenylphosphino)-1,1'-binapthyl) **83** and **84,** respectively (Figure 6). One



83 **84**

Figure 6

example of the use of a BINAP catalyst is in the asymmetric hydrogenation of the arylacrylic acid **85** to furnish the chiral acid **86** with virtually complete asymmetric control (Scheme 29)[44].

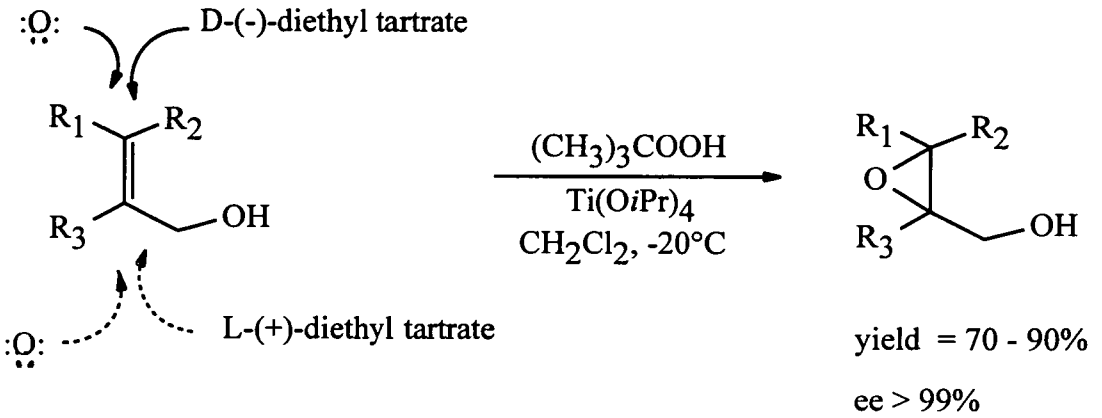


85 **86**

Scheme 29

2.2.2 Asymmetric Epoxidation

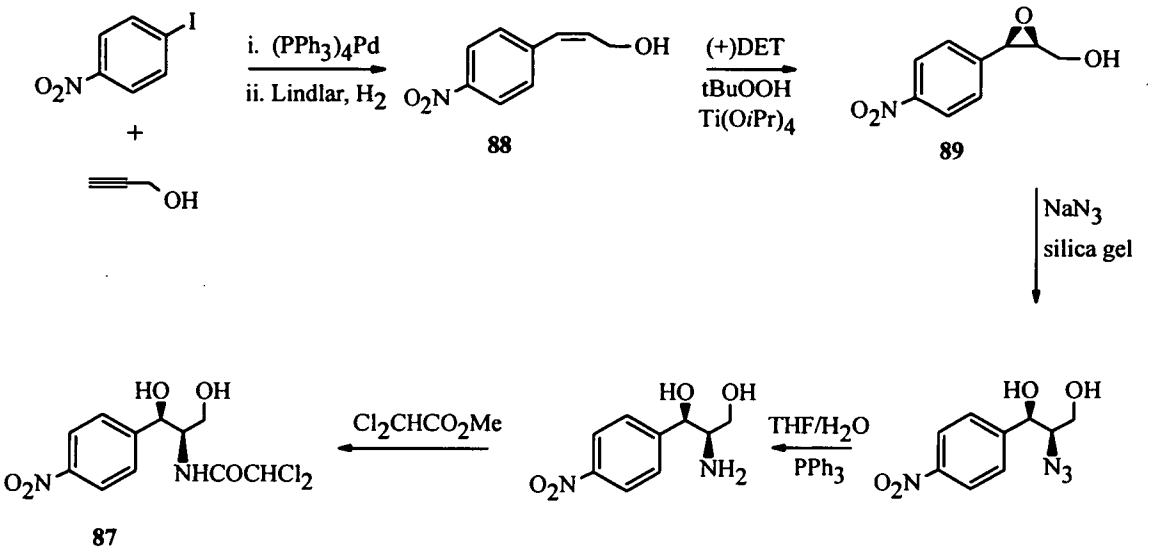
The most widely known catalytic asymmetric reaction is probably the asymmetric epoxidation of allylic alcohols developed by Sharpless in 1980[45]. The procedure involves the epoxidation of allylic alcohols with *t*-butyl hydroperoxide and titanium(IV)isopropoxide in the presence of an optically pure tartrate ester (Scheme 30). The face of the olefin onto which the epoxide is formed is dependant upon



Scheme 30

which enantiomer of the tartrate is used; hence, both isomers of the epoxide can be obtained. Originally the reaction used a stoichiometric amount of titanium catalyst, but it was later found that if molecular sieves were present during the reaction, to remove minute traces of water, the amount of titanium catalyst could be lowered to *ca.* 10%[46].

The Sharpless epoxidation has been used by Rao[47] in his synthesis of the broad-spectrum antibiotic chloramphenicol **87** (Scheme 31). Notably, epoxidation of the

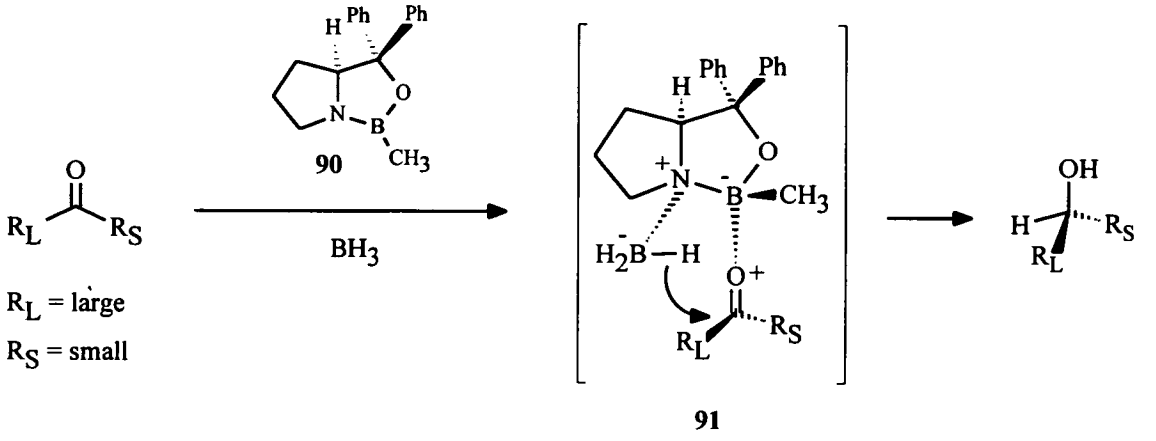


Scheme 31

allylic alcohol **88** furnished the glycidol **89** in 85% yield and with an enantiomeric excess of 95%.

2.2.3 Catalytic Asymmetric Ketone Reduction

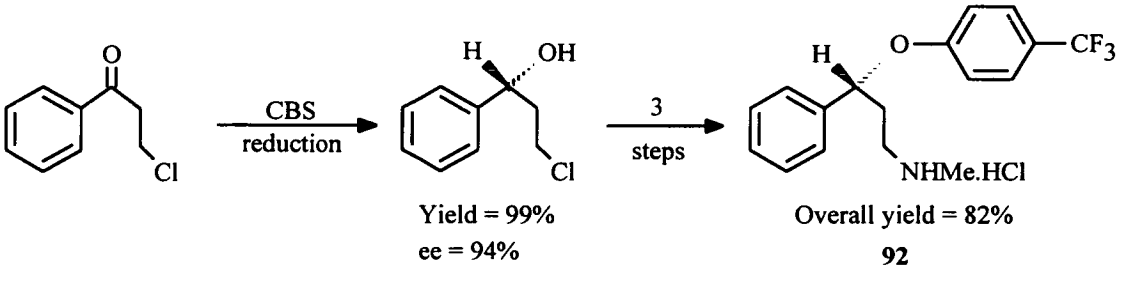
The area of asymmetric ketone reduction has attracted a great deal of attention in recent years and a number of reviews have been published on this topic[48, 49]. The area of catalytic asymmetric reduction was pioneered by Corey and his co-workers using the oxazaborolidine catalyst **90**[50] (Scheme 32). Corey developed a number of such catalysts which exhibit a high level of enantioselectivity in the reduction of carbonyl compounds[51]. As shown in Scheme 32, in this "CBS" reduction (so called after its



Scheme 32

developers, Corey, Bakshi and Shibata), borane is employed as the actual reducing agent. The catalyst holds the borane and the ketone in a fixed orientation such that the hydride from the reducing agent can only be delivered onto one face of the ketone, as shown in the transition state assembly **91**.

Since its conception the CBS reduction has been used in the synthesis of a number of enantiomerically pure products[52, 53] and one such example is the short synthesis of Fluoxetine[54] **92** (Scheme 33).

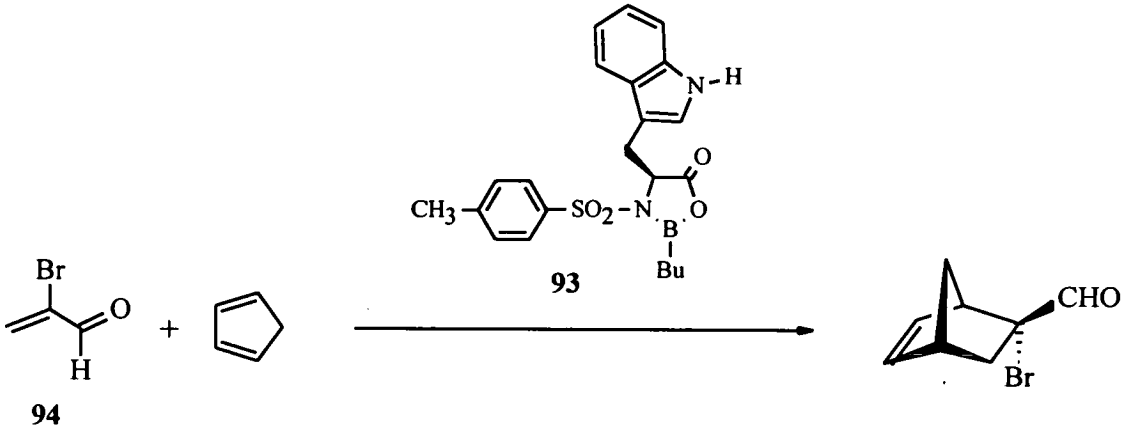


Scheme 33

2.2.4 Catalytic Asymmetric Diels-Alder Reactions

More recently Corey[55] and Helmchen[56] have both developed oxazaborolidines for use as catalysts in asymmetric Diels-Alder reactions. Corey's (*S*)-tryptophan derived

catalyst **93** has imparted excellent levels of asymmetric induction in Diels-Alder reactions such as the one between 2-bromoacrolein **94** and cyclopentadiene (Scheme 34). The high levels of stereoselectivity observed can be explained in terms of steric



Scheme 34

repulsion[55] or due to attractive donor-acceptor interactions[56]. Helmchen[56] proposes the transition state model **95** (Figure 7) based on the following arguments:

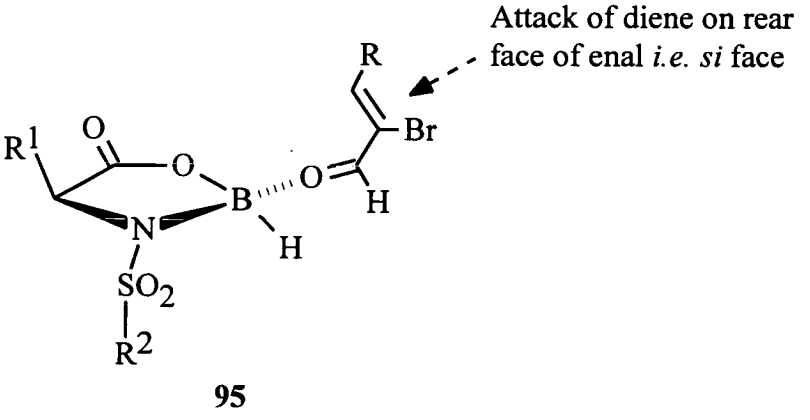


Figure 7

(i) R^1 directs the steric bulk of the R^2SO_2 group to the opposite face of the ring, (ii) R^2SO_2 controls the co-ordination site and defines the boron centre of chirality, (iii) The dienophile oxygen co-ordinates to the boron *syn* to the hydrogen, (iv) The

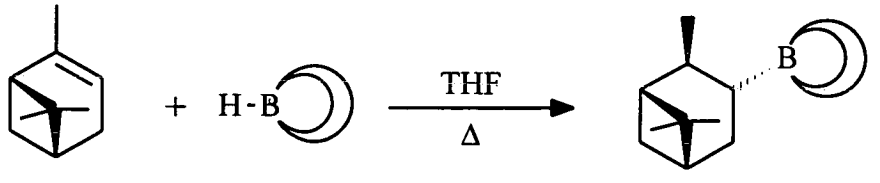
dienophile attacks in the s-*cis* conformation, and (v) The *syn*-planar co-ordination of the B-H and C=O bonds leads to attack of the diene on the *si*-face of the dienophile.

2.3 The Use of Chiral Reagents

In this approach to asymmetric synthesis a chiral reagent is used to impart chirality into a prochiral substrate. Unfortunately, as with the chiral auxiliary methodology, a stoichiometric amount of the reagent is required.

2.3.1 Chiral Boron Reducing Agents

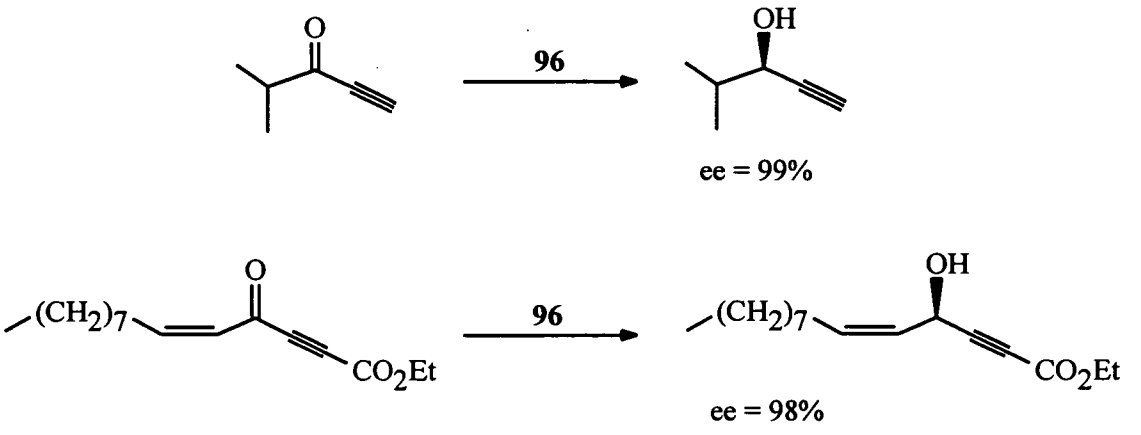
Chiral boron reducing agents have been shown to be extremely valuable in the asymmetric reductions of aldehydes and ketones[57]. A typical example of one of these reagents is Alpine-Borane **96**[58, 59] (Aldrich trade name) derived from 9-BBN **97** (9-borobicyclo[3.3.1]nonane) and (1*R*)-(+)-α-pinene **98** (Scheme 35). Two examples of



98 **97** **96**

Scheme 35

the reductive utility of **96** in an asymmetric context are shown in Scheme 36.

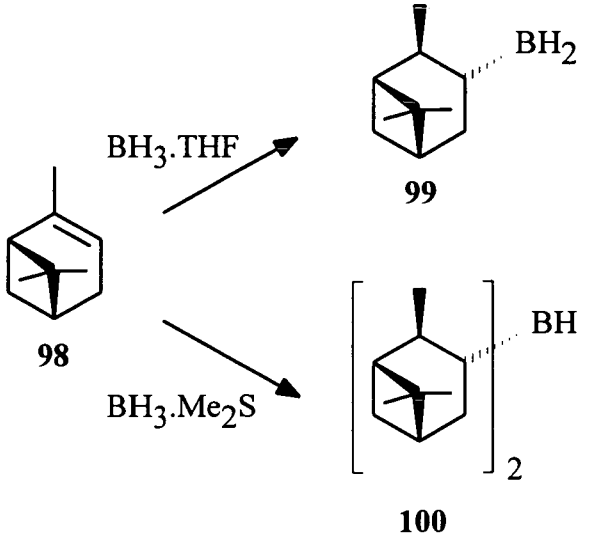


Scheme 36

Since both enantiomers of α-pinene **98** are commercially available, both enantiomeric forms of Alpine-Borane **96** can be used.

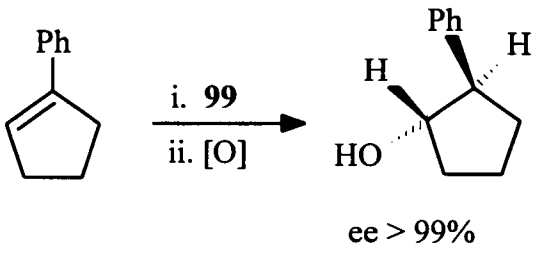
2.3.2 Asymmetric Hydroboration Reagents

There have been a number of terpene-derived hydroboration reagents cited in the literature, two of which are the reagents **99** and **100**[60] derived from α-pinene **98** (Scheme 37). The former is the more reactive of the two, being less hindered.



Scheme 37

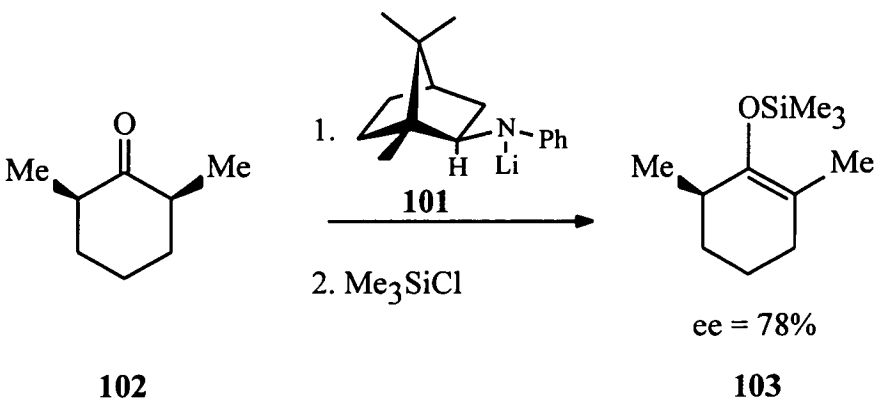
Consequently it is the reagent of choice for the hydroboration of trisubstituted alkenes (Scheme 38).



Scheme 38

2.3.3 Chiral Lithium Amide Bases

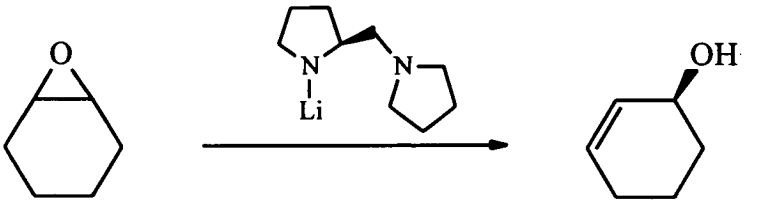
The final class of chiral reagent to be discussed are chiral lithium amide bases[61] such as **101,** which can selectively deprotonate prochiral substrates, and thus allow a chiral product to be furnished (Scheme 39). For example, the selective deprotonation of the prochiral ketone **102** followed by treatment with TMS chloride affords the chiral silyl enol ether **103**, with the (*R*)-configuration, with an good degree of stereoselectivity (Scheme 39)[61].



102 **103**

Scheme 39

These chiral bases can also be employed to carry out enantioselective rearrangement of epoxides to furnish chiral allylic alcohols (Scheme 40).



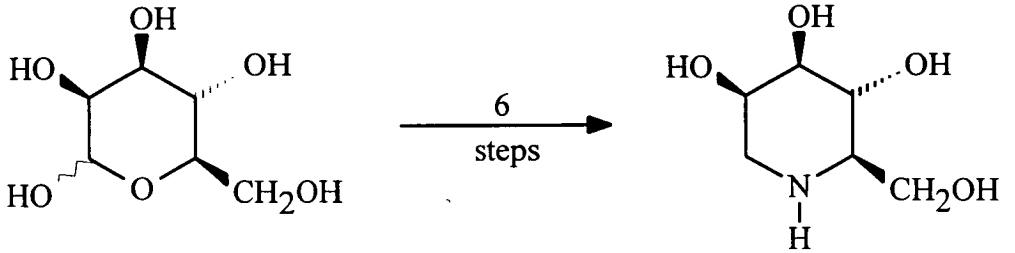
ee = 92%

Scheme 40

3 The Chiral Pool Approach

Another way of obtaining optically-pure compounds is to modify a homochiral compound from the "chiral pool". The "chiral pool" is a term given to the vast number of naturally-occurring compounds such as terpenes, amino acids and carbohydrates. Evans' auxiliary **10** (section 2.1.1) is a good example of this approach as it is derived from the natural amino acid (*S*)-valine **9**.

A more complex example of this approach is the synthesis of the glycosidase inhibitor deoxymannojirimycin **104**, from cheap readily available glucose **105** in six steps and 35% overall yield (Scheme 41)[62].

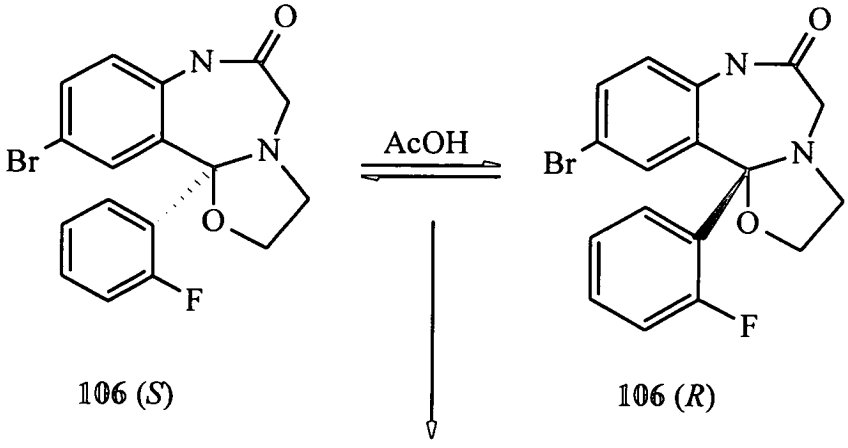


105 **104**

Scheme 41

4. Resolution

The main method employed for the industrial synthesis of pure enantiomers is the resolution of racemic mixtures[63]. The methods of resolution can be divided into three types, the first of which is preferential crystallisation. This technique relies on the fact that one enantiomer crystallises in preference to the other. This technique is most attractive when accompanied by an *in situ* racemisation. One example of this process is the case of the 1,4-benzodiazepinooxazole **106** which undergoes racemisation in acidic solution (Figure 8)[64].

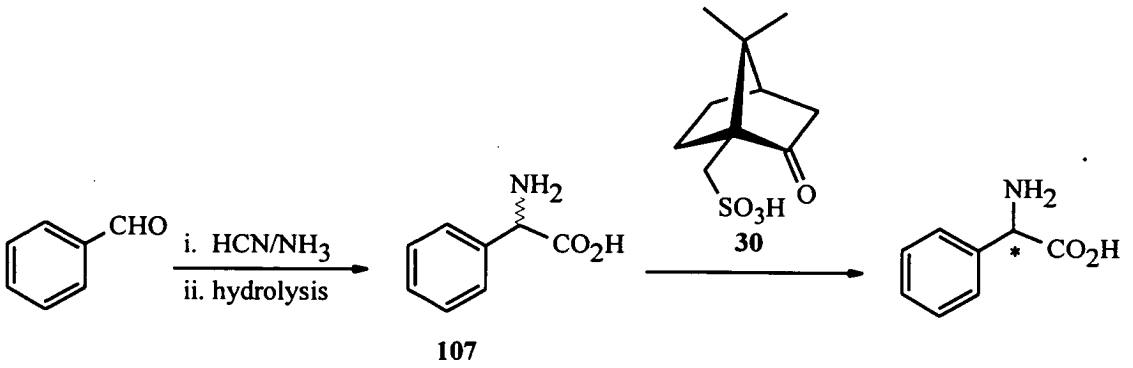


106 (*S*) **106** (*R*)

Pure enantiomer
(*R*) or (*S*)

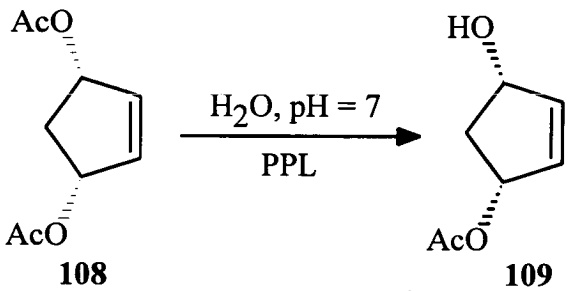
Figure 8

The second method of resolution is diastereomer crystallisation, in which the racemate is reacted with an optically-pure compound to give two diastereomers. Since diastereomers have different physical properties they may crystallise at different rates, and can be separated by classical fractional crystallisation. One of the most commonly used resolving agents is camphorsulphonic acid **30** which has been used successfully to resolve D/L-phenylglycine **107** (Scheme 42)[43].



Scheme 42

The final resolution method is kinetic resolution, which depends on one enantiomer reacting faster than the other with a chiral substrate. In recent years enzyme-catalysed kinetic resolutions have attracted increased attention. For example enzymatic enantioselective hydrolysis of chiral esters is a useful tool for affording optically active acids or alcohols. Alternatively hydrolysis of the prochiral *meso*-diester **108**, with the enzyme Porcine pancreas Lipase (PPL), affords the virtually enantiomerically pure compound **109** in very good yield (86%) (Scheme 43)[65].



Scheme 43

Discussion

Chapter 1

Attempted Synthesis of the Transfigomer 110 of Chirabornox 65

The borneol-derived chiral auxiliary Chirabornox **65** has been shown by Banks *et al*[32] to induce very high levels stereoselectivity in aldol, acylation and alkylation reactions. However, it was found to impart very poor levels of asymmetric induction in Diels-Alder reactions (the reader is directed to the Introduction section 2.1.6). This drawback was ascribed to a lack of steric repulsion between the *N*-acyl moiety and the bornane skeleton in the functionalised auxiliary, resulting in a poor population difference between the s-*trans* and s-*cis* conformations (Figure 9). It is worth noting that the conformers are depicted with their carbonyl functionality's parallel, as this

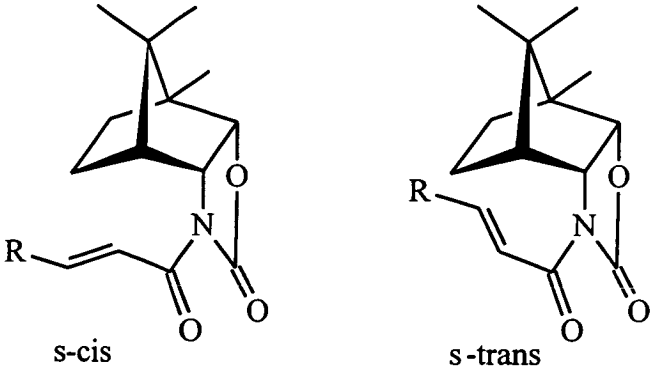


Figure 9

would be the orientation of the molecule when chelated to the Lewis-acid catalyst during reaction. This orientation is not found in the unchelated species since the carbonyl groups repel each other due to their polarities, and consequently, the molecule aligns itself as depicted in Figure 10.

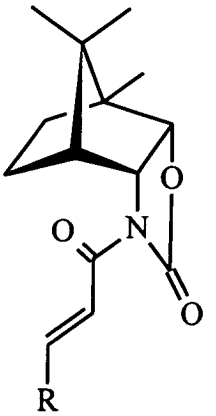


Figure 10

The outcome of fixing the molecule in the chelated form is that the N-C bond is held so that no rotation can occur about it. Unfortunately in the case of Chirabornox it can be seen that rotation about the carbonyl-C_α bond is relatively free to occur, and hence, poor levels of diastereoselectivity are observed with this auxiliary (*cf.* Chiragalox **71**).

In order to improve the ability of the auxiliary to perform well in Diels-Alder reactions, it would be desirable to increase the steric bulk on the side of the bornane skeleton where the reaction occurs. For this to be achieved, one requires a group that is of greater size than the hydrogen at the bridgehead carbon, *i.e.* vicinal to the nitrogen. Examination of the structure of Chirabornox **65** shows that it possesses a methyl group on the opposite bridgehead of the bornane ring. This group serves no useful purpose as far as providing any interaction in the vicinity of the reaction zone. Hence, it would be highly desirable to transpose the methyl group from one side of the bornane skeleton to the other. This transposition would hopefully eliminate the possibility of the carbonyl-C_α rotation due to increased steric repulsion, and consequently improve performance in Diels-Alder reactions (Figure 11).

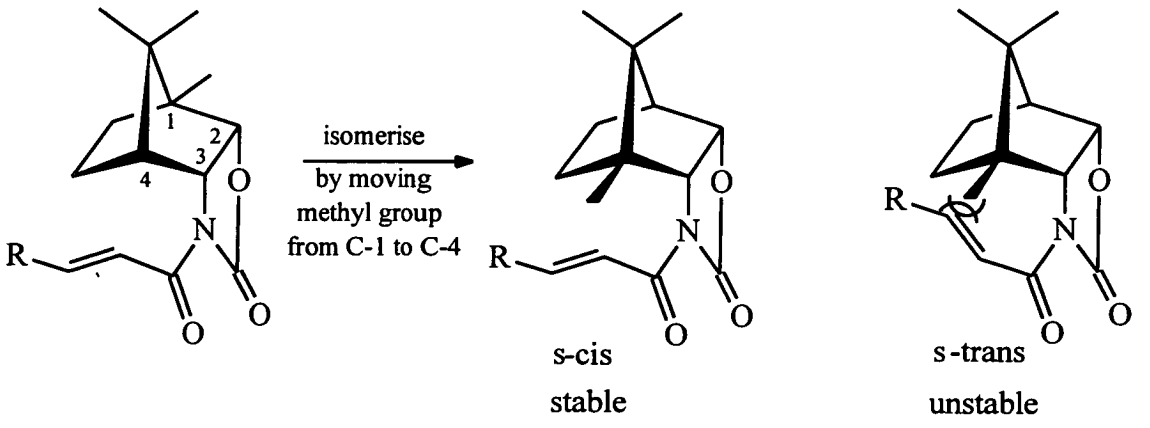
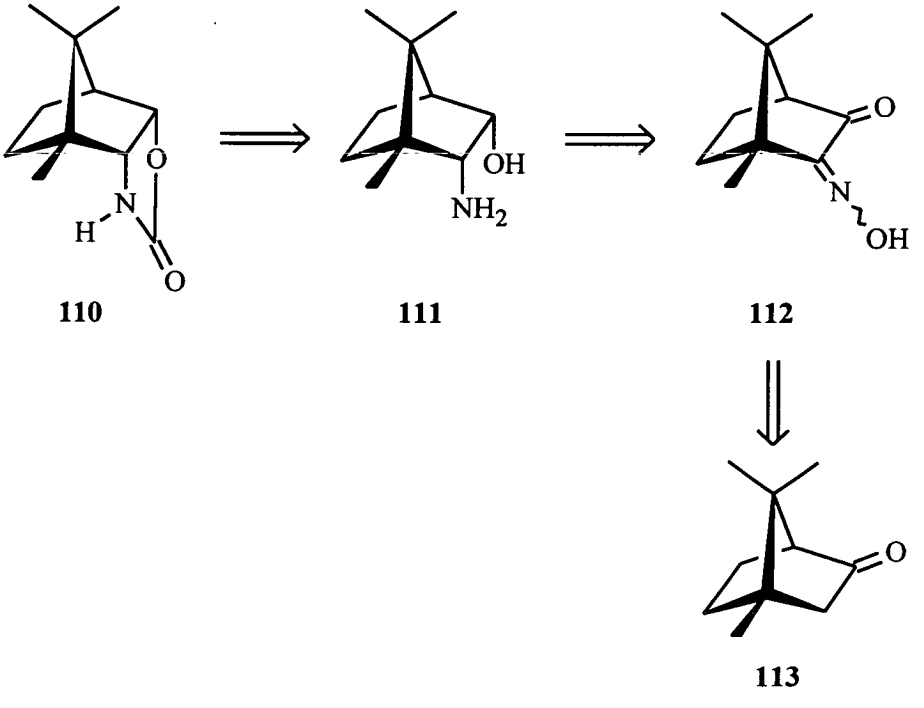


Figure 11

The moving of the methyl group creates a new chiral auxiliary **110** that is essentially a "transfigomer" of **65**.

A retro-synthetic analysis of **110** identifies a number of key intermediates in a proposed synthetic pathway (Scheme 44), *viz. endo-endo*-2-amino-3-hydroxybornane **111**, 2-hydroximinoepicamphor **112** and epicamphor **113**.



Scheme 44

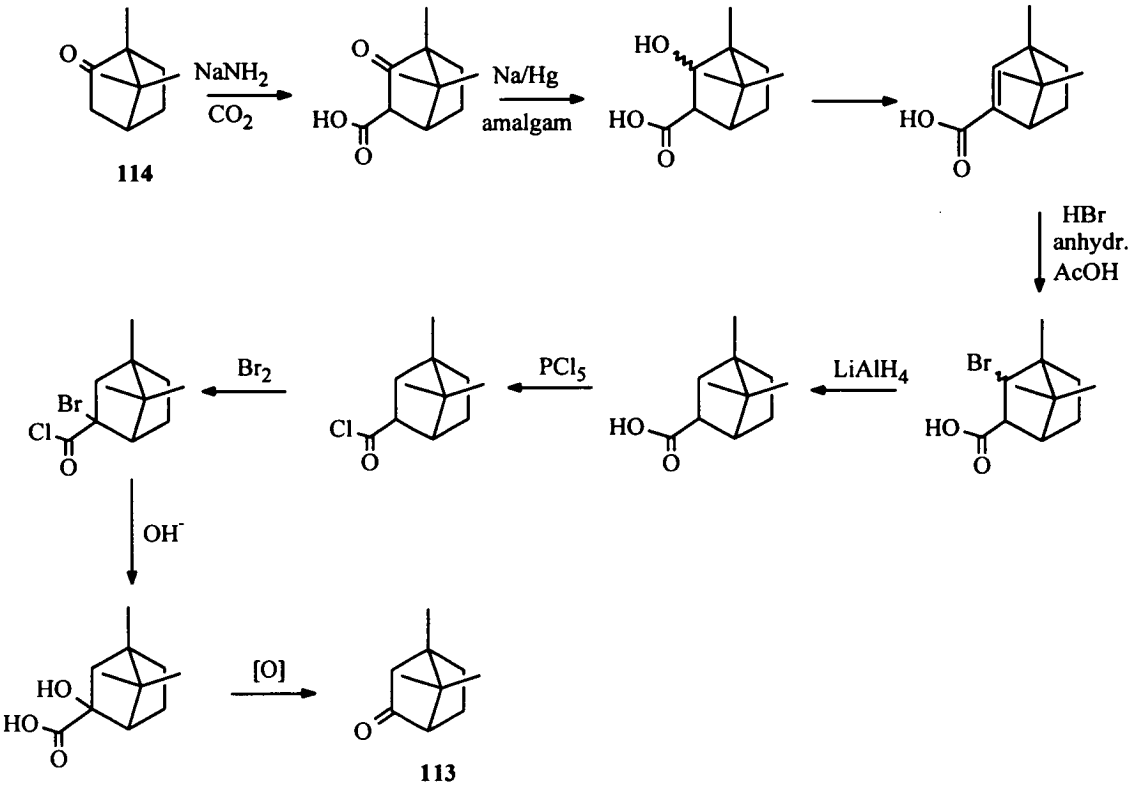
It is obvious from Scheme 44 that the key intermediate in the synthesis of **110** is epicamphor **113** which is an isomer of the naturally-occurring terpene camphor **114**. Epicamphor itself is not found in nature[66], although the potential of epicamphor in synthesis had only begun to be realised when Bredt and Perkin made their prophetic statement [67]:

"....-epicamphor - must be a substance the importance of which, at all events from the chemical point of view, can hardly be less than camphor itself.....

....It is indeed obvious that the study of epicamphor, and especially the careful comparison of the properties of its derivatives with those of camphor, is a problem so attractive that it is not surprising to find evidence that reported efforts have been made from time to time by different investigators to devise some process for the preparation of epicamphor....".

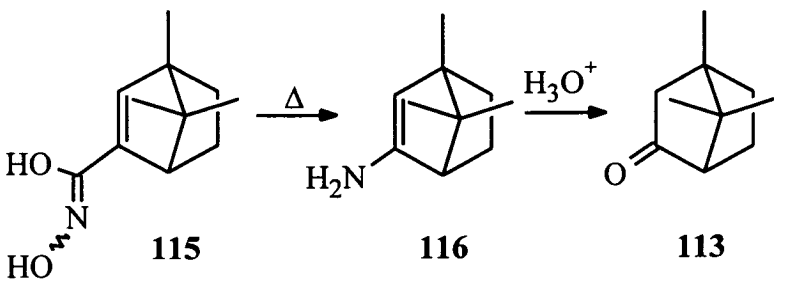
The synthesis of the auxiliary **110** therefore provided an opportunity to further examine the properties of epicamphor, and demonstrate its usefulness in the ever-growing field of asymmetric synthesis.

Epicamphor is chemically derived from camphor **114**, but to do so is not straightforward; indeed, the elaborate synthesis outlined in Scheme 45 takes nine synthetic steps.



Scheme 45

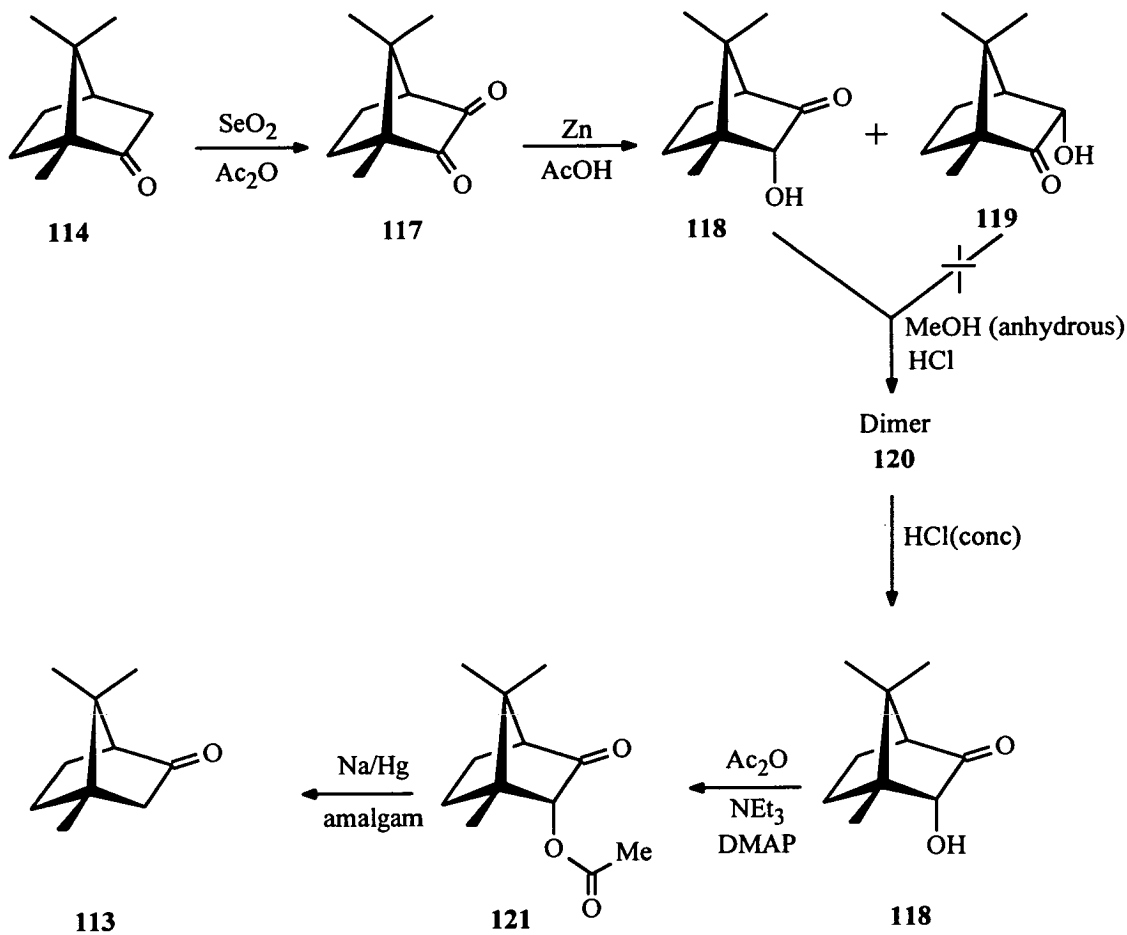
Another route uses the hydroxamic acid **115**, derived from methyl bornene-3-carboxylate, which when heated above its melting point, produced enamine **116** (Scheme 46). Subsequent hydrolysis of this intermediate yields epicamphor **113**[66].



Scheme 46

Neither of the previous two routes are attractive for producing epicamphor on a large scale, so it was decided to adopt the procedure of Huckel and Fechtig[68] for the current work. The synthesis is outlined in Scheme 47 and begins with the preparation

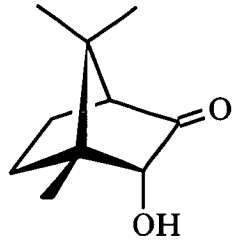
of camphorquinone **117** from camphor **114**, followed by reduction with zinc in acetic acid to give a mixture of *endo*-2-hydroxyepicamphor **118** and *endo*-3-hydroxycamphor **119**, from which the former is separated by formation of dimer **120** and subsequent treatment with hydrochloric acid. In the final steps **118** is acylated to give **121**, which is then reduced with Na/Hg amalgam to furnish epicamphor **113**.



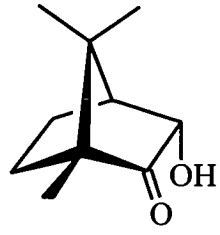
Scheme 47

In the present work, (1*R*)-(+)-camphor **114** was oxidised with selenium dioxide and acetic acid to furnish camphorquinone **117** in excellent yield (96%). The following reduction of **117** with zinc in acetic acid also proceeded with no problems and in high yield (88%) to give a 2:3 mixture of keto-alcohols **118** and **119**,

respectively, the identity of which was confirmed by the presence of both hydroxyl and carbonyl absorbencies in the IR spectrum. Interestingly, this procedure afforded the *endo* isomers selectively (Figure 12), compared to other methods which furnished the *exo* isomers also[69]. The desired **118** could be detected in the mixture by ^{1}H NMR spectroscopy which showed the presence of a singlet at *ca.* δ 3.9 ppm arising from the proton geminal to the hydroxyl group.



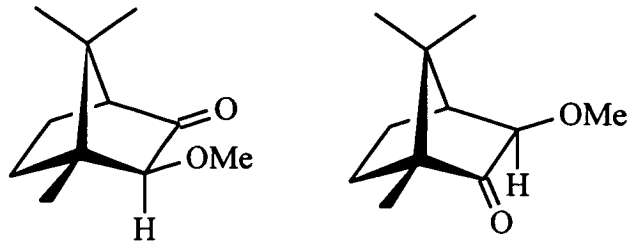
118



119

Figure 12

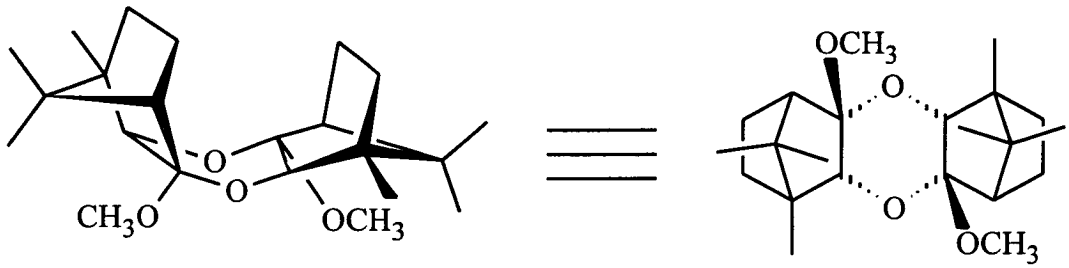
The separation of the two isomeric keto-alcohols was carried out by the method of Huckel *et al*[68], who adopted the procedure of Bredt and Ahrens[70], who in turn had followed the original experiment of Manasse[71], carried out in 1902. The reaction proceeded as described and 2-hydroxyepicamphor **118** was reacted in dry methanol with dry hydrogen chloride gas to form a dimer **120**, which crystallised out of solution in 39% yield as large colourless prisms. The yield is limited by the fact that the keto-alcohol **118** only constitutes 40% of the mixture resulting from the reduction of camphorquinone **117**. It is worth noting that in the previous syntheses, the structure of the dimer was not determined, and Huckel *et al*[68] naively assumed that the product was the "methyl ether of 2-hydroxyepicamphor **118**" with the structure **122** shown in Figure 13.



122 **123**

Figure 13

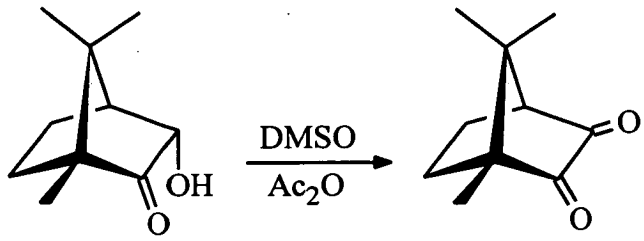
Doubts were originally cast on Huckel's assumption when it was realised that the keto-alcohol **119** didn't react in the same manner to produce **123** (Figure 13). The structure was eventually elucidated by Banks *et al*[72], who in a series of NMR experiments involving nOe techniques, established that the dimer possessed the structure shown in Figure 14.



Structure of dimer **120**

Figure 14

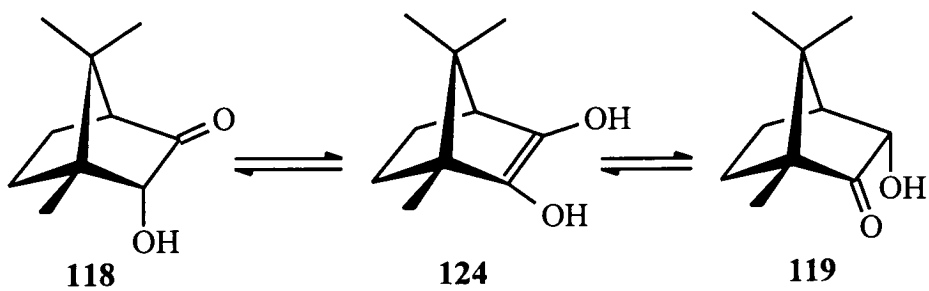
In order to raise the overall yield of **118**, the unreacted 3-hydroxycamphor **119** was recovered by evaporation *in vacuo* of the dimer mother liquors, and recycled back to camphorquinone **117** (in quantitative yield) by treatment with DMSO in acetic anhydride (Scheme 48).



119 **117**

Scheme 48

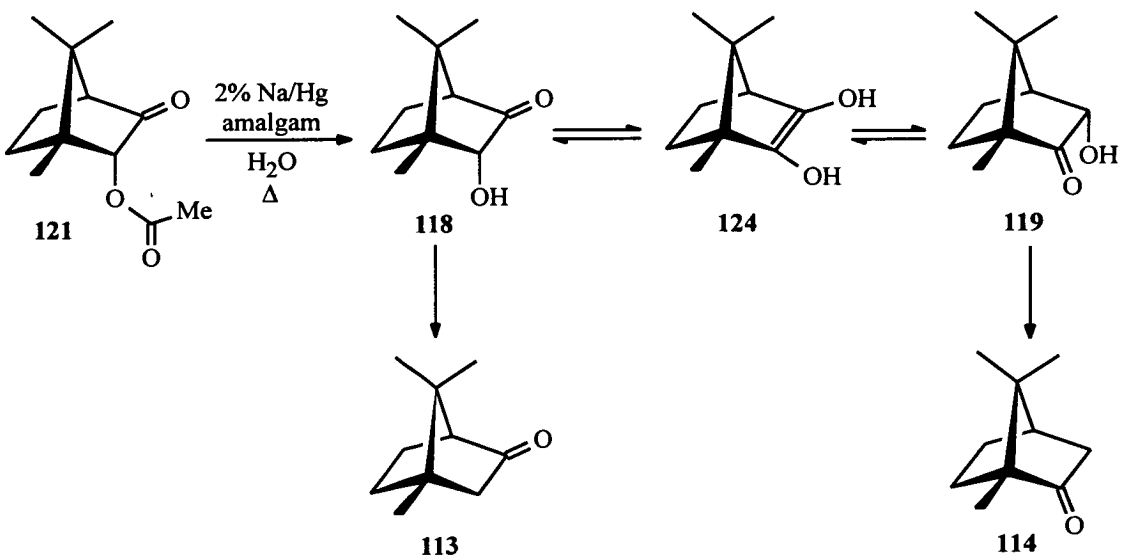
For isolation of pure 2-hydroxyepicamphor **118**, dimer **120** was decomposed by treatment with concentrated hydrochloric acid to give the desired product in high yield (90%). In the subsequent steps, acylation of 2-hydroxyepicamphor **118** was achieved in virtually quantitative yield (98%) using acetic anhydride and triethylamine in the presence of a catalytic amount of DMAP. The resulting acetate **121** needed to be synthesised because reduction of the unprotected keto-alcohol **118** with Na/Hg amalgam suffers from the complication that under alkaline conditions a significant amount of camphor **114** is produced, as well as the desired epicamphor **113**. The reason for this unwanted complication was attributed by Theoren[73] to the fact that under the reaction conditions, **118** undergoes enolisation to **119** *via* the diolene **124**[74] (Scheme 49).



118 **124** **119**

Scheme 49

Reduction of acetate **121** was found to be very dependant upon the composition of the Na/Hg amalgam. When 2% amalgam was used as recorded by Theoren[73], it was found to be a solid and required heating to ensure efficient mixing as a melt. Unfortunately, heating led to a product that was almost a 1:1 mixture of epicamphor **113** and camphor **114**. This disappointing result presumably arises from hydrolysis of the acetate **121** in the aqueous conditions used, thus allowing the enolisation process in Scheme 50 to proceed.

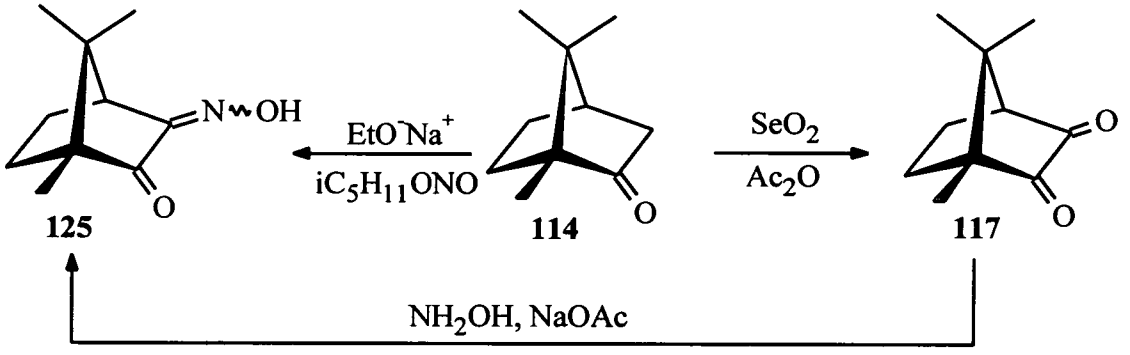


Scheme 50

This problem was overcome successfully by using a 1.5% amalgam, which is a liquid, albeit very thick, and required no heating to allow efficient stirring of the reaction mixture. The procedure worked well on a small scale (24mmol) to produce epicamphor **113** in high yield (88%), but when the scale of the reaction was increased to 71mmol, the product formed was found to be a 4:1 mixture of epicamphor and camphor, respectively. This difficulty presumably arose from the fact that the reaction time was much longer, and consequently allowed hydrolysis and enolisation

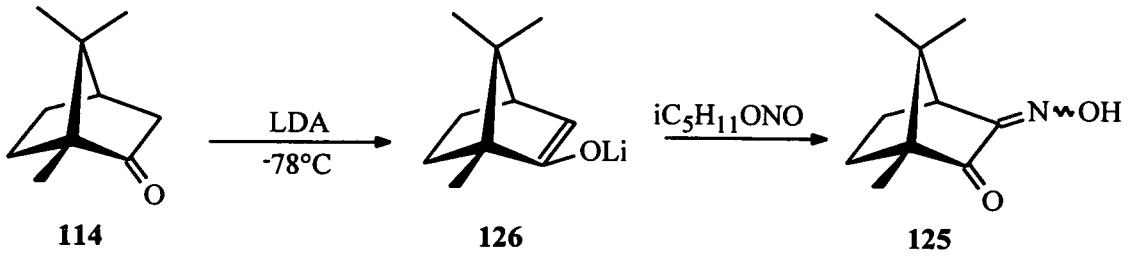
to occur due to poorer mixing of the amalgam with the aqueous suspension on a larger scale.

Owing to the small quantity of epicamphor that had been synthesised, prior to attempts to prepare the transfigomer **110**, it was decided to investigate the α-hydroximination of camphor **114** as a model system. Claisen *et al*[75] had shown that when camphor is treated with isoamylnitrite in the presence of sodium ethoxide, it furnished 3-hydroxyiminocamphor **125** (Scheme 51), *i.e.* the α-position of camphor can be directly aminated. The acidic nature of the α-methylene position of camphor



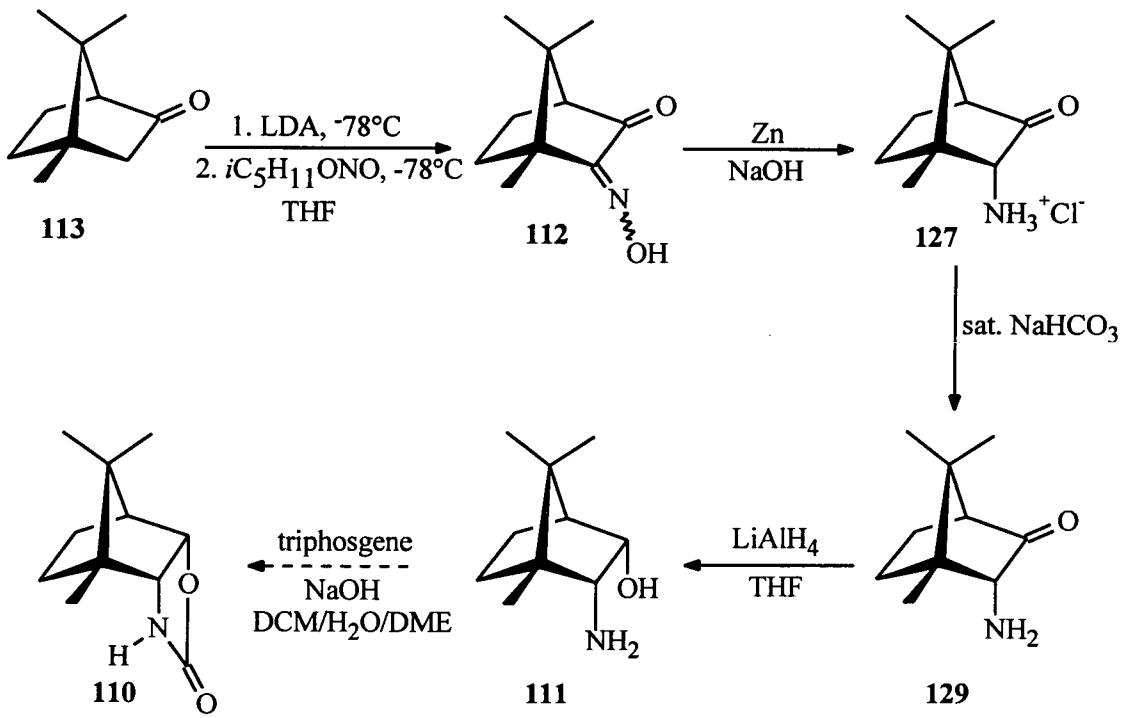
Scheme 51

is further demonstrated by the fact that it can be oxidised by selenium dioxide to camphorquinone **117**[76] (Scheme 51). Interestingly, **125** can also be obtained from camphorquinone **117** by hydroximination of the 3-keto function[77]. Claisen's method of α-hydroximination suffers from poor yields (*ca.* 40%), and in an attempt to improve the procedure, the lithium enolate of camphor **126** was used instead, then cannulated directly into a solution of isoamylnitrite in THF (Scheme 52). Unfortunately the yield was still quite poor (34%), but interestingly the reaction did



Scheme 52

work more successfully when this reverse addition procedure was employed, *i.e.* the enolate was added to the isoamylnitrite. When isoamylnitrite was added directly to the enolate the product afforded was a complex mixture which did not yield the desired product.



Scheme 53

In light of the experiments with camphor itself, it was assumed that α-hydroximination of epicamphor would yield even less product, as a consequence of

the more sterically hindered reaction site (due to the vicinal methyl group). Indeed when the reaction was carried out using the same method employed for the camphor model study, 2-hydroximinoepicamphor **112** was isolated in low yield (16%) (Scheme 53), which NMR indicated was predominantly the *anti* isomer with a small amount of the *syn* isomer (Figure 15) also present.

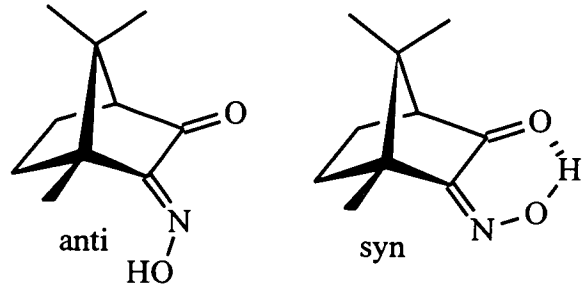
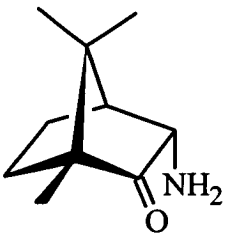


Figure 15

It was expected that the *syn* conformation would be more preferred due to favourable intramolecular hydrogen bonding, but in fact, this is not the case. Cherry *et* al[78] had shown that in 3-hydroximinocamphor **125**, the *syn* isomer is the less stable form. In fact the *anti* isomer is the predominant conformer arising from the formation of intermolecular hydrogen bonds, rather than intramolecular as with the *syn*. On this basis, it is reasonable to assume that the arguments hold true for 2-hydroximinoepicamphor **112**, and account for the composition of the product from the α-hydroximination of epicamphor **113**.

The reduction of the oxime **112** was carried out using zinc dust in sodium hydroxide solution (Scheme 53), and the amino-ketone formed was isolated as its hydrochloride **127** since it was known that the isomeric amino-ketone **128** (Figure

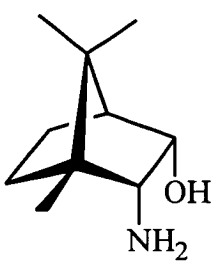
16) was unstable and susceptible to polymerisation. However, for the penultimate stage of the synthesis involving reduction to the amino-alcohol **111**, free amine **129**



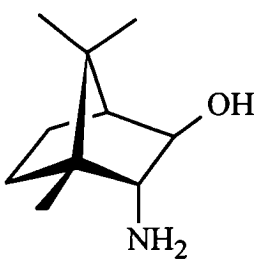
128

Figure 16

was liberated by treatment of the hydrochloride **127** with saturated sodium bicarbonate solution (Scheme 53). Reduction of amino-ketone **129** was carried out with $LiAlH_4$ and TLC showed that the reduction had proceeded with complete consumption of starting material, but upon purification of the product by flash chromatography, what appeared to be a single component by TLC was found to be mixture of components produced in disappointing yield (*ca.* 50%). From ^{13}C NMR spectroscopy, it appeared that the mixture consisted of both the *endo-endo* and the *endo-exo* amino-alcohols **111** and **130** (Figure 17), together with a third unidentified component.



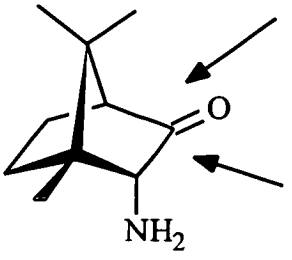
111



130

Figure 17

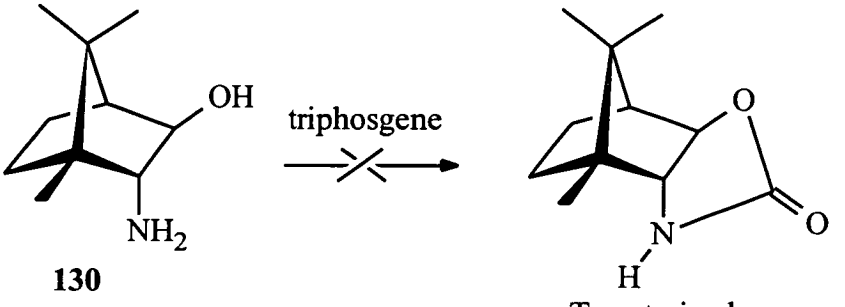
This poor level of stereoselectivity in the ketone reduction presumably arises from the lack of steric repulsion around the carbonyl group. Since the ketone function is situated on the "back" of the bornane skeleton the vicinal hydrogen on the bridgehead carbon imparts no steric control, and consequently, hydride delivery can be achieved from either the upper or lower face of the molecule (Figure 18).



Hydride delivery from either face.

Figure 18

Disappointingly, the final cyclisation stage was not carried out due to insufficient material, but it is easy to envisage that the reaction could be carried out on the inseparable mixture of amino-alcohols **111** and **130**. Since the *endo-endo* isomer **111** should form the oxazolidin-2-one **110**, whereas the *endo-exo* isomer **130** is very unlikely to cyclise as the ring formed would be too strained (Scheme 54).



130

Too strained.

Scheme 54

At this stage, work on the synthesis of the *endo*-transfigomer **110** was abandoned due a to lack of material (the overall yield of the nine stages carried out was only

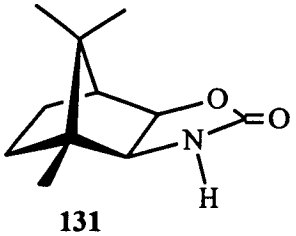
1.8%), and this problem was exacerbated by difficulties in scaling-up the preparation of epicamphor **113**, as well as the time required to complete the route (which was governed by the slow production of dimer crystals **120**). Instead, attention was turned to the synthesis of the *exo*-isomer as described in the next chapter.

Chapter 2

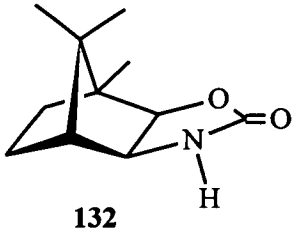
Synthesis and Evaluation of the *exo*-Transfigomer 131 of Chirabornox 65

2.1 Synthesis of Auxiliary 131

After the disappointing progress made in the synthesis of transfigomer **110** (Chapter 1), attention was diverted to the possibility of synthesising the *exo*-isomer **131** (Figure 19), whose analogue **132** (Figure 19) had been synthesised previously, but also proved to perform poorly in Diels-Alder reactions[79] like Chirabornox. This



131



132

Figure 19

poor stereoselectivity once again stems from free rotation of the carbonyl-C_α bond in the *N*-Acyl moiety in the functionalised auxiliary, leading to attack of the diene at either face of the dienophile (Figure 20).

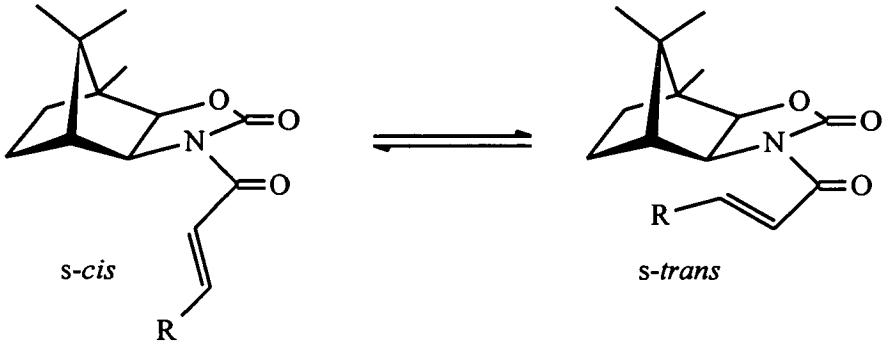


Figure 20

As described in the previous chapter, it was proposed to transpose the "dormant" methyl group from the rear of the bornane ring to the front (and active side) and

eliminate rotation about the carbonyl-C_α bond, due to unfavourable steric interactions. This effect would then allow the dienophile attached to the auxiliary to exist only in its s-*cis* conformation (Figure 21).

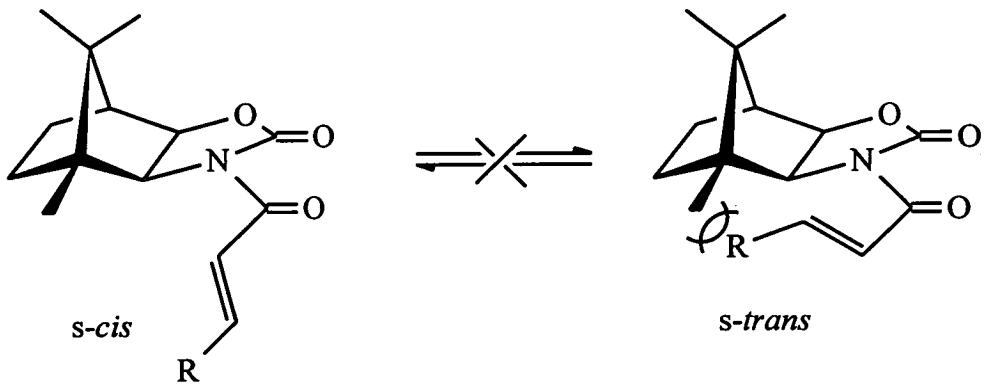
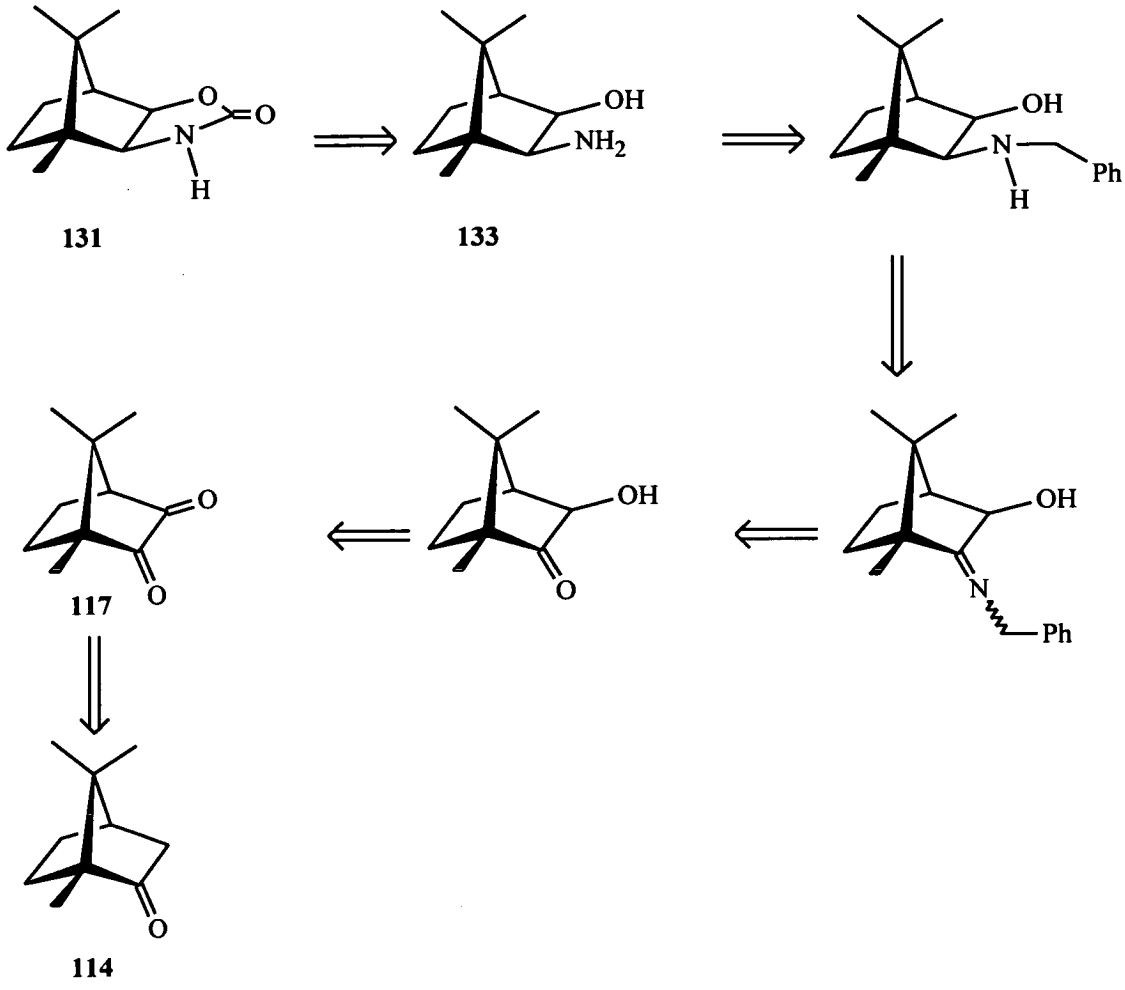


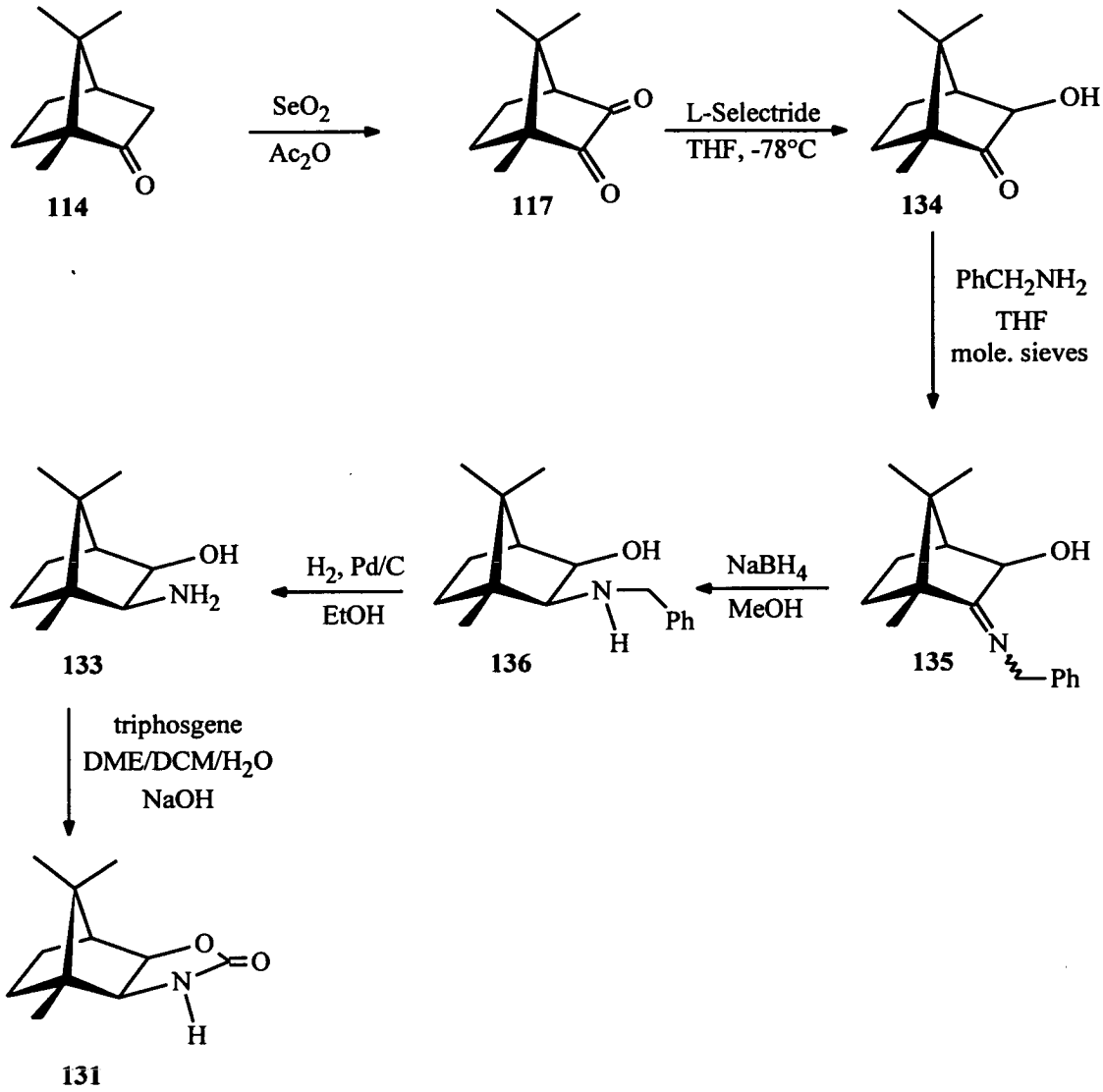
Figure 21

Retro-synthetic analysis of the desired oxazolidin-2-one auxiliary **131** as depicted in Scheme 55 suggested a six-step synthesis from (1*R*)-camphor **114**. Kouklovsky *et*



Scheme 55

al[80] have used amino alcohol **133** as a precursor to oxazoline auxiliaries and it was decided to employ their method of synthesis. For the final stage of ring closure, it was intended to employ a modification of the procedure developed by Pridgen and Prol[81].



Scheme 56

The actual synthetic route used is illustrated in Scheme 56. The initial step once again involved oxidation of (1*R*)-camphor **114** to camphorquinone **117** using selenium dioxide in acetic anhydride. As described earlier this procedure caused no problems, and **117** was furnished in excellent yield (96%). The stereoselective reduction of camphorquinone **117** was effected by treatment with L-Selectride® (lithium tri-*sec*-butylborohydride) in THF at -78°C. Kouklovsky *et al*[80] reported a reaction time of only five minutes, but when this procedure was followed there was

still a significant amount of **117** present in the product mixture. In order to overcome this difficulty, the reaction was allowed to proceed for a period of four hours before quenching, following which the desired keto-alcohol **134** was produced in very high yield (90%) compared to 70% reported previously[80].

Kouklovsky's method[80] was again followed for the preparation of the imine **135**, although once again a longer reaction time was employed, unfortunately the isolated yield was disappointingly low (50%), despite attempts to improve the reaction by raising the temperature and use of other drying agents.

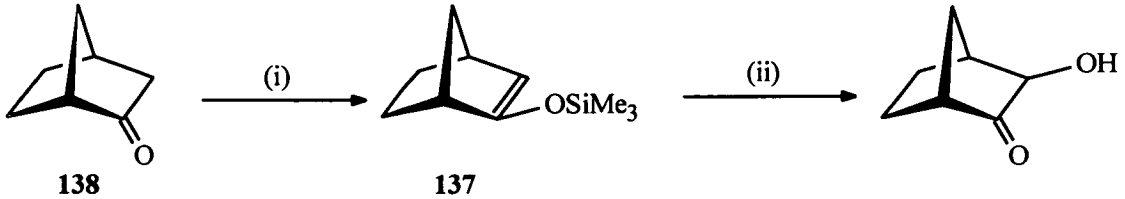
For reduction of the imine **135**, addition of sodium borohydride to a solution of **135** in methanol furnished the desired *exo,exo*-amino alcohol **136** in excellent yield (97%). Subsequent hydrogenation of the protected amino alcohol **136** with 10% Pd/C as catalyst removed the benzyl protecting group cleanly and afforded the primary amino alcohol **133**, again in excellent yield (96%).

For the final step of ring-closure, the amino alcohol **133** was treated with triphosgene and excess sodium hydroxide in a modification of Pidgen and Prol's diphosgene method[81] to furnish the expected oxazolidin-2-one auxiliary **131** in virtually quantitative yield (98%). The synthesis of **131** was achieved in six steps and in a pleasing overall yield of 39% but unfortunately no crystals of the novel auxiliary could be obtained that were of suitable quality for an X-ray structure (unlike its isomer **132**, which had been synthesised previously in our lab., see Structure 1 in the appendix).

The novel auxiliary **131** is a colourless crystalline solid (MP 196.3 - 197.3°C). The ^{13}C NMR spectrum of **131** was seen to contain the eleven signals that one would

expect, in positions comparable to those found for Chirabornox **65**. In the ^{1}H NMR spectrum one can see two doublet of doublets (*J=ca.* 8 and 1Hz) at δ 4.56 and 3.57ppm arising from the protons geminal to the oxygen and nitrogen atoms respectively. It is interesting to note that the proton geminal to the oxygen exhibits a very small coupling with the vicinal bridgehead proton, indicating an angle of *ca.* 90° between the two. This result provides significant evidence in proving that the oxazolidin-2-one ring is in an *exo*-orientation.

Furthermore, the synthetic route chosen, although successful is not especially suitable for large scale work due to the toxicity and cost of certain reagents. These factors are particularly prevalent in the first two stages, where large quantities of selenium dioxide are used, leading to a waste disposal problem, and also the need for large amounts of expensive L-Selectride® (*ca.* £150 per mole). Recent work by Jauch[82] has shown that a modified Rubottom oxidation of bicyclic silyl enol ethers offers a route to bicyclic α-hydroxyketones. The example in Jauch's work that was of particular interest was the α-hydroxylation of the silyl enol ether **137**, which is obtained from bicyclo[2.2.1]heptan-2-one **138** (Scheme 57). It was envisaged that

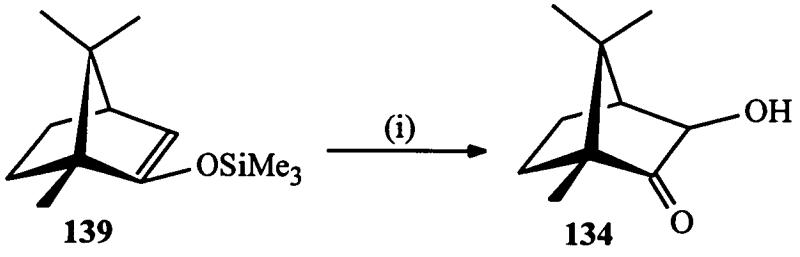


138 **137**

(i) Me_3SiCl, NaI, NEt_3, pentane, CH_3CN
(ii) 1. *m*-CPBA, $NaCO_3$, pentane
2. K_2CO_3, H_2O

Scheme 57

keto-alcohol **134** could also be prepared from the silyl enol ether of camphor **139** by the same method (Scheme 58). Thus the latter was sythesised from (1*R*)-*endo*-(+)-3-bromocamphor **140**, and not camphor itself since its formation under these conditions

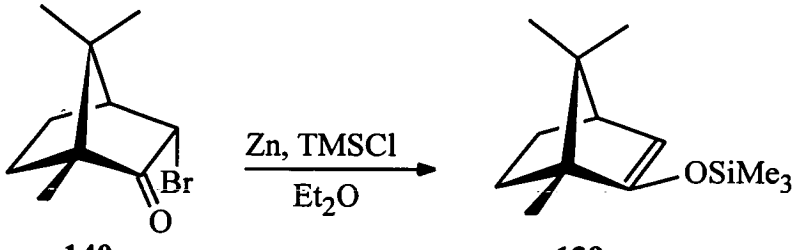


139 **134**

(i) 1. *m*-CPBA, $NaHCO_3$, pentane
2. K_2CO_3, H_2O

Scheme 58

is notoriously difficult, by a modified version of the procedure used by Joshi and Pande[83] (Scheme 59). Typically, a solution of *endo*-bromocamphor **140** and

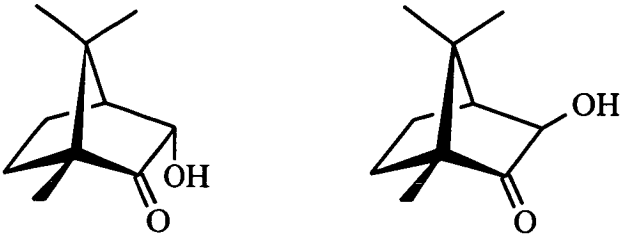


140 **139**

Scheme 59

chlorotrimethylsilane in THF was added to a stirred suspension of activated zinc dust in THF and heated under reflux. After work-up and Kugelrohr distillation, the silyl enol ether **139** was obtained as a colourless liquid in good yield (60%). For the attempted conversion of **139** into **134**, the procedure of Jauch[82] was used, but unfortunately the product was obtained in poor yield (25%), and was also found to be an inseparable 2:1 mixture of two α-hydroxy ketones. The identity of both

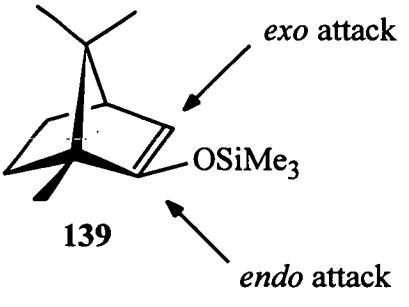
components was determined from the ^{1}H NMR spectrum of the product, which showed a doublet at δ 4.17ppm (J=5.1Hz) arising from the *exo*-hydrogen on the 3-position of the *endo*-hydroxy ketone **119**[69] (predominant product) (Figure 22), and a singlet at δ 3.72ppm, corresponding to the *endo*-hydrogen at the 3-position of the desired keto-alcohol **134** (Figure 22).



119 **134**

Figure 22

This poor result arises from the from the preferential attack of *m*-CPBA on the *endo* face of the enol ether **139** instead of on the *exo* face (Figure 23). Notably, in



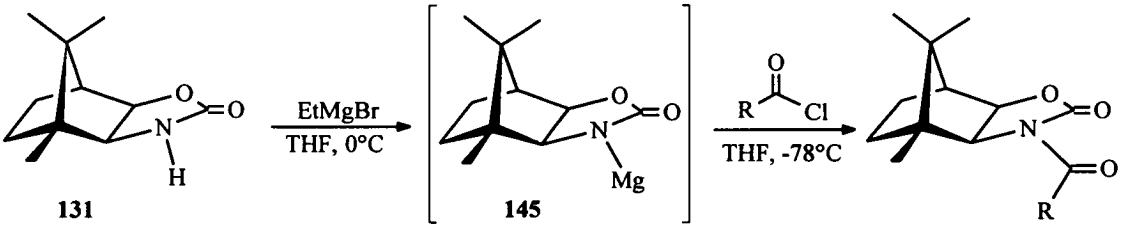
139

Figure 23

the case of the silyl enol ether **137**, attack by *m*-CPBA occurred on the less sterically crowded *exo* face, but for **139** the presence of the methyl groups at the bridging carbon obviously drastically increases the steric bulk on the *exo* face, resulting in the *endo* face being the favourable side of attack.

2.2 Functionalisation of the Auxiliary 131

For the auxiliary **131** to be viable it was essential that it could be easily functionalised. The method used by Evans[7] was employed for the preparation of the *N*-Acyl derivatives **141, 142, 143** and **144**. In each case, the auxiliary was treated with freshly prepared ethylmagnesium bromide at 0°C in THF to form the magnesium species **145** (Scheme 60), which was then reacted with the appropriate acid chloride at -78°C (Scheme 60). Table 1 records the excellent yields obtained for the desired products.



Scheme 60

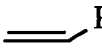
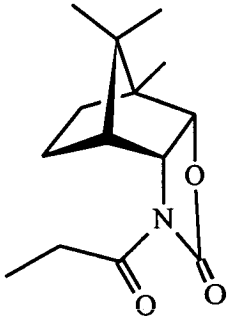
R		Yield
	**141**	88%
	**142**	90%
	**143**	99%
Et	**144**	99%

Table 1. Functionalisation of Auxiliary **131**

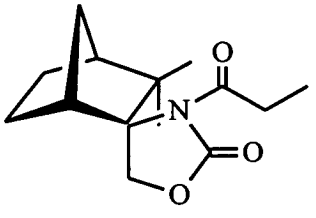
It is worth noting that this method of functionalisation was chosen because of the relatively mild nature of the base used. Stronger bases such as butyllithium can be

employed but such use leads to significantly more ionic intermediates which are known to induce anionic polymerisation, especially in the case of acrylate derivatives[7,84]. As can be seen from Table 1, no such problems arise in the formation of the acrylate **141** with ethylmagnesium bromide as the base. This is due to the magnesium intermediate being considerably less ionic than its lithium counterpart.

It is interesting to note that the propionate derivative **144** is a crystalline solid and has none of the handling difficulties encountered with the corresponding derivatives of Chirabornox **146** and Chiracamphox **147**. The propionate of Chirabornox **146** (Figure 24) is an oil, where the Chiracamphox derivative **147** (Figure 24) has to be crystallised from pentane at -20°C



146



147

Figure 24

2.3 Lewis Acid-Catalysed Asymmetric Diels-Alder Reactions

Once the desired oxazolidin-2-one auxiliary **131** had been successfully synthesised and functionalised, its synthetic utility was studied in a series of asymmetric transformations. The first reactions to be investigated involved Diels-Alder reactions of the acrylate **141**, crotonate **142** and cinnamate **143** with cyclopentadiene.

A significant advance in asymmetric Diels-Alder reactions in recent times has been the increased use of Lewis acid catalysts. The catalysed reactions, as well as proceeding at a greatly enhanced rate, also exhibit dramatically increased levels of regio and stereoselectivity compared to the non-catalysed reactions.

By applying frontier molecular orbital theory[85], the effect can be rationalised as follows. The most important interaction in the standard Diels-Alder reaction, *i.e.* involving an electron rich-diene and an electron-deficient dienophile, is that between the highest occupied molecular orbital (HOMO) of the diene and the lowest unoccupied molecular orbital (LUMO) of the dienophile (Figure 25). Electron withdrawing groups on the dienophile, or the co-ordination of a Lewis acid with a suitable electron donor on the dienophile, lowers the energy of the LUMO (dienophile) relative to that of the HOMO (diene). This leads to the energy difference between the interacting LUMO (dienophile) and HOMO (diene) being reduced, thus giving a greatly accelerated reaction rate.

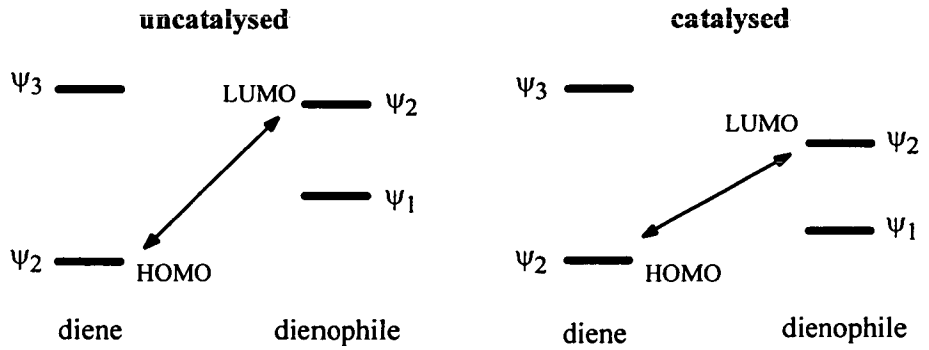
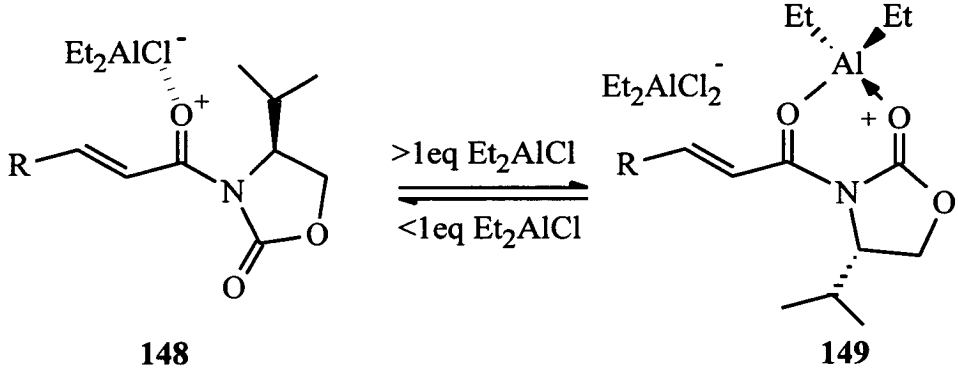


Figure 25

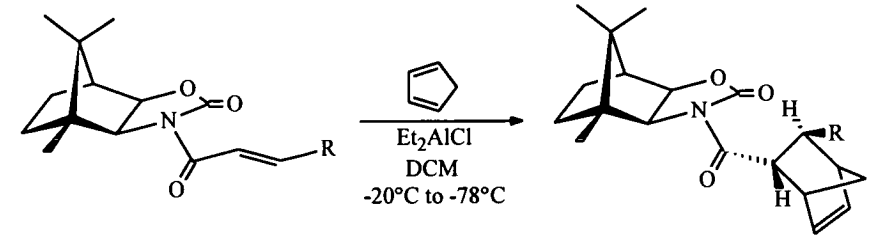
The increase in regio and stereoselectivities arises from a change in the size of the frontier orbital coefficients, which gives rise to greater secondary overlap in certain transition state arrangements, and consequently greater selectivity.

In a study of a number of Lewis acids, Evans *et al*[7] noted that diethylaluminium chloride was the most effective in respect to the Diels-Alder reaction. It was also found that the degree of selectivity increased when greater than one equivalent of catalyst was used. It has been proposed that this effect is due to the complex changing from a monodentate system **148** to a rigid, ionic, highly dienophilic bidentate complex **149** (Scheme 61). The reason for the formation of **149** is the possibility that the catalyst provides itself with a counter ion when surplus catalyst is present.



Scheme 61

The Diels-Alder reactions were carried out by adding diethylaluminium chloride to a cooled, stirred solution of the appropriate dienophile **141**, **142** or **143** and freshly cracked cyclopentadiene (10 equivalents) (Scheme 62). Upon addition of the catalyst, a yellow colour appeared which then faded on completion of reaction.



Scheme 62

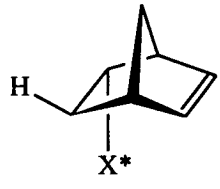
The reactions of the acrylate **141** and crotonate **142** were both carried out at -78°C, but in the case of the less reactive cinnamate **143**, the reaction proceeded at -20°C. The crude products obtained were subjected to flash chromatography to remove excess cyclopentadiene and polymeric material and the resulting material was then examined by 250MHz ^{1}H NMR to determine the selectivity of the reactions. The signals of interest were the doublet of doublets between δ 5.5 and 6.5ppm, that arise from the olefinic protons in the Diels-Alder cycloadduct. Integration of these signals allowed the *endo/exo* selectivities and the diastereomeric excesses to be determined. The results are summarised in Table 2.

Dienophile	**Temp.**	**Yield**	***endo/exo***	***d.e.***
acrylate **141**	-78°C	100%	100 : 0	81%
crotonate **142**	-78°C	92%	100 : 0	>99%
cinnamate **143**	-20°C	100%	100 : 0	>99%

Table 2. Diels-Alder reactions of the acrylate **141**, crotonate **142** and cinnamate **143** with cyclopentadiene.

As can be seen from the table, the yields and the *endo/exo* selectivity achieved were both excellent. In fact, only *endo* isomers were seen to be formed, whilst for the

crotonate **142** and cinnamate **143**, the diastereomeric excesses achieved were virtually perfect and essentially only one product was afforded. The outcome for the acrylate **141** was a little disappointing in that only 81% diastereomeric excess was achieved, arising from a 9:1 mixture of *endo* products. This relatively poor selectivity in the acrylate case obviously arises from a lack of steric repulsion between the acrylate moiety and the methyl group positioned on the front face of the auxiliary. This results in a small amount of the s-*trans* conformer being present, leading to the formation of the second *endo* diastereomer (Figure 26).



X* = auxiliary

Figure 26

These very encouraging results prove that transposition of the "dormant" methyl group from the back to the front of the bornane ring does increase the steric repulsion in the transition state and with a concomitant improvement of the diastereoselectivity of the Diels-Alder reaction. By contrast, in the case of the previously studied *exo* auxiliary **132** diastereomeric excesses for Diels-Alder reactions ranged from only 48-68% with a 4:1 *endo*:*exo* selectivity[79]. The results obtained for transfigomer **131** are in fact comparable to those reported for Evans' (*S*)-valine derived auxiliary **10**[7].

The absolute stereochemistry of the cycloadducts obtained was determined by obtaining an X-ray crystal structure for the crotonate derivative **151** (see Structure 2

in the appendix). The structure clearly shows the adducts are indeed *endo* in nature and also possess the predicted stereochemistry (Figure 27). This result is consistent

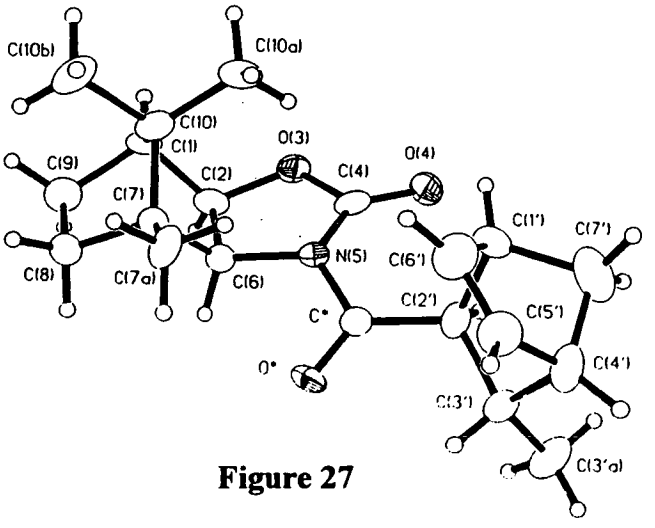
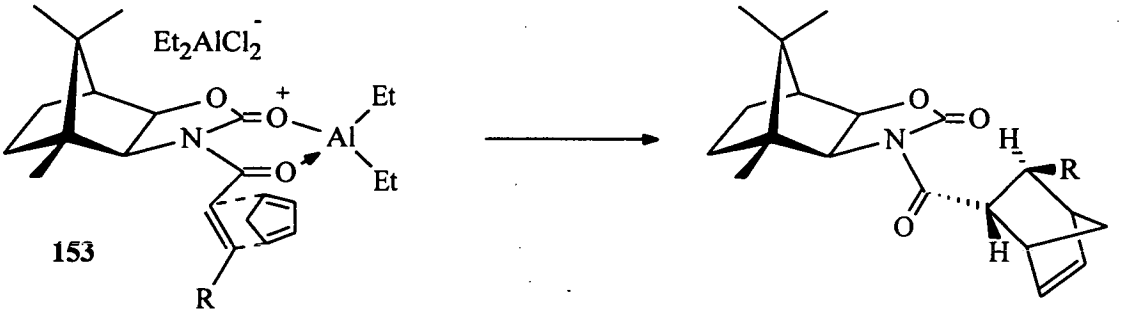


Figure 27

with attack of the diene at the C_α-*si* face of the chelated dienophile in the transition state **153** (Scheme 63).

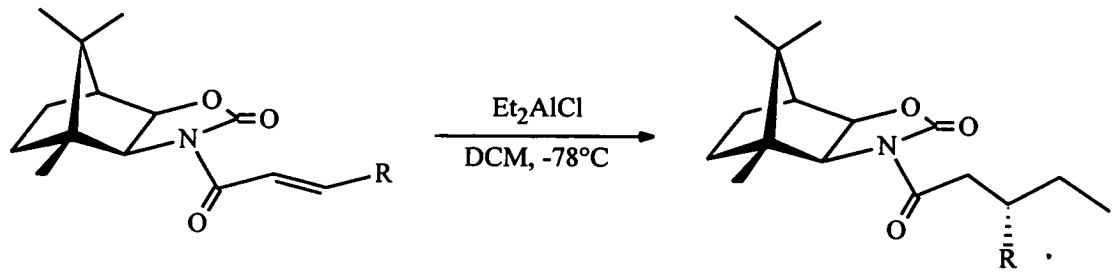


Scheme 63

2.4 Asymmetric 1,4-Conjugate Addition Reactions

As well as acting as a Lewis acid catalyst in Diels-Alder reactions, diethylaluminium chloride can also be used as a highly efficient source of ethyl nucleophiles. By making use of this property, asymmetric 1,4-conjugate addition

reactions were carried out with both the crotonate **142** and cinnamate **143** (Scheme 64).



Scheme 64

Thus, treatment of a solution of **142** or **143** with four equivalents of diethylaluminium chloride at -78°C in methylene chloride furnished the chiral β-branched products **154** and **155**, respectively in quantitative yield. The diastereomeric excesses of the products were determined by high field ^{13}C NMR by integration of the C-H signals arising from the newly formed chiral centres, and the results are recorded in Table 3. This integration technique has been proven to be accurate previously in our group[32b]. This is presumably due to the fact that as the compounds under investigation are diastereomers the relaxation times of the carbon nuclei are virtually indentical. It has been shown that measurement of the relative intensities of carbon signals give diastereomeric excess that are very similar (within 5%) to those obtained from examinations of the corresponding ^{1}H spectrum.

R	Yield	*d.e.*
CH_3 **154**	100%	30%
Ph **155**	100%	78%

Table 3. 1,4-Conjugate addition reactions between Et_2AlCl and the crotonate **142** and cinnamate **143**.

From Table 3 it is evident that the diastereoselectivity obtained in both reactions was rather poor. In the case of the cinnamate-derived product **155** the diastereomeric excess was increased to >95% upon one recrystallisation from cyclohexane with good recovered yield (86%). Palomo *et al*[86] reported that treatment of the crotonate **142** with Et_2AlCl at -78°C in toluene (not methylene chloride) gave a product with 80% *d.e.*. In order to evaluate this claim, their method was repeated, but as with the case where methylene chloride was used, only a 30% *d.e.* was achieved in the product. This poor level of stereoselectivity can be explained by consideration of the transition state for the reaction (Figure 28). From Figure 28 it is evident that the

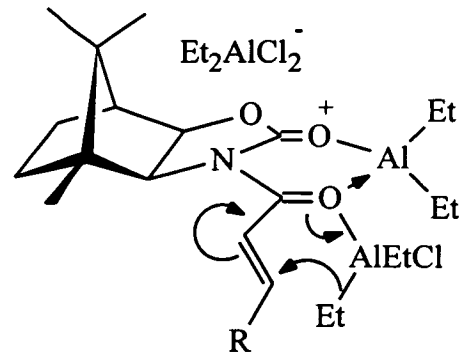
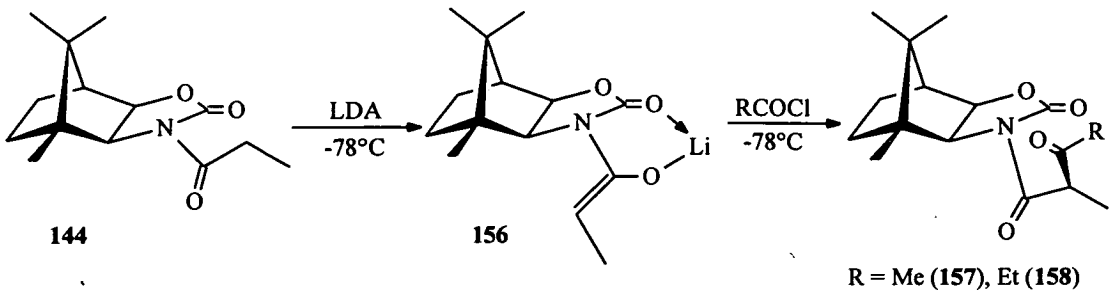


Figure 28

actual site of reaction is relatively distant from the steric bulk of the auxiliary. In consequence less steric repulsion occurs, thus resulting in the poor levels of diastereoselectivity. It can also been seen from Figure 28 that the delivery of the ethyl group preferentially occurs on the lower, *i.e.* C_α-*si* face, of the imide. Due to this reasoning, the absolute stereochemistry, though not determined, has been assigned as (*S*).

2.5 Asymmetric Acylation Reactions

The next series of reactions to be investigated were asymmetric acylations of the propionate derivative **144**. The reactions were carried by the method outlined in Scheme 65, where by the propionate **144** was added to a freshly generated solution of lithium di-isopropylamine (LDA) at -78°C to form the lithium enolate **156**. The appropriate acid chloride was then added to the enolate to yield the desired products **157** and **158**. Acylations were carried out with acetyl and propionyl chloride and the results summarised in Table 4.



Scheme 65

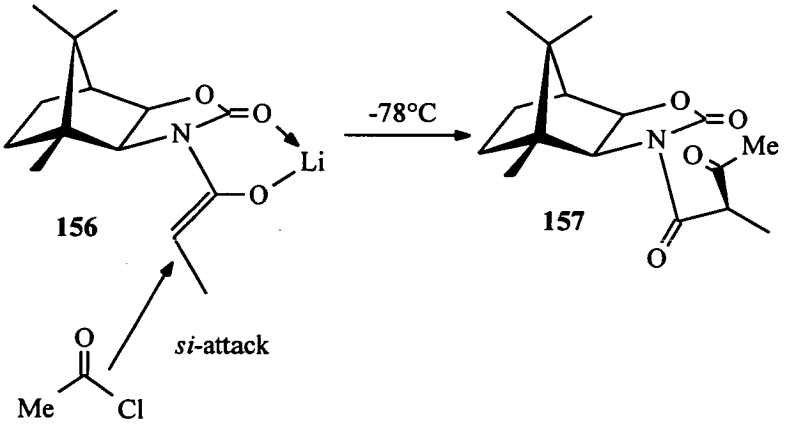
R	Yield	*d.e.*
Me **157**	95%	>99%
Et **158**	72%	>99%

Table 4. Acylation reactions of the propionate **144** with acetyl and propionyl chloride.

Before discussing the outcome, it is worth noting that in acylation reactions there is a delicate balance between sufficient time for complete enolate consumption, and the ensuing problem of racemisation of the newly created chiral centre by residual LDA. In light of this restriction, the reaction with acetyl chloride was allowed to progress for two minutes before quenching, and in the case of propionyl chloride, a reaction time of seven minutes was required for the reaction to proceed to completion.

From Table 4, it can be seen that both reactions proceeded without incident and the two acylated products **157** and **158** were obtained in excellent yield. Analysis of the products by high field ^{1}H and ^{13}C NMR showed that both reactions produced only one diastereomer. Interestingly, there was no problem encountered with *O*-acylation that had been a problem for both Chiragalox **71**[35] and Chirabornox **65**[32].

The absolute stereochemistry of the products was determined by obtaining an X-ray crystal structure of the acylation product **157** derived from acetyl chloride (see Structure 3 in the appendix). From the structure, it can be seen that the orientation of the new chiral centre at the C_α position in the *N*-acyl moiety is (*R*). This result is consistent with the acylation occurring on the C_α-*si* (lower) face of the (*Z*)-enolate **156** derived from the propionate **144** (Scheme 66).

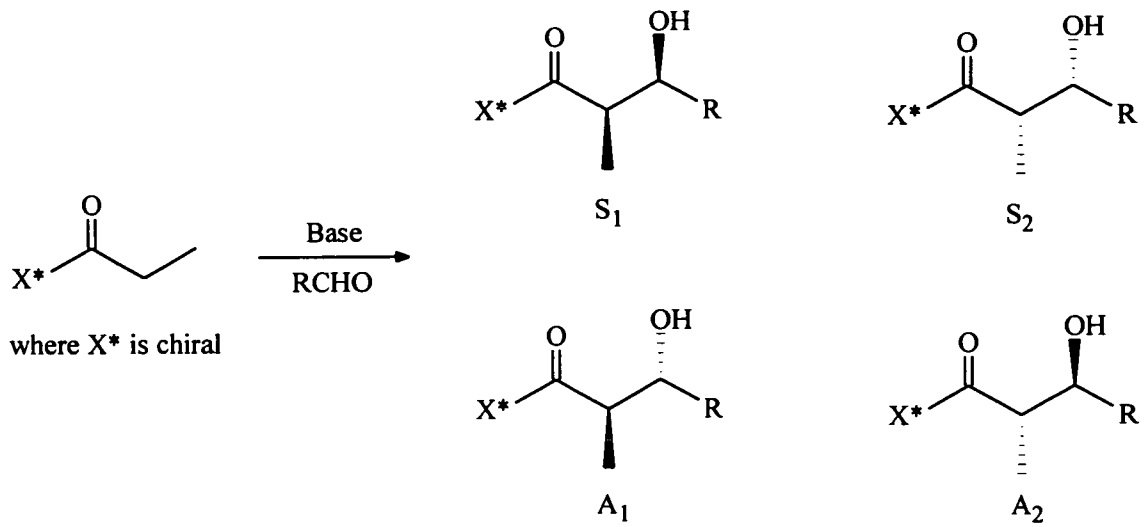


Scheme 66

2.6 Asymmetric Aldol Reactions

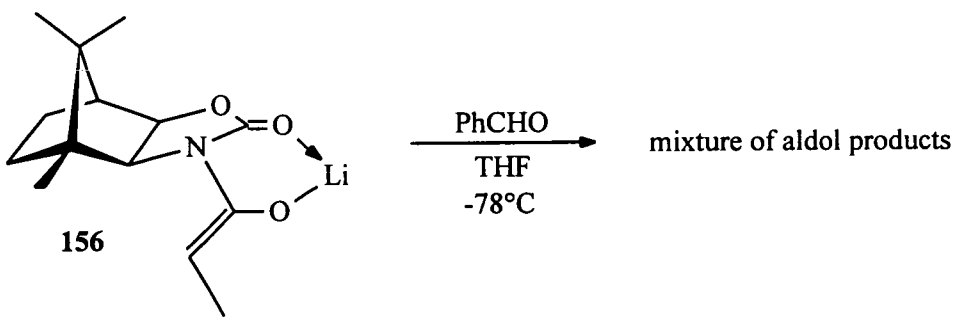
The final series of reactions to be investigated were asymmetric aldol reactions. In such reactions there is the possibility of obtaining four different products (Scheme 67), *viz.* two *syn* isomers S_1 and S_2 and two *anti* isomers A_1 and A_2. The product

obtained depends very much on the auxiliary chosen and on the type of enolate that is used.



Scheme 67

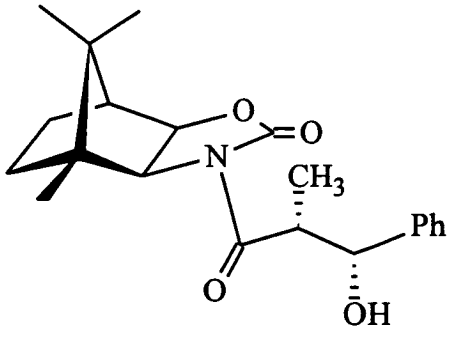
The first aldol reaction to be examined involved the condensation between the lithium enolate **156**, derived from the propionate **144**, and benzaldehyde (Scheme 68).



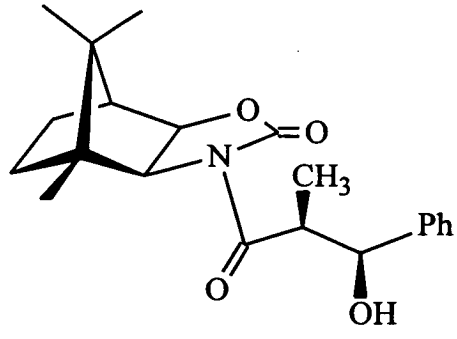
Scheme 68

From an examination of the oily product obtained by high field ^{1}H and ^{13}C NMR spectroscopy, it was evident that the product consisted of a mixture of two major components with a third product present in a smaller amount. Although not proven it

was assumed that the two major components of the product were the two *syn* isomers **159** and **160** (Figure 29).



159



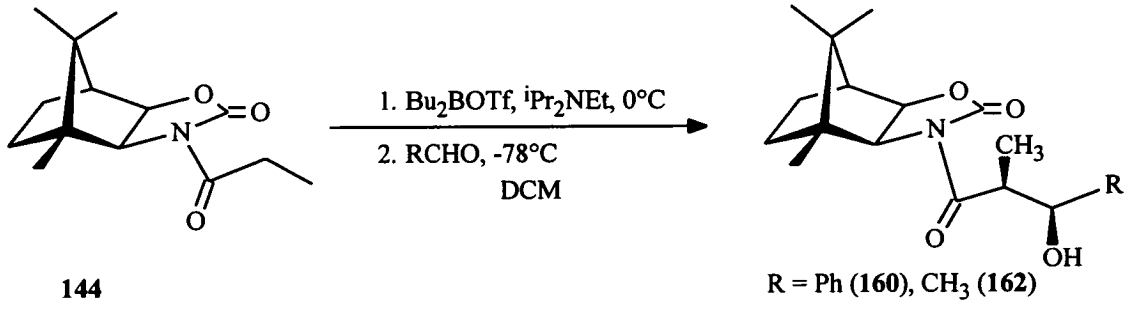
160

Figure 29

The exact composition of the mixture was not closely examined because it had been shown by a number of workers[6,16,34] that lithium-mediated aldol reactions exhibit poor levels of asymmetric induction, and this test reaction just helped to reinforce this point. The poor diastereoselectivity can be attributed to the transition state of the reaction being less "tight" than those set-up by other enolate systems, *e.g.* boron, as discussed later. This arises due to the relatively long Li-O bond lengths[87]. Furthermore, lithium does not possess any true ligands, other than those of solvent, *e.g.* alkyl groups (as with boron, to be discussed later), which can create a greater level of steric interaction in the transition state.

After this poor result (although not unexpected) with the lithium-based enolate, attention was turned to the study of boron-mediated aldol reactions. Evans[6] and others[16] have reported that very high levels of asymmetric induction can be achieved by use of boron enolates rather than lithium enolates.

The boron enolate **161** (Scheme 70) was generated by treating propionate **144** with dibutylboron triflate (Bu_2BOTf) and diisopropylethylamine (Hunig's base), following which the enolate was reacted with the desired aldehyde (Scheme 69). The



144

R = Ph (**160**), CH_3 (**162**)

Scheme 69

results for the aldol reactions between **144** and benzaldehyde and acetaldehyde are summarised in Table 5.

R	Yield	*d.e.*
Ph **160**	67%	99%
CH_3 **162**	38%	99%

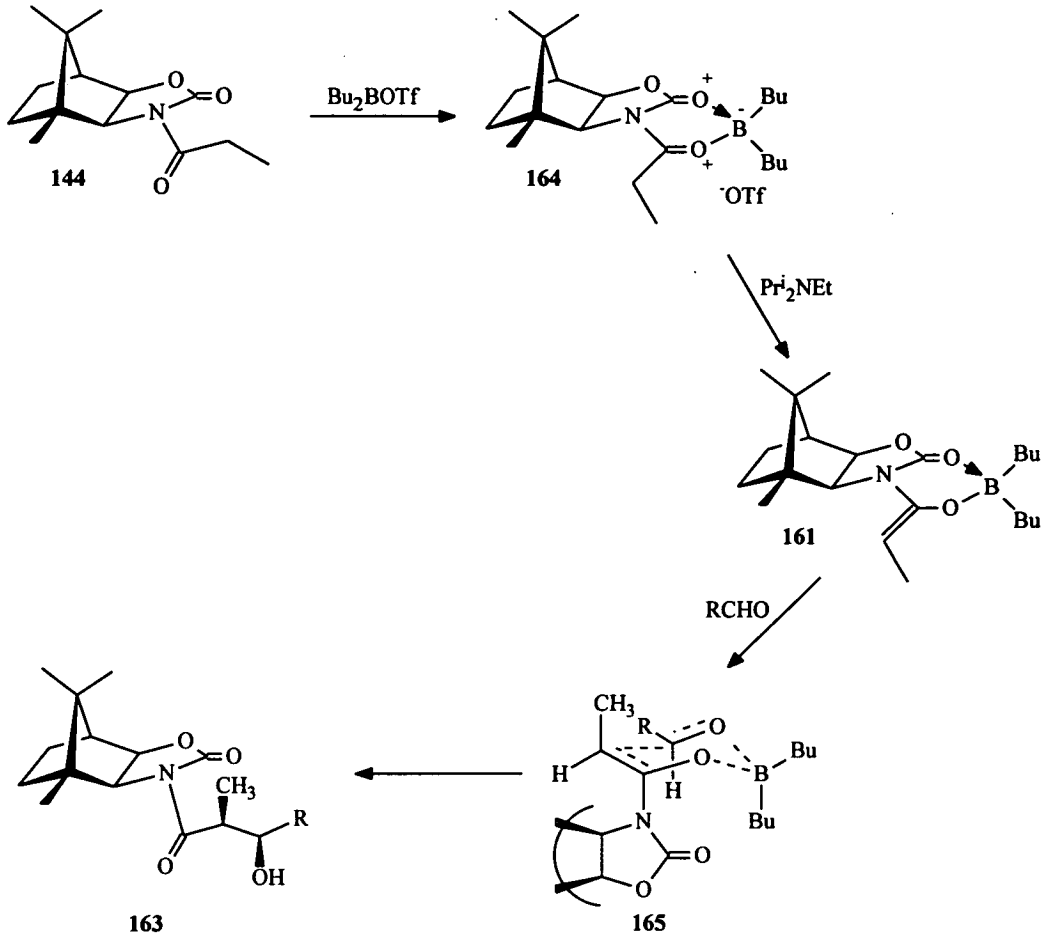
Table 5. Aldol reactions of the propionate **144** with benzaldehyde and acetaldehyde.

The yields of the aldol products were disappointingly low, especially in the case of the product **162** derived from acetaldehyde. This may have been due in some part to the commercial dibutylboron triflate that was used. This reagent is extremely air

and moisture sensitive and deteriorates rapidly, even when thoroughly sealed and stored under anhydrous conditions. It has been reported by other workers[88] that similar problems have been encountered problems with this reagent.

Despite the poor yields, the level of asymmetric induction imparted by the auxiliary is excellent. In both cases, ^{13}C NMR indicated only one product was formed. ^{1}H NMR indicated that the product was a *syn* isomer due the presence of small vicinal coupling constants (J=2.7Hz). This was proven conclusively when the aldol product was cleaved (the reader is directed to Section 2.7). The explanation for this level of stereoselectivity lies in the six-membered transition state that is set up during the reaction, as discussed below.

When the dibutylboron triflate is added to propionate **144**, the boron initially co-ordinates to the carbonyl functions from both the oxazolidin-2-one and *N*-acyl moiety in a tetrahedral arrangement to form complex **164**. Subsequent treatment of **164** with $Pr^{i}_{2}NEt$ yields the (*Z*)-boron enolate **161** (Scheme 70). When the aldehyde is added, the bond from the oxygen of the oxazolidinone carbonyl to the boron is broken and the auxiliary rotates itself through 180° about the N-C bond. This then allows the boron to co-ordinate to the oxygen of the carbonyl function of the incoming aldehyde and the outcome is the formation of the six-membered Zimmerman/Traxler transition state **165** as shown in Scheme 70. It is worth noting that in the transition state **165** the attack of the aldehyde occurs on the C_{α}-*re* face of the enolate since the bulk of the auxiliary shields the C_{α}-*si* face.



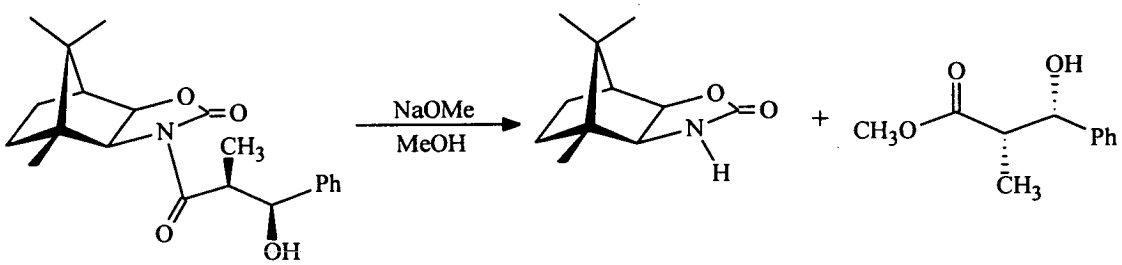
Scheme 70

The vast increase in stereoselectivity resulting from use of boron enolates arises for two reasons. Firstly the B-O bond length is much shorter than the corresponding Li-O length[87], with the result that the transition state is much "tighter". This increases the steric interactions, especially between the auxiliary and the R group of the aldehyde, and results in the R group being forced to adopt an equatorial position in the chair form **165** (Scheme 70). Secondly, as the boron carries alkyl ligands (unlike lithium), the possibility of the R group from the aldehyde residing in an axial position becomes even more unlikely due to 1,3-diaxial interactions that can arise with the axial butyl group on the boron.

2.7 Cleavage of Auxiliary 131

The final test on the utility of the auxiliary **131** to be investigated was the ease with which the auxiliary could be cleaved and recovered without any racemisation. In order to examine this and also to prove the absolute stereochemistry of the aldol reactions discussed in section 2.6, it was decided to cleave the aldol product **160** obtained from the reaction between the propionate **144** and benzaldehyde.

The method of cleavage chosen was to treat **160** with sodium methoxide. This technique yielded the parent auxiliary **131** in high yield (70%) but the expected methyl ester **166** in a rather disappointing yield (30%) (Scheme 71).



160 **131** **166**

Scheme 71

From a comparison of its optical rotation (which was lower than expected, suggesting partial racemisation due to the presence of excess base) value with the known literature value[6], the methyl ester was found to have the (*S*),(*S*) configuration. This is the expected stereochemistry arising from the mechanism discussed in section 2.6. The poor yield of **166** is probably due to the fact that an excess of base (NaOMe)

was used and a retro-aldol process may have taken place, thus destroying the aldol fragment before cleavage.

In retrospect, the cleavage conditions chosen were probably too harsh and a milder method such as using lithium benzyloxide to give the benzyl ester would have been more appropriate. Nevertheless, the auxiliary **131** was recovered in good yield and does indeed prove to be a viable asymmetric tool.

2.8 Conclusion

The main aim in designing and synthesising the auxiliary **131** was to investigate the effectiveness of moving the previously inactive methyl group from the rear to the front of the bornane skeleton. The potency of this move is summarised in Table 6,

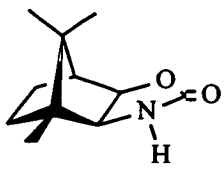
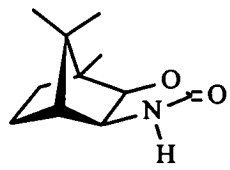
	 **131** ***d.e.***	 **132** ***d.e.***	 **65** ***d.e.***
Type of reaction			
Diels-Alder with cyclopentadiene	81 - 99% (only *endo*)	48 - 68% (4:1 (*endo:exo*))	60 - 90% (4:1 - 99:1 (*endo:exo*))
Conjugate addition of Et_2AlCl	30 - 80%	N/A	11 - 43%
Acylation	99%	N/A	82 - 95% (some O-acylation)
Aldol	99%	N/A	99%

Table 6. Outcome of various asymmetric transformations employing the oxazolidinones **131**, **132** and **65** as chiral auxiliaries

from which it is evident that transposition of the methyl does indeed dramatically increase the degree of asymmetric induction imparted by the newly synthesised auxiliary **131** when compared to Chirabornox **65**. As discussed previously in this

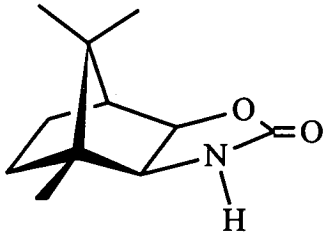
chapter, the methyl group does not possess enough steric bulk for the auxiliary to impart total stereoselectivity, especially in the case the Diels-Alder reaction with the acrylate dienophile (section 2.3) and in 1,4-conjugate addition reactions (section 2.4). On the basis of these results it was deemed desirable to examine the possibility of increasing the steric bulk on the front face of the auxiliary by replacing the methyl with an ethyl group (see Chapter 3).

Chapter 3

Synthesis and Evaluation of a New 10-Methylcamphor-Derived Auxiliary

3.1 Synthesis of Auxiliary 167

As described in Chapter 2, the camphor-derived auxiliary **131** (Figure 30) imparts excellent levels of asymmetric induction in Diels-Alder, acylation and aldol reactions. However **131** displays poor levels of diastereoselectivity in 1,4-conjugate

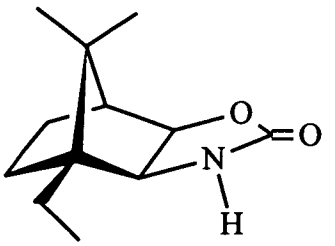


131

Figure 30

addition reactions and in the Diels-Alder reaction of its acrylate **141** with cyclopentadiene. These disappointing results arose from the fact that the methyl group on the front face of the bornane skeleton did not possess enough steric bulk to provide sufficient steric interactions between the auxiliary and the *N*-acyl moiety at which the reaction was occurring to prevent free rotation about the carbonyl-C_α bond (see sections 2.3 and 2.4).

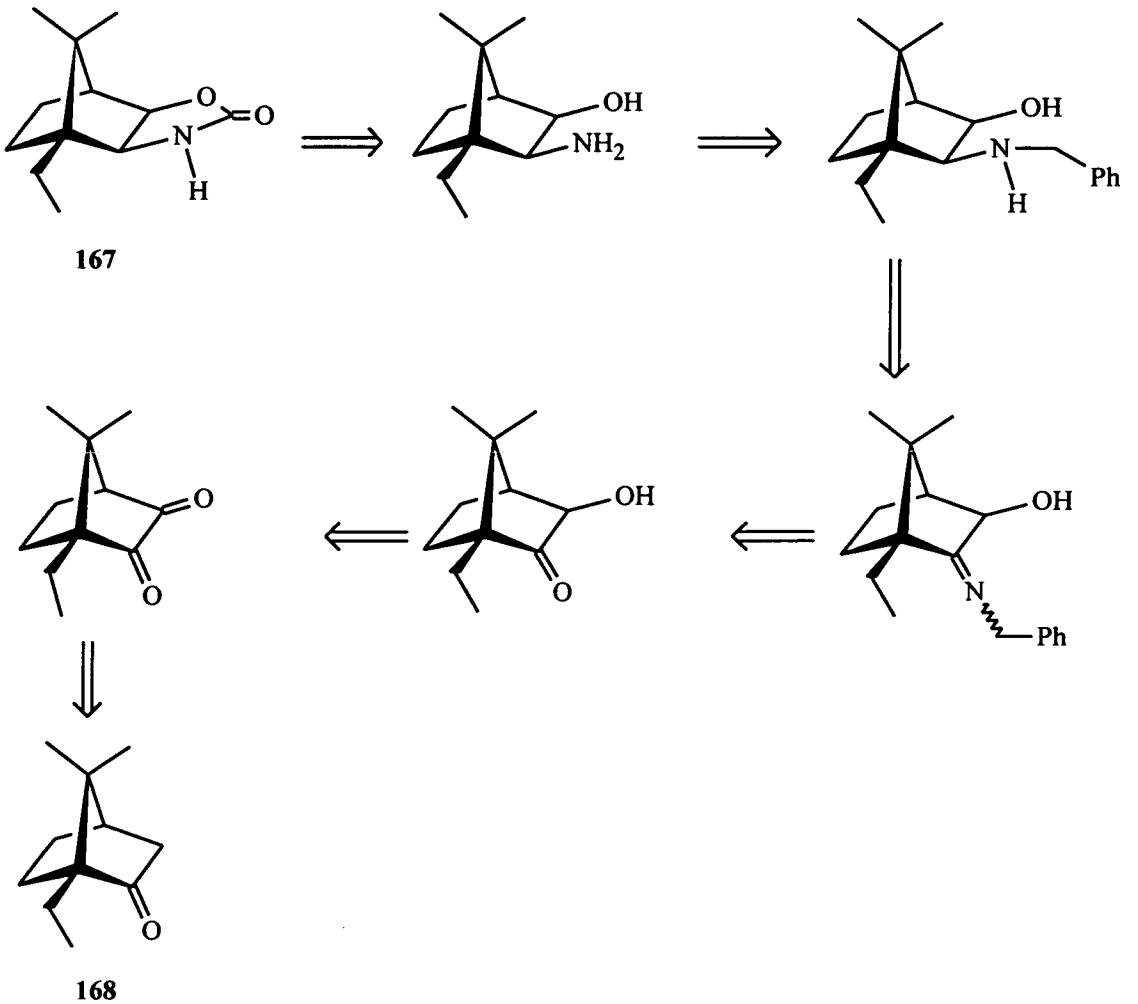
In order to improve the performance in these reactions, it was realised that the methyl group at C-7 needed to be exchanged for a larger functionality. For this reason, it was decided to replace the methyl group by an ethyl group, a change that gives rise to the new oxazolidin-2-one **167** (Figure 31).



167

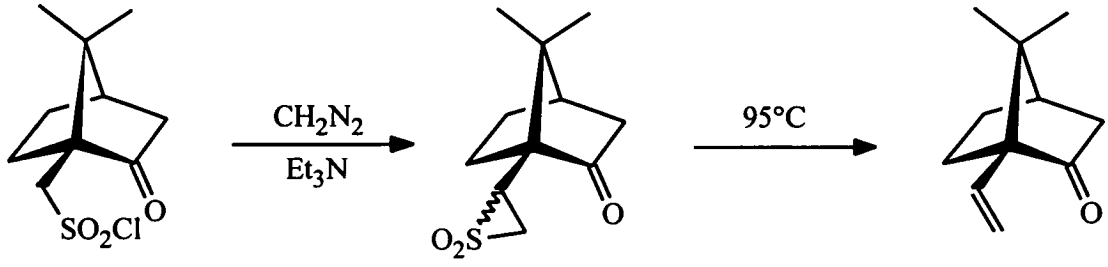
Figure 31

If one assumes that **167** can be synthesised in a similar manner to **131**, retro-synthetic analysis points to 10-methylcamphor **168** as the desired starting material (Scheme 72). Unfortunately 10-methylcamphor **168**, unlike camphor **114**, is not



Scheme 72

commercially available. Moreover no suitable synthetic route was found in the literature that led directly to 10-methylcamphor **168**, although a synthetic method for the preparation of 1-vinylcamphor **169** from 10-camphorsulphonyl chloride **170** was known[89] (Scheme 73). This method relied upon treatment of 10-camphorsulphonyl

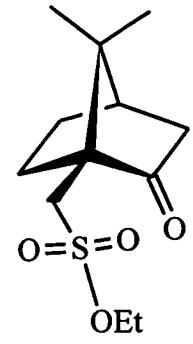


170 **171** **169**

Scheme 73

chloride **170** with diazomethane and triethylamine to form the episulphone **171**, which upon heating led to extrusion of SO_2 and the formation of 1-vinylcamphor **169**. It was then envisaged that hydrogenation of **169** would yield the desired 10-methylcamphor **168**.

The formation of the episulphone **171** was initially attempted using diazomethane generated from Diazald® (*N*-methyl-*N*-nitroso-*p*-toluenesulphonamide) as outlined by Aldrich for use with their Diazald® kit. After purification a colourless crystalline product was furnished in low yield (28%). Examination of this product by high field ^{13}C NMR spectroscopy showed the presence of twelve carbon signals and not eleven as expected for the episulphone **171**. Closer examination of the spectrum suggested that the product was the ethyl sulphonate ester **172** (Figure 32).

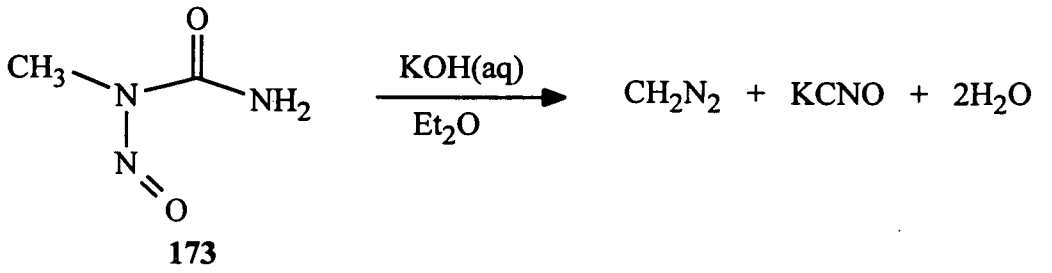


172

Figure 32

This was proven to be the case when the optical rotation value of the product was found to be +46.2° (c = 2.35, $CHCl_3$), which was consistent with the known value for the sulphonate ester **172** ($[\alpha]_D^{21}$ = +43.3° (c = 2.5, $CHCl_3$)[90]. On the basis of this evidence, it is evident that the formation of **172** arose from generation of diazomethane in an ethanolic potassium hydroxide solution. When the diazomethane was distilled out, apparently some ethanol was also carried over, and on treatment with triethylamine, reacted with the sulphonyl chloride **170** to give **172**. In order to overcome this problem and to generate an ethanol-free diazomethane solution, Aldrich have suggested the use of 2-(2-ethoxyethoxy)ethanol as the solvent. This modified method was tried, but gave an unidentified product, that from its ^{13}C NMR spectrum appeared to contain an extra methyl group, *i.e.* it was not the desired episulphone **171**.

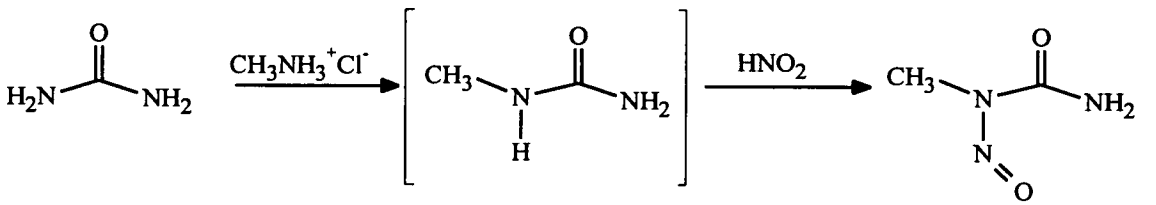
The problems associated with diazomethane generation were eventually overcome by adopting the method of Fischer and Opitz[89] in which nitrosomethylurea **173** is treated with potassium hydroxide (Scheme 74). Since nitrosomethylurea is not



173

Scheme 74

commercially available due to its known carcinogenic properties it was synthesised according to the method of Arndt[91]. Thus treatment of urea **174** with methylamine hydrochloride followed by addition of sodium nitrite gave the methylurea nitrite species **175**, which was then poured into cold sulphuric acid to liberate methylnitrosourea **173** in an acceptable yield (30%) (Scheme 75).



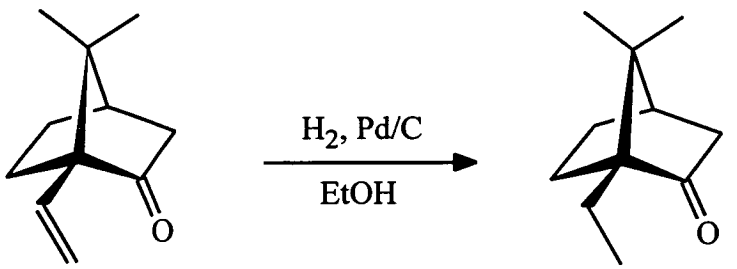
174 **175** **173**

Scheme 75

The synthesis of the episulphone was then attempted according to the method of Fischer and Opitz[89]. Their procedure worked as described and after recrystallisation from methanol at -20°C, a colourless crystalline solid was obtained, but TLC indicated that the product was in fact a mixture of two components. The episulphone **171** is known to be unstable, and even at room temperature, it is reported to decompose[89]. Due to this inherent lack of stability, it was decided to carry on with the synthesis without further purification, and for the next stage, the thermal decomposition of **171** was carried out using the crude material. Upon heating, gas

was seen to be evolved, as reported by Fischer and Opitz, following which the crude product was distilled to furnish the desired 1-vinylcamphor **169** as a waxy solid in good yield (60% based on camphorsulphonyl chloride **170**).

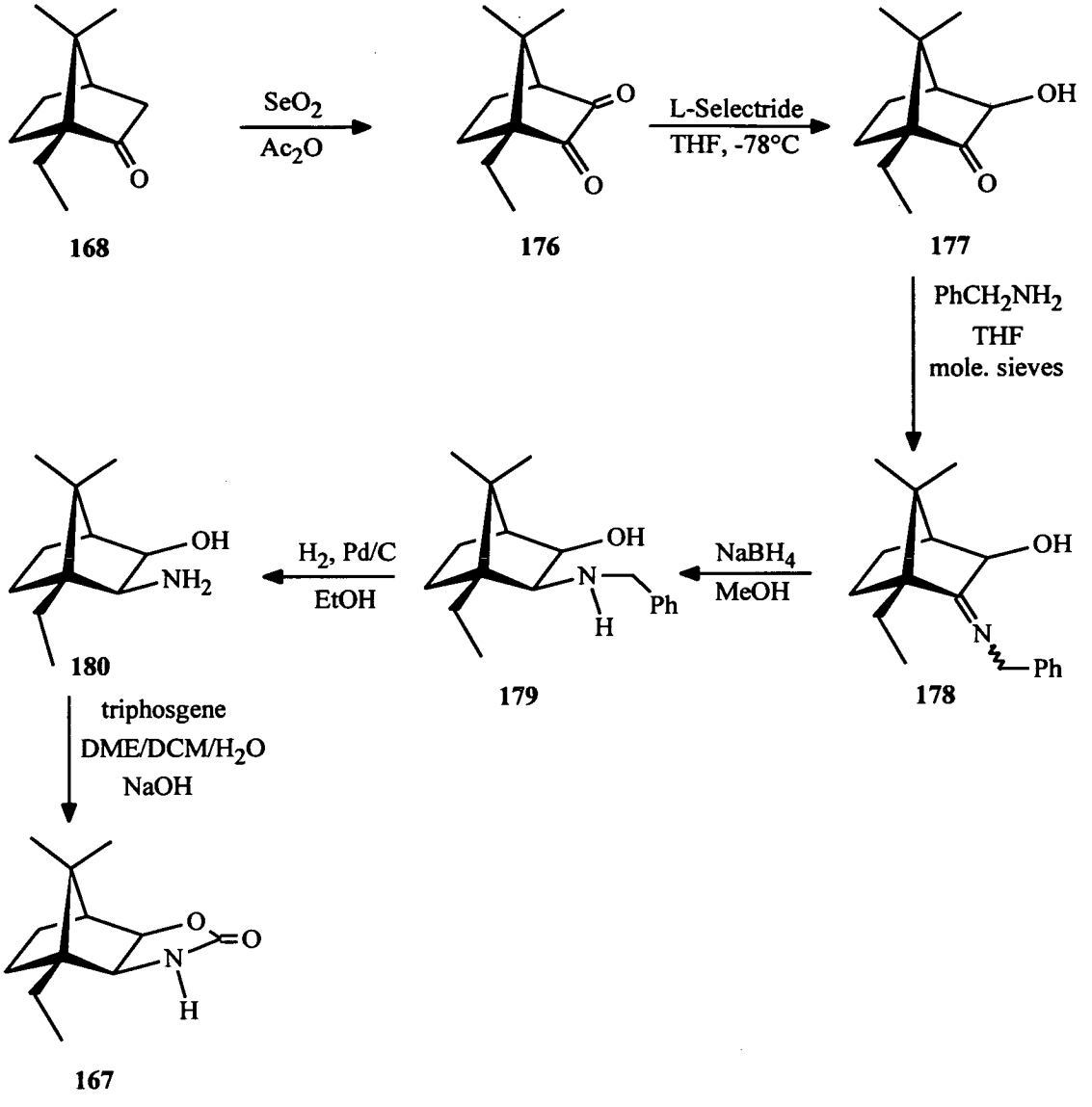
Hydrogenation of 1-vinylcamphor **169** in the presence of 10% Pd/C as catalyst in ethanol gave the desired 10-methylcamphor **168** in excellent yield (93%) (Scheme 76). FT IR analysis of the product showed there to be an absence of any C=C signal. Also comparison of the ^{13}C NMR spectrum of **168** with that of 1-vinylcamphor **169** showed there to be no olefinic signals, and the appearance of CH_2 and CH_3 signals resulting from reduction of the vinyl functionality.



169 **168**

Scheme 76

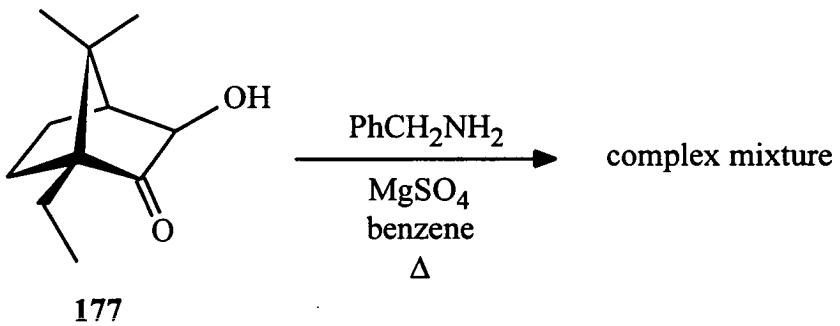
For the synthesis of **167**, the strategy adopted for auxiliary **131** was followed (section 2.1), involving initial formation of quinone **176**, followed by its stereoselective reduction to the keto alcohol **177**. The next stage was to be the synthesis of the imine **178** followed by its stereoselective reduction to the amino alcohol **179**, hydrogenation of which would hopefully yield the deprotected amino alcohol **180**. For the final stage in the synthesis of oxazolidin-2-one **167** outlined in Scheme 77 cyclisation would be effected with triphosgene.



Scheme 77

Thus, treatment of 10-methylcamphor **168** with selenium dioxide in acetic anhydride under reflux afforded 10-methylcamphorquinone **176** in a rather disappointing yield (51%). The amount of selenium dioxide used and the length of reaction time were both varied in an attempt to improve the yield, but the reaction could not be made to progress with any more than *ca.* 50% conversion, although unreacted starting material was recovered for recycling.

The stereoselective reduction of the quinone **176** caused no problems and treatment with L-Selectride® at -78°C in THF gave the desired keto alcohol in excellent yield (91%). Conversion of the latter into imine **178** was initially tried under the same conditions as used previously (the reader is directed to Chapter 2 section 2.1), but treatment with benzylamine and 4Å molecular sieves in THF resulted in no reaction, even after a long period of time. In an attempt to overcome this problem, the reaction was carried out in boiling benzene with magnesium sulphate present to remove the water (Scheme 78). Unfortunately the product obtained was seen by TLC to be a mixture of at least six components, so this method was also discarded.

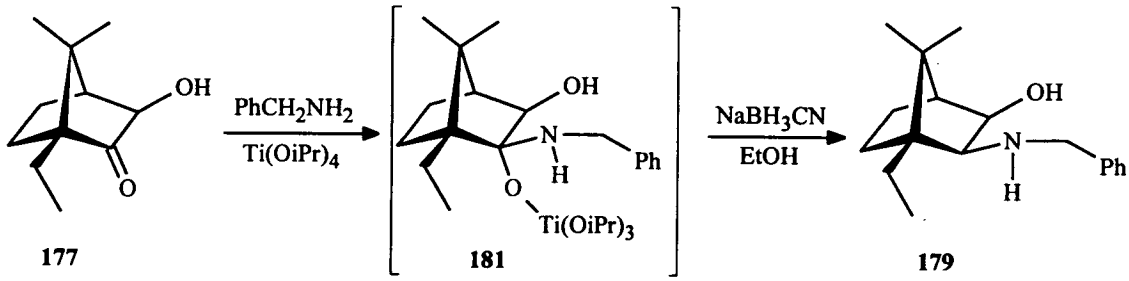


177

Scheme 78

In consequence it was decided to investigate the possibility of forming the amino alcohol **179** directly from the keto alcohol **177**, *i.e.* without going *via* the imine **178**. Mattson *et al*[92] had reported the direct reductive alkylation of amines using titanium(IV)isopropoxide and sodium cyanoborohydride. Their general procedure was followed, and the keto alcohol **177** was stirred with a mixture of benzylamine and titanium(IV)isopropoxide (Scheme 79) until examination of the reaction mixture

by IR spectroscopy showed an absence of any ketone band, which indicated the formation of the stable titanium complex **181** with the loss of isopropylalcohol.



177 **181** **179**

Scheme 79

Dilution of the complex **181** with ethanol, and subsequent treatment with sodium cyanoborohydride (Scheme 79) furnished the desired amino alcohol **179** in reasonable yield (45%). The stereochemistry of the amino alcohol **179** was established by high field ^{1}H NMR spectroscopy. The two doublets present a δ 3.64 and 2.85ppm, arising from the protons geminal to the hydroxy and amino functionalities respectively, both had coupling constants of 7.2Hz. Also, the doublet at δ 1.79ppm due to the bridgehead proton on the bornane ring had a coupling constant of 4.7Hz. All of these couplings are virtually identical to those found for the amino alcohol **136** (Chapter 2), indicating that the newly formed amino alcohol **179** also possessed an *exo, exo* arrangement.

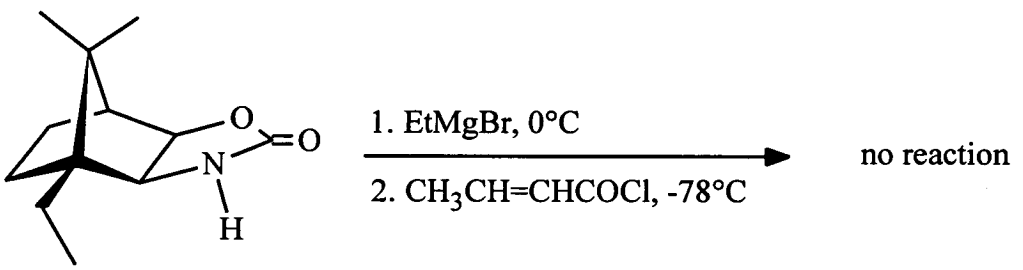
In the next stage, removal of the benzyl protecting group was brought about by hydrogenation of the amino alcohol **179** with 10% Pd/C in ethanol to afford the deprotected amino alcohol **180** in excellent yield (93%).

The final stage of cyclisation to the oxazolidin-2-one auxiliary **167** was achieved using triphosgene in a modified version of the method outlined by Pridgen and Prol[81]. Once again, the procedure progressed without problem and the novel

oxazolidin-2-one **167** was furnished in excellent yield (92%). The overall yield for the synthesis of the auxiliary **167** in seven steps from camphorsulphonyl chloride **170** was only 9%, but despite the poor yield, sufficient material was obtained to allow its synthetic utility in asymmetric operations to be evaluated.

3.2 Functionalisation of Auxiliary 167

The functionalisation of the auxiliary **167** was initially attempted using the same procedure adopted for oxazolidin-2-one **131** (section 2.2). The auxiliary **167** was treated with freshly generated ethylmagnesium bromide at 0°C in THF, cooled to -78°C, and then treated with freshly distilled crotonyl chloride (Scheme 80).

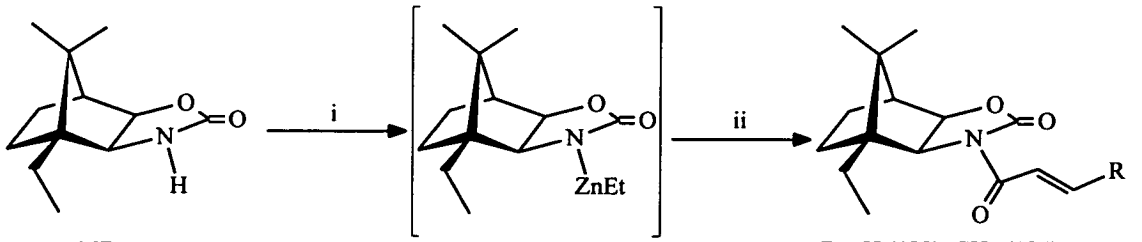


167

Scheme 80

After the mixture was allowed to warm to room temperature, TLC indicated that no reaction had occurred. The reaction mixture was then heated under reflux for *ca.* 24 hours, but even under these conditions, TLC still showed that no reaction had taken place and starting material was recovered in quantitative yield. Other workers in the same laboratory had also encountered similar problems using ethylmagnesium bromide for the functionalisation of the camphene-derived auxiliary Chiracamphox **75**. In order to overcome such problems a new functionalisation procedure, was

developed in which the Grignard reagent was replaced by diethylzinc[37]. Consequently, **167** was treated with diethylzinc at room temperature presumably to form the ethylzinc salt **182**, and the reaction mixture was cooled to -78°C, following which the acid chloride was added (Scheme 81). The reaction mixture was allowed to



167 **182** R = H (**183**), CH_3 (**184**)

(i) Et_2Zn, Et_2O

(ii) RCH=CHCOCl

Scheme 81

warm to room temperature and stirred overnight, after which time the desired *N*-acyl derivatives were isolated albeit in disappointing yield along with significant amounts of unreacted starting material (Table 7). Despite the poor yield of the unsaturated

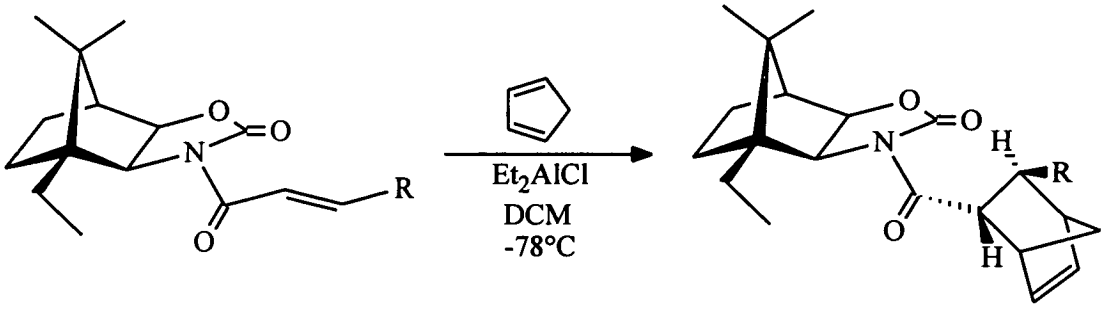
R	**Yield**
H **183**	31%
CH_3 **184**	38%

Table 7 : Functionalisation of the auxiliary **167** using diethylzinc.

carboxamides, enough material was formed to evaluate the potential of the auxiliary, and to determine whether sufficient steric bulk had been created on the front face of the auxiliary to improve the levels of asymmetric induction imparted, particularly in Diels-Alder reactions.

3.3 Asymmetric Diels-Alder Reactions

As in section 2.3 the reactions carried out were those of the acrylate **183** and crotonate **184** derivatives with cyclopentadiene (Scheme 82).



R = H (**183**), CH_3 (**184**) R = H (**185**), CH_3 (**186**)

Scheme 82

The levels of diastereoselectivity achieved were determined by high field ^1H NMR spectroscopy from an examination the doublet of doublets between δ 5.5 and 6.5ppm, arising from the olefinic protons in the Diels-Alder cycloadducts. The outcomes of both reactions are summarised in Table 8. From which it can be seen

Dienophile	Temp.	Yield	*endo:exo*	*d.e.*
acrylate **183**	-78°C	92%	100 : 0	>95%
crotonate **184**	-78°C	91%	100 : 0	>95%

Table 8 : Diels-Alder reaction of the acrylate **183** and crotonate **184** with cyclopentadiene.

that the yields and *endo:exo* selectivity's are excellent, as is the diastereomeric excess for the crotonate product **186**, which is not unexpected. Most important is the reaction of the acrylate dienophile **183** for which the degree of selectivity is greatly improved by comparison with its methyl analogue **141** (section 2.3), resulting in a product **185** with a diastereomeric excess of greater than 95%. This increase in asymmetric induction imparted by **167** is clearly the result of the larger size of the ethyl group compared to that of the methyl. This increased steric bulk means that there is far greater steric repulsion between the auxiliary and its adjacent *N*-acyl moiety such that the s-*trans* conformation of the dienophile in the chelated transition state is unfavourable (Figure 33). In essence, it is the overwhelming preference for

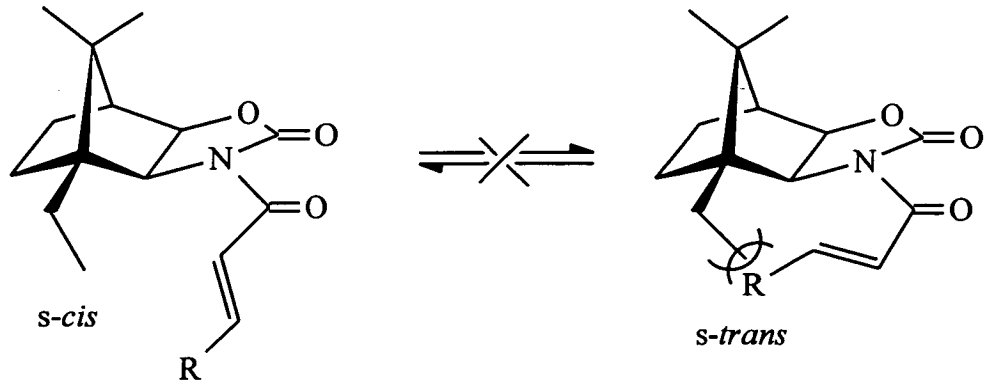


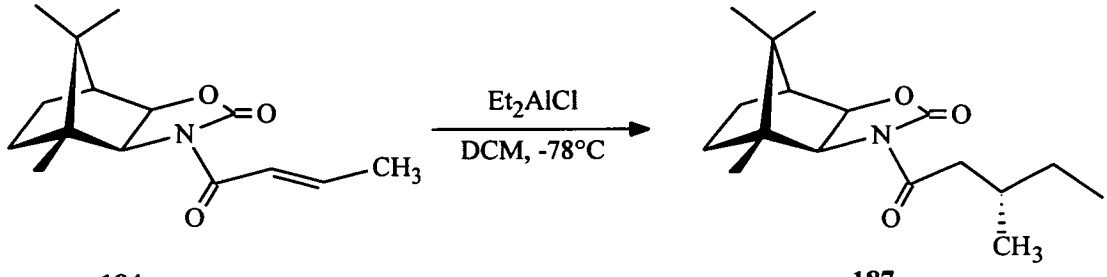
Figure 33

the s-*cis* conformation that leads to the greater degree of stereoselectivity observed in the reaction.

The stereochemistry, although not assigned is likely to be as that shown, *i.e.* resulting from a transition state identical to that observed for the methyl analogue (see Chapter 2, section 2.3).

3.4 Asymmetric 1,4-Conjugate Addition Reactions

In this context, the only reaction to be investigated was the 1,4-conjugate addition reaction between the crotonate derivative **184** and diethylaluminium chloride (Scheme 83). As in the case of the methyl analogue, the reaction proceeded in



184 **187**

Scheme 83

virtually quantitative yield (97%), although examination of the C-H signals arising from the newly formed chiral centre in the high field ^{13}C NMR spectrum of the addition product **187** showed that it had been formed with a diastereomeric excess of only 60%. This level of selectivity is still relatively poor, but it is far greater than that produced by the methyl auxiliary (section 2.4). This increased level of asymmetric induction is clearly due to the site of reaction now being much closer to the bulk of the auxiliary, although the size of the ethyl group is insufficient to raise the level of stereoselectivity to a respectable amount (Figure 34).

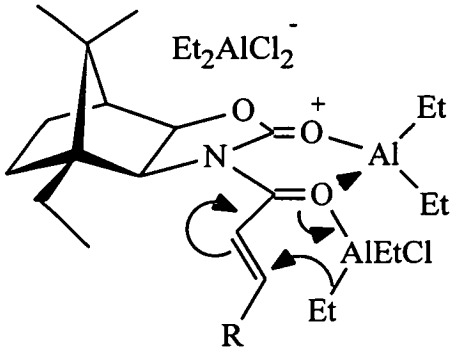


Figure 34

As with the methyl auxiliary **131** (section 2.4) the stereochemistry was assigned as (*S*) at the new β chiral centre, though as before this could not be proven due to lack of material.

3.5 Conclusion

The aim in this section of work was to improve the performance of the camphor-derived auxiliary **131** in the Diels-Alder reaction of the more sterically demanding acrylate dienophile and in the 1,4-conjugate addition reaction of the corresponding crotonate derivative. This aim was realised by increasing the steric bulk on the front

face of the bornane ring by replacing the methyl group with an ethyl group to form the new oxazolidin-2-one auxiliary **167**, which was synthesised from 10-methylcamphor in five steps.

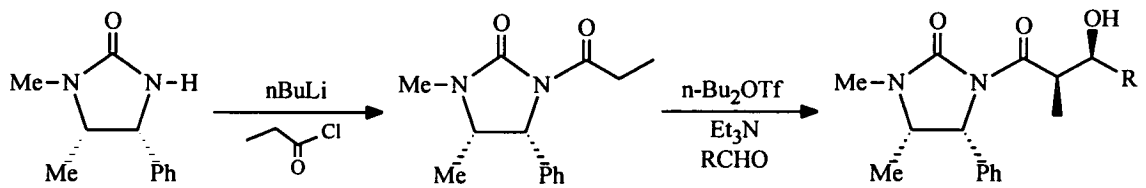
This modification dramatically improved the levels of asymmetric induction imparted by the auxiliary. The diastereomeric excess in the Diels-Alder reaction of the acrylate **183** with cyclopentadiene was >95% compared to only 80% for the corresponding reaction with the methyl analogue **141** (section 2.3). Likewise, for the 1,4-conjugate addition reaction between the crotonate **184** and Et_2AlCl, the diastereomeric excess of the adduct obtained was 60%, which is much greater than the 30% yielded with the crotonate **142** bearing only a methyl substituent (section 2.4).

Overall the new auxiliary **167** performed well, but unfortunately, the difficulties experienced in synthesis resulted in only small amounts being furnished. Consequently large scale reactions using **167** are unlikely to be viable unless an improved synthetic route can be found.

Chapter 4

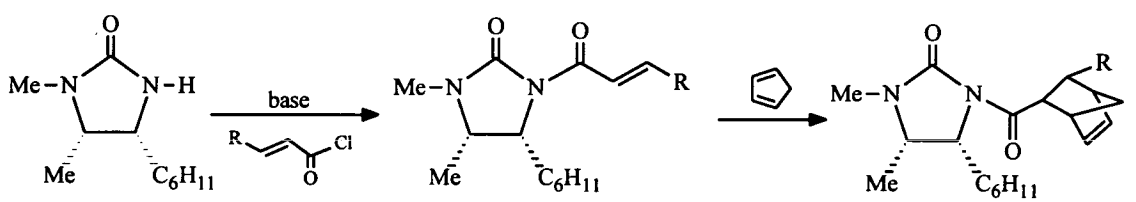
Attempted Synthesis of a New Imidazolidin-2-one Chiral Auxiliary and of a New Diazaborolidine Chiral Catalyst

Recent work carried out by both Davies (see Introduction section 2.1.7) and Roos has demonstrated the effectiveness of imidazolidin-2-one auxiliaries in various asymmetric transformations[42,93-95]. The ephedrine-derived auxiliaries **188** and **189** have been shown to exhibit excellent levels of asymmetric induction in aldol (Scheme 84) and Diels-Alder (Scheme 85) reactions respectively. Diastereomeric



188

Scheme 84

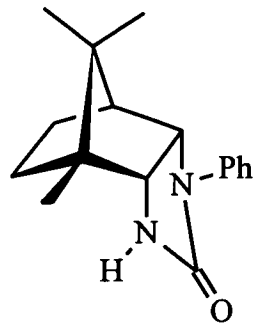


189

Scheme 85

excesses greater than 99% were reported for both reaction types, and in the Diels-Alder reaction, excellent levels of *endo:exo* selectivity were also obtained[93-95].

Encouraged by the excellent results obtained by Roos, it was decided to investigate the possibility of synthesising a camphor-derived imidazolidin-2-one auxiliary; the one chosen to be studied was **190** (Figure 35) similar to the

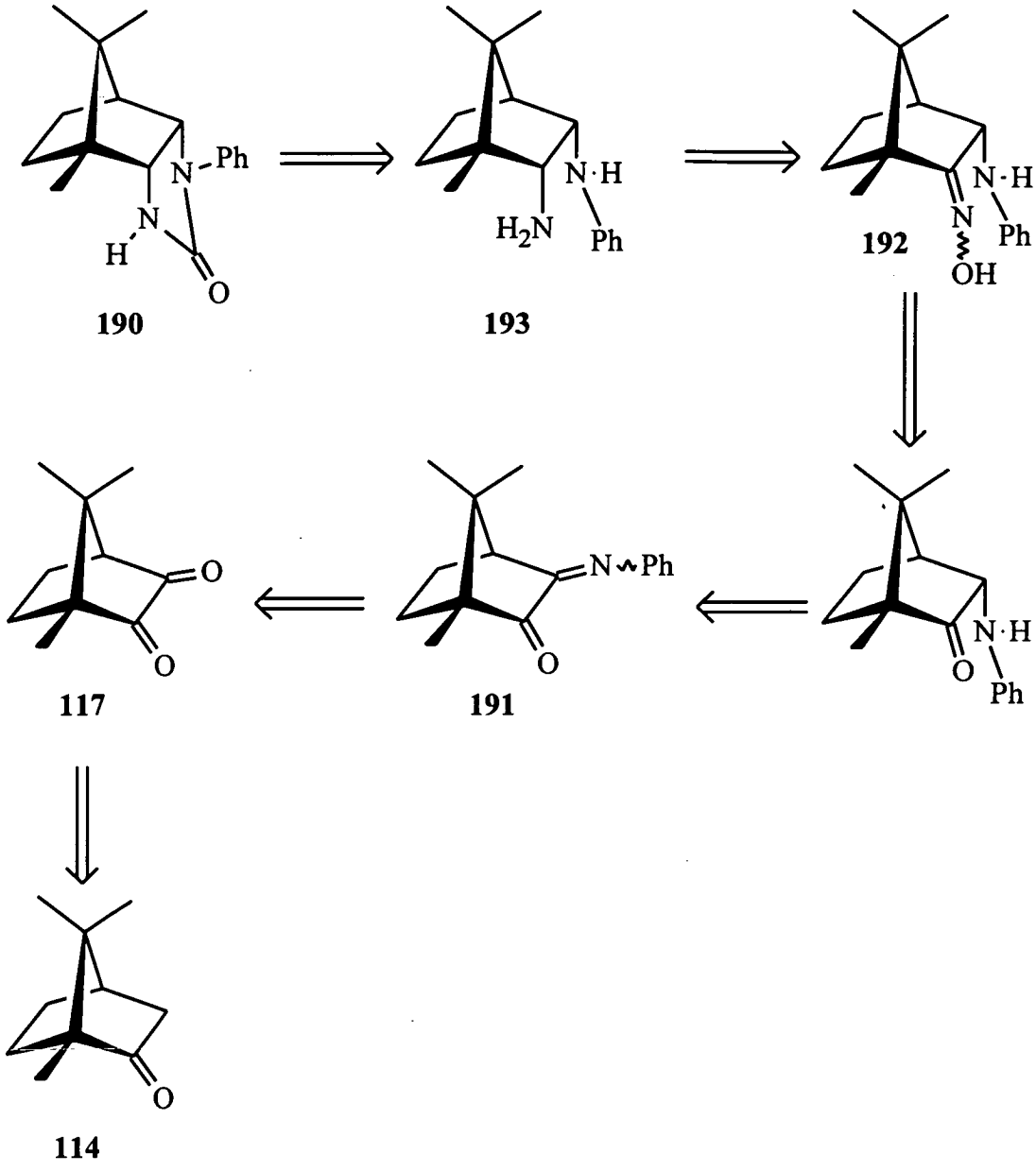


190

Figure 35

transfigomer **110** discussed in Chapter 1. It was envisaged that the methyl group on the front face of the bornane skeleton would help to impart greater steric interaction between the auxiliary bulk and the actual site of reaction, and hopefully, lead to good levels of diastereoselectivity in various reactions.

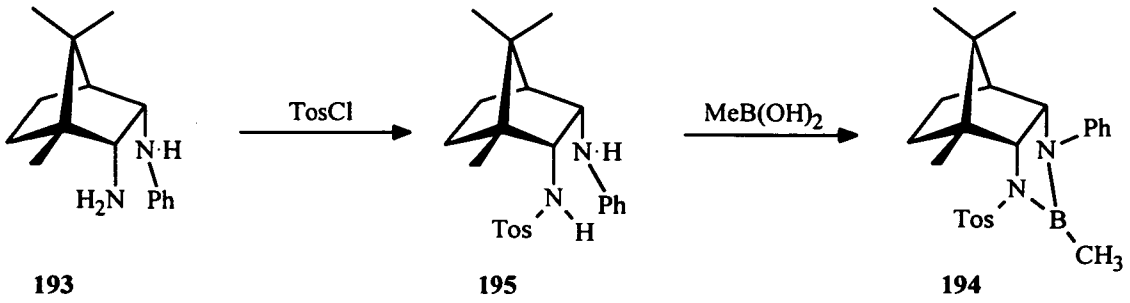
Retro-synthetic analysis of the chosen imidazolidinone **190** is shown in Scheme 86, from which it is evident that a number of key intermediates needed to be synthesised, starting from (1*R*)-camphor **114**. Essentially the synthesis required two



Scheme 86

vital transformations, *viz.* the stereoselective reductions of the imine **191** and of the oxime **192**. The key intermediate in the whole scheme is the *endo, endo* bisamino compound **193** which needs to be synthesised with the desired orientations of the two amino groups in order to be cyclised to the auxiliary **190** by treatment with triphosgene. It should also be noted that the bisamino compound **193** could lead to

the formation of a new diazaborolidine **194** (Scheme 87), which offers possible use as a chiral catalyst in asymmetric Diels-Alder reactions (see Chapter 6). It was

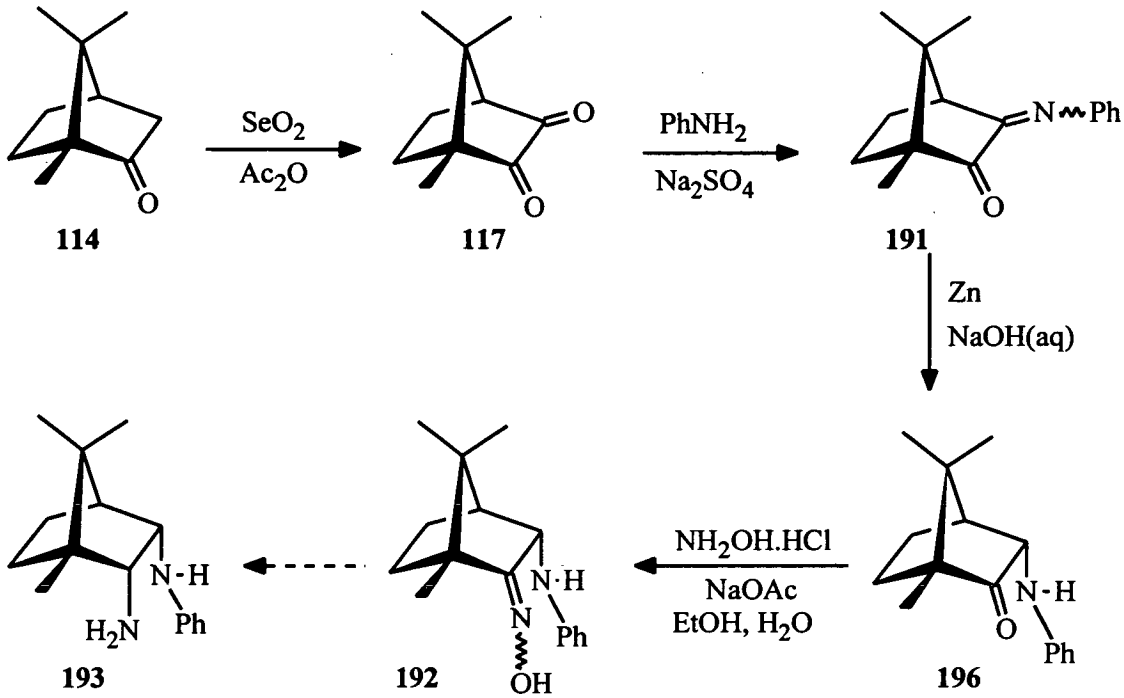


193 **195** **194**

Scheme 87

envisaged that **193** could be treated with *p*-toluenesulphonyl chloride to yield **195**, which in turn could be treated with methylboronic acid to afford the diazaborolidine **194**. It was hoped that if **194** could be obtained the presence of the tosyl and phenyl groups would allow it to act as an efficient catalyst (see Chapter 6 section 6.4 for explanation).

Thus, the main target in this section of work was the synthesis of the bisamino-compound **193**. The route chosen for the synthesis is outlined in Scheme 88.



Scheme 88

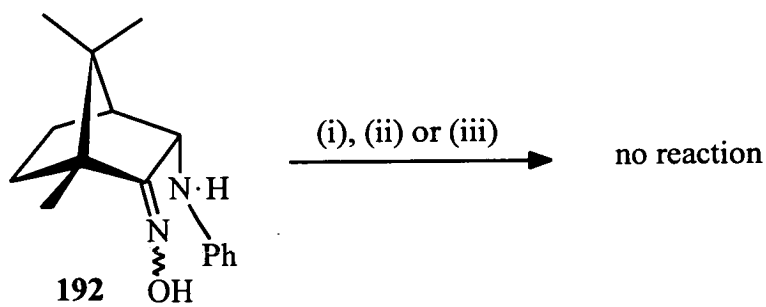
As in the preceding three chapters, the initial step in the synthesis of **190** involved oxidation of (1*R*)-camphor **114** with selenium dioxide in acetic anhydride to furnish camphorquinone **117** in excellent yield (96%).

For the formation of *N*-phenyliminocamphor **191**, the method of Forster and Thornley[96] was followed, whereby equimolar quantities of aniline and camphorquinone **117** are mixed together and then treated with an excess of anhydrous sodium sulphate. The mixture is then heated to *ca.* 100°C for 24 hours. After work-up and recrystalisation, the desired *N*-phenyliminocamphor **191** is afforded in reasonable yield (51%).

Forster and Thornley[96] also reported on the reduction of the imine **191**, but due to the age of the paper (1909), the stereochemistry of the resulting amino ketone **196** was not assigned. In order to clarify the outcome of their work, imine **191** was treated

as reported with zinc dust and sodium hydroxide solution to furnish a pale yellow solid in excellent yield (96%), analysis of which by IR spectroscopy showed the absence of any C=N group, but the retention of the C=O signal and the appearance of an N-H function. The high field ^{1}H NMR spectrum of the product showed the presence of a distorted doublet of doublets at δ 3.98ppm, a pattern that is consistent with the presence of an *exo* proton at the 3-position of the ring *i.e.* the amino function has an *endo* orientation. Thus it is the desired amino ketone **196** that is produced.

Reaction of amino ketone **196** with hydroxylamine hydrochloride and anhydrous sodium acetate in aqueous ethanol furnished the expected oxime **192**, albeit in rather disappointing yield (44%). Moreover, its reduction also proved very problematic and a number of conditions had to be investigated before success was achieved.



192

(i) Zn, NaOH, EtOH, H_2O

(ii) $LiAlH_4$, Et_2O

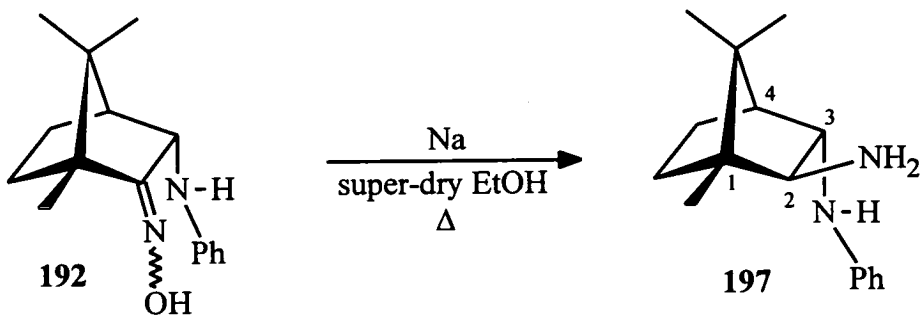
(iii) H_2 (30psi), 10% Pd/C, AcOH

Scheme 89

The first reduction conditions to be attempted were those that had proven to be successful for the reduction of the imine **191**, *i.e.* zinc dust and sodium hydroxide (Scheme 89 i). Unfortunately, even when the present reaction was allowed to proceed

for three days, no reaction was found to take place, and the starting material was recovered unchanged.

A further attempt at the reduction of oxime **192** was carried out using $LiAlH_4$ in dry ether (Scheme 89 ii), but as before, even after prolonged heating no reaction occurred. Even pressure hydrogenation of **192** in acetic acid with a Pd/C catalyst (Scheme 89 iii) failed, but it was eventually discovered that upon treatment of a boiling solution of the oxime **192** in super-dry ethanol with sodium (Scheme 90), reduction did actually occur and the product was furnished in good yield (76%).



192 **197**

Scheme 90

Analysis by IR spectroscopy verified the absence of a C=N group and the appearance of an NH_2 signal. However, examination of the compounds high field ^1H NMR spectrum showed the presence of a sharp singlet at δ 4.12ppm arising from the proton geminal to the new NH_2 group. The fact that this signal was a singlet indicated that the torsion angle between the proton at the 2-position and the one at the 3-position (known to be *exo*) must have been *ca.* 90°, which suggested that the new NH_2 group must have adopted an *exo* orientation, *i.e.* the wrong configuration, and that the compound formed had the *exo, endo* structure **197** (Figure 36). The relative stereochemistry of the two amino functions was proven conclusively by n.O.e

experiments, which showed that irradiation of the signal arising from the *ortho* protons on the phenyl group resulted in *ca.* 4% enhancement in the signal due to the *endo* proton at the 2-position (Figure 36). Final proof of the structure was achieved when an X-ray crystal structure of **197** was obtained (see Structure 4 in the appendix). The crystal structure clearly showed the *exo, endo* arrangement of the amino functions.

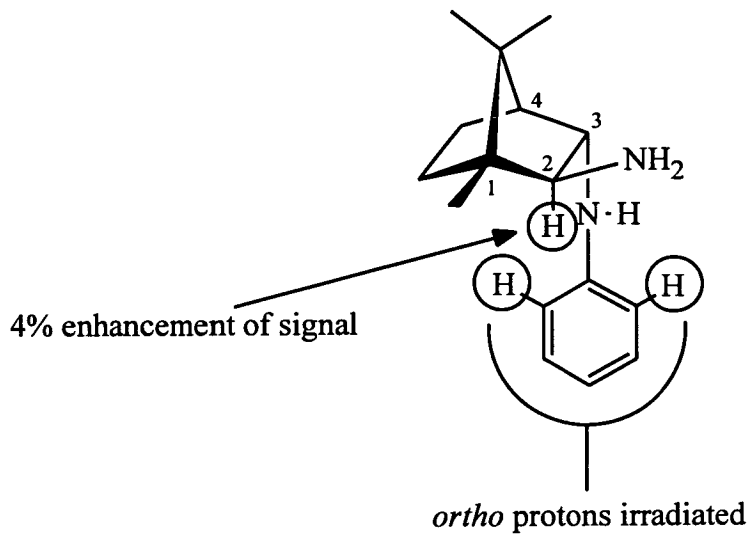


Figure 36

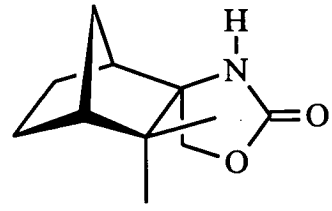
The failure to obtain even minor amounts of the *endo, endo* bisamino compound **193** *via.* reduction of **192** meant that the syntheses of the targeted imidazolidinone **190**, and consequently the diazaborolidine **194** could not be realised and regrettably the work ceased at this stage due to lack of time. However, for work at a future date it may be worthwhile attempting to carry out the reduction of **192** with L-Selectride® which may facilitate attack from the desired direction due to the steric blocking effect of the *endo-N*-phenyl grouping.

Chapter 5

Synthesis and Evaluation of a Novel Spiro-Oxazolidin-2-one 198 Derived From (-)-Isolongifolol 199

5.1 Synthesis of Oxazolidin-2-one 198

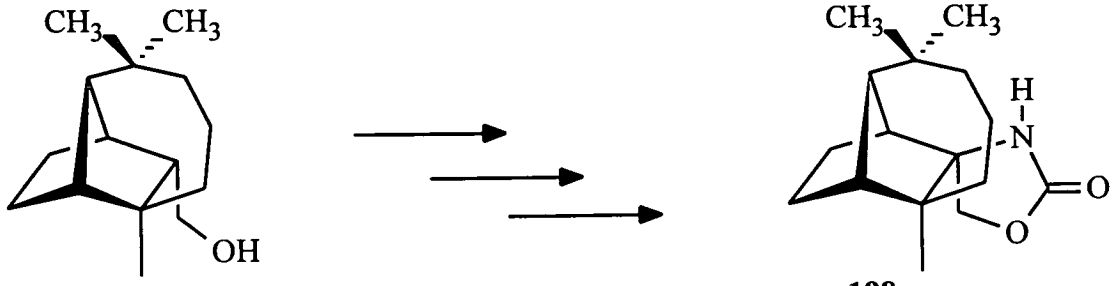
As described previously in the Introduction section 2.1.6 a number of efficient chiral auxiliaries have been synthesised from readily available chiral alcohols *via* a nitrene insertion process[32,33,36]. Banks *et al*[36,37] have reported that excellent levels of diastereoselectivity are imparted by the camphene-derived spiro-oxazolidin-2-one auxiliary Chiracamphox **75** (Figure 37).



75

Figure 37

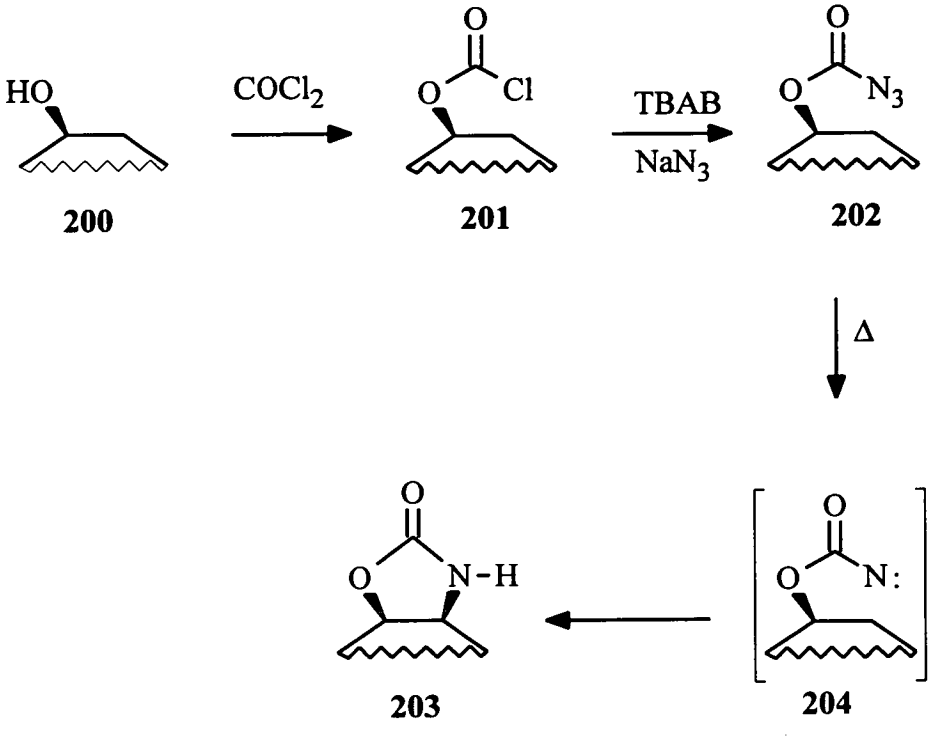
Encouraged by his results, it was decided to attempt the synthesis of a new, but structurally very similar, spiro-oxazolidin-2-one **198** starting from the commercially available and naturally occurring alcohol (-)-isolongifolol **199** (Scheme 91). In a



199 **198**

Scheme 91

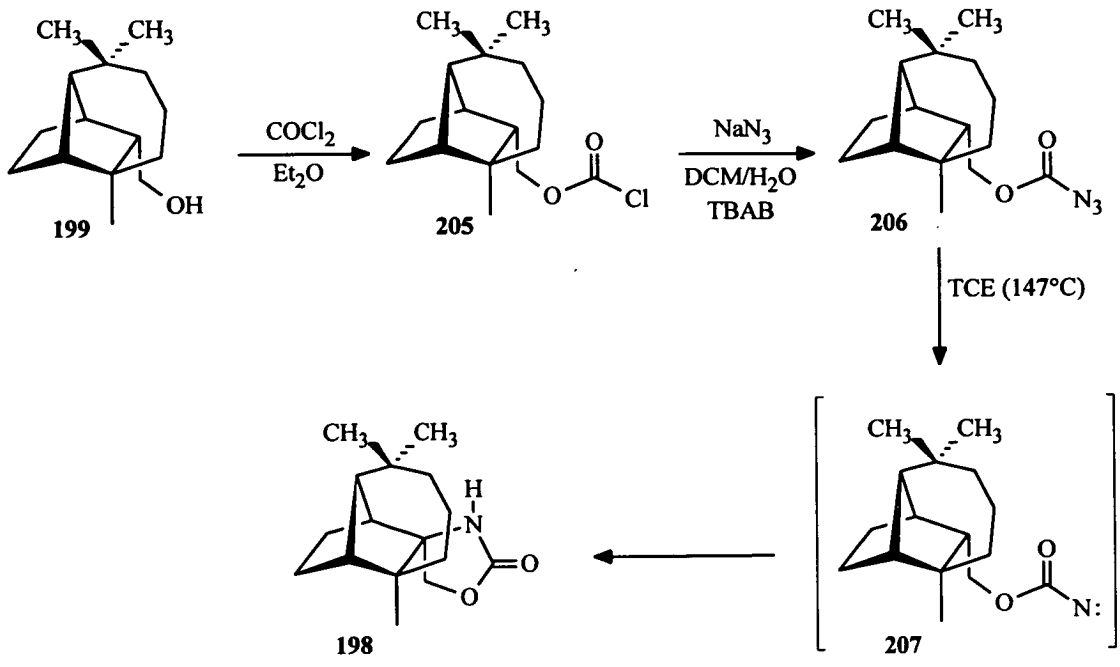
manner similar to that employed for the synthesis of Chiracamphox, it was hoped that the stereospecific nitrene insertion route outlined in Scheme 92 could be employed for the preparation of the desired oxazolidin-2-one **198**.



Scheme 92

Essentially, the route relies on the chosen chiral alcohol **200** first being converted into the corresponding chloroformate **201** and then into the azidoformate **202**. The azidoformate is then thermally decomposed to give the oxazolidin-2-one **203**, *via.* a stereospecific insertion of the generated nitrene **204** into a C-H bond.

The synthesis of the new oxazolidin-2-one **198** is outlined in Scheme 93 and is commenced by treatment of an ethereal solution of (-)-isolongifolol **199** with



Scheme 93

phosgene to furnish the desired chloroformate **205** in virtually quantitative yield (99%). The chloroformate **205** was then treated with sodium azide in a two phase reaction employing tetrabutylammonium bromide (TBAB) as a phase transfer catalyst. This reaction also proceeded very easily and the azidoformate **206** was obtained in very good yield (82%).

The final stage in the synthesis involved the thermal decomposition of the azidoformate **206** to generate the nitrene intermediate **207**, which was expected to insert intramolecularly into the adjacent C-H bond to form the spiro-oxazolidin-2-one **198**. It was already established that the best method for producing nitrenes from azidoformates was by solution thermolysis in 1,1,2,2-tetrachloroethane (TCE). The TCE was chosen as the solvent for two main reasons: firstly its boiling point was high enough (147°C) to ensure smooth decomposition of the azidoformate, and secondly, it has been reported[97] that polychlorinated solvents and especially those

with two geminal chlorine atoms present are inert to nitrene attack. However, the major drawback to TCE is that it is extremely toxic and great care is needed at all times in its use.

The thermolysis was carried out by using a 1% solution of the azidoformate **206** in boiling TCE in order to minimise intermolecular nitrene insertions. Decomposition of the azidoformate occurred quickly and examination of the crude mixture after 30 minutes by TLC showed that the reaction was complete, and significantly, the presence of only one insertion product, *cf.* the synthesis of Chirabornox **65** in which four different insertion products were isolated. After work-up and recrystallisation from xylene, the desired oxazolidin-2-one **198** was isolated in very good yield (62%).

The isolation of only one insertion product, *viz.* **198** in this particular instance is not surprising when the electronic state of the nitrene is considered together with the spacial arrangement of the C-H bonds. Nitrenes are highly reactive monovalent nitrogen species with two non-bonding electrons present. If the electrons are paired, the nitrene is in the singlet state and if they are unpaired, it is in the triplet state. The nitrene **207** generated from the decomposition of **206** obviously reacted in its singlet state, since no evidence was found for the presence of hydrogen abstraction products arising from a triplet nitrene. Moreover, singlet nitrenes prefer to insert into C-H bonds with the preference of tertiary > secondary > primary[98]. Thus, the nitrene **207** had inserted into the nearest tertiary C-H bond to form a 5-membered ring in preference to all the nearby secondary CH_2 groups which offered rings with a minimum size of seven.

The synthesis of the spiro-oxazolidin-2-one **198** was achieved in 51% yield for the three synthetic steps starting from (-)-isolongifolol **199.** Its structure was confirmed by obtaining an X-ray structure which is shown if Figure 38 (see also Structure 5 in the appendix).

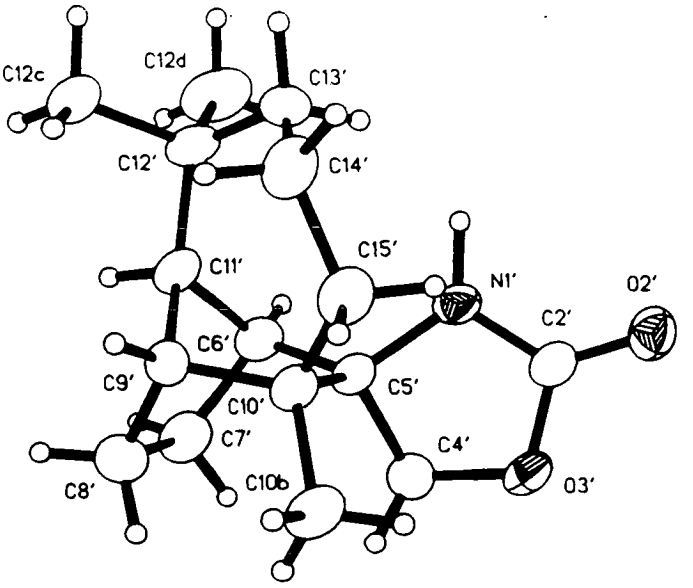
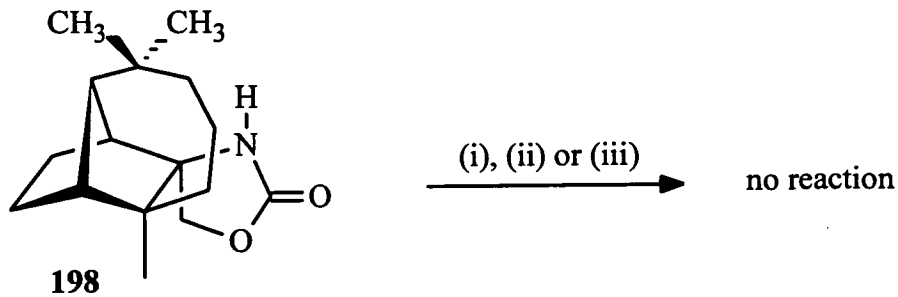


Figure 38

The X-ray structure clearly shows the spiro-centre at C5 and it is virtually identical to the structure of Chiracamphox **75**, apart from the obvious extra hydrocarbon chain from C12 to C10.

5.2 Attempted Functionalisation of the Oxazolidin-2-one 198

After the ease with which the oxazolidin-2-one **198** had been synthesised its functionalisation proved to be a different matter and a number of different and harsh conditions were investigated (Scheme 94).



198

(i) a. $ZnEt_2$, Et_2O
b. $CH_3CHCHCOCl$, -78°C

(ii) a. EtMgBr, THF, 0°C
b. $CH_3CHCHCOCl$, -78°C

(iii) a. nBuLi, THF, -78°C
b. $CH_3CHCHCOCl$, -78°C

Scheme 94

The first set of conditions employed involved the use of diethylzinc followed by the addition of crotonyl chloride (Scheme 94 i), which had proven to be successful with the auxiliary **167** derived from 10-methylcamphor as discussed in Chapter 3. Unfortunately, even after a prolonged period of heating, no reaction occurred and the starting material was recovered in quantitative yield.

The next method to be tried was the one that had worked successfully with the camphor-derived oxazolidin-2-one **131** in Chapter 2. Thus, the spiro-oxazolidin-2-one **198** was treated with freshly generated ethylmagnesium bromide, followed by crotonyl chloride (Scheme 94 ii), but as with the previous method no reaction was found to occur even after prolonged heating and the oxazolidin-2-one **198** was recovered unchanged in quantitative yield.

The final, and most severe conditions attempted to bring about functionalisation of **198** used butyllithium as the base, followed by once again the addition of crotonyl chloride (Scheme 94 iii). Unfortunately, no reaction was observed to take place and the oxazolidinone **198** was recovered in quantitative yield.

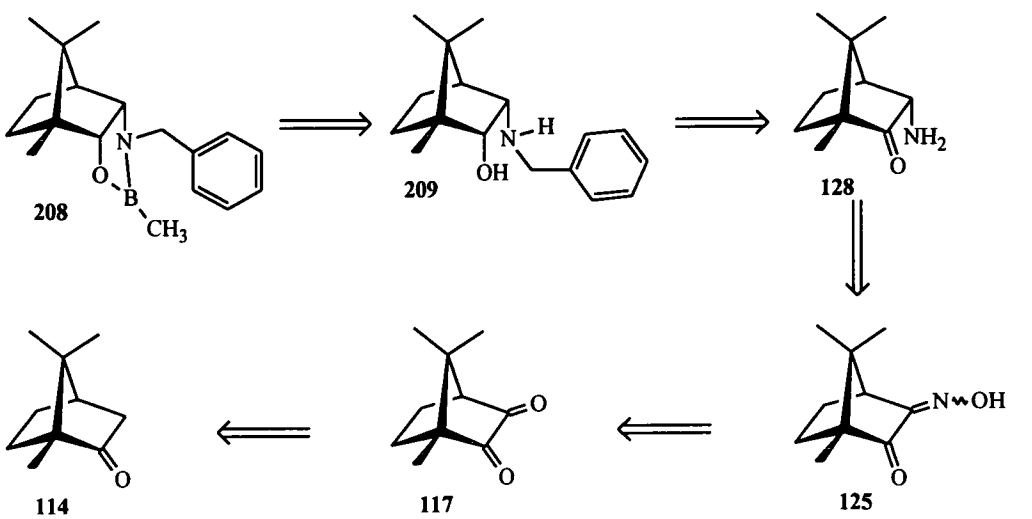
The inability of the spiro-oxazolidin-2-one **198** to be functionalised was surprising, but is presumably due to the nitrogen of the oxazolidinone being too sterically crowded to allow functionalisation. From examination of the X-ray structure of **198** it can be seen that the hydrocarbon chain from the bridging carbon C12 to the carbon atom C10, vicinal to the spiro-centre, is presumably the cause of this steric shielding due to its size and obvious flexibility. So unfortunately as the oxazolidinone could not be functionalised the work on this novel compound was ceased.

Chapter 6

Synthesis and Evaluation of Two Novel Oxazaborolidines 208 and 216

6.1 Synthesis of Oxazaborolidine 208

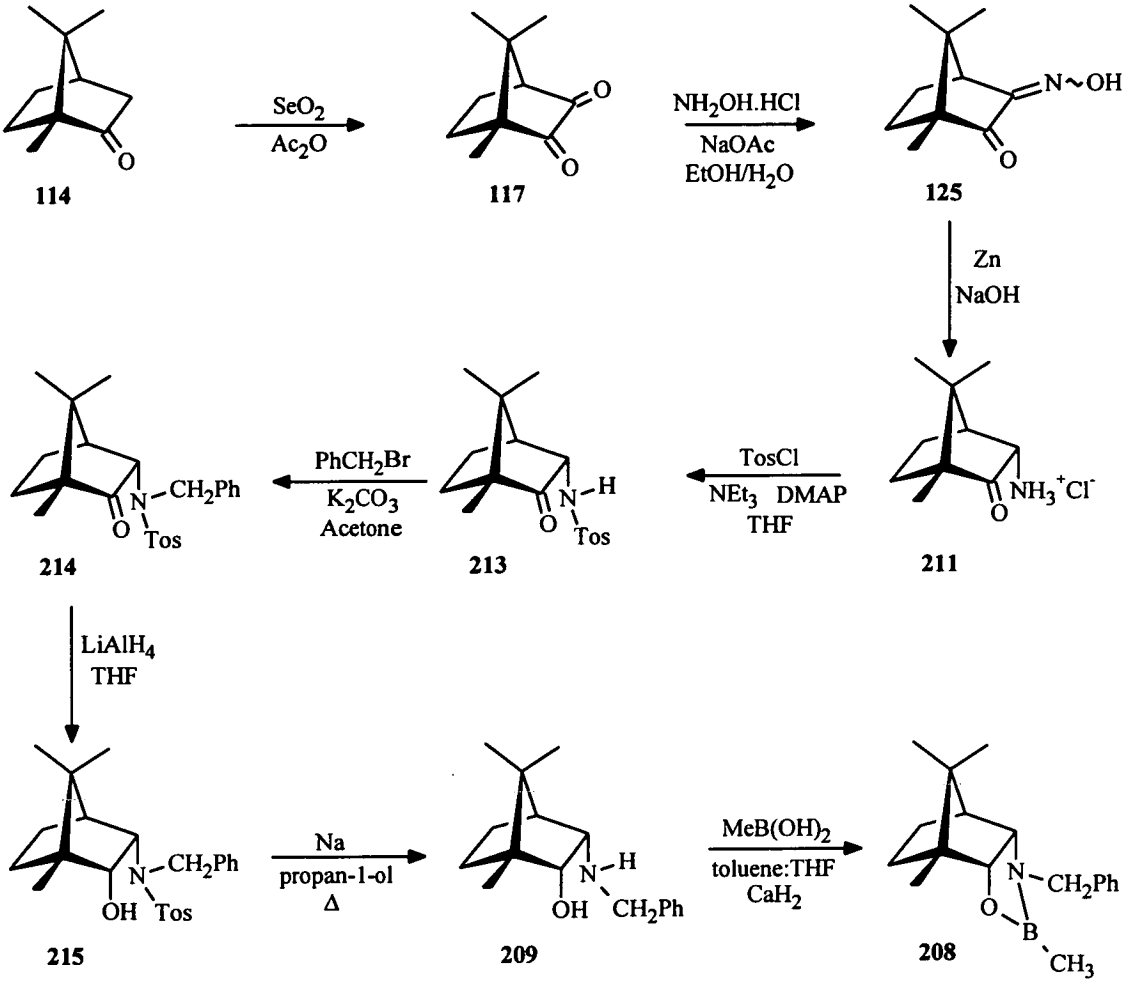
As mentioned in the introduction a great deal of attention has been focused recently on the development of new chiral catalysts, especially for use in asymmetric ketone reduction and Diels-Alder reactions. Examination of previously reported catalysts[48,50,51] show that they are derived principally from α,β-amino alcohols. Since α,β-amino alcohols derived from camphor **114** are well known,[99] it was decided to capitalise on this knowledge and investigate the possibility of preparing new camphor-based chiral catalysts. In order for the catalyst to perform in the Diels-Alder reaction a π-system would have to be incorporated into the molecule in order to facilitate π-stacking in the transition state of the reaction[100]. The initial system chosen to be studied was **208**, and a retro-synthetic analysis for this compound is shown in Scheme 95, giving rise to a number of key intermediates, *viz. endo, endo-*



Scheme 95

amino alcohol **209**, the *endo*-amino ketone **128**, 3-hydroximinocamphor **125** and eventually camphorquinone **117**.

The route chosen for the synthesis of oxazaborolidine **208** is outlined in Scheme 96 and involved conversion of (1*R*)-(+)-camphor **114** into camphorquinone **117** as



Scheme 96

described previously in Chapter 1. The oxime **125** was furnished in quantitative yield by treatment of camphorquinone **117** with hydroxylamine hydrochloride and sodium acetate in aqueous ethanol. The product was found to be approximately a 5:1 mixture of the *anti* and *syn* isomers (Figure 39), a finding that is consistent with the work

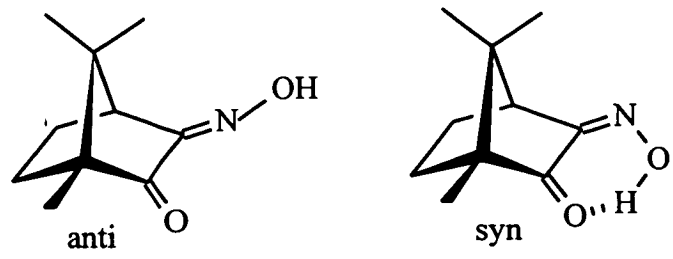
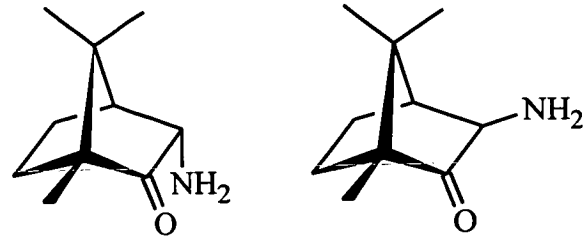


Figure 39

carried out by Cherry *et al*[78] who showed that the *anti* isomer is the more stable conformer and not the *syn* as might be expected from its intramolecular hydrogen bonding capabilities (see also Chapter 1).

The reduction of the oxime **125** was initially attempted by pressure hydrogenation (10psi)[77] over a 10% Pd/C catalyst, but unfortunately this method led to a mixture of *endo* and *exo* amino ketones **128** and **210**, respectively (Figure 40). When the pressure of hydrogen gas was increased to 50psi, the ratio of **128** to **210** was found to



128 **210**

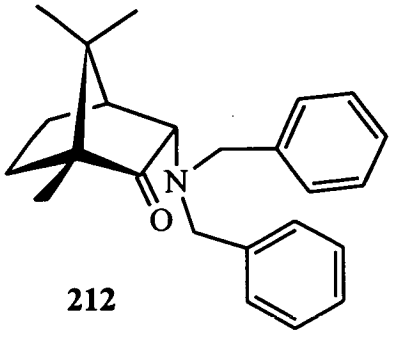
Figure 40

increase, but the pressure could not be raised sufficiently high enough to afford only the *endo* isomer **128**.

In order to circumvent this problem, an alternative reduction procedure was tried using zinc dust in sodium hydroxide solution. This procedure worked well and only the *endo*-amino ketone **128** was produced as a yellow solid, but the compound was found to be prone to polymerisation, and consequently was isolated as its

hydrochloride salt **211**. The stereochemistry of the amine hydrochloride **211** was ascertained from a consideration of its ^{1}H NMR spectrum. In particular, at δ 4.2 ppm a doublet of doublets was present due to the proton geminal to the $NH_3^+Cl^-$ group. Moreover, the main coupling constant from this signal was *ca.* 5.0Hz, which is consistent with an *exo* proton coupling to the bridgehead proton of the bornane ring[69].

It was thought that direct alkylation of the primary amino ketone **128** could not be achieved with benzylbromide since the secondary amino ketone produced would be a stronger base than the starting material **128** and lead to bis-alkylation with the formation of the tertiary amino-ketone **212** (Figure 41). This problem was avoided by

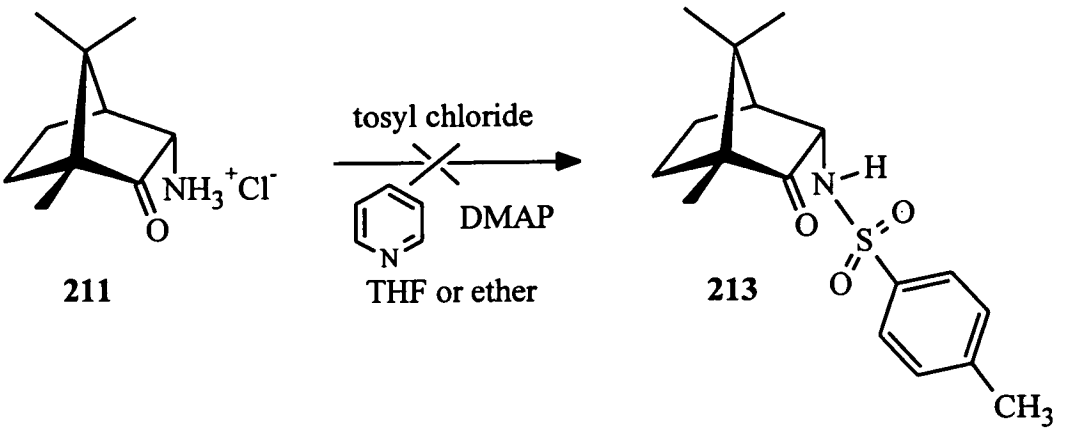


212

Figure 41

protection of the amine **128** with a tosyl group, on the grounds that only mono-substitution would occur due to the deactivation of the amine group by the adjacent δ-positive sulphur centre.

This protection step initially caused some problems in that when the reaction was carried out with tosyl chloride, pyridine and a catalytic amount of DMAP, no reaction was found to occur (Scheme 97). Consequently, a number of parameters



Scheme 97

were altered, including change of solvent from ether to THF without effect. Next, the base was switched from pyridine to triethylamine. This change proved to be the key, and after chromatography, tosyl-amino ketone **213** was isolated as a colourless solid in very high yield (92%).

By comparison, alkylation of **213** presented no problem and the desired tertiary amino ketone **214** was obtained in very high yield (84%) by treatment of **213** with benzylbromide and potassium carbonate in acetone. Subsequent treatment of the tertiary amino ketone **214** with $LiAlH_4$ in THF furnished the amino alcohol **215** in good yield (75%). The identity of the product was confirmed by the loss of the carbonyl absorbance in the IR spectrum and the appearance of a hydroxyl signal. The stereochemistry of **215** was confirmed to be the desired *endo, endo* configuration by the large 8.1Hz coupling present in the doublet of doublets at δ 4.0 ppm in the ^1H NMR spectrum (due to the proton geminal to the OH group coupling with the proton geminal to the amine group). Alternatively, if the reduction had produced the *exo* alcohol instead one would have expected the coupling constant to have been significantly smaller due to the torsion angle between the two protons being *ca* 120°.

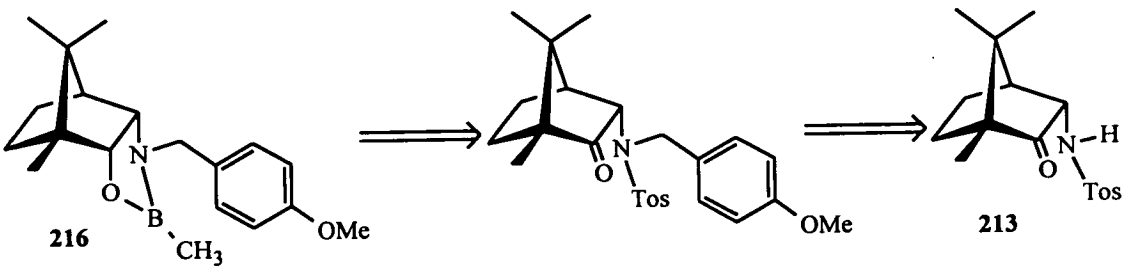
Removal of the tosyl protecting group was achieved with a dissolving metal reduction, involving the addition of an excess of sodium to a solution of **215** in dry propan-1-ol under reflux to yield the secondary amino alcohol **209** in high yield (75%). Clarification of the stereochemistry of **209** was obtained from its ^{1}H NMR spectrum which displayed a doublet of doublet of doublets at δ 3.2 ppm, arising from the proton geminal to the amino function coupling to the *exo* proton geminal to the OH (J = 9.1Hz), and a 4.4Hz coupling arising from the bridgehead proton on the bornane skeleton. All of these couplings are consistent with an *endo, endo* arrangement of the α, β-amino alcohol **209**.

The final stage of cyclisation of the amino alcohol **209** to the oxazaborolidine **208** was carried out using the method of Corey *et al*[55], whereby **209** was treated with methylboronic acid with azeotropic removal of water. The method worked well to give an almost quantitative yield of the oxazaborolidine **208**, which was identified from its ^{11}B NMR spectrum by a broad single peak at δ +34 ppm, consistent with the values reported by Corey for his catalysts[55]. The oxazaborolidine **208** was stored as a solution in methylene chloride under argon. The overall yield of **208** for the eight synthetic steps was a very pleasing 40%.

6.2 Synthesis of Oxazaborolidine 216

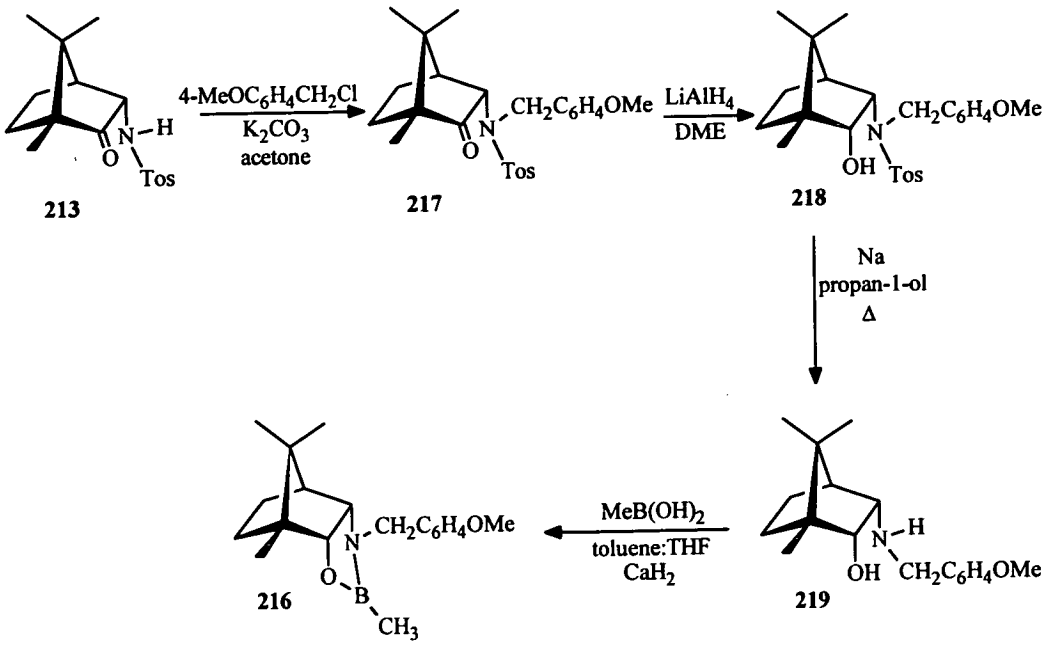
In order to explore electronic effects it was decided to synthesise a second oxazaborolidine **216** which contained a more π-basic aromatic system *viz.* a *p*-methoxyphenyl group. Retro-synthetic analysis for the desired compound **216**

(Scheme 98) showed that the *N*-tosylamino ketone **213** previously synthesised also served as the necessary starting material.



Scheme 98

The route chosen for the synthesis of **216** is shown in Scheme 99 and contained many similar steps to those used for the previous oxazaborolidine **208** (Scheme 96).



Scheme 99

Thus alkylation of **213** proceeded without problems, and on treatment with potassium carbonate and *p*-methoxybenzyl chloride furnished the tertiary amino ketone **217** in high yield (75%). The reduction of **217** with $LiAlH_4$ in THF proved to be very slow and led to a complex mixture of products. Consequently, the solvent

was changed from THF to DME which overcame the problem to yield the amino alcohol **218** in reasonable yield (60%). Once again the *endo* orientation of the hydroxyl function was confirmed from the ^{1}H NMR spectrum in which the signal due to the proton geminal to the OH appeared as a doublet (δ 3.98 ppm) with a splitting of 8Hz.

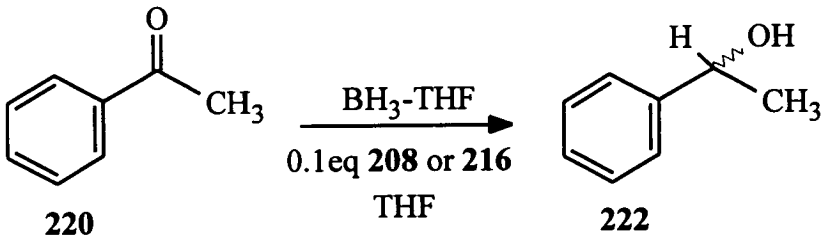
Deprotection of **218** was again successfully carried out by using addition of sodium to a boiling solution of **218** in propan-1-ol. The amino alcohol **219** was isolated in excellent yield, (84%), and as for **209** (section 6.1), the proton geminal to the amino function appeared as a doublet of doublet of doublets at δ 3.17 ppm in the ^{1}H NMR spectrum with 9.1 and 4.4Hz couplings consistent with an *endo, endo* conformation **219**.

The formation of the oxazaborolidine **216** in the ultimate step was carried out by reaction of **219** with methylboronic acid and azeotropic removal of water. The ^{11}B NMR spectrum of **216** showed a single broad peak at δ +34 ppm in keeping with values obtained previously for oxazaborolidines. The overall yield for the eight step synthesis from camphor to **216** was an acceptable 29%.

6.3 Oxazaborolidine Catalysed Ketone Reductions

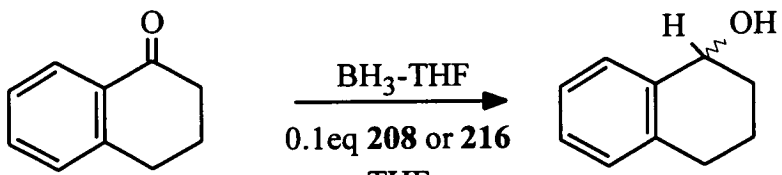
The potential of oxazaborolidines **208** and **216** as possible chiral catalysts was investigated firstly by examining the borane reduction of two unsymmetrical ketones, *viz.* acetophenone **220** and α-tetralone **221**. The conditions employed for the reductions were the same as those used by Corey[51], whereby 0.6 equivalents of borane-THF was added to a solution of the ketone and 0.1 equivalents of the catalyst

in THF at room temperature over several hours. The reductions of acetophenone **220** and α-tetralone **221** did occur to produce the expected alcohols 1-phenyl-ethanol **222** (Scheme 100) and α-tetralol **223** (Scheme 101) respectively, but from



220 **222**

Scheme 100



221 **223**

Scheme 101

the results summarised in Table **9** it is evident that little stereoselectivity, if indeed any was imparted by the presence of catalytic amounts of oxazaborolidines **208** and **216**.

Ketone	Catalyst	Yield	*e.e.*[a]	Configuration of Major Product
acetophenone **220**	**208**	95%	18%	*R*
α-tetralone **221**	**208**	75%	2%	*S*
acetophenone **220**	**216**	86%	0%	/
α-tetralone **221**	**216**	80%	0%	/

Table 9 Borane reduction of acetophenone **220** and α-tetralone **221** in the presence of oxazaborolidines **208** and **216**

[a] *e.e.* determined by optical rotation measurements

These insignificant levels of asymmetric induction clearly indicate the two novel oxazaborolidines **208** and **216** have no future as chiral catalysts for ketone reductions. The apparent reversal of selectivity in the reduction of α-tetralone in the presence of **208** probably resulted from machine error in the optical rotation measurement, and is not due to any mechanistic anomaly. The failure of **208** and **216** to impart significant stereoselectivity may have arisen from the fact that they are derived from α,β-amino alcohols (**209** and **219**) in which there is a secondary hydroxy function. From the published literature on oxazaborolidine ketone reduction catalysts it is now evident that a tertiary hydroxy and a secondary amino function are apparently essential for good enantioselectivity[101]. Another factor that may have influenced the outcome is the ability of the N-B bond of the oxazaborolidine ring to

exist in two resonance forms. It is known that the -NR-BR'- unit is similar to the -CR=CR'- group and can indeed replace it in many compounds[102]. This can be justified by assuming that the electron distribution in the N-B bond can be described by the resonance structure (II) in Figure 42, where π-bonding is introduced.

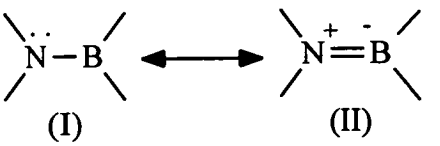


Figure 42

Good evidence is available that these types of bond have considerable π character, and do not contain the polarity that the structure (II) implies. This can explained by the presence of considerable polarity, albeit in the opposite direction, in the original σ-bond. This leads to the net polarity being the difference of the two. If in fact the oxazaborolidines **208** and **216** are existing in the resonance form shown in Figure 43,

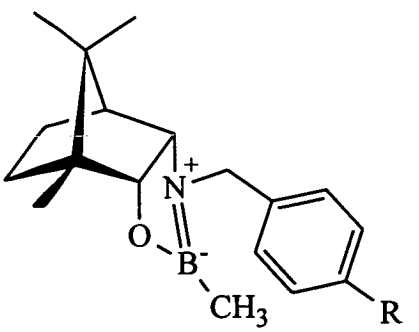
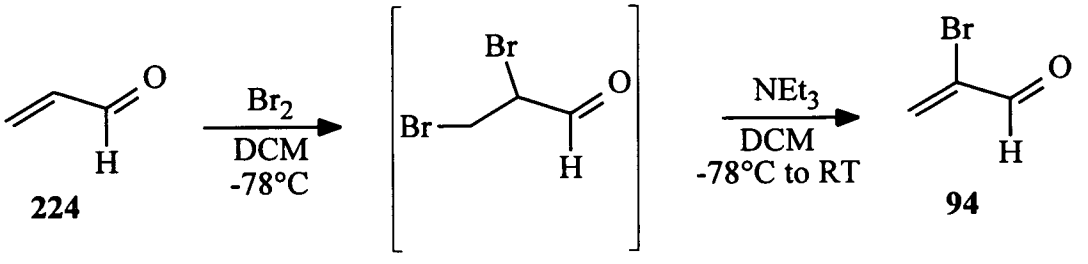


Figure 43

the nitrogen centre cannot bind to the borane reducing agent, and consequently, reduction of the ketone must occur without the influence of the would-be catalyst. Thus, ketone reduction is occurring in a non-asymmetric environment and lacks stereoselctivity.

6.4 Diels-Alder Reaction Between α-Bromoacrolein 94 and Cyclopentadiene Employing Oxazaborolidines 208 and 216 as Catalysts

The Diels-Alder reaction that was chosen to be investigated was that mentioned in the Introduction (section 2.2.4) *viz.* the reaction between the enal, α-bromoacrolein 94, and cyclopentadiene, originally carried out by Corey[55]. Firstly, it was necessary to prepare the α-bromoacrolein and this was achieved by treating acrolein **224** with bromine, at -78°C, followed by triethylamine (Scheme 102). This procedure worked well and **94** was obtained in an acceptable yield (34%).



Scheme 102

α-Bromoacrolein was chosen as the dienophile because it is known that when it chelates to the boron of the oxazaborolidine the bromine atom comes into conflict with the aromatic ring, leading to a change in the geometry from the s-*trans* assembly to the s-*cis* conformer (Figure 44)[55]. This geometry change has been

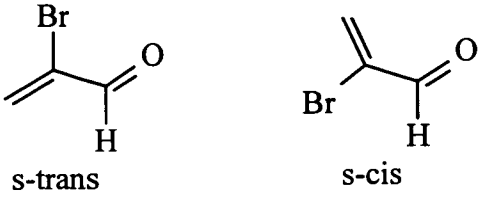
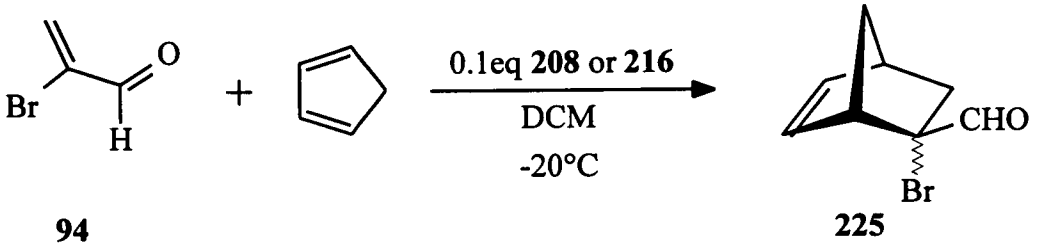


Figure 44

reported for a variety of 2-substituted acroleins and explains the high levels of stereoselectivity observed in their cycloaddition reactions[100].

The Diels-Alder reaction was attempted using the method of Corey[55] whereby a mixture of α-bromoacrolein and an excess of cyclopentadiene was stirred with 0.1 equivalents of **208** or **216** (Scheme 103). In each case, the reaction worked well, in

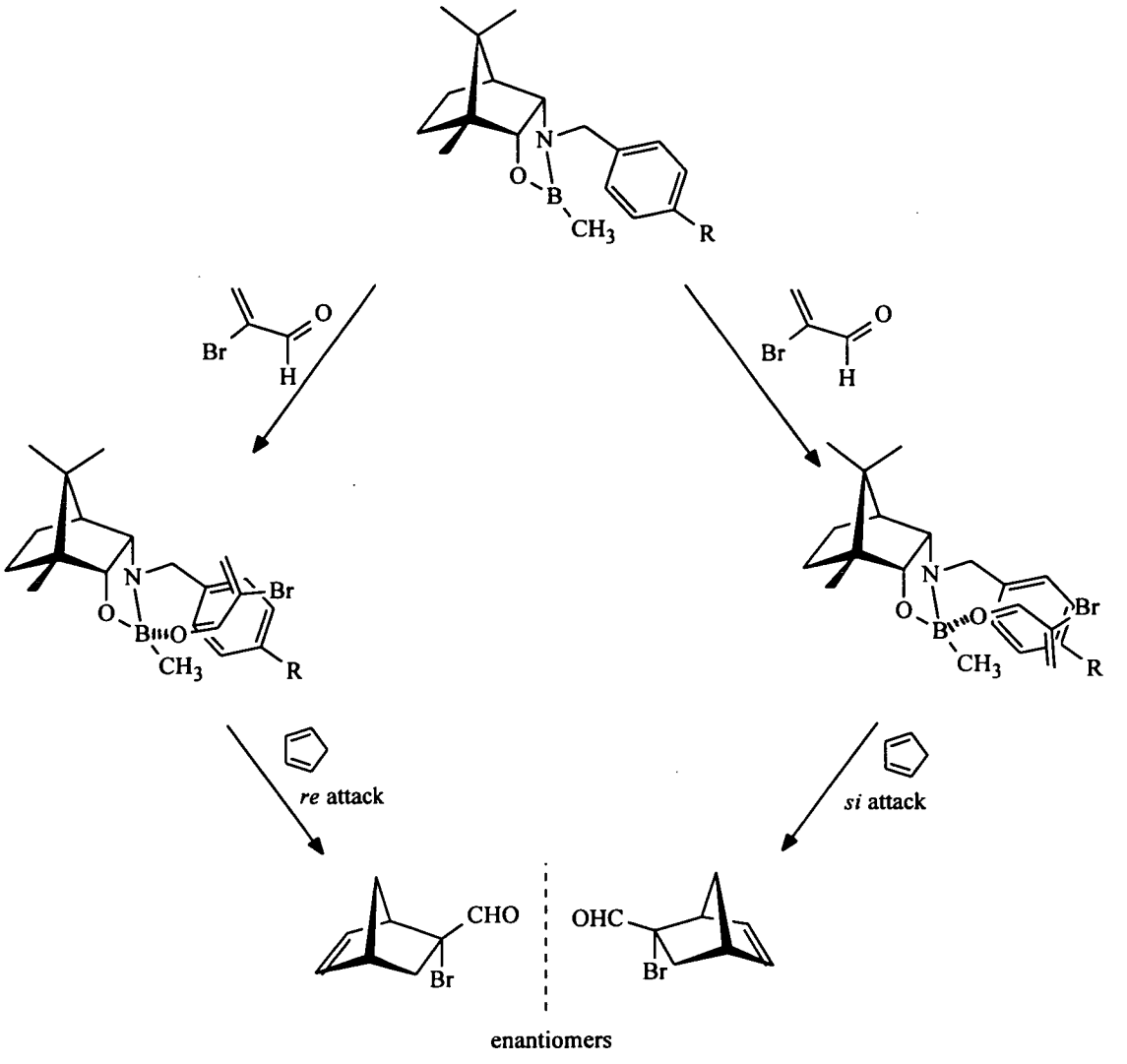


94 **225**

Scheme 103

that it produced the desired aldehyde **225** in quantitative yield, but unfortunately the product was obtained in racemic form, as evidenced by obtaining optical rotation measurements of zero.

The reason for the failure of **208** and **216** to act as asymmetric Diels-Alder catalysts is speculative, but one reason may lie in the fact that there is a lack of one preferred orientation for the enal in the transition state. This lack of preferential alignment is due to there being no excessive steric repulsion between the bromine atom and the aromatic ring in one of the conformations. This results in the diene being able to react on either the *re* or *si* face of the enal, producing a racemic product (Scheme 104).



Scheme 104

There may be other reasons for the failure of **208** and **216** to bring about stereoselectivity. The first of these is that both **208** and **216** lack the presence of a tosyl functionality in the molecule. The previously reported examples of use of oxazaborolidine catalysts[55,56] in Diels-Alder reactions possessed tosyl groups which may impart some steric bias, because upon removal, the enantioselectivity gained drops to virtually zero[103]. Secondly, the established catalysts have much more π-rich

systems present, *e.g.* indole, and replacement of these groups with less π-rich groups such as phenyl, also dramatically lowered the selectivity[100].

In retrospect, it appears that the choice of catalyst suffered from the lack a tosyl functionality, and also, the aromatic systems employed were obviously lacking in the necessary π-stacking ability. These factors (and possibly others) account for the very poor performances of **208** and **216** in the Diels-Alder reaction. In order to rectify the situation, attempts were made to synthesise a catalyst with a tosyl group present, but unfortunately these efforts resulted in failure (see chapter 4).

Experimental

Symbols and Abbreviations

Ar	aromatic
$[\alpha]_D$	specific rotation
b	broad
BP	boiling point
cm	complex multiplet
d	doublet
δ	chemical shift
DMAP	4-dimethylaminopyridine
DME	dimethoxyethane
DMSO	dimethylsulphoxide
eq	equivalents
FAB	fast atom bombardment
FT IR	Fourier transform infrared spectroscopy
J	spin-spin coupling constant
Lit.	literature value
M	mol dm^{-3}
M^+	molecular ion
mmol	millimoles
MP	melting point
m	multiplet
NMR	nuclear magnetic resonance spectroscopy

ppm	parts per million
psi	pounds per square inch
s	singlet
TBAB	tetrabutylammonium bromide
TCE	1,1,2,2-tetrachloroethane
THF	tetrahydrofuran
TLC	thin layer chromatography
t	triplet
q	quartet
ν_{max}	maximum wave number

1. Instrumentation and General Techniques

1.1 NMR Spectroscopy

Routine ^{1}H NMR spectra were obtained using a Joel PMX-60 spectrometer. Higher field spectra were obtained on a Bruker WP-200 SW operating at 200.13 MHz for ^{1}H and at 50.32 MHz for ^{13}C, operated by Mr W. Kerr or on a Bruker AC-250 spectrometer operating at 250.13 MHz for ^{1}H and at 62.9 MHz for ^{13}C, operated by Mr J.R.A. Millar or on a Bruker WH-360 spectrometer operating at 360.13 MHz for ^{1}H and at 90.56 MHz for ^{13}C, operated by Dr D. Reed.

Chemical shifts (δ) are reported in parts per million using tetramethylsilane (δ 0.0) as a reference.

1.2 Infrared Spectroscopy

Infrared spectra were recorded on a Bio-Rad FTS-7 spectrometer. Liquid samples were recorded as thin films and solid samples as nujol mulls, both on sodium chloride plates.

1.3 Mass Spectrometry

FAB and accurate mass measurements were obtained on a Kratos MS-50 TC spectrometer, operated by Mr A. Taylor.

1.4 Elemental Analysis

Elemental analysis for carbon, hydrogen and nitrogen were carried out on a Perkin-Elmer 2400 CHN elemental analyser, operated by Mrs L. Eades.

1.5 X-Ray Crystallography

X-Ray crystal structures were determined on a Stoe STADI-4, four circle diffractometer, operated by Dr A. Blake or by Dr S. Parsons.

1.6 Melting Points

Melting points were measured on a digital Gallenkamp capillary tube apparatus and are uncorrected.

1.7 Optical Rotations

Optical rotations were measured on an Optical Activity AA 1000 polarimeter; readings were taken at 589 nm (the sodium D-line) using a 1 dm cell.

1.8 Flash Column Chromatography

Flash column chromatography was routinely carried out using Merck silica gel 60 (mesh size 0.040 - 0.063 mm) as solid support, and a pressure of 10 p.s.i. of compressed air to aid the elution of solvent.

1.9 Thin Layer Chromatography

For analytical purposes, aluminium backed plates, coated with a 0.2 mm layer of silica gel 60, and containing fluorescent indicator were used. Component spots were visualised by ultra-violet light, iodine vapour or by dipping into a 5% sulphuric acid/ethanol solution followed by gentle flaming.

1.10 Drying and Purification of Solvents

Methylene chloride, DME, toluene and TCE were all dried by distilling from finely divided calcium hydride (Fisons) under an argon or nitrogen atmosphere. THF and ether were dried by distilling from sodium and benzophenone, under an argon or nitrogen atmosphere, the solvent was collected when the deep purple colour, due to sodium benzophenone ketyl, had formed.

1.11 Drying of Glassware and Inert Gases

Before conducting moisture sensitive reactions, reaction flasks were dried thoroughly by heating with a strong Bunsen flame whilst flushing with a strong flow of argon.

Argon gas used for reactions was dried by passing the gas through a series of dreschel vessels containing concentrated sulphuric acid, calcium chloride and self indicating silica gel.

2. Attempted Synthesis of Transfigomer 110

2.1 Synthesis of Camphorquinone 117

This was achieved using the method of Evans *et al*[76].

Selenium dioxide (8.15g, 73.0mmol) was added to a stirred suspension of (1R)-(+)-camphor **114** (10.0g, 66.0mmol) in acetic anhydride (10ml), and the resulting suspension heated under reflux and stirred for 2 hours. A further portion of selenium dioxide (2.10g, 18.9mmol) was then added and reflux continued for a further 2 hours before a final portion of selenium dioxide (1.78g, 16.0mmol) was added. The reaction mixture was then heated under reflux overnight. The mixture was then cooled and neutralised with sodium hydroxide solution (30% w:v, 25ml), and then taken to pH 8. The mixture was then filtered through a pad of celite and washed with ether (250ml) until the filtrate ran colourless. The layers were then separated and the aqueous layer extracted with further ether (2x50ml). The combined organic layers were dried over magnesium sulphate, filtered and evaporated *in vacuo* to give (1*R*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2,3-dione **117** as a bright yellow solid (10.47g, 96%); **MP** = 200.0-200.4°C (EtOH) (Lit[76] = 198-199°C); **FT IR** ν_{max} (nujol) 1746(bs, 2C=O) cm^{-1}.

2.2 Reduction of Camphorquinone 117 Using Zinc and Acetic Acid

The method of Huckel and Fechtig[68] was used.

(1*R*)-Camphorquinone **117** (70.21g, 420.0mmol) was dissolved in the minimum amount of hot acetic acid (*ca.* 60ml), then hot water (600ml) added. The mixture was

then heated to 90-100°C, with mechanical stirring, then zinc dust added in portions until the yellow colour of the solution had faded completely (160g in total). The reaction mixture was then quickly filtered through celite, and hot water (2 litres) used to wash the zinc and celite residue. The filtrate was saturated with sodium chloride and extracted into methylene chloride (4x500ml). The combined organic layers were dried over magnesium sulphate, filtered and evaporated *in vacuo* to give a mixture of **118** and **119** as a colourless solid (43.59g, 62%). Further product was obtained by refluxing the the crushed zinc residue in methylene chloride (500ml) for 4 hours. The mixture was then filtered and evaporated *in vacuo* to give the second crop of the product (18.20g, 26%); **MP** = 202-205°C (Lit[68] = 203-205°C); **FT IR** ν_{max} (nujol) 3420(OH), 1746(C=O) cm^{-1}.

2.3 Isolation of *endo*-2-Hydroxyepicamphor 118 From *endo*-3-Hydroxycamphor 119 *via* Formation of Manassse's Dimer 120

Following the method of Manasse[71], HCl gas (freshly generated from concentrated sulphuric acid and ammonium chloride (90mmol. 0.2eq)) was bubbled into a solution of **118** and **119** (60.9g, 362mmol) in dry methanol (200ml) assisted by a stream of argon. The solution was allowed to stand at room temperature for several days, over which time a number of crops of crystals were recovered. The combined crops of crystals were washed with a little cold pentane to give [(1*R*, 4*S*, 4a*S*, 5a*R*, 6*R*, 9*S*, 9a*S*, 10a*R*)]-1,4:6,9-diisopropano-4a,9a-dimethoxy-1,6-dimethylperhydro-dibenzodioxin **120** as colourless crystals (25.41g, 39%); **MP** = 149-150°C (Lit[70] = 149-150°C); $[\alpha]_D^{21}$ = +178° (c=5.06, EtOH:CH_2Cl_2(8:1)) (Lit[70] = +174.2°); ^{1}**H**

NMR (360.13MHz, $CDCl_3$) δ 3.34(1H, t, J = 1.2 Hz, CHO), 3.18(3H, s, OCH_3), 2.12(1H, dd, J = 4.5, 1.5 Hz, bridgehead), 1.92(1H, ddd, J = 11.8, 9.5, 4.6 Hz), 1.84(1H, ddd, J = 12.1, 9.7, 3.3 Hz), 1.52(1H, tt, J = 11.7, 4.3 Hz), 1.13(1H, tdd, J = 12.2, 3.7, 1.5 Hz), 1.02(3H, s, CH_3), 0.88(3H, s, CH_3), 0.85(3H, s, CH_3) ppm; **^{13}C NMR** (90.56MHz, $CDCl_3$) δ 102.01(C), 78.38(CH), 49.36(C), 49.31(CH_3), 48.75(CH), 45.07(C), 26.36(CH_2), 21.26(CH_2), 20.33(CH_3), 19.37(CH_3), 13.70(CH_3) ppm.

2.4 Regeneration of 118 From Manasse's Dimer 120

Concentrated hydrochloric acid (7.5ml, 5eq) was added to the dimer **120** (5.3g, 15mmol), and the resulting suspension stirred at room temperature for 2.5 hours, after which time further concentrated hydrochloric acid (4ml, 2eq) was added and the reaction mixture allowed to stir overnight. After this time the dimer had completely dissolved. The mixture was then neutralised and raised to pH 8 by the careful addition of powdered sodium carbonate, with stirring. The solution was then saturated with sodium chloride and extracted into methylene chloride (3x75ml). The organic layers were dried over magnesium sulphate, filtered and evaporated *in vacuo* to give (1*R*, 2*R*)-*endo*-2-hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptan-3-one **118** as a colourless solid (4.53g, 90%); **MP** = 219-220°C (hexane) (Lit[68] = 221°C); **^{1}H NMR** (200.13MHz, $CDCl_3$) δ 3.83(1H, bs, OH), 3.10(1H, bs, C<u>H</u>OH), 2.24(1H, dd, J = 4.1, 1.0 Hz, bridgehead), 2.05-1.88(2H, cm), 1.46-1.28(2H, cm), 1.02(3H, s, CH_3), 0.95(3H, s, CH_3), 0.90(3H, s, CH_3) ppm; **^{13}C NMR** (50.3MHz, $CDCl_3$) δ 219.6(C=O), 78.4(CH), 59.3(CH), 50.0(C), 42.8(C), 24.8(CH_2), 24.4(CH_2),

19.1(CH_3), 17.7(CH_3), 12.7(CH_3) ppm; **FT IR** ν_{max} (nujol) 3430(OH), 1745(C=O) cm^{-1}.

2.5 Re-Oxidation of 119 to Camphorquinone 117

Reaction was carried out using the method of Szarek *et al*[104].

To a solution of **119** (5.5g, 33mmol) in DMSO (25ml) was added acetic anhydride (30ml). The resulting mixture was heated to 120°C for 4 hours, after which time TLC (silica, hexane:ether (1:1)) showed no starting material was present. Water was then added and the mixture extracted into ethyl acetate (2x70ml). The combined organic layers were washed with water, dried over magnesium sulphate, filtered and evaporated *in vacuo* to yield camphorquinone **117** (5.47g, 100%).

2.6 Acylation of *endo*-2-Hydroxyepicamphor 118

Achieved using the conditions of Wilson and Price[105].

Acetic anhydride (5.5g, 54mmol, 2eq), triethylamine (5.6g, 55mmol, 2eq) and DMAP (0.3g, 2.7mmol, 0.1eq) were added to a solution of (1*R*, 2*R*)-*endo*-2-hydroxyepicamphor **118** (4.5g, 27mmol) in methylene chloride (20ml). An exothermic reaction ensued, and stirring was then continued for a further 3.5 hours before quenching with dilute hydrochloric acid (0.1M, 10ml), followed by concentrated hydrochloric acid (10ml). The mixture was then extracted into methylene chloride (3x75ml) and the organic layers washed with saturated sodium bicarbonate solution. The organic layer was then dried over magnesium sulphate, filtrered and evaporated *in vacuo* to give (1*R*, 2*R*)-*endo*-2-acetoxy-1,7,7-

trimethylbicyclo[2.2.1]heptan-3-one **121** as a yellow oil, which crystallised on standing to give a pale yellow solid (5.56g, 98%); **MP** = 58.5-59.5°C (Lit[73] = 61-62°C); **^{1}H NMR** (200.13MHz, $CDCl_3$) δ 5.18(1H, d, *J* = 0.9 Hz, CHO), 2.28(1H, d, *J* = 4.8 Hz, bridgehead), 2.19-1.81(2H, cm), 2.12(3H, s, $C\underline{H}_3CO$), 1.52-1.37(2H, cm), 0.99-0.96(9H, 2s, $3CH_3$) ppm; **^{13}C NMR** (50.3MHz, $CDCl_3$) δ 212.5(C=O), 170.1(C=O), 78.5(CH), 59.2(CH), 49.8(C), 43.1(C), 26.0(CH_2), 23.8(CH_2), 20.4(CH_3), 19.2(CH_3), 17.5(CH_3), 12.8(CH_3) ppm; **FT IR** ν_{max} (nujol) 1754(bs, 2C=O) cm^{-1}.

2.7 Preparation of a 1.5% Na/Hg Amalgam

A glove bag containing a flask of mercury (167g) and a beaker with sodium metal (2.54g) was evacuated and purged with nitrogen several times. Small pieces of sodium were then added to the mercury with gentle swirling (**Caution:** latent period before violent exothermic reaction). The glove bag was then evacuated and purged several times to remove mercury vapour before the amalgam was removed. The amalgam was then stored under nitrogen until used.

2.8 Preparation of Epicamphor 113

A modification of the method of Thoren[73] was employed.

The acylated 2-hydroxyepicamphor **121** (5.0g, 24mmol) was added to water (50ml) to give a partial suspension. The mixture was then stirred magnetically over a 1.5% Na/Hg amalgam (see above) for 24 hours. The reaction mixture was then extracted into ether (3x200ml), and the organic layers decanted off. The combined organic

layers were dried over magnesium sulphate, filtered and evaporated *in vacuo* to give (1*S*)-1,7,7-trimethylbicyclo[2.2.1]heptan-3-one **113** as a colourless solid (3.20g, 88%); **MP** = 169-171°C (lit[73] = 179-180°C); $[\alpha]_D^{21}$ = -51.8° (c=5.5, benzene) (Lit[73] = -51.1° (c=10, benzene); **^{1}H NMR** (200.13MHz, $CDCl_3$) δ 2.00-1.48(4H, cm), 1.33-1.17(2H, cm), 0.89-0.59(1H, cm), 0.83(3H, s, CH_3), 0.76(3H, s, CH_3), 0.73(3H, s, CH_3) ppm; **^{13}C NMR** (50.32MHz, $CDCl_3$) δ 217.0(C=O), 60.0(CH), 49.0(CH_2), 46.0(C), 45.4(C), 34.0(CH_2), 21.5(CH_2), 19.0(CH_3), 17.0(CH_3), 14.4(CH_3) ppm; **FT IR** ν_{max} (nujol) 1752(C=O) cm^{-1}.

2.9 Model Reaction: α-Hydroximation of Camphor 114

To dry THF (70ml) at 0°C under argon was added dropwise diisopropylamine (1.5g, 15mmol) followed by dropwise addition of n-butyllithium (12ml, 1.6M in hexanes, 19mmol), and the mixture stirred at 0°C for 30 minutes, then cooled to -78°C. A solution of (1*R*)-(+)-camphor **114** (2.0g, 13mmol) in dry THF (20ml) was then added dropwise and the mixture then stirred at -78°C for 15 minutes. The resulting enolate solution was then cannulated into a solution of *iso*-amylnitrite (1.7g, 14mmol) in dry THF (50ml) under argon at -78°C. The reaction mixture was allowed to warm to room temperature and stirred overnight. Saturated ammonium chloride solution (100ml) was added and the mixture stirred for 30 minutes. The solvent was then removed *in vacuo*, and the aqueous residue extracted into methylene chloride (3x50ml). The combined organic layers were then dried over magnesium sulphate, filtered and evaporated *in vacuo* to give a brown solid. The crude product was purified by flash chromatography (silica, hexane:ethyl acetate (5:1)) to yield (1*R*)-*N*-

hydroxy-3-imino-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one **125** as a yellow solid (0.81g, 34%); **MP** = 154-156°C (Lit[75] = 156-158°C); **FT IR** ν_{max} (nujol) 3445(OH), 1740(C=O), 1641(C=N) cm^{-1}.

2.10 α-Hydroximation of Epicamphor 113

The procedure outlined in section 2.9 was followed using epicamphor **113** (2.12g, 13.9mmol), diisopropylamine (1.55g, 15.3mmol), *n*-butyllithium (10ml, 1.6M in hexanes, 16mmol) and *iso*-amylnitrite. Flash chromatography (silica, hexane:ether (9:1 - 4:1)) gave a 5:1 ratio of *anti* : *syn* isomers of (1*R*)-*N*-hydroxy-2-imino-1,7,7-bicyclo[2.2.1]heptan-3-one **112** as a yellow solid (0.40g, 16%); **MP** = 95-100°C; **^{1}H NMR** (250.13MHz, $CDCl_3$) δ 11.91(1H, bs, C=N-O<u>H</u>), 2.36(1H, d, *J* = 5.1 Hz, bridgehead), 2.13-2.00(1H, cm), 1.94-1.83(1H, cm), 1.80-1.43(2H, cm), 1.11(3H, s, CH_3), 0.96(3H, s, CH_3), 0.92(3H, s, CH_3) ppm; **^{13}C NMR** (69.90MHz, $CDCl_3$) δ (*anti* isomer) 202.72(C=O), 157.43(C=N), 65.68(C), 58.83(CH), 51.94(C), 32.17(CH_2), 22.18(CH_2), 20.31(CH_3), 17.04(CH_3), 10.12(CH_3) ppm; **FT IR** ν_{max} (nujol) 3426(OH), 1742(C=O), 1631(C=N) cm^{-1}; **Accurate mass** found 182.11743 (MH^+), $C_{10}H_{16}NO_2$ requires 182.11810.

2.11 Reduction of *N*-Hydroxy-2-iminoepicamphor 112 Using Zinc

The oxime **112** (0.36g, 2.0mmol) was added to a solution of sodium hydroxide (0.50g, 12mmol) in water (5ml), and stirred until clear. Zinc dust (0.70g, 10mmol) was then added and the mixture vigorously stirred for 40 minutes. The whole reaction mixture was then extracted into ether (2x50ml). The combined organic

layers were cooled in an ice bath and treated with concentrated hydrochloric acid (2ml) then diluted with water (10ml). The aqueous layer was separated and washed with ether (2x25ml), then the water evaporated *in vacuo* to give (1*R*, 2*R*)-*endo*-2-amino-1,7,7-trimethylbicyclo[2.2.1]heptan-3-one hydrochloride **127** as a colourless solid (0.37g, 91%); **MP** = 224-226°C; $[\alpha]_D^{21}$ = +5.6° (c=1.00, H_2O); **^{1}H NMR** (250.13MHz, D_2O) δ 3.82(1H, s, C<u>H</u>$NH_3^+Cl^-$); 2.48(1H, d, *J* = 5.4 Hz, bridgehead), 2.23-2.13(1H, cm), 1.85-1.69(1H, cm), 1.60-1.49(1H, cm), 1.42-1.31(1H, cm), 1.11(3H, s, CH_3), 1.01(3H, s, CH_3), 0.97(3H, s, CH_3) ppm; **^{13}C NMR** (62.90MHz, D_2O) δ 214.78(C=O), 61.60(CH), 58.94(CH), 49.05(C), 44.84(C), 25.56(CH_2), 23.72(CH_2), 18.28(CH_3), 16.66(CH_3), 11.96(CH_3) ppm; **FT IR** ν_{max} (nujol) 1752(C=O) cm^{-1}; **Accurate mass** found 168.13889 (MH^+), $C_{10}H_{18}NO$ requires 168.13384.

2.12 Attempted Reduction of 129 Using $LiAlH_4$

Amine hydrochloride 127 (0.46g, 2.3mmol) was dissolved in saturated sodium bicarbonate solution (25ml), stirred for 5 minutes, then extracted into methylene chloride (3x50ml). The organic layers were dried over magnesium sulphate, filtered and evaporated *in vacuo* to give a pale yellow gum. The resulting free amine **129** (0.21g, 1.3mmol) in dry THF (10ml) was then added to a stirred suspension of lithiumaluminium hydride (0.15g, 4.0mmol, 3eq) in dry THF (25ml). The mixture was then heated under reflux overnight, after which time TLC (silica, hexane:ether (1:1)) showed no evidence of starting material. The reaction mixture was then cooled and treated with water (0.5ml), followed by sodium hydroxide solution (15% w:v,

0.5ml) and water (2ml), then stirred for 30 minutes and filtered. The THF was then removed *in vacuo* and the aqueous residue extracted into methylene chloride (3x50ml). The combined organic layers were then dried over magnesium sulphate, filtered and evaporated *in vacuo* to give a colourless solid. The solid was purified by flash chromatography (silica, hexane:ether (1:1)), to isolate a single spot on the TLC as a yellow oil (0.11g). The oil was found to be a complex mixture of products.

3. Synthesis and Evaluation of the Novel Auxiliary 131

3.1 Stereoselective Reduction of Camphorquinone 117 Using L-Selectride®

A modification of Kouklovsky *et al*'s method[80] was used.

To a solution of camphorquinone **117** (4.40g, 26.5mmol) in dry THF (50ml) at -78°C under argon, was added a solution of L-Selectride® (28ml, 1.0M in THF, 28mmol, 1.1eq). The reaction mixture was then stirred at -78°C for 4 hours then quenched by the addition of a solution of hydrochloric acid in methanol (3.0M, 18ml) at the same temperature, and stirred for 10 minutes. The THF was then evaporated *in vacuo* and the aqueous residue extracted into methylene chloride (3x50ml). The organic layers were then dried over magnesium sulphate, filtered and evaporated *in vacuo* to give a yellow oil. The oil was purified by flash chromatography (silica, hexane:ether (95:5)) to give (1*R*, 3*R*)-*exo*-3-hydroxy-1,7,7-trimethylbicyclo[2.2.1]-heptan-2-one **134** as a colourless oil (3.99g, 90%); **^{13}C NMR** (50.32MHz, $CDCl_3$) δ 220.4(C=O), 77.2(CH), 69.4(C), 49.2(CH), 46.6(C), 28.4(CH_2), 25.0(CH_2), 20.8(CH_3), 19.9(CH_3), 8.8(CH_3) ppm; **FT IR** ν_{max} (thin film) 3440(OH), 1748(C=O) cm^{-1}.

3.2 Formation of the Imine 135

Again a modification of the Kouklovsky method[80] was employed.

To a solution of the keto alcohol **134** (2.06g, 12.3mmol) in dry THF (50ml) under argon was added benzylamine (2.9g, 27mmol), and 4Å molecular sieves (3.12g, dried under vacuum at 90°C for 1 hour). The reaction mixture was then stirred at room temperature for 3 days. The mixture was then filtered through a pad of celite

and washed with ether. The solvent was removed *in vacuo* to give a yellow oil. The oil was then purified by flash chromatography (silica, hexane:ether (9:1-4:1)) to give (1*R*, 3*R*)-*N*-benzyl-3-imino-*exo*-3-hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptane **135** as a colourless solid (3.17g, 50%); $[\alpha]_D^{21}$ = -45.2° (c=1.05, $CHCl_3$) (Lit[80] = -46° (c=1.11, $CHCl_3$)); **^{13}C NMR** (50.32MHz, $CDCl_3$) δ 181.6(C=N), 140.6(Ar C), 128.0(2Ar CH), 127.3(2Ar CH), 126.2(Ar CH), 69.8(CH), 54.3(CH_2), 51.9(C), 50.0(CH), 44.2(C), 32.3(CH_2), 19.1(CH_3), 19.0(CH_3), 18.3(CH_2), 11.7(CH_3) ppm; **FT IR** ν_{max} (nujol) 3145(OH), 1674(C=N) cm^{-1}.

3.3 Stereoselective Reduction of the Imine 135 Using $NaBH_4$

Kouklovsky's procdure[80] was followed.

Sodium borohydride (10.50g, 276.3mmol, 10eq) was added in small portions to a stirred solution of the imine **135** (7.10g, 27.6mmol) in methanol (150ml). The reaction mixture was then allowed to stir at room temperature for 5.5 hours. Saturated sodium chloride solution (75ml) was then added and the mixture stirred for 10 minutes, then extracted into methylene chloride (3x100ml). The organic layers were then combined, dried over magnesium sulphate, filtered and evaporated *in vacuo* to give (1*R*, 2*S*, 3*R*)-*N*-benzyl-*exo*-2-amino-*exo*-3-hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptane **136** as a clear colourless oil (6.90g, 97%); **^{1}H NMR** (250.13MHz, $CDCl_3$) δ 7.35-7.25(5H, cm, Ph), 3.77(2H, s, $PhC\underline{H}_2$), 3.63(1H, d, *J* = 7.3 Hz, C<u>H</u>OH), 2.70(1H, d, *J* = 7.3 Hz, C<u>H</u>NH), 1.80(1H, d, *J* = 4.5 Hz, bridgehead), 1.66-1.51(2H, cm), 1.09-0.83(2H, cm), 1.01(3H, s, CH_3), 0.87(3H, s, CH_3), 0.77(3H, s, CH_3) ppm; **^{13}C NMR** (62.90MHz, $CDCl_3$) δ 139.52(Ar C),

128.31(2Ar CH), 127.99(2Ar CH), 127.07(Ar CH), 74.35(CH), 69.66(CH), 55.20(CH_2), 50.94(CH), 48.13(C), 46.41(C), 36.21(CH_2), 23.61(CH_2), 21.58(CH_3), 21.01(CH_3), 11.63(CH_3) ppm; **FT IR** ν_{max} (thin film) 3357(bs, HN and OH) cm^{-1}.

3.4 Removal of Benzyl Group from Amino Alcohol 136

Kouklovsky's method[80] was employed once more.

A solution of the amino alcohol **136** (2.34g, 9.03mmol) in methanol (60ml) was stirred with 10% Pd/C (0.30g, *ca.* 0.1eq) under a hydrogen atmosphere for 48 hours. The reaction mixture was then filtered through a pad of celite and evaporated *in vacuo* to give (1*R*, 2*S*, 3*R*)-*exo*-2-amino-*exo*-3-hydroxy-1,7,7-trimethylbicyclo-[2.2.1]heptane **133** as a colourless solid (1.47g, 96%); **^{1}H NMR** (200.13MHz, $CDCl_3$) δ 3.62(1H, d, *J* = 7.4 Hz, C<u>H</u>OH), 3.02(3H, bs, NH_2 and OH), 2.84(1H, d, *J* = 7.4 Hz, C<u>H</u>NH_2), 1.74(1H, d, *J* = 4.5 Hz, bridgehead), 1.64-1.42(2H, cm), 1.20-0.80(2H, cm), 1.00(3H, s, CH_3), 0.85(3H, s, CH_3), 0.73(3H, s, CH_3) ppm; **^{13}C NMR** (50.32MHz, $CDCl_3$) δ 75.0(CH), 62.4(CH), 50.9(CH), 47.8(C), 46.5(C), 35.74(CH_2), 23.8(CH_2), 21.7(CH_3), 20.7(CH_3), 11.9(CH_3) ppm; **FT IR** ν_{max} (nujol) 3391(NH_2), 3297(NH_2), 3155(OH) cm^{-1}.

3.5 Formation of Oxazolidin-2-one Auxiliary 131

A solution of 6M sodium hydroxide (2ml) was added to the amino alcohol **133** (0.50g, 3.0mmol) in DME (20ml). The reaction mixture was then cooled to -5°C (ice/salt) and treated with a solution of triphosgene (0.38g,1.28mmol) in anhydrous

methylene chloride (10ml). The mixture was then stirred at this temperature for 1 hour, then warmed to room temperature and stirred for a further 2.5 hours. The reaction mixture was then extracted into methylene chloride (3x10ml). The combined organic layers were then dried over magnesium sulphate, and subsequent filtration and evaporation *in vacuo* gave (1*S*, 2*R*, 6*S*, 7*R*)-*exo*-3-oxa-*exo*-5-aza-7,10,10-trimethyltricyclo[5.2.1.$0^{2,6}$]decan-4-one **131** as a colourless solid (0.57g, 98%); **MP** = 196.3-197.3°C (cyclohexane:ethyl acetate); $[\alpha]_D^{21}$ = +1.2° (c=1.02, CH_2Cl_2); **^{1}H NMR** (250MHz,$CDCl_3$) δ 7.25(1H, bs, NH), 4.56(1H, dd, *J* = 8.6, 0.5 Hz, CHO), 3.57(1H, dd, *J* = 8.1, 1.3 Hz, CHN), 2.08(1H, d, *J* = 5.1 Hz, bridgehead), 1.76-1.68(1H, cm), 1.51-1.39(2H, cm), 1.05(3H, s, CH_3), 0.96-0.93(1H, cm),0.89(3H, s, CH_3), 0.86(3H, s, CH_3) ppm; **^{13}C NMR** (50.32MHz,$CDCl_3$) δ 160.9(C=O), 84.0(CH), 65.4(CH), 47.9(CH), 47.4(C), 46.1(C), 32.6(CH_2), 22.9(CH_3), 22.8(CH_2), 19.0(CH_3), 10.5(CH_3) ppm; **FT IR** ν_{max} (nujol) 3286 and 3176(NH), 1756 and 1714(C=O) cm^{-1}; **Accurate mass** found 196.13312(MH^+), $C_{11}H_{18}NO_2$ requires 196.13375; **Elemental analysis** found 67.2% C, 9.2% H, 7.1% N, $C_{11}H_{17}NO_2$ requires 67.6% C, 8.8% H, 7.2% N.

3.6 Preparation of the Silyl Enol Ether of Camphor 139

A modified version of the procedure used by Joshi and Pande[83] was employed.

To a stirred suspension of activated zinc dust (2.20g, 33.6mmol) in dry THF (25ml) under argon, was added dropwise a solution of *endo*-3-bromocamphor **140** (5.05g,

21.9mmol) and chlorotrimethylsilane (3.62g, 33.2mmol), in dry THF (50ml). The reaction mixture was then heated under reflux for 24 hours, then allowed to cool to room temperature. The mixture was then filtered through a pad of celite and subsequent evaporation *in vacuo* of the filtrate yielded a sticky colourless solid. Kugelrohr distillation (56°C, 1mbar) of the solid yielded (1*R*)-2-trimethylsilyloxybicyclo[2.2.1]hept-2-ene **139** as a colourless liquid (2.91g, 60%); **^{1}H NMR** (250.13MHz, $CDCl_3$) δ 4.61(1H, d, *J* = 3.5 Hz, C=CH), 2.16(1H, t, *J* = 3.5 Hz, bridgehead), 1.86-1.78(1H, cm), 1.46-1.35(1H, cm), 1.11-1.04(1H, cm), 0.89-0.81(1H, cm), 0.85(6H, s, $2CH_3$), 0.70(3H, s, CH_3), 0.17(9H, s, $OSi(CH_3)_3$) ppm; **^{13}C NMR** (62.90MHz, $CDCl_3$) δ 160.25($(CH_3)_3SiO\underline{C}$=CH), 103.34(C=$\underline{C}$H), 54.56(C), 53.17(C), 49.30(CH), 31.07(CH_2), 27.14(CH_2), 19.98(CH_3), 19.61(CH_3), 9.82(CH_3), -0.08($(CH_3)_3$) ppm; **FT IR** ν_{max} (thin film) 1616(C=C) cm^{-1}.

3.7 Attempted Synthesis of Keto Alcohol 134 from the Silyl Enol Ether of Camphor 139

The method of Jauch[82] was adopted for this reaction.

m-Chloroperoxybenzoic acid (1.55g, 8.96mmol) and sodium hydrogen carbonate (2.0g, 22mmol, 3eq) were suspended in dry pentane (30ml), under argon. The mixture was then stirred at room temperature for 10 minutes, then cooled to -25°C, then a solution of the silyl enol ether **139** (1.47g, 6.56mmol) was added. The reaction mixture was allowed to stir at -25°C for 6 hours then warmed to room temperature

and stirred overnight. The mixture was then filtered and the residue washed with a little cold ether. Potassium iodide paper indicated peroxides were present in the filtrate so a little sodium sulphite solution was added, and the mixture subsequently separated and the organic layers then evaporated *in vacuo*. The residue was then stirred vigorously with a half saturated solution of potassium carbonate (28g in 50ml of water) for 24 hours. The aqueous mixture was then extracted into methylene chloride (5x50ml), and the organic layers dried over magnesium sulphate, filtered and evaporated *in vacuo* to give a sticky yellow solid. The crude product was subjected to flash chromatography (silica, hexane:ether (9:1-4:1)) to give a colourless solid (0.28g, 25%). Examination of the ^{1}H NMR spectrum showed a doublet at δ 4.17 (J = 5.1 Hz) ppm arising from **119** and a singlet at δ 3.72ppm arising from **134**. Integration of these signals indicated that the solid was a 2:1 mixture of the keto alcohols **119** and **134** respectively; **FT IR** ν_{max} (nujol) 3455(OH), 1745(C=O) cm^{-1}.

3.8 Functionalisation of Auxiliary 131

3.8.1 Preparation of the Acrylate 141

Ethyl bromide (0.21g, 1.9mmol) was added to magnesium turnings (0.04g, 1.6mmol) in dry THF (6ml) under argon. When the magnesium had dissolved dry THF (15ml) was added and the mixture cooled to 0°C and treated with a solution of auxiliary **131** (0.20g, 1.0mmol) and quinol (10mg) in dry THF (10ml). After 15 minutes the reaction mixture was cooled to -78°C and freshly distilled acryloyl chloride (0.17g,

2.1mmol) added. The mixture was then stirred for 15 minutes, and the temperature then raised to 0°C for 40 minutes, then allowed to warm to room temperature. After 90 minutes the reaction was quenched with saturated ammonium chloride solution and the mixture concentrated *in vacuo.* The aqueous residue was then extracted into methylene chloride (3x20ml). The combined organic layers were dried over magnesium sulphate, and subsequent filtation and evaporation *in vacuo* yielded a yellow oil. The oil was subjected to flash chromatography (silica, hexane:ether (4:1)) to give (1*S*, 2*R*, 6*S*, 7*R*)-*N*-acryloyl-*exo*-3-oxa-*exo*-5-aza-7,10,10-trimethyltricyclo[5.2.1.$0^{2,6}$]decan-4-one **141** as a colourless solid (0.22g, 88%); **MP** = 93.4-94.7°C (hexane); $[\alpha]_D^{21}$ = +82.7° (c=1.00,CH_2Cl_2); **^{1}H NMR** (250.13MHz, $CDCl_3$) δ 7.46(1H, dd, *J* = 17.0, 10.4 Hz, proton of =CH_2 *trans* to proton on adjacent carbon), 6.48(1H, dd, *J* = 17.0, 1.8 Hz, proton of =CH_2 *cis* to proton on adjacent carbon), 5.84(1H, dd, *J* = 10.4, 1.8 Hz, C<u>H</u>=CH_2) 4.50(1H, dd, *J* = 8.0, 0.63 Hz, CHO), 4.45(1H, d, *J* = 8.0 Hz, CHN), 2.14(1H, d, *J* = 5.1 Hz, bridgehead), 1.87-1.71(1H, cm), 1.60-1.48(1H, cm), 1.29-1.15(1H, cm), 1.08-0.94(1H, cm), 0.99(3H, s, CH_3), 0.91(3H, s, CH_3), 0.87(3H, s, CH_3) ppm; **^{13}C NMR** (62.90MHz, $CDCl_3$) δ 165.47(C=0), 154.78(C=O), 131.71(CH_2), 127.69(CH), 81.30(CH), 69.66(CH), 50.01(C), 47.45(CH), 46.33(C), 33.10(CH_2), 22.62(CH_3 and CH_2), 19.50(CH_3), 11.90(CH_3) ppm; **FT IR** ν_{max} (nujol) 1787, 1758(C=O), 1695(C=O), 1616(C=C) cm^{-1}; **Accurate mass** found 250.14451(MH^+), $C_{14}H_{20}NO_3$ requires 250.14432.

3.8.2 Preparation of Crotonate 142

This was prepared by the same general procedure as for the acrylate (see section 3.8.1), using ethyl bromide (0.21g, 1.9mmol, 1.6eq), magnesium turnings (0.03g, 1.2mmol, 1.1eq), auxiliary **131** (0.23g, 1.2mmol) and freshly distilled crotonyl chloride (0.20g, 1.9mmol, 1.6eq). Flash chromatography as above yielded (1*S*, 2*R*, 6*S*, 7*R*)-*N*-crotonoyl-*exo*-3-oxa-*exo*-5-aza-7,10,10-trimethyltricyclo[5,2,1,$0^{2,6}$]decan-4-one **142** as a colourless solid (0.28g, 90%); **MP** = 141.4-143.4°C (cyclohexane); $[\alpha]_D^{21}$ = +46.0° (c= 0.50, CH_2Cl_2); **^{1}H NMR** (250.13MHz, $CDCl_3$) δ 7.25-7.03(2H, cm, CH=CH), 4.49-4.41(2H, cm, CHO and CHN), 1.92(3H, dd, *J* = 6.5, 1.2 Hz, CH=CH_3), 1.89-1.80(1H, cm), 1.52(1H, ddd, *J* = 11.8, 11.8, 4.5 Hz, CH_2), 1.22(1H, dt, *J* = 9.2, 4.0 Hz, CH_2), 1.06-1.00(1H, cm), 0.98(3H, s, CH_3), 0.89(3H, s, CH_3), 0.86(3H, s, CH_3) ppm; **^{13}C NMR** (62.90MHz, $CDCl_3$) 165.49(C=O), 154.86(C=O), 146.16(CH), 122.10(CH), 81.06(CH), 65.58(CH), 49.89(C), 47.45(CH), 46.28(C), 33.07(CH_2), 22.61(CH_2+CH_3), 19.44(CH_3), 18.32(CH_3), 11.85(CH_3) ppm; **FT IR** ν_{max} (nujol) 1758(C=O), 1682(C=O), 1632(C=C) cm^{-1}; **Accurate mass** found 264.16015(MH^+), $C_{15}H_{22}NO_3$ requires 264.15997.

3.8.3 Preparation of Cinnamate 143

This was prepared by the general procedure as in section 3.8.1, using ethyl bromide (0.30g, 2.8mmol, 1.2eq), magnesium turnings (0.06g, 2.5mmol, 1.1eq), auxiliary **131**

(0.43g, 2.2mmol) and freshly distilled cinnamoyl chloride (0.51g, 3.1mmol, 1.4eq). The only difference in procedure was that the reaction mixture was allowed to stir at room temperature overnight due to slower reaction. Flash chromatography as in section 3.8.1 gave (1*S*, 2*R*, 6*S*, 7*R*)-*N*-cinnamoyl-*exo*-3-oxa-*exo*-5-aza-7,10,10-trimethyltricyclo-[5.2.1.$0^{2,6}$]decan-4-one **143** a colourless solid (0.71g, 100%); **MP** = 141.5-142.5°C (cyclohexane); $[\alpha]_D^{21}$ = +149.6° (c=1.03,CH_2Cl_2); **^{1}H NMR** (250.13MHz, $CDCl_3$) δ 7.91(1H, d, *J* = 15.7 Hz, COC<u>H</u>=CH), 7.80(1H, d, *J* = 15.8 Hz, C=C<u>H</u>Ph), 7.61-7.57(2H, cm, Ph), 7.39-7.34(3H, cm, Ph), 4.51(2H, s, CHO and CHN), 2.16(1H, d, *J* = 5.1 Hz, bridgehead), 1.81-1.75(1H, cm), 1.56(1H, dt, *J* = 12.4, 4.6 Hz, CH_2), 1.31-1.21(1H, cm), 1.05-1.03(1H, cm), 1.03(3H, s, CH_3), 0.95(3H, s, CH_3), 0.88(3H, s, CH_3) ppm; **^{13}C NMR** (62.90MHz, $CDCl_3$) δ 165.69(C=O), 154.95(C=O), 145.74(CH), 134.44(Ar C), 130.36(Ar CH), 128.65(2 Ar CH), 128.39(2 Ar CH), 117.32(CH), 81.15(CH), 65.75(CH), 50.10(C), 47.45(CH), 46.32(C), 33.09(CH_2), 22.61(CH_2 and CH_3), 19.50(CH_3), 11.93(CH_3) ppm;**FT IR** ν_{max} (nujol) 1764(C=O), 1678(C=O), 1618(C=C) cm^{-1}; **Accurate mass** found 326.17662(MH^+), $C_{20}H_{24}NO_3$ requires 326.17526.

3.8.4 Preparation of the Propionate 144

Again the product was made by the protocol outlined in section 3.8.1, using ethyl bromide (0.76g, 7.0mmol, 1.4eq), magnesium turnings (0.15g, 6.2mmol, 1.3eq), auxiliary **131** (0.95g, 4.9mmol) and freshly distilled propionyl chloride (0.84g,

9.1mmol, 1.8eq). Flash chromatography (as in section 3.8.1) yielded (1*S*, 2*R*, 6*S*, 7*R*)-*N*-propionyl-*exo*-3-oxa-*exo*-5-aza-7,10,10-trimethyltricyclo-[5.2.1.$0^{2,6}$]decan-4-one **144** as a colourless solid (1.21g, 99%); **MP** = 89.1-90.3°C (pentane/cyclohexane); $[\alpha]_D^{21}$ = +55.2° (c=1.00,CH_2Cl_2); **^{1}H NMR** (250 MHz, $CDCl_3$) δ 4.46(1H, dd, *J* = 8.0, 0.8 Hz, CHO), 4.34(1H, d, *J* = 8.0 Hz, CHN), 2.93(1H, dq, *J* = 17.5, 7.2 Hz, CH<u>H</u>CH_3), 2.84(1H, dq, *J* = 17.5, 7.3 Hz, C<u>H</u>HCH_3), 2.17(1H, d, *J* = 5.1 Hz, bridgehead), 1.78(1H, dddd, *J* = 13.2, 11.8, 5.2, 3.9 Hz, CH_2), 1.51(1H, ddd, *J* = 16.4, 11.9, 4.5 Hz, CH_2), 1.25-1.13(1H, cm), 1.12(3H, t, *J* = 7.4 Hz, CH_3), 0.96(3H, s, CH_3), 0.88(3H, s, CH_3), 0.85(3H, s, CH_3), 1.05-0.80(1H, cm) ppm; **^{13}C NMR** (62.90 MHz,$CDCl_3$) δ 174.48(C=O), 154.90(C=O), 81.20(CH), 65.66(CH), 49.75(C), 47.46(CH), 46.26(C), 33.12(CH_2), 29.20(CH_2), 22.60(CH_2 and CH_3), 19.43(CH_3), 11.88(CH_3), 8.52(CH_3) ppm; **FT IR** ν_{max} (nujol) 1787, 1767(C=0), 1712(C=O) cm^{-1}; **Accurate mass** found 252.15964(MH^+), $C_{14}H_{22}NO_3$ requires 252.15997.

3.9 Asymmetric Diels-Alder Reactions

3.9.1 Diels-Alder Reaction Between the Crotonate 142 and Cyclopentadiene

To a solution of the crotonate **142** (0.21g, 0.78mmol) in dry methylene chloride (20ml) at -78°C under argon was added freshly cracked cyclopentadiene (0.52g, 7.8mmol, 10eq.). Diethylaluminium chloride (0.7ml, 1.8M in toluene, 1.3mmol, 1.6eq.) was then added and the reaction mixture stirred at -78°C for 20minutes until

the yellow colour had faded, then quenched with saturated ammonium chloride solution. The mixture was then extracted into methylene chloride (3x20ml) and the combined organic layers dried over magnesium sulphate. Subsequent filtration and evaporation *in vacuo* gave a pale yellow solid. The solid was subjected to flash chromatography (silica, hexane:ether (4:1)) to yield (1*S*, 2*R*, 6*S*, 7*R*)-*N*-((3'*R*, 4'*S*, 5'*S*, 6'*R*)-5'-methylbicyclo[2.2.1]heptene-4'-carbonyl)-*exo*-3-oxa-*exo*-5-aza-7,10,10-trimethyltricyclo[5.2.1.$0^{2,6}$]decan-4-one **151** as a colourless solid (0.24g, 92%); **MP** = 174.3-175.3°C (cyclohexane); $[\alpha]_D^{21}$ = +178° (c= 1.00, CH_2Cl_2); **^{1}H NMR** (360.13MHz, $CDCl_3$) δ 6.35(1H, dd, *J* = 5.6, 3.2 Hz, C=CH), 5.78(1H, dd, *J* = 5.7, 2.7 Hz, CH=C), 4.44(1H, d, *J* = 8.1 Hz, CHO), 4.35(1H, d, *J* = 8.1 Hz, CHN), 3.55(1H, dd, *J* = 4.4, 3.4 Hz, cycloadduct bridgehead CH), 3.28(1H,s, CH), 2.47(1H, d, *J* = 1.4 Hz, cycloadduct bridgehead CH), 2.12(1H, d, *J* = 5.1Hz, auxiliary bridgehead), 2.12-2.06(1H, cm), 1.81-1.72(1H, cm), 1.44(1H, d, *J* = 1.7 Hz, CH), 1.54-1.41(2H, cm), 1.22-1.13(1H, cm), 1.06(3H, d, *J* = 7.1 Hz, $CHC\underline{H}_3$), 1.02(3H, s, CH_3), 1.00-0.89(1H, cm), 0.86(3H, s, CH_3), 0.81(3H, s, CH_3) ppm; **^{13}C NMR** (50.32MHz, $CDCl_3$) δ 174.2(C=O), 154.7(C=O), 139.7(CH), 130.8(CH), 81.0(CH), 65.7(CH), 51.7(CH), 49.6(C), 49.0(CH), 47.5(CH and CH_3), 47.1(CH_2), 46.2(C), 35.1(CH), 33.2(CH_2), 22.6(CH and CH_2), 20.2(CH_3), 19.2(CH_3), 11.9(CH_3) ppm; **FT IR** ν_{max} (nujol) 1757(C=0), 1705(C=O) cm^{-1}; **Accurate mass** found 330.20691(MH^+), $C_{20}H_{28}NO_3$ requires 330.20691; **Elemental analysis** found 72.6% C, 8.1% H, 4.6% N, $C_{20}H_{27}NO_3$ requires 72.9% C, 8.3% H, 4.3% N.

3.9.2 Diels-Alder Reaction Between the Cinnamate 143 and Cyclopentadiene

The reaction protocol was as that described in section 3.9.1, using cinnamate **143** (0.19g, 0.59mmol), cyclopentadiene (0.40g, 6.1mmol, 10eq) and diethylaluminium chloride (0.5ml, 1.8M in toluene, 0.9mmol, 1.5eq). The only difference in conditions was that the reaction was stirred at -78°C for 15 minutes then warmed to -20°C and stirred for 40 minutes before quenching. Flash chromatography yielded (1*S*, 2*R*, 6*S*, 7*R*)-*N*-((3'*R*, 4'*S*, 5'*S*, 6'*R*)-5'-phenylbicyclo[2.2.1]heptene-4'-carbonyl)-*exo*-3-oxa-*exo*-5-aza-7,10,10-trimethyltricyclo[5.2.1.$0^{2,6}$]decan-4-one **152** as a colourless solid(0.23g, 99%); **MP** = 176.5-178°C; $[\alpha]_D^{21}$ = +169.3 (c=1.05, CH_2Cl_2); **^{1}H NMR** (250.13MHz, $CDCl_3$) δ 7.27-7.16(5H, cm, Ph), 6.54(1H, dd, *J* = 5.6, 3.2 Hz, HC=C<u>H</u>), 5.96(1H, dd, *J* = 5.6, 2.8 Hz, C<u>H</u>=CH), 4.44(1H, d, *J* = 8.2 Hz, CHO), 4.37(1H, d, *J* = 8.1 Hz, CHN), 4.22(1H, dd, *J* = 5.3, 3.4 Hz, CHCO), 3.51(1H, bs), 3.37(1H, dd, *J* = 5.3, 1.8 Hz, CHPh), 2.99(1H, bs), 2.15(1H, d, *J* = 5.1 Hz, cycloadduct bridgehead CH), 1.97(1H, d, *J* = 8.7 Hz, auxiliary bridgehead), 1.79-1.52(3H, cm), 1.30-1.10(1H, cm), 1.07(3H, s, CH_3), 1.06-0.73(1H, cm), 0.90(3H, s, CH_3), 0.88(3H, s, CH_3) ppm; **^{13}C NMR** (62.90MHz, $CDCl_3$) δ 173.82(C=O), 154.64(C=O), 143.76(Ar C), 40.25(CH), 132.06(CH), 128.27(2 Ar CH), 127.40(2 Ar CH), 125.87(Ar CH), 81.09(CH), 65.78(CH), 50.99(CH), 49.72(C), 49.12(CH), 48.13(CH_2), 47.53(CH), 47.42(CH), 46.26(C), 45.61(CH), 33.20(CH_2), 22.60(CH_2 and CH_3), 19.29(CH_3), 11.98(CH_3) ppm; **FT IR** ν_{max} (nujol) 1760(C=O), 1703(C=O) cm^{-1}; **Accurate mass** found 392.22334(MH^+) $C_{25}H_{30}NO_3$ requires 392.22257.

3.9.3 Diels-Alder Reaction Between the Acrylate 141 and Cyclopentadiene

Procedure as described for the crotonate in section 3.9.1 using acrylate **141** (0.18g, 0.72mmol), cyclopentadiene (0.48g, 7.3mmol, 10eq) and diethylaluminium chloride (0.6ml, 1.8M in toluene, 1.1mmol, 1.5eq), yielded (1*R*, 2*R*, 6*S*, 7*R*)-*N*-((3'*R*, 4'*S*, 6'*R*)-5'-bicyclo[2.2.1]heptene-4'-carbonyl)-*exo*-3-oxa-*exo*-5-aza-7,10,10-trimethyl-tricyclo[5.2.1.$0^{2,6}$]decan-4-one **150** as a colourless solid (0.22g, 99%). The *d.e.* of this crude material was determined by integration of the doublet of doublets at δ 6.26(0.9H, *J* = 5.6, 3.1 Hz), 6.16(0.1H, *J* = 5.1, 2.6 Hz), 5.98(0.1H, *J* = 5.1, 2.5 Hz) and 5.85(0.9H, *J* = 5.6, 2.8 Hz) ppm. Recrystalisation of the crude material afforded the major isomer; **^{1}H NMR** (250.13MHz, $CDCl_3$) δ 6.26(1H, dd, *J* = 5.6, 3.1 Hz, C<u>H</u>=CH), 5.85(1H, dd, *J* = 5.6, 2.8 Hz, CH=C<u>H</u>), 4.45(1H, d, *J* = 8.0 Hz, CHO), 4.34(1H, d, *J* = 8.1 Hz, CHN), 4.06(1H, dt, *J* = 8.3, 4.2 Hz, COC<u>H</u>CH_2), 3.36(1H, bs), 2.92(1H, bs), 2.14(1H, d, *J* = 5.0 Hz, auxiliary bridgehead), 1.83-0.92(8H, cm), 1.04(3H, s, CH_3), 0.88(3H, s, CH_3), 0.84(3H, s, CH_3) ppm; **^{13}C NMR** (62.90MHz, $CDCl_3$) δ 174.61(C=O), 154.78(C=O), 138.37(CH), 130.77(CH), 81.07(CH), 65.87(CH), 50.45(CH_2), 49.76 (C), 47.59(CH), 46.82(CH), 46.27(C), 42.97 (CH), 42.69(CH), 33.29(CH_2), 28.06(CH_2), 22.65(CH_2 and CH_3), 19.31(CH_3), 12.02(CH_3) ppm; **FT IR** ν_{max} (nujol) 1769(C=O), 1711(C=O) cm^{-1}; **Accurate mass** found 316.19215(MH^+), $C_{19}H_{26}NO_3$ requires 316.19127.

3.10 Asymmetric 1,4-Conjugate Addition Reactions

3.10.1 Conjugate Addition of Diethylaluminium Chloride to Cinnamate 143

Diethylaluminium chloride (1.7ml, 1.8M in toluene, 3.1mmol, 4eq) was added to a solution of the cinnamate **143** (0.25g, 0.77mmol) in dry methylene chloride (20ml) at -78°C under argon. The mixture was stirred at -78°C for 3 hours then quenched with saturated ammonium chloride solution. The reaction mixture was then separated and extracted into methylene chloride (3x20ml) and the combined organic layers dried over magnesium sulphate. The organic layers were then filtered and evaporated *in vacuo* to yield a colourless solid (0.27g, 99%). The *d.e.* of this crude product was determined by comparison of the intensities of the following signals in its ^{13}C spectrum: δ 81.11(0.89CH), 80.96(0.11CH), 65.68(0.89CH), 65.49(0.11CH), 29.60(0.89CH_2) and 29.42(0.11CH_2) ppm. The product was recrystallised from cyclohexane to give (1*S*, 2*R*, 6*S*, 7*R*)-*N*-(3'*S*-phenyl-pentanoyl)-*exo*-3-oxa-*exo*-5-aza-7,10,10-trimethyltricyclo[5.2.1.$0^{2,6}$]decan-4-one **155** as an enantiomerically pure colourless solid (0.24g, 86%); **MP** = 135.1-136.4°C (cyclohexane); $[\alpha]_D^{21}$ = +59.5° (c=1.10, CH_2Cl_2); **^{1}H NMR** (250.13MHz, $CDCl_3$) δ 7.30-7.13(5H, cm, Ph), 4.37(1H, d, *J* = 8.0 Hz, CHO), 4.23(1H, d, *J* = 8.0 Hz, CHN), 3.36-3.24(1H, cm), 3.20-3.09(1H, cm), 2.10(1H, d, *J* = 5.0 Hz, auxiliary bridgehead), 1.81-1.42(4H, cm), 1.26-1.10(2H, cm), 1.00-0.78(1H, cm), 0.98(3H, s, CH_3), 0.85(3H, s, CH_3), 0.79(3H, t, *J* = 7.4 Hz, $CH_2C\underline{H}_3$), 0.73(3H, s, CH_3) ppm; **^{13}C NMR** (62.90MHz, $CDCl_3$) δ 172.29(C=O), 154.85(C=O), 143.66(Ar C), 128.11(2 Ar CH), 127.73(2 Ar CH), 126.15(Ar CH), 81.13(CH), 65.69(CH), 49.72(C), 47.45(CH), 46.27(C), 43.17(CH), 41.72(CH_2), 33.11(CH_2), 29.62(CH_2), 22.58(CH_2 and CH_3), 19.56(CH_3), 11.74(CH_3), 11.61(CH_3) ppm; **FT IR** ν_{max} (nujol) 1774(C=O), 1698(C=O) cm^{-1}; **Accurate mass** found 356.22623(MH^+), $C_{22}H_{30}NO_3$ requires 356.22257; **Elemental**

analysis found 74.0% C, 9.0% H, 4.1% N, $C_{22}H_{29}NO_3$ requires 74.3% C, 8.6% H, 3.9% N.

3.10.2 Conjugate Addition of Diethylaluminium Chloride to Crotonate 142

The procedure outlined in section 3.10.1 was again followed, using the crotonate **142** (0.28g, 1.1mmol) and diethylaluminium chloride (2.4ml, 1.8M in toluene, 4.3mmol, 4eq), to give (1*S*, 2*R*, 6*S*, 7*R*)-*N*-(3'*S*-methyl-pentanoyl)-*exo*-3-oxa-*exo*-5-aza-7,10,10-trimethyltricyclo[5.2.1.$0^{2,6}$]decan-4-one **154** as a colourless gum (0.31g, 98%). The product was a mixture of diastereomers which proved to be inseparable by flash chromatography; **^{1}H NMR** (250.13MHz, $CDCl_3$) δ (both diastereomers) 4.46(1H, dd, *J* = 8.0, 0.6 Hz, CHO), 4.37(1H, d, *J* = 8.0 Hz, CHN), 3.04-2.53(3H, cm), 2.13(1H, d, *J* = 5.1 Hz, auxiliary bridgehead), 1.98-1.71(2H, cm), 1.58-1.04(3H, cm), 1.02-0.81(16H, cm) ppm; **^{13}C NMR** (62.90MHz, $CDCl_3$) δ 173.28(C=O), 154.87(C=O), 81.06(CH), 65.64(CH), 49.77(C), 47.46(CH), 46.27(C), 42.29(CH_2), 33.16(CH_2), 31.19(0.35 CH), 31.08(0.65CH), 29.27(0.65CH_2), 29.09(0.35CH_2), 22.61(CH_2 and CH_3), 19.43(CH_3), 18.98(CH_3), 12.01(CH_3), 11.09(CH_3) ppm; **FT IR** ν_{max} (thin film) 1770(C=O), 1700(C=O) cm^{-1}.

3.11 Asymmetric Acylation Reactions

3.11.1 Acylation of 144 with Acetyl Chloride

n-Butyllithium (0.5ml, 1.6M in hexanes, 0.8mmol, 1.1eq.) was added dropwise to a solution of diisopropylamine (0.1g, 1.0mmol, 1.4eq.) in anhydrous THF (5ml) at 0°C under argon. The resulting mixture was stirred at 0°C for 30 minutes then cooled to -78°C. A solution of the propionate **144** (0.18g, 0.72mmol) in anhydrous THF (10ml) was then added dropwise over a period of 10 minutes, then stirred for 30 minutes. Freshly distilled acetyl chloride (0.17g, 2.2mmol, 3eq.) was then added and the mixture stirred for 2 minutes, then quenched with saturated ammonium chloride solution. The mixture was concentrated *in vacuo* and the aqueous residue extracted into methylene chloride (3x20ml). The organic layers were dried over magnesium sulphate, filtered and evaporated *in vacuo* to yield (1*S*, 2*R*, 6*S*, 7*R*)-*N*-((2'*R*)-methyl-3-oxobutanoyl)-*exo*-3-oxa-*exo*-5-aza-7,10,10-trimethyltricyclo-[5.2.1.$0^{2,6}$]decan-4-one **157** as a pale yellow solid (0.2g, 95%); **MP** = 104-106°C (cyclohexane); $[\alpha]_D^{21}$ = -37.8° (c= 1.02, CH_2Cl_2); **^{1}H NMR** (250.13MHz, $CDCl_3$) δ 4.53-4.44(2H, dd overlapping a q, CHO and C<u>H</u>CH_3), 4.34(1H, d, *J* = 7.9 Hz, CHN), 2.27(3H, s, $COCH_3$), 2.11(1H, d, *J* = 5.1 Hz, auxiliary bridgehead), 1.84-1.72(1H, cm), 1.59-1.47(1H, cm), 1.33(3H, d, *J* = 7.3 Hz, CHC<u>H</u>$_3$) 1.24-1.13(1H, cm), 1.04-0.95(1H, cm), 1.02(3H, s, CH_3), 0.93(3H, s, CH_3), 0.87(3H, s, CH_3) ppm; **^{13}C NMR** (62.90MHz, $CDCl_3$) δ 205.16(C=O), 170.06(C=O), 155.08(C=O), 81.72(CH), 65.92(CH), 52.91(CH), 50.35(C), 47.60(CH), 46.25(C), 33.21(CH_2), 28.19(CH_3), 22.68(CH_3), 22.65(CH_2), 19.26(CH_3), 12.22(CH_3), 11.98(CH_3) ppm; **FT IR** ν_{max} (nujol) 1779(C=O), 1707 (bs, 2C=O) cm^{-1}; **Accurate mass** found 294.17118(MH^+), $C_{16}H_{24}NO_4$ requires 294.17053; **Elemental analysis** found 65.7% C, 8.2% H, 4.8% N, $C_{16}H_{23}NO_4$ requires 65.5% C, 7.9% H, 4.8% N.

3.11.2 Acylation of 144 with Propionyl Chloride

Same general protocol as in section 3.11.1, using *n*-butyllithium (0.5ml, 1.6M in hexanes, 0.8mmol, 1.1eq), diisopropylamine (0.11g, 1.1mmol, 1.5eq), propionate **144** (0.18g, 0.72mmol) and freshly distilled propionyl chloride (0.30g, 3.2mmol, 4eq). Reaction time was 7 minutes yielding a (1*S*, 2*R*, 6*S*, 7*R*)-*N*-((2'*R*)-methyl-3-oxopentanoyl)-*exo*-3-oxa-*exo*-5-aza-7,10,10-trimethyltricyclo[5.2.1.$0^{2,6}$]decan-4-one **158** as a colourless solid (0.16g, 72%); **MP** = 101.0-102.7°C; $[\alpha]_D^{21}$ = -21.0° (c=1.75, CH_2Cl_2); **^{1}H NMR** (250.13MHz, $CDCl_3$) δ 4.53-4.44(2H, dd overlapping a q, CHO and C<u>H</u>CH_3), 4.34(1H, d, *J* = 7.9 Hz, CHN), 2.70(1H, dq, *J* = 18.2, 7.4 Hz, C<u>H</u>HCH_3), 2.58(1H, dq, *J* = 18.2, 7.2 Hz, CH<u>H</u>CH_3), 2.09(1H, d, *J* = 5.1 Hz, auxiliary bridgehead), 1.85-1.71(1H, cm), 1.58-1.46(1H, cm), 1.31(3H, d, *J* = 7.2 Hz, COCHC<u>H</u>$_3$), 1.28-1.13(1H, cm), 1.03(3H, s, CH_3), 1.02(3H, t, *J* = 7.3 Hz, CH_2C<u>H</u>$_3$), 0.98-0.80(1H, cm), 0.91(3H, s, CH_3), 0.86(3H, s, CH_3) ppm; **^{13}C NMR** (62.90MHz, $CDCl_3$) δ 208.03(C=O), 170.28(C=O), 155.03(C=O), 81.67(CH), 65.87(CH), 52.26(CH), 50.32(C), 47.57(CH), 46.21(C), 33.77(CH_2), 33.18(CH_2), 22.66(CH_3), 22.61(CH_2), 19.18(CH_3), 12.60(CH_3), 11.97(CH_3), 7.40(CH_3) ppm; **FT IR** ν_{max} (nujol) 1767(C=O), 1714(C=O), 1693(C=O) cm^{-1}; **Accurate mass** found 308.18412(MH^+), $C_{17}H_{26}NO_4$ requires 308.18618; **Elemental analysis** found 66.2% C, 8.5% H, 4.5% N, $C_{17}H_{25}NO_4$ requires 66.4% C, 8.2% H, 4.6% N.

3.12 Asymmetric Aldol Reactions

3.12.1 Aldol Reaction Between Lithium Enolate of 144 and Benzaldehyde

Butyllithium (0.5ml, 1.6M in hexanes, 0.8mmol, 1.2eq) was added dropwise to a solution of diisopropylamine (0.09g, 0.89mmol, 1.3eq) in dry THF (5ml) at 0°C. The resulting mixture was stirred at 0°C for 30 minutes then cooled to -78°C and treated with a solution of the propionate **144** (0.17g, 0.68mmol) in dry THF (10ml), dropwise over 10 minutes. The reaction mixture was allowed to stir for 30 minutes then treated with a solution of freshly distilled bezaldehyde (0.12g, 1.13mmol, 1.6eq) in dry THF (5ml). The mixture was stirred for 5 minutes then quenched by the addition of a saturated solution of ammonium chloride (10ml). The mixture was then concentrated *in vacuo* and the aqueous residue extracted with methylene chloride (3x25ml). The combined organic layers were dried over magnesium sulphate, filtered and evaporated *in vacuo* to give a pale yellow oil (0.25g, 100%). Analysis of the crude product by high field NMR spectroscopy showed it to be a mixture three components (two of which were *syn* isomers).

3.12.2 Aldol Reaction Between Boron Enolate of 144 and Benzaldehyde

Dibutylboron triflate (0.7ml, 1.0M in CH_2Cl_2, 0.70mmol, 1.1eq) was added to a solution of propionate **144** (0.16g, 0.64mmol) in dry methylene chloride (10ml) at 0°C under argon. The mixture was then treated dropwise with diisopropylethylamine (0.15g, 1.2mmol, 1.8eq) in dry methylene chloride (2ml), then stirred at 0°C for 30 minutes. The reaction mixture was then cooled to -78°C and a solution of freshly

distilled benzaldehyde (0.10g, 9.4mmol, 1.5eq.) in dry methylene chloride (1ml) added and stirred for 30 minutes. The reaction mixture was then warmed to room temperature and stirred for 50 minutes before quenching with pH 7 buffer solution (30ml). The reaction mixture was then extracted into methylene chloride (3x10ml).The solvent removed *in vacuo* to give a yellow liquid which was taken up in methanol (30ml) cooled to 0°C and treated with 30% hyrogen peroxide (1ml). The reaction mixture was then stirred at room temperature overnight, sodium sulphite solution (10ml) was added and the mixture evaporated *in vacuo*. The aqueous residue was extacted into methylene chloride (3x20ml) and the combined organic layers dried over magnesium sulphate, filtered and evaporated *in vacuo* to give a pale yellow gum. The gum was purified by flash chromatography (silica, hexane:diethyl ether (100:0-0:100)) to yield (1*S*, 2*R*, 6*S*, 7*R*)-*N*-((3'*S*)-hydroxy-(2'*S*) methyl-3'-phenylpropionyl)-*exo*-3-oxa-*exo*-5-aza-7,10,10-trimethyltricyclo-[5.2.1.$0^{2,6}$]decan-4-one **160** as a colouless solid (0.21g, 67%); **MP** = 128.8-130.3°C; $[\alpha]_D^{21}$ = +14.3 (c=0.95, CH_2Cl_2); **^{1}H NMR** (250.13MHz, $CDCl_3$) δ 7.39-7.21(5H, cm, Ph), 5.10(1H, t, *J* = 2.8 Hz, C<u>H</u>OH), 4.46(1H, dd, *J* = 8.0, 0.7 Hz, CHO), 4.39(1H, d, *J* = 8.0 Hz, CHN), 4.12(1H, dq, *J* = 7.0, 3.4 Hz, C<u>H</u>CH_3), 3.38(1H, d, *J* = 2.4 Hz, OH), 2.15(1H, d, *J* = 5.1 Hz, auxiliary bridgehead), 1.83-1.74(1H, cm), 1.61-1.49(1H, cm), 1.27-1.15(1H, cm), 1.17(3H, d, *J* = 7.1 Hz, CHC<u>H</u>$_3$), 1.07-0.96(1H, cm), 0.98(3H, s, CH_3), 0.90(3H, s, CH_3), 0.88(3H, s, CH_3) ppm; **^{13}C NMR** (62.90MHz, $CDCl_3$) δ 177.96(C=O), 154.14(C=O), 141.13(Ar C), 128.07(2Ar CH), 127.17(Ar CH), 126.00(2Ar CH), 81.19(CH), 72.58(CH), 65.37(CH), 49.99(C), 47.49(CH), 46.34(C), 44.30(CH), 33.16(CH_2), 22.60(CH_2 and CH_3), 19.50(CH_3), 11.74(CH_3), 10.88(CH_3)

ppm; **FT IR** ν_{max} (nujol) 3480(OH), 1777(C=O), 1674(C=O) cm^{-1}; **Accurate mass** found 358.20311(MH^+), $C_{21}H_{28}NO_4$ requires 358.20183.

3.12.3 Aldol Reaction Between Boron Enolate of 144 and Acetaldehyde

Procedure as in section 3.12.1, using dibutylboron triflate (0.9ml, 1.0M in CH_2Cl_2, 0.90mmol, 1.1eq), diisopropylethylamine (0.14g, 1.1mmol, 1.3eq), propionate **144** (0.20g, 0.80mmol) and acetaldehye (0.3g, 9eq). Flash chromatography as in section 3.12.1 yielded cleaved auxiliary(0.07g, 46%), and (1*S*, 2*R*, 6*S*, 7*R*)-*N*-((3'*R*)-hydroxy-(2'*S*)-methyl-butanoyl)-*exo*-3-oxa-*exo*-5-aza-7,10,10-trimethyltricyclo-[5.2.1.$0^{2,6}$]-decan-4-one **162** as a colourless solid (0.09g, 38%); **MP** = 151.0-152.1°C; $[\alpha]_D^{21}$ = +42.9 (c=0.95, CH_2Cl_2); **^{1}H NMR** (250.13MHz, $CDCl_3$) δ 4.44(1H, dd, *J* = 8.0, 0.6 Hz, CHO), 4.40(1H, d, *J* = 8.0 Hz, CHN), 4.14-4.04(1H, cm, C<u>H</u>OH), 3.70(1H, dq, *J* = 7.2, 2.7 Hz, COC<u>H</u>(CH_3)), 3.14(1H, d, *J* = 2.1 Hz, OH), 2.13(1H, d, *J* = 5.1 Hz, auxiliary bridgehead), 1.86-1.72(1H, cm), 1.58-1.46(1H, cm), !.25-1.18(1H, cm), 1.22(3H, d, *J* = 7.2 Hz, COCH(C<u>H</u>$_3$)), 1.14(3H, d, *J* = 6.5 Hz, CH(OH)C<u>H</u>$_3$), 1.06-0.95(1H, cm), 0.97(3H, s, CH_3), 0.86(6H, bs, $2CH_3$) ppm; **^{13}C NMR** (62.90MHz, $CDCl_3$) δ 178.25(C=O), 154.27(C=O), 81.11(CH), 66.66(CH), 65.23(CH), 49.89(C), 47.40(CH), 46.29(C), 43.01(CH), 33.08(CH_2), 22.56(CH_2 and CH_3), 19.45(CH_3), 19.28(CH_3), 11.71(CH_3), 10.51(CH_3) ppm; **FT IR**

ν_{max} (nujol) 3543(OH), 1765(C=O), 1689(C=O) cm^{-1}; **Accurate mass** found 296.18755(MH^+), $C_{16}H_{26}NO_4$ requires 296.18618; **Elemental analysis** found 64.69% C, 8.42% H, 4.59% N, $C_{16}H_{25}NO_4$ requires 65.06% C, 8.53% H, 4.74% N.

3.13 Nucleophillic Cleavage of Benzaldehde Aldol Product 160

The aldol product **160** (0.22g, 0.62mmol) in anhydrous methanol (10ml) at 0°C under argon was treated with a solution of sodium methoxide (1.1eq, 0.70mmol) in dry methanol (1ml). The reaction mixture was then stirred at 0°C for 15minutes then water(10ml) added and the reaction mixture concentrated *in vacuo*. The aqueous residue was extracted into methylene chloride (3x10ml) and the organic layers combined, dried over magnesium sulphate, filtered and evaporated *in vacuo* to give a pale yellow solid. The solid was purified by flash chromatography (silica, hexane:ether (9:1 - 1:1)) to give cleaved auxiliary **131** (0.08g, 66%) and 2(*S*),3(*S*)-methyl-2-methyl-3-hydroxy-3-phenyl propionate **166** as a pale yellow gum (0.03g, 28%); $[\alpha]_D^{21}$ = -13.2° (c=1.00, $CHCl_3$) (Lit[6] = +23.2° (c=3.2 $CHCl_3$) (*R*,*R* enantiomer)); **^{1}H NMR** (250.13MHz, $CDCl_3$) δ 7.35-7.25(5H, cm, Ph), 5.10(1H, d, *J* = 3.2 Hz, $CHCH_3$), 3.67(3H, s, CH_3O), 2.94(1H, bs, OH), 2.78(1H, dq, *J* = 7.2, 4.1 Hz, $CHCH_3$), 1.12(3H, d, *J* = 7.2 Hz, CH_3).

4. Synthesis and Evaluation of the Novel Auxiliary 167

4.1 Attempted Synthesis of Episulphone 171 Using Diazald®

(a.) Preparation Of Diazomethane

The procedure outlined by Aldrich for use with their mini-Diazald® kit was used. Ethanol (20ml) was added to a solution of potassium hydroxide (10.0g, 179mmol) in water (16ml). The reaction flask was warmed to *ca.* 60°C with a water bath and a solution of Diazald® (*N*-methyl-*N*-nitroso-*p*-toluenesulphonamide) (10.17g, 48.00mmol) in ether (100ml) was then added dropwise over a period of 30 minutes. The distilled diazomethane (approx. 33mmol) was collected in a flask, which was cooled to -20°C, with potassium hydroxide pellets and ether (50ml) already present in the vessel.

(b.) Attempted Synthesis (**Note**- All glassware used had Clear-Seal joints, no ground glass was used.)

The ethereal diazomethane solution (*ca.* 33mmol) (from part a.) was dried over potassium hydroxide pellets for 2 hours, then transferred to a 500ml 3-necked flask. Triethylamine (3.34g, 33.1mmol) and ether (50ml) were added and the resulting mixture cooled to 0°C. A solution of (1*S*)-(+)-10-camphorsulphonyl chloride **170** (6.34g, 25.3mmol) in ether (100ml) was then added dropwise over 1 hour. The mixture was then allowed to warm to room temperature and stirred overnight. The reaction mixture was then concentrated *in vacuo* and filtered. The solid was washed with ether and subsequent evaporation *in vacuo* of the filtrate gave a yellow oil. The

crude product was recrystallised from methanol at -20°C to give colourless crytstals which were further purified by flash chromatography (silica, hexane:ether (9:1-4:1))to give a colourless solid (1.86g, 28%) which was identified as the ethylsulphonate ester **172**; **MP** = 44.2-45.2°C (Lit[90] = 47°C); $[\alpha]_D^{21}$ = +46.2° (c=2.35, $CHCl_3$) (Lit[90] = +43.3° (c=2.5, $CHCl_3$)); **^{1}H NMR** (250.13MHz, $CDCl_3$) δ 4.35(1H, dq, *J* = 9.8, 7.2 Hz, $CH_3C\underline{H}HO$), 4.30(1H, dq, *J* = 9.8, 7.0 Hz, $CH_3CH\underline{H}O$), 3.56(1H, d, *J* = 15.1 Hz, $C\underline{H}HSO_2$), 2.95(1H, d, *J* = 15.1 Hz, $CH\underline{H}SO_2$), 2.47-2.30(2H, cm), 2.11-1.88(2H, cm), 1.72-1.57(1H, cm), 1.45-1.30(1H, cm), 1.37(3H, t, *J* = 7.1 Hz, $CH_2C\underline{H}_3$), 1.08(3H, s, CH_3), 0.85(3H, s, CH_3) ppm; **^{13}C NMR** (62.90MHz, $CDCl_3$) δ 214.41(C=O), 66.75(CH_2), 57.74(C), 47.79(C), 46.47(CH_2), 42.52(CH), 42.32(CH_2), 26.67(CH_2), 24.64(CH_2), 19.59(CH_3), 19.49(CH_3), 14.90(CH_3) ppm; **FT IR** ν_{max} (nujol) 1741(C=O) cm^{-1}.

4.2 Preparation of Nitrosomethylurea 173

The method of Arndt[91] was followed.

Concentrated hydrochloric acid (50ml) was added to a 25-30% solution of aqueous methylamine (50g, 375mmol) until the mixture was acidic to methyl red indicator. Water (125ml) was then added, followed by urea **174** (75g, 1.2mol), and the mixture heated under reflux for 3 hours. The reaction mixture was allowed to cool to room temperature, and sodium nitrite (26.0g, 375mmol) added and the mixture cooled to 0°C. The cooled reaction mixture was then slowly added, with mechanical stirring, to a flask containing ice (150g) and concentrated sulphuric acid (25g), cooled in an ice/salt bath. The solid produced was filtered off and washed with a little cold water,

then dried *in vacuo* at room temperature to give nitrosomethylurea **173** as a pale pink solid (37g, 30%); **MP** = 121-122°C (Lit[91] = 123-124°C).

4.3 Preparation of Episulphone 171 Using Nitrosomethylurea 173

(a.) Preparation of Diazomethane

Note: as in section 4.1 no ground glass was used.

A mixture of potassium hydroxide (50%, 20ml) and ether (70ml) was cooled to 5°C and treated with nitrosomethylurea **173** (5.71g, 57.1mmol) with shaking. The mixture was then heated to 50°C with a water bath and the ethereal diazomethane solution distilled into a flask at -20°C containing ether (70ml) and potassium hydroxide pellets (this gave approx. 30mmol of diazomethane).

(b.) Synthesis of Episulphone **171**

The method of Fischer and Opitz[89] was followed.

The ethereal diazomethane solution (30mmol) was dried over potassium hydroxide for 2.5 hours then transferred to a 500ml 3 necked flask. Triethylamine (3.10g, 30.7mmol) and ether (50ml) were then added and the solution cooled to 0°C. A solution of (1*S*)-(+)-10-camphorsulphonyl chloride **170** (6.02g, 24.0mmol) in ether (100ml) was then added dropwise over 1 hour, and the mixture then stirred at 0°C for 2 hours. The reaction mixture was then concentrated *in vacuo*, filtered and evaporated *in vacuo* to give an orange oil. The oil was recrystallised from methanol at -20°C to give a colourless solid. TLC showed this solid to be a mixture of two components but due to the unstability of the episulphone **171** no further purification

was carried out; **MP** = 77-79°C (Lit[89] = 83-85°C), **FT IR** ν_{max} (nujol) 1745(C=O) cm^{-1}.

4.4 Preparation of 1-Vinyl-camphor 169 From Episulphone 171

Again Fischer and Opitz's method[89] was followed.

The crude episulphone **171** (1.12g, 4.91mmol) (from section 4.3) was heated to 95°C in a small flask, with a condenser fitted, for 30 minutes, during which time gas was seen to be evolved. The resulting crude yellow liquid was distilled on a Kugelrohr (3mmHg, 120°C) to give (1*R*)-1-vinyl-7,7-dimethylbicyclo[2.2.1]hepan-2-one **169** as a colourless waxy solid (0.57g, 60% based on camphorsulphonyl chloride); **MP** = 62-64°C (Lit[89] = 64-65°C); $[\alpha]_D^{21}$ = +16.4° (c=2.15, MeOH); **^{1}H NMR** (250.13MHz, $CDCl_3$) δ 5.76(1H, dd, *J* = 17.6, 11.1 Hz, C<u>H</u>=CH_2), 5.33(1H, dd, *J* = 11.1, 1.7 Hz, proton of =CH_2 *cis* to H), 5.16(1H, dd, *J* = 17.6, 1.7 Hz, proton of =CH_2 *trans* to H), 2.40(1H, ddd, *J* = 18.3, 4.6, 2.2 Hz, CH<u>H</u>CO), 2.11-1.81(4H, cm, including bridgehead), 1.48-1.32(2H, cm), 0.88(3H, s, CH_3) 0.87(3H, s, CH_3) ppm; **^{13}C NMR** (62.90MHz, $CDCl_3$) δ 217.11(C=O), 131.98(<u>C</u>H=CH_2), 118.76(CH=<u>C</u>H_2), 63.90(C), 48.29(C), 43.41(CH_2), 43.15(CH), 26.71(CH_2), 25.67(CH_2), 19.90(CH_3), 19.13(CH_3) ppm; **FT IR** ν_{max} (nujol) 1747(C=O), 1640(C=C) cm^{-1}.

4.5 Synthesis of 10-Methylcamphor 168

10% Pd/C (0.70g, 0.1eq) was added to a solution of vinylcamphor **169** (6.25g, 38.1mmol) in ethanol (80ml). The reaction mixture was then stirred under an atmosphere of hydrogen for 16 hours. The mixture was then filtered through a pad of

celite and the filtrate evaporated *in vacuo* to give (1*R*)-1-ethyl-7,7-dimethylbicyclo[2.2.1]heptan-2-one **168** as a clear colourless liquid (5.81g, 93%); $[\alpha]_D^{21}$ = +24.8° (c=2.85, EtOH); **^{1}H NMR** (250.13MHz, $CDCl_3$) δ 2.30(1H, ddd, *J* = 18.1, 4.8, 3.3 Hz, C<u>H</u>HCO), 2.02-1.93(1H, cm, bridgehead), 1.92-1.15(7H, cm), 0.98(3H, t, *J* = 7.6 Hz, $CH_2C\underline{H}_3$), 0.94(3H, s, CH_3), 0.85(3H, s, CH_3) ppm; **^{13}C NMR** (62.90MHz, $CDCl_3$) δ 219.74(C=O), 60.17(C), 47.17(C), 43.36(CH and CH_2), 26.72(CH_2), 26.31(CH_2), 20.22(CH_3), 19.71(CH_3), 18.18(CH_2), 9.43(CH_3) ppm; **FT IR** ν_{max} (thin film) 1741(C=O) cm^{-1}.

4.6 Synthesis of 10-Methyl-camphorquinone 176

Selenium dioxide (11.1g, 100mmol, 3eq) was added to a solution of 10-methyl-camphor **168** (5.95g, 35.8mmol) in acetic anhydride (30ml), and the mixture then heated under reflux for 48 hours. A further portion of selenium dioxide (11g, 99mmol, 3eq) was added and reflux continued for another 24 hours. The mixture was allowed to cool and neutralised with 30% sodium hydroxide solution, then taken to pH 8, and filtered through a pad of celite. The solid residue was washed with ether until the ether ran colourless (*ca.* 1.5 litres). The filtrate was separated and the organic layer dried over magnesium sulphate, filtered and evaporated *in vacuo* to give a yellow oil. The oil was subjected to flash chromatography (silica, hexane:ether (95:5)) to give (1*R*)-1-ethyl-7,7-dimethylbicyclo[2.2.1]heptan-2,3-dione **176** as a yellow solid (3.26g, 51%); **MP** = 56.0-56.7°C (methanol/water); $[\alpha]_D^{21}$ = -157° (c=1.00, CH_2Cl_2); **^{1}H NMR** (250.13MHz, $CDCl_3$) δ 2.51(1H, d, *J* = 4.9 Hz, bridgehead), 2.17-2.04(1H, cm), 1.97-1.86(1H, cm), 1.76-1.51(3H, cm), 1.46-

1.32(1H, cm), 1.02(3H, t, J = 7.6 Hz, $CH_2C\underline{H}_3$), 1.00(3H, s, CH_3), 0.89(3H, s, CH_3) ppm; **^{13}C NMR** (62.90MHz, $CDCl_3$) δ 204.69(C=O), 202.78(C=O), 61.27(C), 58.11(CH), 42.76(C), 26.44(CH_2), 21.75(CH_2), 21.28(CH_3), 17.82(CH_2), 17.65(CH_3), 9.19(CH_3) ppm; **FT IR** ν_{max} (nujol) 1756(bs, 2C=O) cm^{-1}; **Accurate mass** found 181.12301(MH^+), $C_{11}H_{17}O_2$ requires 181.12285.

4.7 Stereoselective Reduction of 176 With L-Selectride®

L-Selectride® (25ml, 1.0M in THF, 25mmol, 1.1eq) was added to a solution of 10-methyl-camphorquinone **176** (4.00g, 22.2mmol) in dry THF (80ml) at -78°C under argon. The reaction mixture was allowed to stir at -78°C for 1.5 hours, then quenched by the addition of a 3M solution of hydrochloric acid in methanol (40ml) and stirred at -78°C for 20 minutes. The THF was then removed *in vacuo* and the aqueous residue extracted into methylene chloride (3x100ml). Subsequent drying over magnesium sulphate, filtration and evaporation *in vacuo* of the combined organic layers gave an unpleasant smelling yellow liquid. The liquid was purified by flash chromatography (silica, hexane:ether (9:1 - 3:1)) to give (1*R*, 3*R*)-*exo*-3-hydroxy-1-ethyl-7,7-dimethylbicyclo[2.2.1]heptan-2-one **177** as a clear colourless oil (3.64g, 91%); $[\alpha]_D^{21}$ = +77.3° (c=1.5, CH_2Cl_2); **^{1}H NMR** (250.13MHz, $CDCl_3$) δ 3.65(1H, s, C$\underline{H}$OH), 3.25(1H, bs, CHO$\underline{H}$), 2.00-1.87(2H, cm, includes bridgehead), 1.71-1.28(3H, cm), 1.22-1.04(1H, cm), 0.97-0.79(10H, cm, including $3CH_3$) ppm; **^{13}C NMR** (62.90MHz, $CDCl_3$) δ 220.42(C=O), 77.15(CH), 59.89(C), 49.35(CH), 47.00(C), 24.78($2CH_2$), 21.00(CH_3), 20.54(CH_3), 17.65(CH_2), 9.16(CH_3) ppm; **FT**

IR ν_{max} (thin film) 3459(OH), 1749(C=O) cm^{-1}; **Accurate mass** found 183.13843(MH^+), $C_{11}H_{19}O_2$ requires 183.13851.

4.8 Attempted Formation of the Imine 178

Benzylamine (0.56g, 5.2mmol, 1.8eq), freshly distilled from zinc dust, and 4Å molecular sieves (*ca.* 1.0g, dried under vacuum at 90°C for 1 hour) were added to a solution of the keto-alcohol **177** (0.52g, 2.9mmol) in dry THF (30ml) under argon. The reaction mixture was then stirred at room temperature for 48 hours. After this time TLC (silica, hexane:ether (1:1)) indicated no reaction had occured, so the mixture was filtered and evaporated to give recovered starting material (0.50g, 96%).

4.9 Formation of the *exo-exo*-Amino-Alcohol 179 Directly From 177

The general procedure outlined by Mattson *et al*[92] was used.

A mixture of the keto-alcohol **177** (1.05g, 5.77mmol), benzylamine (0.64g, 6.0mmol, 1.0eq) and titanium(IV)isopropoxide (2.07g, 7.92mmol, 1.4eq) were stirred together at room temperature with the exclusion of moisture for 1 hour, FT IR spectroscopy then showed the absence of any ketone band. Ethanol (7ml) was then added followed by the addition of sodium cyanoborohydride (0.25g, 4.0mmol, 0.7eq), and the reaction mixture stirred at room temperature for 22 hours. Water (2ml) was added and the mixture filtered and concentrated *in vacuo*. The residue was dissolved in ethyl acetate and again filtered and evaporated *in vacuo* to yield a cloudy, creamy coloured oil. The oil was purified by flash chromatography (silica, hexane:ether (95:5 - 4:1)) to give (1*R*, 2*S*, 3*R*)-*N*-benzyl-*exo*-2-amino-*exo*-3-hydroxy-1-ethyl-7,7-

dimethylbicyclo-[2.2.1]heptane **179** as a clear colourless oil (0.70g, 45%); $[\alpha]_D^{21}$ = -44.0° (c=1.50, CH_2Cl_2); **^{1}H NMR** (250.13MHz, $CDCl_3$) δ 7.35-7.25(5H, cm, Ph), 3.75(2H, s, $PhC\underline{H}_2$), 3.64(1H, d, *J* = 7.2 Hz, C<u>H</u>OH), 2.85(1H, d, *J* = 7.2 Hz, C<u>H</u>NH), 1.79(1H, d, *J* = 4.7 Hz, bridgehead), 1.78-1.57(1H, cm), 1.50-1.16(4H, cm), 1.11-0.82(1H, cm), 0.99(3H, s, CH_3), 0.90(3H, t, *J* = 7.5 Hz, $CH_2C\underline{H}_3$), 0.75(3H, s, CH_3) ppm; **^{13}C NMR** (62.90MHz, $CDCl_3$) δ 139.33(Ar C), 128.39(2Ar CH), 128.08(2Ar CH), 127.21(Ar CH), 74.02(CH), 67.12(CH), 55.64(CH_2), 52.06(C), 51.45(CH), 46.74(C), 32.70(CH_2), 23.29(CH_2), 21.98(CH_3), 21.21(CH_3), 19.22(CH_2), 9.38(CH_3) ppm; **FT IR** ν_{max} (thin film) 3357(OH), 3330(NH) cm^{-1}; **Accurate mass** found 274.21663(MH^+), $C_{18}H_{28}NO$ requires 274.21709.

4.10 Removal of Benzyl Group from Amino-alcohol 179

10% Pd/C (0.16g, 0.3eq) was added to a solution of the amino alcohol **179** (0.66g, 2.4mmol) in ethanol (15ml) and the reaction mixture stirred under an atmosphere of hydrogen for 48 hours. The mixture was then filtered through a pad of celite, then evaporated *in vacuo* to give a very pale yellow oil. The oil was purified by dry flash chromatography (silica, ether:methanol (100:0 - 0:100)) to give (1*R*, 2*S*, 3*R*)-*exo*-2-amino-*exo*-3-hydroxy-1-ethyl-7,7-dimethylbicyclo[2.2.1]heptane **180** as a colourless waxy solid (0.41g, 93%); **MP** = >270°C decomposes; $[\alpha]_D^{21}$ = -44.2° (c=1.00, CH_2Cl_2); **^{1}H NMR** (250.13MHz, $CDCl_3$) δ 3.55(1H, d, *J* = 7.5 Hz, C<u>H</u>OH), 2.99(1H, d, *J* = 7.5 Hz, C<u>H</u>NH_2), 2.48(3H, bs, OH and NH_2), 1.78(1H, d, *J* = 4.7 Hz, bridgehead), 1.64-1.51(1H, cm), 1.46-1.34(2H, cm), 1.24-0.74(3H, cm), 0.97(3H, s, CH_3), 0.88(3H, t, *J* = 7.4 Hz, $CH_2C\underline{H}_3$), 0.72(3H, s, CH_3) ppm; **^{13}C NMR**

(62.90MHz, $CDCl_3$) δ 74.75(CH), 58.82(CH), 51.31(C), 51.11(CH), 46.83(C), 32.22(CH_2), 23.51(CH_2), 22.07(CH_3), 20.63(CH_3), 19.10(CH_2), 9.18(CH_3) ppm; **FT IR** ν_{max} (nujol) 3453 and 3328(NH_2) cm^{-1} both superimposed on a bs(OH); **Accurate mass** found 184.17109(MH^+), $C_{11}H_{22}NO$ requires 184.17014.

4.11 Formation of the Oxazolidin-2-one Auxiliary 167

The primary amino alcohlol **180** (0.38g, 2.1mmol) in DME (10ml) was treated with a solution of sodium hydroxide (2.0ml, 6M in water, 12mmol, 6eq), then cooled to -5°C (ice/salt). Triphosgene (0.28g, 0.94mmol, 0.4eq) in methylene chloride (8ml) was then added and the mixture stirred for 1 hour at -5°C, then at room temperature for a further 1.5 hours. TLC (silica, cyclohexane:ethyl acetate (2:1)) indicated reaction was complete, so water (20ml) was added and the mixture extracted into methylene chloride (3x50ml). The combined organic layers were dried over magnesium sulphate, filtered and evaporated *in vacuo* to give a pale brown solid. The crude product was subjected to dry flash chromatography (silica, hexane:ether (100:0 - 0:100)) to give (1*S*, 2*R*, 6*S*, 7*R*)-*exo*-3-oxa-*exo*-5-aza-7-ethyl-10,10-dimethyl-tricyclo[5.2.1.$0^{2,6}$]decan-4-one **167** as a very pale yellow crystalline solid (0.40g, 92%); **MP** = 138.0-140.0°C (xylene/cyclohexane); $[\alpha]_D^{21}$ = -10.0° (c=1.25, CH_2Cl_2); **^{1}H NMR** (250.13MHz, $CDCl_3$) δ 7.21(1H, bs, NH), 4.54(1H, d, *J* = 8.1 Hz, CHO), 3.72(1H, dd, *J* = 8.1, 0.9 Hz, CHN), 2.06(1H, d, *J* = 5.1 Hz, bridgehead), 1.78-1.65(1H, cm), 1.53-1.16(3H, cm), 1.10-0.78(2H, cm), 1.03(3H, s, CH_3), 0.84(3H, t, *J* = 7.5 Hz, $CH_2\underline{CH}_3$), 0.83(3H, s, CH_3) ppm; **^{13}C NMR** (62.90MHz, $CDCl_3$) δ 161.03(C=O), 83.84(CH), 62.40(CH), 51.18(C), 48.14(CH), 46.51(C), 29.27(CH_2),

23.26(CH_3), 22.59(CH_2), 19.02(CH_3), 18.15(CH_2), 9.28(CH_3) ppm; **FT IR** ν_{max} (nujol) 3253(NH), 3141(NH), 1733(C=O), 1713(C=O) cm^{-1}; **Accurate mass** found 210.14970(MH^+), $C_{12}H_{20}NO_2$ requires 210.14940; **Elemental analysis** found 68.7% C, 9.1% H, 6.5% N, $C_{12}H_{19}NO_2$ requires 68.9% C, 9.1% H, 6.7% N.

4.12 Functionalisation of Auxiliary 167

4.12.1 Attempted Functionalisation of 167 *via* its Magnesium Salt

Ethyl bromide (0.23g, 2.1mmol, 2eq) was added to magnesium turnings (0.03g, 1.2mmol, 1.3eq) in dry THF (4ml) under argon. When all the magnesium had dissolved dry THF (10ml) was added and the mixture cooled to 0°C, and treated with a solution of the auxiliary **167** (0.20g, 0.96mmol) in dry THF (12ml), then stirred at 0°C for 20 minutes. The mixture was then cooled to -78°C and crotonyl chloride (0.18g, 1.7mmol, 1.8eq) added. The mixture was warmed to room temperature and stirred for 2 hours after which time TLC (silica, hexane:ether (1:1)) indicated no reaction had occured, so the reaction mixture was then heated under reflux for 20 hours. After this time TLC (silica, hexane:ether (1:1)) showed still no reaction had occured, so the reaction was quenched by the addition of saturated ammonium chloride solution, and the THF then removed *in vacuo*. The residue was extracted into methylene chloride (3x50ml), dried over magnesium sulphate, filtered and evaporated to give starting material **167** (0.2g, 100%).

4.12.2 Formation of the Crotonate 184 Using Diethylzinc

Diethylzinc (1.0ml, 1.0M in hexanes, 1.0mmol, 1.1eq) was added to a solution of the auxiliary **167** (0.18g, 0.86mmol) in dry ether (12ml) under argon, and the mixture stirred at room temperature for 1 hour. The reaction mixture was then cooled to -78°C and treated with crotonyl chloride (0.30g, 2.9mmol, 3eq), then allowed to warm to room temperature and stirred for 1.5 hours. The mixture was warmed to 25°C and stirred for 4 hours, then left to stir at room temperature overnight, after which time TLC (silica, hexane:ether (1:1)) indicated the reaction had proceeded to about 50% completion. The reaction was quenched by the careful addition of saturated sodium bicarbonate solution, then treated with a 1:1 mixture of 1M hydrochloric acid and saturated ammonium chloride solution until two distinct layers were observed. The layers were then separated and the aqueous further extracted with ether (3x50ml). The combined organic layers were dried over magnesium sulphate, filtered and evaporated *in vacuo* to give a yellow oil. The oil was purified by flash chromatography (silica, hexane:ether (95:5 - 8:1)) to give unreacted auxiliary **167** (0.06g, 33%) and (1*S*, 2*R*, 6*S*, 7*R*)-*N*-crotonoyl-*exo*-3-oxa-*exo*-5-aza-7-ethyl-10,10-dimethyltricyclo[5.2.1.$0^{2,6}$]-decan-4-one **184** as a colourless solid (0.90g, 38%); **MP** = 134-136°C; $[\alpha]_D^{21}$ = +48.7° (c=0.75, CH_2Cl_2); **^{1}H NMR** (250.13MHz, $CDCl_3$) δ 7.25-7.03(2H, cm, C<u>H</u>=C<u>H</u>), 4.54-4.45(2H, cm, CHO and CHN), 2.11(1H, d, *J* = 5.0 Hz, bridgehead), 1.92(3H, d, *J* = 5.2 Hz, C=CHC<u>H</u>$_3$), 1.82-1.70(2H, cm), 1.63-1.51(1H, cm), 1.30-1.12(3H, cm), 0.98(3H, s, CH_3), 0.95(3H, t, *J* = 7.4 Hz, $CH_2C\underline{H}_3$), 0.89(3H, s, CH_3) ppm; **^{13}C NMR** (62.90MHz, $CDCl_3$) δ 165.66(C=O), 155.13(C=O), 145.90(<u>C</u>H=C), 122.60(C=<u>C</u>H), 81.11(CH), 63.91(CH), 53.13(C),

47.93(CH), 46.80(C), 29.26(CH_2), 23.53(CH_3), 22.31(CH_2), 19.42(CH_3), 18.34(CH_2 and CH_3), 9.72(CH_3) ppm; **FT IR** ν_{max} (nujol) 1759(C=O), 1690(C=O), 1634(C=C) cm^{-1}; **Accurate mass** found 278.17594(MH^+), $C_{16}H_{24}NO_3$ requires 278.17562.

4.12.3 Preparation of the Acrylate 183 Using Diethylzinc

The procedure in section 4.12.2 was repeated using auxiliary **167** (0.26g, 1.2mmol), quinol (*ca.* 10mg), diethylzinc (1.4ml, 1.0M in hexanes, 1.4mmol, 1.1eq) and acryloyl chloride (0.36g, 4.0mmol, 3 eq). Purification as before yielded unreacted auxiliary **167** (0.13g, 50%) and (1*S*, 2*R*, 6*S*, 7*R*)-*N*-acryloyl-*exo*-3-oxa-*exo*-5-aza-7-ethyl-10,10-dimethyltricyclo[5.2.1.$0^{2,6}$]decan-4-one **183** as a colourless solid (0.1g, 31%); **MP** = 84.0-86.0°C (hexane); $[\alpha]_D^{21}$ = +66.8° (c=0.75, $CHCl_3$); **^{1}H NMR** (250.13MHz, $CDCl_3$) δ 7.42(1H, dd, *J* = 17.0, 10.3 Hz, C<u>H</u>=CH_2), 6.48(1H, dd, *J* = 17.0, 1.7 Hz, proton of CH=C<u>H</u>$_2$ *trans* to H), 5.85(1H, dd, *J* = 10.5, 1.7 Hz, proton of CH=C<u>H</u>$_2$ *cis* to H), 4.54(1H, distorted d, *J* = 8.0 Hz, CHO), 4.50(1H, distorted d, *J* = 8.2 Hz, CHN), 2.14(1H, d, *J* = 5.0 Hz, bridgehead), 1.86-1.73(1H, cm), 1.66-1.54(1H, cm), 1.33-1.15(3H, cm), 1.07-0.96(1H, cm), 1.00(3H, s, CH_3), 0.98(3H, t, *J* = 7.3 Hz, CH_2C<u>H</u>$_3$), 0.91(3H, s, CH_3) ppm; **^{13}C NMR** (62.90MHz, $CDCl_3$) δ 165.69(C=O), 155.07(C=O), 130.94(<u>C</u>H=CH_2), 128.19(CH=<u>C</u>H_2), 81.36(CH), 64.00(CH), 53.27(C), 47.95(CH), 46.88(C), 29.31(CH_2), 23.54(CH_3), 22.34(CH_2), 19.48(CH_3), 18.39(CH_2), 9.74(CH_3) ppm; **FT IR** ν_{max} (nujol) 1759(C=O), 1698(C=O), 1616(C=C) cm^{-1}; **Accurate mass** found 264.15964(MH^+), $C_{15}H_{22}NO_3$ requires 264.15997.

4.13 Asymmetric Diels-Alder Reactions

4.13.1 Diels-Alder Reaction Between the Crotonate 184 and Cyclopentadiene

A solution of the crotonate **184** (0.08g, 0.29mmol) in dry methylene chloride (10ml) was cooled to -78°C under argon, and treated with freshly cracked cyclopentadiene (0.23g, 3.5mmol, 12eq) in dry methylene chloride (3ml). Diethylaluminium chloride (0.3ml, 1.8M in toluene, 0.54mmol, 1.6eq) was added and the reaction stirred at -78°C for 20 minutes. Saturated ammonium chloride solution was added and the mixture stirred for 5 minutes, then extracted into methylene chloride (3x50ml). The organic layers were dried over magnesium sulphate, filtered and evaporated *in vacuo* to give a yellow oil. The crude product was then subjected to flash chromatography (silica, hexane:ether (8:1 - 4:1)) to give (1*S*, 2*R*, 6*S*, 7*R*)-*N*-((3'*R*, 4'*S*, 5'*S*, 6'*R*)-5'-methylbicyclo[2.2.1]hept-1'-ene-4'-carbonyl)-*exo*-3-oxa-*exo*-5-aza-7-ethyl-10,10-dimethyltricyclo[5.2.1.$0^{2,6}$]decan-4-one **186** as a pale yellow gum (which partially solidified on standing) (0.09g, 91%); $[\alpha]_D^{21}$ = +88.0° (c=2.00, $CHCl_3$); **^{1}H NMR** (250.13MHz, $CDCl_3$) δ 6.36(1H, dd, *J* = 5.7, 3.2 Hz, C<u>H</u>=CH), 5.78(1H, dd, *J* = 5.7, 2.8 Hz, CH=C<u>H</u>), 4.45(2H, s, CHO and CHN), 3.64(1H, dd, *J* = 4.6, 3.4 Hz, COC<u>H</u>CH(CH_3)), 3.27(1H, bs, cycloadduct bridgehead), 2.48(1H, bs, cycloadduct bridgehead), 2.13-2.06(2H, cm, including auxiliary bridgehead), 1.83-1.41(4H, cm), 1.27-0.80(4H, cm), 1.08(3H, d, *J* = 7.1 Hz, C<u>H</u>$_3$CH), 1.02(3H, s, CH_3), 0.89(6H, t and s, *J* = 7.5 Hz, $CH_2C\underline{H}_3$ and CH_3) ppm; **^{13}C NMR** (62.90MHz, $CDCl_3$) δ 174.41(C=O), 155.05(C=O), 139.79(<u>C</u>H=CH), 130.74(CH=<u>C</u>H), 81.04(CH), 63.98(CH), 53.00(C), 51.90(CH), 49.09(CH), 47.97(CH), 47.67(CH), 47.18(CH_2), 46.80(C), 35.32(CH), 29.17(CH_2), 23.54(CH_3), 22.34(CH_2), 20.26(CH_3),

19.25(CH_3), 18.08(CH_2), 9.64(CH_3) ppm; **FT IR** ν_{max} (thin film) 1771(C=O), 1703(C=O), 1657(C=C) cm^{-1}; **Accurate mass** found 344.22271(MH^+), $C_{21}H_{30}NO_3$ requires 344.22257.

4.13.2 Diels-Alder Reaction Between the Acrylate 183 and Cyclopentadiene

Reaction conditions were as in section 4.13.1 using the acrylate **183** (0.14g, 0.53mmol), cyclopentadiene (0.35g, 5.3mmol, 10eq) and diethylaluminium chloride (0.4ml, 1.8M in toluene, 0.7mmol, 1.4eq). Purification as before yielded (1*S*, 2*R*, 6*S*, 7*R*)-*N*-((3'*R*, 4'*S*, 6'*R*)-bicyclo[2.2.1]hept-1'-ene-4'-carbonyl)-*exo*-3-oxa-*exo*-5-aza-7-ethyl-10,10-dimethyltricyclo[5.2.1.$0^{2,6}$]decan-4-one **185** as a colourless solid (0.16g, 92%); **MP** = 97.0-99.0°C (hexane); $[\alpha]_D^{21}$ = +100.0° (c=1.75, $CHCl_3$); **^{1}H NMR** (250.13MHz, $CDCl_3$) δ 6.27(1H, dd, *J* = 5.6, 3.0 Hz, C<u>H</u>=CH), 5.81(1H, dd, *J* = 5.7, 2.8 Hz, CH=C<u>H</u>), 4.45(2H, s, CHO and CHN), 4.16(1H, dt, *J* = 8.0, 3.6 Hz, COC<u>H</u>CH_2), 3.34(1H, bs, cycloadduct bridgehead), 2.93(1H, bs, cycloadduct bridgehead), 2.12(1H, d, *J* = 5.0 Hz, auxiliary bridgehead), 1.84-1.70(2H, cm), 1.62-1.51(2H, cm), 1.46-1.41(2H, cm), 1.30-1.10(3H, cm), 1.04(3H, s, CH_3), 1.00-0.84(1H, cm), 0.91(3H, t, *J* = 7.4 Hz, $CH_2C\underline{H}_3$), 0.90(3H, s, CH_3) ppm; **^{13}C NMR** (62.90MHz, $CDCl_3$) δ 174.68(C=O), 155.09(C=O), 138.43(<u>C</u>H=CH), 130.65(CH=<u>C</u>H), 81.10(CH), 64.13(CH), 53.07(C), 50.52(CH_2), 48.00(CH), 47.03(CH), 46.82(C), 43.01(CH), 42.75(CH), 29.21(CH_2), 28.08(CH_2), 23.57(CH_3), 22.34(CH_2), 19.30(CH_3), 18.16(CH_2), 9.67(CH_3) ppm; **FT IR** ν_{max} (nujol) 1759(C=O), 1707(C=O) cm^{-1}; **Accurate mass** found 330.20714(MH^+), $C_{20}H_{28}NO_3$ requires 330.20692.

4.14 Conjugate Addition of Diethylaluminium Chloride to the Crotonate 184

A solution of the crotonate **184** (0.14g, 0.50mmol) in dry methylene chloride (15ml) under argon was cooled to -78°C. Diethylaluminium chloride (1.2ml, 1.8M in toluene, 2.1mmol, 4eq) was added and the reaction mixture stirred at -78°C for 20 minutes, then saturated ammonium chloride solution added and the mixture stirred for 5 minutes. The mixture was then separated and further extracted into methylene chloride (3x50ml). The combined organic layers were dried over magnesium sulphate, filtered and evaporated *in vacuo* to give (1*S*, 2*R*, 6*S*, 7*R*)-*N*-(3'*S*-methyl-pentanoyl)-*exo*-3-oxa-*exo*-5-aza-7-ethyl-10,10-dimethyltricyclo-[5.2.1.$0^{2,6}$]decan-4-one (and its diastereomer) as a colourless oil (0.15g, 97%); **^{1}H NMR** (250.13MHz, $CDCl_3$) δ 4.46(2H, s, CHO and CHN), 3.05(0.8H, dd, *J* = 15.8, 5.6 Hz, COCHH(major isomer)), 2.81(0.4H, d, *J* = 6.7 Hz, $COCH_2$(minor isomer)), 2.63(0.8H, dd, *J* = 15.8, 8.1 Hz, COCHH(major isomer)), 2.10(1H, d, *J* = 6.7 Hz, bridgehead), 1.95(1H, octet, *J* = 6.5 Hz, $CHCH_3$), 1.84-1.70(1H, cm), 1.57(1H, td, *J* = 12.7, 4.1 Hz, CH_2), 1.46-0.79(21H, cm) ppm; **^{13}C NMR** (62.90MHz, $CDCl_3$) δ 173.38(C=O), 155.06(C=O), 81.09(CH), 63.97(CH), 53.05(C), 48.00(0.2CH), 47.91(0.8CH), 46.80(C), 42.67(0.2CH_2), 42.57(0.8CH_2), 31.22(CH), 29.28(2CH_2), 25.31(CH_3), 22.30(CH_2), 19.39(CH_3), 19.00(CH_3), 18.34(CH_2), 11.27(0.2CH_3), 11.06(0.8CH_3), 9.73(CH_3) ppm; **FT IR** ν_{max} (thin film) 1770(C=O), 1705(C=O) cm^{-1}; **Accurate mass** found 308.22239(MH^+), $C_{18}H_{30}NO_3$ requires 308.22257.

5. Attempted Synthesis of the Imidazolidin-2-one 190

5.1 Preparation of the *N*-Phenyl Imine 191

To aniline (12.8g, 138mmol) (freshly distilled from CaH_2) was added camphorquinone **117** (20.2g, 122mmol) followed by anhydrous sodium sulphate (vast excess). The reaction mixture was then heated to 90-100°C for 24 hours, then cooled to room temperature and treated with water (200ml). The mixture was then extracted into ether (3x100ml), and the ether layers then washed with a saturated solution of sodium chloride. The organic layers were then dried over magnesium sulphate, filtered and evaporated *in vacuo* to give a sticky orange solid. The crude product was then recrystalised from hexane to give (1*R*)-*N*-phenyl-3-imino-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one **191** as long yellow needles(15.1g, 51%); **MP** = 108.0-109.3°C (hexane) (Lit[96] = 109°C); $[\alpha]_D^{21}$ = +563.5° (c=1.00, CH_2Cl_2); **^{1}H NMR** (80.13MHz, $CDCl_3$) δ 7.42-6.81(5H, cm, Ph), 2.78(1H, dbs, *J* = 4.6 Hz, bridgehead), 2.08-1.51(4H, cm), 1.07(3H, s, CH_3), 0.94(3H, s, CH_3), 0.87(3H, s, CH_3) ppm; **^{13}C NMR** (90.56MHz, $CDCl_3$) δ 206.15(C=O), 171.57(C=N), 149.25(Ar C), 128.66(2Ar CH), 124.97(Ar CH), 120.06(2Ar CH) 57.79(C), 49.74(CH), 44.23(C), 29.83(CH_2), 24.08(CH_2), 20.66(CH_3), 17.20(CH_3), 8.78(CH_3) ppm; **FT IR** ν_{max} (nujol) 1744(C=O), 1663(C=N), 1651(C=C) cm^{-1}; **Accurate mass** found 242.15568(MH^+), $C_{16}H_{20}NO$ requires 242.15449.

5.2 Reduction of Imine 191 Using Zinc

The imine **191** (6.16g, 25.6mmol) was added to a solution of sodium hydroxide (4.72g, 118mmol) in water (60ml) to give a partial suspension. Zinc dust (4.2g, 65mmol) was then added and the reaction mixture left to stir for 48 hours at room temperature. The reaction mixture was then extracted into ether (3x100ml) and the combined ether layers dried over magnesium sulphate, filtered and evaporated *in vacuo* to give (1*R*, 3*S*)-*N*-phenyl-*endo*-3-amino-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one **196** as a pale yellow solid (6.00g, 96%); **MP** = 79.0-80.3°C (pentane); $[\alpha]_D^{21}$ = +82.4° (c=1.75, CH_2Cl_2); **^{1}H NMR** (80.13MHz, $CDCl_3$) δ 7.31-7.10(2H, cm, Ar), 6.86-6.60(3H, cm, Ar), 4.00-3.95(1H, m, CHN), 2.78-2.45(1H, cm, bridgehead), 1.80-1.13(4H, cm), 1.08(3H, s, CH_3), 1.05(3H, s, CH_3), 1.02(3H, s, CH_3) ppm; **^{13}C NMR** (90.56MHz, $CDCl_3$) δ 218.16(C=O), 149.70(Ar C), 129.02(2Ar CH), 117.87(Ar CH), 113.10(2Ar CH), 62.12(CH), 58.22(C), 48.43(CH), 44.06(C), 32.48(CH_2), 19.65(CH_3), 19.24(CH_3), 18.70(CH_2), 9.19(CH_3) ppm; **FT IR** ν_{max} (nujol) 3374(N-H), 1738(C=O) cm^{-1}; **Accurate mass** found 244.1713(MH^+), $C_{16}H_{22}NO$ requires 244.17014.

5.3 Preparation of the Oxime 192 from *endo*-3-*N*-Phenylaminocamphor 196

Endo-3-*N*-phenylaminocamphor **196** (5.02g, 20.7mmol) in ethanol (80ml) was treated with anhydrous sodium acetate (20.28g, 247.2mmol, 2eq) and hydroxylamine hydrochloride (8.20g, 118mmol, 5.70eq) in water (45ml). The reaction mixture was then heated under reflux for 48 hours, after which time TLC (silica, hexane:ether (3:1)) showed total consumption of the starting material. The mixture was allowed to

cool to room temperature then poured onto ice (100g) and then saturated with sodium chloride. The mixture was then extracted into methylene chloride (3x100ml) and the combined organic layers dried over magnesium sulphate, filtered and evaporated *in vacuo* to give a brown oil. The oil was purified by flash chromatography (silica, hexane:ether (9:1)) to give (1*R*, 3*S*)-*N*-phenyl-2-hydroximino-*endo*-3-amino-1,7,7-trimethylbicyclo[2.2.1]heptane **192** as a colourless solid (2.33g, 44%); **MP** = 151.5-153.5°C (hexane:cyclohexane (1:1)); $[\alpha]_D^{21}$ = +132.3° (c=1.00, CH_2Cl_2); **^{1}H NMR** (200.13MHz, $CDCl_3$) δ 7.25-7.17(2H, m, Ar), 6.81-6.68(3H, m, Ar), 4.41(1H, dbs, *J* = 4.1 Hz, CHN), 2.40-2.36(1H, m, bridgehead), 1.85-1.06(4H, cm), 1.01(6H, s, $2CH_3$), 0.94(3H, s, CH_3) ppm; **^{13}C NMR** (50.32MHz, $CDCl_3$) δ 167.7(C=N), 148.0(Ar C), 129.0(2Ar CH), 117.8(Ar CH), 113.8(2Ar CH), 55.4(CH), 52.1(C), 48.8(CH), 46.3(C), 33.0(CH_2), 19.2(CH_3 and CH_2), 19.0(CH_3), 11.4(CH_3) ppm; **FT IR** ν_{max} (nujol) 3403(OH), 3276(NH), 1601(C=N) cm^{-1}; **Accurate mass** found 259.18212(MH^+), $C_{16}H_{23}N_2O$ requires 259.18104.

5.4 Preparation of Super-Dry Ethanol

The method outlined in Vogel's Comprehensive Organic Synthesis[106] was followed. To a flame dried one litre round bottomed flask, fitted with a dropping funnel and condenser, all under argon, was added magnesium turnings (2.50g) and iodine (0.25g) followed by ethanol (50ml). A vigorous reaction occured, and the mixture heated until the iodine colour had disappeared. More ethanol (450ml) was then added and the mixture heated under reflux for 30 minutes before distillation and collection. The collected ethanol was stored over 4Å molecular sieves.

5.5 Reduction of the Oxime 192 With Sodium in Super-Dry Ethanol

To a refluxing solution of the oxime **192** (1.50g 5.81mmol) in super-dry ethanol (80ml) was added small pieces of sodium metal (7.0g, 40mmol, 52eq) over a period of one hour. The reaction mixture was then heated under reflux for a further two hours before being evaporated, *in vacuo,* to dryness. Water (80ml) was then added and the mixture extracted into methylene chloride (4x100ml). The organic layers were combined dried over magnesium sulphate, filtered and evaporated to give an orange oil. The oil was purified by flash chromatography (silica, hexane:ether (9:1)) to give (1*R*, 2*S*, 3*S*)-*endo*-3-*N*-phenyl-amino-*exo*-2-amino-1,7,7-trimethylbicyclo-[2.2.1]-heptane **197** as a yellow solid (1.08g, 76%); **MP** = 115.2-117.0°C (cyclohexane); $[\alpha]_D^{21}$ = +88.2° (c=1.10, CH_2Cl_2); **^{1}H NMR** (360.13MHz, $CDCl_3$) δ 7.97-7.87(2H, m, Ar), 7.46-7.25(3H, m, Ar), 4.40(1H, bs, C<u>H</u>NHPh), 4.12(1H, s, C<u>H</u>NH_2), 2.81(1H, d, *J* = 4.4 Hz, bridgehead), 2.69-2.66(1H, cm), 2.25-2.01(5H, bcm, including NH_2 and NH protons), 1.78(3H, s, CH_3), 1.67-1.60(1H, cm), 1.51(3H, s, CH_3), 1.47(3H, s,CH_3) ppm; **^{13}C NMR** (50.32MHz, $CDCl_3$) δ 148.0(Ar C), 129.0(2Ar CH), 116.8(Ar CH), 113.2(2Ar CH), 68.6(CH), 63.5(CH), 63.3(C), 48.4(C), 47.3(CH), 36.5(CH_2), 21.3(CH_3), 19.6(CH_3), 18.9(CH_2), 11.6(CH_3) ppm; **FT IR** ν_{max} (nujol) 3378(NH), 3316(bs, NH_2), 1600(Ar C=C) cm^{-1}; **Accurate mass** found 245.20227(MH^+), $C_{16}H_{25}N_2$ requires 245.20177; **Elemental analysis** found 78.43% C, 9.63% H, 11.59% N, $C_{16}H_{24}N_2$ requires 78.69% C, 9.84% H, 11.48% N.

5.6 Attempted Reduction of Oxime 192 Using Zinc

The oxime **192** (0.54g, 2.1mmol) was dissolved in ethanol, then added to a solution of sodium hydroxide (0.77g, 19mmol) in water (15ml). Activated zinc dust (0.94g, 14mmol) was then added and the reaction mixture stirred at room temperature for 3 days. Analysis of the mixture by TLC (silica, hexane:ether (3:1)) showed no reaction had occured. The starting material was then recovered as a colourless solid.

5.7 Attempted reduction of the Oxime 192 Using $LiAlH_4$

To a stirred suspension of lithium aluminium hydride (0.29g, 7.6mmol, 3eq) in dry ether under argon was added dropwise a solution of the oxime **192** (0.53g, 2.0mmol) in dry ether (20ml). The reaction mixture was then heated under reflux for 24 hours after which time TLC (silica, hexane:ether (3:1)) indicated no reaction had taken place, so the starting material was recovered using the same work-up procedure as in section 7.5.

5.8 Attempted Reduction of Oxime 192 Using Pressure Hydrogenation

The oxime **192** (0.50g, 1.9mmol) was dissolved in glacial acetic acid (100ml) then 10% Pd/C (0.05g, 0.10eq) was added. The reaction mixture was then agitated under an atmosphere of hydrogen at 30psi for 24 hours. After this time TLC (silica, hexane:ether (3:1)) showed no evidence of reaction. The mixture was then filtered through a pad of celite and then evaporated *in vacuo* to give recovered starting material.

6. Synthesis of the Spiro-Oxazolidin-2-one 198

6.1 Formation of Chloroformate 205

(-)-Isolongifolol **199** (4.14g, 18.6mmol) in ether was added to a solution of phosgene (29ml, 1.93M in toluene, 56mmol, 3eq) and stirred at room temperature for 24 hours. After this time the solvent was removed *in vacuo* to give (1*S*, 11*S*)-11-methylchloroformate-3,3,7-trimethyltricyclo[5.3.1.$0^{2,8}$]undecane **205** as a clear colourless oil (5.27g, 99%); $[\alpha]_D^{21}$ = -33.8° (c=1.80, CH_2Cl_2); **^{1}H NMR** (200.13MHz, $CDCl_3$) δ 4.36(2H, d, *J* = 8.7 Hz, CH_2O), 2.39-2.30(1H, cm, bridgehead), 2.16(1H, bs), 2.03(1H, bs), 1.74-1.15(11H, cm), 1.00(3H, s, CH_3), 0.96(3H, s, CH_3), 0.84(3H, s, CH_3) ppm; **^{13}C NMR** (50.3MHz, $CDCl_3$) δ 150.5(C=O), 71.7(CH_2), 61.6(CH), 45.6(CH), 45.3(CH), 43.9(CH_2), 40.7(CH), 40.5(C), 39.5(CH_2), 33.1(C), 32.4(CH_3), 29.6(CH_3), 25.6(CH_2), 23.1(CH_3), 21.3(CH_2), 21.2(CH_2) ppm; **FT IR** ν_{max} (thin film) 1776(C=O) cm^{-1}; **Nominal mass** found 285(MH^+), $C_{16}H_{26}O_2{}^{35}Cl$ requires 285, and 287(MH^+), $C_{16}H_{26}{}^{37}Cl$ requires 287.

6.2 Formation of Azidoformate 206

The chloroformate **205** (5.14g, 18.1mmol) in methylene chloride (20ml) was added to a solution of sodium azide (2.40g, 36.9mmol, 2eq) and TBAB (50mg) in water (20ml) at 0°C. The reaction mixture was then warmed to room temperature and stirred for 24 hours. The mixture was then separated and the aqueous extracted into methylene chloride (2x50ml). The organic layers were combined, dried over

magnesium sulphate, filtered and evaporated *in vacuo* to give a yellow oil. The crude product was purified by dry flash chromatography (silica, hexane:ether (9:1)) to give (1*S*, 11*S*)-11-methylazidoformate-3,7,7-trimethyltricyclo[5.3.1.$0^{2,8}$]undecane **206** as a clear colourless oil (4.43g, 82%); $[\alpha]_D^{21}$ = -48.5° (c=1.70, CH_2Cl_2); **^{1}H NMR** (250.13MHz, $CDCl_3$) δ 4.21(2H, d, *J* = 7.5 Hz, $C\underline{H}_2O$), 2.29-2.22(1H, cm, bridgehead), 2.11(1H, bs), 1.91(1H, bs), 1.61-1.12(11H, cm), 0.95(3H, s, CH_3), 0.91(3H, s, CH_3), 0.80(3H, s, CH_3) ppm; **^{13}C NMR** (50.3MHz, $CDCl_3$) δ 157.2(C=O), 67.7(CH_2), 61.5(CH), 45.6(CH), 45.2(CH), 43.9(CH_2), 40.6(CH), 40.3(C), 39.4(CH_2), 33.0(C), 32.3(CH_3), 29.4(CH_3), 25.6(CH_2), 23.0(CH_3), 21.2(CH_2), 21.1(CH_2) ppm; **FT IR** ν_{max} (thin film) 2135(N_3), 1757(C=O) cm^{-1}; **Nominal mass** found 292(MH^+) $C_{16}H_{26}N_3O_2$ requires 292.

6.3 Formation of Spiro-Oxazolidin-2-one 198 *via* a Nitrene Insertion

A solution of the azidoformate **206** (4.33g, 15.6mmol) in TCE (80ml) was added dropwise, over a period of 45 minutes, into TCE (320ml) at 147°C. After addition was complete the reaction mixture was heated under reflux for a further 30 minutes, after which time TLC (silica, cyclohexane:ethyl acetate (2:1)) indicated the presence of one product and no starting material. The solvent was removed *in vacuo* and the residue dissolved in methylene chloride (100ml), then stirred with activated charcoal for 10 minutes. The mixture was then filtered through a pad of celite and the solvent removed *in vacuo* to give an off white solid. The crude product was recrystallised from xylene to give the oxazolidinone **198** as a colourless crystalline solid (2.42g, 62%); **MP** = 151-152°C (xylene); $[\alpha]_D^{21}$ = -14.0° (c=1.00, CH_2Cl_2); **^{1}H NMR**

(250.13MHz, $CDCl_3$) δ 5.22(1H, bs, NH), 4.44(1H, d, J = 9.2 Hz, CHHO), 4.17(1H, d, J = 9.3 Hz, CHHO), 2.21-2.16(1H, cm, bridgehead), 2.02-1.18(12H, cm), 1.05(3H, s, CH_3), 1.02(3H, s, CH_3), 1.00(3H, s, CH_3) ppm; **^{13}C NMR** (50.3MHz, $CDCl_3$) δ 158.6(C=O), 71.9(CH_2), 68.6(C), 63.0(CH), 48.6(CH), 46.9(C), 45.1(CH), 40.1(CH_2), 37.3(CH_2), 33.2(CH_3), 32.3(C), 30.6(CH_3), 26.7(CH_3), 26.4(CH_3), 23.8(CH_2), 20.5(CH_2) ppm; **FT IR** ν_{max} (nujol) 3372 and 3330(NH), 1747(C=O) cm^{-1}; **Accurate mass** found 264.19666(MH^+), $C_{16}H_{26}NO_2$ requires 264.19635.

6.4 Attempted Functionalisation of 198

6.4.1 *via* Deprotonation Using Diethylzinc

Diethylzinc (1.1ml, 1.0M in hexanes, 1.1mmol, 1.1eq) was added dropwise to a solution of the oxazolidinone **198** (0.25g, 0.94mmol) in dry ether (50ml) under argon. The resulting mixture was stirred at room temperature for 1 hour then cooled to -78°C and treated with freshly distilled crotonyl chloride (0.3g, 3mmol, 3eq). The reaction mixture was warmed to room temperature and stirred for 2 hours, then heated under reflux for 22 hours. After this time TLC (silica, cyclohexane:ethyl acetate (2:1)) indicated no reaction had occured, so the reaction was stopped and worked up as in section 4.12.2 to give unreacted starting material (0.25g, 100%).

6.4.2 *via* Deprotonation Using a Grignard Reagent

Ethyl bromide (0.30g, 2.8mmol) was added to magnesium turnings (0.03g, 1.0mmol) in dry THF (5ml) under argon. When all the magnesium had dissolved the reaction mixture was cooled to 0°C and dry THF (10ml) added followed by a solution of **198**

(0.25g, 0.94mmol) in dry THF (10ml). The mixture was stirred at 0°C for 30 minutes then cooled to -78°C and treated with freshly distilled crotonyl chloride (0.25g, 2.4mmol). The mixture was then allowed to stir at room temperature for 24 hours, then heated under reflux for a further 24 hours, but after this time TLC (silica, cyclohexane:ethyl acetate (2:1)) showed no evidence of reaction. The mixture was then cooled, quenched with saturated ammonium chloride solution and the THF removed *in vacuo*. The residue was extracted into methylene chloride (3x50ml) and the organic layers dried over magnesium sulphate, filtered and evaporated *in vacuo* to give unreacted oxazolidin-2-one **198** (0.25g, 100%).

6.4.3 *via* Deprotonation Using *n*-Butyllithium

A solution of **198** (0.35g, 1.3mmol) in dry THF (10ml) at -78°C under argon, was treated dropwise with *n*-butyllithium (0.90ml, 1.6M in hexanes, 1.5mmol), and stirred for 40 minutes. Freshly distilled crotonyl chloride (0.30g, 2.9mmol) was then added, and the solution allowed to warm to room temperature and stirred for 70 hours. TLC (silica, cyclohexane:ethyl acetate (2:1)) showed no reaction had occurred, so DMAP (20mg) was added in an attempt to activate the acid chloride, but after a further 22 hours still no reaction was observed. The reaction was then quenched by the addition of saturated sodium bicarbonate solution and the THF removed *in vacuo*. The residue was extracted into methylene chloride (2x50ml), and the organic layers combined, dried over magnesium sulphate, filtered and evaporated *in vacuo* to yield unreacted **198** (0.35g, 100%).

7. Synthesis and Evaluation of Oxazaborolidines 208 and 216

7.1 Preparation of (1*R*)-Camphorquinone-3-oxime 125

(1*R*)-Camphorquinone **117** (12.95g, 77.90mmol) in ethanol (100ml) was treated with anhydrous sodium acetate (11.5g, 140mmol) and hydroxylamine hydrochloride (5.41g, 77.9mmol) in water (50ml). The mixture was then heated under reflux for 70 minutes after which time TLC (silica, hexane:ether (1:1)) showed the reaction to be complete. The reaction mixture was then cooled to room temperature and poured onto ice (100g), then saturated with sodium chloride. The mixture was then extracted into methylene chloride (3x100ml). The organic layers were then combined, dried over magnesium sulphate, filtered and then evaporated *in vacuo* to give (1*R*)-3-hydroximino-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one **125** as a pale yellow solid (14.10g, 100%); **MP** = 153.6-156.6°C (Lit.[75]=154-156°C); $[\alpha]_D^{21}$ = +233° (c=1.50, EtOH); **FT IR** ν_{max} (nujol) 3417(OH), 1741(C=O), 1642(C=N) cm^{-1}; **Accurate mass** found 168.13879(MH^+), $C_{10}H_{18}NO$ requires 168.13884.

7.2 Reduction of Oxime 125 With Zinc

The oxime **125** (93.1g, 514mmol) was added to a solution of sodium hydroxide (100g, 4.35mol) in water (700ml) and stirred until the solution went clear. Zinc dust (118.80g, 1.81mol) was then added in portions (temperature rise noted) and the reaction mixture stirred for 30 minutes. The mixture (including zinc) was then extracted with ether (2x500ml). The organic layers were then cooled in ice and

treated with concentrated hydrochloric acid (20g, 51.2ml), then diluted with water (200ml). The layers were then separated and the aqueous washed with ether (2x200ml). The aqueous layer was then evaporated *in vacuo* to give (1*R*, 3*S*)-*endo*-3-amino-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one hydrochloride **211** as a colourless solid (91.86g, 88%); **MP** = 224.2-225.7°C; $[\alpha]_D^{21}$ = +14° (c=1.00, H_2O); **^{1}H NMR** (250.13MHz, D_2O) δ 4.05(1H, dd, *J* = 5.0, 0.9 Hz, C<u>H</u>$NH_3^+Cl^-$), 2.50-2.47(1H, m, bridgehead), 2.06-1.86(2H, cm), 1.57-1.34(1H, cm), 1.12-0.88(1H, cm), 1.05(3H, s, CH_3), 0.95(3H, s, CH_3), 0.93(3H, s, CH_3) ppm; **^{13}C NMR** (62.90MHz, D_2O) δ 216.90(C=O), 59.09(C), 56.81(CH), 46.03(CH), 44.58(C), 31.39(CH_2), 18.95(CH_3), 18.54(CH_2), 17.69(CH_3), 8.29(CH_3) ppm; **FT IR** ν_{max} (nujol) 3355 and 3350(NH), 1752(C=O) cm^{-1}; **Accurate mass** found 168.13879(MH^+), $C_{10}H_{17}NO$ requires 168.13884.

7.3 Synthesis of Tosyl-Amino Ketone 213

Amine hydrochloride **211** (10.0g, 49mmol) was suspended in dry THF (400ml) under argon and treated dropwise with triethylamine (9.95g, 100mmol, 2eq) followed by DMAP (0.60g, 5mmol). A solution of *p*-toluenesulphonyl chloride (9.35g, 49mmol) in dry THF (100ml) was then added dropwise and the reaction mixture heated under reflux overnight. The mixture was then cooled and water (200ml) added and the reaction mixture left to stir at room temperature for 2 days. The THF was then removed *in vacuo*, then saturated sodium bicarbonate solution (100ml) was added and the mixture extracted into methylene chloride (3x100ml). The organic layers were combined, dried over magnesium sulphate, filtered and evaporated *in*

vacuo to give a yellow oil. The oil was quickly purified by flash chromatography (silica, ether as eluent) and evaporated *in vacuo* to give (1*R*, 3*S*)-*N*-toluenesulphonyl-*endo*-3-amino-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one **213** as a colourless solid (14.40g, 92%); **MP** = 102.8-104.2°C (cyclohexane); $[\alpha]_D^{21}$ = +44.3° (c=1.65, CH_2Cl_2); **^{1}H NMR** (200.13MHz, $CDCl_3$) δ 7.78-7.22(2H, m, Ar), 7.32-7.25(2H, m, Ar), 4.93(1H, d, *J* = 3.2 Hz, NH), 3.66-3.62(1H, m, CHNH), 2.40(3H, s, CH_3), 2.35-2.31(1H, m, bridgehead), 1.83-1.62(2H, cm), 1.29-1.20(1H, cm), 1.02-0.89(1H, cm), 0.96(3H, s, CH_3), 0.88(3H, s, CH_3), 0.81(3H, s, CH_3) ppm; **^{13}C NMR** (62.90MHz, $CDCl_3$) δ 215.55(C=O), 143.58(Ar C), 135.95(Ar C), 129.59(2Ar CH), 127.10(2Ar CH), 60.46(CH), 58.23(C), 48.24(CH), 43.90(C), 32.08(CH_2), 21.38(CH_3), 19.53(CH_3), 18.90(CH_2), 18.88(CH_3), 9.01(CH_3) ppm; **FT IR** ν_{max} (nujol) 3311 and 3256(2NH), 1746 and 1732(2C=O) cm^{-1}; **Accurate mass** found 322.14828(MH^+), $C_{17}H_{24}NO_3S$ requires 322.14769.

7.4 Reaction of Tosyl-Amino Ketone 213 with Benzyl Bromide

To the tosyl-amino ketone **213** (10.06g, 30mmol) in acetone (400ml) was added anhydrous potassium carbonate (6.27g, 45mmol, 1.5eq) followed by benzyl bromide (8.07g, 47mmol, 1.5eq). The resulting mixture was then heated under reflux overnight, after which TLC (silica, hexane:ether (1:1)) showed reaction to be complete. The reaction mixture was then cooled, filtered and evaporated *in vacuo* to give an orange oil. The oil was then triturated with pentane to give (1*R*, 3*S*)-*N*-*p*-toluenesulphonyl-*N*-benzyl-*endo*-3-amino-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one **214** as a fluffy colourless solid (10.39g, 84%); **MP** = 95.1-96.1°C; $[\alpha]_D^{21}$ = +24.1°

(c=1.10, CH_2Cl_2); **^{1}H NMR** (200.13MHz, $CDCl_3$) δ 7.76-7.59(2H, cm, Ar), 7.36-7.19(7H, cm, Ar), 4.57(1H, d, *J* = 15.4 Hz, PhCHH), 4.35(1H, d, *J* = 15.4 Hz, PhCHH), 3.85-3.82(1H, cm, CHN), 2.42-2.35(1H, cm, bridgehead), 2.41(3H, s, CH_3), 1.57-1.54(2H, cm), 1.46-1.35(1H, cm), 0.90(3H, s, CH_3), 0.82-0.71(1H, cm), 0.79(6H, s, $2CH_3$) ppm; **^{13}C NMR** (50.32MHz, $CDCl_3$) δ 212.4(C=O), 143.4(Ar C), 136.7(Ar C), 135.8(Ar C), 129.5(2Ar CH), 128.8(2Ar CH), 128.0(3Ar CH), 127.4(2Ar CH), 64.6(CH), 58.8(C), 50.5(CH_2), 49.5(CH), 43.1(C), 29.4(CH_2), 20.2(CH_3), 19.2(CH_2), 19.1($2CH_3$), 9.4(CH_3) ppm; **FT IR** ν_{max} (nujol) 1746(C=O) cm^{-1}; **Accurate mass** found 412.19463(MH^+), $C_{24}H_{30}NO_3S$ requires 412.19465.

7.5 Reduction of Ketone 214 Using $LiAlH_4$

A solution of the ketone **214** (4.90g, 12mmol) in dry THF (50ml) was added dropwise to a stirred suspension of lithium aluminium hydride (0.58g, 15mmol) in dry THF (200ml) under argon. The reaction mixture was then heated under reflux for 4 days, then allowed to cool. Water (1ml) was then added followed by sodium hydroxide solution (15%, 1ml) and a further portion of water (3ml). The mixture was stirred for 15 minutes then filtered and the THF removed *in vacuo*. The aqueous residue was then extracted into ether (4x50ml) and the organic layers combined, dried over magnesium sulphate, filtered and evaporated *in vacuo* to give a pale yellow solid. The crude product was purified by flash chromatography (silica, hexane:ethyl acetate (100:1 - 5:1)) to yield (1*R*, 2*R*, 3*S*)-*N*-*p*-toluenesulphonyl-*N*-benzyl-*endo*-2-hydroxy-*endo*-3-amino-1,7,7-trimethylbicyclo[2.2.1]heptane **215** as a colourless solid (3.73g, 75%); **MP** = 153.9-155.2°C; **$[\alpha]_D^{21}$** = +25.2°(c=1.35,

CH_2Cl_2); **^{1}H NMR** (200.13MHz, $CDCl_3$) δ 7.71-7.65(2H, cm, Ar), 7.45-7.17(7H, cm, Ar), 4.50(1H, d, *J* = 17.8 Hz, PhCHH), 4.22(1H, d, *J* = 17.7 Hz, PhCHH), 4.00(1H, dd, *J* = 8.07, 2.76 Hz, CHO), 3.85-3.79(1H, cm, CHN), 3.21(1H, d, *J* = 3.04 Hz, OH), 2.43(3H, s, CH_3), 2.06-1.94(1H, cm), 1.75-1.71(1H, cm), 1.48-0.74(3H, cm), 0.91(3H, s, CH_3), 0.89(3H, s, CH_3), 0.84(3H, s, CH_3) ppm; **^{13}C NMR** (50.32MHz, $CDCl_3$) δ 143.8(Ar C), 139.2(Ar C), 133.5(Ar C), 129.5(2Ar CH), 128.0(2Ar CH), 127.7(2Ar CH), 126.5(Ar CH), 126.2(2Ar CH), 75.4(CH), 60.3(CH), 51.3(CH_2), 49.7(C), 49.1(CH), 45.5(C), 25.5(CH_2), 21.4(CH_3), 19.8(CH_2), 19.3(2CH_3), 14.1(CH_3) ppm; **FT IR** ν_{max} (nujol) 3539(OH) cm^{-1}; **Accurate mass** found 414.20943(MH^+), $C_{24}H_{32}NO_3S$ requires 414.21029.

7.6 Removal of Tosyl Group From 215 by a Dissolving Metal Reduction

The amino alcohol **215** (1.70g, 4.1mmol) was dissolved in dry propan-1-ol (40ml) and the solution then brought to reflux. Sodium metal (2.00g, 87mmol, 21eq) was then added as small pieces over a period of 60 minutes. The resulting mixture was then heated under reflux for 3.5 hours, then left to stir at room temperature overnight. The solvent was then removed *in vacuo* and water (100ml) added and the mixture then extracted into ether (3x100ml). The combined organic layers were dried over magnesium sulphate, filtered and evaporated *in vacuo* to give an orange oil. The oil was purified by flash chromatography (silica, hexane:ether (5:1 - 0:100)) to give (1*R*, 2*R*, 3S)-*N*-benzyl-*endo*-2-hydroxy-*endo*-3-amino-1,7,7-trimethylbicyclo[2.2.1]-heptane **209** as a sticky yellow solid (0.80g, 75%); **$[\alpha]_D^{21}$** = +3.0° (c=2.00, CH_2Cl_2); **^{1}H NMR** (200.13MHz, $CDCl_3$) δ 7.39-7.23(5H, cm, Ph), 3.79-3.65(1H, cm, CHOH),

3.71(2H, d, J = 0.92 Hz, $PhCH_2$), 3.20(1H, ddd, J = 9.11, 4.39, 0.98 Hz, CHN), 1.86-1.73(2H, cm), 1.48-0.72(3H, cm), 0.90(6H, s, $2CH_3$), 0.88(3H, s, CH_3) ppm; **^{13}C NMR** (50.32MHz, $CDCl_3$) δ 139.8(Ar C), 128.3(2Ar CH), 127.9(2Ar CH), 126.9(Ar CH), 72.6(CH), 56.3(CH), 53.2(CH_2), 49.4(C), 48.8(CH), 45.1(C), 25.3(CH_2), 19.8(CH_3), 18.7(CH_2), 18.2(CH_3), 14.3(CH_3) ppm; **FT IR** ν_{max} (nujol) 3290(NH) cm^{-1}; **Accurate mass** found 260.20144(MH^+), $C_{17}H_{26}NO$ requires 260.20289.

7.7 Formation of the Oxazaborolidine 208

The method of Corey[55] was adopted.

The amino alcohol **209** (0.74g,2.9mmol) was dissolved in a mixture of toluene (180ml) and THF (90ml) under argon, then treated with methylboronic acid (0.18g, 3.0mmol). The reaction mixture was then heated under reflux for 24 hours with a soxhlet extractor (with CaH_2 in the thimble) fitted. The mixture was then cooled and evaporated *in vacuo* to give the oxazaborolidine **208** as a yellow gum (0.78g, 97%) (the product was then dissolved in dry methylene chloride (15ml) and kept as a solution under argon.); **^{11}B NMR** (64.21MHz, CH_2Cl_2) δ 34.6 ppm.

7.8 Reaction of Ketone 213 with *p*-Methoxybenzyl Chloride

This was carried out using the same procedure as outlined in section 7.4 using the amino ketone **213** (3.72g, 11.6mmol), 4-methoxybenzyl chloride (2.73g, 17.4mmol, 1.5eq) and potassium carbonate (2.40g, 17.4mmol, 1.5eq) in acetone (150ml). The reaction was allowed to reflux for 48 hours before work-up and purification as

before, yielded (1*R*, 3*S*)-*N*-*p*-toluenesulphonyl-*N*-*p*-methoxybenzyl-*endo*-3-amino-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one **217** as a colourless solid (3.80g, 75%); **MP** = 129.0-130.6°C (methanol); $[\alpha]_D^{21}$ = +18.8° (c=1.60, CH_2Cl_2); **^{1}H NMR** (200.13MHz, $CDCl_3$) δ 7.68(2H, apparent doublet, Ar), 7.72-7.13(4H, cm, Ar), 6.82-6.69(2H, cm, Ar), 4.59(1H, d, *J* = 15.2 Hz, ArCHH), 4.26(1H, d, *J* = 15.2 Hz, ArCHH), 3.76(1H, d, *J* = 4.3 Hz, CHN), 3.68(3H, s, OCH_3), 2.34(3H, s, CH_3), 2.31(1H, bs, bridgehead), 1.57-1.28(3H, cm), 0.87-0.74(1H, cm), 0.86(3H, s, CH_3), 0.75(3H, s, CH_3), 0.74(3H, s, CH_3) ppm; **^{13}C NMR** (50.32MHz, $CDCl_3$) δ 212.2(C=O), 158.7(Ar C), 143.1(Ar C), 135.8(Ar C), 129.9(Ar CH), 129.2(Ar CH), 128.3(Ar C), 128.1(Ar CH), 127.1(2Ar CH), 113.4(Ar CH), 113.1(2Ar CH), 64.2(CH), 58.5(C), 54.8(CH_3), 49.7(CH_2), 49.2(CH), 42.9(C), 29.2(CH_2), 21.1(CH_3), 20.0(CH_2), 18.9($2CH_3$), 9.2(CH_3) ppm; **FT IR** ν_{max} (nujol) 1748 cm^{-1}; **Accurate mass** found 440.18915($M-H^+$), $C_{25}H_{30}NO_4S$ requires 440.18956; **Elemental analysis** found 67.73% C, 6.98% H, 3.07% N, $C_{25}H_{31}NO_4S$ requires 68.03% C, 7.03% H, 3.17% N.

7.9 Reduction of Ketone 217 Using $LiAlH_4$

A solution of the ketone **217** (2.53g, 5.74mmol) in dry DME (30ml) was added to a stirred suspension of lithium aluminium hydride (1.10g, 28.9mmol, 5eq) in dry DME (25ml) under argon. The reaction mixture was then heated under reflux for 24 hours. The mixture was then cooled and water (1.5ml) added followed by sodium hydroxide solution (15%, 1.5ml) and more water (5ml), and the mixture left to stir for 20 minutes. The mixture was then filtered and the DME removed *in vacuo* and the

aqueous residue then extracted into ether (3x50ml). The combined organic layers were dried over magnesium sulphate, filtered and evaporated *in vacuo* to give a yellow gum. The gum was purified by flash chromatography (silica, hexane:ether (9:1-4:1)) to give (1*R*, 2*R*, 3*S*)-*N*-*p*-methoxybenyl-*N*-*p*-toluenesulphonyl-*endo*-2-hydroxy-*endo*-3-amino-1,7,7-trimethylbicyclo[2.2.1]heptane **218** as a colourless solid (1.50g, 60%); **MP** = 68-69°C; $[\alpha]_D^{21}$ = +34.3° (c=1.25, CH_2Cl_2); **^{1}H NMR** (360.13MHz, $CDCl_3$) δ 7.67-7.64(2H, m, Ar), 7.32-7.25(4H, cm, Ar), 6.85-6.81(2H, m, Ar), 4.43(1H, d, *J* = 17.3 Hz, ArC<u>H</u>H), 4.15(1H, d, *J* = 17.3 Hz, ArCH<u>H</u>), 3.98(1H, d, *J* = 8.0 Hz, C<u>H</u>OH), 3.81-3.75(1H, cm, CHN), 3.77(3H, s, OCH_3), 3.18(1H, bs, OH), 2.42(3H, s, CH_3), 1.99(1H, ddd, *J* = 12.7, 9.4, 3.9 Hz, bridgehead), 1.73-1.71(1H, m), 1.46-1.39(1H, cm), 1.30-1.24(1H, cm), 1.16-1.11(1H, cm), 0.90(3H, s, CH_3), 0.88(3H, s, CH_3), 0.84(3H, s, CH_3) ppm; **^{13}C NMR** (50.32MHz, $CDCl_3$) δ 158.2(Ar C), 143.7(Ar C), 133.6(Ar C), 131.1(Ar C), 129.5(2Ar CH), 127.8(2Ar CH), 127.5(2Ar CH), 113.5(2Ar CH), 75.5(CH), 60.4(CH), 55.0(CH_3), 50.9(C), 49.8(CH_2), 49.1(CH), 45.5(C), 25.6(CH_2), 21.4(CH_3), 19.9(CH_2), 19.3(2CH_3), 14.1(CH_3) ppm; **FT IR** ν_{max} (nujol) 3541(OH) cm^{-1}; **Accurate mass** found 442.20467($M-H^+$), $C_{25}H_{32}NO_4S$ requires 442.2051.

7.10 Removal of Tosyl Group From 218 by a Dissolving Metal Reduction

Sodium metal (1.40g, 60.9mmol, 24eq) was added to a solution of amino alcohol **218** (1.10g, 2.48mmol) in dry propan-1-ol (25ml) under reflux over a period of 20 minutes. The mixture was heated under reflux for a further 5 hours, then stirred at room temperature overnight. The solvent was then removed *in vacuo*, then water

(5ml) was added and the mixture extacted into ether (3x50ml). The combined organic layers were dried over magnesium sulphate, filtered and evaporated *in vacuo* to give a yellow oil. The crude product was then purified by flash chromatography (silica, hexane:ether (1:1)) to give (1*R*, 2*R*, 3*S*)-*N*-*p*-methoxybenzyl-*endo*-2-hydroxy-*endo*-3-amino-1,7,7-trimethylbicyclo[2.2.1]heptane **219** as a pale yellow solid (0.60g, 84%); **MP** = 71.5-72.3°C (pentane); $[\alpha]_D^{21}$ = +27.8° (c=1.05, CH_2Cl_2); **^{1}H NMR** (360.13MHz, $CDCl_3$) δ 7.25-7.20(2H, cm, Ar), 6.87-6.83(2H, cm, Ar), 3.77(3H, s, OCH_3), 3.67-3.59(3H, cm, overlapping signals, $ArCH_2$ and C<u>H</u>OH), 3.17(1H, ddd, *J* = 9.1, 4.4, 1.3 Hz, C<u>H</u>N), 3.00-2.30(2H, bs, NH and OH), 1.81-1.74(2H, cm), 1.44-1.32(2H, cm), 1.25-0.93(1H, cm), 0.88(6H, s, $2CH_3$), 0.86(3H, s, CH_3) ppm; **^{13}C NMR** (50.32MHz, $CDCl_3$) δ 158.5(Ar C), 131.7(Ar C), 129.1(2Ar CH), 113.6(2Ar CH), 72.4(CH), 56.1(CH), 55.0(CH_3), 52.4(CH_2), 49.4(C), 48.6(CH), 45.1(C), 25.2(CH_2), 19.8(CH_3), 18.7(CH_2), 18.1(CH_3), 14.3(CH_3) ppm; **FT IR** ν_{max} (nujol) 3332(NH), 3127(OH) cm^{-1}; **Accurate mass** found 290.21165(MH^+), $C_{18}H_{28}NO_2$ requires 290.21200; **Elemental analysis** found 74.3% C, 9.3% H, 4.7% N, $C_{18}H_{27}NO_2$ requires 74.7% C, 9.3% H, 4.8% N.

7.11 Formation of Oxazaborolidine 216

The same procedure as in section 7.7 was used, using the amino alcohol **219** (0.74g, 2.6mmol) to give the oxazaborolidine **216** (0.80g, 100%); **^{11}B NMR** (64.21MHz, CH_2Cl_2) δ 34.6 ppm.

7.12 Attempted Asymmetric Ketone Reductions

7.12.1 Reduction of Acetophenone 220 in the Presence of Oxazaborolidine 208

The method of Corey[51] was followed.

Acetophenone **220** (0.95g, 7.9mmol) was added to dry THF (25ml) under argon, followed by addition of the oxazaborolidine **208** (0.20g, 0.71mmol, 0.1eq) in methylene chloride (5ml). BH_3-THF (4.8ml, 1.0M in THF, 4.8mmol, 0.6eq) was then added dropwise over a period of 8 hours. The reaction mixture was then quenched by the addition of saturated sodium bicarbonate solution (15ml) and left to stir for 30 minutes. The mixture was extracted into methylene chloride (3x50ml), and the combined organic layers dried over magnesium sulphate, filtered and evaporated *in vacuo* to give a pale yellow liquid. The crude mixture was then subjected to flash chromatography (silica, hexane:ether (4:1)) to give phenethylalcohol **222** as a colourless liquid (0.86g, 95%); $[\alpha]_D^{21}$ = +8.2° (c=3.05, MeOH) (Lit.[107] = +45.5° (c=3.0, MeOH)); **FT IR** ν_{max} (thin film) 3373(OH) cm^{-1}.

7.12.2 Reduction of Acetophenone 220 in the Presence of Oxazaborolidine 216

The same procedure as in section 7.12.1 was employed using oxazaborolidine **216** (0.1eq), acetophenone **220** (0.89g, 7.4mmol) and BH_3-THF (4.5ml, 1.0M in THF, 4.5mmol, 0.6eq), which led to the formation of phenethylalcohol **222** as a colourless liquid (0.78g, 86%); $[\alpha]_D^{21}$ = 0.0° (c=3.00, MeOH); **FT IR** ν_{max} (thin film) 3372(OH) cm^{-1}.

7.12.3 Reduction of α-Tetralone 221 in the Presence of Oxazaborolidine 208

Reaction conditions were as described in section 7.12.1, using oxazaborolidine **208** (0.1eq), α-tetralone **221** (1.07g, 7.30mmol) and BH_3-THF (4.4ml, 1.0M in THF,

4.4mmol, 0.6eq) which gave α-tetralol **223** as a clear colourless oil (0.80g, 75%); $[\alpha]_D^{21}$ = +0.6° (c=3.45, $CHCl_3$) (Lit.[108]= +32° (c=2.5, $CHCl_3$); **FT IR** ν_{max} (thin film) 3344(OH) cm^{-1}.

7.12.4 Reduction of α-Tetralone 221 in the Presence of Oxazaborolidine 216

Again section 7.12.1's conditions were used with oxazaborolidine **216** (0.1eq), α-tetralone **221** (1.02g, 6.98mmol) and BH_3-THF (4.2ml, 1.0M in THf, 4.2mmol, 0.6eq) to give α-tetralol **223** as a clear colourless oil (0.83g, 80%); $[\alpha]_D^{21}$ = 0.0° (c=2.00, $CHCl_3$); **FT IR** 3343(OH) cm^{-1}.

7.13 Preparation of α-Bromoacrolein 94

Acrolein **224** (17.86g, 319mmol) was added to dry methylene chloride(110ml) under argon, and the solution cooled to -78°C. A solution of bromine (56.0g, 350mmol) in dry methylene chloride (80ml), was then added over a period of 2 hours. Triethylamine (40.08g, 397mmol) in methylene chloride (70ml) was then added over 1.5 hours (reaction mixture was seen to turn a blue colour) and then allowed to warm to room temperature and stirred overnight. The solvent was removed *in vacuo,* and the crude product redissolved in ether, filtered and the ether evaporated *in vacuo* at room temperature. The crude product was then Kugelrhor distilled to give α-bromo-acrolein **94** as a colourless oil (14.54g, 34%); **BP** = 55°C at 40mmHg (Lit.[55]= 50°C at 30 mmHg); **FT IR** ν_{max} (thin film) 1670(C=O), 1599(C=C) cm^{-1}.

7.14 Attempted Asymmetric Diels-Alder Reaction Between α-Bromoacrolein 94 and Cyclopentadiene

7.14.1 Using Oxazaborolidine 208 as Catalyst

The oxazaborolidine **208** (0.1eq) in dry methylene chloride (25ml) was cooled to -20°C (salt/ice) then freshly distilled α-bromoacrolein **94** (0.21g, 1.56mmol) added followed by dropwise addition of freshly cracked cyclopentadiene (0.88g, 13mmol). The mixture was then was then stirred at -20°C for 13 hours. The solvent was then removed *in vacuo* and purified by flash chromatography (silica, hexane:ether (4:1)) to give 2-bromo-2-carbonylbicyclo[2.2.1]hept-5-ene **225** as a pale yellow oil (0.43g, 100%); $[\alpha]_D^{21}$ = 0.0° (c=5.2, CH_2Cl_2); **^{1}H NMR** (60MHz, $CDCl_3$) δ 9.7(1H, s, COH), 6.6(1H, dd, *J* = 5.0, 3.0 Hz, CH=C), 6.3(1H, dd, *J* = 5.0, 3.0 Hz, C=CH), 3.5-1.0(6H, cm) ppm; **FT IR** ν_{max} (thin film) 1722(C=O) cm^{-1}.

7.14.2 Using 216 as Catalyst

The same procedure was followed as in 7.14.1 with α-bromoacrolein (0.15g, 1.1mmol) and cyclopentadiene (0.75g, 11mmol). As before chromatography yielded racemic **225** as a pale yellow oil (0.21g, 94%).

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Appendix

Structure 1

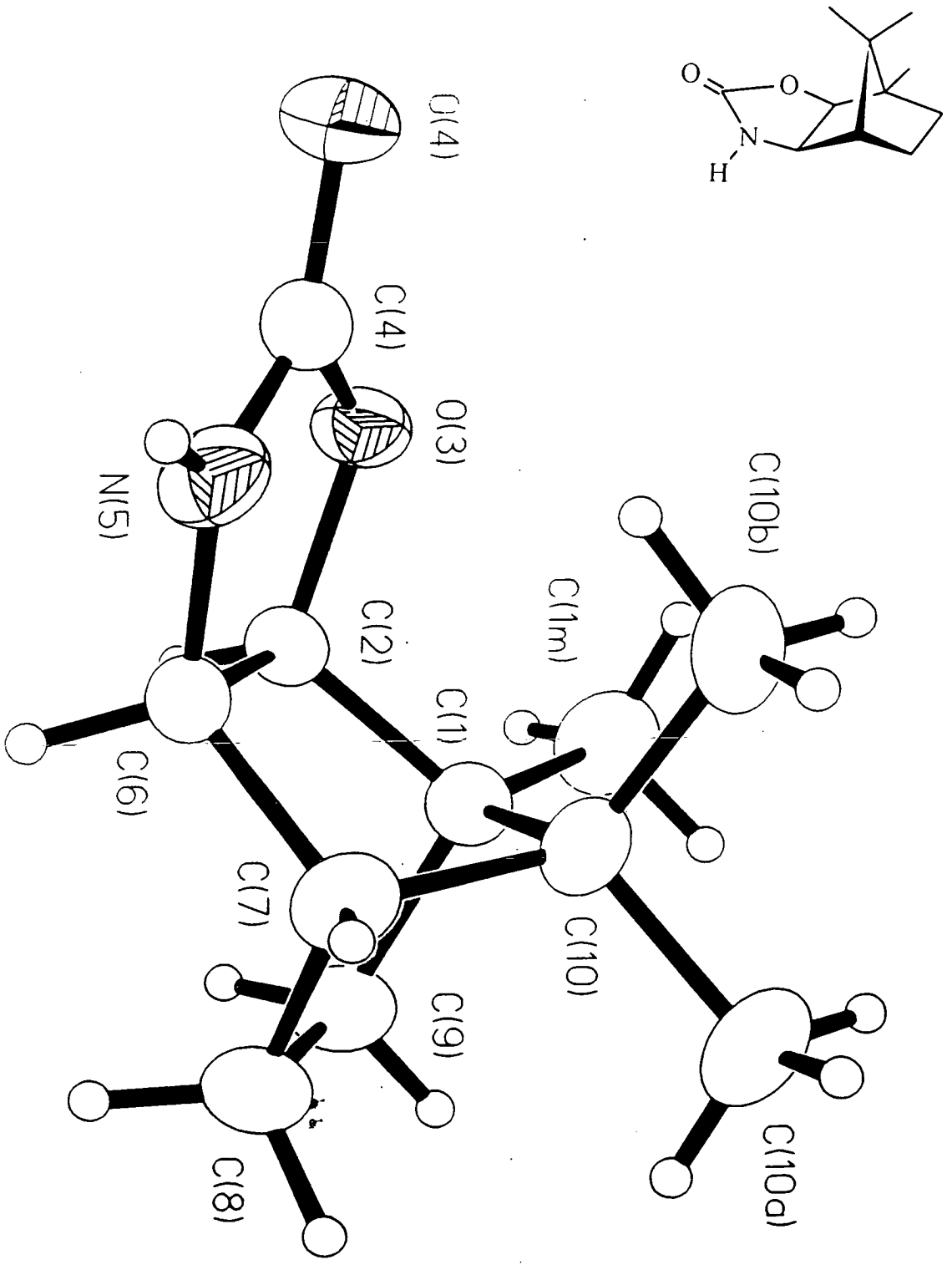


Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for 1. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
C(1)	-499(3)	4954(3)	6265(1)	48(1)
C(1M)	-1646(4)	6741(4)	6369(1)	72(1)
C(2)	154(3)	3982(3)	6856(1)	46(1)
O(3)	1037(2)	5225(2)	7301(1)	57(1)
C(4)	2850(3)	4646(3)	7410(1)	59(1)
O(4)	3822(3)	5413(3)	7800(1)	86(1)
N(5)	3309(3)	3234(3)	7032(1)	62(1)
C(6)	1742(3)	2613(3)	6652(1)	51(1)
C(7)	1844(4)	2972(3)	5957(1)	59(1)
C(8)	55(4)	2001(3)	5708(1)	78(1)
C(9)	-1552(4)	3330(4)	5930(1)	71(1)
C(10)	1361(3)	5099(3)	5876(1)	52(1)
C(10A)	968(4)	5642(4)	5202(1)	79(1)
C(10B)	2855(4)	6520(4)	6095(1)	74(1)

Table 3. Selected bond lengths [A] and angles [deg] for 1.

C(1)-C(1M)	1.509(3)
C(1)-C(2)	1.528(3)
C(1)-C(9)	1.543(3)
C(1)-C(10)	1.558(3)
C(2)-O(3)	1.445(2)
C(2)-C(6)	1.537(3)
O(3)-C(4)	1.354(3)
C(4)-O(4)	1.215(3)
C(4)-N(5)	1.329(3)
N(5)-C(6)	1.443(3)
C(6)-C(7)	1.538(3)
C(7)-C(8)	1.526(4)
C(7)-C(10)	1.544(3)
C(8)-C(9)	1.541(4)
C(10)-C(10A)	1.541(3)
C(10)-C(10B)	1.524(3)
C(1M)-C(1)-C(2)	114.0(2)
C(1M)-C(1)-C(9)	115.7(2)
C(2)-C(1)-C(9)	102.1(2)
C(1M)-C(1)-C(10)	118.2(2)
C(2)-C(1)-C(10)	103.8(2)
C(9)-C(1)-C(10)	101.0(2)
O(3)-C(2)-C(1)	115.0(2)
O(3)-C(2)-C(6)	105.3(2)
C(1)-C(2)-C(6)	104.7(2)
C(4)-O(3)-C(2)	109.7(2)
O(4)-C(4)-N(5)	129.0(2)
O(4)-C(4)-O(3)	120.9(2)
N(5)-C(4)-O(3)	110.1(2)
C(4)-N(5)-C(6)	113.4(2)
N(5)-C(6)-C(2)	101.2(2)
N(5)-C(6)-C(7)	118.7(2)
C(2)-C(6)-C(7)	102.5(2)
C(8)-C(7)-C(6)	103.8(2)
C(8)-C(7)-C(10)	102.3(2)
C(6)-C(7)-C(10)	105.1(2)
C(7)-C(8)-C(9)	102.5(2)
C(8)-C(9)-C(1)	104.4(2)
C(7)-C(10)-C(1)	93.3(2)
C(10A)-C(10)-C(7)	112.8(2)
C(10A)-C(10)-C(1)	112.7(2)
C(10B)-C(10)-C(7)	116.7(2)
C(10B)-C(10)-C(1)	116.5(2)
C(10A)-C(10)-C(10B)	105.0(2)

Symmetry transformations used to generate equivalent atoms:

Selected torsion angles for MRBFVP

-48.49	(0.23)	C1M - C1 - C2 - O3
-174.00	(0.16)	C9 - C1 - C2 - O3
81.36	(0.19)	C10 - C1 - C2 - O3
-163.52	(0.18)	C1M - C1 - C2 - C6
70.97	(0.19)	C9 - C1 - C2 - C6
-33.67	(0.18)	C10 - C1 - C2 - C6
-119.46	(0.18)	C1 - C2 - O3 - C4
-4.78	(0.20)	C6 - C2 - O3 - C4
-175.18	(0.19)	C2 - O3 - C4 - O4
5.84	(0.22)	C2 - O3 - C4 - N5
176.57	(0.22)	O4 - C4 - N5 - C6
-4.55	(0.25)	O3 - C4 - N5 - C6
1.37	(0.22)	C4 - N5 - C6 - C2
112.45	(0.21)	C4 - N5 - C6 - C7
2.03	(0.19)	O3 - C2 - C6 - N5
123.70	(0.16)	C1 - C2 - C6 - N5
-121.05	(0.17)	O3 - C2 - C6 - C7
0.62	(0.20)	C1 - C2 - C6 - C7
175.64	(0.18)	N5 - C6 - C7 - C8
-73.96	(0.19)	C2 - C6 - C7 - C8
-77.24	(0.24)	N5 - C6 - C7 - C10
33.16	(0.22)	C2 - C6 - C7 - C10
71.84	(0.21)	C6 - C7 - C8 - C9
-37.38	(0.20)	C10 - C7 - C8 - C9
1.74	(0.22)	C7 - C8 - C9 - C1
162.67	(0.19)	C1M - C1 - C9 - C8
-72.95	(0.19)	C2 - C1 - C9 - C8
33.90	(0.21)	C10 - C1 - C9 - C8
178.78	(0.19)	C8 - C7 - C10 - C10B
70.58	(0.24)	C6 - C7 - C10 - C10B
-59.50	(0.24)	C8 - C7 - C10 - C10A
-167.71	(0.19)	C6 - C7 - C10 - C10A
56.81	(0.17)	C8 - C7 - C10 - C1
-51.39	(0.20)	C6 - C7 - C10 - C1
56.24	(0.24)	C1M - C1 - C10 - C10B
-71.05	(0.20)	C2 - C1 - C10 - C10B
-176.59	(0.18)	C9 - C1 - C10 - C10B
-65.21	(0.26)	C1M - C1 - C10 - C10A
167.50	(0.19)	C2 - C1 - C10 - C10A
61.96	(0.23)	C9 - C1 - C10 - C10A
178.36	(0.19)	C1M - C1 - C10 - C7
51.07	(0.17)	C2 - C1 - C10 - C7
-54.46	(0.18)	C9 - C1 - C10 - C7

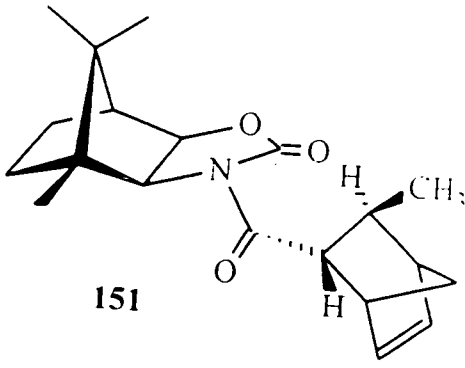
Table 4. Anisotropic displacement parameters (A^2 x 10^3) for 1. The anisotropic displacement factor exponent takes the form: -2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
C(1)	43(1)	51(1)	51(1)	-1(1)	1(1)	-1(1)
C(1M)	62(1)	77(2)	78(2)	5(1)	0(1)	22(1)
C(2)	47(1)	45(1)	47(1)	-2(1)	3(1)	-8(1)
O(3)	64(1)	55(1)	51(1)	-12(1)	-4(1)	1(1)
C(4)	67(1)	55(1)	54(1)	6(1)	-6(1)	-13(1)
O(4)	97(1)	86(1)	76(1)	-2(1)	-31(1)	-32(1)
N(5)	57(1)	67(1)	62(1)	4(1)	-11(1)	14(1)
C(6)	64(1)	40(1)	50(1)	0(1)	-5(1)	3(1)
C(7)	67(1)	62(1)	48(1)	-3(1)	6(1)	17(1)
C(8)	112(2)	63(1)	60(1)	-12(1)	-20(1)	-1(2)
C(9)	69(2)	81(2)	64(1)	-2(1)	-17(1)	-17(1)
C(10)	48(1)	58(1)	49(1)	10(1)	4(1)	5(1)
C(10A)	86(2)	92(2)	58(1)	22(1)	7(1)	11(2)
C(10B)	61(1)	72(2)	89(2)	28(1)	4(1)	-12(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for 1.

	x	y	z	U(eq)
H(1M1)	-2746(4)	6452(4)	6614(1)	87
H(1M2)	-872(4)	7665(4)	6577(1)	87
H(1M3)	-2049(4)	7245(4)	5980(1)	87
H(2)	-883(3)	3292(3)	7039(1)	56
H(5)	4213(42)	2516(34)	7105(12)	75
H(6)	1406(3)	1317(3)	6738(1)	61
H(7)	3015(4)	2577(3)	5767(1)	71
H(8A)	-89(4)	745(3)	5874(1)	94
H(8B)	85(4)	1925(3)	5268(1)	94
H(9A)	-2401(4)	2676(4)	6204(1)	85
H(9B)	-2273(4)	3813(4)	5589(1)	85
H(10A)	2154(4)	5714(4)	4983(1)	94
H(10B)	165(4)	4696(4)	5016(1)	94
H(10C)	340(4)	6854(4)	5188(1)	94
H(10D)	3934(4)	6492(4)	5823(1)	89
H(10E)	2313(4)	7773(4)	6097(1)	89
H(10F)	3261(4)	6191(4)	6502(1)	89

Structure 2



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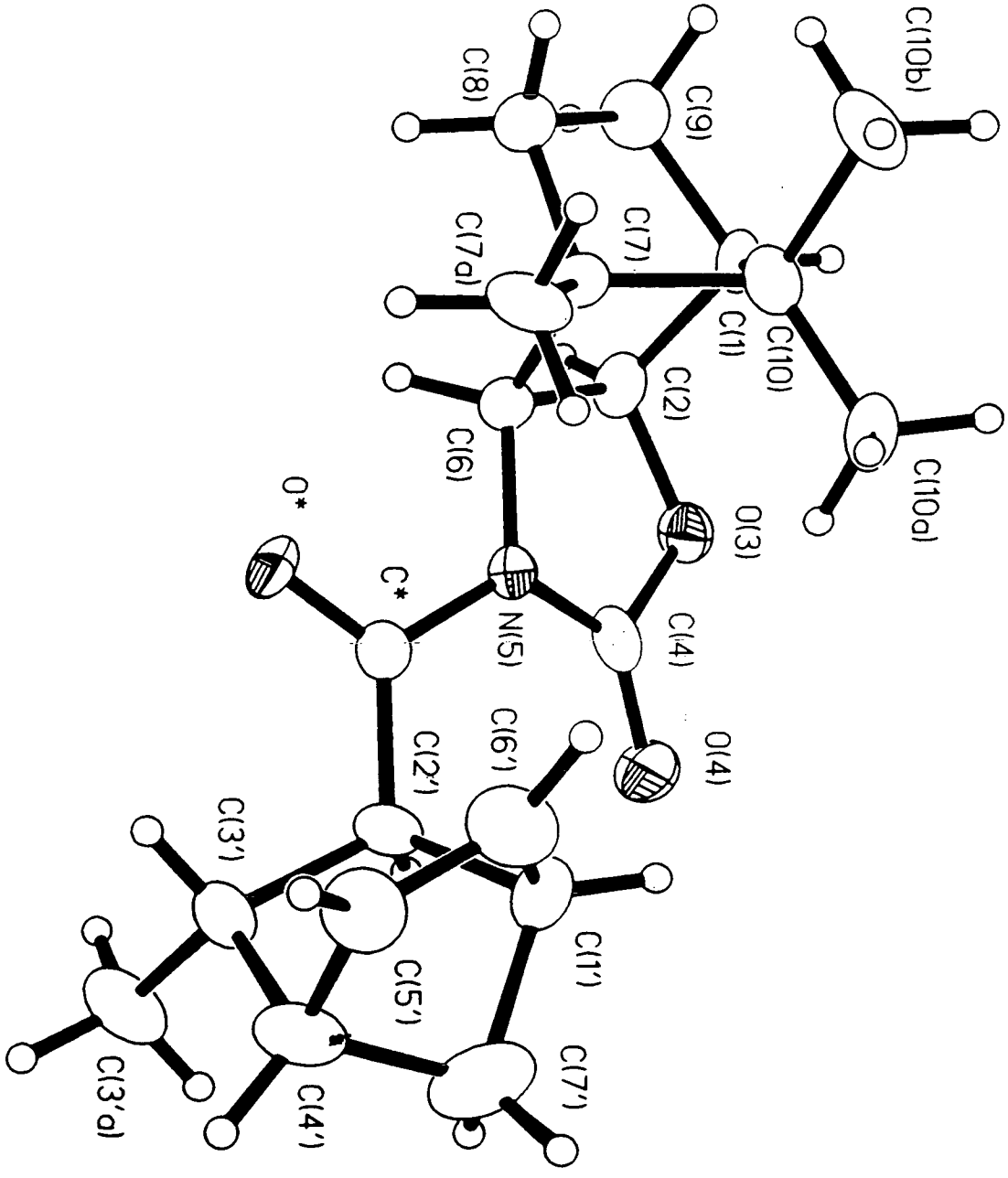

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for AUXDAA. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
C(1)	4586(9)	-120(8)	4838(3)	26(2)
C(2)	3303(10)	1065(7)	4897(3)	27(2)
O(3)	4219(7)	2376(5)	4923(2)	27(1)
C(4)	3618(10)	3175(8)	4512(3)	27(2)
O(4)	4078(8)	4331(5)	4485(2)	35(1)
N(5)	2498(8)	2465(6)	4161(2)	21(1)
C(6)	2205(11)	1093(7)	4357(3)	24(2)
C(7)	3045(9)	-104(7)	4026(3)	22(2)
C(7A)	2736(12)	-81(8)	3405(3)	35(2)
C(8)	2232(11)	-1324(8)	4324(3)	30(2)
C(9)	3275(12)	-1335(8)	4890(3)	35(2)
C(10)	5092(11)	-146(8)	4220(3)	29(2)
C(10A)	6330(10)	1006(8)	4008(3)	34(2)
C(10B)	6057(12)	-1457(8)	4054(3)	40(2)
C*	1289(10)	2998(7)	3757(3)	22(2)
O*	120(7)	2265(5)	3577(2)	31(1)
C(1')	3355(11)	4593(8)	3214(3)	33(2)
C(2')	1538(10)	4402(7)	3566(3)	24(2)
C(3')	34(11)	4940(8)	3178(3)	28(2)
C(3'A)	-1183(13)	5994(8)	3446(3)	41(2)
C(4')	1151(12)	5455(8)	2674(3)	34(2)
C(5')	1882(12)	4225(8)	2398(3)	36(2)
C(6')	3183(12)	3711(9)	2717(3)	40(2)
C(7')	2902(14)	5959(9)	2956(3)	49(3)

Table 3. Bond lengths [A] and angles [deg] for AUXDAA.

C(1)-C(2)	1.514(10)
C(1)-C(10)	1.542(10)
C(1)-C(9)	1.548(11)
C(2)-O(3)	1.469(9)
C(2)-C(6)	1.533(10)
O(3)-C(4)	1.347(9)
C(4)-O(4)	1.203(9)
C(4)-N(5)	1.376(9)
N(5)-C*	1.419(9)
N(5)-C(6)	1.464(9)
C(6)-C(7)	1.563(10)
C(7)-C(7A)	1.521(9)
C(7)-C(8)	1.534(10)
C(7)-C(10)	1.563(11)
C(8)-C(9)	1.567(11)
C(10)-C(10B)	1.539(10)
C(10)-C(10A)	1.548(11)
C*-O*	1.205(8)
C*-C(2')	1.486(10)
C(1')-C(6')	1.498(11)
C(1')-C(7')	1.536(11)
C(1')-C(2')	1.585(11)
C(2')-C(3')	1.541(11)
C(3')-C(3'A)	1.521(10)
C(3')-C(4')	1.554(11)
C(4')-C(5')	1.495(11)
C(4')-C(7')	1.531(12)
C(5')-C(6')	1.325(11)

C(2)-C(1)-C(10)	104.6(6)
C(2)-C(1)-C(9)	102.9(6)
C(10)-C(1)-C(9)	102.4(6)
O(3)-C(2)-C(1)	114.8(6)
O(3)-C(2)-C(6)	104.9(5)
C(1)-C(2)-C(6)	104.8(6)
C(4)-O(3)-C(2)	110.4(5)
O(4)-C(4)-O(3)	121.2(7)
O(4)-C(4)-N(5)	128.7(7)
O(3)-C(4)-N(5)	110.1(6)
C(4)-N(5)-C*	126.9(6)
C(4)-N(5)-C(6)	111.5(6)
C*-N(5)-C(6)	118.9(6)
N(5)-C(6)-C(2)	102.6(6)
N(5)-C(6)-C(7)	119.4(6)
C(2)-C(6)-C(7)	102.7(6)
C(7A)-C(7)-C(8)	114.9(6)
C(7A)-C(7)-C(6)	116.0(6)
C(8)-C(7)-C(6)	102.3(5)
C(7A)-C(7)-C(10)	116.0(6)
C(8)-C(7)-C(10)	101.8(6)
C(6)-C(7)-C(10)	103.9(6)
C(7)-C(8)-C(9)	103.3(6)
C(1)-C(9)-C(8)	102.8(6)
C(10B)-C(10)-C(1)	112.1(6)
C(10B)-C(10)-C(10A)	106.2(6)
C(1)-C(10)-C(10A)	116.6(6)
C(10B)-C(10)-C(7)	112.3(6)
C(1)-C(10)-C(7)	93.6(5)
C(10A)-C(10)-C(7)	115.9(6)
O*-C*-N(5)	117.5(6)

O*-C*-C(2')	123.0(6)
N(5)-C*-C(2')	119.5(6)
C(6')-C(1')-C(7')	100.1(6)
C(6')-C(1')-C(2')	107.0(6)
C(7')-C(1')-C(2')	98.5(7)
C*-C(2')-C(3')	115.6(6)
C*-C(2')-C(1')	112.5(6)
C(3')-C(2')-C(1')	102.9(5)
C(3'A)-C(3')-C(2')	113.2(6)
C(3'A)-C(3')-C(4')	114.4(6)
C(2')-C(3')-C(4')	102.9(6)
C(5')-C(4')-C(7')	99.9(7)
C(5')-C(4')-C(3')	105.5(6)
C(7')-C(4')-C(3')	101.2(6)
C(6')-C(5')-C(4')	108.1(7)
C(5')-C(6')-C(1')	107.5(7)
C(4')-C(7')-C(1')	93.9(6)

Symmetry transformations used to generate equivalent atoms:

Torsion angles for AUXDAA

C10	C1	C2	O3	-79.6(7)
C9	C1	C2	O3	173.7(6)
C10	C1	C2	C6	34.9(7)
C9	C1	C2	C6	-71.8(6)
C1	C2	O3	C4	121.7(6)
C6	C2	O3	C4	7.3(7)
C2	O3	C4	O4	173.7(7)
C2	O3	C4	N5	-6.9(8)
O4	C4	N5	C*	-15.7(12)
O3	C4	N5	C*	165.0(6)
O4	C4	N5	C6	-177.0(8)
O3	C4	N5	C6	3.6(8)
C4	N5	C6	C2	1.0(7)
C*	N5	C6	C2	-162.0(6)
C4	N5	C6	C7	-111.6(7)
C*	N5	C6	C7	85.4(8)
O3	C2	C6	N5	-4.7(7)
C1	C2	C6	N5	-126.0(6)
O3	C2	C6	C7	119.7(6)
C1	C2	C6	C7	-1.5(7)
N5	C6	C7	C7A	-47.6(9)
C2	C6	C7	C7A	-160.1(6)
N5	C6	C7	C8	-173.4(6)
C2	C6	C7	C8	74.1(6)
N5	C6	C7	C10	80.9(7)
C2	C6	C7	C10	-31.6(7)
C7A	C7	C8	C9	162.0(6)
C6	C7	C8	C9	-71.4(6)
C10	C7	C8	C9	35.8(7)
C2	C1	C9	C8	73.4(7)
C10	C1	C9	C8	-34.9(7)
C7	C8	C9	C1	-0.9(7)
C2	C1	C10	C10B	-167.7(6)
C9	C1	C10	C10B	-60.7(8)
C2	C1	C10	C10A	69.5(7)
C9	C1	C10	C10A	176.6(6)
C2	C1	C10	C7	-51.8(7)
C9	C1	C10	C7	55.2(6)
C7A	C7	C10	C10B	-65.5(8)
C8	C7	C10	C10B	60.0(7)
C6	C7	C10	C10B	166.0(5)
C7A	C7	C10	C1	178.7(6)
C8	C7	C10	C1	-55.8(6)
C6	C7	C10	C1	50.3(6)
C7A	C7	C10	C10A	56.8(9)
C8	C7	C10	C10A	-177.8(6)
C6	C7	C10	C10A	-71.7(7)
C4	N5	C*	O*	-163.4(7)
C6	N5	C*	O*	-3.3(9)
C4	N5	C*	C2'	18.2(10)
C6	N5	C*	C2'	178.3(6)
O*	C*	C2'	C3'	8.2(10)
N5	C*	C2'	C3'	-173.4(6)
O*	C*	C2'	C1'	-109.5(8)
N5	C*	C2'	C1'	68.8(8)
C6'	C1'	C2'	C*	61.3(8)
C7'	C1'	C2'	C*	164.6(6)
C6'	C1'	C2'	C3'	-63.8(7)
C7'	C1'	C2'	C3'	39.5(7)
C*	C2'	C3'	C3'A	109.5(7)
C1'	C2'	C3'	C3'A	-127.5(7)
C*	C2'	C3'	C4'	-126.5(6)

C1'	C2'	C3'	C4'	-3.5(7)
C3'A	C3'	C4'	C5'	-167.1(7)
C2'	C3'	C4'	C5'	69.7(7)
C3'A	C3'	C4'	C7'	89.2(8)
C2'	C3'	C4'	C7'	-34.0(7)
C7'	C4'	C5'	C6'	33.4(8)
C3'	C4'	C5'	C6'	-71.2(8)
C4'	C5'	C6'	C1'	-0.2(9)
C7'	C1'	C6'	C5'	-33.0(9)
C2'	C1'	C6'	C5'	69.2(8)
C5'	C4'	C7'	C1'	-49.8(7)
C3'	C4'	C7'	C1'	58.3(7)
C6'	C1'	C7'	C4'	49.8(8)
C2'	C1'	C7'	C4'	-59.2(6)

Table 4. Anisotropic displacement parameters (A^2 x 10^3) for AUXDAA. The anisotropic displacement factor exponent takes the form: -2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
C(1)	14(4)	36(5)	29(4)	6(4)	2(3)	-2(3)
C(2)	21(4)	36(5)	23(4)	3(4)	0(3)	-3(4)
O(3)	24(3)	31(3)	26(3)	1(2)	-8(2)	1(2)
C(4)	19(4)	34(5)	28(4)	-6(4)	-3(4)	8(4)
O(4)	32(3)	27(3)	46(3)	-5(3)	-16(3)	-7(3)
N(5)	16(3)	22(3)	24(3)	0(3)	1(3)	2(3)
C(6)	21(4)	25(4)	27(4)	9(3)	4(3)	-1(3)
C(7)	22(4)	21(4)	22(4)	1(3)	0(3)	-2(3)
C(7A)	46(5)	23(4)	34(4)	-5(4)	-6(4)	10(4)
C(8)	27(5)	26(5)	38(5)	4(3)	-2(3)	-3(4)
C(9)	34(5)	38(5)	32(4)	7(4)	9(4)	3(4)
C(10)	24(4)	36(5)	28(4)	0(4)	2(3)	5(4)
C(10A)	19(4)	46(5)	39(4)	7(4)	7(4)	1(4)
C(10B)	35(5)	43(5)	42(5)	3(4)	10(4)	18(4)
C*	18(4)	24(4)	23(4)	0(3)	6(3)	3(3)
O*	19(3)	29(3)	44(3)	7(3)	-9(3)	-10(3)
C(1')	23(4)	40(5)	37(4)	7(4)	-3(4)	-8(4)
C(2')	32(4)	15(4)	25(4)	-4(3)	1(4)	3(3)
C(3')	24(4)	30(4)	29(4)	3(4)	-1(3)	5(4)
C(3'A)	46(6)	37(5)	41(5)	-3(4)	1(4)	22(4)
C(4')	50(5)	24(4)	27(4)	1(3)	-2(4)	4(4)
C(5')	37(5)	44(5)	25(4)	2(4)	5(4)	2(4)
C(6')	42(5)	45(5)	35(5)	5(4)	22(4)	9(5)
C(7')	68(7)	44(6)	35(5)	2(4)	2(5)	-23(5)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for AUXDAA.

	x	y	z	U(eq)
H(1)	5615(9)	-119(8)	5086(3)	31
H(2)	2506(10)	949(7)	5209(3)	32
H(6)	925(11)	938(7)	4427(3)	29
H(7A1)	1443(12)	-52(8)	3329(3)	42
H(7A2)	3318(12)	697(8)	3250(3)	42
H(7A3)	3257(12)	-874(8)	3244(3)	42
H(8A)	2464(11)	-2159(8)	4115(3)	36
H(8B)	892(11)	-1219(8)	4380(3)	36
H(9A)	2414(12)	-1218(8)	5203(3)	41
H(9B)	3968(12)	-2179(8)	4941(3)	41
H(10A)	7557(10)	890(8)	4145(3)	41
H(10B)	6347(10)	1013(8)	3612(3)	41
H(10C)	5842(10)	1839(8)	4141(3)	41
H(10D)	5324(12)	-2199(8)	4177(3)	48
H(10E)	6190(12)	-1496(8)	3660(3)	48
H(10F)	7246(12)	-1501(8)	4224(3)	48
H(1')	4485(11)	4536(8)	3417(3)	40
H(2')	1610(10)	4973(7)	3884(3)	29
H(3')	-733(11)	4210(8)	3061(3)	33
H(3'1)	-2105(13)	6296(8)	3192(3)	50
H(3'2)	-1764(13)	5625(8)	3768(3)	50
H(3'3)	-422(13)	6736(8)	3552(3)	50
H(4')	532(12)	6084(8)	2439(3)	40
H(5')	1484(12)	3874(8)	2054(3)	43
H(6')	3879(12)	2926(9)	2643(3)	48
H(7'A)	3821(14)	6240(9)	2696(3)	59
H(7'B)	2686(14)	6648(9)	3224(3)	59

Structure 3

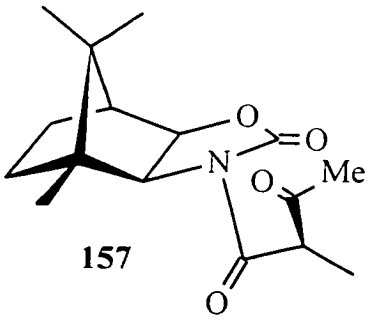

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Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for AUXDIN. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
C(1)	6644(4)	5(4)	79(2)	29(1)
C(2)	5424(4)	-355(3)	-211(2)	28(1)
O(3)	5090(3)	-1484(2)	-108(1)	30(1)
C(4)	3962(4)	-1565(4)	147(2)	26(1)
O(4)	3476(3)	-2425(2)	246(1)	34(1)
N(5)	3521(3)	-532(3)	274(2)	24(1)
C(6)	4388(4)	324(3)	80(2)	26(1)
C(7)	5142(4)	992(3)	533(2)	28(1)
C(7A)	4368(5)	1479(4)	1012(2)	33(1)
C(8)	5830(5)	1835(4)	147(2)	35(1)
C(9)	6851(5)	1155(4)	-159(2)	36(1)
C(10)	6259(4)	237(3)	704(2)	28(1)
C(10A)	5921(5)	-763(4)	1065(2)	33(1)
C(10B)	7283(4)	835(4)	1039(2)	38(1)
C(11)	2290(4)	-277(4)	442(2)	27(1)
O(11)	1953(3)	663(2)	428(2)	36(1)
C(12)	1441(4)	-1189(4)	641(2)	29(1)
C(13)	122(4)	-766(5)	764(3)	49(1)
C(14)	1961(4)	-1710(4)	1180(2)	31(1)
O(14)	2673(3)	-1211(3)	1487(1)	43(1)
C(15)	1529(5)	-2839(4)	1316(2)	39(1)
C(1')	5049(4)	9916(4)	3048(2)	31(1)
C(2')	4168(4)	9421(4)	2617(2)	28(1)
O(3')	3762(3)	8323(2)	2748(1)	33(1)
C(4')	2504(4)	8264(4)	2782(2)	28(1)
O(4')	1954(3)	7416(3)	2846(1)	37(1)
N(5')	2003(3)	9286(3)	2749(2)	28(1)
C(6')	2968(4)	10121(4)	2661(2)	30(1)
C(7')	3287(4)	10931(3)	3151(2)	32(1)
C(7A')	2172(5)	11463(4)	3437(3)	55(2)
C(8')	4226(5)	11710(4)	2856(2)	39(1)
C(9')	5423(5)	11008(4)	2780(2)	37(1)
C(10')	4181(5)	10273(4)	3543(2)	33(1)
C(0A')	3578(5)	9365(4)	3901(2)	42(1)
C(0B')	4905(6)	10978(5)	3974(2)	56(2)
C(11')	738(5)	9536(4)	2666(2)	37(1)
O(11')	440(3)	10457(3)	2542(2)	65(1)
C(12')	-237(5)	8654(5)	2749(2)	42(1)
C(13')	-1549(5)	9085(6)	2614(4)	75(2)
C(14')	-184(5)	8255(4)	3359(2)	40(1)
O(14')	261(4)	8828(3)	3732(1)	50(1)
C(15')	-743(7)	7157(5)	3485(3)	67(2)

Table 3. Selected bond lengths [A], angles and torsions [deg] for AUXDIN.

C(1)-C(2)	1.528(6)
C(1)-C(9)	1.538(6)
C(1)-C(10)	1.549(6)
C(2)-O(3)	1.455(5)
C(2)-C(6)	1.539(6)
O(3)-C(4)	1.341(5)
C(4)-O(4)	1.201(5)
C(4)-N(5)	1.388(5)
N(5)-C(11)	1.401(6)
N(5)-C(6)	1.471(5)
C(6)-C(7)	1.564(6)
C(7)-C(7A)	1.516(6)
C(7)-C(8)	1.558(6)
C(7)-C(10)	1.560(6)
C(8)-C(9)	1.546(7)
C(10)-C(10B)	1.529(6)
C(10)-C(10A)	1.535(6)
C(11)-O(11)	1.211(5)
C(11)-C(12)	1.513(6)
C(12)-C(13)	1.522(6)
C(12)-C(14)	1.521(7)
C(14)-O(14)	1.211(5)
C(14)-C(15)	1.499(7)
C(1')-C(2')	1.504(7)
C(1')-C(9')	1.536(7)
C(1')-C(10')	1.546(7)
C(2')-O(3')	1.452(5)
C(2')-C(6')	1.542(6)
O(3')-C(4')	1.340(6)
C(4')-O(4')	1.206(5)
C(4')-N(5')	1.368(6)
N(5')-C(11')	1.392(6)
N(5')-C(6')	1.467(6)
C(6')-C(7')	1.559(7)
C(7')-C(7A')	1.510(7)
C(7')-C(8')	1.547(6)
C(7')-C(10')	1.550(7)
C(8')-C(9')	1.548(7)
C(10')-C(0A')	1.539(7)
C(10')-C(0B')	1.538(7)
C(11')-O(11')	1.212(6)
C(11')-C(12')	1.513(7)
C(12')-C(14')	1.514(8)
C(12')-C(13')	1.524(8)
C(14')-O(14')	1.218(6)
C(14')-C(15')	1.506(7)
C(2)-C(1)-C(9)	103.1(4)
C(2)-C(1)-C(10)	104.5(3)
C(9)-C(1)-C(10)	102.2(4)
O(3)-C(2)-C(1)	114.2(4)
O(3)-C(2)-C(6)	105.8(3)
C(1)-C(2)-C(6)	104.6(3)
C(4)-O(3)-C(2)	111.2(3)
O(4)-C(4)-O(3)	122.3(4)
O(4)-C(4)-N(5)	128.4(4)
O(3)-C(4)-N(5)	109.2(4)
C(4)-N(5)-C(11)	125.5(4)
C(4)-N(5)-C(6)	112.2(3)

C(11)-N(5)-C(6)	120.7(3)
N(5)-C(6)-C(2)	101.3(3)
N(5)-C(6)-C(7)	119.1(4)
C(2)-C(6)-C(7)	102.7(3)
C(7A)-C(7)-C(8)	114.9(4)
C(7A)-C(7)-C(10)	117.2(4)
C(8)-C(7)-C(10)	101.0(3)
C(7A)-C(7)-C(6)	115.7(4)
C(8)-C(7)-C(6)	101.3(4)
C(10)-C(7)-C(6)	104.5(3)
C(9)-C(8)-C(7)	103.7(3)
C(1)-C(9)-C(8)	103.4(4)
C(10B)-C(10)-C(10A)	105.7(4)
C(10B)-C(10)-C(1)	112.8(4)
C(10A)-C(10)-C(1)	115.7(4)
C(10B)-C(10)-C(7)	112.6(3)
C(10A)-C(10)-C(7)	116.3(4)
C(1)-C(10)-C(7)	93.8(3)
O(11)-C(11)-N(5)	118.8(4)
O(11)-C(11)-C(12)	122.8(4)
N(5)-C(11)-C(12)	118.4(4)
C(11)-C(12)-C(13)	110.6(4)
C(11)-C(12)-C(14)	110.6(4)
C(13)-C(12)-C(14)	108.7(4)
O(14)-C(14)-C(15)	122.4(4)
O(14)-C(14)-C(12)	120.4(4)
C(15)-C(14)-C(12)	117.2(4)
C(2')-C(1')-C(9')	104.0(4)
C(2')-C(1')-C(10')	104.4(4)
C(9')-C(1')-C(10')	102.2(4)
O(3')-C(2')-C(1')	114.9(4)
O(3')-C(2')-C(6')	105.2(3)
C(1')-C(2')-C(6')	104.1(4)
C(4')-O(3')-C(2')	111.0(4)
O(4')-C(4')-O(3')	122.4(4)
O(4')-C(4')-N(5')	128.0(4)
O(3')-C(4')-N(5')	109.5(4)
C(4')-N(5')-C(11')	125.9(4)
C(4')-N(5')-C(6')	112.5(4)
C(11')-N(5')-C(6')	119.9(4)
N(5')-C(6')-C(2')	101.2(3)
N(5')-C(6')-C(7')	119.7(4)
C(2')-C(6')-C(7')	103.1(4)
C(7A')-C(7')-C(8')	115.8(4)
C(7A')-C(7')-C(10')	116.4(5)
C(8')-C(7')-C(10')	101.2(4)
C(7A')-C(7')-C(6')	115.8(4)
C(8')-C(7')-C(6')	101.9(4)
C(10')-C(7')-C(6')	103.6(3)
C(7')-C(8')-C(9')	103.5(4)
C(1')-C(9')-C(8')	103.3(4)
C(0A')-C(10')-C(0B')	105.1(4)
C(0A')-C(10')-C(7')	116.6(4)
C(0B')-C(10')-C(7')	113.6(4)
C(0A')-C(10')-C(1')	116.8(4)
C(0B')-C(10')-C(1')	110.9(4)
C(7')-C(10')-C(1')	94.0(4)
O(11')-C(11')-N(5')	119.5(5)
O(11')-C(11')-C(12')	121.6(5)
N(5')-C(11')-C(12')	118.9(5)
C(11')-C(12')-C(14')	109.1(4)
C(11')-C(12')-C(13')	110.4(5)
C(14')-C(12')-C(13')	110.0(5)
O(14')-C(14')-C(15')	122.2(5)

O(14')-C(14')-C(12')	120.3(5)
C(15')-C(14')-C(12')	117.4(5)
C(9)-C(1)-C(2)-O(3)	173.1(3)
C(10)-C(1)-C(2)-O(3)	-80.4(4)
C(9)-C(1)-C(2)-C(6)	-71.8(4)
C(10)-C(1)-C(2)-C(6)	34.7(4)
C(1)-C(2)-O(3)-C(4)	120.5(4)
C(6)-C(2)-O(3)-C(4)	6.1(5)
C(2)-O(3)-C(4)-O(4)	176.3(4)
C(2)-O(3)-C(4)-N(5)	-5.0(5)
O(4)-C(4)-N(5)-C(11)	-14.0(7)
O(3)-C(4)-N(5)-C(11)	167.4(4)
O(4)-C(4)-N(5)-C(6)	-179.7(4)
O(3)-C(4)-N(5)-C(6)	1.7(5)
C(4)-N(5)-C(6)-C(2)	1.9(4)
C(11)-N(5)-C(6)-C(2)	-164.5(4)
C(4)-N(5)-C(6)-C(7)	-109.7(4)
C(11)-N(5)-C(6)-C(7)	83.9(5)
O(3)-C(2)-C(6)-N(5)	-4.6(4)
C(1)-C(2)-C(6)-N(5)	-125.5(4)
O(3)-C(2)-C(6)-C(7)	119.0(4)
C(1)-C(2)-C(6)-C(7)	-1.9(4)
N(5)-C(6)-C(7)-C(7A)	-50.8(5)
C(2)-C(6)-C(7)-C(7A)	-161.6(4)
N(5)-C(6)-C(7)-C(8)	-175.8(3)
C(2)-C(6)-C(7)-C(8)	73.4(4)
N(5)-C(6)-C(7)-C(10)	79.6(4)
C(2)-C(6)-C(7)-C(10)	-31.2(4)
C(7A)-C(7)-C(8)-C(9)	162.1(4)
C(10)-C(7)-C(8)-C(9)	34.9(4)
C(6)-C(7)-C(8)-C(9)	-72.4(4)
C(2)-C(1)-C(9)-C(8)	72.6(4)
C(10)-C(1)-C(9)-C(8)	-35.7(4)
C(7)-C(8)-C(9)-C(1)	0.2(5)
C(2)-C(1)-C(10)-C(10B)	-167.9(4)
C(9)-C(1)-C(10)-C(10B)	-60.7(4)
C(2)-C(1)-C(10)-C(10A)	70.2(4)
C(9)-C(1)-C(10)-C(10A)	177.4(4)
C(2)-C(1)-C(10)-C(7)	-51.4(4)
C(9)-C(1)-C(10)-C(7)	55.8(4)
C(7A)-C(7)-C(10)-C(10B)	-63.9(5)
C(8)-C(7)-C(10)-C(10B)	61.7(5)
C(6)-C(7)-C(10)-C(10B)	166.6(4)
C(7A)-C(7)-C(10)-C(10A)	58.3(5)
C(8)-C(7)-C(10)-C(10A)	-176.1(4)
C(6)-C(7)-C(10)-C(10A)	-71.3(5)
C(7A)-C(7)-C(10)-C(1)	179.4(4)
C(8)-C(7)-C(10)-C(1)	-54.9(4)
C(6)-C(7)-C(10)-C(1)	49.9(4)
C(4)-N(5)-C(11)-O(11)	-164.9(4)
C(6)-N(5)-C(11)-O(11)	-0.4(6)
C(4)-N(5)-C(11)-C(12)	15.7(6)
C(6)-N(5)-C(11)-C(12)	-179.8(4)
O(11)-C(11)-C(12)-C(13)	4.6(6)
N(5)-C(11)-C(12)-C(13)	-176.0(4)
O(11)-C(11)-C(12)-C(14)	-115.8(5)
N(5)-C(11)-C(12)-C(14)	63.5(5)
C(11)-C(12)-C(14)-O(14)	22.8(6)
C(13)-C(12)-C(14)-O(14)	-98.8(5)
C(11)-C(12)-C(14)-C(15)	-158.8(4)
C(13)-C(12)-C(14)-C(15)	79.6(5)
C(9')-C(1')-C(2')-O(3')	174.6(3)
C(10')-C(1')-C(2')-O(3')	-78.6(4)

C(10')-C(1')-C(2')-C(6')	35.9(4)
C(1')-C(2')-O(3')-C(4')	122.0(4)
C(6')-C(2')-O(3')-C(4')	8.3(5)
C(2')-O(3')-C(4')-O(4')	174.5(4)
C(2')-O(3')-C(4')-N(5')	-6.9(5)
O(4')-C(4')-N(5')-C(11')	-14.0(8)
O(3')-C(4')-N(5')-C(11')	167.6(4)
O(4')-C(4')-N(5')-C(6')	-179.0(4)
O(3')-C(4')-N(5')-C(6')	2.6(5)
C(4')-N(5')-C(6')-C(2')	2.4(5)
C(11')-N(5')-C(6')-C(2')	-163.6(4)
C(4')-N(5')-C(6')-C(7')	-109.9(5)
C(11')-N(5')-C(6')-C(7')	84.1(5)
O(3')-C(2')-C(6')-N(5')	-6.1(4)
C(1')-C(2')-C(6')-N(5')	-127.3(4)
O(3')-C(2')-C(6')-C(7')	118.3(4)
C(1')-C(2')-C(6')-C(7')	-2.9(4)
N(5')-C(6')-C(7')-C(7A')	-48.1(6)
C(2')-C(6')-C(7')-C(7A')	-159.4(4)
N(5')-C(6')-C(7')-C(8')	-174.7(4)
C(2')-C(6')-C(7')-C(8')	74.0(4)
N(5')-C(6')-C(7')-C(10')	80.5(5)
C(2')-C(6')-C(7')-C(10')	-30.8(4)
C(7A')-C(7')-C(8')-C(9')	162.6(4)
C(10')-C(7')-C(8')-C(9')	35.8(5)
C(6')-C(7')-C(8')-C(9')	-70.8(5)
C(2')-C(1')-C(9')-C(8')	73.9(4)
C(10')-C(1')-C(9')-C(8')	-34.5(5)
C(7')-C(8')-C(9')-C(1')	-0.9(5)
C(7A')-C(7')-C(10')-C(0A')	55.6(6)
C(8')-C(7')-C(10')-C(0A')	-178.0(4)
C(6')-C(7')-C(10')-C(0A')	-72.7(5)
C(7A')-C(7')-C(10')-C(0B')	-66.8(6)
C(8')-C(7')-C(10')-C(0B')	59.6(5)
C(6')-C(7')-C(10')-C(0B')	164.9(4)
C(7A')-C(7')-C(10')-C(1')	178.3(4)
C(8')-C(7')-C(10')-C(1')	-55.3(4)
C(6')-C(7')-C(10')-C(1')	50.0(4)
C(2')-C(1')-C(10')-C(0A')	69.7(5)
C(9')-C(1')-C(10')-C(0A')	177.8(4)
C(2')-C(1')-C(10')-C(0B')	-170.0(4)
C(9')-C(1')-C(10')-C(0B')	-61.9(5)
C(2')-C(1')-C(10')-C(7')	-52.9(4)
C(9')-C(1')-C(10')-C(7')	55.2(4)
C(4')-N(5')-C(11')-O(11')	-166.7(5)
C(6')-N(5')-C(11')-O(11')	-2.8(8)
C(4')-N(5')-C(11')-C(12')	14.8(7)
C(6')-N(5')-C(11')-C(12')	178.7(4)
O(11')-C(11')-C(12')-C(14')	-117.2(6)
N(5')-C(11')-C(12')-C(14')	61.3(6)
O(11')-C(11')-C(12')-C(13')	3.8(8)
N(5')-C(11')-C(12')-C(13')	-177.7(5)
C(11')-C(12')-C(14')-O(14')	22.1(7)
C(13')-C(12')-C(14')-O(14')	-99.1(6)
C(11')-C(12')-C(14')-C(15')	-160.1(5)
C(13')-C(12')-C(14')-C(15')	78.7(7)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters (A^2 x 10^3) for AUXDIN. The anisotropic displacement factor exponent takes the form: -2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
C(1)	23(2)	35(2)	30(2)	-1(2)	2(2)	2(2)
C(2)	38(2)	23(2)	22(2)	1(2)	5(2)	2(2)
O(3)	31(2)	26(2)	32(2)	-2(1)	8(1)	2(1)
C(4)	27(2)	29(3)	23(2)	-3(2)	-3(2)	4(2)
O(4)	35(2)	25(2)	41(2)	1(2)	1(2)	0(2)
N(5)	22(2)	26(2)	25(2)	0(2)	1(2)	4(2)
C(6)	30(2)	25(2)	23(2)	1(2)	-2(2)	2(2)
C(7)	28(2)	27(2)	28(2)	-4(2)	1(2)	-2(2)
C(7A)	38(3)	35(3)	26(2)	-6(2)	3(2)	4(2)
C(8)	45(3)	28(2)	33(3)	1(2)	3(2)	-6(2)
C(9)	37(3)	38(2)	33(3)	-1(2)	5(2)	-7(2)
C(10)	26(2)	31(2)	26(2)	0(2)	2(2)	1(2)
C(10A)	33(2)	37(3)	30(3)	2(2)	-1(2)	7(2)
C(10B)	33(3)	46(3)	35(3)	-6(2)	1(2)	1(2)
C(11)	28(2)	33(3)	22(2)	-4(2)	-6(2)	3(2)
O(11)	33(2)	34(2)	42(2)	-4(2)	-1(2)	8(2)
C(12)	24(2)	40(3)	25(2)	-11(2)	-3(2)	1(2)
C(13)	24(3)	58(3)	63(4)	-10(3)	7(3)	-1(3)
C(14)	21(2)	46(3)	27(2)	-7(2)	1(2)	-8(2)
O(14)	48(2)	55(2)	25(2)	-4(2)	-4(2)	-18(2)
C(15)	37(3)	49(3)	29(3)	5(2)	-4(2)	-11(3)
C(1')	23(2)	32(2)	39(3)	1(2)	-2(2)	-3(2)
C(2')	27(2)	31(3)	25(2)	-3(2)	6(2)	2(2)
O(3')	26(2)	29(2)	43(2)	-10(2)	2(2)	0(2)
C(4')	34(3)	31(3)	20(2)	-6(2)	1(2)	2(2)
O(4')	43(2)	33(2)	36(2)	-6(2)	2(2)	-8(2)
N(5')	20(2)	34(2)	30(2)	5(2)	2(2)	0(2)
C(6')	27(2)	34(3)	29(2)	9(2)	3(2)	2(2)
C(7')	34(3)	25(2)	38(3)	1(2)	12(2)	3(2)
C(7A')	48(3)	34(3)	82(4)	-11(3)	30(3)	-3(3)
C(8')	40(3)	27(2)	51(3)	7(2)	13(3)	-5(2)
C(9')	34(3)	41(3)	37(3)	-3(2)	8(2)	-5(2)
C(10')	41(3)	33(3)	26(2)	-4(2)	4(2)	-7(2)
C(0A')	53(3)	42(3)	30(3)	2(2)	0(3)	-6(3)
C(0B')	71(4)	62(4)	35(3)	-10(3)	-1(3)	-24(3)
C(11')	32(3)	45(3)	34(3)	11(2)	1(2)	0(2)
O(11')	32(2)	68(3)	95(3)	41(2)	-1(2)	8(2)
C(12')	31(3)	52(3)	42(3)	-6(3)	6(2)	-7(3)
C(13')	22(3)	95(5)	109(6)	7(5)	-8(3)	-7(3)
C(14')	37(3)	44(3)	39(3)	-12(3)	17(2)	-12(3)
O(14')	64(2)	50(2)	36(2)	-15(2)	19(2)	-20(2)
C(15')	94(5)	54(3)	55(4)	-15(3)	30(4)	-40(4)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for AUXDIN.

	x	y	z	U(eq)
H(1)	7343(4)	-482(4)	30(2)	35
H(2)	5445(4)	-208(3)	-613(2)	33
H(6)	3975(4)	791(3)	-190(2)	31
H(7AA)	3711(5)	1922(4)	853(2)	40
H(7AB)	4001(5)	916(4)	1242(2)	40
H(7AC)	4910(5)	1920(4)	1244(2)	40
H(8A)	6202(5)	2398(4)	375(2)	42
H(8B)	5259(5)	2158(4)	-122(2)	42
H(9A)	6732(5)	1176(4)	-565(2)	43
H(9B)	7678(5)	1422(4)	-70(2)	43
H(10A)	6666(5)	-1175(4)	1149(2)	40
H(10B)	5530(5)	-537(4)	1415(2)	40
H(10C)	5344(5)	-1204(4)	851(2)	40
H(10D)	7951(4)	342(4)	1135(2)	46
H(10E)	7614(4)	1423(4)	816(2)	46
H(10F)	6915(4)	1118(4)	1383(2)	46
H(12)	1387(4)	-1726(4)	344(2)	35
H(13A)	-217(4)	-427(5)	428(3)	58
H(13B)	-414(4)	-1356(5)	877(3)	58
H(13C)	168(4)	-243(5)	1067(3)	58
H(15A)	1918(5)	-3068(4)	1666(2)	46
H(15B)	629(5)	-2850(4)	1359(2)	46
H(15C)	1769(5)	-3321(4)	1014(2)	46
H(1')	5741(4)	9461(4)	3159(2)	38
H(2')	4526(4)	9459(4)	2242(2)	34
H(6')	2813(4)	10503(4)	2310(2)	36
H(7AD)	2460(5)	11946(4)	3731(3)	65
H(7AE)	1697(5)	11865(4)	3160(3)	65
H(7AF)	1646(5)	10913(4)	3603(3)	65
H(8'A)	4406(5)	12327(4)	3093(2)	47
H(8'B)	3911(5)	11962(4)	2495(2)	47
H(9'A)	5617(5)	10921(4)	2382(2)	45
H(9'B)	6137(5)	11321(4)	2970(2)	45
H(0AA)	3125(5)	8883(4)	3653(2)	50
H(0AB)	4211(5)	8964(4)	4104(2)	50
H(0AC)	3004(5)	9686(4)	4169(2)	50
H(0BA)	5447(6)	10535(5)	4205(2)	67
H(0BB)	5400(6)	11510(5)	3776(2)	67
H(0BC)	4301(6)	11338(5)	4214(2)	67
H(12B)	-62(5)	8062(5)	2494(2)	50
H(13D)	-1611(5)	9331(6)	2226(4)	90
H(13E)	-2155(5)	8520(6)	2679(4)	90
H(13F)	-1714(5)	9680(6)	2868(4)	90
H(15D)	-650(7)	6980(5)	3881(3)	81
H(15E)	-1622(7)	7181(5)	3389(3)	81
H(15F)	-333(7)	6614(5)	3257(3)	81

Structure 4

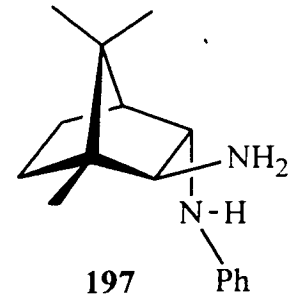

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Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for 1. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
C(1)	1243(1)	8850(5)	2828(3)	51(1)
C(1A)	1308(2)	9568(7)	1578(4)	79(1)
C(2)	1845(1)	7584(5)	3690(3)	45(1)
N(2)	2187(1)	6171(5)	3075(2)	65(1)
C(3)	1534(1)	6525(5)	4605(3)	44(1)
N(3)	1948(1)	6801(4)	5954(2)	51(1)
C(1')	1775(1)	5951(5)	6945(3)	48(1)
C(2')	1387(2)	4222(5)	6793(3)	63(1)
C(3')	1279(2)	3338(7)	7835(4)	80(1)
C(4')	1542(2)	4150(8)	9053(4)	84(1)
C(5')	1913(2)	5837(8)	9204(4)	76(1)
C(6')	2026(2)	6745(6)	8180(3)	61(1)
C(4)	809(1)	7373(6)	4210(3)	58(1)
C(5)	869(2)	9535(6)	4671(4)	75(1)
C(6)	1172(2)	10518(5)	3727(4)	71(1)
C(7)	617(1)	7544(5)	2743(3)	55(1)
C(7A)	566(2)	5582(6)	2046(4)	76(1)
C(7B)	-67(2)	8617(7)	2097(4)	90(1)

Table 3. Selected bond lengths [A], angles and torsions [deg] for 1.

C(1)-C(1A)	1.502(5)
C(1)-C(6)	1.534(5)
C(1)-C(7)	1.553(4)
C(1)-C(2)	1.557(4)
C(2)-N(2)	1.480(4)
C(2)-C(3)	1.538(4)
C(3)-N(3)	1.461(3)
C(3)-C(4)	1.541(4)
N(3)-C(1')	1.379(4)
C(1')-C(6')	1.391(4)
C(1')-C(2')	1.396(5)
C(2')-C(3')	1.373(5)
C(3')-C(4')	1.382(5)
C(4')-C(5')	1.354(6)
C(5')-C(6')	1.366(5)
C(4)-C(7)	1.532(5)
C(4)-C(5)	1.533(5)
C(5)-C(6)	1.532(5)
C(7)-C(7A)	1.514(5)
C(7)-C(7B)	1.548(4)

C(1A)-C(1)-C(6)	114.1(3)
C(1A)-C(1)-C(7)	117.0(3)
C(6)-C(1)-C(7)	101.3(2)
C(1A)-C(1)-C(2)	115.8(2)
C(6)-C(1)-C(2)	103.8(2)
C(7)-C(1)-C(2)	102.8(2)
N(2)-C(2)-C(3)	111.7(2)
N(2)-C(2)-C(1)	119.2(2)
C(3)-C(2)-C(1)	102.9(2)
N(3)-C(3)-C(2)	111.6(2)
N(3)-C(3)-C(4)	116.0(2)
C(2)-C(3)-C(4)	103.3(2)
C(1')-N(3)-C(3)	121.8(2)
N(3)-C(1')-C(6')	119.8(3)
N(3)-C(1')-C(2')	122.9(3)
C(6')-C(1')-C(2')	117.1(3)
C(3')-C(2')-C(1')	120.6(3)
C(2')-C(3')-C(4')	120.9(4)
C(5')-C(4')-C(3')	118.7(4)
C(4')-C(5')-C(6')	121.4(4)
C(5')-C(6')-C(1')	121.2(4)
C(7)-C(4)-C(5)	103.9(3)
C(7)-C(4)-C(3)	102.6(2)
C(5)-C(4)-C(3)	107.0(3)
C(6)-C(5)-C(4)	101.2(3)
C(5)-C(6)-C(1)	105.5(3)
C(7A)-C(7)-C(4)	114.7(3)
C(7A)-C(7)-C(7B)	105.9(3)
C(4)-C(7)-C(7B)	113.7(3)
C(7A)-C(7)-C(1)	116.3(3)
C(4)-C(7)-C(1)	93.1(2)
C(7B)-C(7)-C(1)	113.2(3)

Table 4. Bond lengths [A], angles and torsions [deg] for 1.

C(1)-C(1A)	1.502(5)
C(1)-C(6)	1.534(5)
C(1)-C(7)	1.553(4)
C(1)-C(2)	1.557(4)
C(2)-N(2)	1.480(4)
C(2)-C(3)	1.538(4)
C(3)-N(3)	1.461(3)
C(3)-C(4)	1.541(4)
N(3)-C(1')	1.379(4)
C(1')-C(6')	1.391(4)
C(1')-C(2')	1.396(5)
C(2')-C(3')	1.373(5)
C(3')-C(4')	1.382(5)
C(4')-C(5')	1.354(6)
C(5')-C(6')	1.366(5)
C(4)-C(7)	1.532(5)
C(4)-C(5)	1.533(5)
C(5)-C(6)	1.532(5)
C(7)-C(7A)	1.514(5)
C(7)-C(7B)	1.548(4)

C(1A)-C(1)-C(6)	114.1(3)
C(1A)-C(1)-C(7)	117.0(3)
C(6)-C(1)-C(7)	101.3(2)
C(1A)-C(1)-C(2)	115.8(2)
C(6)-C(1)-C(2)	103.8(2)
C(7)-C(1)-C(2)	102.8(2)
N(2)-C(2)-C(3)	111.7(2)
N(2)-C(2)-C(1)	119.2(2)
C(3)-C(2)-C(1)	102.9(2)
N(3)-C(3)-C(2)	111.6(2)
N(3)-C(3)-C(4)	116.0(2)
C(2)-C(3)-C(4)	103.3(2)
C(1')-N(3)-C(3)	121.8(2)
N(3)-C(1')-C(6')	119.8(3)
N(3)-C(1')-C(2')	122.9(3)
C(6')-C(1')-C(2')	117.1(3)
C(3')-C(2')-C(1')	120.6(3)
C(2')-C(3')-C(4')	120.9(4)
C(5')-C(4')-C(3')	118.7(4)
C(4')-C(5')-C(6')	121.4(4)
C(5')-C(6')-C(1')	121.2(4)
C(7)-C(4)-C(5)	103.9(3)
C(7)-C(4)-C(3)	102.6(2)
C(5)-C(4)-C(3)	107.0(3)
C(6)-C(5)-C(4)	101.2(3)
C(5)-C(6)-C(1)	105.5(3)
C(7A)-C(7)-C(4)	114.7(3)
C(7A)-C(7)-C(7B)	105.9(3)
C(4)-C(7)-C(7B)	113.7(3)
C(7A)-C(7)-C(1)	116.3(3)
C(4)-C(7)-C(1)	93.1(2)
C(7B)-C(7)-C(1)	113.2(3)

C(1A)-C(1)-C(2)-N(2)	-37.3(4)

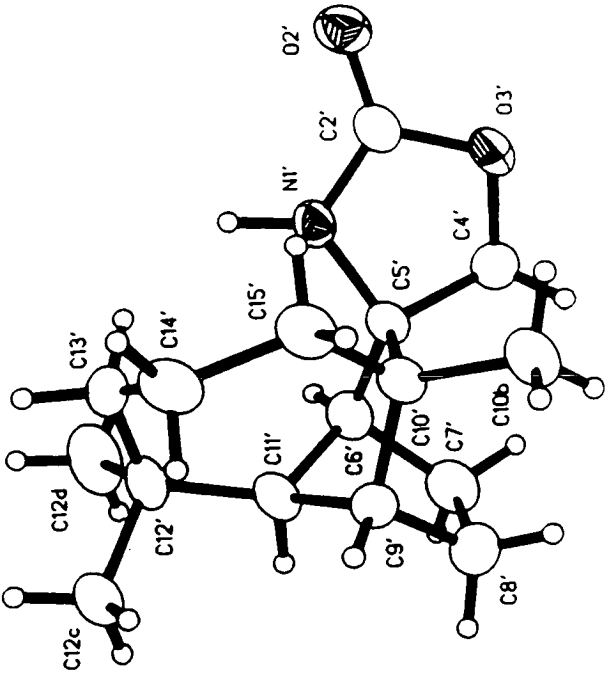
C(6)-C(1)-C(2)-N(2)	-163.2(2)
C(7)-C(1)-C(2)-N(2)	91.6(3)
C(1A)-C(1)-C(2)-C(3)	-161.6(3)
C(6)-C(1)-C(2)-C(3)	72.5(3)
C(7)-C(1)-C(2)-C(3)	-32.7(3)
N(2)-C(2)-C(3)-N(3)	103.1(3)
C(1)-C(2)-C(3)-N(3)	-127.8(3)
N(2)-C(2)-C(3)-C(4)	-131.7(3)
C(1)-C(2)-C(3)-C(4)	-2.6(3)
C(2)-C(3)-N(3)-C(1')	-178.7(3)
C(4)-C(3)-N(3)-C(1')	63.4(4)
C(3)-N(3)-C(1')-C(6')	-158.1(3)
C(3)-N(3)-C(1')-C(2')	26.3(4)
N(3)-C(1')-C(2')-C(3')	174.2(3)
C(6')-C(1')-C(2')-C(3')	-1.6(5)
C(1')-C(2')-C(3')-C(4')	0.9(5)
C(2')-C(3')-C(4')-C(5')	-0.3(6)
C(3')-C(4')-C(5')-C(6')	0.4(6)
C(4')-C(5')-C(6')-C(1')	-1.2(5)
N(3)-C(1')-C(6')-C(5')	-174.2(3)
C(2')-C(1')-C(6')-C(5')	1.7(5)
N(3)-C(3)-C(4)-C(7)	160.1(3)
C(2)-C(3)-C(4)-C(7)	37.7(3)
N(3)-C(3)-C(4)-C(5)	51.0(4)
C(2)-C(3)-C(4)-C(5)	-71.3(3)
C(7)-C(4)-C(5)-C(6)	-36.3(3)
C(3)-C(4)-C(5)-C(6)	71.9(3)
C(4)-C(5)-C(6)-C(1)	0.8(3)
C(1A)-C(1)-C(6)-C(5)	160.6(3)
C(7)-C(1)-C(6)-C(5)	33.9(3)
C(2)-C(1)-C(6)-C(5)	-72.5(3)
C(5)-C(4)-C(7)-C(7A)	176.5(3)
C(3)-C(4)-C(7)-C(7A)	65.1(4)
C(5)-C(4)-C(7)-C(7B)	-61.4(4)
C(3)-C(4)-C(7)-C(7B)	-172.8(3)
C(5)-C(4)-C(7)-C(1)	55.7(3)
C(3)-C(4)-C(7)-C(1)	-55.7(3)
C(1A)-C(1)-C(7)-C(7A)	62.4(4)
C(6)-C(1)-C(7)-C(7A)	-172.8(3)
C(2)-C(1)-C(7)-C(7A)	-65.7(3)
C(1A)-C(1)-C(7)-C(4)	-178.0(3)
C(6)-C(1)-C(7)-C(4)	-53.3(3)
C(2)-C(1)-C(7)-C(4)	53.8(3)
C(1A)-C(1)-C(7)-C(7B)	-60.6(4)
C(6)-C(1)-C(7)-C(7B)	64.2(3)
C(2)-C(1)-C(7)-C(7B)	171.3(3)

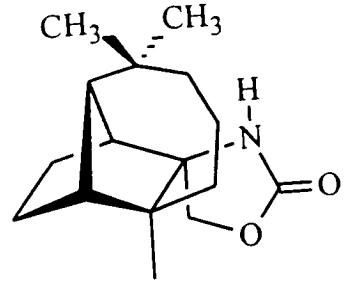
Symmetry transformations used to generate equivalent atoms:

Table 5. Anisotropic displacement parameters (A^2 x 10^3) for 1. The anisotropic displacement factor exponent takes the form: -2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
C(1)	44(2)	43(2)	64(2)	8(2)	17(1)	-1(1)
C(1A)	66(2)	86(3)	79(2)	31(2)	15(2)	-2(2)
C(2)	42(2)	46(2)	47(2)	-2(2)	14(1)	-3(1)
N(2)	56(2)	80(2)	65(2)	-2(2)	28(1)	18(2)
C(3)	39(1)	39(2)	51(2)	-3(2)	12(1)	-1(1)
N(3)	59(1)	49(2)	47(1)	-5(1)	18(1)	-9(1)
C(1')	43(2)	52(2)	52(2)	4(2)	19(1)	4(2)
C(2')	67(2)	60(2)	65(2)	8(2)	26(2)	-5(2)
C(3')	73(2)	74(3)	103(3)	22(3)	42(2)	-1(2)
C(4')	82(3)	113(4)	68(3)	31(3)	37(2)	13(3)
C(5')	72(2)	104(3)	57(2)	4(2)	26(2)	7(3)
C(6')	57(2)	74(2)	54(2)	1(2)	20(2)	7(2)
C(4)	42(2)	65(2)	70(2)	4(2)	22(2)	-6(2)
C(5)	71(2)	65(2)	99(3)	-7(2)	42(2)	21(2)
C(6)	67(2)	40(2)	104(3)	-1(2)	23(2)	7(2)
C(7)	39(2)	50(2)	69(2)	9(2)	7(2)	-1(2)
C(7A)	71(2)	63(2)	76(2)	0(2)	-3(2)	-17(2)
C(7B)	44(2)	99(3)	112(3)	28(3)	8(2)	8(2)

Structure 5





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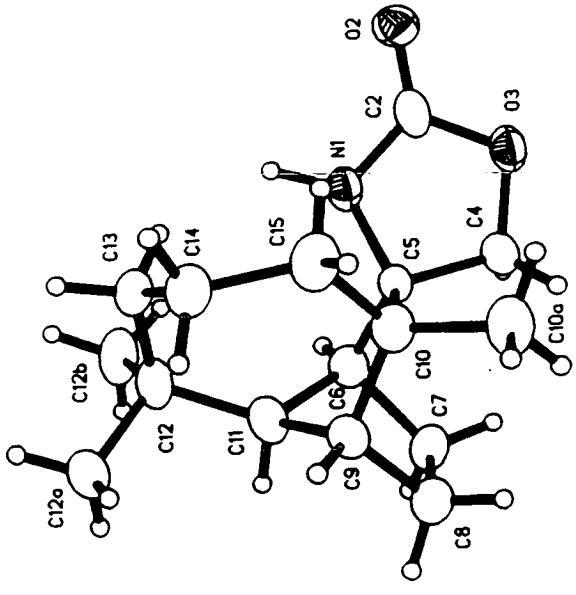

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for NOROAM. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
N(1)	-573(6)	-2783(3)	-205(4)	31(1)
C(2)	-425(7)	-3358(3)	-1046(4)	31(1)
O(2)	-87(5)	-3257(2)	-2057(3)	36(1)
O(3)	-718(5)	-4114(2)	-604(3)	36(1)
C(4)	-1395(7)	-4005(3)	526(4)	33(1)
C(5)	-745(6)	-3147(3)	939(4)	27(1)
C(6)	-2049(6)	-2709(3)	1683(4)	30(1)
C(7)	-2564(7)	-3319(4)	2640(5)	36(1)
C(8)	-931(7)	-3324(4)	3459(5)	38(1)
C(9)	315(7)	-2737(3)	2849(4)	31(1)
C(10)	982(6)	-3130(3)	1759(4)	31(1)
C(10A)	1747(7)	-4002(4)	1946(5)	41(1)
C(11)	-1021(7)	-2075(3)	2421(5)	33(1)
C(12)	-462(7)	-1209(3)	1998(5)	34(1)
C(12A)	29(9)	-698(4)	3063(5)	44(2)
C(12B)	-2042(8)	-795(4)	1392(6)	46(2)
C(13)	1045(7)	-1172(3)	1193(4)	34(1)
C(14)	2630(7)	-1696(4)	1521(5)	36(1)
C(15)	2481(7)	-2617(4)	1262(5)	37(1)
N(1')	1753(5)	-1843(3)	-2923(4)	32(1)
C(2')	911(6)	-1225(3)	-2393(4)	32(1)
O(2')	-211(5)	-1267(3)	-1674(3)	38(1)
O(3')	1508(5)	-479(2)	-2755(3)	36(1)
C(4')	2674(7)	-658(4)	-3658(5)	36(1)
C(5')	3356(6)	-1546(3)	-3438(4)	28(1)
C(6')	3880(7)	-1973(3)	-4520(4)	33(1)
C(7')	5121(8)	-1383(4)	-5155(5)	46(2)
C(8')	6795(8)	-1416(4)	-4392(5)	45(2)
C(9')	6333(6)	-2028(3)	-3427(4)	31(1)
C(10')	5063(6)	-1620(3)	-2625(4)	30(1)
C(10B)	5670(8)	-780(4)	-2133(6)	45(2)
C(11')	5222(7)	-2652(3)	-4161(4)	34(1)
C(12')	4737(7)	-3514(3)	-3734(5)	36(1)
C(12C)	6386(7)	-4042(4)	-3774(6)	44(1)
C(12D)	3390(10)	-3891(4)	-4588(7)	60(2)
C(13')	4030(7)	-3565(3)	-2537(5)	39(1)
C(14')	5056(8)	-3104(4)	-1598(5)	44(2)
C(15')	4811(7)	-2163(4)	-1534(5)	38(1)

Table 3. Selected bond lengths [A], angles and torsions [deg] for NOROAM

N(1)-C(2)	1.355(7)
N(1)-C(5)	1.463(6)
C(2)-O(2)	1.222(6)
C(2)-O(3)	1.345(6)
O(3)-C(4)	1.440(6)
C(4)-C(5)	1.544(7)
C(5)-C(6)	1.522(7)
C(5)-C(10)	1.613(7)
N(1')-C(2')	1.350(7)
N(1')-C(5')	1.472(6)
C(2')-O(2')	1.225(6)
C(2')-O(3')	1.360(7)
O(3')-C(4')	1.434(6)
C(4')-C(5')	1.545(7)
C(5')-C(6')	1.501(7)
C(5')-C(10')	1.600(7)
C(2)-N(1)-C(5)	113.1(4)
O(2)-C(2)-O(3)	122.1(4)
O(2)-C(2)-N(1)	128.9(5)
O(3)-C(2)-N(1)	109.0(4)
C(2)-O(3)-C(4)	108.0(4)
O(3)-C(4)-C(5)	105.5(4)
N(1)-C(5)-C(6)	114.3(4)
N(1)-C(5)-C(4)	96.7(4)
C(6)-C(5)-C(4)	112.2(4)
N(1)-C(5)-C(10)	115.6(4)
C(6)-C(5)-C(10)	101.9(4)
C(4)-C(5)-C(10)	116.9(4)
C(2')-N(1')-C(5')	111.7(4)
O(2')-C(2')-N(1')	129.2(5)
O(2')-C(2')-O(3')	121.0(5)
N(1')-C(2')-O(3')	109.8(4)
C(2')-O(3')-C(4')	106.0(4)
O(3')-C(4')-C(5')	106.5(4)
N(1')-C(5')-C(6')	116.3(4)
N(1')-C(5')-C(4')	94.7(4)
C(6')-C(5')-C(4')	112.8(4)
N(1')-C(5')-C(10')	115.0(4)
C(6')-C(5')-C(10')	102.7(4)
C(4')-C(5')-C(10')	115.9(4)
C(5)-N(1)-C(2)-O(2)	-171.7(5)
C(5)-N(1)-C(2)-O(3)	8.3(6)
O(2)-C(2)-O(3)-C(4)	-169.2(5)
N(1)-C(2)-O(3)-C(4)	10.8(5)
C(2)-O(3)-C(4)-C(5)	-24.4(5)
C(2)-N(1)-C(5)-C(6)	-139.6(5)
C(2)-N(1)-C(5)-C(4)	-21.5(5)
C(2)-N(1)-C(5)-C(10)	102.5(5)
O(3)-C(4)-C(5)-N(1)	26.4(5)
O(3)-C(4)-C(5)-C(6)	146.0(4)
O(3)-C(4)-C(5)-C(10)	-96.8(5)
N(1)-C(5)-C(6)-C(11)	-94.0(5)
C(4)-C(5)-C(6)-C(11)	157.2(4)
C(10)-C(5)-C(6)-C(11)	31.4(5)
N(1)-C(5)-C(6)-C(7)	160.1(4)
C(4)-C(5)-C(6)-C(7)	51.3(5)
C(10)-C(5)-C(6)-C(7)	-74.5(5)

C(11)-C(6)-C(7)-C(8)	-37.2(5)
C(6)-C(7)-C(8)-C(9)	-1.4(5)
C(7)-C(8)-C(9)-C(10)	-70.9(5)
C(7)-C(8)-C(9)-C(11)	39.0(5)
C(8)-C(9)-C(10)-C(10A)	-51.7(6)
C(11)-C(9)-C(10)-C(10A)	-157.5(4)
C(8)-C(9)-C(10)-C(15)	-169.7(4)
C(11)-C(9)-C(10)-C(15)	84.6(5)
C(8)-C(9)-C(10)-C(5)	68.9(5)
C(11)-C(9)-C(10)-C(5)	-36.9(5)
N(1)-C(5)-C(10)-C(9)	128.1(4)
C(6)-C(5)-C(10)-C(9)	3.5(5)
C(4)-C(5)-C(10)-C(9)	-119.2(4)
N(1)-C(5)-C(10)-C(10A)	-110.1(5)
C(6)-C(5)-C(10)-C(10A)	125.4(4)
C(4)-C(5)-C(10)-C(10A)	2.7(6)
N(1)-C(5)-C(10)-C(15)	8.3(6)
C(6)-C(5)-C(10)-C(15)	-116.3(5)
C(4)-C(5)-C(10)-C(15)	121.0(5)
C(5)-C(6)-C(11)-C(12)	81.1(6)
C(7)-C(6)-C(11)-C(12)	-167.1(5)
C(5)-C(6)-C(11)-C(9)	-51.6(4)
C(7)-C(6)-C(11)-C(9)	60.1(4)
C(10)-C(9)-C(11)-C(6)	53.7(5)
C(8)-C(9)-C(11)-C(6)	-61.0(4)
C(10)-C(9)-C(11)-C(12)	-80.7(6)
C(8)-C(9)-C(11)-C(12)	164.5(5)
C(6)-C(11)-C(12)-C(13)	-75.2(7)
C(9)-C(11)-C(12)-C(13)	44.7(7)
C(6)-C(11)-C(12)-C(12A)	163.6(5)
C(9)-C(11)-C(12)-C(12A)	-76.5(6)
C(6)-C(11)-C(12)-C(12B)	47.5(6)
C(9)-C(11)-C(12)-C(12B)	167.4(5)
C(12A)-C(12)-C(13)-C(14)	75.4(6)
C(12B)-C(12)-C(13)-C(14)	-168.2(5)
C(11)-C(12)-C(13)-C(14)	-45.6(7)
C(12)-C(13)-C(14)-C(15)	77.9(6)
C(13)-C(14)-C(15)-C(10)	-56.2(7)
C(9)-C(10)-C(15)-C(14)	-25.1(7)
C(10A)-C(10)-C(15)-C(14)	-148.4(5)
C(5)-C(10)-C(15)-C(14)	89.1(6)
C(5')-N(1')-C(2')-O(2')	-162.0(5)
C(5')-N(1')-C(2')-O(3')	17.0(6)
O(2')-C(2')-O(3')-C(4')	-174.8(5)
N(1')-C(2')-O(3')-C(4')	6.1(5)
C(2')-O(3')-C(4')-C(5')	-25.3(5)
C(2')-N(1')-C(5')-C(6')	-147.8(5)
C(2')-N(1')-C(5')-C(4')	-29.5(5)
C(2')-N(1')-C(5')-C(10')	92.0(5)
O(3')-C(4')-C(5')-N(1')	31.9(5)
O(3')-C(4')-C(5')-C(6')	153.0(4)
O(3')-C(4')-C(5')-C(10')	-88.9(5)
N(1')-C(5')-C(6')-C(7')	159.0(5)
C(4')-C(5')-C(6')-C(7')	51.1(6)
C(10')-C(5')-C(6')-C(7')	-74.4(5)
N(1')-C(5')-C(6')-C(11')	-96.2(5)
C(4')-C(5')-C(6')-C(11')	155.9(4)
C(10')-C(5')-C(6')-C(11')	30.3(5)
C(5')-C(6')-C(7')-C(8')	71.8(6)
C(11')-C(6')-C(7')-C(8')	-39.2(5)
C(6')-C(7')-C(8')-C(9')	1.0(6)
C(7')-C(8')-C(9')-C(10')	-72.0(5)
C(7')-C(8')-C(9')-C(11')	37.6(5)

C(8')-C(9')-C(10')-C(10B)	-159.0(5)
C(11')-C(9')-C(10')-C(15')	-170.6(4)
C(8')-C(9')-C(10')-C(15')	84.1(5)
C(11')-C(9')-C(10')-C(5')	68.4(5)
C(8')-C(9')-C(10')-C(5')	-37.0(5)
N(1')-C(5')-C(10')-C(9')	131.5(4)
C(6')-C(5')-C(10')-C(9')	4.1(5)
C(4')-C(5')-C(10')-C(9')	-119.4(4)
N(1')-C(5')-C(10')-C(10B)	-105.4(5)
C(6')-C(5')-C(10')-C(10B)	127.2(5)
C(4')-C(5')-C(10')-C(10B)	3.7(6)
N(1')-C(5')-C(10')-C(15')	12.3(6)
C(6')-C(5')-C(10')-C(15')	-115.1(5)
C(4')-C(5')-C(10')-C(15')	121.5(5)
C(5')-C(6')-C(11')-C(12')	83.2(6)
C(7')-C(6')-C(11')-C(12')	-165.4(5)
C(5')-C(6')-C(11')-C(9')	-50.4(5)
C(7')-C(6')-C(11')-C(9')	61.0(4)
C(10')-C(9')-C(11')-C(12')	-81.6(6)
C(8')-C(9')-C(11')-C(12')	165.2(5)
C(10')-C(9')-C(11')-C(6')	52.6(4)
C(8')-C(9')-C(11')-C(6')	-60.7(4)
C(6')-C(11')-C(12')-C(13')	-72.4(6)
C(9')-C(11')-C(12')-C(13')	47.6(7)
C(6')-C(11')-C(12')-C(12C)	165.9(5)
C(9')-C(11')-C(12')-C(12C)	-74.0(6)
C(6')-C(11')-C(12')-C(12D)	50.2(7)
C(9')-C(11')-C(12')-C(12D)	170.3(5)
C(11')-C(12')-C(13')-C(14')	-48.2(7)
C(12C)-C(12')-C(13')-C(14')	72.2(6)
C(12D)-C(12')-C(13')-C(14')	-171.0(5)
C(12')-C(13')-C(14')-C(15')	78.4(7)
C(13')-C(14')-C(15')-C(10')	-53.3(7)
C(9')-C(10')-C(15')-C(14')	-27.7(7)
C(10B)-C(10')-C(15')-C(14')	-151.0(5)
C(5')-C(10')-C(15')-C(14')	86.2(6)

Table 4. Bond lengths [A], angles and torsions [deg] for NOROAM

N(1)-C(2)	1.355(7)
N(1)-C(5)	1.463(6)
C(2)-O(2)	1.222(6)
C(2)-O(3)	1.345(6)
O(3)-C(4)	1.440(6)
C(4)-C(5)	1.544(7)
C(5)-C(6)	1.522(7)
C(5)-C(10)	1.613(7)
C(6)-C(11)	1.539(7)
C(6)-C(7)	1.546(7)
C(7)-C(8)	1.554(8)
C(8)-C(9)	1.539(7)
C(9)-C(10)	1.521(7)
C(9)-C(11)	1.556(8)
C(10)-C(10A)	1.538(8)
C(10)-C(15)	1.550(7)
C(11)-C(12)	1.546(8)
C(12)-C(13)	1.518(7)
C(12)-C(12A)	1.523(8)
C(12)-C(12B)	1.541(8)
C(13)-C(14)	1.526(8)
C(14)-C(15)	1.520(8)
N(1')-C(2')	1.350(7)
N(1')-C(5')	1.472(6)
C(2')-O(2')	1.225(6)
C(2')-O(3')	1.360(7)
O(3')-C(4')	1.434(6)
C(4')-C(5')	1.545(7)
C(5')-C(6')	1.501(7)
C(5')-C(10')	1.600(7)
C(6')-C(7')	1.555(8)
C(6')-C(11')	1.555(7)
C(7')-C(8')	1.543(9)
C(8')-C(9')	1.544(8)
C(9')-C(10')	1.524(6)
C(9')-C(11')	1.558(7)
C(10')-C(10B)	1.539(7)
C(10')-C(15')	1.558(8)
C(11')-C(12')	1.527(8)
C(12')-C(13')	1.512(8)
C(12')-C(12C)	1.534(8)
C(12')-C(12D)	1.539(8)
C(13')-C(14')	1.520(9)
C(14')-C(15')	1.532(9)
C(2)-N(1)-C(5)	113.1(4)
O(2)-C(2)-O(3)	122.1(4)
O(2)-C(2)-N(1)	128.9(5)
O(3)-C(2)-N(1)	109.0(4)
C(2)-O(3)-C(4)	108.0(4)
O(3)-C(4)-C(5)	105.5(4)
N(1)-C(5)-C(6)	114.3(4)
N(1)-C(5)-C(4)	96.7(4)
C(6)-C(5)-C(4)	112.2(4)
N(1)-C(5)-C(10)	115.6(4)
C(6)-C(5)-C(10)	101.9(4)
C(4)-C(5)-C(10)	116.9(4)
C(5)-C(6)-C(11)	106.7(4)
C(5)-C(6)-C(7)	107.7(4)

C(6)-C(7)-C(8)	102.8(4)
C(9)-C(8)-C(7)	102.8(4)
C(10)-C(9)-C(8)	111.1(4)
C(10)-C(9)-C(11)	105.0(4)
C(8)-C(9)-C(11)	98.7(4)
C(9)-C(10)-C(10A)	113.8(4)
C(9)-C(10)-C(15)	111.4(5)
C(10A)-C(10)-C(15)	104.7(4)
C(9)-C(10)-C(5)	101.7(4)
C(10A)-C(10)-C(5)	112.0(4)
C(15)-C(10)-C(5)	113.7(4)
C(6)-C(11)-C(12)	124.6(5)
C(6)-C(11)-C(9)	92.6(4)
C(12)-C(11)-C(9)	122.2(4)
C(13)-C(12)-C(12A)	107.7(5)
C(13)-C(12)-C(12B)	108.2(5)
C(12A)-C(12)-C(12B)	107.9(5)
C(13)-C(12)-C(11)	117.4(4)
C(12A)-C(12)-C(11)	107.2(4)
C(12B)-C(12)-C(11)	108.1(4)
C(12)-C(13)-C(14)	116.6(4)
C(15)-C(14)-C(13)	116.0(5)
C(14)-C(15)-C(10)	120.1(5)
C(2')-N(1')-C(5')	111.7(4)
O(2')-C(2')-N(1')	129.2(5)
O(2')-C(2')-O(3')	121.0(5)
N(1')-C(2')-O(3')	109.8(4)
C(2')-O(3')-C(4')	106.0(4)
O(3')-C(4')-C(5')	106.5(4)
N(1')-C(5')-C(6')	116.3(4)
N(1')-C(5')-C(4')	94.7(4)
C(6')-C(5')-C(4')	112.8(4)
N(1')-C(5')-C(10')	115.0(4)
C(6')-C(5')-C(10')	102.7(4)
C(4')-C(5')-C(10')	115.9(4)
C(5')-C(6')-C(7')	107.7(4)
C(5')-C(6')-C(11')	107.1(4)
C(7')-C(6')-C(11')	98.2(4)
C(8')-C(7')-C(6')	103.0(5)
C(7')-C(8')-C(9')	103.3(5)
C(10')-C(9')-C(8')	109.7(4)
C(10')-C(9')-C(11')	105.1(4)
C(8')-C(9')-C(11')	98.8(4)
C(9')-C(10')-C(10B)	114.4(4)
C(9')-C(10')-C(15')	110.8(4)
C(10B)-C(10')-C(15')	103.8(4)
C(9')-C(10')-C(5')	101.9(4)
C(10B)-C(10')-C(5')	112.8(4)
C(15')-C(10')-C(5')	113.5(4)
C(12')-C(11')-C(6')	124.1(5)
C(12')-C(11')-C(9')	123.2(4)
C(6')-C(11')-C(9')	92.3(4)
C(13')-C(12')-C(11')	116.6(4)
C(13')-C(12')-C(12C)	108.8(5)
C(11')-C(12')-C(12C)	106.5(4)
C(13')-C(12')-C(12D)	108.3(5)
C(11')-C(12')-C(12D)	108.6(5)
C(12C)-C(12')-C(12D)	107.7(5)
C(12')-C(13')-C(14')	115.9(5)
C(13')-C(14')-C(15')	117.2(5)
C(14')-C(15')-C(10')	119.9(5)

C(5)-N(1)-C(2)-O(2)	-171.7(5)

C(5)-N(1)-C(2)-O(3)	
O(2)-C(2)-O(3)-C(4)	-169.2(5)
N(1)-C(2)-O(3)-C(4)	10.8(5)
C(2)-O(3)-C(4)-C(5)	-24.4(5)
C(2)-N(1)-C(5)-C(6)	-139.6(5)
C(2)-N(1)-C(5)-C(4)	-21.5(5)
C(2)-N(1)-C(5)-C(10)	102.5(5)
O(3)-C(4)-C(5)-N(1)	26.4(5)
O(3)-C(4)-C(5)-C(6)	146.0(4)
O(3)-C(4)-C(5)-C(10)	-96.8(5)
N(1)-C(5)-C(6)-C(11)	-94.0(5)
C(4)-C(5)-C(6)-C(11)	157.2(4)
C(10)-C(5)-C(6)-C(11)	31.4(5)
N(1)-C(5)-C(6)-C(7)	160.1(4)
C(4)-C(5)-C(6)-C(7)	51.3(5)
C(10)-C(5)-C(6)-C(7)	-74.5(5)
C(5)-C(6)-C(7)-C(8)	73.7(5)
C(11)-C(6)-C(7)-C(8)	-37.2(5)
C(6)-C(7)-C(8)-C(9)	-1.4(5)
C(7)-C(8)-C(9)-C(10)	-70.9(5)
C(7)-C(8)-C(9)-C(11)	39.0(5)
C(8)-C(9)-C(10)-C(10A)	-51.7(6)
C(11)-C(9)-C(10)-C(10A)	-157.5(4)
C(8)-C(9)-C(10)-C(15)	-169.7(4)
C(11)-C(9)-C(10)-C(15)	84.6(5)
C(8)-C(9)-C(10)-C(5)	68.9(5)
C(11)-C(9)-C(10)-C(5)	-36.9(5)
N(1)-C(5)-C(10)-C(9)	128.1(4)
C(6)-C(5)-C(10)-C(9)	3.5(5)
C(4)-C(5)-C(10)-C(9)	-119.2(4)
N(1)-C(5)-C(10)-C(10A)	-110.1(5)
C(6)-C(5)-C(10)-C(10A)	125.4(4)
C(4)-C(5)-C(10)-C(10A)	2.7(6)
N(1)-C(5)-C(10)-C(15)	8.3(6)
C(6)-C(5)-C(10)-C(15)	-116.3(5)
C(4)-C(5)-C(10)-C(15)	121.0(5)
C(5)-C(6)-C(11)-C(12)	81.1(6)
C(7)-C(6)-C(11)-C(12)	-167.1(5)
C(5)-C(6)-C(11)-C(9)	-51.6(4)
C(7)-C(6)-C(11)-C(9)	60.1(4)
C(10)-C(9)-C(11)-C(6)	53.7(5)
C(8)-C(9)-C(11)-C(6)	-61.0(4)
C(10)-C(9)-C(11)-C(12)	-80.7(6)
C(8)-C(9)-C(11)-C(12)	164.5(5)
C(6)-C(11)-C(12)-C(13)	-75.2(7)
C(9)-C(11)-C(12)-C(13)	44.7(7)
C(6)-C(11)-C(12)-C(12A)	163.6(5)
C(9)-C(11)-C(12)-C(12A)	-76.5(6)
C(6)-C(11)-C(12)-C(12B)	47.5(6)
C(9)-C(11)-C(12)-C(12B)	167.4(5)
C(12A)-C(12)-C(13)-C(14)	75.4(6)
C(12B)-C(12)-C(13)-C(14)	-168.2(5)
C(11)-C(12)-C(13)-C(14)	-45.6(7)
C(12)-C(13)-C(14)-C(15)	77.9(6)
C(13)-C(14)-C(15)-C(10)	-56.2(7)
C(9)-C(10)-C(15)-C(14)	-25.1(7)
C(10A)-C(10)-C(15)-C(14)	-148.4(5)
C(5)-C(10)-C(15)-C(14)	89.1(6)
C(5')-N(1')-C(2')-O(2')	-162.0(5)
C(5')-N(1')-C(2')-O(3')	17.0(6)
O(2')-C(2')-O(3')-C(4')	-174.8(5)
N(1')-C(2')-O(3')-C(4')	6.1(5)
C(2')-O(3')-C(4')-C(5')	-25.3(5)
C(2')-N(1')-C(5')-C(6')	-147.8(5)

C(2')-N(1')-C(5')-C(10')	92.0(5)
O(3')-C(4')-C(5')-N(1')	31.9(5)
O(3')-C(4')-C(5')-C(6')	153.0(4)
O(3')-C(4')-C(5')-C(10')	-88.9(5)
N(1')-C(5')-C(6')-C(7')	159.0(5)
C(4')-C(5')-C(6')-C(7')	51.1(6)
C(10')-C(5')-C(6')-C(7')	-74.4(5)
N(1')-C(5')-C(6')-C(11')	-96.2(5)
C(4')-C(5')-C(6')-C(11')	155.9(4)
C(10')-C(5')-C(6')-C(11')	30.3(5)
C(5')-C(6')-C(7')-C(8')	71.8(6)
C(11')-C(6')-C(7')-C(8')	-39.2(5)
C(6')-C(7')-C(8')-C(9')	1.0(6)
C(7')-C(8')-C(9')-C(10')	-72.0(5)
C(7')-C(8')-C(9')-C(11')	37.6(5)
C(8')-C(9')-C(10')-C(10B)	-53.7(6)
C(11')-C(9')-C(10')-C(10B)	-159.0(5)
C(8')-C(9')-C(10')-C(15')	-170.6(4)
C(11')-C(9')-C(10')-C(15')	84.1(5)
C(8')-C(9')-C(10')-C(5')	68.4(5)
C(11')-C(9')-C(10')-C(5')	-37.0(5)
N(1')-C(5')-C(10')-C(9')	131.5(4)
C(6')-C(5')-C(10')-C(9')	4.1(5)
C(4')-C(5')-C(10')-C(9')	-119.4(4)
N(1')-C(5')-C(10')-C(10B)	-105.4(5)
C(6')-C(5')-C(10')-C(10B)	127.2(5)
C(4')-C(5')-C(10')-C(10B)	3.7(6)
N(1')-C(5')-C(10')-C(15')	12.3(6)
C(6')-C(5')-C(10')-C(15')	-115.1(5)
C(4')-C(5')-C(10')-C(15')	121.5(5)
C(5')-C(6')-C(11')-C(12')	83.2(6)
C(7')-C(6')-C(11')-C(12')	-165.4(5)
C(5')-C(6')-C(11')-C(9')	-50.4(5)
C(7')-C(6')-C(11')-C(9')	61.0(4)
C(10')-C(9')-C(11')-C(12')	-81.6(6)
C(8')-C(9')-C(11')-C(12')	165.2(5)
C(10')-C(9')-C(11')-C(6')	52.6(4)
C(8')-C(9')-C(11')-C(6')	-60.7(4)
C(6')-C(11')-C(12')-C(13')	-72.4(6)
C(9')-C(11')-C(12')-C(13')	47.6(7)
C(6')-C(11')-C(12')-C(12C)	165.9(5)
C(9')-C(11')-C(12')-C(12C)	-74.0(6)
C(6')-C(11')-C(12')-C(12D)	50.2(7)
C(9')-C(11')-C(12')-C(12D)	170.3(5)
C(11')-C(12')-C(13')-C(14')	-48.2(7)
C(12C)-C(12')-C(13')-C(14')	72.2(6)
C(12D)-C(12')-C(13')-C(14')	-171.0(5)
C(12')-C(13')-C(14')-C(15')	78.4(7)
C(13')-C(14')-C(15')-C(10')	-53.3(7)
C(9')-C(10')-C(15')-C(14')	-27.7(7)
C(10B)-C(10')-C(15')-C(14')	-151.0(5)
C(5')-C(10')-C(15')-C(14')	86.2(6)

Table 5. Anisotropic displacement parameters (A^2 x 10^3) for NOROAM
The anisotropic displacement factor exponent takes the form:
-2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
N(1)	38(2)	22(2)	33(2)	-1(2)	-8(2)	-1(2)
C(2)	33(3)	23(3)	37(3)	-6(2)	-10(2)	0(2)
O(2)	39(2)	38(2)	29(2)	-3(2)	-1(1)	-4(2)
O(3)	42(2)	23(2)	42(2)	-4(2)	3(2)	-3(2)
C(4)	35(3)	27(3)	36(3)	-4(2)	1(2)	-1(2)
C(5)	34(3)	19(2)	28(2)	0(2)	4(2)	0(2)
C(6)	28(3)	29(3)	34(2)	0(2)	-5(2)	0(2)
C(7)	38(3)	29(3)	41(3)	5(2)	3(2)	-6(2)
C(8)	46(3)	31(3)	38(3)	3(2)	-1(2)	-3(3)
C(9)	34(3)	28(3)	30(2)	-3(2)	-3(2)	-3(2)
C(10)	25(3)	29(3)	38(3)	3(2)	-4(2)	2(2)
C(10A)	34(3)	35(3)	54(3)	1(3)	-8(3)	6(2)
C(11)	33(3)	28(3)	39(3)	-4(2)	-6(2)	1(2)
C(12)	37(3)	22(2)	44(3)	-2(2)	-5(2)	0(2)
C(12A)	58(4)	32(3)	42(3)	-5(3)	-2(3)	-10(3)
C(12B)	44(3)	28(3)	65(4)	6(3)	-1(3)	4(2)
C(13)	41(3)	25(3)	35(3)	2(2)	0(2)	-7(2)
C(14)	35(3)	32(3)	42(3)	0(3)	-3(2)	-4(2)
C(15)	24(3)	35(3)	53(3)	5(3)	-5(2)	0(2)
N(1')	24(2)	23(2)	50(2)	-2(2)	-3(2)	1(2)
C(2')	26(3)	28(3)	43(3)	-3(2)	-4(2)	5(2)
O(2')	31(2)	41(2)	43(2)	-3(2)	2(2)	6(2)
O(3')	41(2)	24(2)	42(2)	-2(2)	5(2)	7(2)
C(4')	36(3)	33(3)	38(3)	3(2)	3(2)	2(2)
C(5')	29(3)	24(3)	31(2)	-5(2)	1(2)	2(2)
C(6')	37(3)	30(3)	33(2)	1(2)	-4(2)	2(2)
C(7')	52(4)	39(3)	48(3)	5(3)	3(3)	9(3)
C(8')	46(3)	35(3)	54(3)	5(3)	11(3)	-1(3)
C(9')	26(2)	30(3)	36(2)	-5(2)	0(2)	-2(2)
C(10')	28(3)	28(3)	33(2)	-9(2)	-3(2)	0(2)
C(10B)	36(3)	36(3)	61(4)	-18(3)	-8(3)	0(3)
C(11')	38(3)	26(3)	37(3)	-8(2)	-3(2)	4(2)
C(12')	38(3)	22(3)	47(3)	-3(2)	-6(2)	1(2)
C(12C)	41(3)	29(3)	62(4)	-4(3)	2(3)	5(2)
C(12D)	53(4)	40(4)	87(5)	-9(4)	-31(4)	-3(3)
C(13')	33(3)	25(3)	59(3)	11(3)	7(3)	1(2)
C(14')	49(3)	47(3)	35(3)	10(3)	5(2)	17(3)
C(15')	34(3)	40(3)	40(3)	2(3)	-4(2)	7(2)

Table 6. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for NOROAM

	x	y	z	U(eq)
H(1N)	-381(6)	-2195(3)	-438(4)	37
H(4A)	-2638(7)	-4031(3)	500(4)	39
H(4B)	-955(7)	-4431(3)	1035(4)	39
H(6A)	-3011(6)	-2473(3)	1253(4)	36
H(7A)	-3555(7)	-3115(4)	3028(5)	43
H(7B)	-2819(7)	-3860(4)	2337(5)	43
H(8A)	-1187(7)	-3120(4)	4211(5)	46
H(8B)	-458(7)	-3873(4)	3527(5)	46
H(9A)	1219(7)	-2518(3)	3349(4)	37
H(10A)	2753(7)	-3973(4)	2453(5)	61
H(10B)	2071(7)	-4215(4)	1212(5)	61
H(10C)	904(7)	-4363(4)	2271(5)	61
H(11A)	-1723(7)	-1965(3)	3071(5)	40
H(12A)	1017(9)	-937(4)	3463(5)	66
H(12B)	-939(9)	-693(4)	3561(5)	66
H(12C)	295(9)	-141(4)	2838(5)	66
H(12D)	-1729(8)	-255(4)	1120(6)	69
H(12E)	-2958(8)	-744(4)	1926(6)	69
H(12F)	-2426(8)	-1132(4)	752(6)	69
H(13A)	624(7)	-1347(3)	445(4)	40
H(13B)	1395(7)	-603(3)	1130(4)	40
H(14A)	3605(7)	-1485(4)	1122(5)	44
H(14B)	2875(7)	-1628(4)	2332(5)	44
H(15A)	3547(7)	-2877(4)	1511(5)	45
H(15B)	2389(7)	-2677(4)	440(5)	45
H(1N')	1473(5)	-2435(3)	-2762(4)	39
H(4'A)	2097(7)	-614(4)	-4401(5)	43
H(4'B)	3617(7)	-270(4)	-3623(5)	43
H(6'A)	2923(7)	-2177(3)	-4988(4)	40
H(7'A)	5313(8)	-1575(4)	-5923(5)	55
H(7'B)	4654(8)	-832(4)	-5192(5)	55
H(8'A)	7748(8)	-1613(4)	-4827(5)	54
H(8'B)	7077(8)	-878(4)	-4084(5)	54
H(9'A)	7323(6)	-2271(3)	-3036(4)	37
H(10D)	6698(8)	-869(4)	-1661(6)	67
H(10E)	4778(8)	-551(4)	-1672(6)	67
H(10F)	5921(8)	-401(4)	-2743(6)	67
H(11B)	5869(7)	-2745(3)	-4841(4)	41
H(12G)	6858(7)	-4017(4)	-4527(6)	66
H(12H)	6110(7)	-4607(4)	-3594(6)	66
H(12I)	7222(7)	-3835(4)	-3215(6)	66
H(12J)	3819(10)	-3861(4)	-5354(7)	91
H(12K)	2323(10)	-3588(4)	-4556(7)	91
H(12L)	3192(10)	-4460(4)	-4390(7)	91
H(13C)	2877(7)	-3341(3)	-2555(5)	47
H(13D)	3953(7)	-4138(3)	-2325(5)	47
H(14C)	4803(8)	-3339(4)	-863(5)	52
H(14D)	6257(8)	-3210(4)	-1730(5)	52
H(15C)	5620(7)	-1953(4)	-923(5)	46
H(15D)	3623(7)	-2060(4)	-1272(5)	46