

Asymmetric Synthesis Using a Camphene-Derived Chiral Auxiliary

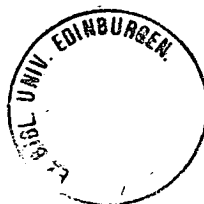
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Thesis presented for the degree of

Doctor of Philosophy

The University of Edinburgh

1997



Declaration

I declare that this thesis is my own composition, that the work of which it is a record has been carried out by 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 the 14th of January 1992, the date of my admission as a research student.

3/9/97

Paul Thorburn

To Malcolm and both Ians

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Courses Attended

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

- 1 Current Topics in Organic Chemistry, various speakers, Department of Chemistry, University of Edinburgh, 3 years attendance.
- 2 Organic Research Seminars, various speakers, Department of Chemistry, University of Edinburgh, 3 years attendance.
- 3 Royal Society of Chemistry, Perkin Division (Scottish Section), annual meetings, various speakers, 3 years attendance.
- 4 Merck, Sharp and Dohme, Medicinal Chemistry Lectures, Prof. R. Baker and Dr. P. Leeson, Department of Chemistry, University of Edinburgh, three years attendance
- 5 NMR of Biological Molecules, Dr. J. Parkinson and Dr. I. Sadler, Department of Chemistry, University of Edinburgh, 1993.
- 6 Chemical Development in the Pharmaceutical Industry, Smith-Kline Beecham, various speakers, Department of Chemistry, University of Edinburgh, 1993.
- 7 Industrial Fine Organic Chemistry, Prof. A. McKillop (University of East Anglia), Department of Chemistry, University of Edinburgh, 1993.
- 8 Industrial Biocatalysts, Smith-Kline Beecham, various speakers, Department of Chemistry, University of Edinburgh, 1994.
- 9 25th Sheffield Stereochemical Meeting, various speakers, Sheffield, 1991.
- 10 Royal Society of Chemistry, Heterocyclic Group, 2 years attendance.

Abstract

The synthesis of a novel spiro-oxazolidin-2-one chiral auxiliary from both enantiomers of the common terpene camphene is described. The compound is formed *via* nitrene insertion and its structure has been determined by both NMR spectroscopy and X-ray diffraction studies. Evaluation of the functionalisation conditions for this hindered oxazolidin-2-one have been carried out and it has been observed that zinc salts give superior yields of *N*-acyl products compared to the use of the orthodox lithium or halomagnesium salts. It has been demonstrated that using suitable conditions the auxiliary is capable of inducing high degrees of stereoselectivity in a variety of enolate reactions including alkylation, acylation and aldol condensation. Unsaturated acyl derivatives undergo Diels-Alder cycloaddition with cyclopentadiene in the presence of diethylaluminium chloride to give adducts with very high diastereomeric excess. Michael additions of aluminium reagents to these acyl derivatives also give high diastereomeric excesses where the possibility of formation of a cationic intermediate exists. When such intermediates cannot be formed, in particular addition of trialkyl aluminium reagents, very low diastereomeric excesses are observed. 1,4-Conjugate addition of magnesium reagents is dependent on the presence of copper catalysts but the reactions proceed with high stereoselectivity and the intermediate enolates may be readily alkylated with equal selectivity. In many cases the so formed adducts have been cleaved to give the newly created chiral fragments in high optical purity and chemical yield with almost complete recovery of the auxiliary (>90%). The application of a combination of stereoselective 1,4 conjugate addition and aldol condensation reactions has been applied to the synthesis of a number of substituted β -carboxy- γ -lactones (paraconic acids). The stereochemistry of these target molecules has been readily created with a high degree of specificity in very good chemical yield. In one attempted synthesis use of a surprisingly stereoselective lithium enolate aldol condensation is described. The origins of this selectivity have been proposed after considering the selectivities of a number of different substrates. However removal of the chiral product fragment from the auxiliary leaving both intact has been found to be highly dependant on both the functionality and stereochemistry of the adduct. Further applications of the auxiliary to short natural product synthesis and the potential of these routes is also briefly described.

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1. Introduction

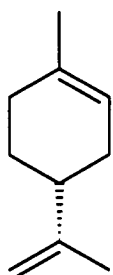
1.1 Chirality

1.1.1 The Importance of Chirality

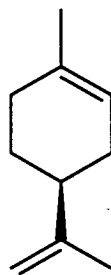
Over the past twenty years asymmetric synthesis has grown from little more than an academic curiosity to a thriving research field with immense potential. Industrial applications of the techniques devised for asymmetric synthesis are now widespread. The importance of this arm of organic chemistry stems from the different biological properties of the optical isomers of a compound¹. These differences are a consequence of the main building blocks of life (amino acids and sugars) being chiral and occurring only in one enantiomeric form. The interactions of each enantiomer of a chemical with a biological system become diastereotopic in nature and hence non-equivalent.

The differences exhibited, range from the innocent fact that (*R*)- and (*S*)-limonine **1**, taste of oranges and lemon respectively, to more sinister examples in the fields of pharmaceuticals and agrochemicals. Thus, it is now recognised that with many chiral drugs the enantiomer of the beneficial compound has deleterious effects. For many drugs the side-effects associated with the unwanted enantiomer make administration of the racemate unacceptable. The classic example of this phenomenon was the prescription of racemic thalidomide **2** for morning sickness during pregnancy. Although the (*S*)-enantiomer was of low toxicity and possessed the desired beneficial effects, the inactive (*R*)-antipode was highly toxic to the developing foetus and caused severe deformities. The anaesthetic ketamine **3** cannot be administered as the racemate since the (*R*)-enantiomer causes central nervous

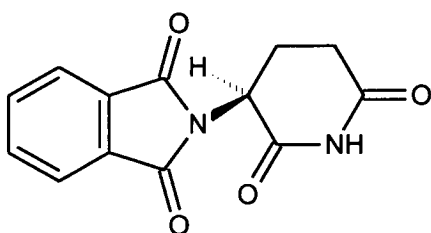
system excitation, which inhibits anaesthesia and can cause patients to emerge from anaesthesia during operations².



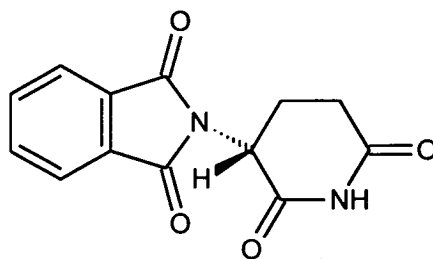
(*R*)-1



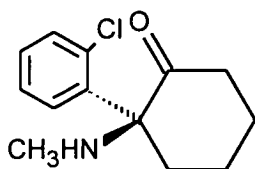
(*S*)-1



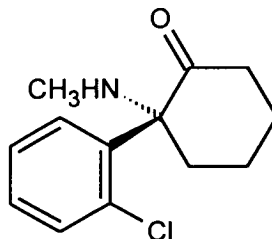
(*S*)-2



(*R*)-2



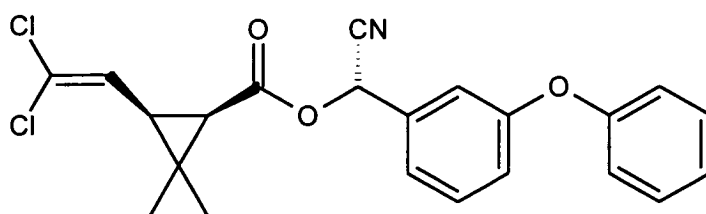
(*S*)-3



(*R*)-3

Of great environmental and industrial importance is the asymmetric synthesis of the pyrethrin-type insecticides such as cypermethrin **4**³. These contain three chiral centres and thus have eight possible isomers, only one of which is active. Thus a non-stereocontrolled synthesis would yield a product with only 12.5% of the activity of the pure enantiomer. This would represent not only an undesirable waste and

expense on an industrial-scale synthesis, but would also be a needless burden on the environment.



4

Much legislation now covers the application of chiral compounds in the pharmaceutical industry; in the agrochemical industry the larger scale and desire to be seen to be responsible to the environment make a shift to enantioselective synthesis a wise option.

1.1.2 Methods of Obtaining Single Enantiomers

Obtaining enantiomerically pure compounds can in effect be done in three ways. Firstly by starting with an enantiomerically pure compound and elaborating it to the target molecule. The starting materials for this method must be readily available and of high enantiomeric purity (importantly the correct enantiomer must be available). These compounds are invariably obtained from natural sources (or controlled biological systems) and the elaboration of chiral non-racemic molecules from this source is known as the 'Chiral Pool' approach. The second method is the separation of enantiomers by resolution, which involves the formation of diastereomeric pairs (either covalent or ionic in nature) These can then be separated by physical means, such as crystallisation and standard chromatography (covalent pairs) (Figure 1). Chromatography on a chiral stationary phase causes diastereomeric interactions such

that retention of enantiomers becomes non-equivalent and thus they can be separated. Two important variations to classical resolution are kinetic resolution (formation of the diastereomeric pairs in unequal quantities) and deracemisation (a continuous process of kinetic resolution and racemisation of the remaining unwanted enantiomer). Unfortunately, with the exception of the final variation a maximum yield of only 50% can be obtained unless the material can be recycled. Further classical resolution can be laborious, low yielding and unpredictable as to its outcome.

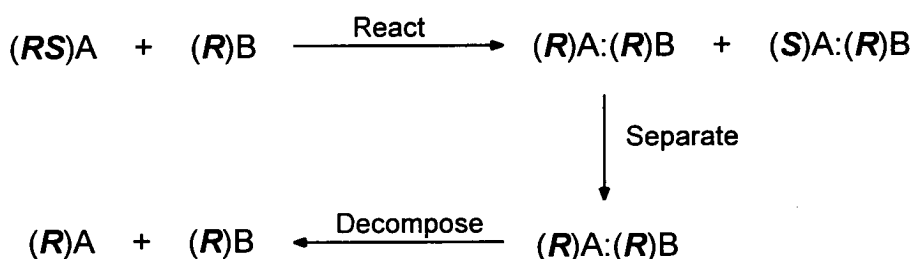


Figure 1

By far the most important method as far as this project is concerned is directed asymmetric synthesis from prochiral starting materials. This approach is discussed in more detail here and is the only area which will be reviewed. Previous workers have reviewed the whole field and the reader is directed towards the relevant thesis^{4,5}. In the context of the brief review of asymmetric γ -lactone synthesis which follows, these approaches are mentioned where applied. There are three ways in which this form of enantioselective synthesis can be achieved. Firstly, the use of chiral auxiliaries (the method exploited by this work and to which greatest emphasis is given in the following review) which involves the attachment of the prochiral

substrate to a chiral molecule in order to induce the sense of chirality in the newly formed chiral centre. Reagent-controlled synthesis relies on a chiral molecule finding one face (or group) of a prochiral substrate more favourable for reaction than the other. This effect may also be achieved by the use of stoichiometric quantities of a chiral ligand to modify a simple reagent *e.g.* an organometallic. Finally, asymmetric catalysis which requires only a small amount of chiral information is undoubtedly the most efficient method of obtaining chiral non-racemic compounds. Here binding and activation of the substrate and/or reagent in an asymmetric environment induces the desired stereochemistry in the reaction. Such catalysts can be biological (enzymes) or man-made (very often dependent on main-group, transition or lanthanide metals for their activity) and can often be recovered for re-use.

These three methods all rely on energy differences in the possible diastereomeric transition states. This is in contrast to the classical methods of resolution which rely on different physical properties of the diastereomers (solubility, chromatographic mobility, *etc.*). Thus a simple transition state is raised in energy from its reactants by the difference in free energy $\Delta G^\ddagger$. For the formation of a pair of enantiomers, the transition states are the same, therefore $\Delta G^\ddagger$ is the same, hence the products are equally favourable and formed in equal quantities. However in an asymmetric environment the transition states are no longer equivalent since they are diastereomeric in nature and a difference in the free energy of the states is produced : $\Delta\Delta G^\ddagger$ (Figure 2). It is the magnitude of this difference which effects the extent of asymmetric induction. For almost complete asymmetric induction at room

temperature, a $\Delta\Delta G^\ddagger$ of approximately 13 KJ.mol⁻¹ is necessary. By lowering the temperature, a smaller difference in free energy is required to produce the same selectivity due to the reduction in the overall distribution of energy between the molecules. Since lowering the temperature also reduces molecular motion, more highly defined transition states are obtained which consequently show greater asymmetric bias, manifesting itself in greater selectivities.

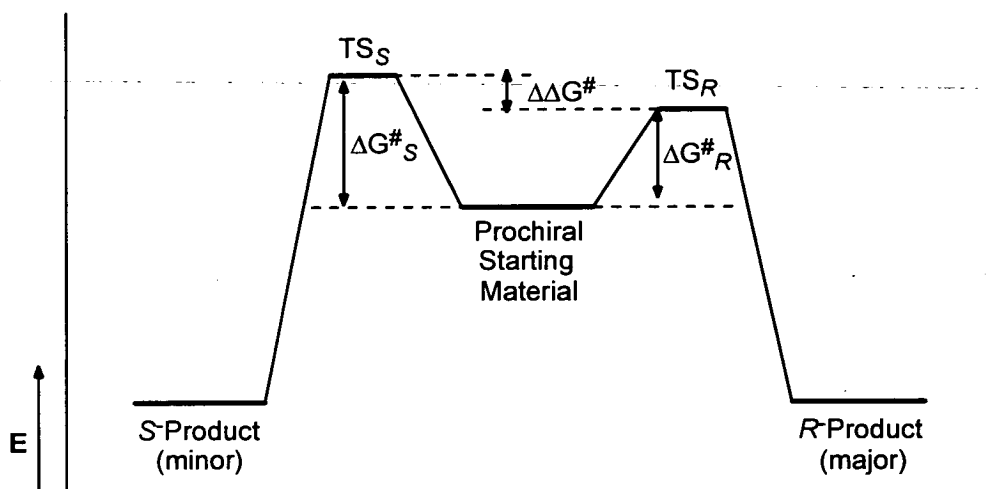


Figure 2

The majority of progress in asymmetric synthesis has come about as a result of the use and understanding of main group and transition metals in these reactions. The vast majority of chiral auxiliaries, reagents and catalysts rely on these metals for co-ordination (especially chelation leading to highly rigid transition states) and activation of the substrates.

1.2 Methods of Asymmetric Synthesis

A brief review of some of the most important methods in directed asymmetric synthesis will be presented. The majority of this survey is given over to relayed

stereochemical induction, *i.e.* chiral auxiliary controlled synthesis. The two potentially more significant fields of reagent and catalyst controlled asymmetric induction are covered more briefly.

1.2.1 Auxiliary Controlled Asymmetric Synthesis

As the field of asymmetric synthesis grew rapidly in the early 80's, the use of chiral auxiliaries became one of the most popular methods for the synthesis of chirally pure organic compounds. This was largely due to the more frequent successes obtained at this time using this methodology. Now that major advances in chiral reagent and catalyst controlled asymmetric synthesis have been made, chiral auxiliaries have lost their dominant position, but due to their wide scope and predictability they are still popular especially for research purposes. The approach amounts to linking a prochiral substrate **S** to an optically pure compound (the auxiliary, **A***) and then carrying out a subsequent reaction(s) on the functionalised auxiliary **A*S** under conditions such that a new chiral centre(s) is produced with a high bias to one configuration(**A*P***). Following purification the new chiral product **P*** is cleaved off and the auxiliary preferably recovered for future use.

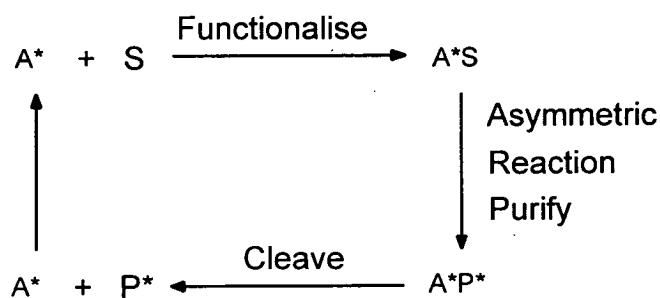
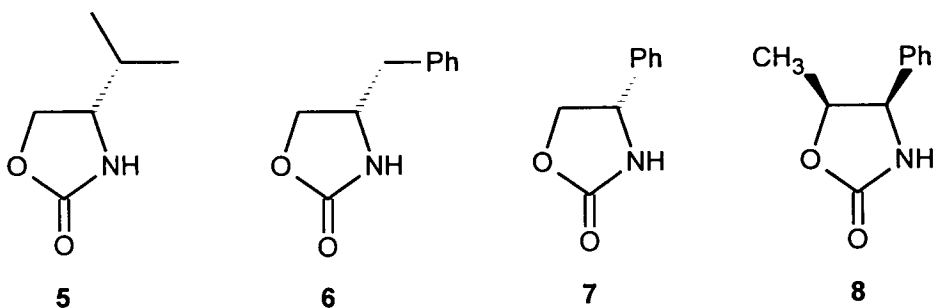


Figure 3

The auxiliary should preferably be available in both enantiomeric forms in an optically pure state. Further to this attachment of the substrate should be facile, high yielding and flexible with regard to the functional groups that can be present. The diastereomeric excess (d.e.) of the reactions should be high (preferably greater than 80%). Obviously it is an advantage for the auxiliary to impart crystallinity to the adduct so as to facilitate purification. Finally, removal of the chiral auxiliary must be possible without racemisation of any of the chiral centres formed. It is also a great advantage if the auxiliary can be recovered in high yield and be easily purified (a further advantage of crystallinity).

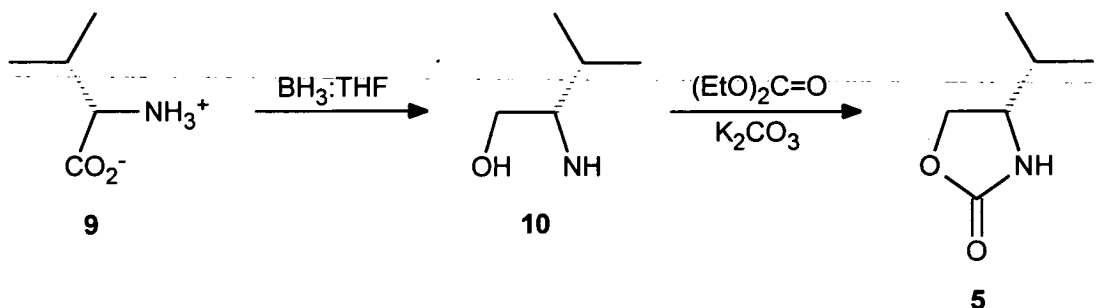
1.2.1.1 Oxazolidin-2-one Chiral Auxiliaries

Since this project is intrinsically based on the application of the oxazolidin-2-one function to asymmetric induction, this area will be covered in greatest detail. A number of natural-product derived oxazolidin-2-one chiral auxiliaries **5-8** have been synthesised and widely used previously⁶. Most have been derived from α -amino acid precursors by short and relatively simple synthetic routes; an exception is the readily accessible auxiliary **8** which is synthesised from norephedrine and induces



stereochemistry of the opposite sense to that given by auxiliaries derived from natural *L*-amino acids.

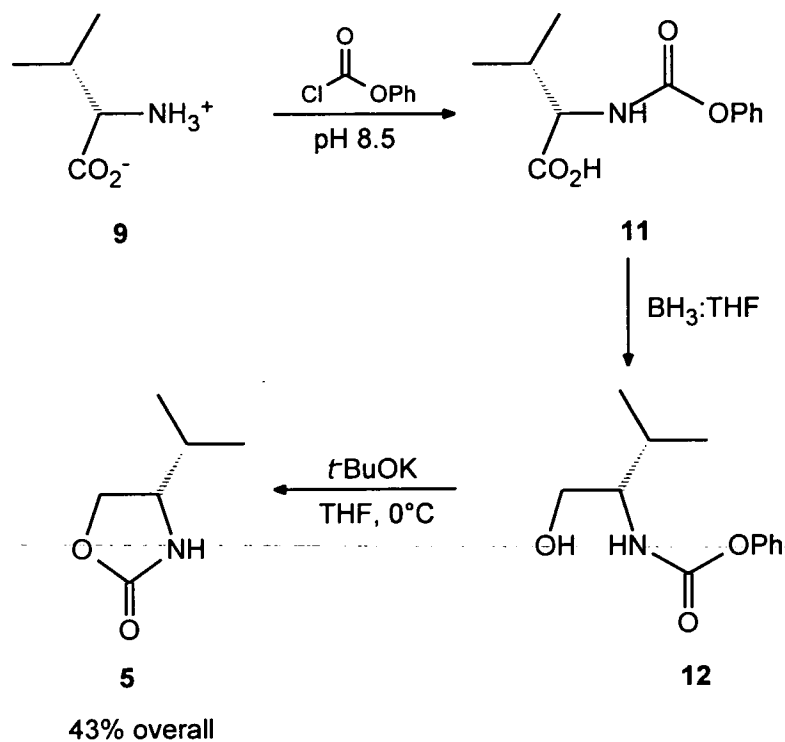
The general basis of the synthesis relies on the reduction of the α -amino acid to the β -amino alcohol followed by cyclocarbamation. Evans' original synthesis relied on reduction of the α amino acid with $\text{BH}_3\text{:THF}$ complex followed by cyclisation using diethyl carbonate under basic conditions.



Scheme 1

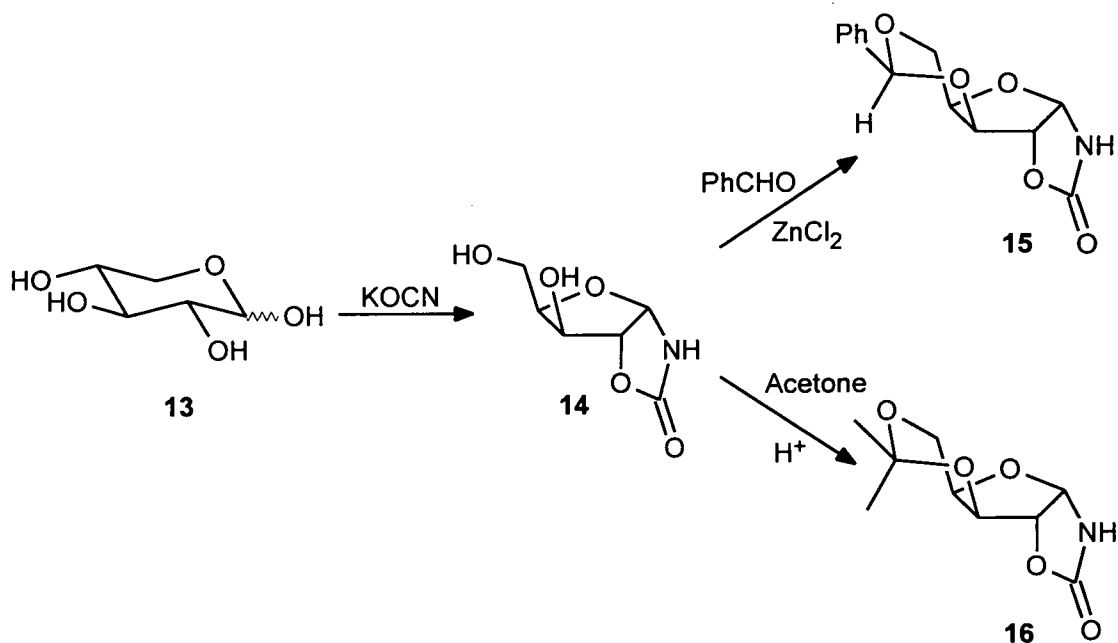
Various alterations have been made to this route with most attempting to avoid isolation of the intermediate β -amino alcohols due to the high water solubility of the lower molecular weight alcohols, in particular valinol. A one-pot reduction and cyclisation method was developed by workers at Smith-Kline & French, a procedure that relied on a BH_3/BF_3 reduction followed by cyclocarbamation using diphosgene and aqueous alkali⁷.

Another relies on the use of the *N*-phenyloxycarbonyl-protected amino acid, *e.g.* **11**, which is reduced with borane to afford an *N*-protected amino-alcohol **12** which is cyclised under basic conditions to give **5**⁸. Although this process is not a single pot procedure, the facile isolation and purification of the intermediates, together with a reasonable overall yield make this method advantageous.



Scheme 2

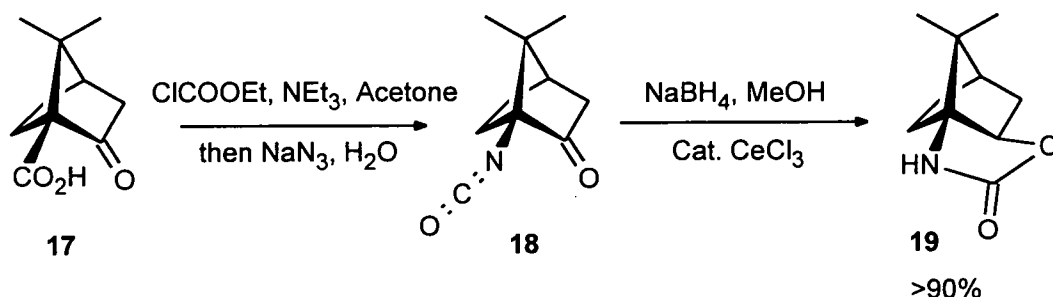
Although not a general method, a very inexpensive and simple route to chiral oxazolidin-2-ones has been developed by Köll⁹ based on the addition



Scheme 3

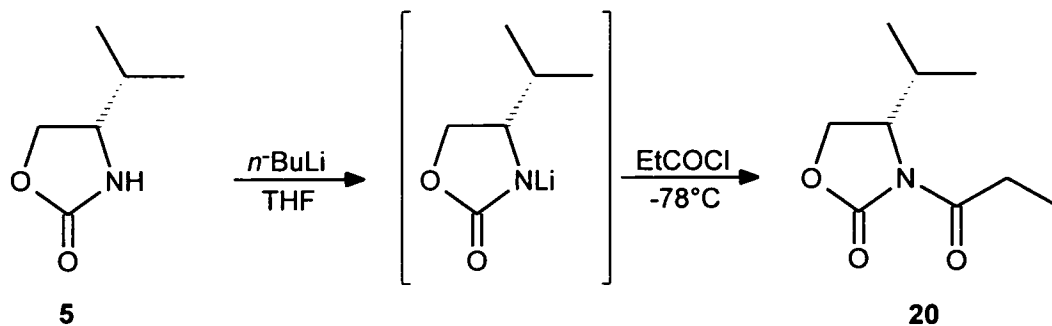
cyanate to *D*-xylose **13**. Following the formation of the heterocycle **14**, the remaining two hydroxyls are protected as either the benzylidene **15** or *iso*-propylidene **16** derivatives. These oxazolidin-2-ones were subsequently used in resolution schemes but have not yet been evaluated as chiral auxiliaries.

A further oxazolidin-2-one auxiliary has recently been developed by Chinese workers¹⁰, this time based on a terpene structure. The starting material, ketopinic acid **17**, itself obtained by the oxidation of camphor, was treated with ethyl chloroformate, triethylamine and sodium azide to form an acyl azide which rearranged *in situ* to give the isocyanate **18**. **18** Was then reduced and cyclised by treatment with sodium borohydride in the presence of ceric chloride to provide the oxazolidin-2-one **19** in >90% yield.



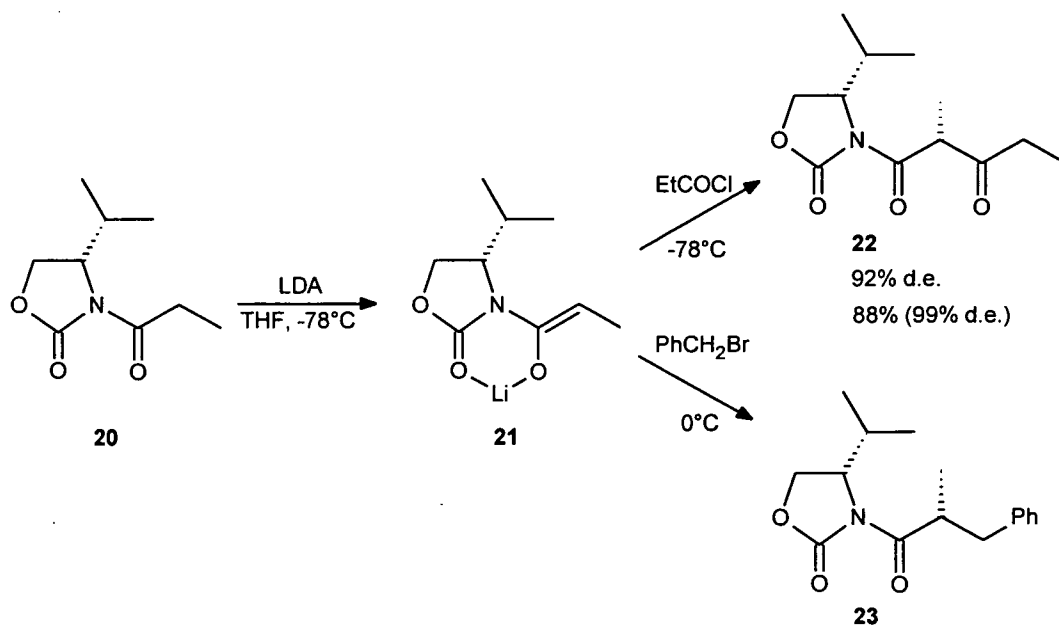
Scheme 4

These chiral oxazolidin-2-ones are readily derivatised by reaction of their metal salts (most commonly Na, Li⁶ or MgX¹¹), prepared by deprotonation with suitable organometallics, with acid chlorides to give acyl and enoyl derivatives.



Scheme 5

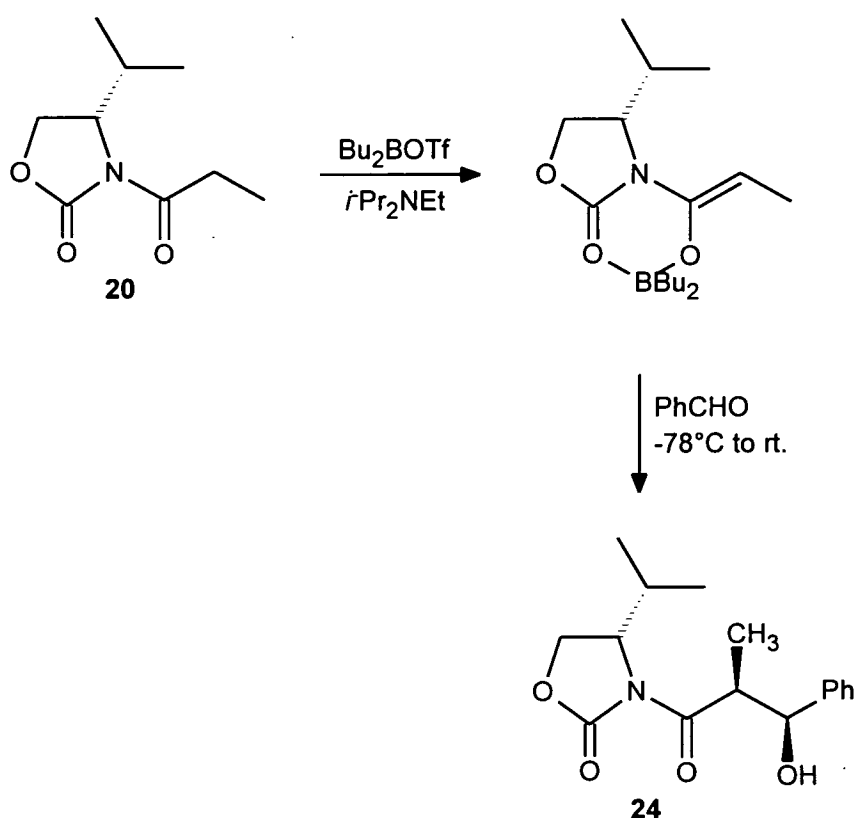
An extensive range of asymmetric reactions have now been performed on these functionalised oxazolidin-2-ones making their use one of the most versatile and reliable strategies in asymmetric synthesis. Evans found that geometrically defined N -acyloxazolidin-2-one enolates could readily be generated by treatment of imides such as **20** with powerful hindered bases and that these $Z(O)$ enolates, *e.g.* **21**, reacted with a very high degree of stereofacial selection with a wide range of acylating¹² and alkylating¹³ agents. This high diastereomeric excess combined with the normally



Scheme 6

crystalline nature of adducts such as **22** and **23** meant that single diastereomers were readily isolated by recrystallisation. The specific formation of the *Z*(*O*) enolate on deprotonation with strong non-nucleophilic bases such as lithium diisopropylamide (LDA) or sodium hexamethyldisilazide (NaHMDS) has been explained by evoking a transition state for proton abstraction as described in 2.3.1. Once generated the alkali metal enolate is chelated by the oxazolidin-2-one carbonyl such that an incoming electrophile reacts preferentially on the face opposite the steric controlling group, *i.e.* the upper face of enolate **21** in Scheme 6.

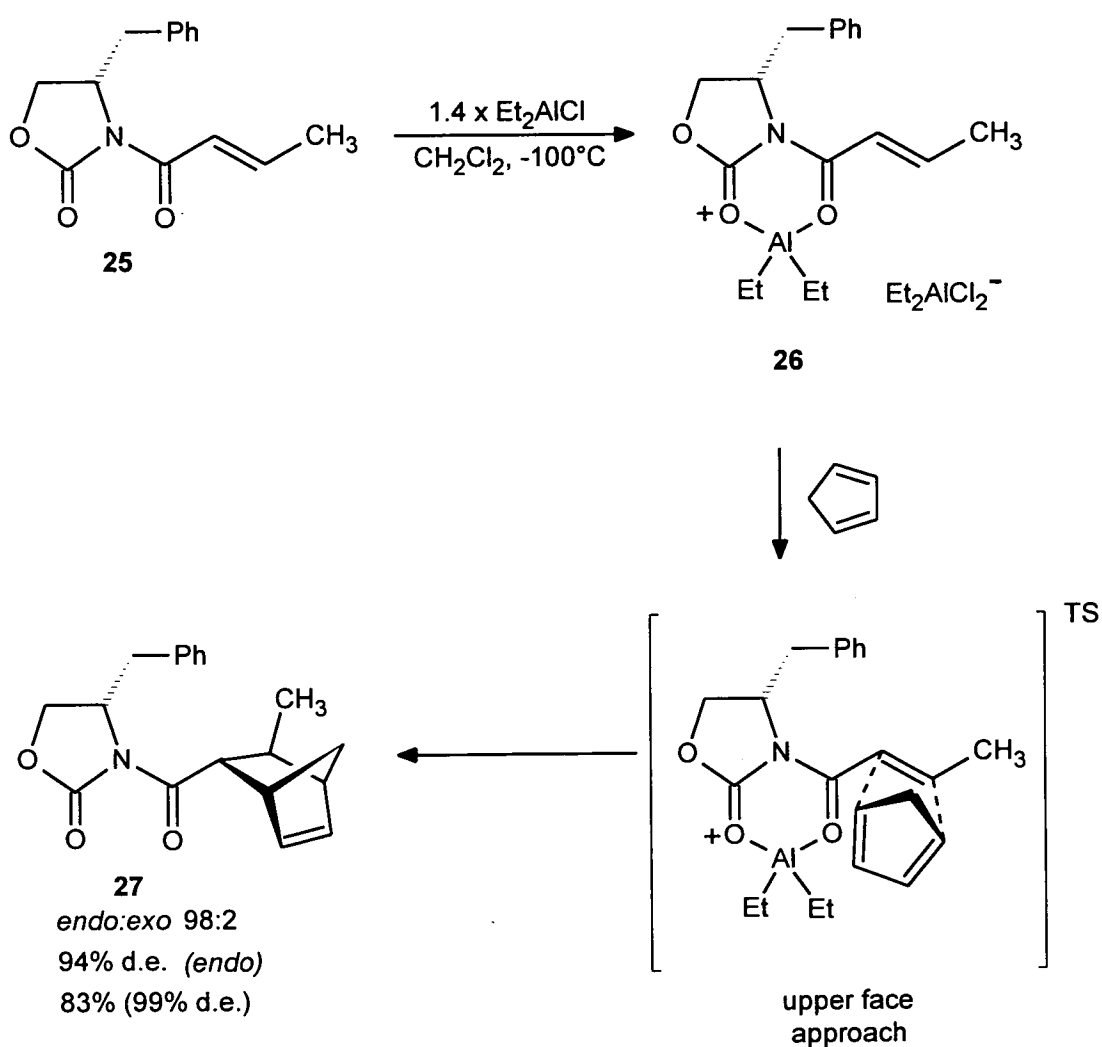
Perhaps the most elegantly used asymmetric reaction is the aldol condensation of the propionate-derived dibutylboron enolates which show very high degrees of selectivity^{6, 14}. The reaction in this case proceeds without chelation to



Scheme 7

the oxazolidinone carbonyl and is controlled by factors discussed in 2.4.2. The formation of the *syn* product **24** is primarily the result of the enolate geometry and the nature of the transition state which governs even the non-asymmetric version of this reaction (Zimmerman Traxler model). However, the absolute stereochemistry is determined by the auxiliary.

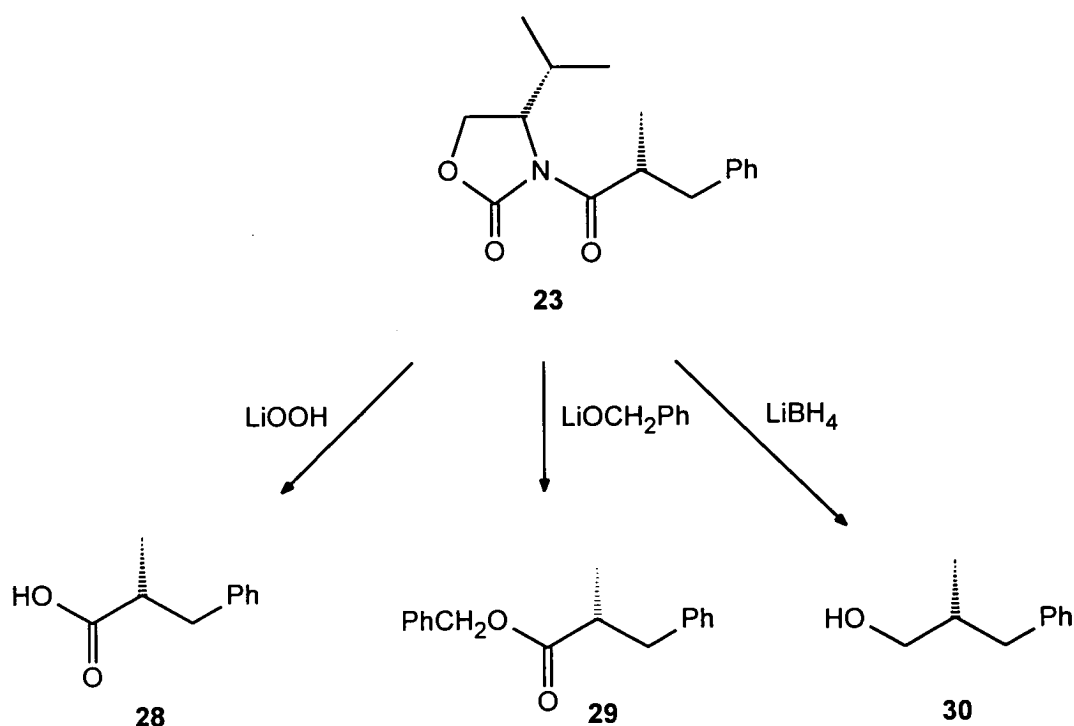
Diels-Alder cycloaddition reactions of unsaturated imides proceed with high selectivity when the phenylalanine-derived auxiliary **6** is used^{11,15}. The imide **25** in its chelated and activated state **26**, reacts rapidly at low temperature with:



Scheme 8

cyclopentadiene creating the four new chiral centres of the adduct **27** with almost complete stereocontrol. The nature and stoichiometry of the catalyst is highly important and this is discussed more fully in 2.5.2. Almost complete *endo*-selectivity is observed upon condensation with cyclopentadiene and the reaction generally shows very high regio-, stereo- and enantioselectivity for a wide range of dienes, including cases of intramolecular reaction

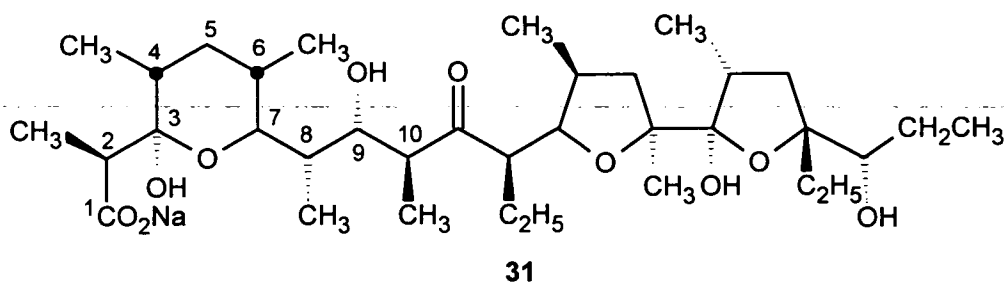
Following completion of the reaction, removal of the chiral fragment can be achieved by a variety of methods leading to a wide range of functionality in the fragment. The most widely used are solvolysis with lithium hydroperoxide¹⁶ to give the acid **28**, cleavage with lithium benzyloxide¹³ to provide the benzyl ester **29** and reductive cleavage with lithium borohydride¹⁷ to give the alcohol **30**. With suitable



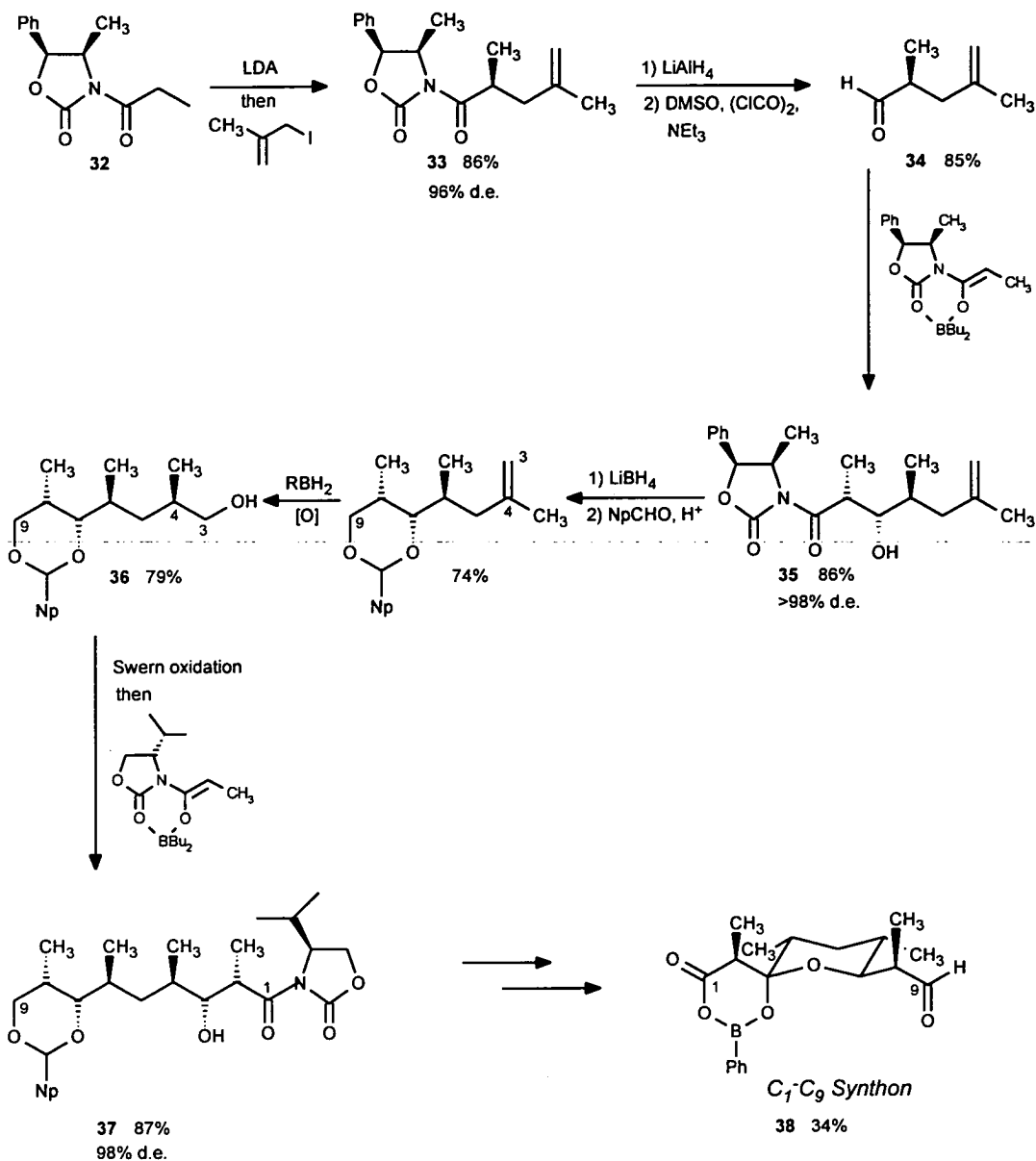
Scheme 9

protection required in some cases, the reaction gives not only a high yield of the chiral fragment without racemisation but also allows the auxiliary to be recovered in similar yield.

A combination of asymmetric alkylation and aldol reactions is exemplified in the synthesis of the C₁₋₉ synthon **38** of the polyether anti-biotic Ferensimycin **31**¹⁸.



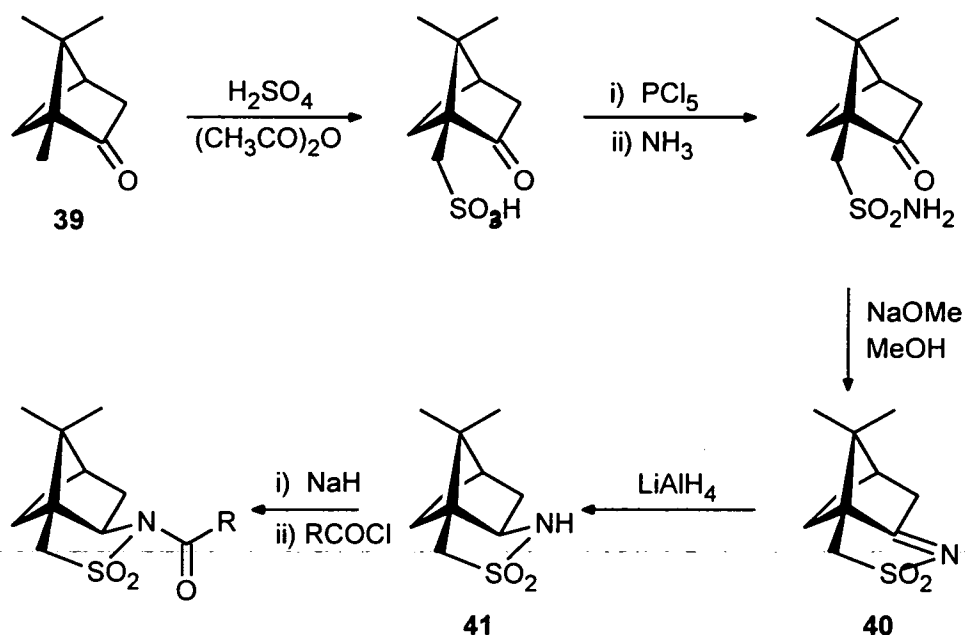
Thus, alkylation of the lithium enolate of **32** with 2-methyl allyl iodide proceeded to give the alkylated adduct **33** with 96% d.e.. This was reductively cleaved and then reoxidised to give the chiral aldehyde **34** which was subsequently reacted with the boron enolate of **32** with equally high diastereoselection to give the *syn* aldol product **35**¹⁹. After reductive removal of this fragment and its protection as its 1,3-naphthylidene acetal, a modestly diastereoselective (84:16) hydroboration reaction was used to create the C₄ chiral centre in **36**. The aldehyde was obtained by mild oxidation and condensed with the boron enolate of **20** to afford **37** with *syn* stereochemistry in the opposite sense to that forming the C_{7,8} stereocentres. Removal of the auxiliary from **37** and further manipulation provided the protected C₁₋₉ synthon **38**.



Scheme 10

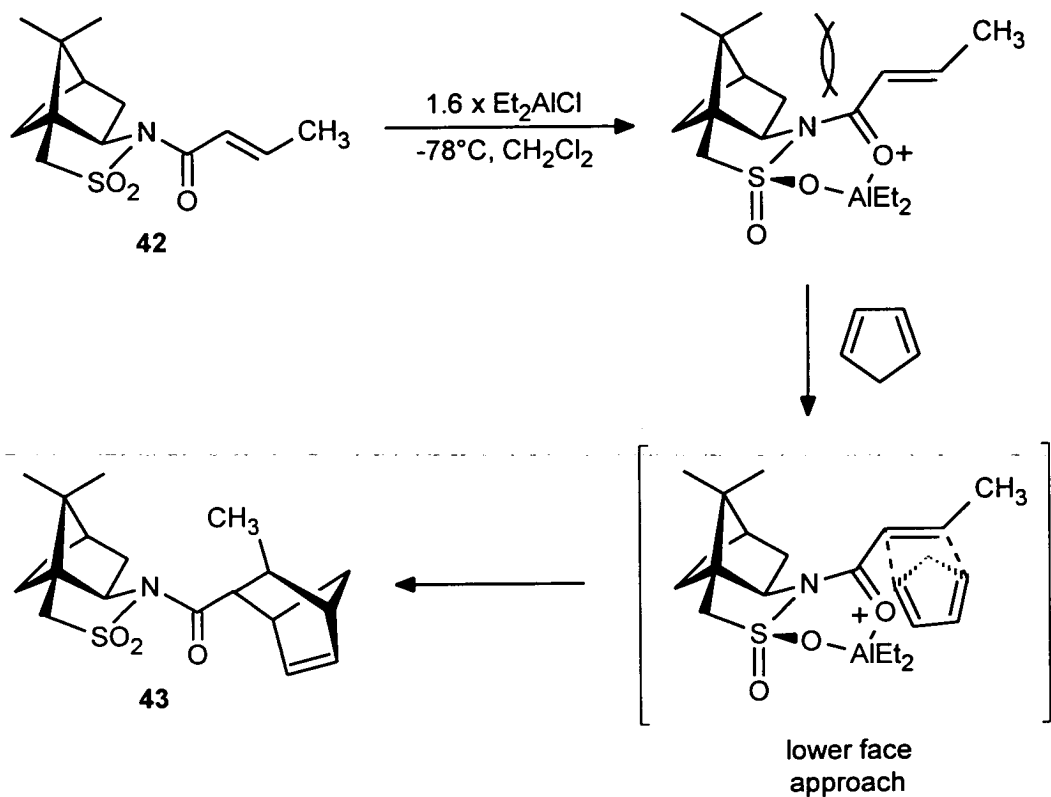
1.2.1.2 Oppolzer's Camphor Sultam

Oppolzer has developed the camphor sultam **41** as an highly effective chiral auxiliary²⁰. First synthesised in 1938 by Shriner²¹ from camphor **39**, the route shown is the one used by Oppolzer and provides a very good overall yield of this versatile auxiliary.



Scheme 11

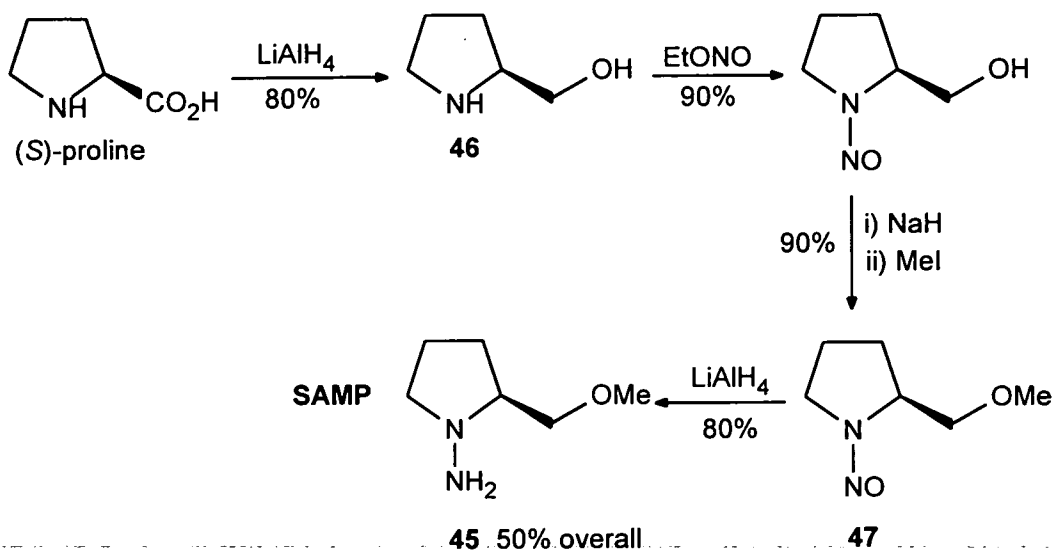
Functionalisation is carried out by analogous methods to those of Evans and most of the reactions described for the oxazolidin-2-one auxiliaries can also be carried out using this sultam as the source of chirality. Diastereoselectivities of many of the reactions are often slightly higher than those achieved with the oxazolidin-2-one auxiliary controlled reactions²². The main steric controlling group of the auxiliary is the dimethyl bridge which in the example of the Diels-Alder reaction of the chelated imide **42** can be seen to block the upper face of the dieneophile. In particular, it is worth noting that the $\text{C}_\alpha\text{-C=O}$ bond is held in the *s-cis* conformation to avoid steric interactions with the bornane skeleton whilst retaining good π -overlap with the rest of the conjugated system. Removal of the auxiliary from adducts such as **43** can be achieved under conditions similar to those used for the oxazolidinone adduct with yields and optical purities being generally equally high.



Scheme 12

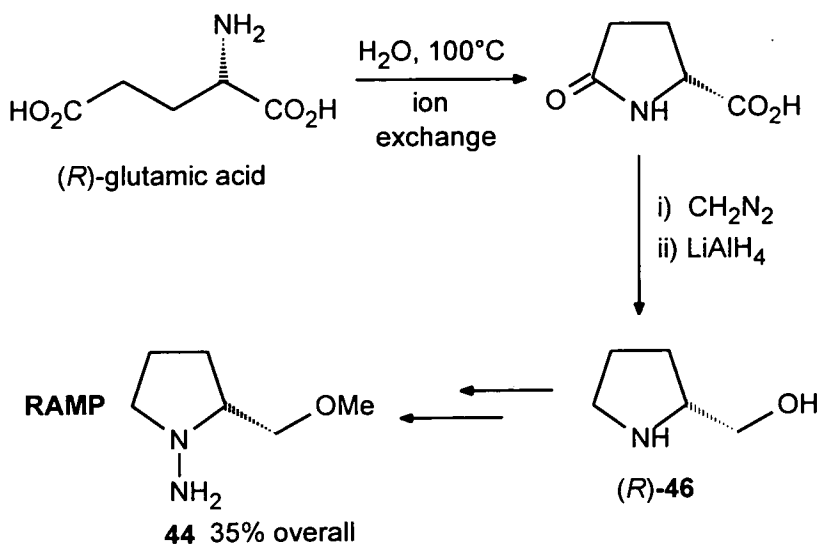
1.2.1.3 Asymmetric Alkylation of Chiral Hydrazones

A very effective and relatively simple approach to the asymmetric synthesis of α -alkylated ketones has been developed by Enders²³. The auxiliaries (*R*)- and (*S*)-1-amino-2-(methoxymethyl)pyrrolidine (RAMP and SAMP, 44 & 45) can be prepared from (*R*)- or (*S*)-proline by a sequence of reduction, nitrosation, and after hydroxyl protection, reduction of the nitroso group to yield the hydrazine.



Scheme 13

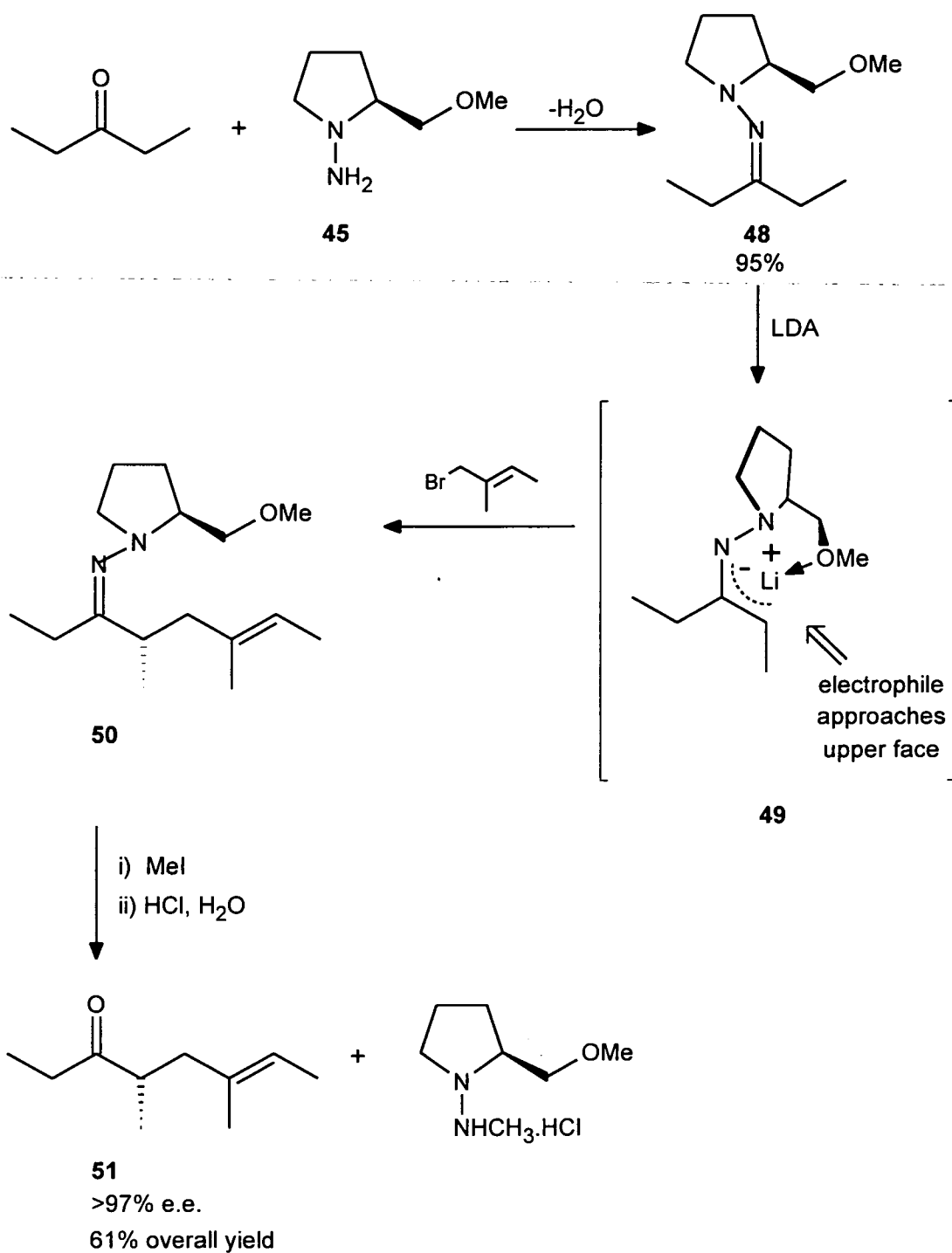
Due to the higher cost of (*R*)-proline, the (*R*)-prolinol required to produce **44** is better obtained from (*R*)-glutamic acid *via* cyclisation and reduction.



Scheme 14

The hydrazines can be condensed with a variety of ketones (most often symmetrical) to form a hydrazone which is readily deprotonated. In the example shown in Scheme 15, deprotonation of **48** with LDA generates the *Z*-(*N*) aza-allyl anion which is believed to adopt the conformation **49** as depicted with the lithium

counter-ion held by chelation to the ether oxygen. Alkylation on the face opposite the chelating group gives the adduct **50** with high d.e. In this case the auxiliary had



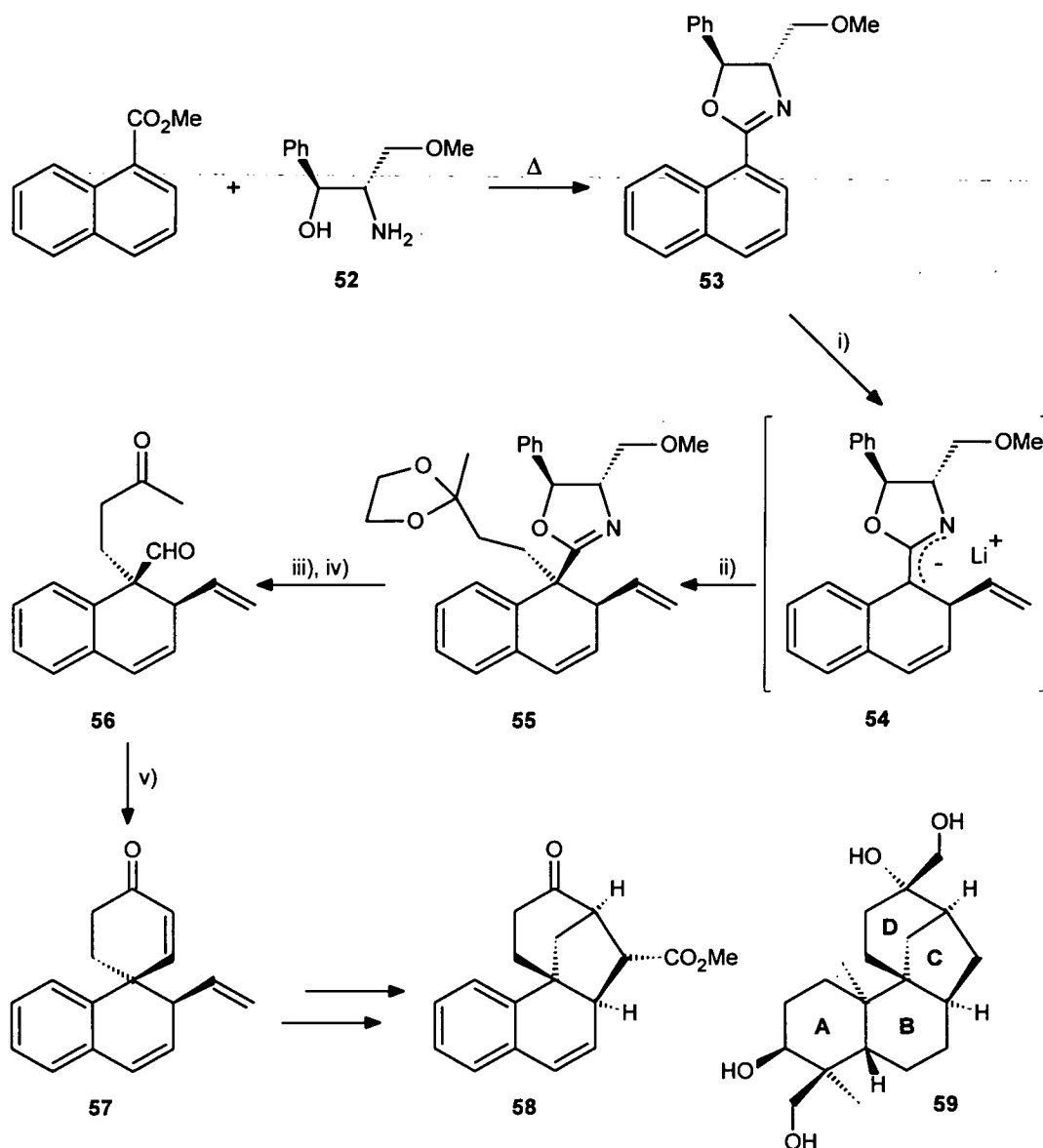
Scheme 15

to be removed by acidic hydrolysis of the preformed methylhydrazonium salt, a method that does not allow facile recycling of the auxiliary. The ketone (*S*)-**51**, the alarm pheromone of the daddy long legs was obtained in >97% e.e. in 61% overall yield²⁴. Ozonolytic cleavage of the alkylated hydrazone adduct, which was not an option in this case, does allow recycling of the auxiliary *via* reduction of the nitroso compound **47** that is so obtained.

1.2.1.4 Conjugate Addition to Chiral Oxazoline Substituted Naphthalenes

A further example of a chiral aza-allyl anion is demonstrated by Meyers' use of the methoxymethylene-substituted oxazolines derived from auxiliary **52**; these have been used in the control of many asymmetric reaction types²⁵. The example shown in Scheme 16, demonstrates not only the ability of the oxazoline heterocycle to control the stereochemical outcome of conjugate addition, but also the activating effect of the oxazoline on the naphthalene²⁶. The oxazoline **53** was formed by condensation of methyl α -naphthoic acid with the amino-alcohol **52**. Initial delivery of the nucleophile to **53** is considered to be sigmatropic in nature²⁷ from the initial metal-bound complex. The delivery is to the face opposite the methoxymethylene substituent (the oxazoline is prevented from rotation due to the necessity of the nitrogen being correctly positioned) resulting in the formation of the aza-allyl anion **54**. The electrophile then reacts with **54** on the opposite face to the Michael-added substituent. The *trans*-disposition of the two added groups in **55** is characteristic of this reaction, it is thought that the electrophile always adds to the face opposite the

Michael substituent irrespective of the preference of the auxiliary. It should be noted that in this reaction the methoxymethylene substituent does not appear to influence the selectivity of the Michael addition by acting as a chelating ligand. The use of *tert*-leucinol-derived oxazolines in similar reactions has provided comparable and often improved selectivities, merely through the influence of steric bulk²⁸. After



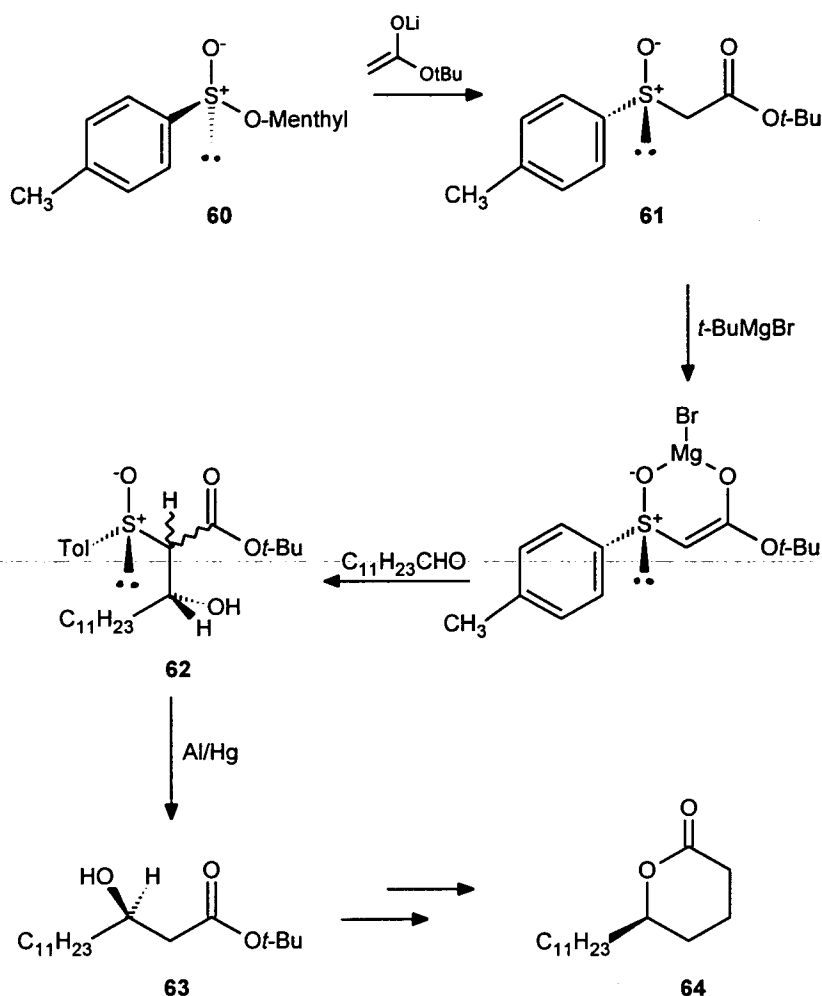
Conditions : i) MeLi, Bu₃SnCH=CH₂, -45°C, THF; ii) 2-methyl-2-(2-iodoethyl)-1,3-dioxolan, RT; iii) MeOTf, CH₂Cl₂ then NaBH₄, MeOH/THF, then H⁺; iv) TsOH; v) KOH, MeOH.

Scheme 16

removal of the auxiliary and deprotection, intramolecular aldol condensation of **56** provided the highly functionalised spiro-cyclohexanone derivative **57** as a single enantiomer. This was achieved in good yield in only five steps from simple α -naphthoic ester. This represented a model synthesis of the **A**, **B** and **D** rings of the tetracyclic compound aphidicolin **59**²⁹. The **C** ring was constructed by functional group conversion followed by a further intramolecular aldol condensation. The six-membered ring so obtained was ring contracted *via* a Wolff rearrangement to the five membered ring of **58**.

1.2.1.5 Chiral Sulfoxides

Unsymmetrically substituted sulfoxides are stable tetrahedral chiral centres due to the sulphur lone pair and have been used as a source of chirality in a number of reaction types³⁰. The sulfoxide **61**, obtained by reaction of *t*-butylacetate enolate on optically pure menthyl *p*-toluene sulphinatate **60**³¹, is readily deprotonated to give what is presumed to be a chelated enolate. This was condensed with the long chain aldehyde to create the two new chiral centres in the adduct **62**, although one of these is destroyed in the reductive cleavage of the auxiliary which gives the β -hydroxy ester **63** with >80% e.e. This was then chain extended and lactonised to give δ -hexadecanolide **64**, the oriental wasp pheromone³².

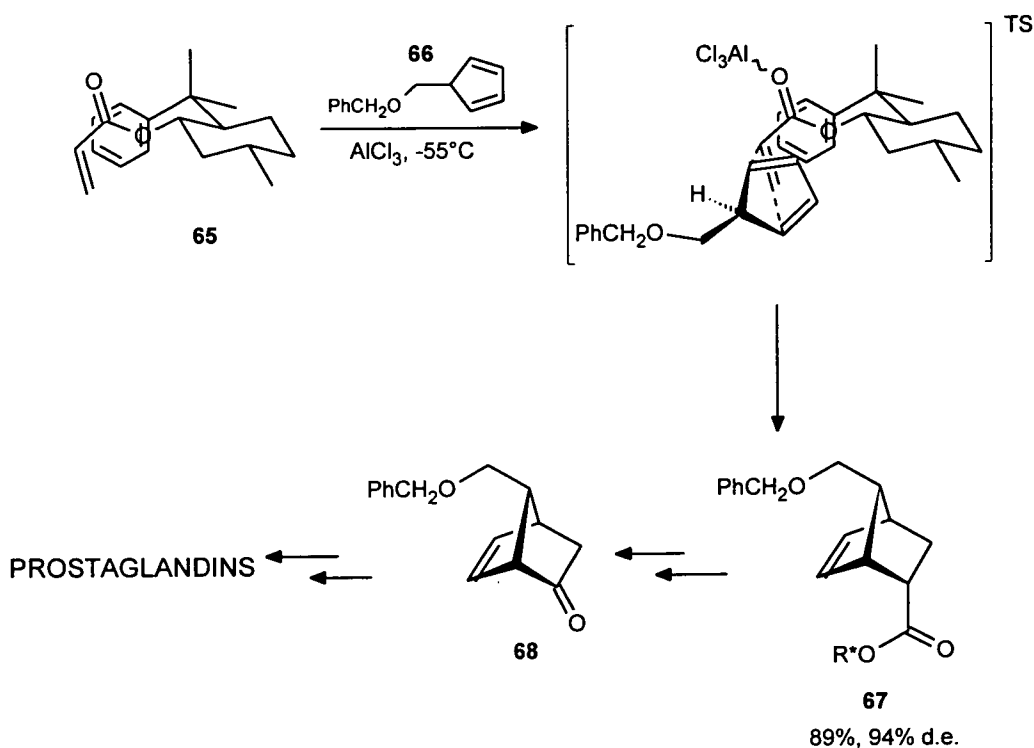


Scheme 17

1.2.1.6 Chiral Induction Without Chelation *via* 8-Phenylmenthol

Although chelation is highly important in many asymmetric transformations, it is still possible to obtain highly diastereoselective reactions which are not dependent on the conformation being fixed by chelation. The Diels-Alder condensation of the acrylate ester **65** of 8-phenylmenthol is an early example of auxiliary controlled asymmetric synthesis³³. Control of the addition of the substituted cyclopentadiene **66** was of great importance to the enantioselective synthesis of prostaglandins since it allowed access to the crucial intermediate **68**. Upon co-ordination with aluminium trichloride

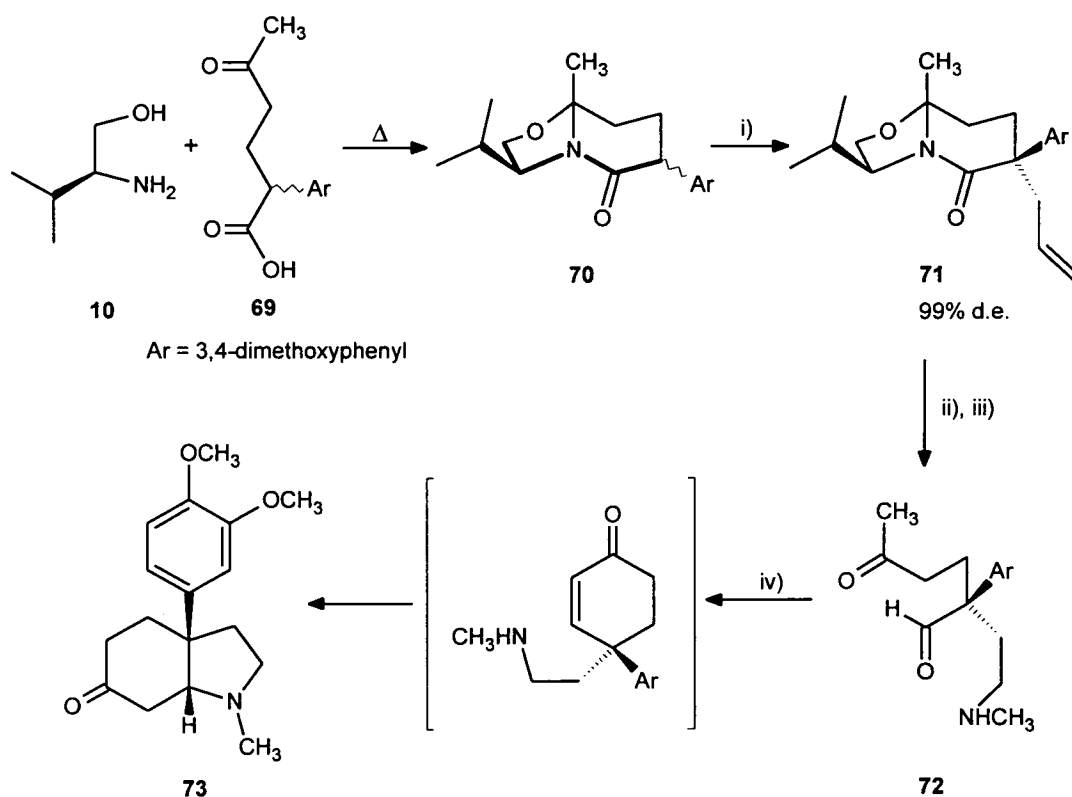
it is believed that the acrylate assumes the conformation shown in Scheme 18 due to a combination of steric factors, as well as favourable aryl-acrylate π -system stacking³⁴. Obviously only one face of the dienophile is accessible and *endo*-selectivity is controlled by secondary orbital interactions (see 2.5.1) as well as steric constraints for this substituted cyclopentadiene (crucially controlling the bridgehead stereochemistry as well). The d.e. of the product **67** was high and importantly the auxiliary was easily removed under mild conditions. It should be noted that more modern auxiliaries can control such reactions even more specifically, but this result was a highly significant early example and use of this auxiliary (and its naphthyl analogue) is still regularly reported today.



Scheme 18

1.2.1.7 Chiral Bicyclic Lactams

Meyers has recently developed a system applicable to induction of chirality *via* alkylation and 1,2- or 1,4-addition of organometallics³⁵. This does not rely on chelation to form a defined transition state but rather relies on the rigid nature of the bicyclic compound. The alkylation sequence is of particular value since chiral non-racemic quaternary centres are readily generated, a reaction that is difficult with many other systems. An example of the efficiency of this approach is the synthesis of the scelerium alkaloid, mesembrine **73** by a very concise route: The chiral source is a simple amino alcohol such as *S*-valinol **10**, which is condensed with the α -aryl δ -keto acid **69**, giving a mixture of diastereomers of **70**, which upon treatment with *sec*-



Conditions : i) *s*-BuLi, then allyl bromide, THF, -20°C; ii) OsO₄ (cat.), NaIO₄, Et₂O/H₂O, then MeNH₂, NaBH₃CN; iii) LiAlH₃OEt, then Bu₄NH₂PO₄; iv) 4 M NaOH

Scheme 19

-butyl lithium gave the same enolate. This enolate reacted with allyl bromide, on the lower face, to give the quaternary adduct **71** as essentially a single diastereomer in good yield. The amino functionality was introduced by oxidative cleavage followed by imine formation and *in situ* reduction. After reduction to an aminal and mild acidic cleavage, the keto aldehyde **72** was obtained; base treatment not only induced the aldol condensation to produce a γ,γ -disubstituted cyclohexenone, but this spontaneously underwent intramolecular Michael addition to create the second chiral centre. The synthesis provided the unnatural enantiomer of mesembrine **73**³⁶ in 22% overall yield with an optical rotation equal in magnitude to that obtained from natural sources.

Further, a wide variety of functionalisation and condensation reactions allows such adducts as **71** to be converted into a great variety of highly substituted carbo- and heterocyclic products with high enantiomeric purity³⁷.

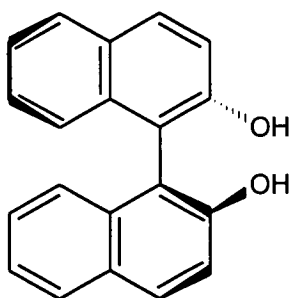
1.2.2 Reagent Controlled Asymmetric synthesis

Reagent controlled asymmetric synthesis offers the advantage that the enantiomerically enriched product is obtained in a single step as opposed to the three-step auxiliary mediated sequence. Furthermore an auxiliary approach often leads to a specific or limited range of functionality, which may not be desired in the target. Counter to this a stoichiometric quantity of chiral information is still required and if complete asymmetric induction is not achieved, one faces the more difficult task of enantiomeric *verse* diastereomeric enrichment. Two major classes of chiral reagent

appear to be in use, viz those which are intrinsically chiral, and those which bear chiral modifiers.

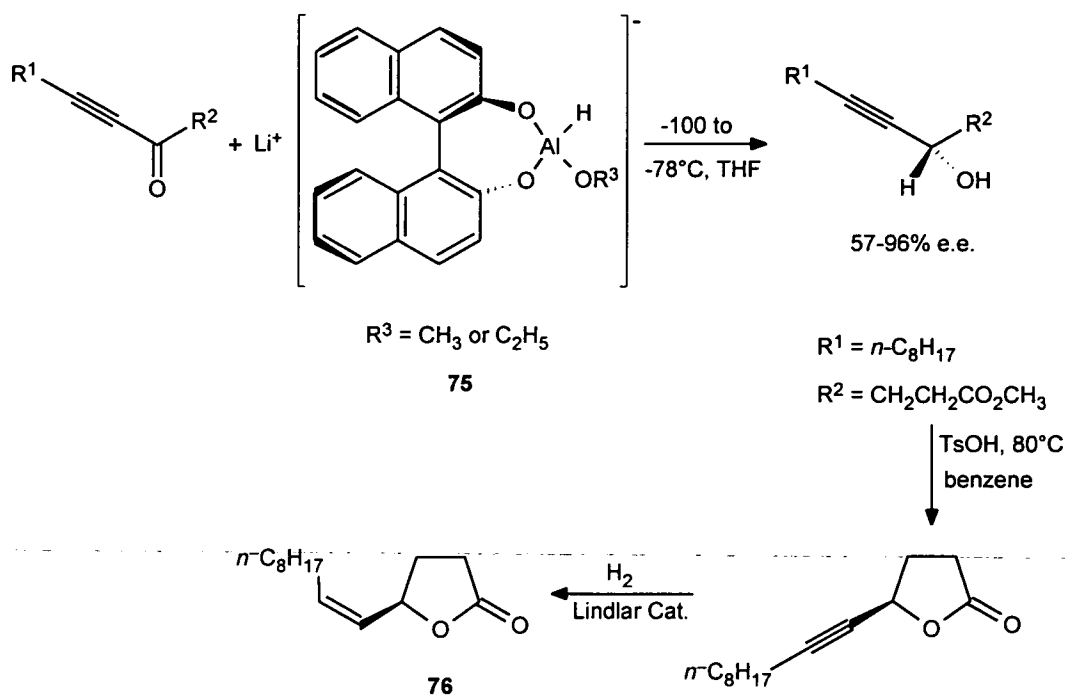
1.2.2.1 Reduction using a Binaphthol-Modified Aluminium Hydride Reagent

Chiral modifiers for lithium aluminium hydride have been used for a number of years to provide enantioselective reducing reagents³⁸. A particularly effective example is Noyori's use of the C_2 symmetric, axially-chiral binaphthol ligand *S*-(-)-2,2'-dihydroxy-1,1'-dinaphthyl (BINOL) **74** and its enantiomer³⁹.



74

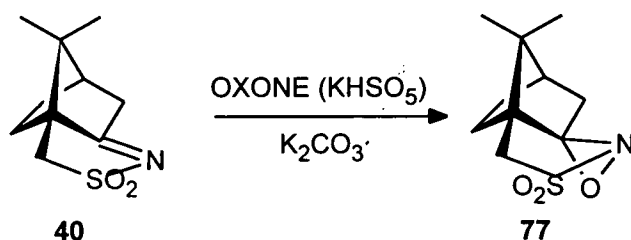
Mixing of lithium aluminium hydride with an alcohol (normally methanol) and the optically pure diol in THF forms the reagent known as BINAL-H **75**, which effects highly enantioselective reductions of various acetylinic ketones. Enantiomeric excesses of between 57 and 96% were observed (and generally greater than 84%) in this relatively simple reaction. An example of its application is shown in Scheme 20 which illustrates the straight forward synthesis of one enantiomer of the Japanese beetle pheromone **76**, a simple γ -substituted γ -lactone. For a comparable example of reagent controlled reduction see 1.3.1.3, and for a catalytic enantioselective approach to mono-substituted γ -lactones using a similar axially chiral ligand see 1.2.3.1.



Scheme 20

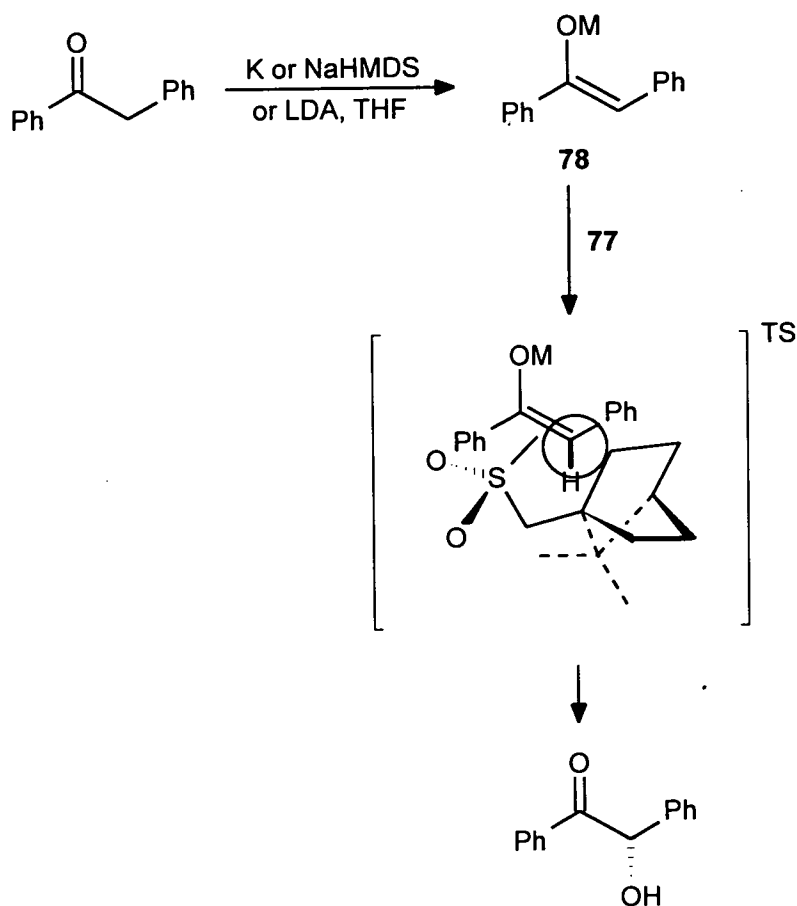
1.2.2.2 Asymmetric Oxidation using an Enantiomerically Pure Oxaziridine

Davies has developed an enantiofacially selective electrophilic oxidising agent derived from the intermediate **40** used in the synthesis of Oppolzer's sultam **41**⁴⁰.



Racemic *N*-sulphonyloxaziridines have been used with chiral enolates in the asymmetric synthesis of α -hydroxycarboxylic acid equivalents⁴¹. The reagent **77** offers an alternative approach to these auxiliary controlled methods. The prochiral

potassium enolate of benzylphenyl ketone **78** ($M = K$) reacts with **77** to give (*S*)-benzoin in 73% yield with 93% e.e. The sodium enolate provides an equally high selectivity (95% e.e.) with a similar yield. However the reaction is highly substrate dependent and very sensitive to counter-ion, solvent changes (*e.g.* addition of HMPA) and duration of reaction. For example the lithium enolate gives an enantiomeric excess. of only 68% in a slightly lower yield. This is partly due to less specific formation of the *Z*(*O*)-enolate; attempts to counter this by the addition of

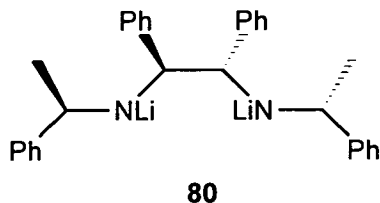
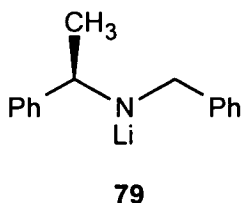


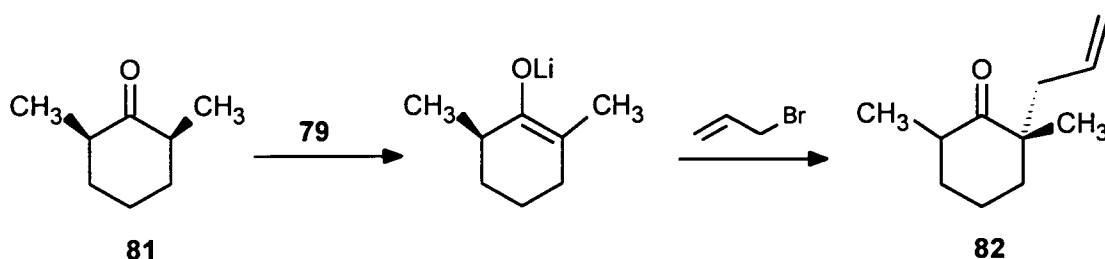
Scheme 21

HMPA resulted in a stereodefined enolate, but with a much reduced enantiomeric excess (6%). Over a wide range of substrates and reaction conditions the enantioselectivity varied drastically (3-95%), but for suitable cases the reagent can be highly effective.

1.2.2.3 Homochiral Lithium Amide Bases (HCLAs)

HCLAs (e.g. **79** and **80**) have become important reagents in asymmetric synthesis, having found applications not only in the generation of enantiomerically enriched enolates from *meso*-compounds, but also in enantioselective rearrangements, kinetic resolution and as non-covalently bonded auxiliaries in enolate and anionic reactions⁴². Further to acting as bases, their nucleophilic character has been used in the synthesis of β -amino carboxylic acid derivatives by Michael-addition reactions⁴³. A simple example of chiral base methodology is the enantioselective alkylation of the *meso*-ketone **81**. Preferential removal of the one proton gives a scalemic (chiral non-racemic) enolate which is then alkylated, although the stereoselectivity of this early example to give **82** was rather modest (25% e.e.)⁴⁴.

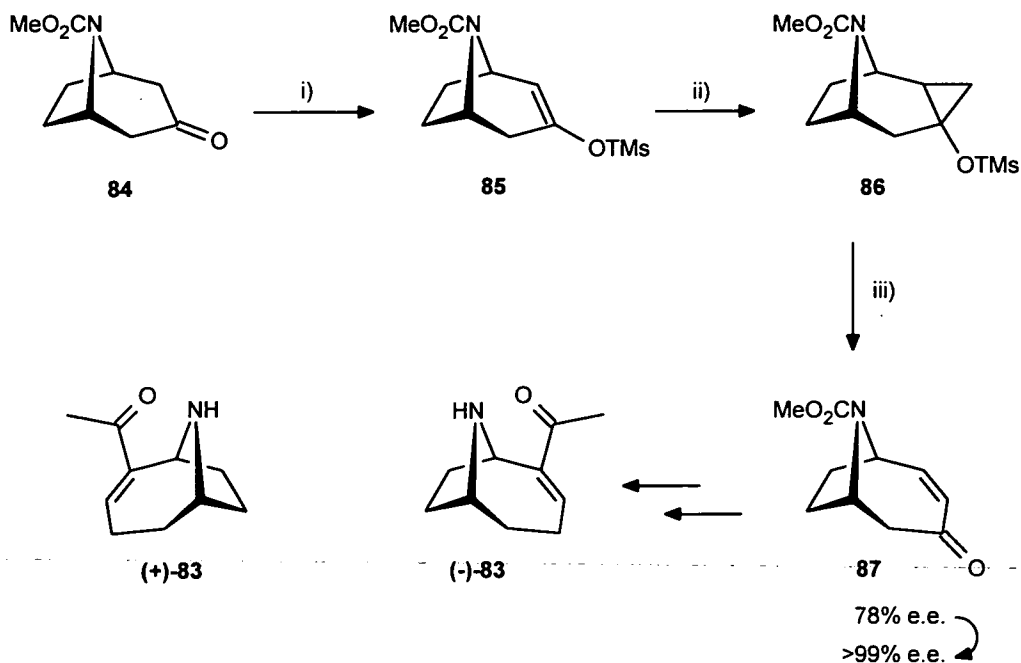




Scheme 22

A recent and more effective example of this approach is the enantioselective synthesis of the unnatural (-) enantiomer of (+)-anatoxin-a **83**⁴⁵, a powerful agonist of the acetylcholine receptor and highly toxic. The route is based on the enantioselective ring expansion of the simple tropinone system **84**. By deprotonation with the doubly lithiated base **80** and *in situ* trapping of the enolate with TMS chloride in the presence of lithium chloride to give the enol silane **85** with 78% e.e. It should be noted that in many cases addition of metal salts has been found to have beneficial effects on the selectivities of HCLA reactions.

In subsequent steps, cyclopropanation of the enol silane gave **86** which underwent a ring expansion reaction in the presence of ferric chloride to yield the eight-membered ring enone **87**, which was obtained as a single enantiomer by recrystallisation. Michael addition of an anionic acyl equivalent to this intermediate and further manipulation yielded (-)-**83** with an optical rotation equal in magnitude to the natural material.

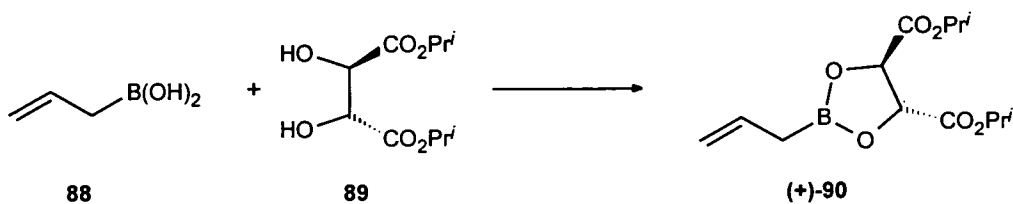


Conditions : i) **80**, TMSCl, THF; ii) ZnEt_2 , ICH_2Cl ; iii) FeCl_3 , NaOAc, DMF/MeOH.

Scheme 23

1.2.2.4 Allylation using Diisopropyltartrate-modified Allylborinate Reagents

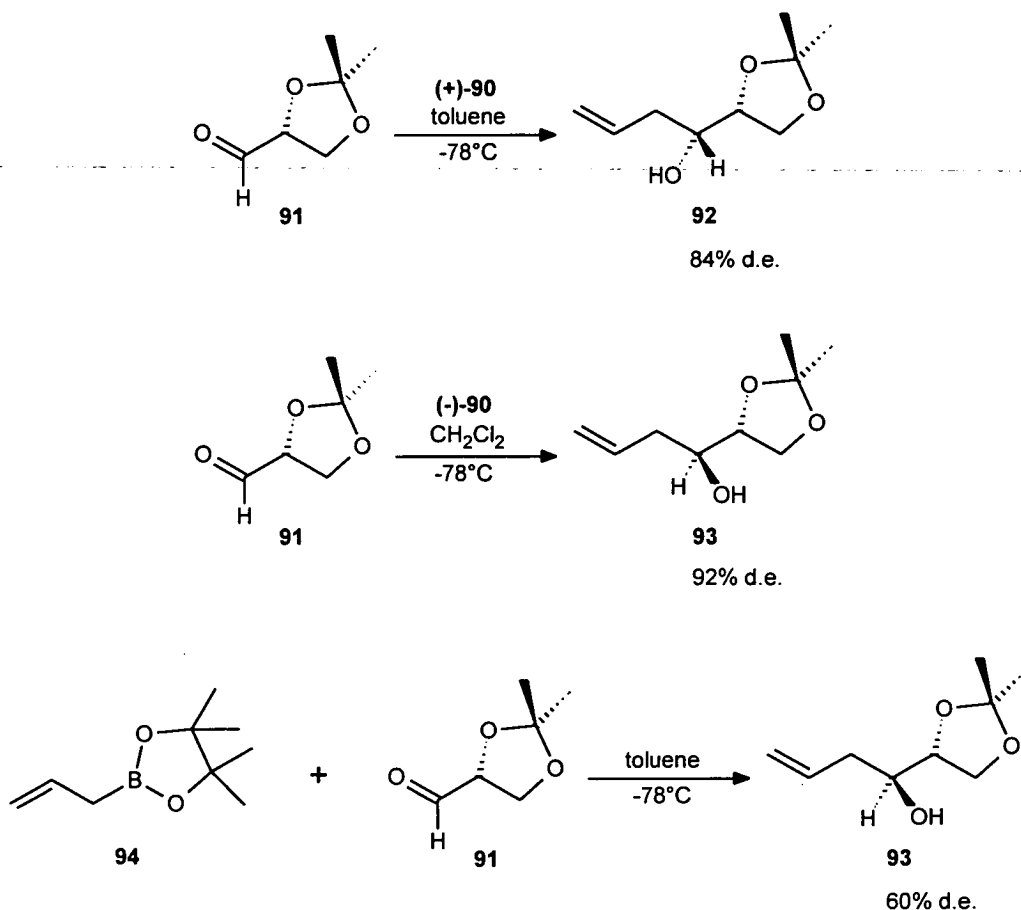
The metal of these active allyl systems bears the chiral inductor groups and is itself lost in the reaction. Reagent **90** is prepared via esterification of the allyl boronic acid **88** with diisopropyltartrate **89**, and reacts with a range of achiral aldehydes to give



Scheme 24

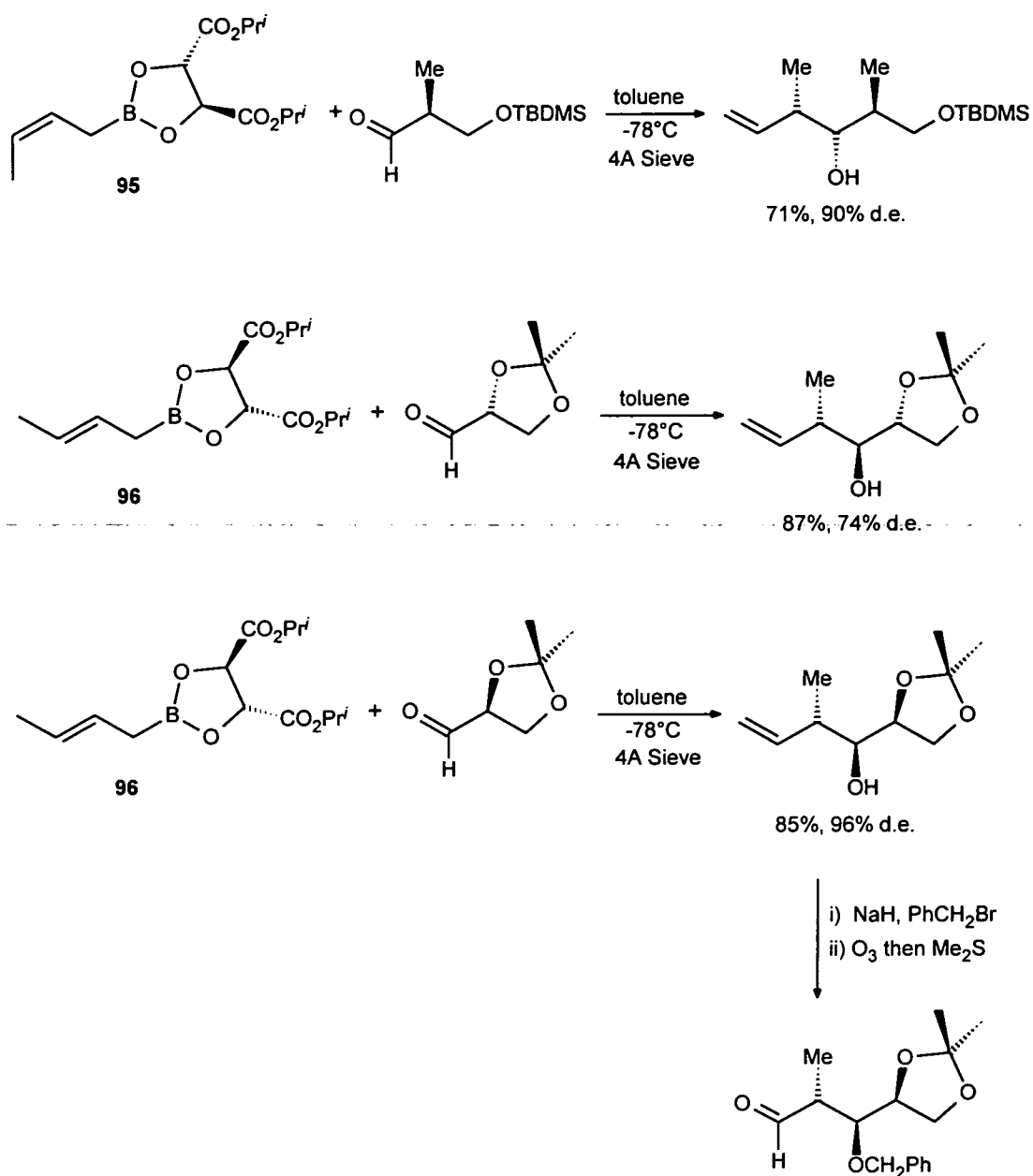
good yields of products in 79-87% e.e.⁴⁶. The power of this method is such that condensation of them, even with mis-matched chiral aldehydes (those that would naturally give the opposite selectivity with an achiral reagent), proceed with high selectivity in the manner predicted for the boron reagent.

In the first example, it can be seen that upon condensation of (+)-**90** with the



Scheme 25

mis-matched aldehyde **91** the reaction proceeds with high selectivity to give the product **92** in 84% d.e. By comparison, use of the matched pair ((-)-**90**) gives the diastereomer **93** with 92% d.e. It should be noted that the aldehyde **91** also reacts with the achiral allyl boronate **94**, derived from pinacol, to give the diastereomer **93** with 60% d.e.⁴⁶.



Scheme 26

The reaction with the corresponding (*Z*)- or (*E*)-crotyl systems (**95** and **96** respectively), allows the generation of a second chiral centre in either a *syn* or *anti* manner with respect to the newly-formed hydroxyl group⁴⁷. The second method is particularly useful since upon oxidative cleavage of the vinyl group, an *anti*-aldol product is obtained⁴⁸.

It can clearly be seen that both the matched and mis-matched selectivities are still reasonably high for these reactions even though four products are now possible. Throughout this work Roush proposes that stereoelectronic effects are dominant in bringing about this selectivity as can be seen in the two possible transition states shown Figure 4. The value of the C_2 chiral inductor in this case is obvious.

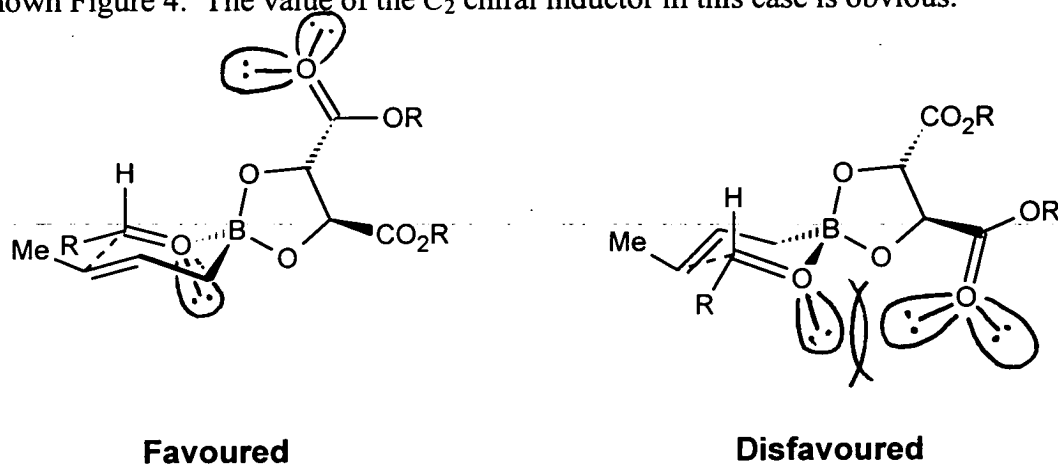


Figure 4

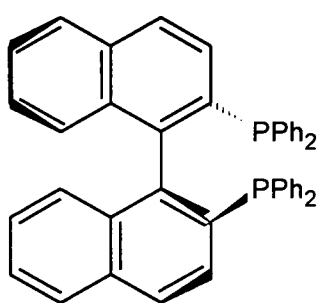
1.2.3 Catalyst Controlled Asymmetric Synthesis

Catalytic asymmetric synthesis offers the advantages of asymmetric reagent controlled synthesis without the requirement of a stoichiometric quantity of chiral information. This obviously makes it the most economic method of asymmetric synthesis and as such the most likely to be adopted by industry. The required quantities of catalyst varies from reaction to reaction (0.1 to 40 mol%), but depends mostly on the competitive rates for catalysed to non-catalysed reaction. Interestingly, due to the non-linear feature of chiral amplification⁴⁹, many catalytic reactions can be run with non-homochiral (scalemic) catalyst and still yield enantimerically pure

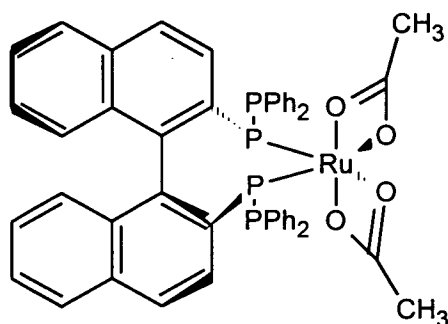
products. In many cases, the active catalyst or its chiral ligands can be easily recovered after the reaction.

1.2.3.1 Asymmetric Hydrogenations using a Chiral Transition Metal Complex

Asymmetric catalytic hydrogenation of prochiral alkene and ketone functions rates as one of the potentially most important industrial methods of enantioselective synthesis. This is due to the simplicity of the reaction and economy both in terms of the reagent and the small quantity of chiral information required. Noyori has probably contributed most to this field and the ligand developed by him, (2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP) **97** is undoubtedly one of the most effective⁵⁰. Thus, the high pressure reduction of prochiral alkenes by hydrogen in the presence of transition metal (ruthenium or rhodium) catalysts bearing this ligand is highly efficient given that the substrate bears a nearby polar group (enantiomeric excesses often approach 100%).



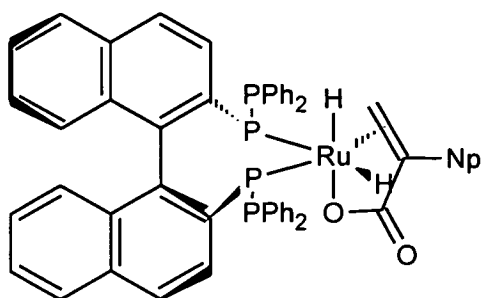
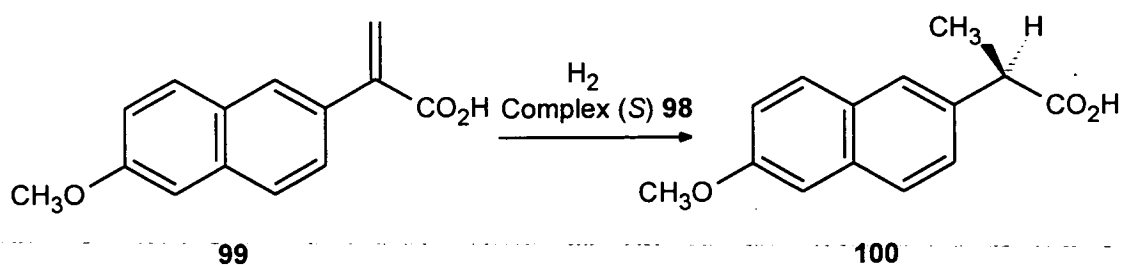
97



98

For example, the substituted acrylic acid **99** is reduced to the non-steroidal anti-inflammatory drug *S*-Naproxen **100** with 99% e.e. when hydrogenated in the presence of the (*S*)-BINAP ruthenium complex **98**⁵¹. The requirement of an adjacent

polar group is proposed to be due to a tight transition state which is formed when the substrate chelates to the metal centre *via* both the π -system and the polar group, *e.g.* **101**. This allows selective delivery of the hydrogen atoms that are also bound to the metal centre to one face of the substrate.

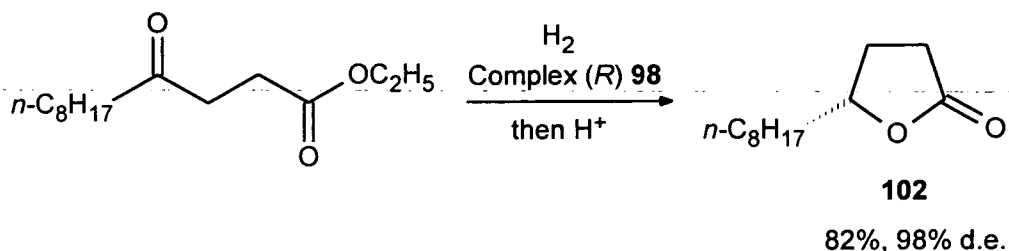


101

Scheme 27

Ketones that bear a polar group three carbons or less distant can also be reduced with virtual complete selectivity. An example that compliments the reduction of acetylinic ketones using the chiral reagent BINAL-H (**1.2.2.1**) is the facile synthesis of γ -substituted γ -lactones. Thus, 4-oxocarboxylic esters are readily reduced, provided that the catalyst has been activated by pretreating it with a small quantity of hydrogen chloride, to produce a mixture of the corresponding hydroxy ester and lactone. Treatment of this crude product with acid yields desired the γ -

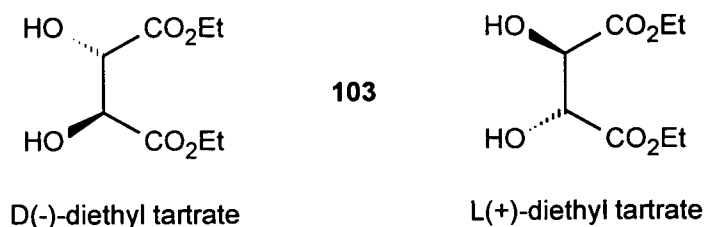
lactone with enantiomeric excesses of 98-99.5%⁵². A typical example of this procedure is the facile synthesis of the rove beetle pheromone **102** which shows that this method rates as the most efficient enantioselective synthesis of simple γ -substituted γ -lactones available. An excellent review of asymmetric ketone reduction is available and covers both reagent and catalytic methods⁵³.



Scheme 28

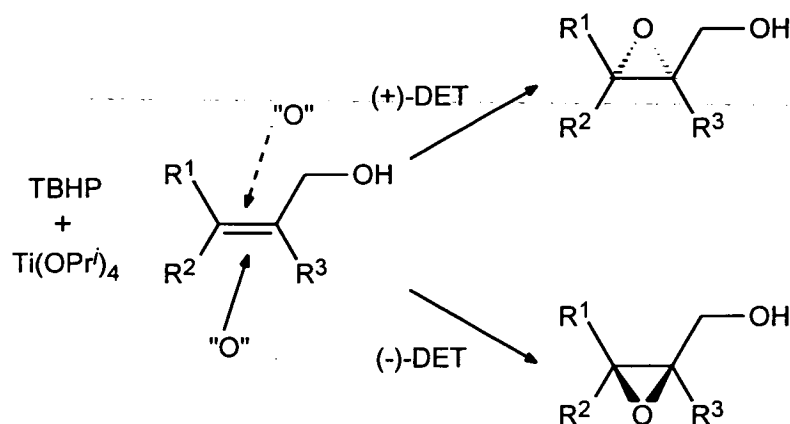
1.2.3.2 Asymmetric Oxidation of Alkenes

Sharpless has developed two methods of asymmetric oxidation that have subsequently been adopted by a great number of research workers. These are catalytic asymmetric epoxidation⁵⁴ and dihydroxylation⁵⁵. The first method is the epoxidation of allylic



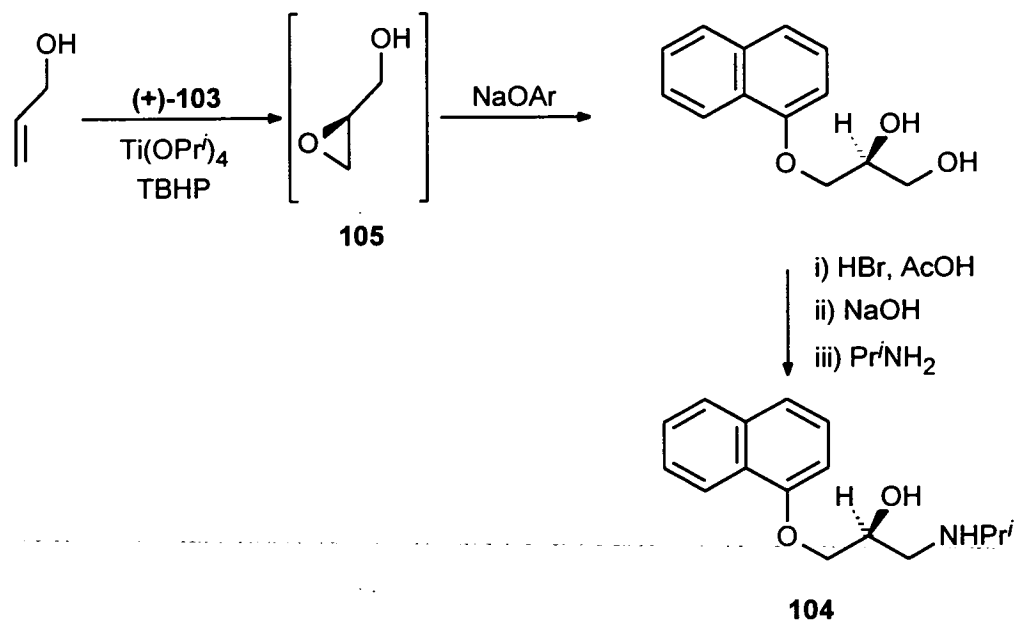
alcohols with an alkyl peroxide using a titanium catalyst bearing *D*-or *L*-diethyl tartrate ligands (DET) **103**. The reaction was originally developed as a reagent

controlled method, but it was found later that under strictly anhydrous conditions the reaction could be carried out catalytically (10-15% of **103**). The active catalyst is believed to be a complex dimeric species and only allylic alcohols are good substrates. By contrast, homoallylic alcohols are poor substrates, while isolated alkenes are unaffected in the presence of an alternative allylic site.



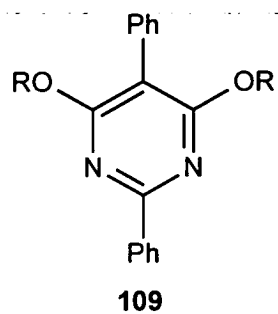
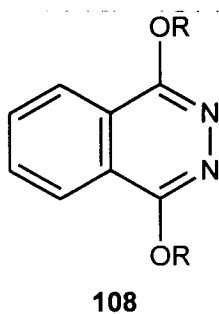
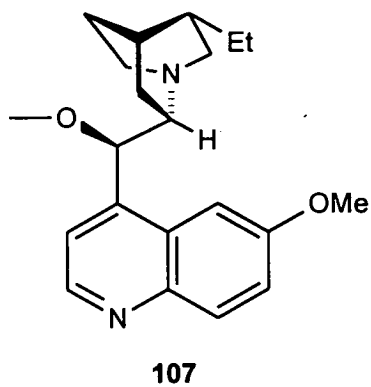
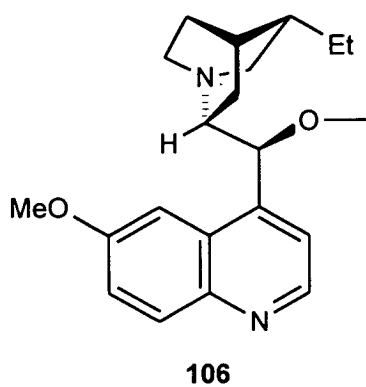
Scheme 29

The synthesis of the β -andergenic blocking agent, (2*S*)-propanolol **104**, illustrates an application of Sharpless's process⁵⁶. The unstable glycidol **105**, which is prone to a degenerate form of the Payne rearrangement under the reaction conditions, is trapped *in situ* with sodium naphthoxide; thereafter straight forward functionalisation yields the drug **104** as a single enantiomer in good overall yield. An alternative epoxidation procedure has been developed by Jacobsen⁵⁷ which gives extremely high enantioselectivities with unfunctionalised alkenes. In this case the manganese catalyst, is once again used with a cheap re-oxidant and although only developed recently, the process is finding many applications.

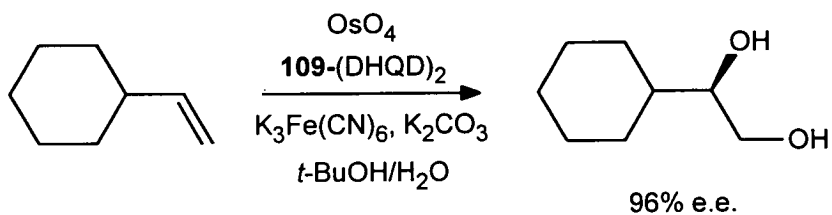
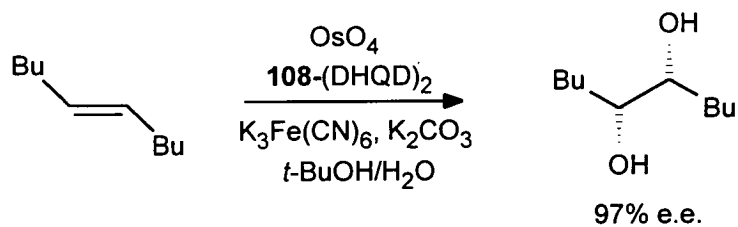


Scheme 30

A complementary functionalisation procedure for alkenes is asymmetric dihydroxylation (AD). AD is carried out by catalytic osmium (VIII) oxidation in the presence of a chiral ligand and a cheap re-oxidant. Sharpless has probably developed the most effective chiral ligands, which are heterocycles substituted by dihydroquinine (DHQ) **106**, or dihydroquinidine (DHQD) **107** moieties to give effectively an enantiomeric pair of catalysts. Phthalazine ligands **108**⁵⁸ give good selectivities with 1,1-, 1, 2-di and tri-substituted alkenes, but generally poor selectivity with terminal alkenes (except styrene). The pyrimidine ligands **109**⁵⁹ have been developed subsequently and were shown to possess complementary selectivity to **108**, giving high selectivity with terminal alkenes. The active catalyst in both cases is proposed to be a chelated mono-osmium complex. The other possible chelation sites of ligands **108** and **109** are believed to adopt an unfavourable conformation. Although these reactions use very little ligand and catalyst (1 mol % of each), at



R = **106** or **107**

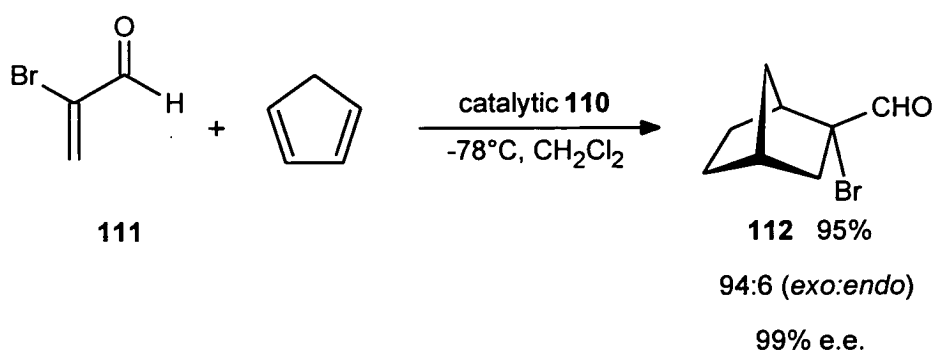
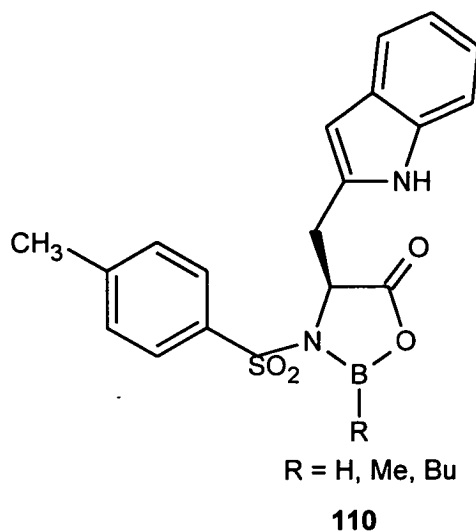


Scheme 31

lower temperatures it is possible to use even less ligand and still obtain good selectivity. Thus, a much lower concentration of ligand (0.01 mol %) can be used in relation to both the osmium catalyst (1 mol %) and the substrate; but even under these conditions little non-ligand controlled reaction takes place showing the rate acceleration effect that the ligands have on the catalyst.

1.2.3.3 Catalytic Asymmetric Diels-Alder Cycloaddition

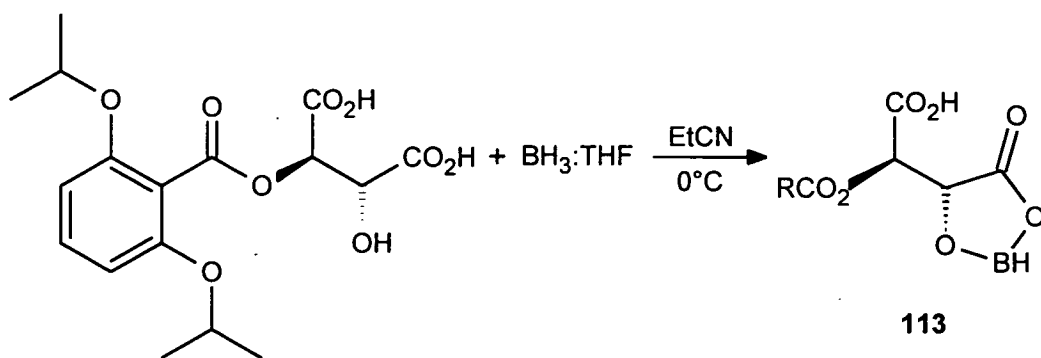
Corey has developed the tryptophan-derived oxazaborolidine catalyst **110**, this Lewis acidic catalyst has proved highly effective in controlling Diels Alder reactions with very high enantioselectivity⁶⁰. Thus in the presence of 5 mol% of **110**, at low temperature the aldehyde **111** gives the adduct **112** with cyclopentadiene in 95% yield. 94:6 Diastereoselectivity (exo/endo) was observed and the reaction proceeded with greater than 99% enantioselectivity. This highly selective reaction is believed to be due to two factors, firstly the aldehyde is known to prefer a *S-cis* conformation. On binding to the boron the alkene is thought to undergo π -stacking interactions with the electron rich indole ring. The tosyl group is necessary for good enantioselectivity but it is not but it is not as yet clear how it functions in this catalyst.



Scheme 32

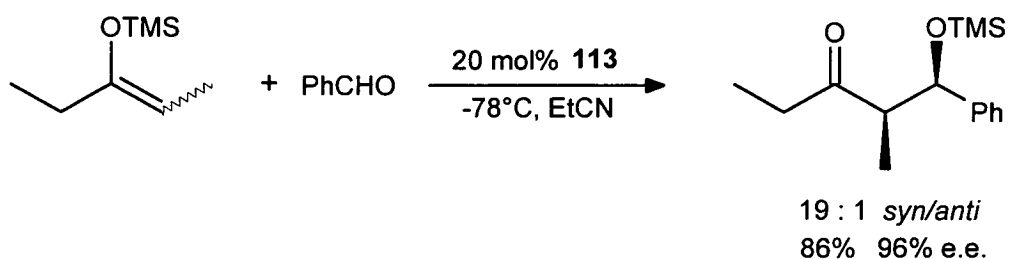
1.2.3.4 Catalytic Asymmetric Aldol Condensation

Although asymmetric aldol condensations have been achieved for many years using methodologies in which the chiral information is covalently bound to one of the reacting species (substrate, auxiliary or reagent control), a catalytic approach to this problem has only recently been successful. Yamamoto has used the chiral acyloxyborane (CAB) complex **113** in a catalytic asymmetric version of the Lewis



Scheme 33

acid mediated Mukaiyama condensation of silyl enol ethers and ketene acetals⁶¹. As illustrated in Scheme 34, aldol condensations carried out in the presence of 20 mol % of CAB catalyst **113** proceeded in good yield and with excellent relative and absolute stereocontrol. In fact a wide range of silyl enolates and aldehydes undergo similar reaction with a good selectivity that is independent of the geometry



Scheme 34

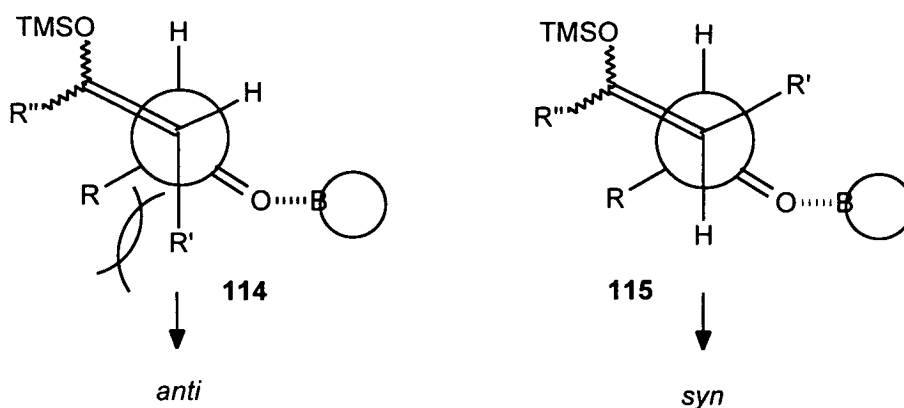
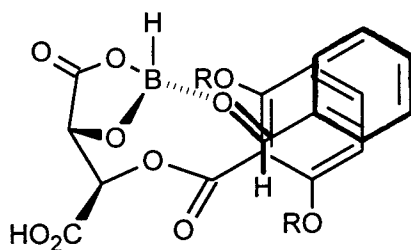


Figure 5

of the enol component. An acyclic transition state such as **115**, as opposed to **114** (Figure 5) has been proposed to explain the high relative stereochemical control. Asymmetric induction in this transition state is believed to stem from shielding of one face of the aldehyde by the aromatic ester as in **116**. This is believed to control the face of the enol that reacts due to the preference for a *syn* product. It has been suggested that π -stacking effects may be operating and a transition state such as **116** has been proposed for the reaction with benzaldehyde. However, this argument is tempered by the findings that even simple aliphatic aldehydes show good selectivity in this reaction. In essence, the reaction shows the power of this catalyst, which is uncommon in that it is capable of introducing asymmetry in a number of different reaction types.



116

1.3 Asymmetric Synthesis of γ -Lactones

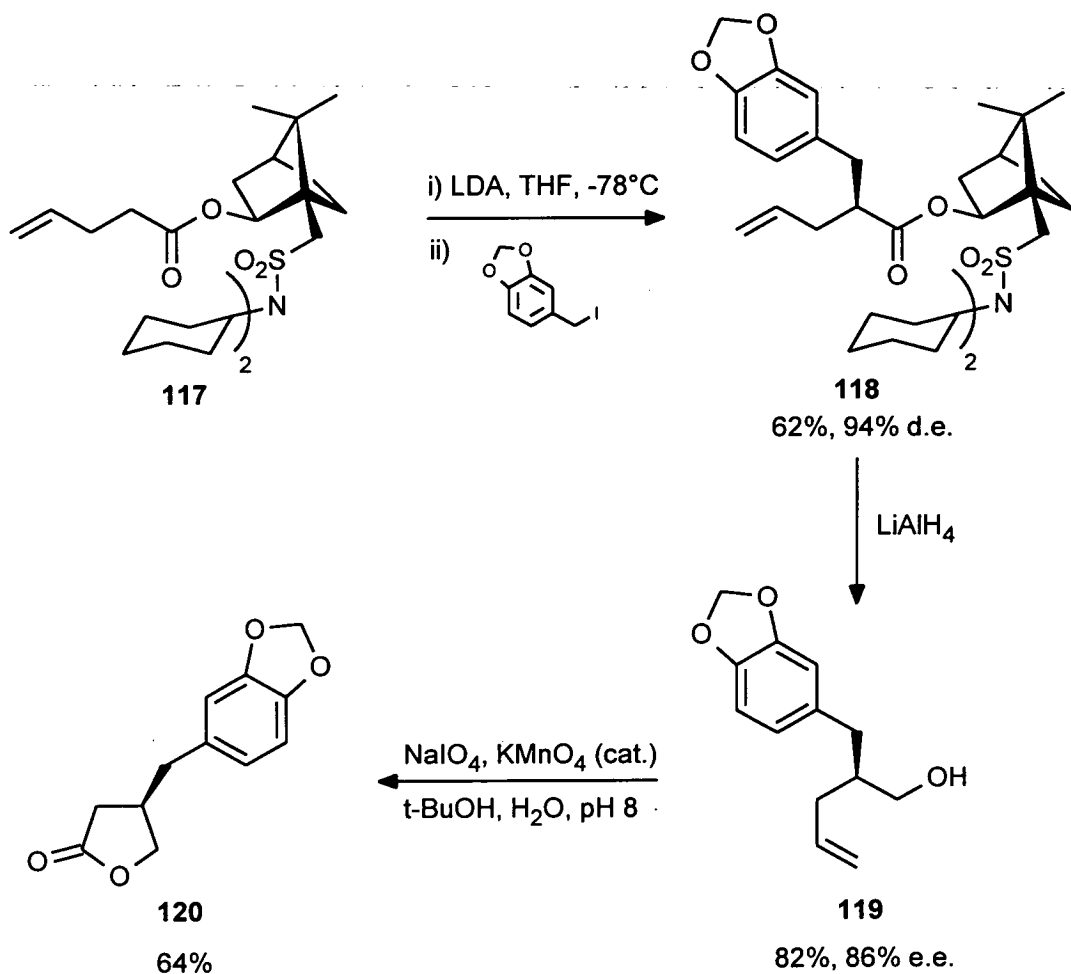
As the latter part of this thesis is concerned with the asymmetric synthesis of polysubstituted γ -lactones, it seemed pertinent include a short review of some of the methods available for the enantioselective synthesis of such compounds. In view of the importance of the γ -lactone functionality in natural products, and the subsequent quantity of work that has been carried out on their asymmetric synthesis, it would be impossible to present a complete review here. Instead, a small number of syntheses of γ -lactones bearing one, two and three chiral centres, respectively will be discussed. In particular, attention will be focused on the use of chemical methods of asymmetric induction to form such chiral centres, but the importance of biological and 'Chiral Pool' approaches will also be highlighted. A number of other γ -lactone syntheses are also discussed in other sections and these are cross referenced.

1.3.1 Asymmetric Synthesis of γ -Lactones Possessing One Chiral Centre

1.3.1.1 Synthesis of a Simple β -Substituted γ -Lactone

A simple synthesis β -substituted γ -lactones in a non-racemic fashion is illustrated by the use of Oppolzers' dicyclohexylsulphonamide-substituted borneol auxiliary in an asymmetric alkylation reaction. Costa⁶² found that compared with alkylation of the corresponding piperonyl acetate ester with allyl bromide (using the opposite enantiomer of the auxiliary) that alkylation of **117** with piperonyl iodide gave the adduct **118** with a considerably better diastereomeric excess (94% vs. 78%). This result was presumed to be due to the greater bulk of piperonyl iodide upon reaction with the intermediate enolate. The alcohol **119** was obtained by reductive cleavage

of **118** with lithium aluminium hydride and was shown to have an enantiomeric excess of 86% by examination of its acetate in the presence of the chiral shift reagent $\text{Eu}(\text{hfc})_3$. Subsequent oxidation of the unsaturated alcohol **119** under Leumieux-Ruddoff conditions afforded the *R* (+)- γ -lactone **120**, a key intermediate in lignan synthesis, in 31% overall yield.

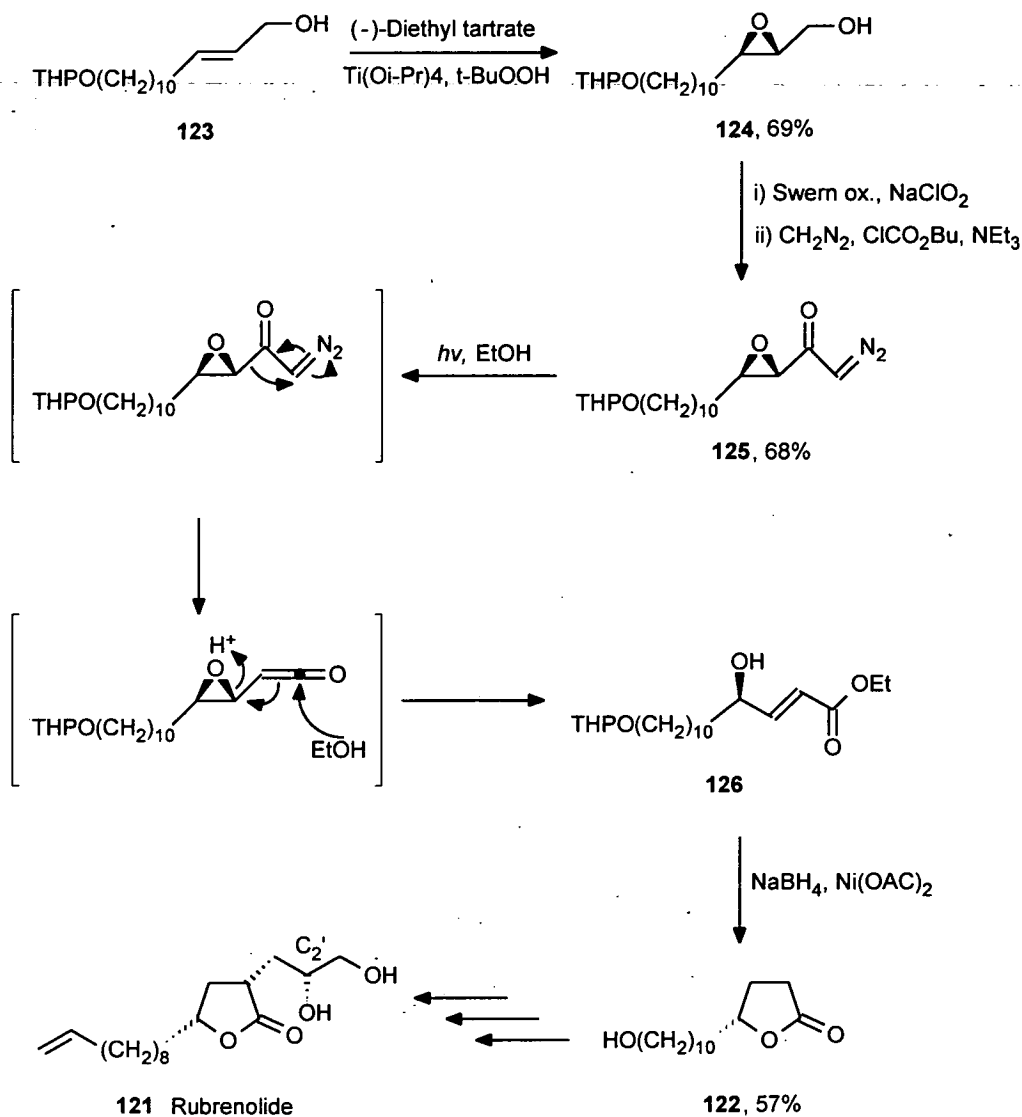


Scheme 35

1.3.1.2 Synthesis of a Simple γ -Substituted γ -Lactone, a Precursor to

Rubrenolide

In the synthesis of the γ -lactone rubrenolide **121**⁶³, the γ -substituted γ -lactone **122** was the key intermediate, and was obtained by a route dependent on the author's own novel photo-induced rearrangement α,β -epoxy diazomethylketones to produce γ -secondary α,β unsaturated alcohols⁶⁴. Initially the γ -chiral centre was produced *via*



$[\alpha]_D^{20} = +21.2^\circ$ (CHCl₃), (Lit. $+21^\circ$)

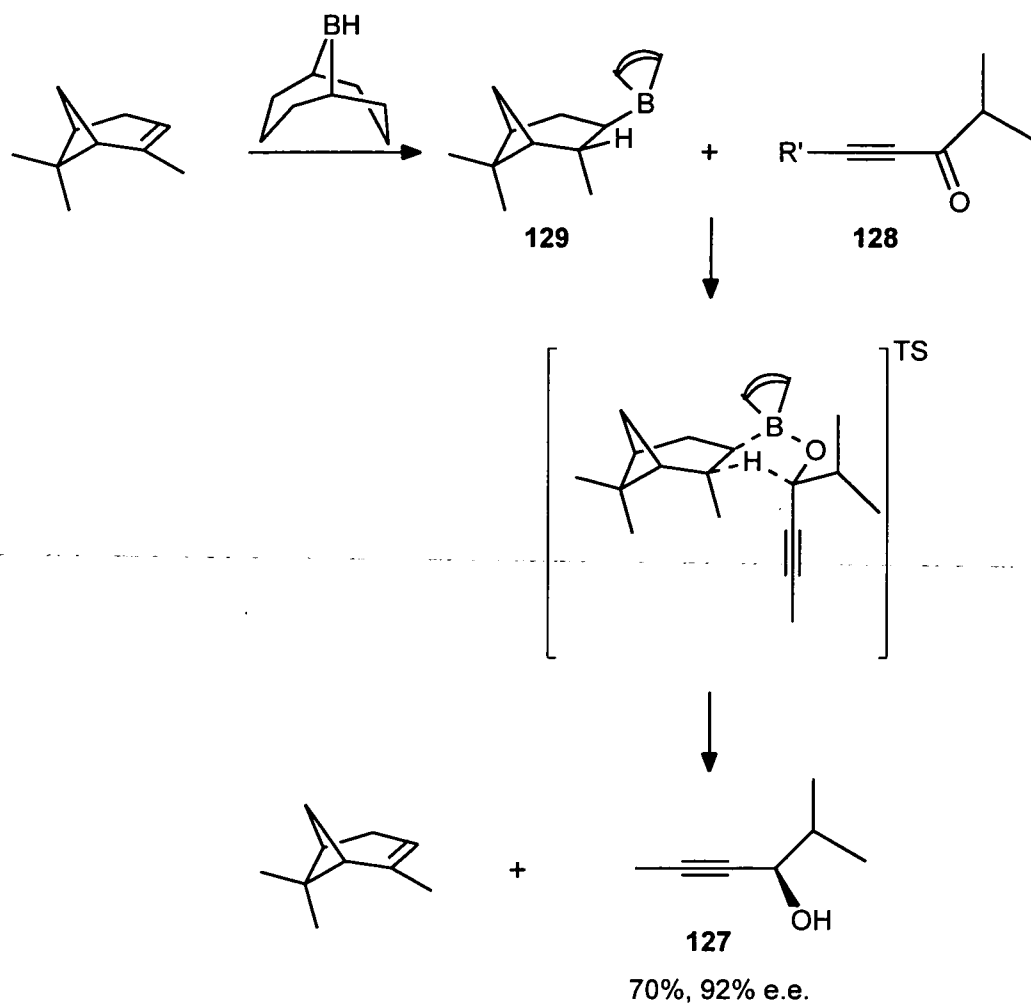
Scheme 36



Sharpless epoxidation⁵⁴ of the allylic alcohol **123** to give the *R,R*-epoxy alcohol **124**. Thereafter a two-stage oxidation yielded the corresponding acid, which on condensation with diazomethane provided the α,β -epoxy diazomethylketone **125**. Upon irradiation the latter underwent a Wolff rearrangement to give the epoxy-ketene, solvolysis of which proceeded with rearrangement and loss of chirality at the β -centre to provide the unsaturated γ -hydroxy ester **126**. Reduction and acidic work-up provided the desired lactone **122** in 27% overall yield from the allylic alcohol **123**. The synthesis of the natural enantiomer of rubrenolide **121**, was completed by the introduction of the side chain and in doing so, disproved the original assignment of stereochemistry at C₂.

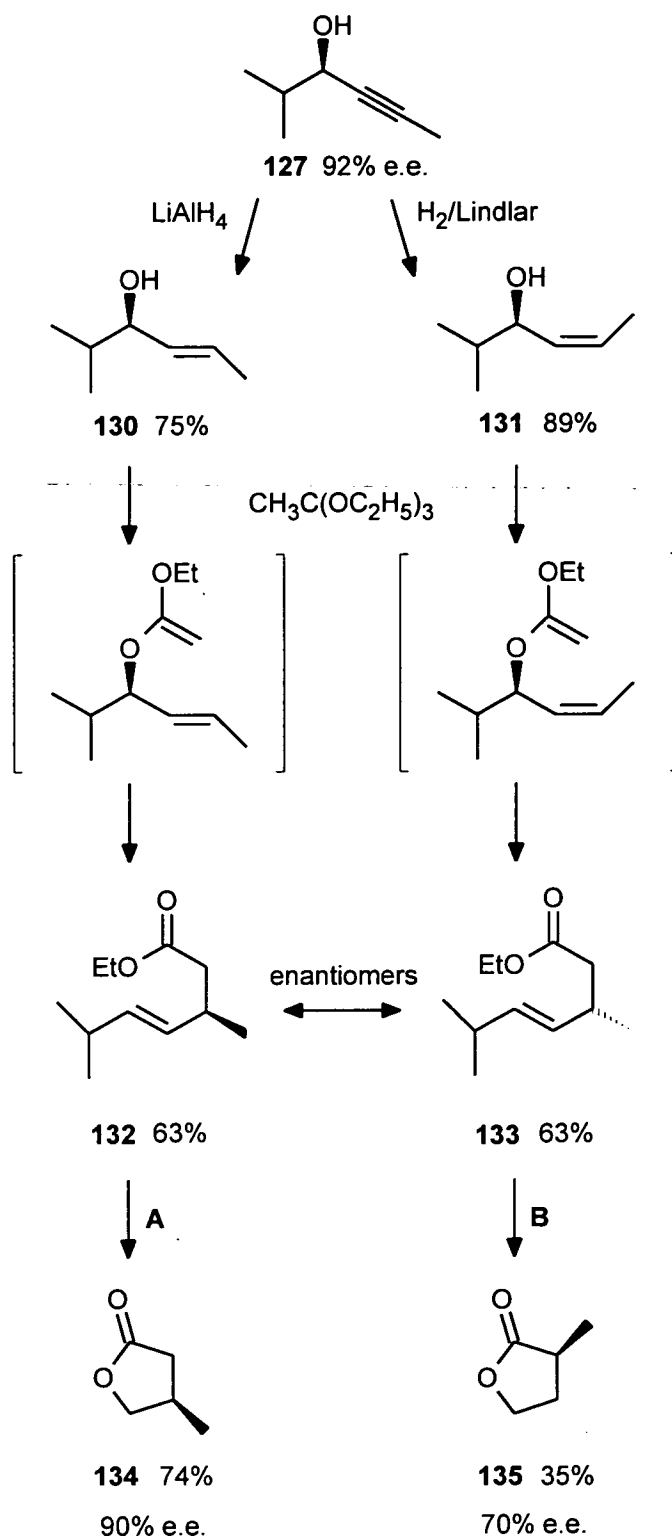
1.3.1.3 A Divergent Synthesis of Either Enantiomer of Simple α - or β -Substituted γ -Lactones

Midland has described a highly versatile route to either enantiomer of both α - and β -mono-substituted lactones, starting from the same enantiomerically enriched propargylic secondary alcohol **127** (92% e.e.)⁶⁵. This was prepared by asymmetric reduction of the ketone **128** using *B*-3-pinanyl-9-BBN **129** (Alpine borane) which proceeds via the transition state shown in Scheme 37. It should be noted that α -pinene of only 92% e.e. was used in the synthesis, however, since enantiomerically-pure α -pinene is commercially available⁶⁶ this and all other enantiomeric excesses mentioned henceforth could be increased accordingly. The versatility of the synthesis comes from the use of a Claisen-Cope rearrangement of the partially reduced enol ethers of the allylic alcohols **130** and **131**. Thus, a choice of reduction conditions gave rise to either an *E*- or *Z*-alkene, and subsequently led to transfer of



Scheme 37

chirality with either retention or inversion of the sense of the stereocentre. The final variation of changing the reduction/oxidation order of esters **132** and **133** allows access to either enantiomer of α - or β -substituted γ -lactones **134** and **135** with 90 and 70% e.e., respectively. Chirality transfer *via* the Claisen-Cope rearrangement was essentially quantitative but racemisation was noted to occur in route **B** during the final oxidation step. It should be noted that the alkyl substituent of the propargylic alcohol (Pr^i) which is lost in the final steps was chosen to give the greatest combination of asymmetric induction upon reduction and stereochemical integrity during the subsequent chirality transfer.

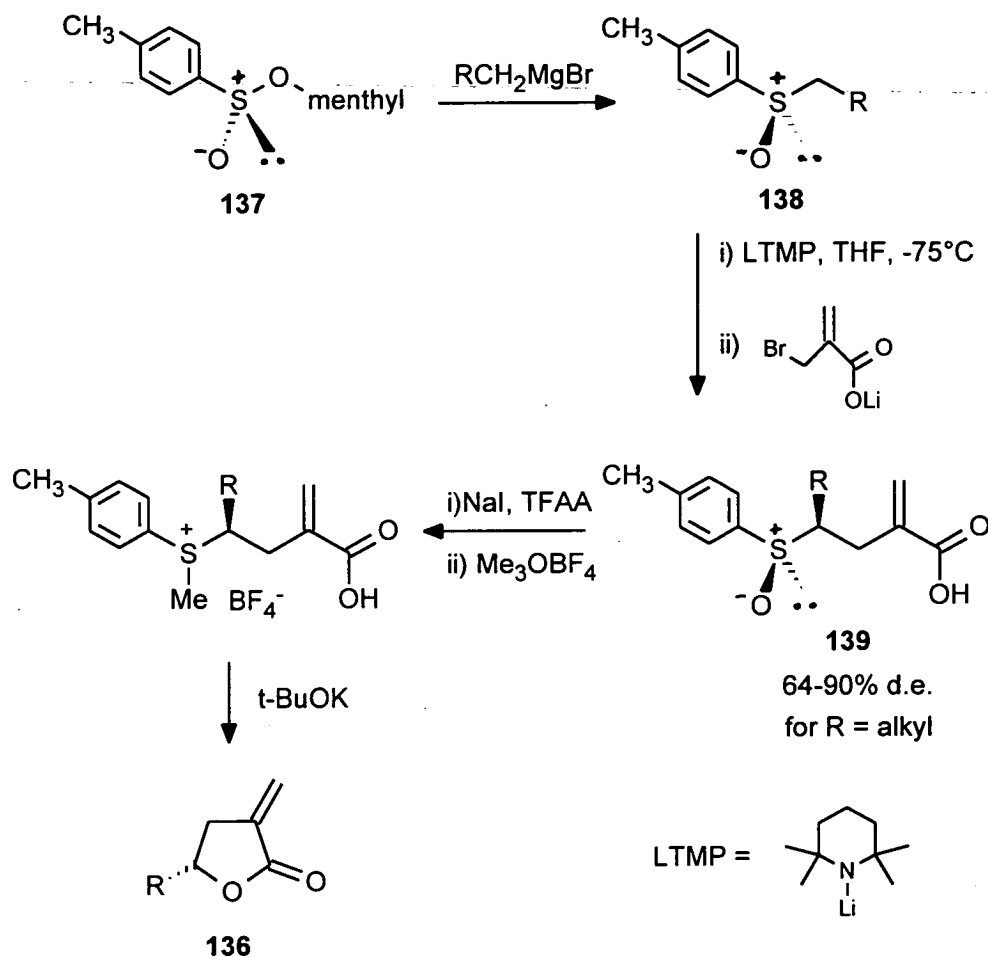


Conditions : A : O_3 then NaBH_4 . B : i) LiAlH_4 ; ii) O_3 then Me_2S ; iii) CrO_3 , H_2SO_4 , Me_2CO .

Scheme 38

1.3.1.4 Synthesis of α -Methylene γ -Substituted γ -Lactones

Due to their biological properties (2.7.1) and their occurrence in many natural products, α -methylene γ -lactones are very significant targets for asymmetric synthesis. Bravo⁶⁷ has developed an efficient route to chirally pure γ -substituted α -methylene γ -lactones **136** based on the diastereoselective alkylation of chiral non-



Scheme 39

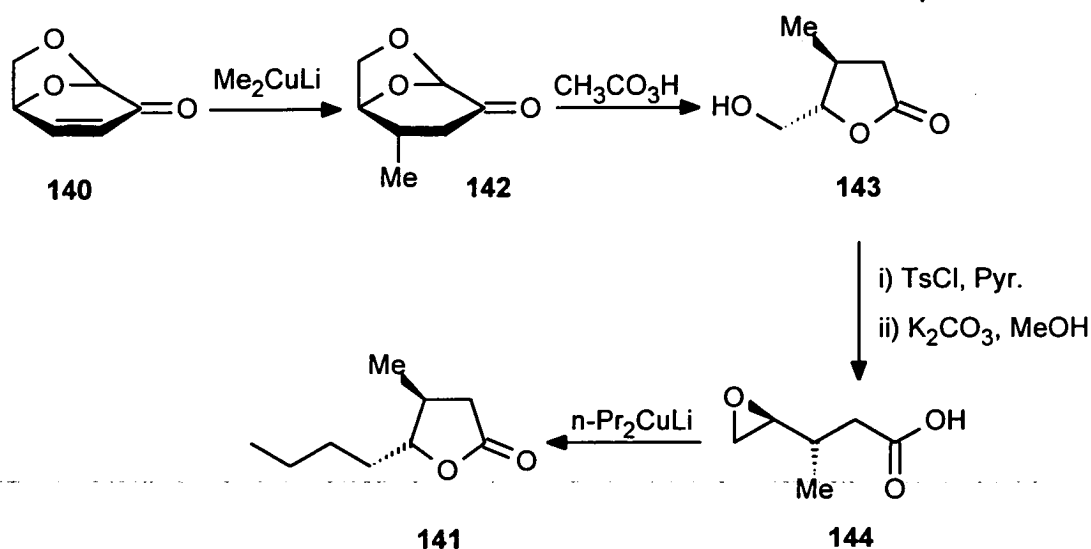
racemic sulfoxides. The sulfoxides **138** were formed from (-)-*S*-menthyl-*p*-toluene sulphinates **137** and deprotonated with lithium tetramethyl piperidide (LTMP) which gave better selectivity than use of LDA. Alkylation with lithium α -

bromomethacrylate proceeded with moderate to good diastereoselection and the resulting diastereomers of **139** were readily separated by chromatography. A sequence of reduction, *S*-methylation and base-induced intramolecular displacement of the sulphonium group (with inversion of configuration) furnished the optically pure lactones **136** in good overall yield (48-55%).

1.3.2 Asymmetric Synthesis of γ -Lactones Possessing Two Chiral Centres

1.3.2.1 A 'Chiral Pool' Approach to *trans*-Whisky Lactone

Ebata has used the readily available homochiral starting material, levoglucosonide **140**, in the synthesis of a number of β,γ -substituted γ -lactones including *trans*-whisky lactone **141**⁶⁸. The chiral building block, formed by pyrolysis of cellulose, is first treated with the Gillman reagent which adds in a stereoselective manner to the α -face of the enone moiety to give **142**. This creates the two chiral centres of the natural product, the lactone system **143** being revealed by oxidative cleavage of the protected keto-aldehyde with peracetic acid. After formation of the tosylate, direct organometallic coupling may have been possible, but the authors elected instead to form the epoxide **144** which was reacted with the relevant dialkylcopperlithium reagent to form the lactone **141** in 37% overall yield from **140**. This route is obviously quite versatile, but although the γ -centre may easily be inverted (Mitsunobu reaction), the β -centre is governed by the starting material which is only available as one enantiomer. It is also evident that by reaction of the enolate formed in the initial 1,4-conjugate addition step with a suitable electrophile, that this route could be extended to the synthesis of γ -lactones with three chiral centres.

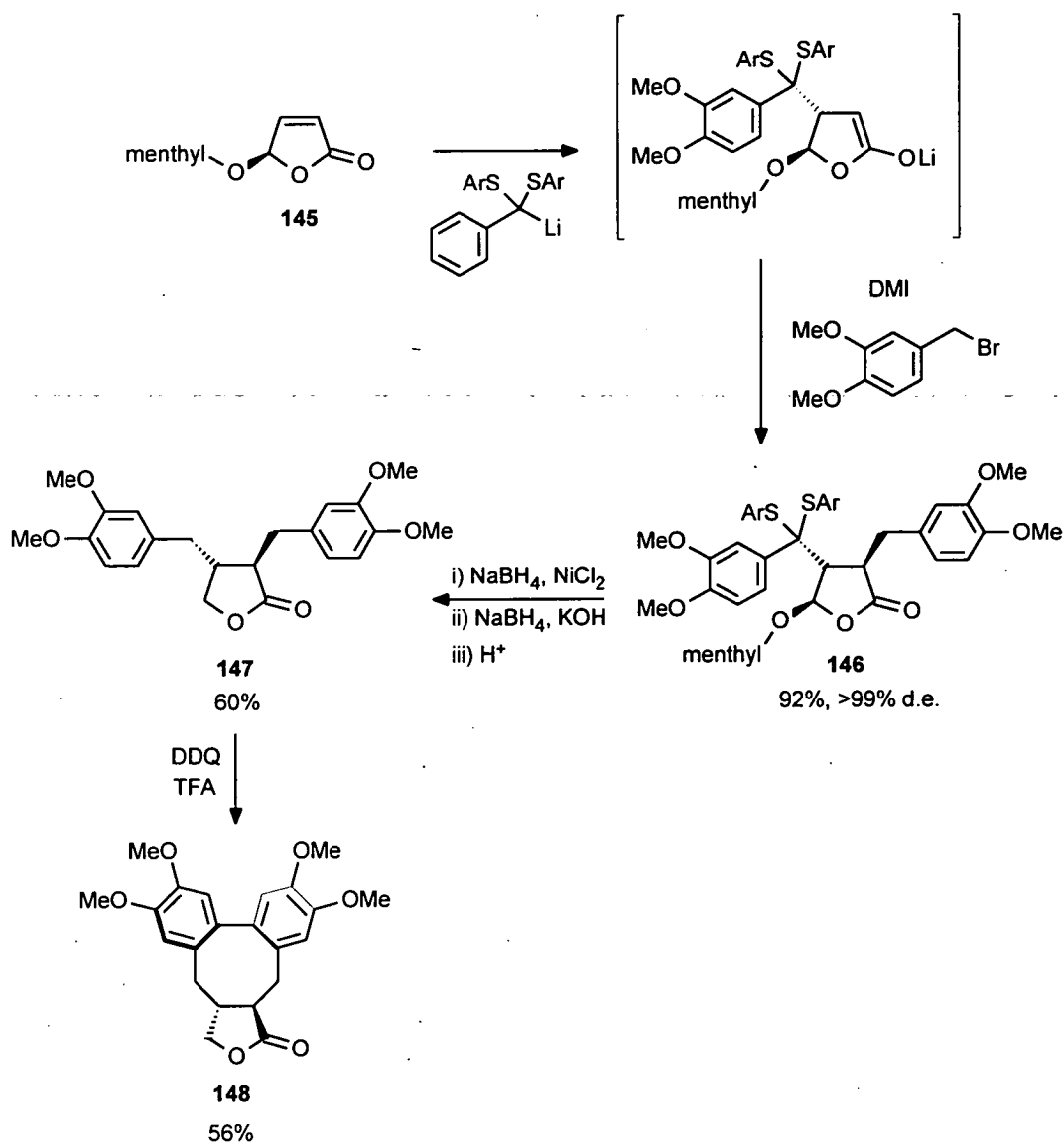


Scheme 40

1.3.2.2 Synthesis of Lignan Lactones *via* a Chiral Michael Acceptor

Pelter⁶⁹ has applied tandem addition of an aromatic dithioacetal anion to the highly stereodifferentiating Michael acceptor 5-(1-menthyloxy)furan-2(5H)-one **145** and trapping of the intermediate enolate with a substituted benzyl halide in the enantioselective synthesis of lignan lactones. The initial Michael addition occurs *trans* to the menthyloxy substituent, and the enolate so formed reacts with an alkylating agent on the face opposite the bulky aromatic dithioacetal. The resulting *trans, trans*-configuration was verified by the small vicinal ¹H coupling constants of the respective methines. The adduct **146** was reductively desulphurised and cleaved reductively from the menthol auxiliary to form the *trans*-di-substituted lactone **147**. Owing to the stereochemistry of the lactone, oxidative coupling of the aromatic rings by DDQ in TFA gave a single plane of chirality in the diphenyl unit. Thus, (+)-5-

detigloyloxysteganolide **148** was obtained in 31% overall yield by a four-pot reaction sequence.



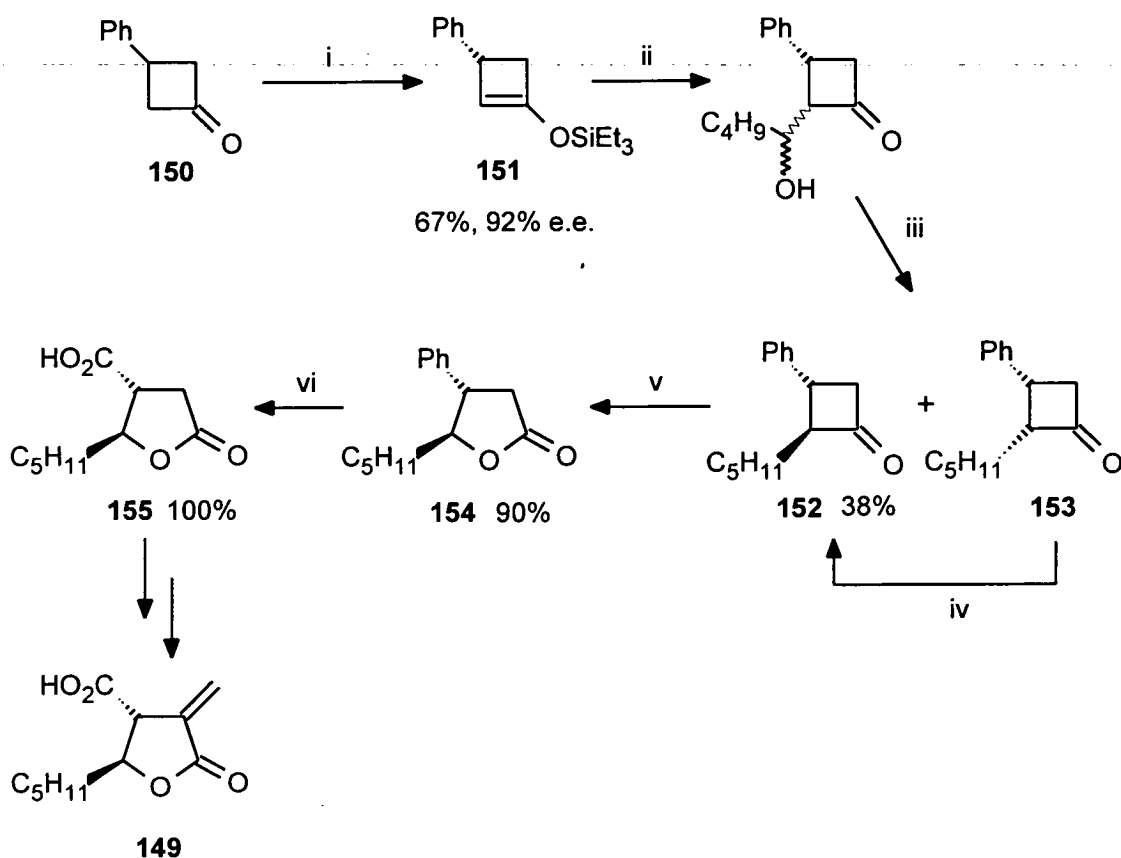
Scheme 41

1.3.2.3 Synthesis of an α -Methylene β,γ -Di-substituted γ -Lactone *via* HCLA

Methodology

Honda⁷⁰ has used deprotonation of symmetrical 3-substituted cyclobutanones with a homochiral lithium amide (HCLA) base, combined with oxidative cleavage of the

four membered ring in the synthesis of a number of enantiomerically pure substituted γ -lactones, *e.g.* (-)-methylenolactocin **149**, an anti-tumour anti-biotic isolated from *penicillium sp.*, which had previously been synthesised by Greene⁷¹ (see 2.7.2 for a related example). Deprotonation of the cyclobutanone **150** with lithium (*S,S'*)- α,α' -dimethyldibenzylamide, followed by trapping with TES chloride, provided the silyl enolether **151** with 92% e.e. in 67% chemical yield. Aldol condensation and



Conditions : i) lithium (*S,S'*)- α,α' -dimethyldibenzylamide, THF, -100°C, then TESCl; ii) *n*-C₄H₉CHO, TbaF, THF, 0°C; iii) Ac₂O, Pyr., DMAP; then DBU, Δ ; then H₂, Pd/C; iv) cat. NaH, THF; v) H₂O₂, AcOH; vi) RuCl₃, HIO₄.

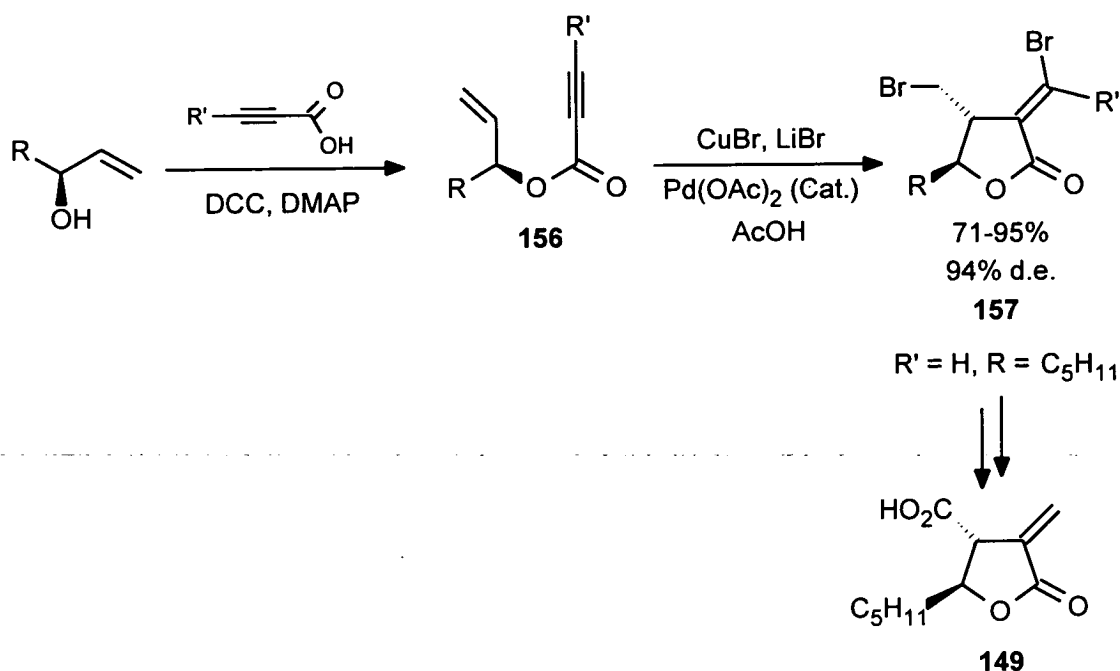
Scheme 42

subsequent elimination, followed by hydrogenation afforded the two diastereomeric cyclobutanones **152** and **153** in a *ca.* 2:1 ratio. This mixture was equilibrated to 20:1 before Baeyer-Villiger oxidation to the lactone **154** which was purified by chromatographic removal of the minor *cis*-isomer. Oxidative cleavage of the phenyl group under Sharpless conditions⁷² gave the paraconic acid **155**, an intermediate in Greene's synthesis of **149**, in 23% overall yield. Finally use of the mild α -methylenation procedure developed by Greene was all that was required to obtain **149**.

1.3.2.4 Synthesis of α -Methylene- β,γ -Di-substituted γ -Lactones *via*

Halocyclisation

The majority of syntheses so far discussed have relied on the lactonisation of specifically constructed γ -hydroxy acids, apart from the use of ring expansion *via* Baeyer-Villiger oxidation. Lu has made use of palladium-catalysed halo-cyclisation of allyl 2-alkynoate esters **156** to give a highly stereospecific route to *cis*- β,γ -disubstituted α -alkylidene- γ -lactones **157**⁷³. By the use of readily accessible homochiral allylic alcohols (from reduction of enones and ynones), the procedure provides a rapid access to γ -lactones which can be readily transformed into more highly functionalised molecules *via* the pendant alkyl and vinyl halides. It is worth noting that lower and inverted selectivity was observed with propargylic esters. In a later paper⁷⁴, details have been given of the synthesis of both enantiomers of methylenolactocin **149** from each enantiomer of oct-1-en-3-ol in 15% overall yield.



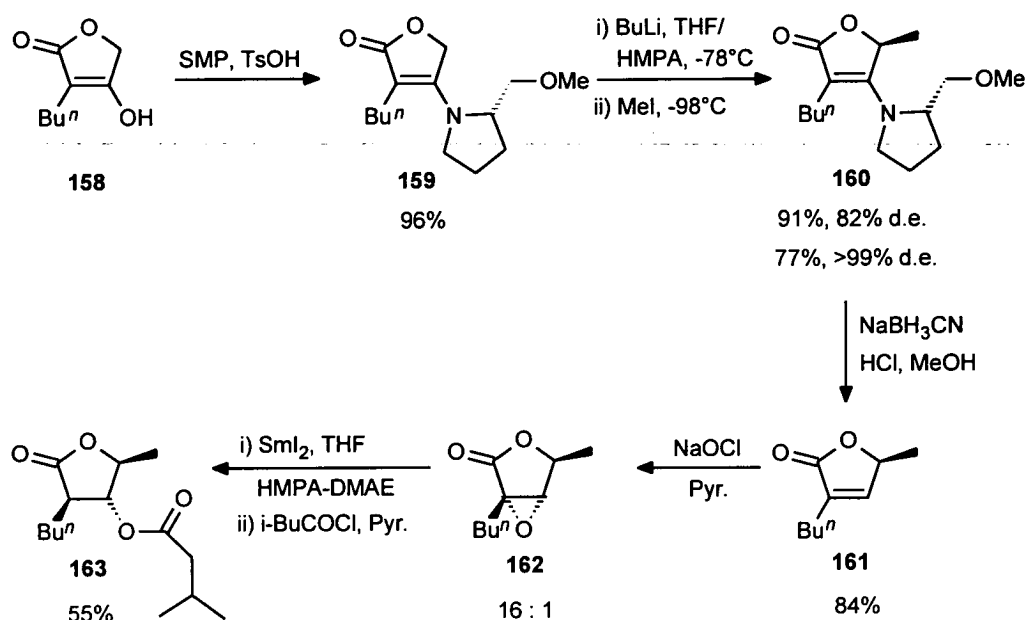
Scheme 43

1.3.3 Asymmetric Synthesis of γ -Lactone Possessing Three Chiral Centres

1.3.3.1 Total Synthesis of Blastmycinone

Node has made use of the readily available chiral auxiliary (*S*)-2-methoxymethylpyrrolidine (SMP)⁷⁵, to control the regio- and stereo-selectivity of alkylation of α -butyltetronic acid **158**, synthesised from tetronic acid by the method of Ramage⁷⁶. Upon deprotonation of the enamine **159**, it is believed that the C $_{\alpha}$ -lithium tautomer **B** is favoured due to chelation from methoxy group on the auxiliary over the O-lithium furan structure **B** (Figure 6). Consequently, alkylation is directed

to this face to give **160** from which the auxiliary was reductively cleaved to provide the γ -substituted butanolide **161**. Stereoselective epoxidation, followed by regiospecific reductive ring-opening of the epoxide **162** with samarium(II)iodide furnished the skeleton of (+)-blastmycinone, which required only esterification to provide the target **163** in 22% yield, in six steps.



Scheme 44

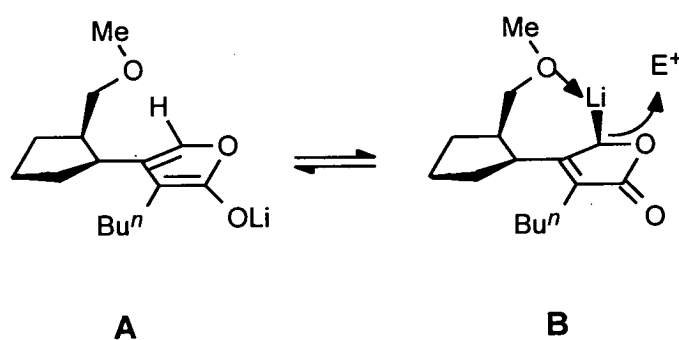
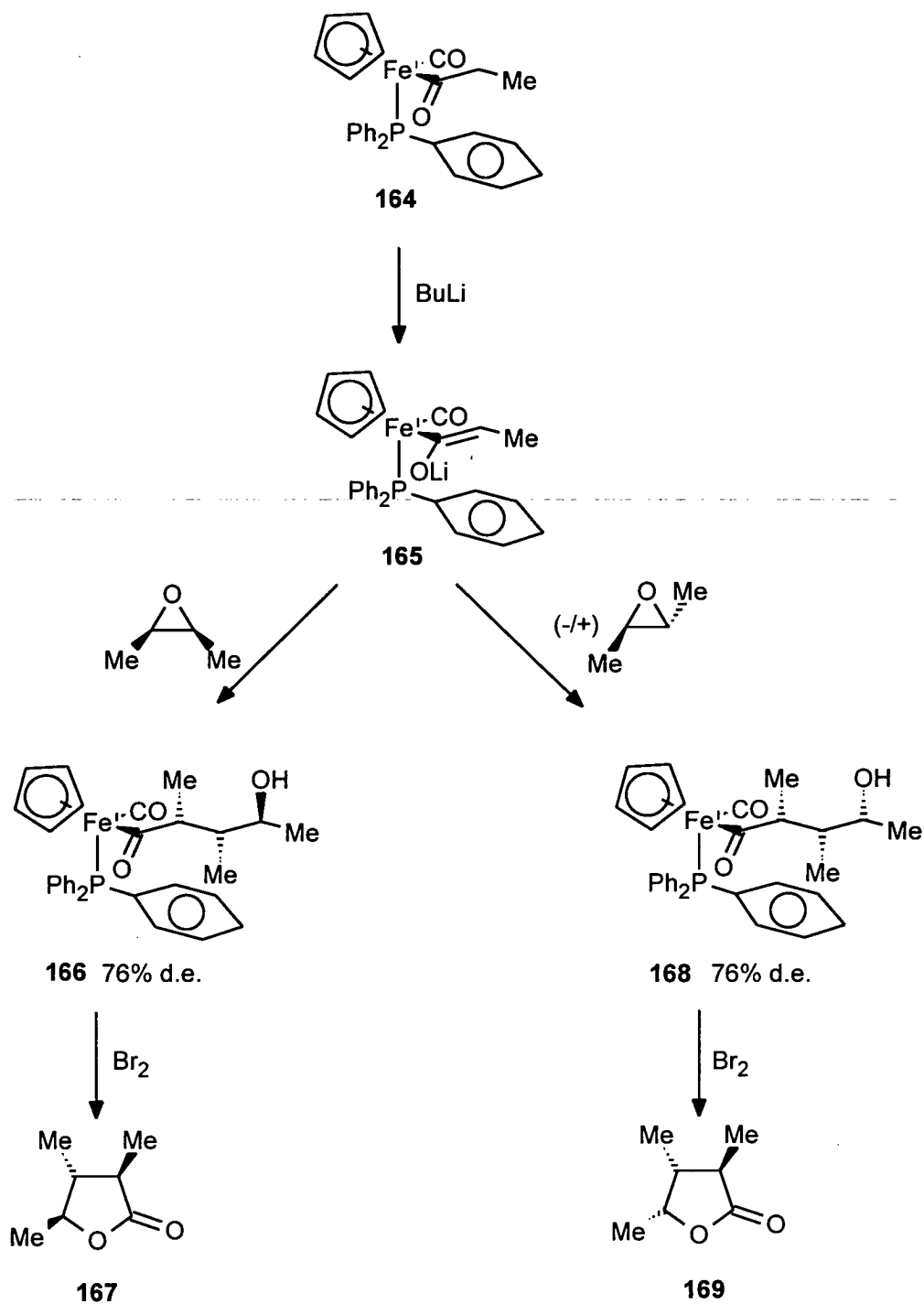


Figure 6

1.3.3.2 Chiral Recognition in the Synthesis of Tri-substituted γ -Lactones

Davies has used his chiral iron auxiliary in the formal enantioselective synthesis of mono-, di- and tri-substituted γ -lactones⁷⁷. The respective papers describe the use of the racemic auxiliary, but since both enantiomers of the auxiliary are readily available, individual synthesis of each enantiomer is possible. In Scheme 45 all structures are shown for the *R*-auxiliary. Thus, deprotonation of the propionyl derivative **164** with butyl-lithium gave the expected *Z*(*O*) enolate **165** which was reacted with *meso cis*-but-2-ene oxide to furnish the adduct **166** with 76% d.e. The major diastereomer was isolated by chromatography and upon oxidation, cleavage occurred to give the tri-substituted lactone **167**. This result shows that the *R*-enolate **165** prefers to react with the *R*-centre of the *meso*-epoxide. Reaction with racemic *trans*-but-2-ene oxide provided the adduct **168** with an identical d.e., which was cleaved to give the lactone **169**. This demonstrated that the enolate has reacted preferentially with *R,R-trans*-but-2-ene oxide and pointed to a transition state similar to that of the reaction above. This property of chiral recognition is a hallmark of this auxiliary, which has also proved effective in the synthesis of γ -, α,γ - and β,γ -substituted γ -lactones as described in further publications. The preference for reaction with a *R*-epoxide centre is thought to be due to avoidance of steric interaction between the methyl group on the epoxide and the iron centre of the auxiliary, as shown in Figure 7.



Scheme 45

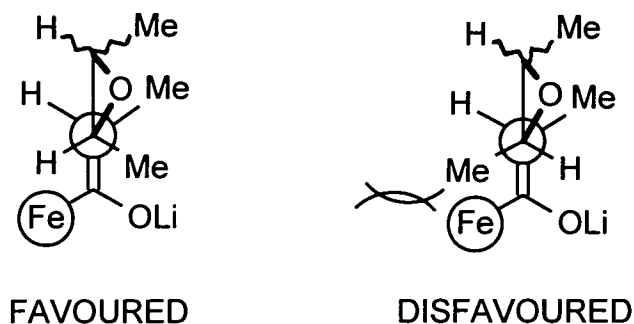
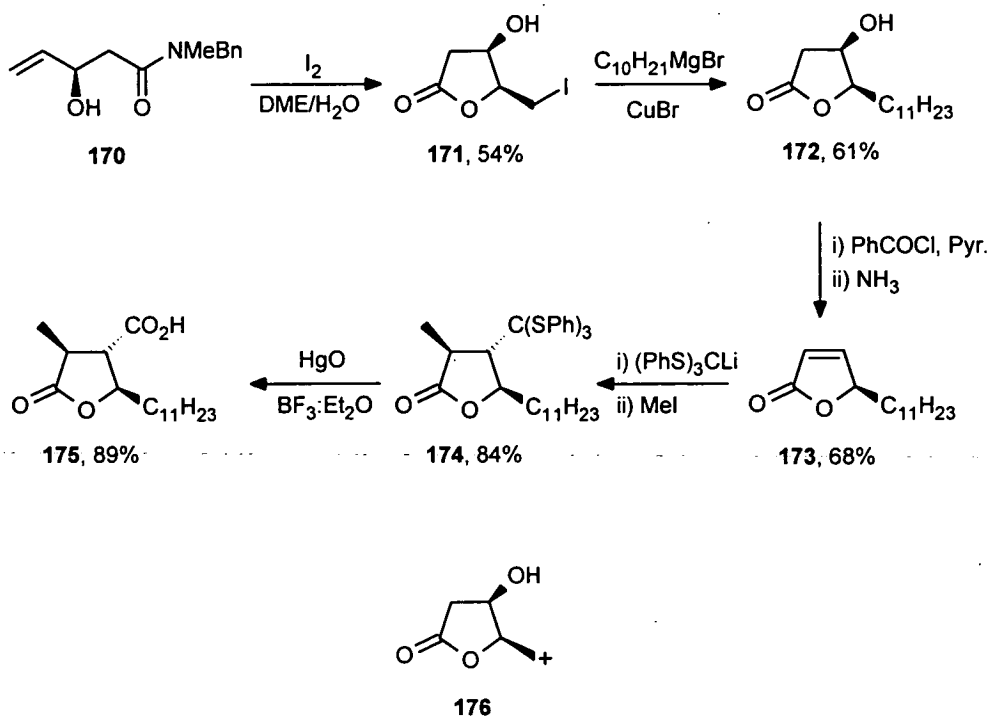


Figure 7

1.3.3.3 Tri-substituted γ -Lactones *via* a Chiral Butenolide Synthon

An important method of enantioselective synthesis of tri-substituted γ -lactones is the use of chiral butenolides (*cf.* 1.3.2.2). Takahata's synthesis of nephrosteranic acid shown in Scheme 46 illustrates this approach⁷⁸. The chiral starting material, (*R*)-*N*-benzyl-*N*-methyl-3-hydroxy-4-pentenamide **170**, was obtained from a racemic mixture *via* enzymatic resolution. The unwanted (*S*)-enantiomer was converted into its acetate using a lipase and vinylacetate, and then removed to give a 44% yield of **170** with 99% e.e.. Iodolactonisation of the latter yielded the *cis*-lactone **171** due to the directing effect of the allylic hydroxyl group. Coupling of this compound with a Grignard-derived cuprate gave a good yield of **172**, which was then subjected to a two-step elimination process to furnish the homochiral butenolide **173**. Conjugate addition of the anionic carboxylate synthon, tris(phenylthio)methyl lithium, to **173** followed by enolate trapping with methyl iodide provided a good yield of the adduct **174** with 96% e.e. (by HPLC). The C₄-stereocentre has thus been used to control the absolute stereochemistry at the C₂- and C₃-stereocentres with excellent *trans*-, *trans*-



Scheme 46

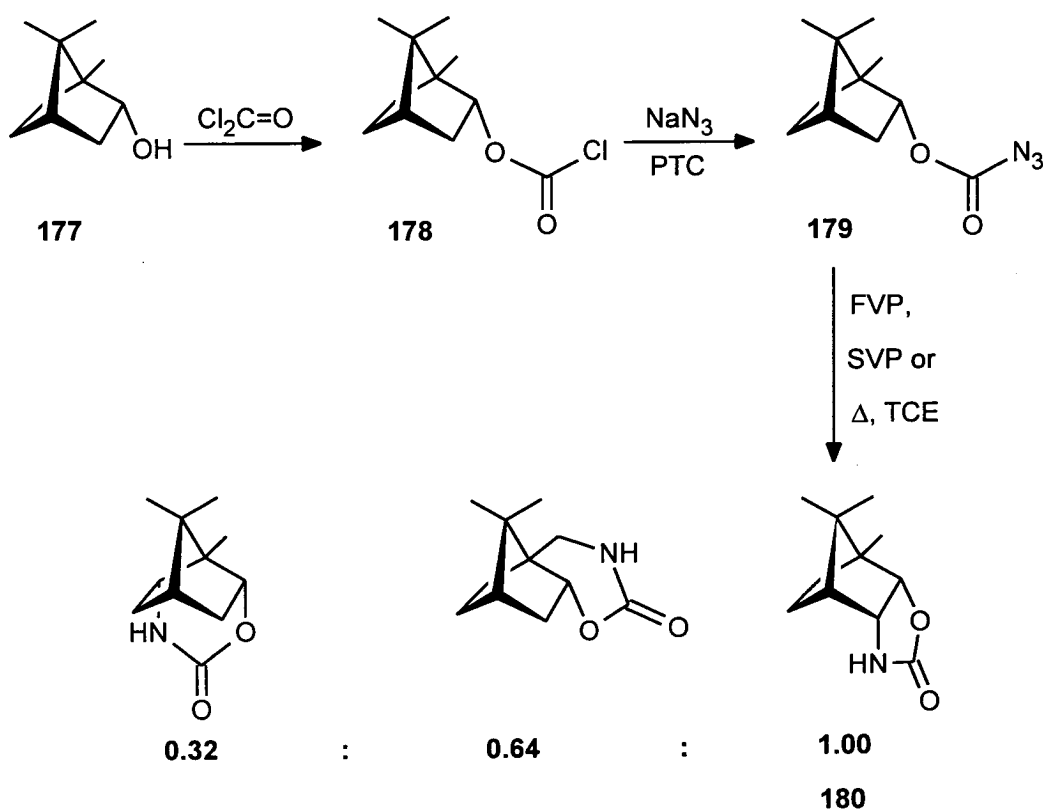
selectivity. Subsequent desulphurisation yielded the target material, nephrosteranic acid **175**, in 17% overall yield from **170** and with 98% e.e. Thus the compound **171** can be considered as a highly stereodifferentiating equivalent to the synthon **176**

2 Discussion

2.1 The Conception and Synthesis of a Camphene-Derived Chiral Auxiliary

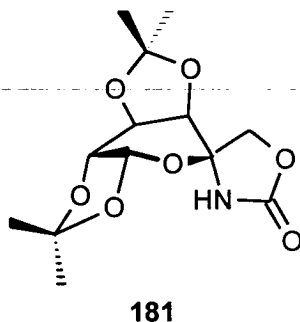
2.1.1 Chiral Auxiliaries Derived From Chiral Alcohols *via* Nitrene Insertion

During investigations of the potential of an enantioselective nitrene insertion reaction by Thomson⁷⁹, Dawson observed the formation of intramolecular nitrene insertion products from the bornyl azidoformate **179** upon heating. Speculating on the potential of these products as chiral auxiliaries (in particular **180**), Dawson and Banks⁸⁰ developed an effective route to these compounds, shown in Scheme 47. In view of the considerable quantities of **180** that could be easily obtained in a pure state from readily available borneol **177**, it was decided to undertake an investigation into its utility as chiral auxiliary.

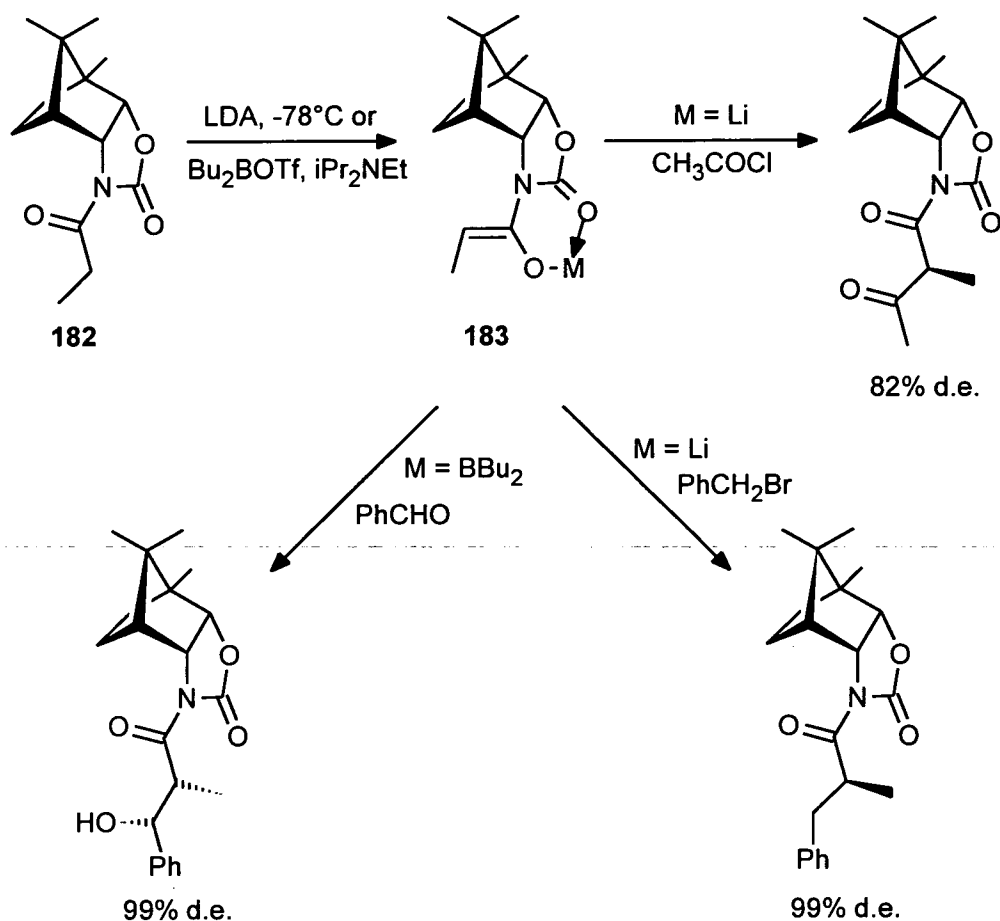


Scheme 47

Following the discovery and elaboration of this route to chiral oxazolidin-2-one and oxazin-2-one auxiliaries from other chiral alcohols, a large number of auxiliaries have been synthesised and evaluated. This work has been carried out by the former and then latterly by Gaur^{4, 81}, Grant^{5, 82} and MacDougal⁸³. The most useful of these have been **180** (Chirabornox) and **181** (Chiragalox) which is galactose based.

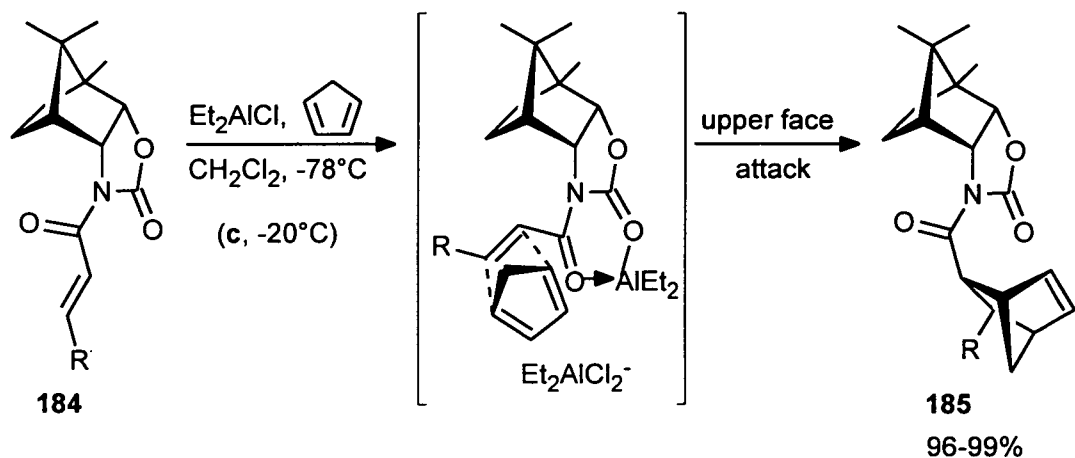


A thorough evaluation of **180** and **181** has shown that although these reagents have proved to be effective for the control of stereochemistry in many reactions neither possesses the desirable broad scope of utility which could be hoped for. Thus, **180** has proved to be highly effective in controlling the stereochemical outcome of alkylation and acylation reactions of lithium enolate **183** ($M = Li$) of the propionyl derivative **182**. Furthermore the stereoselectivity of aldol condensations of the boron enolate **183** ($M = BBU_2$) are also controlled by the asymmetric bias of Chirabornox (Scheme 48). However, the synthetic utility of the enoyl derivatives **184a-c** in Lewis-acid catalysed Diels-Alder reactions is low except where the β -carbon bears a large group (*e.g.* for phenyl), and consequently, adducts **185a & b** are formed with low to moderate diastereomeric excesses. (Scheme 49).



Scheme 48

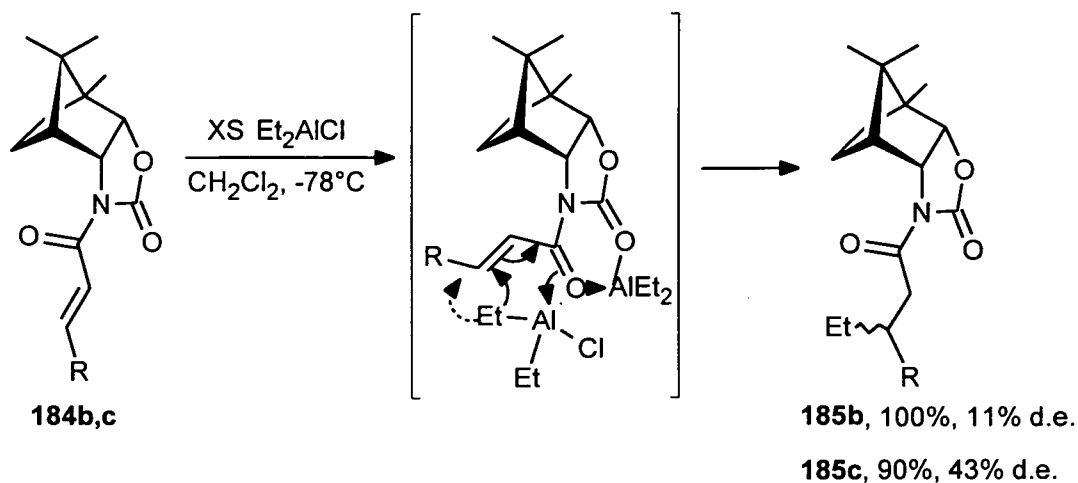
The low specificity of the Diels-Alder reaction is considered to be due to the inability of the auxiliary to control the rotamer preference of the $\text{C}_\alpha\text{-C=O}$ bond effectively, thus allowing each face of the unsaturated system to be exposed to the incoming enophile. For similar reasons, 1,4 conjugate additions to these systems show extremely poor diastereoselectivity as witnessed by the conjugate addition of diethylaluminium chloride to **184b** & **c**, which proceeded to give β alkylated products **186b** & **c** with only 11% and 43% d.e., respectively (Scheme 50).



		<i>endo:exo</i>	d.e., <i>endo</i>
185a	R = H	96:4	59%
185b	R = CH ₃	100:0	71%
185c	R = Ph	100:0	99%

Scheme 49

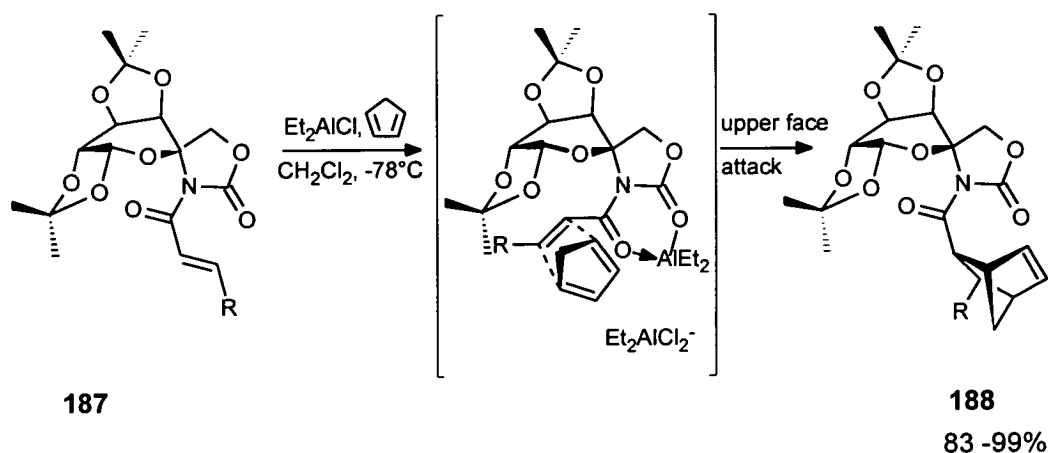
From these results it was obvious that **180** does not have suitably placed steric controlling groups that can both influence the preferred rotamer (in derivative **184**) and effectively shield one face of the prochiral function^{5, 82}. Thus, an obvious quality for an improved chiral auxiliary is to have bulky groups which are capable of not only limiting



Scheme 50

the conformational freedom of the reactive functionality, but simultaneously blocking one face to an incoming reagent.

To a considerable extent these desires were achieved with the design and synthesis of Chiragalox **181**. The performance of its enoyl derivatives in Lewis-acid catalysed Diels-Alder reactions with cyclopentadiene was considerably better than those derived from **180**, and in the case of 1,4-conjugate addition reactions of diethylaluminium chloride, a d.e. that would be synthetically useful was obtained. It can clearly be seen in Scheme 51, that in the chelated intermediate the conformation of the alkene moiety is controlled by both the pyranose ring and an isopropylidene acetal



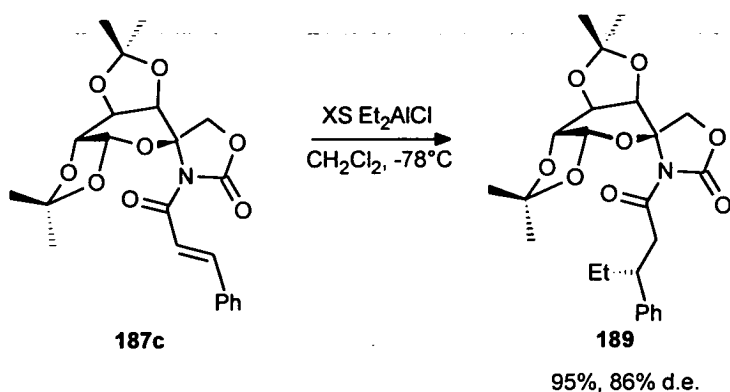
		<i>endo:exo</i>	d.e., <i>endo</i>
188a	R = H	98:2	80%
188b	R = CH ₃	99:1	82%
188c	R = Ph	98:2	92%

Scheme 51

function. Facial shielding is also provided by these groups and because of the favourability of the diene reacting to give an *endo*-adduct due to secondary orbital interactions, it is obvious that one diastereomeric product is strongly favoured. In fact for the Diels-Alder cycloaddition of cyclopentadiene catalysed by

diethylaluminium chloride, there is little room for improvement except in the case of the acryloyl derivative **187a**.

That the facial shielding is now effecting the β prochiral centre is demonstrated by the dramatic increase in the selectivity of the conjugate addition of diethylaluminium chloride to **187c** to a more useful d.e. of 86%. Obviously similar interactions to those encountered in the Diels-Alder reaction now provided a defined transition state for this less sterically demanding reaction.

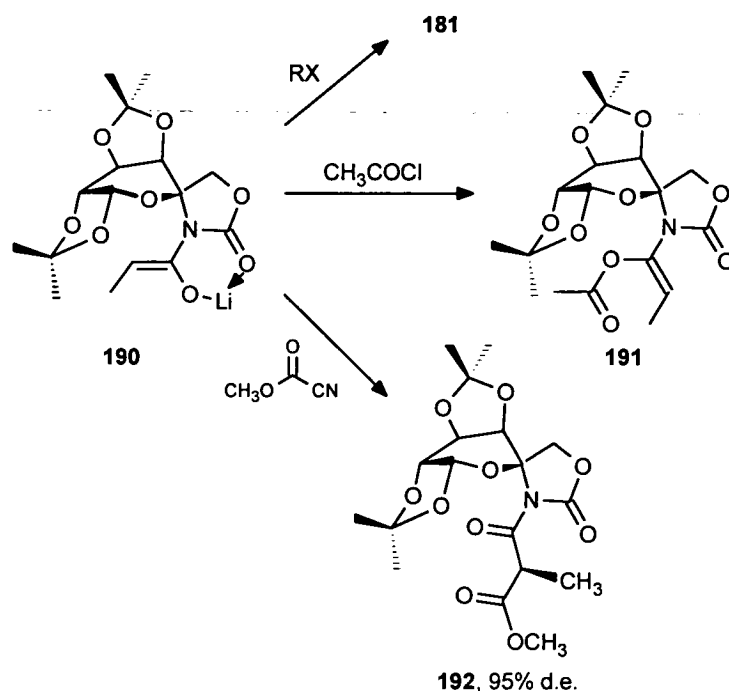


Scheme 52

A major limitation of **181** as a widely applicable chiral auxiliary is its poor performance in enolate chemistry. Thus, excluding the case of the exceptional lithium-mediated aldol condensations^{4, 81}, metal enolates bearing **181** are almost universally ineffective in the creation of new C α stereocentres by their reaction with a wide range of electrophiles.

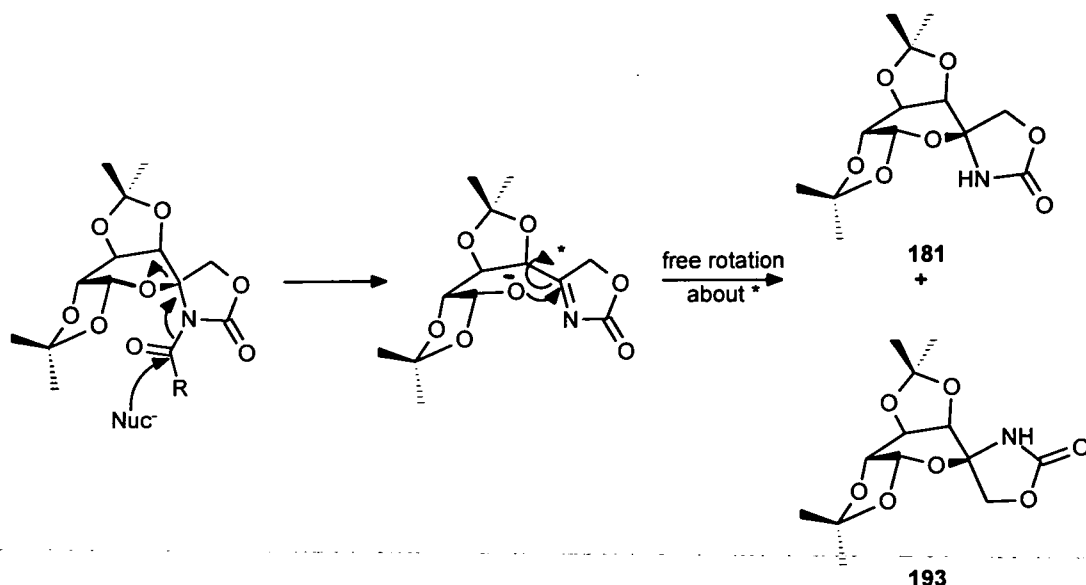
Both lithium- and sodium-enolates *e.g.* **190** failed to react with active alkyl halides such as allyl bromide and benzyl bromide, but instead as the reaction temperature is increased, they decomposed to give the anion of **181** presumably by elimination of methylketene. It is still unclear whether this is due to increased steric effects, metal chelation to acetal and/or pyranose oxygens, or some form of electronic effect. Whatever effect has caused the change in reactivity of these enolates, it has certainly altered their pattern of reactivity when more reactive electrophiles are used.

For example, reaction with acyl chlorides led exclusively to *O*-acylated products **191** and thus failed to generate a new stereocentre. Only in the case of reaction with the highly *C*-selective reagent methylcyano formate (Manders reagent⁸⁴) was a new C_{α} stereocentre generated (**192**) and reassuringly with a high diastereomeric excess. This propensity to undergo *O*-acylation is shown to only a very limited extent in the acylation of the corresponding enolate of **182**.



Scheme 53

A major problem associated with **181** is that upon cleavage of adducts by the routine methods the auxiliary cannot be recovered in a suitable form for reuse. Instead a mixture of **181** and its anomer **193** (ratio 44:56) was obtained from which it proved impossible to separate **181**⁴. A plausible mechanism (shown in Scheme 54) for this process is the cleavage of the pyranose ring to give the alkoxide anion and a heterocyclic moiety which can undergo free rotation to give either spiro-oxazolidin-2-one upon ring closure. The problems associated with the enolate chemistry of **181** and the inability to recycle it have restricted the utility of this auxiliary.

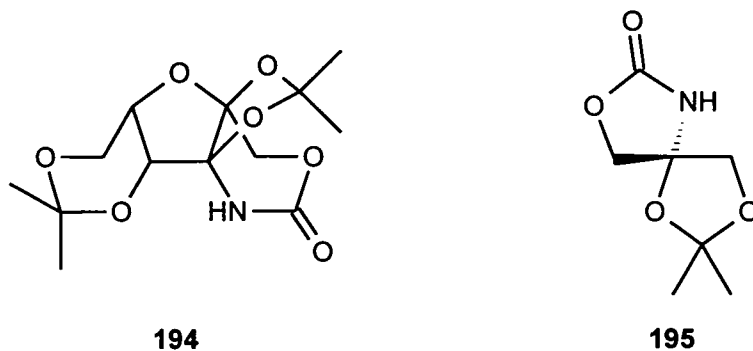


Scheme 54

From the above it appears that to have an effective and broadly applicable chiral auxiliary one requires well situated steric controlling groups and preferably a lack of functionality which can cause unwanted chelation and/or stereoelectronic effects.

2.1.2 Synthesis of Chiracamphox

Potential starting alcohols for chiral oxazolidin-2-one synthesis by the nitrene insertion strategy had for the most part been exhausted by previous workers. Consequently, if this strategy was to be used in the synthesis of an improved chiral oxazolidin-2-one auxiliary then other carefully selected alcohol precursors would need to be examined. A slight deviation towards this pathway had already been made by Gaur⁴ and Banks⁸⁰ with the synthesis of the gluconic acid-derived auxiliary **194** and the solketal-based spiro-oxazolidin-2-one **195** which is ultimately derived from cleavage of *D*-mannitol.



The first compound to be examined was the common unsaturated terpene (+) and (-) camphene **196** (Figure 8), structures which obviously contain a striking asymmetric bias. That this initial choice was so surprisingly successful is witnessed by the fact that the search for further improvements was halted so that the chemistry of one of its oxazolidin-2-one derivatives could be fully investigated.

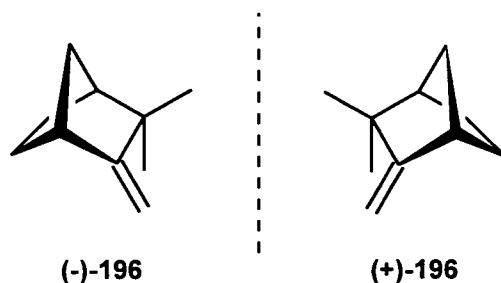


Figure 8

There was one major problem associated with synthesising a chiral auxiliary from camphene, *viz* its propensity to undergo racemisation under acidic conditions. This not only put limitations on the nature of the route, but also meant that obtaining the starting material with the required optical purity became a problem. Neither antipode of camphene is commercially available in greater than 50% e.e., and consequently, this source was of no use for the preparation of a chiral auxiliary, although it should be noted that some early work on the route to an oxazolidin-2-one product was carried out using material from this source. The process of racemisation of camphene is known to be caused by two different carbocation rearrangements; the Nametkin rearrangement⁸⁵ and a [1,6]-H shift⁸⁶, both of which are shown in Figure 9.

The Nametkin rearrangement involves a [1,2]-sigmatropic shift of a methyl to give the enantiomer of the original carbocation.

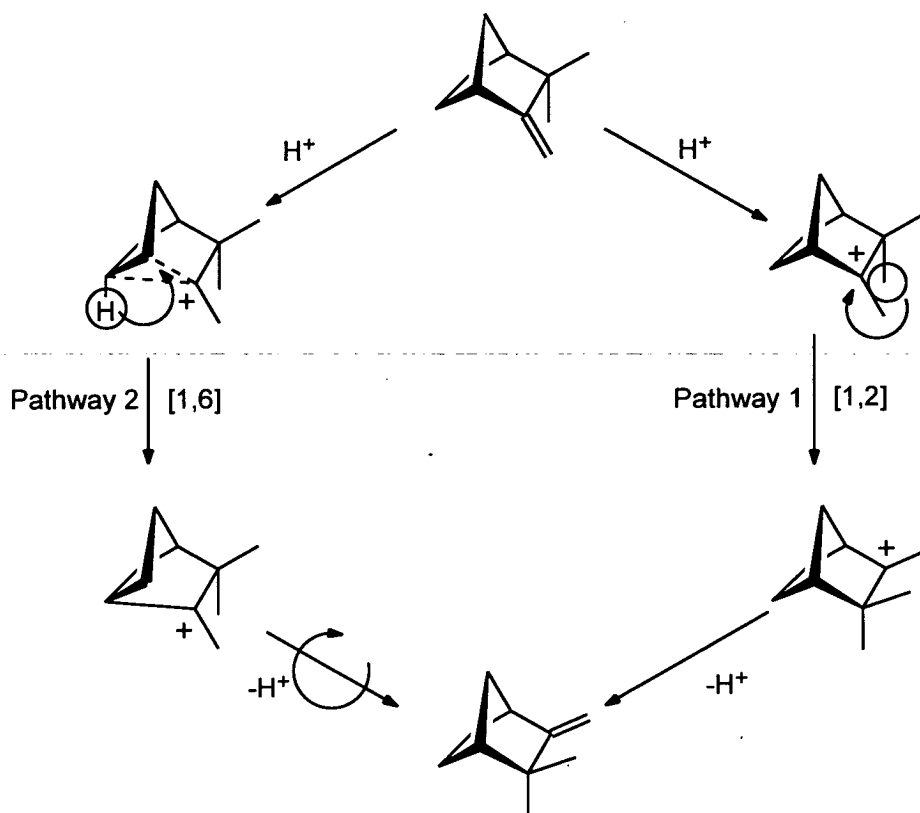
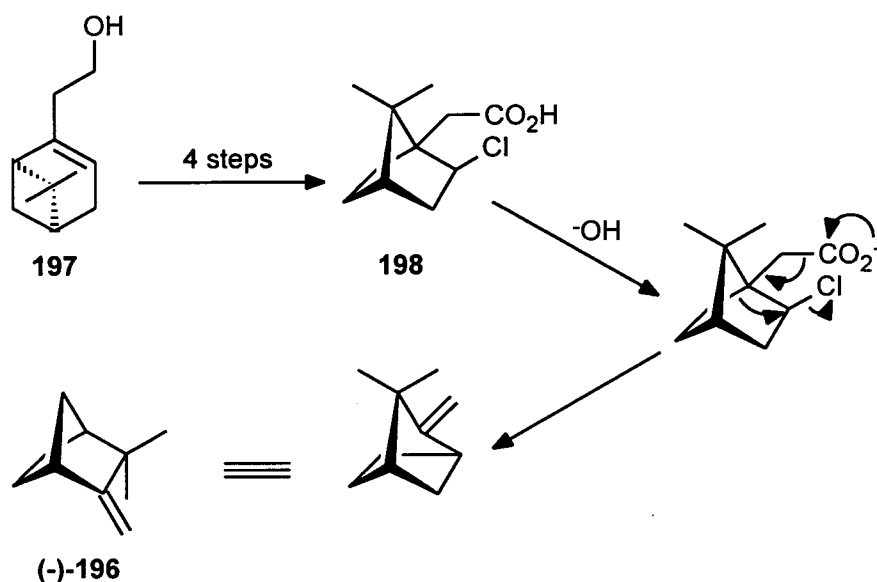


Figure 9

It has been shown that the second mechanism competes with the Nametkin rearrangement and that both normally occur to different extents depending on the conditions of racemisation. The nature of the second mechanism has been determined to be a [1,6]-H shift of the carbocation which results in racemisation without rearrangement of the vinyl or geminal methyl groups. This was shown by the retention of the C_8 - ^{14}C ($=\underline{C}H_2$) label on racemisation under conditions where this mechanism predominated. The use of reaction conditions where the Nametkin rearrangement is favoured leads to the label being found statistically between C_8 and the geminal methyls.

Although carbocation rearrangements were an initial problem to the project they also proved to be its solution, in that a number of terpene-derived compounds

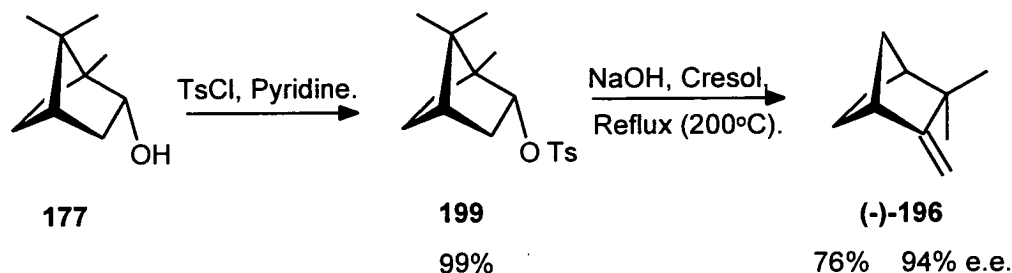
can be rearranged to give either enantiomer of camphene in high optical purity. The route quoted to give (-)-196 of the highest optical purity⁸⁷ was the solvolysis of 2-chloroapocamphanic acid **198** which can be synthesised in four steps from commercially available nopol **197** (Scheme 55). The reaction involves decarboxylation followed by chloride elimination and the rearrangement is quoted not to occur with concomitant racemisation. Unfortunately, problems were encountered in purifying the intermediates with reasonable recovery and the five synthetic steps, which proceeded with a modest overall yield, made the route unappealing.



Scheme 55

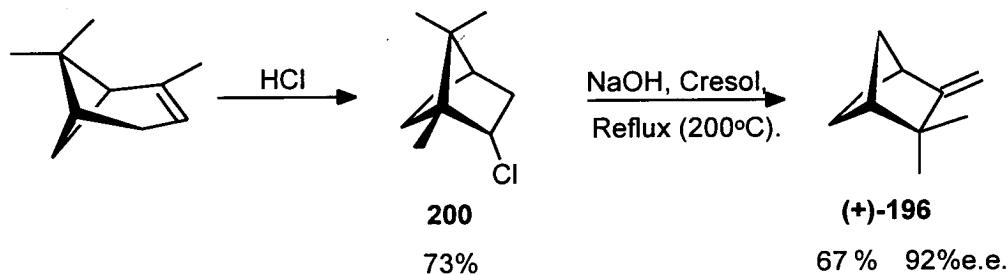
A shorter synthesis of (-)-196, involving the solvolysis of (-)-bornyl tosylate **199**, which itself was prepared by tosylation of (-)(1*S*)-borneol **177** in pyridine in near quantitative yield, was attempted using the literature conditions of heating a solution of **199** under reflux in methanol with calcium oxide or in acetic acid with sodium acetate⁸⁸. However, even after prolonged heating only traces of terpene material was formed and starting material was recovered in high yield in both cases. Other conditions were tried such as heating with triethylamine, both neat and in

alcoholic solution, heating with aqueous sodium hydroxide (emulsified with detergent) as well as alcoholic alkali but similar results were obtained.



Scheme 56

A chance lead suggested the use of sodium hydroxide in boiling cresol and this procedure was found to provide a high yield of (-)-camphene with acceptable optical purity (Scheme 56). However, the conditions were not ideal for a number of practical and safety reasons, but after some modification, better conditions of boiling in ethylene glycol/tetraglyme with one equivalent of cresol and excess sodium hydroxide yielded camphene in good yield (78%) and similar optical purity ($[\alpha]_D^{20} = -106.5^\circ$, ($c = 20$,

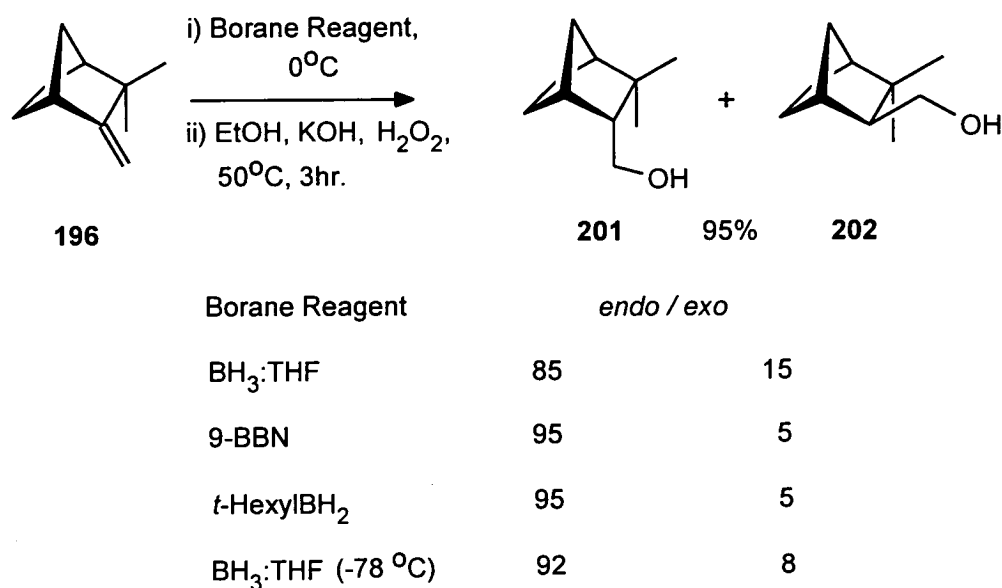


Scheme 57

ether), ~92% e.e.) following purification by distillation. (+)-Camphene of similar quality was obtained under similar conditions (Scheme 57), by solvolysis of bornyl chloride **200**, itself was prepared from (+)- α -pinene (92% e.e.) by reaction with hydrogen chloride in chloroform at -10°C . Under these conditions the terpene skeleton undergoes a Wagner-Meerwein rearrangement to give the bornane skeleton⁸⁹.

The chosen route to the desired oxazolidin-2-one derivative was *via* hydroboration to form the known alcohol, camphenol. This alcohol exists in two diastereomeric forms, but one *endo*-camphenol **201** appeared upon examination of molecular models to be more interesting than *exo*-camphenol **202** on the grounds of the potential insertion products and their viability as chiral auxiliaries.

Literature conditions⁹⁰ for the hydroboration of camphene with $\text{BH}_3\cdot\text{THF}$ complex and subsequent oxidation gave a near quantitative yield of **201** and **202** in a ratio of 85:15 (Scheme 58). This mixture was virtually inseparable by column chromatography, at least on any scale that would have been useful for the synthesis of the potential auxiliary.

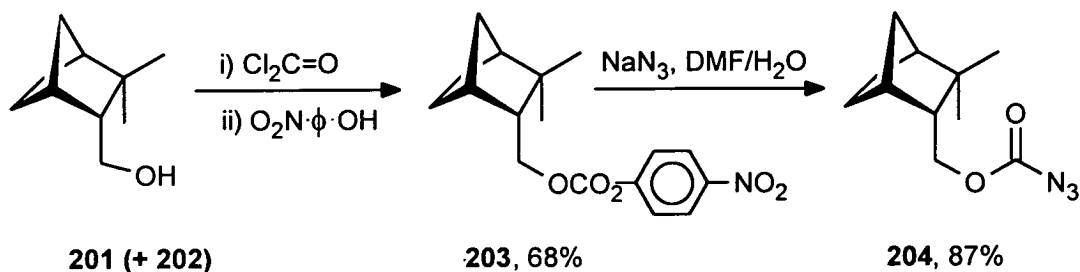


Scheme 58

In an effort to improve the ratio in favour of *endo*-camphenol, reduction with more hindered borane reagents was attempted. To this end, camphene was treated with 9-borobicyclo[3.3.1]nonane (9-BBN)⁹¹ and *t*-hexylborane⁹² in the hope that increased steric interactions would favour the *endo*-product. Reaction of **196** with 9BBN was observed to give a 95:5 mixture of **201** and **202**, respectively in near quantitative yield. This result came as no great surprise considering the increased

steric demands of the cyclooctane ligand. In contrast, *t*-hexylborane gave only a 50% yield when reacted in 1:2 ratio with camphene, although *endo* selectivity was almost identical to that obtained with 9-BBN. On the other hand, reaction in a 1:1 ratio gave a quantitative yield and similar selectivity. This indicated that only one B-H bond of *t*-hexylborane was used, so that as with 9-BBN, only one third of the potential reducing power of borane was used with these expensive reagents. A further complication was the need to remove the alcohols (1,4-dihydroxycyclooctane and 2,3-dimethylbutan-2-ol) produced from the borane ligands by chromatography or fractional distillation in contrast to the use of $\text{BH}_3\text{:THF}$, where the camphenols can be carried forward after simple isolation.

As an alternative form of purification from the minor *exo*-alcohol, fractional crystallisation was considered. Unfortunately, the mixed alcohols are a rather soft low-melting and highly soluble substance, and obviously not a serious candidate for fractional crystallisation. A more crystalline derivative was needed, preferably one which could be included in the synthetic route without the addition of any further steps. The most suitable candidates with respect to minimal disruption of the route were the substituted camphenyl formates where the leaving group was liable to impart crystallinity to the compound. Consequently, camphenyl aryloxycarbonates in which the aromatic moiety was suitably substituted with electron-withdrawing groups were synthesised. Of a number of cases, the *p*-nitro-phenoxy carbonate derivative ⁹³ **203** proved to be crystalline. Unfortunately, fractional crystallisation did not affect the diastereomer ratio as witnessed by ^1H NMR spectroscopy. Nonetheless, the primary consideration that the aryloxy group would be readily displaced by azide ion was achieved, since the reaction of the mixed carbonate with sodium azide in $\text{DMF/H}_2\text{O}$ (95:5) proceeded in high yield (Scheme 59).



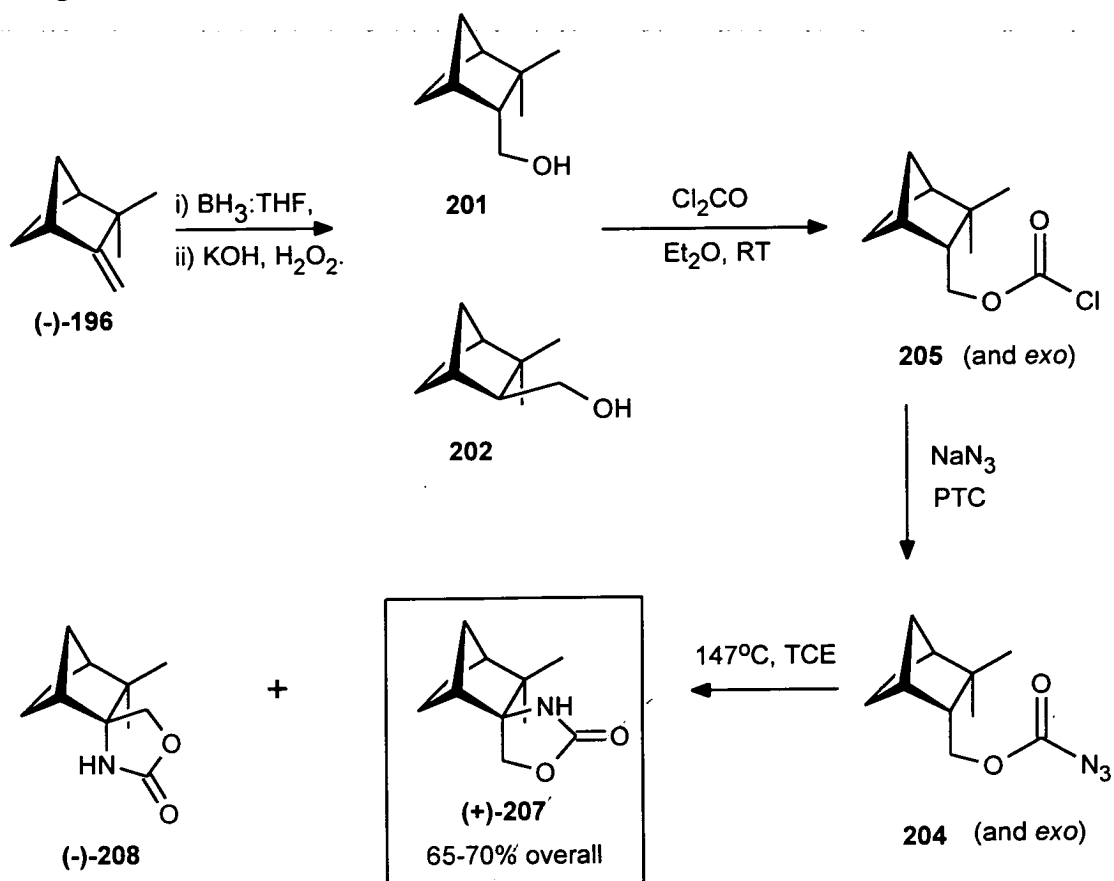
Scheme 59

It seemed reasonable to assume that one might be more successful in using a group which would impart a greater degree of crystallinity. A likely candidate appeared to be the trinitrophenoxy derivative, which could have an added advantage in that the displacement by azide ion may have been possible under more convenient phase-transfer conditions. Unfortunately, due to the proposed scale of the final synthesis this did not appear to be the way forward since the idea of handling mole quantities of dried picric acid was viewed with some trepidation. Work towards purifying an intermediate was abandoned after finding that French workers⁹⁴ had failed to increase the diastereomer ratio of the mono-acid phthalate derivative of **201/202** by fractional crystallisation.

The most convenient improvement to this first step was almost trivial and discovered during scale-up of the synthesis. In order to avoid the considerable exotherm produced upon the addition of $\text{BH}_3\cdot\text{THF}$ to camphene at orthodox reaction temperatures of between 0 and -10°C when working on a mole scale, the reaction was conducted at -78°C and allowed to warm to room temperature over a period of eight hours. A slight exotherm was noted when the reaction reached -30°C , and it is assumed that this is the temperature at which the reaction becomes favourable. Examination of the crude material by high field ^1H NMR spectroscopy showed a slight increase in the proportion of the *endo*-isomer **201** (9:1) which was sufficient to improve the purification of the final oxazolidin-2-one mixture.

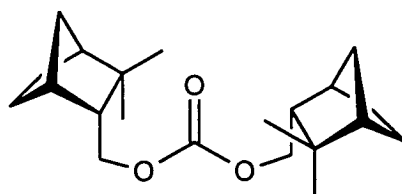
Since separation on a large scale was not feasible, this mixture was carried through the synthesis as depicted in Scheme 60; thus addition of the alcohol and

triethylamine to a large excess of phosgene in toluene gave the chloroformate **205** in high yield. Unfortunately there was a tendency to form considerable quantities of the carbonate **206**, which produced problems in the final stage of the synthesis. In an attempt to counter this problem, the method of Dawson and Banks⁸⁰ was used whereby the alcohol was reacted with a large excess of phosgene in the absence of base. The reaction is rather slow with the secondary alcohol **177** (see Scheme 47), but was found to be relatively fast for camphenol. Moreover the large excess of phosgene used by Banks



Scheme 60

in an effort to prevent carbonate formation, was found to be unnecessary, and reaction with 1.2 equivalents of phosgene for 24 hours provided a quantitative yield of the chloroformate **205**. This outcome is presumably due to the considerably lower reactivity of the chloroformate compared to phosgene.

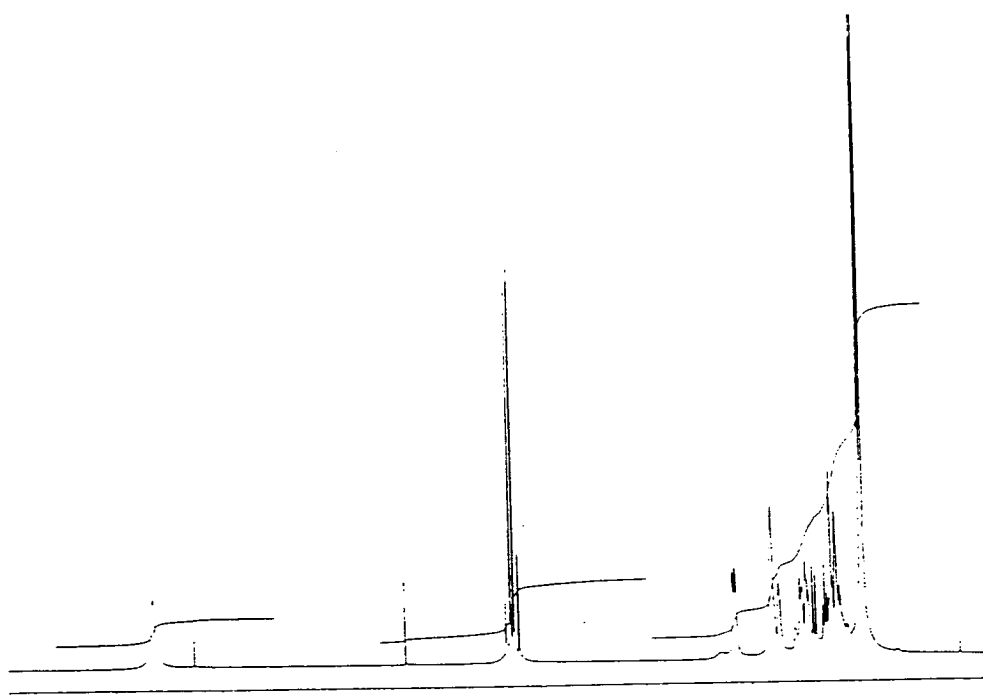


206

Treatment of **205** in CH_2Cl_2 with aqueous sodium azide under phase-transfer conditions using tetrabutylammonium bromide (TBAB) as catalyst, gave a near quantitative yield of the azidoformate **204**. In the next step, thermolytic formation of the nitrenoformate was conducted under a variety of conditions: flash vacuum pyrolysis (FVP), spray vacuum pyrolysis (SVP)⁹⁵ and solution thermolysis in an inert solvent. The product distribution of all these methods was virtually identical except that the latter procedure showed a propensity towards tar formation. FVP provided a high yield of insertion product, but unfortunately was of limited use due to the small scale on which it was possible to operate. Although SVP has proved to be more useful for the synthesis of large quantities of nitrene insertion products^{4,5}, it proved to be impractical in this particular case due to a technical point. The problem was that the back-heat from the vertical furnace tended to cause thermolysis in the fine spray nozzle (0.2 mm diameter) which is in a temperature zone of 150-200 °C. This had not been a problem previously since any thermolysis products formed had been liquid at this temperature, but in this case, the insertion products invariably crystallised in the fine aperture whilst only a fraction of the way through the pyrolysis run.

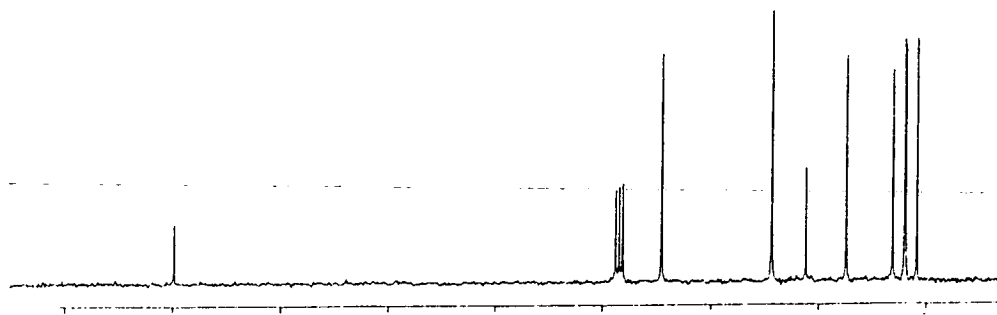
By contrast, solution thermolysis of **204** in boiling tetrachloroethane (TCE, 147°C) proved much more amenable to large scale preparation. Dropwise addition of **204** dissolved in TCE to the boiling solvent to give a final concentration of 2% (w/v) provided a high yield of insertion products, and also a tolerable level of tar and hydrogen abstraction products. In fact, the only insertion products found in the reaction mixture were the spiro compounds **207** and **208** derived from the *endo*- and

exo-azidoformates, respectively. Proof that the major insertion product was the spiro-oxazolidin-2-one **207** was obtained initially by examination of NMR data. The ^{13}C NMR spectrum of the major product contained a new quaternary centre (68.9 ppm) and also showed the loss of one CH (Figure 10b), which indicated insertion into a methine group. The latter could only be that bearing the methylenoxy group or the adjacent bridgehead. In the ^1H NMR spectrum, the signals of the diastereotopic methylenoxy protons were present as two distorted doublets (δ 4.21 ppm, $J = 9.0\text{ Hz}$ and δ 4.29 ppm, $J = 9.0\text{ Hz}$) (Figure 10a), but had insertion into the bridgehead methine occurred these signals would have been split further into a pair of doublets of doublets. Final confirmation of the structure was obtained by X-ray diffraction, the ORTEP structure of which is shown in Figure 10c.



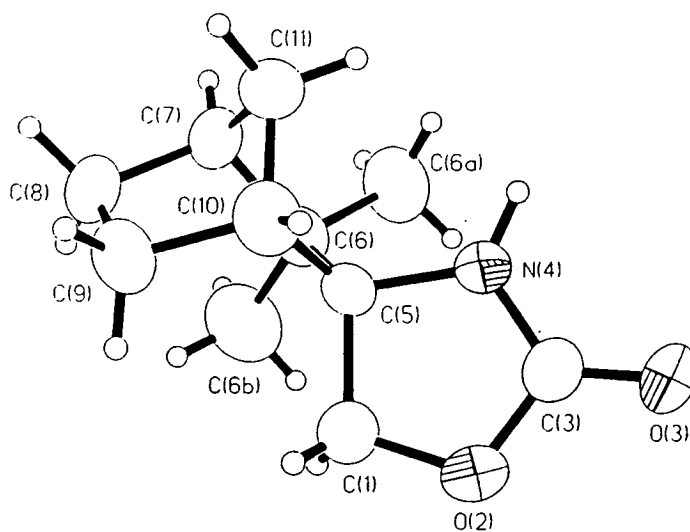
200 MHz ^1H NMR Spectrum of **207**

Figure 10a



50.3 MHz ^{13}C NMR Spectrum of **207**

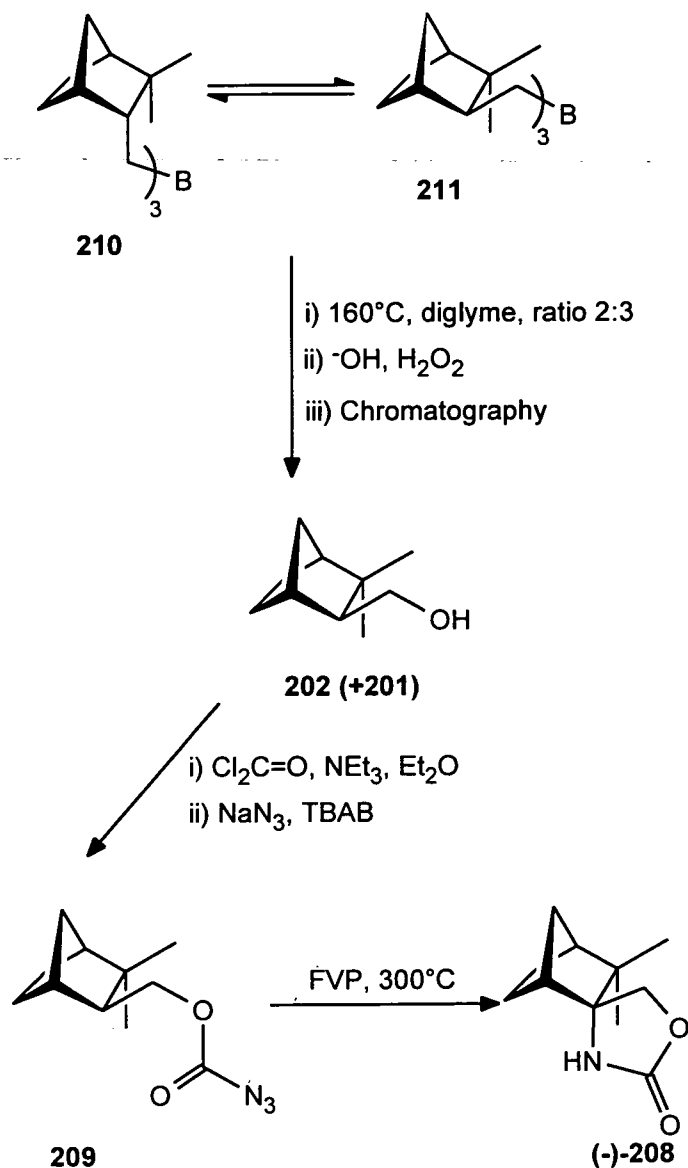
Figure 10b



ORTEP Drawing of the X-ray Structure of **207**

Figure 10c

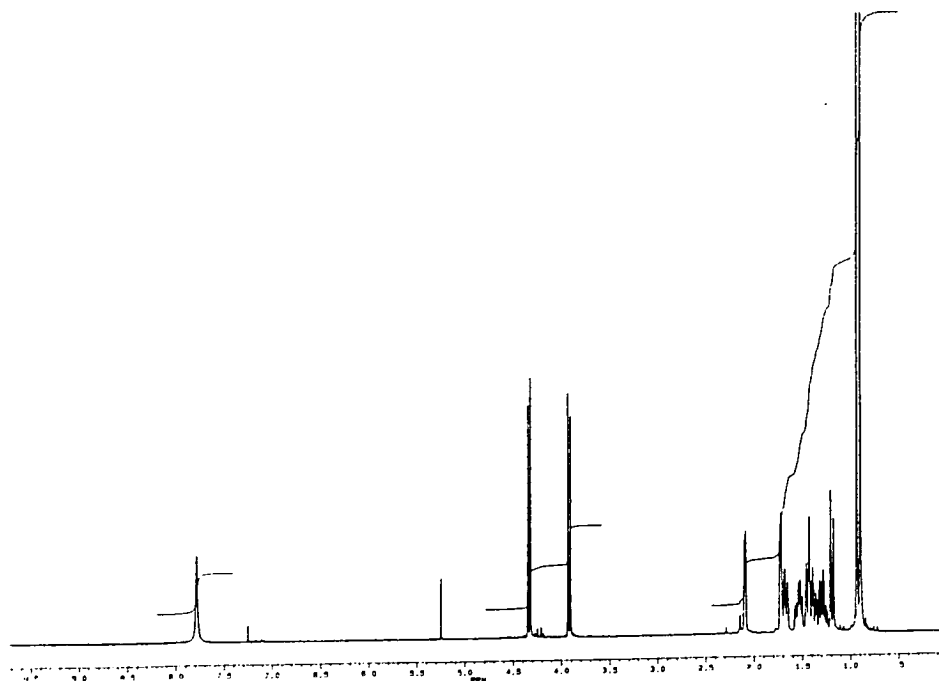
The minor insertion product was found to be derived from the *exo*-azidoformate **209** by independent synthesis. Thus, *exo*-camphenol **202** was prepared by thermal isomerisation of the initially formed mixture of boranes (**210** and **211**) in boiling diglyme⁹⁶ for three days, followed by oxidation to yield the *exo*- and *endo*-alcohols as a 3:2 mixture, respectively (Scheme 61). Repeated chromatography



Scheme 61

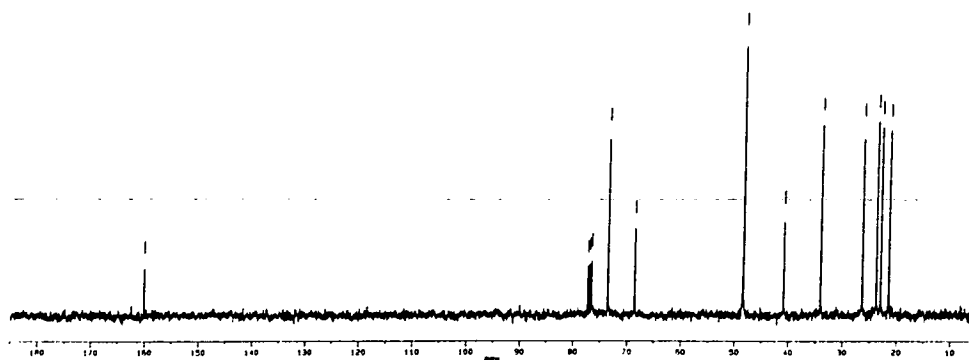
(three times on silica gel, elution with hexane:ether 4:1) afforded a sample of the mixed alcohols containing >85% of **202**. This mixture was carried through the

synthesis as described previously, FVP of **209** yielding a crystalline solid, from which the minor component **208** was obtained in 70% yield. The structure of the *exo*-analogue **208** was again assigned by NMR analysis, which established that a new quaternary carbon had appeared (signal at 68.6ppm and concomitant loss of one CH). The ^1H NMR spectra of **208** also contained the characteristic pair of doublets (4.34ppm, $J = 9.0$ Hz; 3.91ppm, $J = 9.0$ Hz) from the diastereotopic methylenoxy protons, indicating the spiro nature of the compound (Figures 11a and b).



360 MHz ^1H NMR Spectrum of **208**

Figure 11a



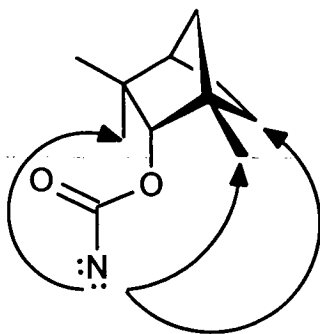
90 MHz ^{13}C NMR Spectrum of **208**

Figure 11b

The rationale for the propensity to form the spiro-compound is quite convincing. Not only are tertiary $C-H$ bonds much more reactive towards nitrene insertion than primary or secondary $C-H$ bonds⁹⁷, but the transition state required to form a five-membered ring is geometrically favourable. Furthermore the transition state required to attain an insertion into the adjacent bridge head *i.e.* formation of a six membered ring is less geometrically favourable. The only other possible sites for attack, *viz* the methylene bridge and the two geminal methyls, are not only less reactive but would also have to be formed through even less favourable transition states, which lead to seven-membered rings.

The exclusive formation of a spiro-oxazolidin-2-one product has previously been noted for methyleneoxy azidoformates where the requisite methine exists. For example, galactose-based **181** is the exclusive insertion product obtained upon thermolysis of the azide precursor, although the yield is only moderate (53%) due to

the formation of copious amounts of tar. It is also in contrast to many terpenoid-based azidoformates, which tend to form a number of insertion products *e.g.* **180** is formed in 35% yield along with two other diastereomers (Scheme 47). In a similar manner, the fenchol-derived nitrenoformate forms several insertion products⁸⁰ (Figure 12).



Insertion Sites of Fenchyl Nitrenoformate

Figure 12

The formation of a sole insertion product from the thermal decomposition of **204** is highly desirable since in cases where a variety of products have been formed, tedious chromatographic separation has been necessary. Thus, it was extremely pleasing to find only one insertion product for each azidoformate diastereomer; and had it not been for the *exo*-contaminant, isolation of the auxiliary **207** would have been trivial.

Due to difficulties in separating the two oxazolidin-2-ones by silica gel chromatography (R_f of *exo*- and *endo*-isomers are 0.55 and 0.50, respectively, 1:1 hexane/ethylacetate) purification of large quantities of **207** was performed by fractional crystallisation, from dichloromethane/cyclohexane by slow evaporation initially, but latterly by recrystallisation from hot xylene which has proved to be much more efficient. Purity was monitored by both ^1H NMR spectroscopy and optical rotation measurement, the latter being particularly useful due to the fact that

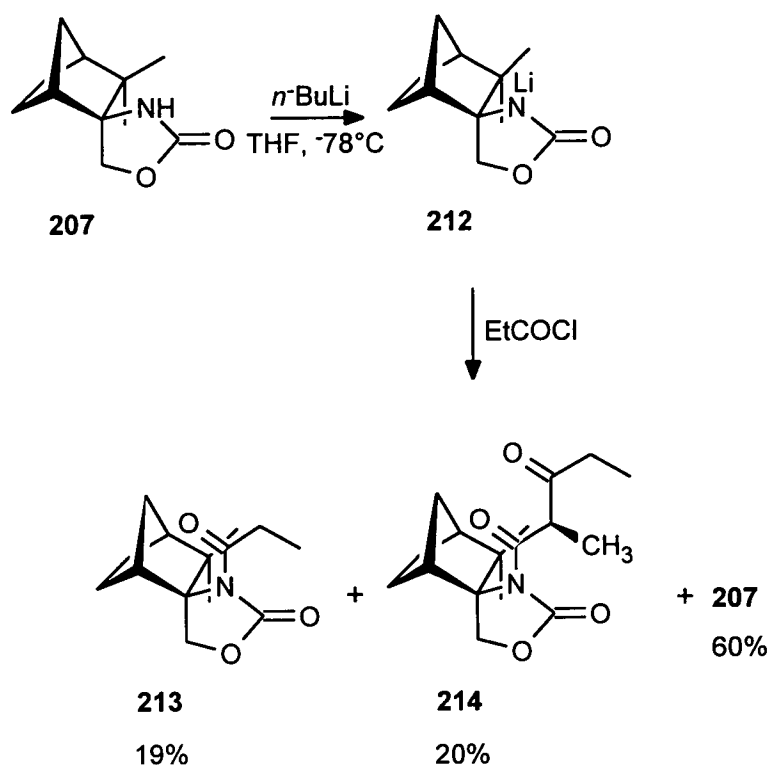
diastereomeric contaminant **208** had a value and sign of optical rotation very similar to that of the unwanted antipode. Once all of the above information had been acquired it became relatively easy to synthesise up to 100g quantities of each enantiomer of Chiracamphox quite readily in 60-70% yield starting from camphene.

2.2 Functionalisation of Chiracamphox

Functionalisation of oxazolidin-2-one chiral auxiliaries with acyl- and enoyl-moieties has routinely been achieved *via* deprotonation of the relatively acid N-*H* by organometallics such as *n*-butyl lithium⁶ or methylmagnesium bromide¹¹. The resulting lithium or bromomagnesium salts are subsequently reacted at low temperature, with the relevant acid halide.

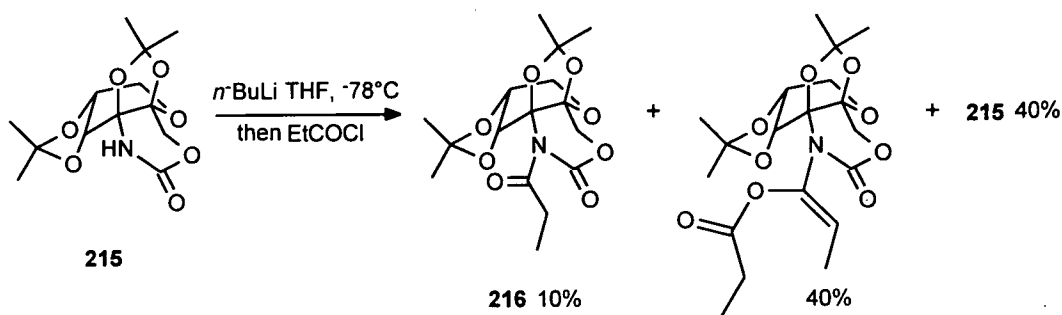
2.2.1 Synthesis of the Propionyl Imide of Chiracamphox (207)

Deprotonation using *n*-butyl lithium, followed by reaction with propionyl chloride, has been found to be highly effective for the synthesis of *N*-propionyl derivatives of oxazolidin-2-ones such as Evans' valine derived auxiliary **5** or Chirabornox **180**.



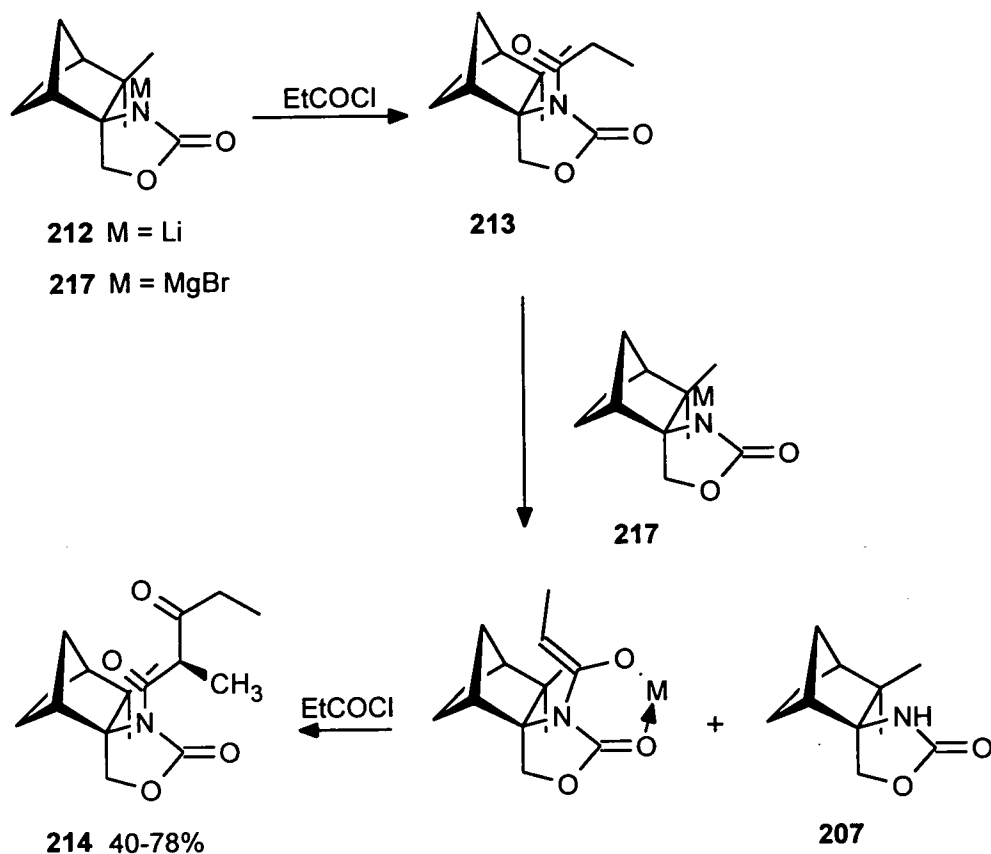
Scheme 62

Attempts to use this procedure to prepare the *N*-propionyl derivative **213** via the lithium salt of chiracamphox **212** led to a very low yield (19%) of the desired product, together with the *C*-acylated adduct **214** (20%) and recovered starting material (60%). The formation of this type of diacylated species had been noted before by McDougal⁸³, when attempting to functionalise the fructose-derived oxazolinone **215** under similar conditions. The rationale for the formation of such products is clear when one compares the steric crowding at the nitrogen in these highly hindered oxazolidin-2-ones/oxazinones with the far more open position in oxazolidin-2-ones such as **5** or **180**.



Scheme 63

Obviously, the lithium salts of these hindered oxazolidin-2-ones / oxazolinones are much less nucleophilic than their counterparts, and thus more likely to deprotonate the *N*-propionyl imide formed than to react directly with the acid chloride. The enolate formed from **213** is predominantly *C*-acylated to give **214** with concomitant production of one equivalent of auxiliary. It should be noted that *C*-acylation under these condition was found to be highly stereospecific, a pointer to the future potential of the auxiliary (Scheme 64)

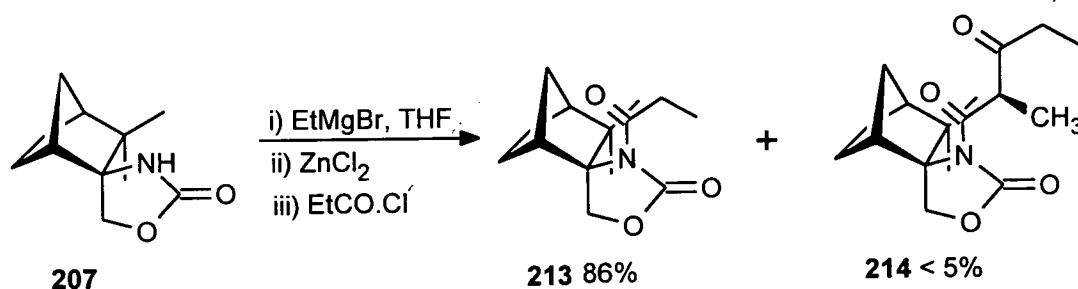


Scheme 64

The solution to the problem in the case of **215** was straightforward since Evans¹¹ had recently published an improved synthesis of *N*-enoyl imides by using the considerably less basic *N*-bromomagnesium salts, which are prepared by reacting the oxazinone with methylmagnesium bromide at 0°C in THF. Thus, use of this procedure with the fructose based auxiliary **215** gave a 92% yield of the desired *N*-propionyl oxazolidin-2-one **216**. When the same procedure was used on a small scale (200mg) with **207**, a similar dramatic increase in yield to 78% was obtained. Unfortunately, on attempting to use the procedure for the synthesis of gram quantities of the propionyl imide, the yield dropped to as low as 40%, even by the use of

reversed addition procedures. In essence, even the less basic bromomagnesium salt **217** was showing its basic character due to the severe steric demands which reduced its nucleophilicity. It may have been possible to have increased the yield again by use of a combination of reverse addition, high dilution and a large excess of acid halide, but once again, these changes would have become less practical on further scale-up.

It was evident that an even softer counter ion was needed. Initially, a zinc salt was formed by transmetalation of the *N*-bromomagnesium salt with anhydrous zinc chloride in THF. Reaction of this salt with propionyl chloride (initial addition at -78°C) at room temperature led to a slow reaction which produced only required imide **213** and a variable quantity of starting material. The initially modest yields (60-70%) were increased to much more acceptable 86% by the use of glove-box techniques to handle the anhydrous zinc chloride. The small loss of yield was presumed to be due to slight contamination of the extremely hygroscopic zinc chloride with atmospheric moisture.

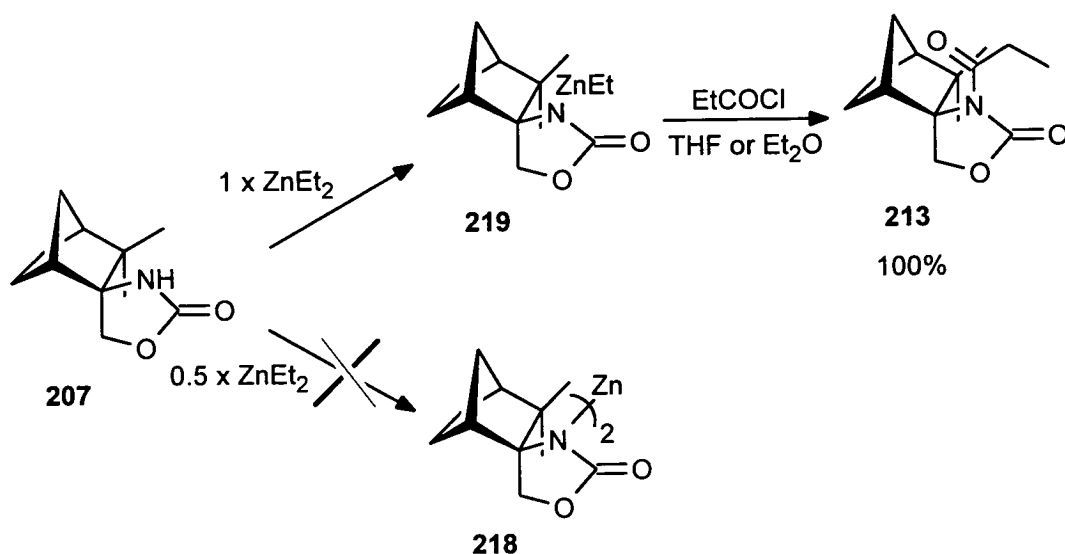


Scheme 65

The reasoning had obviously paid off; no appreciable diacylated product was ever detected in these reactions and the yield was independent of scale or mixing conditions. Although the reaction was reasonably efficient, it was clearly desirable to

have a simpler and more robust procedure which was not so prone to drastic reductions in yield due to a failing in technique [one worker failed to achieved a yield greater than 20% while using this procedure even after a considerable number of attempts]. To this end, it was argued that if transmetalation with a zinc salt was so facile then direct deprotonation with an organozinc reagent may also prove feasible.

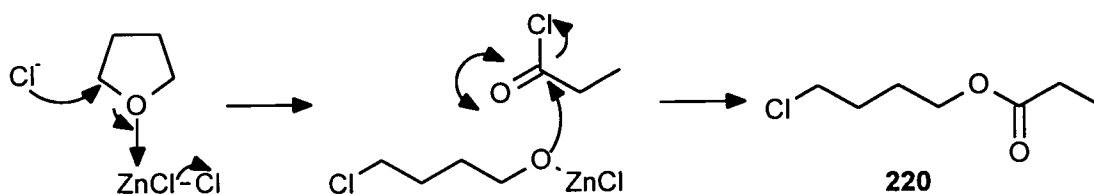
The most commonly used and commercially available zinc reagent is diethylzinc. Consequently, formation of the zinc salt of **207**, by deprotonation with this reagent was attempted. Thus, a solution of **207** in THF was treated with 0.5 equivalents of diethyl zinc at 0°C for one hour before cooling the mixture to -78°C and adding an excess of propionyl chloride. Monitoring by TLC showed that a large proportion of auxiliary had failed to react even after two days. Following work-up and chromatographic isolation of the product, a yield of only 50% of **213** was obtained and 48% of auxiliary was recovered. This outcome indicated that the bis-



Scheme 66

oxazolidin-2-one zinc salt **218** had not formed, but due probably to steric constraints, half of the available auxiliary had been transformed into the *N*-ethylzinc salt **219**.

Since it appeared that the species **219** formed readily and reacted cleanly with the acid chloride, reaction with 1.1 equivalents of diethyl zinc was attempted. A large excess of propionyl chloride was used since it was anticipated that a considerable quantity could be consumed in side reactions. Monitoring of the reaction by TLC showed that complete consumption of **207** had occurred within 24 hours, and after work-up and chromatography, **213** was isolated in ~100% yield, as an oil. Unfortunately, it was contaminated to slight extent by an unknown compound, the majority of which had been removed by chromatography. Nonetheless, recrystalliation proved to be difficult and reduced the purified yield considerably. This slightly volatile compound had a characteristic sweet smell and had often been noted in the crude products from other methods (lithium and bromomagnesium salts), but not to such a considerable extent except by the transmetalation method (zinc chloride). A sample was purified by distillation and characterised; surprisingly it was found to be 4-chlorobutyl propionate **220**, most likely formed by



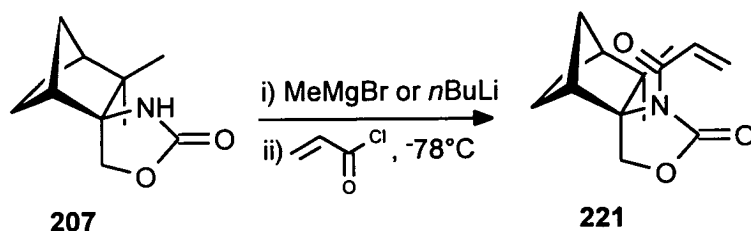
Scheme 67

the Lewis-acid catalysed cleavage of the solvent THF by the acid chloride. This known reaction is normally noted to produce an alkyl halide and an ester, but with

cyclic THF, the halo-ester is formed⁹⁸. This finding pointed to a change of solvent, but unwilling to change too drastically in case of any other detrimental effects, it was decided to continue with an ether solvent. By using diethyl ether instead, the products formed from ether cleavage would be highly volatile and thus removed with the solvent. The sole problem appeared to be the lack of solubility of **207** in diethyl ether, but it was found that upon treatment of a suspension in this solvent with diethyl zinc solution at room temperature the auxiliary dissolved rapidly. The reaction proceeded smoothly with a complete transformation of auxiliary to the imide, and no other involatile products being formed. After subjecting the crude product to high vacuum it was possible to obtain the pure compound by recrystallisation from pentane (-30°C) with high recovery.

2.2.2 Synthesis of the *N*-Acryloyl Imide of Chiracamphox

Preparation of the parent acryloyl imide **221** was attempted by use of the bromomagnesium salt, but disappointingly the isolated yield was a mere 29%. The *N*-substitution, was shown by the presence of two carbonyls in the IR spectrum and the characteristic oxazolidin-2-one carbonyl in the ¹³C NMR spectrum at 155.5 ppm, making the possibility of *O*-acylation⁴ unlikely. Even after a number of attempts this yield was never improved. However Gaur had noted⁴ that the acryloyl imide of **180** was not formed from the lithiated oxazolidin-2-one in THF but on changing the reaction solvent to CH₂Cl₂, a moderate yield was obtained. The same conditions were attempted with **207**, but TLC showed only the formation of a base-line spot and work-up yielded an intractable glassy, polymer. Evans¹¹ noted an alternative

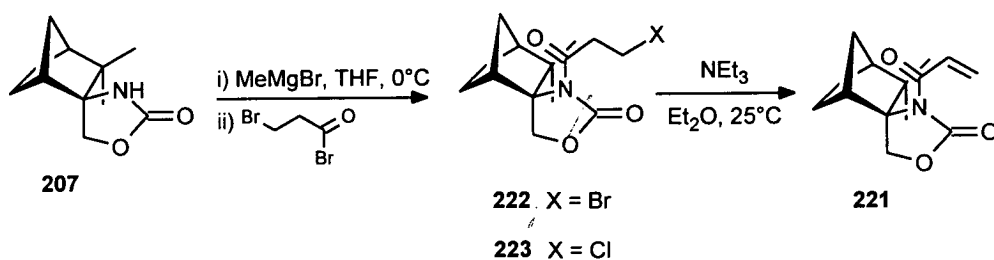


AUX MgBr : 29%

AUX.Li : polymer only

Scheme 68

procedure to the direct preparation of oxazolidin-2-one acrylates. By using this method, **207** was first transformed into its 3-bromopropionyl imide **222** which was expected to readily eliminated hydrogen bromide upon treatment with triethylamine and furnish the acryloyl imide in good yield.

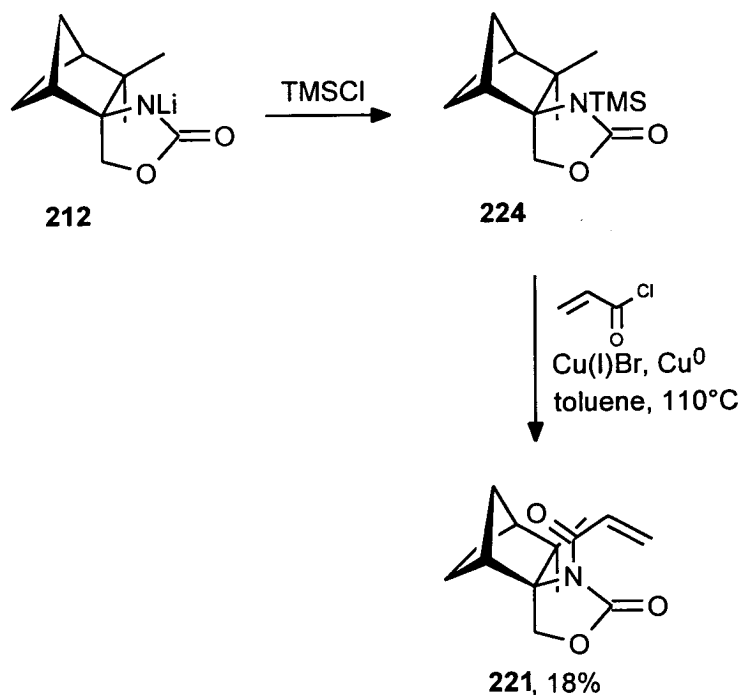


Scheme 69

Nonetheless, on following this two-step procedure, a crude yield of only 20% of the acryloyl imide was obtained and this was heavily contaminated with an unknown compound, which could not be removed by chromatography. Even on attempts to distil out the impurity under high vacuum, the acryloyl imide polymerised despite the presence of a stabiliser (galvanoxyl). The recovery of considerable quantities of **207** hinted at the elimination of hydrogen bromide from the acid bromide. In an attempt to make the more stable chloro intermediate **223**, the reaction

was repeated with 3-chloropropionyl chloride, but again the major component isolated proved to be the starting material. This reaction was also attempted using the ethylzinc salt **219**, but again only starting material was obtained.

Kocienski had noted⁹⁹ that preparation of acrylates of many oxazolidin-2-ones has proved to be problematic. Consequently, he has developed a procedure whereby the oxazolidin-2-one is transformed to an *N*-trimethylsilyl derivative and then reacted with the acid chloride. Using this procedure the **207** was converted *via* its lithium salt to its *N*-trimethylsilane derivative **224** which was isolated but not purified and was then reacted directly with acryloyl chloride in boiling toluene in the presence of copper bromide and copper bronze as catalysts. Kocienski has noted that such reactions are slow (periods of up to 60 hours were required), but even after five days, only 18% of the acryloyl imide **221** was obtained.

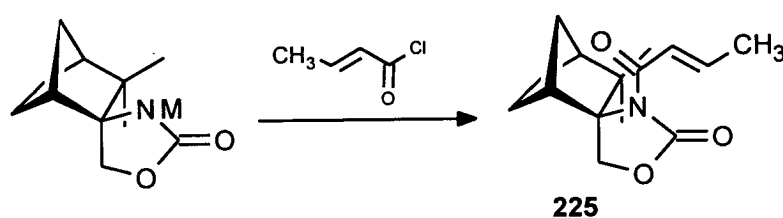


Scheme 70

In summary, low yields, coupled with the propensity to polymerisation, of this acryloyl imide certainly detract from its considerable potential in asymmetric synthesis. A reliable method for its preparation would certainly be an important goal for the future¹⁰⁰.

2.2.3 Synthesis of Substituted Acryloyl Imides of Chiracamphox

The preparation of the crotonyl imide **225** from the bromomagesium salt of **207** proved to be straightforward, and after chromatographic isolation, a yield of 82% of this highly crystalline and important intermediate was obtained. However, since



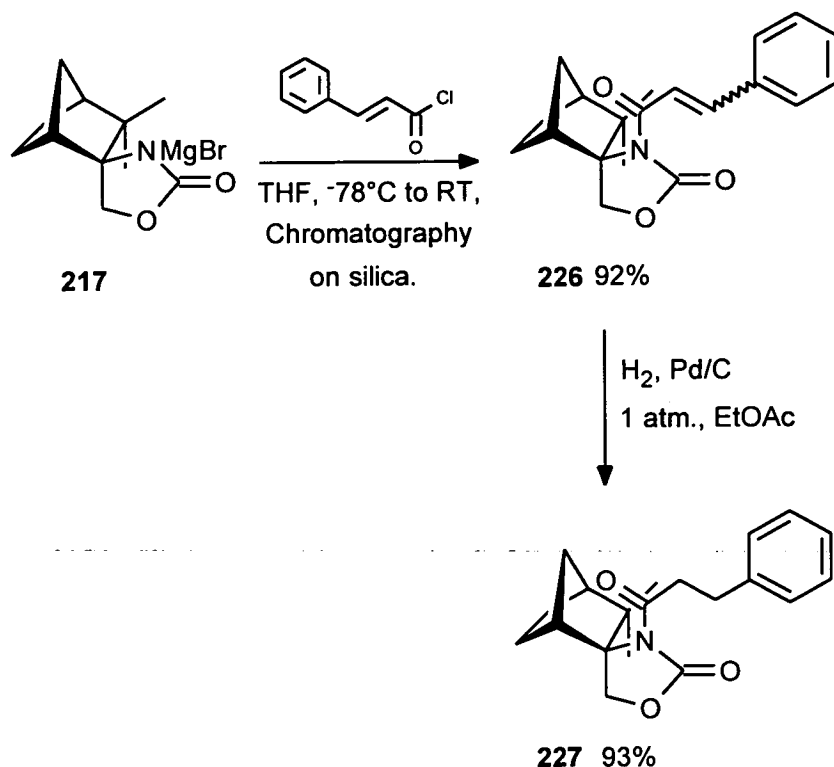
M	solvent	yield
MgBr	THF	82%
ZnEt	Et ₂ O	93%

Scheme 71

much of the work carried out later during this research relied heavily on both enantiomers of this molecule and since multi-gram quantities of **225** were prepared regularly, a higher yielding and cleaner reaction (avoiding chromatography) was desired. In this respect, use of the idealised diethyl zinc deprotonation procedure gave a much cleaner reaction and led to a 70% yield of pure **225** after recrystallisation. Chromatography of the mother liquors took the overall yield to

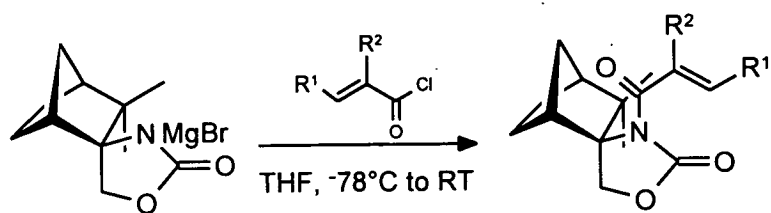
93%. It thus appears that the use of zinc salt is generally preferable to halomagnesium salts in the preparation of acyl and enoyl imides of **207**.

The reaction of the bromomagnesium salt of **207** with cinnamoyl chloride appeared to proceed smoothly to give the desired compound. After purification by chromatography on silica, ^1H - and ^{13}C -NMR spectroscopy clearly showed the presence of a contaminant which was suspected to be an isomer. The ^{13}C shift for the oxazolidin-2-one carbonyl group in the major component was as expected, whilst the impurity showed a very close value (155.8 and 156.5 ppm, respectively). In addition, the absence of an imine stretch in the IR spectrum indicated that the impurity was unlikely to be the *O*-acylated species. It was suspected that the minor compound could be the *cis* isomer. Hence the mixture was re-chromatographed, but this step only succeeded in increasing the amount of the contaminant. Consequently, this mixture was taken into dichloromethane and stirred with silica overnight, resulting in the formation of a near 1:1 mixture of isomers. Moreover, the IR spectrum of the mixture was identical to that of the initial material, clearly indicating no change in functionality. The mixture of presumably *cis* and *trans* isomers was hydrogenated over 5% Pd/C to give a 93% yield of the 3-phenylpropionyl imide **227**. From the evidence available, it was evident that acid-catalysed *cis/trans* isomerisation is occurring on the surface of the silica, making purification of **226** by this method of



Scheme 72

chromatography futile. Chromatography on neutral alumina could have been performed, but fortunately this highly crystalline compound was produced in a relatively clean reaction and an 86% yield of the pure product could be obtained by a single recrystallisation of the crude product. Other substituted enoyl derivatives such as methacryloyl and tigloyl imides (**228** and **229**) were also obtained by reaction of the respective acid chlorides with the bromomagnesium salt of **207** in yields of 92% and 79%, respectively. It thus appears that only the unsubstituted acryloyl derivative **221** is at all problematic to synthesise



	R^1	R^2	yield
226	Ph	H	86%
228	H	CH_3	92%
229	CH_3	CH_3	79%

Scheme 73

2.3 Alkylation and Acylation of Metal Enolates of Acyl Imides of Chiracamphox

2.3.1 Stereospecific Metal Enolate Formation

Probably the most important feature of this and the following chapter is the ability to generate geometrically pure metal enolates. Without this control, no amount of chelation or facial shielding would be able to produce diastereomerically pure products. Deprotonation of acyl compounds of the type **230** with powerful kinetic bases such as LDA can lead almost specifically to either *E(O)*- or *Z(O)*-enolates dependant on the nature of the substituent X^{101} (Figure 13).

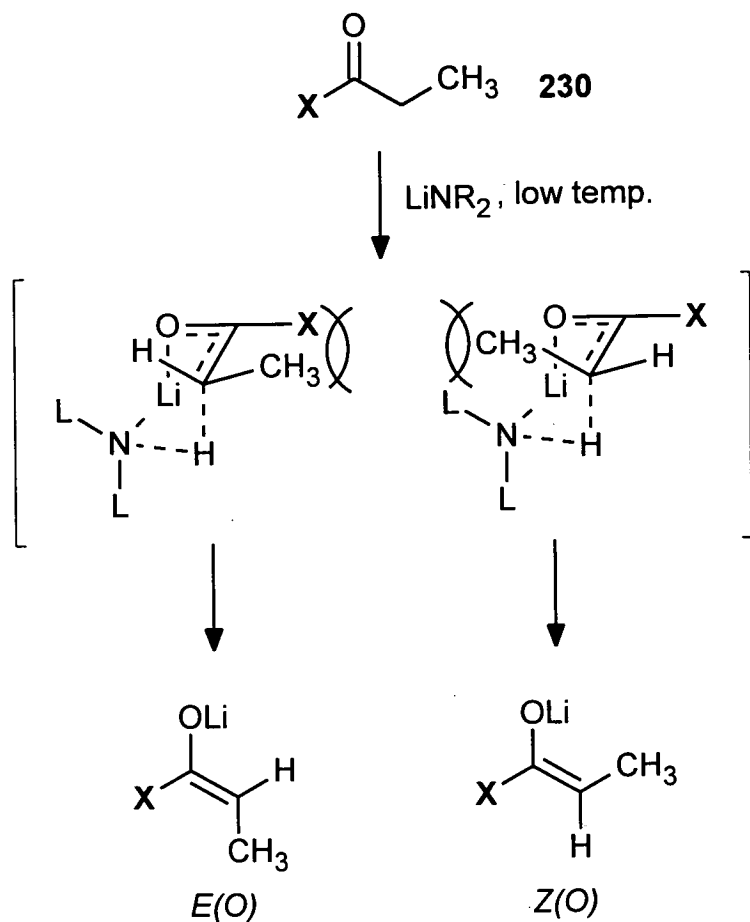
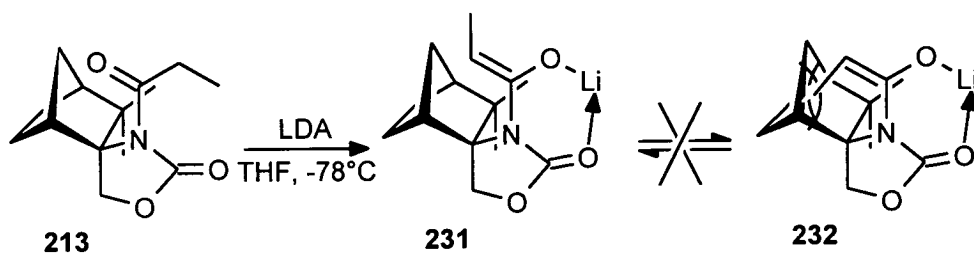


Figure 13

When **X** is small, *e.g.* an ester or ethyl ketone, the *E(O)*-enolate is preferred due to the minimisation of steric interaction between the methyl group and the substituents of the lithium amide (isopropyl). On the other hand, as the bulk of the group **X** is increased, there is a change-over in selectivity, since the main concern is to avoid **X** to methyl interaction; this is particularly pronounced for tertiary amides since the planar nature of the amide link (conservation of π overlap) introduces severe interactions within the developing *E(O)*-enolate. Because, acyl oxazolidinones can be considered to be sterically equivalent to tertiary amides, the high preference for the formation of the *Z(O)*-enolate **231** is clearly seen. This enolate is covalent in nature at low temperature, hence it is not prone to interconversion with its geometric isomer. Furthermore the *Z(O)*-enolate exists in the chelated form and it can clearly be seen that the *E(O)*-enolate **232** would be less stable due to severe steric interactions with the bicycloheptane ring (Scheme 74).



Scheme 74

2.3.2 Alkylation Reactions

Although alkylation of metal enolates of oxazolidinone *N*-acyl imides has proved to be an important source of C_α -alkyl substituted carboxylic acids and their derivatives,

many problems have been encountered with this reaction^{4, 5}. The major problem lies in the relatively low reactivity of such enolates towards even activated alkylating reagents, *viz.* allyl and benzyl halides, compared to other electrophiles such as acyl halides and aldehydes. At the higher temperatures that are required for reaction with these electrophiles, the enolates themselves are no longer stable. They appear to decompose *via* elimination of the relevant ketene, which is no doubt prone to dimerisation/polymerisation, leaving the metalated auxiliary (Figure 14). In at least one case the metalated auxiliary was seen to react with the electrophile (benzyl bromide) to give the *N*-benzylated oxazolidinone⁸³.

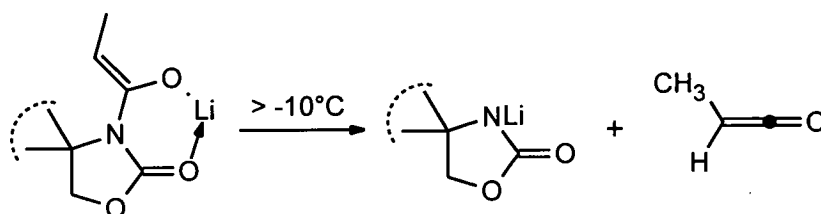
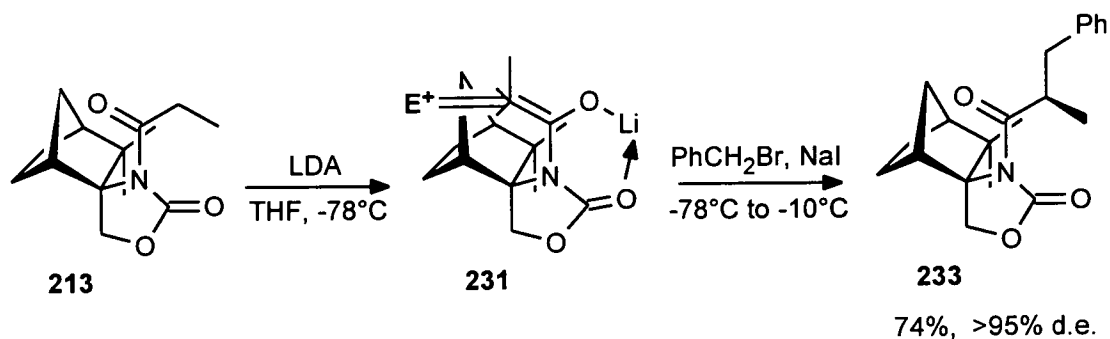


Figure 14

For most oxazolidinone auxiliaries careful choice of the reaction temperature can minimise this side-reaction whilst allowing alkylation to occur. Thus, with 3-alkyl substituted *N*-acyloxazolidinones such as those of Evans' valine-derived auxiliary **5**, or relatively non-hindered terpenoid oxazolidinone **180**, lithium enolates must be reacted around -10°C , whereas for the less stable and consequently more reactive sodium enolates, a temperature between -20 and -30°C is necessary. With the use of less reactive alkylating reagents, *e.g.* ethyl iodide, the problems return and alkylation of the lithium enolate of **180** with this alkyl halide gave only a 6% yield of the C_{α} -alkylated product, although only as a single diastereomer^{5,82}.

With some highly hindered oxazolidinones it has proved impossible to obtain any C_α -alkylated product whatsoever. As noted previously, reaction of lithium enolates of the propionyl imide of **181** (see 2.1.1) with benzyl or allyl bromides led only to the recovery of starting material and considerable quantities of cleaved auxiliary. It was unclear whether this was due to a mere increase in steric hindrance or to adverse chelating/stereoelectronic effects of the numerous acetal oxygens. The performance of the more hindered Chiracamphox imides in these reactions could obviously shed some light on this question.

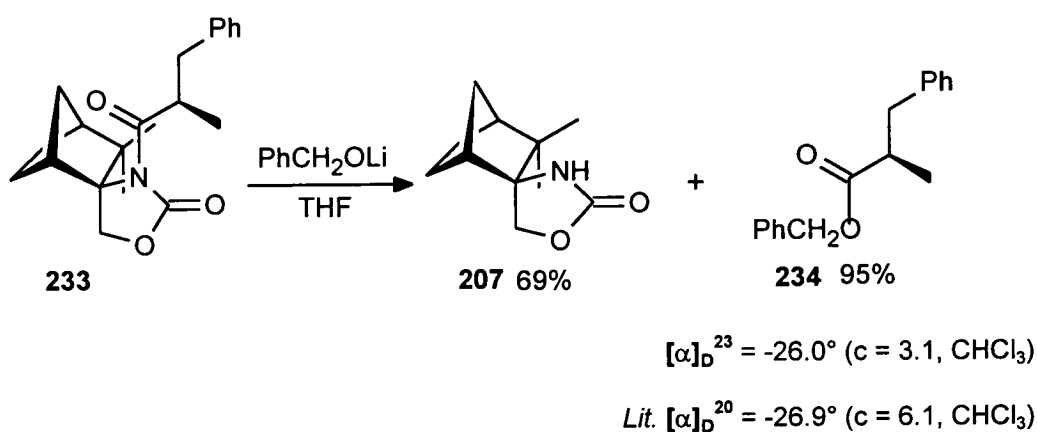
Dawson and Grant^{5,82} had developed slightly improved conditions for the reaction of benzyl bromide with the lithium enolate **183**. They found that addition of anhydrous sodium iodide produced an increase in yield from 62% to 80%. The same conditions were also used by Gaur and McDougal with the propionyl imides of **180** and **215**, respectively, but on this occasion with no improvement in the outcome.



Scheme 75

Under the same condition, the lithium enolate **231** underwent reaction with benzyl bromide at -18 to -10°C over 16 hours to give the benzylated adduct **233** in 74% yield (Scheme 75). Only a small quantity of starting material remained unreacted although around 20% of the auxiliary had formed. A considerable number

of minor products were also present and an initial d.e. of 84% was assigned to the reaction. This was proved to be highly pessimistic following the synthesis of the authentic diastereomer **238** (*vide infra*); in whose ^1H NMR spectrum, the H_{1b} signal appeared as a doublet at 3.45 ppm ($J = 9.0$ Hz). This resonance was completely absent in the ^1H NMR spectrum of the crude reaction product and consequently a d.e. of >95% was assigned. As depicted in Scheme 76, the adduct **233** was cleaved by treatment with lithium benzyloxide, to give (2*R*)-benzyl-2-methyl-3-phenylpropionate in 95% yield.

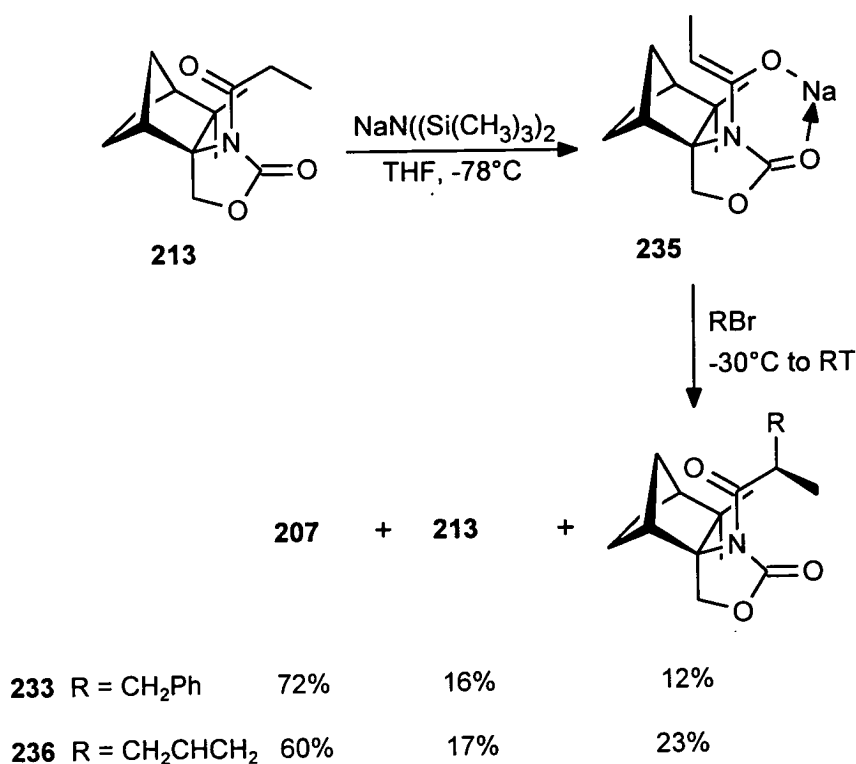


Scheme 76

From the evidence, the lithium enolate of **213** clearly undergoes alkylation reactions, albeit slowly. This indicates that the lack of reactivity of the sugar-based oxazolidin-2-one imide enolates, *e.g.* **190**, is due either to chelation or stereoelectronic effects from the many oxygen atoms, rather than being purely steric in origin.

Since the alkylation reaction was far from clean, and the yield was certainly open to improvement, the use of the sodium enolate **235** for benzylation was

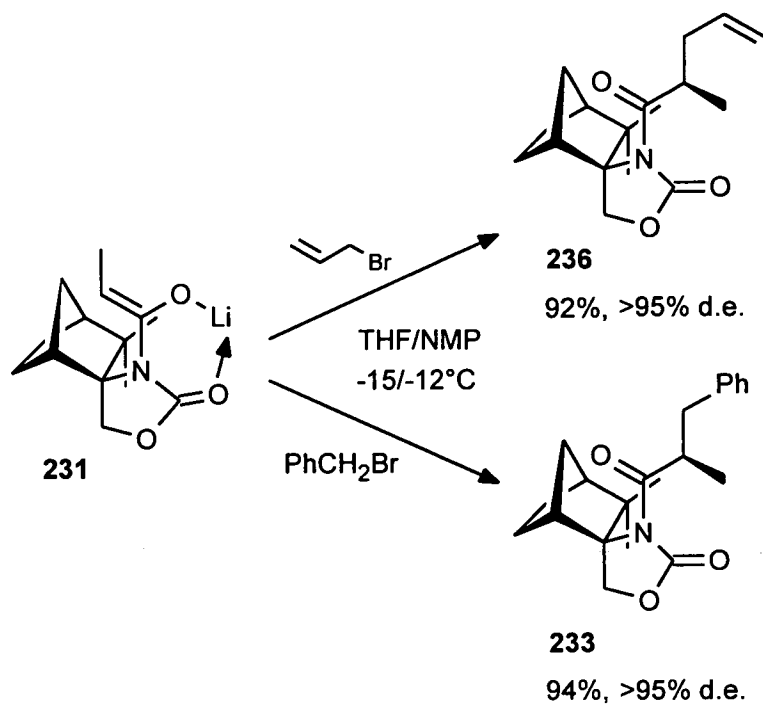
attempted. Thus, after deprotonation at -78°C , benzyl bromide was added and the reaction allowed to reach -30°C . After 5 hours at this temperature, the reaction was allowed to slowly warm to room temperature over a three hour period and then quenched. TLC indicated considerable quantities of the auxiliary to be present as well as starting material, together with the benzylated adduct. After removal of the auxiliary **207** by chromatography (72% yield), the remainder of the reaction mixture was examined by 250 MHz ^1H NMR, which confirmed the presence of unreacted **213** and the product **233**, which was present as a single diastereomer; calculated yields for the two compounds were 16% and 12%, respectively. Repetition of the same procedure with allyl bromide gave **207** (60%), **213** (17%) and apparently, a single diastereomer of the allyl adduct **236** albeit in the low yield of 23% (see Scheme 77).



Scheme 77

These results clearly demonstrate the instability of the sodium enolate **235**, which is also relatively unreactive towards alkylating agents. Clearly, the synthetic utility of this reaction appears to be limited unless conditions can be idealised. The use of polar co-solvents is known to dramatically increase the reactivity of many enolates. Oppolzer has regularly used the highly polar hexamethylphosphoramide (HMPA) in alkylation reactions of enolates of *N*-acyl camphor sultam derivatives, and generally obtained high yields¹⁰². However, the use of HMPA is limited due to its high toxicity and considerable safety legislation surrounding its use. After a recommendation by A. I. Meyers, regarding the encouragement of the editors of Organic Synthesis for the authors of procedures to use *N*-methylpyrrolidinone (NMP) in place of HMPA, it was decided to attempt the reaction with this co-solvent. Working under slightly more concentrated conditions, the lithium enolate was generated and then treated with benzyl bromide. Anhydrous NMP was added until it formed approximately 30% of the solvent mixture and the reaction was then warmed to -12°C. After only 2 hours the reaction was complete, with virtually no auxiliary being formed and only a trace of starting material remaining. Analysis of the product by 200 MHz ¹H NMR spectroscopy showed that only a single diastereomer was present (>95% d.e.) and following chromatography, the pure crystalline product **233** was isolated in 94% yield (Scheme 78).

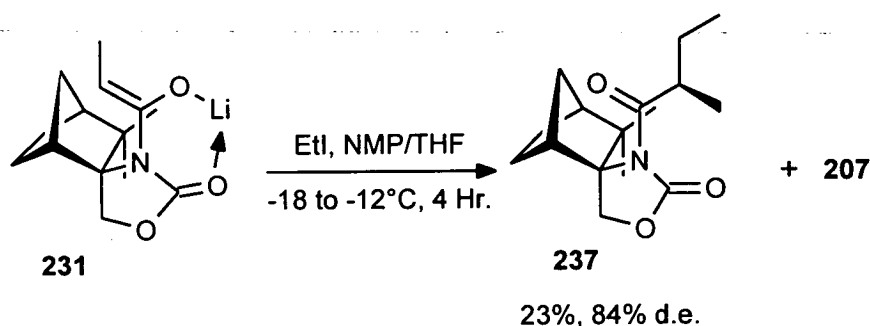
Following the same procedure with allyl bromide at -15°C, the adduct **236** was isolated in 92% yield as a low-melting solid with a d.e. of >95% being assigned to the crude product, although this was somewhat tentative in the absence of an authentic diastereomer.



Scheme 78

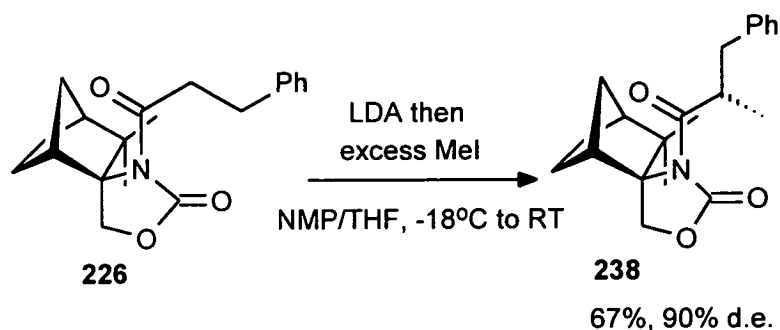
On the basis of these results, it is evident that the use of the polar co-solvent has reduced the strength of the *Li-O* bond and thus increased the reactivity of the enolate towards these alkylating agents without unduly reducing the thermal stability of the enolate. In view of the ease of alkylation of **231** in the presence of NMP with active alkylating agents, it was decided to attempt an alkylation with less reactive ethyl iodide, especially since this had proved to be troublesome with enolate **183** (*vide supra*). By carrying out the reaction as before, a crude product was obtained that consisted mostly of cleaved auxiliary. The two faster eluting components were freed from auxiliary, ¹H NMR spectroscopy showed that the combined mixture consisted of the two C_α isomers of **237** in a ratio of 92:8 (84% d.e.), in 23% yield. Further chromatography allowed pure **237** to be isolated in 19%.

This outcome showed that even although **231** is a more hindered enolate than **183**, the yield obtained using NMP as a co-solvent was three times that of the latter (see Scheme 48). It seems fitting that these conditions should, in the future be applied to **183** in an attempt to increase its scope for alkylation reactions. It should also be noted that Grant did not observe any diastereomeric product; however the analysis was carried out on the crude product which contained only 6% of the alkylated material and as such it was probably beyond the detection limit.



Scheme 79

In order to determine the diastereomeric excess of the initial benzylation reaction it was considered that one could form the diastereomeric mixture from reaction of a metal salt of **207** with racemic 2-methyl-3-phenyl-propionyl chloride, or alternatively prepare the diastereomer specifically. The latter approach appeared to be the more interesting from the point of view of using a more complex enolate as well as being able to investigate the reactivity of such an enolate towards methylation. By coincidence, the 3-phenylpropionyl imide **227** was in hand having been synthesised by catalytic hydrogenation while proving that the



Scheme 80

cinnamate **226** underwent *cis/trans* isomerisation on silica (see 2.2.4). Treatment under the same conditions used for the benzylation reaction, but with a large excess of methyl iodide, gave a crude reaction product, analysis of which by 200 MHz ^1H NMR spectroscopy indicated the presence of starting material (20%) and the two diastereomers **238** and **233** in a ratio of 18:1 (90% d.e.). Chromatographic isolation of the major product gave the 2'*S* isomer **238** in 67% yield. The lower d.e. compared to direct benzylation of **231**, is assumed to be the result of reaction with the smaller methyl electrophile, which has fewer steric restrictions, since the geometric integrity of the enolate is unlikely to be altered by the large substituent

In summary, the auxiliary **207** is highly effective in controlling the stereochemical outcome of alkylation of metal enolates with active alkyl halides, but the best yields and shortest reaction times are achieved only by use of polar co-solvents such as NMP.

2.3.3 Acylation Reactions

In simple terms, the acylation of lithium enolate such as **231** is essentially a more rapid version of alkylation, but there are some complicating factors. Firstly *O*- as

well as *C*-acylation is possible, and in some cases it is also possible for an *O*-acylated product to act as the acylating agent and reform the enolate such that equilibration to the *C*-acylated product is observed¹⁰³ (Figure15).

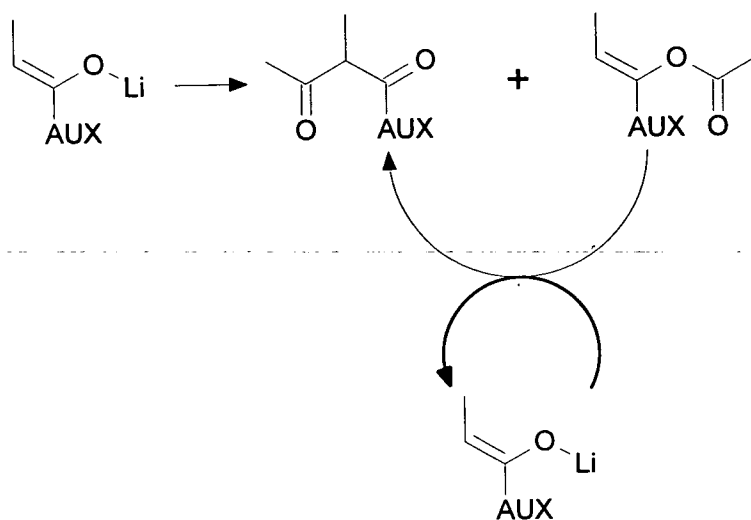


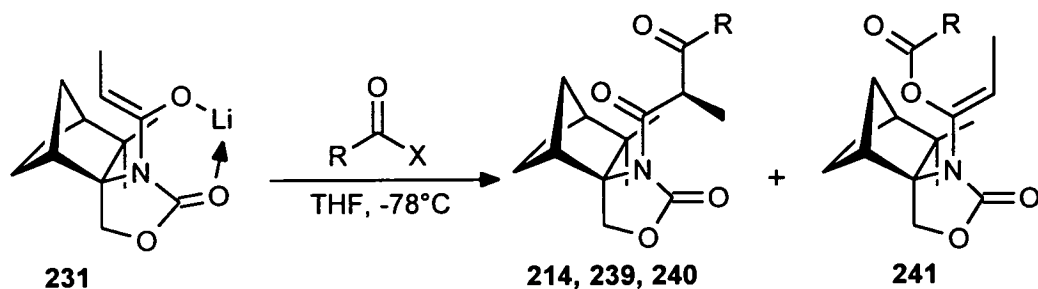
Figure 15

The proportion of *C*- to *O*-acylation depends on a number of factors, including addition rate and order. In some cases, pure *O*-acylation has been observed, as in the reaction of lithium enolates of imides bearing the sugar-based auxiliaries **181** and **215** (see 2.1.1), but in most cases only a few percent is observed. The second complication is the possibility of facile epimerisation of the newly created chiral centre as it is part of a β -keto imide system. Normally, this is not observed to any great extent, presumably due to the fact that deprotonation of the acylated adduct, by any slight excess of LDA would only be possible by the type of transition state depicted in 2.3.1. That is to say, that in imides such as **213**, only the pro-*R* diastereotopic proton is readily removed by alkali amide bases. In acylated adducts, the pro-*R* protons have already been replaced, leaving only the pro-*S* proton

which is more difficult to abstract. Evans has also noted that under various enolisation conditions deprotonation occurs at the less hindered site γ to the imide carbonyl (*vide infra*).

Solutions of the enolate **231** in THF at -78°C were treated with both acetyl and propionyl chloride and allowed to react for only a short period of time before being quenched. In each case TLC showed only minor traces of both starting material and cleaved auxiliary. The crude products were analysed by high field ^1H - and ^{13}C -NMR spectroscopy which showed that for acetylation, two isomers were present in a ratio of 19:1. However, the minor component showed no signals in the ^{13}C NMR spectrum corresponding closely to the C_{α} methine carbon or the β -keto signal of the major isomer. Furthermore, a quarternary carbon was present at 117 ppm and a distinct quartet at 5.40 ppm was seen in the proton spectra. Such signals are distinctive features of an O-acylated product and it was surmised that the contaminant was of the type **241**, thus allowing a d.e. of $>95\%$ to be assigned to the reaction. Interestingly, purification by chromatography on silica led to a slight degree of epimerisation (*ca.* 5%), as witnessed by high-field NMR analysis. In fact the signals observed had been completely absent in the crude reaction mixture and closely resembled the major diastereomer. In light of this observation it would seem prudent to carry out chromatography of such adducts on neutral alumina instead of slightly acidic silica.

The ^1H NMR spectrum of the propionyl adduct **214** was very complex so that traces of its opposite diastereomer were difficult to observe. However, the ^{13}C NMR spectrum showed only one signal attributable to the C_{α} methine carbon;



	R	X	d.e.	yield
239	CH ₃	Cl	>95%	84%
214	C ₂ H ₅	Cl	>95%	68%
240	CH ₃ O	CN	91%	69%

Scheme 81

consequently, a d.e. of >95% was assigned. A final acylation was performed using the highly *C*-selective reagent, methyl cyanoformate (Manders reagent)⁸⁴. Treatment of the enolate **231** with this reagent, followed by a rapid quench, yielded a crystalline product which was analysed by high-field NMR spectroscopy, which showed that the material consisted of a mixture of the two diastereomers of **240**. Integration of the methoxy signals between 3.8 and 3.6 ppm showed that they were present in a ratio of 21:1, giving a d.e. of 91%. As noted previously in 2.1.1, this relatively soft electrophile reacted with the enolate **190** solely at carbon, the only acylating reagent which does so.

Since the pattern of *O*-acylation does not seem to be caused by steric effects and is reversed by use of a particularly soft electrophile, one could anticipate that the enolate **190**, where the nitrogen is subject to an anomeric effect¹⁰⁴, is a somewhat

harder nucleophile than the more orthodox oxazolidin-2-one analogues. Although Chiracamphox is clearly a highly hindered auxiliary, it does not suffer from the low and altered reactivity patterns displayed by the sugar-based oxazolidin-2-ones **181** and **215** in alkylation or acylation reactions.

The stereochemistry of the adducts **214**, **239**, **240** has not been definitely assigned, but is presumed to be as shown by comparison to similar systems (*e.g.* the Chirabornox analogues). It should also be noted that cleavage of these adducts with retention of their stereochemical integrity is virtually impossible. They must first be transformed, *e.g.* into the corresponding β -alcohol (*i.e.* aldol type product) by stereospecific reduction¹⁰⁵, before cleavage can be performed. Nevertheless, a highly significant application of these β -keto imides is that used by Evans in the synthesis of a number of polyketide macrocycles. Thus, the less hindered γ -hydrogen can be abstracted by LDA to form enolates which undergo highly specific aldol condensations, controlled by the α -stereocentre¹⁰⁶.

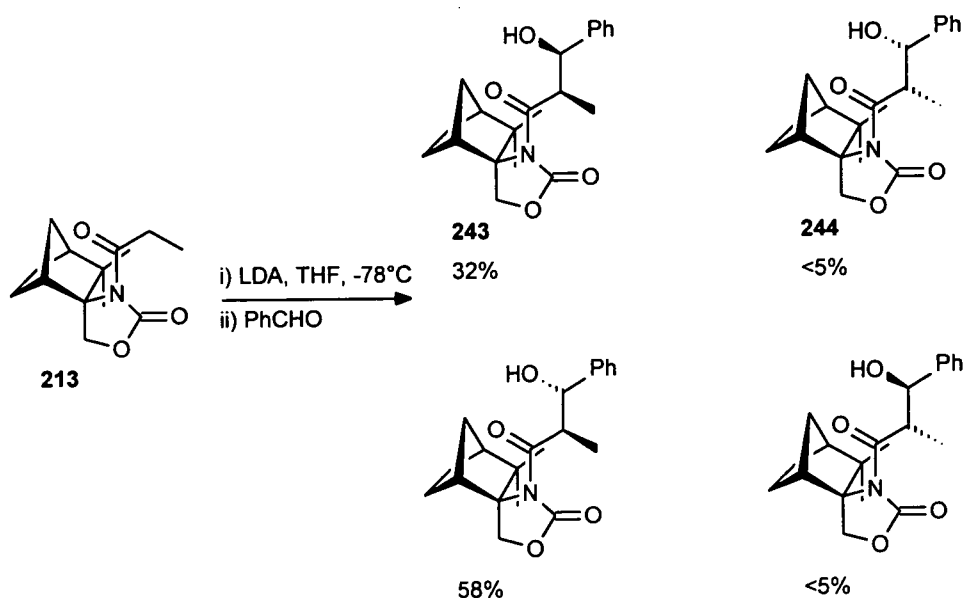
2.4 Asymmetric Aldol Condensation Reactions

Asymmetric aldol condensation of acyl-substituted oxazolidin-2-ones is possibly one of the most widely used reactions of this class of chiral auxiliary. Evans has made extensive use of this reaction in the synthesis of polyketide macrolactides¹⁰⁷ and many other workers have used such aldol products in variety of asymmetric syntheses. The versatility of the reaction stems from the possibility of creating specifically up to three of the four possible diastereomers from the same chemical entities. Thus, reliable methods are available for the synthesis of both of the *syn* and one of the *anti*-isomers. Generally, greatest success has been achieved using enolates of metals such as boron¹⁰⁸, titanium¹⁰⁹ and tin¹¹⁰. Poorer selectivities have been obtained with alkali metal enolates. The following two sections discuss the results obtained in lithium- and boron-mediated aldol reactions using the propionyl imide **213** of Chiracamphox **207**.

2.4.1 Aldol Condensation of Lithium Enolates

It had previously been shown that the auxiliary **180** like other contemporary auxiliaries, showed poor selectivity in lithium-enolate aldol condensations. In sharp contrast, the sugar- auxiliaries **181** and **215** proved to be surprisingly selective in such reactions^{5,81,83}. It was not clear where this selectivity came from, but it was possibly due to better placing of the steric-control groups, chelation of the lithium to one of the many available oxygens, or perhaps the anomeric nature of the oxazolidin-2-one (at least in **181**). Indeed, very much the same questions that were posed by the altered pattern of reactivity of these enolates, as discussed in the section 2.1.1. If

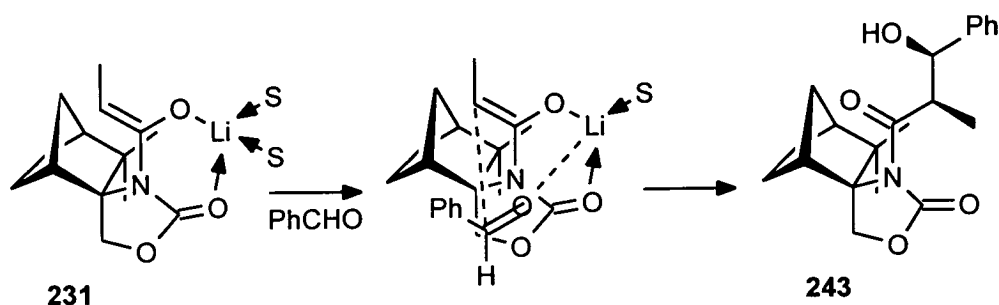
these effects were steric in origin one might expect Chiracamphox to perform well in comparison to the sugar based auxiliaries. The *Z*(*O*) lithium enolate **231** was formed from **213** (as in 2.3.2) and treated with benzaldehyde. A short reaction period was allowed in order that a kinetic product mixture, rather than an equilibrated thermodynamic product would be obtained. The crude isolated product was examined by high-field ^1H - and ^{13}C -NMR spectroscopy, which showed that two major diastereomers had been formed in the ratio 2:1.



Scheme 82

This poor selectivity is consistent with the results obtained by Grant with the auxiliary **180**, and by many others. In fact, the low selectivity is believed to arise from a combination of ill-defined co-ordination of the lithium atom and the long *Li-O* bond, which produces a less crowded transition state, such that steric controlling groups are less likely to be effective. The minor product was identified as a *syn*

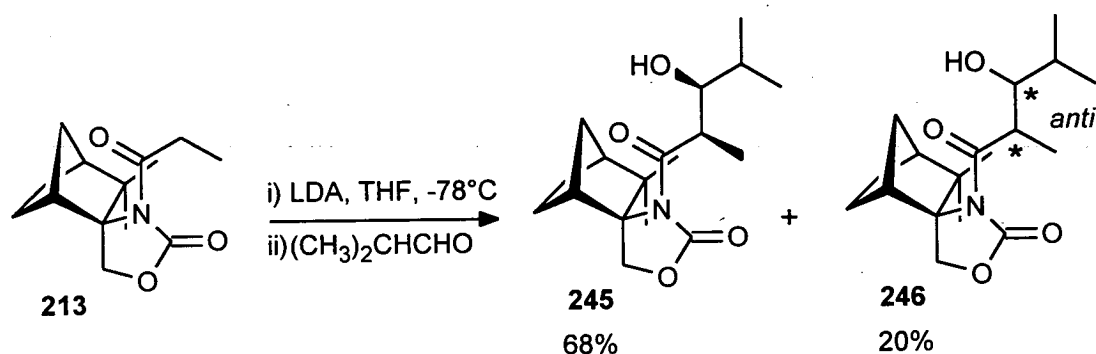
diastereomer by its small CHOH-CHC=O coupling constant ($J = 3.0 \text{ Hz}$)¹¹¹, and although not isolated, comparison to the *syn* product obtained from the boron-enolate reaction (*vide infra*) allowed assignment of the configuration as 2'*R*, 3'*R*, i.e. adduct **243**. It is believed that this adduct is the product from reaction of the *si*-face of the chelated enolate with the *re*-face of the aldehyde (Scheme 83). The major product was seen to be an *anti* diastereomer (the most chemically reasonable is depicted) from its considerably larger CHOH-CHC=O coupling constant (8.0 Hz). Clearly, this reaction had not shown the selectivity of the sugar-based auxiliaries, indicating that factors other than steric controlling groups are important in highly selective lithium-enolate aldol condensations.



Scheme 83

Reaction of the lithium-enolate **231** with one other aldehyde was attempted. Both Grant⁴ and Gaur⁵ had noted low yields upon the reaction of acetaldehyde with lithium enolates, presumably due to competitive deprotonation of the aldehyde. Consequently, the more hindered isobutyraldehyde was used since this appeared to be less prone to deprotonation (Scheme 84). The reaction gave a high yield of aldol products which were examined by high-field ¹H- and ¹³C-NMR spectroscopy which indicated that only two major diastereomers were present in a ratio of 7 : 2, a d.e. of

55% (*syn:anti*) was assigned and the two diastereomers separated by chromatography. The major product **245** possessed a CHOH-CHC=O coupling constant of 2.5 Hz, showing it to be *syn*. Its absolute stereochemistry has been assigned as 2'*R*, 3'*S* by comparison to the diastereomeric product from the corresponding boron-mediated reaction (*vide infra*).



Scheme 84

The minor component is believed to be an *anti*-isomer (CHOH-CHC=O $J = 8.0$ Hz), but has not been definitely identified. Although the diastereomeric excess is only moderate, the simplicity of the reaction, coupled with the facile isolation of the product, means that it may be used synthetically. Further investigation into the limits of lithium-mediated aldol reactions were not carried out until a surprisingly selective aldol condensation was used during an attempted synthesis of a natural product (**2.7.6**). This discovery spurred on a brief investigation of the steric effects of both C_α -substituents on the enolate and that from the bulk of the aldehyde used in the reaction.

2.4.2 Aldol Condensation of Dialkylboron Enolates

The use of dialkylboron enolates has become the method of choice for the stereospecific formation of aldol products from acyl oxazolidin-2-ones. Depending on the presence, or absence of Lewis acids, and their exact nature, three of the four possible diastereomers can easily be obtained. In this short study the procedure for the synthesis of the non-chelated *syn* product is used. Thus, the dibutylboron-enolate, was generated by treatment of the propionate **213** with dibutylboron triflate at low temperature followed by addition of the hindered tertiary amine, diisopropylamine. The latter abstracts a proton from the Lewis-acid complexed

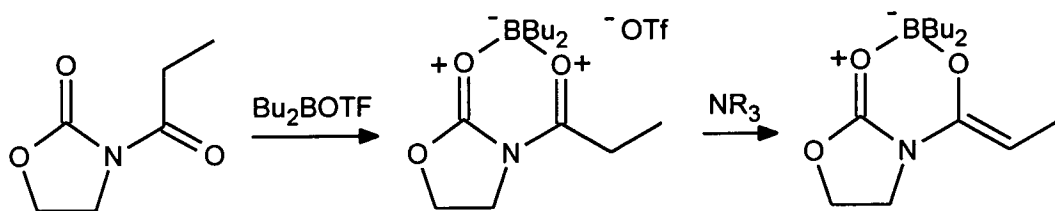
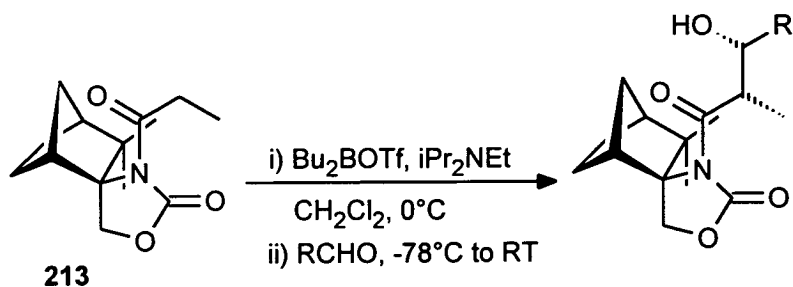


Figure 17

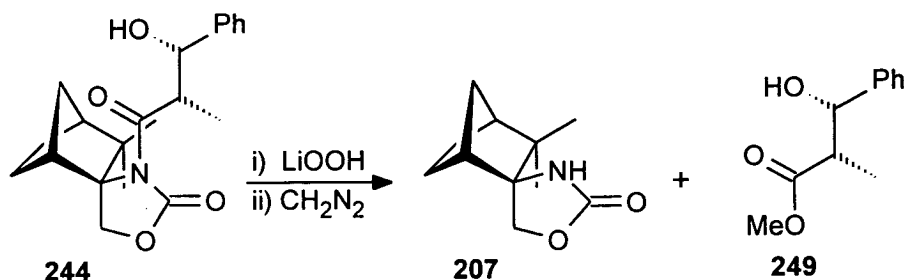
propionate to form selectively the *Z*(*O*)-enolate as depicted in Figure 17. This enolate was reacted with three aldehydes as shown in Scheme 85. The addition was carried out at low temperature, but the slowness of the reaction necessitated a period at room temperature for completion. The products (**244**, **247** and **248**) were formed in good yield, with high diastereomeric excesses and found to have CHOH-CHC=O coupling constants of 5.0, 3.0 and 3.0 Hz. Further the ^{13}C NMR shifts of the C_α methyls were 12.0, 10.8 and 10.5 ppm, respectively, in keeping with the *syn* stereochemistry¹¹¹.



	R	syn:anti	d.e. (syn)	yield
244	Ph	>98:2	>95%	94%
247	CH_3	>98:2	>95%	92%
248	$(\text{CH}_3)_2\text{CH}$	>98:2	>95%	96%

Scheme 85

The absolute stereochemistry of the benzaldehyde adduct **244** was determined by hydrolytic cleavage with lithium hydroperoxide (Scheme 86), which does not cause equilibration or retro-aldol reaction that can be encountered when using hydroxides. This cleavage afforded the β-hydroxy-acid which was methylated with diazomethane before isolation. The magnitude and sign of the optical rotation of the resulting ester **249** corresponded to the 2'S, 3'S diastereomer of the adduct, indicating that the *re*-face of the enolate had reacted with the *si*-face of the aldehyde.



Scheme 86

This stereochemistry fits with the transition state depicted in Figure 18. On approach of the aldehyde, the chelated intermediate is broken down since boron having a maximum co-ordination number of four must relinquish the carbonyl chelation to bind the aldehyde. The transition state leading to the *syn* product is then formed; this is based on the Zimmerman-Traxler model¹¹² and it can be seen that due to the specific enolate geometry, the methyl occupies an axial position. The bulk of both the oxazolidin-2-one and the axial boron ligand lead to large 1,3-diaxial interactions with the aldehyde substituent in the alternative *anti*-transition state. Consequently, this group adopts an equatorial position, and although chelation no longer exists to lock the oxazolidin-2-one and hence direct the steric control groups, it still obviously adopts a single conformation relative to the enolate moiety (Figure 19). It is believed that dipole-dipole interactions cause an *anti*-disposition of the carbonyl and the enolised oxygen to be adopted¹¹³. Though this would lead to a lessening of the shielding of the enolate, the large bulk of the dibutylboron moiety, which is attached covalently to the oxygen, can only be accommodated on the outer face of the enolate. The reaction gives the boronate ester which after oxidative cleavage yields the *re, si* aldol product. In summary, Chiracamphox has been shown to be effective in stereo-control of this important reaction.

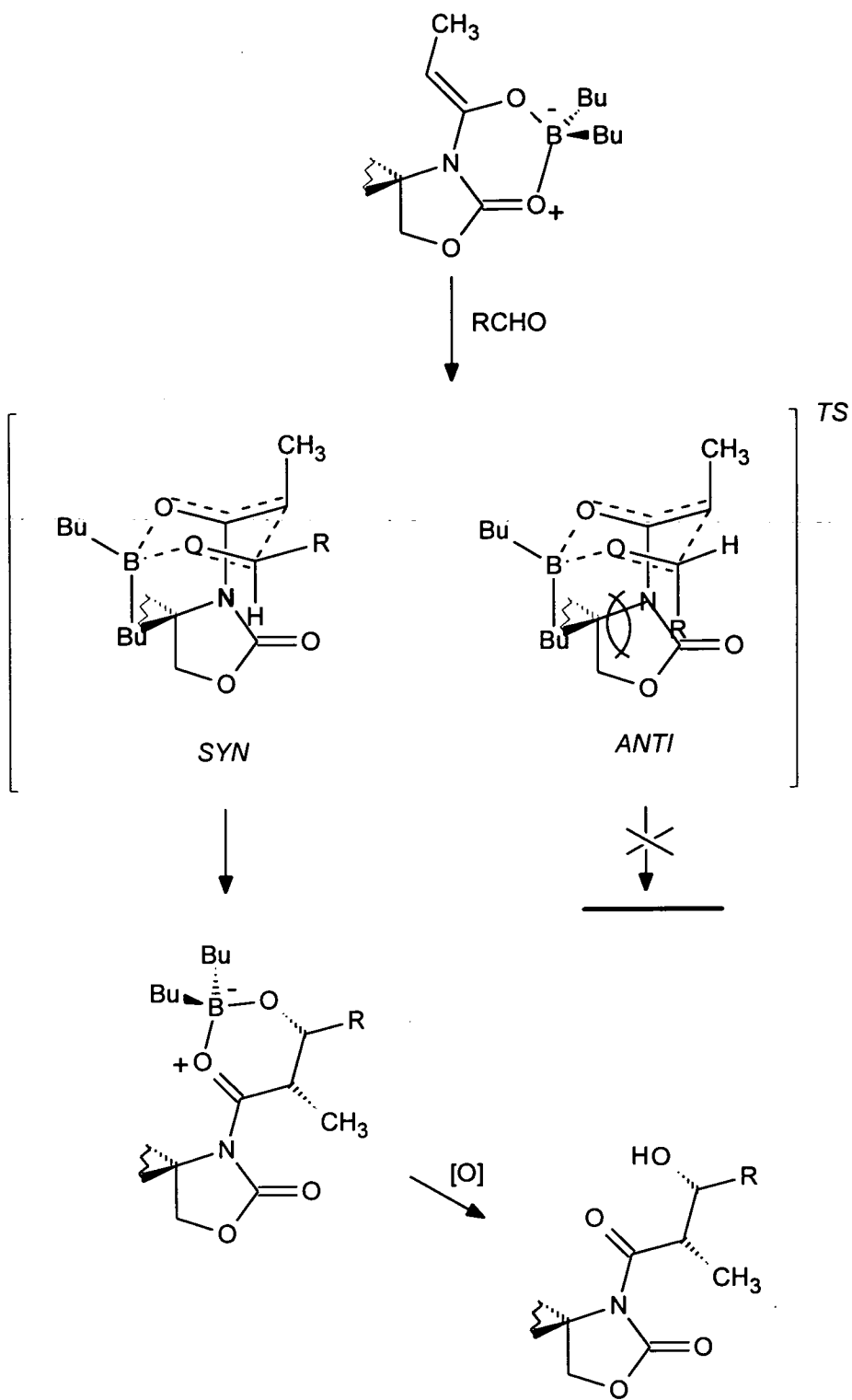


Figure 18

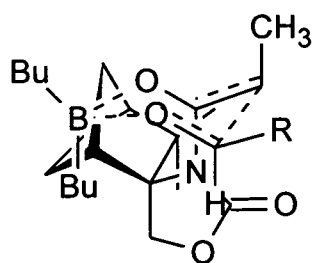


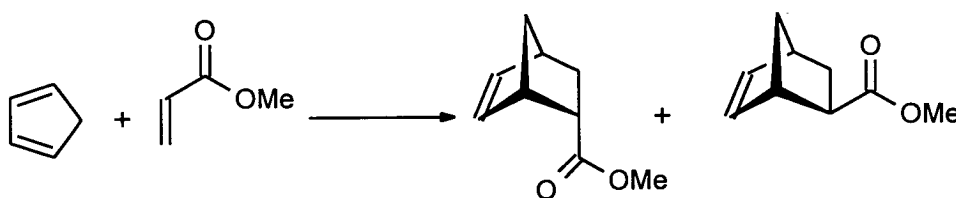
Figure 19

2.5 Asymmetric Diels-Alder Cycloaddition Reactions

There are few reactions which can compare with the Diels-Alder cycloaddition for the number of chiral centres which can be set up in a single synthetic step. The high level of control of relative stereochemistry inherent in the reaction means that its use in an asymmetric environment is a powerful tool for the synthesis of chiral non-racemic fragments. A considerable amount of work has been carried out on asymmetric Diels-Alder cycloaddition-reactions and a review detailing these approaches is available²².

2.5.1 Lewis Acid Catalysts in the Diels-Alder Cycloaddition Reaction

Progress in chiral auxiliary-controlled asymmetric Diels-Alder cycloaddition reactions has come about as a result of the understanding and use of Lewis acid catalysts. For many years it has been known that the use of Lewis acids gives a greater degree of relative stereochemical control in the non-asymmetric reaction¹¹⁴.



Conditions	<i>endo</i>	<i>exo</i>
0°C	88%	12%
0°C + AlCl ₃	96%	4%

Scheme 87

This is ably explained by consideration of the frontier orbitals of the reaction. For the most common Diels-Alder reactions, an electron-rich diene reacts with an electron-deficient alkene (the dienophile). As shown in the FMO diagram for the uncatalysed reaction the low lying highest occupied molecular orbital (HOMO) of the diene interacts with the lowest unoccupied molecular orbital (LUMO) of the electron deficient dienophile (Figure 20).

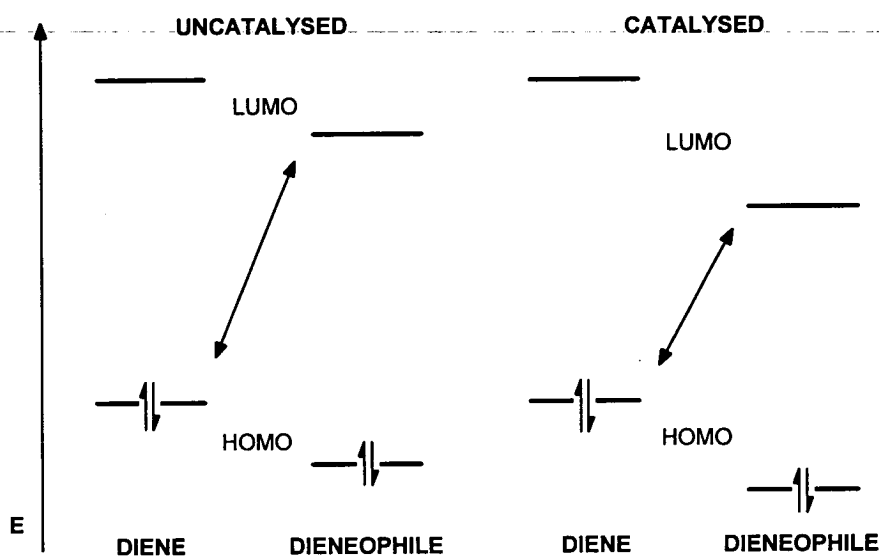


Figure 20

As the energy gap between the interacting orbitals becomes smaller, the overlap is greater, and this becomes the kinetically favoured reaction pathway. This means that a given reaction will proceed most readily by the route where the interacting orbitals are closest in energy. Consequently any method of reducing the energy gap between the HOMO and the LUMO increases the reaction rate *via* this pathway. This can effectively be achieved in two ways, by raising the energy of the HOMO of the diene or by lowering the energy of the LUMO of dienophile. The

latter is by far the most commonly used method of catalysis since simple co-ordination of a Lewis acid to the electronegative site of an electron-withdrawing group lowers the electron density of the conjugated alkene. This results in a consequent lowering of the energy of both the HOMO and the LUMO of the alkene due to a reduction in electron-pair repulsion. This lowers the energy gap between the interacting HOMO and LUMO making reaction *via* the catalysed route more favourable compared to the non-catalysed route. By working at low temperatures the energy difference between the transition states can be exploited so that the reaction operates purely by the catalysed route. A highly important feature of co-ordination of the dienophile is that changes in the size of the frontier molecular orbital coefficients on the individual atoms means that the reaction becomes more regio- and stereoselective as a result of increase in the energy gaps between various transition states. This alteration in the coefficients occurs as the Lewis acid pulls electron density out of the unsaturated system. Hence, the HOMO has a larger coefficient on the oxygen and the LUMO must have a larger coefficient on the carbonyl carbon.

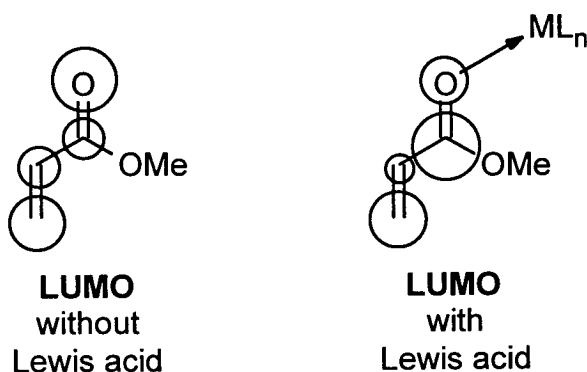


Figure 21

This large coefficient increases the preference for secondary orbital overlap, and a greater *endo*-selectivity is noted for Lewis acid catalysed reactions with cyclic dienes.

Greater regioselectivity with unsymmetrical dienes is similarly brought about by the concomitant alterations to the sizes of the coefficients on the C_α and C_β atoms.

For oxazolidin-2-one acyl imide systems, Lewis acids can lead to reaction through chelated transition states. The most successful approach has undoubtedly been that adopted by Evans^{11,15}, who employed diethylaluminium chloride, a Lewis acid capable of chelating two carbonyls *via* loss of chloride anion, which is stabilised as a complex ion with a further molecule of the Lewis acid. The cationic nature of the transition state means that the dienophile is particularly electron deficient. From an FMO point of view, this not only makes the reaction more regio- and stereoselective, but also increases its rate considerably *versus* the non-catalysed reaction, to the extent that it becomes the sole reaction pathway.

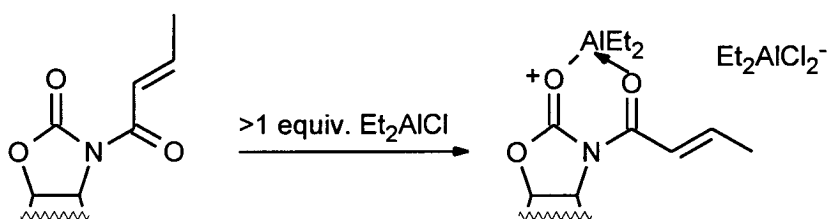
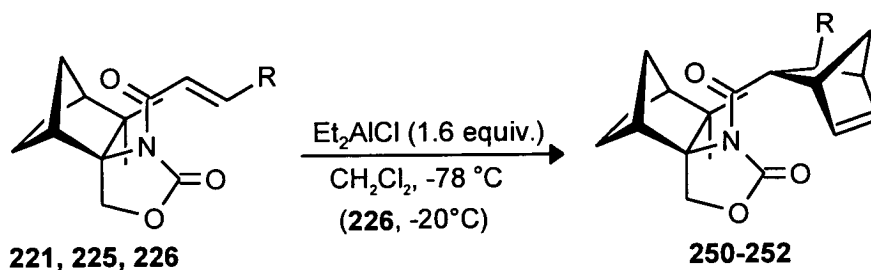


Figure 22

2.5.2 Asymmetric Diels-Alder Reaction of Unsaturated Imides of Chiracamphox

The acryloyl, crotonyl and cinnamoyl imides (**221**, **225** and **226**, respectively) were subjected to Diels-Alder cycloaddition reactions with cyclopentadiene under the conditions used by Evans. Thus, a cooled solution of the imide was treated with freshly cracked cyclopentadiene, and once the solution had recooled, it was then treated with 1.6 equivalents of diethylaluminium chloride. The order of addition is

quite important as prechelation of the imides can lead to polymerisation, or 1,4-conjugate addition of an ethyl group from the aluminium reagent (see 2.6.2). The completion of reaction was witnessed by loss of colour associated with the

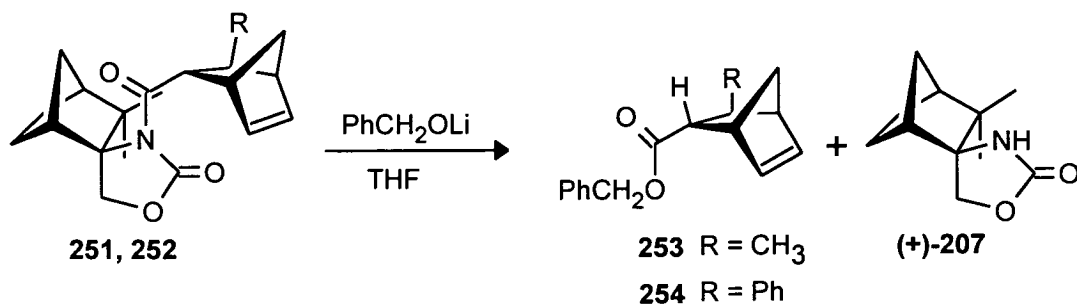


	R	yield	<i>endo/exo</i>	d.e. (<i>endo</i>)
250	H	95%	>98:2	95%
251	CH ₃	98%	>98:2	>95%
252	Ph	97%	>98:2	>95%

Scheme 88

conjugated cationic intermediate, since this conjugation is lost as the reaction proceeds. The relative rate of reaction varied with the bulk of the substituent, the particularly slow reaction rate of the cinnamoyl imide being attributed to the extra stabilisation imparted by conjugation with the phenyl ring. The rates were considerably slower than those reported for the same imides of Chirabornox^{5, 82}, hinting that the transition state was higher in energy and possibly more crowded, thus suggesting the possibility of greater interaction with steric-controlling groups. The products were routinely isolated and then freed from polymeric cyclopentadiene by rapid chromatography. The crude products thus obtained were analysed by high-field ¹H NMR spectroscopy which indicated that essentially a single diastereomer had

formed in each case and d.e.'s of 95% or greater were consequently assigned to these reactions. The proton spectra of the acryloyl adduct **250** was slightly less clean, but no definite signals attributable to the *endo*-diastereomer could be observed, and in this instance a d.e. of >95% has been provisionally assigned to the reaction. This outcome is a startling increase in d.e. compared to the results obtained with same imides of **180** (2.1.1), which for the acryloyl imide proceeded with a d.e. of only 59%. This increase is attributed to low C_{α} -C=O rotor control rather than poor facial shielding since one C_{α} -face is known to be highly shielded in enolate reactions. The control of the C_{α} -C=O rotor in imides **221**, **225** and **226** appears to be due mostly to the unfavourable interaction with the methylene bridge of the bicycloheptane system. Examination of molecular models shows a severe clash between a hydrogen atom of the acrylate moiety and the H_{11a} atom on the bridge in the *s-trans* conformation, and on this premise, the reaction is assumed to occur *via* the *s-cis* conformation. This also appears to be the preferred conformer of the chelated Chirabornox imides, but obviously not to the same extent. As the reaction is inherently highly *endo*-selective because of secondary π -overlap with the imide carbonyl, it appears that the *exo*-methyl of the auxiliary is the most important steric controlling group shielding the



Scheme 89

C_{α} -*si* face of the C_{α} -C=O *s-cis* rotamer. This was confirmed by cleaving the newly-formed bicycloheptenes from the auxiliary (Scheme 89). Thus, the crotonyl and cinnamoyl adducts, **252** and **251**, were treated with lithium benzyloxide¹³, a strongly nucleophilic reagent which is known not to epimerise the C_{α} centre of such adducts. Upon treatment with this reagent, two products were formed and these were isolated and identified as the desired esters **253** and **254** together with recovered auxiliary. For both cases, high chemical yields were obtained and comparison of optical rotation of the esters obtained showed that the magnitude was within experimental error of the literature values. The sign of rotation was positive, showing that the C_{α} centres of the esters **253** and **254** were *S* and *R* (note, inversion of priorities due to phenyl substitution), respectively and consequently, are derived from C_{α} -*re* face attack. Thus cyclopentadiene approaches

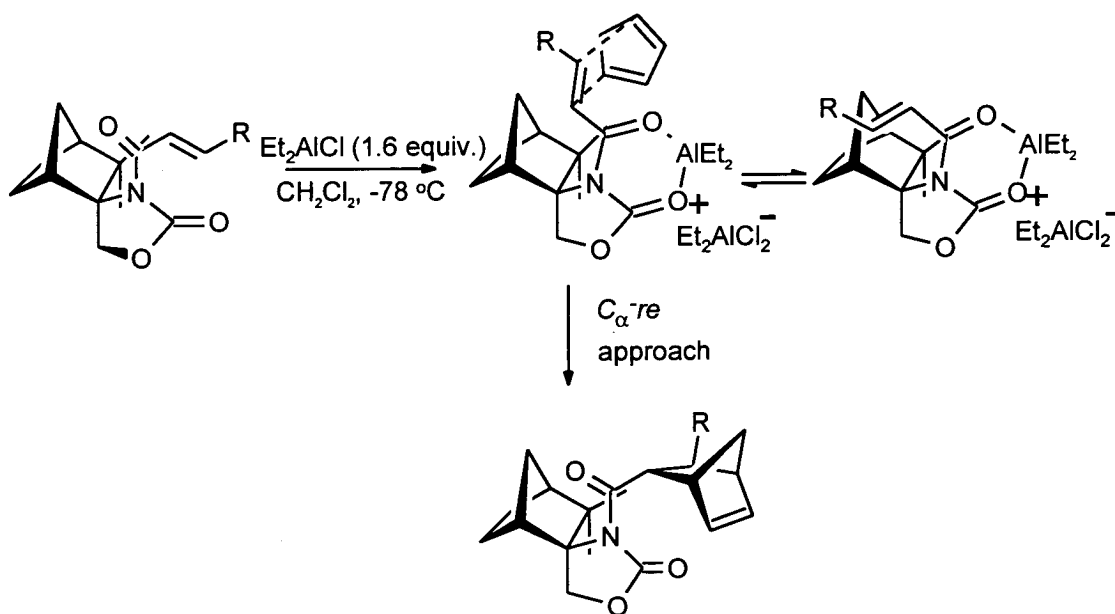
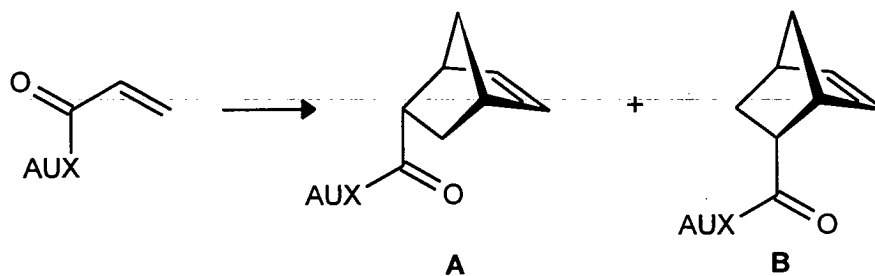


Figure 23

only in the conformation shown in the general transition state in Figure 23 to the upper face of the complex. The selectivity displayed for the acrylate reaction is higher not only than that obtained with the sugar-derived auxiliaries **181** and **215**, but also the contemporary auxiliaries developed by Evans (**5**, **6**) and Oppolzer (**41**). As can be seen in Figure 24 the selectivity is comparable to that obtained using sultam **41** without the need to resort to drastic low temperature conditions.



Auxiliary	Et ₂ AlCl equiv.	solvent	temp °C	yield %	A/B	endo/exo selectivity	d.e. % (endo)
(+)-207	1.6	CH ₂ Cl ₂	-78	95	B	>98:2	95
180	1.3	CH ₂ Cl ₂	-78	100	A	96:4	59
181	1.4	CH ₂ Cl ₂	-78	83	A	98:2	80
5	1.4	CH ₂ Cl ₂	-100	81*	B	>99:1	86
6	1.4	CH ₂ Cl ₂	-100	78*	B	>99:1	90
41	1.5	C ₂ H ₅ Cl	-130	83	A	99.5:0.5	93

* Purified Yield

Figure 24

Overall it appears that Chiracamphox is an effective chiral auxiliary for the control of cycloaddition reactions. The main limiting factor is the difficulty in preparing the important acrylate imide **221** and its instability (2.2.3).

2.6 Asymmetric 1,4-Conjugate Addition to Unsaturated Imides of 207 and Related Reactions

1,4-Conjugate addition in asymmetric synthesis is a highly important process, in that it not only allows the synthesis of chiral centres β to electron-withdrawing groups, but the reaction can be extended to the formation of α -chiral centres *via* enolate trapping reactions. Control of the absolute stereochemistry of these newly-formed chiral centres is possible *via* auxiliary control of either the Michael acceptor or the nucleophile, the effect of neighbouring chiral centres, *e.g.* γ or the use of chiral ligands for the nucleophile. Only the first of these methods is relevant to this work and as such will be discussed in some detail; further information on the other methods is available in a review of this thriving field¹¹⁵.

2.6.1 Auxiliary Controlled 1,4-Conjugate Addition Reactions

The use of unsaturated systems bearing chiral auxiliaries for the generation of new chiral centres by Michael addition is a broad-ranging and adaptable method. A very wide range of carbon nucleophiles are effective in this reaction as shown in Figure 25. Further to this heteroatom substitution of the β -centre is also being actively developed, thus nitrogen⁴³ and silicon¹¹⁶ nucleophiles have all been used effectively (the latter is an hydroxyl equivalent upon oxidation). Quenching of the resulting enolate may be by protonation or by a wide variety of carbon or heteroatom electrophiles.

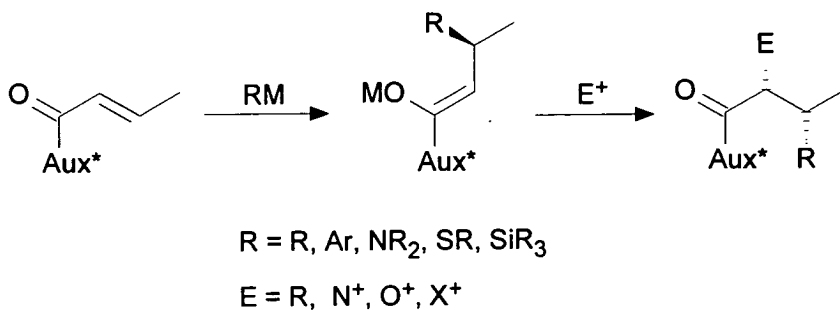
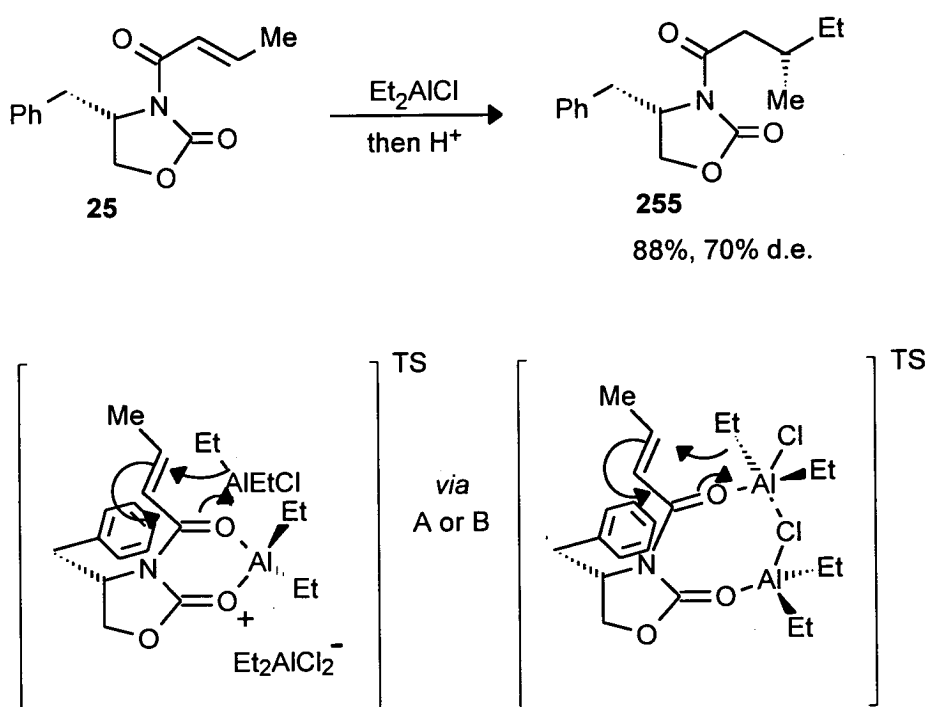


Figure 25

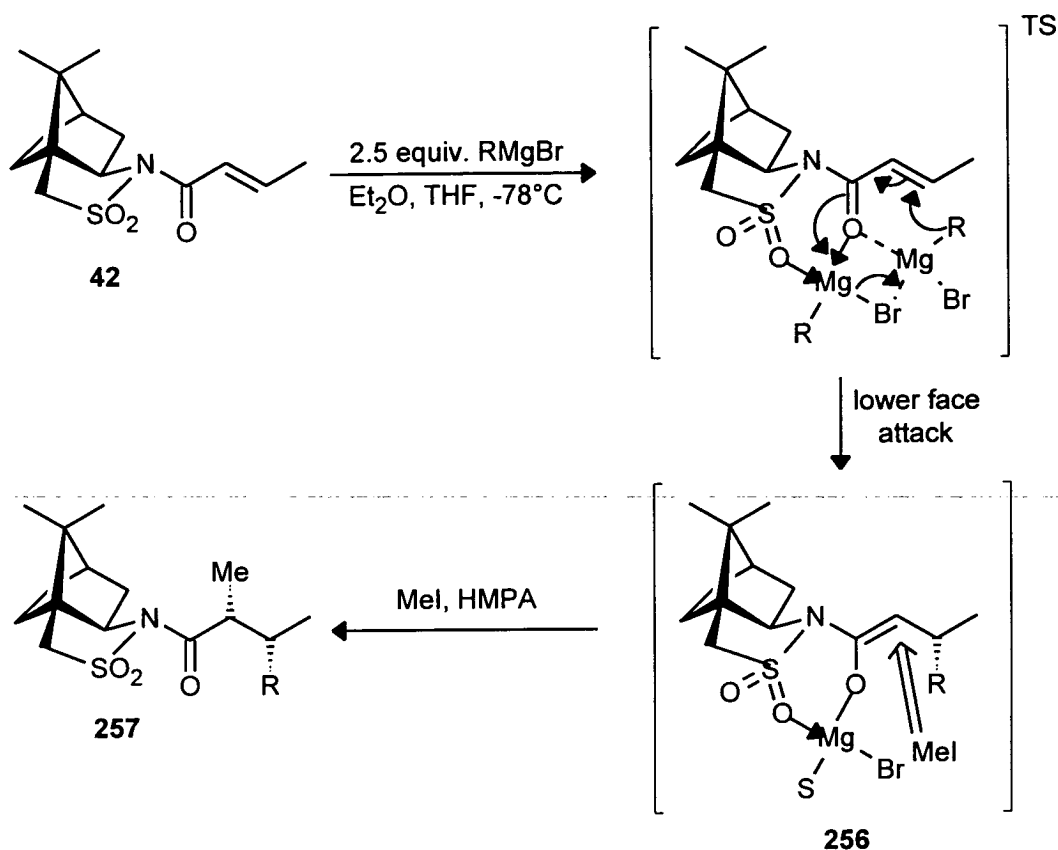
Kunz has found that a variety of dialkylaluminium chlorides can be effectively added in high yield with good diastereoselectivity to enoyl imides of Evans' phenylalanine-derived auxiliary, *e.g.* **25**¹¹⁷. The reaction is believed to occur through a chelated transition state, which allows the benzyl moiety to shield one face of the alkene. The exact nature of the transition state is unclear, although two plausible possibilities exist. Firstly, one based on the chelated intermediate **A**, which is used by Evans to explain the effectiveness of diethylaluminium chloride catalysed



Scheme 90

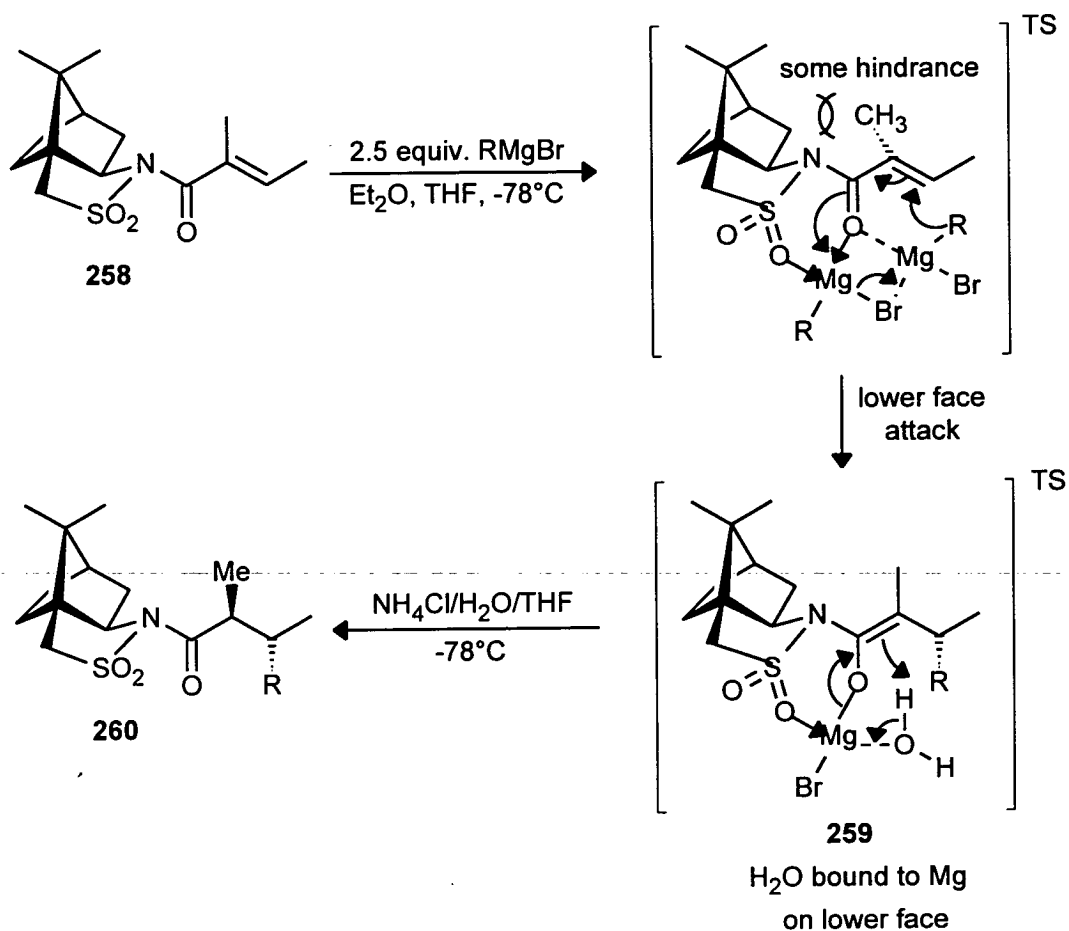
Diels-Alder cycloadditions to unsaturated oxazolidinone imides. This necessitates that the imide carbonyl chelates one aluminium centre whilst also binding the second equivalent of the reagent so that it may deliver the ethyl nucleophile to the unshielded face of the β -prochiral centre. Kunz has proposed an alternative transition state in which an eight-membered chelation system is produced *via* a chloride bridge between two aluminums. Although support for this nature of bonding is readily available (the dimeric nature of aluminium halides, *etc.*), the geometry of the eight-membered ring invites scepticism of this transition state. In order to obtain good overlap of the oxygen lone-pairs with the aluminium centres, the imide carbonyl would have to be distorted by some 30° from the plane of the oxazolidinone ring, which would obviously severely disrupt the π -overlap as envisaged by Evans^{13, 15}. Although protonation of the enolate to give **255** is shown here, Kunz has also described C_α -hydroxylation of the enolate by using an oxaziridine reagent or molecular oxygen to give effectively a transposed aldol substitution pattern.

The two imides of Oppolzer's sultam demonstrate two alternative methods to obtain α -methyl β -alkyl carboxylic acid equivalents. Addition of the Grignard reagent to the crotonyl imide **42**¹¹⁸ is believed to proceed through a transition state where one equivalent of the Grignard reagent is chelated between the imide carbonyl and a sulfoxide. Oppolzer believes that the pyrimidalisation of the nitrogen leads to attack from the lower *si*-face due to the nitrogen lone pair as well as shielding by the bornane skeleton. The chelated magnesium enolate can then be quenched with methyl iodide, which attacks the C_α *re*-face to give the *2R*, *3R* carboxylic acid equivalent **257**.



Scheme 91

An alternative approach to this target is addition of the Grignard reagent to the tigloyl imide **258**. The initial transition state is presumed to be similar to that of the simple crotonyl imide, even though there is the potential for steric hindrance between the C_α methyl and the bornane skeleton. It is believed that in protonation of the enolate **259**, the in-coming water molecule binds to the magnesium atom first, and the proton is then delivered to the C_α *si*-face of the enolate to give the diastereomeric 2*S*, 3*R* carboxylic acid equivalent **260**.



Scheme 92

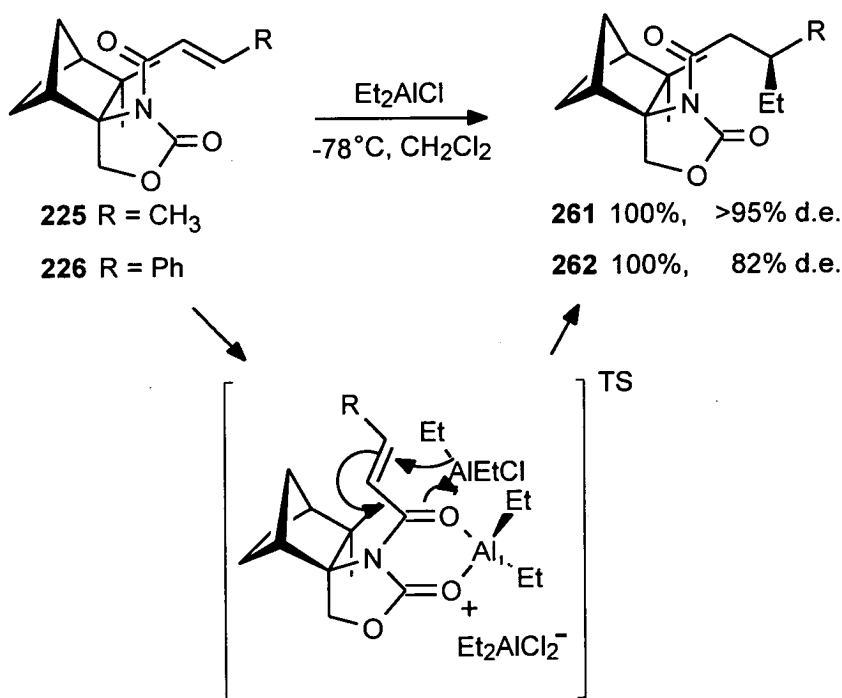
Due to the possibility of interchanging both the substituents and the incoming nucleophiles/electrophiles at the C_{α} - and C_{β} -centres, this type of conjugate addition is a highly versatile form of asymmetric induction.

2.6.2 1,4-Conjugate Addition of Diethylaluminium Chloride to Unsaturated Imides of Chiracamphox

It was known that the crotonyl imide of **180** showed extremely poor selectivity in the conjugate addition of diethylaluminium chloride to give only 11% d.e., presumably due to the inability of **180** to control either the rotomer preference of the C_{α} - $C=O$

bond, or effectively shield the β -face (see Scheme 48, 2.1.1). It was hoped that as the selectivity of the Diels-Alder reaction for imides of **207** was considerably higher than those of **180**, that this increase in selectivity would also be present in these conjugate addition reactions.

When **225** was treated with diethylaluminium chloride at -78°C in CH_2Cl_2 it required some three hours to lose the deep yellow colour compared to a mere 15 minutes for the same reaction with the imide of **180**. This showed that this imide was less reactive presumably due to the molecule not being able to react in all the conformations open to **185b**, due to more effective rotor control and also an increase in steric effects even on the more open face. Nonetheless, a quantitative yield of the adduct **261** was obtained and neither high-field ^1H - or ^{13}C -NMR spectroscopy of the crude product showed any trace of the other diastereomer. Concern that the

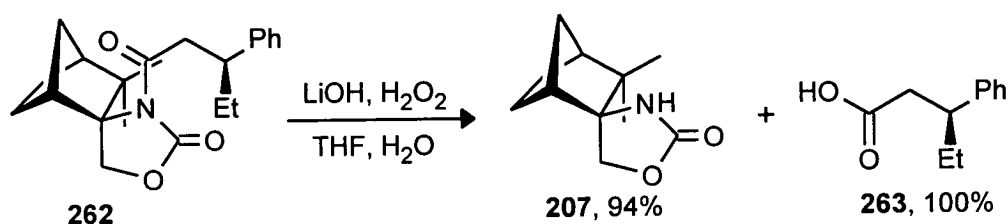


Scheme 93

diastereomers would possibly not show significant chemical shift differences in these spectra, due to the separation of the chiral centre from the auxiliary, was unfounded as the less hindered **180** adduct showed clear differences. Consequently a d.e. of >95% was assigned to the material, far in excess of that obtained with **180**. The cinnamoyl imide **226** was treated in a similar manner and it was anticipated that as this reaction was more selective for the imide **185c** than **185b**, that a single diastereomer would be obtained as before. The reaction proceeded very slowly with the initially formed deep red colour being retained for over 8 hours at -78°C. The reaction was allowed to warm to -20°C overnight, whereupon it was found that the colour had faded. After isolation, the product **262** was analysed by high-field ¹H- and ¹³C-NMR spectroscopy which clearly showed the presence of the diastereomer, a d.e. of 82% was determined upon integration of the respective H_{1a} and H_{1b} resonances. It seemed strange that the cinnamoyl imide should give a less selective reaction than the crotonyl imide, unless allowing the reaction to warm had caused a lowering in selectivity. The reaction was repeated, allowing it to go to completion without raising the temperature above -78°C. The time required for complete reaction was 72 hours, but once the product had been isolated, analysis by ¹H NMR spectroscopy showed that the diastereomeric ratio was unchanged. Interestingly, when the reaction was repeated, adding the imide to the cooled solution of the organometallic (the more orthodox procedure for such conjugate addition reactions), the formation of a lime yellow solution was observed. Furthermore, this reaction occurred within only two hours at -78°C, but the product ratio of **262** remained unchanged. It is believed that this may represent the formation of a less reactive

(possibly aggregate) complex when diethylaluminium chloride is added to the initial excess of the imide. However, the latter procedure does appear to be the more expedient than that initially reported.

Cleavage of the β -ethyl adduct **262** with lithium hydroperoxide yielded (3*S*) 3-phenyl pentanoic acid **263** with an optical rotation of $-49.3^{\circ 119}$; for a chelated transition state this must have been the product of *si*-face attack at the β -centre. Considering a transition state based on the Evans' type chelation system, it is clear that a combination of the *exo*-methyl and the methylene bridge of the camphene skeleton provide a pocket that both prevents the *s-trans* conformation forming and adequately shields the *re*-face of the C_{β} prochiral centre.



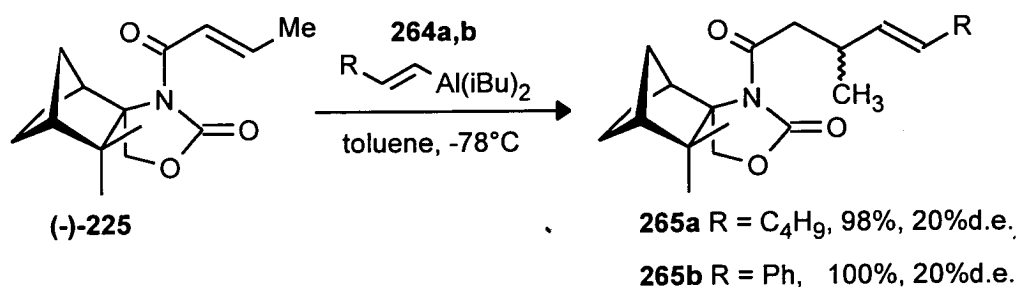
Scheme 94

It should be noted that changes in the solvent polarity do not appear to effect the selectivity of the reaction; **207** and **180** imides were reacted in CH_2Cl_2 , whilst Kunz¹¹⁷ and the Spanish workers¹²⁰ used toluene (in some cases CH_2Cl_2), but importantly Doyle¹²¹ observed that no change in selectivity occurred using either solvent, or on lowering the reaction temperature with imides of a system related to **180**. That solvent polarity changes such as these do not affect the outcome of these reactions, supports the proposal by Kunz¹²² that delivery of the ethyl group is a reaction more akin to a [1,5] sigmatropic migration than anionic nucleophilic attack.

2.6.3 Reaction of Unsaturated Imides of Chiracamphox with Aluminium Vinyl

Reagents

Due to the interest developed in the synthesis of natural products as described later in this thesis (2.7), the conjugate addition of vinyl moieties became a prime concern. As the vinyl moieties are synthons for carboxylic acid functions, their exact nature was of little concern compared with the stereoselectivity of their addition to the crotonyl imide. Due to the ease with which vinyl aluminium reagents could be prepared, it was decided to attempt their addition first, since the corresponding lithium and copper reagents were known to be tedious to prepare. The first vinyl alane to be tried was *trans*-hex-1-enyl diisobutylaluminium **264a**, prepared from 1-hexyne and DIBALH¹²³. The crotonyl imide was treated with **264a** and the reaction observed to occur within 2 hours. Upon isolation, the product was found to be a mixture of two diastereomers (d.e. 20%). *trans*-Integrity in the product was shown since the vinyl signals of the diastereomers had the same chemical shift, whereas the presence of the *cis*-isomer would probably have been shown by a shift of *ca.* 1 ppm¹²⁴. Addition of the styryl alane reagent **264b**, derived from phenylacetylene, was also attempted, this also gave a product with a d.e. of 20%. This low selectivity



Scheme 95

presumably reflects the inability to form a cationic chelated intermediate as with diethylaluminium chloride. However, compared to Kunz's findings¹²² that trialkylaluminiums do not react with unsaturated oxazolidin-2-one imides, the delivery of the vinyl group appears to be facile.

It must be assumed that a closed transition state is unlikely due to the maximum of tetrahedral co-ordination for aluminium. In order to minimise steric and dipolar effects, the intermediates shown in Figure 26 could be considered as favourable. A plausible explanation for the low selectivity is that delivery of the vinyl unit to the less shielded face would bring the bulk of an *iso*-butyl group into conflict with the methylene bridge and the *exo*-methyl of the auxiliary. Consequently attack at this face is as high in energy as attack from the more hindered face where the isobutyl encounters no steric repulsion. It is assumed that a similar process operates with **264b**, since the greater bulk of the phenyl group appears to have caused little increase in the stereoselectivity of the reaction due to it being far from the reactive site.

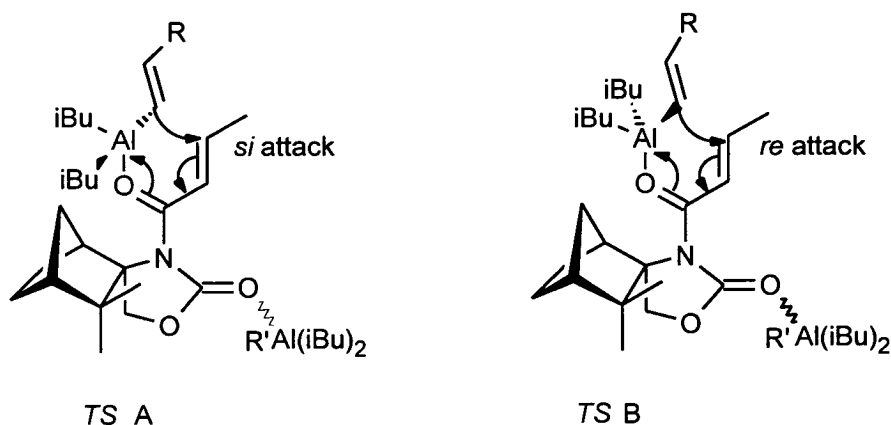


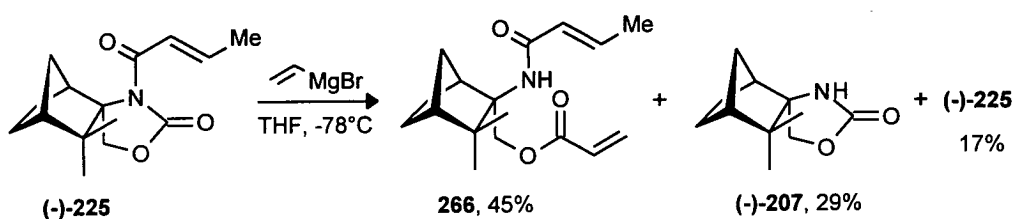
Figure 26

Abandoning aluminium reagents, since synthesis of the chloro-analogues would have been tiresome, resulted in a switch to the readily available vinyl magnesium bromide as a source of the vinyl group.

2.6.4 1,4-Addition of Grignard Reagents to Unsaturated Imides

Oppolzer has noted that addition of copper(I)salts to Grignard reagents, prior to the addition of unsaturated sultam imides, inverted the stereochemical outcome for the C_{α} -methyl systems¹²⁵. Unfortunately he did not expand this observation to the non-substituted systems. In light of this, it was decided to investigate the uncatalysed reaction first, since it appeared that this could lead to the desired (*S*)-stereocentre by reaction of vinylmagnesium bromide with (-)-225.

Treatment of (-)-**225** with 2.5 equivalents of vinylmagnesium bromide at -78°C in THF produced a yellow colour indicative of a highly polar complex. After quenching, and work-up three components were isolated by chromatography, viz., (-)-**225** (17%), cleaved auxiliary (29%) and a slow running crystalline material (45%).



Scheme 96

Because of its polarity this compound did not appear to be the 1,4-adduct. Moreover high-field ^1H NMR spectroscopy clearly showed five alkene resonances, while ^{13}C NMR spectroscopy displayed four alkene signals (3 x CH, 1 x CH₂), and crucially, the absence of an oxazolidinone carbonyl. The oxazolidin-2-one ring had clearly

been cleaved because the diastereotopic methylene signals had shifted from the normal position of 4.0-4.3 ppm to 4.39 ppm and 5.09 ppm, together with a significant change in the normally immutable coupling constants of 9.0 Hz to 11.5 Hz. From the forgoing information, and the appearance of an NH signal, the compound was deduced to be the amido-ester **266**. Consistent mass spectral and infra-red spectroscopic measurements were also obtained for this compound, which is obviously formed by attack on the oxazolidinone carbonyl with the amido moiety acting as a leaving group. Similarly, the cleaved auxiliary is formed by 1,2 attack at the *exo*-carbonyl with the oxazolidinone as the stabilised leaving group (Figure 27).

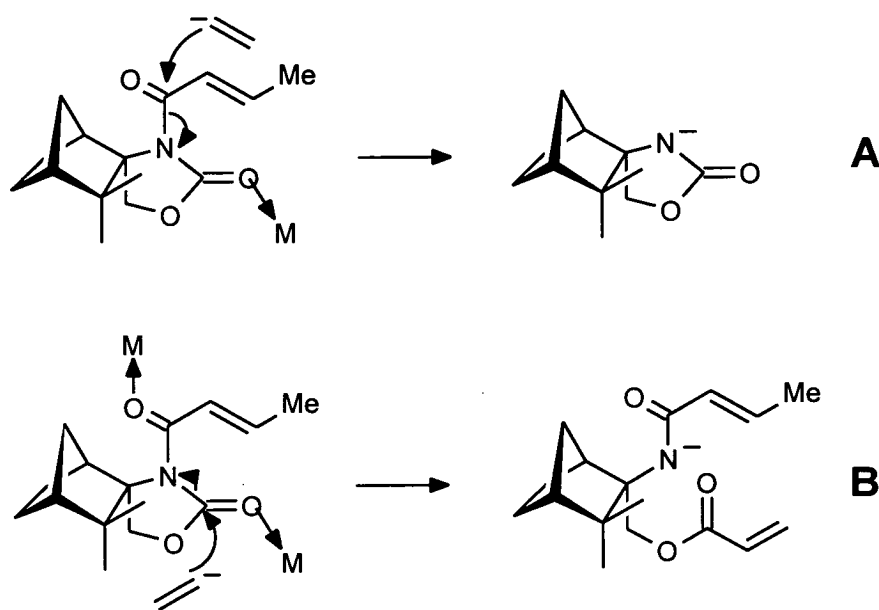


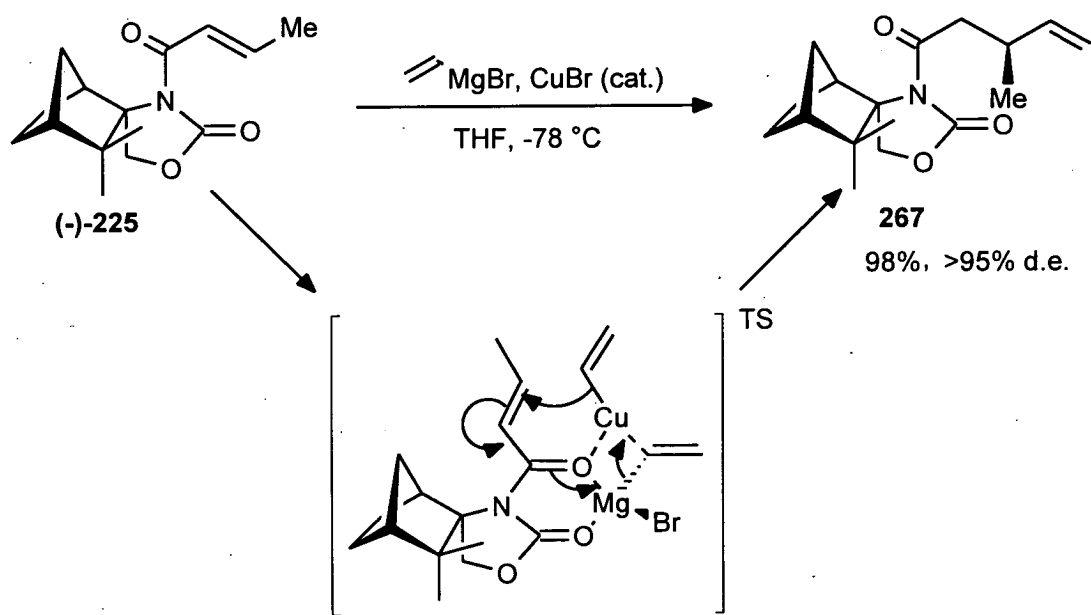
Figure 27

Unfortunately, when this reaction was performed only a very limited high field NMR spectroscopy service was available and a number of experiments were carried out before this compound was unequivocally identified. Firstly, (-)-**225** was treated with only 1.1 equivalents of vinylmagnesium bromide since under these

conditions, Oppolzer had noted that no reaction occurred with the sultams, but merely served to chelate the imides¹¹⁸. By contrast, in our case little amido-ester **266** was observed, but 68% of cleaved auxiliary was obtained. A similar result was found when 2.5 equivalents of reagent were used, but the reaction carried out in diethyl ether. In this case, 8% of **266** was obtained but the major product was still (-)-**207**. In an attempt to force the reaction to proceed in a 1,4-manner, it was decided to define the transition state by pre-chelating the imide with diethylaluminium chloride. The first attempt was surprisingly unsuccessful, no problems were observed with competitive addition of ethyl groups on use of 1.3 equivalents of this Lewis acid, but on addition of 1.1 equivalents of vinylmagnesium bromide the colour of the complex was lost and no sign of the reaction was detected even after 3 hours, 92% of starting material was recovered. The reaction was repeated, but this time using 2.5 equivalents of vinylmagnesium bromide, again all colour disappeared after the addition of only *ca.* 0.3 equivalents of Grignard reagent. The diethylaluminium dichloride was obviously reacting with the vinylmagnesium bromide and presumably the vinyl group was being delivered to the chelated aluminium. The removal of excess Lewis acid would give rise to a non-chelated system such as **B** in Figure 27. The major difference with these final conditions was that (-)-**225** was almost completely converted into **266** (66%) and auxiliary (18%). It can only be assumed that the Lewis acids co-ordinated to the two carbonyls to make this a highly electron-deficient system. Consequently, 1,2 attack is favoured over 1,4 attack and the carbonyl of the oxazolidin-2-one becomes the most activated of the pair. It was thus apparent that vinylmagnesium bromide was too hard a nucleophile to add in a

conjugate manner to the soft β -position, and instead attacked the harder carbonyl, with the use of Lewis acids merely compounding the problem. Even though there was doubt about which stereochemistry would be produced from a copper-catalysed reaction it was decided to try this avenue of approach in any case.

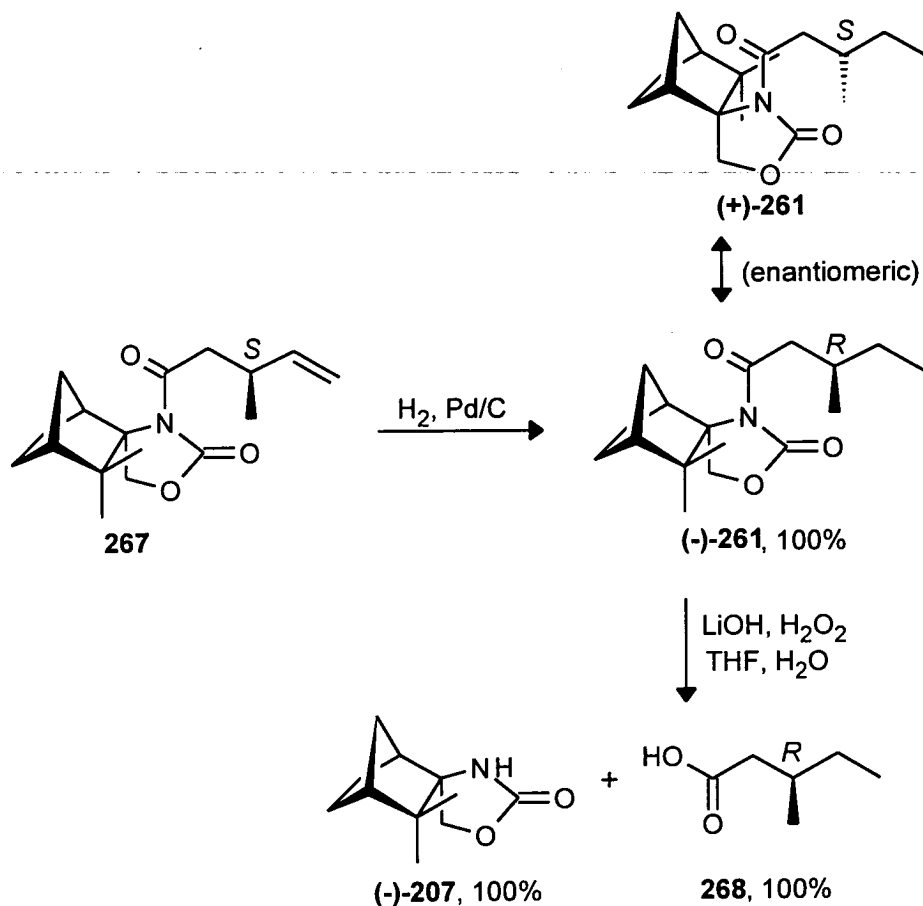
Reaction of (-)-**225** with vinyl magnesium bromide in the presence of a catalytic amount of copper(I) bromide (20 mol%) proceeded smoothly to give a 1,4-conjugate addition product as verified by low-field ^1H NMR spectroscopy. TLC analysis of the reaction mixture also indicated that no appreciable quantities of other material had been formed. High-field ^1H - and ^{13}C -NMR spectroscopy showed that the material was essentially a single diastereomer of the 1,4-adduct.



Scheme 97

In order to determine the absolute stereochemistry at the of the β -centre, the alkene moiety in **267** was hydrogenated over Pd/C to give the saturated β -ethyl adduct. The enantiomeric *S* diastereomer (+)-**261** was already known, so the reduced

material was compared with this compound (^1H NMR and $[\alpha]_D$) and appeared to be identical except for the sign of optical rotation. The new stereocentre in the hydrogenated product was thus assigned as *R*, but so that its identity as (-)-261 could be conclusively proven, this adduct was cleaved with lithium hydroperoxide under normal conditions to give (*R*) 3-methylpentanoic acid 268; this indicated that the



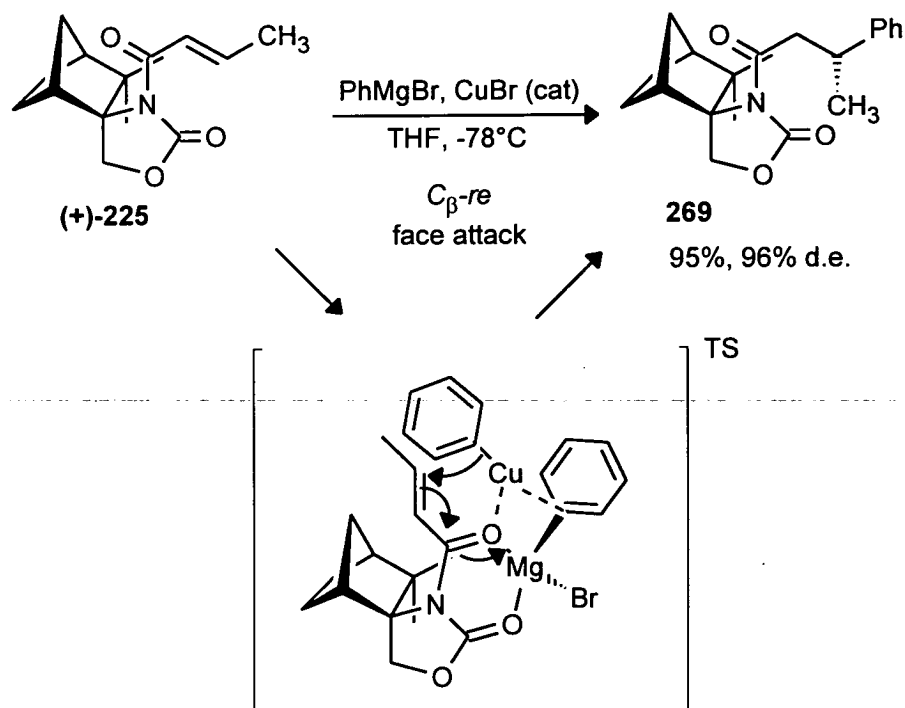
Scheme 98

stereocentre in the vinyl adduct was *S* (note, change of priorities). The formation of the *S*-stereocentre by this reaction can be explained by invoking a transition state similar to that postulated by Oppolzer for the addition of an alkyl Grignard to sultam imides without copper catalysis. In this case a molecule of the Grignard reagent is chelated between the two carbonyls, locking the molecule in the same geometry as

that produced by diethylaluminium chloride chelation. It is proposed that a molecule of vinyl copper is then bound to the imide carbonyl and *via* the π -bond to the vinyl group of the Grignard reagent (or possibly *via* the bromine). Due to shielding by the so-called 'alkyl pocket', the vinyl group is delivered from the soft copper atom to the *si*-face of the β -centre. In the process the chelated magnesium traps out the enolate and a molecule of vinyl copper is reformed (or copper bromide which could continue to catalyse the reaction). Since the selectivities of the diethylaluminium chloride and copper-catalysed vinyl Grignard additions are both high, it is not unreasonable to believe that the transition states through which they proceed will be geometrically similar. It was found later that the use of a large excess of Grignard was not necessary (contrast with Oppolzers findings that 2 equivalents are required for non-copper catalysed reaction with alkyl magnesium halides, one for chelation and the second as the nucleophile) and that 1.3 equivalents with 0.2 equivalents of copper(I) bromide sufficed, this lends some support to the mechanism above.

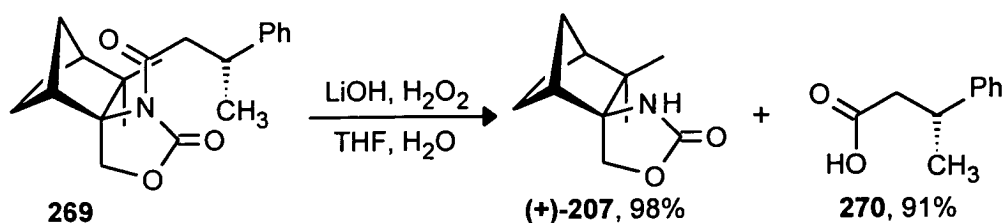
To extend the utility of this conjugate addition, reaction of (+)-225 with phenylmagnesium bromide was attempted. Thus, the crotonyl imide was added dropwise to a solution of phenylmagnesium bromide (3 equivalents) and copper(I)bromide (0.2 equivalents) in THF at -78°C . A transient yellow colour was noted as each drop was added, and after 30 minutes the starting material was seen to have been consumed and a single product spot was observed by TLC analysis. The crude product was isolated in high yield and examined by high-field ^1H NMR spectroscopy, which showed only ~2% of the minor diastereomer to be present; this could be said with some certainty since a mixture of the diastereomers was in hand

(2.7.4). A d.e. of 96% was assigned and as **269** was highly crystalline, it was easily purified to give a single diastereomer. Interestingly the resonances of the methylene



Scheme 99

protons of the oxazolidin-2-one moiety, showed a similar large shift for the diastereomers as was noted for the α -benzyl propionate adducts **233** and **238**. Also, the signals from these nuclei in the major isomer correspond closely to the minor diastereomer of the β -ethylated adduct **262** and *visa versa*. Although this was a first indication that the stereochemistry was opposite to that of **262**, it was proved by cleavage of the adduct from the auxiliary by treatment under standard conditions with lithium hydroperoxide, to yield the acid **270**. **270** Had an optical rotation of -44.3° (*Lit.* -57^{125}), which showed that the stereocentre was *R*. On this basis it is believed that a similar transition state to that proposed for vinyl conjugate addition is operating in this highly selective reaction.



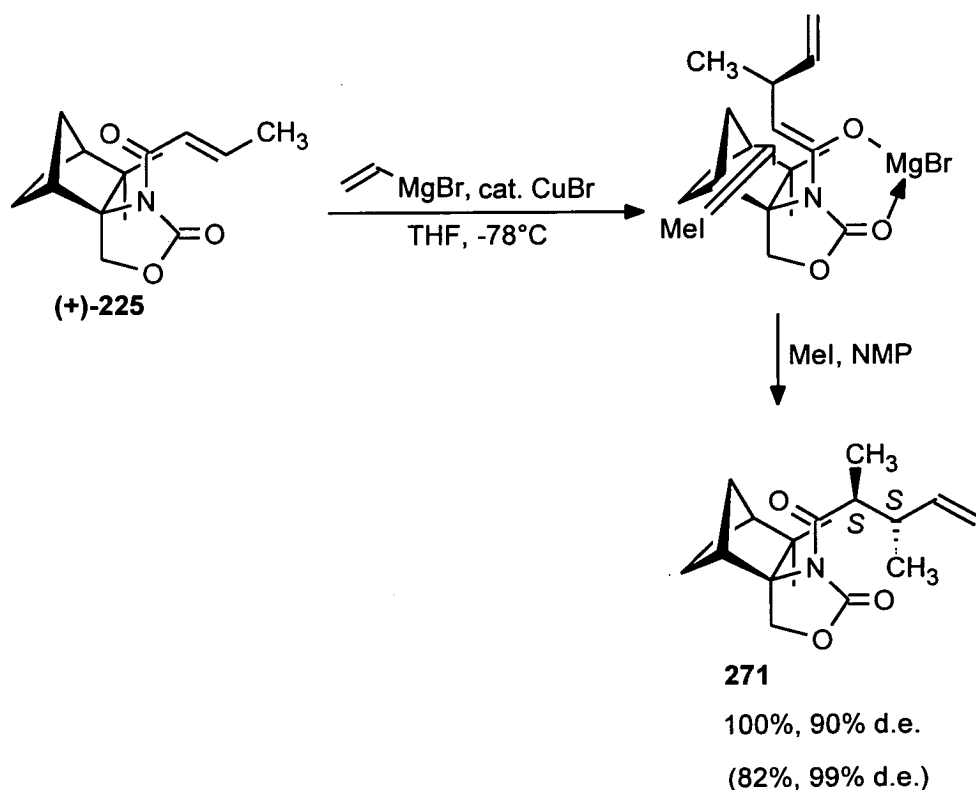
Scheme 100

Further work will obviously be needed to show that these reactions are general and also that addition of a saturated Grignard reagent is also possible with similar selectivity.

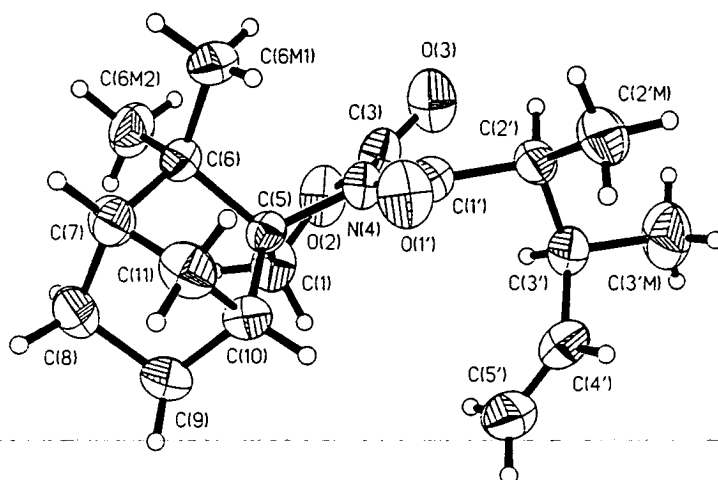
2.6.5 Electrophilic Quenching of Intermediate Enolates

To further extend the utility of this stereochemical induction it was decided to react the intermediate enolate with an electrophile other than proton. This would not only demonstrate the possibility of forming two contiguous chiral centres, but give a direct picture of enolate geometry, if one assumes chelation control in the electrophilic alkylation reaction; this would help to confirm the proposed transition state. The possibility of using only a small excess of organometallic reagent meant that in the electrophilic quench, fewer side reactions would be encountered. Oppolzer achieved methylation of such enolate intermediates by using the polar co-solvent HMPA (*ca.* 30 equivalents)^{102, 118}, but due to health risks with this solvent, *N*-methylpyrrolidinone NMP was used as a substitute as it had performed well in the activation of lithium enolates (2.3.2). Thus, after conjugate addition was completed, methyl iodide was added followed by NMP as the reaction was warmed to -15°C. This procedure led to rapid reaction to give a near quantitative yield of the α -methyl

β -vinyl adduct **271**. High field ^1H NMR spectroscopy indicated that a second diastereomer was present (almost certainly the C_α diastereomer), integration of the respective H_{1a} and H_{1b} resonances, indicated 90% d.e.. Unlike the non- α -substituted adduct **267**, **271** was crystalline presumably due to reduction in the degrees of freedom caused by the α -substituent. An X-ray structure of **271** was determined (Figure 27a) and this clearly showed the stereochemistry to be $2S, 3S$ (note, opposite enantiomer to **267**, but also inversion of priorities at the β -centre due to α -methylation). The stereochemistry of the α -centre clearly corresponded to the $Z(O)$ enolate being formed *via* the *s-cis* conformation in the transition state (see Scheme 97).



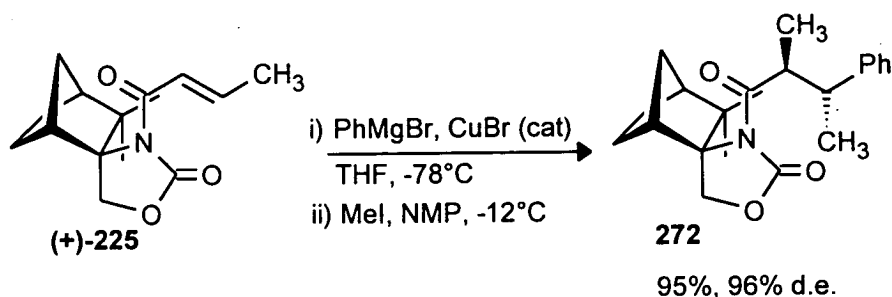
Scheme 101



ORTEP Drawing of the X-ray Structure of 271

Figure 27a

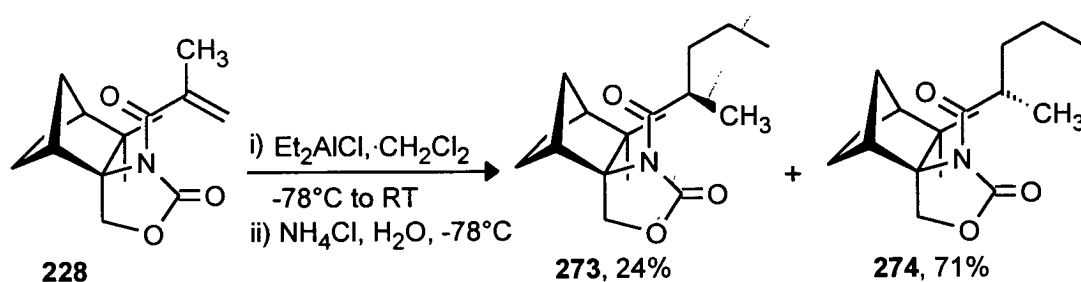
Using the same conditions as before for phenyl Grignard addition and enolate trapping with methyl iodide, gave almost a single diastereomer of **272** (96% d.e. by integration of H_{1a} and H_{1b} resonances). The product was isolated in high yield, but as yet, it has not been cleaved to prove the stereochemistry at the α -centre. However, it is assumed to be *S* considering the nature of the reactions involved.



Scheme 102

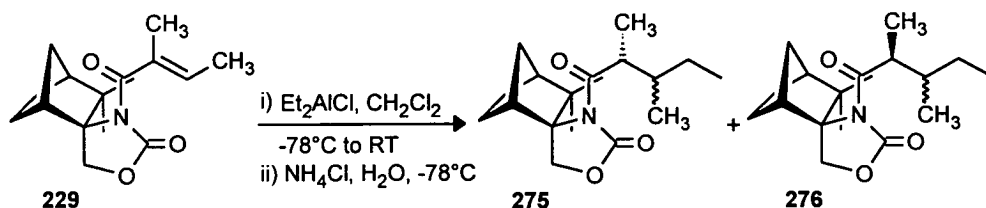
2.6.6 Attempted Stereocontrol of Enolate Protonations

A brief investigation has been carried out into the possibility of using protonation of enolates derived by 1,4-addition to C α -substituted unsaturated imides. Two imides were chosen, viz, methacryloyl **228** and tigloyl **229** whose synthesis has been described in 2.2.3. Due to the simplicity of the diethylaluminium chloride addition, this reaction was carried out first and **228** chosen as the substrate since only one chiral centre can be formed. Unlike the other reactions carried out with diethylaluminium chloride, the colour of the cationic complex was seen to persist even at room temperature for a number of hours. The reaction was quenched with aqueous THF at -78°C and the product isolated. TLC analysis showed the presence of two compounds in the reaction mixture, whose high-field ¹H NMR spectra indicated the two diastereomers **273** and **274**, in a ratio of 3:8 (45% d.e.). The provisional assignment of the stereochemistry of the products was based on the chromatographic mobility of the diastereomers, those of type **273** are known to be more rapidly eluted.



Scheme 103

The reaction was repeated using **229** as substrate, and again after a slow reaction, TLC analysis indicated the formation of two products. Again ^1H NMR spectroscopy appeared to show the presence of two products, but after separation by chromatography, analysis of each fraction by ^{13}C NMR spectroscopy showed them to contain two diastereomers in almost equal proportions. It is assumed that the chromatographically separable fractions represent the C_α diastereomers, giving a diastereoselection at this centre of 3:1. It is presumed that conjugate addition is essentially non-specific, but protonation of the resulting enolates (what ever their geometry) shows a slight specificity. The diastereomers were neither separated nor identified and it appears that this procedure is of limited use.



Scheme 104

Addition of other organometalics have been attempted but the results have proved inconclusive and are not reported here. Generally a combination of 1,4-conjugate addition and alkylation would seem to be preferable in the synthesis of α,β -substituted carboxylic acid equivalents.

2.7. Enantioselective Synthesis of a Class of Di- and Tri-

Substituted γ -Lactones: the Paraconic Acids

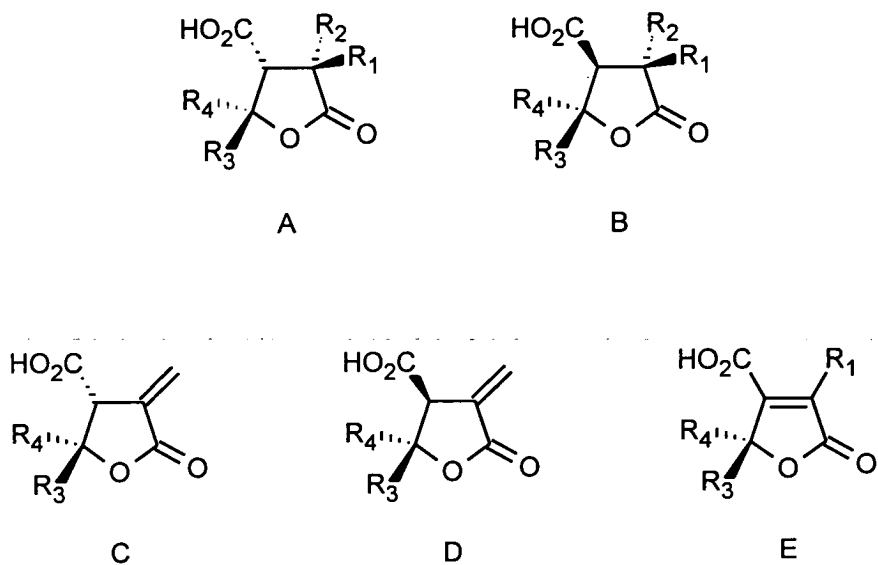
Due to the wide range of reactions which Chiracamphox was capable of controlling with a high degree of stereoselectivity, it was obvious that a suitable concluding piece of research would be to apply the auxiliary to a natural product synthesis. To demonstrate its broad scope, the synthesis of a natural product which demanded the use of more than one type of asymmetric reaction seemed logical. In the interest of efficiency it was preferable if these reactions derived their asymmetric bias from the same chiral auxiliary. The desire to induce all the asymmetry from the auxiliary would mean that all the chiral centres would have to be formed reasonably close to the auxiliary. This encouraged us to seek a natural product with a number of contiguous chiral centres. Given that a number of stereocentres would be present, it would be pleasing to obtain a general route that could produce all of the possible stereoisomers with only minor adaptations to the synthesis (made easier by the availability of both enantiomers of the auxiliary).

2.7.1 The Nature and Biological Properties of the Paraconic Acids

A class of natural products that fitted the above criteria were the paraconic acids (4-carboxy- γ -lactones) shown by the general formulas A to E (Figure 28)¹²⁷. These compounds are most commonly substituted by methyl or methylene on C₃ and an aliphatic side chain on C₅ of variable length. They have been isolated from various species of bacteria and fungi. Of particular interest were the C₅ long-chain

compounds which occur in many species of lichens and have also been obtained from cell cultures.

Representative Paraconic Acids



Name	Form	R ₁	R ₂	R ₃	R ₄	[α] _D ^o
Dihydroprotolichesterinic acid (-)-278	A	H	CH ₃	CH ₃ (CH ₂) ₁₂	H	-49.5
Roccellaric acid (+)-277	B	H	CH ₃	H	CH ₃ (CH ₂) ₁₂	+28.7
Nephromopsinic acid	B	H	CH ₃	CH ₃ (CH ₂) ₁₂	H	-85
Methylenolactocin 149	C	—	—	CH ₃ (CH ₂) ₄	H	-6.8
Protolichesterinic acid	C	—	—	CH ₃ (CH ₂) ₁₂	H	-13
allo-Protolichesterinic acid	D	—	—	CH ₃ (CH ₂) ₁₂	H	-102
Lichesterinic acid	E	CH ₃	—	CH ₃ (CH ₂) ₁₂	H	-32

Figure 28

It is believed that the biosynthesis of the long-chain lichen acids is the same as that of the common fatty acids until the correct length of side chain has been created¹²⁸. The condensation of acetyl coenzyme A is believed to proceed to an intermediate such as A (Figure 29). At this point most of the polyketide units of the chain have been reduced, but it is possible that the β -hydroxy still exists (the required oxygen may be introduced later by reoxidation of the methylene group). Intermediate A or possibly its activated malonate form is then condensed with oxalylacetic acid to yield the unsaturated tricarbonyl compound B, which undergoes decarboxylation with concomitant rearrangement to produce the α -methylene paraconic acid C. This can either be reduced to the saturated analogues or the sensitive α -methylene functionality can be isomerised to the fully conjugate internal alkene to provide the full range of paraconic acids.

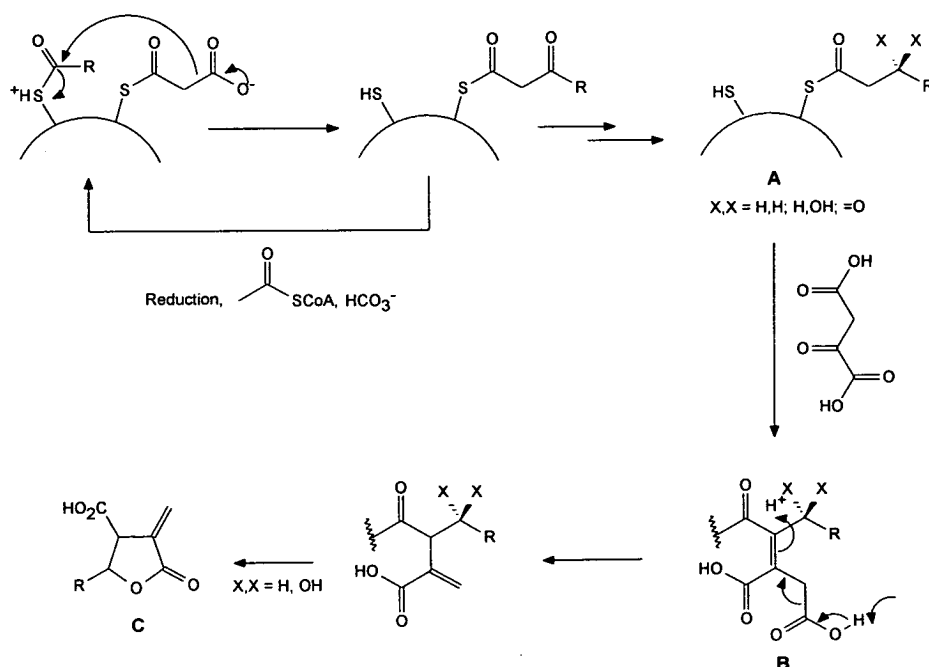


Figure 29

The greatest biological activity of the lichen acids (and their smaller homologues) is shown by the α -methylene substituted compounds, which are noted to be effective cytotoxic agents; many anti-bacterial and anti-viral compounds derive their activity from the an α -methylene lactone function¹²⁹. It is believed that this activity is caused by the Michael addition of biological nucleophiles (thiols, amines) to the reactive unsaturated systems. An example of the proposed method of action is shown in Figure 30. Thus, the sulphydryl groups of a cystine or glutathione residue in an enzyme are irreversibly alkylated by these molecules. Not only are these groups often implicated in the active sites of enzymes but modification of the tertiary structure of the protein may also be induced upon alkylation in less significant areas. The high cytotoxicity of the related sesquiterpene α -methylene γ -lactones is believed to be due to inhibition of DNA synthesis and/or transcription¹³⁰.

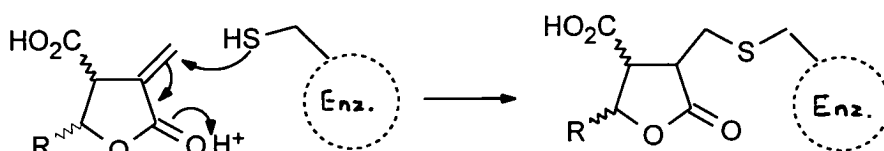
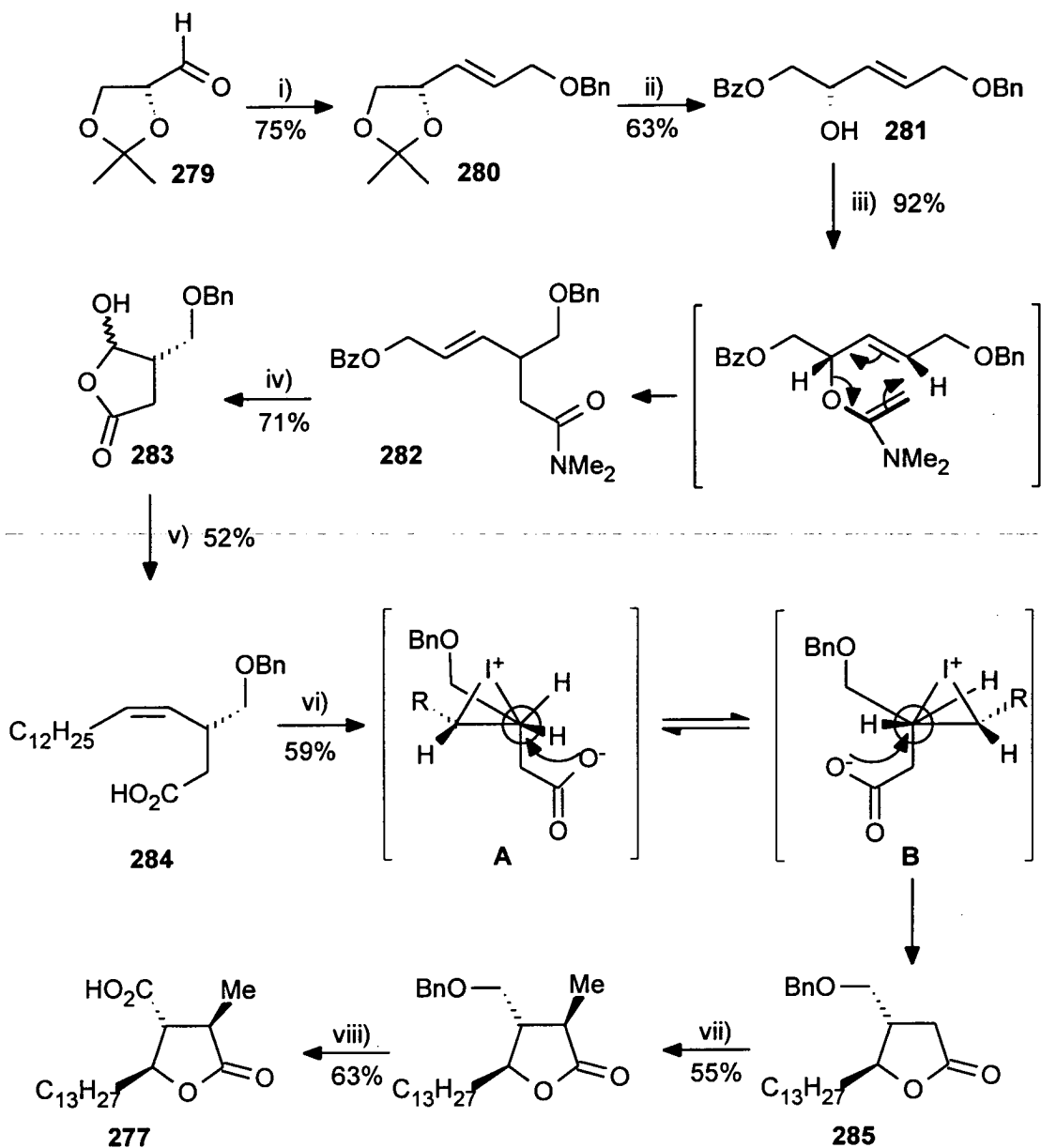


Figure 30

Neighbouring electron-withdrawing groups (unsaturated esters, cyclopentanones, etc.) are known to increase the biological activity of α -methylene compounds. Also the presence of neighbouring hydroxyls has been noted to increase the rate of condensation of α -methylene γ -lactones with sulphur-containing amino acids¹³¹. The high toxicity of these compounds has so far prevented many of them from being used clinically, but much work is being done in this field due to the obvious potential.

2.7.2 Asymmetric Synthesis of Paraconic Fatty Acids

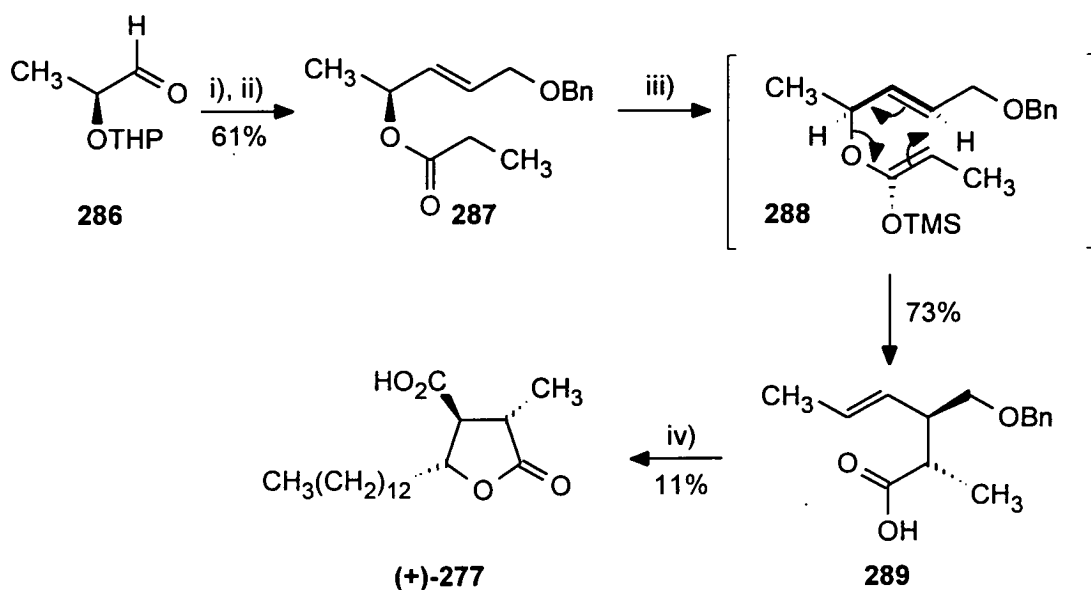
In 1994 Mulzer described three stereospecific routes to both enantiomers of roccellaric acid **277** and its C₃ diastereomer dihydroprotolichesterinic acid **278**¹³². The first route starts from (*R*)-2,3-isopropylideneglyceraldehyde **279**, which by a sequence of Wittig reaction, reduction and benzyl protection yielded the intermediate **280**. Subsequent re-ordering of the protection, then provided the allylic alcohol **281**, which was then condensed with *N,N* dimethylacetamide dimethylacetal *via* an Eshenmoser-Claisen rearrangement¹³³ to give the unsaturated amide **282**. Hydrolysis and oxidative cleavage of the latter gave the acylal **283**, which was found to exist to the extent of 0.5% in the ring-opened form (by NMR analysis) and as such reacted smoothly with the long chain Wittig reagent to give the γ,δ unsaturated acid **284**. Iodo-cyclisation of **284** appeared to proceed exclusively through the transition state **B**, which alleviates 1,3-allylic strain present in the alternative transition state, and after radical dehalogenation the lactone **285** was obtained. The final C-C bond forming step of the synthesis could arguably be considered its downfall, *viz.* reaction of the lithium enolate of lactone **285** to produce a 3:1:1 mixture of the desired lactone, its C₃-stereoisomer and the α,α -dimethyl lactone, albeit in high combined yield. This mixture was first separated by chromatography, following which deprotection and oxidation provided the target compound, (-)-**277** in 1.5% overall yield from (*R*)-2,3-isopropylidene glyceraldehyde. The synthesis thus also provided a 0.5% yield of (-)-**278**.



Conditions : i) **a** $(i\text{-PrO})_2\text{P(O)CH}_2\text{CO}_2\text{Et}$, $t\text{-BuOK}$, -78°C ; **b** DIBALH, -78°C ; **c** NaH, DMF, 40°C , BnCl; ii) **a** MeOH, TsOH; **b** BzCl, Pyr., 0°C ; iii) $\text{CH}_3\text{C(OCH}_3)_2\text{N(CH}_3)_2$, toluene, reflux; iv) **a** NaOH, MeOH; **b** O_3 , MeOH, -78°C then PPh_3 ; v) $\text{C}_{12}\text{H}_{25}\text{CH=PPh}_3$, -78°C ; vi) **a** $\text{I}_2\text{-KI}$, K_2CO_3 , THF/ H_2O ; **b** Bu_3SnH , AIBN, toluene, reflux; vii) LDA, -78°C , MeI; viii) **a** H_2/Pd , MeOH; **b** PDC, DMF.

Scheme 105

A more stereospecific and higher yielding route to the natural enantiomer was then described as shown in Scheme 106. Lactic acid was transformed into (*S*)-*O*-THP-2-oxypropionaldehyde **286** by a known procedure. Thus, as with the previous route a sequence of Wittig condensation, reduction, benzylation and mild acid deprotection gave the allylic alcohol, which was converted in a straight forward manner into the propionate ester **287**. The allyl enol ether **288** required for the Ireland-Claisen rearrangement¹³⁴, was generated from **287** by deprotonation with LDA followed by trapping as the TMS ether. At room temperature **288** underwent stereoselective rearrangement to give the α -methyl γ,δ -unsaturated acid, **289** together with 15% of its C_α diastereomer. This low specificity cannot easily be attributed to



Conditions : i) As for Scheme 105 i), ii) **a**; ii) (CH₃CH₂CO)₂O, DMAP, Pyr.; iii) LDA, TMSCl, -78°C to RT; iv) As for Scheme 105 iv) **b** to vi), viii).

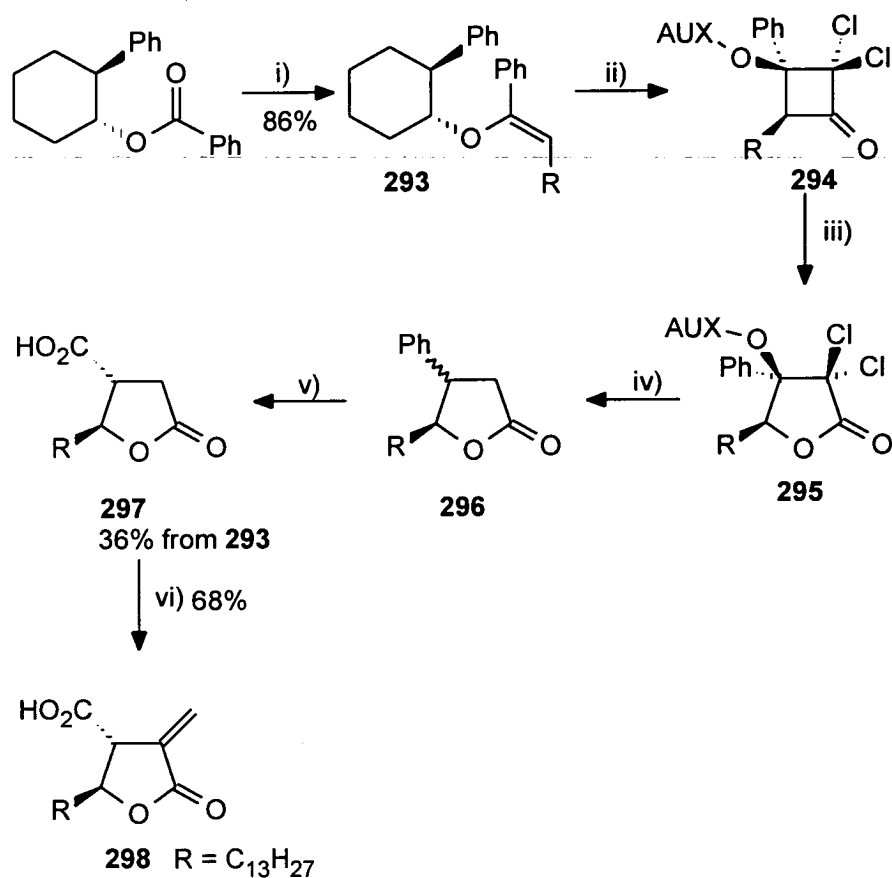
Scheme 106

such a stereospecific reaction as the Claisen rearrangement, but it may arise from the formation of a minor quantity of the *E(O)*-enolate upon deprotonation of **287** with LDA.

The acid **289** was treated as for the previous route, iv) **b** to viii) in Scheme 105, missing only the methylation step to give natural (+)-roccellaric acid in 5.2% overall yield from **286** (the minor isomer produced in the Claisen rearrangement was removed at an earlier stage by recrystallisation). A final synthesis of (+)-**277** and (+)-**278** was performed, starting from diacetone-*D*-glucose, but since the final steps were the same as the initial route it was not particularly stereospecific, nor was it high yielding. The second route rates as the most efficient and stereoselective of the three and is also reasonably adaptable, but due to its length and low yield, the route was open to much improvement.

Recently Greene has examined the enantioselective synthesis of some α -methylene substituted paraconic acids, one of which, viz. protolichesterinic acid **298**¹³⁵ is detailed below. Since the α -methylene functionality is highly prone to isomerisation it was introduced in the final stages. Asymmetry was induced *via* the chiral auxiliary, (1*R*)-*trans*-2-phenyl cyclohexanol, whilst the reactive functionality of the enol ether **293** was formed *via* the Takai *Z(O)*-selective alkylidenation procedure¹³⁶. The purified *Z(O)*-enol ether was treated *in situ* with dichloroketene to give a 9:1 mixture (80% d.e.) of the diastereomers of the cyclobutanone **294**. Due to the instability of the latter, and the lactone **295** formed from it *via* Bayer Villiger oxidation, the diastereomeric purity could not be raised easily. Reductive removal of

the auxiliary followed by hydrogenation gave a mixture of the *cis* and *trans* lactones **296**. The carboxyl group was unmasked by oxidation under the Sharpless⁷² conditions and the ester generated *via* diazomethane. Equilibration with DBU gave the *trans* isomer, which was separated by chromatography and hydrolysed to give acid **297**. Following recrystallisation to increase the enantiomeric purity, **297** was



Conditions : i) $\text{C}_{13}\text{H}_{27}\text{CHBr}_2$, Zn, TiCl_4 , $\text{THF}/\text{CH}_2\text{Cl}_2/\text{TMEDA}$; ii) Cl_3COCl , Zn, Et_2O ; iii) MCPBA, NaHCO_3 , CH_2Cl_2 ; iv) $\text{Cr}(\text{ClO}_4)_2$, acetone/ H_2O ; H_2 , Pd/C; v) RuCl_3 , NaIO_4 , CH_2N_2 ; DBU; 6 M hydrochloric acid; vi) $\text{MeOMgOCO}_2\text{Me}$, DMF, 135°C ; HCHO , PhNHCH_3 , H_2O (buffered).

Scheme 107

shown to be homochiral by analysis of the Mosher's ester¹³⁷ of a derivative using ¹⁹F NMR spectroscopy. In the final step, the acid **297** was α -methylenated by a mild two-step reaction developed by the authors in the synthesis of the related methylenolactocin **149**⁷¹ (see also 1.3.2.3-4). Thus in 11 steps and an overall yield of 17%, enantiomerically pure **298** was obtained; the enantiomer was synthesised by an exactly analogous route.

2.7.3 Choice of Target and Retrosynthesis

The initial target chosen was roccellaric acid **277** which was not known to have been synthesised enantiospecifically (the paper detailing its first enantiospecific synthesis was published by Mulzer around the same time and was thus not found in a *Chemical Abstracts* search, but was found latter when the synthesis was underway).

When roccellaric acid is depicted in its open chain form (as in Figure 31 it can be seen that the hydroxyl group and the C_α substituent are *syn*. Consequently, with R^1 as the chiral auxiliary a *syn* selective aldol condensation could be used to form bond **a**. Disconnection of this bond gives a mono-substituted succinic acid derivative, which can be further disconnected in three ways. The formation of bond **b** was discounted due to the desire to use only a single chiral auxiliary. By contrast disconnection **c** was practical with R^1 as the auxiliary, provided the synthesis was carried out by Michael addition of a methyl nucleophile to an unsaturated system which carried a β substituent that was a carboxylic acid synthon. Similarly disconnection **d** was worthwhile since addition of an anionic carboxylic acid synthon to the readily available crotonyl imide would be capable of creating the new

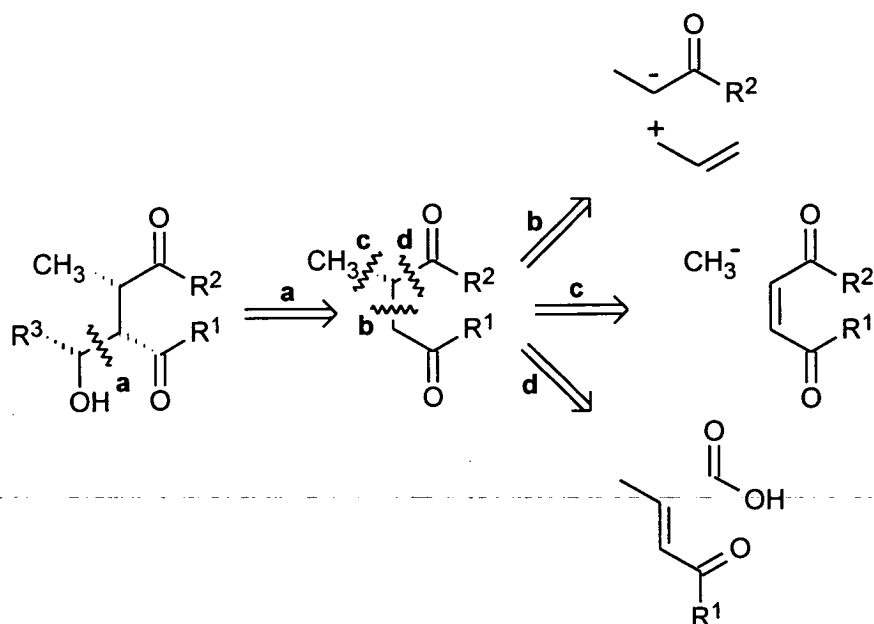


Figure 31

stereocentre in a non-racemic fashion. Given similar chelated transition states, the use of either reaction would allow the generation of the desired stereochemistry at this centre from either enantiomeric form of the auxiliary. On these grounds it was decided to use the most straightforward method to control the aldol condensation to give the required 4*R* and 5*S* stereocentres in (+)-**277**. Thus, for use of the *Z*(*O*) dibutylboron enolate under conditions to give a *syn* product with the indicated stereocentres, the (+) enantiomer of Chiracamphox was required, with the appropriate choice of unsaturated substrate and Michael reagent (Figure 32).

In order to create the correct stereochemistry in the Michael addition with (+)-**207**, it was necessary to make disconnection **c**, *i.e.* add a methyl group to the unsaturated system bearing the carboxylate synthon. This would be the case provided that the Michael reaction proceeded through a chelated transition state and delivered the nucleophile to the C_β *re* face. An alkene moiety was chosen as the

synthon for the carboxylic acid since it would have little effect on the outcome of the subsequent asymmetric aldol reaction, and moreover, the true functionality could be revealed by a variety of mild oxidative methods.

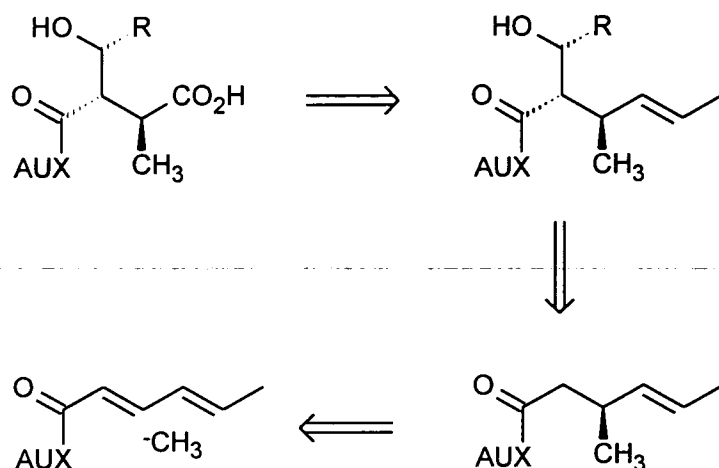
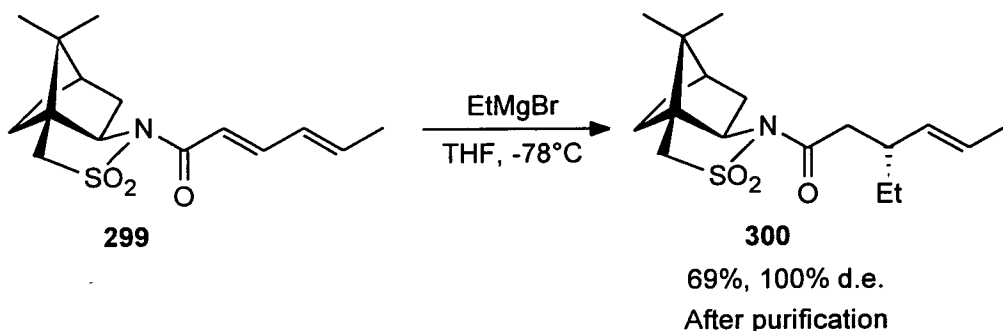


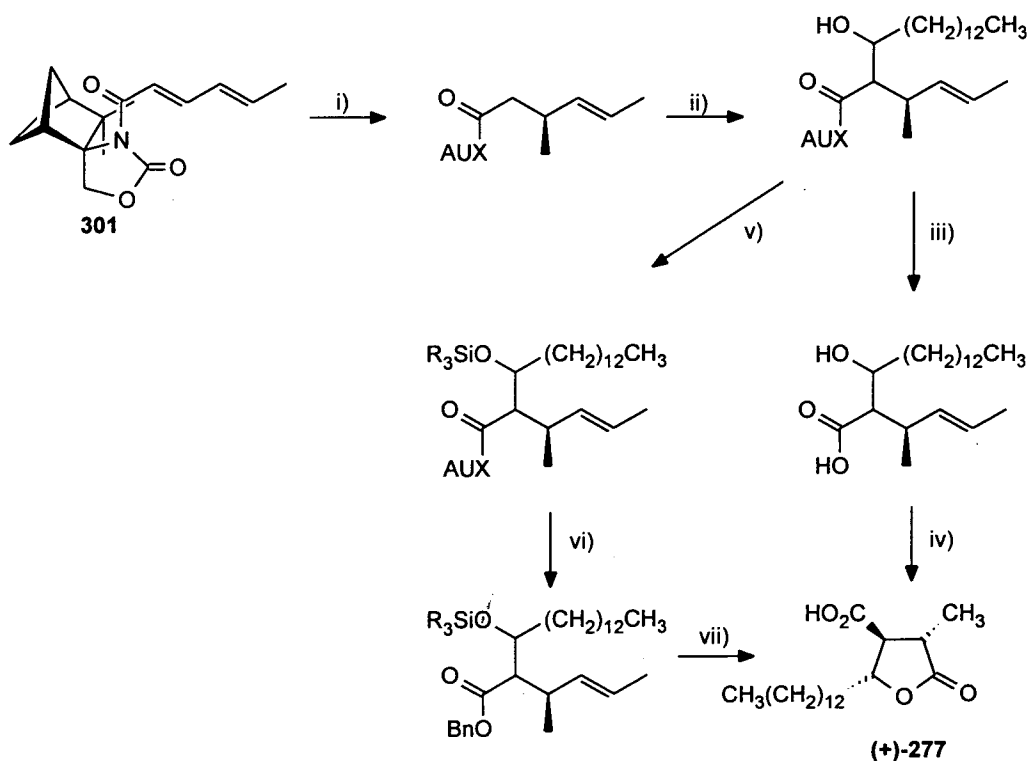
Figure 32

The chosen sorbyl imide was a readily available system and both regio- and stereo-selective conjugate addition had been carried out with a similar system. Thus Oppolzer had reported¹¹⁸ the selective 1,4-conjugate addition of ethylmagnesium bromide to the sorbyl camphorsultam **299**, which proceeded with high stereoselectivity to give the adduct **300** (Scheme 108). This contrasted with L-selectride[®] reduction which proceeded in a 1,6-manner.



Scheme 108

For the planned synthesis outlined in Figure 32, (+)-**207** was to be functionalised *via* the bromomagnesium salt to give the sorbyl imide which was then to be treated with a methyl organometallic to give the Michael adduct. This was then to be subjected to an aldol condensation with tetradecanal using the dibutylboron enolate, to give the *syn* aldol product, and thus create the remaining stereocentres. From here, two paths were considered, firstly hydrolytic cleavage, the mono-acid product of which could be subjected to ozonolysis without hydroxyl protection to give the target¹³⁸. In the second pathway, base stable protection of the hydroxyl group with cleavage from the auxiliary by lithium benzyloxide would give a product



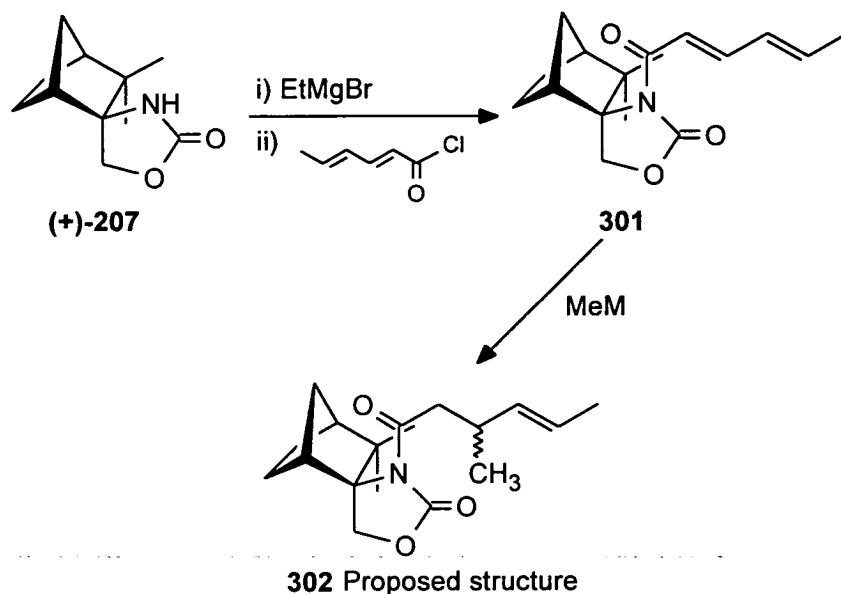
Proposed Conditions : i) MeM, (M = metal); ii) Buⁿ₂OTf, Pr^f₂NEt, CH₃(CH₂)₁₂CHO; iii) LiOOH; iv) O₃; v) R₃SiX, base; vi) BnOLi; vii) Oxidation then H₂, Pd/C.

Scheme 109

suitable for a wide range of oxidative conditions. Finally, hydrogenation under acidic conditions would not only cleave the benzyl group, but also remove an acid-labile protecting group and encourage lactonisation to the target.

2.7.4 Michael Addition Reactions with Sorbyl Imide 301

The imide **301** was prepared by treatment of the bromomagnesium salt of (+)-**207** with sorbyl chloride, which is readily prepared from sorbic acid and thionyl chloride¹¹⁸. As for most substituted enoyl systems, a high yield of the desired product was obtained (92%) by this standard procedure. Unfortunately, the intermediate was non-crystalline and also highly prone to polymerisation, but it could be stored indefinitely when refrigerated and stabilised with a trace of galvanoxyl. Initially Oppolzers method¹³⁹ of addition of methyl copper to the diethylaluminium chloride chelated imide was attempted. Thus, a 1:1 mixture of diethylaluminium chloride and methylcopper (5 equivalents) [prepared *in situ* from copper bromide:dimethyl sulphide complex and methyl lithium at -40°C] in toluene was treated with **301** at -78°C and the reaction warmed to -20°C. After 30 minutes, TLC analysis showed complete reaction had occurred and the product was isolated in quantitative yield. Unfortunately ¹H- and ¹³C-NMR spectroscopy revealed that the product was a 3:2 mixture of what was presumed to be the two diastereomers of **302**. Although *cis/trans* isomerisation of the remaining double bond was a possibility, it was thought unlikely since this had not been noted by Oppolzer under Grignard conditions (*vide supra*). Copper-catalysed addition of the Grignard reagent was then



Entry	RM	catalyst	solvent	temp °C	yield %	Product ratio
1	MeCu/ Et ₂ AlCl	none	toluene	-78 to -20	100	3 : 2
2	MeMgI	CuBr	THF	-78 to -20	95	3 : 2
3	MeMgI	CuI	THF	-78 to -20	95	3 : 2
4	MeMgBr	CuBr	THF	-78 to -20	95	3 : 2
5	Me ₂ CuLi	none	toluene	-78	100	2 : 1

Scheme 110

attempted. Thus, addition of **301** to methylmagnesium iodide and copper bromide at -78°C produced a deep orange colour, indicative of a polarised, chelated complex. The reaction mixture was warmed to -20°C, and after 30 minutes reaction was found to be complete from TLC analysis. Upon isolation, an identical product to the previous experiment was obtained, in which the ratio was again found to be 3:2. Subsequently, two further slight variations to this approach were performed. Firstly, addition of **301** to methylmagnesium iodide was carried out in the presence of copper iodide, and secondly, the reaction was repeated with the corresponding mixture of

bromides. It would have been expected that these changes might have brought some changes in the transition state due to variation in the halide used and subsequent alteration of the steric factors and bonding distances to the metal centre. Nonetheless, the ratios of the product obtained were essentially identical. Finally, use of the Gillman reagent, dimethylcopper lithium¹⁴⁰, was attempted. The reagent was prepared from copper iodide and methyl lithium (1:2) at -78°C in toluene. Upon addition of **301**, a deep red-orange colour formed, which faded over 20 minutes when the temperature was raised to -20°C. TLC analysis showed the reaction to be complete, and after isolation of the product, high field ¹H- and ¹³C-NMR spectroscopy showed these conditions had produced the same two products, albeit in the slightly improved ratio of 2:1.

It seemed highly unlikely that this variety of reactions could produce such consistent diastereomeric excesses since variations in metals and solvents would be expected to have a considerable effects on the outcome of asymmetric reactions. Consequently, one was forced to consider the occurrence of *cis/trans* isomers of the pendant allyl group (*i.e.* structure **303**, Scheme 111) as opposed to the diastereomers at C₃. The simple solution of picking out the three bond vinyl coupling in the ¹H NMR spectrum and identifying whether the *trans* substitution pattern was being retained was not possible since both signals overlapped. Even though the resulting haystack of signal may have been simplified by decoupling of the adjacent methyl group, the resulting overlapping multiplets would still have been difficult to interpret reliably. However, a similar shift in the characteristic H_{1b} resonance of **302** was noted compared to that of the C₃ diastereomers of the related compound **265a**,

produced by *trans*-alkenyl-alane addition, with presumed geometrical integrity (2.6.3). This was taken to indicate a similar degree of difference in the steric environment of C_{3'}. Comparison of the ¹³C NMR spectra of these two mixtures revealed a slight, albeit significant difference. In the alane product **265a**, the only atoms which showed different chemical shifts for each isomer were C_{2'} and C_{3'}, each being split by only 0.3 ppm. The alkene signals appeared as two lines only, showing no sign of the diastereomeric nature of the product. By contrast the alkenic carbons of **302** were each clearly split into two lines with the low and high field signals being shifted by 0.8 and 0.5 ppm respectively. This observation fitted with *cis/trans* isomerism since a shift of around 1 ppm is normally noted between the two isomers¹²³. Furthermore, it is known that a larger difference occurs for the allylic carbons (*ca.* 6 ppm), this was clearly demonstrated here in that the two C_{3'} signals were at 30.6 and 25.4 ppm respectively, giving a difference of 5.1 ppm. Consequently, it was considered that the C_{3'} stereocentre may have been created in a stereoselective fashion, but *cis/trans* isomerism had been operating.

Since *cis* alkenic and allylic signals have a down field shift relative to the signals of the *trans* isomer, it was possible to identify the geometry of the major component. Unsurprisingly, the *trans* isomer appeared to be the major product from all the reactions. Initially, this was assumed to be due to Lewis acid (*e.g.* MgX₂) isomerising the bond through a cationic intermediate as shown in Figure 33. Evans has noted that *cis/trans* isomerisation occurs with *cis*-crotonyl substituted oxazolidin-2-one imides under Diels-Alder reaction conditions, catalysed by

diethylaluminium chloride¹⁸. A conjugated diene system such as **301** would be expected to undergo as facile isomerisation under such conditions.

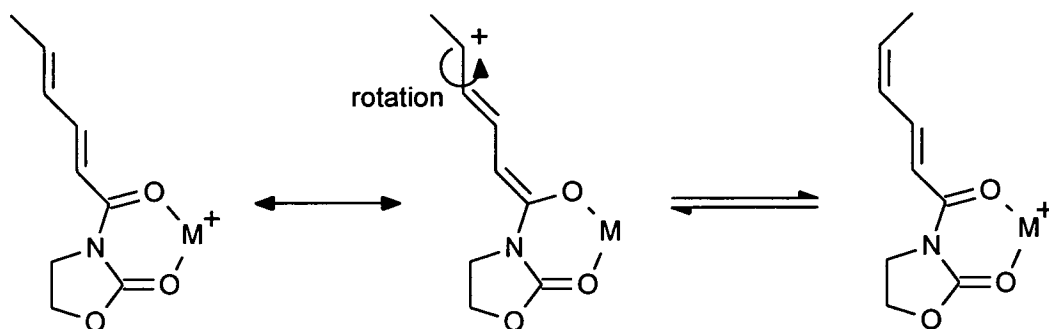
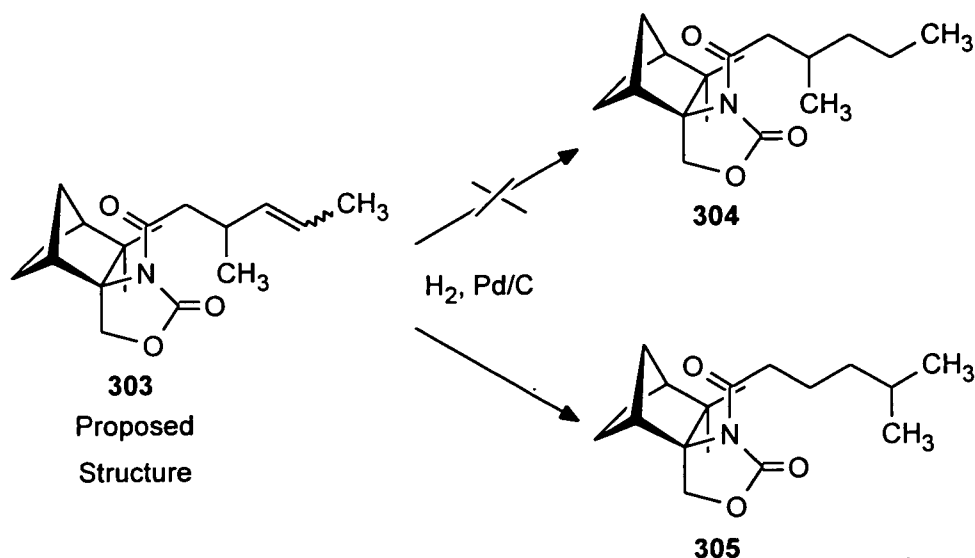


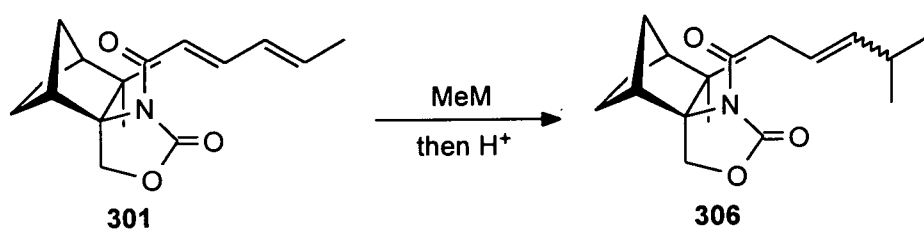
Figure 33

If such a mechanism operated, then once conjugate addition had occurred and conjugation was lost, the conformation would be frozen. However, it was surprising in the light of these observations that Oppolzer did not encounter a similar isomerisation of the sorbyl imide **299**. In an effort to understand the reaction, the mixture of presumed *cis/trans* isomers **303** was hydrogenated at atmospheric pressure over 5% Pd/C, in anticipation of the formation of a single diastereomer of **304**. Examination of the ¹³C NMR spectrum of the product clearly showed a single isomer to be present and this appeared to fit well with the expected structure. However, the proton spectrum was completely inconsistent with such a structure, which would have been expected to display two singlet methyls, a doublet methyl and a triplet methyl. The spectrum appeared to show four singlet methyls, or more correctly two singlet methyls and a doublet of integral 6. This is consistent with the presence of an isopropyl group and consequently the structure **305** was assigned.



Scheme 112

This outcome indicated that 1,6-conjugate addition had occurred thus forming no chiral centre. As to the nature of the unsaturated product, either an α,β or β,γ unsaturated system was possible, but the first was easily discounted since the imide carbonyl stretch occurred at 1711 cm^{-1} (*cf.* 1690 cm^{-1} for the crotonyl imide **225**) whilst the alkene proton shifts were at 5.4-5.6 ppm (*cf.* 7 ppm for **225**).



Scheme 113

The formation of **306** rather than its regioisomer was to be expected since quenching of a dienolate system with a hard electrophile like a proton is always noted to give the thermodynamically less stable non-conjugated product¹⁴¹. It has been calculated that there is a larger coefficient on the C_α centre in the frontier molecular

orbitals of this type of system than on C_γ . Since the reaction is energetically very favourable and kinetically controlled, FMO interactions rather than the thermodynamic stabilities of the products govern the outcome, with protonation on the C_α centre giving the final product. Addressing the question of why the *cis/trans* isomers were obtained, the most plausible explanation for this outcome is that the two rotamers (Figure 34) about the β,γ sigma bond in the chelated form of **301** are approximately of equal energy. Consequently, 1,6-addition gives the two geometric isomers about the newly created β,γ double bond in the dienolate, and protonation at C_α then locks this configuration.

Critical examination of the spectra of the initial conjugate addition products that had been assigned structures **302**, and then **303**, showed that the β,γ unsaturated isomers (**306**) fitted better than the products of 1,4-addition. As ever simple in hindsight. It thus appeared that the 1,6-addition of methyl metal reagents was highly favoured for the dienoyl system **301**, and consequently, this approach to the generation of the stereocentre was abandoned. However, one final experiment was carried out on this substrate. Since these methyl reagents had never been used with the other unsaturated imides of **207**, a reaction that was known to favour 1,4-conjugate addition was tried with this diene. When **301** was treated with diethylaluminium chloride under standard conditions (2.6.2), this led to reaction at an intermediate rate compared to the crotonyl and cinnamoyl imides. However, when the product was isolated it was seen to be a mixture of two isomers in a ratio of 4:9. Interestingly, there were considerable shifts to the alkenic carbons, far greater than those observed in the 1,6-methyl addition products, and on this basis *cis/trans*

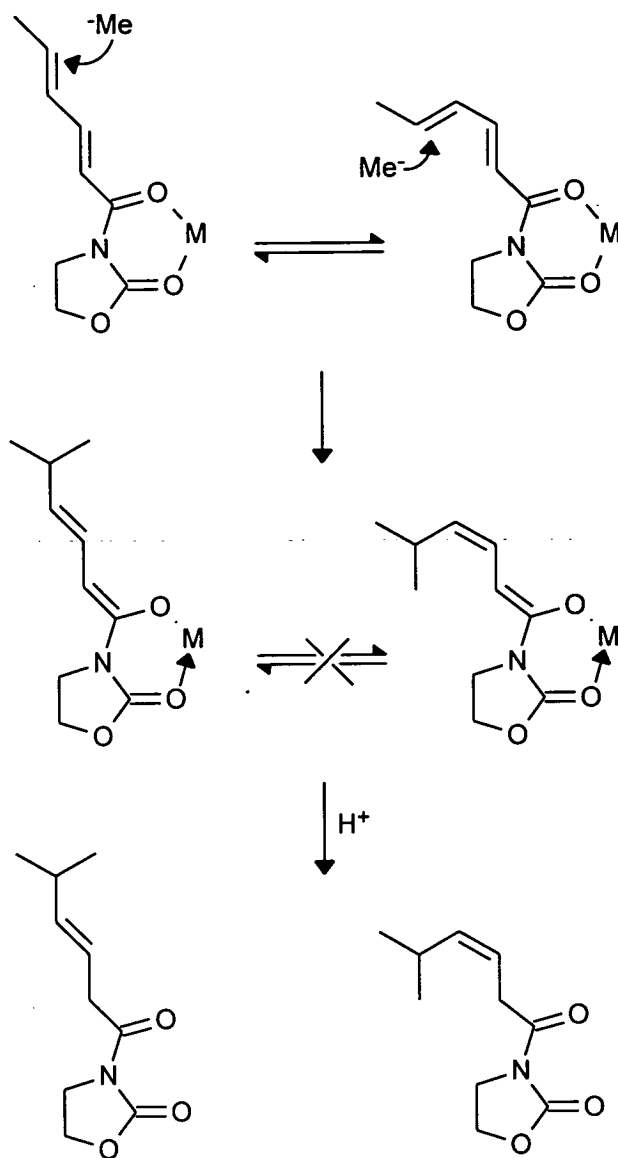
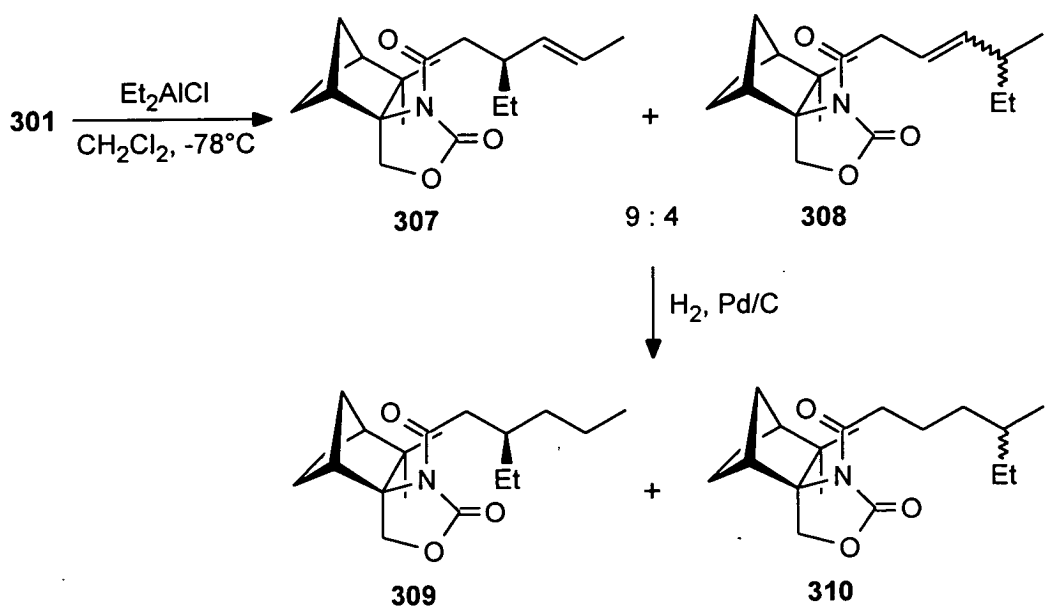


Figure 34

isomerisation appeared unlikely. Certain features of the proton spectrum appeared to fit closely with those expected for a 1,4-adduct (γ,δ unsaturated), viz. a pair of doublet of doublets at 2.9 and 2.7 ppm, due to the two α protons and a multiplet approximating to a quintet at 1.96 ppm, due to the β proton. The structure **307** has been assigned on the basis of previous findings, and its diastereomer was not apparent in the mixture. However, the signals for the minor component included a

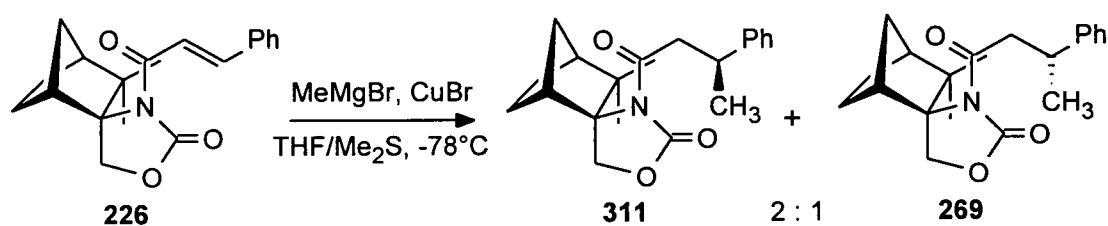
complex multiplet at 3.50 ppm with an integral of two, and a complex multiplet at 2.37 ppm with an integral of one. Comparison to the spectra of **306**, showed that the compound was probably a 1,6-adduct, *i.e.* **308**. The mixture was hydrogenated and then analysed by high field NMR spectroscopy, which clearly showed the presence of two compounds ascribed to the β adduct **309** and the δ adduct **310**. It is assumed that the latter compound may be present as a mixture of diastereomers, but that the separation of the chiral centre from the auxiliary means that the mixture appears to be a single compound when analysed by NMR spectroscopy. It is apparent that this imide shows a high degree of propensity for 1,6-addition, despite the use of a reaction which would be envisaged to show a preference for 1,4-addition.



Scheme 114

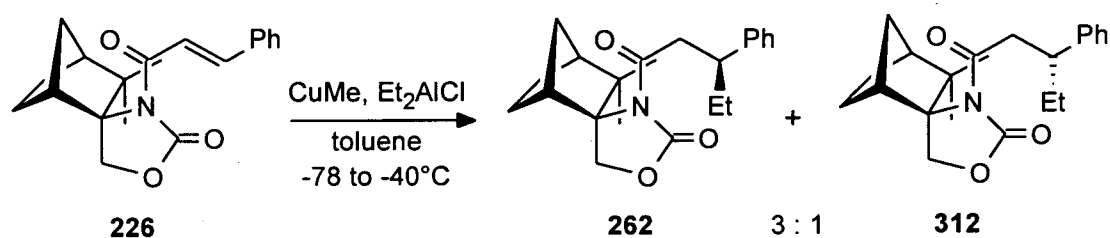
Although the vinyl group is commonly used as a carboxylate synthon, phenyl is equally suited to this purpose, since it can be cleaved by exhaustive ozonolysis, or by a catalytic quantity of ruthenium trichloride in the presence of an oxidant.

Hurby¹⁴² has reported that 1,4-conjugate addition of methylmagnesium bromide to substituted cinnamoyl imides of oxazolidin-2-one **7** show a high degree of stereoselectivity when carried out in the presence of copper bromide:dimethylsulphide complex in the mixed solvent system of dimethylsulphide and THF. On attempting to repeat these reactions with the cinnamoyl imide **226**, very poor selectivity was observed (33% d.e.), and the major product was tentatively assigned as the (3'*S*) 3-phenylbutanoyl derivative **311** whilst the minor product was identified as the diastereomer **269** (2.6.4) (Scheme 115).—Compound, **311** was presumed to have been formed *via* a closed transition state, whereas the other product was possibly formed *via* an open transition state due to dimethylsulphide acting as a ligand for the metal. This would clearly expose the other face of the alkene (in the *s-cis* conformation) to the incoming nucleophile since the alternative *s-trans* conformation would lead to an unfavourable interaction between the β hydrogen and the oxazolidin-2-one oxygen. This was clearly in contrast to the result obtained by Hurby.



Scheme 115

Attempts were made using Oppolzer's method¹³⁹ of addition of copper methyl to the chelated imide as previously tried with the imide **301** (Scheme 116). Essentially the imide was added to a five-fold excess of the 1:1 copper methyl/diethylaluminium chloride mixture at -78°C, and after the reaction was complete, the product was isolated and analysed by high field ¹H- and ¹³C-NMR spectroscopy. Two products were found, but neither was related to those obtained in the previous reaction, nor was there evidence for 1,2 addition (no cleaved auxiliary) or attack on the oxazolidin-2-one carbonyl (absence of what would have been a distinctive acetate signal, *cf.* non copper-catalysed vinyl addition to crotonyl imide **2.6.4**). Notably the doublet methyl signal was absent, and instead a triplet was present, thus indicating that an ethyl group was present. It was realised that this group must have been delivered from the diethylaluminium chloride, and on comparison of the spectra to that of the pure authentic adduct **262** (**2.6.2**) it was seen that the compound was indeed the (3'*R*)-ethylated product. On comparing the crude spectrum of the authentic **262** to this new reaction mixture, it was seen that the minor diastereomer



Scheme 116

was the other component of the reaction mixture, *i.e.* **312**. The d.e. of this reaction was a mere 50%, considerably lower than reaction under standard conditions.

On the basis of these findings it appeared that this area was very complicated. Addition of methyl copper to **301** proceeded smoothly, albeit to form the 1,6-methylated product, while the cinnamoyl imide was ethylated in a surprisingly non-specific manner with no methyl adduct detected. Due to the difficulties encountered in forming a β -methyl product with the correct stereochemistry by these approaches, it was decided to change the target slightly, and work towards the synthesis of the stereoisomer (-)-**278** is described next.

2.7.5 Enantioselective Synthesis of Dihydroprotolichesterinic Acid ((-)-**278**)

The target chosen was the known compound (-)-**278** which has the opposite stereochemistry in the aldol moiety to (+)-**277**, but the same stereochemistry at the lactone C_α centre. As a consequence of using the opposite enantiomer of the auxiliary to control the aldol stereochemistry, the order of substitution/addition of the groups around the Michael centre had to be reversed. Figure 35 shows schematically

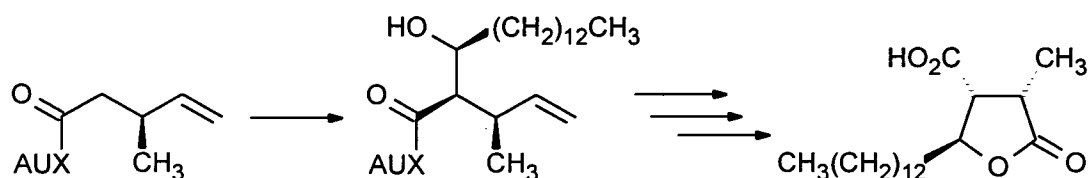
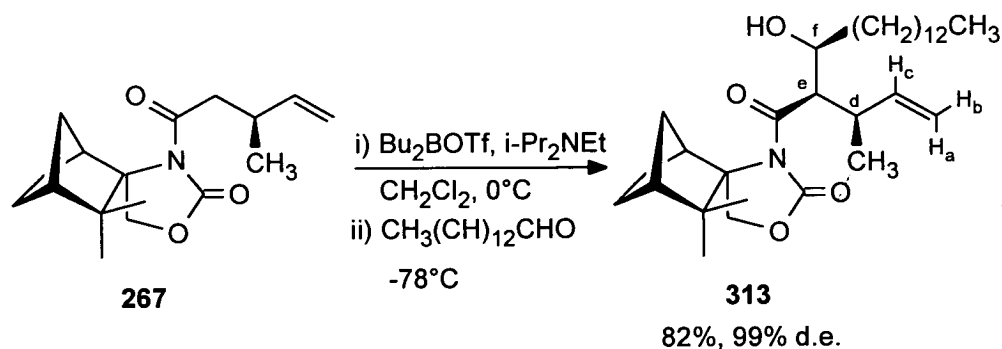
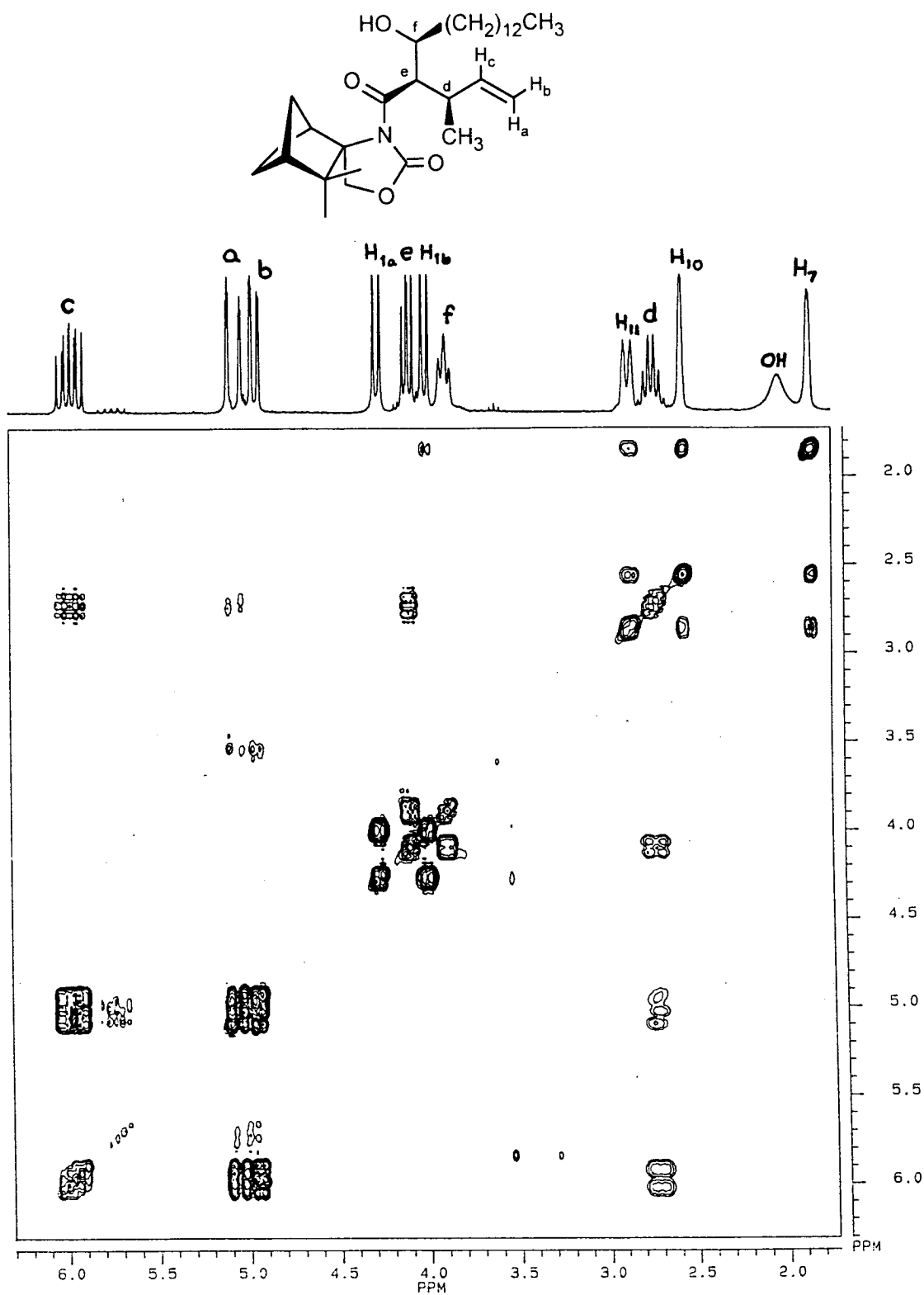


Figure 35

the required transformation. Synthesis of the required intermediate is described in 2.6.3-4. The adduct **267** was thus readily obtained from (-)-**207** in two steps, as essentially a single diastereomer, in 92% yield. The aldehyde, tetradecanal, required for the aldol condensation, although commercially available (expensive and of low purity) was prepared by pyridinium chlorochromate oxidation¹⁴³ of tetradecanol and purified by column chromatography. The dibutylboron enolate of the adduct **267** was generated with dibutylboron triflate and diisopropylamine, then treated with tetradecanal at -78°C, and the reaction allowed to proceed at room temperature (Scheme 117). High field ¹H NMR spectroscopy of the crude product showed that none of the opposite *syn* diastereomer was present (*vide infra*), but due to the absence of authentic material and the complex nature of the spectrum, no definitive *syn/anti* ratio could be determined. The aldol product **313** was separated from the starting material (18% recovery), and the aldehyde self condensation-products, by chromatography and obtained in 82% yield.



Scheme 117



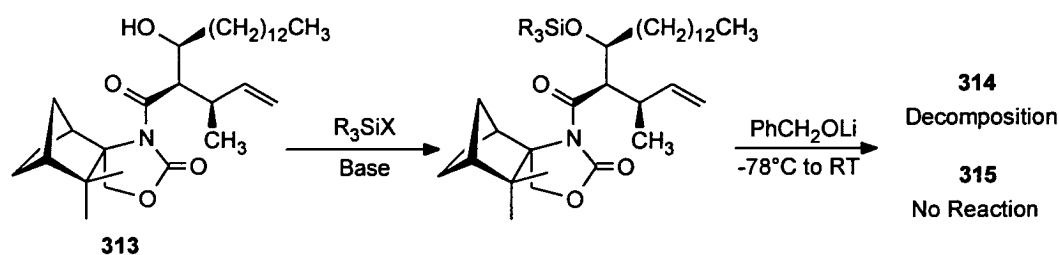
2D- ^1H NMR Spectrum of Aldol Product 313

Figure 36

Both high field ^1H - and ^{13}C -NMR spectroscopy of the purified material showed only a single diastereomer (>95% d.e.), and by performing a 2-D NMR experiment (Figure 36) the proton resonances of **313** were determined as follows. The lowest field signal of a ddd at 5.96 ppm was assigned as **c** and is clearly coupled to the two higher-field vinyl resonances. The coupling constant of the dt at 5.05 was 17.2 Hz indicating it to be *trans* to **c** *i.e.* proton **a**. The other vinyl signal, observed as a dt at 4.93 ppm ($J = 10.0$ Hz), was clearly proton **b**. The signal from **c** was coupled to the sextet at 2.71 ppm showing this to be proton **d** ($J_{\text{c,d}} = 8.0$, $J_{\text{d,e}} = 7.5$ Hz). This multiplet was also coupled to the dd at 4.08 ppm which was thus assigned as proton **e** ($J = 6.5$, 7.5 Hz). The smaller coupling constant was assigned as the **e** to **f** coupling, it is clearly seen in the 2D spectra. Geminal coupling between $\text{H}_{1\text{a}}$ and $\text{H}_{1\text{b}}$ of the auxiliary, as well as the coupling between $\text{H}_{11\text{a}}$ and both H_{10} and H_7 was also apparent. Since a coupling constant of 6.4 Hz between the C_α and carbinol protons (**e** to **f**) had been determined, this allowed reasonably confident assignment of the stereochemistry as *syn* (6.5 Hz is at the top end of the range of coupling constants observed for *syn* products)¹¹² and thus considering the nature of the reaction, the absolute configuration was assumed to be 2'*R*, 3'*S*.

The next step was to cleave the fragment, believed to contain all the necessary chiral centres, from the auxiliary. This was to be carried out with lithium benzyloxide so that the benzyl ester of the acid could be obtained. One condition for the removal of an aldol product fragment from an oxazolidin-2-one with lithium benzyl oxide is that the hydroxyl group must be protected, since the highly basic conditions will induce a retro-aldol reaction as well as equilibrating the product.

Protection of the hydroxyl group as the trimethylsilyl (TMS) ether was chosen, so that hydrogenation under acidic condition would cleave the benzyl ester and easily remove this protecting group in the final step to furnish the lactone. Straightforward treatment of **313** with TMS chloride and pyridine in ether led to complete conversion into the ether **314** within 30 minutes. This material was isolated and used directly in the next reaction. However, treatment of **314** with lithium benzyloxide under standard¹³ conditions gave no reaction after 30 minutes at room temperature. Slowly a number of products began to form, and after 48 hours all of the starting material had been consumed. By that time a total of eight products had been formed, one of which was auxiliary, but none of which were isolated.



	R ₃ Si	X	base	yield
314	TMS	Cl	pyridine	100%
315	TBDMS	Cl	imidazole	0%
315	TBDMS	OTf	NEt ₃	>95%

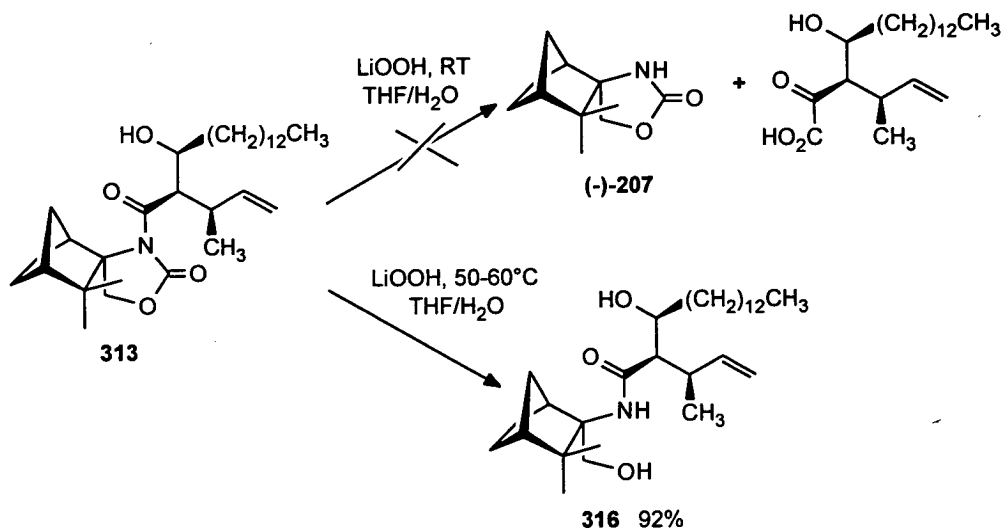
Scheme 118

It was apparent that due to presumed hindrance of the *exo*-carbonyl, the cleavage reaction was slow, thus allowing deprotection of the TMS ether and subsequent equilibration and retro-aldol reactions to occur. To overcome this problem, use of a more stable silyl protecting group *viz.* *t*-butyldimethylsilyl

(TBDMS) was attempted. Thus, treatment of **313** with TBDMS chloride using imidazole as base¹⁴⁴ gave no reaction even after hours at room temperature and finally at 35°C. This lack of reactivity contrasted with the ease of TMS protection and clearly showed that the hydroxyl was relatively hindered. Consequently, the more powerful silylating agent TBDMS triflate¹⁴⁵ was employed with triethylamine as a base. Under these conditions, reaction occurred rapidly and a near quantitative yield of the TBDMS ether **315** was obtained. When **315** was treated with lithium benzyloxide no reaction was seen to occur after 6 hours at room temperature. Even after 36 hours only a slight trace of a reaction product was detected by TLC analysis. This was identified later as the amido alcohol **316** (*vide infra*), and was presumably formed due to ingress of water; 90% of starting material was recovered from the reaction. This result signalled the end of this cleavage route since it appeared that a considerable amount of time, effort and valuable material would have to be expended to find a suitable protecting group with low bulk and acceptable stability.

In a different approach, hydrolytic cleavage of the fragment was attempted with hydroperoxide anion, which due to its low basicity did not require prior protection of the hydroxyl¹⁶. Upon treating **313** with lithium hydroxide and hydrogen peroxide in aqueous THF at room temperature no reaction occurred even after 30 hours. From this outcome it appeared that even without a bulky protecting group, the long alkyl and β branched chains were shielding the outer face of the *exo*-carbonyl, while the auxiliary was blocking the inner face equally well from the small and powerful hydroperoxide nucleophile. In an attempt to force the reaction it was heated under reflux for 3 hour after which time all starting material had been

consumed. Unfortunately a single product was formed, but no auxiliary was detected and this indicated that a reaction other than cleavage of the product fragment had occurred. When the compound was isolated, high field ^1H NMR spectroscopy showed that the new chiral fragment was still intact. The long chain and the vinyl group were still present, and the aldol and β -branched regions were relatively unchanged as was most of the bicyclic auxiliary. However, the H_{1a} and H_{1b} resonances had changed drastically, and although still a pair of doublets, both had moved upfield by 0.22 and 0.24 ppm, respectively. Also, the geminal coupling constant of these protons, normally 9.0 Hz for a wide range of auxiliary derivatives, had changed to 11.5 Hz. These features were highly reminiscent of **266**, the product of vinyl addition to the oxazolidin-2-one carbonyl of the crotonyl imide **225** (see 2.6.4), and suggested that hydrolysis of the oxazolidin-2-one ring had occurred. Further evidence was found in the proton spectrum in that the broad deuterium exchangeable signal at 3.3 ppm was now of integral two, while a broad singlet had appeared at 5.78 ppm. This signal was not lost on deuteration and was assigned as a secondary amide. Infrared spectroscopy also confirmed the presence of these functional groups. Conclusive proof of structure **316** was found in the ^{13}C NMR spectrum by the absence of the oxazolidin-2-one carbonyl. In addition, the C-N quaternary had moved from 76.1 ppm to 68.4 ppm, whilst the CH_2O signal had shifted from 71.8 ppm to 61.3 ppm (*cf. endo*-camphenol, 60.8 ppm). Clearly the reaction had stopped after cleavage of the more reactive imide type bond (amide and oxazolidin-2-one as comparable leaving groups), leaving the amide link even though excess reagent was present.



Scheme 119

Since **313** would almost definitely adopt a conformation in which the C_α hydrogen points towards the auxiliary shielding groups, the two alkyl chains on this atom will thus point in the opposite direction, *i.e.* over the outer face of the *exo*-carbonyl. Considering the bulk of the β -branched chain and the probability that the long alkyl chain fold back on itself in a highly polar solvent, Figure 36a shows how these two groups could be blocking the outer face of the *exo*-carbonyl.

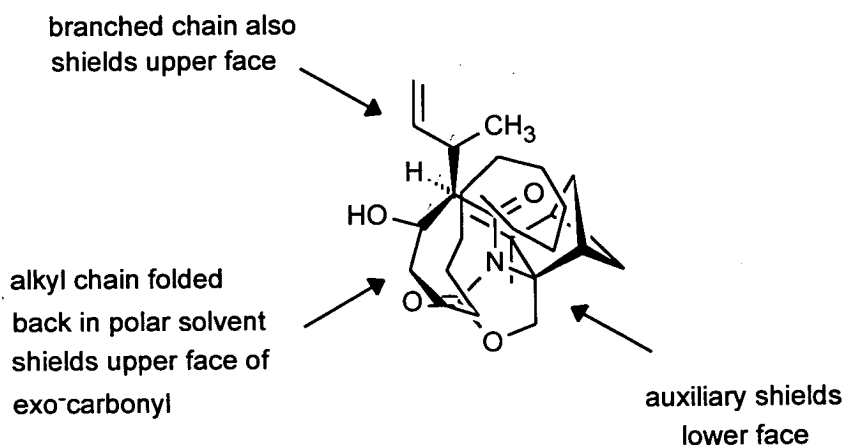


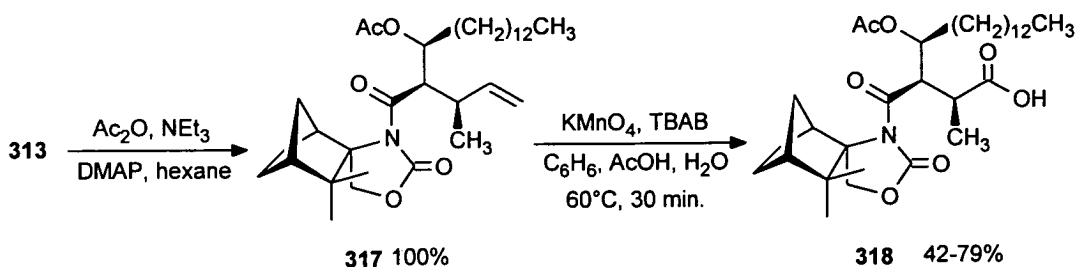
Figure 36a

The second route had thus failed, and at the same time shown that no matter how small a protecting group was used, the lithium benzyloxide cleavage reaction was unlikely to occur. It was assumed that other cleavage methods, *e.g.* bromomagnesium methoxide¹⁴⁶ or even the recently developed lithium trimethylaluminium benzylthiolate complex¹⁴⁷, would be equally ineffective. A very different approach to the problem was obviously needed. One possible method involved preparing the aldol product without the long alkyl chain and only attaching it at the end of the synthesis, although this would greatly lengthen and complicate the synthesis. The other option was to see if one of the chains could be used to deliver rather than hinder the nucleophile. A practical approach to this end involved cleavage of the double bond to give the carboxylic acid, before removing the fragment from the auxiliary. It was hoped that this approach would assist the solvolysis *via* a neighbouring group effect, but it was questionable whether the carboxylate anion would be sufficiently nucleophilic to displace the auxiliary and form the reactive succinic anhydride intermediate. If this was possible, the addition of extra steps to the route could be avoided provided that the protection group for the oxidation step was chosen such that it could be removed under alkaline conditions; this would also eliminate any hindrance problems caused by the protecting group. Although ozonolysis without protection may have been possible¹³⁸, a more convenient oxidation method was attempted initially. For a wide range of oxidising reactions, simple acetate protection appeared to be adequate and also suited the cleavage conditions perfectly. Protection was initially achieved by treatment of **313** with acetic anhydride and triethylamine in ether using DMAP as a catalyst. The

acetate **317** was isolated quantitatively, but the reaction had been rather sluggish. Slow DMAP-catalysed reactions with hindered alcohols are known to be caused by solvent polarity owing to stabilisation of the reactive intermediate¹⁴⁸. This was shown to be the case in this instance since on changing the solvent to hexane, the reaction was complete in under 30 minutes.

Considering the low aqueous solubility of the substrate, the phase-transfer catalysed permanganate oxidation conditions developed by Starks¹⁴⁹ appeared interesting. A trial reaction using similar conditions, but different phase-transfer catalyst, to oxidise 1-tetradecene failed to give any reaction. However, it was found that on addition of acetic acid the reaction proceeded rapidly at room temperature. This was not surprising when one considers that a proton source greatly enhances the power of permanganate as an oxidant. As a further test, the conjugate addition product **267** was oxidised under the new conditions, but no reaction occurred until the temperature was raised to 45°C, whereupon all starting material was consumed within 30 minutes. ¹H- and ¹³C-NMR spectroscopy of the crude material showed that the acid had been formed in an estimated 80% yield. The protected aldol product **317** was then oxidised by this procedure as shown in Scheme 120, but no reaction was seen until 60°C, when once again the reaction was complete after 30 minutes at this temperature. The crude material was isolated and chromatographed to yield three products; the first minor product appeared by ¹H NMR spectroscopy to be a cleaved fragment and has not been identified; the second was a mixture of two compounds, one of which was a cleaved fragment, and the other major component

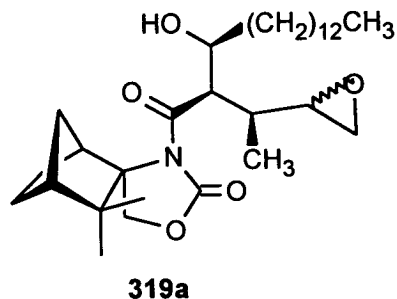
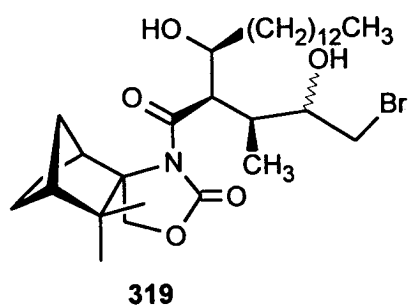
still attached to the auxiliary. The final product was identified as the desired acid **318** as described below and isolated in 52% yield.

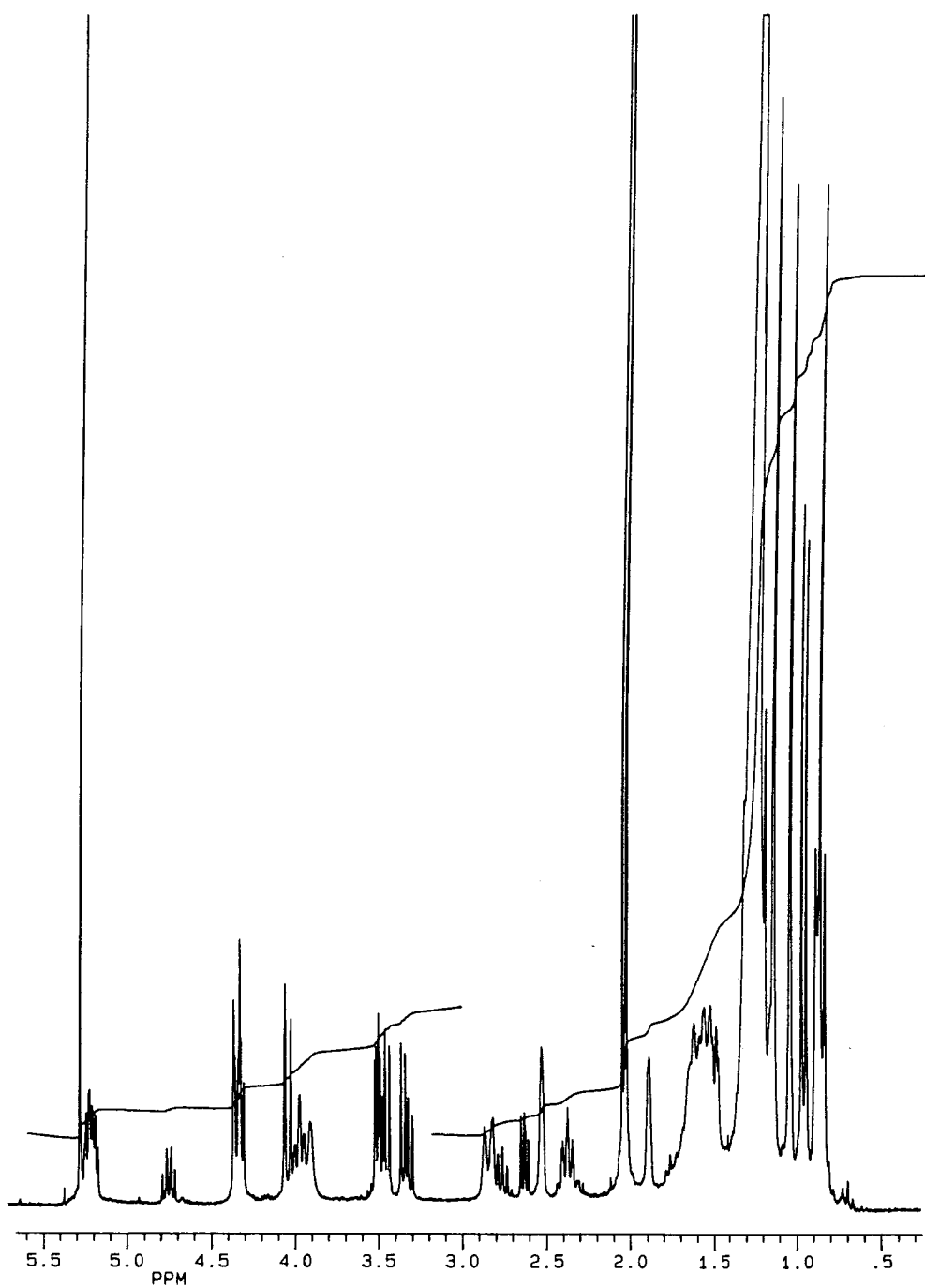


Scheme 120

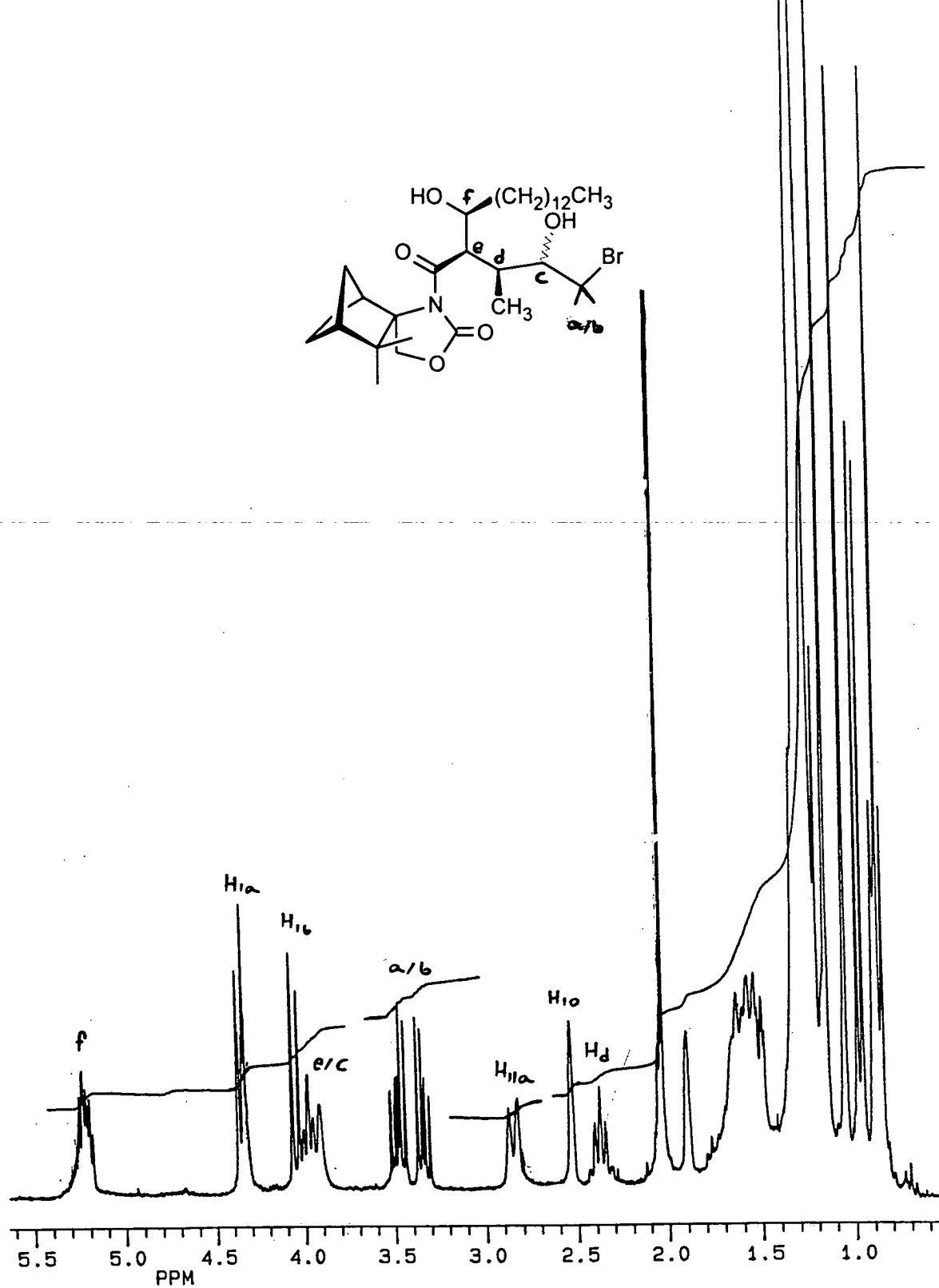
^1H NMR spectroscopy of the isolated compound showed the absence of the vinyl moiety, but the aldol linkage and the acetate protection were clearly unaffected. The methine at the chiral centre α to C_2' had simplified from a sextet to a quintet, but most importantly, the ^{13}C NMR spectrum showed four distinct carbonyl resonances. The FAB mass spectrum of the compound showed only a small protonated molecular ion but a large peak 60 units lower due to elimination of acetic acid. A second attempt at the reaction was carried out on a larger scale, but this time only a 42% yield was obtained. It must be noted that Starks had observed that oxidation of the catalyst was a problem on occasions, and consequently, a large quantity of the phase transfer-catalyst had been used. On re-examining the ^1H NMR spectrum of the second chromatographic fraction, an interesting observation was made, at 3.35 ppm a distinct eight-line pattern was present, this was partly overlapped but appeared in the form of a pair of doublet of doublets (see Figure 37; *N.B.* the signals due to the impurity (integral = 0.5) have been removed in the second spectrum for clarity).

Considering the reaction, this pattern would fit with a heteroatom substituted diastereotopic methylene coupled to a methine, *e.g.* a vicinal diol. Examination of the spectra revealed a resonance at 3.8 ppm, which would fit the adjacent secondary carbinol proton and this group was also present in the ^{13}C spectrum (73.3 ppm), but the primary carbinol ^{13}C resonance was clearly absent. Given that the proton substitution pattern had been identified, the nature of the heteroatom substitution was now unclear. In the ^{13}C spectrum a methylene was present at 35.3 ppm, and by checking against a number of similar long-chain aldol products synthesised at that time (*vide infra*), it was noted that the highest alkyl chain resonance was at 32 ppm. Considering the heteroatoms possible from the mixture (O, N, Br) and calculating the empirical chemical shifts, only one fitted this methylene shift, *viz.* bromine. The proton chemical shifts (3.32 and 3.48 ppm) also correlated far better with this substitution than hydroxyl. Unfortunately, the FAB mass spectrum did not show the expected parent ion or any ion with the bromine isotope pattern. However, it did show the MH^+ ion of the epoxide **319a**, *i.e.* elimination of hydrogen bromide from the halohydrin **319**.





250 MHz ^1H NMR Spectrum of Permanganate Oxidation By-product
(Original Spectrum)



^1H NMR Signals attributed to Compound 319

Figure 37

With the by-product provisionally identified, its formation needed to be understood; a proposed mechanism is shown below in Figure 38.

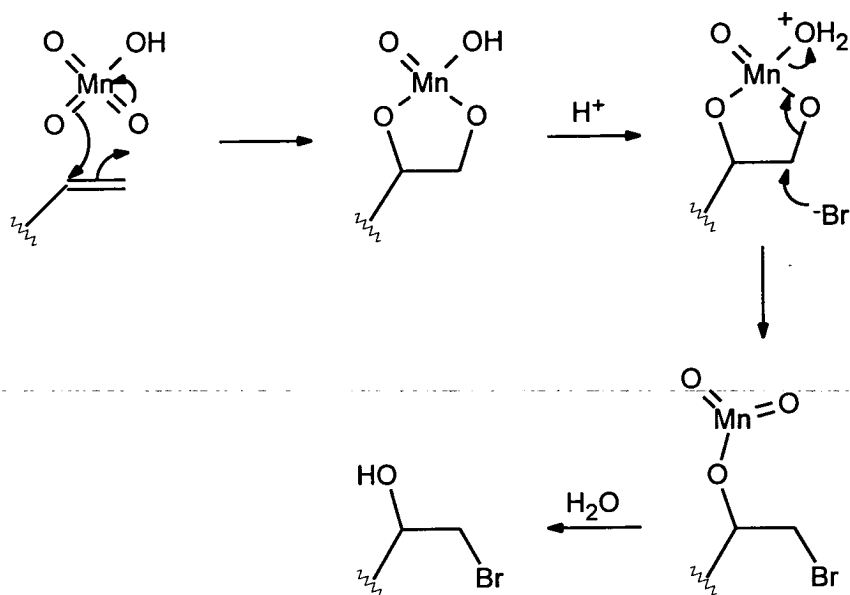
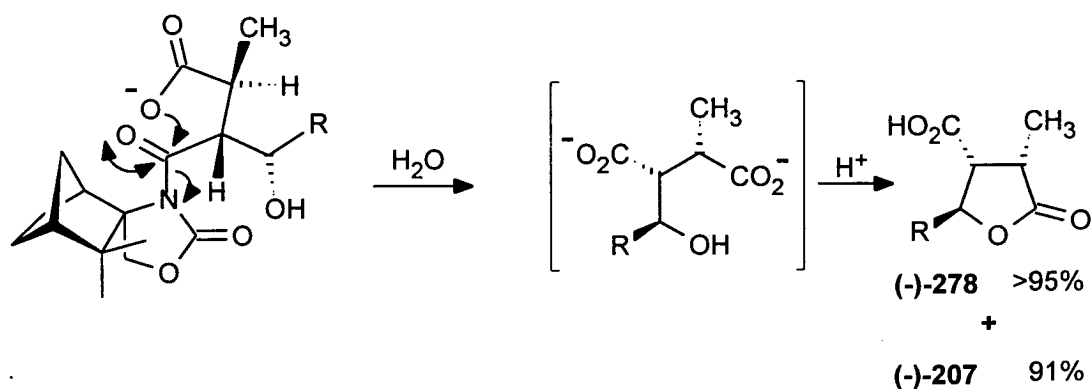


Figure 38

Since this mechanism requires protonation of the oxidation intermediate, it may explain why Starks did not observe this reaction since he used non-acidic conditions. One aspect was still highly surprising considering the reaction was carried out at 60°C, namely that a single diastereomer had apparently been formed. The minor impurity did not possess an auxiliary fragment, and it set aside, the spectrum was very clean. It would be of interest to investigate the origin of this diastereoselectivity, but the origin of the side reaction was now obvious and its prevention straightforward, *viz.* reduction of the phase-transfer catalyst concentration. After repeating the reaction with only 5% of catalyst and a slightly higher ratio of oxidant a 79% yield of **318** was obtained and only a trace of the **319** was observed by TLC in the crude reaction mixture.

The acid **318** was treated with lithium hydroxide using a greater than normal concentration of hydrogen peroxide (five-fold) in aqueous THF. This procedure gave a slow, but very clean reaction to produce after five days only (-)-**207** and a very slow running spot, as observed by TLC. After work-up, 91% of (-)-**207** was recovered, and the other compound was obtained as a waxy solid in approximately quantitative yield, but on recrystallisation only a 15% yield of (-)-**278** was isolated. This material was analysed by ^1H - and ^{13}C -NMR spectroscopy which showed that it was a single diastereomer; these and all other spectral data correlated exactly with those reported by Mulzer¹³². The melting-point and optical rotation were both slightly higher than

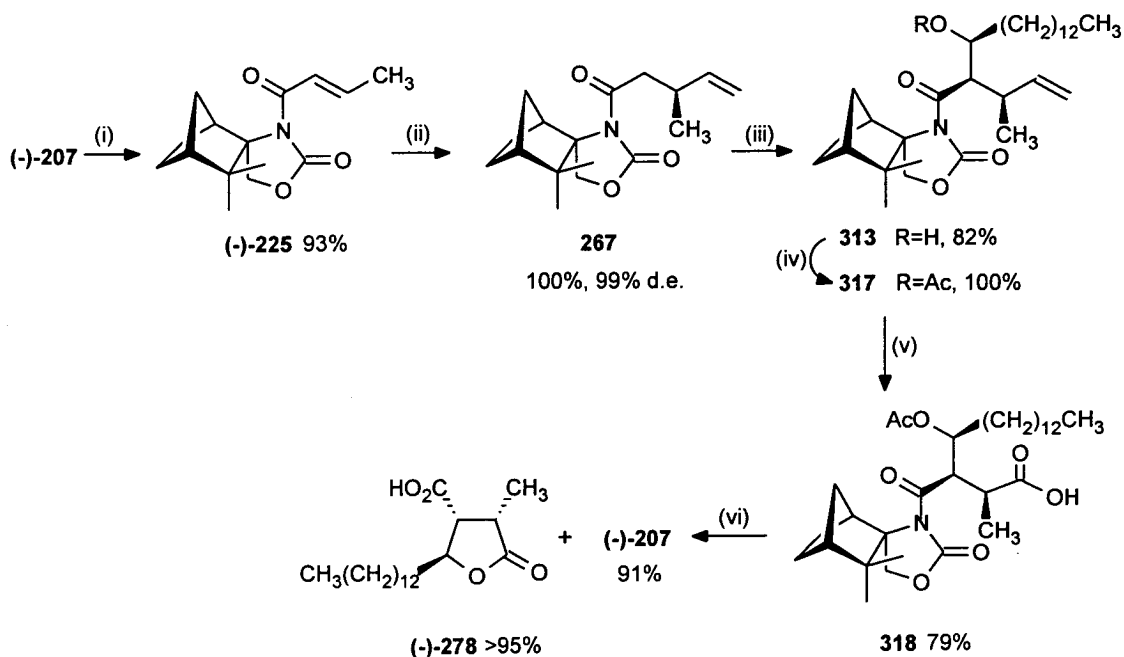


Scheme 121

the values obtained by Mulzer, but the melting-point was identical to one reported as literature reference¹⁵⁰. Unfortunately, upon attempting to isolate the remainder of the product, it could no longer be crystallised and an attempt to chromatograph this highly polar substance resulted in its decomposition. As this left the question of how pure the crude product was, the reaction was repeated and a 110% mass balance of the lactone was isolated. High-field ^1H - and ^{13}C -NMR spectroscopy showed that

apart from solvent impurity, only a trace of any product other than lactone was present, giving a yield of >95% in this final step.

It was assumed that the reaction is occurring *via* attack of the carboxylate anion on the *exo*-carbonyl to form a succinic anhydride intermediate which would rapidly hydrolyse to give the salt of the product. However, lowering of the hydrogen peroxide concentration led to the formation of a non-cleaved product that has yet to be identified, thus indicating that the nucleophile must be a peroxy species. It was originally proposed that this could be the percarboxylate anion, but this was



Conditions : i) ZnEt_2 , Et_2O , rt, then *E*-crotonyl chloride -78°C to 35°C , 3 hr; ii) $\text{CH}_2=\text{CHMgBr}$ (1.3 equiv.), CuBr (0.2 equiv.), -78°C , then addition to sat. $\text{NH}_4\text{Cl}/\text{THF}$ 0°C ; iii) *n*- Bu_2BOTf , *i*- Pr_2NEt , CH_2Cl_2 , 0°C , then $\text{CH}_3(\text{CH}_2)_{12}\text{CHO}$, -78°C to rt; iv) Ac_2O , NEt_3 , DMAP, hexane; v) KMnO_4 , TBAB, $\text{C}_6\text{H}_6/\text{AcOH}/\text{H}_2\text{O}$, 60°C ; vi) LiOH , H_2O_2 (30%, 100 equiv.), $\text{THF}/\text{H}_2\text{O}$, rt, 5 days.

Scheme 122

discounted as the percarboxylate anion would not be stable under these conditions. However, the ease with which this cleavage reaction proceeds by a neighbouring group effect clearly contrasts with the results obtained using the more orthodox procedures (see Addendum). Overall, a yield of 57% of (-)-dihydroprotolichesterinic acid **278** has been obtained by a short and adaptable route; over 140 times the yield of the previous synthesis and obtained in less than half the number of steps.

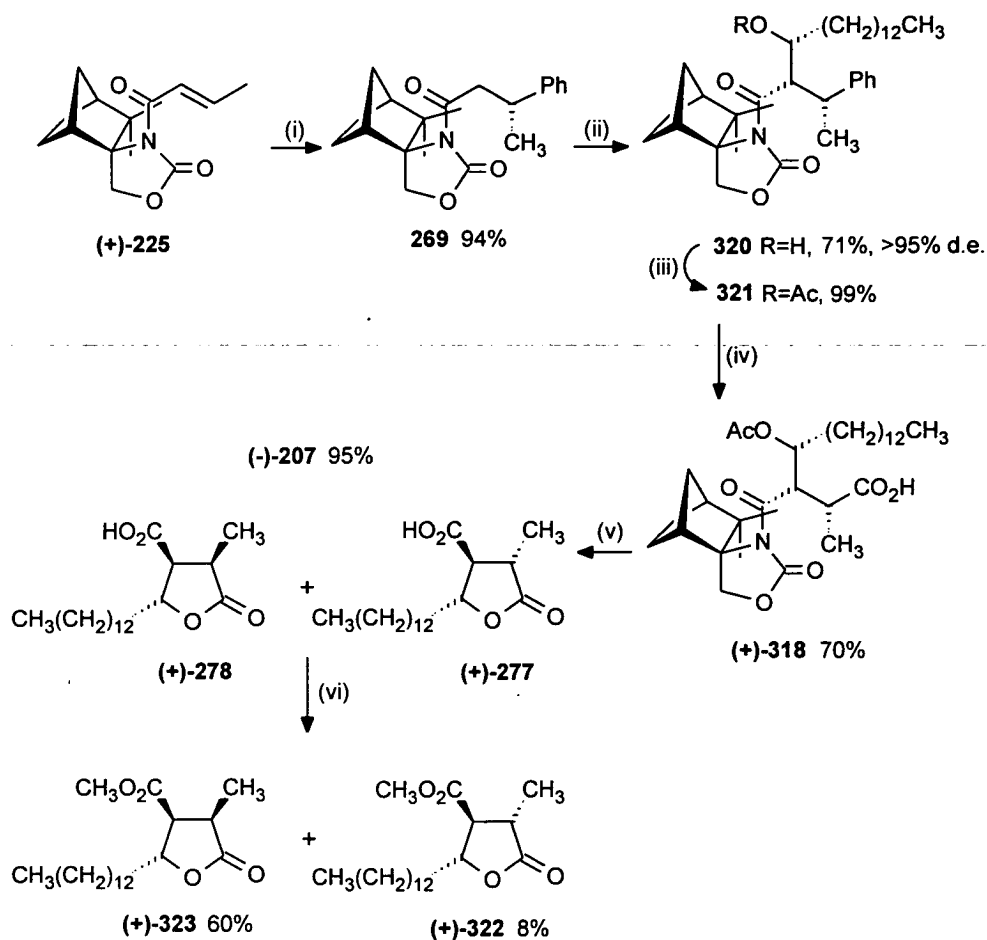
2.7.6 Synthesis of the (+)-Dihydroprotolichesterinic Acid Using Phenyl as a Carboxyl Equivalent.

Although the synthesis of dihydroprotolichesterinic acid had been achieved using the vinyl group as a carboxylate synthon, it appeared that there could be some advantages in the use of phenyl as a carboxylate equivalent. Firstly the adduct **269** was known to be crystalline making its isolation and purification a simple matter. Secondly, if the diastereomeric product **311** (2.7.4) could be obtained, then this route could possibly be used to synthesis **277** since the later steps would already be familiar. Investigation of the addition of phenylmagnesium bromide to the crotonyl imide (+)-**225** (2.6.4) showed that a highly selective addition had occurred (96% d.e.) in a high yield. The stereochemical outcome of this reaction was proven by optical comparison of the cleaved fragment, which showed that the addition was in the same sense as that of vinyl Grignard, *i.e.* the β -stereocentre was *R*. The boron enolate of this adduct was formed under standard conditions and reacted smoothly with tetradecanal to provide the aldol product in 71% yield. Once, again chromatography was required to remove starting material (27%), and also aldehyde self condensation products, and although

only a single diastereomer was observed by NMR spectroscopy, the assigned d.e. of >95% is only provisional. As before, the main problem of the reaction is the somewhat low conversion, which is presumably due to competitive self-condensation of the aldehyde. The relative stereochemistry was confirmed as *syn* by extracting the CHOHCHC=O coupling constant and observing it to be 5.0 Hz. In the next step, **320** was transformed into its acetate **321** using acetic anhydride, triethylamine and DMAP. Surprisingly, it was found to be crystalline, thus allowing simple isolation and removal of any traces of diastereomers. Unfortunately, crystals of the quality required for X-ray diffraction could not be grown, and consequently, the confirmation of the stereocentres had to await cleavage of the fragment from the auxiliary. Interestingly, the ^1H NMR spectrum of both **320** and **321** showed that one of the geminal methyls of the camphene skeleton was highly shielded by the ring current generated from the phenyl group; the respective resonances for the two compounds were 0.12 and 0.13 ppm.

The phenyl group of the **321** was then oxidised by the Sharpless method⁷², using catalytic ruthenium trichloride with sodium periodate as re-oxidant. Heating of the mixture at 35°C for 6 hours gave complete reaction and the desired acid (+)-**318** was isolated in 70% yield after chromatography. All spectral data was consistent with the enantiomer obtained in section 2.7.5. The material was then treated with lithium hydroxide and hydrogen peroxide under the adapted conditions, where it reacted slowly with the formation of an intermediate which appeared (by TLC) to decompose to the target material. This is presumed to be due to faster removal of the acetate protection than cleavage from the auxiliary. On this occasion, quenching of

the peroxide was carried out by addition to a suspension of 5% palladium on alumina, which catalytically decomposed the peroxide¹⁵¹.



Conditions : i) PhMgBr (3 equiv.), CuBr (0.2 equiv.), -78°C , then addition to sat. $\text{NH}_4\text{Cl}/\text{THF}$ 0°C ; ii) $n\text{-Bu}_2\text{BOTf}$, $i\text{-Pr}_2\text{NEt}$, CH_2Cl_2 , 0°C , then $\text{CH}_3(\text{CH}_2)_{12}\text{CHO}$, -78°C to rt; iii) Ac_2O , NEt_3 , DMAP, hexane; iv) RuCl_3 , NaIO_4 , $\text{CH}_3\text{CN}/\text{CCl}_4/\text{H}_2\text{O}$, 35°C ; v) LiOH , H_2O_2 (30%, 100 equiv.), $\text{THF}/\text{H}_2\text{O}$, rt, 6 days; vi) CH_2N_2 , MeOH .

Scheme 123

A crude yield of 106% of the acid was obtained, but when this was analysed by high field ^1H and ^{13}C NMR spectroscopy, it could be seen that there was a small

quantity of **277** as well as the major product **278** (doublet of triplet at 4.45 ppm and quartet at 4.67 ppm respectively) in the ratio 1 : 10. It was obvious that either some aldol equilibration or epimerisation α to the lactone carbonyl was occurring during alkaline hydrolysis or subsequent acidic workup. The pathway could easily be identified since if aldol equilibration was occurring, then unnatural (-)-**277** would have been formed. If the product had been formed *via* C_α -epimerisation (*i.e.* α to the carboxyl in (+)-**318**) then the sign of optical rotation would be positive (natural enantiomer). Unfortunately, it was known that these acids are extremely difficult to chromatograph, consequently, they were first converted to their methyl esters by treatment with diazomethane. The esters **322** and **323** were readily separated by chromatography and isolated in 8 and 60% yields from the crude cleavage mixture, respectively. The spectroscopic and optical rotation measurements showed the major component **323** to be the ester of the target material, (+)-dihydroprotolichesterinic acid, which was formed in an overall yield of 27% from the auxiliary. The minor component was identified as the methyl ester of roccellaric acid and was found to possess a positive optical rotation. This result showed that the configuration of the C_α centre was now *S* and indicated that inversion of this stereocentre had occurred. It seems difficult to attribute this inversion to epimerisation of the C_α centre (*i.e.* α to the lactone carbonyl) in the cleaved product since these compounds are known to be relatively stable under alkaline conditions. Furthermore, though base catalysed epimerisation of this centre under non-aqueous conditions in the methyl esters **322** and **323** is well documented^{132,152} this would not be favourable under aqueous conditions. However, as workup of the reaction was performed using strong acid, acid catalysed

enolisation could occur, epimerising this centre. Though the reaction was only taken to pH 2, 6 M hydrochloric acid was used and high concentration due to inadequate mixing may have been the contributory factor. That equilibration can occur in this final stage, suggests that careful idealisation of this solvolysis reaction should be performed in the future.

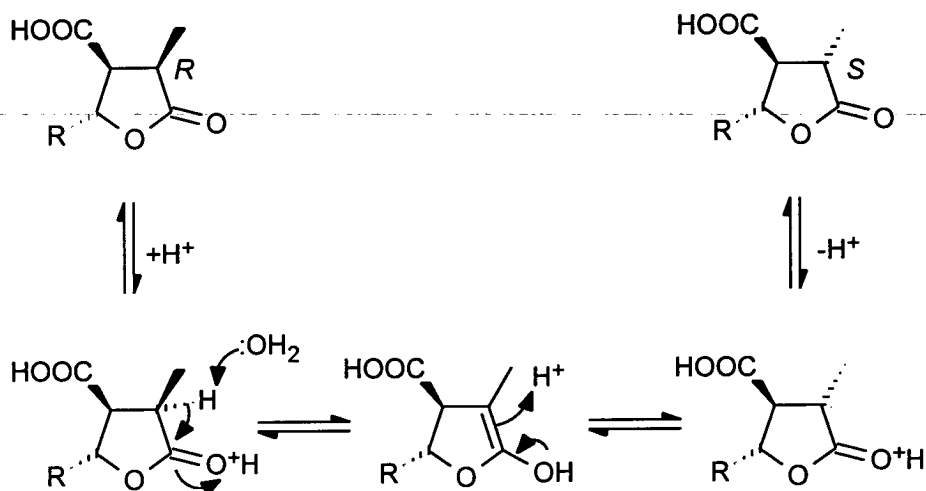


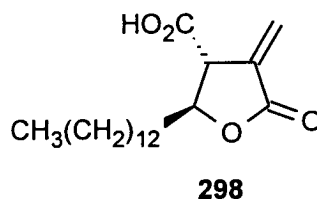
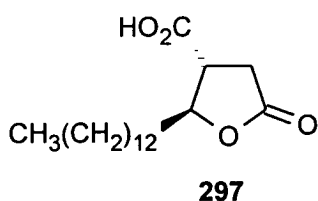
Figure 39

In conclusion, the use of the phenyl equivalent for the carboxyl group in the synthesis of this type of lactone system has been shown to be equally effective to the use of a vinyl group. Furthermore, the advantage of crystallinity in a number of the intermediates makes purification on a large scale much simpler. The lower overall yield obtained in this synthesis was not considered to be particularly relevant since no effort has as yet been expended to idealise the route.

2.7.7 Synthesis of a 5-Substituted Paraconic Acid : a Formal Synthesis

of (-)-Protolichesterinic Acid **298**

Since the use of this general route had great potential for the general synthesis of 3,5-substituted paraconic acids, it was considered worthwhile to adapt it to the synthesis of unsaturated γ -lactones, and in particular to the more biologically active α -methylene paraconic acids (**2.7.1**). As described in **2.7.2**, Greene has developed an effective α -methylenation procedure for paraconic acids which proceeds under mild conditions without concomitant migration of the double bond to an *endo*-cyclic position^{71,135}. Significant to ourselves, was the fact that the α -methylene unit is added in the final step, and the crucial intermediate in the synthesis of protolichesterinic acid **298**, *i.e.* 5-substituted paraconic acid **297** could be readily obtained by our route merely by eliminating the Michael addition step.

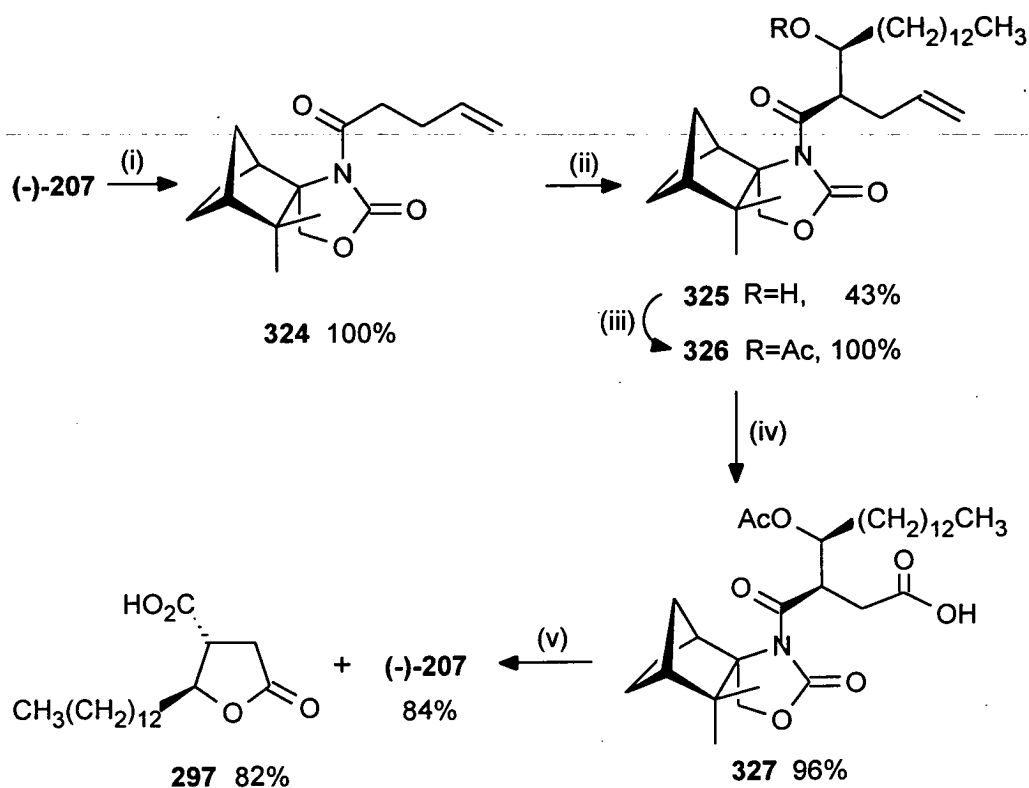


Since the oxidation of a vinyl or phenyl group was facile, the respective 3-substituted propionyl imides **324** and **227** were considered as potential starting materials. This gave a five-step synthesis, but it was also considered that this could have been shortened even further by use of the 3-carbomethoxy propionyl imide which according to Evans should undergo a clean boron mediated aldol condensation¹⁴. The vinyl substituted imide was chosen since all of the reagents

were in hand. Thus, the relevant acid chloride was obtained *via* treatment with thionyl chloride and then reacted with the ethylzinc salt of (-)-**207** to give a quantitative yield of the non-crystalline imide **324**. Conversion of the resulting imide into its *Z(O)*-dibutylboron enolate, and subsequent reaction with tetradecanal gave a rather low yield of the aldol product **325**. Surprisingly, in this case, as the solution reached room temperature, unlike any other boron aldol condensations performed, the reaction mixture turned jet black. This does not appear to be a spurious observation since repetition of the reaction gave an identical result. The ^1H NMR spectrum of the crude reaction mixture contained starting material, the aldol product, aldehyde self condensation-products and an unidentified product. Due to the obvious complexity of the spectrum, no information could be gained as to the diastereoselectivity of the reaction, although a single aldol product was readily isolated by chromatography. The *syn*-stereochemistry of the product was shown by a CHOH.CHC=O coupling constant of 4.5 Hz and the absolute configuration assumed from the nature of the reaction. In the next steps, DMAP-catalysed acetylation and permanganate oxidation using the phase-transfer catalysed reaction conditions as before, provided a 96% yield of the required acid **327**. All spectral data gathered for this compound was consistent with the expected structure. In particular, the diastereotopic C_α protons were present as a distinctive pair of doublet of doublets as would be expected. The acid **327** was treated as before with lithium hydroperoxide to yield after work up the crude lactone **297** for which high field NMR spectroscopy showed that only the *trans* isomer was present. The compound was isolated by

recrystallisation from hexane to give the pure product in 82% yield. The optical rotation for **297** was equal in sign and value to that obtained by Greene.

The overall yield for this short and versatile synthesis is 32% and provided the problems of the aldol condensation can be overcome, it would represent a highly effective route to this class of compounds.



Conditions : i) ZnEt_2 , Et_2O , rt, then pent-4-enoyl chloride -78°C to 35°C , 3 hr; ii) $n\text{-Bu}_2\text{BOTf}$, $i\text{-Pr}_2\text{NEt}$, CH_2Cl_2 , 0°C , then $\text{CH}_3(\text{CH}_2)_{12}\text{CHO}$, -78°C to rt; iii) Ac_2O , NEt_3 , DMAP, hexane; iv) KMnO_4 , TBAB, $\text{C}_6\text{H}_6/\text{AcOH}/\text{H}_2\text{O}$, 60°C ; v) LiOH , H_2O_2 (30%, 100 equiv.), $\text{THF}/\text{H}_2\text{O}$, rt, 6 days.

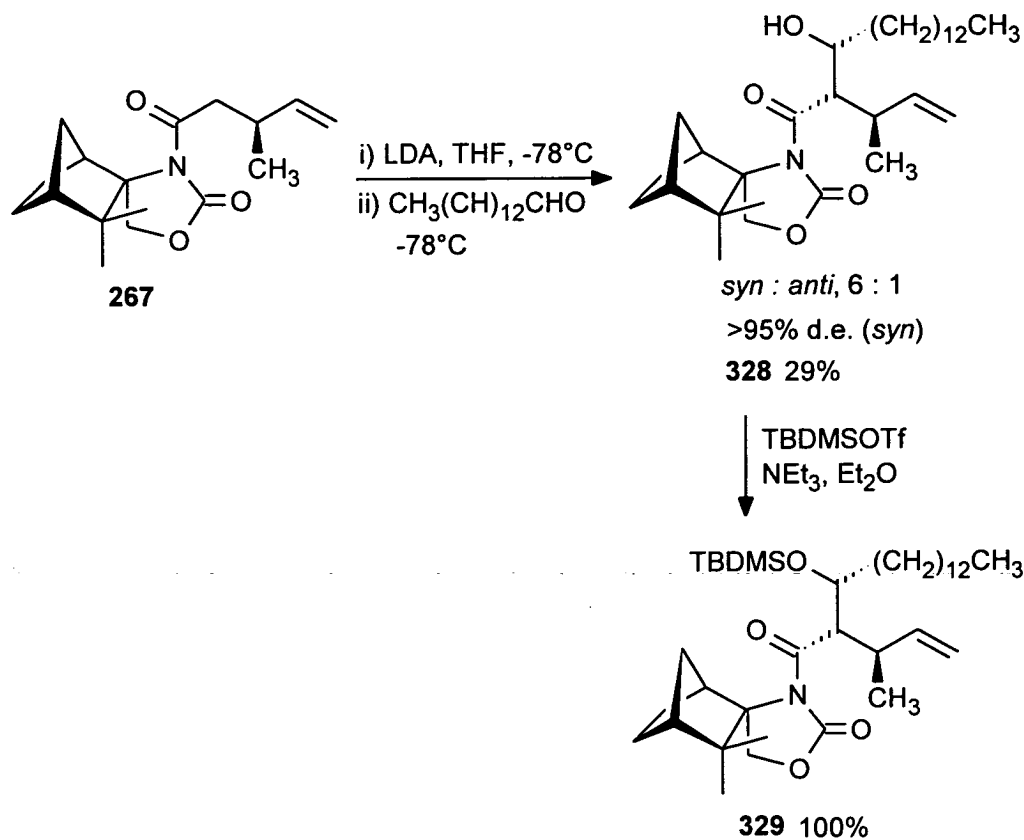
Scheme 124

2.7.8 Attempted Synthesis of Roccellaric Acid : the Use of a surprisingly

Selective Lithium Mediated *syn*-Aldol Condensation Reaction

With the basic principles of the synthesis of this class of tri-substituted γ -lactones in hand, the synthesis of various stereoisomers was a valuable target, especially the original target molecule, roccellaric acid (+)-**277**. Starting from the imide **267**, the necessary approach would require a so-called non-Evans *syn*-aldol condensation to set up the 4*S*, 5*R* stereocentres of (+)-**277**. There are many ways of obtaining the non-Evans product in a highly specific manner¹⁵⁴, but initially, a lithium aldol condensation was carried out since some degree of selectivity has been noted sometimes with this reaction. Consequently, Michael product **267** was treated with LDA, and then teradecanal under near normal conditions. After 1 hour, TLC showed that no more product was being formed, and apart from self-condensation products of the aldehyde, only starting material and two aldol products appeared to have formed.

The crude product was analysed by high field ¹H- and ¹³C-NMR spectroscopy, with the former showing that there was no Evans *syn* product present (absence of dd at 4.08 ppm, for the C $_{\alpha}$ methine) but little else. The vinyl resonances in the carbon spectrum allowed a crude estimate of the diastereomeric ratio (7:1), which is believed to represent the *syn/anti* selectivity. Although not impressive, the fact that the minor isomer could be easily removed by chromatography, gave the reaction some potential. Unfortunately, the starting material was extremely difficult to separate from the aldol product which was consequently converted into its TBDMS ether **321** (this was before the futility of this route was evident in the synthesis of (-)-**278**) using TBDMS triflate, in 96% yield. The unreacted imide **267**



Scheme 125

was recovered in 48% yield. The proton resonances of **329** were identified from a 2D ^1H NMR spectroscopic experiment, not detailed here, but which was found to be in accord with the desired structure. Two problems needed to be addressed; the low conversion and the inability to separate the aldol product from the residual starting material. Even after a number of attempts, no conversion of greater than 29% had been achieved, and moreover, reactions carried out on a larger scale only proceeded in slightly lower yield. The second problem was solved more easily by use of finer flash silica (40-60 μm vs. 60 μm) with a lower loading. The C_α proton resonance of **328** appeared as a dd at 3.83 ppm ($J = 9.0, 4.0$ Hz), the larger coupling constant was matched with the adjacent allyl methine. This meant that the coupling constant to the

carbinol was 4.0 Hz, and indicated that *syn* stereochemistry had been created in the aldol condensation.

A brief investigation was carried out in order to determine the cause of such selectivity. It was already known that the reaction of the lithium enolate of the propionate imide **213** with the hindered aldehyde, isobutyraldehyde, gave a moderately high degree of stereoselectivity. Furthermore, the main product was the diastereomer opposite to that obtained in the reaction of the corresponding boron enolate. In addition, the next most abundant product was an *anti*-isomer although, again it was not known which particular one was formed. The diastereoselection of the reaction of this enolate with less hindered aldehydes was thus attempted. Likewise, a model of the more hindered enolate of **267** was also reacted with two straight chain aldehydes and isobutyraldehyde. The chosen model was the *iso*-valeryl imide **330**, which was easily obtained in quantitative yield by treatment of the ethyl zinc salt of (+)-**207** with isovaleryl chloride. Similarly, the lithium enolate of the even more hindered imide **269** was reacted with tetradecanal. Figure 40 summarises the results of these reactions.

It can clearly be seen that for the simple non-hindered enolate, increasing the aldehyde bulk gives greater diastereoselection. Whilst increasing the bulk of the enolate substituent gives better diastereoselection for less hindered aldehydes. Given that in each case, the minor product appears to be an *anti* isomer, these findings can be rationalised if the reaction is occurring *via* a closed transition state with the lithium chelated by the carbonyl group of the oxazolidin-2-one moiety. There is strong evidence that it is a chelated transition state, since the products **245** and **328**

Percentage Conversion and *Syn:Anti* Ratio of the Products of Reaction between Lithium Enolates of Imides of 207 and three Aldehydes

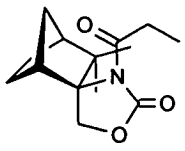
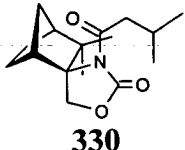
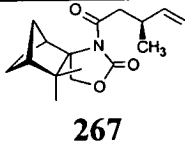
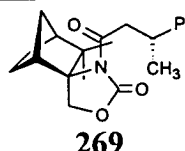
Imide \ RCHO	Pentyl	Tetradecyl	isopropyl
 213	70% 3 : 2	60% 2 : 1	90% 7 : 2
 330	45% predominatly one diastereomer	30% predominatly one diastereomer	45% predominatly one diastereomer
 267		32% 7 : 1 no Evans <i>syn</i> detected	
 269		40% >5 : 1 no Evans <i>syn</i> detected	

Figure 40

are known to be the non-Evans *syn* diastereomers. The drop in selectivity with decreasing bulk of aldehyde in the reaction of the propionate enolate is readily explained as there is no longer sufficient steric interaction (1,3 diaxial) with the oxazolidin-2-one(A, Figure 41), thus allowing transition states such as **B** or possibly its twist boat equivalent **C**. The latter transition state would alleviate much of the steric interaction of the aldehyde substituent with oxazolidin-2-one moiety. However, with a very bulky enolate substituent, 1,3-interaction with the pseudo axial

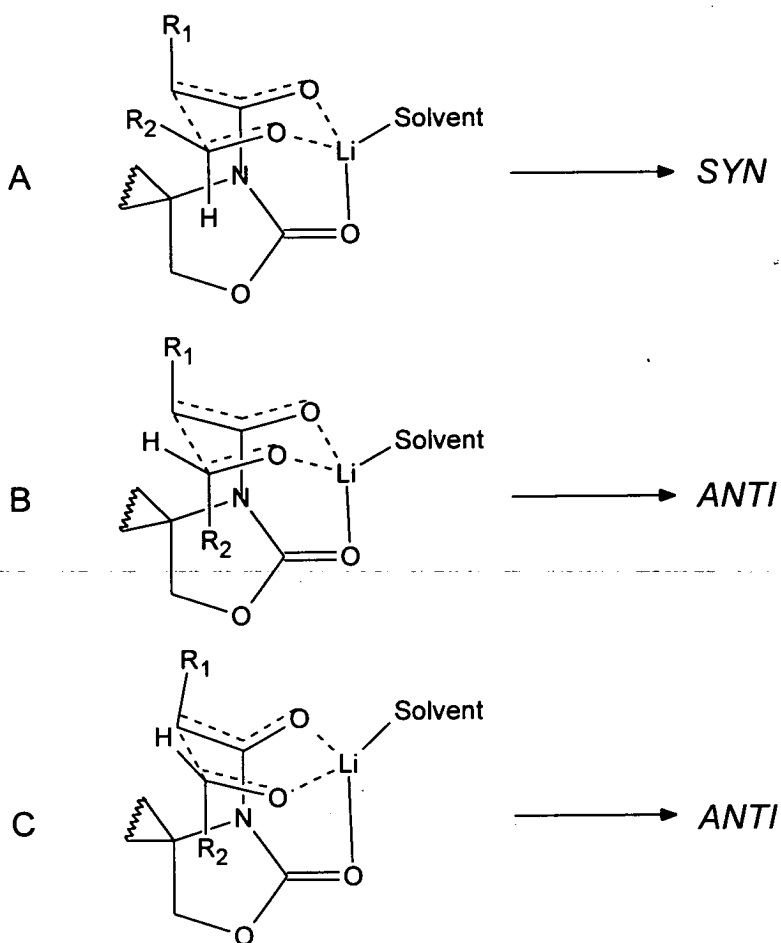


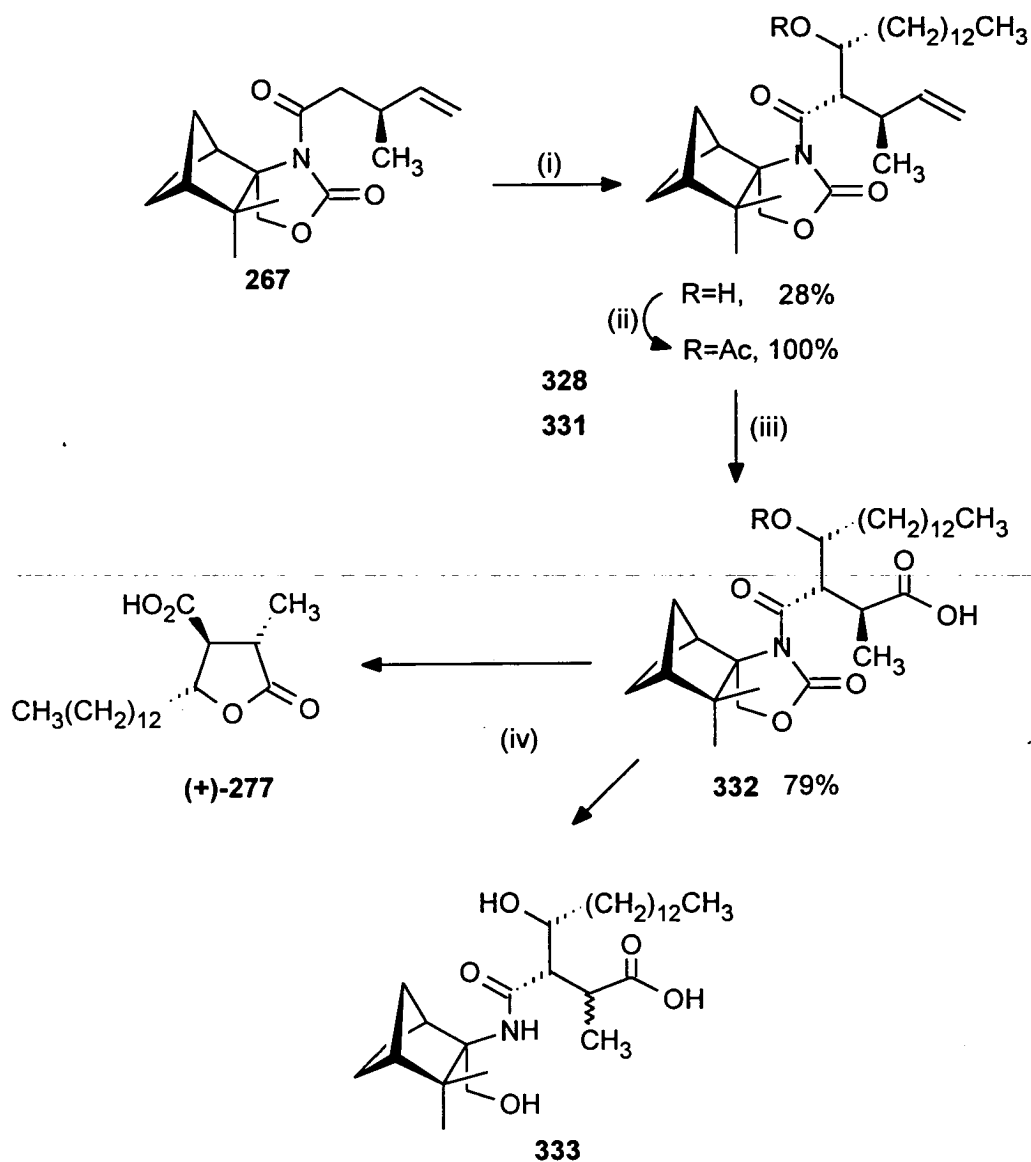
Figure 41

proton could destabilise this conformation, and make this pathway less favourable than A, leading to the observed increase *syn/anti* diastereoselection. The reaction of both types of enolate appear to be more selective for the chelation controlled *syn* product than many contemporary auxiliaries (5, 180), undoubtedly due to better shielding of the opposite face.

After purification, **328** was protected as its acetate **331** by using acetic anhydride and DMAP in hexane (the reaction of this aldol product in ether was

particularly slow). In turn, **331** was oxidised with potassium permanganate under phasetransfer conditions described in the previous sections to give the acid **332** in 68% yield. The ^1H NMR spectrum of this material confirmed the loss of the vinyl group and showed the appearance of a very broad signal at 8.6 ppm. It also showed that the protecting group, aldol region and signals for the auxiliary were all as might be expected. Unfortunately, the expected quintet from the methine α to the carboxyl group was overlapped by the H_{11a} resonance and only one peak of the presumed methyl doublet could be seen since the other was also overlapped by the alkyl chain resonances. The ^{13}C NMR spectrum showed only three carbonyl signals, viz. imide, acetate and oxazolidin-2-one, and furthermore it was apparent that the α methine resonance (to carboxyl) was absent. FT-IR spectroscopy showed that the material was an acid (broad absorbance at 3100 cm^{-1}), while FAB mass spectroscopy gave a small MH_2^+ peak (5%) and a larger $\text{MH}_2^+ - 60$ peak (55%) arising from loss of acetic acid. When the ^{13}C NMR spectrum was re-run with a lower intensity pulse and a longer delay period, the carboxylic acid and methine carbons which were originally absent appeared as normal intensity peaks. In fact, re-running the proton spectrum also showed more structure in the α proton signal, and this time, it did approximate the expected quintet.

Compound **332** was then subjected to hydrolysis with lithium hydroperoxide under the adapted conditions. The reaction progressed slowly, and after six days, all of the starting material had been consumed, but no auxiliary was detected by TLC. Upon isolation, the mixture was found to be composed of three compounds. The two major components have tentatively been assigned as the diastereomers **333**, formed



Conditions : i) LDA, THF, then $CH_3(CH_2)_{12}CHO$, $-78^\circ C$; ii) Ac_2O , NEt_3 , DMAP, hexane; iii) $KMnO_4$, $n-BuN_4Br$, $C_6H_6/AcOH/H_2O$, $60^\circ C$; iv) $LiOH$, H_2O_2 (30%, 100 equiv.), THF/ H_2O , rt, 6 days.

Scheme 126

by cleavage of the oxazolidin-2-one ring. This assignment was based on the comparison of the NMR spectra of the material with compounds such as **266** and **316**. Further to this FAB mass spectroscopy gave dehydration products of the

proposed structure, although the MH^+ ion was negligible. That the compounds are diastereomeric at the chiral centre α to the carboxyl group is proposed in light of the findings detailed in 2.7.6. The formation of this product was both highly surprising and disappointing, but its implications may be significant in understanding the factors governing the proposed assisted cleavage mechanism. In the proposed transition state for the cleavage of (-)-278 from the auxiliary (Scheme 121), the steric hinderance between the auxiliary and the carbinol/long alkyl chain is minimised. However, for the deprotected form of 332, interaction of these to groups would be severe (Figure 42).

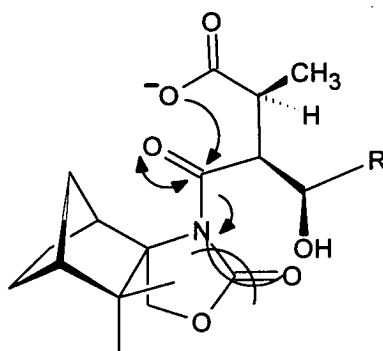


Figure 42

In essence, the above findings indicate that the preparation of (+)-277 by this route may be impossible. However, it may be possible to remove the fragment corresponding to (+)-277 from the adduct with (+)-207. This would be able to proceed through a similar transition state to that shown in Figure 4. In essence, it appears that cleavage of these larger fragments may depend on the diastereomeric relationship between the auxiliary and the aldol stereocentres.

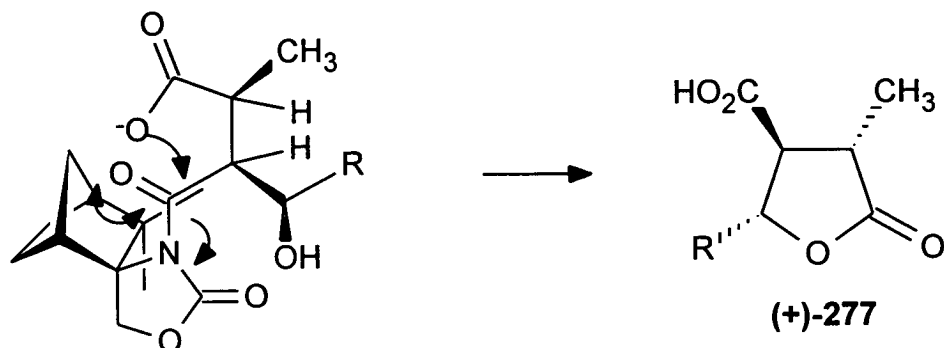


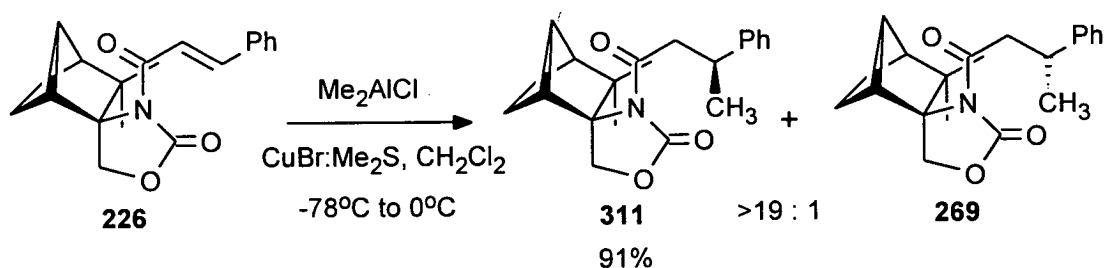
Figure 43

2.7.9 Summary

It has now been demonstrated that the reaction sequence of 1,4-conjugate addition and aldol reactions has the potential to be used in the synthesis of all of the stereoisomers of a variety of di-substituted paraconic acids. The range of functionality which can be introduced at C₃ and C₅ is very broad, and furthermore, the simple synthesis of C₅ mono-substituted paraconic acids, when combined with Greene's α -methylenation procedure allows the rapid high yielding synthesis of many analogues of the more biologically active α -methylene paraconic acids. The most important work to be carried out directly from this area must be the synthesis of roccellaric acid from (+)-207, a reaction that would required the selective synthesis of a Michael adduct such as 311. Further adaptation of the cleavage conditions to allow the removal of auxiliary from fragments such as 332 would also be worthwhile. To extend the scope of the synthesis, the application of *anti*-aldol reactions in the synthesis of 4,5-*cis*-paraconic acids must also be attempted.

Addendum

The synthesis of Michael adduct **311** was tackled again before handing the task of synthesis of (+)-**277** over to a 4th year project student. It was considered that this might be possible using Kunz's method¹²⁴ of addition of dimethylaluminium chloride to imide **226** under the influence of u.v. light (methylaluminium compounds appear to require radical conditions to add to oxazolidin-2-one imides). However, the low yields obtained and moderate diastereomeric excess together with the awkward reaction conditions made this route unappealing. Interestingly, a paper was published demonstrating that trimethylaluminium delivers methyl groups to enones under copper-catalysis in contrast to the reluctance of this transformation without such catalysis¹⁵³. Although trimethylaluminium was of no use since chelation of the acyl oxazolidin-2-one would not occur, it was surmised that copper-catalysis might be a better method of activation than u.v. irradiation. The reaction was performed by treatment of a solution of dimethylaluminium chloride in dichloromethane at 0°C



Scheme 127

with copper chloride:dimethylsulphide complex. The imide **226** was then added to this mixture at -78°C and the reaction allowed to warm to 0°C where TLC analysis showed the reaction to be complete. The crude material was isolated, and shown to be composed of the two diastereomers **311** and **269** in the ratio $>19 : 1$, indicating a diastereomeric excess of $>90\%$, and recrystallisation provided the pure adduct **311** in 91% yield (Scheme 127). This important observation has demonstrated that a route based on the initially attempted method (2.7.3) is once again an option for the synthesis of roccellaric acid.

The nature of the assisted cleavage has still not been identified conclusively, though the reaction seems to depend on the presence of hydrogen peroxide, it does not appear probable that the nucleophilic species could be a percarboxylate anion due to its instability in aqueous media. furthermore, it is questionable whether the simple carboxylate anion would be sufficiently nucleophilic to displace the oxazolidinone moiety. However, it has been suggested by Dr. J. Knight that this could be rationalised if the carboxylate anion was involved in hydrogen bonding the relatively electron deficient hydrogen of a peroxide anion and thus assisting in the delivery of this nucleophile to the *exo*-carbonyl.

3 Experimental

Instrumentation and General Techniques

i. NMR Spectroscopy

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

ii. Infrared Spectroscopy

Infrared spectra were recorded on a Bio-Rad FTS-7 spectrometer. Continuous wave spectra were recorded on a Perkin-Elmer 781 spectrometer. Liquid samples were recorded as thin films and solid samples as carbon tetrachloride mulls, both on sodium chloride plates.

iii. Mass Spectrometry

FAB and accurate mass measurements were obtained on a Kratos MS-50 TC spectrometer, operated by Mr A. Taylor. EI spectra were recorded on a AEI MS 902 instrument by Miss E. Stevenson.

iv. 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.

v. 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 R. O. Gould.

vi. Melting Points

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

vii. 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.

viii. 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.

ix. 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.

x. Drying and Purification of Solvents

Dichloromethane, 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.

xi. 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.

xii Moisture Sensitive Reactions

All moisture sensitive reactions were carried out in dry, freshly distilled solvents, under an argon atmosphere using oven or flame dried glass ware.

Symbols and Abbreviations

AIBN	2,2' azobis(<i>iso</i> -butyronitrile)
Ar	aromatic
$[\alpha]_D$	specific rotation
b	broad
Bn	benzyl
BP	boiling point
Bu	butyl
Bz	benzoyl
cm	complex multiplet
d	doublet
δ	chemical shift
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DMAP	4-dimethylaminopyridine
DME	dimethoxyethane
DMF	<i>N,N</i> -dimethylformamide
EI	electron impact
equiv.	equivalents
Et	ethyl
FAB	fast atom bombardment
FT IR	Fourier transform infrared spectroscopy
<i>J</i>	spin-spin coupling constant
<i>Lit.</i>	literature value
m	multiplet
M	mol dm ⁻³
M ⁺	molecular ion
mmol	millimoles
Me	methyl
MP	melting point

MS	mass spectroscopy
NMR	nuclear magnetic resonance spectroscopy
<i>o,m,p</i>	<i>ortho, meta, para</i>
PDC	Pyridinium dichromate
Ph	phenyl
ppm	parts per million
Pr	propyl
s	singlet
TBAB	tetrabutylammonium bromide
TCE	1,1,2,2-tetrachloroethane
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
t	triplet
q	quartet
quat	quaternary
$\nu_{\max}$	maximum wave number

3.1 Preparation of Chiracamphox

3.1.1 Preparation of Bornyl Toluene Sulphonate 199

(-) (1*S*) Borneol **177** (154g, 1.00 mole) in pyridine (500 ml) was added to a stirred solution of toluene sulphonyl chloride (240g, 1.25 mole) and *N,N*-4-dimethylaminopyridine (0.5g) in pyridine (300ml) at 0°C. After 48 hours at room temperature considerable quantities of pyridinium hydrochloride had precipitated and TLC (1:4, cyclohexane/ethylacetate) indicated complete consumption of starting material. The reaction mixture was poured into ice/water (8000 ml) and stirred manually until this melted, the resulting white precipitate was filtered then washed with copious water and air dried under suction. The white powder was taken up in hexane (800 ml) leaving toluene sulphonic acid undissolved, dried with anhydrous sodium sulphate then filtered and evaporated to yield (1*S*) *endo*-2-toluenesulphonyl-1,7,7-Trimethylbicyclo[2.2.1]heptane **199** as a colourless crystalline solid (304g, 99%) MP = 67-68°C (from hexane); ¹H NMR (60 MHz, CDCl₃) δ 7.9(2H, d, *J* = 8 Hz, CH's *o* to SO₃), 7.5(2H, d, *J* = 8.0 Hz, CH's *m* to SO₃), 4.75(1H, dm, *J* = 10.0 Hz, CHO), 2.55(3H, s, CH₃-Ar), 2.3-1.1(7H, cm's), 0.9(6H, s, 2 x CH₃), 0.8(3H, s, CH₃) ppm.

3.1.2 Preparation of (-)-Camphene 196

Powdered sodium hydroxide (120g, 3.0 mole) was dissolved with mechanical stirring in ethanediol (1500 ml) containing cresol (mixed isomers) (110g, 1.02 mole) at 60°C. Bornyl toluene sulphonate **199** (302g, 0.98 mole) dissolved in tetraglyme (400 ml)

was then added and the stirred solution heated under reflux. After 44 hours the reaction was cooled slightly, followed by distillation of camphene (130-165°C) into a receiver containing a vigorously stirred mixture of ether (100 ml) and sodium hydroxide solution (10%, 100 ml) to remove acidic impurities. [NB. Camphene regularly solidifies in the condenser and can be melted by use of a hot air blower. Also a wide bore slanted T-piece is preferable to an orthodox distillation receiver head as the latter invariably blocks and is difficult to free.] After addition of pentane (100 ml) the organic layer was separated and the aqueous extracted with pentane (2x50 ml). The combined organics were dried over sodium hydroxide pellets, decanted, then evaporated to one third volume and distilled from vigorously stirred molten sodium through a 20 cm insulated vigreux column collecting the fraction from 155 to 160 °C to yield (*1S*)-2,2 Dimethyl-3-methylene-bicyclo[2.2.1]heptane (-)-196 as a waxy low melting solid (101g, 76%) $[\alpha]_D = -106.5^\circ\text{C}$ (c = 20, ether); ^1H NMR (60 MHz, CDCl_3) δ 4.7(2H, 2 x s, =CH₂), 2.75(1H, bs, bridgehead CH), 2.0-1.0(7H, cm), 1.15, 1.10(6H, 2 x s, 2 x CH₃) ppm.

3.1.3 Preparation of Bornyl Chloride 200

A solution of (+)- α -pinene (390g, 2.87 mole) in chloroform (800 ml) was dried over molecular sieves (4Å) then cooled to -15°C (salt/ice) under argon. Dry hydrogen chloride was passed into this solution steadily over 2.5 hours until a steady stream passed through indicating saturation. The solution was allowed to warm to room temperature and stand for one hour. Argon was blown through the solution to remove excess hydrogen chloride, then the solvent removed *in vacuo* [FUME

HOOD]. The resulting paste was recrystallised from ethanol/methanol (plus a small quantity of water) to give two crops (300g & 36g, 73%) of *(1R) endo-2-chloro-1,7,7-Trimethylbicyclo[2.2.1]heptane* MP = 128-130°C [Lit. MP = 132°C]⁸⁹; ¹H NMR (250 MHz, CDCl₃) δ 4.16(1H, ddd, *J* = 10.5, 4.5, 2.5 Hz, CHCl), 2.45(1H, cm), 2.05(1H, cm), 1.75(1H, cm), 1.65(1H, cm), 1.4-1.2(3H, cm), 0.92(3H, s, CH₃), 0.86(6H, s, 2 x CH₃) ppm; ¹³C NMR (62.9 Mhz, CDCl₃) δ 67.8(CHCl), 50.7, 47.8(2 x quat), 44.8(bridgehead CH), 40.1, 28.0, 27.9(3 x CH₂), 20.5, 18.4, 13.2(3 x CH₃) ppm.

3.1.4 Preparation of (+)-Camphene 196

This was carried out as for 3.1.2 using the following quantities. Sodium hydroxide (160g, 4 mole), cresols (170 ml, 1.8 mole), ethylene glycol (700 ml)*, triglyme (300 ml)*[†] and bornyl chloride **200** (300g, 1.75 mole). The reaction was heated under reflux for 72 hours, then isolation carried out as before to yield *(1R)-2,2 Dimethyl-3-methylene-bicyclo[2.2.1]heptane (+)-196* (160g, 67%) [α]_D = +102° (c = 20, ether).

* Note, considerably less solvent is required for this solvolysis than that of the tosylate as the latter tends to become exceedingly viscous.

[†] Substituted for tetraglyme due to availability and economy.

3.1.5 Preparation of (2S)-endo-Camphenol 201

A 2l three neck flask flushed with argon was charged with camphene (-)-**196** (100g, 0.74 mole) and THF (150 ml), cooled to -78°C then borane:THF complex (370 ml, 1M in THF, 0.37 mole) was added *via* syringe over one hour. The reaction

mixture was allowed to warm to *Ca* -30°C over 4 hours, a slight exotherm was noted at this temperature. The reaction was allowed to reach room temperature over 2 hours and stirred for a further two hours. Ethanol (20 ml) was added to quench the reaction, followed by sodium hydroxide solution (20g, 0.5 mole in 100 ml water). Hydrogen peroxide (150 ml, ~30% w/v, ~1.5 mole) was added [CAUTION!] over 20 minutes and the reaction mixture heated to 50°C for 3 hours. After cooling sodium sulphite solution (60g in 200 ml water) was added [the presence of peroxides was checked with potassium iodide starch paper]. Following evaporation of two thirds of the organics, water (300 ml) was added then the mixture extracted with hexane (4 x 250 ml) and the combined organics washed with sodium sulphite solution (100 ml, 10%), water (3x200 ml) and brine (200 ml). The organics were dried over magnesium sulphate, filtered evaporated and subjected to high vacuum to yield (*2R*)-*endo*-3,3 Dimethyl-bicyclo[2.2.1]heptane-2-methanol **201** as a sticky colourless solid (112g, 98%, *endo* : *exo* *Ca*. 9:1) ¹H NMR (250 MHz, CDCl₃) δ 3.58(1H, d, *J* = 7.0 Hz, CH₂OH), 3.56(1H, d, *J* = 7.0 Hz, CH₂OH), 2.23(1H, bs, H₂), 1.85(1H, bs, OH), 1.70(1H, bs, H₁), 1.67-1.47(4H, cm), 1.38-1.20(2H, cm), 1.16(1H, dt, *J* = 10.5, 2.0 Hz, H₇), 0.95(3H, s, CH₃), 0.80(3H, s, CH₃) ppm; ¹³C NMR (62.9 MHz, CDCl₃) δ 60.8(CH₂OH), 52.3(CHCH₂OH), 48.9(CH), 39.5(CH), 36.9(CH₂), 36.6(quat, C(CH₃)₂), 32.4(CH₃), 24.2(CH₂), 20.3(CH₃), 20.1(CH₂) ppm; FT IR (thin film) ν_{max} 3300(broad, OH), 2960(CH) cm⁻¹; MS (EI) 136(35%, M⁺-H₂O), 123(16), 121(32), 111(26), 93(84).

NB (*2S*)-*endo*-camphenol was obtained in a similar manner.

3.1.6 Preparation of *endo*-Camphenol Chloroformate **205**

To an argon flushed three neck flask charged with phosgene solution (500 ml, 20% in toluene, 1.93 M, 0.97 mole) at 0°C was added the above mixture of camphenols **201** and **202** (112g, 0.727 mole, ~90% *endo*) in dry ether (200 ml) *via* a pressure equalised addition funnel over 30 minutes. The reaction was stirred at room temperature for 20 hours when IR analysis showed the reaction to be complete by the presence of a single carbonyl stretch and no hydroxyl stretch. Hydrogen chloride, excess phosgene and solvents were evaporated [FUME-HOOD] and the oil subjected to high vacuum to yield (160g. 94%) of ((2*R*)-*endo*) 3,3 Dimethyl-bicyclo[2.2.1]heptane-2-methylchloroformate **205** contaminated by *ca.* 10% of its *exo* diastereomer BP= 90°C (1mm Hg); ¹H NMR (200 MHz, CDCl₃) δ 4.32(2H, d, *J* = 8.0 Hz, CH₂O), 2.23(1H, bs, H₂), 1.85-1.71(2H, cm), 1.69-1.50(2H, cm), 1.4-1.1(4H, cm), 1.00(3H, s, CH₃), 0.85(3H, s, CH₃) ppm; ¹³C NMR (50.3 MHz, CDCl₃) δ 150.4(quat, C=O), 71.6(CH₂O), 48.8, 48.3(CH's), 40.0(CH), 37.0(CH₂), 32.1(CH₃), 24.3(CH₂), 20.5(CH₃), 20.3(CH₂) ppm; FT IR (thin film) ν_{max} 2960(CH), 1775(C=O), 1470 cm⁻¹.

NB. (2*S*)-*endo*-camphenol chloroformate was obtained in an identical manner.

3.1.7 Preparation of Camphenol Azidoformate **204**

The chloroformate **205** (158g, 0.65 mole) in dichloromethane (1000 ml) was added to a vigorously, mechanically stirred solution of sodium azide (85g, 1.31 mole) and tetra-*n*-butylammonium bromide (1.0g) in water (500 ml) at 0°C over 30 minutes. After stirring for 6 hours IR analysis of an aliquot indicated complete reaction (azide

and carbonyl stretches of approximately equal intensity). After separation followed by extraction with DICHLOROMETHANE (3 x 200 ml), the combined organics were washed with water (3 x 200 ml) and brine (200 ml). Drying over magnesium sulphate, filtration, evaporation and subjection to high vacuum afforded ((2*R*)-*endo*) 3,3 Dimethyl-bicyclo[2.2.1]heptane-2-methylazidoformate **204** contaminated by *ca.* 10% of its *exo* diastereomer as an oil (155g, 98%) ^1H NMR (200 MHz, CDCl_3) δ 4.21(2H, d, $J = 9.0$ Hz, CH_2O), 2.20(1H, bs, H_2), 1.76(1H, cm), 1.7-1.5(4H, cm), 1.4-1.2(2H, cm) 1.19(1H, td, $J = 9.0, 2.0$ Hz, H_7), 0.98(3H, s, CH_3), 0.85(3H, s, CH_3) ppm; ^{13}C NMR (50.3 MHz, CDCl_3) δ 157.4(quat, C=O), 67.8(CH_2O), 48.8, 48.4($\text{CH}'\text{s}$), 39.9(CH), 37.0(CH_2), 36.9(quat, $\text{C}(\text{CH}_3)_2$), 32.1(CH_3), 24.3(CH_2), 20.5(CH_3), 20.3(CH_2) ppm; FT IR (thin film) ν_{max} 2960(CH), 2193, 2138(N_3), 1760, 1733($\text{C}=\text{O}$) cm^{-1} ; MS (FAB) 242(62%, M^+), 170(54), 137(44).

NB. (2*S*)-*endo*-camphenol azidoformate was obtained in an identical manner.

3.1.8 Preparation of Chiracamphox (+)-**207** by Solution Thermolysis.

Azidoformate **204** (51g, 0.21 mole) in dry TCE (250 ml) was added *via* pressure equalising funnel over 40 minutes to vigorously refluxing, mechanically stirred TCE (2200 ml) under an argon atmosphere. Heating was continued for a further 15 minutes then the reaction mixture (golden brown in colour) was allowed to cool. TCE was removed *in vacuo*, two 50 ml portions of xylene were added and evaporated to azeotropically remove the remaining TCE and the black residue subjected to high vacuum. The resulting semi-crystalline mass was triturated with cyclohexane, filtered then taken up in dichloromethane, treated with activated

charcoal, filtered and evaporated. Two recrystallisations from xylene gave the pure compound (21.5g). Chromatography of the mother liquors on silica, elution with hexane to hexane:ether:dichloromethane (3:1:1) and subsequent recrystallisation from xylene increased the yield of (5*S*, 7*S*, 10*R*)-2-oxa-4-aza-6,6-dimethyl-7,10-methylenespiro[4.5]decan-3-one (+)-**207** to (27.9g, 68%). **MP**= 226.5-227.5 °C (from xylene); $[\alpha]_{\text{D}}^{20} = +51.8^{\circ}$ (c = 5.0, dichloromethane); **R_f** = 0.50 (1:1, cyclohexane/ethylacetate) **¹H NMR** (200 MHz, CDCl₃) δ 7.76(1H, b, N-H), 4.29(1H, d, *J* = 9.0 Hz, H_{1a}), 4.21(1H d, *J* = 9.0 Hz, H_{1b}), 2.14(1H, m, H₁₀), 1.79(1H, m), 1.73(1H, m), 1.625-1.39(2H, m), 1.38-1.125(3H, m), 0.955(3H, s, CH₃), 0.929(3H, s, CH₃) ppm; **¹³C NMR** (50.3 MHz, CDCl₃) δ 159.7(quat, oxazolidinone C=O), 69.0(CH₂O), 48.6, 48.5(CH's, C₇ & C₁₀), 42.21(quat, C₅), 34.80(CH₂, C₁₁), 26.06, 23.84(2 x CH₃), 23.64, 21.53(CH₂'s, C₈ & C₉) ppm; **FT IR** (KBr disc) ν_{max} 3240, 3134(N-H), 2970(C-H), 1749(C=O) cm⁻¹; **MS** (EI) 195(35%, M⁺), 152(16), 127(93), 126(71), 112(88.8); **Accurate mass** (FAB) (MH⁺) Found 196.13390; C₁₁H₁₈NO₂ requires 196.13375; **Elemental analysis**, Found 67.83% C, 8.65% H, 7.18% N, C₁₁H₁₇NO₂ requires 67.65% C, 8.78% H, 7.18% N.

NB. (5*R*, 7*R*, 10*S*)-2-oxa-4-aza-6,6-dimethyl-7,10-methylenespiro[4.5]decan-3-one (+)-**207** has been prepared in an analogous manner; in 63% yield $[\alpha]_{\text{D}} = -51.0^{\circ}$ (c = 5, dichloromethane).

3.1.9 Preparation of Chiracamphox 207 by Flash Vacuum Pyrolysis

Azidoformate **204** (3.77g) was placed in the inlet of the flash vacuum pyrolysis apparatus and heated to 90°C under a vacuum of 0.5-0.1m bar for three hours. After this time 2.50g (11.2 mmol) of **204** was volatilised and passed through the furnace at 300°C. After cooling the solid deposited at the furnace mouth was collected and after preadsorption on magnesium sulphate was chromatographed on silica, gradient elution (hexane to ether) to yield a colourless crystalline solid with physical data consistent with the product of **3.1.8**.

3.1.10 Preparation of *exo*-Camphenol via Thermal Isomerisation of the Intermediate Camphenylboranes 210/211

Camphene (13.6g, 0.1 mole) under argon in an ice cooled flask was dissolved in a solution of borane:THF complex (50 ml, 1 M in THF, 0.05 mole, 1.5 equivalents of B-H). This solution was stirred at room temperature for 17 hours, then most of the THF was removed under vacuum and the residue diluted with dry diglyme (90 ml). A further portion of borane complex (10 ml, 0.01 mole) was added as it has been noted that excess borane accelerates thermal isomerisation⁹⁶. The remaining THF was removed under vacuum until the reaction mixture boiled at >162°C at atmospheric pressure (bath temperature ~190°C) (all transfers carried out under argon). The mixture was heated under reflux for 22 hours then after cooling was quenched with ethanol (30 ml). Sodium hydroxide (5.0g, 0.125 mole) in water (25 ml) and then hydrogen peroxide (40 ml, ~30%, ~0.4 mole) were added with caution and the mixture kept at ~50°C for three hours. After work up as for **3.1.5** a sticky,

off white solid was obtained. Integration of the ^1H NMR signal of H_{1a} and H_{1b} showed that it was a 3:2 mixture of *exo*- and *endo*- camphenols. The material was chromatographed on silica (50g per 1g of alcohols), eluting with hexane:ether (3:1). The leading fractions were collected then evaporated and rechromatographed twice in similar manner. At the end of this procedure a 4:1 mixture of *exo*- and *endo*-camphenols was obtained (2.25g, 14 %). The following physical data was collected for the major isomer ((2*S*)-*exo*) 3,3 Dimethyl-bicyclo[2.2.1]heptane-2-methanol **202** ^1H NMR (200 MHz, CDCl_3) δ 3.53(1H, dd, $J = 10.5, 6.0$ Hz, CH_2OH), 3.30(1H, dd, $J = 10.5, 9.0$ Hz, CH_2OH), 2.50(1H, s, OH), 2.07(1H, d, $J = 4.0$ Hz, H_2), 1.7-1.45(4H, cm), 1.38-0.95(4H, cm), 0.97(3H, s, CH_3), 0.85(3H, s, CH_3) ppm; ^{13}C NMR (50.3 MHz, CDCl_3) δ 63.0(CH_2OH), 56.2(CH), 49.0(CH), 40.4(CH), 35.6(CH_2), 29.3(CH_2), 27.9(CH_3), 23.8(CH_2), 23.5(CH_3) ppm; IR (thin film) ν_{max} 3300(broad, OH), 2960(CH) cm^{-1} .

3.1.11 Preparation of *exo*-Camphenol Chloroformate

exo-Camphenol **202** (2.15g, 14 mmol., ~80%) and triethylamine (2.1g, 20 mmol.) in ether (30 ml) were added drop wise to an ice cold solution of phosgene (30 ml, 1.92 M in toluene, 57 mmol.) over 20 minutes with vigorous stirring. After 24 hours at room temperature the reaction was observed to be complete by IR analysis. the solution was filtered and evaporated to yield ((2*S*)-*exo*) 3,3 Dimethyl-bicyclo[2.2.1]heptane-2-methylchloroformate together with its *endo* diastereomer as an oil (2.65g, 82 %). Physical data for the major isomer was ^1H NMR (200 MHz, CDCl_3) δ 4.25(1H, dd, $J = 10.5, 7.0$ Hz, CH_2O), 4.12(1H, dd, $J = 10.5, 9.0$ Hz,

CH₂O), 2.06(1H, d, J = 4.5 Hz, H₂), 1.80-1.50(4H, cm), 1.50-1.00(4H, cm), 1.04(3H, s, CH₃), 0.92(3H, s, CH₃) ppm; ¹³C NMR (50.3 MHz, CDCl₃) δ 150.5(quat, C=O), 73.2(CH₂O), 51.8(CH), 49.0(CH), 40.7(CH), 35.7(CH₂), 29.1(CH₃), 27.6(CH₂), 23.7(CH₂ & CH₃) ppm; IR (thin film) $\nu_{\max}$ 2960(CH), 1770(C=O), 1160 cm⁻¹.

3.1.12 Preparation of *exo*-Camphenol Azidoformate **209**

Chloroformate (2.25g, 13.5 mmol., ~80%), in dichloromethane (30 ml) was treated with sodium azide (3.6g, 4 equiv.) and tetra-*n*-butylammonium bromide (100 mg) in water (20 ml). After 24 hours work up as for **3.1.7** yielded ((2*S*)-*exo*) 3,3 Dimethylbicyclo[2.2.1]heptane-2-methylazidoformate **209** together with its *endo* diastereomer as a slightly yellow oil (2.79g, 100%) ¹H NMR (200 MHz, CDCl₃) δ 4.13(1H, dd, J = 11.0, 7.0, CH₂O), 4.00(1H, dd, J = 11.0, 9.0, CH₂O), 2.02(1H, d, J = 3.5 Hz, H₂), 1.78-1.47(4H, cm), 1.40-1.00(4H, cm), 1.00(3H, s, CH₃), 0.90(3H, s, CH₃) ppm; ¹³C NMR (50.3 MHz, CDCl₃) δ 157.4(quat, C=O), 69.5(CH₂O), 52.0(CH), 49.0(CH), 40.7(CH), 39.8(quat, C(CH₃)₂), 35.7(CH₂), 29.1(CH₂), 27.7(CH₃), 23.7(CH₂ & CH₃) ppm; IR (thin film) $\nu_{\max}$ 2960(CH), 2180, 2115(N₃), 1760, 1725(C=O), 1280 cm⁻¹.

3.1.13 Flash Vacuum Pyrolysis of *exo*-Camphenol Azidoformate **209**

Azidoformate **209** (2.60g) was treated as for **3.1.8** which resulted in 1.78g (7.4 mmol.) being volatilised. A colourless residue was collected from the trap and the end of the pyrolysis tube (1.42g, 68 % mass balance). This was examined by ¹H NMR and shown to be a mixture of the spiro-oxazolidinones, this time predominantly the *exo*-derived diastereomer. The residue was recrystallised from

toluene to give (5*R*, 7*S*, 10*R*)-2-oxa-4-aza-6,6-dimethyl-7,10-methylenespiro[4.5]decan-3-one **208** (0.62g, 43 %) **MP** = 226.0-226.8°C (from toluene); $[\alpha]_D^{20} = -39.5^\circ$ (C = 2.3, dichloromethane); **R_f** = 0.55 (1:1, cyclohexane/ethylacetate); **¹H NMR** (360 MHz, CDCl₃) δ 4.34(1H, d, *J* = 9.0 Hz, H_{1a}), 3.91(1H, d, *J* = 9.0 Hz, H_{1b}), 2.09(1H, d, *J* = 4.5 Hz, H₁₀), 1.72(1H, s, H₇), 1.68(1H, ddt, *J* = 12.0, 9.0, 3.0 Hz), 1.54(1H, tdd, *J* = 13.0, 5.0, 2.0 Hz), 1.44(1H, dm, *J* = 11.0 Hz, H_{11a}), 1.39(1H, tdd, *J* = 13.0, 4.5, 3.0 Hz), 1.27(1H, tdd, *J* = 12.0, 5.0, 4.0 Hz), 1.18(1H, dt, *J* = 10.7, 1.6 Hz, H_{11b}), 0.93(3H, s, CH₃), 0.90(3H, s, CH₃) ppm; **¹³C NMR** (90.5 MHz, CDCl₃) δ 160.1(quat, oxazolidinone C=O), 73.5(CH₂O), 68.6(quat, C-N), 48.5(2 x CH), 40.9(quat, C(CH₃)₂), 34.1(CH₂, C₁₁), 26.4(CH₃), 23.7(CH₂), 23.0(CH₃), 21.4(CH₂) ppm; **FT IR** (KBr disc) $\nu_{\max}$ 3240, 3125(NH), 2960(CH), 1760(C=O) cm⁻¹; **MS** (FAB) 196(76, MH⁺), 135(18), 107(15); **Accurate mass** (FAB) (MH⁺) Found 196.13328; C₁₁H₁₈NO₂ requires 196.13375; **Elemental analysis**, Found 67.48% C, 8.35% H, 7.13% N, C₁₁H₁₇NO₂ requires 67.65% C, 8.78% H, 7.18% N.

3.1.14 Preparation of *endo*-Camphenol *p*-Nitrophenyl Carbonate **203**

Chloroformate **205** (3.09g, 13.3 mmol.) in ether (30 ml) was added to *p*-nitrophenol (1.9g, 13.5 mmol) and triethylamine (1.4g, 13.5 mmol) in ether (50 ml) at 0°C. After 48 hours at room temperature the suspension was filtered and the filtrate washed with sodium bicarbonate solution (3 x 15 ml), water and brine. After drying the solvent was evaporated to yield a low melting solid. Chromatography failed to separate the diastereomers, but did yield a crystalline solid (2.80g, 68%, **MP** = 47-49°C).

Recrystallisation of this material also failed to alter the diastereomer ratio, as witnessed by ^1H NMR spectroscopy. ((2*R*)-*endo*/(2*S*)-*exo*) 3,3 Dimethyl-bicyclo[2.2.1]heptane-2-methyl *p*-nitrophenyl carbonate **203** MP = 51-52°C (from hexane); R_f = 0.35 (1:1, hexane/toluene); ^1H NMR (60 MHz, CDCl_3) δ 8.35(2H, d, J = 9.0 Hz, CH's *m* to *OR*), 7.4(2H, d, J = 9.0 Hz, CH's *o* to O), 4.4(2H, d, J = 8.0 Hz, CH_2O), 2.35(1H, cm, CHCH_2O), 2.0-1.0(8H, cm's), 1.1(3H, s, CH_3), 0.95(3H, s, CH_3) ppm; IR (thin film) ν_{max} 3110, 3090(Ar CH), 2960(CH), 1760(C=O), 1615, 1595(Ar C=C), 1520, 1350(NO_2), 855(Ar C-H) cm^{-1} ; MS (FAB) 320(4%, MH^+), 302(6), 290(10), 171(10), 137(55).

3.1.15 Preparation of *endo*-Camphenol Azidoformate **204** From *endo*-

Camphenol *p*-Nitrophenyl Carbonate **203**.

A stirred solution of the carbonate **203** (1.05g, 3.3 mmol) in wet *N,N*-dimethylformamide (20 ml + 1 ml water), was treated with sodium azide (1.5g, 23 mmol., 7 equiv.). A yellow colour rapidly appeared (*p*-nitrophenolate anion) and after stirring overnight TLC showed that all starting material had been consumed. Ether (40 ml) was added and after filtration the solvents were removed *in vacuo*. The residue was taken up in dichloromethane, washed with copious water, dried filtered and evaporated to yield a yellow oil which was identified as the azidoformate **204** (0.61g, 87%).

3.2 Functionalisation of Chiracamphox

3.2.1 Preparation of Propionyl Imide 213 *via* the Lithium Salt of 207

A solution of oxazolidin-2-one **207** (490mg, 2.51 mmol.) in dry THF (10 ml) under argon at -78°C was treated with *n*-butyl lithium (1.7 ml, 1.6 M in hexanes, 2.72 mmol.) and stirred for thirty minutes. Freshly distilled propionyl chloride (420mg, 4.55 mmol.) in dry THF (2 ml) was added rapidly and after 30 minutes the reaction was allowed to warm to room temperature. TLC analysis (4:1, cyclohexane/ethylacetate) showed that **207** and two other faster eluting components were present. After 2 hours no change was apparent so the reaction was quenched with sodium bicarbonate solution (10 ml), concentrated *in vacuo* and extracted with dichloromethane (3 x 30 ml). After washing with water then brine, drying over magnesium sulphate, filtration and evaporation a gum was obtained. Chromatography on silica, eluting with hexane to hexane:ether (4:1) yielded (5*S*, 7*S*, 10*R*)-*N*-propionyl-2-oxa-4-aza-6,6-dimethyl-7,10-methylenespiro[4.5]decan-3-one **213** as an oil which later solidified (120mg, 19%) MP= 52-53.5 °C (from pentane); $[\alpha]_D^{20} = +110.5^\circ$ (c = 6.3, dichloromethane); $R_f = 0.60$ (4:1, cyclohexane/ethylacetate); $^1\text{H NMR}$ (200 MHz, CDCl_3) δ 4.26(1H, d, $J = 9.0$ Hz, H_{1a}), 3.98(1H, d, $J = 9.0$ Hz, H_{1b}), 2.96(1H, dq, $J = 18.5, 8.0$ Hz, $\text{CH}_3\text{CH}_2\text{CO}$), 2.88(1H, dq, $J = 18.5, 8.0$ Hz, $\text{CH}_3\text{CH}_2\text{CO}$), 2.65(1H, m, H_{10}), 1.79(1H, m), 1.64-1.11(6H, cm), 1.10(3H, s, CH_3), 1.088(3H, t, $J = 8.0$ Hz, $\text{CH}_3\text{CH}_2\text{CO}$), 1.028(3H, s, CH_3) pm; $^{13}\text{C NMR}$ (50.3 MHz, CDCl_3) δ 174.74(quat, $\text{RC}=\text{ON}$), 155.74(quat,

oxazolidinone C=O), 75.07(quat, C-N), 70.68($\underline{\text{C}}\text{H}_2\text{O}$), 49.04(CH, C₁₀), 47.47(quat, $\underline{\text{C}}(\text{CH}_3)_2$), 45.00(CH, C₇), 38.20(CH₂, C₁₁), 30.54($\underline{\text{C}}\text{H}_2\text{CO}$), 25.60(CH₃), 23.99, 22.54(2xCH₂), 21.10(CH₃), 8.65($\underline{\text{C}}\text{H}_3\text{CH}_2$) ppm; **FT IR** (thin film) ν_{max} 1775 (oxazolidinone C=O), 1710 (R.C=O) cm^{-1} ; **MS** (FAB) 252(58%, MH^+), 196(84), 135(66); **Accurate mass** (FAB) (MH^+) Found 252.15852; C₁₄H₂₂NO₃ requires 252.15997; **Elemental analysis**, Found 66.96% C, 8.41% H, 5.48% N, C₁₄H₂₁NO₃ requires 66.89% C, 8.43% H, 5.58% N.

Further elution gave a colourless solid- **214** (180mg, 20%) (see **3.3.10** for physical data) contaminated with *ca.* 10% of its C_a diastereomer. Elution with ether gave **207** (300mg, 60%).

3.2.2 Preparation of Propionyl Imide 213 via the bromomagnesium salt of 207

Oxazolidin-2-one **207** (630mg, 3.2 mmol) in dry THF (10 ml) was added drop wise to a freshly prepared solution of methylmagnesium bromide (3.6 mmol) [from magnesium (88mg, 3.7 mmol) and methylbromide (4 ml, 2M in ether, 8 mmol)] in dry THF under argon at 0°C. After stirring for 30 minutes the reaction was cooled to -78°C then treated with freshly distilled propionyl chloride (580mg, 6.2 mmol) in dry THF (10 ml). After allowing the reaction mixture to warm to ambient temperature, monitoring by TLC (4:1, cyclohexane/ethylacetate) showed the formation of the same three products as **3.2.1** but the fastest eluting was by far the strongest. Work up as for **3.2.1** yielded a gum (1070mg) which was chromatographed on silica, elution hexane to hexane:ether (4:1) yielded **213** as a colourless gum which solidified (640mg, 78 %) (physical data as for **3.2.1**). Further elution (3:1) yielded **214** (180mg, 18 %), then (ether) **207** (20g, 3 %).

3.2.3 Preparation of Propionyl Imide **213** via the Chlorozinc salt of **207**

Oxazolidin-2-one **207** (3.90g, 20.0 mmol) in dry THF (30 ml) was added over 10 minutes to a freshly prepared solution of ethylmagnesium bromide (22.1 mmol) [magnesium (0.53g) and ethylbromide (3.5g)] in dry THF (150 ml) under argon at 0°C. After 30 minutes finely crushed anhydrous zinc chloride (2.95g, 24.0 mmol) was added [AVOID EXPOSURE TO MOISTURE] and the reaction stirred for 1 hour before cooling to -78°C (formation of white precipitate). Freshly distilled propionyl chloride (2.6g, 28.1 mmol) was added and the reaction allowed to warm to room temperature. Monitoring by TLC (1:4, cyclohexane/ethylacetate), indicated that after 24 hours no further product was being formed (a small quantity of **207** was still present but **214** was absent). After quenching with saturated ammonium chloride solution (60 ml), the THF was removed *in vacuo*, followed by extraction with dichloromethane (3x100 ml) washing with saturated ammonium chloride, sodium bicarbonate solution then brine, drying with magnesium sulphate, filtration and evaporation *in vacuo* yielded an oil. Chromatography on silica, eluting hexane:ether (4:1) yielded a colourless solid **213** (4.32g, 86%), which could be recrystallised from pentane (-30°C). Elution with ether gave unreacted **207** 0.51g, 13%).

3.2.4 Preparation of Propionyl Imide *via* the “Zinc salt” of 207 in THF;

Deprotonation of 207 with 0.5 Equivalents of Diethylzinc

A solution of **207** (3.92g, 20.1 mmol) in dry THF (80 ml) at 0°C was treated with diethylzinc (10.5 ml, 1.0 M in hexanes, 10.5 mmol) over 15 minutes and stirred at this temperature for one hour. After cooling to -78°C, then addition of propionyl chloride (2.70g, 29.2 mmol) the reaction was allowed to warm to room temperature. Monitoring by TLC (4:1, cyclohexane/ethylacetate) over a period of 24 hours showed that the presence of **207** and **213** and a faster running component; however no **214** was present. Even after 48 hours considerable quantities of **207** were still present, and quenching and work up as for **3.2.3** yielded an oil containing crystals of **207**, which was chromatographed on silica to give **213** (2.54g, 50%) and recovered **207** (1.88g, 48%).

3.2.5 Preparation of Propionyl Imide **213 *via* the Ethylzinc Salt of **207**;**

Deprotonation of 207 with 1.1 Equivalents of Diethylzinc

The procedure of **3.2.4** was followed using **207** (3.92g, 20.1 mmol), diethylzinc (21 ml, 1.0 M in hexanes, 21 mmol) and propionyl chloride (6.20g, 67 mmol). After 24 hours at room temperature then 4 hours at 35 °C TLC (4:1, cyclohexane/ethylacetate) showed the presence of only **213** and a faster eluting component. Quenching , work up and chromatography as for **3.2.3** yielded **213** as a gum (5.30g, >100% mass balance) slightly contaminated by ester **220**; recrystallisation from pentane gave the pure compound.

3.2.6 Preparation of Propionyl Imide 213 *via* the Ethylzinc salt of 207 in Ether

A suspension of **207** (1.96g, 10.1 mmol) in dry ether (100 ml) under argon at ambient temperature was treated slowly with diethylzinc (10.5 ml, 1.0 M in hexane, 10.5 mmol) whereupon the undissolved auxiliary went into solution. After 1 hour the reaction was cooled to -78°C and treated with propionyl chloride (2.30g, 25 mmol) then allowed to warm to room temperature. After stirring for 24 hours TLC (4:1, cyclohexane/ethylacetate) showed complete reaction and an absence of the faster running spot. Quenching with ammonium chloride solution followed by extraction with ether (3 x 50 ml), washing with saturated ammonium chloride, sodium bicarbonate and brine: then drying over magnesium sulphate, filtration and evaporation yielded an oil. After being subject to high vacuum almost pure **213** was obtained as gum (2.61g, 104% mass balance) was recrystallised from pentane (-30°C) (2.23g, 89% recovery).

3.2.7 Preparation of Acryloyl Imide 221 *via* the Bromomagnesium salt of **207**.

Auxiliary **207** (5.0g, 24.5 mmol) in dry THF (40 ml) was added to a freshly prepared solution of methylmagnesium bromide (30.0 mmol) [from magnesium (720mg, 30 mmol) and methyl bromide (20 ml, 2.0 M in ether, 40 mmol)] in dry ether at 0°C under an argon atmosphere. After 30 minutes the reaction mixture was cooled to -78°C then treated with freshly distilled acryloyl chloride (7.50g, 83 mmol) in dry THF (30 ml). After warming to room temperature and stirring for 16 hours TLC

indicated that no more product was being formed. The reaction was quenched with saturated sodium hydrogencarbonate solution, stirred for 20 minutes then the solvent removed *in vacuo* and the residue extracted into dichloromethane (3x150 ml). After washing with water then brine the organic layers were dried over magnesium sulphate, filtered and evaporated to afford an oil (8.43g). The oil was chromatographed on silica, eluting hexane to hexane/ether(3:1) to yield (5*S*, 7*S*, 10*R*)-*N*-acryloyl-2-oxa-4-aza-6,6-dimethyl-7,10-methylenespiro[4.5]decan-3-one **221** as a colourless solid (1.82g, 29%) **MP**= 132-133.5°C (from dichloromethane/hexane); $[\alpha]_D^{20} = +140^\circ$ (c = 1.75, CHCl₃); **R_f** = 0.40 (4:1, cyclohexane/ethylacetate); **¹H NMR** (200 MHz, CDCl₃) δ 7.18(1H, dd, *J* = 17.0, 10.5 Hz, CH=CH₂), 6.32(1H, dd, *J* = 16.0, 2.0 Hz, CH=CH₂), 5.70(1H, dd, *J* = 10.5, 2.0 Hz, CH=CH₂), 4.28(1H, d, *J* = 9.0 Hz, H_{1a}), 4.02(1H, d, *J* = 9.0 Hz, H_{1b}), 2.69(1H, dm, *J* = 10.5 Hz, H_{11a}), 2.63(1H, bs, H₁₀), 1.79(1H, bs, H₇), 1.63-1.30(2H, cm), 1.23(1H, dt, *J* = 10.5, 1.5 Hz, H_{11b}), 1.20-1.05(2H, m), 1.08, 0.94(6H, 2xs, 2xCH₃) ppm; **¹³C NMR** (50.3 MHz, CDCl₃) δ 165.8(quat, RC=O), 155.5(quat, oxazolidinone C=O), 129.5(CH=CH₂), 75.2(quat, C-N), 70.8(CH₂O), 48.9(CH, C₁₀), 47.4(quat, C(CH₃)₂), 44.8(CH, C₇), 37.9(CH₂, C₁₁), 25.7(CH₃), 23.8, 22.4(2 x CH₂), 21.0(CH₃) ppm; **FT IR** (CCl₄) $\nu_{\max}$ 1786 (oxazolidinone C=O *str*), 1690(R.C=O *str*) cm⁻¹; **MS** (FAB) 250(15%, MH⁺), 196(40), 135(32), 107(24); **Accurate mass** (FAB) (MH⁺) Found 250.14335; C₁₄H₂₀NO₃ requires 250.14432; **Elemental analysis**, Found 67.59% C, 7.83% H, 5.61% N, C₁₄H₁₉NO₃ requires 67.43% C, 7.69% H, 5.62% N.

3.2.8 Attempted Preparation of Acryloyl Imide 221 via the Lithium salt of

207.

Auxiliary **207** (710mg, 3.65 mmol) in dry dichloromethane (40 ml) under argon at -78°C was treated with *n*-butyl lithium (2.2 ml, 1.6 M in hexane, 3.5 mmol) and after one hour freshly distilled acryloyl chloride (650mg, 7.2 mmol) in dichloromethane (10 ml) was added; on warming to room temperature the reaction mixture became cloudy. TLC (4:1, cyclohexane/ethylacetate) indicated only base line material, quenching and work-up followed by evaporation yielded an intractable polymeric glass.

3.2.9 Attempted Preparation of Acryloyl Imide 221 via the *N*-3

Bromopropionyl derivative 222.

Auxiliary **207** (1.07g, 5.5 mmol) in dry THF (10 ml) was added to a preformed solution of methylmagnesium bromide (5.75 mmol) in THF (20 ml) under argon at 0°C, after 30 minutes 3 bromopropionyl chloride (1.1g, 6.5 mmol) was added and the reaction mixture warmed to 35°C for 12 hours. TLC showed the presence of both **207** and a compound of similar R_f to **221**. Ether (60 ml) was added and the organics washed with saturated ammonium chloride solution, extracted with ether (2 x 30 ml) then dried with magnesium sulphate and filtered. The filtrate was treated with triethylamine (6 ml, vast excess) for three hours, washed with 1:1 saturated ammonium chloride solution/1M hydrochloric acid (100 ml) extracted with ether dried, filtered and evaporated. The resulting gum was chromatographed on silica eluting hexane:ether (4:1) to provide a yellow oil (220mg) which contained **221** but

also a large quantity of an unidentified contaminant (could not be separated by chromatography or high vacuum distillation (decomposition)).

3.2.10 Attempted Preparation of the 3-chloropropionyl Imide 223 via the Bromomagnesium salt of 207.

A solution of the bromomagnesium salt of **207** (2.15 mmol) in dry THF (20 ml) [see 3.2.2] under argon at -78°C was treated with 3-chloropropionyl chloride (500mg, 3.2 mmol) and the reaction allowed to warm to room temperature. After stirring for a protracted period of time TLC (4:1, cyclohexane/ethylacetate) showed only starting material was present. Standard work up gave almost pure **207** (400mg, 95%).

3.2.11 Attempted Preparation of the N-3-chloropropionyl Imide 223 via the Chlorozinc salt of 207

A solution of the bromomagnesium salt of **207** (2.00 mmol) in dry THF (20 ml) under argon at 0°C was treated with freshly prepared anhydrous zinc chloride (390mg, 2.86 mmol) and after stirring for 30 minutes cooled to -78°C. 3-Chloropropionyl chloride (500mg, 3.2 mmol) and the reaction allowed to warm to room temperature. After stirring for 18 hours TLC (4:1, cyclohexane/ethylacetate) showed that starting material was present together with two faster eluting components. Quenching and work up as for 3.2.3 gave a gum (1.1g) which was subjected to chromatography on silica, gradient elution hexane-ether to give a mobile oil (460 mg) followed by an oil (150mg); neither of these compounds has been

identified. Finally elution with ether gave **207** (400mg, 105% mass balance) as a colourless crystalline powder.

3.2.12 Preparation of Acryloyl Imide **221** via the *N*-TMS Derivative of **207**.

Auxiliary **207** (1.95g, 10.0 mmol) in dry THF (100 ml) under argon at -78°C was treated with *n*-butyl lithium (6.5 ml, 1.6 M in hexane, 10.4 mmol). After 30 minutes trimethylsilyl chloride (2.6 ml, 3.03 g, 28 mmol) in THF (10 ml) was added and the reaction mixture allowed to warm to room temperature and stirred for 2 hours. Volatiles were removed *in vacuo* and the residue taken up in dry toluene (50 ml) and filtered (under an argon atmosphere). Copper(II)chloride (2.0g, 20 mmol) and fine copper powder (50mg, "bronze") were added followed by acryloyl chloride (4.5g, 50 mmol); the reaction mixture was then heated under reflux for 60 hours under a nitrogen atmosphere. TLC (4:1, cyclohexane/ethylacetate) showed that some **221** was present, a further quantity of propionyl chloride (1g, 11 mmol) was added and heating continued for 60 hours. TLC showed that no more **221** was forming so the reaction was evaporated *in vacuo* and the residue chromatographed on silica. Elution with hexane then hexane:ether 10:1, 4:1 provided **221** as a sticky solid (445mg, 18 %), further elution with ether gave **207** as a colourless solid (1.52g, 78 %).

3.2.13 Preparation of Crotonyl Imide **225** via the Bromomagnesium salt of **207**.

A solution of the bromomagnesium salt of **207** (20 mmol) in dry THF (200 ml) [see 3.2.2] under argon at -78°C was treated with freshly distilled crotonyl chloride (2.4g,

23 mmol) in THF (7 ml) and the reaction mixture allowed to warm to room temperature. After 4 hours the reaction was quenched with saturated ammonium chloride, evaporated then extracted with dichloromethane (3 x 100 ml), washed with sodium bicarbonate, water and brine (50 ml of each) then dried over magnesium sulphate. After filtering evaporation gave a yellow gum which was chromatographed on silica, eluent hexane:ether 4:1, to give after evaporation colourless needles of (5*S*, 7*S*, 10*R*)-*N*-*trans*-crotonoyl-2-oxa-4-aza-6,6-dimethyl-7,10-methylenespiro[4.5]decan-3-one **225** (4.31g, 82%) MP= 114.9-115.6°C (from cyclohexane); $[\alpha]_D^{20} = +145.2^\circ$ (c = 2.1, dichloromethane); $R_f = 0.38$ (4:1, cyclohexane/ethylacetate); $^1\text{H NMR}$ (200 MHz, CDCl_3) δ 6.98(2H, cm, $\text{CH}=\text{CH}$), 4.28(1H, d, $J = 9.0$ Hz, H_{1a}), 4.01(1H, d, $J = 9.0$ Hz, H_{1b}), 2.75-2.60(2H, cm, H_{10} & H_{11a}), 1.86(3H, d, $J = 4.5$ Hz, $\text{CH}=\text{CH}.\text{CH}_3$), 1.80(1H, bs, H_7), 1.8-1.4(3H, cm), 1.24(1H, dt, $J = 10.5, 1.0$ Hz, H_{11b}), 1.20-1.00(1H, cm), 1.10(3H, s, CH_3), 0.96(3H, s, CH_3) ppm; $^{13}\text{C NMR}$ (50.3 MHz, CDCl_3) δ 166.0(quat, $\text{RC}=\text{O}$), 155.7(quat, oxazolidinone $\text{C}=\text{O}$), 144.6($\text{CH}=\text{CHC}=\text{O}$), 123.9($\text{CH}=\text{CHC}=\text{O}$), 75.2(quat, C-N), 70.8(CH_2O), 49.0(CH, C_{10}), 47.5(quat, $\text{C}(\text{CH}_3)_2$), 45.1(CH, C_7), 38.0(CH_2 , C_{11}), 25.8($=\text{CHCH}_3$), 23.9, 22.5(2 x CH_2), 21.2, 18.1(2 x CH_3) ppm; **FT IR** (thin film) ν_{max} 3055, 2970(CH *str*), 1774(oxazolidinone $\text{C}=\text{O}$), 1693(R.C=O), 1636(C=C) cm^{-1} ; **MS** (FAB) 264(16%, MH^+), 196(76), 135(35), 107(32); **Accurate mass** (FAB) (MH^+) Found 264.15977; $\text{C}_{15}\text{H}_{22}\text{NO}_3$ requires 264.15997; **Elemental analysis**, Found 68.61% C, 7.66% H, 5.33% N, $\text{C}_{15}\text{H}_{21}\text{NO}_3$ requires 68.40% C, 8.04% H, 5.32% N.

3.2.14 Preparation of Crotonyl Imide 225 via the Ethylzinc salt of 207 in Ether

207 (3.90g, 19.5 mmol), in ether (180 ml) was treated with diethylzinc (22 ml, 1.0 M, 22 mmol) at room temperature then cooled to -78°C . Freshly distilled crotonyl chloride (7.10g, 68 mmol) added and the reaction allowed to warm to room temperature. After heating to 30°C for 2 hours TLC showed the reaction to be complete. Work up as for 3.2.6 and recrystallisation from hexane provided (-)-225 (3.52g), chromatography of the mother liquors, followed by recrystallisation from hexane/pentane gave a further crop (1.25g, 93% in total). $[\alpha]_{\text{D}} = -144^{\circ}$ ($c = 1.9$).

3.2.15 Preparation of the Cinnamoyl Imide 226 via the Bromomagnesium salt of 207.

207 (1.97g, 10.1 mmol) in dry THF (20ml) was added to methyl magnesium bromide (11.6 mmol) in THF (60 ml) under argon at 0°C . After 30 minutes this was cooled to -78°C and treated with freshly distilled cinnamoyl chloride (2.00g, 12.0 mmol). After 17 hours at room temperature TLC (4:1, cyclohexane/ethylacetate) indicated almost complete reaction; quenching and work up as for 3.2.2 gave a yellow gum which solidified. This was recrystallised* from dichloromethane/hexane to give (5*S*, 7*S*, 10*R*)-*N*-trans-cinnamoyl-2-oxa-4-aza-6,6-dimethyl-7,10-methylenespiro[4.5]decan-3-one 226 as faintly yellow crystals (2.84g, 87%) $\text{MP} = 98.0\text{--}99.8^{\circ}\text{C}$ (from dichloromethane/hexane); $[\alpha]_{\text{D}}^{20} = +148.1^{\circ}$ ($c = 2.1$, dichloromethane); $R_{\text{f}} = 0.47$ (4:1, cyclohexane/ethylacetate); $^1\text{H NMR}$ (200 MHz, CDCl_3) δ 7.72(2H, s, $\text{CH}=\text{CH}$), 7.59-7.50(2H, cm, Ph), 7.40-7.25(3H, cm, Ph), 4.31(1H, d, $J = 9.0$ Hz, $\text{H}_{1\text{a}}$), 4.06(1H, d, $J = 9.0$ Hz, $\text{H}_{1\text{b}}$), 2.80(1H, dm, $J = 10.5$ Hz,

H_{11a}), 2.72(1H, bs, H₁₀), 1.83(1H, bs, H₇), 1.8-1.4(3H, cm), 1.30(1H, dm, $J = 10.5$ Hz, H_{11b}), 1.25-1.05(1H, m), 1.13(3H, s, CH₃), 1.03(3H, s, CH₃) ppm; ¹³C NMR (50.3 MHz, CDCl₃) δ 166.1(quat, RC=O), 155.8(quat, oxazolidinone C=O), 144.5(CH=CHC=O), 134.5(quat, Ph), 130.2(CH, Ph), 128.5, 128.1(2 x CH, 2 x CH, Ph), 119.3(CH=CHC=O), 75.3(quat, C-N), 70.8(CH₂O), 48.9(CH, C₁₀), 47.5(quat, C(CH₃)₂), 45.0(CH, C₇), 38.0(CH₂, C₁₁), 25.8(CH₃), 23.9, 22.5(2 x CH₂), 21.15(CH₃) ppm; FT IR (CCl₄ mull) $\nu_{\max}$ 3040(Ar CH), 2960(CH), 1770(oxazolidinone C=O), 1690(RC=O), 1620(C=C), 789, 775 cm⁻¹; MS (FAB) 326(22%, MH⁺), 196(25), 136(16), 107(18); Accurate mass (FAB) (MH⁺) Found 326.17566; C₂₀H₂₄NO₃ requires 326.17562; Elemental analysis, Found 73.95% C, 6.8% H, 4.32% N, C₂₀H₂₃NO₃ requires 73.81% C, 7.1% H, 4.31% N.

* Chromatography on silica yielded colourless crystals which contained ~10% of a closely related compound, probably the *cis* isomer (by ¹H & ¹³C NMR spectroscopy). Rechromatography of this mixture only increased the impurity to ~30% and stirring over silica in dichloromethane for 20 hours gave a near 1:1 mixture; TLC showed no decomposition and IR spectra were essentially unchanged.

3.2.16 Catalytic Hydrogenation of *cis/trans* Cinnamoyl Imide 207

226 (650mg, ~1:1 *cis/trans*, 2.0 mmol) was dissolved in ethylacetate (30 ml) and stirred with 10% Pd/C (100mg) under a hydrogen atmosphere for three hours. TLC (4:1, cyclohexane/ethylacetate) indicated complete reduction and the catalyst was filtered off onto a celite pad. The filtrate was evaporated and then hexane (10 ml) was added then evaporated, this was repeated twice. The resulting gum was crystallised

from pentane (-30°C) to yield two crops of (5*S*, 7*S*, 10*R*)-*N*-3-phenylpropionyl-2-oxa-4-aza-6,6-dimethyl-7,10-methylenespiro[4.5]decan-3-one **227** as colourless needles (610mg, 93%) **MP** = 80.6-81.2°C (from pentane); $[\alpha]_D^{20} = +96.2^\circ$ ($c = 1.8$, dichloromethane); **R_f** = 0.99 (4:1, cyclohexane/ethylacetate); **¹H NMR** (250 MHz, CDCl₃) δ 7.30-7.14(5H, cm, Ph), 4.27(1H, d, $J = 9.0$ Hz, H_{1a}), 3.96(1H, d, $J = 9.0$ Hz, H_{1b}), 3.28(1H, ddd, $J = 16.8, 9.1, 6.5$ Hz, CH₂C=O), 3.15(1H, ddd, $J = 17.0, 8.0, 7.0$ Hz, CH₂C=O), 2.97(1H, ddd, $J = 14.0, 7.0, 6.5$ Hz, CH₂Ph), 2.91(1H, ddd, $J = 14.0, 9.5, 7.0$ Hz, CH₂Ph), 2.73(1H, dm, $J = 10.5$ Hz, H_{11a}), 2.63(1H, bs, H₁₀), 1.83(1H, d, $J = 2.0$ Hz, H₇), 1.68-1.42(3H, cm), 1.29(1H, dt, $J = 10.5, 1.5$ Hz, H_{11b}), 1.2-1.0(1H, cm), 1.12(3H, s, CH₃), 0.94(3H, s, CH₃) ppm; **¹³C NMR** (62.9 MHz, CDCl₃) δ 173.1(quat, RC=O), 155.7(quat, oxazolidinone C=O), 140.6(quat, Ph), 128.4(2 x CH, Ph), 128.2(2 x CH, Ph), 125.9(CH, Ph), 75.3(quat, C-N), 70.7(CH₂O), 49.1(CH, C₁₀), 47.4(quat, C(CH₃)₂), 44.9(CH, C₇), 38.6, 38.2, 30.6(3 x CH₂), 25.6(CH₃), 23.9, 22.5(2 x CH₂), 21.1(CH₃) ppm; **FT IR** (CCl₄) $\nu_{\max}$ 3027(Ar CH), 2966(CH), 1780(oxazolidinone C=O), 1706(RC=O) cm⁻¹; **MS** (FAB) 328(100%, MH⁺), 312(36), 196(96); **Accurate mass** (FAB) (MH⁺) Found 328.18953; C₂₀H₂₆NO₃ requires 328.19127; **Elemental analysis**, Found 73.06% C, 8.01% H, 4.17% N, C₂₀H₂₅NO₃ requires 73.35% C, 7.70% H, 4.28% N.

3.2.17 Preparation of Methacryloyl Imide 228 via the Bromomagnesium salt of

207.

A freshly prepared solution of the bromomagnesium salt of **207** (14.9 mmol) in THF (80 ml) was cooled to -78°C then treated with freshly distilled methacryloyl chloride (2.10g, 20.1 mmol) in THF (5 ml) and stirred at ambient temperature for 20 hours. After this time TLC (4:1, cyclohexane/ethylacetate) indicated that no more product was forming and the reaction was quenched with aqueous sodium bicarbonate and worked up as for 3.2.2 The resulting oil was chromatographed on silica, eluting hexane:ether (4:1) to yield a thick colourless oil (3.70g, 94%) which was recrystallised from pentane (-30°C) to yield fine white crystals of (5*S*, 7*S*, 10*R*)-*N*-methacryloyl-2-oxa-4-aza-6,6-dimethyl-7,10-methylenespiro[4.5]decan-3-one **228** (two crops-3.62g, 92%). **MP** = 67.0 - 67.7°C (from pentane); $[\alpha]_{\text{D}}^{20} = +138^{\circ}$ ($c = 1.55$, dichloromethane); **R_f** = 0.32 (4:1, cyclohexane/ethylacetate); **¹H NMR** (250 MHz, CDCl₃) δ 5.21(1H, q, $J = 1.5$ Hz, =CH₂), 5.12(1H, d, $J = 1.0$ Hz, =CH₂), 4.37(1H, d, $J = 9.0$ Hz, H_{1a}), 4.08(1H, d, $J = 9.0$ Hz, H_{1b}), 2.84(1H, dt, $J = 10.5, 1.5$ Hz, H_{11a}), 2.51(1H, d, $J = 1.5$ Hz, H₁₀), 1.98(3H, t, $J = 1.5$ Hz, =C(C=O)CH₃), 1.88(1H, d, $J = 1.5$ Hz, H₇), 1.7-1.4(3H, cm), 1.25(1H, dt, $J = 10.5, 1.5$ Hz, H_{11b}), 1.2-1.1(1H, cm), 1.14, 1.101(6H, 2 x s, 2 x CH₃) ppm; **¹³C NMR** (62.9 MHz, CDCl₃) δ 171.7(quat, RC=O), 155.5(quat, oxazolidinone C=O), 142.0(quat, C=CH₂), 117.0(C=CH₂), 75.6(quat, C-N), 71.4(CH₂O), 49.5(CH, C₁₀), 47.2(quat, C(CH₃)₂), 45.1(CH, C₇), 37.8(CH₂, C₁₁), 27.0(CH₃), 23.9, 22.6(2 x CH₂, C₈ & C₉), 21.6(CH₃), 19.4(=C(CO)CH₃) ppm; **FT IR** (CCl₄) ν_{max} 2296(CH), 1790(oxazolidinone C=O), 1697(RC=ON), 1319, 1278, 1206, 1070 cm⁻¹; **MS** (FAB) 264(47%, MH⁺), 196(20),

135(60), 107(30), 93(29); **Elemental analysis**, Found 68.45% C, 8.25% H, 5.24% N, C₁₅H₂₁NO₃ requires 68.40% C, 8.04% H, 5.32% N.

3.2.18 Preparation of Tigloyl Imide **229** via the Bromomagnesium salt of **207**.

A freshly prepared solution of the bromomagnesium salt of **207** (10.0 mmol) in THF (120 ml) was cooled to -78°C then treated with freshly distilled tigloyl chloride (1.65g, 13.9 mmol) [freshly prepared from tiglic acid and thionyl chloride] in THF (5 ml) and stirred at ambient temperature for 16 hours. After this time TLC (4:1, cyclohexane/ethylacetate) indicated that <5% of **207** was present, and the reaction was quenched with aqueous sodium bicarbonate and worked up as for **3.2.2**. The resulting oil was chromatographed on silica, eluting hexane:ether (4:1) to yield a thick colourless gum (2.32g) which was recrystallised from cyclohexane to yield fine white crystals of (5*S*, 7*S*, 10*R*)-*N*-methacryloyl-2-oxa-4-aza-6,6-dimethyl-7,10-methylenespiro[4.5]decan-3-one **229** (2.18g, 79 %) MP = 71.9-72.6°C (from cyclohexane); $[\alpha]_D^{20} = +148.9^\circ$ (c = 2.5, dichloromethane); $R_f = 0.46$ (4:1, cyclohexane/ethylacetate); $^1\text{H NMR}$ (200 MHz, CDCl₃) δ 5.90(1H, qq, $J = 7.0, 1.5$ Hz, =CHCH₃), 4.37(1H, d, $J = 9.0$ Hz, H_{1a}), 4.07(1H, d, $J = 9.0$ Hz, H_{1b}), 2.86(1H, dm, $J = 10.5$ Hz, H_{11a}), 2.43(1H, d, $J = 1.5$ Hz, H₁₀), 1.85(1H, d, $J = 1.8$, H₇), 1.82(3H, cm, =(C=O)CH₃), 1.70(3H, dq, $J = 7.0, 1.0$ Hz, =CHCH₃), 1.65-1.36(3H, cm), 1.21(1H, dt, $J = 10.5, 1.5$ Hz, H_{11b}), 1.18-1.09(1H, cm), 1.13(6H, s, 2 x CH₃) ppm; $^{13}\text{C NMR}$ (50.3 MHz, CDCl₃) δ 172.4(quat, RC=O), 155.8(quat, oxazolidinone C=O), 134.0(quat, =C(C=O)CH₃), 130.6(=CHCH₃), 75.7(quat, C-N), 71.4(CH₂O), 49.7(CH, C₁₀), 47.1(quat, C(CH₃)₂), 45.2(CH, C₇), 37.6(CH₂, C₁₁), 26.4(CH₃), 23.9,

22.7(2 x CH₂), 21.8(CH₃), 13.6, 13.5(C(CH₃)=CHCH₃) ppm; **FT IR** (CCl₄) $\nu_{\max}$ 2966(CH), 1793(oxazolidinone C=O), 1690(RC=ON), 1288 cm⁻¹; **MS** (FAB) 278(100%, MH⁺), 262(58), 196(64), 135(79);

3.3 Asymmetric Alkylation Reactions

Preparation of Lithium Diisopropylamide (LDA)

This was invariably prepared *in situ*, immediately prior to use; a typical example is given for the preparation on a 2 mmol scale. Diisopropylamine (220mg, 2.2 mmol) in dry THF (20ml) at 0°C under argon was treated dropwise with *n*-butyl lithium (1.25ml, 1.6M in hexanes, 2.0 mmol) and the solution stirred for 30 minutes. The resulting solution of LDA (2 mmol) was cooled to -78°C and used immediately.

3.3.1 Reaction of the *Z*(*O*) Lithium Enolate of Propionyl Imide **213** with

Benzyl Bromide Catalysed by Sodium Iodide

Propionyl imide **213** (490mg, 1.95 mmol) in dry THF (5ml) was added dropwise to a freshly prepared solution of LDA (2.0 mmol) in THF (20ml) at -78°C under argon and stirred for 30 minutes. Benzyl bromide (1.0g, 5.8 mmol) was added followed by sodium iodide (300mg, 2.0 mmol), and the reaction allowed to reach -10°C over 18 hours. At this point TLC (4:1, cyclohexane/ethylacetate) indicated that most of the starting material had been consumed; the reaction was quenched with saturated ammonium chloride solution and THF evaporated *in vacuo*. After addition of water, the residue was extracted with dichloromethane (3 x 40ml), washed with water then brine, dried, filtered and evaporated. The resulting oil was subjected to high vacuum to remove excess benzyl bromide then analysed by high field ¹H NMR spectroscopy, the absence of the doublet at 3.45 ppm due to **238** allowed a diastereomeric excess of >95% to be assigned. Chromatography on silica, hexane/ether (4:1) yielded a solid

(490mg, 74%) which was recrystallised from cyclohexane/hexane (382mg, 78% recovery) to give pure (5*S*, 7*S*, 10*R*)-*N*-(2'*R*)-2'-methyl-3'-phenylpropionyl-2-oxa-4-aza-6,6-dimethyl-7,10-methylene spiro[4.5]decan-3-one **233**. **MP**= 106.5-106.9°C (from cyclohexane/hexane); $[\alpha]_D^{20} = +51.2^\circ$ ($c = 1.7$, dichloromethane); $R_f = 0.52$ (4:1, cyclohexane/ethylacetate); $^1\text{H NMR}$ (200 MHz, CDCl_3) δ 7.30-7.13(5H, cm, Ph), 4.28(1H, d, $J = 9.0$ Hz, H_{1a}), 4.08-3.97(1H, cm, CHCO), 4.02(1H, d, $J = 9.0$ Hz, H_{1b}), 3.21(1H, dd, $J = 13.0, 6.0$ Hz, CH_2Ph), 2.72(1H, dt, $J = 10.5, 1.5$ Hz, H_{11a}), 2.66(1H, bs, H_{10}), 2.50(1H, dd, $J = 13.0, 9.0$ Hz, CH_2Ph), 1.79(1H, bs, H_7), 1.60-1.41(3H, cm), 1.29(1H, dt, $J = 10.5, 1.0$ Hz, H_{11b}), 1.2-1.1(1H, cm), 1.10(3H, s, CH_3), 1.06(3H, d, $J = 7.0$ Hz, CHCH_3), 0.78(3H, s, CH_3) ppm; $^{13}\text{C NMR}$ (50.32 MHz, CDCl_3) δ 177.1(quat, RC=ON), 155.4(quat, oxazolidinone C=O), 139.4(quat, Ph), 129.1(2 x CH, Ph), 128.0(2 x CH, Ph), 125.9(CH, Ph), 75.4(quat, $\underline{\text{C}}\text{-N}$), 70.6($\underline{\text{C}}\text{H}_2\text{O}$), 49.1(CH, C_{10}), 47.2(quat, $\underline{\text{C}}(\text{CH}_3)_2$), 45.0(CH, C_7), 40.9(CH, $\underline{\text{C}}\text{HCH}_2\text{Ph}$), 39.6(CH_2 , $\underline{\text{C}}\text{H}_2\text{Ph}$), 38.3(CH_2 , C_{11}), 25.4(CH_3), 24.0, 22.5(2 x CH_2 , C_8 & C_9), 21.0(CH_3), 16.7(CHCH_3) ppm; **FT IR** (CCl_4) ν_{max} 3026, 2964(CH), 1780(oxazolidinone C=O), 1708(RC=ON), 1457, 1365, 1278, 1075 cm^{-1} ; **MS** (FAB) 342(100%, MH^+), 326(24), 196(80), 135(32); **Accurate mass** (FAB) (MH^+) Found 342.20551; $\text{C}_{21}\text{H}_{28}\text{NO}_3$ requires 342.20692; **Elemental analysis**, Found 74.10% C, 8.07% H, 4.09% N, $\text{C}_{21}\text{H}_{27}\text{NO}_3$ requires 73.86% C, 7.98% H, 4.10% N.

3.3.2 Cleavage of Benzylated Adduct 233 using Lithium Benzyloxide

Benzyl alcohol (170mg, 1.6 mmol) in THF (20ml) at -78°C under argon was treated with *n*-butyl lithium (0.55ml, 1.6 M in hexanes, 0.9 mmol). After 30 minutes benzyl adduct **233** (270mg, 0.7 mmol) in THF (2ml) was added and the reaction mixture allowed to reach room temperature. After 2 hours TLC indicated complete consumption of the starting material and the formation of both auxiliary and a rapidly eluting, UV active component. The reaction was quenched with saturated ammonium chloride solution then the solvent was removed *in vacuo* and the products extracted into dichloromethane (3 x 20ml). Drying, filtration and evaporation gave an oil and crystals; chromatography on silica eluting hexane/ether (5:1), gave an oil (190mg, 95%), identified as (2'*R*)-benzyl 2'-methyl-3'-phenylpropionate **234** $[\alpha]_{\text{D}}^{23} = -26.0^{\circ}$ (c = 3.1, CHCl₃), $[\text{Lit } \alpha]_{\text{D}}^{20} = -26.9^{\circ}$ (c = 6.1, CHCl₃)¹³, ¹H NMR (200 MHz, CDCl₃) δ 7.34-7.12(10H, cm, 2 x Ph), 5.07(2H, s, CH₂O), 3.04(1H, dd, *J* = 12.5, 6.0 Hz, PhCH₂CH), 2.89-2.64(2H, cm, PhCH₂CH), 1.18(3H, d, *J* = 7.0 Hz, CH₃) ppm; ¹³C NMR (50.3 MHz, CDCl₃) δ 175.8(quat, C=O), 139.1, 135.9(q's, 2 x Ph), 128.9, 128.4, 128.3, 128.0, 126.2(CH's, Ph's), 66.0(CH₂O), 41.4(CH), 39.6(CH₂Ph), 16.7(CH₃) ppm; FT IR (CCl₄) ν_{max} 3062, 3027(Ar, CH), 2970, 2934(CH), 1734(C=O), 1604(Ar C=C), 1495, 1454, 1165, 746, 697 cm⁻¹.

Further elution (ether) provided **207** (130mg, 96%)

3.3.3 Reaction of the *Z(O)* Sodium Enolate of Propionyl Imide **213** with

Benzyl Bromide

Propionyl imide **213** (500mg, 2.0 mmol) in dry THF (10ml) was added over 1 hour to a solution of sodium hexamethyldisilazine (3.3ml, 0.6 M in toluene, 2.1 mmol) in THF (20ml) at -78°C under argon. After stirring for thirty minutes benzyl bromide (1.0g, 5.8 mmol, ~3 equiv.) in THF (2ml) was added and the reaction warmed over 1 hour to -30°C then held at this temperature for 4 hours before being allowed to warm to ambient temperature. TLC showed a large quantity of **207** to be present together with **213** and a UV active component. After quenching and work up as for 3.3.1 a semi-crystalline mass was obtained, this was chromatographed to remove auxiliary (280mg, 72%) and the faster eluting fractions combined, then analysed by high field ¹H NMR spectroscopy. This showed **213** and **233** to be present in a ratio of 4:3, with no sign of the opposite diastereomer **238**, thus a yield of 12% was calculated and a d.e. of >95% assigned.

3.3.4 Reaction of the *Z(O)* Sodium Enolate of Propionyl Imide **213** with Allyl

Bromide

A solution of the sodium enolate of **213** (2.0 mmol) was prepared as 3.3.3 and treated with freshly distilled allyl bromide (0.78g, 6.5 mmol) in THF (2ml) then warmed over 1 hour to -30°C. After 3.5 hours at this temperature the reaction was allowed to reach ambient temperature where TLC showed a large proportion of **207** together with smaller quantities of starting material and the presumed allyl adduct. Removal of the auxiliary (240mg, 62% recovery) as for 3.3.3 and high field ¹H NMR

spectroscopy of the remainder showed starting material and a single diastereomer of the allyl adduct **236** in a 2:3 ratio. The product was not isolated but a yield of 23% was calculated.

3.3.5 Reaction of the *Z*(*O*) Lithium Enolate of Propionyl Imide **213 with**

Benzyl Bromide in THF/*N*-Methylpyrrolidinone (NMP)

A solution of the lithium enolate of propionyl imide **213** (2.0 mmol) in THF (11ml) was prepared as **3.3.1** then treated at -78°C with freshly distilled benzyl bromide (1.0g, 5.8 mmol), followed by NMP (5ml, anhydrous), and the reaction allowed to reach -15°C over 1 hour. After 2 hours TLC (4:1, cyclohexane/ethylacetate) showed the reaction to be complete and it was quenched with saturated ammonium chloride solution and solvents evaporated *in vacuo* (benzyl bromide and NMP at 2mm Hg), after addition of water (20 ml), the residue was extracted with ether/hexane 1:2 (3 x 40 ml), washed with water (5 x 30ml), then brine (20ml), dried over magnesium sulphate, filtered then evaporated to yield a gum (710mg, 105% mass balance). High field ¹H NMR spectroscopy showed only one diastereomer of **233** to be present (>95% d.e.) and only a trace of starting material. Chromatography on silica, eluting hexane/ether 6:1, 4:1 yielded **233** as a solid (640mg, 94%) which was recrystallised from cyclohexane/hexane (525mg, 82% recovery).

3.3.6 Reaction of the *Z*(*O*) Lithium Enolate of Propionyl Imide **213** with Allyl Bromide in THF/*N*-Methylpyrrolidinone (NMP)

A solution of the lithium enolate of propionyl imide **213** (2.0 mmol) in THF (11ml) was prepared as 3.3.1 and treated at -78°C with freshly distilled allyl bromide (1.03g, 8.5 mmol) followed by NMP (5ml) then warmed over 1 hour to -12°C. After 4 hours at this temperature TLC showed virtual complete consumption of starting material and only a trace of auxiliary. The reaction was quenched and worked up as for 3.3.5 to yield a pale yellow oil. High field ¹H NMR spectroscopy showed only one diastereomer of **236** to be present (>95% d.e.) and only a trace of starting material and auxiliary. Chromatography on silica, eluting hexane:ether 6:1, 4:1 yielded (5*S*, 7*S*, 10*R*)-*N*-(2'*R*)-2'-methylpent-4-enoyl-2-oxa-4-aza-6,6-dimethyl-7,10-methylenespiro[4.5] decan-3-one **236** as an oil which slowly crystallised to a low melting solid (535mg, 92%); [α]_D²⁰ = +87.7° (c = 2.0, dichloromethane); *R*_f = 0.56 (4:1, cyclohexane/ethylacetate); ¹H NMR (200 MHz, CDCl₃) δ 5.69(1H, dddd, *J* = 17.0, 10.0, 7.5, 6.0 Hz, CH=CH₂), 4.97(1H, dq, *J* = 17.0, 2.0 Hz, CH=CH₂), 4.90(1H, dm, *J* = 10.0 Hz, CH=CH₂), 4.22(1H, d, *J* = 9.0 Hz, H_{1a}), 3.95(1H, d, *J* = 9.0 Hz, H_{1b}), 3.66(1H, qt, *J* = 7.0, 6.0 Hz, CH₃CH), 2.70(1H, dm, *J* = 10.5 Hz, H_{11a}), 2.52(1H, bs, H₁₀), 2.45(1H, dtt, *J* = 14.0, 6.0, 1.5 Hz, CH₂=CHCH₂), 1.98(1H, dtt, *J* = 14.0, 7.5, 1.0 Hz, CH₂=CHCH₂), 1.75(1H, bs, H₇), 1.56-1.31(3H, cm), 1.19(1H, d, *J* = 10.5 Hz, H_{11b}), 1.1-1.0(1H, cm), 1.04(3H, s, CH₃), 1.00(3H, d, *J* = 7.0 Hz, CH₃CH), 0.89(3H, s, CH₃) ppm; ¹³C NMR (50.3 MHz, CDCl₃) δ 177.1(quat, RC=ON), 155.4(quat, oxazolidinone C=O), 135.6(CH₂=CH), 116.6(CH₂=CH), 75.4(quat, C-N), 70.6(CH₂O), 49.2(CH, H₁₀), 47.2(quat, C(CH₃)₂), 45.0(CH, H₇),

38.3(2 x CH₂, H₁₁ & CH₂=CHCH₂), 37.7(CHC=O), 25.9(CH₃), 24.0, 22.5(2 x CH₂, C₈ & C₉), 21.1(CH₃), 16.8(CH₃CH) ppm; **FT IR** (CCl₄) $\nu_{\max}$ 3077, 3037, 2967(CH), 1784(oxazolidinone C=O), 1707(RC=ON), 1640(C=C), 1458, 1364, 1280, 1204, 1070 cm⁻¹; **MS** (FAB) 292(56%, MH⁺), 205(74), 196(81), 187(53), 177(35), 159(40), 135(78); **Accurate mass** (FAB) (MH⁺) Found 292.19048; C₁₇H₂₆NO₃ requires 292.19127.

3.3.7 Reaction of the *Z*(*O*) Lithium Enolate of Propionyl Imide **213** with Ethyl Iodide in THF/*N*-Methylpyrrolidinone (NMP)

A solution of the lithium enolate of propionyl imide **213** (1.99 mmol) in THF (10ml) was prepared as **3.3.1** and treated at -78°C with freshly distilled ethyl iodide (1.3g, 8.3 mmol), followed by NMP (5ml) then warmed over 1 hour to -12°C. After 4 hours at this temperature TLC showed that most starting material had either reacted or had decomposed to auxiliary. The reaction was quenched and worked up as for **3.3.5** to yield a sticky solid. Chromatography on silica removed the auxiliary and the combined faster eluting components (130mg, 23%) were analysed by high field ¹H and ¹³C NMR spectroscopy which showed no starting material to be present. The mixture appeared to be that of the two C_α diastereomers in a ratio of 92:8 (84% d.e.). The major isomer was isolated by chromatography on silica eluting, hexane:ether (6:1) to give (5*S*, 7*S*, 10*R*)-*N*-(2'*R*)-2'-methylbutanoyl-2-oxa-4-aza-6,6-dimethyl-7,10-methylenespiro[4.5]decan-3-one (110mg, 19%). *R*_f = 0.52 (4:1, cyclohexane/ethylacetate); ¹H NMR (250 MHz, CDCl₃) δ 4.21(1H, d, *J* = 9.0 Hz, H_{1a}), 3.93(1H, d, *J* = 9.0 Hz, H_{1b}), 3.47(1H, sextet, *J* = 6.7 Hz, CHC=O), 2.71(1H,

dm, $J = 10.5$ Hz, H_{11a}), 2.52(1H, bs, H_{10}), 1.80-1.65(2H, cm), 1.52-1.00(6H, cm) 1.04(3H, s, CH_3), 0.98(3H, d, $J = 6.8$ Hz, CH_3CH), 0.90(3H, s, CH_3), 0.82(3H, t, $J = 7.4$ Hz, CH_3CH_2) ppm; ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 177.7(quat, $RC=O$), 155.3(quat, oxazolidinone $C=O$), 75.2(quat, $C-N$), 70.5(CH_2O), 49.2(CH , C_{10}), 47.1(quat, $C(CH_3)_2$), 44.9(CH , C_7), 39.8($CHC=O$), 38.2(CH_2 , C_{11}), 26.6(CH_2CH_3), 25.7(CH_3), 23.9, 22.4(CH_2s), 20.9(CH_3), 16.7(CH_3CH), 11.33(CH_3CH_2) ppm; FT IR (thin film) ν_{max} 2962(CH), 1778(oxazolidinone $C=O$), 1704($RC=ON$) cm^{-1} .

3.3.8 Reaction of the *Z*(*O*) Lithium Enolate of 3-Phenylpropionyl Imide 227

with Methyl Iodide in THF/*N*-Methylpyrrolidinone (NMP)

3-Phenylpropionyl imide **227** (330mg, 1.01 mmol) in dry THF (4ml) was added to a solution of LDA (1.08 mmol) in THF (10ml) at $-78^\circ C$ under argon over 15 minutes and stirred for 40 minutes. Methyl iodide (1.4g, 9.9 mmol), freshly distilled from CaH_2 was added followed by NMP (5ml, anhydrous). After stirring for 3 hours at $-18^\circ C$ the reaction was allowed to warm to room temperature over 2 hours when TLC showed two UV active components together with the starting material. Quenching and work up as for **3.3.4** yielded a colourless gum (350mg, >100% mass balance). High field ^1H NMR spectroscopy showed the presence of starting material (24%) and the diastereomeric products in a ratio of 18:1 (d.e. 90%). Chromatographic separation as **3.3.4** gave (5*S*, 7*S*, 10*R*)-*N*-(2'*S*)-2'-methyl-3'-phenylpropionyl-2-oxa-4-aza-6,6-dimethyl-7,10-methylenespiro[4.5]decan-3-one **238** as a colourless gum (228mg, 67%); $[\alpha]_D^{20} = +201.7^\circ$ ($c = 2.5$, dichloromethane); $R_f = 0.60$ (4:1, cyclohexane/ethylacetate); ^1H NMR (250 MHz, $CDCl_3$) δ 7.29-7.12(5H, cm, Ph),

4.09(1H, d, $J = 8.8$ Hz, H_{1a}), 4.05(1H, cm, CHC=O), 3.45(1H, d, $J = 8.8$ Hz, H_{1b}), 2.89(1H, dd, $J = 13.3, 8.9$ Hz, CH₂Ph), 2.79(1H, d, $J = 10.5$ Hz, H_{11a}), 2.71(1H, dd, $J = 13.3, 6.7$ Hz, CH₂Ph), 2.26(1H, bs, H₁₀), 1.80(1H, bs, H₇), 1.53-1.20(4H, cm), 1.23(3H, d, $J = 6.6$ Hz, CH₃CH), 1.1-1.0(1H, cm), 1.06(3H, s, CH₃), 0.97(3H, s, CH₃) ppm; ¹³C NMR (50.3 MHz, CDCl₃) δ 177.4(quat, RC=ON), 155.7(quat, oxazolidinone C=O), 139.3(quat, Ph), 128.9(2 x CH, Ph), 128.1(2 x CH, Ph), 126.2(CH, Ph), 75.5(quat, C-N), 70.7(CH₂O), 49.4(CH, C₁₀), 47.1(quat, C(CH₃)₂), 44.5(CH, C₇), 40.9(CH₂Ph), 38.2(CH₂, C₁₁), 25.6(CH₃), 23.9, 22.5(2 x CH₂, C₈ & C₉), 21.1(CH₃), 17.6(CH₃CH) ppm; FT IR (thin film) ν_{max} 3032, 2963(CH), 1786(oxazolidinone C=O), 1701(RC=ON), 1603(Ar C=C), 1454, 1368, 1282, 1072 cm⁻¹; MS (FAB) 342(40%, MH⁺), 326(6), 196(62), 135(53); **Accurate mass** (FAB) (MH⁺) Found 342.20613; C₂₁H₂₈NO₃ requires 342.20692.

3.3.9 Acylation of the *Z*(*O*) Lithium Enolate of Propionyl Imide 213 with Acetyl Chloride

A solution of the lithium enolate of propionyl imide **213** (2.08 mmol) in THF (35ml) was prepared as **3.3.1** then cooled to -78°C. Freshly distilled acetyl chloride (240mg, 3.06 mmol) in THF (2ml) was added rapidly, the reaction stirred for 2 minutes then quenched with saturated ammonium chloride solution (5ml). After warming to room temperature THF was removed *in vacuo* and after the addition of water (10ml) the product was extracted into dichloromethane (3 x 30ml), washed with water then brine and dried over magnesium sulphate. After filtration and evaporation the solid obtained (610 mg, >100% mass balance) was examined by high field ¹H and ¹³C

spectroscopy which indicated that two isomers were present in a ratio of 19:1, the *C*- and *O*-acylated products respectively. A diastereomeric excess of >95% was assigned to the reaction. Chromatography on silica, eluting hexane/ether (4:1) yielded a colourless solid which was recrystallised from cyclohexane/hexane to yield colourless needles (493mg, 84%) of almost pure (5*S*, 7*S*, 10*R*)-*N*-(2'*R*)-2'-methyl-3-oxobutanoyl)-2-oxa-4-aza-6,6-dimethyl-7,10-methylenespiro[4.5]decan-3-one **239** (a few percent of the *C_α* diastereoisomer had appeared, presumably as a result of epimerisation on silica). **MP**=107.6-108.4 °C (from cyclohexane/hexane); $[\alpha]_D^{20} = +40.7^\circ$ (*c* = 2.25, dichloromethane); **R_f** = 0.28 (4:1, cyclohexane/ethylacetate); **¹H NMR** (250 MHz, CDCl₃) δ 4.40(1H, d, *J* = 9.0 Hz, H_{1a}), 4.27(1H, q, *J* = 7.0 Hz, CH₃CH), 4.01(1H, d, *J* = 9.0 Hz, H_{1b}), 2.85(1H, dt, *J* = 10.5, 1.5 Hz, H_{11a}), 2.56(1H, d, *J* = 1.0 Hz, H₁₀), 2.25(3H, s, CH₃CO), 2.21(1H, bs, H₇), 1.6-1.3(3H, cm), 1.30(3H, d, *J* = 7.0 Hz, CH₃CH), 1.28(1H, dt, *J* = 10.5, 1.5 Hz, H_{11b}), 1.12(1H, td, *J* = 9.0, 3.0 Hz), 1.09, 1.07(6H, 2 x s, 2 x CH₃) ppm; **¹³C NMR** (62.9 MHz, CDCl₃) δ 204.6(quat, CH₃C=O), 170.2(quat, RC=ON), 156.0(quat, oxazolidinone C=O), 75.7(quat, C-N), 71.2(CH₂O), 54.4(CH₃CH), 49.5(CH, C₁₀), 47.6(quat, C(CH₃)₂), 44.8(CH, C₇), 38.3(CH₂, C₁₁), 28.0(CH₃C=O), 25.9(CH₃), 24.0, 22.5(2 x CH₂, C₈ & C₉), 21.2(CH₃), 13.1(CH₃CH) ppm; **FT IR** (CCl₄) $\nu_{\max}$ 2968(C-H *str*), 1782(oxazolidinone C=O *str*), 1727(CH₃C=OC *str*), 1713(RC=ON *str*), 1293, 1072 cm⁻¹; **MS** (FAB) 294(47%, MH⁺), 250(24, MH⁺-CH₃CHO), 196(57), 180(20), 152(25), 135(50), 107(50); **Accurate mass** (FAB) (MH⁺) Found 294.17076, C₁₆H₂₄NO₄ requires 294.17053; **Elemental analysis**, Found 65.46% C, 7.60% H, 4.75% N, C₁₆H₂₃NO₄ requires 65.49% C, 7.91% H, 4.78% N.

3.3.10 Acylation of the *Z*(*O*) Lithium Enolate of Propionyl Imide **213** with

Propionyl Chloride

A solution of the lithium enolate of **213** (1.99 mmol) in dry THF (25 ml) prepared as for **3.3.1** at -78°C under argon was treated with freshly distilled propionyl chloride (270mg, 2.97 mmol) in THF (2ml) and quenched after 2 minutes. Work up as for **3.4.1** yielded a solid that was examined by high field ^1H and ^{13}C NMR spectroscopy, which indicated that though some starting material and *O*-acylated material were present only a single diastereomer was present in >95% d.e. (no satellite to CH_3CH in the ^{13}C NMR spectra which was apparent in a purified sample due slight epimerisation on silica). The crude material was purified by recrystallisation from methanol/water to give a colourless crystalline solid (420mg, 68%) which was identified as (5*S*, 7*S*, 10*R*)-*N*-(2'*R*)-2'-methyl-3-oxopentanoyl)-2-oxa-4-aza-6,6-dimethyl-7,10-methylenespiro [4.5]decan-3-one **214** MP = $118.2\text{--}119.2^{\circ}\text{C}$ (from methanol/water); $[\alpha]_{\text{D}}^{20} = +38.1^{\circ}$ ($c = 5.35$, dichloromethane); $R_f = 0.35$ (4:1, cyclohexane/ethylacetate); ^1H NMR (200 MHz, CDCl_3) δ 4.28(1H, d, $J = 9.1$ Hz, H_{1a}), 4.24(1H, q, $J = 7.0$ Hz, CH_3CH), 3.99(1H, d, $J = 9.0$ Hz, H_{1b}), 2.71(1H, dm, $J = 7.0$ Hz, H_{11a}), 2.66(1H, dq, $J = 15.0, 7.0$ Hz, CH_3CH_2), 2.49(1H, dq, $J = 15.0, 7.0$ Hz, CH_3CH_2), 2.55(1H, bs, H_{10}), 1.82(1H, bs, H_7), 1.60-1.38(2H, cm), 1.33-1.24(1H, cm), 1.27(3H, d, $J = 7.0$ Hz, CHCH_3), 1.24-1.0(2H, cm), 1.07(6H, s, 2 x CH_3), 1.01(3H, t, $J = 7.0$ Hz, CH_3CH_2) ppm; ^{13}C NMR (50.3 MHz, CDCl_3) δ 207.3(quat, $\text{CH}_2\text{C}=\text{O}$), 170.4(quat, $\text{RC}=\text{ON}$), 156.0(quat, oxazolidinone $\text{C}=\text{O}$), 75.7(quat, C-N), 71.1(CH_2O), 53.8(CH_3CH), 49.4(CH, C_{10}), 47.6(quat, $\text{C}(\text{CH}_3)_2$), 44.8(CH, C_7),

38.3(CH₂, C₁₁), 33.4(CH₃CH₂), 25.9(CH₃), 24.0, 22.4(2 x CH₂, C₈ & C₉), 21.1(CH₃), 13.5(CH₃CH), 7.4(CH₃CH₂) ppm; **FT IR** (CCl₄) $\nu_{\max}$ 1775(oxazolidinone C=O *str*), 1720(CH₂C=OC *str*), 1710(RC=ON) cm⁻¹; **MS** (FAB) 308(52%, MH⁺), 196(92), 135(30), 107(39); **Accurate mass** (FAB) (MH⁺) Found 308.18655; C₁₇H₂₆NO₄ requires 308.18618; **Elemental analysis**, Found 66.49% C, 8.17% H, 4.54% N, C₁₇H₂₅NO₄ requires 66.41% C, 8.20% H, 4.56% N.

3.3.11 Acylation of the *Z*(*O*) Lithium enolate of Propionyl Imide **213** with

Methylcyanoformate (Mander's Reagent)

A solution of the lithium enolate of **213** (2.00 mmol) in dry THF (25 ml) prepared as for **3.3.1** at -78°C under argon was treated with freshly distilled methylcyanoformate (240mg, 2.76 mmol) in THF (2ml) and quenched after 3 minutes. Work up as for **3.4.1** yielded a solid which was examined by high field ¹H- and ¹³C-NMR spectroscopy, which indicated a d.e. of 92% from integration of the methoxy signals between 3.8-3.6 ppm. The remainder was recrystallised from ethylacetate/cyclohexane to yield colourless prisms (392mg, (corrected 69%)) of (*5S*, *7S*, *10R*)-*N*-(*2'S*)-*2'*-carbomethoxypropionyl-2-oxa-4-aza-6,6-dimethyl-7,10-methylenespiro[4.5]decan-3-one **240** **MP** = 147.2-147.8°C (from ethylacetate/cyclohexane); $[\alpha]_{\text{D}}^{20} = +69.7^\circ$ (c = 1.3, dichloromethane); **R_f** = 0.28 (4:1, cyclohexane/ethylacetate); **¹H NMR** (250 MHz, CDCl₃) δ 4.32(1H, d, *J* = 9.0 Hz, H_{1a}), 4.21(1H, q, *J* = 7.0 Hz, CH₃CH), 4.03(1H, d, *J* = 9.0 Hz, H_{1b}), 3.67(3H, s,

OCH_3), 2.83(1H, dm, $J = 10.5$ Hz, H_{11a}), 2.59(1H, dm, $J = 1.0$ Hz, H_{10}), 1.85(1H, bs, C_7), 1.60-1.36(3H, cm), 1.38(3H, d, $J = 7.0$ Hz, CH_3CH), 1.28(1H, dt, $J = 10.5, 1.0$ Hz, H_{11b}), 1.12(3H, s, CH_3), 1.08(3H, s, CH_3) ppm; ^{13}C NMR (62.9 MHz, CDCl_3) δ 171.1(quat, $\text{C}=\text{O}$), 169.8(quat, $\text{C}=\text{O}$), 155.7(quat, oxazolidinone $\text{C}=\text{O}$), 75.8(quat, $\text{C}-\text{N}$), 71.1(CH_2O), 52.1(CH_3O), 49.4 (CH , C_{10}), 47.8(quat, $\text{C}(\text{CH}_3)_2$), 47.3(CH_3CH), 44.8(CH , C_7), 38.3(CH_2 , C_{11}), 25.7(CH_3), 34.0, 22.5(2 x CH , C_8 & C_9), 21.2(CH_3), 14.0(CH_3CH) ppm; FT IR (CCl_4) ν_{max} 2956(CH), 1784(oxazolidinone $\text{C}=\text{O}$), 1742($\text{RC}=\text{O.O}$), 1714($\text{RC}=\text{ON}$), 1281, 1021 cm^{-1} ; MS (FAB) 310(52%, MH^+), 309(M^+), 294(10), 278(28), 196(78), 135(50), 107(46), 102(100); **Accurate mass** (FAB) (MH^+) Found 310.16579; $\text{C}_{16}\text{H}_{24}\text{NO}_5$ requires 310.16545; **Elemental analysis**, Found 62.02% C, 7.67% H, 4.52% N, $\text{C}_{16}\text{H}_{23}\text{NO}_5$ requires 62.10% C, 7.67% H, 4.53% N.

3.4 Asymmetric Aldol Condensation Reactions

3.4.1 Aldol Condensation of the *Z(O)* Lithium Enolate of Propionyl Imide **213** with Benzaldehyde

A solution of the lithium enolate of propionyl imide **213** (2.03 mmol) in THF (25ml) was prepared as **3.3.1** then treated at -78°C with freshly distilled benzaldehyde (280mg, 2.6 mmol) and stirred for 3 minutes before being quenched with saturated ammonium chloride solution (5ml). Solvent was removed *in vacuo* and the residue extracted into dichloromethane (3 x 20ml), washed with water then brine, dried then filtered and evaporated. After being subjected to high vacuum (to remove excess benzaldehyde) the resulting gum (740mg, 105% mass balance) was analysed by high field ¹H and ¹³C NMR spectroscopy. The ¹H NMR spectra showed the presence of one *syn*- (**243**) and one *anti*-product (CHOH signals d, 5.13 ppm, *J* = 2.9 Hz and t, 4.60 ppm, *J* = 8.2 Hz) in the ratio 7:13, together with traces of the other two diastereomers (<5%). The individual compounds were not isolated.

3.4.2 Aldol condensation of the *Z(O)* Lithium Enolate of Propionyl Imide **213** with Isobutyraldehyde

A solution of the lithium enolate of propionyl imide **213** (2.0 mmol) in THF (20ml) was prepared as **3.3.1** then treated at -78°C with freshly distilled isobutyraldehyde (280mg, 3.9 mmol) in THF (0.5ml). After stirring for 3 mins the reaction was quenched with saturated ammonium chloride solution (5ml) and worked up as for **3.4.1** to provide a colourless crystalline solid (620mg, 97%). High field ¹H NMR

spectroscopy indicated that apart from the presence of some **207** and **213** the product was predominantly two aldol condensation products. The two main products were separated by chromatography on silica eluting with hexane:ether (4:1) to yield firstly the minor product (130mg, 20%) (*5S, 7S, 10R*)-*N*-(2'*R, 3'R*)-3'-hydroxy-2',4'-dimethylpentanoyl-2-oxa-4-aza-6,6-dimethyl-7,10-methylenespiro[4.5]decan-3-one

246 MP = 154.5-155.8°C (from hexane) R_f = 0.36 (4:1, cyclohexane /ethylacetate);

^1H NMR (360 MHz, CDCl_3) δ 4.22(1H, d, J = 9.0 Hz, H_{1a}), 3.94(1H, d, J = 9.0 Hz, H_{1b}), 3.77(1H, dq, J = 8.0, 7.0 Hz, CHC=O), 3.28(1H, ddd, J = 10.5, 8.0, 4.0 Hz, CHOC), 3.04(1H, d, J = 10.5 Hz, OH), 2.80(1H, dm, J = 10.5 Hz, H_{11a}), 2.41(1H, bs, H_{10}), 1.77(1H, bs, H_7), 1.69(1H, cm, $\text{CH}(\text{CH}_3)_2$), 1.55-1.33(3H, s, CH_3), 1.18(1H, d, J = 10.5 Hz, H_{11b}), 1.03(3H, s, CH_3), 1.01(3H, d, J = 7.0 Hz, CH_3CH), 0.98(3H, s, CH_3), 0.87(3H, d, J = 7.0 Hz, $(\text{CH}_3)_2\text{CH}$), 0.81(3H, d, J = 7.0 Hz, $(\text{CH}_3)_2\text{CH}$), ppm;

^{13}C NMR (250 MHz, CDCl_3) δ 179.1(quat, RC=ON), 155.4(quat, oxazolidinone C=O), 76.6(CHOH), 75.7(quat, C-N), 70.7(CH_2O), 49.3(CH , C_{10}), 47.4(quat, $\text{C}(\text{CH}_3)_2$), 45.0(CH , C_7), 39.9(CHC=O), 38.3(CH_2 , C_{11}), 30.7($(\text{CH}_3)_2\text{CH}$), 25.7(CH_3), 24.1, 22.5(CH_2), 21.1(CH_3), 19.3, 18.7($(\text{CH}_3)_2\text{CH}$), 10.3(CHCH_3) ppm.

Followed by the major product **245** as a gum recrystallised from hexane (430mg, 68%) (*5S, 7S, 10R*)-*N*-(2'*R, 3'S*)-3'-hydroxy-2',4'-dimethylpentanoyl-2-oxa-4-aza-6,6-dimethyl-7,10-methylenespiro[4.5]decan-3-one **245** MP = 133.5-134.5°C (from cyclohexane/hexane) [Cf. **248** : MP = 132-134°C, Mixed sample with **245** : MP = 110-120°C]; R_f = 0.32 (4:1, cyclohexane/ethylacetate); ^1H NMR (360 MHz, CDCl_3) δ 4.31(1H, d, J = 9.0 Hz, H_{1a}), 4.06(1H, qd, J = 7.0, 2.5 Hz, CHC=O), 4.03(1H, d, J = 9.0 Hz, H_{1b}), 3.55(1H, dt, J = 8.5, 2.5 Hz, CHOH), 2.95(1H, d, J = 2.5 Hz, OH),

2.77(1H, dm, $J = 10.5$ Hz, H_{11a}), 2.60(1H, bs, H_{10}), 1.69(1H, cm, $CH(CH_3)_2$), 1.65-1.58(1H, cm), 1.52-1.46(2H, cm), 1.19(1H, dt, $J = 10.5, 4.5$ Hz), 1.20-1.10(1H, cm), 1.14(3H, s, CH_3), 1.11(3H, d, $J = 7.0$ Hz, CH_3CH), 1.03(6H, d + s, $J = 7.0$ Hz, CH_3CH & CH_3), 0.90(3H, d, $J = 7.0$ Hz, CH_3CH) ppm; ^{13}C NMR (90.6 MHz, $CDCl_3$) δ 177.9, (quat, $RC=ON$), 157.0, (quat, oxazolidinone $C=O$), 79.5, ($CHOH$), 76.3, (quat, $C-N$), 71.2, (CH_2O), 49.6, (C_{10}), 47.3, (quat, $C(Me)_2$), 44.9, (CH , $C7$), 41.5, ($CHCO$), 38.3, (CH_2C_{11}), 30.2, ($CH(CH_3)_2$), 26.0, (CH_3), 24.2, (CH_2), 22.5, (CH_2), 21.2, (CH_3), 19.9, ($CHCH_3$), 15.6, ($CH(CH_3)_2$), 15.1, ($CH(CH_3)_2$) ppm; FT IR (CCl_4) ν_{max} 3520(OH), 2961(CH), 1779(oxazolidinone $C=O$), 1697($RC=ON$) cm^{-1} .

3.4.3 Aldol condensation of the *Z(O)* Dibutylboron Enolate of Propionyl

Imide 213 with Benzaldehyde

A solution of **213** (580mg, 2.3 mmol) in dry dichloromethane (20ml) at $-78^\circ C$ under argon was treated successively with dibutylboron triflate (2.55ml, 1.0 M in dichloromethane, 2.55 mmol) then diisopropylethylamine (360mg, 2.8 mmol) in dichloromethane (2ml). The solution was allowed to warm to $0^\circ C$, stirred for 30 minutes then cooled to $-78^\circ C$. Freshly distilled benzaldehyde (380mg, 2.8 mmol) dichloromethane (2ml) was added and the reaction allowed to warm to room temperature. After three hours TLC (4:1, cyclohexane/ethylacetate) showed an absence of starting material and the reaction was quenched with pH 7 phosphate buffer. After separating the layers and extracting with dichloromethane (3 x 30ml) the organics were evaporated before being redissolved in methanol (20 ml) and

treated with hydrogen peroxide (2ml, 30% w/v, vast excess) at 0°C. After stirring at room temperature for 3 hours the peroxide was quenched with sodium sulphite then the solvents removed *in vacuo*. The residue was extracted with dichloromethane (3 x 30 ml) washed with water then brine and dried over magnesium sulphate before being filtered and evaporated. The resulting gum was analysed by high field ^1H NMR spectroscopy which showed that a single isomer was present. This was chromatographed on silica; gradient elution from hexane to hexane:ether (3:1) to yield a colourless crystalline powder (770g, 94%) (5*S*, 7*S*, 10*R*)-*N*-(2'*S*,3'*S*)-3'-hydroxy-2'-methyl-3'-phenylpropionyl-2-oxa-4-aza-6,6-dimethyl-7,10-methylenespiro[4.5]decan-3-one **244** MP = 154.0-155.2°C (from cyclohexane); $[\alpha]_{\text{D}}^{20} = +138.5^\circ$ (c= 4.1, dichloromethane); $R_f = 0.24$ (4:1, cyclohexane/ethylacetate); ^1H NMR (200 MHz, CDCl_3) δ 7.36-7.22(5H, cm, Ph), 4.89(1H, d, $J = 5.0$ Hz, CH_2OH), 4.16(1H, d, $J = 9.0$ Hz, H_{1a}), 4.02(1H, qd, $J = 7.0, 5.0$ Hz, CH_3CH), 3.62(1H, d, $J = 9.0$ Hz, H_{1b}), 3.19(1H, bs, OH), 2.73(1H, dm, $J = 10.5$ Hz, H_{11a}), 2.32(1H, bs, H_{10}), 1.81(1H, d, $J = 1.5$ Hz, H_7), 1.55-1.20(3H, cm), 1.24(3H, d, $J = 7$ Hz, CH_3CH), 1.17-0.88(2H, cm), 1.08, 0.96(6H, 2 x s, 2 x CH_3) ppm; ^{13}C NMR (50.3 MHz, CDCl_3) δ 177.0(quat, RC=ON), 155.4(quat, oxazolidinone C=O), 141.6(quat, Ph), 128.0(2 x CH, Ph), 127.3(CH, Ph), 126.2(2 x CH, Ph), 75.6(quat, C-N), 75.0(CH_2OH), 70.63(CH_2O), 49.2(CH, C_{10}), 47.1(quat, $\text{C}(\text{CH}_3)_2$), 45.6, 44.4(2 x CH), 38.1(CH_2 , C_{11}), 25.5(CH_3), 23.8, 22.4(2 x CH_2 , C_8 & C_9), 20.9(CH_3), 12.0(CH_3CH) ppm; FT IR (CCl_4) ν_{max} 3494(OH), 2971(CH), 1782(oxazolidinone C=O), 1713.5(RC=ON) cm^{-1} ; MS (EI) 358(25%, MH^+), 340(100, MH^+-18), 196(40), 145(100%), 135(25); Accurate mass (FAB) (MH^+)

Found 358.19910; $C_{21}H_{28}NO_4$ requires 358.20183; **Elemental analysis**, Found 70.50% C, 7.91% H, 3.83% N, $C_{21}H_{27}NO_4$ requires 70.55% C, 7.62% H, 3.92% N.

3.4.4 Cleavage of Aldol Product 244 with Lithium Hydroperoxide and

Isolation as the Methyl Ester 249

Aldol product **244** (360mg, 1.01 mmol) was dissolved in THF (20ml); lithium hydroxide (110mg, 2.38 mmol) in water (8ml) was added followed by hydrogen peroxide 91.2 ml, ~30%, ~12 mmol). The reaction was stirred at room temperature for 16 hours then saturated sodium bicarbonate (2ml) added and the THF removed *in vacuo*. The reaction mixture was extracted with dichloromethane (2 x 20ml), then taken to pH 2 with 6 M hydrochloric acid and extracted with dichloromethane (3 x 20ml), dried, filtered and evaporated to leave a gum (180mg). This was dissolved in methanol (20ml) and treated with diazomethane (~3 mmol) [Prepared from dizald[®] (1.1g, 5 mmol) and sodium hydroxide (1.1g, 19.3 mmol); in ether (10 ml), ethanol (2.5 ml) and water (2 ml) by the standard method. Then distilled directly into the reaction flask.]¹⁵⁴ then the reaction stirred for 2 hours. after flushing with argon for 30 minutes to remove excess diazomethane, the solvents were removed *in vacuo* and the residue subjected to rapid chromatography to yield a thick oil; identified as (2'S,3'S)-methyl-3'-hydroxy-2'-methyl-3'-phenylpropionate **249** $[\alpha]_D^{20} = -19.2^\circ$ (c = 4.4, dichloromethane) [Lit. $[\alpha]_D^{20} = -23.0^\circ$ (c = 0.32, $CHCl_3$)]¹⁴; ¹H NMR (200 MHz, $CDCl_3$) δ 7.35-7.19(5H, cm, Ph), 5.03(1H, d, $J = 4.5$ Hz, CHOH), 3.60(3H, s, CH_3O), 3.25(1H, bs, OH), 2.75(1H, qd, $J = 7.0, 4.5$ Hz, CH_3CH), 1.10(3H, d, $J = 7.0$ Hz, CH_3CH) ppm; ¹³C NMR (90.6 MHz, $CDCl_3$) δ 175.6(quat, C=O), 141.4(quat,

Ph), 127.9(2 x CH, Ph), 127.2(CH, Ph), 125.7(2 x CH, Ph), 73.6(CHOH), 51.5(CH₃O), 46.4(CHC=O), 10.70(CH₃CH) ppm; **FT IR** (thin film) $\nu_{\max}$ 3470(OH), 3055, 3033(Ar CH), 2980(CH), 1734(C=O), 1455, 770, 701 cm⁻¹; **MS** (FAB) 195(15%, MH⁺), 177(68, -H₂O), 121(100), 91(94).

3.4.5 Aldol Condensation of the *Z*(*O*) Dibutylboron Enolate of Propionyl

Imide 213 with Acetaldehyde

A solution of the dibutylboron enolate of **213** (2.4 mmol) [prepared from **213** 600mg, dibutylboron triflate (2.6ml, 1.0M in dichloromethane, 2.6 mmol) and diisopropylethylamine (380mg, 2.95 mmol) as for **3.4.3**] in dichloromethane (20ml) at -78°C was treated with acetaldehyde (500mg, 11.4 mmol) in dichloromethane (1ml) and stirred at room temperature for 4 hours, when TLC (4:1, cyclohexane/ethylacetate) indicated that no more product was forming. The reaction was quenched and worked up as for **3.4.1** to yield a yellow solid, high field ¹H NMR of which showed that a single *syn* diastereomer was present. Chromatography on silica eluting hexane-hexane:ether (3:1) yielded the desired product as a solid which was recrystallised from hexane/cyclohexane to give pure (5*S*, 7*S*, 10*R*)-*N*-(2'*S*, 3'*R*)-3'-hydroxy-2'-methlybutanoyl-2-oxa-4-aza-6,6-dimethyl-7,10-methylenespiro [4.5] decan-3-one **247** (660mg, 92%) MP= 133-134°C (from hexane/cyclohexane); $[\alpha]_D^{20} = +114^\circ$ (c = 1.95, dichloromethane); **R_f** = 0.10 (4:1, cyclohexane/ethylacetate); ¹H NMR (360 MHz, CDCl₃) δ 4.32(1H, d, *J* = 9.0 Hz, H_{1a}), 4.07(1H, dq, *J* = 6.5, 3.0 Hz, CHCO), 4.05(1H, d, *J* = 9.0 Hz, H_{1b}), 3.61(1H,

dq, $J = 7.0, 3.0$ Hz, CHOH), 3.04(1H, bs, OH), 2.76(1H, dm, $J = 10.5$ Hz, H_{11a}), 2.66(1H, d, $J = 1.5$ Hz, H_{10}), 1.85(1H, bs, H_7), 1.65-1.57(1H, cm), 1.55-1.44(2H, cm), 1.30(1H, dt, $J = 10.5, 1.5$ Hz, H_{11b}), 1.24(3H, d, $J = 7.0$ Hz, CH_3CHOH), 1.18(1H, cm), 1.14(3H, d, $J = 6.4$ Hz, CH_3CHCO), 1.14(13H, s, CH_3), 1.00(3H, s, CH_3) ppm; ^{13}C NMR (50.3 MHz, CDCl_3) δ 178.5(quat, RC=ON), 155.5(quat, oxazolidinone C=O), 75.7(quat, C-N), 70.9(CH_2O), 68.0(CHOH), 49.3(CH , C_{10}), 47.5(quat, $\text{C}(\text{CH}_3)_2$), 45.0, 44.2(2 x CH , C_{10} & CHCO), 38.3(CH_2 , C_{11}), 25.7(CH_3), 24.1, 22.6(2 x CH_2 , C_8 & C_9), 21.1(CH_3), 19.6(CH_3CHOH), 10.8(CH_3CHCO) ppm; FT IR (CCl_4) ν_{max} 3540(OH), 2975(CH), 1790(oxazolidinone C=O), 1705(RC=ON), 1280 cm^{-1} ; MS (EI) 296(100%, MH^+), 278(60, $\text{MH}^+ - 18$), 196(100), 135(60), 107(40); **Accurate mass** (FAB) (MH^+) Found 296.18662; $\text{C}_{16}\text{H}_{26}\text{NO}_4$ requires 296.18618; **Elemental analysis**, Found 64.72% C, 8.65% H, 4.64% N, $\text{C}_{16}\text{H}_{25}\text{NO}_4$ requires 65.05% C, 8.54% H, 4.74% N.

3.4.6 Aldol Condensation of the *Z*(O) Dibutylboron Enolate of Propionyl

Imide 213 with Isobutyraldehyde

A solution of the dibutylboron enolate of **213** (2.47 mmol) [prepared from **213** (620mg), dibutylboron triflate (2.7ml, 1.0M in dichloromethane, 2.7 mmol) and diisopropylethylamine (400mg, 3.1 mmol)] in dichloromethane (18ml) at -78°C was treated with isobutyraldehyde (280mg, 3.9 mmol) in dichloromethane (1ml) and stirred at room temperature for 4 hours, when TLC (4:1, cyclohexane/ethylacetate) indicated that no more product was forming. The reaction was quenched and worked up as for **3.4.1** to yield a yellow solid, high field ^1H NMR of which showed that a

single *syn* diastereomer was present. Chromatography on silica eluting hexane-hexane:ether (3:1) yielded the desired product as a solid which was recrystallised from hexane to give pure (5*S*, 7*S*, 10*R*)-*N*-(2'*S*,3'*R*)-3'-hydroxy-2',4'-dimethylpentanoyl-2-oxa-4-aza-6,6-dimethyl-7,10-methylenespiro[4.5]decan-3-one **248** (760mg, 96%) **MP** = 132-134°C (from hexane); $[\alpha]_D^{20} = +79.8^\circ$ (c = 1.25, dichloromethane); **R_f** = 0.26 (4:1, cyclohexane/ethylacetate); **¹H NMR** (360 MHz, CDCl₃) δ 4.30(1H, d, *J* = 9.0 Hz, H_{1a}), 4.03(1H, d, *J* = 9.0 Hz, H_{1b}), 3.84(1H, dq, *J* = 7.0, 3.0 Hz, CHCO), 3.40(1H, dd, *J* = 8.0, 3.0 Hz, CHOH), 2.94(1H, bs, OH), 2.76(1H, dm, *J* = 10.5 Hz, H_{11a}), 2.62(1H, m, H₁₀), 1.83(1H, d, *J* = 2.0 Hz, H₇), 1.6(1H, cm, CH(CH₃)₂), 1.60-1.56(1H, cm), 1.47-1.43(2H, cm), 1.27(1H, d, *J* = 10.5 Hz, H_{11b}), 1.18(3H, d, *J* = 7.0 Hz, CH₃CHCO), 1.18-1.10(1H, cm), 1.12(3H, s, CH₃), 0.99(3H, s, CH₃), 0.96(3H, d, *J* = 7.0 Hz, CH₃CH), 0.84(3H, d, *J* = 7.0 Hz, CH₃CH) ppm; **¹³C NMR** (90.6 MHz, CDCl₃) δ 178.6(quat, RC=ON), 155.3(quat, oxazolidinone C=O), 77.1(CHOH), 75.6(quat, C-N), 70.8(CH₂O), 49.4(CH, C₁₀), 47.5(quat, C(CH₃)₂), 45.0(CH, C₇), 40.7(CHC=O), 38.2(CH₂, C₁₁), 30.6(CH(CH₃)₂), 25.6(CH₃), 24.0, 22.5(2 x CH₂, C₈ & C₉), 21.1(CH₃), 18.8(2 x CH₃), 10.4(CH₃) ppm; **FT IR** (CCl₄) $\nu_{\max}$ 3540(OH), 2965(CH), 1790(oxazolidinone C=O), 1695(RC=ON), 1554, 1277 cm⁻¹; **MS** (EI) 324(5%, MH⁺), 306(5, MH⁺-18), 196(20), 130(100); **Accurate mass** (FAB) (MH⁺) Found 324.21466; C₁₈H₃₀NO₄ requires 324.21748; **Elemental analysis**, Found 66.78% C, 9.19% H, 4.29% N, C₁₈H₂₉NO₄ requires 66.83% C, 9.04% H, 4.33% N.

3.5 Asymmetric Diels-Alder Reactions

3.5.1 Diethylaluminium Chloride Catalysed Asymmetric Diels-Alder

Cycloaddition of Cyclopentadiene to Acryloyl Imide 221

Acryloyl imide **221** (350mg, 1.4 mmol) in dry dichloromethane (10ml) at -78°C under argon was treated successively with freshly cracked cyclopentadiene (1.0g, 14 mmol) and diethylaluminium chloride (1.25ml, 1.8 M in toluene, 2.25 mmol, 1.6 equiv). A very faint transient yellow colour was seen to form and after 5 minutes the reaction was quenched with saturated ammonium chloride solution (5ml) then allowed to warm to room temperature. Extraction with dichloromethane (3 x 20ml) followed by washing, drying over magnesium sulphate, filtration and evaporation yielded a sticky solid. Rapid chromatography on silica, eluent hexane to ether removed cyclopentadiene dimer and polymer to yield colourless crystals (450mg, 100%). 360 MHz ^1H NMR showed that the adduct was present as almost a single diastereomer (d.e. 95%) and this was recrystallised from dichloromethane/hexane to yield pure (5*S*, 7*S*, 10*R*) *N*-(4'*R*)-endo-bicyclo[2.2.1]heptene-4'-carbonyl-2-oxa-4-aza-6,6-dimethyl-7,10-methylene-spiro[4.5]decanone **250** MP = $158.5\text{--}159.3^{\circ}\text{C}$ (from dichloromethane/hexane); $[\alpha]_{\text{D}}^{20} = +218^{\circ}$ ($c = 4.9$, dichloromethane); $R_{\text{f}} = 0.56$ (4:1, cyclohexane/ethylacetate); ^1H NMR (360 MHz, CDCl_3) δ 6.18(1H, dd, $J = 5.5$, 3.0 Hz, $\text{CH}=\text{CH}$), 5.84(1H, dd, $J = 5.5$, 3.0 Hz, $\text{CH}=\text{CH}$), 4.25(1H, d, $J = 9.0$ Hz, $\text{H}_{1\text{a}}$) 3.96(1H, d, $J = 9.0$ Hz, $\text{H}_{1\text{b}}$), 3.56(1H, ddd, $J = 9.0$, 4.5, 3.5 Hz, $\text{CHC}=\text{O}$), 3.34(1H, bs, adduct bridge head), 2.84(1H, bs, adduct bridge head), 2.69(1H, dm, $J = 10.5$ Hz, $\text{H}_{11\text{a}}$), 2.53(1H, bs, H_{10}), 1.86(1H, ddd, $J = 11.5$, 9.0, 4.0 Hz, $\text{CH}_2\text{CHC}=\text{O}$),

1.79(1H, d, $J = 2.5$ Hz, H_7), 1.55(1H, cm), 1.48-1.38(2H, cm), 1.33 (1H, d, $J = 8.0$ Hz), 1.27(1H, ddd, $J = 11.5, 4.5, 2.5$ Hz, $\text{CH}_2\text{CHC=O}$), 11.22(1H, dt, $J = 10.5, 2.5$ Hz, H_{11b}), 1.11(3H, s, CH_3), 0.97(3H, s, CH_3) ppm; ^{13}C NMR (90.6 MHz, CDCl_3) δ 175.2(quat, RC=ON), 155.7(quat, oxazolidinone C=O), 137.4 (CH), 132.4(CH), 75.2(quat, C-N), 70.8(CH_2O), 50.0($\text{CH}_2\text{CHC=O}$), 49.3(CH, C_{10}), 47.4 (quat, $\text{C}(\text{CH}_3)_2$), 46.5, 44.9, 44.6, 42.6(4 x CH), 38.4 (CH_2 , C_{11}), 30.6(CH_2), 25.8(CH_3), 24.1, 22.6(2 x CH_2 , C_8 & C_9), 21.2(CH_3) ppm; FT IR (CCl_4) ν_{max} 1779(oxazolidinone C=O), 1706.5(RC=ON) cm^{-1} ; MS (FAB) 316(67%, MH^+), 250(14, $\text{MH}^+ - \text{C}_5\text{H}_6$), 196(30), 135(17), 121(20, $\text{MH}^+ - 195$); Accurate mass (FAB) (MH^+) Found 316.19135; $\text{C}_{19}\text{H}_{26}\text{NO}_3$ requires 316.19127; Elemental analysis, Found 71.91% C, 7.84% H, 4.64% N, $\text{C}_{19}\text{H}_{25}\text{NO}_3$ requires 72.34% C, 7.99% H, 4.44% N.

3.5.2 Diethylaluminium Chloride Catalysed Asymmetric Diels-Alder

Cycloaddition of Cyclopentadiene to Crotonoyl Imide 225

A solution of crotonate **225** (650mg, 2.47 mmol) and cyclopentadiene (0.8g, 12.1 mmol) in dichloromethane at -78°C under argon was treated with diethylaluminium chloride (2.2ml, 1.8 M in toluene, 4.0 mmol, 1.6 equiv.) in an identical manner to **3.5.1** but in this case a reaction time of 20 minutes was required. Quenching and work up and chromatography as for **3.5.1** yielded colourless crystals (800mg, 98%). High field ^1H NMR spectroscopy showed only a single diastereomer to be present (>95% d.e.). The material was recrystallised from dichloromethane/hexane to yield colourless crystals of pure (5*S*, 7*S*, 10*R*) *N*-(4'*R*, 5*S'*)-4'-endo-5'-methyl-

bicyclo[2.2.1]heptene-4'-carbonyl-2-oxa-4-aza-6,6-dimethyl-7,10-methylene-spiro[4.5]decanone **251** MP= 181.7-183.0°C (from dichloromethane/hexane); $[\alpha]_D^{20} = +251.8^\circ$ (c = 1.5, dichloromethane); $R_f = 0.56$ (4:1, cyclohexane/ethylacetate); $^1\text{H NMR}$ (200 MHz, CDCl_3) δ 6.33(1H, dd, $J = 5.5, 3.0$ Hz, $\text{CH}=\text{CH}$), 5.72(1H, dd, $J = 5.5, 2.5$ Hz, $\text{CH}=\text{CH}$), 4.26(1H, d, $J = 9.0$ Hz, H_{1a}), 4.01(1H, d, $J = 9.0$ Hz, H_{1b}), 3.35(2H, cm), 2.68-2.63(2H, cm), 2.45(1H, d, $J = 1.5$ Hz, H_{10}), 1.95(1H, cm, CH_3CH), 1.79(1H, d, $J = 2.0$ Hz, H_7), 1.64(1H, d, $J = 8.5$ Hz), 1.58-1.38(5H, cm), 1.23(1H, dt, $J = 11.0, 1.5$ Hz, H_{11b}), 1.25-0.90(2H, cm), 1.16(3H, s, CH_3), 1.05(3H, d, $J = 7.0$ Hz, CH_3CH), 0.93(3H, s, CH_3) ppm; $^{13}\text{C NMR}$ (50.3 MHz, CDCl_3) δ 174.7(quat, $\text{RC}=\text{ON}$), 155.6(quat, oxazolidinone $\text{C}=\text{O}$), 139.0(CH, $\text{CH}=\text{CH}$), 131.3(CH, $\text{CH}=\text{CH}$), 75.4(quat, C-N), 70.6(CH_2O), 49.2, 49.1(2 x CH), 47.8(CH), 47.3(quat, $\text{C}(\text{CH}_3)_2$), 47.2(CH_2 adduct), 44.9(CH, C_7), 38.4(CH_2 , C_{11}), 37.2(CH), 25.6(CH_3), 24.0, 22.5(2 x CH_2 , C_8 & C_9), 21.0, 20.41(CH_3 , CH_3CH) ppm; FT IR (CCl_4) ν_{max} 2963(CH), 1782(oxazolidinone $\text{C}=\text{O}$), 1705($\text{RC}=\text{ON}$), 1279, 1203, 1073 cm^{-1} ; MS (FAB) 330(51%, MH^+), 264(12, $\text{MH}^+ - \text{C}_5\text{H}_6$), 196(35), 135(64), 107(71), 91(77); Accurate mass (FAB) (MH^+) Found 330.20635; $\text{C}_{20}\text{H}_{28}\text{NO}_3$ requires 330.20692; Elemental analysis, Found 72.80% C, 8.42% H, 4.40% N, $\text{C}_{20}\text{H}_{27}\text{NO}_3$ requires 72.90% C, 8.27% H, 4.25% N.

3.6.3 Diethylaluminium Chloride Catalysed Asymmetric Diels-Alder

Cycloaddition of Cyclopentadiene to Cinnamoyl Imide **226**

A solution of cinnamoyl imide **226** (490mg, 1.51 mmol) and cyclopentadiene (600g, 9.1 mmol) in dichloromethane at -78°C under argon was treated with

diethylaluminium chloride (1.35 ml, 1.8 M in toluene, 2.4 mmol, 1.6 equiv.) in an identical manner to **3.5.1** then the reaction was warmed to -18°C where they deep orange colour faded over 45 minutes. Quenching and work up and chromatography as for **3.5.1** yielded colourless crystals (600mg). High field ¹H NMR spectroscopy showed only a single diastereomer to be present (>95% d.e.). The material was recrystallised from dichloromethane/hexane to yield colourless crystals (550mg, 93%) of pure (5*s*, 7*S*, 10*R*) *N*-(4'*S*, 5*R'*)-4'-endo-5'-methyl-bicyclo[2.2.1]heptene-4'-carbonyl-2-oxa-4-aza-6,6-dimethyl-7,10-methylene-spiro[4.5]decanone **252 MP** = 153.2-153.8°C (from dichloromethane); [α]_D²⁰ = +267° (c = 1.0, dichloromethane); *R*_f = 0.56 (4:1, cyclohexane/ethylacetate); ¹H NMR (200 MHz, CDCl₃) δ 7.34-7.13(5H, cm, Ph), 6.54 (1H, dd, *J* = 5.5, 3.0 Hz, CH=CH), 5.91(1H, dd, *J* = 5.5, 3.0 Hz, CH=CH), 4.26(1H, d, *J* = 9.0 Hz, H_{1a}), 4.09(1H, dd, *J* = 5.5, 3.0 Hz, CHC=O), 3.97(1H, d, *J* = 9.0 Hz, H_{1b}), 3.60(1H, bs, adducthead), 3.26(1H, dd, *J* = 5.5, 1.5 Hz, PhCH), 2.92(1H, d, *J* = 1.5 Hz, adduct bridgehead), 2.8-2.6(2H, cm), 1.97(1H, d, *J* = 8.5 Hz), 1.85(1h, d, *J* = 2.0 Hz, H₇), 1.61-1.35(4H, cm), 1.30(1H, dm, *J* = 10.5 Hz, H_{11b}), 1.16-0.98(1H, cm), 1.16(CH₃), 1.02(CH₃) ppm; ¹³C NMR (50.3 MHz, CDCl₃) δ 174.1(quat, RC=ON), 155.5(quat, oxazolidinone C=O), 144.0(quat, Ph), 139.5(CH=CH), 132.4(CH=CH), 128.3(2 x CH, Ph), 127.4(2 x CH, Ph), 125.9(CH, Ph), 75.4(quat, C-N), 70.6(CH₂O), 51.3, 49.8, 49.0(3 x CH), 48.1(CH₂, adduct bridge), 47.8, 47.7(2 x CH), 47.4(C(CH₃)₂), 44.8(CH, C₇), 38.4(CH₂, C₁₁), 25.9(CH₃), 24.0, 22.5(2 x CH₂, C₈ & C₉), 21.0(CH₃) ppm; FT IR (CCl₄) $\nu_{\max}$ 3063, 3034(Ar CH), 2968(CH), 1780(oxazolidinone C=O), 1705(RC=ON), 1282 cm⁻¹; MS (FAB) 392(11%, MH⁺), 326(6, MH⁺-C₅H₆), 196(70), 131(42), 91(100, C₇H₇⁺);

Accurate mass (FAB) (MH^+) Found 392.22390; $C_{25}H_{30}NO_3$ requires 392.22257;

Elemental analysis, Found 76.48% C, 7.66% H, 3.49% N, $C_{25}H_{29}NO_3$ requires 76.68% C, 7.47% H, 3.58% N.

3.5.4 Cleavage of Diels-Alder Adduct 251 using Lithium Benzyloxide

Benzyl alcohol (200mg, 1.9 mmol) in THF (20ml) at $-78^\circ C$ under argon was treated with *n*-butyl lithium (0.65ml, 1.5 M in hexanes, 1.0 mmol). After 30 minutes Diels-Alder adduct **251** (300mg, 0.9 mmol) in THF (2ml) was added and the reaction mixture allowed to reach room temperature. After 25 minutes TLC indicated complete consumption of the starting material and the formation of both auxiliary and a rapidly eluting component. The reaction was quenched with saturated ammonium chloride solution then the solvent was removed *in vacuo* and the products extracted into dichloromethane (3 x 20ml). Drying, filtration and evaporation gave a gum; chromatography on silica eluting hexane:ether (9:1), gave an oil (200mg, 91%) identified as (4'*R*, 5*S'*)-benzyl-4'-endo-5'-methyl-bicyclo[2.2.1]heptene-4'-carboxylate **253** $[\alpha]_D^{20} = +127.1^\circ$ ($c = 2.44$, dichloromethane) [*lit.* $[\alpha]_D^{20} = +130^\circ$ ($c = 2.08$, $CHCl_3$)]¹¹; ^1H NMR (200 MHz, $CDCl_3$) δ 7.43-7.30(5H, cm, Ph), 6.28(1H, dd, $J = 5.5, 3.0$ Hz, $CH=CH$), 5.98(1H, dd, $J = 5.5, 3.0$ Hz, $CH=CH$), 5.09(2H, AB q, $J = 12.5$, $PhCH_2O$), 3.16(1H, bs, bridgehead CH), 2.50-2.46(2H, cm), 1.89(1H, m, CH_3CH), 1.59-1.49(2H, cm), 1.21(3H, d, $J = 7.0$ Hz, CH_3CH) ppm; ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 174.3(C=O), 136.3(quat, Ph), 133.1($CH=CH$), 128.3(2 x CH, Ph), 127.8(2 x CH, Ph), 127.7(CH, Ph), 65.7($PhCH_2$), 52.4(CH), 48.7(CH), 45.8(CH_2 & CH), 37.7(CH), 20.8(CH_3) ppm; FT IR (thin film) ν_{max} 1730(C=O), 1610-1570(C=C), 1450, 1220, 1010, 710, 690 cm^{-1} ; MS (FAB) 259(26%, MH^+).

Further elution (4:1 to 1:1) provided benzyl alcohol, then auxiliary (160mg, 90%).

3.5.4 Cleavage of Cinnamate Cyclopentadiene Adduct 253 using Lithium

Benzyloxide

Diels-Alder adduct 252 (350mg, 0.9 mmol) in THF (2ml) was added to as solution of lithium benzyl oxide (1.05 mmol) in THF (20ml) at -78°C and the reaction mixture allowed to reach room temperature. After 35 minutes TLC indicated complete consumption of the starting material and the formation of both auxiliary and a rapidly eluting, UV active component. The reaction was quenched with saturated ammonium chloride solution then the was solvent removed *in vacuo* and the products extracted into dichloromethane (3 x 20ml). Drying, filtration and evaporation gave a gum; chromatography on silica eluting hexane:ether (9:1), gave an gum (260mg, 95%) identified as (4'*R*, 5'*S*)-benzyl-4'-endo-5'-methyl-bicyclo[2.2.1]heptene-4'-carboxylate **254** [α]_D²⁰ = +124.4° (c = 2.36, dichloromethane) [*lit.* [α]_D²⁰ = +121° (c = 1.33, CHCl₃)]¹¹; ¹H NMR (200 MHz, CDCl₃) δ 7.51-7.16(10H, cm, 2 x Ph), 6.43(1H, dd, *J* = 5.5, 3.0 Hz, CH=CH), 6.07(1H, dd, *J* = 5.5, 3.0 Hz, CH=CH), 5.13(2H, AB q, *J* = 12.5, PhCH₂O), 3.33(1H, bs, bridgehead CH), 3.17(1H, cm, CHC=O), 3.08-3.04(2H, cm), 1.81(1H, cm), 1.62-1.56(2H, cm) ppm; ¹³C NMR (50.3 MHz, CDCl₃) δ 173.8(C=O), 144.0(quat, Ph), 138.9(CH=CH), 136.1(quat, Ph), 134.2(CH=CH), 128.3(4 x CH, Ph), 127.8(2 x CH, Ph), 127.3(2 x CH, Ph), 125.8(CH, Ph), 66.0(PhCH₂), 52.1(CH), 48.1(CH), 47.3(CH), 46.2(CH₂), 29.5(CH) ppm; FT IR (thin film) $\nu_{\max}$ 3062,3029(Ar, vinyl CH), 2980(CH) 1731(C=O), 1640-1590(C=C), 1490, 11454 cm⁻¹; MS (FAB) 321(14%, MH⁺).

Further elution (4:1 to 1:1) provided benzyl alcohol, then auxiliary (170mg, 97%).

3.6 Asymmetric Conjugate Addition Reactions

3.6.1 1,4 Conjugate Addition of Diethylaluminium Chloride to Crotonyl Imide

225

A solution of crotonyl imide **225** (390mg, 1.48 mmol) in dry dichloromethane (30ml) at -78°C under argon was treated with diethylaluminium chloride (3.3ml, 1.8 M. in toluene, 5.9 mmol). A strong yellow coloration was seen to form, which then disappeared after 3 hours at -78°C. The reaction was then poured into rapidly stirred saturated ammonium chloride solution (60ml) and allowed to warm to room temperature. The lower layer was separated and the aqueous layer extracted with dichloromethane (2 x 30ml); the combined organics were then washed with water, dried over magnesium sulphate and evaporated. The resulting colourless gum (460mg, >100% mass balance) was analysed by high field ^1H and ^{13}C NMR which showed that a single diastereomer was present; which was identified as (5*S*, 7*S*, 10*R*)-*N*-(3'*S*)-3'-methylpentanoyl-2-oxa-4-aza-6,6-dimethyl-7,10-methylenespiro[4.5]decan-3-one **261** [α]_D²⁰ = +98.7° (c = 1.25, dichloromethane); *R*_f = 0.56 (4:1, cyclohexane/ethylacetate); ^1H NMR (200 MHz, CDCl₃) δ 4.26(1H, d, *J* = 9.0 Hz, H_{1a}), 3.98(1H, d, *J* = 9.0 Hz, H_{1b}), 2.83(1H, dd, *J* = 16.5, 5.5 Hz, CHHC=O), 2.80-2.62(2H, cm, C_{11a} & C₁₀), 2.60(1H, dd, *J* = 16.5, 8.0 Hz, CHHC=O), 1.87(1H, octet, *J* = 5.5 Hz, CH₃CH), 1.81(1H, bs, H₇), 1.62-1.09(7H, cm), 1.09, 0.95(6H, 2 x s, 2 x CH₃), 0.86(3H, d, *J* = 7.0 Hz, CH₃CH), 0.84(1H, dd, *J* = 10.0, 4.5 Hz, CH₃CH₂) ppm; ^{13}C NMR (50.3 MHz, CDCl₃) δ 173.4(quat, RC=ON), 155.7(quat, oxazolidinone C=O), 75.2(quat, C-N), 70.7(CH₂O), 49.1(CH,

C₁₀), 47.4(quat, C(CH₃)₂), 45.0(CH, C₇), 43.6(CH₂O), 38.2(CH₂, C₁₁), 31.0(CH₃CH), 29.2(CH₃CH₂), 25.6(CH₃), 24.0, 22.5(2 x CH₂, C₈ & C₉), 21.1(CH₃), 19.0(CH₃CH), 11.2(CH₃CH₂) ppm; FT IR (thin film) $\nu_{\max}$ 2966(CH), 1787.5(oxazolidinone C=O), 1710.5(RC=ON), cm⁻¹; MS (FAB) 294(8%, MH⁺), 196(15), 154(3), 136(3); Accurate mass (FAB) (MH⁺) Found 294.20567; C₁₇H₂₈NO₃ requires 294.20692.

3.6.2 1,4 Conjugate Addition of Diethylaluminium Chloride to Cinnamoyl

Imide 226

Cinnamoyl imide **225** (440mg, 1.35 mmol) in dichloromethane (30ml) was treated with diethylaluminium chloride (3.3ml, 1.8 M. in toluene, 5.9 mmol) in an identical manner to **3.8.1** to give a deep orange solution. The reaction was held at -78°C for 18 hours after which it was warmed to -20°C, at which temperature the colour was observed to disappear gradually*. Quenching and work up as for **3.8.1** provided a colourless crystalline solid (490mg, 100%). ¹H and ¹³C NMR spectroscopy indicated a 82% d.e.. The material was recrystallised from dichloromethane/hexane to yield pure (5*S*, 7*S*, 10*R*)-*N*-(3'*S*)-3'-phenylpentanoyl)-2-oxa-4-aza-6,6-dimethyl-7,10-methylenespiro[4.5] decan-3-one **262** MP= 99.3-100.7°C (from dichloromethane/hexane); [α]_D²⁰ = +127.4° (c = 1.45, dichloromethane); R_f = 0.33 (9:1, hexane/ethylacetate); ¹H NMR (250 MHz, CDCl₃) δ 7.30-7.15(5H, Ph), 4.10(1H, d, *J* = 9.0 Hz, H_{1a}), 3.48(1H, dd, *J* = 14.5, 8.5 Hz, CH₂C=O), 3.47(1H, d, *J* = 9.0 Hz, H_{1b}), 2.72(1H, dm, *J* = 10.5 Hz, H_{11a}), 2.20(1H, d, *J* = 2.0 Hz, H₁₀), 1.80(1H, t, *J* = 1.5 Hz, H₇), 1.76-1.58(2H, cm), 1.54-1.24(3H, cm), 1.19(1H, dt, *J* = 10.5, 1.5 Hz, H_{11b}), 1.07(3H, s, CH₃), 1.0-0.85(1H, cm), 0.97(3H, s, CH₃), 0.78(3H, t,

$J = 7.0$ Hz, CH_3CH_2) ppm; ^{13}C NMR (50.3 MHz, CDCl_3) δ 173.0(quat, $\text{RC}=\text{ON}$), 156.0(quat, oxazolidinone $\text{C}=\text{O}$), 143.7(quat, Ph), 128.1, 127.6, 126.2(2 + 2 + 1 CH, Ph), 75.4(quat, C-N), 70.6(CH_2O), 49.2(CH, C_{10}), 47.0(quat, $\text{C}(\text{CH}_3)_2$), 44.7, 44.4(2 x CH, C_7 & CHPh), 42.4($\text{CH}_2\text{C}=\text{O}$), 38.1(CH_2 , C_{11}), 29.8(CH_3CH_2), 25.7(CH_3), 25.4, 23.8(2 x CH_2 , C_8 & C_9), 21.0(CH_3), 11.8(CH_3CH_2) ppm; **FT IR** (CCl_4) ν_{max} 3034, 2964(CH), 1784(oxazolidinone), 1710($\text{RC}=\text{ON}$), 1284, 1072 cm^{-1} ; **MS** (FAB) 356(40%, MH^+), 340(16), 196(57), 161(18), 159(24), 135(29), 131(43), 119(75), 91(100); **Accurate mass** (FAB) (MH^+) Found 356.22241; $\text{C}_{22}\text{H}_{30}\text{NO}_3$ requires 356.22257; **Elemental analysis**, Found 74.13% C, 8.22% H, 3.84% N, $\text{C}_{22}\text{H}_{29}\text{NO}_3$ requires 74.32% C, 8.23% H, 3.94% N.

* An identical reaction was carried out holding the reaction at -78°C for 72 hours by which time the colour of the reaction had faded; the resulting product was found to have an identical d.e. to that produced as above. However, when the imide was added to the cooled diethylaluminium chloride solution the reaction was complete with in 2 hours, an identical yield and d.e. were obtained.

3.6.3 Cleavage of 1,4 Conjugate Adduct 262 with Lithium Hydroperoxide

Adduct **262** (420mg, 1.18 mmol) in THF (15ml) was treated with lithium hydroxide (100mg, 2.4 mmol) in water (5ml) and hydrogen peroxide (1.1ml, 30% vol., ~11 mmol) at room temperature. After stirring for 2 hours TLC indicated completion of reaction, saturated sodium bicarbonate solution (2ml) was added followed by saturated sodium sulphite [until negative to starch iodide paper] and the solvent

removed *in vacuo*. The aqueous was extracted with dichloromethane (2 x 20ml), saturated with sodium chloride and acidified to pH 2 with concentrated hydrochloric acid. Extraction with dichloromethane (3 x 20ml) drying, filtration and evaporation gave (3'S)-3'-phenylpentanoic **263** as an oil (220mg, 105% mass balance) $[\alpha]_D^{20} = +49.3^\circ$ (c = 9.5, benzene), [Lit. $[\alpha]_D = +54.2^\circ$ (c = 30, benzene)]¹¹⁹; ¹H NMR (200 MHz, CDCl₃) δ 7.27(5H, cm, Ph), 3.03(1H, cm, CH), 2.67(2H, cm, CH₂C=O), 1.75(1H, cm, CH₃CH₂), 1.67(1H, cm, CH₃CH₂), 0.82(3H, t, *J* = 7.5 Hz, CH₃) ppm; ¹³C NMR (50.3 MHz, CDCl₃) δ 178.9(quat, C=O), 143.4(quat, Ph), 128.3(2 x CH, Ph), 127.3(2 x CH, Ph), 126.3(CH, Ph), 43.3(CH₂C=O), 41.0(CH), 28.9(CH₃CH₂), 11.7(CH₃) ppm; FT IR (thin film) $\nu_{\max}$ 3060, 3032(Ar, CH), 2900(broad, OH), 1712(C=O), 1493 cm⁻¹; MS (FAB) 179(100%, MH⁺), 161(76), 131(52).

3.6.4 1,4 Conjugate Addition of *trans*-1-Hexenyldiisobutylaluminium **264a** to Crotonyl Imide (-)-**225**

A solution of *trans*-1-hexenyl diisobutylaluminium **264a** was prepared by treating 1-hexyne (26g, 38 mmol) in dry toluene (50ml) under argon with diisobutylaluminium hydride (25ml, 1.5 M in toluene, 37.5 mmol) at room temperature. The resulting solution was heated at 50°C for 3 hours then cooled and the solution (~0.4 M) stored in a pressure bottle.

A solution of crotonyl imide (-)-**225** (520mg, 1.98 mmol), in dry toluene (20 ml) at -78°C under argon was treated with the freshly prepared solution of *trans*-1-hexenyl aluminium **264a** (15ml, ~6 mmol). After 2 hours the starting material had been consumed and the reaction was quenched by pouring it into rapidly stirred

saturated ammonium chloride solution (30ml). After extraction into dichloromethane (3 x 30ml) washing, drying, filtration and evaporation a thick oil was obtained (640mg, 98%). This was shown to contain two diastereomers in a ratio of 1:1.46 (20% d.e.) by comparison of a number of proton resonances in the high field ^1H NMR spectra. The two compounds were inseparable by chromatography on silica and the physical data given is for the mixture of (5*S*, 7*S*, 10*R*)-*N*-(3'*S*/*R*)-3'-methylnon-4'-enoyl-2-oxa-4-aza-6,6-dimethyl-7,10-methylenespiro[4.5]decan-3-one **265a** R_f = 0.56 (4:1, cyclohexane/ ethylacetate); ^1H NMR (80 MHz, CDCl_3) δ 5.38-5.22(2H, cm, $\text{CH}=\text{CH}$), 4.32(1H, d, J = 9.0 Hz, H_{1a}), 3.90(1H, d, J = 9.0 Hz, H_{1b}), 2.97-2.58(4H, cm, $\text{CHCH}_2\text{C}=\text{O}$, C_{11a}), 2.58(1H, bs, H_{10}), 2.0-1.7(2H, cm), 1.5-0.8(21H, cm), 1.06(3H, s, CH_3), 0.92(6H, s + t, J = 10.5 Hz, CH_3 & CH_2CH_3) ppm; ^{13}C NMR (50.3 MHz, CDCl_3) δ 172.6, 172.5(quat, $\text{RC}=\text{ON}$, major/minor), 155.6(quat, oxazolidinone $\text{C}=\text{O}$), 134.0, 129.0($\text{CH}=\text{CH}$), 75.1(quat, $\text{C}-\text{N}$), 70.6(CH_2O), 49.0(CH , C_{10}), 47.2(quat, $\text{C}(\text{CH}_3)_2$), 44.80(CH , C_7), 43.9, 43.6($\text{CHC}=\text{O}$), major/minor), 38.1(CH_2 , C_{11}), 33.2, 32.9($\text{CHCH}=\text{CH}$, major/minor), 31.9, 31.4($\text{CH}=\text{CHCH}_2$, major/minor), 25.7(CH_3), 23.9, 22.4(2 x CH_2 , C_8 & C_9), 21.8(CH_3), 22.0, 20.5(CH_2CH , major/minor), 13.7(CH_2CH_3) ppm; FT IR (thin film) ν_{max} 2963(CH str), 1786(oxazolidinone $\text{C}=\text{O str}$), 1712.5($\text{RC}=\text{ON str}$) cm^{-1} ; MS (FAB) 348(48%, MH^+), 332(9), 304(6), 196(59), 153(38, $\text{RCH}=\text{C}=\text{OH}^+$), 152(28), 151(31), 135(42), 107(52); Accurate mass (FAB) (MH^+) Found 348.25157; $\text{C}_{21}\text{H}_{34}\text{NO}_3$ requires 348.25387.

3.6.5 1,4 Conjugate Addition of *trans*-2-Styryldiisobutylaluminium 264b to

Crotonyl Imide (-)-225

A solution of *trans*-2-styryldiisobutylaluminium 264b was prepared by treating phenyl acetylene (3.80g, 37.5 mmol) in dry toluene (50ml) under argon with aluminium hydride (25ml, 1.5 M in toluene, 37.5 mmol) at room temperature. The resulting yellow solution was heated at 50°C for 3 hours to produce a plum red solution, which was then cooled and stored in a pressure bottle (~0.4 M).

Crotonyl imide (-)-225 (530mg, 2.02 mmol) in dry toluene (20ml) was treated in an identical manner to 3.8.3 with the reagent 264b. After quenching and work up a semi-crystalline product was obtained (760mg, 103 %), which was analysed by ¹H NMR spectroscopy to reveal a d.e. of 18%. Again the diastereomers were inseparable by chromatography on silica and the physical data given is for the mixture of (5*S*, 7*S*, 10*R*)-*N*-(3'*S*/*R*)-3'-methyl-5'-phenylpent-4'-enoyl-2-oxa-4-aza-6,6-dimethyl-7,10-methylenespiro[4.5]decan-3-one 265b MP = 128.5-130.5°C (from ether/hexane); *R*_f = 0.46 (4:1, cyclohexane/ethylacetate); ¹H NMR (80 MHz, CDCl₃) δ 7.37-7.15(5H, cm, Ph), 6.54(2H, cm, CH=CH), 4.28(0.41H, d, *J* = 9.0 Hz, H_{1a} minor), 4.20(0.59H, d, *J* = 9.0 Hz, H_{1a} major), 3.97(0.59H, d, *J* = 9.0 Hz, H_{1b} major), 3.82(0.41H, d, *J* = 9.0 Hz, H_{1b} minor), 3.24-2.59(5H, cm, CHCH₂C=O, C_{11a} & C₁₀), 1.82(1H, bs, H₇), 1.7-1.2(5H, cm), 1.2-0.85(9H, 3 x CH₃ (complex)) ppm; ¹³C NMR (62.9 MHz, CDCl₃) δ 172.6, 172.4(quat, RC=ON major/minor), 155.9, 155.7(quat, oxazolidinone C=O), 137.2, 137.1(quat, Ph), 134.5, 134.3(CH=CHPh), 128.7, 128.6(CH=CHPh), 128.3, 128.2(2 x CH, Ph), 126.9, 126.8(CH, Ph), 125.8(2 x CH, Ph), 75.3(quat, C-N), 70.7, 70.6(CH₂O), 49.1, 49.0(CH, C₁₀), 47.3, 47.2(C(CH₃)₂),

44.9, 44.8(CH, C₇), 43.7, 43.4(CH₂C=O), 38.2(CH₂, C₁₁), 34.1, 33.3(CHCH=CH), 25.8(CH₃), 23.9, 22.4(2 x CH₂, C₈ & C₉), 21.0(CH₃), 20.043, 20.1(CH₃CH) ppm; FT IR (CCl₄) $\nu_{\max}$ 2962(CH), 1786(oxazolidinone C=O), 1706(RC=ON), 1366, 1287, 1073 cm⁻¹; MS (FAB) 368(60%, MH⁺), 281(17), 196(45), 131(44); **Accurate mass** (FAB) (MH⁺) Found 368.22526; C₂₃H₃₀NO₃ requires 368.22257.

3.6.6 Attempted Conjugate Addition of Vinylmagnesium Bromide to Crotonyl Imide (-)-225 (2.5 Equivalents in THF)

A solution of crotonyl imide (-)-225 (240mg, 0.91 mmol) in dry THF (15ml) at -78°C under argon was treated with vinylmagnesium bromide (2.3ml, 1M in THF, 2.3 mmol) to give a yellow solution. After 3 hours monitoring by TLC showed that a considerable quantity of starting material had been consumed and two slow running spots had appeared. The reaction mixture was poured into rapidly stirred saturated ammonium chloride solution and after warming to room temperature solvent was evaporated in vacuo. Extraction with dichloromethane followed by drying, filtration and evaporation provided a yellow gum (280mg). ¹H and ¹³C NMR spectroscopy confirmed the presence of starting material, auxiliary and a third component which did not appear to be the target material. Flash chromatography, gradient elution hexane:ether (4:1 to 2:1 to 0:1) allowed the isolation of (-)-225 (40mg, 17%), (-)-225 (50mg, 29%) and finally a crystalline compound (120mg, 45%) identified as amidoester (1*S*, 2*S*, 4*R*)-2-*N*-crotonylamino-3,3-dimethyl-bicyclo[2.2.1]heptane-2-methylacrylate **266** MP = 100-103°C decomposes to polymer (from cyclohexane);

$[\alpha]_D^{20} = +0.8^\circ$ ($c = 1.9$, dichloromethane); $R_f = 0.39$ (1:1, cyclohexane/ethylacetate); $^1\text{H NMR}$ (200 MHz, CDCl_3) δ 6.67(1H, dq, $J = 15.0, 7.0$ Hz, $\text{CH}_3\text{CH}=\text{CH}$), 6.26(1H, dd, $J = 17.0, 2.0$ Hz, $\text{CH}_2=\text{CH}$), 6.00(1H, dd, 17.0, 10.5 Hz, $\text{CH}_2=\text{CH}$), 5.80 (1H, dq, $J = 15.0, 1.5$, $\text{CH}_3\text{CH}=\text{CH}$), 5.70(1H, dd, $J = 10.5, 1.5$ Hz, $\text{CH}_2=\text{CH}$), 5.09(1H, d, $J = 11.5$ Hz, CH_2O), 4.39(1H, d, $J = 11.5$ Hz, CH_2O), 2.20(1H, bs, H_{10}), 1.86(1H, d, $J = 10.5$ Hz, H_{11a}), 1.74(3H, dd, $J = 7.0, 2.0$ Hz, $\text{CH}_3\text{CH}=\text{CH}$), 1.57-1.0(5H, cm), 1.12(1H, d, $J = 10.5$ Hz, H_{11b}), 1.04(3H, s, CH_3), 1.02(3H, s, CH_3) ppm; $^{13}\text{C NMR}$ (50.3 MHz, CDCl_3) δ 165.8, 165.7(2 x q, $\text{NC}=\text{O}$ & $\text{OC}=\text{O}$), 138.8($\text{CH}_3\text{CH}=\text{CH}$), 130.1($\text{CH}_2=\text{CH}$), 128.3, 125.6($\text{CH}_2=\text{CH}$ & $\text{CH}_3\text{CH}=\text{CH}$), 65.3(quat, C-N), 61.8(CH_2O), 50.2(CH, C_{10}), 47.1(CH, C_7), 45.5(quat, $\text{C}(\text{CH}_3)_2$), 34.3(CH_2 , C_{11}), 26.0 (CH_3), 22.9, 22.3(2 x CH_2 , C_8 & C_9), 20.6(CH_3), 17.3($\text{CH}_3\text{CH}=\text{CH}$) ppm; FT IR (CCl_4) ν_{max} 3371, 3292(NH), 3066(vinyl C=C), 2969(CH), 1726(RC=OO), 1715(RC=ON), 1670, 1632(C=C), 1538 cm^{-1} ; MS (FAB) 292(3%, MH^+), 220(14), 196(36), 152(64), 135(100); Accurate mass (FAB) (MH^+) Found 292.19409; $\text{C}_{17}\text{H}_{26}\text{NO}_3$ requires 292.19127.

3.6.7 Attempted Conjugate Addition of Vinylmagnesium Bromide to Crotonyl

Imide (-)-225 (1.2 Equivalents in Toluene)

Treatment of (-)-225 (260mg, 0.99 mmol) in toluene (25ml) at -60°C gave a persistent yellow colour, on warming to -40°C this faded over 40 minutes. Work up as before gave a semi-crystalline gum, TLC and 60 MHz $^1\text{H NMR}$ showed that it was mostly (-)-225 and (-)-207. Chromatographic separation gave (-)-225 (68mg, 26%) and auxiliary (130mg, 68%) as well as a trace of the amido-alcohol 266.

3.6.8 Attempted Conjugate Addition of Vinylmagnesium Bromide to Crotonyl Imide (-)-225 (2.5 Equivalents in Ether)

Reaction of (-)-225 (270mg, 1.02 mmol) in ether in an identical manner to 3.6.5 at -90 to -60°C, provided after work up a mixture of (-)-225 (30mg, 12%), (-)-207 (135mg, 68%) and amidoester 266 (25mg, 8%).

3.6.9 Attempted Conjugate Addition of Vinylmagnesium Bromide (1.1 Equiv.) to Crotonyl Imide (-)-225 Prechelated with Diethylaluminium Chloride

(-)-225 (260mg, 0.99 mmol) in dry toluene (40ml) at -60°C was treated with diethylaluminium chloride (0.80ml, 1.8 M in toluene, 1.3 mmol) to give a yellow solution, after 15 minutes vinylmagnesium bromide (1.1ml, 1M in THF, 1.1 mmol) was added. The colour rapidly faded as this was added but even after 3 hours at -78°C TLC showed only starting material. This was recovered in 92% yield after quenching and work up.

3.6.10 Attempted 1,4 Conjugate Addition of Vinylmagnesium Bromide (2.5 Equiv.) to Crotonyl Imide (-)-225 Prechelated with Diethylaluminium Chloride

The reaction was repeated as for 3.6.9 but vinylmagnesium bromide (4ml, 4 mmol) was added. This lead to similar rapid decolorisation but after 2 hours all starting material had been consumed and the reaction was quenched. Extractive work up and

chromatography as **3.6.5** gave auxiliary (35mg, 18%), followed by the amido-ester **266** (190mg, 66%).

3.6.11 Copper (I) Catalysed Asymmetric 1,4 Conjugate Addition of Vinylmagnesium Bromide to Crotonyl Imide (-)-**225**

A suspension of copper(I)bromide (800mg, 5.6 mmol) in dry THF (100ml) at 0°C was treated [slow addition at first] with vinylmagnesium bromide (67ml, 1M in THF, 67 mmol) to form a black solution which after 30 minutes was cooled to -78°C. Crotonyl imide (-)-**225** (7.11g, 27.0 mmol) in THF (50ml) was then added over 45 minutes via syringe pump. After 30 minutes this was warmed to -15°C for two hours*, then poured into rapidly stirred saturated ammonium chloride solution, solvent evaporated in vacuo and the product extracted into dichloromethane. This was washed, dried, filtered and evaporated to give a yellow oil which was essentially a single spot by TLC. Rapid chromatography gave (5*R*, 7*SR*, 10*S*)-*N*-(3'*S*)-3'-methylpent-4-enoyl-2-oxa-4-aza-6,6-dimethyl-7,10-methylenespiro[4.5]decan-3-one **267** as a colourless oil (7.70g, 98%) [α]_D²⁰ = -106.5° (c = 3.1, dichloromethane); *R*_f = 0.52 (4:1, cyclohexane/ethylacetate); ¹H NMR (360 MHz, CDCl₃) δ 5.77(1H, ddd, *J* = 17.0, 10.5, 7.0 Hz, CH=CH₂), 5.01(1H, dt, *J* = 17.0, 1.5 Hz, CH=CH₂), 4.92(1H, dt, *J* = 10.5, 1.5 Hz, CH=CH₂), 4.29(1H, d, *J* = 9.0 Hz, H_{1a}), 4.00(1H, d, *J* = 9.0 Hz, H_{1b}), 2.91(1H, dd, *J* = 16.0, 7.0 Hz, CH₂CH), 2.84(1H, dd, *J* = 16.0, 7.0, CHCH), 2.73(1H, dm, *J* = 10.5 Hz, H_{11a}), 2.69(1H, septet, *J* = 7.0 Hz, CH₂=CHCH), 1.81(1H, d, *J* = 2.0 Hz, H₇), 1.58(1H, cm), 1.50-1.36(2H, cm), 1.260(1H, d, *J* = 10.5 Hz, H_{11b}), 1.16-1.10(1H, cm), 1.11(3H, s, CH₃), 1.02(3H, d, *J* = 7.0 Hz, CH₃CH), 0.98(CH₃)

ppm; ^{13}C NMR (90.5 MHz, CDCl_3) δ 172.5(quat, $\text{RC}=\text{ON}$), 155.7(quat, oxazolidinone $\text{C}=\text{O}$), 142.7($\text{CH}_2=\underline{\text{C}}\text{H}$), 113.0($\underline{\text{C}}\text{H}_2=\text{CH}$), 75.3(quat, $\text{C}-\text{N}$), 70.7(CH_2O), 49.2(CH , C_{10}), 47.4($\underline{\text{C}}(\text{CH}_3)_2$), 45.0(CH , C_7), 43.4($\text{CH}_2\text{C}=\text{O}$), 38.2(CH_2 , C_{11}), 33.8($\text{CH}_2=\text{CH}\underline{\text{C}}\text{H}$), 25.8(CH_3), 24.0, 22.5(2 x CH_2 , C_8 & C_9), 21.1(CH_3), 19.7($\underline{\text{C}}\text{H}_3\text{CH}$) ppm; FT IR (thin film) ν_{max} 3080, 3040(vinyl CH), 2965(CH), 1785(oxazolidinone $\text{C}=\text{O}$), 1710($\text{RC}=\text{ON}$), 1640($\text{C}=\text{C}$) cm^{-1} ; MS (FAB) 292.953%, MH^+ , 205(45), 196(65), 135(64), 107(57); Accurate mass (FAB) (MH^+) Found 292.18994; $\text{C}_{17}\text{H}_{26}\text{NO}_3$ requires 292.19127.

* NB. It has been found that use of only 1.3 equivalents of vinyl magnesium bromide gives the same reaction product and the reaction appears to go to completion within 1 hour at -78°C .

3.6.12 Catalytic Hydrogenation of 1,4 Conjugate Adduct 267

The adduct **267** (1.80g, 6.2 mmol) was hydrogenated at atmospheric pressure in the presence of 5% palladium on charcoal (200mg) for 2 hours. Filtration through celite and evaporation yielded (*5R*, *7R*, *10S*)-*N*-(*3'R*)-*3'*-methylpentanoyl-2-oxa-4-aza-6,6-dimethyl-7,10-methylenespiro[4.5]decan-3-one (-)-**261** as a gum (1.82g, quantitative) $[\alpha]_{\text{D}}^{20} = -96^\circ$ ($c = 2$, dichloromethane); other physical data as for the enantiomer.

3.6.13 Cleavage of Adduct (-)-261 with Lithium Hydroperoxide

Adduct (-)-261 (1.80g, 6.14 mmol) in THF (25ml) was treated with lithium hydroxide (500mg, 12.0 mmol) in water (6ml) and hydrogen peroxide (4ml, 30% vol., ~20 mmol) at room temperature. After stirring for 4 hours TLC indicated completion of reaction. Peroxides were quenched by stirring the reaction over palladium/alumina for 2 hours and work up was carried out as for 3.6.3. The residue was bulb to bulb distilled to yield (3*R*)-3-methylpentanoic 268 as an oil (710mg, 100% mass balance) BP = 150°C, 25mm Hg; $[\alpha]_D^{20} = -5.05^\circ$ (c = 4.4, CHCl₃) [*Lit.* $[\alpha]_D^{20} = -6.48^\circ$ (c = -4.07, CHCl₃)]¹⁵⁵; ¹H NMR (200 MHz, CDCl₃) δ 11.6(1H, b, OH), 2.33(1H, dd, *J* = 15.0, 6.0 Hz, CH₂C=O), 2.11(1H, dd, *J* = 15.0, 7.0 Hz, CH₂C=O), 1.86(1H, sextet, *J* = 7.0 Hz, CH), 1.48-1.11(2H, cm, CH₃CH₂), 0.87(3H, t, *J* = 7.5 Hz, CH₃) ppm; ¹³C NMR (50.3 MHz, CDCl₃) δ 180.2(quat, C=O), 41.1(CH₂C=O), 31.6(CH), 29.1(CH₃CH₂), 11.1(CH₃) ppm; FT IR (thin film) $\nu_{\max}$ 3050(broad, OH), 2960(CH), 1714(C=O), 1409, 1290, 1206, 938 cm⁻¹.

3.6.14 Copper (I) Catalysed Asymmetric 1,4 Conjugate Addition of

Phenylmagnesium Bromide to Crotonyl Imide (-)-225

A solution of phenylmagnesium bromide (~30 mmol) [prepared from magnesium (720mg) and bromobenzene (4.7g, 30 mmol) in dry THF (120ml) at 0°C] was treated with copper(I)bromide (290mg, 2.0 mmol) to form a colourless suspension; which after 30 minutes was cooled to -78°C. Crotonyl imide (+)-225 (2.63g, 10.0 mmol) in THF (50ml) was then added dropwise over 15 minutes (formation of a transient yellow colour) and the resulting slurry stirred for a further 45 minutes. After this

time TLC showed complete consumption of starting material and the reaction mixture was quenched and worked up as for **3.6.11**. A colourless solid (3.52g, 103%) was obtained, high field ^1H NMR of which indicated that the minor diastereomer was present to an extent of *ca.* 2%, 96% d.e. This material was subjected to rapid chromatography giving (5*S*, 7*S*, 10*R*)-*N*-(3'*R*)-3'-phenylbutanoyl-2-oxa-4-aza-6,6-dimethyl-7,10-methylenespiro [4.5]decan-3-one **269** as a colourless solid which was recrystallised from cyclohexane/hexane (3.21g, 94%) MP = 110.1-110.7°C (from cyclohexane); $[\alpha]_{\text{D}}^{20} = +79.5^\circ$ (*c* = 1.35, dichloromethane); ^1H NMR (250 MHz, CDCl_3) δ 7.6-7.1(5H, cm, Ph), 4.26(1H, d, *J* = 9.0Hz, $\text{H}_{1\text{a}}$), 3.97(1H, d, *J* = 9.0 Hz, $\text{H}_{1\text{b}}$), 3.40-3.09(3H, cm), 2.60(1H, dt, *J* = 10.5, 2.5 Hz, $\text{H}_{11\text{a}}$), 2.52(1H, bs, H_{10}), 1.76(1H, d, *J* = 2.0 Hz, 1.58-1.36(2H, cm), 1.29(1H, cm), 1.29(3H, d, *J* = 7.0 Hz, CH_3CH), 1.23(1H, dt, *J* = 10.5, 1.5 Hz, $\text{H}_{11\text{b}}$), 1.14-1.06(1H, cm), 1.08(3H, s, CH_3), 0.75(3H, s, CH_3) ppm; ^{13}C NMR (62.9 MHz, CDCl_3) δ 172.4(quat, RC=ON), 155.7(quat, oxazolidinone C=O), 145.8(quat, Ph), 128.2, 126.9(4 x CH, Ph), 126.0(CH, Ph), 75.8(quat, C-N), 70.7(CH_2O), 49.0(CH, C_{10}), 47.3(quat, $\text{C}(\text{CH}_3)_2$), 45.0($\text{CH}_2\text{C=O}$), 44.9(CH, C_7), 38.1(CH_2 , C_{11}), 35.7(PhCH), 25.5(CH_3), 24.0, 22.5(CH_2 's), 22.0, 21.0(2 x CH_3) ppm; FT IR (CCl_4) ν_{max} 3032(Ar CH), 2970, 2900(CH), 1782(oxazolidinone C=O), 1708(RC=ON), 1366, 1280 cm^{-1} ; MS (FAB) 342(90%, MH^+), 326(66), 196(87), 135(59), 105(100); Accurate mass (FAB) (MH^+) Found 342.20942; $\text{C}_{21}\text{H}_{28}\text{NO}_3$ requires 342.20692; Elemental analysis, Found 73.54% C, 8.09% H, 4.15% N, $\text{C}_{21}\text{H}_{27}\text{NO}_3$ requires 73.86% C, 7.98% H, 4.10% N.

3.6.14 Cleavage of Adduct 269 with Lithium Hydroperoxide

Adduct **269** (820mg, 2.40 mmol) in THF (20ml) was treated with lithium hydroxide (220mg, 5.0 mmol) in water (4ml) and hydrogen peroxide (2ml, 30% vol., ~20 mmol) at room temperature. After stirring for 1 hours TLC indicated completion of reaction, quenching and work up was carried out as for **3.6.3** and the residue bulb to bulb distilled to yield (3'*R*)-3'-phenylbutanoic **270** as an oil (360mg, 91% mass balance) BP = 160°C, 1mm Hg; $[\alpha]_{\text{D}}^{20} = -46^{\circ}$ (c = 5.1, CHCl₃) [*Lit.* $[\alpha]_{\text{D}}^{20} = -57.2^{\circ}$ (c = 9.8, CHCl₃)]¹²⁶; ¹H NMR (200 MHz, CDCl₃) δ 11.1(1H, b, OH), 7.40-7.19(5H, cm, Ph), 3.31(1H, sextet, *J* = 7.0 Hz, CH), 2.72(1H, dd, *J* = 15.5, 7.0 Hz, CH₂C=O), 2.60(1H, dd, *J* = 15.5, 7.0 Hz, CH₂C=O), 1.36(3H, t, *J* = 7.0 Hz, CH₃) ppm; ¹³C NMR (50.3 MHz, CDCl₃) δ 178.9(quat, C=O), 145.3(quat, Ph), 128.4(2 x CH, Ph), 126.6(2 x CH, Ph), 126.4(CH, Ph), 42.5(CH₂C=O), 36.0(CH), 21.7(CH₃) ppm; FT IR (thin film) ν_{max} 3060, 3030(Ar, CH), 2900(broad, OH), 1712(C=O), 1493 cm⁻¹.

The initial organic extract provided (+)-**207** (460mg, 98%)

3.6.15 Copper (I) Catalysed Asymmetric 1,4 Conjugate Addition of

Vinylmagnesium Bromide to Crotonyl Imide (+)-**225** and Methylation of the Resulting Enolate

A suspension of copper(I)bromide (54mg, 0.38 mmol) in dry THF (15ml) at 0°C was treated with vinylmagnesium bromide (3.1ml, 1M in THF, 3.1 mmol) to form a black solution which after 30 minutes was cooled to -78°C. Crotonyl imide (+)-**225** (510mg, 1.94 mmol) in THF (5ml) was then added over 15 minutes. After 45 minutes NMP(10ml) was added and the reaction warmed to -20°C for 4 hours.

Quenching and work up as for **3.3.5** provided a sticky solid (590mg, 100%). This was analysed by high field ^1H NMR which indicated that a presumed C_α diastereomer was present to the extent of 5% giving a d.e. of 90%. Rapid chromatography (hexane:ether (4:1)) and recrystallisation from hexane gave (5*S*, 7*S*, 10*R*)-*N*-(2'*S*, 3'*S*)-2', 3'-dimethylpent-4-enoyl-2-oxa-4-aza-6,6-dimethyl-7,10-methylenespiro[4.5]decan-3-one **271** as a crystalline solid (480mg, 82%) **MP** = 91.5-92.7°C (from hexane) $[\alpha]_D^{20} = +148.4^\circ$ ($c = 3.1$, dichloromethane); $R_f = 0.56$ (4:1, cyclohexane/ethylacetate); ^1H NMR (250 MHz, CDCl_3) δ 5.57(1H, ddd, $J = 16.0, 11.0, 8.5$ Hz, $\text{CH}=\text{CH}_2$), 4.95(1H, dm, $J = 16.0$ Hz, $\text{CH}=\text{CH}_2$), 4.93(1H, dm, $J = 11.0$ Hz, $\text{CH}=\text{CH}_2$), 4.26(1H, d, $J = 9.0$ Hz, H_{1a}), 3.95(1H, d, $J = 9.0$ Hz, H_{1b}), 3.49(1H, dq, $J = 8.5, 7.0$ Hz, H_2), 2.82(1H, dm, $J = 10.5$, H_{11a}), 2.38(1H, septet, $J = 6.7$ Hz, H_3), 1.80(1H, bs, H_7), 1.55-1.34(3H, cm), 1.23(1H, dt, $J = 10.5, 1.5$ Hz, H_{11b}), 1.10-1.00(1H, cm), 1.08(3H, s, CH_3), 1.06(3H, d, $J = 7.0$ Hz, CH_3CH), 0.96(CH_3), 0.91(3H, d, $J = 7.0$ Hz, CH_3CH) ppm; ^{13}C NMR (62.9 MHz, CDCl_3) δ 177.2(quat, $\text{RC}=\text{ON}$), 155.8(quat, oxazolidinone $\text{C}=\text{O}$), 140.8($\text{CH}_2=\text{CH}$), 115.0($\text{CH}_2=\text{CH}$), 75.7(quat, $\text{C}-\text{N}$), 71.0(CH_2O), 49.5(CH , C_{10}), 47.4($\text{C}(\text{CH}_3)_2$), 45.0(CH , C_7), 43.4($\text{CH}_2\text{C}=\text{O}$), 41.6($\text{CH}_2=\text{CHCH}$), 38.2(CH_2 , C_{11}), 25.6(CH_3), 24.2, 22.6(2 x CH_2 , C_8 & C_9), 21.2(CH_3), 18.5, 15.4(2 x CH_3CH) ppm; **FT IR** (thin film) ν_{max} 3040(vinyl CH), 2970(CH), 1786(oxazolidinone $\text{C}=\text{O}$), 1706($\text{RC}=\text{NO}$) cm^{-1} ; **MS** (FAB) 306(65%, MH^+), 290(10), 219(65), 196(79), 135(58); **Accurate mass** (FAB) (MH^+) Found : 306.20742; $\text{C}_{17}\text{H}_{26}\text{NO}_3$ requires 306.20692.

3.6.16 Copper (I) Catalysed Asymmetric 1,4 Conjugate Addition of Phenylmagnesium Bromide to Crotonyl Imide (+)-225 and Methylation of the Intermediate Enolate

A solution of phenylmagnesium bromide (~13.7 mmol) [prepared as for 3.3.5] in dry THF (30ml) at 0°C was treated with copper(I)bromide (80mg, 0.6 mmol) to form a colourless suspension; which after 30 minutes was cooled to -78°C. Crotonyl imide (+)-225 (1.20g, 4.56 mmol) in THF (15ml) was then added dropwise over 15 minutes (formation of a transient yellow colour) and the resulting slurry stirred for a further 45 minutes. Freshly distilled methyl iodide (4.2g, 29.6 mmol) was added, followed by NMP (20ml) and the reaction mixture stirred at -20 to -12°C for 4 hours. After this time TLC showed complete consumption of starting material and the reaction mixture was quenched and worked up as for 3.3.5. A colourless solid (1.6g) was obtained, high field ¹H NMR of which showed predominantly one diastereomer (96% d.e.). This material was subjected to rapid chromatography giving (5*S*, 7*S*, 10*R*)-*N*-(2'*S*,3'*R*)-2'-methyl-3'-phenylbutanoyl-2-oxa-4-aza-6,6-dimethyl-7,10-methylenespiro[4.5]decan-3-one **272** as a colourless solid which was recrystallised from cyclohexane (1.50g, 93%) MP = °C (from cyclohexane); [α]_D²⁰ = +32.1° (c = 4.2, dichloromethane); R_f = 0.56 (4:1, cyclohexane:ethylacetate); ¹H NMR (250 MHz, CDCl₃) δ 7.31-7.24(2H, cm, Ph), 7.21-7.14(3H, cm, Ph), 4.29(1H, d, *J* = 9.0Hz, H_{1a}), 3.96(1H, d, *J* = 9.0 Hz, H_{1b}), 3.89(1H, dq, *J* = 10.0, 6.5 Hz, CHC=O), 3.00(1H, dq, *J* = 10.0, 7.0 Hz, PhCH), 2.90(1H, dm, *J* = 10.5 Hz, H_{11a}), 2.62(1H, bs, H₁₀), 1.85(1H, bs, H₇), 1.61-1.41(3H, cm), 1.31(1H, dt, *J* = 10.5, 1.5 Hz, H_{11b}), 1.3-1.1(1H, cm), 1.20(3H, d, *J* = 7.0 Hz, CH₃CH), 1.13(3H, s, CH₃), 1.02(3H, s, CH₃),

0.97(3H, d, $J = 6.5$ Hz, CH_3CH) ppm; ^{13}C NMR (62.9 MHz, CDCl_3) δ 177.6(quat, RC=ON), 155.7(quat, oxazolidinone C=O), 144.3(quat, Ph), 128.2, 127.6(4 x CH, Ph), 126.3(CH, Ph), 75.7(quat, C-N), 71.0(CH_2O), 49.5(CH, C_{10}), 47.5(quat, $\text{C}(\text{CH}_3)_2$), 45.0(CHC=O & C_7), 43.7(PhCH), 38.4(CH_2 , C_{11}), 25.5(CH_3), 24.2, 22.6(CH_2 's), 22.2, 20.2, 17.0(3 x CH_3), ppm; FT IR (CCl_4) ν_{max} 3032(Ar CH), 2970, 2900(CH), 1782(oxazolidinone C=O), 1708(RC=ON), 1366, 1280 cm^{-1} ; MS (FAB) 342(90%, MH^+), 326(66), 196(87), 135(59), 105(100); **Accurate mass** (FAB), Found : 342.20942; $\text{C}_{21}\text{H}_{28}\text{NO}_3$ requires 342.20692; **Elemental analysis**, Found : 73.54% C, 8.09% H, 4.15% N, $\text{C}_{21}\text{H}_{27}\text{NO}_3$ requires 73.86% C, 7.98% H, 4.10% N.

3.6.17 1,4 Conjugate Addition of Diethylaluminium Chloride to Methacryloyl

Imide 228 and Proton Quenching of the Intermediate Enolate

A solution of methacryloyl imide **228** (250mg, 0.96 mmol) in dry dichloromethane (15ml) at -78°C under argon was treated with diethylaluminium chloride (2.1ml, 1.8 M. in toluene, 3.8 mmol). A pale yellow colour formed, which then disappeared after stirring overnight at room temperature. After re-cooling to -78°C the reaction was stirred rapidly then saturated ammonium chloride solution/THF (1:1, 10ml) added and the reaction allowed to warm to room temperature. The lower layer was separated and the aqueous extracted with dichloromethane (2 x 30ml); the combined organics were then washed with water, dried over magnesium sulphate and evaporated. The resulting colourless gum (280mg, 99% mass balance) was analysed by high field ^1H NMR which showed that two diastereomer were present in a ratio of 8:3, giving a d.e. of 45%. The compounds were separated by chromatography on

silica, eluting hexane:ether (6:1) to provide (5*S*, 7*S*, 10*R*)-*N*-(2'*S*)-2'-methylpentanoyl-2-oxa-4-aza-6,6-dimethyl-7,10-methylenespiro[4.5]decan-3-one **273** as a low melting solid (70mg, 24%) $[\alpha]_{\text{D}}^{20} = +142^{\circ}$ ($c = 0.7$, dichloromethane); $R_f = 0.67$ (4:1, cyclohexane/ethylacetate); $^1\text{H NMR}$ (250 MHz, CDCl_3) δ 4.27(1H, d, $J = 9.0$ Hz, H_{1a}), 3.98(1H, d, $J = 9.0$ Hz, H_{1b}), 3.58(1H, sextet, $J = 6.5$ Hz, CHC=O), 2.81(1H, dm, $J = 10.5$ Hz, H_{11a}), 2.57(1H, bs, H_{10}), 1.82(1H, bs, H_7), 1.64-1.56(2H, cm), 1.50-1.40(2H, cm), 1.34-1.00(6H, cm), 1.14(3H, d, $J = 6.5$ Hz, CH_3CH), 1.11(3H, s, CH_3), 0.98(3H, s, CH_3), 0.84(3H, t, $J = 7.0$ Hz, CH_3CH_2) ppm; $^{13}\text{C NMR}$ (62.9 MHz, CDCl_3) δ 178.1(quat, RC=ON), 155.5(quat, oxazolidinone C=O), 75.4(quat, C-N), 70.8(CH_2O), 49.4(CH , C_{10}), 47.4(quat, $\text{C}(\text{CH}_3)_2$), 45.1(CH , C_7), 38.7(CHC=O), 38.4(CH_2 , C_{11}), 36.3(CH_2), 25.6(CH_3), 24.1, 22.6(2 x CH_2), 21.1(CH_3), 20.3(CH_2), 17.8(CH_3CH), 13.9(CH_3CH_2) ppm; **FT IR** (CCl_4) ν_{max} 2958, 2872(CH), 1783(oxazolidinone C=O), 1702(RC=ON), 1280 cm^{-1} ; **MS** (FAB) 294(100%, MH^+), 278(16)196(45).

Further elution provided the major diastereomer (5*S*, 7*S*, 10*R*)-*N*-(2'*R*)-2'-methylpentanoyl-2-oxa-4-aza-6,6-dimethyl-7,10-methylenespiro[4.5]decan-3-one **274** as a gum (210mg, 71%) $[\alpha]_{\text{D}}^{20} = +94.7^{\circ}$ ($c = 2.4$, dichloromethane); $R_f = 0.62$ (4:1, cyclohexane/ethylacetate); $^1\text{H NMR}$ (250 MHz, CDCl_3) δ 4.24(1H, d, $J = 9.0$ Hz, H_{1a}), 3.96(1H, d, $J = 9.0$ Hz, H_{1b}), 3.62(1H, sextet, $J = 6.5$ Hz, CHC=O), 2.96(1H, dm, $J = 10.5$ Hz, H_{11a}), 2.55(1H, bs, H_{10}), 1.79(1H, bs, H_7), 1.78-1.62(2H, cm), 1.55-1.38(2H, cm), 1.34-1.21(5H, cm), 1.14-1.05(1H, cm), 1.08(3H, s, CH_3), 1.02(3H, d, $J = 6.5$ Hz, CH_3CH), 0.95(3H, s, CH_3), 0.84(3H, t, $J = 7.0$ Hz, CH_3CH_2) ppm; $^{13}\text{C NMR}$ (62.9 MHz, CDCl_3) δ 178.0(quat, RC=ON), 155.4(quat,

oxazolidinone C=O), 75.3(quat, C-N), 70.6(CH₂O), 49.3(CH, C₁₀), 47.2(quat, C(CH₃)₂), 45.0(CH, C₇), 38.3(CH₂, C₁₁), 38.2(ChC=O), 35.7(CH₂), 25.7(CH₃), 24.0, 22.5(2 x CH₂), 21.0(CH₃), 20.1(CH₂), 17.2(CH₃CH), 13.8(CH₃CH₂) ppm; FT IR (CCl₄) $\nu_{\max}$ 2969(CH), 1779(oxazolidinone C=O), 1704(RC=ON), 1456, 1365, 1280, 1203, 1072 cm⁻¹; MS (FAB) 294(100%, MH⁺), 278(16), 196(45).

3.6.18 1,4 Conjugate Addition of Diethylaluminium Chloride to Tigloyl

Imide 229 and Proton Quenching of the Intermediate Enolate

A solution of Tigloyl imide **229** (270mg, 0.98 mmol) in dry dichloromethane (15ml) at -78°C under argon was treated with diethylaluminium chloride (2.2ml, 1.8 M. in toluene, 4.0 mmol). A lime yellow colour formed, this persisted as the temperature was raised over a number of hours; even after 3 hours at room temperature little of the colour had faded. The reaction was stirred overnight, by which time it was colourless; it was then recooled to -78°C. The reaction was quenched and worked up as for **3.3.5** providing a colourless gum (300mg, 100% mass balance). This was analysed by high field ¹H NMR which showed that two diastereomer were present in a ratio of 3:1. The components were separated by chromatography on silica, eluting hexane:ether (6:1) to provide the minor fraction (80mg, 27%), high field ¹H and ¹³C NMR spectroscopy of which showed it to be a 1:1 mixture of presumably C_β diastereomers. Similarly the major fraction (220mg, 73%), was also seen to be a 1:1 mixture of diastereomers.

3.7. Enantioselective Synthesis of Paraconic Acids

3.7.1 Preparation of Sorbyl Imide 301

A solution of the chloromagnesium salt of (+)-207 was formed in the standard manner from auxiliary (1.95g, 10.0 mmol) in THF (100ml) and butyl magnesium bromide (5ml, 2 M in THF, 10.0 mmol), then treated with freshly distilled sorbyl chloride (1.43g, 11.0 mmol) (prepared from sorbic acid and thionyl chloride¹³⁹). After stirring at room temperature for 14 hours the reaction was seen to be complete and was quenched before work up as for 3.2.2. Chromatography on silica, eluent hexane:ether, 5:1; provided a gum, stabilised before evaporation by the addition of galvanoxyl (10mg) (2.66g, 92%) identified as (5*S*, 7*S*, 10*S*) *N*-hex-2,4-dienoyl-2-oxa-4-aza-6,6-dimethyl-7,10-methylenespiro[4.5]decan-3-one **301** $[\alpha]_D^{20} = +133.9^\circ$ ($c = 2.4$, dichloromethane); $R_f = 0.42$ (4:1, cyclohexane/ethylacetate); ^1H NMR (200 MHz, CDCl_3) δ 7.26(1H, dd, $J = 15.0, 10.0$ Hz, $\text{CH}=\text{CH}$), 6.94(1H, d, $J = 15.0$ Hz, $\text{CH}=\text{CH}$), 6.21(1H, dd, $J = 15.0, 10.0$ Hz, $\text{CH}=\text{CH}$), 6.15(1H, dq, $J = 15.0, 6.0$ Hz, $\text{CH}=\text{CH}$), 4.26(1H, d, $J = 9.0$ Hz, H_{1a}), 3.99(1H, d, $J = 9.0$ Hz, H_{1b}), 2.72-2.65(2H, m, H_{10} & H_{11a}), 1.77(4H, bs + d, $J = 6.0$ Hz, H_7 & $=\text{CHCH}_3$), 1.67-1.30(3H, cm), 1.22(1H, d, $J = 10.5$ Hz, H_{11b}), 1.15-1.00(1H, cm), 1.07(1H, s, CH_3), 0.94(3H, s, CH_3) ppm; ^{13}C NMR (50.3 MHz, CDCl_3) δ 166.4(quat, $\text{RC}=\text{ON}$), 155.6(quat, oxazolidinone $\text{C}=\text{O}$), 145.2, 139.6, 130.1, 120.1(4 x CH, diene), 75.2(quat, C-N), 70.7(CH_2O), 48.9(CH, C_{10}), 47.5(quat, $\text{C}(\text{CH}_3)_2$), 45.1(CH, C_7), 38.0(CH_2 , C_{11}), 25.8(CH_3), 23.9, 2.5(2 x CH_2 , C_8 & C_9), 21.1(CH_3), 18.5($=\text{CHCH}_3$) ppm; FT IR

(thin film) $\nu_{\max}$ 3097, 3028(alkenic CH), 2930(CH), 1780, 1770(oxazolidinone C=O), 1683(RC=ON), 1635, 1602(C=C) cm^{-1} ; MS (FAB) 290(80%, MH^+), 274(17), 219(16), 196(50); **Accurate mass** (FAB) (MH^+) Found 290.17454; $\text{C}_{17}\text{H}_{24}\text{NO}_3$ requires 290.17562.

3.7.2 Conjugate Addition of Methyl Copper to Sorbyl Imide **301** Catalysed by Diethylaluminium Chloride

Copper(I)bromide (960mg, 6.6mmol) and dimethyl sulphide (420mg, 13.2 mmol) were stirred together for 10 minutes, then excess volatiles remove by purging with argon. Toluene (20ml) was then added and the reaction mixture cooled to -40°C before treating with methyllithium (4.8ml, 1.4 M in ether, 6.6 mmol), to give a greenish slurry. Diethylaluminium chloride (3.7ml, 1.8 M in toluene, 6.7 mmol) was added at -78°C to give a deep lime green slurry to which was added the sorbyl imide **301** (385mg, 1.3 mmol) in toluene (5ml). After 30 minutes the reaction was warmed to -20°C and stirred for 30 minutes when TLC indicated complete reaction to a single product. The mixture was poured into rapidly stirred ammonium chloride solution, then extracted with ether (2 x 30ml), washed with brine, dried and evaporated to give a slightly yellow gum (100%). 60 MHz ^1H NMR a relatively clean spectrum, but. High field ^1H NMR spectroscopy clearly showed that the H_{1b} doublet at 3.9 ppm to be further split, indicating that two products were present in a ratio of 2:3. This ratio of products was also displayed by certain ^{13}C resonances. These products were originally thought to be the diastereomers of NNN but were later shown to be (5*S*, 7*S*,

10R) *N*-(*cis/trans*) 5'-methyl-hex-3'-enoyl)-2-oxa-4-aza-6,6-dimethyl-7,10-methylenespiro [4.5] decan-3-one was obtained $R_f = 0.52$ (4:1, cyclohexane/ethylacetate); $^1\text{H NMR}$ (250 MHz, CDCl_3) δ 5.45-5.22(2H, cm, CH=CH), 4.22(0.6H, d, $J = 9.0$ Hz, H_{1a} (major)), 4.21(0.4H, d, $J = 9.0$ Hz, H_{1a} (minor)), 3.95(0.6H, d, $J = 9.0$ Hz, H_{1b} (major)), 3.93(0.4H, d, $J = 9.0$ Hz, H_{1b} (minor)), 3.66-3.25(2H, cm, CH_2CO), 2.64(1H, d, $J = 10.5$ Hz, H_{11a}), 2.56(1H, b, H_{10}), 2.48(0.6H, cm, CHCH_3 (major)), 2.150(0.4H, cm, CHCH_3 (minor)), 1.73(1H, d, $J = 1.5$ Hz, H_7), 1.60-1.25(3H, cm), 1.16(1H, d, $J = 10.5$ Hz, H_{11b}), 1.1-0.8(13H, complex, 4 x CH_3 & 1H) ppm; $^{13}\text{C NMR}$ (62.9 MHz, CDCl_3) δ 172.2, 171.8(quat, RC=ON), 155.3 (quat, oxazolidinone), 141.1, 140.3(CH=CH), 118.6, 118.1(CH=CH), 74.8(quat, C-N), 70.4(CH_2O), 48.7(CH, C_{10}), 47.1(quat, $\text{C}(\text{CH}_3)_2$), 44.6(CH, C_7), 40.4(CH_2CO (minor)), 37.9(CH_2 , C_{11}), 35.2(CH_2CO (major)), 30.6, 26.3(CHCH_3 (minor, major)), 25.4, 25.3(CH_3), 23.7, 22.4(2 x CH_2 , C_8 & C_9), 22.2, 21.8, 20.8(CH_3 's) ppm; **FT IR** (thin film) ν_{max} 3040(alkene CH), 2961(CH), 1784(oxazolidinone C=O), 1711(RC=ON), 1464, 1281, 1074 cm^{-1} ; **MS** (FAB) 306(94%, MH^+), 290(36), 196(86), 180(17), 152(30), 135(72); **Accurate mass** (FAB) (MH^+) Found 306.20799; $\text{C}_{18}\text{H}_{28}\text{NO}_3$ requires 306.20692.

3.7.3 Conjugate Addition of Methylmagnesium Iodide to Sorbyl Imide 301 in the Presence of Copper(I)Iodide

Methylmagnesium iodide (5.5ml, 1.0 M in ether, freshly prepared, 5.5 mmol) was added to copper(I)iodide in dry THF (30ml) under argon at 0°C. After 10 minutes the yellow mixture was cooled to -78°C and **301** (580mg, 2.0 mmol) in THF (10ml) added over 10 minutes; the resulting orange slurry was stirred for 15 minutes then allowed to warm slowly to -20°C and held at this temperature for 90 minutes. TLC indicated complete reaction and the mixture was poured in to rapidly stirred ammonium chloride solution, THF was removed *in vacuo* and after extractive work up with dichloromethane a yellow (galvanoxyl traces) gum was obtained (610mg, 100%). Once again high field ^1H and ^{13}C NMR spectroscopy showed the same two isomers in essentially the same ratio (3:2).

3.7.4 Conjugate Addition of Methylmagnesium Iodide to Sorbyl Imide 301 in the Presence of Copper(I)Bromide

Reaction 3.7.3 was repeated using copper(I)bromide (60mg, 0.4 mmol) in place of copper (I) iodide with identical quantities of methyl magnesium iodide and **301**. The addition of the later was performed over 20 minutes and the reaction held at -78°C for 55 hours. After quenching and work up as for 3.7.3 high field ^1H NMR spectroscopy showed that the same products were formed in identical yield to the previous reactions (3:2).

3.7.5 Conjugate Addition of Methylmagnesium Bromide to Sorbyl Imide 301 in the Presence of Copper(I)Bromide

Methylmagnesium bromide (9mmol) was prepared freshly in THF (30ml) and cooled to 0°C under argon; copper(I)bromide (100mg, 0.7 mmol) was added and stirred for 20 minutes before cooling to -78°C. **301** (870mg, 3.0 mmol) in THF (15ml) was added over 15 minutes to give an orange slurry and after 1 hour at -78°C the reaction was warmed to -20°C and held at this temperature for 2.5 hours. Quenching and work up as for **3.7.3** yielded a yellow gum (920mg, 100%), high field ¹H NMR spectroscopy of this showed that the same products were formed in identical ratios to the previous reactions (3:2).

3.7.6 Conjugate Addition of Dimethylcopper Lithium to Sorbyl Imide 301

A stirred suspension of copper(I)iodide (600mg, 3.0 mmol) in toluene (20ml) at -40°C under argon was treated with methyl lithium (4.3ml, 1.4 M in ether, 6.0 mmol) to form a faintly yellow solution. After 20 minutes this was cooled to -78°C then **301** (290mg, 1.0 mmol) in toluene (6ml) was added to give a deep red-orange solution. This was warmed over 1 hour to -40°C (by removal of excess dry ice from the Dewar bath); the colour slowly started to faded at this temperature and after 20 minutes TLC indicated complete reaction. Quenching and work up as for **3.7.3** yielded a yellow gum (300mg, 99%), high field ¹H NMR of this showed that the same products were formed in identical ratios to the previous reactions (3:2).

3.7.7 Catalytic Hydrogenation of Adduct 306

Adduct **306** (470mg, 1.54 mmol) was hydrogenated at atmospheric pressure over palladium/charcoal (100mg, 5%) for 3 hours. After filtration through a celite pad, solvent was evaporated to yield a pale yellow gum (470mg, 99%) identified as (5*S*, 7*S*, 10*R*) *N*-5'-methylhexanoyl-2-oxa-4-aza-6,6-dimethyl-7,10-methylenespiro[4.5]decan-3-one **305** R_f = 0.48 (4:1, cyclohexane/ethylacetate); ^1H NMR (MHz, CDCl_3) δ 4.22(1H, d, J = 9.0 Hz, H_{1a}), 3.94(1H, d, J = 9.0 Hz, H_{1b}), 2.84(1H, ddd, J = 17.0, 8.5, 6.5 Hz, $\text{CH}_2\text{C}=\text{O}$), 2.73-2.63(2H, cm, $\text{CH}_2\text{C}=\text{O}$), 2.60(1H, bs, H_{10}), 1.76(1H, bs, H_7), 1.57-1.35(6H, cm), 1.23-1.08(4H, cm), 1.05(3H, s, CH_3), 0.90(3H, s, CH_3), 0.79(6H, d, J = 6.5 Hz, $(\text{CH}_3)_2\text{CH}$) ppm; ^{13}C NMR (MHz, CDCl_3) δ 173.9(quat, $\text{RC}=\text{ON}$), 155.5(quat, oxazolidonone $\text{C}=\text{O}$), 74.9(quat, C-N), 70.50(CH_2O), 48.9(CH, C_{10}), 47.30(quat, $\text{C}(\text{CH}_3)_2$), 44.9(CH, C_7), 38.1, 38.0(2 x CH_2 , C_{11} & $\text{CH}_2\text{C}=\text{O}$), 37.1(CH_2), 27.5($\text{CH}(\text{CH}_3)_2$), 25.5(CH_3), 23.9, 22.4(3 x CH_2), 22.2($\text{C}(\text{CH}_3)_2$), 21.0(CH_3) ppm; **Accurate mass** (FAB), Found : 308.22196; $\text{C}_{18}\text{H}_{30}\text{NO}_3$ 308.22257.

3.7.8 Conjugate Addition of Diethylaluminium Chloride to Sorbyl Imide 301

301 (590mg, 2.0 mmol) in dry dichloromethane (40ml) at -78°C under argon was treated with diethylaluminium chloride (4.5ml, 1.8 M in toluene, 8.0 mmol). to form a deep red-orange coloured solution. After 10 minutes this had faded to orange and

after 1 hour to yellow; a pale yellow colour persisted and this was presumed to be due to galvanoxy. The reaction was quenched and worked up as for **3.6.1** (630mg, 100%). 60 M HZ ^1H NMR distinctly showed two isomers (H_{1a} and H_{1b} resonances) and high field ^1H and ^{13}C NMR confirmed this giving a ratio of 5:2. The product was identified as a mixture of *trans* (5*S*, 7*R*, 10*S*) *N*-((3'*S*) 3'-ethyl-hex-4-enoyl)-2-oxa-4-aza-6,6-dimethyl-7,10-methylenespiro[4.5]decan-3-one **307** (minor) and *cis/trans* (5*S*, 7*R*, 10*S*) *N*-((3'*R/S*) 5'-methyl-hept-3-enoyl)-2-oxa-4-aza-6,6-dimethyl-7,10-methylene-spiro[4.5] decan-3-one **308** (major) ^1H NMR (250 MHz, CDCl_3) δ 5.53-5.08(2H, cm, $\text{CH}=\text{CH}$), 4.25(0.7H, d, $J = 9.0$ Hz, H_{1a}), 4.23(0.3H, d, $J = 9.0$ Hz, H_{1a}), 3.96(0.7H, d, 9.0 Hz, H_{1b}), 3.91(0.3H, d, $J = 9.0$ Hz, H_{1b}), 3.51(1H, cm, CH_2CO), 2.95-2.63(2H, CH_2CO & H_{11a}), 2.60(0.7H, bs, H_{10} (major)), 2.53(0.3H, bs, H_{10} (minor)), 2.370(0.3H, cm, $\text{CHCH}=\text{CH}$ (minor)), 1.962(0.7H, pentet, $J = 7.0$ Hz, $\text{CHCH}=\text{CH}$ (major)), 1.77(1H, bs, C_7), 1.56(2H, cm), 1.40(2H, cm), 1.19(3H, cm), 1.07,1.06(3H, 2 x s, CH_3), 0.90(6H, 2 x s, 2 x d, CH_3 & CH_3CH), 0.78,0.76(3H, 2 x t, CH_3CH_2) ppm; FT IR (thin film) ν_{max} 3037(vinyl CH *str*), 2964, 1789(oxazolidinone $\text{C}=\text{O}$ *str*), 1706.5($\text{RC}=\text{ON}$ *str*), 1459 cm^{-1} ; MS (FAB) 320(45%, MH^+), 196(55), 135(40), 123(37), 107(51).

3.7.9 Hydrogenation of the mixture of **307** and **308**

Adducts **307** and **308** (4:9, 180mg, 0.55 mmol) in ethylacetate (15ml) were hydrogenated at atmospheric pressure in the presence of palladium/charcoal (50mg, 5%) for 2 hours. Isolation as for **3.7.7** provided an oil(180mg, 100%) identified as a

mixture of the saturated 1,4 adduct **309** and the saturated 1,6 adduct **310** ^1H NMR (250 MHz, CDCl_3) δ 4.26(1H, d, $J = 9.0$ Hz, H_{1a}), 3.99(0.7H, d, $J = 9.0$ Hz, H_{1b} (major)), 3.97(0.3H, d, $J = 9.0$ Hz, H_{1b} (minor)), 2.97-2.82(0.7H, cm, CH_2CO (major)), 2.76(0.6H, dd, $J = 7.0, 2.0$ Hz, $\text{CH}_2\text{C}=\text{O}$ (minor)), 2.78-2.66(1.7H, cm, $\text{CH}_2\text{C}=\text{O}$ (major) + H_{11a}), 2.63(1H, bs, H_{10}), 1.9-1.8(0.3H, cm, $\text{CHCH}_2\text{C}=\text{O}$ (minor)), 1.8(1H, bs, H_7), 1.6-1.4(5H, cm), 1.40-1.15(6H, cm), 1.15-1.05(2H, cm), 1.10(3H, s, CH_3), 0.96(0.9H, s, CH_3), 0.95(2.1H, s, CH_3 (minor)), 0.85-0.75(6H, cm, 2 x CH_3) ppm; ^{13}C NMR (62.9 MHz, CDCl_3) δ 174.1, 173.7(quat, $\text{RC}=\text{ON}$), 155.7(quat, oxazolidinone), 75.2, 75.1(quat, C-N), 70.6(CH_2O), 49.1(CH, C_{10}), 48.5(quat, $\text{C}(\text{CH}_3)_2$), 47.4(CH, C_7), 41.0, 38.2, 37.3, 35.7, 35.4 (CH_2 's), 29.1, 26.0(CH 's), 25.6(CH_3), 24.0, 22.5, 22.0(CH_2 's), 21.9(CH_3), 19.5(CH_2), 18.9, 14.2, 11.1, 10.5(CH_3 's) ppm

3.7.10 Copper (I) Catalysed Conjugate Addition of Methylmagnesium Bromide to Cinnamoyl Imide **226** in THF/Dimethylsulphide

Methylmagnesium bromide (3.0 mmol) in THF/dimethylsulphide (20ml, 1:1) was treated with copper(I)bromide:dimethylsulphide complex (610mg, 3.0 mmol) in dimethylsulphide (5ml) at 0°C . After 30 minutes the resulting green mixture was cooled to -78°C and **226** (320mg, 1.0 mmol) in THF (5ml) added over 10 minutes before warming to 0°C . Quenching and work up as for 3.7.3 [FUMEHOOD] gave a gum (340mg, 100%) which by integration of the H_{1b} ^1H NMR spectrum signal was shown to be a mixture of **311** (d, 3.63 ppm, $J = 9.0$ Hz) and its diastereomer **269** (d, 3.97 ppm, $J = 9.0$ Hz) in the ratio 2:1.

3.7.11 Attempted Conjugate Addition of Methylcopper to Diethylaluminium

Chloride Chelated Cinnamoyl Imide **226**

Copper(I)bromide:dimethylsulphide complex (1.03g, 5.0 mmol) in toluene (33ml) was treated with methyllithium (3.6ml, 1.4 M in ether, 5.0 mmol) at -40°C. After 20 minutes this was cooled to -78°C and diethylaluminium chloride (2.8ml, 1.8 M in toluene, 5.0 mmol) was added and after a further 20 minutes **226** (320mg, 1.0 mmol) in toluene (2ml) added dropwise. TLC showed no reaction at this temperature but after slowly warming to 0°C the reaction was complete in a further 20 minutes. Workup and isolation as for **3.7.2** gave a gum 360 mg, 100%) which was shown by ¹H- and ¹³C-NMR spectroscopy to consist of a mixture of the β-ethylated adducts **262** (H_{1a}, 4.07 ppm, d, *J* = 9.0 Hz) and **312** (H_{1a}, 4.21 ppm, d, *J* = 9.0 Hz) in the ratio 3:1.

3.7.12 Aldol Condensation of the *Z*(*O*) Dibutyl Boron Enolate of **267** with

Tetradecanal

Adduct **267** (2.92g, 10.0 mmol.) in dry dichloromethane (80ml) at -78°C under argon was treated with dibutyl boron triflate (11.0ml, 1.0 M in dichloromethane, 11.0 mmol.), then diisopropylethylamine (1.68g, 13.0 mmol.) in dichloromethane (3ml) was added dropwise and the reaction mixture allowed to warm to 0°C, then stirred for 30 minutes. The reaction was re-cooled to -78°C and treated with tetradecanal

(2.75g, 13.0 mmol.) in dichloromethane (15ml) and allowed to warm to room temperature and stirred for 14 hours. After quenching with saturated ammonium chloride solution the organic layer was separated and evaporated. The residue was dissolved in methanol (70ml) and treated with hydrogen peroxide (4ml, 30%) for 4 hours before being quenched with saturated sodium sulphite solution (40ml). After removal of methanol *in vacuo*, the aqueous was extracted with dichloromethane (4 x 50ml), dried, filtered and evaporated to give a thick yellow oil. This was chromatographed on silica (300g, C60, 40-60 μ m), gradient elution hexane/ether, 9:1 to 8:1 to give starting material (0.53g, 18%), further elution, 6:1 to 4:1 provided (5*R*, 7*R*, 10*S*) *N*-(2'*R*, 3'*S*)-2'-((*R*)- α -vinylehtyl)-3'-hydroxyhexadecanoyl-2-oxa-4-aza-6,6-dimethyl-7,10-methylenespiro[4.5]decan-3-one **313** (4.12g, 81.6%) as a colourless gum. $[\alpha]_D^{20} = -129.5^\circ$ ($c = 3.7$, dichloromethane); $R_f = 0.46$ (4:1, cyclohexane/ethylacetate); $^1\text{H NMR}$ (250 MHz, CDCl_3) δ 5.96(1H, ddd, $J = 17.0, 10.0, 8.0$ Hz, $\text{CH}=\text{CH}_2$), 5.05(1H, dt, $J = 17.0, 1.5$ Hz, $\text{CH}=\text{CH}_2$), 4.93(1H, dd, $J = 10.0, 1.5$ Hz, $\text{CH}=\text{CH}_2$), 4.26(1H, d, $J = 9.0$ Hz, H_{1a}), 4.08(1H, dd, $J = 7.5, 6.5$ Hz, $\text{CHC}=\text{O}$), 3.99(1H, d, $J = 9.0$ Hz, H_{1b}), 3.87(1H, cm, on D_2O shake-t, $J = 7.0$ Hz, CHOH), 2.84(1H, d, $J = 10.5$ Hz, H_{11a}), 2.71(1H, sextet, $J = 7.5$ Hz, $\text{CHCH}=\text{CH}_2$), 2.54(1H, bs, H_{10}), 2.09(1H, d, $J = 4.0$ Hz, lost on D_2O shake, OH), 1.83(1H, d, 1.5 Hz, H_7), 1.65-1.45(5H, cm), 1.22(24H, s & cm, CH_2 's & H_{11b}), 1.10(3H, s, CH_3), 1.06(3H, d, $J = 7.0$ Hz, CH_3CH), 0.99(3H, s, CH_3), 0.85(3H, t, $J = 6.5$ Hz, CH_3CH_2) ppm; $^{13}\text{C NMR}$ (62.9 MHz, CDCl_3) δ 173.9(quat, $\text{RC}=\text{ON}$), 156.6(quat, oxazolidinone $\text{C}=\text{O}$), 142.4($\text{CH}_2=\text{CH}$), 114.1($\text{CH}_2=\text{CH}$), 76.11(quat, C-N), 71.8(CHOH), 70.9(CH_2O), 53.2(CHCO), 49.6(CH, C_{10}), 46.9(quat, $\text{C}(\text{CH}_3)_2$),

44.6(CH, C₇), 38.4(CH₂, C₁₁), 37.1(CHCH=CH₂), 32.7, 31.7, 29.4. 29.1(CH₂'s), 26.2(CH₃), 26.0, 24.1, 22.5, 22.4(CH₂'s), 21.0(CH₃), 17.2(CH₃CH), 13.8(CH₃CH₂) ppm; **FT IR** (thin film) $\nu_{\max}$ 3498(OH *str*), 3080, 3042, 2925,(CH *str*), 1781(oxazolidinone C=O *str*), 1702(RC=ON *str*) cm⁻¹; **MS** (FAB) 504(5%, MH⁺), 486(10, MH⁺-H₂O), 399(12), 291(21), 196(50), 135(37) 107(38); **Accurate mass** (FAB) (MH⁺) Found 504.40476; C₃₁H₅₄NO₄ requires 504.40528.

3.7.13 Protection of Aldol Product 313 as its Trimethylsilyl Ether

Aldol product **313** (1.06g, 2.0 mmol) in ether (25ml) was treated with pyridine (280mg, 3.1 mmol) and trimethylsilyl chloride (280mg, 2.5 mmol) at 0°C then allowed to warm to room temperature. After 30 minutes TLC (neutral Al₂O₃, 9:1 hexane/ether) showed complete consumption of starting material and the reaction mixture was evaporated and the solvent replaced by hexane then filtered through a plug of neutral alumina (30g) eluting with hexane/ether 9:1. The crude oil obtained ((5*R*, 7*R*, 10*S*) *N*-(2'*R*, 3'*S*)-2'-((*R*)- α -vinylehtyl)-3'-trimethylsiloxyhexadecanoyl-2-oxa-4-aza-6,6-dimethyl-7,10-methylenespiro[4.5]decan-3-one **314** (1.15mg, 105% mass balance)) was used in the next reaction with out further purification or characterisation.

3.7.14 Reaction of the Trimethylsilyl Protected Aldol Product 314 with Lithium Benzyloxide

Benzylalcohol (660mg, 6.1 mmol) in dry THF (20ml) at -78°C under argon was treated with *n*-butyl lithium (1.25ml, 1.6 m.in hexane, 2.0 mmol). After 20 minutes **314** (1.15mg, crude, 2.0 mmol) in THF (5ml) was added and the reaction allowed to warm to room temperature. After 30 minutes, TLC showed no reaction, after 48 hours all starting material had been consumed to be replaced by eight different products, one of which appeared by TLC to be auxiliary, none were isolated or characterised.

3.7.15 Attempted Protection of Aldol Product 313 as its *t*-Butyldimethylsilyl

Ether using *t*-Butyldimethylsilyl chloride (TBDMSCl) and Imidazole

The aldol product **313** (1.07g, 2.0 mmol) in dry THF (5ml) was added to a stirred mixture of imidazole (280mg, 4.1 mmol) and TBDMSCl (310mg, 2.2 mmol) at -20°C and warmed to room temperature. The reaction was monitored by TLC, but even after one day at 35°C no reaction was observed. Quenching and standard aqueous work up provided starting material (1.10g, 100%)

3.7.16 Protection of Aldol Product 313 as its *t*-Butyldimethylsilyl Ether using *t*-Butyldimethylsilyltriflate (TBDMSOTf) and Triethylamine

The aldol product **313** (480mg, 0.95 mmol) in dry THF (15ml) at -78°C under argon was treated with TBDMSOTf (320mg, 1.1 mmol) in THF (2ml) followed by triethylamine (190mg, 1.9 mmol) in ether (2ml). The reaction was warmed to room temperature and after 1 hour TLC showed almost complete reaction (ca. 90%), after stirring over night no further change was seen. A further 0.2 equivalent of TBDMSOTf was added and after 2 hours TLC showed only a trace of starting material. The reaction was quenched with water and the THF evaporated, after the addition of water (20ml) the product was extracted into dichloromethane (2 x 30ml), washed with water, dried over magnesium sulphate and evaporated to give an oil which was chromatographed rapidly on a small silica column; eluent hexane/ether 9:1 to give (5*R*, 7*R*, 10*S*) *N*-(2'*R*, 3'*S*)-2'-((*R*)- α -vinylehtyl)-3'-*t*-butyldimethylsiloxyhexadecanoyl-2-oxa-4-aza-6,6-dimethyl-7,10-methylenespiro[4.5]decan-3-one **315** (560g, 96%) $[\alpha]_D^{20} = -98^\circ$ (c = 1.7, dichloromethane); $R_f = 0.82$ (9:1, hexane/ethylacetate); $^1\text{H NMR}$ (250 MHz, CDCl_3) δ 5.89(1H, ddd, $J = 17.0, 10.0, 8.5$ Hz, $\text{CH}=\text{CH}_2$), 5.00(1H, dq, $J = 17.0, 0.5$ Hz, $\text{CH}=\text{CH}_2$), 4.88(1H, dd, $J = 10.0, 2.0$ Hz, $\text{CH}=\text{CH}_2$), 4.23(1H, d, $J = 9.0$ Hz, H_{1a}), 4.03(1H, dd, $J = 9.0, 5.5$ Hz, $\text{CHC}=\text{O}$), 3.94(1H, d, $J = 9.0$ Hz, H_{1b}), 3.91(1H, cm, CHO), 2.94(1H, d, $J = 10.5$ Hz, H_{11a}), 2.58(1H, sextet, $J = 8.0$ Hz, $\text{CHCH}=\text{CH}_2$), 2.50(1H, bs, H_{10}), 1.84(1H, bs, H_7), 1.65-1.30(6H, cm), 1.23(22H, s, CH_2 's), 1.2-1.0(1H, cm), 1.10(3H, s, CH_3), 1.07(3H, d, $J = 7.0$ Hz, CH_3CH), 1.00(3H, s, CH_3),

0.86(12H, cm, (CH₃)₃C & CH₃CH₂), 0.05, 0.04(6H, 2 x s, Si(CH₃)₂) ppm; ¹³C NMR (62.9 MHz, CDCl₃) δ 174.2(quat, RC=ON), 156.0(quat, oxazolidinone C=O), 141.8(CH=CH₂), 114.3(CH=CH₂), 76.2(quat, C-N), 73.1(CHO), 70.9(CH₂O), 53.8(CHCO), 49.8(CH, C₁₀), 47.2(quat, C(CH₃)₂), 44.8(CH, C₇), 38.6(CHCH=CH₂), 38.5(CH₂, C₁₁), 33.3, 31.8, 29.8, 29.6, 29.5, 29.2(CH₂'s), 26.5(CH₃), 25.94(C(CH₃)₃), 24.2, 22.6, 22.6(CH₂'s), 21.3(CH₃), 18.3(CH₃CH), 18.0(quat, SiC(CH₃)₃), 14.0(CH₃CH₂), -4.1, -4.7(Si(CH₃)₂) ppm; FT IR (thin film) ν_{max} 2925(CH), 17.86(oxazolidinone C=O), 1703.5(RC=ON), 1641(C=C) cm⁻¹; MS (FAB) 618(2%, M⁺-H), 602(2), 560(9), 486(9), 423(7), 365(8), 327(34), 291(17), 252(11), 196(12).

3.7.17 Attempted Cleavage of the *t*-Butyldimethylsilyl Protected Aldol

Producted 315 with Lithium Benzyloxide

Benzylalcohol (250mg, 2.3 mmol) in dry THF (20ml) at -78°C under argon was treated with *n*-butyl lithium (0.53ml, 1.6 m.in hexane, 0.85 mmol). After 20 minutes TBDMS ether **315** (450mg, 0.75 mmol) in THF (5ml) was added and the reaction warmed to room temperature. TLC after 1 hour showed no reaction. Finally after 36 hours TLC showed a very faint trace (<<10%) of a very slow running product to be present. This was not auxiliary and was later tentatively identified by TLC comparison to be the amido-alcohol **316** presumably formed due to ingress of water during the long reaction period. The reaction was quenched and starting material recovered.

3.7.18 Attempted Cleavage of the Unprotected Aldol Product 313 using Lithium Hydroperoxide

Aldol product **313** (100mg, 0.2 mmol) in THF (6ml) was treated with hydrogen peroxide (0.16ml, 30%, 1.6 mmol) in water (1ml) and lithium hydroxide (17mg, 0.4 mmol) in water (1ml) after stirring for 12 hours no reaction was observed by TLC. A similar quantity of lithium hydroxide and hydrogen peroxide were added but after a further 18 hours no reaction had occurred. The reaction was heated under reflux for 3 hours, after which TLC showed that starting material had been completely consumed, a single very slow running spot had formed and no auxiliary was observed. The solvent was evaporated, water (5ml) added and after acidification with 6M hydrochloric acid the product was extracted into ether (2 x 20ml). The extract was washed with water, brine, dried, filtered and evaporated to give a gum which was chromatographed on silica, eluent hexane/ether, 2:1 + 2% acetic acid to give a gum (90mg, 92%) identified as *(1S, 2R)-N-(2'R, 3'S)-2'-((R)-α-vinylehtyl)-3'-hydroxyhexadecanoyl-2' amino 3,3-dimethyl-bicyclo[2.2.1]heptane-2-methanol* **316** $[\alpha]_D^{20} = -6.4^\circ$ (c = 2.5, dichloromethane); $R_f = 0.52$ (1:2, cyclohexane/ethylacetate); $^1\text{H NMR}$ (250 MHz, CDCl_3) δ 5.98(1H, ddd, $J = 17.5, 10.5, 7.5$ Hz, $\text{CH}=\text{CH}_2$), 5.78(1H, s, NH), 5.07(1H, dt, $J = 17.5, 1.5$ Hz, $\text{CH}=\text{CH}_2$), 5.01(1H, dq, $J = 10.5, 1.0$ Hz, $\text{CH}=\text{CH}_2$), 4.04(1H, d, $J = 11.5$ Hz, H_{1a}), 3.80(1H, dd, $J = 12.0, 7.0$ Hz, CHOH), 3.75(1H, d, $J = 11.5$ Hz, H_{1b}), 3.3(2H, b, OH), 2.66(1H, sextet, $J = 7.0$ Hz, $\text{CHCH}=\text{CH}_2$), 2.54(1H, d, $J = 2.5$ Hz, H_{10}), 2.16(1H, dd, $J = 7.5, 5.0$ Hz, $\text{CHC}=\text{O}$), 1.80-1.77(2H, overlapped dm & bs, H_{11} & H_7), 1.60-1.30(5H, cm), 1.21(24H, CH_2 's

& 2H), 1.06(3H, d, $J = 7.0$ Hz, $\underline{\text{C}}\text{H}_3\text{CH}$), 1.06(3H, s, CH_3), 0.97(3H, s, CH_3), 0.83(3H, t, $J = 7.0$ Hz, $\underline{\text{C}}\text{H}_3\text{CH}_2$) ppm; ^{13}C NMR (62.9 MHz, CDCl_3) δ 173.1(quat, $\text{RC}=\text{ON}$), 141.9($\underline{\text{C}}\text{H}=\text{CH}_2$), 114.4($\text{CH}=\underline{\text{C}}\text{H}_2$), 71.5(CHOH), 68.4(quat, $\text{C}-\text{N}$), 61.3(CH_2OH), 58.6($\underline{\text{C}}\text{HC}=\text{O}$), 50.2(CH , C_{10}), 45.5(quat, $\underline{\text{C}}(\text{CH}_3)_2$), 44.1(CH , C_7), 35.5($\underline{\text{C}}\text{HCH}=\text{CH}_2$), 34.6, 33.4, 31.7, 29.5, 29.4, 29.2(CH_2 's), 26.9(CH_3), 26.3, 22.9, 22.8, 22.5(4 x CH_2), 21.1(CH_3), 17.9($\underline{\text{C}}\text{H}_3\text{CH}$), 14.0($\underline{\text{C}}\text{H}_3\text{CH}_2$) ppm; FT IR (thin film) ν_{max} 3380(OH, NH), 2925(CH), 1745($\text{C}=\text{O}$), 1646($\text{C}=\text{C}$) cm^{-1} ; MS (FAB) 479(26%, MH_2^+), 477(14, M^+), 309(23), 196(22), 135(36), 107(39); Accurate mass (FAB)(MH^+) Found 478.42592, $\text{C}_{30}\text{H}_{56}\text{NO}_3$ requires 478.42602.

3.7.19 Acetylation of Aldol Product 313

Aldol product **313** (3.93g, 7.81 mmol) in hexane (60ml) was treated successively with triethylamine (1.20g, 11.2 mmol), *N,N*-dimethylaminopyridine (72mg, 0.6 mmol), and freshly distilled acetic anhydride (1.20g, 11.2 mmol) and stirred protected from atmospheric moisture for 12 hours. TLC indicated complete reaction, 1 M hydrochloric acid (20ml) was added and the mixture stirred for 2 minutes before being separated then extracted with hexane (2 x 30ml). The organics were washed twice with water, then sodium bicarbonate and finally brine (all 20ml) before being dried, filtered and evaporated. The crude yellow oil so obtained was rapidly chromatographed on silica, eluent hexane/ether 6:1 to yield (5*R*, 7*R*, 10*S*) *N*-(2'*R*, 3'*S*)-2'-((*R*)- α -vinylehtyl)-3'-acetoxyhexadecanoyl-2-oxa-4-aza-6,6-dimethyl-7,10-methylenespiro[4.5]decan-3-one **317** as a colourless gum which slowly crystallised

(4.26g, 99%); MP = 47.7-49.0°C (neat); $[\alpha]_D^{20} = -121.5^\circ$ (c = 1.9, dichloromethane); $R_f = 0.63$ (4:1, cyclohexane/ethylacetate); $^1\text{H NMR}$ (250 MHz, CDCl_3) δ 5.81(1H, ddd, J 17.0, 10.5, 8.0 Hz, $\text{CH}=\text{CH}_2$), 5.21(1H, ddd, J = 11.0, 5.5, 2.0 Hz, CHO), 4.90(1H, ddd, J = 17.0, 1.5, 1.0 Hz, $\text{CH}=\text{CH}_2$), 4.89(1H, ddd, J = 10.5, 1.5, 1.0 Hz, $\text{CH}=\text{CH}_2$), 4.29(1H, d, J = 9.0 Hz, H_{1a}), 4.26(1H, dd, J = 9.0, 5.5 Hz, $\text{CHC}=\text{O}$), 3.97(1H, d, J = 9.0 Hz, H_{1b}), 2.85(1H, dm, J = 10.5 Hz, H_{11a}), 2.65(1H, sextet, J = 8.0 Hz, $\text{CHCH}=\text{CH}_2$), 2.56(1H, bs, H_{10}), 1.98(3H, s, CH_3COO), 1.84(1H, bs, H_7), 1.69-1.44(4H, cm), 1.35-1.10(3H, cm), 1.22(22H, CH_2 's), 1.10(3H, s, CH_3), 1.07(3H, d, J = 7.0 Hz, CH_3CH), 0.98(3H, s, CH_3), 0.85(3H, t, J = 6.5 Hz, CH_3CH_2) ppm; $^{13}\text{C NMR}$ (62.9 MHz, CDCl_3) δ 172.6(quat, $\text{RC}=\text{ON}$), 169.9(quat, $\text{CH}_3\text{C}=\text{OO}$), 156.0(quat, oxazolidinone $\text{C}=\text{O}$), 141.8($\text{CH}=\text{CH}_2$), 114.2($\text{CH}=\text{CH}_2$), 76.2(quat, C-N), 72.9(CHO), 70.9(CH_2O), 50.4($\text{CHC}=\text{O}$), 49.6(CH, C_{10}), 47.0(quat, $\text{C}(\text{CH}_3)_2$), 44.8(CH, C_7), 38.4(CH_2 , C_{11}), 36.9($\text{CHCH}=\text{CH}_2$), 31.8, 30.0, 29.5, 29.4, 29.2(CH_2 's), 26.2(CH_3), 25.7, 24.3, 22.6, 22.5(4 x CH_2), 21.0, 20.8(CH_3 & $\text{CH}_3\text{C}=\text{OO}$), 17.0(CH_3CH), 14.0(CH_3CH_2) ppm; **FT IR** (thin film) ν_{max} 1785(oxazolidinone $\text{C}=\text{O}$), 17434(acetate $\text{C}=\text{O}$), 1704($\text{RC}=\text{ON}$), 1639($\text{C}=\text{C}$) cm^{-1} ; **MS** (FAB) 547(8%, MH_2^+), 545(6%, M^+), 487(31, $\text{MH}_2^+ - \text{CH}_3\text{CO}_2\text{H}$), 291(38), 196(27), 135(36), 107(39); **Accurate mass** (FAB) (MH^+) Found 546.41887; $\text{C}_{33}\text{H}_{56}\text{NO}_3$ requires 546.41585; **Elemental analysis**, Found 72.76% C, 9.67% H, 2.56% N, $\text{C}_{33}\text{H}_{55}\text{NO}_5$ requires 72.62% C, 10.16% H, 2.57% N.

3.7.20 Phase Transfer Catalysed Permanganate Oxidation of Acetate Protected

Aldol Product 31

Alkene 317 (0.95g, 1.74 mmol) in benzene (20ml) and acetic acid (8ml) was treated with potassium permanganate (2.20g, 14.0 mmol) in water (14ml) and tetrabutylammonium bromide (40mg, 7 mol%) added. The mixture was stirred rapidly and heated to 60°C, TLC (1:2 cyclohexane/ethylacetate + 1% acetic acid) of a sodium sulphite quenched aliquot removed after 30 minutes indicated complete consumption of starting material. The reaction was cooled to room temperature and quenched by the addition of solid sodium sulphite until both phases became colourless. The product was extracted into hexane (2 x 30ml), washed with water (5 x 30ml) then brine, dried over magnesium sulphate, filtered and evaporated. The resulting gum was chromatographed on silica (60g), gradient elution hexane/ether/acetic acid 80:20:0, 75:25:1, 66:33:1. The eluent was evaporated to a volume of 50ml, then washed with water (4 x 30ml), then brine, dried, filtered and evaporated to yield (5*R*, 7*R*, 10*S*) *N*-(2'*R*, 3'*S*)-2'-((*R*)- α -carboxyethyl)-3'-acetoxylhexadecanoyl-2-oxa-4-aza-6,6-dimethyl-7,10-methylenespiro[4.5]decan-3-one 318 as a colourless glass (770mg, 79%); $[\alpha]_D^{20} = -98.2^\circ$ ($c = 2.0$, dichloromethane); $R_f = 0.41$ (2:1, cyclohexane/ethylacetate + 2% AcOH) ^1H NMR (250 MHz, CDCl_3) δ 5.14(1H, cm, CHO), 4.53(1H, dd, $J = 9.5, 4.5$ Hz, CHC=O), 4.31(1H, d, $J = 9.0$ Hz, H_{1a}), 4.04(1H, d, $J = 9.0$ Hz, H_{1b}), 2.95(1H, dq, $J = 9.5, 7.5$ Hz, CHCO_2H), 2.81(1H, dm, $J = 10.0$ Hz, H_{11a}), 2.53(1H, bs, H_{10}), 2.01(3H, s, $\text{CH}_3\text{C=OO}$), 1.85(1H, bs, H_7), 1.60-1.37(6H, cm), 1.31(3H, d, $J = 7.5$ Hz, CH_3CH),

1.40-1.10(22H, s, CH₂'s & 3H, cm), 1.12(3H, s, CH₃), 0.96(3H, s, CH₃), 0.85(3H, t, $J = 6.5$ Hz, CH₃CH₂) ppm; ¹³C NMR (62.9 MHz, CDCl₃) δ 180.5(quat, CO₂H), 173.2(quat, RC=ON), 170.2(quat, CH₃C=OO), 155.7(quat, oxazolidinone C=O), 76.3(quat, C-N), 71.6(CHO), 70.9(CH₂O), 49.6, 48.6(2 x CH, $\underline{\text{C}}\text{HC}=\text{O}$ & C₁₀), 47.3(quat, $\underline{\text{C}}(\text{CH}_3)_2$), 44.7(CH, C₇), 38.6($\underline{\text{C}}\text{HCO}_2\text{H}$), 38.5(CH₂, C₁₁), 31.8, 30.7, 29.5, 29.4, 29.3, 29.2, 29.1, 25.8(CH₂'s), 25.5(CH₃), 24.3, 22.5(2 x CH₂, C₈ & C₉), 21.0, 20.6(CH₃ & $\underline{\text{C}}\text{H}_3\text{C}=\text{OO}$), 14.5, 14.0($\underline{\text{C}}\text{H}_3\text{CH}_2$ & $\underline{\text{C}}\text{H}_3\text{CH}$) ppm; FT IR (thin film) ν_{max} 3250(b, CO₂H), 2926(CH), 1791(b, CO₂H & oxazolidinone C=O), 1742(CH₃C=OO), 1713(d, RC=ON), 1465, 1386, 1281, 1228 cm⁻¹; MS (FAB) 565(34%, MH₂⁺), 505(88%, MH₂⁺-CH₃CO₂H), 196(100), 135(71); **Accurate mass** (FAB) (MH⁺) Found 564.38988; C₃₂H₅₄NO₇ requires 564.39003.

3.7.21 Cleavage of Acetate Protected Acid 318 by Lithium Hydroperoxide;

Preparation of (-)-Dihydroprotolichesterinic Acid (-)-278

The acetate protected acid (-)-278 (740 mg, 1.3 mmol) in THF (15ml) was treated with hydrogen peroxide (10ml, 30%, ~100 mmol, 16 equiv. per lithium hydroxide) and finely powdered lithium hydroxide (270mg, 6.6 mmol) added. After stirring for 5 days at room temperature starting material was completely consumed. TLC (2:1 CE + 1% acetic acid) of an acid quenched aliquot showed auxiliary and a slow running component to be present. The reaction was quenched by slow addition to a stirred solution of sodium sulphite (13g) in water (150ml) at 0°C then saturated sodium carbonate (20ml) added and the THF removed *in vacuo* [large volume flask

required due to foaming]. The resulting aqueous was extracted with ether (3 x 50ml) the organics dried and evaporated to yield (-)-**207** (230mg, 91%). The aqueous was acidified with 6M hydrochloric acid to pH 2 and extracted into dichloromethane (3 x 60ml), washed with water (100ml), brine (50ml), dried, filtered and evaporated to yield a colourless crystalline solid (110% mass balance). High field ^1H and ^{13}C NMR spectroscopy showed that some of the other isomers were present but to an extent of less than 5%. A yield of 95% was assigned and the product identified as (-)-dihydroprotolichesterinic acid, (3*S*, 4*R*, 5*S*)-4-carboxy-3-methyl-5-tridecyl-oxolan-2-one (-)**278** MP= 105.1-105.8°C (from hexane/cyclohexane) [*Lit.* MP = 106°C]¹⁵⁰; $[\alpha]_{\text{D}}^{20} = -53.0^\circ$ (c = 1.75, CHCl₃) [*Lit.* $[\alpha]_{\text{D}}^{20} = -49.5^\circ$ (c = 1.75, CHCl₃)]¹³²; ^1H NMR (250 MHz, CDCl₃) δ 9.44(1H, broad, CO₂H), 4.68(1H, q, *J* = 6.5 Hz, H₅), 3.14(1H, dd, *J* = 9.5, 6.0 Hz, H₄), 3.01(1H, dq, *J* = 9.5, 7.5 Hz, H₃), 1.66(2H, cm, CH₂CHO), 1.46(2H, cm, CH₂CH₂CHO), 1.28(3H, d, *J* = 7.5 Hz, CH₃CH), 1.23(20H, s, CH₂'s), 0.86(3H, t, *J* = 6.5 Hz, CH₃CH₂), ppm; ^{13}C NMR (62.9 MHz, CDCl₃) δ 177.2, 175.6(q's, CO₂H & CO₂R), 79.3(CH, C₅), 49.7(CH, C₄), 36.8(CH, C₃), 34.5, 31.8, 29.5, 29.5, 29.5, 29.4, 29.3, 29.2, 29.1, 25.2, 22.6(CH₂'s), 14.0, 11.6(2 x CH₃) ppm; FT IR (CCl₄) ν_{max} 2990(b, COO-H *str*), 2960, 2920, 2851(CH *str*), 1743(C=O), 1713(C=O), 1552, 1240 cm⁻¹; MS (FAB) 654(65%, dimer 2H⁺), 653(26, dimer H⁺), 327(100, MH⁺), 309(24, MH⁺-18), 292(26), 281(19), 283(17), 263(10), 217(12).

3.7.22 Aldol Condensation of the *Z*(*O*) Dibutyl Boron Enolate of **269** with

Tetradecanal

The Michael adduct **269** (1.03g, 3.02 mmol) in dry dichloromethane (50ml) at -78°C under argon was treated with dibutylborontriflate (3.3ml, 1.0 M in dichloromethane, 3.3 mmol) then diisopropylethylamine (0.56g, 4.34 mmol) in dichloromethane (4ml) as for **3.7.12**. Tetradecanal (830mg, 3.93 mmol) in dichloromethane (10ml) was added at -78°C and after 14 hours TLC showed that reaction had ceased. Work up as for **3.7.12** provided a yellow gum which partially crystallised (starting material), this was chromatographed on silica (100g, C60, 40-60mm) eluting hexane/ether 9:1, 6:1 to provide starting material (280g, 27%), then 4:1, 3:1 to furnish (5*S*, 7*S*, 10*R*) *N*-(2'*S*, 3'*R*)-2'-((*R*)- α -methylbenzyl)-3'-hydroxyhexadecanoyl-2-oxa-4-aza-6,6-dimethyl-7,10-methylenespiro[4.5]decan-3-one **320** (1.18g, 71%) as a colourless gum; $[\alpha]_D^{20} = +72.3^\circ$ ($c = 2.7$, dichloromethane); $R_f = 0.43$ (4:1, cyclohexane/ethylacetate); ^1H NMR (250 MHz, CDCl_3) δ 7.30-7.15(4H, cm, Ph), 7.09-7.03(1H, cm, Ph), 4.88(1H, dd, $J = 11.0, 5.0$ Hz, $\text{CHC}=\text{O}$), 4.14(1H, d, $J = 9.0$ Hz, H_{1a}), 4.07(1H, ddm, $J = 7.5, 4.5$ Hz, CHOH), 3.94(1H, d, $J = 9.0$ Hz, H_{1b}), 3.18(1H, dq, $J = 11.0, 7.0$ Hz, PhCH), 2.55-2.50(2H, s & d overlapped, H_{10} & H_{11a}), 2.11(1H, bs, OH), 1.62(1H, bs, H_7), 1.71-1.04(10H, cm), 1.23(22H, bs, CH_2 's), 0.93(3H, s, CH_3), 0.85(3H, t, $J = 6.5$ Hz, CH_3CH_2), 0.12(3H, s, CH_3) ppm; ^{13}C NMR (62.9 MHz, CDCl_3) δ 173.1(quat, $\text{RC}=\text{ON}$), 157.0(quat, oxazolidinone $\text{C}=\text{O}$), 145.6(quat, Ph), 128.2 (2 x CH, Ph), 127.7(2 x CH, Ph), 126.0 (CH, Ph), 76.0 (quat, C-N), 71.9(CHOH), 70.6(CH_2O), 53.88($\text{CHC}=\text{O}$), 49.3(CH, C_{10}), 46.7(quat, $\text{C}(\text{CH}_3)_2$), 44.7(CH, C_7), 39.0(PhCH),

38.4(CH₂, C₁₁), 31.8, 31.1, 29.5, 29.4, 29.22, 26.6(CH₂'s), 24.5(CH₃), 24.1, 22.5(1 & 2 x CH₂), 20.8, 20.1(CH₃ & CH₃CH), 14.0 (CH₃CH₂) ppm; **FT IR** (thin film) $\nu_{\max}$ 3491(OH), 3032, 2924, 2852(CH), 1778, 1763(oxazolidinone C=O), 1702(RC=ON), 1457, 1360, 1283 cm⁻¹; **MS** (FAB) 554(3%, MH⁺), 536(13, MH⁺-H₂O), 341(42, retro-aldol), 196(43), 131(36), 105(77), 91(57, C₇H₇⁺); **Accurate mass** (FAB) (MH⁺) Found : 554.4180; C₃₅H₅₆NO₄ requires 554.4209.

3.7.23 Acetylation of Aldol Product 320

Aldol product **320** (1.04g, 1.88 mmol) in hexane (40ml) was treated as **3.7.19** with triethylamine (285mg, 2.8 mmol), DMAP (18mg, 0.09 mmol) and acetic anhydride (270mg, 2.7 mmol). After 30 minutes TLC indicated that the reaction was complete (single product) and work up as for **3.7.19** provided (5*S*, 7*S*, 10*R*) *N*-(2'*S*, 3'*R*)-2'-((*R*)- α -methylbenzyl)-3'-acetoxyhexadecanoyl-2-oxa-4-aza-6,6-dimethyl-7,10-methylenespiro [4.5]decan-3-one **321** as a colourless crystalline solid (1.10g, 99%) which recrystallised from hexane (0.88g, 80% recovery) **MP**= 105.7-106.4°C (from hexane); $[\alpha]_D^{20} = +115.3^\circ$ (c = 1.9, dichloromethane); **R_f** = 0.57 (4:1, cyclohexane/ethylacetate); **¹H NMR** (250 MHz, CDCl₃) δ 7.27-7.14(4H, cm Ph), 7.09-7.02(1H, cm, Ph), 5.38(1H, ddd, *J* = 11.0, 4.0, 2.0 Hz, CHOH), 4.84(1H, dd, *J* = 11.0, 4.0 Hz, CHC=O), 4.20(1H, d, *J* = 9.0 Hz, H_{1a}), 3.91(1H, d, *J* = 9.0 Hz, H_{1b}), 3.15(1H, dq, *J* = 11.0, 7.0 Hz, PhCH), 2.57-2.53(2H, cm, H₁₀ & H_{11a}), 2.00(3H, s, CH₃CO₂), 1.72(1H, cm), 1.64(1H, bs, H₇), 1.51-1.08(7H, cm), 1.30(3H, d, *J* = 7.0 Hz, CH₃CH), 1.23(22H, s, CH₂'s), 0.94(3H, s, CH₃), 0.86(3H, t, *J* = 6.5 Hz,

CH₃CH₂), 0.13(3H, CH₃) ppm; ¹³C NMR (62.9 MHz, CDCl₃) δ 171.9(quat, RC=ON), 169.9(quat, CH₃C=OO), 155.8(quat, oxazolidinone C=O), 145.33(quat, Ph), 128.1(2 x CH, Ph), 127.5(2 x CH, Ph), 75.9(quat, C-N), 72.7(CHO), 70.6(CH₂O), 51.0(CHC=O), 49.3(CH, C₁₀), 46.7(quat, C(CH₃)₂), 44.7(CH, C₇), 39.0(PhCH), 38.3(CH₂, C₁₁), 31.7, 29.5, 29.4, 29.2, 29.1, 29.0(CH₂'s), 24.4(CH₃), 24.1, 22.5(1 & 2 x CH₂), 20.8, 20.7, 19.9(3 x CH₃), 14.0(CH₃CH₂) ppm; FT IR (CCl₄) ν_{max} 2925, 2855(CH), 1787(oxazolidinone C=O), 1740(acetate C=O), 1701(RC=ON) cm⁻¹; MS (FAB) 596(2%, MH⁺), 554(5), 536(30, MH⁺-60), 432(5), 341(55), 196(30), 135(30) 131(48), 107(37); **Accurate mass** (FAB) (MH⁺) Found 596.42926; C₃₇H₅₈NO₅ requires 596.43150; **Elemental analysis**, Found 74.50% C, 9.70% H, 2.36% N, C₃₇H₅₇NO₅ requires 74.58% C, 9.64% H, 2.35% N.

3.7.24 Ruthenium Catalysed Oxidation of Acetate Protected Aldol Product 321

The protected aldol product **321** (2.84g, 5.14 mmol) in CCl₄ (12ml) was added to a stirred suspension of sodium periodate (15.9g, 75 mmol) in acetonitrile/water (12ml of each), followed by ruthenium trichloride (60mg, 0.3 mmol) and the mixture heated at 40°C. After 8 hours TLC (2:1 cyclohexane/ethyl acetate + 1% acetic acid) showed that the reaction was complete; the mixture was acidified to pH 2 then the product extracted into ether/hexane (1:1, 3 x 50 ml). The organics were washed with water, brine, dried, filtered and evaporated to give a green oil. This was chromatographed on silica (100g), eluting hexane/ether/acetic acid 80:20:0, 75:25:1, 66:33:1 to give a hard colourless glass (2.11g, 73%) identified as (5*S*, 7*S*, 10*R*) *N*-(2'*S*, 3'*R*)-2'-((*S*)-α-

carboxyethyl)-3'-*acetoxyhexadecanoyl*-2-*oxa*-4-*aza*-6,6-*dimethyl*-7,10-

methylenespiro [4.5]*decan*-3-one (+)-**318** $[\alpha]_D^{20} = +97.2^\circ$ (c = 2.2, dichloromethane); other physical data as for the enantiomer **318**.

3.7.25 Cleavage of Acetate Protected Acid (+)-**318**

The acetate protected acid (+)-**318** (830mg, 1.47 mmol) in THF (15ml) was treated with hydrogen peroxide (15ml, 30%, ~100 mmol, 20 equiv. per lithium hydroxide) and finely powdered lithium hydroxide (310mg, 7.5 mmol) added. After stirring for 6 days at room temperature starting material was completely consumed, though a number of products had apparently formed. Quenching of the peroxide with 5% palladium on alumina (~100mg), and work up as for 3.7.21 gave an off-white solid (510mg, 106% mass balance). High field ^1H and ^{13}C NMR spectroscopy showed this to be a mixture of dihydroprotolichesterinic **278** (q, 4.67 ppm) acid and roccellaric acid **277** (dq, 4.45), in the ratio (4:1) together with some minor unidentified impurities.

3.7.26 Methylation and Subsequent Separation of Mixed Lactones **278** and **277**

The above mixture of lactones (460mg, 1.41mmol) in methanol (20ml) and ether (10ml) was treated at 0°C with diazomethane (from *N*-nitrosomethylurea (1.2g, 12 mmol) and potassium hydroxide (5ml of 50%) in ether (20ml)) until a persistent yellow colour developed. After 30 minutes excess diazomethane was removed with

a vigorous stream of argon, the solution evaporated and the residue chromatographed on silica; hexane:ether 20:1 to 9:1 to give roccellaric acid methyl ester *methyl-(3S, 4S, 5R)-4-carboxy-3-methyl-5-tridecyl-oxolan-2-one (+)-322* (40mg, 8%) $[\alpha]_{\text{D}}^{20} = +26.0^{\circ}$ (c = 2.5, CHCl₃) [Lit. $[\alpha]_{\text{D}}^{20} = +23$ (c = 1.5)]¹³²; $R_f = 0.49$ (4:1, cyclohexane/ethylacetate); ¹H NMR (250 MHz, CDCl₃) δ 4.40(1H, ddd, $J = 9.5, 8.0, 4.5$ Hz, H₅), 3.73(3H, s, OCH₃), 2.91(1H, dt, $J = 11.5, 7.0$ Hz, H₃), 2.61(1H, dd, $J = 11.5, 9.5$ Hz, H₄), 1.67(2H, cm), 1.28(3H, d, $J = 7.0$ Hz, CH₃CH), 1.21(22H, bs, CH₂'s), 0.83(3H, t, $J = 7.0$ Hz, CH₃CH₂) ppm; ¹³C NMR (62.9 MHz, CDCl₃) δ 176.6(quat, lactone C=O), 171.0(quat, C=OOCH₃), 79.3(CH, C₅), 53.9(CH, C₄), 52.4(OCH₃), 39.7(CH, C₃), 36.9, 34.7, 31.7, 29.4, 29.3, 29.2, 29.1, 29.0, 25.1, 22.5(CH₂'s), 14.2, 13.9(2 x CH₃) ppm; FT IR (thin film) ν_{max} 2928, 2852(CH), 1783, 1740(C=O), 1457, 1436, 1256, 1171, 1003 cm⁻¹; MS (FAB) 341(100%, MH⁺), 326(21), 281(46).

Further elution provided (+)-dihydroprotolichesterinic acid *methyl-(3R, 4S, 5R)-4-carboxy-3-methyl-5-tridecyl-oxolan-2-one (+)-323* (290mg, 60%) $[\alpha]_{\text{D}}^{20} = +48.6^{\circ}$ (c = 1.4, CHCl₃) [Lit. $[\alpha]_{\text{D}}^{20} = -47^{\circ}$ (c = 0.64, CHCl₃)]¹³²; $R_f = 0.42$ (4:1, cyclohexane:ethylacetate); ¹H NMR (250 MHz, CDCl₃) δ 4.65(1H, q, $J = 6.5$ Hz, H₅), 3.70(3H, s, OCH₃), 3.08(1H, dd, $J = 9.0, 6.0$ Hz, H₄), 2.93(1H, dq, $J = 9.0, 7.5$ Hz, H₃), 1.60(2H, cm), 1.21(22H, bs, CH₂'s), 1.17(3H, d, $J = 7.5$ Hz, CH₃CH), 0.83(3H, t, $J = 7.0$ Hz, CH₃CH₂) ppm; ¹³C NMR (62.9 MHz, CDCl₃) δ 177.1(quat, lactone C=O), 170.4(quat, C=OOCH₃), 79.3(CH, C₅), 51.9(OCH₃), 49.8(CH, C₄), 36.9(CH, C₃), 34.5, 31.7, 29.4, 29.3, 29.2, 29.1, 29.0, 25.2, 22.5(CH₂'s),

13.9($\underline{\text{CH}_3\text{CH}_2}$), 11.7($\underline{\text{CH}_3\text{CH}}$) ppm; **FT IR** (CCl_4) ν_{max} 2932, 2855(CH), 1784(C=O), 1742(C=O), 1464, 1438, 1203, 989 cm^{-1} ; **MS** (FAB) 682(Dimer, M_2H_2^+), 341(100%, MH^+), 325(45), 309(44), 295(47), 281(46).

3.7.27 Preparation of Pent-4-enoyl Imide of 324 via Diethyl Zinc Deprotonation

A suspension of auxiliary (-)-**207** (3.30g, 16.9 mmol), in ether (130 ml) at room temperature under argon was treated with diethyl zinc (18.0ml, 1.0 M in hexanes, 18.0 mmol) and stirred for 45 minutes. After cooling to -78°C the solution was treated with pent-4-enoyl chloride (6.0g, 60 mmol, in 4ml ether) (freshly prepared by boiling pent-4-enoic acid (5.0g, 50mmol) and thionyl chloride (8.0g, 67 mmol) for 30 minutes and distilling (6.0g, 100%, **BP.** 120-125 $^\circ\text{C}$)) and the reaction allowed to warm to room temperature. After 5 hours ($\sim 15^\circ\text{C}$) the reaction was seen to be nearly complete, after a further 2 hours at 25°C TLC showed no starting material and a single product spot. The reaction was quenched and worked up as for **3.2.6** to provided a colourless oil. This was chromatographed on silica, eluting hexane/ether 8:1, 4:1 to give (5*R*, 7*R*, 10*S*)-*N*-pent-4-enoyl-2-oxa-4-aza-6,6-dimethyl-7,10-methylenespiro[4.5]decan-3-one **324** as a oil (4.95g, 105% mass balance); $[\alpha]_{\text{D}}^{20} = -92.7^\circ$ ($c = 3.5$, dichloromethane); $R_f = 0.47$ (4:1, cyclohexane/ethylacetate); **^1H NMR** (250 MHz, CDCl_3) δ 5.82(1H, ddt, $J = 17.0, 10.0, 6.5$ Hz, $\underline{\text{CH}}=\text{CH}_2$), 5.04(1H, dq, $J = 17.0, 2.0$ Hz, $\text{CH}=\underline{\text{CH}_2}$), 4.96(1H, ddt, $J = 10.0, 2.0, 1.5$ Hz, $\text{CH}=\underline{\text{CH}_2}$), 4.29(1H, d, $J = 9.0$ Hz, H_{1a}), 4.01(1H, d, $J = 9.0$ Hz, H_{1b}), 3.05(1H, ddd, $J = 17.0, 8.0, 7.0$ Hz, $\text{CH}_2\text{C=O}$), 2.89(1H, ddd, $J = 17.0, 7.5, 7.0$ Hz, $\text{CH}_2\text{C=O}$), 2.72(1H, dm, $J = 10.5$ Hz,

H_{11a}), 2.65(1H, d, $J = 1.5$ Hz, H₁₀), 2.43-2.29(2H, cm, CH₂CH=CH₂), 1.82(1H, d, $J = 1.5$ Hz, H₇), 1.60-1.42(3H, cm), 1.28(1H, dt, $J = 10.5, 1.5$ Hz, H_{11b}), 1.20-1.08(1H, cm), 1.12(3H, s, CH₃), 0.96(3H, s, CH₃) ppm; ¹³C NMR (62.9 MHz, CDCl₃) δ 173.2(quat, RC=ON), 155.8(quat, oxazolidinone C=O), 136.9(CH=CH₂), 115.2(CH=CH₂), 75.2(quat, C-N), 70.7(CH₂O), 49.1(CH, C₁₀), 47.5(quat, C(CH₃)₂), 45.0(CH, C₇), 38.2(CH₂, C₁₁), 36.3(CH₂C=O), 28.4(CH₂CH=CH₂), 25.7(CH₃), 24.0, 22.6(2 x CH₂, C₈ & C₉), 21.1(CH₃) ppm; FT IR (thin film) $\nu_{\max}$ 3040(alkenic CH), 2964(CH), 1782(oxazolidinone CH), 1707(RC=ON), 1643(C=C), 1367, 1288, 1205, 1072 cm⁻¹; MS (FAB) 278(38%, MH⁺), 196(57), 173(38), 135(55), 107(51); **Accurate mass** (FAB) (MH⁺) Found 278.17424; C₁₆H₂₄NO₃ requires 278.17562.

3.7.28 Aldol Condensation of the *Z*(*O*) Dibutylboron Enolate of Pent-4-enoyl

Imide 324 with Tetradecanal

A solution of pent-4-enoyl imide **324** (3.92g, 14.2 mmol) in dry dichloromethane (100ml) was treated as in 3.7.12 with dibutylboron triflate (15.6ml, 1.0 M in dichloromethane, 15.6 mmol) and di-isopropylethylamine (2.38g, 18.5 mmol) in dichloromethane (3ml), followed by tetradecanal (4.0g, 18.9 mmol) in dichloromethane (20ml) at -78°C. On warming to room temperature the reaction (surprisingly) turned deep purple-brown, after 2 hours TLC showed no further formation of product and the reaction was quenched and worked up as for 3.7.12. Chromatography on silica (300g, C60, 40-60mm), gradient elution hexane/ether 6:1,

4:1, 3:1, of the resulting oil provided (5*R*, 7*R*, 10*S*) *N*-(2'*R*, 3'*S*)-2'-allyl-3'-hydroxyhexadecanoyl-2-oxa-4-aza-6,6-dimethyl-7,10-methylenespiro[4.5] decan-3-one **325** as a colourless oil (2.95g, 43%); $[\alpha]_D^{20} = -100.7^\circ$ ($c = 2.0$, dichloromethane); $^1\text{H NMR}$ (250 MHz, CDCl_3) δ 5.81(1H, ddt, $J = 17.0, 10.5, 7.0$ Hz, $\text{CH}=\text{CH}_2$), 5.04(1H, dq, $J = 17.0, 2.0$ Hz, $\text{CH}=\text{CH}_2$), 4.93(1H, dt, $J = 10.0, 2.0$ Hz, $\text{CH}=\text{CH}_2$), 2.26(1H, d, $J = 9.0$ Hz, H_{1a}), 4.06(1H, dt, $J = 9.0, 4.5$ Hz, $\text{CHC}=\text{O}$), 3.99(1H, d, $J = 9.0$ Hz, H_{1b}), 3.72(1H, td, $J = 6.0, 4.5$ Hz, CHOH), 2.79(1H, d, $J = 10.5$ Hz, H_{11a}), 2.53-2.44(3H, cm, OH, H_{10} , $\text{CH}_2\text{CH}=\text{CH}_2$), 2.31(1H, ddd, $J = 14.5, 6.5, 5.0$ Hz, $\text{CH}_2\text{CH}=\text{CH}_2$), 1.81(1H, bs, H_7), 1.57-1.38(5H, cm), 1.3-1.1(2H, cm), 1.20(22H, s, CH_2 's), 1.08(3H, s, CH_3), 0.95(3H, s, CH_3), 0.82(3H, t, $J = 6.5$ Hz, CH_3CH_2) ppm; $^{13}\text{C NMR}$ (62.9 MHz, CDCl_3) δ 175.4(quat, $\text{RC}=\text{ON}$), 156.0(quat, oxazolidinone $\text{C}=\text{O}$), 135.8($\text{CH}=\text{CH}_2$), 116.4($\text{CH}=\text{CH}_2$), 76.0(quat, C-N), 72.7(CHOH), 70.8(CH_2O), 49.4(CH , H_{10}), 48.3($\text{CHC}=\text{O}$), 47.0(quat, $\text{C}(\text{CH}_3)_2$), 44.8(CH , H_7), 38.3(CH_2 , C_{11}), 33.8($\text{CH}_2=\text{CHCH}_2$), 31.7, 29.4, 29.4, 29.1, (CH_2 's), 26.1(CH_3), 25.9, 24.1, 22.5, 22.5(4 x CH_2), 21.0(CH_3), 13.9(CH_3CH_2), ppm; **FT IR** (thin film) ν_{max} 3473(OH), 3040, 2925(CH), 1785(oxazolidinone $\text{C}=\text{O}$), 1705($\text{RC}=\text{ON}$), 1642($\text{C}=\text{C}$), 1465, 1366, 1281, 1204, 1072 cm^{-1} ; **MS** (FAB) 490(3%, MH^+), 472(12, MH^+-18), 277(17), 196(49), 135(40), 107(44); **Accurate mass** (FAB) (MH^+) Found 490.39412; $\text{C}_{30}\text{H}_{52}\text{NO}_4$ requires: 490.38963.

3.7.29 Acetylation of Aldol Product Aldol product 325.

Aldol product **325** (2.47g, 5.05 mmol) in hexane (60ml) was treated as **3.7.19** with triethylamine (0.75g, 7.5 mmol), DMAP (50mg, 0.37 mmol) and acetic anhydride (0.75g, 7.5 mmol). After 20 minutes TLC indicated that the reaction was complete (single spot) and work up as for **3.7.20** provided (5*R*, 7*R*, 10*S*) *N*-(2'*R*, 3'*S*)-2'-allyl-3'-acetoxyhexadecanoyl-2-oxa-4-aza-6,6-dimethyl-7,10-methylenespiro[4.5]decan-3-one **326** (2.71g, 102% mass balance) as a colourless oil; $[\alpha]_D^{20} = -74.6^\circ$ ($c = 1.75$, dichloromethane); $^1\text{H NMR}$ (250 MHz, CDCl_3) δ 5.73(1H, ddt, $J = 17.0, 10.0, 6.5$ Hz, $\text{CH}=\text{CH}_2$), 5.07(1H, cm, overlapping $\text{CH}=\text{CH}_2$ & CHO), 5.02(1H, dq, $J = 17.0, 2.0$ Hz, $\text{CH}=\text{CH}_2$), 4.94(1H, dq, $J = 10.0, 2.0$ Hz, $\text{CH}=\text{CH}_2$), 4.26(1H, d, $J = 9.0$ Hz, H_{1a}), 4.22(1H, dt, $J = 10.0, 4.0$ Hz, $\text{CHC}=\text{O}$), 4.06(1H, d, $J = 9.0$ Hz, H_{1b}), 2.73(1H, d, $J = 10.5$ Hz, H_{11a}), 2.55(1H, ddd, $J = 14.5, 10.0, 6.5$ Hz, $\text{CH}_2\text{CH}=\text{CH}_2$), 2.53(1H, bs, H_{10}), 2.19(1H, ddd, $J = 14.5, 6.0, 4.0$ Hz, $\text{CH}_2\text{CH}=\text{CH}_2$), 1.98(3H, s, CH_3CO_2), 1.79(1H, bs, H_7), 1.57-1.40(5H, cm), 1.3-1.1(2H, cm), 1.20(22H, s, CH_2 's), 1.09(3H, s, CH_3), 0.91(3H, s, CH_3), 0.83(1H, t, $J = 6.5$ Hz, CH_3CH_2) ppm; $^{13}\text{C NMR}$ (62.9 MHz, CDCl_3) δ 172.6(quat, $\text{RC}=\text{ON}$), 170.4(quat, CH_3CO_2), 156.0(quat, oxazolidinone $\text{C}=\text{O}$), 135.6($\text{CH}=\text{CH}_2$), 116.3($\text{CH}=\text{CH}_2$), 75.9(quat, C-N), 73.4(CHOAc), 70.7(CH_2O), 49.4(CH , C_{10}), 47.0(quat, $\text{C}(\text{CH}_3)_2$), 46.8($\text{CHC}=\text{O}$), 44.2(CH , C_7), 38.4(CH_2 , C_{11}), 31.7, 31.7($\text{CH}_2=\text{CHCH}_2$ & CH_2CHOAc), 29.7, 29.5, 29.4, 29.3, 29.2, 29.11(CH_2 's), 25.9(CH_3), 25.5, 24.3, 22.6, 22.5(4 x CH_2), 21.0, 20.7(CH_3 & CH_3CO_2), 14.0(CH_3CH_2) ppm; FT IR (thin film) ν_{max} 3038, 2928, 2835(CH), 1785(oxazolidinone $\text{C}=\text{O}$), 1739($\text{CH}_3\text{C}=\text{OO}$), 1707($\text{RC}=\text{ON}$), 1644($\text{C}=\text{C}$), 1463, 1388, 1280, 1240, 1072 cm^{-1} ; MS (FAB) 532(2%, MH^+), 472(25,

MH⁺-60), 385(6), 357(4), 277(37), 196(27); **Accurate mass** (FAB) (MH⁺) Found : 532.40185; C₃₂H₅₄NO₅ requires: 532.40020.

3.7.30 Phase Transfer Catalysed Permanganate Oxidation of Acetate Protected

Aldol Product 326

Acetate protected alkene **326** (1.07g, 2.02 mmol) was treated in an identical manner to **3.7.20** with potassium permanganate (2.55g, 16.2 mmol), tetrabutylammonium chloride (30mg) in benzene (20ml), acetic acid (10ml), and water (15ml) at a temperature of 70°C. TLC indicated the reaction to be complete after 30 minutes and work up as for **3.7.19** yielded a colourless gum. This was chromatographed as before to yield a glass (1.03g, 96%) identified as (*5R*, *7R*, *10S*) *N*-(2'*R*, 3'*S*)-2'-methylenecarboxy-3'-acetoxylhexadecanoyl-2-oxa-4-aza-6,6-dimethyl-7,10-methylenespiro[4.5]decan-3-one **327**; [α]_D²⁰ = -87° (c = 2.7, dichloromethane); **R_f** = 0.60 (2:1, cyclohexane/ethylacetate + 1% AcOH); **¹H NMR** (250 MHz, CDCl₃) δ 5.13(1H, td, *J* = 6.0, 2.0 Hz, CHO), 4.53(1H, dt, *J* = 10.5, 2.5 Hz, CHC=O), 4.27(1H, d, *J* = 9.0 Hz, H_{1a}), 4.13(1H, d, *J* = 9.0 Hz, H_{1b}), 3.00(1H, dd, *J* = 17.5, 11.5 Hz, CH₂CO₂H), 2.47(1H, dd, *J* = 17.5, 3.5 Hz, CH₂CO₂H), 1.98(3H, s, CH₃CO₂), 1.81(1H, bs, H₇), 1.58-1.37(5H, cm), 1.3-1.1(2H, cm), 1.22(22H, s, CH₂'s), 1.11(3H, s, CH₃), 0.93(3H, s, CH₃), 0.85(3H, t, *J* = 6.5 Hz, CH₃CH₂) ppm; **¹³C NMR** (62.9 MHz, CDCl₃) δ 178.3(quat, CO₂H), 172.4(quat, RC=ON), 170.6(quat, CH₃C=OO), 156.0(quat, oxazolidinone C=O), 75.9(quat, C-N), 72.3(CHO), 70.7(CH₂O), 49.4(CH, C₁₀), 47.3(quat, C(CH₃)₂), 44.4(CH, C₇), 38.4(CH₂, C₁₁), 32.3(CH₂CO₂H),

31.8, 29.5, 29.4, 29.3, 29.2, 29.1, 26.8(CH₂'s), 25.6(CH₃), 24.3, 22.5(CH₂'s), 21.1, 20.6(CH₃ & CH₃CO₂), 14.0(CH₃CH₂) ppm; **FT IR** (thin film) $\nu_{\max}$ 3102(broad, CO₂H), 3040, 2926, 2851(CH), 1788(broad, C=OOH & oxazolidinone C=O), 1741(C=OOR), 1712(RC=ON), 1467, 1360, 1284, 1236, 1073, 1019 cm⁻¹; **MS** (FAB) 550(4%, MH⁺), 490(38, MH⁺-60), 196(38), 135(33), 107(34); **Accurate mass** (FAB) (MH⁺) Found 550.37089; C₃₁H₅₂NO₁₇ requires 550.374378.

3.7.31 Lithium Hydroperoxide Cleavage of Acetate Protected Acid 327;

Preparation of the (-)-Protolichesterinic Acid Precursor 297

The acetate protected acid **327** (1.03g, 1.9mmol) in THF (20ml) was treated with hydrogen peroxide (15ml, 30%, ~40 mmol, 4 equiv. per lithium hydroxide) and finely powdered lithium hydroxide (400mg, 9.4mmol) added. After stirring for 6 days at room temperature starting material was completely consumed. TLC (2:1 cyclohexane/ethylacetate + 1% acetic acid) of an acid quenched aliquot showed auxiliary and a slow running component to be present. The reaction was quenched as for **3.7.21** and the THF removed *in vacuo* [large volume flask required due to foaming]. The resulting aqueous was extracted with ether (3 x 50ml) the organics dried and evaporated to yield (-)-**207** (190mg, 84%). The aqueous was acidified with concentrated hydrochloric acid to pH 3 and extracted into dichloromethane (3 x 60ml), washed with water (100ml), brine (50ml), dried, filtered and evaporated to yield a colourless crystalline solid (170mg, 82%). High field ¹H and ¹³C NMR spectroscopy showed this to be (4*R*, 5*S*)-4-carboxy-5-tridecyl-oxolan-2-one **297 MP**

= 111.5-113.0°C (from hexane/cyclohexane) [*Lit.* MP = 109-111°C (from ethylacetate/hexane)]¹³⁵; [α]_D²⁰ = -40.7° (c = 0.9, CHCl₃) [*Lit.* [α]_D²⁰ = -41° (c = 0.5, CHCl₃)]¹³⁵; ¹H NMR (MHz, CDCl₃) δ 8.6(1H, b, CO₂H), 4.61(1H, td, *J* = 7.0, 5.0 Hz, H₅), 3.08(1H, ddd, *J* = 10.0, 8.0, 7.0 Hz, H₄), 2.93(1H, dd, *J* = 17.5, 8.0 Hz, H₃), 2.80(1H, dd, *J* = 17.5, 10.0 Hz, H₃'), 1.81-1.70(2H, cm), 1.55-1.40(2H, cm), 1.25(20H, bs, CH₂'s), 0.87(3H, t, *J* = 6.5 Hz, CH₃CH₂) ppm; ¹³C NMR (MHz, CDCl₃) δ 176.0, 174.2(q's, C=O), 81.7(CH, C₅), 45.3(CH, C₄), 35.3(CH₂, C₃), 31.8, 31.75, 29.5, 29.4, 29.3, 29.2, 29.1, 25.0, 22.6(CH₂'s), 14.0(CH₃CH₂) ppm; FT IR (CCl₄) $\nu_{\max}$ 3110(OH), 2920, 2645, 1750, 1717(C=O), 1461, 1393, 1242, 1197cm⁻¹; MS (FAB) 626(19%, dimer, M₂H₂⁺), 313(100, MH⁺), 297(44), 217(74); **Elemental analysis**, Found 68.4% C, 10.0% H, C₁₈H₃₂O₄ requires 69.2% C, 10.3% H.

3.7.32 Aldol Condensation of the *Z*(*O*) Lithium Enolate of 267 with

Tetradecanal

Michael adduct **267** (2.31g, 7.9 mmol) in THF (20ml) was added over 1 hour by syringe pump to a solution of lithium diisopropylamide (8.7 mmol) [prepared as **3.3**] in THF (40ml) at -78°C under argon. After 30 minutes tetradecanal (2.44g, 11.5 mmol) in THF (20ml) was added and the reaction stirred for 1.5 hours. TLC (4:1 cyclohexane:ethylacetate) showed no further formation of product and the reaction was quenched with saturated ammonium chloride and THF evaporated *in vacuo*. The product was extracted into dichloromethane (3 x 100ml), washed with water then brine, dried, filtered and evaporated to give a thick yellow oil. This was

chromatographed on silica (300g, C60, 40-60mm); gradient elution hexane/ether 8:1, 6:1, to give starting material (1.10g, 48%), 6:1; 4:1; to give the major aldol product (1.15g, 28% (57% for reacted starting material), and finally its diastereomer **313** (160mg, 4%). The major product was provisionally assigned as (5*R*, 7*R*, 10*S*) *N*-(2'*S*, 3'*R*)-2'-((*R*)- α -vinylehtyl)-3'-hydroxyhexadecanoyl-2-oxa-4-aza-6,6-dimethyl-7,10-methylenespiro[4.5]decan-3-one **328**. $[\alpha]_D^{20} = -88.2^\circ$ ($c = 2.9$, dichloromethane); ^1H NMR (250 MHz, CDCl_3) δ 5.69(1H, ddd, $J = 17.0, 10.0, 8.5$ Hz, $\text{CH}=\text{CH}_2$), 5.10(1H, dm, $J = 17.0$ Hz, $\text{CH}=\text{CH}_2$), 5.01(1H, dd, $J = 10.0, 2.0$ Hz, $\text{CH}=\text{CH}_2$), 4.31(1H, d, $J = 9.0$ Hz, H_{1a}), 3.96(1H, d, $J = 9.0$ Hz, H_{1b}), 3.83(1H, dd, $J = 9.0, 4.0$ Hz, $\text{CHC}=\text{O}$), 3.71(1H, cm, CHOH), 3.20(1H, d, $J = 10.5$ Hz, H_{11a}), 2.86(1H, dm, $J = 9.0$ Hz, OH), 2.76(1H, sextet, $J = 7.0$ Hz, $\text{CH}-\text{CH}=\text{CH}_2$), 2.55(1H, bs, H_{10}), 1.88(1H, bs, H_7), 1.62-1.40(5H, cm), 1.40-1.10(2Hcm), 1.21(22H, s, CH_2 's), 1.12(3H, s, CH_3), 1.05(3H, s, CH_3), 0.99(3H, d, $J = 7.0$ Hz, CH_3CH), 0.84(3H, t, $J = 6.5$ Hz, CH_3CH_2) ppm; ^{13}C NMR (62.9 MHz, CDCl_3) δ 177.3(quat, $\text{RC}=\text{ON}$), 156.0(quat, oxazolidinone $\text{C}=\text{O}$), 141.0($\text{CH}=\text{CH}_2$), 115.4($\text{CH}=\text{CH}_2$), 76.6(quat, C-N), 71.4(CHOH), 71.2(CH_2O), 51.7($\text{CHC}=\text{O}$), 49.6(CH, C_{10}), 47.1(quat, $\text{C}(\text{CH}_3)_2$), 44.6(CH, C_7), 39.2($\text{CHCH}=\text{CH}_2$), 38.4(CH_2 , C_{11}), 36.4, 31.8, 29.5, 29.4, 29.2(CH_2 's), 25.9(CH_3), 25.9, 24.2(CH_2 's), 22.5(2 x CH_2), 21.1(CH_3), 17.7(CH_3CH), 14.0(CH_3CH_2) ppm; FT IR (thin film) ν_{max} 2930(CH), 1789(oxazolidinone $\text{C}=\text{O}$), 1704($\text{RC}=\text{ON}$), 1639($\text{C}=\text{C}$) cm^{-1} ; MS (FAB) 504(15%, MH^+), 486(20, $\text{MH}^+ - \text{H}_2\text{O}$), 399(39), 291(52, retro-aldol), 196(100), 135(66); Accurate mass (FAB) (MH^+) Found : 504.40696; $\text{C}_{31}\text{H}_{54}\text{NO}_4$ requires 504.40528.

3.7.33 Protection of Aldol Product 328 as its *t*-Butyldimethylsilyl Ether using *t*-

Butyldimethylsilyltriflate (TBDMSOTf) and Triethylamine

Aldol product **328** (370mg, 0.73 mmol) contaminated by **267** in dry THF (7ml) at -78°C under argon was treated with TBDMSOTf (240mg, 0.9 mmol) in THF (1ml) followed by triethylamine (130mg, 1.3 mmol) in ether (1ml). The reaction was warmed to room temperature and after 1 hour TLC showed complete reaction. The reaction was quenched with water and the THF evaporated, after the addition of water (20ml), the product was extracted into dichloromethane (2 x 30ml), washed with water, dried and evaporated to give an oil which was chromatographed on silica, eluent hexane/ether 9:1 to give (5*R*, 7*R*, 10*S*) *N*-(2'*S*, 3'*R*)-2'-((*R*)- α -vinylehtyl)-3'-*t*-butyldimethylsiloxy-hexadecanoyl-2-oxa-4-aza-6,6-dimethyl-7,10-methylenespiro[4.5]decan-3-one **329** (560g, 96%) as a colourless gum $[\alpha]_D^{20} = -52.7^\circ$ ($c = 1.75$, dichloromethane); $R_f = 0.80$ (9:1, hexane/ethylacetate); $^1\text{H NMR}$ (250 MHz, CDCl_3) δ 5.92(1H, ddd, $J = 17.0, 10.5, 6.5$ Hz, $\text{CH}=\text{CH}_2$), 4.98(1H, d, $J = 17.0$ Hz, $\text{CH}=\text{CH}_2$), 4.96(1H, d, $J = 10.5$ Hz, $\text{CH}=\text{CH}_2$), 4.24(1H, d, $J = 9.0$ Hz, H_{1a}), 4.17(1H, dt, $J = 6.5, 4.0$ Hz, CHO), 4.08(1H, t, $J = 6.5$ Hz, $\text{CHC}=\text{O}$), 3.93(1H, d, $J = 9.0$ Hz, H_{1b}), 2.88(1H, d, $J = 10.5$ Hz, H_{11a}), 2.61(1H, sextet, $J = 6.5$ Hz, $\text{CHCH}=\text{CH}_2$), 2.53(1H, bs, H_{10}), 1.85(1H, bs, H_7), 1.7-1.3(6H, cm), 1.24(22H, CH_2 's), 1.12(3H, s, CH_3), 1.02(3H, s, CH_3), 0.94(3H, d, $J = 6.5$ Hz, CH_3CH), 0.85(12H, complex, $\text{C}(\text{CH}_3)_2$ & CH_3CH_2), 0.05, 0.04(6H, 2 x s, $\text{Si}(\text{CH}_3)_2$) ppm; $^{13}\text{C NMR}$ (62.9 MHz, CDCl_3) δ 173.3(quat, $\text{RC}=\text{ON}$), 156.0(quat, oxazolidinone $\text{C}=\text{O}$), 142.4($\text{CH}=\text{CH}_2$), 113.0($\text{CH}=\text{CH}_2$), 76.2(quat, C-N), 71.0(CHO), 70.9(CH_2O),

52.5($\underline{\text{C}}\text{HC}=\text{O}$), 49.6(CH , C_{10}), 47.0(quat, $\underline{\text{C}}(\text{CH}_3)_2$), 44.7(CH , C_7), 38.4(CH_2 , C_{11}), 36.6($\underline{\text{C}}\text{HCH}=\text{CH}_2$), 32.7, 31.8, 29.7, 29.5, 29.2(CH_2 's), 26.32(CH_3), 25.8($\text{SiC}(\underline{\text{C}}\text{H}_3)_3$), 24.2, 23.5, 22.7, 22.6(4 x CH_2), 21.2(CH_3), 18.0(quat, $\text{Si}\underline{\text{C}}(\text{CH}_3)_3$), 15.4, 14.0(2 x CH_3), -4.4, -4.7($\text{Si}(\underline{\text{C}}\text{H}_3)_2$) ppm; **FT IR** (thin film) ν_{max} 2929, 1789(oxazolidinone $\text{C}=\text{O}$ *str*), 1704($\text{RC}=\text{ON}$ *str*), 1639($\text{C}=\text{C}$ *str*) cm^{-1} ; **MS** (FAB) 619(0.5%, M^+), 603($\text{MH}_2^+ - 18$), 561(8, $\text{M}^+ - \text{iso-butyl}$), 487(1, $\text{M}^+ - \text{TBDMS}$), 423(3), 365(3), 327(10), 196(7), 135(8), 107(18).

3.7.34 Preparation of *iso*-Valeryl Imide 330

(+)-**207** (1.94g, 1.0 mmol) in ether (80 ml) was treated as for 3.2.6 with diethylzinc (11ml, 1.0M in hexane, 11.0 mmol) and *iso*-valeryl chloride (3.03g, 25 mmol) and allowed to react overnight. After workup and isolation as for 3.2.6 the resulting oil was subjected to high vacuum (removal of any ester formed through ether cleavage) then chromatographed on silica eluting with heane/ether 9:1 to yield (*5S*, *7S*, *10R*) *N*-*iso*-valeryl-2-oxa-4-aza-6,6-dimethyl-7,10-methylenespiro [4.5]decan-3-one **330** as an oil (2.74g, 99%) $[\alpha]_{\text{D}}^{20} = +91.1^\circ$ ($c = 4.4$, dichloromethane); ^1H NMR (250 MHz, CDCl_3) δ 4.27(1H, d, $J = 9.0$ Hz, H_{1a}), 3.99(1H, d, $J = 9.0$ Hz, H_{1b}), 3.05(1H, d, $J = 7.0$ Hz, $\text{CH}_2\text{C}=\text{O}$), 2.89(1H, d, $J = 7.0$ Hz, $\text{CH}_2\text{C}=\text{O}$), 2.8-2.7(1H, cm), 2.63(1H, d, $J = 1.5$ Hz, H_{10}), 2.11(1H, septet, $J = 7.0$ Hz, $\underline{\text{C}}\text{H}(\text{CH}_3)_2$), 1.81(1H, d, $J = 1.5$ Hz, H_7), 1.58-1.40(3H, cm), 1.27(1H, dt, $J = 10.5, 1.5$ Hz, H_{11b}), 1.18-1.05(1H, cm), 1.10(3H, s, CH_3), 0.96(3H, s, CH_3) 0.93(3H, d, $J = 7.0$ Hz, $\underline{\text{C}}\text{H}_3\text{CH}$), 9.10(3H, d, $J = 7.0$ Hz, $\underline{\text{C}}\text{H}_3\text{CH}$) ppm; ^{13}C NMR (62.9 MHz, CDCl_3) δ 173.3(quat, $\text{RC}=\text{ON}$), 155.8(quat,

oxazolidinone C=O), 75.2(quat, C-N), 70.7(CH₂O), 49.1(CH, C₁₀), 47.4(quat, C(CH₃)₂), 45.5(CH₂C=O), 45.0(CH, C₇), 38.3(CH₂, C₁₁), 25.7(CH₃), 24.8(CH(CH₃)₂), 23.8, 22.6(2 x CH₂, C₈ & C₉), 22.4, 22.3(CH(CH₃)₂), 21.1(CH₃) ppm; FT IR (thin film) $\nu_{\max}$ 2960(CH), 1778(oxazolidinone CH), 1709(RC=ON), 1469, 1368, 1299, 1281 cm⁻¹; MS (FAB) 280(38%, MH⁺), 196(72); **Accurate mass** (FAB) (MH⁺) Found 280.18999; C₁₆H₂₆NO₃ requires 280.19127.

3.7.35 Aldol Condensation of Lithium Enolates of Imides 215, 330, and 269 with Selected Aldehydes

Reactions were carried out on a 1-2 mmol scale as for 3.4.1, using between 1.1 and 3 equivalents of the aldehyde. The reactions were quenched once TLC indicate that no more product was forming and worked up as before to provide a crude product. This was analysed by high field ¹H and ¹³C NMR spectroscopy which allowed an estimate of both the conversion to aldol products and the diastereomeric excess. In all cases only two significant aldol products were observed.

a) Reaction of lithium enolate of the propionyl imide **213** with hexanal proceeded with 70% conversion to a mixture with a 25% d.e. of the chelation controlled *syn* aldol product and a lesser quantity of a presumed chelation controlled *anti* aldol product. Chromatography allowed isolation of firstly the anti isomer (*5S*, *7S*, *10R*)-*N*-(2'*R*, 3'*R*)-3'-hydroxy-2'-methyloctanoyl-2-oxa-4-aza-6,6-dimethyl-7,10-methylenespiro[4.5]decan-3-one as a gum ¹H NMR (250 MHz, CDCl₃) δ 4.29(1H, d, *J* = 9.0 Hz, H_{1a}), 4.01(1H, d, *J* = 9.0 Hz, H_{1b}), 3.69(1H, quintet, *J* = 7.0 Hz,

CHC=O), 3.55(1H, cm, CHOH), 2.99(1H, bs, OH), 2.28(1H, dm, $J = 10.5$ Hz, H_{11a}), 2.50(1H, bs, H_{10}), 1.83(1H, bs, H_7), 1.6-0.96(13H, cm), 1.09(3H, s, CH_3), 1.09(3H, d, $J = 7.0$ Hz, CH_3CH), 1.01(3H, s, CH_3), 0.82(3H, t, $J = 6.5$ Hz, CH_3CH_2) ppm; ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 177.5(quat, RC=ON), 156.5(quat, oxazolidinone C=O), 76.1(quat, C-N), 74.5($\underline{C}HOH$), 71.0(CH_2O), 49.5(CH, C_{10}), 47.2(quat, $\underline{C}(CH_3)_2$), 44.8, 44.2(CH 's), 38.3(CH_2 , C_{11}), 34.9, 31.5(CH_2 's), 26.0(CH_3), 24.9, 24.1, 22.5, 22.4(CH_2 's), 21.3(CH_3), 15.3($\underline{C}H_3CH$), 13.8($\underline{C}H_3CH_2$) ppm.

Followed by the major *syn* product (5*S*, 7*S*, 10*R*)-*N*-(2'*R*, 3'*S*)-3'-hydroxy-2'-methybutanoyl-2-oxa-4-aza-6,6-dimethyl-7,10-methylenespiro[4.5]decan-3-one NN as a crystalline solid **MP** = 78.6-79.8°C (from hexane); ^1H NMR (250 MHz, $CDCl_3$) δ 4.31(1H, d, $J = 9.0$ Hz, H_{1a}), 4.02(1H, d, $J = 9.0$ Hz, H_{1b}), 3.94(1H, cm, $\underline{C}HOH$), 3.81(1H, qd, $J = 7.0, 2.5$ Hz, CHC=O), 2.76(1H, d, $J = 2.5$ Hz, OH), 2.77(1H, dm, $J = 10.5$ Hz, H_{11a}), 2.58(1H, bs, H_{10}), 1.85(1H, d, $J = 2.0$ Hz, H_7), 1.74-1.41(6H, cm), 1.39-1.25(6H, cm), 1.2-1.1(1H, cm), 1.13(3H, s, CH_3), 1.10(3H, d, $J = 7.0$ Hz, CH_3CH), 1.01(3H, s, CH_3), 0.86(3H, t, $J = 6.5$ Hz, CH_3CH_2) ppm; ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 178.6(quat, RC=ON), 155.6(quat, oxazolidinone C=O), 75.8(quat, C-N), 71.5($\underline{C}HOH$), 70.8(CH_2O), 49.3(CH, C_{10}), 47.4(quat, $\underline{C}(CH_3)_2$), 45.0(CH, C_7), 42.5($\underline{C}HC=O$), 38.3(CH_2 , C_{11}), 33.7, 31.7(CH_2 's), 25.8(CH_3), 25.6, 24.1, 22.5, 22.4(CH_2 's), 21.1(CH_3), 13.9($\underline{C}H_3CH_2$), 10.6($\underline{C}H_3CH$) ppm; **MS** (FAB) 353(86%, MH^+), 334(100, $MH^+ - H_2O$), 196(74).

b) Reaction of lithium enolate of the propionyl imide **213** with tetradecanal proceeded with 60% conversion to a mixture of the *syn*- and *anti*-diastereomers in a 2:1 ratio. The products were not isolated or further characterised.

d) Reaction of lithium enolate of the *iso*-valyroyl imide **330** with hexanal proceeded with 45% conversion to give predominately the *syn* diastereomer. The products were not isolated or further characterised.

d) Reaction of lithium enolate of the *iso*-valyroyl imide **330** with tetradecanal proceeded with 30% conversion to give predominately the *syn* diastereomer. The products were not isolated or further characterised.

e) Reaction of lithium enolate of the *iso*-valyroyl imide **330** with tetradecanal proceeded with 45% conversion to give predominately the *syn* diastereomer. The products were not isolated or further characterised.

f) Reaction of lithium enolate of the 3-phenylbutanoyl imide **NN** with tetradecanal proceeded with 40% conversion to a mixture of the *syn*- and *anti*-diastereomers in a 5:1 ratio. The products were not isolated or further characterised

3.7.36 Acetylation of Aldol Product **328**

Aldol product **328** (2.90g, 5.8 mmol) in hexane (40ml) was treated with triethylamine (0.88g, 8.7 mmol), DMAP (70mg, 0.5 mmol) and freshly distilled acetic anhydride (0.87g, 8.7 mmol) as for **3.7.19**. After 30 minutes TLC (4:1, cyclohexane/ether) showed the reaction to be complete, work up as before yielded (*5R*, *7R*, *10S*) *N*-(*2'S*, *3'R*)-*2'-((R)-α-vinylehtyl*)-*3'-acetoxyhexadecanoyl-2-oxa-4-aza-6,6-dimethyl-7,10-methylenespiro[4.5]decan-3-one* **331** as a colourless oil (3.15g, 100%); $[\alpha]_D^{20} = -93.7^\circ$ ($c = 3.35$, dichloromethane); $R_f = 0.36$ (9:1, hexane/ethylacetate); $^1\text{H NMR}$

(250 MHz, CDCl₃) δ 5.79(1H, ddd, J = 17.5, 10.0, 6.5 Hz, CH=CH₂), 5.30(1H, td, J = 7.5, 3.5 Hz, CHO), 5.01(1H, dt, J = 10.0, 1.5 Hz, CH=CH₂), 5.00(1H, 1H, dt, J = 17.5, 1.5 Hz, CH=CH₂), 4.37(1H, dd, J = 8.5, 6.5 Hz, CHC=O), 4.24(1H, d, J = 9.0 Hz, H_{1a}), 3.89(1H, d, J = 9.0 Hz, H_{1b}), 2.87(1H, dm, J = 10.5 Hz, H_{11a}), 2.54(1H, sextet, J = 6.5 Hz, CHCH=CH₂), 2.49(1H, bs, H₁₀), 1.94(3H, s, CH₃CO₂), 1.83(1H, bs, H₇), 1.7(1H, cm), 1.60-1.47(4H, cm), 1.21(22H, s, CH₂'s), 1.3-1.0(2H, cm), 1.10(3H, s, CH₃), 1.00(3H, d, J = 6.5 Hz, CH₃CH), 0.99(3H, s, CH₃), 0.84(3H, t, J = 6.5 Hz, CH₃CH₂) ppm; ¹³C NMR (62.9 MHz, CDCl₃) δ 172.5(quat, RC=ON), 170.0(quat, CH₃CO₂), 156.1(quat, oxazolidinone C=O), 140.6(CH=CH₂), 114.7(CH=CH₂), 76.2(quat, C-N), 72.8(CHO), 70.9(CH₂O), 49.5(2 x CH, C₁₀ & CHC=O), 47.1(quat, C(CH₃)₂), 44.6(CH, C₇), 38.1(CH₂, C₁₁), 37.3(CHCH=CH₂), 31.7, 29.5, 29.4, 29.3, 29.2, 26.7(CH₂'s), 25.8(CH₃), 24.4, 24.2, 22.6, 22.5(4 x CH₂), 21.0(CH₃ & CH₃CO₂), 14.4, 14.0(CH₃CH & CH₃CH₂) ppm; FT IR (thin film) $\nu_{\max}$ 2927, 2855, 1784.5(oxazolidinone C=O *str*), 1743(CH₃C=OO *str*), 1705(RC=ON *str*), 1281, 1242t cm⁻¹; MS (FAB) 547(4%, MH⁺), 487(87, MH⁺-60), 399(44), 291(100)196(73), 135(83); **Accurate mass** (FAB) (MH⁺) Found 546.41216; C₃₃H₅₆NO₅ requires 546.41585.

3.7.37 Phase Transfer Catalysed Permanganate Oxidation of Acetate Protected

Aldol Product 331

Acetate protected aldol product **331** (1.21g, 2.22 mmol) was treated in an identical manner to **3.7.20** with potassium permanganate (2.80g, 1.77 mmol), TBAB (0.30g, 0.9 mmol) in benzene (30ml), acetic acid (10ml), and water (15ml). TLC indicated the reaction to be complete after 45 minutes and work up as before yielded a colourless gum. This was chromatographed as before to yield a glass (850mg, 68%) identified as (5*R*, 7*R*, 10*S*) *N*-(2'*S*, 3'*R*)-2'-((*R*)- α -carboxyethyl)-3'-acetoxylhexadecanoyl-2-oxa-4-aza-6,6-dimethyl-7,10-methylenespiro[4.5]decan-3-one **332** $[\alpha]_D^{20} = -175.6^\circ$ ($c = 3.3$, dichloromethane); $^1\text{H NMR}$ (MHz, CDCl_3) δ 9.5(1H, b, CO_2H), 5.31(1H, td, $J = 7.5, 3.0$ Hz, CHOAc), 4.60(1H, dd, $J = 7.5, 6.5$ Hz, CHC=ON), 4.27(1H, d, $J = 9.0$ Hz, H_{1a}), 3.98(1H, d, $J = 9.0$ Hz, H_{1b}), 2.84(1H, d, $J = 10.5$ Hz, H_{11a}), 2.80(1H, quintet, $J = 6.5$ Hz, CHCH_3), 2.52(1H, bs, H_{10}), 1.96(3H, s, CH_3CO_2), 1.84(1H, bs, H_7), 1.7-1.4(6H, cm), 1.3-1.1(3H, cm), 1.21(22H, CH_2 's), 1.19(3H, d, partially obscured, CH_3CH), 1.11(3H, s, CH_3), 1.00(3H, s, CH_3), 0.84(3H, t, $J = 6.2$ Hz, CH_3CH_2) ppm; $^{13}\text{C NMR}$ (MHz, CDCl_3) δ 179.7(quat, CO_2H), 171.6(quat, RC=ON), 156.1(quat, oxazolidinone C=O), 76.4(quat, C-N), 72.4(CHOAc), 71.0(CH_2O), 49.6(CH , C_{10}), 47.1(quat, $\text{C}(\text{CH}_3)_2$), 47.0(CHC=ON), 44.6(CH , C_7), 39.2(CHCH_3), 38.4(CH_2 , C_{11}), 31.7, 31.3, 29.5, 29.4, 29.3, 29.2, 26.7(CH_2 's), 25.9(CH_3), 25.0, 24.2, 22.6, 22.5(CH_2 's), 21.0, 20.9(CH_3 & CH_3CO_2), 14.0, 13.5(CH_3CH_2 & CH_3CH) ppm; FT IR (thin film) ν_{max} 3186(broad, CO_2H), 2936, 2855(CH), 1787(acid and oxazolidinone C=O), 1744(CH_3CO_2),

1708(RC=ON), 1463, 1390, 1283, 1227 cm^{-1} ; **MS** (FAB) 565(5%, MH_2^+), 563(4, MH^+), 505(56, $\text{MH}_2^+ - 60$), 487(25), 459(9), 308(10), 265(27), 196(64), 135(55); **Accurate mass** (FAB) (MH^+) Found 564.38615; $\text{C}_{32}\text{H}_{54}\text{NO}_7$ requires 564.39003.

3.7.38 Lithium Hydroperoxide Hydrolysis of Acetate Protected Acid 332

Acetate protected acid **332** (520mg, 0.95 mmol) was dissolved in THF (20ml) and hydrogen peroxide (10ml, 30%, ~100 mmol) added. Lithium hydroxide (210mg, 5.0 mmol) in water (3ml) was then added and the reaction stirred for 6 days when starting material was shown to be absent by TLC; however no cleaved auxiliary was observed. The remaining peroxide was destroyed catalytically by the addition of 5% palladium on alumina, then the THF evaporated. The aqueous was extracted with ethylacetate, then taken to pH 2 with 6 M hydrochloric acid and extracted with dichloromethane (3 x 20ml). The acid extract was washed with water then brine, dried filtered and evaporated to yield a colourless solid (350mg). High field ^1H and ^{13}C NMR spectroscopy of this material indicate that it was composed of a minor component and two major components, all of which appeared to retain a terpenoid moiety. The two major components have been tentatively assigned as the C_α diastereomers of the amido-alcohol **333**. The basic structure of the products (i.e. ring opening) was shown by the distinctive geminal coupling constants of the methanol protons (11.5 & 12.0 Hz, compare amido-alcohol **266**, $J = 11.5$ Hz). **^1H NMR** (250 MHz, CDCl_3) δ 7.1(1H, CO_2H), 6.17(0.3H, bs, NH), 5.98(0.7H, bs, NH), 5.35-5.25(0.3H, cm, CHOH), 5.15-5.05(0.7H, cm, CHOH), 4.57(0.3H, dd, $J = 7.0, 8.0$ Hz,

CHC=O), 4.33(0.7H, d, $J = 11.5$ Hz, CH₂O), 4.23(0.3H, d, $J = 12.0$ Hz, CH₂O), 4.02(0.7H, dd, $J = 13.5, 13.0$ Hz, CHC=O), 3.80(0.3H, d, $J = 12.0$ Hz, CH₂O), 3.72(0.7H, d, $J = 11.5$ Hz, CH₂O), 3.15-2.65(cm, H_{11a} + CHCH₃), 2.53, 2.35(bs's, H₁₀), 1.9-0.9(ca. 46H, cm), 0.82(3H, t, $J = 7.0$ Hz, CH₂CH₃) ppm; MS (FAB) 504(2%, MH⁺), 478(14, MH⁺-18).

3.7.39 Copper Catalysed Conjugate Addition of Dimethylaluminium Chloride to Cinnamoyl Imide **226**

Copper(I)bromide:dimethylsulphide complex (31mg, 0.15 mmol) in dichloromethane (10ml) was treated with dimethylaluminium chloride (3.8ml, 1M in hexane, 3.8 mmol) at 0°C and after stirring for five minutes, cooled to -78°C. Imide **226** (250mg, 77 mmol) in dichloromethane (2ml) was added dropwise and the reaction slowly warmed to 0°C and TLC showed the reaction to be complete. Workup as for **3.6.1** yielded the crude adduct **311** which was shown by ¹H NMR spectroscopy to contain <5% of the diastereomer **269** (>90% d.e.). Recrystallisation from hexane furnished pure (5*S*, 7*S*, 10*R*)-*N*-(3'*S*)-3'-phenylbutanoyl-2-oxa-4-aza-6,6-dimethyl-7,10-methylenespiro [4.5]decan-3-one **311** (240mg, 91%) MP = 132-134°C (from hexane); [α]_D²⁰ = +124.7° (c = 1.35, dichloromethane); ¹H NMR (250 MHz, CDCl₃) δ 7.3-7.1(5H, cm, Ph), 4.16(1H, d, $J = 9.0$ Hz, H_{1a}), 3.63(1H, d, $J = 9.0$ Hz, H_{1b}), 3.42(1H, dd, $J = 15.0, 8.0$ Hz, CH₂C=O), 2.99(1H, dd, $J = 15.0, 6.0$ Hz, CH₂C=O), 2.72(1H, d, $J = 10.5$ Hz, H_{11a}), 2.35(1H, bs, H₁₀), 1.81(1H, d, $J = 2.0$ Hz, 1.55-1.20(6H, cm), 1.31(3H, d, $J = 7.0$ Hz, CH₃CH), 1.09(3H, s, CH₃), 0.98(3H, s, CH₃)

ppm; ^{13}C NMR (62.9 MHz, CDCl_3) δ 172.8(quat, RC=ON), 156.0(quat, oxazolidinone C=O), 145.6(quat, Ph), 127.8, 126.9(4 x CH, Ph), 126.2(CH, Ph), 75.4(quat, C-N), 70.7(CH_2O), 49.2(CH, C_{10}), 47.2(quat, $\text{C}(\text{CH}_3)_2$), 44.7(CH, C_7), 44.2($\text{CH}_2\text{C=O}$), 38.2(CH_2 , C_{11}), 36.9(PhCH), 25.8(CH_3), 23.9, 22.5(CH_2 's), 22.2, 21.1(2 x CH_3) ppm; **FT IR** (nujol mull) ν_{max} 1780(oxazolidinone C=O), 1702(RC=ON) cm^{-1} ; **MS** (FAB) 342(100%, MH^+); **Accurate mass** (FAB) (MH^+) Found 342.20725; $\text{C}_{21}\text{H}_{28}\text{NO}_3$ requires 342.20692.

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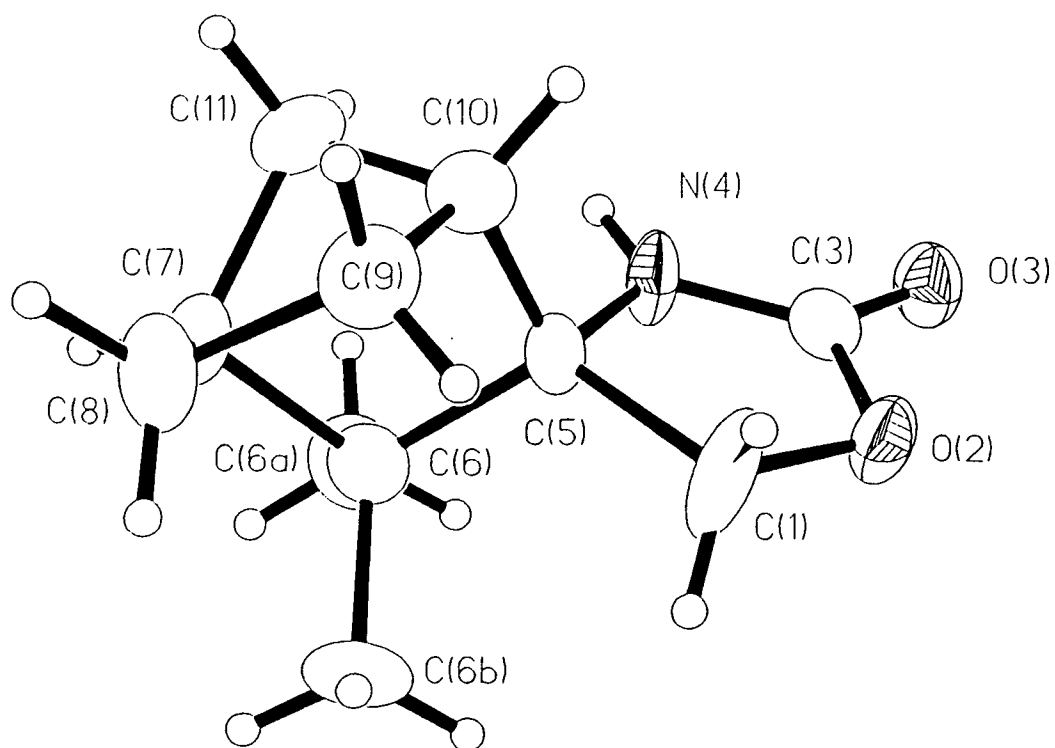
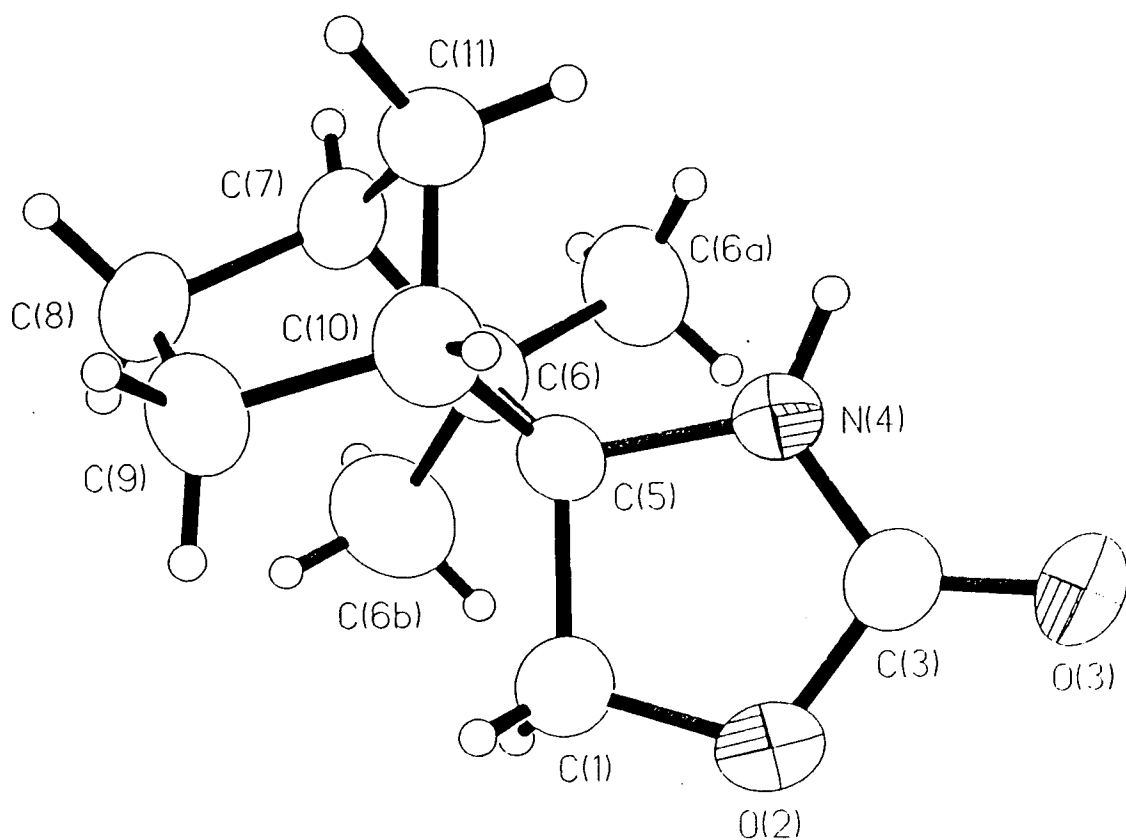
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5 Appendix

5.1 X-ray Structures Of Chiracamphox 207

(Two molecules per unit cell)



STRUCTURE DETERMINATION SUMMARY

Crystal Data

Empirical Formula	$C_{11} H_{17} N O_2$
Color; Habit	Colourless column
Crystal Size (mm)	0.54 x 0.23 x 0.19
Crystal System	Orthorhombic
Space Group	$P2_1^2 2_1^2 2_1$
Unit Cell Dimensions	$\underline{a} = 8.9831(10) \text{ \AA}$ $\underline{b} = 11.0255(5) \text{ \AA}$ $\underline{c} = 20.9573(10) \text{ \AA}$
Volume	$2075.7(10) \text{ \AA}^3$
Z	8
Formula Weight	195.3
Density(calc.)	1.250 Mg/m^3
Absorption Coefficient	$.085 \text{ mm}^{-1}$
F(000)	848

Data Collection

Diffractometer Used	Stoe Stadi-4
Radiation	MoK α (λ = .71073 Å)
Temperature (K)	295 .
Monochromator	Highly oriented graphite crystal
2 θ Range	5.0 to 45.0°
Scan Type	ω -2 θ
Standard Reflections	3 measured every 120 minutes
Index Ranges	$-9 \leq h \leq 9$, $0 \leq k \leq 11$ $0 \leq l \leq 22$
Reflections Collected	2907
Independent Reflections	2665 (R_{int} = 1.99%)
Observed Reflections	1817 ($F > 4.0\sigma(F)$)
Absorption Correction	N/A

Solution and Refinement

System Used	Siemens SHELXTL
Solution	Direct Methods
Refinement Method	Full-Matrix Least-Squares
Quantity Minimized	$\sum w(F_o - F_c)^2$
Absolute Structure	N/A
Extinction Correction	$\chi = .0011(3)$, where $F^* = F [1 + 0.002\chi F^2 / \sin(2\theta)]^{-1/4}$
Hydrogen Atoms	Riding model, fixed isotropic U
Weighting Scheme	$w^{-1} = \sigma^2(F) + .0007F^2$
Number of Parameters Refined	254
Final R Indices (obs. data)	R = 3.86 %, wR = 5.03 %
R Indices (all data)	R = 6.81 %, wR = 5.64 %
Goodness-of-Fit	1.31
Largest and Mean Δ/σ	.003, .001
Data-to-Parameter Ratio	7.2:1
Largest Difference Peak	.28 eÅ ⁻³
Largest Difference Hole	-.16 eÅ ⁻³

Table 1. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement coefficients ($\text{\AA}^2 \times 10^3$)

	x	y	z	U(eq)
C(1)	3515(4)	9166(3)	3819(3)	77(2)
O(2)	2054(2)	8697(2)	3831(1)	59(1)
C(3)	2109(4)	7473(3)	3882(2)	45(1)
O(3)	999(3)	6859(2)	3906(1)	59(1)
N(4)	3517(3)	7117(2)	3893(2)	58(1)
C(5)	4602(3)	8098(3)	3862(2)	45(1)
C(6)	5771(4)	7928(3)	3299(2)	47(1)
C(6A)	5446(5)	6799(3)	2894(2)	70(2)
C(6B)	5838(5)	9006(4)	2849(2)	81(2)
C(7)	7230(4)	7728(3)	3672(2)	56(1)
C(8)	7799(4)	8924(3)	3954(2)	65(2)
C(9)	6612(4)	9228(3)	4453(2)	61(1)
C(10)	5607(4)	8105(3)	4449(2)	55(1)
C(11)	6685(4)	7096(3)	4277(2)	63(2)
C(1')	1539(4)	12189(3)	3709(3)	73(2)
O(2')	2985(2)	12657(2)	3821(1)	59(1)
C(3')	2918(4)	13886(3)	3870(2)	49(1)
O(3')	4020(3)	14497(2)	3946(2)	67(1)
N(4')	1528(3)	14245(3)	3823(2)	60(1)
C(5')	443(3)	13259(3)	3791(2)	46(1)
C(6')	-794(4)	13443(3)	3262(2)	46(1)
C(6A')	-533(5)	14579(3)	2860(2)	70(2)
C(6B')	-921(5)	12368(4)	2814(2)	71(2)
C(7')	-2207(4)	13613(3)	3677(2)	54(1)
C(8')	-2750(4)	12413(3)	3953(2)	66(2)
C(9')	-1489(4)	12088(3)	4417(2)	63(2)
C(10')	-485(4)	13223(3)	4407(2)	56(1)
C(11')	-1602(4)	14225(3)	4274(2)	61(1)

* Equivalent isotropic U defined as one third of the trace of the orthogonalized U_{ij} tensor

Table 2. Bond lengths (Å)

C(1)-O(2)	1.410 (4)	C(1)-C(5)	1.532 (5)
O(2)-C(3)	1.355 (4)	C(3)-O(3)	1.206 (4)
C(3)-N(4)	1.325 (4)	N(4)-C(5)	1.456 (4)
C(5)-C(6)	1.591 (5)	C(5)-C(10)	1.526 (5)
C(6)-C(6A)	1.534 (5)	C(6)-C(6B)	1.519 (5)
C(6)-C(7)	1.542 (5)	C(7)-C(8)	1.532 (5)
C(7)-C(11)	1.527 (6)	C(8)-C(9)	1.531 (6)
C(9)-C(10)	1.532 (5)	C(10)-C(11)	1.518 (5)
C(1')-O(2')	1.418 (4)	C(1')-C(5')	1.546 (5)
O(2')-C(3')	1.360 (4)	C(3')-O(3')	1.208 (4)
C(3')-N(4')	1.314 (5)	N(4')-C(5')	1.461 (4)
C(5')-C(6')	1.583 (5)	C(5')-C(10')	1.537 (5)
C(6')-C(6A')	1.528 (5)	C(6')-C(6B')	1.517 (5)
C(6')-C(7')	1.549 (5)	C(7')-C(8')	1.524 (5)
C(7')-C(11')	1.523 (5)	C(8')-C(9')	1.534 (6)
C(9')-C(10')	1.543 (5)	C(10')-C(11')	1.519 (5)

Table 3. Bond angles (°)

O(2)-C(1)-C(5)	108.1(3)	C(1)-O(2)-C(3)	109.4(3)
O(2)-C(3)-O(3)	122.1(3)	O(2)-C(3)-N(4)	109.3(3)
O(3)-C(3)-N(4)	128.5(3)	C(3)-N(4)-C(5)	114.7(3)
C(1)-C(5)-N(4)	98.5(2)	C(1)-C(5)-C(6)	117.9(3)
N(4)-C(5)-C(6)	112.8(3)	C(1)-C(5)-C(10)	114.9(3)
N(4)-C(5)-C(10)	111.3(3)	C(6)-C(5)-C(10)	102.0(3)
C(5)-C(6)-C(6A)	112.3(3)	C(5)-C(6)-C(6B)	113.3(3)
C(6A)-C(6)-C(6B)	107.4(3)	C(5)-C(6)-C(7)	101.6(3)
C(6A)-C(6)-C(7)	109.1(3)	C(6B)-C(6)-C(7)	113.2(3)
C(6)-C(7)-C(8)	110.8(3)	C(6)-C(7)-C(11)	102.4(3)
C(8)-C(7)-C(11)	100.4(3)	C(7)-C(8)-C(9)	102.7(3)
C(8)-C(9)-C(10)	103.3(3)	C(5)-C(10)-C(9)	110.9(3)
C(5)-C(10)-C(11)	100.5(3)	C(9)-C(10)-C(11)	102.6(3)
C(7)-C(11)-C(10)	93.9(3)	O(2')-C(1')-C(5')	106.7(3)
C(1')-O(2')-C(3')	109.5(3)	O(2')-C(3')-O(3')	122.0(3)
O(2')-C(3')-N(4')	109.7(3)	O(3')-C(3')-N(4')	128.4(3)
C(3')-N(4')-C(5')	114.4(3)	C(1')-C(5')-N(4')	98.5(2)
C(1')-C(5')-C(6')	117.9(3)	N(4')-C(5')-C(6')	113.9(3)
C(1')-C(5')-C(10')	114.7(3)	N(4')-C(5')-C(10')	110.1(3)
C(6')-C(5')-C(10')	102.1(3)	C(5')-C(6')-C(6A')	112.5(3)
C(5')-C(6')-C(6B')	112.7(3)	C(6A')-C(6')-C(6B')	108.1(3)
C(5')-C(6')-C(7')	101.4(3)	C(6A')-C(6')-C(7')	109.7(3)
C(6B')-C(6')-C(7')	112.4(3)	C(6')-C(7')-C(8')	111.8(3)
C(6')-C(7')-C(11')	102.9(3)	C(8')-C(7')-C(11')	100.7(3)
C(7')-C(8')-C(9')	102.0(3)	C(8')-C(9')-C(10')	103.5(3)
C(5')-C(10')-C(9')	110.5(3)	C(5')-C(10')-C(11')	100.7(3)
C(9')-C(10')-C(11')	101.9(3)	C(7')-C(11')-C(10')	93.6(3)

Table 4. Anisotropic displacement coefficients ($\text{\AA}^2 \times 10^3$)

	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C(1)	41(2)	47(2)	142(4)	-1(2)	9(3)	-6(3)
O(2)	43(1)	47(2)	85(2)	9(1)	-4(2)	1(1)
C(3)	41(2)	50(2)	45(2)	-1(2)	3(2)	-3(2)
O(3)	35(1)	60(2)	82(2)	-6(1)	-2(1)	1(1)
N(4)	35(2)	35(2)	103(3)	2(1)	2(2)	3(2)
C(5)	38(2)	31(2)	67(3)	1(1)	4(2)	-3(2)
C(6)	52(2)	44(2)	46(2)	-5(2)	-1(2)	-3(2)
C(6A)	83(3)	67(3)	61(3)	-10(2)	4(2)	-22(2)
C(6B)	103(4)	72(3)	68(3)	-6(3)	9(3)	16(2)
C(7)	31(2)	50(2)	88(3)	-1(2)	9(2)	-14(2)
C(8)	40(2)	58(2)	98(3)	-5(2)	-9(2)	-13(2)
C(9)	70(2)	49(2)	64(3)	-6(2)	-10(2)	-16(2)
C(10)	60(3)	56(3)	49(2)	-6(2)	0(2)	-1(2)
C(11)	62(2)	46(2)	81(3)	0(2)	-27(2)	4(2)
C(1')	45(2)	42(3)	132(4)	6(2)	-9(2)	-9(3)
O(2')	45(1)	47(2)	85(2)	5(1)	0(1)	4(1)
C(3')	47(2)	45(2)	55(2)	2(2)	-4(2)	4(2)
O(3')	37(1)	56(2)	107(2)	-6(1)	-5(2)	8(2)
N(4')	32(2)	39(2)	109(3)	1(1)	-12(2)	-6(2)
C(5')	40(2)	36(2)	61(3)	1(1)	-2(2)	-4(2)
C(6')	50(2)	46(2)	42(2)	-5(2)	0(2)	2(2)
C(6A')	74(3)	71(3)	66(3)	-9(2)	-7(2)	18(2)
C(6B')	84(3)	69(3)	59(3)	-3(2)	-6(2)	-16(2)
C(7')	42(2)	48(2)	72(3)	2(2)	-6(2)	6(2)
C(8')	49(2)	59(2)	89(3)	-4(2)	10(2)	11(2)
C(9')	74(3)	57(3)	57(2)	-10(2)	11(2)	15(2)
C(10')	71(3)	49(2)	47(2)	-2(2)	-17(2)	0(2)
C(11')	66(2)	49(2)	67(3)	4(2)	16(2)	-9(2)

The anisotropic displacement factor exponent takes the form:

$$-2\pi^2(h^2a^{*2}U_{11} + \dots + 2hka^*b^*U_{12})$$

Table 5. H-Atom coordinates ($\times 10^4$) and isotropic displacement coefficients ($\text{\AA}^2 \times 10^3$)

	x	y	z	U
H(1A)	3664	9699	4176	80
H(1B)	3676	9613	3432	80
H(4)	3782	6331	3916	80
H(6A1)	6172	6738	2560	80
H(6A2)	5506	6095	3163	80
H(6A3)	4468	6849	2711	80
H(6B1)	6556	8849	2519	80
H(6B2)	4874	9119	2660	80
H(6B3)	6116	9725	3077	80
H(7)	7962	7270	3441	80
H(8A)	7841	9532	3627	80
H(8B)	8764	8841	4145	80
H(9A)	6053	9934	4333	80
H(9B)	7050	9359	4865	80
H(10)	5077	7990	4842	80
H(11A)	7446	6998	4595	80
H(11B)	6192	6338	4199	80
H(1'A)	1319	11566	4015	80
H(1'B)	1461	11854	3288	80
H(4')	1261	15031	3805	80
H(6A4)	-1303	14663	2545	80
H(6A5)	-540	15274	3136	80
H(6A6)	416	14520	2652	80
H(6B4)	-1678	12516	2500	80
H(6B5)	21	12258	2605	80
H(6B6)	-1165	11650	3051	80
H(7')	-2971	14072	3467	80
H(8'A)	-2881	11804	3631	80
H(8'B)	-3667	12521	4181	80
H(9'A)	-955	11392	4265	80
H(9'B)	-1855	11922	4838	80
H(10)	102	13324	4786	80
H(11C)	-2330	14316	4606	80
H(11D)	-1127	14987	4187	80

TORSION ANGLES FOR MECHIR #1018 for PT/IG in P2(1)2(1)2(1)

C5	C1	O2	C3	0.5					
C1	O2	C3	O3	179.5					
C1	O2	C3	N4	-0.9	C10'	C5'	C6'	C7'	5.6
O2	C3	N4	C5	1.0	C5'	C6'	C7'	C8'	-75.6
O3	C3	N4	C5	-179.4	C5'	C6'	C7'	C11'	31.6
O2	C1	C5	N4	0.1	C6A'	C6'	C7'	C8'	165.2
O2	C1	C5	C6	121.6	C6A'	C6'	C7'	C11'	-87.5
O2	C1	C5	C10	-118.2	C6B'	C6'	C7'	C8'	44.9
C3	N4	C5	C1	-0.7	C6B'	C6'	C7'	C11'	152.2
C3	N4	C5	C6	-125.8	C6'	C7'	C8'	C9'	67.0
C3	N4	C5	C10	120.3	C11'	C7'	C8'	C9'	-41.6
C1	C5	C6	C6A	-110.9	C7'	C8'	C9'	C10'	6.8
C1	C5	C6	C6B	10.9	C1'	C5'	C10'	C9'	-62.6
C1	C5	C6	C7	132.7	C1'	C5'	C10'	C11'	-169.7
N4	C5	C6	C6A	2.8	N4'	C5'	C10'	C9'	-172.6
N4	C5	C6	C6B	124.7	N4'	C5'	C10'	C11'	80.3
N4	C5	C6	C7	-113.6	C6'	C5'	C10'	C9'	66.1
C10	C5	C6	C6A	122.3	C6'	C5'	C10'	C11'	-41.0
C10	C5	C6	C6B	-115.8	C8'	C9'	C10'	C5'	-76.1
C10	C5	C6	C7	5.9	C8'	C9'	C10'	C11'	30.2
C5	C6	C7	C8	-74.9	C6'	C7'	C11'	C10'	-56.2
C5	C6	C7	C11	31.4	C8'	C7'	C11'	C10'	59.3
C6A	C6	C7	C8	166.3	C5'	C10'	C11'	C7'	59.5
C6A	C6	C7	C11	-87.4	C9'	C10'	C11'	C7'	-54.3
C6B	C6	C7	C8	46.9					
C6B	C6	C7	C11	153.1					
C6	C7	C8	C9	67.2					
C11	C7	C8	C9	-40.5					
C7	C8	C9	C10	6.1					
C1	C5	C10	C9	-62.2					
C1	C5	C10	C11	-170.1					
N4	C5	C10	C9	-173.0					
N4	C5	C10	C11	79.1					
C6	C5	C10	C9	66.5					
C6	C5	C10	C11	-41.4					
C8	C9	C10	C5	-75.9					
C8	C9	C10	C11	30.7					
C6	C7	C11	C10	-56.3					
C8	C7	C11	C10	57.9					
C5	C10	C11	C7	60.1					
C9	C10	C11	C7	-54.4					
C5'	C1'	O2'	C3'	-8.5					
C1'	O2'	C3'	O3'	-177.7					
C1'	O2'	C3'	N4'	2.5					
O2'	C3'	N4'	C5'	5.2					
O3'	C3'	N4'	C5'	-174.6					
O2'	C1'	C5'	N4'	10.3					
O2'	C1'	C5'	C6'	133.1					
O2'	C1'	C5'	C10'	-106.5					
C3'	N4'	C5'	C1'	-9.6					
C3'	N4'	C5'	C6'	-135.2					
C3'	N4'	C5'	C10'	110.7					
C1'	C5'	C6'	C6A'	-110.7					
C1'	C5'	C6'	C6B'	12.0					
C1'	C5'	C6'	C7'	132.2					
N4'	C5'	C6'	C6A'	4.0					
N4'	C5'	C6'	C6B'	126.0					
N4'	C5'	C6'	C7'	-113.0					
C10'	C5'	C6'	C6A'	122.7					
C10'	C5'	C6'	C6B'	-114.7					

5.2 X-ray Structure of Adduct 271

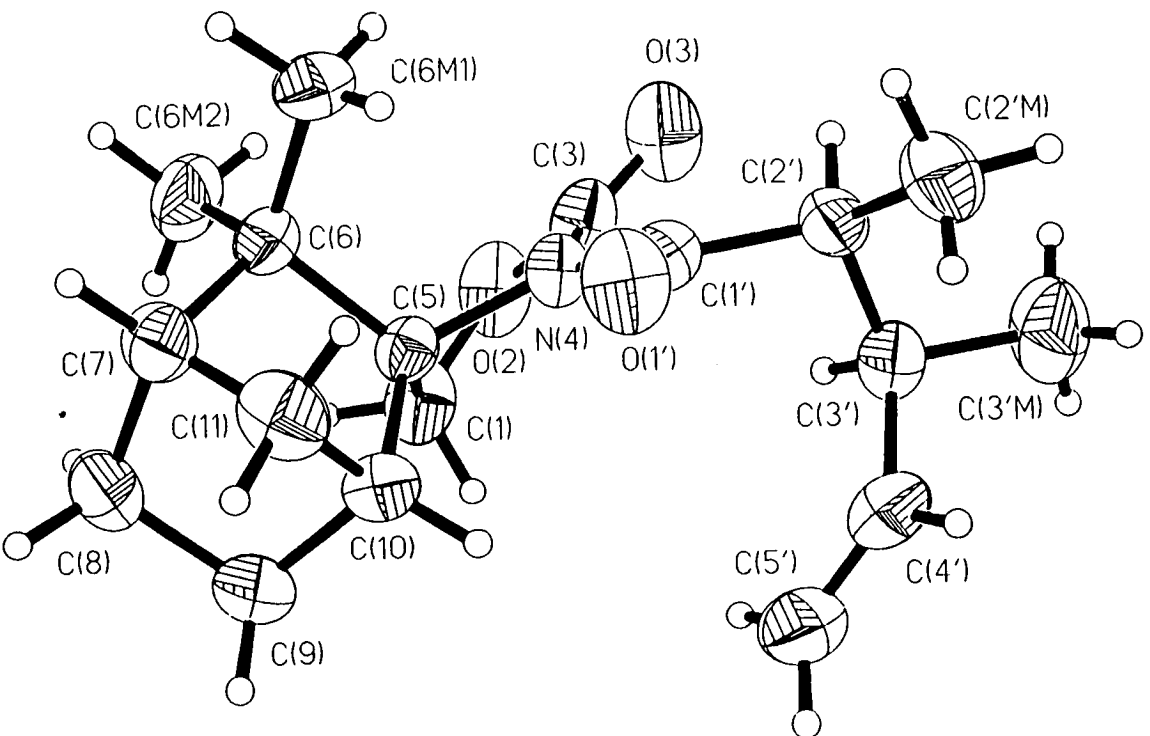


Table 1. Crystal data and structure refinement for 1.

Identification code	ptnben
Empirical formula	$C_{18}H_{27}NO_3$
Formula weight	305.41
Temperature	296(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1$
Unit cell dimensions	$a = 7.432(2)$ Å $\alpha = 90^\circ$ $b = 14.912(4)$ Å $\beta = 96.89(3)^\circ$ $c = 7.603(3)$ Å $\gamma = 90^\circ$
Volume, Z	836.5(5) Å ³ , 2
Density (calculated)	1.212 Mg/m ³
Absorption coefficient	0.082 mm ⁻¹
F(000)	332
Crystal size	1.50 x 1.25 x 0.75 mm
θ range for data collection	2.70 to 30.05°
Limiting indices	$-10 \leq h \leq 10$, $0 \leq k \leq 21$, $0 \leq l \leq 10$
Reflections collected	2534
Independent reflections	2534 ($R_{int} = 0.0000$)
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2534 / 1 / 204
Goodness-of-fit on F^2	1.053
Final R indices [$I > 2\sigma(I)$]	$R1 = 0.0613$, $wR2 = 0.1534$
R indices (all data)	$R1 = 0.0671$, $wR2 = 0.1606$
Absolute structure parameter	0(2)
Extinction coefficient	0.011(9)
Largest diff. peak and hole	0.444 and -0.261 eÅ ⁻³

Table 2. Atomic coordinates [$\times 10^4$] and equivalent isotropic displacement parameters [$\text{\AA}^2 \times 10^3$] for 1. $U(\text{eq})$ is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	$U(\text{eq})$
C(1)	1722(3)	3747(2)	9880(4)	49(1)
O(2)	712(2)	4053(2)	8238(3)	57(1)
C(3)	1076(3)	3505(2)	6920(4)	47(1)
O(3)	330(3)	3564(2)	5450(3)	65(1)
N(4)	2466(2)	2921(1)	7588(2)	37(1)
C(5)	3392(2)	3295(1)	9307(3)	34(1)
C(6)	5018(3)	3957(2)	9058(3)	40(1)
C(6M1)	5726(4)	3813(2)	7254(3)	55(1)
C(6M2)	4595(5)	4960(2)	9194(4)	59(1)
C(7)	6463(3)	3624(2)	10567(3)	47(1)
C(8)	5854(4)	3795(2)	12410(3)	57(1)
C(9)	4387(4)	3070(2)	12530(3)	56(1)
C(10)	4245(3)	2611(2)	10688(3)	43(1)
C(11)	6255(3)	2606(2)	10424(4)	53(1)
C(1')	2838(3)	2103(2)	6807(3)	39(1)
O(1')	4230(2)	1713(1)	7277(3)	56(1)
C(2')	1371(3)	1696(2)	5461(3)	42(1)
C(2'M)	2156(4)	908(2)	4523(4)	59(1)
C(3')	-275(3)	1436(2)	6436(3)	45(1)
C(3'M)	-1831(5)	1047(3)	5127(6)	78(1)
C(4')	246(4)	790(2)	7919(4)	54(1)
C(5')	175(5)	958(3)	9596(4)	66(1)

Table 3. Bond lengths [Å] and angles [°] for 1.

C(1)-O(2)	1.450(4)	C(1)-C(5)	1.522(3)
O(2)-C(3)	1.345(3)	C(3)-O(3)	1.190(3)
C(3)-N(4)	1.400(3)	N(4)-C(1')	1.398(3)
N(4)-C(5)	1.509(3)	C(5)-C(10)	1.544(3)
C(5)-C(6)	1.589(3)	C(6)-C(6M2)	1.534(4)
C(6)-C(6M1)	1.542(3)	C(6)-C(7)	1.556(3)
C(7)-C(11)	1.528(5)	C(7)-C(8)	1.545(4)
C(8)-C(9)	1.546(4)	C(9)-C(10)	1.551(4)
C(10)-C(11)	1.531(4)	C(1')-O(1')	1.203(3)
C(1')-C(2')	1.529(3)	C(2')-C(2'M)	1.527(4)
C(2')-C(3')	1.554(4)	C(3')-C(4')	1.497(4)
C(3')-C(3'M)	1.545(4)	C(4')-C(5')	1.307(5)
O(2)-C(1)-C(5)	104.4(2)	C(3)-O(2)-C(1)	108.7(2)
O(3)-C(3)-O(2)	122.9(2)	O(3)-C(3)-N(4)	128.8(2)
O(2)-C(3)-N(4)	108.3(2)	C(1')-N(4)-C(3)	124.3(2)
C(1')-N(4)-C(5)	126.7(2)	C(3)-N(4)-C(5)	108.9(2)
N(4)-C(5)-C(1)	96.2(2)	N(4)-C(5)-C(10)	116.8(2)
C(1)-C(5)-C(10)	112.4(2)	N(4)-C(5)-C(6)	113.6(2)
C(1)-C(5)-C(6)	114.7(2)	C(10)-C(5)-C(6)	103.6(2)
C(6M2)-C(6)-C(6M1)	106.9(2)	C(6M2)-C(6)-C(7)	112.9(2)
C(6M1)-C(6)-C(7)	109.4(2)	C(6M2)-C(6)-C(5)	115.6(2)
C(6M1)-C(6)-C(5)	111.4(2)	C(7)-C(6)-C(5)	100.5(2)
C(11)-C(7)-C(8)	101.0(2)	C(11)-C(7)-C(6)	102.1(2)
C(8)-C(7)-C(6)	111.4(2)	C(7)-C(8)-C(9)	102.9(2)
C(8)-C(9)-C(10)	103.2(2)	C(11)-C(10)-C(5)	103.9(2)
C(11)-C(10)-C(9)	99.1(2)	C(5)-C(10)-C(9)	107.4(2)
C(7)-C(11)-C(10)	94.5(2)	O(1')-C(1')-N(4)	120.2(2)
O(1')-C(1')-C(2')	121.7(2)	N(4)-C(1')-C(2')	118.0(2)
C(2'M)-C(2')-C(1')	109.7(2)	C(2'M)-C(2')-C(3')	113.4(2)
C(1')-C(2')-C(3')	108.6(2)	C(4')-C(3')-C(3'M)	110.5(3)
C(4')-C(3')-C(2')	111.9(2)	C(3'M)-C(3')-C(2')	110.9(3)
C(5')-C(4')-C(3')	125.1(3)		

Symmetry transformations used to generate equivalent atoms:

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SYNTHESIS OF ENANTIOMERICALLY PURE (5S)-4-AZA-2-OXA-6,6-DIMETHYL-7,10-METHYLENE-5-SPIRO[4.5]DECAN-3-ONE, A NOVEL CHIRAL OXAZOLIDIN-2-ONE FROM (-)-CAMPHENE FOR USE AS A RECYCLABLE CHIRAL AUXILIARY IN ASYMMETRIC TRANSFORMATIONS

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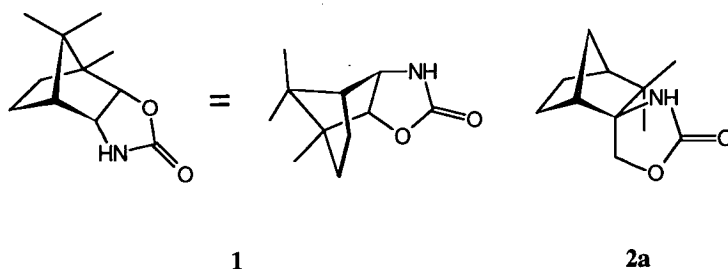
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Abstract- By an intramolecular nitreno-mediated route (-)-camphene is transformed into a novel spiro-oxazolidin-2-one whose efficiency as a chiral auxiliary is highlighted by the excellent levels of chiral induction attained in an array of asymmetric transformations such as the Diels -Alder, conjugate addition, aldol condensation, alkylation and acylation reactions.

Preparative access to chiral oxazolidin-2-ones, whether as reagents for asymmetric manipulations¹ or as chiral derivatising agents (CDA) for the resolution of racemic amines *etc.*, employ direct cyclocarbamation of relatively expensive optically pure β -amino alcohols, or resort to the tedious separation of similarly prepared racemic analogues.² We have recently reported the enantiospecific synthesis of a terpenoid-derived tricyclic oxazolidin-2-one (**1**) from readily available [(1S)-*endo*]-(-)-borneol by a nitreno-mediated route and demonstrated its usefulness as a chiral auxiliary in a variety of asymmetric transformations³ and as a CDA for the resolution of racemic amines, carboxylic acids and alcohols.⁴ The reagent (**1**) performed well in acylation, alkylation and aldol reactions but Lewis-acid mediated Diels-Alder reactions were disappointing. The reason for this unsatisfactory diastereoselection was thought to be steric in origin and reflected the

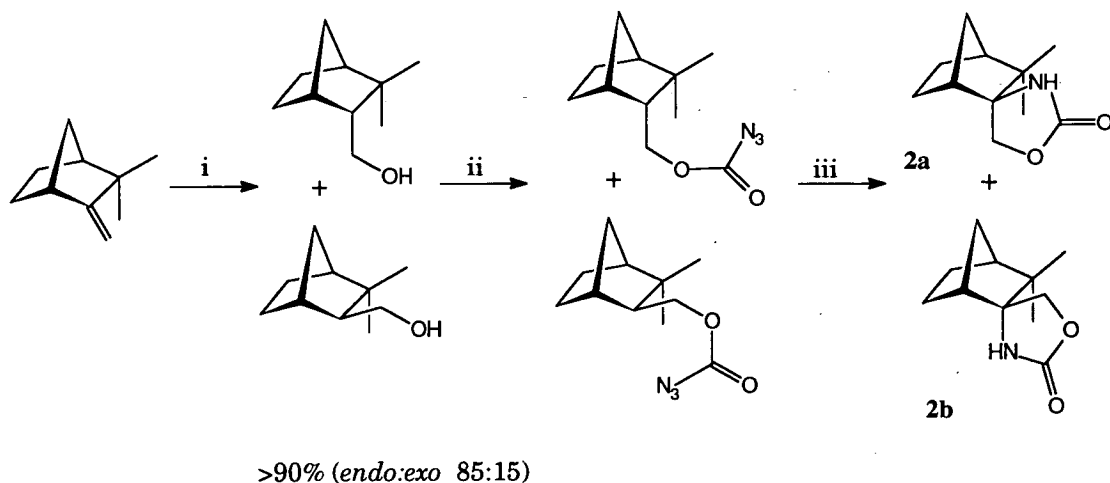
We dedicate this paper to our friend and colleague Professor Alan Katritzky, FRS on the occasion of his 65th birthday and in recognition of his many pioneering contributions to, and stentorian enthusiasm for, heterocyclic chemistry.

inability of **1** to provide the required topological bias to control rotameric preference in the conformations adopted by its *N*-substituted acryloyl derivatives.



With this in mind, we have designed a camphene-based oxazolidin-2-one (**2a**) with the necessary control element, *i.e.* masked *tert*-butyl group, to improve π -face discrimination and bring about very high levels of diastereoselection in Diels-Alder reactions and other asymmetric transformations. In this connection it is worth noting that due to propitious blocking of different faces of the oxazolidin-2-one ring in auxiliaries (**1**) and (**2a**), products of the opposite stereochemical sense will result in the ensuing diastereoselective processes.

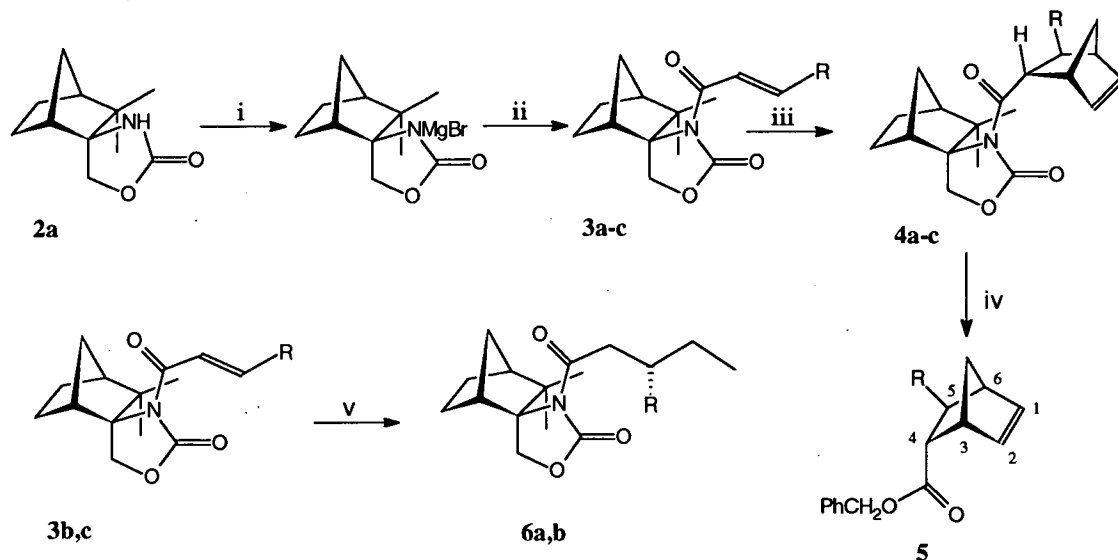
For the preparation of the new chiral reagent (**2a**) in an optically pure state we used the same device of intramolecular nitrene delivery as before. This process outlined in Scheme 1 was achieved *via* hydroboration



Scheme 1

Reagents and conditions: i, BH_3 :THF then KOH, H_2O_2 ; ii, 3COCl_2 , 1.1NEt₃ (>95%) isolate then 2NaN_3 , PTC (>95%); iii, thermolysis in TCE, 147°C, (65-70%).

of (-)-camphene⁵ which yielded predominantly *endo*-camphenol in excellent yield (>90%, *endo:exo* 85:15). Conversion of the isomeric alcohols into their azidoformates *via* the chloroformate and subsequent thermolysis by dropwise addition to boiling 1,1,2,2-tetrachloroethane (TCE) at 2-3% concentration gave a 90% yield of an epimeric mixture of the spiro-oxazolidin-2-ones (**2a**) and (**2b**) from which **2a** was isolated in 65-70% yield after two fractional crystallisations from CH₂Cl₂: cyclohexane.⁶ The spiro-oxazolidin-2-ones (**2a**) and (**2b**) could also be easily separated by flash chromatography on silica using ether: n-hexane as eluent.



Scheme 2

Reagents and conditions: i, MeMgBr, THF; ii, RCH=CHCOCl, -78°C, (**3a**, R=H, **3b**, R=Me, **3c**, R=Ph; yields: 29, 80, 87% respectively); iii, cyclopentadiene, 1.6 Et₂AlCl, CH₂Cl₂ -78°C; iv, 1.5 PhCH₂OH/BuⁿLi, THF, -78°C to room temperature; v, 4 Et₂AlCl, -78°C (**6a**, R=Me, **6b**, R=Ph; yields: 100, 100% respectively).

In order to prepare the chiral unsaturated carboximides (**3a-c**) as dienophiles for the Diels-Alder reactions, we adopted the method of Evans⁷ whereby the oxazolidin-2-one (**2a**) was treated successively with MeMgBr and the appropriate α,β -unsaturated acid chloride in THF under carefully controlled conditions (Scheme 2). Cycloaddition of **3a-c** with freshly cracked cyclopentadiene in CH₂Cl₂ occurred at -78°C in the presence of 1.6 equiv. of Et₂AlCl as Lewis-acid promoter to produce adducts (**4a-c**) in almost quantitative yield. From the results of these reactions shown in Table 1 it is evident that auxiliary (**2a**) induces significantly

higher levels of diastereoselection in the Diels-Alder reactions than the corresponding reactions with **1**.⁸ Moreover, cleavage of **4b** and **4c** with lithium benzyl oxide afforded the 4*S*, 5*S* benzyl esters (**5b**) [91%, $[\alpha]_D = +127^\circ$ (20°C, *c* = 2.44, CH₂Cl₂)] and (**5c**) [95%, $[\alpha]_D = +124^\circ$ (22°C, *c* = 2.36, CH₂Cl₂)] of opposite sign to those obtained with **1** but identical to those derived with Evans' (*S*)-valinol-based oxazolidin-2-one.⁷ In both cases auxiliary (**2a**) was recovered unchanged in 90% and 97%, respectively.

Table 1. Et₂AlCl-promoted reactions of dienophiles (**3a-c**) with cyclopentadiene to produce (**4a-c**) including corresponding yields for analogues derived from (**1**).

Compound	%Yield 4a-c (corresponding % yield for 1)	de %* (corresponding de% for 1)
3a , R=H	98 (98)	>95 (60)
3b , R=Me	99 (96)	99 (60)
3c , R=Ph	97 (99)	98 (99)

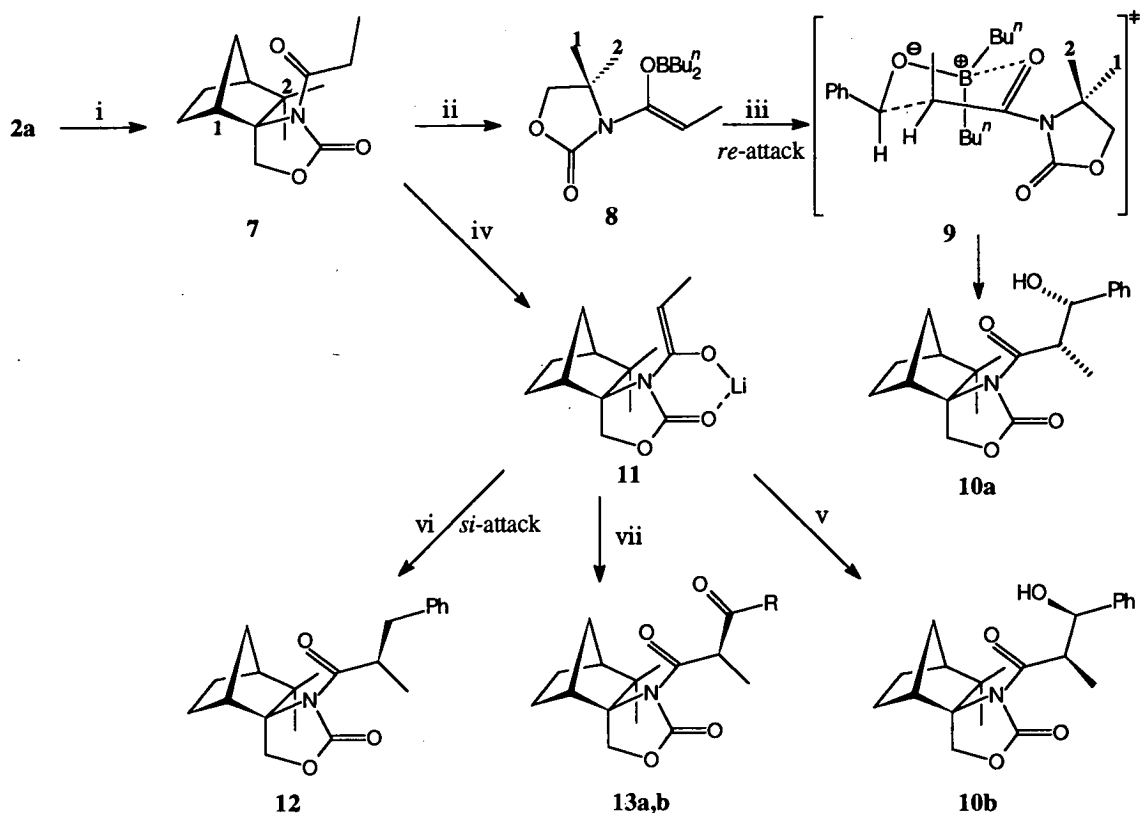
*Diastereoisomeric excesses (de) were determined by 360 MHz ¹H nmr spectroscopy.

With the crotonoyl and cinnamoyl derivatives (**3b**) and (**3c**) in hand we decided to investigate the stereochemical outcome of their 1,4-conjugate addition reaction with Et₂AlCl (4 equiv.). Both chiral unsaturated carboximides readily underwent β-alkylation reactions from the re-face to give products (**6a**) and (**6b**) in quantitative yield with excellent diastereoselection (**6a**, de 99%; **6b**, de 90%) when compared to the corresponding adducts from **1** (11%, 43%de respectively). In each case cleavage of the adduct with lithium hydroperoxide afforded the chirally pure pentanoic acid, *e.g.* 3*S*-phenyl, in quantitative yield with almost complete recovery of the auxiliary.

On the basis of the markedly increased steric shielding provided by the new auxiliary (**2a**) *vis-à-vis* (**1**) in the foregoing reactions, we synthesised the crystalline *N*-propionyl derivative (**7**) (78% yield) as shown in Scheme 3 in order to probe its effectiveness as a chiral auxiliary in aldol, alkylation and acylation reactions. The aldol condensation was studied involving both chiral boron (**8**) and lithium enolates (**11**) in reactions with PhCHO in CH₂Cl₂. Excellent diastereoselection was observed with the dibutylboron enolate (**8**) (de 95%) and the major aldol product (**10a**) was determined to be *erythro* by high field ¹H nmr spectroscopy (*J* = 5.2 Hz) with the *threo*-products accounting for less than 5% of the crude reaction mixture. Subsequent cleavage of **10a** with lithium hydroperoxide followed by methylation with diazomethane afforded methyl

(2*S*, 3*S*)-2-methyl-3-hydroxy-3-phenyl propionate [94%, $[\alpha]_D = -19.2^\circ$ (18°C, $c = 4.4$, CH_2Cl_2)]⁹ which verified the assigned stereochemistry as shown in Scheme 3.

By comparison, only moderate diastereoselectivity was found in the case of the lithium-chelated (*Z*)-enolate (11) generated from **7** with freshly prepared Pr^i_2NLi (*erythro:threo* 81:19, *erythro* de 31%). A noteworthy feature of this reaction is that the *erythro*-isomer (10a) generated using boron is diastereomerically opposed to its isomer (10b) obtained with lithium as the counter-ion, this reversal in topicity arising because of the cyclic chelate (11).



Scheme 3

Reagents and conditions: i, 3.0 M MeMgBr in Et_2O , THF, 0°C then -78°C , EtCOCl ; ii, 1 M di-*n*-butylboron triflate in CH_2Cl_2 , 0°C , Pr^i_2EtN ; iii, -78°C , PhCHO ; iv, 1.1 Pr^i_2NLi , 0°C , THF; v, -78°C , PhCHO ; vi, -78°C , PhCH_2Br , NaI then -10°C ; vii, -78°C , RCOCl , (13a, $\text{R}=\text{Me}$, 13b, $\text{R}=\text{Et}$); yields: 90, 97% respectively).

The poor levels of stereoregulation found in the lithium enolate-mediated reaction matches those results obtained for chiral auxiliary (1) and PhCHO ,³ in keeping with similar results reported by other groups for

chiral auxiliaries derived from (1*S*, 2*R*)-norephedrine¹⁰ and (+)-camphor.¹¹ The greater diastereoselectivity achieved with the use of the boron enolate (**8**) is comparable to the auxiliaries just mentioned and can be rationalised in terms of the Zimmerman-Traxler six-membered cyclic transition state (**9**)¹² in which only the C $_{\alpha}$ -*re* face is open to attack.

It has been suggested by Heathcock¹³ that the lithium cation can simultaneously coordinate three oxygen atoms in the transition state, which in turn orients the auxiliary in such a way that the two enolate faces are differentiated. On the other hand, boron bears two butyl substituents and can coordinate only two oxygens as depicted in (**9**). Since boron enolates are not very reactive species it is necessary that the aldehydic carbonyl be activated before aldol addition can occur. The required carbonyl-activation is brought about by coordination with a Lewis acid. In the absence of an external Lewis acid this activation must be provided by the boron atom and it follows that in the closed transition state (**9**) boron is coordinated with oxygen from the enolate and aldehyde and can no longer be coordinated with the oxazolidinone carbonyl group.

The opposite sense of diastereofacial bias imparted by **2a** when compared to **1** is further reflected in the alkylation of the chelated lithium enolate (**11**) with PhCH₂Br at -10°C in the presence of NaI which proceeded from the less hindered *si*-face to produce α -alkylated **12** with *R*-configuration in 74% yield with a de of 84%. By comparison the analogous reaction with **1** gave the (*S*)-alkylated product in 80% yield with a de of >99%. Similarly, reaction between lithium enolate (**11**) and acyl chlorides at -78°C produced *C*-acylated derivatives (**13a**) and (**13b**) in high chemical and optical yield (**13a** de 86%, **13b** de >90%). This result compares well with the selectivity found for the associated reactions reported for **1** (R=Me, yield 88%, de 82%; R=Et, yield 89%, de >99%).³

On the basis of these preliminary results it is evident that the (-)-camphene-derived spirooxazolidin-2-one (**2a**) constitutes a powerful new addition to the existing armoury of preparatively useful chiral auxiliaries. For most asymmetric transformations, and especially Lewis acid-mediated Diels-Alder reactions, it offers exceptionally high levels of diastereofacial differentiation, and in this respect, it is superior to its predecessor, the likewise terpenoid-based tricyclic oxazolidin-2-one (**1**). An added benefit to **2a** is that its optical antipode is readily accessible from (+)-camphene, which in turn can be obtained from cheap (+)- α -pinene in two steps, thereby allowing preparative access to both enantiomeric products in a range of asymmetric manipulations.

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Exploiting Steric Shielding: Tuning Terpenoid-Derived Oxazolidin-2-ones as Chiral Auxiliaries for the Diels-Alder Reaction

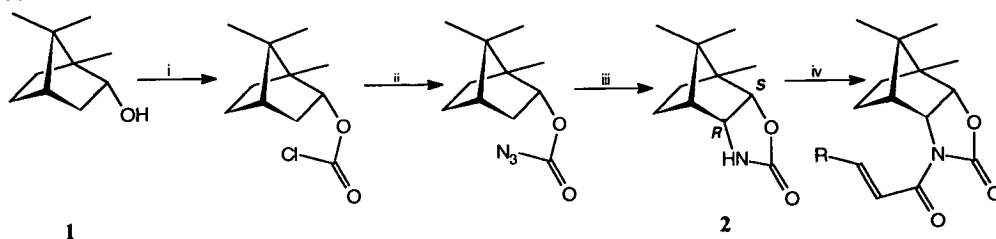
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Abstract: Preparative methodology is described for access to three different terpenoid-derived oxazolidin-2-ones **4**, **8**, and **11**, of which the latter, obtained from camphene in four steps, provides virtually complete asymmetric induction when acting as a chiral auxiliary in Diels-Alder cycloaddition reactions with cyclopentadiene.

Following the seminal work by Evans¹ on the development of chiral oxazolidin-2-ones as auxiliaries in asymmetric reactions there have been numerous efforts² to design more efficient variants including a recent report by us³ on the promising use of the enantiomerically pure 4,5-disubstituted oxazolidinone **2** which is sterically constrained by the rigid bornyl system. Preparative access to **2** was achieved by a nitrene-mediated three-step sequence from (-)-borneol **1** as depicted in Scheme 1 and although high levels of asymmetric induction were observed with **2** in alkylation, acylation and aldol reactions, Diels-Alder reactions were much less effective (Table 1) due to insufficient π -topological bias provided by the auxiliary when bearing acryloyl substituents.

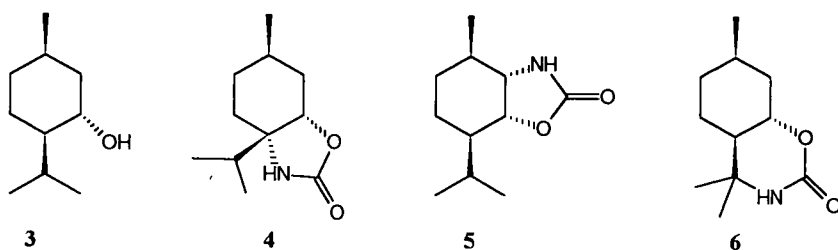


Scheme 1. Reagents and conditions: (i) phosgene, triethylamine, toluene-ether, 0°C, 4h; (ii) sodium azide, tetrabutylammonium bromide, dichloromethane-water, 25°C, 4h; (iii) flash vacuum thermolysis (300°C, 0.02 mmHg); (iv) *n*-butyl lithium, or methylmagnesium bromide followed by the appropriate α,β -unsaturated acid chloride (R = H, Me, Ph).

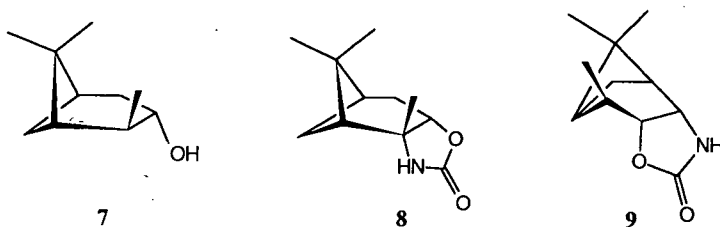
In this letter we describe the preparation of other likewise terpenoid-based oxazolidin-2-ones with the aim of introducing the necessary control element to bring about improved π -face discrimination in Diels-Alder reactions. For each new homochiral reagent the same synthetic protocol as used for **2** was employed and involved chloroformylation of the terpene alcohol followed by conversion into the corresponding azidoformate

and thermolysis under flash vacuum conditions⁴ or in boiling 1,1,2,2-tetrachloroethane (TCE). In the final step to the required chiral dienophiles for use in asymmetric Diels-Alder reactions, the isolated oxazolidin-2-ones were functionalised at nitrogen with the appropriate α,β -unsaturated acid chloride by prior treatment with *n*-butyl lithium, or alternatively, methylmagnesium bromide to avoid polymerisation which could be a problem with acryloyl chloride.

The first terpene alcohol to be used as starting material was inexpensive *iso*-menthol **3** which was converted readily into the desired azidoformate in quantitative yield. Unfortunately when subjected to flash vacuum thermolysis, the latter gave rise to a mixture of two oxazolidin-2-ones **4** and **5** from nitrene insertion at C-2 and C-6, together with the six-membered oxazinone **6** originating from nitrene attack on the *iso*-propyl group, in the ratio of 7:1:2 respectively. The major oxazolidinone **4** could be isolated, albeit as a thick syrup (51%), but further applications of this auxiliary were not pursued when attempts to functionalise it resulted in the formation of thick gums which proved extremely difficult to purify.



Greatly improved crystallinity was found from the same sequence of reactions when (-)-3-pinanol **7** was used as starting material. Thermolysis of its azidoformate under flash vacuum conditions (300°C, 0.02 mmHg) afforded a mixture consisting of oxazolidin-2-ones **8** and **9** in the ratio 3:1, reflecting the tendency of the nitrene intermediate to insert preferentially into *tertiary* C-H bonds compared with *secondary* C-H bonds. The major isomer could be easily isolated in 65% yield as colourless crystals (m.p. 155.5-156.0°C; $[\alpha]_D = -71.5^\circ$ ($c = 3.36$, CH_2Cl_2)) following trituration with diethyl ether and recrystallisation from ethyl acetate.



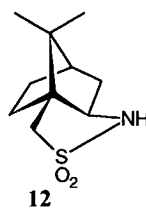
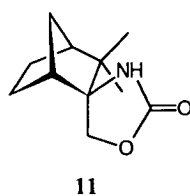
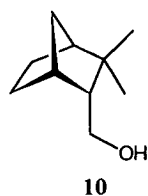
Disappointingly, the sterically crowded oxazolidin-2-one **8** imparted only poor levels of asymmetric induction in Et_2AlCl -mediated Diels-Alder cycloadditions of its *N*-acryloyl, *N*-crotonoyl, and *N*-cinnamoyl derivatives with cyclopentadiene (Table 1). This outcome is reflected in the X-ray structure of **8** (Fig. 1a) at 150K which establishes that both of its faces, and in consequence, those of the acrylate derivatives, are hindered to a similar degree, one by the methyl substituent adjacent to nitrogen and the other by the bridging methylene group of the four-membered ring of the terpenoid moiety.

Table 1. Diastereoselection in Lewis-acid catalysed Diels-Alder Cycloadditions of Chiral Acrylate Derivatives of Oxazolidin-2-ones **2**, **8**, and **11** with Cyclopentadiene

Auxiliary Aux*H	R	Temp (°C)	Yield (%)	<i>endo:exo</i>	<i>endo</i> d.e. ^a A(R):B(S)
 2	H	-78	98	96:4	59
	Me	-78	96	100:0	71
	Ph	-20	99	100:0	99
 8	H	-78	92	93:7	25
	Me	-78	100	97:3	33
	Ph	-20	96	95:5	32
 11	H	-78	98	>99:1	95
	Me	-78	99	>99:1	99
	Ph	-78	97	>99:1	99

^aDetermined by 360MHz ¹H NMR spectroscopy.

For this reason we chose *endo*-camphenol **10** (prepared from (-)-camphene by hydroboration followed by treatment with KOH/H₂O₂)⁵ as the starting material and by a similar reaction process, albeit decomposition of the azidoformate in boiling TCE, to our pleasure obtained in 70% yield after recrystallisation from CH₂Cl₂/cyclohexane the spiro-oxazolidin-2-one **11** in enantiomerically pure form as a colourless crystalline compound (m.p. 226-227°C, [α]_D = +48°(c = 5.1, CH₂Cl₂)) whose structure was confirmed by X-ray crystallography (Fig.1b). The sole formation of **11** is notable when compared to the two previous processes, but can be explained by the overwhelming bias for nitrene insertion at C-3 to form a five-membered ring and the more sterically demanding option of attack at C-4 to afford a much less favoured six-membered ring.



The efficiency of **11** as a chiral control element in the corresponding Diels-Alder reactions of its acrylate derivatives with excess cyclopentadiene are also given in Table 1. From the data it is evident that cycloaddition is regulated with much higher diastereoselectivity than that previously obtained with **4** and **8**. In each case *endo*-diastereoselection is *virtually complete* (in favour of adduct **A**), and to our knowledge, well in excess of levels attained by conventional chiral oxazolidin-2-ones⁶ derived from amino acids, and even Oppolzer's camphor sultam **12**⁷, which requires temperatures as low as -130°C to bring about a comparable outcome for the acryloyl (R = H) dienophile.

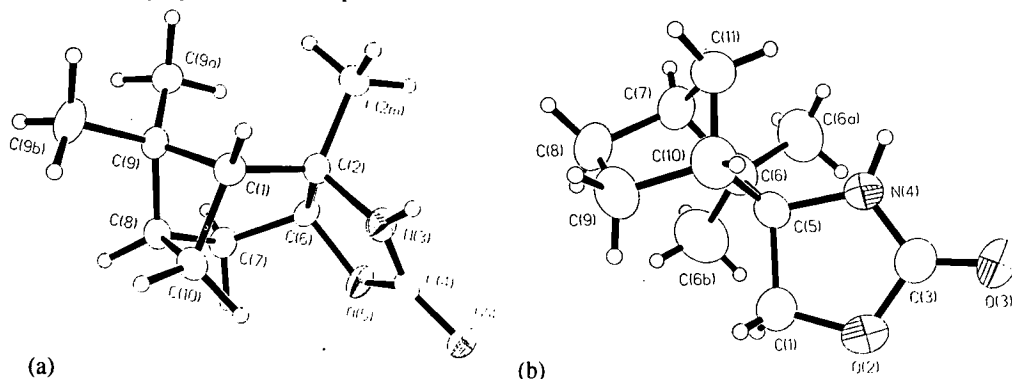


Figure 1. ORTEP drawings of (a) oxazolidin-2-one **8** derived from (-)-pinanol, and (b) spirooxazolidin-2-one **11** derived from *endo*-camphenol.

This exceptional quality of asymmetric induction imparted by spirooxazolidin-2-one **11** is undoubtedly the result of propitious shielding of one of its faces by the masked *tert*-butyl group (see Fig. 1b), an effect that is extended to its acrylate derivatives such that cyclopentadiene can approach from one direction only.

Thus, we have successfully developed a powerful new addition to the panoply of chiral oxazolidin-2-ones for asymmetric chemical conversions. Work is now in progress to exploit and expand the synthetic usefulness of this new reagent and details will be reported in due course.

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Chiracamphox

A Practical and Highly Versatile Reagent for use in Asymmetric Transformations

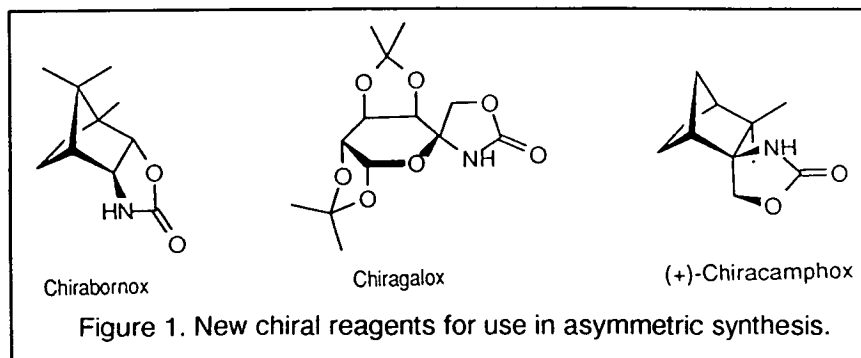
Banks, M.R.^a; Cadogan, J.I.G.^b; Gosney, I.^a; Hodgson, P.K.G.^c and Thorburn, P.^a,

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b) Department of Chemistry, Imperial College of Science, Technology and Medicine, South Kensington, London SW7 2AY, England;
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Abstract : *Chiracamphox, a new and highly crystalline terpenoid-based spiro-oxazolidin-2-one, which proves to be a widely effective chiral auxiliary by contemporary standards, shows many practical advantages, including availability in both enantiomeric forms and benefits from ease of recyclability.*

Over the last decade there has been sustained interest in the development and use of optically-pure oxazolidin-2-ones as chiral auxiliaries (1) due to the breadth of asymmetric reactions which their derivatives undergo with good levels of diastereoselection. Combined with this function, further valuable facets such as the ease of determination of diastereomer ratios, facile purification and straight-forward cleavage of adducts with recovery of the auxiliary, make these reagents one of the most reliable and versatile tools in the armoury of organic chemists for the synthesis of homochiral fragments.

of chiral reagents including those shown in Figure 1, all of which can be obtained in an optically-pure state in multi-gram quantities. Each auxiliary possesses its own areas of strength and all are highly crystalline in nature and consequently impart good crystallinity to derivatives such that diastereomeric purity can be raised in each case by simple recrystallisation. Chirabornox (2)



For the past five years, our laboratory has been actively seeking access to more preparatively useful chiral oxazolidin-2-ones by elaboration of compounds from the 'Chiral Pool'. The outcome has been the synthesis of a number

displays high selectivity in enolate chemistry whilst Chiragalox (3) is more suited to enoyl chemistry such as Diels-Alder cycloadditions, though both are effective resolving agents.

Chiracamphox (4) is particularly useful in cases where a high degree of shielding is necessary to provide adequate diastereoselection; coupled with this it is efficient in a wide range of asymmetric transformations and generally affords adducts with high diastereomeric excesses (d.e.). An added benefit of chiracamphox is that both enantiomers are readily available.

Both N-acyl and N-enoyl derivatives are readily prepared (Scheme 1, typical procedure) in

generally high yields (5) via halomagnesium salts

effective in a range of asymmetric aldol

condensations with a variety of

aldehydes as exemplified by the

excellent quality of diastereocontrol in

the condensation with benzaldehyde to

furnish a product with virtually

complete syn-stereoselection (Scheme 2).

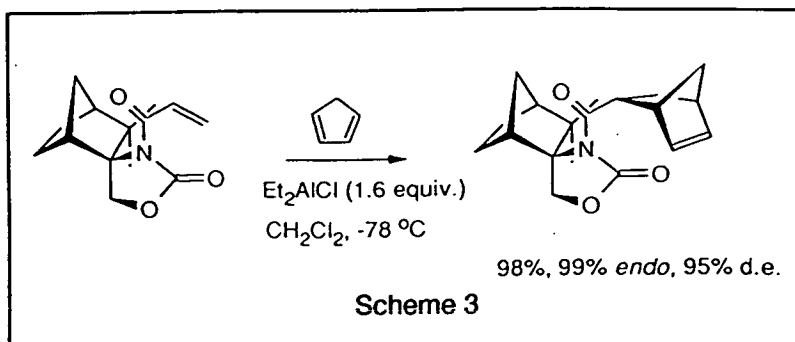
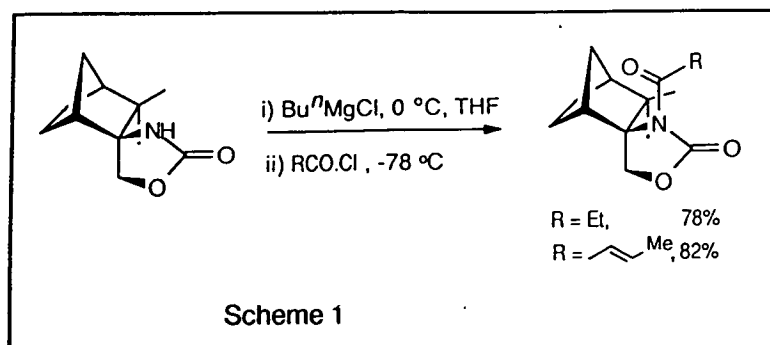
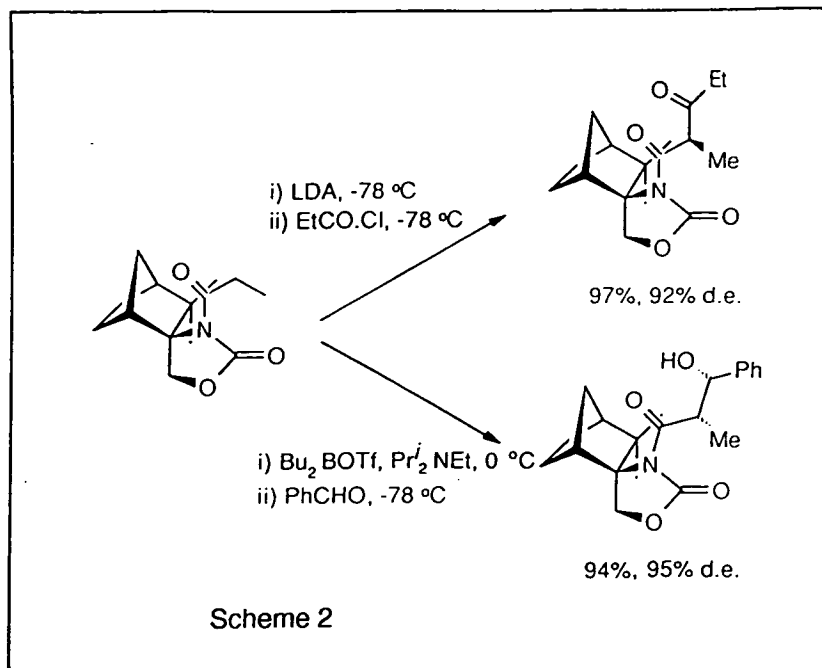
The beneficial shielding action of the conformationally fixed geminal methyl

of chiracamphox. For the preparation of the propionyl imide ($R=Et$) on a large scale, it is advantageous to add one equivalent of anhydrous zinc chloride to the halomagnesium salt prior to the addition of the acid chloride.

Treatment of the propionyl imide with a variety of bases gives access to alkali metal enolates which react with a high degree of stereospecificity with acyl and reactive alkyl halides to furnish crystalline, readily purified adducts as shown in Scheme 2. In aldol reactions the corresponding lithium enolates unsurprisingly (6) give products with low d.e., but boron enolates (7) have proved very

groups of Chiracamphox is particularly evident in the stereocontrol of Lewis-acid catalysed asymmetric Diels-Alder cycloadditions and 1,4-conjugate additions to its enoyl derivatives.

Diethylaluminium chloride proves to be an effective catalyst for Diels-Alder reactions, and even in the most difficult case involving the N-acryloyl dienophile (8), convenient laboratory conditions (as

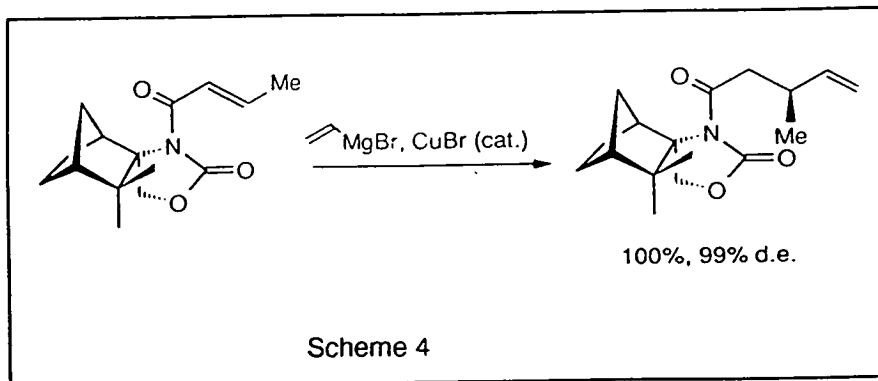


exemplified in the experimental section) bring about almost complete asymmetric induction upon reaction with cyclopentadiene (Scheme 3). Both aluminium reagents (9) and magnesium reagents (10) (the latter only in the presence of copper catalysts) undergo exclusive 1,4-conjugate additions to give β -alkyl carboxylic acid equivalents virtually as a single diastereomer in quantitative

Typical experiment:

Preparation of crotonyl imide: To a dry, argon flushed, flask charged with Chiracamphox (3.90g, 20 mmol.) and dry THF (180ml), is added butylmagnesium chloride (10.5ml, 2M in THF, 21 mmol.) at 0°C. After 15 min. the vessel is cooled to -78°C and freshly distilled crotonyl chloride (2.4, 23

mmol.) in THF (7ml) added via a syringe. After 4 hours at room temperature aqueous work-up and evaporation yields a yellow solid, flash chromatography of which (silica, hexane / ether, 4:1) followed by evaporation affords the imide as colourless

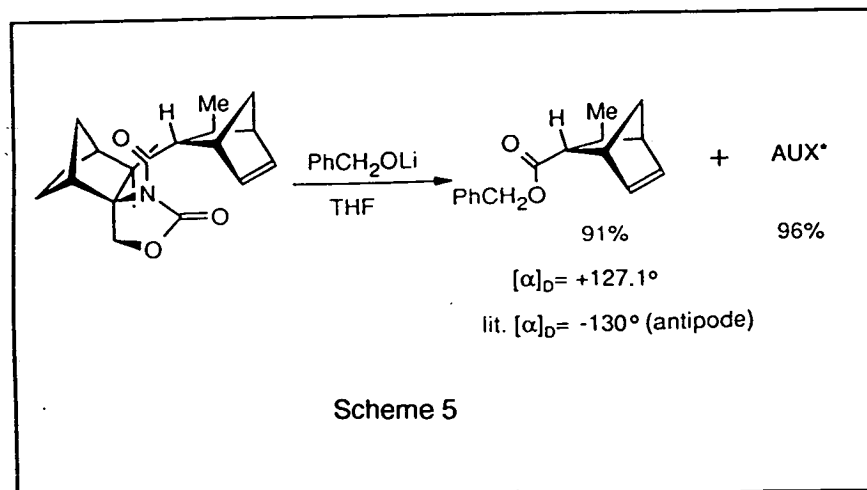


yield, e.g., copper-catalysed addition of vinyl Grignard to the N-crotonyl imide derived from (-)-Chiracamphox as shown in (Scheme 4).

The majority of derivatives and chiral adducts of Chiracamphox are highly crystalline and can be readily purified by a single recrystallisation to yield diastereomerically pure compounds. In each case, subsequent cleavage with reagents such as lithium hydroperoxide (11), or lithium benzyloxide (1a) as exemplified in Scheme 5 for the Diels-Alder cycloadduct, furnishes high yields of the homochiral fragment together with almost complete recovery of the auxiliary (AUX*) for re-use.

needles (4.31g, 82%), mp= 113-114 °C, $[\alpha]_D^{25} = +145.20$ (c=2.1, CH₂Cl₂).

Preparation of cyclopentadiene adduct: To a dry, argon flushed, flask charged with crotonyl imide (0.65g, 2.47 mmol.) and dry CH₂Cl₂ (25ml) at -78°C, freshly distilled cyclopentadiene (0.8g, 12.1 mmol.) in CH₂Cl₂ (3ml) is added followed by diethylaluminium chloride (2.2ml, 1.8M in toluene, 4 mmol.), both via syringe. After 20 min. the initial yellow colouration fades and the reaction is quenched with NH₄Cl/H₂O and aqueous work-up followed by rapid chromatography on silica affords



colourless crystals (800mg, 98%). High-field ¹H NMR

spectroscopy shows only one diastereomer (99% d.e.).

Recrystallisation from CH₂Cl₂/hexane yields fine colourless crystals of the cyclopentadiene adduct (760mg, 93%), mp= 182-183 °C, $[\alpha]_D^{25} = +251.80$ (c=1.5, CH₂Cl₂).

Keywords :

R/asymmetric reactions, R/aldol condensation, SM/alkali metal enolates SM/boron enolates, SM/chiral auxiliary, R/1,4 conjugate addition, R/Diels-Alder cycloaddition, SM/diethylaluminium chloride, SM/enoylimides, SM/oxazolidin-2-ones; SM/propionyl imide.

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29.643.58 (-)-Chiracamphox

500 mg

(5R-4-Aza-2-oxa-6,6-dimethyl-7,10-methylene-5-spiro(4.5)decan-3-one



0040-4039(95)00560-9

A Concise Synthesis of (-)-Dihydroprotolichesterinic Acid *via* Consecutive Stereocontrolled 1,4-Conjugate Addition and *syn*-Aldol Condensation Reactions

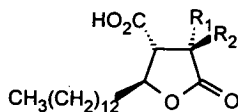
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Middlesex TW16 7LN, England

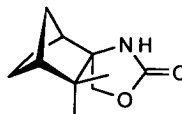
Abstract : (-)-Dihydroprotolichesterinic acid **1a** is synthesised in 6 steps and 57% overall yield by a strategy employing the camphene-derived chiral auxiliary **2** to construct the three contiguous stereogenic centres in consecutive stereocontrolled 1,4-conjugate addition and *syn*-aldol reactions.

Interest in the enantioselective synthesis of paraconic fatty acids has grown in recent years due to their biological significance. In particular, the tri-substituted γ -lactone (-)-dihydroprotolichesterinic acid [(3*S*, 4*R*, 5*S*)-4-carboxy-3-methyl-5-tridecyl-oxolan-2-one] **1a** is noted to be a potent antibacterial agent,¹ while (-)-protolichesterinic acid **1b**, recently synthesised enantiospecifically by Greene,² is known to possess anti-bacterial, anti-fungal, anti-tumoral and growth regulating properties.³ The first enantiospecific synthesis of **1a** was carried out recently by Mulzer⁴ in 14 steps from (3*R*)-2,3-isopropylidene glyceraldehyde with an overall yield of 0.4%, while its enantiomer was obtained by a similar route in 0.5% from di-isopropylidene-*D*-glucose.



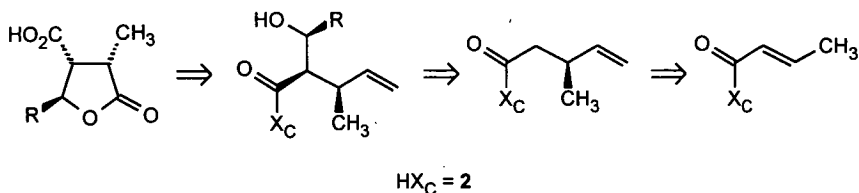
1a, R₁ = CH₃, R₂ = H

1b, R₁, R₂ = =CH₂



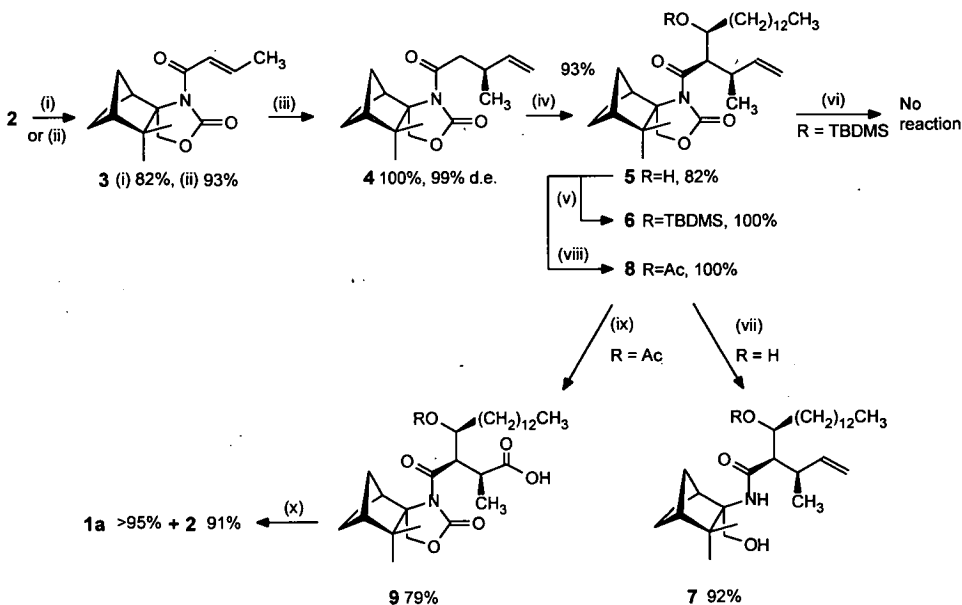
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Herein we describe a much more concise and efficient synthesis of **1a** in which our recently developed camphene-derived chiral auxiliary **2** [(*-*)-Chiracamphox]⁵ is used to construct the three contiguous chiral centres *via* the successful strategy of consecutive stereocontrolled 1,4-conjugate addition and *syn*-aldol condensation reactions. In retrosynthetic analysis (Scheme 1) we masked the lactone carboxyl function as a vinyl group.



Scheme 1

The synthesis begins with the crotonyl imide **3** which is conveniently prepared either by reaction of the bromomagnesium salt⁶ of **2** with crotonyl chloride in 82% yield, or in 93% yield *via* the ethylzinc salt, a procedure developed by us^{5c} to avoid *C*-acylation in the synthesis of acyl imides (Scheme 2).

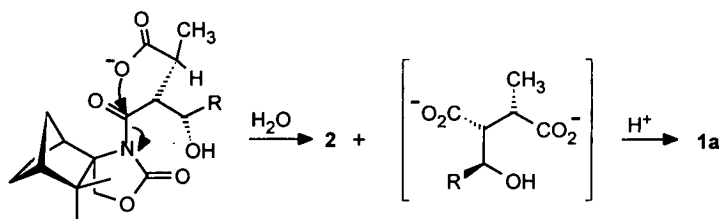


Scheme 2.

Reaction conditions: (i) EtMgBr, THF, 0°C, then *E*-crotonyl chloride, -78°C to rt. (ii) ZnEt₂, Et₂O, rt, then *E*-crotonyl chloride -78°C to 35°C, 3 hr. (iii) CH₂=CHMgBr (2.5 equiv.), CuBr (0.4 equiv.), -78°C to -20°C, then addition to sat. NH₄Cl/THF 0°C. (iv) *n*-Bu₂BOTf, *i*-Pr₃NEt, CH₂Cl₂, -78°C to 0°C, then CH₃(CH₂)₁₂CHO, -78°C to rt. (v) TBDMSTf, THF, -78°C to rt. (vi) PhCH₂OLi, THF, -78°C to rt, 5 days. (vii) LiOH, H₂O₂, THF/H₂O, 50°C, 3 hr. (viii) Ac₂O, NEt₃, DMAP, hexane. (ix) KMnO₄, *n*-Bu₄NBr, C₆H₆/AcOH/H₂O, 50°C, 1/2 hr. (x) LiOH, H₂O₂ (30%, 100 equiv.), THF/H₂O, rt, 5 days.

1,4-Conjugate addition of vinylmagnesium bromide to **3** under copper catalysis led to the quantitative formation of adduct **4** with near complete stereoselection. The absolute configuration of the new stereocentre in **4** was determined after catalytic reduction (H_2 , 10% Pd/C, ethyl acetate, 1 atm.) of **4**, followed by cleavage with lithium hydroperoxide⁷ to give (3*R*)-3-methylpentanoic acid $[\alpha]_{\text{D}}^{18} = +4.5^\circ$ ($c = 2.0$, CHCl_3), *lit.*⁸ $[\alpha]_{\text{D}}^{23} = +6.42^\circ$ ($c = 4.03$, CHCl_3).

In the second stereocontrolled step, the dibutylboron enolate of **4** produced under standard conditions⁹ was treated with tetradecanal to give the *syn*-aldol product **5** (CHOH.CHCO , $J = 6.4$ Hz) in 82% yield as a single diastereomer. Initially **5** was converted into its TBDMS ether **6**, but this failed to cleave when treated with lithium benzyloxide,¹⁰ presumably due to shielding of the imide carbonyl by the long alkyl chain/TBDMS group. It was found that use of the smaller TMS ether grouping led to deprotection and subsequent decomposition of the aldol product due to the prolonged reaction time required. An attempt was made to cleave the unprotected aldol product **5**, but this failed to react with lithium hydroperoxide under mild conditions and gave only the β -amido alcohol **7**, formed by *endo*-cyclic attack in 92% yield when heated to 50°C . Not discouraged, we next investigated the possibility of assisted solvolysis of the desired fragment from the auxiliary. To this end, **5** was protected as its acetate **8** which was then oxidatively cleaved with potassium permanganate under modified phase-transfer conditions of Starks¹¹ to give the acid **9** in 79% yield. Treatment of **9** with lithium hydroperoxide (5 equiv.) under adapted conditions (see Scheme 2) led to the slow but complete removal of the chiral fragment in the required manner, and to our pleasure, the desired lactone **1a**. In this step it is believed that the neighbouring carboxylate (or percarboxylate) anion may be assisting in the cleavage of the imide bond by its attack on the *exo*-carbonyl (Scheme 3).



Scheme 3.

The crystalline lactone **1a** was isolated in >95% yield [m.p. = 105.1 – 105.8°C (from hexane/cyclohexane), *lit.*¹² m.p. = 106°C , $[\alpha]_{\text{D}} = -53.0^\circ$ ($c = 1.75$, CHCl_3), *lit.*⁴ $[\alpha]_{\text{D}} = -49.5^\circ$ ($c = 1.75$, CHCl_3) and consistent spectroscopic data] whilst **2** was recovered in 91% yield with complete stereochemical integrity.

Thus an overall yield of 57% of chirally pure **1a** in six steps has been achieved, considerably shorter and higher yielding than the previous synthesis.⁴ Our route represents a viable and easily adapted method for the formation of 4-carboxy- γ -lactones containing three contiguous chiral centres. We are at present attempting to apply this methodology to other similar systems as well as demonstrating the utility of **2** and its enantiomer in the synthesis of other small- and medium-sized chirally pure fragments.

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Mini-Review

Exerting Face-Stereoselective Shielding: Design of an Enantiomeric Pair of Camphene-based Oxazolidin-2-ones for Use as Recyclable Chiral Auxiliaries in Asymmetric Synthesis

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Preparative methodology is described for access to a range of enantiomerically pure oxazolidin-2-ones by chemical elaboration of naturally-occurring compounds (terpenes, carbohydrates) *via* a stereospecific intramolecular nitrene insertion reaction. The effectiveness and limitations of these reagents as chiral control elements in the form of their *N*-acyl derivatives for an array of asymmetric transformations is reported. In particular, the efficiency of the spiro-oxazolidin-2-one (+)-**3** obtained from (–)-camphene is highlighted by the virtually complete stereoselection attained in such reactions as the Diels-Alder, conjugate addition, aldol, alkylation and acylation reactions. An added benefit to **3** is that its enantiomer (–)-**3** is also readily accessible from (+)-camphene, thereby allowing preparative access to *both* enantiomeric products in a range of asymmetric manipulations. Both reagents are readily cleaved from the newly created chiral moieties and can be recycled. This exceptional quality of asymmetric induction imparted by (+)-**3** is highlighted by a concise synthesis of the tri-substituted lactone (–)-dihydroprotolichesterinic acid in 57% overall yield *via* consecutive ste-

reo-controlled 1,4-conjugate addition and *syn*-aldol reactions.

Keywords: Asymmetric synthesis, chiral auxiliaries, oxazolidin-2-ones

INTRODUCTION

Over the last decade there has been sustained interest in the development and use of optically-pure oxazolidin-2-ones as chiral auxiliaries [1] due to the breadth of asymmetric reactions which their derivatives undergo with good levels of diastereoselection. Combined with this function, facile purification and straight forward cleavage of adducts with recovery of the auxiliary, make these reagents one of the most reli-

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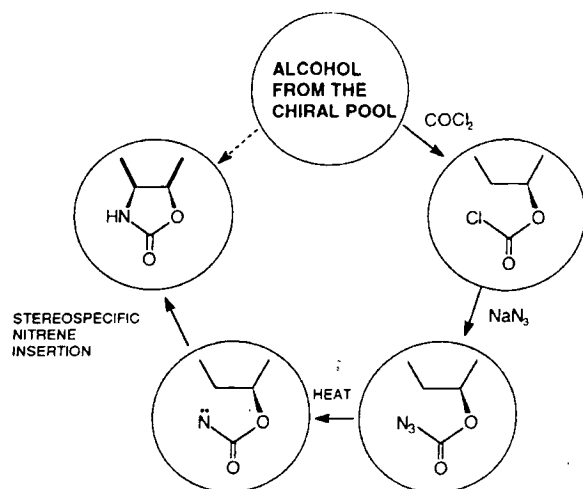


FIGURE 1 Synthetic protocol *via* intramolecular nitrene insertion process

able and versatile tools in the armoury of organic chemists for the synthesis of homochiral fragments.

For the past five years, our laboratory has been actively seeking access to more preparatively useful chiral oxazolidin-2-ones by chemical elaboration of naturally-occurring compounds (terpenes, carbohydrates) from the 'Chiral Pool'. Our approach is depicted in Fig. 1 and involved in the key step an efficient and stereospecific intramolecular nitrene-insertion reaction.

The outcome has been the synthesis of a number of chiral reagents including those shown in Fig. 2, all of which can be obtained in an enantiomerically pure state in multi-gram quantities. Each auxiliary possesses its own areas of strength and all are highly crystalline in nature

and consequently impart good crystallinity to derivatives such that diastereomeric purity can be raised in each case by simple recrystallisation.

The Chemistry of Chirabornox 1

Evaluation of the auxiliaries 1 and 2 has shown that while they have proved to be effective reagents for the control of stereochemistry in many reactions, neither shows the desirable broad scope of utility that could be hoped for. Thus, Chirabornox 1 has proved to be highly effective in controlling the stereochemical outcome of alkylation and acylation reactions of lithium enolate 4 [2]. In each case, the sense of diastereofacial bias is readily rationalised in terms of attack at the C_{α} -*Re* face of the lithium-chelated (*Z*)-enolate 4. It is also worth noting an improvement in the yield for the reaction of 4 with benzyl bromide from 62 to 80% by the judicious addition of sodium iodide to the reaction mixture. The stereoselectivity of aldol condensations of boron enolates 5 of the propionyl derivative of 1 are also controlled by the asymmetric bias of Chirabornox as illustrated in Scheme 1. For example, condensation of 5 with benzaldehyde furnished a single diastereomerically pure *erythro*-adduct in 52% yield. In both these transformations, racemisation-free removal of the oxazolidinone auxiliary is readily achieved by adoption of Evans' transesterification procedure with lithium benzyloxide [1a].

Unfortunately the synthetic utility of the enoyl derivatives 6a-c in Lewis-acid catalysed Diels-

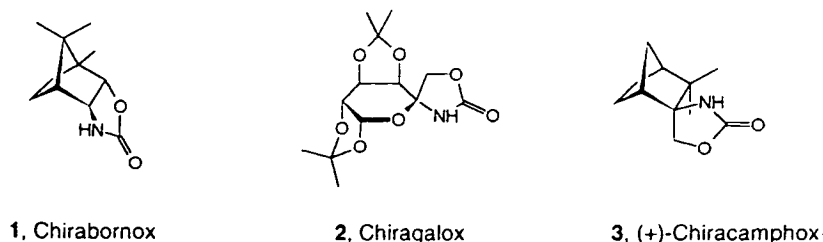
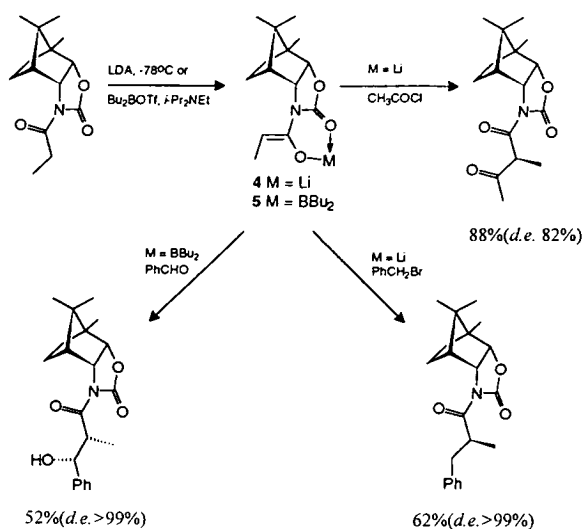


FIGURE 2 New chiral reagents for use in asymmetric synthesis.



SCHEME 1

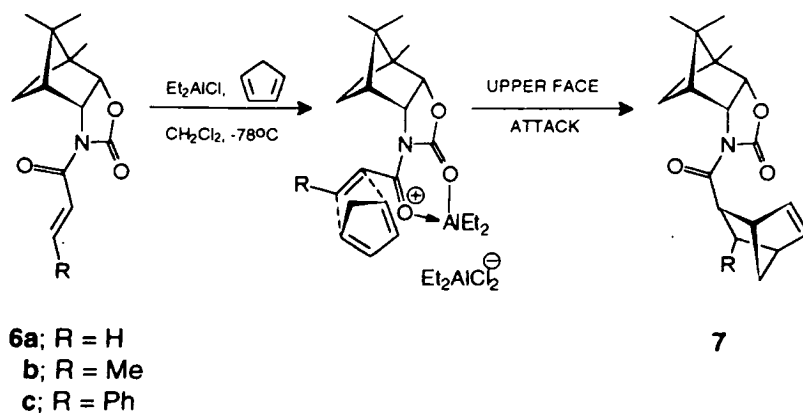
Alder reactions is low except where the β -carbon bears a large group (e.g. for phenyl **6c** 99% *d.e.*), as adducts **7a** and **b** are formed with 59% and 60% *d.e.*, respectively (Scheme 2).

The low specificity of the latter Diels-Alder reactions is considered to be due to the inability of the auxiliary **1** to control the rotamer preference of the $\text{C}_\alpha\text{-C=O}$ bond effectively, thus allowing each face of the unsaturated system to be exposed to the incoming enophile, *i.e.* the dienophile can react in either the *s-trans* or *s-cis* conformation despite the adjacent enantiopure bornyl substituent and the presence of a Lewis-acid catalyst [Et_2AlCl or $\text{TiCl}_2(\text{OPr}^i)_2$] to bring

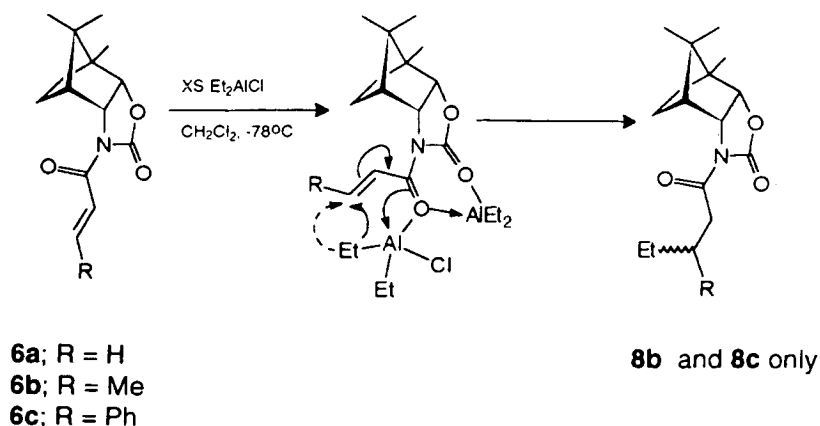
about bidentate chelation and freeze the *N*-carbonyl rotor. For similar reasons, 1,4 conjugate additions to these systems show extremely poor diastereoselectivity as witnessed by the conjugate addition of diethylaluminium chloride to the crotonate and cinnamate proceeding to give alkylated products (**8b** and **c**) with only 11% and 43% *d.e.*, respectively (Scheme 3).

The Chemistry of *exo*-Chirabornox **9**

From these results it is obvious that Chirabornox **1** does not have suitably placed steric controlling groups that can both influence the preferred rotamer and effectively shield one face of the prochiral functions. Thus, an obvious quality for an improved chiral auxiliary is to have bulky (preferably alkyl) regions which are capable of not only limiting the conformational freedom of the reactive functionality but simultaneously blocking one face to an incoming reagent. This steric bias can, in principle, be effected by transposition of the passive methyl group from the rear of the bornane ring to the front, *i.e.* proximal to the active site of the auxiliary. Hitherto, access to such an isomer of **1** has eluded us, but recently we have managed to prepare the *exo*-variant **9**, albeit not by an intramolecular nitrene-insertion reaction [3], [4]. We surmised that with chelation control this transposition of steric bias



SCHEME 2

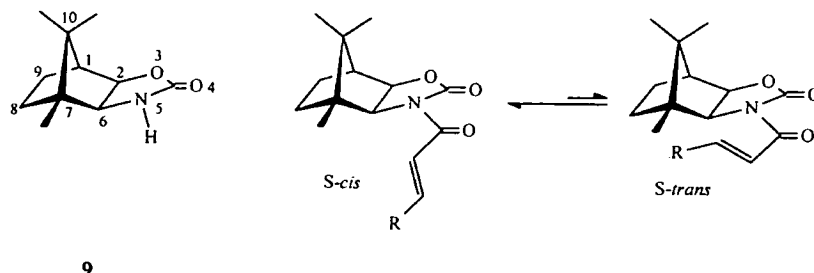


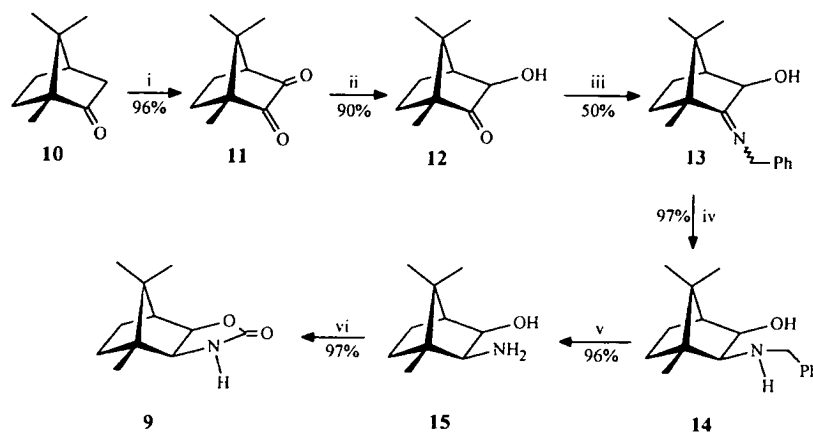
SCHEME 3

should lead to an increase in steric repulsion between the *N*-acryloyl moiety and the bornane ring in the *S-trans* conformer, and thus lead to better stereoselection *via* the *S-cis* conformer during Diels-Alder reactions (Fig. 3).

The synthesis of **9** in an enantiomerically pure state was achieved in a six-step process in 39% overall yield starting from (1*R*)-camphor **10** as depicted in Scheme 4 [5]. Thus, oxidation of **10** to camphorquinone **11** using selenium dioxide in acetic anhydride was followed by stereoselective reduction with L-Selectride® in tetrahydrofuran (THF) to afford the desired *exo*- α -hydroxyketone **12** exclusively. We sought to avoid the disposal problems associated with the first step, and the expense of the second, by direct conversion of **10** into **12** *via* its silylenol ether and subsequent oxidation with *m*-chloroperoxybenzoic acid [6], but this approach led to an inseparable 2:1 mixture

of *endo*- and *exo*-isomers. In the next step, **12** was transformed into the corresponding *N*-benzylimine **13** by treatment with benzylamine in THF in the presence of 4Å molecular sieves, albeit in only 50% yield. Attempts to improve the yield by varying the reaction temperature and the nature of the dehydrating agent failed, but reduction of imine **13** with sodium borohydride in methanol proceeded smoothly to yield the desired *exo,exo*-hydroxy-*N*-benzylamine **14**, which was deprotected by catalytic hydrogenation with 10% palladium on charcoal to afford *exo,exo*-hydroxyamine **15**. Finally, treatment of **15** with triphosgene and excess sodium hydroxide [7] led to the virtually quantitative formation of the desired oxazolidin-2-one **9**, which after recrystallisation from cyclohexane:ethyl acetate yielded colourless crystals (m.p. = 196.3–197.3°C). Unfortunately, the crystals formed were unsuitable for

FIGURE 3 *S-cis* versus non-chelation *S-trans* conformation.



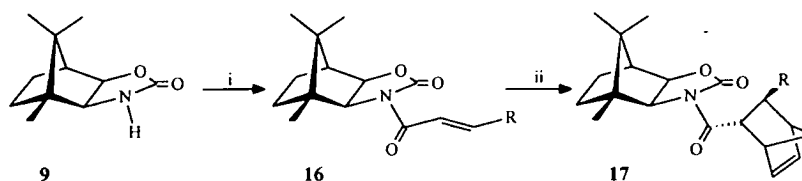
SCHEME 4 Reagents and conditions: (i), SeO_2 , Ac_2O , reflux, 24h; (ii), L-selectride®, THF, -78°C , 4h; (iii), PhCH_2NH_2 , $4\text{\AA}$ molecular sieves, THF, r.t., 72h; (iv), NaBH_4 , MeOH, r.t., 5.5h; (v), 10% Pd-C, H_2 , EtOH; (vi), triphosgene, DME/DCM/ H_2O , NaOH.

an X-ray crystal structure, but the absolute stereochemistry of the novel auxiliary **9** was proven conclusively by obtaining an X-ray structure for the crotonate Diels-Alder adduct **17b** (*vide infra*).

A significant advance in asymmetric Diels-Alder reactions in recent times has been the increased use of Lewis-acid catalysts to control rotameric preference [1d-f]. When compared to non-catalysed Diels-Alder reactions, catalysed versions proceed at greatly enhanced rates as well as with dramatically increased levels of regio- and stereo-selectivity. Thus, the required unsaturated carboximides **16** are easily prepared in excellent yield (89–99%) by treatment of **9** with freshly prepared ethylmagnesium bromide at 0°C in THF followed by the appropriate acid chloride at -78°C (Scheme 5). The Diels-Alder reactions were carried out by judicious addition of diethylaluminium chloride (1.6 equiv.) to a cooled stirred solution of the appropriate diono-

phile **16** (1 equiv.) and freshly cracked cyclopentadiene (10 equiv.) in dichloromethane. The addition of catalyst to the reaction mixture was accompanied by a yellow colouration which faded on completion of the reaction. The reactions of the acrylate **16a** and crotonate **16b** were carried out at -78°C , whilst the less reactive cinnamate **16c** needed to be warmed to -20°C before reaction would occur.

In each case, reaction occurred in almost quantitative yield and the diastereomeric product ratios were determined by high-field (250 MHz) NMR spectroscopic analysis of the crude product after filtration through silica gel to remove excess cyclopentadiene. The resonances of interest were the two doublet of doublets between δ 5.5 and 6.5 due to the olefinic protons in the cycloadducts **17**. Integration of these signals allowed both the *endo/exo* selectivities and the diastereomeric excesses (*d.e.*) to be measured.



SCHEME 5 Reagents and conditions: (i), EtMgBr , THF, 0°C , $\text{RCH} = \text{CHCOCl}$, -78°C , **16a**, R = H (88%), **16b**, R = Me (90%), **16c**, R = Ph (99%); (ii), Et_2AlCl , cyclopentadiene, DCM, -78°C (-20°C for **16c**), **17a**, R = H (100%), **17b**, R = Me (92%), **17c**, R = Ph (100%).

The results are summarised in Table I and clearly demonstrate the efficiency of **9** (*versus 1*) as a chiral control element in Lewis-acid mediated Diels-Alder reactions. In each case *endo*-diastereoselection is exceptionally good and well in excess of levels previously attained with oxazolidin-2-one **1** [2], although the relatively poor level of diastereoselection (81% *d.e.*) obtained with acrylate **16a** presumably reflects the lack of sufficient steric repulsion between the acrylate moiety and the methyl group on the front face of the auxiliary to bring about overwhelming population differences between the chelated *S-cis* and *S-trans* conformers. Nonetheless, the benefit of introducing a methyl group onto the front face of the auxiliary **9** is underlined when the results of the corresponding Diels-Alder reaction with **1** are considered. In this case, *endo:exo* selectivities of only *ca.* 4:1 are observed with corresponding low levels of diastereoselection in the range of 48–68% [8].

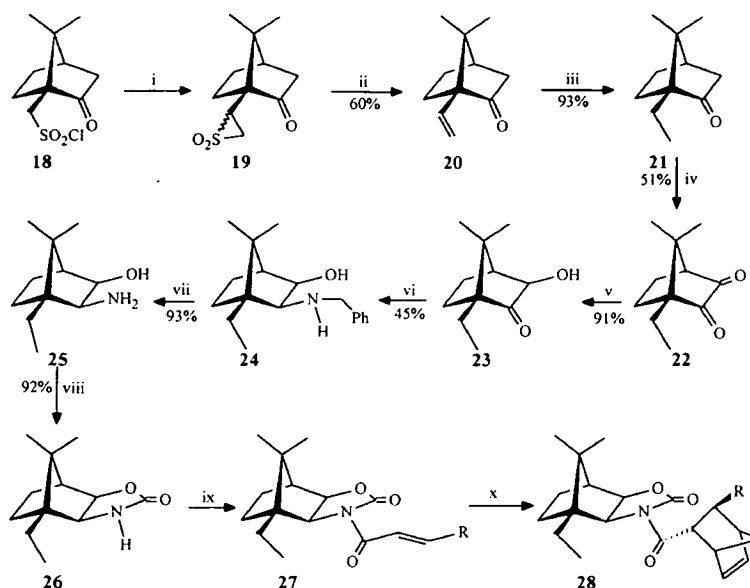
The absolute stereochemical outcome of the cycloadducts **17** was determined by obtaining an X-ray crystal structure for the crotonyl-derived adduct **17b** [2], which showed that attack of the diene occurred on the C_α-Si face of the chelated dienophile, *i.e.* opposite to that obtained with the *endo*-variant **1**.

In order to improve on the selectivity provided by auxiliary **9** in Lewis-acid mediated Diels-Alder reactions involving the acrylate derivative **16a**, it was decided to increase the steric bulk at the front face of the auxiliary by replacing the methyl group at C-7 with an ethyl group to create the homologue **26** with the required topological bias to control the rotameric prefer-

ence. To this end, a synthetic route similar to that adopted for **9** was followed as outlined in Scheme 6, starting from 10-methylcamphor **21**, which can be prepared in a three-step sequence from commercially available 10-camphorsulfonyl chloride **18**. Thus, treatment of **18** with diazomethane followed by neat thermolysis of the crude episulphone **19** produced methylenecamphor **20** as a waxy solid in 60% yield after Kugelrohr distillation. Catalytic hydrogenation of the latter using 10% palladium on charcoal in ethanol gave rise to the desired 10-methylcamphor **21** in excellent yield (93%), but subsequent treatment with selenium dioxide in acetic anhydride under reflux afforded 10-methylcamphorquinone **22** in only 51% yield. Variation of both reaction time and stoichiometry failed to improve the yield, but fortunately unreacted starting material could be recovered and recycled. Stereoselective reduction of **22** proceeded smoothly with L-Selectride[®] to yield hydroxy ketone **23** in 91% yield. Attempts to prepare the *N*-benzylimine derivative of **23** (*cf.* Scheme 4) failed; variation of temperature and dehydration agent led only to complex mixtures, but the problem was circumvented by direct synthesis of **24** in 45% yield by reductive amination of **23** using titanium(IV) isopropoxide and sodium cyanoborohydride [9]. The *exo,exo*-stereochemistry of **24** was verified by comparison of its ¹H NMR spectrum with that of the methyl analogue **14**. In essence, three doublets appeared at δ 3.64, 2.85 and 1.79 ppm due to the protons attached to C-3, C-2 and C-4, respectively with corresponding coupling constants of 7.2, 7.2 and 4.7 Hz, which are almost identical to those displayed by **14**.

TABLE I Diethylaluminium chloride-promoted asymmetric Diels-Alder reactions of unsaturated carboximides derived from auxiliaries **9** and **26** with cyclopentadiene

Dienophile	Temp/°C	Yield (%)	<i>endo:exo</i>	<i>d.e.</i> (%) (corresponding <i>d.e.</i> for 1)
16a	–78	100	100:0	81 (59)
16b	–78	92	100:0	>99 (60)
16c	–20	100	100:0	>99 (99)
27a	–78	92	100:0	>95
27b	–78	91	100:0	>99



SCHEME 6 Reagents and conditions: (i), CH_2N_2 , Et_2O , 0°C , 3h; (ii), 95°C ; (iii), 10% Pd-C, H_2 , EtOH ; (iv), SeO_2 , Ac_2O ; (v), L-Selectride®, THF, -78°C ; (vi), $\text{Ti(IV)O}^i\text{Pr}$, PhCH_2NH_2 , EtOH , NaBH_3CN ; (vii), 10% Pd-C, H_2 , EtOH ; (viii), triphosgene, $\text{DME/DCM}/\text{H}_2\text{O}$, NaOH ; (ix), Et_2Zn , $\text{RCH} = \text{CHCOCl}$, 25°C , **27a**, $\text{R} = \text{H}$ (31%), **b**, $\text{R} = \text{Me}$ (33%); (x), Et_2AlCl , cyclopentadiene, DCM , -78°C , **28a**, $\text{R} = \text{H}$ (92%), **b**, $\text{R} = \text{Me}$ (91%).

The final steps in the synthesis were achieved in a straight-forward manner by catalytic hydrogenation of **24** followed by treatment of the resulting α,β -amino alcohol **25** with triphosgene to afford the desired oxazolidin-2-one **26** as pale-yellow fluffy crystals (m.p. = $138\text{--}140^\circ\text{C}$ from xylene/cyclohexane). Disappointingly, the overall yield of **26** for the eight-step synthetic sequence from 10-camphorsulfonyl chloride was only 9%, but sufficient material was obtained to evaluate its synthetic utility in Lewis-acid mediated Diels-Alder reactions.

The propitious shielding by the ethyl group introduced at C-7 in oxazolidin-2-one **26** was reflected initially in the failure of our first attempts to prepare its *N*-acryloyl derivatives using freshly prepared ethylmagnesium bromide as described previously; only starting material was recovered even after boiling under reflux for *ca.* 24 hours. This obstacle was overcome by utilizing an alternative procedure developed by us [10], whereby the auxiliary was treated with diethylzinc at room temperature followed by cooling to -78°C and subsequent reaction with the

TABLE II Et_2AlCl -mediated asymmetric Diels-Alder reactions of chiral unsaturated carboximides **29a-c** and cyclopentadiene^a

Dienophile	Temp/ $^\circ\text{C}$	Yield(%)	<i>endo:exo</i>	<i>endo d.e.</i> (%) ^{c,d}
29a	-78	83 (88) ^b	98:2 (98:2)	80 (79)
29b	-78	98 (91)	99:1 (98:2)	89 (77)
29c	-78 to -20	99	98:2	92

^aReactions run at -78°C in methylene chloride using 1.4 equiv. of Et_2AlCl .

^bFigures in parentheses for corresponding reactions with (*S*)-valinol-derived oxazolidinone [1e] under identical reaction conditions.

^cRatios determined by 360 MHz ^1H NMR spectroscopy.

^dAbsolute configuration of the preferred diastereomer: **30a**, 4'S; **30b**, 4'S, 5'R; **30c**, 4'R, 5'R.

appropriate acid chloride (Scheme 6). Even so, acrylate **27a** and crotonate **27b** were obtained in only 31% and 38% yields respectively, along with significant amounts of unreacted **26**.

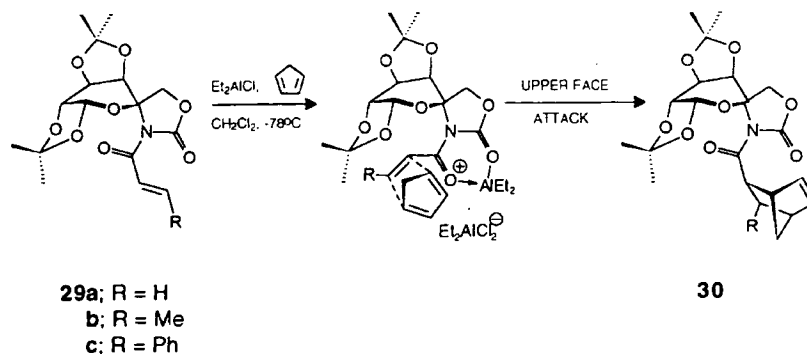
The degree of stereoselectivity (*d.e.*%) for the Diels-Alder reaction of the difficult to prepare dienophiles **27** with cyclopentadiene was determined as before by integration of the signals arising from the olefinic protons in the high field ^1H NMR spectra of the cycloadducts **28**. Table II shows that the *endo:exo* selectivity is excellent in both cases, and in particular that the *d.e.* for the acrylate **27a** is increased to >95% from 81% for its homologue **16a**.

The outcome of these experiments demonstrate unequivocally that the reason for the poor diastereoselection in Diels-Alder reactions of cyclopentadiene with **1** as the chiral control element is steric in origin and that transposition of the dormant methyl group from C-1 into the vicinity of the reaction site at C-7 is sufficient to improve π -face discrimination to acceptable levels. This can be raised to even higher levels by the introduction of an ethyl group instead of a methyl, but the synthesis of the required auxiliary **26** needs eight steps starting from commercially available 10-camphorsulphonyl chloride **18**, and can be achieved, disappointingly in only 9% overall yield.

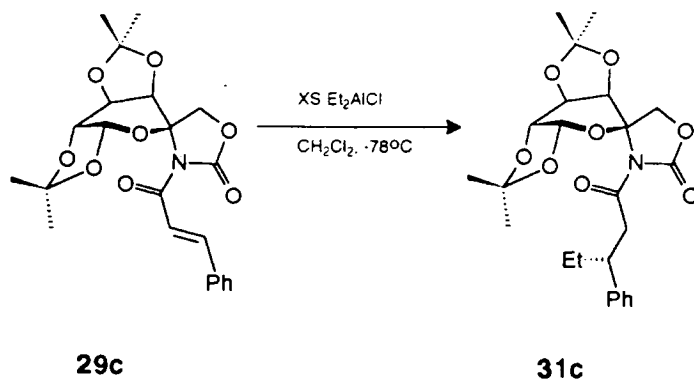
The Chemistry of Chiragalox 2

To a considerable extent the problems associated with the auxiliaries **1**, **9** and **26** were circumvented with the synthesis of Chiragalox **2**, a spiro-oxazolidin-2-one derived from D-(+)-galactose by the aforementioned intramolecular nitrene process [11]. The performance of derivatives of **2** in Lewis-acid catalysed Diels-Alder reactions with cyclopentadiene was considerably better than that of terpenoid-derived **1**, and in 1,4 conjugate additions of diethylaluminium chloride, diastereomeric excesses that were synthetically useful could be obtained. It can clearly be seen in Scheme 7 that in chelated intermediate the conformation of the alkene moiety is controlled by the pyranose ring and isopropylidene acetal function. Facial shielding is also provided by these groups and because of the favourability of the diene reacting to give an *endo*-adduct due to secondary orbital interactions it is obvious that one diastereomeric product **30** is strongly favoured. In fact for the Diels-Alder cycloaddition of cyclopentadiene catalysed by diethylaluminium chloride there is no room for improvement except in the case of the acryloyl derivative **29a** (see Table II).

That the facial shielding is now affecting the β -prochiral centre is demonstrated by the dra-



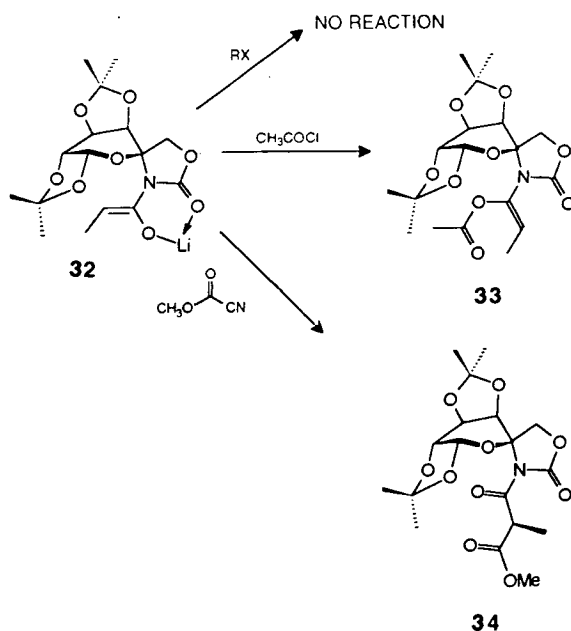
SCHEME 7



SCHEME 8

matic increase in the selectivity of the conjugate addition of diethylaluminium chloride to cinnamoyl derivative **29c** and the isolation of **31c** with a more useful *d.e.* of 86% (Scheme 8). A transition state such as that shown in Scheme 7 indicates the probable interactions that could have increased the rotamer differentiation and facial shielding.

Despite these improvements, a major limitation of Chiralox **2** as a widely applicable chiral auxiliary is its poor performance in enolate chemistry. Thus, apart from the exceptional lithium-mediated aldol condensations, *i.e.* without recourse to the use of hazardous and expensive di-*n*-butyltriflate as a mediating agent, metal enolates bearing **2** (Scheme 9) are invariably in-



SCHEME 9

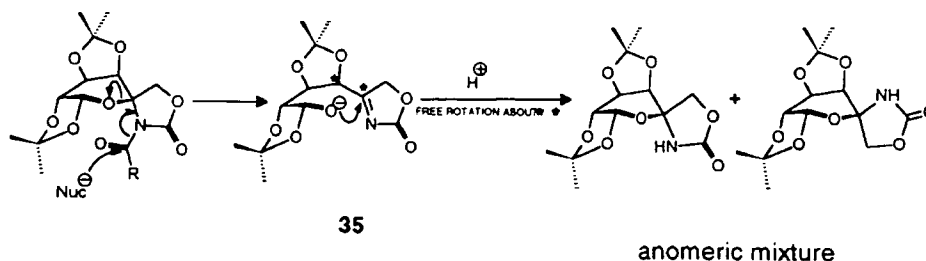
effective in the creation of new stereocentres by their reaction with a wide range of electrophiles. Thus, lithium (and sodium) enolates of the type **32** fail to react with active alkyl halides such as allyl bromide and benzyl bromide, but instead as the reaction temperature is increased, decompose to give the anion of **2**, presumably by elimination of methylketene. It is still unclear whether this is due to increased steric effects, metal chelation to acetal and/or pyranose oxygens or some form of electronic effect. Whatever effect has caused the change in reactivity of these enolates it has certainly altered their pattern of reactivity when more reactive electrophiles are used. Reaction with acyl chlorides lead exclusively to *O*-acylated products such as **33**, and thus a failure to generate a new stereocentre. Only in the case of the highly *C*-selective Manders reagents was a new C_α -stereocentre generated to afford **34**, and reassuringly with a high diastereomeric excess. This propensity to undergo *O*-acylation is shown to only a very limited extent (*ca.* 15%) in the acylation of the corresponding enolate of **1** (see Scheme 1).

Detailed studies have also established that the recovered galactose-derived chiral auxiliary **2** undergoes epimerisation to varying degrees about the spiro-carbon atom upon cleavage of its adducts by routine methods, *i.e.* with lithium borohydride or lithium benzyloxide. A plausible mechanism for this process is shown in Scheme 10 and involves ring-opening of the pyranose ring in **2** to form the alkoxide ion **35** which can undergo free rotation to give both anomers upon ring-closure. The problems associated with the

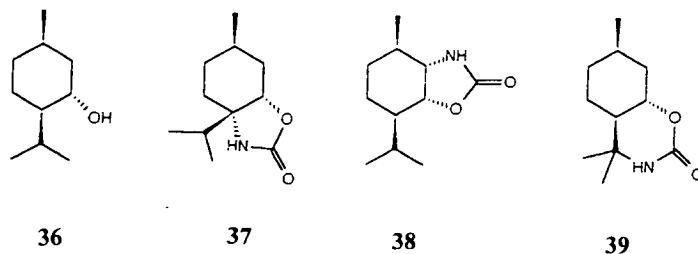
enolate chemistry of **2** and the inability to recycle it fully have restricted the potential of this auxiliary.

New Terpene-Derived Oxazolidinones

From the above it is evident that to have an effective and broadly applicable chiral control agent, one requires well situated steric controlling groups and preferably a lack of functionality which can cause unwanted chelation and/or stereoelectronic effects. In addition, for oxazolidin-2-one-based auxiliaries, there is an important need to protect the ring carbonyl from nucleophilic attack by providing steric shielding, and hence promote exocyclic cleavage of the elaborated *N*-acyl fragment [12]. With this in mind, we designed and synthesised a range of further terpenoid-based oxazolidin-2-ones [13] with the initial aim of introducing the necessary control element to bring about improved π -facial discrimination in Diels-Alder reactions. For each new homochiral reagent the same synthetic protocol as used for **1** (and **2**) was employed and involved chloroformylation of the terpene alcohol followed by conversion into the corresponding azidoformate and thermolysis under flash vacuum conditions [14] or in boiling 1,1,2,2-tetrachloroethane (TCE). In the final step to the required chiral dienophiles for use in asymmetric Diels-Alder reactions, the isolated oxazolidin-2-ones were functionalised at nitrogen with the appropriate α,β -unsaturated acid chloride by prior treatment with *n*-butyl lithium, or alternatively, methylmagnesium bromide to avoid po-



SCHEME 10



lymerisation which could be a problem with acryloyl chloride.

The first terpene alcohol to be used as starting material was inexpensive *iso*-menthol **36** which was converted readily into the desired azidoformate in quantitative yield. Unfortunately when subjected to flash vacuum thermolysis, the latter gave rise to a mixture of two oxazolidin-2-ones **37** and **38** from nitrene insertion at C-2 and C-6, together with the six-membered oxazinone **39** originating from nitrene attack on the *iso*-propyl group, in the ratio of 7:1:2 respectively. The major oxazolidinone **37** could be isolated, albeit as a thick syrup (51%), but further applications of this auxiliary were not pursued when attempts to functionalise it resulted in the formation of thick gums which proved extremely difficult to purify.

Greatly improved crystallinity was found from the same sequence of reactions when (–)-3-pinanol **40** was used as starting material. Thermolysis of its azidoformate under flash vacuum conditions (300°C, 0.02 mmHg) afforded a mixture consisting of oxazolidin-2-ones **41** and **42** in the ratio 3:1, reflecting the tendency of the nitrene intermediate to insert preferentially into *tertiary* C-H bonds compared with *secondary* C-H

bonds. The major isomer could be easily isolated in 65% yield as colourless crystals (m.p. 155.5–156.0°C; $[\alpha]_D = 71.5^\circ$ $c = 3.36$, CH_2Cl_2) following trituration with diethyl ether and recrystallisation from ethyl acetate.

Disappointingly, the sterically crowded oxazolidin-2-one **41** imparted only poor levels of asymmetric induction in Et_2AlCl -mediated Diels-Alder cycloadditions of its *N*-acryloyl, *N*-crotonoyl, and *N*-cinnamoyl derivatives with cyclopentadiene (Table III). This outcome is reflected in the X-ray structure of **41** at 150 K [13] which establishes that both of its faces, and in consequence, those of the acrylate derivatives, are hindered to a similar degree, one by the methyl substituent adjacent to nitrogen and the other by the bridging methylene group of the four-membered ring of the terpenoid moiety.

The Chemistry of Chiracamphox 3

With this in mind, we have designed the (–)-camphene-based oxazolidin-2-one **3** [(+)-Chiracamphox] [15] with the necessary control element, *i.e.* masked *tert*-butyl group, to improve π -face discrimination and bring about very high levels of diastereoselection in Diels-Alder reac-

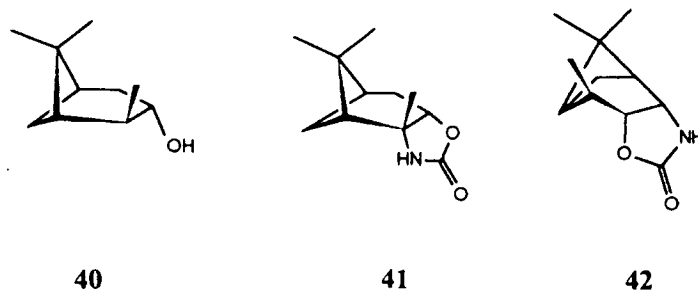


TABLE III Diastereoselection in Lewis-acid catalysed Diels-Alder cycloadditions of chiral acrylate derivatives of oxazolidin-2-ones **1** and **41** with Cyclopentadiene

Auxiliary (Aux*H)	R	Temp/°C	Yield(%)	<i>endo:exo</i>	<i>endo d.e. (%)</i> ^a (A(R):B(S))
1	H	-78	98	96:4	59
1	Me	-78	96	100:0	71
1	Ph	-20	99	100:0	99
41	H	-78	92	93:7	25
41	Me	-78	100	97:3	33
41	Ph	-20	96	95:5	32

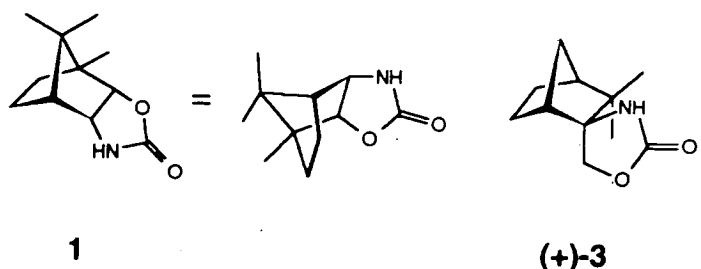
^aDetermined by 360 MHz ¹H NMR spectroscopy.

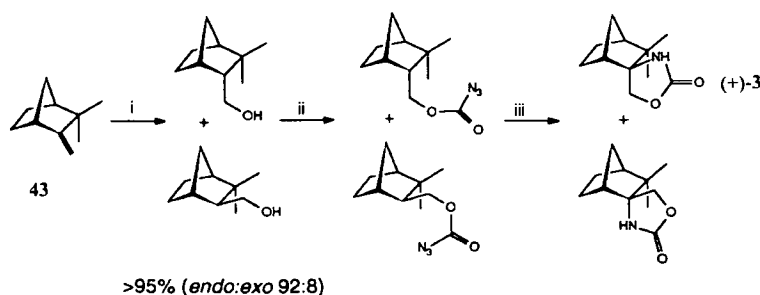
tions and other asymmetric transformations. In this connection it is worth noting that due to propitious blocking of different faces of the oxazolidin-2-one ring in auxiliaries **1** and (+)-**3** products of the opposite stereochemical sense result in the ensuing diastereoselective processes.

For the preparation of the novel chiral reagent (+)-**3** in an optically pure state, we used the same synthetic device of intramolecular nitrene delivery as before. This process is outlined in Scheme 11 and was achieved *via* hydroboration of (-)-camphene **43** [16] which yielded, after oxidation, predominantly *endo*-camphenol (>95%, *endo:exo* 92:8). Conversion of the isomeric alcohols into their azidoformates *via* the chloroformate and subsequent thermolysis by dropwise addition to boiling 1,1,2,2-tetrachloroethane (TCE) at 2–3% concentration gave a 90% yield of a mixture of

the spiro-oxazolidin-2-ones (+)-**3** and its epimer, from which the former was isolated in 65–70% yield after two fractional crystallisations from CH₂Cl₂:cyclohexane in enantiomerically pure form as a colourless crystalline compound (m.p. 226–227°C, [α]_D = +48° (c = 5.1, CH₂Cl₂)) [17] whose structure was confirmed by X-ray crystallography [13]. The sole formation of (+)-**3** is notable when compared to the two previous processes, but can be explained by the overwhelming bias for nitrene insertion at C-3 to form a five-membered ring and the more sterically demanding option of attack at C-4 to afford a much less favoured six-membered ring.

In order to prepare the chiral unsaturated carboximides **44a–c** as dienophiles for Diels-Alder reaction, we adopted the method of Evans [1e] whereby the oxazolidin-2-one **3** was treated suc-





SCHEME 11 Reagents and conditions: (i), BH_3 :THF (-78°C) then KOH, H_2O_2 ; (ii), 1.2equiv. COCl_2 (>95%) isolate then 2NaN_3 , PTC(>95%); (iii), thermolysis in TCE, 147°C , (65–70%).

cessfully with MeMgBr and the appropriate α,β -unsaturated acid chloride in THF under carefully controlled conditions (Scheme 12). Cycloaddition of **44a–c** with freshly cracked cyclopentadiene in CH_2Cl_2 occurred at -78°C in the presence of 1.6 equiv. of Et_2AlCl as Lewis-acid promoter to produce adducts **45a–c** in almost quantitative yield. From the results of these reactions shown in Table IV it is evident that auxiliary **3** induces significantly higher levels of diastereoselection in the Diels-Alder reactions than the corresponding reactions with **1** and **2** [18]. Moreover, cleavage of **45b** and **45c** with lithium benzyl oxide afforded the 4S, 5S benzyl esters **46b** [91%, $[\alpha]_D = +127^\circ$ (20°C , $c = 2.44$, CH_2Cl_2)] and **46c** [95%, $[\alpha]_D = +124^\circ$ (22°C , $c =$

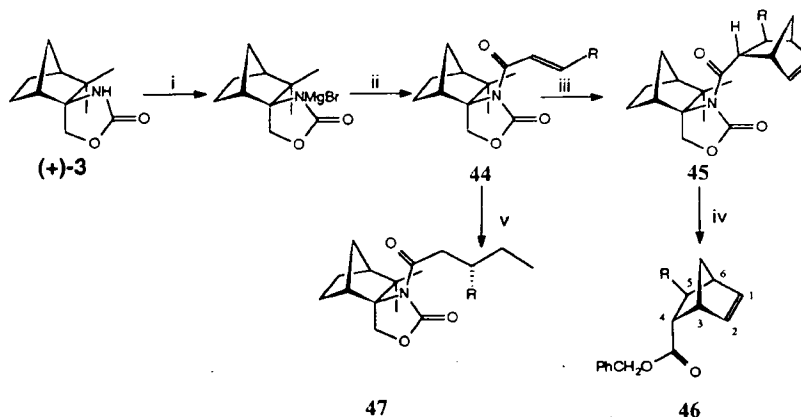
TABLE IV Et_2AlCl -promoted reactions of dienophiles **44a–c** with cyclopentadiene to produce **45a–c** including corresponding yields for analogues derived from **1**

Compound	Yield(%)	d.e.(%) ^a
44a , R=H	98 (98) ^b	>95 (60)
44b , R=Me	99 (96)	99 (60)
44c , R=Ph	97 (99)	98 (99)

^aDiastereomeric excesses (d.e.) were determined by 360 MHz ^1H NMR spectroscopy.

^bFigures in parentheses for corresponding reactions with **1** under identical conditions.

2.36, CH_2Cl_2)] of opposite sign to those obtained with **1**, but identical to those derived with Evans' (S)-valinol-based oxazolidin-2-one [**1e**]; in both cases auxiliary **3** was recovered unchanged in 90% and 97%, respectively.



SCHEME 12 Reagents and conditions: (i), MeMgBr , THF; (ii), $\text{RCH}=\text{CHCOCl}$, -78°C , (**44a**, R = H, **44b**, R = Me, **44c**, R = Ph; yields: 29, 80, 87% respectively); (iii), cyclopentadiene, 1.6equiv. Et_2AlCl , CH_2Cl_2 , -78°C ; (iv), 1.5equiv. $\text{PhCH}_2\text{OH}/\text{Bu}^\text{n}\text{Li}$, THF, -78°C to room temperature; (v), 4equiv. Et_2AlCl , -78°C (**47a**, R = Me, **47b**, R = Ph; yields: 100, 100% respectively).

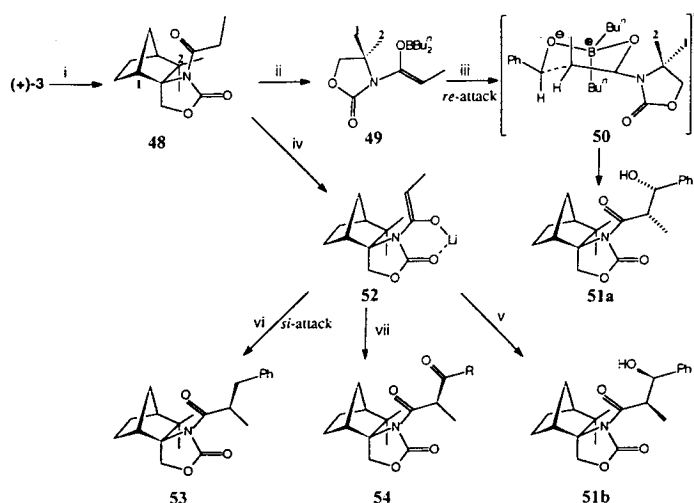
With the crotonoyl and cinnamoyl derivatives **44b** and **44c** in hand we decided to investigate the stereochemical outcome of their 1,4-conjugate addition reaction with Et_2AlCl (4 equiv.). Both chiral unsaturated carboximides readily underwent β -alkylation reactions from the *re*-face to give products **47a** and **47b** in quantitative yield with excellent diastereoselection (**47a**, *d.e.* 99%; **47b**, *d.e.* 90%) when compared to the corresponding adducts from **1** (11%, 43% *d.e.* respectively). In each case cleavage of the adduct with lithium hydroperoxide afforded the enantiomerically pure pentanoic acid, *e.g.* 3*S*-phenyl, in quantitative yield with almost complete recovery of the auxiliary without racemisation (*cf.* **2**).

On the basis of the markedly increased steric shielding provided by the new auxiliary **3** *vis-à-vis* **1** in the foregoing reactions, we synthesised the crystalline *N*-propionyl derivative **48** (78% yield) as shown in Scheme 13 in order to probe its effectiveness as a chiral auxiliary in aldol, alkylation and acylation reactions. The aldol condensation was studied involving both chiral boron **49** and lithium enolates **52** in reactions with PhCHO in CH_2Cl_2 . Excellent diastereoselection was observed with the dibutylboron enolate **49** (*d.e.* 95%) and the major aldol product

51a was determined to be *erythro* by high field ^1H NMR spectroscopy ($J = 5.2$ Hz) with the *threo*-products accounting for less than 5% of the crude reaction mixture. Subsequent cleavage of **51a** with lithium hydroperoxide followed by methylation with diazomethane afforded methyl (2*S*, 3*S*)-2-methyl-3-hydroxy-3-phenyl propionate [94%], $[\alpha]_D = -19.2^\circ$ (18°C, $c = 4.4$, CH_2Cl_2) [19] which verified the assigned stereochemistry as shown in Scheme 13.

By comparison, only moderate diastereoselectivity was found in the case of the lithium-chelated (*Z*)-enolate **52** generated from **48** with freshly prepared Pr_2NLi (*erythro:threo* 81:19, *erythro d.e.* 31%). A noteworthy feature of this reaction is that the *erythro*-isomer **51a** generated using boron is diastereomerically opposed to its isomer **51b** obtained with lithium as the counterion, this reversal in topicity arising because of the cyclic chelate **52**.

The poor levels of stereoregulation found in the lithium enolate-mediated reaction in Scheme 13 matches those results obtained for chiral auxiliary **1** and PhCHO [2], in keeping with similar results reported by other groups for chiral auxiliaries derived from (1*S*, 2*R*)-norephedrine [20] and (+)-camphor [21]. The greater diastereose-



SCHEME 13 Reagents and conditions: (i), 1.1equiv. Et_2Zn in hexane:ether, 20°C then -78°C , 3equiv. EtCOCl ; (ii), 1M di-*n*-butylboron triflate in CH_2Cl_2 , 0°C , Pr_2EtN ; (iii), -78°C , PhCHO; (iv), 1.1equiv. Pr_2NLi , 0°C , THF; (v), -78°C , PhCHO; (vi), -78°C , PhCH_2Br , NaI then -10°C ; (vii), -78°C , RCOCl , (**54a**, $\text{R} = \text{Me}$, **54b**, $\text{R} = \text{Et}$); yields: 90, 97% respectively).

lectivity achieved with the use of the boron enolate **49** is comparable to the auxiliaries just mentioned and can be rationalised in terms of the Zimmerman-Traxler six-membered cyclic transition state **50** in which only the C_α -*Re* face is open to attack.

It has been suggested by Heathcock [22] that the lithium cation can simultaneously coordinate with three oxygen atoms in the transition state, which in turn orients the auxiliary in such a way that the two enolate faces are differentiated. On the other hand, boron bears two butyl substituents and can coordinate with only two oxygens as depicted in **50**. Since boron enolates are not very reactive species it is necessary that the aldehydic carbonyl be activated before aldol addition can occur. The required carbonyl-activation is brought about by coordination with a Lewis acid. In the absence of an external Lewis acid this activation must be provided by the boron atom and it follows that in the closed transition state **50** boron is coordinated with oxygen from the enolate and aldehyde and can no longer be coordinated with the oxazolidinone carbonyl group.

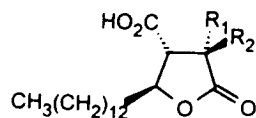
The opposite sense of diastereofacial bias imparted by (+)-**3** when compared to **1** is further reflected in the alkylation of the chelated lithium enolate **52** with PhCH_2Br at -10°C in the presence of NaI which proceeded from the less hindered *si*-face to produce α -alkylated **53** with *R*-configuration in >90% yield and a *d.e.* of 99%. By comparison, the analogous reaction with **1** gave the (*S*)-alkylated product in 80% yield with a *d.e.* of >99%. Similarly, reaction between lithium enolate **52** and acyl chlorides at -78°C produced *C*-acylated derivatives **54a** and **54b** in

high chemical and optical yield (**54a** *d.e.* 86%, **54b** *d.e.* >90%). This result compares well with the selectivity found for the associated reactions reported for **1** ($\text{R}=\text{Me}$, yield 88%, *d.e.* 82%; $\text{R}=\text{Et}$, yield 89%, *d.e.* >99%) [2].

On the basis of these preliminary results, it is evident that the (–)-camphene-derived spirooxazolidin-2-one **3** [(+)-Chiracamphox] constitutes a powerful new addition to the existing armoury of preparatively useful chiral auxiliaries. For most asymmetric transformations, and especially Lewis acid-mediated Diels-Alder reactions, it offers exceptionally high levels of diastereofacial differentiation, and in this respect, it is superior to its predecessor, the likewise terpenoid-based tricyclic oxazolidin-2-one **1**.

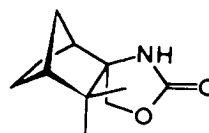
Application of (–)-Chiracamphox to the Synthesis of Paraconic Fatty Acid **55a**

The exceptional quality of asymmetric induction imparted by (+)-**3** [and its enantiomer, (–)-Chiracamphox] is undoubtedly the result of propitious shielding of one of its faces by the masked *tert*-butyl group, an effect that is extended to its pro-chiral precursors. We have exploited this effect further and expanded the preparative usefulness of Chiracamphox **3** to the enantioselective synthesis of paraconic fatty acids, a group of naturally-occurring compounds of topical interest due to their biological significance. In particular, the tri-substituted γ -lactone, (–)-dihydroprotolichesterinic acid [(3*S*, 4*R*, 5*S*)-4-carboxy-3-methyl-5-tridecyl-oxolan-2-one] **55a** is noted to be a potential antibacterial agent [23], while (–)-protolichesterinic acid **55b**, recently synthesised

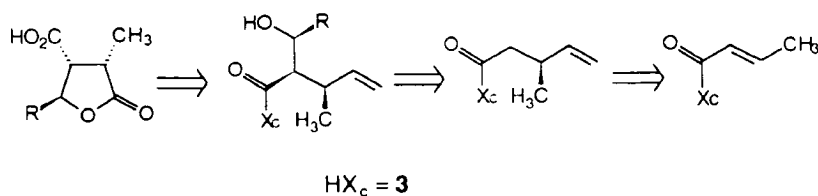


55a , $\text{R}_1 = \text{CH}_3$, $\text{R}_2 = \text{H}$

55b , $\text{R}_1, \text{R}_2 = =\text{CH}_2$



(–)-**3**



SCHEME 14 Retrosynthetic analysis of 55.

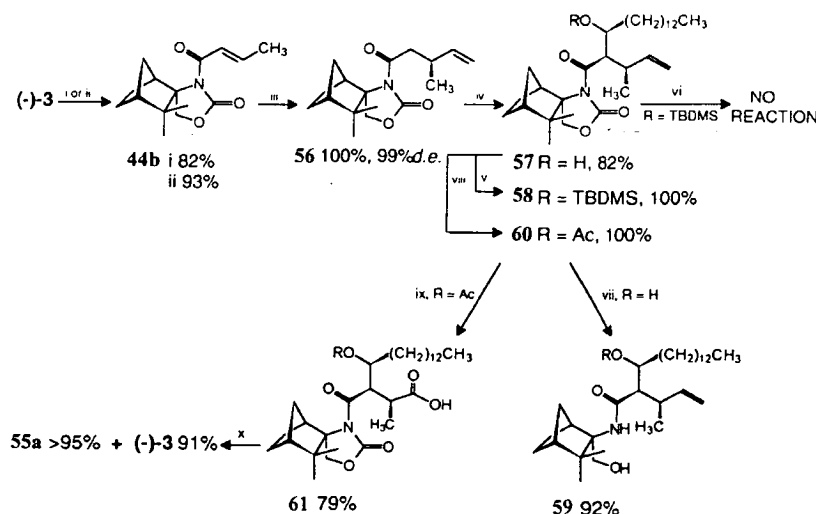
enantioselectively by Greene [24], is known to possess anti-bacterial, anti-fungal, anti-tumoral and growth regulation properties [25]. The first enantioselective synthesis of **55a** was carried out recently by Mulzer [26] in 14 steps from (3*R*)-2,3-isopropylidene glyceraldehyde with an overall yield of 0.4%, while its enantiomer was obtained by a similar route in 0.5% from di-isopropylidene-*D*-glucose.

We have now described a much more concise and efficient synthesis of **55a** [27] in which our recently developed (+)-camphene-derived chiral auxiliary **3** [(−)-Chiracamphox] is used to construct the three contiguous chiral centres *via* the successful strategy of consecutive stereocontrolled 1,4-conjugate addition and *syn*-aldol con-

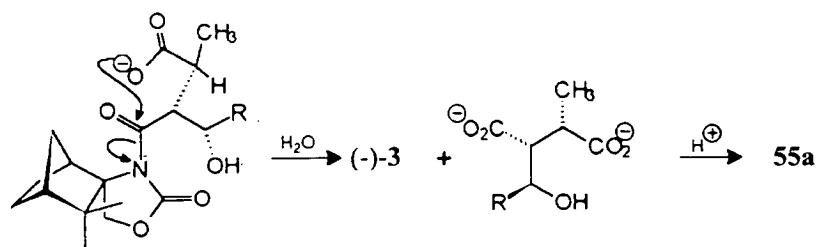
densation reactions. In retrosynthetic analysis we masked the lactone carboxyl function as a vinyl group (Scheme 14).

The synthesis begins with the crotonyl imide **44b** which is conveniently prepared either by reaction of the bromomagnesium salt of (−)-**3** with crotonyl chloride in 82% yield, or in 93% yield *via* the ethylzinc salt, a procedure developed by us (*vide supra*) to avoid C-acylation in the synthesis of acyl imides (Scheme 15).

1,4-Conjugate addition of vinylmagnesium bromide to **44b** under copper catalysis led to the quantitative formation of adduct **56** with near complete stereoselection. The absolute configuration of the new stereocentre in **56** was determined after catalytic reduction (H_2 , 10% Pd/C,



SCHEME 15 Reaction conditions: (i), EtMgBr, THF, 0°C, then *E*-crotonyl chloride, −78°C to rt; (ii), ZnEt₂, Et₂O, rt, then *E*-crotonyl chloride −78°C to 35°C, 3 hr; (iii), CH₂CHMgBr (2.5 equiv.), CuBr (0.4 equiv.), −78°C to −20°C, then addition to sat. NH₄Cl/THF 0°C; (iv) *n*-Bu₂BOTf, *i*-Pr₂NEt, CH₂Cl₂, −78°C to 0°C, then CH₃(CH₂)₁₂CHO, −78°C to rt; (v), TBDMSOTf, THF, −78°C to rt, 5 days; (vi), LiOH, H₂O₂, THF/H₂O, 50°C, 3 hr; (vii), Ac₂O, NEt₃, DMAP, hexane; (viii), KMnO₄, *n*-Bu₄NBr, C₆H₆/AcOH/H₂O, 50°C, 1/2 hr; (ix), LiOH, H₂O₂ (30%, 100 equiv.), THF/H₂O, rt, 5 days.



SCHEME 16

ethyl acetate, 1 atm.) of **56**, followed by cleavage with lithium hydroperoxide [28] to give (3*R*)-3-methylpentanoic acid [α]_D = +4.5° (*c* = 2.0, CHCl₃), *lit.* [29] [α]_D²³ = +6.42° (*c* = 4.03, CHCl₃).

In the second stereocontrolled step, the dibutylboron enolate of **56** produced under standard conditions [20] was treated with tetradecanal to give the *syn*-aldol product **57** (CHOH.CHCO, *J* = 6.4 Hz) in 82% yield as a single diastereomer. Initially **57** was converted into its TBDMS ether **58**, but this failed to cleave when treated with lithium benzyloxide, presumably due to shielding of the imide carbonyl by the long alkyl chain/TBDMS group. It was found that use of the smaller TMS ether grouping led to deprotection and subsequent decomposition of the aldol, but this failed to react with lithium hydroperoxide under mild conditions and gave only the β -amido alcohol **59**, formed by *endo*-cyclic attack in 92% yield when heated to 50°C. Not discouraged, we next investigated the possibility of assisted solvolysis of the desired fragment from the auxiliary. To this end, **57** was protected as its acetate **60** which was then oxidatively cleaved with potassium permanganate under modified phase-transfer conditions of Starks [30] to give the acid **61** in 79% yield. Treatment of **61** with lithium hydroperoxide (5 equiv.) under adapted conditions (see Scheme 16) led to the slow but complete removal of the chiral fragment in the required manner, and to our pleasure, the desired lactone **55a**. In this step it is believed that the neighbouring carboxylate (or percarboxy-

late) anion may be assisting in the cleavage of the imide bond by its attack on the *exo*-carbonyl (Scheme 16).

The crystalline lactone **55a** was isolated in >95% yield [m.p. = 105.1–105.8°C (from hexane/cyclohexane), *lit.* [31] m.p. = 106°C. [α]_D = -53.0° (*c* = 1.75, CHCl₃), *lit.* [26] [α]_D = -49.5° (*c* = 1.75, CHCl₃)] and consistent spectroscopic data] whilst (-)-**3** was recovered in 91% yield with complete stereochemical integrity.

Thus an overall yield of 57% of chirally pure **55a** in six steps has been achieved, considerably shorter and higher yielding than the previous synthesis [26]. Our route represents a viable and easily adapted method for the formation of 4-carboxy- γ -lactones containing three contiguous chiral centres. We are at present attempting to apply this methodology to other similar systems as well as demonstrating the utility of (-)-**3** and its enantiomer in the synthesis of other small- and medium-sized enantiomerically pure fragments.

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- [4] We have prepared the *exo*-variant of **1** from *exo*-borneol [obtained by L-Selectride reduction of (1*R*)-camphor] using our nitreno-mediated route to construct the oxazolidin-2-one ring (G.B. patent application No. 901268.0, filing date 7th July 1990); see also Bonner, M. P. and Thornton, E. R. (1991). *J. Am. Chem. Soc.*, 113, 1299 for an alternative synthesis from (1*R*)-(-)-camphorquinone by conversion into the corresponding *exo,exo*-aminoalcohol followed by cyclocarbamation.
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- [18] See Tanaka, K., Uno, H., Osuga, H. and Suzuki, H. (1993). *Tetrahedron Asym.*, 4, 629, for the striking observation that the *endo*-diastereoselectivity in the reaction of the crotonoyl dienophile from **1** with cyclopentadiene in the presence of $\text{TiCl}_2(\text{OPr})_2$ is dramatically raised (47 to 84%) on changing the solvent from CH_2Cl_2 to toluene. Since our original observation [2] we have also discovered that the diastereoselectivity can be improved by changing the order of addition of Lewis Acid promoter to last.
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Asymmetric Diels-Alder Reactions Employing Modified Camphor-Derived Oxazolidin-2-one Chiral Auxiliaries

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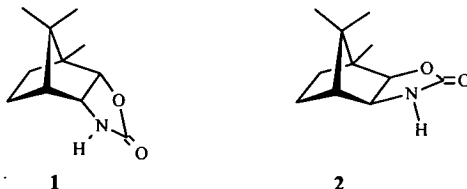
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Abstract: Transposition of the dormant methyl group from C-1 in chiral oxazolidin-2-one **2** to C-7 in a six step synthetic sequence from (1*R*)-camphor **5** creates a novel transfigomer **4** with sufficient π -topological bias to induce excellent levels of asymmetric induction in Lewis-acid catalysed Diels-Alder reactions of its α , β -unsaturated carboximide derivatives with cyclopentadiene. Further modification of **4** by replacement of the C-7 methyl group with an ethyl substituent raises the level of diastereoselectivity for the acrylate derivative **11a** from 81 to >95% *d.e.*.

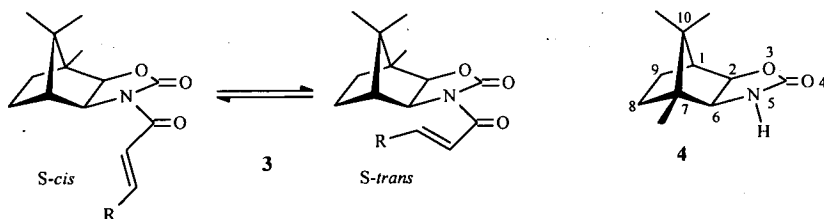
Introduction

The pioneering work of Evans¹ on the utilisation of optically-pure oxazolidin-2-ones derived from α -amino acids as chiral auxiliaries for use in asymmetric synthesis has inspired development of more efficient variants derived from other natural sources such as terpenes² and carbohydrates.³ As part of on-going studies in this area, we have synthesised the *endo*- and *exo*-variants **1**⁴ and **2**⁵ respectively, both of which are sterically constrained by the rigid bornyl system, and demonstrated their usefulness as chiral reagents in a variety of asymmetric transformations. In particular, these auxiliaries have proved to be effective in achieving high levels



of asymmetric induction in alkylation, acylation and aldol reactions, but Diels-Alder cycloadditions were much less successful due to the lack of sufficient π -topological bias imparted by the auxiliary when bearing *N*-acryloyl substituents, *e.g.* **3**. The origin of the poor stereoselection arises from the free rotation of the carbonyl- C_α bond in the *N*-acryloyl moiety of the dienophile. This allows attack by the diene on both enantiofaces, *i.e.* the dienophile can react in either the *S-trans* or *S-cis* conformation despite the adjacent enantiopure bornyl substituent and the presence of a Lewis-acid catalyst [Et_2AlCl or $\text{TiCl}_2(\text{OPr}^i)_2$], which brings about bidentate chelation and freezes the *N*-carbonyl rotor. In order to render the faces diastereotopic and bring about

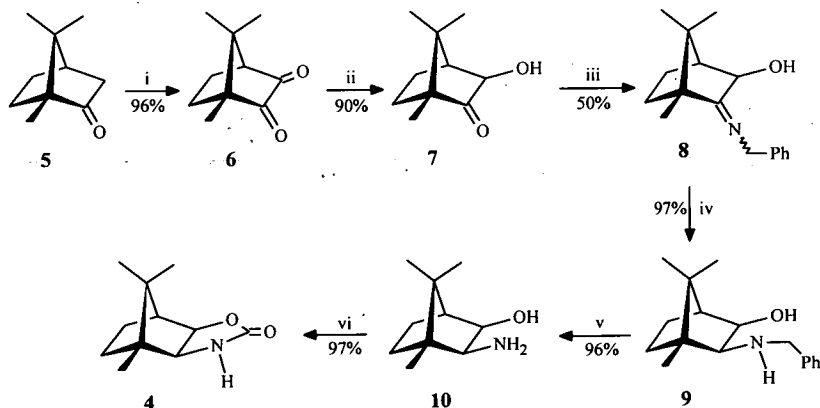
asymmetric induction, it is clearly necessary to modify the chiral framework in systems such as **2** (and **1**). This steric bias can, in principle, be effected by transposition of the passive methyl group from the rear of the bornane ring to the front, *i.e.* proximal to the active site of the auxiliary, and hence create the positional isomer **4**. We surmised that with chelation control this transposition of steric bias should lead to an increase in steric repulsion between the *N*-acryloyl moiety and the bornane ring in the *S-trans* conformer, and thus lead to better stereoselection *via* the *S-cis* conformer during Diels-Alder reactions. Palomo and co-workers have recently reported the synthesis of **4** in a communication,⁶ but hitherto they have only described the Diels-Alder reaction on the crotonyl derivative **11b**.



Results and Discussion

1. Synthesis of (1*S*, 2*R*, 6*S*, 7*R*, *exo*)-3-oxa-5-aza-7,10,10-trimethyltricyclo[5.2.1.0]decan-4-one **4**

The synthesis of isomer **4** in an optically pure state was achieved in a six-step process in 39% overall yield starting from (1*R*)-camphor **5** (Scheme 1). Thus, following the previous work carried out by Langlois and co-workers,⁷ oxidation of **5** to camphorquinone **6** using selenium dioxide in acetic anhydride⁸ was followed by



Scheme 1. Reagents and conditions: (i), SeO₂, Ac₂O, reflux, 24h; (ii), L-selectride®, THF, -78°C, 4h; (iii), PhCH₂NH₂, 4A molecular sieves, THF, r.t., 72h; (iv), NaBH₄, MeOH, r.t., 5.5h; (v), 10% Pd-C, H₂, EtOH; (vi), triphosgene, DME/DCM/H₂O, NaOH.

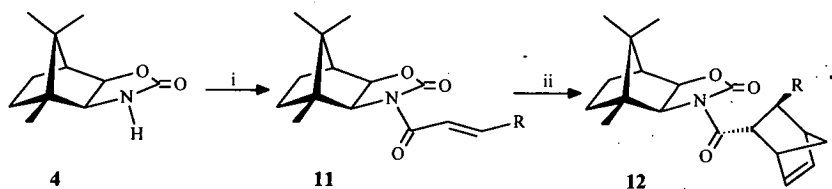
stereoselective reduction with L-Selectride® in tetrahydrofuran (THF) to afford the desired *exo*- α -hydroxyketone **7** exclusively. We sought to avoid the disposal problems associated with the first step, and the expense of the second, by direct conversion of **5** into **7** via its silylenol ether⁹ and subsequent oxidation with *m*-chloroperoxybenzoic acid, but this approach led to an inseparable 2:1 mixture of *endo*- and *exo*-isomers. In the next step, **7** was transformed into the corresponding *N*-benzylimine **8** by treatment with benzylamine in THF in the presence of 4Å molecular sieves, albeit in only 50% yield. Attempts to improve the yield by varying the reaction temperature and the nature of the dehydrating agent failed, but reduction of imine **8** with sodium borohydride in methanol proceeded smoothly to yield the desired *exo,exo*-hydroxy-*N*-benzylamine **9**, which was deprotected by catalytic hydrogenation with 10% palladium on charcoal to afford *exo,exo*-hydroxyamine **10**. Finally, treatment of **10** with triphosgene and excess sodium hydroxide¹⁰ led to the virtually quantitative formation of the desired oxazolidin-2-one **4**, which after recrystallisation from cyclohexane:ethyl acetate yielded colourless crystals (m.p. = 196.3–197.3°C). Unfortunately, the crystals formed were unsuitable for an X-ray crystal structure but the absolute stereochemistry of the novel auxiliary **4** was proven conclusively by obtaining an X-ray structure for the crotonate Diels–Alder adduct **12b** (*vide infra*).

2. Utility of chiral auxiliary **4** in Diels–Alder cycloaddition reactions

A significant advance in asymmetric Diels–Alder reactions in recent times has been the increased use of Lewis-acid catalysts to control rotameric preference.¹ When compared to non-catalysed Diels–Alder reactions, catalysed versions proceed at greatly enhanced rates as well as with dramatically increased levels of regio- and stereo-selectivity.

The required unsaturated carboximides **11** are easily prepared in excellent yield (89–99%) by treatment of the oxazolidin-2-one auxiliary **4** with freshly prepared ethylmagnesium bromide at 0°C in THF followed by the appropriate acid chloride at -78°C (Scheme 2). The Diels–Alder reactions were carried out by addition of diethylaluminium chloride (1.6 equiv.) to a cooled stirred solution of the appropriate dienophile **11** (1 equiv.) and freshly cracked cyclopentadiene (10 equiv.) in dichloromethane. The addition of catalyst to the reaction mixture was accompanied by a yellow colouration which faded on completion of the reaction. The reactions of the acrylate **11a** and crotonate **11b** were carried out at -78°C, whilst the less reactive cinnamate **11c** needed to be warmed to -20°C before reaction would occur.

In each case, reaction occurred in almost quantitative yield and the diastereomeric product ratios were determined by high-field NMR spectroscopic (250 MHz) analysis of the crude product after filtration through silica gel to remove excess cyclopentadiene. The resonances of interest were the two doublet of doublets between δ 5.5 and 6.5 due to the olefinic protons in the cycloadducts **12**. Integration of these signals allowed the *endo/exo* selectivities and the diastereomeric excesses (*d.e.*) to be measured.



Scheme 2. Reagents and conditions: (i), EtMgBr, THF, 0°C, RCH=CHCOCl, -78°C, **11a**, R = H (88%), **11b**, R = Me (90%), **11c**, R = Ph (99%); (ii), Et₂AlCl, cyclopentadiene, DCM, -78°C (-20°C for **11c**), **12a**, R = H (100%), **12b**, R = Me (92%), **12c**, R = Ph (100%).

The results are summarised in Table 1 and clearly demonstrate the efficiency of **10** as a chiral control element in Lewis-acid mediated Diels-Alder reactions. In each case *endo*-diastereoselection is exceptionally good and well in excess of levels previously attained with chiral oxazolidin-2-one **1**,⁴ although the relatively poor level of diastereoselection (81% *d.e.*) obtained with acrylate **11a** presumably reflects the lack of sufficient steric repulsion between the acrylate moiety and the methyl group on the front face of the auxiliary to bring about overwhelming population differences between the chelated *S-cis* and *S-trans* conformers. Nonetheless, the benefit of introducing a methyl group onto the front face of the auxiliary **10** is underlined when the results of the corresponding Diels-Alder reaction of **2** are considered. In this case, *endo:exo* selectivities of only *ca.* 4:1 are observed with corresponding low levels of diastereoselection in the range of 48-68%.¹¹

Table 1. Diethylaluminium chloride-promoted asymmetric Diels-Alder reactions of unsaturated carboximides derived from auxiliaries **4** and **21** with cyclopentadiene^a

Dienophile	Temp/°C	Yield (%)	<i>endo:exo</i>	<i>d.e.</i> (%) (corresponding <i>d.e.</i> for 1)
11a	-78	100	100:0	81 (60)
11b	-78	92	100:0	>99 (60)
11c	-20	100	100:0	>99 (99)
22a	-78	92	100:0	>95
22b	-78	91	100:0	>99

^a Methylene chloride was used as solvent with Et₂AlCl (1.6equiv.) as catalyst.

The absolute stereochemical outcome of the products was determined by obtaining an X-ray crystal structure for the crotonyl-derived adduct **12b** (Fig. 1), which showed that attack of the diene occurred on the C_α-*si* face of the chelated dienophile, *i.e.* opposite to that obtained with the *endo*-variant **1**.⁴

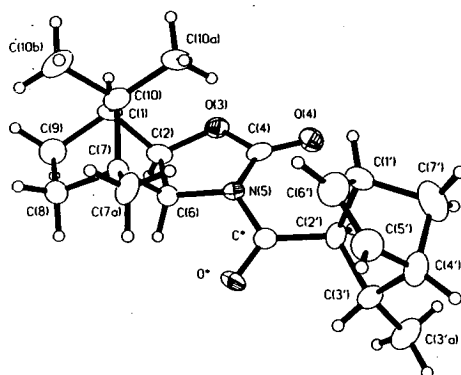


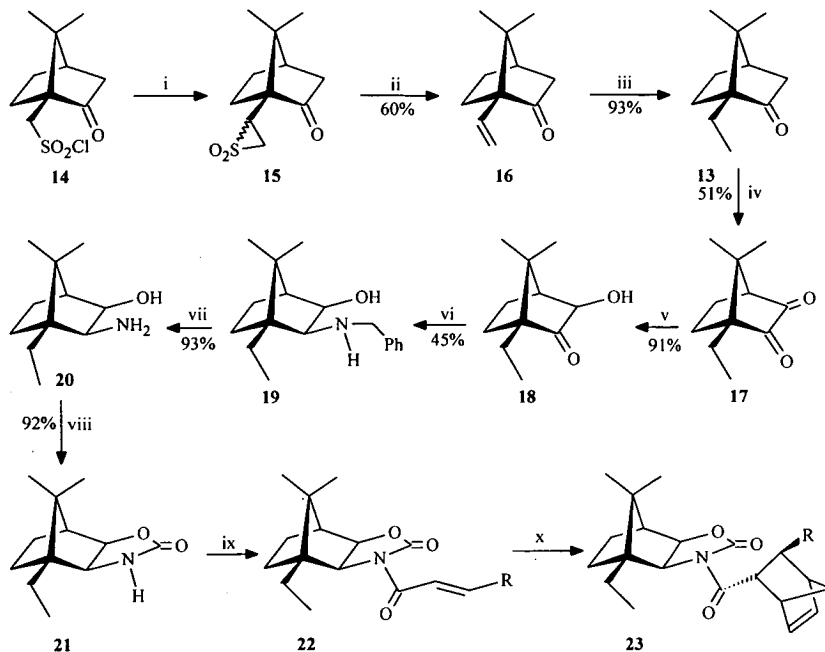
Figure 1. View of the X-ray Structure of Diels-Alder Adduct 12b.

3. Synthesis of (1*S*, 2*R*, 6*S*, 7*R*)-3-oxa-5-aza-7-ethyl-10,10-dimethyl-tricyclo[5.2.1.0^{2,6}]decan-4-one 21

In order to improve on the selectivity provided by the auxiliary **4** in Lewis-acid mediated Diels-Alder reactions involving the acrylate derivative **11a**, it was decided to increase the steric bulk at the front face of the auxiliary by replacing the methyl group at C-7 with an ethyl group to create the homologue **21** with the required topological bias to control the rotameric preference. To this end, a synthetic route similar to that adopted for **4** was followed as outlined in Scheme 3, starting from 10-methylcamphor **13**, which can be prepared in a three-step sequence from commercially available 10-camphorsulfonyl chloride **14**. Thus, treatment of **14** with diazomethane followed by neat thermolysis of the crude episulphone **15** produced methylenecamphor **16** as a waxy solid in 60% yield after Kügelrohr distillation. Catalytic hydrogenation of the latter using 10% palladium on charcoal in ethanol gave rise to the desired 10-methylcamphor **13** in excellent yield (93%), but subsequent treatment with selenium dioxide in acetic anhydride under reflux afforded 10-methylcamphorquinone **17** in only 51% yield. Variation of both reaction time and stoichiometry failed to improve the yield, but fortunately unreacted starting material could be recovered and recycled. Stereoselective reduction of **17** proceeded smoothly with L-Selectride® to yield hydroxy ketone **18** in 91% yield. Attempts to prepare the *N*-benzylimine derivative of **18** (*cf.* Scheme 1) failed; variation of temperature and dehydration agent led only to complex mixtures, but the problem was circumvented by direct synthesis of **19** in 45% yield by reductive amination of **18** using titanium(IV)isopropoxide and sodium cyanoborohydride.¹² The *exo*, *exo*-stereochemistry of **19** was verified by comparison of its ¹H NMR spectrum with that of the methyl analogue **9**. In essence, three doublets appeared at δ 3.64, 2.85 and 1.79 ppm due to the protons attached to C-3, C-2 and C-4, respectively with corresponding coupling constants of 7.2, 7.2 and 4.7 Hz, which are almost identical to those displayed by **9**.

The final steps in the synthesis were achieved in a straight-forward manner by catalytic hydrogenation of **19** followed by treatment of the resulting α,β-amino alcohol **20** with triphosgene to afford the desired oxazolidin-2-one **21** as pale-yellow fluffy crystals (m.p. = 138–140°C from xylene/cyclohexane). The overall

yield of **21** for the eight-step synthetic sequence from 10-camphorsulfonyl chloride was only 9%, but sufficient material was obtained to evaluate its synthetic utility in Lewis-acid mediated Diels-Alder reactions.



Scheme 3. Reagents and conditions: (i), CH_2N_2 , Et_2O , 0°C , 3h; (ii), 95°C ; (iii), 10% Pd-C, H_2 , EtOH ; (iv), SeO_2 , Ac_2O ; (v), L-Selectride[®], THF, -78°C ; (vi), $\text{Ti(IV)O}^i\text{Pr}$, PhCH_2NH_2 , EtOH , NaBH_3CN ; (vii), 10% Pd-C, H_2 , EtOH ; (viii), triphosgene, DME/DCM/ H_2O , NaOH ; (ix), Et_2Zn , $\text{RCH}=\text{CHCOCl}$, 25°C , **22a**, $\text{R} = \text{H}$ (31%), **b**, $\text{R} = \text{Me}$ (33%); (x), Et_2AlCl , cyclopentadiene, DCM, -78°C , **23a**, $\text{R} = \text{H}$ (92%), **b**, $\text{R} = \text{Me}$ (91%).

4. Lewis-acid mediated Diels-Alder reactions utilising auxiliary **21**

Our initial attempts to prepare *N*-acryloyl derivatives of **21** using freshly prepared ethylmagnesium bromide as described previously failed, and only starting material was recovered even after boiling under reflux for *ca.* 24 hours. This obstacle was overcome by utilising an alternative procedure developed by us,¹³ whereby the auxiliary was treated with diethylzinc at room temperature followed by cooling to -78°C and subsequent reaction with the appropriate acid chloride (Scheme 3). Even so, acrylate **22a** and crotonate **22b** were obtained in only 31% and 38% yields respectively, along with significant amounts of unreacted **21**. This difficulty in bringing about the functionalisation of **21** is presumably a consequence of the increased steric hindrance arising from the incorporation of an ethyl group at C-7.

The degree of stereoselectivity (*d.e.*%) for the Diels-Alder reaction of dienophiles **22** with cyclopentadiene was determined as before by integration of the signals arising from the olefinic protons in the high field ^1H NMR spectra of the cycloadducts **23**. Table 1 shows that the *endo:exo* selectivity is excellent in

both cases, and in particular that the *d.e.* for the acrylate **22a** is increased to >95% from 81% for its homologue **11a**.

In conclusion, these experiments show that the reason for the poor diastereoselection in Diels–Alder reactions of cyclopentadiene with **1** and **2** as the chiral control elements is clearly steric in origin and that transposition of the dormant methyl group from C-1 into the vicinity of the reaction site at C-7 is sufficient to improve π -face discrimination to acceptable levels. These can be raised to even higher levels by the introduction of an ethyl group instead of a methyl, although synthesis of the required auxiliary **21** requires eight steps starting from commercially available 10-camphorsulphonyl chloride **14**.

Experimental

Melting points are uncorrected. ^1H and ^{13}C NMR spectra were obtained on a Bruker AC-250 operating at 250 MHz or 62.9 MHz or on a Bruker WH-360 operating at 360 MHz or 90.6 MHz respectively. IR spectra were recorded on a Biorad FTS-7 spectrometer and accurate mass measurements determined on a Kratos MS 50TC mass spectrometer. Elemental analyses were determined on a Perkin Elmer 2400 CHN elemental analyser. Tetrahydrofuran and ether were distilled prior to use from sodium/benzophenone ketyl and methylene chloride was distilled from finely divided (Fisons) calcium hydride. Thin layer chromatography was carried out on silica gel 60 F₂₅₄ plates and visualised by UV irradiation and/or dipping the plate into a solution of concentrated sulphuric acid in ethanol (5:95) followed by gentle flaming. Flash chromatography was conducted using silica gel 60 (220–240 mesh). All reagents were used as supplied by commercial sources unless otherwise stated. For all X-ray structures reported, atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.

(1R, 3R, exo)-3-Hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (7). A modification of Langlois *et al.*'s method⁷ was used. To a solution of camphorquinone **6**⁸ (4.40g, 26.5mmol) in dry THF (50ml) at -78°C under argon, was added a solution of L-Selectride[®] (28ml of a 1.0M solution, 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 **7** as a colourless oil (3.99g, 90%); ^{13}C NMR (50.32MHz, CDCl_3) δ 220.39(C=O), 77.17(CH), 69.36(C), 49.15(CH), 46.61(C), 28.45(CH₂), 20.84(CH₃), 19.89(CH₃), 8.85(CH₃) ppm; FT IR ν_{max} (thin film) 3440(OH), 1748(C=O) cm^{-1} .

(1R, 3R, exo)-N-Benzyl-3-imino-3-hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptane (8). Again a modification of the Langlois method⁷ was employed. To a solution of the keto alcohol **7** (2.06g, 12.3mmol) in dry THF (50ml) under argon was added benzylamine (2.89g, 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 **8** as a colourless solid (3.17g, 50%); ^{13}C NMR (50.32MHz, CDCl_3) δ 181.56(C=N), 140.58(Ar C), 128.05(2Ar CH), 127.29(2Ar CH), 126.18(Ar CH), 69.81(CH), 54.31(CH_2), 51.95(C), 49.99(CH), 44.15(C), 32.31(CH_2), 19.14(CH_3), 19.03(CH_3), 18.29(CH_2), 11.66(CH_3) ppm; FT IR ν_{max} (nujol) 3145(OH), 1674(C=N) cm^{-1} .

(**1R**, **2S**, **3R**, *exo*)-*N*-Benzyl-2-amino-3-hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptane (**9**).⁷ Sodium borohydride (10.50g, 276.3mmol, 10eq) was added in small portions to a stirred solution of the imine **8** (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 **9** as a clear colourless oil (6.90g, 97%); ^1H NMR (250.13MHz, CDCl_3) δ 7.35-7.25(5H, cm, Ph), 3.77(2H, s, PhCH_2), 3.63(1H, d, $J = 7.3$ Hz, CHOH), 2.70(1H, d, $J = 7.3$ Hz, CHNH), 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} .

(**1R**, **2S**, **3R**, *exo*)-2-Amino-3-hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptane (**10**).⁹ A solution of the amino alcohol **9** (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 **10** as a colourless solid (1.47g, 96%); ^1H NMR (200.13MHz, CDCl_3) δ 3.62(1H, d, $J = 7.4$ Hz, CHOH), 3.02(3H, bs, NH_2 and OH), 2.84(1H, d, $J = 7.4$ Hz, CHNH_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 75.02(CH), 62.43(CH), 50.86(CH), 47.79(C), 46.53(C), 35.74(CH_2), 23.79(CH_2), 21.73(CH_3), 20.73(CH_3), 11.86(CH_3) ppm; FT IR ν_{max} (nujol) 3391(NH_2), 3297(NH_2), 3155(OH) cm^{-1} .

(**1S**, **2R**, **6S**, **7R** *exo*)-3-Oxa-5-aza-7,10,10-trimethyltricyclo[5.2.1.0^{2,6}]decan-4-one (**4**). A solution of 6M NaOH (2ml) was added to the amino alcohol **10** (0.50g, 2.96mmol) 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 **4** as a colourless solid (0.57g, 98%); m.p. = $196.3\text{--}197.3^\circ\text{C}$ (cyclohexane:ethyl acetate) (Lit.⁶ = $202\text{--}204^\circ\text{C}$); $[\alpha]_{\text{D}}^{21} = +1.2^\circ$ ($c=1.02$, CH_2Cl_2); ^1H 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, CH₃), 0.96–0.93(1H, cm), 0.89(3H, s, CH₃), 0.86(3H, s, CH₃) ppm; ¹³C NMR (50.32MHz, CDCl₃) δ 160.91(C=O), 83.99(CH), 65.43(CH), 47.94(CH), 47.36(C), 46.08(C), 32.64(CH₂), 22.94(CH₃), 22.76(CH₂), 18.97(CH₃), 10.46(CH₃) ppm; FT IR $\nu_{\max}$ (nujol) 3286(NH), 1756(C=O) cm⁻¹; (Found: m/z , 196.13312 (MH⁺), C₁₁H₁₈NO₂ requires 196.13375); (Found: C, 67.2; H, 9.2; N, 7.1. C₁₁H₁₇NO₂ requires C, 67.6; H 8.8, N 7.2%.)

(*1S*, *2R*, *6S*, *7R*, *exo*)-*N*-Acryloyl-3-oxa-5-aza-7,10,10-trimethyltricyclo[5.2.1.0^{2,6}]decan-4-one (**11a**). Ethyl bromide (0.21g, 1.93mmol) was added to magnesium turnings (0.04g, 1.67mmol) 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 **4** (0.20g, 1.03mmol) 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, 2.09mmol) 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 filtration and evaporation *in vacuo* yielded a yellow oil. The oil was subjected to flash chromatography (silica, hexane:ether (4:1)) to give **11a** as a colourless solid (0.22g, 88%); m.p. = 93.4–94.7°C (hexane); $[\alpha]_D^{21} = +82.7^\circ$ ($c=1.00$, CH₂Cl₂); ¹H NMR (250.13MHz, CDCl₃) δ 7.46(1H, dd, J = 17.0, 10.4 Hz, proton of =CH₂ trans to proton on adjacent carbon), 6.48(1H, dd, J = 17.0, 1.8 Hz, proton of =CH₂ cis to proton on adjacent carbon), 5.84(1H, dd, J = 10.4, 1.8 Hz, CH=CH₂) 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, CH₃), 0.91(3H, s, CH₃), 0.87(3H, s, CH₃) ppm; ¹³C NMR (62.90MHz, CDCl₃) δ 165.47(C=O), 154.78(C=O), 131.71(CH₂), 127.69(CH), 81.30(CH), 69.66(CH), 50.01(C), 47.45(CH), 46.33(C), 33.10(CH₂), 22.62(CH₃ and CH₂), 19.50(CH₃), 11.90(CH₃) ppm; FT IR $\nu_{\max}$ (nujol) 1787, 1758(C=O), 1695(C=O), 1616(C=C)cm⁻¹; (Found: m/z , 250.14451 (MH⁺), C₁₄H₂₀NO₃ requires 250.14432).

(*1S*, *2R*, *6S*, *7R*, *exo*)-*N*-Crotonoyl-3-oxa-5-aza-7,10,10-trimethyltricyclo[5.2.1.0^{2,6}]decan-4-one (**11b**). Prepared by the same general procedure as above giving **11b** as a colourless solid (0.28g, 90%); m.p. = 141.4–143.4°C (cyclohexane); $[\alpha]_D^{21} = +46.0^\circ$ ($c=0.50$, CH₂Cl₂); ¹H NMR (250.13MHz, CDCl₃) 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=CH₃), 1.89–1.80(1H, cm), 1.52(1H, ddd, J = 11.8, 11.8, 4.5 Hz, CH₂), 1.22(1H, dt, J = 9.2, 4.0 Hz, CH₂), 1.06–1.00(1H, cm), 0.98(3H, s, CH₃), 0.89(3H, s, CH₃), 0.86(3H, s, CH₃) ppm; ¹³C NMR (62.90MHz, CDCl₃) 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(CH₂),

22.61(CH₂+CH₃), 19.44(CH₃), 18.32(CH₃), 11.85(CH₃) ppm; FT IR $\nu_{\max}$ (nujol) 1758(C=O), 1682(C=O), 1632(C=C) cm⁻¹; (Found: m/z , 264.16015 (MH⁺), C₁₅H₂₂NO₃ requires 264.15997).

(1S, 2R, 6S, 7R, exo)-N-Cinnamoyl-3-oxa-5-aza-7,10,10-trimethyltricyclo[5.2.1.0^{2,6}]decan-4-one (11c).

Prepared by the general procedure as above to give **11c** a colourless solid (0.71g, 100%); m.p. = 141.5–142.5°C (cyclohexane); $[\alpha]_D^{21} = +149.6^\circ$ (c=1.03, CH₂Cl₂); ¹H NMR (250.13MHz, CDCl₃) δ 7.91(1H, d, J = 15.7 Hz, COCH=CH), 7.80(1H, d, J = 15.8 Hz, C=CHPh), 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, 12.4, 4.6 Hz, CH₂), 1.31–1.21(1H, cm), 1.05–1.03(1H, cm), 1.03(3H, s, CH₃), 0.95(3H, s, CH₃), 0.88(3H, s, CH₃) ppm; ¹³C NMR (62.90MHz, CDCl₃) 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(CH₂), 22.61(CH₂ and CH₃), 19.50(CH₃), 11.93(CH₃) ppm; FT IR $\nu_{\max}$ (nujol) 1764(C=O), 1678(C=O), 1618(C=C) cm⁻¹; (Found: m/z , 326.17662 (MH⁺), C₂₀H₂₄NO₃ requires 326.17526).

(1S, 2R, 6S, 7R, exo)-N-((3'R, 4'S, 5'S, 6'R)-5'-Methylbicyclo[2.2.1]heptene-4'-carbonyl)-3-oxa-5-aza-7,10,10-trimethyltricyclo[5.2.1.0^{2,6}]decan-4-one (12b).

To a solution of the crotonate **11b** (0.21g, 0.78mmol) in dry methylene chloride (20ml) at -78°C under argon was added freshly cracked cyclopentadiene (0.52g, 7.83mmol, 10eq.). Diethylaluminium chloride (0.7ml of a 1.8M solution, 1.26mmol, 1.6eq.) was then added and the reaction mixture stirred at -78°C for 20minutes, 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 **12b** as a colourless solid (0.24g, 92%); m.p. = 174.3–175.3°C (cyclohexane); $[\alpha]_D^{21} = +178^\circ$ (c= 1.00, CH₂Cl₂); ¹H NMR (360.13MHz, CDCl₃) 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 = 5.1 Hz, 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, CHCH₃), 1.02(3H, s, CH₃), 1.00–0.89(1H, cm), 0.86(3H, s, CH₃), 0.81(3H, s, CH₃) ppm; ¹³C NMR (50.32MHz, CDCl₃) δ 174.22(C=O), 154.74(C=O), 139.74(CH), 130.75(CH), 80.97(CH), 65.70(CH), 51.70(CH), 49.65(C), 49.01(CH), 47.51(CH and CH₃), 47.10(CH₂), 46.20(C), 35.08(CH), 33.19(CH₂), 22.59(CH and CH₂), 20.24(CH₃), 19.23(CH₃), 11.92(CH₃) ppm; FT IR $\nu_{\max}$ (nujol) 1757(C=O), 1705(C=O) cm⁻¹; (Found: m/z , 330.20691(MH⁺), C₂₀H₂₈NO₃ requires 330.20691); (Found: C, 72.6; H, 8.1; N, 4.6. C₂₀H₂₇NO₃ requires C, 72.9; H, 8.3; N, 4.3%).

(1S, 2R, 6S, 7R, exo)-N-((3'R, 4'S, 5'S, 6'R)-5'-Phenylbicyclo[2.2.1]heptene-4'-carbonyl)-3-oxa-5-aza-7,10,10-trimethyltricyclo[5.2.1.0^{2,6}]decan-4-one (12c).

Reaction protocol as that described above except reaction temperature was -20°C gave **12c** as a colourless solid(0.23g, 99%); m.p. = 176.5–178°C; $[\alpha]_D^{21} =$

+169.3 (c=1.05, CH₂Cl₂); ¹H NMR (250.13MHz, CDCl₃) δ 7.27–7.16(5H, cm, Ph), 6.54(1H, dd, *J* = 5.6, 3.2 Hz, CH=CH), 5.96(1H, dd, *J* = 5.6, 2.8 Hz, CH=CH), 4.44(1H, d, *J* = 8.2 Hz, CHO), 4.37(1H, d, *J* = 8.1 Hz, CHN), 4.22(1H, dd, 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, CH₃), 1.06–0.73(1H, cm), 0.90(3H, s, CH₃), 0.88(3H, s, CH₃) ppm; ¹³C NMR (62.90MHz, CDCl₃) 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(CH₂), 47.53(CH), 47.42(CH), 46.26(C), 45.61(CH), 33.20(CH₂), 22.60(CH₂ and CH₃), 19.29(CH₃), 11.98(CH₃) ppm; FT IR ν_{max} (nujol) 1760(C=O), 1703(C=O) cm⁻¹; (Found: *m/z*, 392.22334 (MH⁺) C₂₅H₃₀NO₃ requires 392.22257).

(1*R*, 2*R*, 6*S*, 7*R*, *exo*)-*N*-((3'*R*, 4'*S*, 6'*R*)-5'-Bicyclo[2.2.1]heptene-4'-carbonyl)-3-oxa-5-aza-7,10,10-trimethyltricyclo[5.2.1.0^{2,6}]decan-4-one (12a). Procedure as described previously for 12b yielded 12a as a colourless solid (0.22g, 99%); ¹H NMR (250.13MHz, CDCl₃) δ (major isomer) 6.26(1H, dd, *J* = 5.6, 3.1 Hz, CH=CH), 5.85(1H, dd, *J* = 5.6, 2.8 Hz, CH=CH), 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, COCHCH₂), 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, CH₃), 0.88(3H, s, CH₃), 0.84(3H, s, CH₃) ppm; ¹³C NMR (62.90MHz, CDCl₃) δ 174.61(C=O), 154.78(C=O), 138.37(CH), 130.77(CH), 81.07(CH), 65.87(CH), 50.45(CH₂), 49.76 (C), 47.59(CH), 46.82(CH), 46.27(C), 42.97 (CH), 42.69(CH), 33.29(CH₂), 28.06(CH₂), 22.65(CH₂ and CH₃), 19.31(CH₃), 12.02(CH₃) ppm; FT IR ν_{max} (nujol) 1769(C=O), 1711(C=O) cm⁻¹; (Found: *m/z*, 316.19215 (MH⁺), C₁₉H₂₆NO₃ requires 316.19127).

(1*S*, 2*R*, 6*S*, 7*R*, *exo*)-*N*-((3'*R*, 4'*S*, 5'*S*, 6'*R*)-5'-Methylbicyclo[2.2.1]hept-1'-ene-4'-carbonyl)-3-oxa-5-aza-7-ethyl-10,10-dimethyltricyclo[5.2.1.0^{2,6}]decan-4-one (23b). Same procedure as above gave 23b as a pale yellow gum (which partially solidified on standing) (0.09g, 91%); [α]_D²¹ = +88.0° (c=2.00, CHCl₃); ¹H NMR (250.13MHz, CDCl₃) δ 6.36(1H, dd, *J* = 5.7, 3.2 Hz, CH=CH), 5.78(1H, dd, *J* = 5.7, 2.8 Hz, CH=CH), 4.45(2H, s, CHO and CHN), 3.64(1H, dd, *J* = 4.6, 3.4 Hz, COCHCH(CH₃)), 3.27(1H, bs, cycloadduct bridgehead), 2.48(1H, bs, cycladduct 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, CH₃CH), 1.02(3H, s, CH₃), 0.89(6H, t and s, *J* = 7.5 Hz, CH₂CH₃ and CH₃) ppm; ¹³C NMR (62.90MHz, CDCl₃) δ 174.41(C=O), 155.05(C=O), 139.79(CH=CH), 130.74(CH=CH), 81.04(CH), 63.98(CH), 53.00(C), 51.90(CH), 49.09(CH), 47.97(CH), 47.67(CH), 47.18(CH₂), 46.80(C), 35.32(CH), 29.17(CH₂), 23.54(CH₃), 22.34(CH₂), 20.26(CH₃), 19.25(CH₃), 18.08(CH₂), 9.64(CH₃) ppm; FT IR ν_{max} (thin film) 1771(C=O), 1703(C=O), 1657(C=C) cm⁻¹; (Found: *m/z*, 344.22271 (MH⁺), C₂₁H₃₀NO₃ requires 344.22257).

(1*S*, 2*R*, 6*S*, 7*R*, *exo*)-*N*-((3'*R*, 4'*S*, 6'*R*)-Bicyclo[2.2.1]hept-1'-ene-4'-carbonyl)-3-oxa-5-aza-7-ethyl-10,10-dimethyltricyclo[5.2.1.0^{2,6}]decan-4-one (23a). Reaction conditions as before gave 23a as a colourless solid

(0.16g, 92%); m.p. = 97.0-99.0°C (hexane); $[\alpha]_D^{21} = +100.0^\circ$ ($c=1.75$, CHCl_3); ^1H NMR (250.13MHz, CDCl_3) δ 6.27(1H, dd, $J = 5.6, 3.0$ Hz, $\text{CH}=\text{CH}$), 5.81(1H, dd, $J = 5.7, 2.8$ Hz, $\text{CH}=\text{CH}$), 4.45(2H, s, CHO and CHN), 4.16(1H, dt, $J = 8.0, 3.6$ Hz, COCHCH_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_2CH_3), 0.90(3H, s, CH_3) ppm; ^{13}C NMR (62.90MHz, CDCl_3) δ 174.68($\text{C}=\text{O}$), 155.09($\text{C}=\text{O}$), 138.43($\text{CH}=\text{CH}$), 130.65($\text{CH}=\text{CH}$), 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($\text{C}=\text{O}$), 1707($\text{C}=\text{O}$) cm^{-1} ; (Found: m/z , 330.20714 (MH^+), $\text{C}_{20}\text{H}_{28}\text{NO}_3$ requires 330.20692).

(1R)-1-Vinyl-7,7-dimethylbicyclo[2.2.1]heptan-2-one (16).¹⁴ A solution of (1S)-(+)-10-camphorsulphonyl chloride **14** (6.02g, 23.98mmol) in ether (100ml) was added dropwise over 1 hour to an ethereal solution of diazomethane (30mmol). The mixture was stirred at 0°C for 2 hours and then concentrated *in vacuo*, filtered and evaporated *in vacuo* to give an orange oil which was recrystallised from methanol at -20°C to give colourless crystals of episulphone **15**. Owing to its instability the crude episulphone **15** (1.12g, 4.91mmol) was heated to 95°C (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 **16** as a colourless waxy solid (0.57g, 60% based on camphorsulphonyl chloride); m.p. = 62-64°C (Lit¹⁴ = 64-65°C); $[\alpha]_D^{21} = +16.4^\circ$ ($c=2.15$, MeOH); ^1H NMR (250.13MHz, CDCl_3) δ 5.76(1H, dd, $J = 17.6, 11.1$ Hz, $\text{CH}=\text{CH}_2$), 5.33(1H, dd, $J = 11.1, 1.7$ Hz, proton of $=\text{CH}_2$ cis to H), 5.16(1H, dd, $J = 17.6, 1.7$ Hz, proton of $=\text{CH}_2$ trans to H), 2.40(1H, ddd, $J = 18.3, 4.6, 2.2$ Hz, CHHCO), 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($\text{C}=\text{O}$), 131.98($\text{CH}=\text{CH}_2$), 118.76($\text{CH}=\text{CH}_2$), 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($\text{C}=\text{O}$), 1640($\text{C}=\text{C}$) cm^{-1} .

(1R)-1-Ethyl-7,7-dimethylbicyclo[2.2.1]heptan-2-one (13). 10% Pd/C (0.70g, 0.1eq) was added to a solution of vinylcamphor **16** (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 **13** as a clear colourless liquid (5.81g, 93%); $[\alpha]_D^{21} = +24.8^\circ$ ($c=2.85$, EtOH); ^1H NMR (250.13MHz, CDCl_3) δ 2.30(1H, ddd, $J = 18.1, 4.8, 3.3$ Hz, CHHO), 2.02-1.93(1H, cm, bridgehead), 1.92-1.15(7H, cm), 0.98(3H, t, $J = 7.6$ Hz, CH_2CH_3), 0.94(3H, s, CH_3), 0.85(3H, s, CH_3) ppm; ^{13}C NMR (62.90MHz, CDCl_3) δ 219.74($\text{C}=\text{O}$), 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($\text{C}=\text{O}$) cm^{-1} .

(1R)-1-Ethyl-7,7-dimethylbicyclo[2.2.1]heptan-2,3-dione (17). Selenium dioxide (11.10g, 100mmol, 3eq) was added to a solution of 10-methyl-camphor **13** (5.95g, 35.8mmol) in acetic anhydride (30ml), and the

mixture then heated under reflux for 48 hours. A further portion of selenium dioxide (11.01g, 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 **17** as a yellow solid (3.26g, 51%); m.p. = 56.0–56.7°C (methanol/water); $[\alpha]_D^{21} = -157^\circ$ ($c=1.00$, CH_2Cl_2); ^1H 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_2CH_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} ; (Found: m/z , 181.12301 (MH^+), $\text{C}_{11}\text{H}_{17}\text{O}_2$ requires 181.12285).

(1R, 3R, exo)-3-Hydroxy-1-ethyl-7,7-dimethylbicyclo[2.2.1]heptan-2-one (18). L-Selectride[®] (25ml of a 1.0M solution, 25mmol, 1.1eq) was added to a solution of 10-methyl-camphorquinone **17** (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 total volume) 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 **18** as a clear colourless oil (3.64g, 91%); $[\alpha]_D^{21} = +77.3^\circ$ ($c=1.5$, CH_2Cl_2); ^1H NMR (250.13MHz, CDCl_3) δ 3.65(1H, s, CHOH), 3.25(1H, bs, CHOH), 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 3 CH_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(2 CH_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} ; (Found: m/z , 183.13843 (MH^+), $\text{C}_{11}\text{H}_{19}\text{O}_2$ requires 183.13851).

(1R, 2S, 3R, exo)-N-Benzyl-2-amino-3-hydroxy-1-ethyl-7,7-dimethyl-bicyclo[2.2.1]heptane (19). The general procedure outlined by Mattson *et al*¹² was used. A mixture of **18** (1.05g, 5.77mmol), benzylamine (0.64g, 5.98mmol, 1.0eq) and titanium(IV)isopropoxide (2.07g, 7.92mmol, 1.4eq) were stirred together at room temperature under a drying tube for 1 hour, FT IR then showed the absence of any ketone band. Ethanol (7ml) was then added followed by the addition of sodium cyanoborohydride (0.25g, 3.97mmol, 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 **19** as a clear colourless oil (0.70g, 45%); $[\alpha]_D^{21} = -44.0^\circ$ ($c=1.50$, CH_2Cl_2); ^1H NMR

(250.13MHz, CDCl₃) δ 7.35-7.25(5H, cm, Ph), 3.75(2H, s, PhCH₂), 3.64(1H, d, J = 7.2 Hz, CHOH), 2.85(1H, d, J = 7.2 Hz, CHNH), 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, CH₃), 0.90(3H, t, J = 7.5Hz, CH₂CH₃), 0.75(3H, s, CH₃) ppm; ¹³C NMR (62.90MHz, CDCl₃) 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(CH₂), 52.06(C), 51.45(CH), 46.74(C), 32.70(CH₂), 23.29(CH₂), 21.98(CH₃), 21.21(CH₃), 19.22(CH₂), 9.38(CH₃) ppm; FT IR $\nu_{\max}$ (thin film) 3357(OH), 3330(NH) cm⁻¹; (Found: m/z , 274.21663 (MH⁺), C₁₈H₂₈NO requires 274.21709).

(1*R*, 2*S*, 3*R*, *exo*)-2-Amino-3-hydroxy-1-ethyl-7,7-dimethylbicyclo[2.2.1]heptane (**20**). 10% Pd/C (0.16g, 0.3eq) was added to a solution of the amino-alcohol **19** (0.66g, 2.42mmol) in methanol (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 **20** as a colourless waxy solid (0.41g, 93%); m.p. = >270°C decomposes; $[\alpha]_D^{21}$ = -44.2° (c =1.00, CH₂Cl₂); ¹H NMR (250.13MHz, CDCl₃) δ 3.55(1H, d, J = 7.5 Hz, CHOH), 2.99(1H, d, J = 7.5 Hz, CHNH₂), 2.48(3H, bs, OH and NH₂), 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, CH₃), 0.88(3H, t, J = 7.4 Hz, CH₂CH₃), 0.72(3H, s, CH₃) ppm; ¹³C NMR (62.90MHz, CDCl₃) δ 74.75(CH), 58.82(CH), 51.31(C), 51.11(CH), 46.83(C), 32.22(CH₂), 23.51(CH₂), 22.07(CH₃), 20.63(CH₃), 19.10(CH₂), 9.18(CH₃) ppm; FT IR $\nu_{\max}$ (nujol) 3453 and 3328(NH₂) cm⁻¹ both superimposed on a bs(OH); (Found: m/z , 184.17109 (MH⁺), C₁₁H₂₂NO requires 184.17014).

(1*S*, 2*R*, 6*S*, 7*R*, *exo*)-3-Oxa-5-aza-7-ethyl-10,10-dimethyltricyclo[5.2.1.0^{2,6}]decan-4-one (**21**). The primary amino alcohol **20** (0.38g, 2.08mmol) in DME (10ml) was treated with a solution of sodium hydroxide (2ml of a 6M solution, 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 **21** as a very pale yellow crystalline solid (0.40g, 92%); m.p. = 138.0-140.0°C (xylene/cyclohexane); $[\alpha]_D^{21}$ = -10.0° (c =1.25, CH₂Cl₂); ¹H NMR (250.13MHz, CDCl₃) 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, CH₃), 0.84(3H, t, J = 7.5 Hz, CH₂CH₃), 0.83(3H, s, CH₃) ppm; ¹³C NMR (62.90MHz, CDCl₃) δ 161.03(C=O), 83.84(CH), 62.40(CH), 51.18(C), 48.14(CH), 46.51(C), 29.27(CH₂), 23.26(CH₃), 22.59(CH₂), 19.02(CH₃), 18.15(CH₂), 9.28(CH₃) ppm; FT IR $\nu_{\max}$ (nujol) 3253(NH), 3141(NH),

1733(C=O), 1713(C=O) cm^{-1} ; (Found: m/z , 210.14970 (MH^+), $\text{C}_{12}\text{H}_{20}\text{NO}_2$ requires 210.14940); (Found: C, 68.7; H, 9.1; N, 6.5. $\text{C}_{12}\text{H}_{19}\text{NO}_2$ requires C, 68.9; H, 9.1; N, 6.7%)

(1S, 2R, 6S, 7R, exo)-N-Crotonyl-3-oxa-5-aza-7-ethyl-10,10-dimethyltricyclo[5.2.1.0^{2,6}]decan-4-one (22b).

Diethylzinc (1.0ml of a 1.0M solution, 1.00mmol, 1.1eq) was added to a solution of the auxiliary **21** (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, 2.87mmol, 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. 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 into 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 **21** (0.06g, 33%) and **22b** as a colourless solid (0.90g, 38%); m.p. = $134\text{--}136^\circ\text{C}$; $[\alpha]_{\text{D}}^{21} = +48.7^\circ$ ($c=0.75$, CH_2Cl_2); ^1H NMR (250.13MHz, CDCl_3) δ 7.25–7.03(2H, cm, $\text{CH}=\text{CH}$), 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, $\text{C}=\text{CHCH}_3$), 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_2CH_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($\text{CH}=\text{C}$), 122.60($\text{C}=\text{CH}$), 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} ; (Found: m/z , 278.17594 (MH^+), $\text{C}_{16}\text{H}_{24}\text{NO}_3$ requires 278.17562).

(1S, 2R, 6S, 7R, exo)-N-Acryloyl-3-oxa-5-aza-7-ethyl-10,10-dimethyltricyclo[5.2.1.0^{2,6}]decan-4-one (22a).

Procedure as above yielded unreacted auxiliary **21** (0.13g, 50%) and **22a** as a colourless solid (0.10g, 31%); m.p. = $84.0\text{--}86.0^\circ\text{C}$ (hexane); $[\alpha]_{\text{D}}^{21} = +66.8^\circ$ ($c=0.75$, CHCl_3); ^1H NMR (250.13MHz, CDCl_3) δ 7.42(1H, dd, $J = 17.0$, 10.3 Hz, $\text{CH}=\text{CH}_2$), 6.48(1H, dd, $J = 17.0$, 1.7 Hz, proton of $\text{CH}=\text{CH}_2$ trans to H), 5.85(1H, dd, $J = 10.5$, 1.7 Hz, proton of $\text{CH}=\text{CH}_2$ 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_2CH_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($\text{CH}=\text{CH}_2$), 128.19($\text{CH}=\text{CH}_2$), 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} ; (Found: m/z , 264.15964 (MH^+), $\text{C}_{15}\text{H}_{22}\text{NO}_3$ requires 264.15997).

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