Development and Applications of a New Chiral Auxiliary

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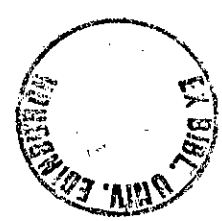

DECLARATION

I declare that this thesis is my own composition and that I have made a substantial contribution to the work described herein, such a contribution being clearly indicated. In addition, I declare that this work 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, University of Edinburgh, under the supervision of Dr. I. Gosney since 1st October 1989, the date of my admission as a research student.

Keith Grant

For Mum, Dad, my big sister Janet, and for Christine.

Acknowledgements

During my three years work I have received a lot of help from a number of people. I would like to start by thanking my supervisor Dr. Ian Gosney for providing me with the opportunity to do this PhD thesis, and also Professor Sir John Cadogan for his continued interest in the work. Dr. Malcolm R. Banks is also to be thanked for his combination of sound advice and cutting sense of humour. Many thanks are due to Mr. John Millar for the countless spectra which were run on the 200 MHz NMR, some done at very short notice. I would like to thank Miss Heather Grant also in this respect.

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Needless to say, I thank all the of the boys in laboratory 64 for making my research time very bearable, namely "Suneey-Boy" Gaur, John Wastle, David Maden, Derek Kilgour, Douglas MacDougall and Paul Thorburn, particularly for their sense of humour.

contd over

The S.E.R.C are to be thanked for their financial support over my three years and also British Petroleum Ltd who have provided generous funding for the purchase of chemicals and the cost for patenting some aspects of the work (G.B. Application No. 9100893, 39pp, Filing date June 1991). Last but certainly not least, I give my warmest and most heartfelt thanks to Suneel Gaur; without his encouragement, friendship and selfless help I am sure I would not be in a position to submit my thesis at all.

Courses Attended

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

Organic Research Seminars, Department of Chemistry, University of Edinburgh (3 years attendance).

Current Developments in Organic Chemistry, various speakers, Department of Chemistry, University of Edinburgh, (2 years attendance).

Merck, Sharp and Dohme, Medicinal Chemistry Lectures, Prof. R. Baker *et al*, Department of Chemistry, University of Edinburgh, (2 years attendance).

Royal Society of Chemistry, Perkin Division, Heterocyclic group, Postgraduate Symposia (3 years attendance).

Recent advances in the Synthesis and Activity of Agrochemicals, Schering Agrochemicals, various speakers, Department of Chemistry, University of Edinburgh, 1992.

Discovery, Development and Pharmacology of Zoladex for Treatment of Prostate Cancer- I.C.I. Pharmaceuticals, various speakers, Department of Chemistry, University of Edinburgh, 1992.

Aspects and Applications of NMR spectroscopy - Dr. I. Sadler, Dr. D. Reed and Dr. J. Parkinson, Department of Chemistry, University of Edinburgh, 1992.

25th Sheffield Stereochemical Meeting, various speakers, Sheffield, 1991.

Smith, Kline and French Research Symposium on "Chirality in Drug Design and Synthesis", various speakers, Cambridge, 1990.

I have attended and passed the Departmental german course, February 1990.

ABSTRACT

An *endo*-borneol based oxazolidinone **77** was used in a series of asymmetric transformations to assess its worth as a chiral auxiliary. In regard to titanium catalysed Diels-Alder reactions with cyclopentadiene, the acrylate and crotonate derivatives **87** and **101** exhibited poor selectivity; the acrylate displayed an optimum ratio of *endo* products of 2:1 and the crotonate of 3:1. Furthermore, the selectivity was shown to be dependent upon the order of addition of the reagents. The cinnamate derivative **102** reacted very sluggishly under the same conditions and only *ca.* 20% of the starting material was consumed after three days. When diethylaluminium chloride was employed as catalyst, the selectivity of **87** increased to 4:1 and that of the **101** increased to 6:1. Only **102** showed almost complete selectivity using this catalyst. The dienophile **87** reacted with isoprene to give a 2:1 mixture of products using titanium catalysts and 5:1 using diethylaluminium chloride catalyst.

In regard to alkylation reactions, the lithium enolate **110** of the propionyl derivative of **77** condensed stereospecifically with benzyl bromide, but ethyl tosylate was inert to this nucleophile. Reaction of **110** with acetyl and propionyl chloride formed products with high selectivity, but small amounts of concomitant *O*-acylation occurred. Only reaction with methyl cyanoformate (Mander's reagent) occurred wholly at carbon, with a selectivity of 10:1. The reaction of this enolate with benzoyl chloride was stereospecific, but large amounts of enol product were also formed in this particular case.

The enolate **110** underwent aldol condensation with isobutyraldehyde with 48% d.e. and 29% d.e. with acetaldehyde. However, the latter reaction was marred by the sluggishness of its reaction and the formation of dehydration products. The corresponding chlorotitanium enolate

reacted with benzaldehyde to form a 6 : 5 ratio of *anti* : *syn* products. Use of excess Lewis acid furnished solely *anti* products. The analogous zinc enolate **132** was found to be completely unreactive towards even benzaldehyde complexed with diethylaluminium chloride and underwent chemical cleavage in boiling tetrahydrofuran.

The lithium enolate **110** reacted with *N*-bromosuccinimide to give a 6:1 ratio of epimeric products; the corresponding boron enolate reacted to give a ratio of 60:1. The α-bromo carboximide **133A** underwent nucleophilic substitution with azide ion under phase-transfer conditions to furnish the corresponding azidocarboximide **134A** without detectable epimerisation, which in turn underwent cleavage under mild Seebach conditions to furnish the azido benzyl ester **135**, which is the pre-cursor to the amino acid (L)-(+)-alanine.

The resolution of racemic 2-methylcyclohexanol was effected by reaction of the chloroformate **147** of the alcohol with the lithiated thione derivative **149** of the auxiliary. Analysis of the diastereomers by normal phase HPLC yielded an α-value of 1.34.

Reaction of an anhydrous methanolic solution of *endo*-2-hydroxyepicamphor **160** with dry HCl gas furnished a stable, crystalline solid, first synthesised in 1902. The molecule was shown by high resolution electron impact mass spectrometry to be a dimer of formula $C_{22}H_{36}O_4$. Furthermore, the stereochemical structure of this molecule was solved by NOE difference spectroscopy.

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Chapter seven

The attempted synthesis of the structural isomer (84) of Chirabornox *via* (-)-epicamphor (154) 154

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"I will destroy the wisdom of the wise;
the intelligence of the intelligent I will frustrate"
"....For the foolishness of God is wiser than man's wisdom,
and the weakness of God is stronger than man's strength"

1 Corinthians chapter 1 verses 19 and 25.

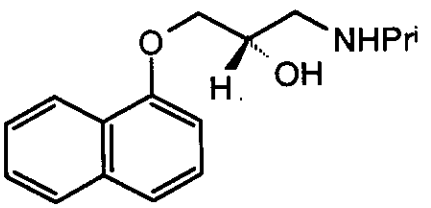
"The fear of the Lord is the beginning of knowledge,
but fools despise wisdom and discipline."

Proverbs chapter 1 verse 7.

INTRODUCTION

The need for optical purity

A recent survey of commercial drugs conducted by Ariens[1] showed that of the 1850 drugs on the market, 570 of them are sold as single isomers. Optical purity can be of paramount importance, for example (-) - propanolol **1** is a β-blocker for the treatment of heart disease; however its enantiomer acts as a contraceptive.



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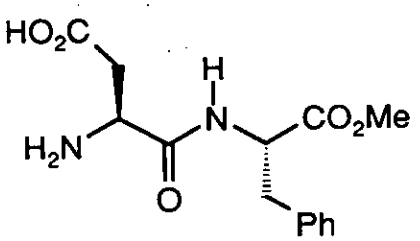
Other examples include the dipeptide sweetner aspartame. Only the isomer shown **2** is sweet tasting, the other three are bitter; the (*R*,*R*) form of chloramphenicol **3** is antibacterial, its (*S*,*S*) isomer is inactive.



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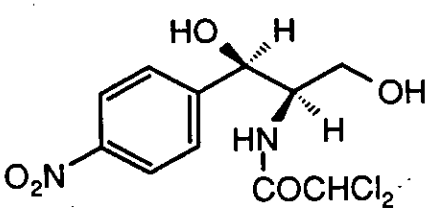

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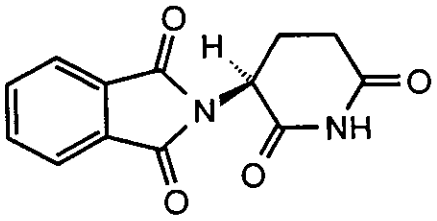
It can be dangerous therefore to assume that in a racemic mixture only one isomer is active and the other isomers are inactive or harmless; no more painful example of this is the case of the drug Thalidomide **4** which was sold as a racemate. Both isomers interconvert *in vivo* and both act as sedatives; however the (*S*)-(-) form shown also causes dreadful foetal deformalities. It is obvious that the need for obtaining separate isomers and the testing of each one is essential (as directed now by the Food and



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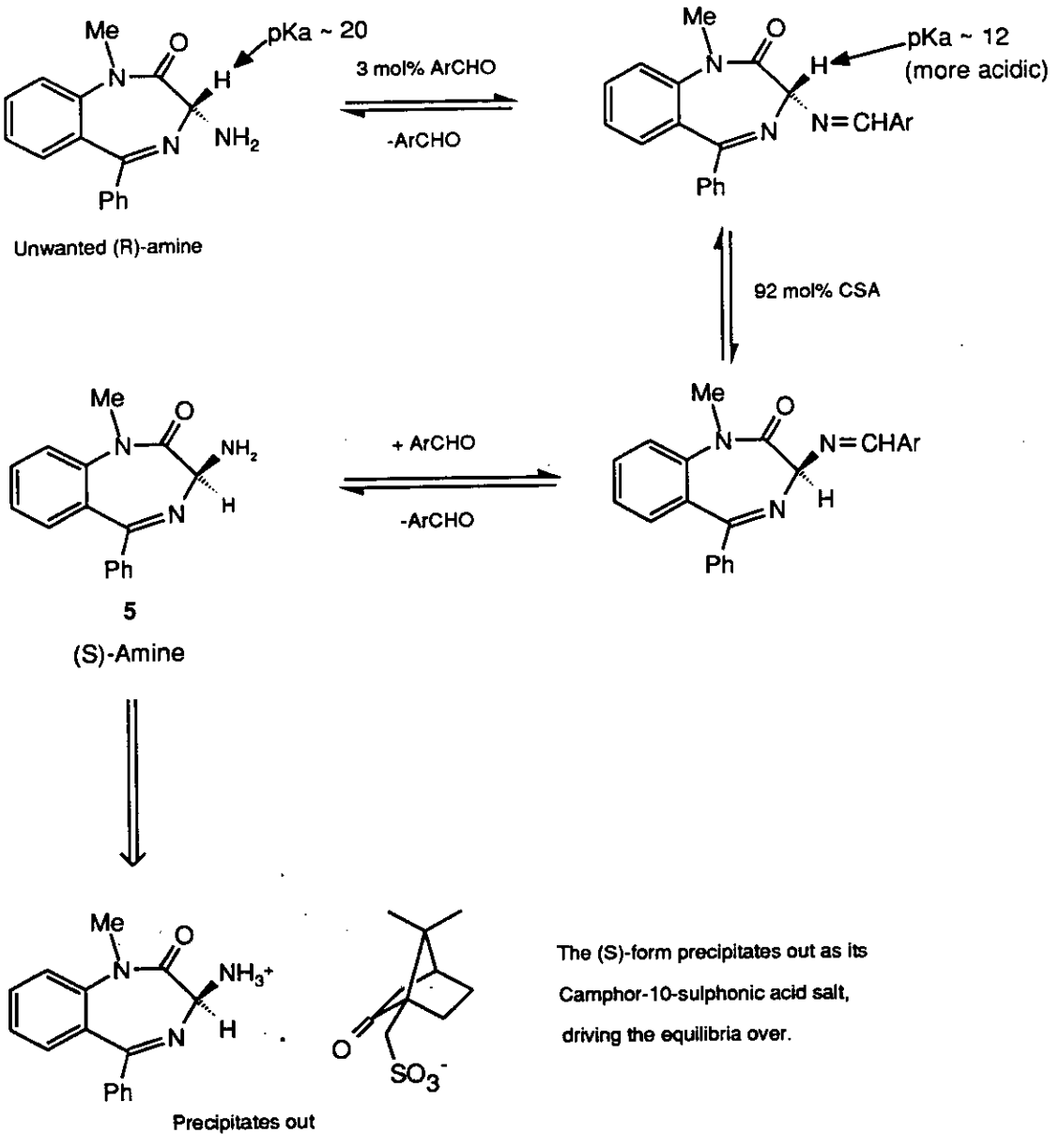
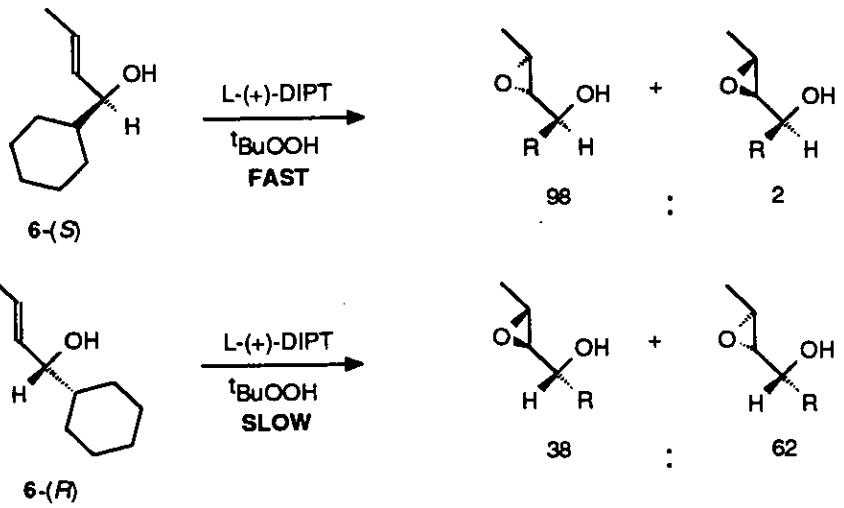
Drug Administration (FDA)) if future disasters are to be avoided.There follows a review of the various methods for obtaining chirally pure compounds.

1.1 Resolution

Industries' disaffection towards resolution stems from the fact that it can be an expensive process and unless the isomers concerned are in some equilibrium situation, at least half of the material consists of the unwanted isomer(s). However, in some cases,resolution is both commercially viable and the method of choice. For example Reider *et al*[2] have used an elegant method for the conversion of a racemate to a single enantiomer **5** which is the precursor to an extremely potent Cholecystokinin (CCK) antagonist (Scheme 1). Another branch of this field includes kinetic resolution where one enantiomer reacts faster with a chiral reagent than the other to produce diastereomers in unequal amounts, and in an ideal situation one should be formed with the complete exclusion of the other. An example of this kind of resolution is the Sharpless epoxidation of the chiral allylic alcohol (*S*)- and (*R*)-(*E*)-cyclohexyl propenyl carbinol **6**[3]. The (*S*)-form reacts over one hundred times faster than the (*R*)-form. This reaction will be discussed in more detail in the asymmetric catalytic synthesis section, but it shows how the two fields are inextricably intertwined.


Me
pKa ~ 20
3 mol% ArCHO
-ArCHO
pKa ~ 12
(more acidic)
N=CHAr
Ph
Unwanted (R)-amine
92 mol% CSA
+ ArCHO
-ArCHO
5
(S)-Amine
Precipitates out
The (S)-form precipitates out as its
Camphor-10-sulphonic acid salt,
driving the equilibria over.

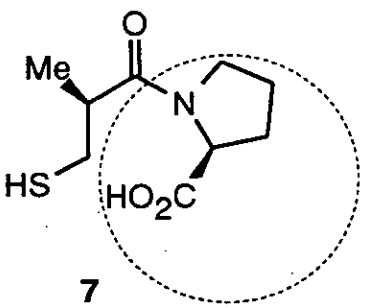
Scheme 1


L-(+)-DIPT
tBuOOH
FAST
98
2
6-(S)
L-(+)-DIPT
tBuOOH
SLOW
38
62
6-(R)

1.2 The "Chiral Pool" approach

It is obviously an attractive proposition to be able to use starting materials which are cheap, readily available and have their own chirality built-in. The set of naturally occurring chiral molecules (or "Chiral Pool") broadly encompasses amino acids, carbohydrates and terpenes.

Amino acids are one of the oldest sources of optical activity and are used for a wide variety of products, for example the angiotensin-converting enzyme (ACE) inhibitor Captopril **7** incorporates L-proline into its structure; ampicillin **8** makes use of D-phenylglycine and 6-amino penicillamic acid,another "chiral pool" molecule.



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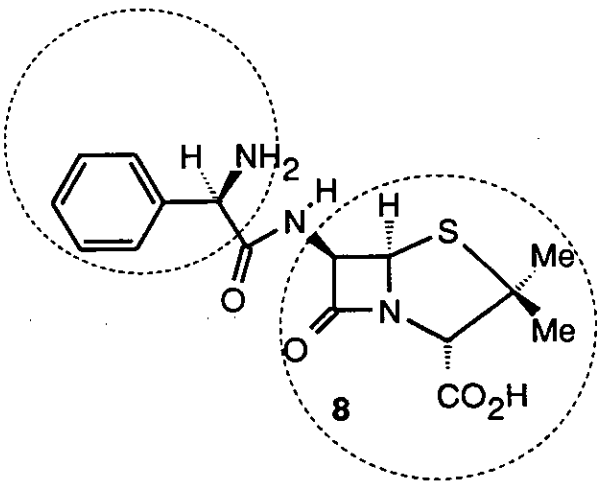

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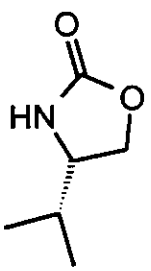
Evans' (*S*)-valinol derived auxiliary **9**[4] is a good example of the use of a chiral amino acid building block for the synthesis of a new chiral reagent, but this example will be discussed further in the section regarding chiral auxiliaries.



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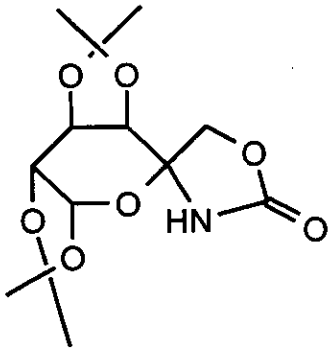
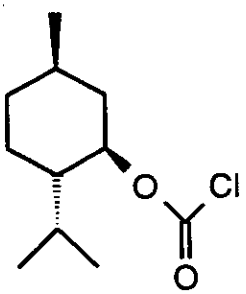
Carbohydrates are another cheap source of readily available homochiral compounds. An example of this is the conversion of D-galactose into Chiragalox **10**, a chiral auxiliary synthesised by Gaur[5] which has been shown to exhibit high levels of selectivity in a variety of asymmetric transformations. The major disadvantage in the use of carbohydrates is that they are generally only available in one enantiomeric form.



10

Terpenes are not commonly used as building blocks for incorporation into larger systems, but are used commonly as templates for resolutions, chiral reagents or chiral auxiliaries. For example, (-)-menthyl chloroformate **11** has been used by Westley *et al*[6] for the resolution of a variety of alcohols, via diastereomeric carbonates. The (1*R*)-(+)-α-pinene derived borane reagent **12** has been used to reduce butanal with complete selectivity[7].



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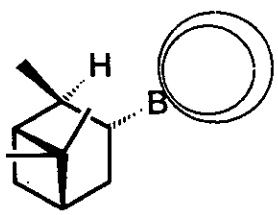

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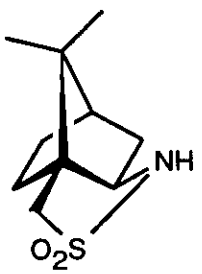
D-(+)-Camphor has been exploited by Oppolzer *et al* in the synthesis of a number of auxiliaries[8,9], notably **13**, the details of which will be discussed later.



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1.3 Asymmetric synthesis

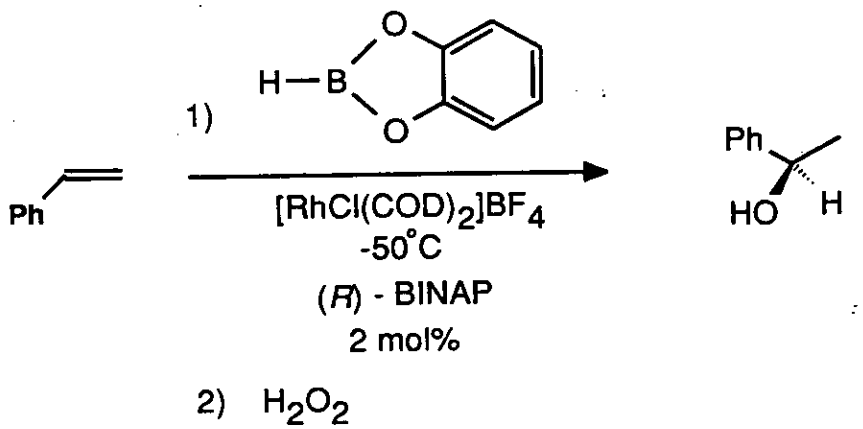
Despite Louis Pasteur's historic discovery of the phenomenon of stereoisomerism as early as 1848, the goal of selectively synthesising one isomer out of a possible two or more only began to be realised 20 to 30 years ago. The asymmetric environment required to convert a prochiral centre into an sp^3 hybridised carbon with bias towards a particular isomer can be provided in two ways, by asymmetric catalysis or by chiral auxiliaries; there follows a short review of the former and a more detailed review of the latter.

1.4 Asymmetric catalysis

In this field an asymmetric reagent is used to catalytically provide the stereochemical bias in the reaction; this is not the situation when chiral auxiliaries are employed as in this instance the substrate provides the bias. Asymmetric catalysis can be subdivided into six reaction types (i) hydroborations, (ii) reduction of ketones,(iii) Diels-Alder reactions,(iv) aldol reactions,(v) reductive alkylations and (vi) epoxidations; this is not an exhaustive list, but encompasses the more frequently encountered catalytic types.

1.4.1 Asymmetric catalytic hydroborations

This has been most elegantly demonstrated by Hayashi *et al*[10] in which prochiral alkenes have been reacted with catecholborane in the presence of a rhodium catalyst and 2 mol% of a chiral biphosphine ligand to produce chiral alcohols, on oxidation with hydrogen peroxide. For example, styrene can be hydroborated to (*R*)-1-phenyl ethanol, with 81% ee using a cationic rhodium catalyst in the presence of (*R*)-BINAP (Scheme 2). The methodology is elegant in that one does not require a stoichiometric amount of chiral information *i.e.* the chiral environment does not come from the substrate or the hydroborating reagent. As a result the borane products produced are directly enantiomeric.In addition,the high regioselectivity obtained is in contrast to that obtained by Burgess *et al*[11] in which the rhodium catalyst is not cationic and poorer regioselectivites as well as enantioselectivities were observed.

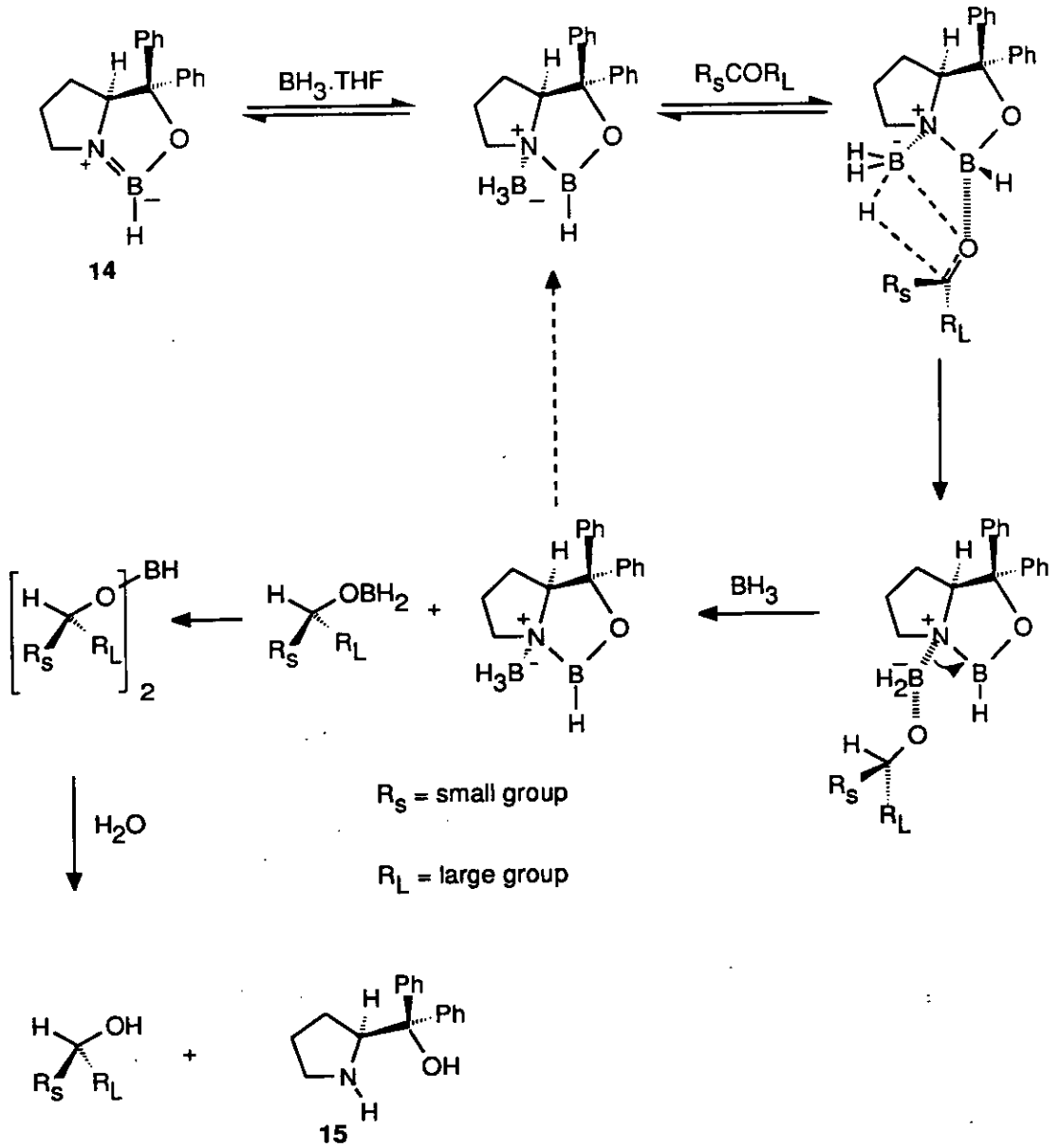


Scheme 2

1.4.2 Asymmetric reduction of ketones

The best example of asymmetric catalytic reduction would have to be the so-called "Molecular Robot" devised by Corey *et al*[12,13]. Using 0.05 equivalents of the oxazaborolidine **14** in the presence of 0.6 equivalents of BH_3 a variety of ketones were reduced with very high ee's. The reagent

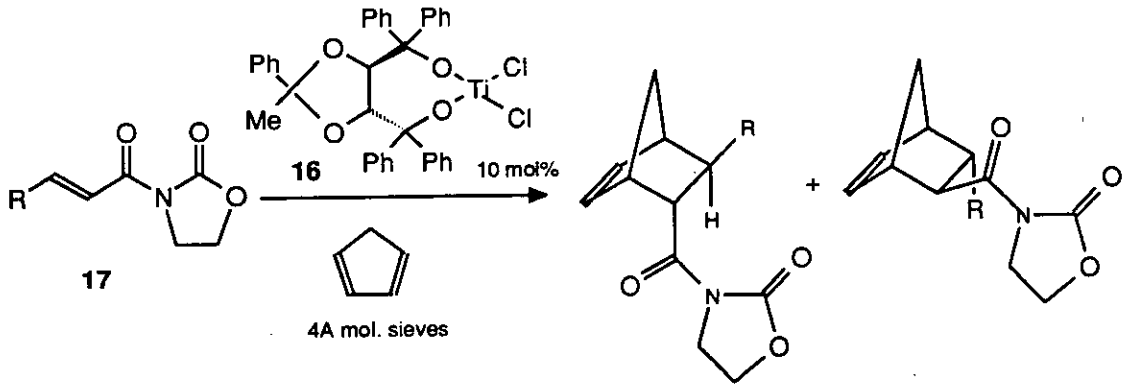
can then be continously re-used in the catalytic cycle (Scheme 3). Upon work-up, the diphenylprolinol ligand **15** can be recovered and re-used.



Scheme 3

1.4.3 Asymmetric catalytic Diels-Alder reactions

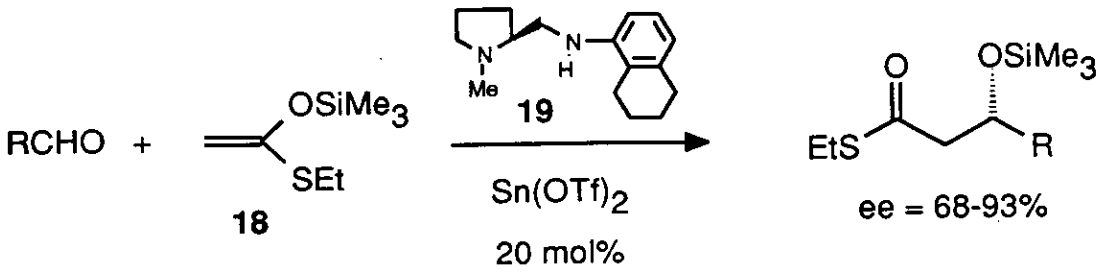
Narasaka *et al*[14] have reported the use of the chiral titanium catalyst **16** for the conversion of α,β unsaturated oxazolidinone carboximide **17** to cyclopentadiene adducts with good to excellent enantiomeric excesses.The author indicated that the selectivity observed is highly sensitive to the



substituents of the ketal protecting group. However, a later study by Corey *et al*[15] revealed that substitution of the gem-phenyl groups in the catalyst for other aryl groups of varying electron donating/withdrawing character could also adversely affect the selectivity observed. Here the electron donating/withdrawing properties of the aromatic rings affect the selectivity by favouring/disfavouring the formation of a π-donor-acceptor interaction with the dienophile, helping to sterically hinder one face of the alkene. Such a hypothesis is reinforced by further studies[16] in which another chiral oxazaborolidinone is employed with a π-basic indole ring, which it is proposed, is the source of excellent enantiomeric excesses.

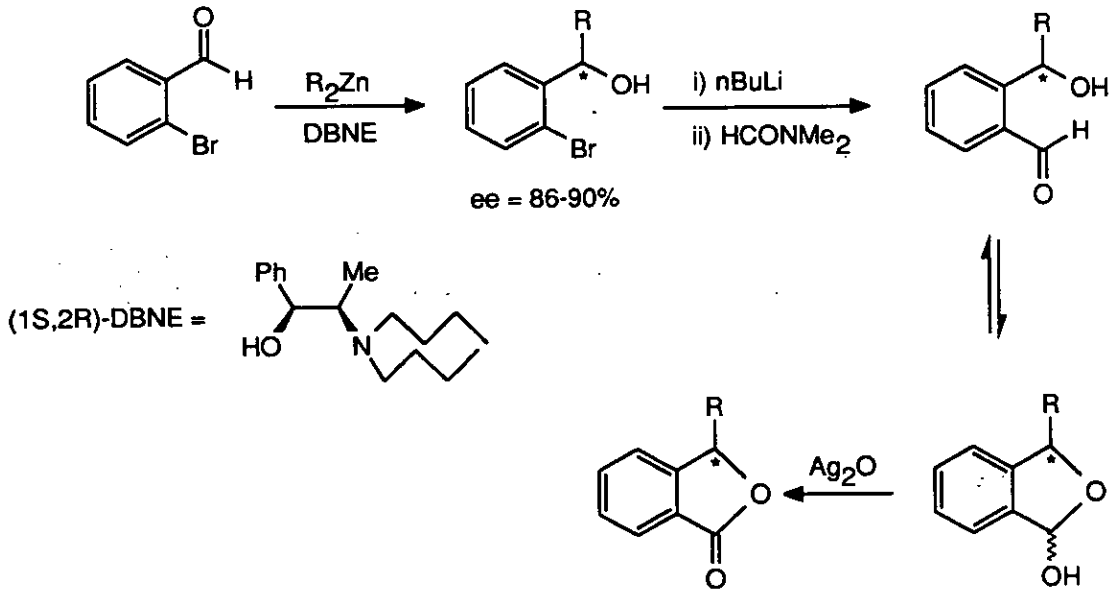
1.4.4 Asymmetric catalytic aldol reactions

Mukaiyama *et al*[17] have employed a chiral tin Lewis acid for use in aldol condensations of the trimethylsilyl enol ether of *S*-ethyl ethanethioate **18** with various aldehydes. Good to excellent enantiomeric excesses are reported, the source of the asymmetric induction being the chiral diamine, (*S*)-1-methyl-2-[(N-1-(5,6,7,8-tetrahydronaphthyl) amino) methyl] pyrrolidine **19**. This is reported to be the first α-unsubstituted system which undergoes aldol reactions in a highly stereoselective manner, using only a catalytic amount of chiral information.



1.4.5 Asymmetric reductive alkylations

Enantioselective alkylations to aldehydes has been achieved by Soai *et al*[18] using N,N-dibutylnorephedrine (DBNE) in the synthesis of optically active phthalides (Scheme 4). Although only the (1*S*,2*R*) form of DBNE is shown, the (1*R*,2*S*)-form was also used by the authors to achieve intermediate secondary alcohols of opposite stereochemistry.

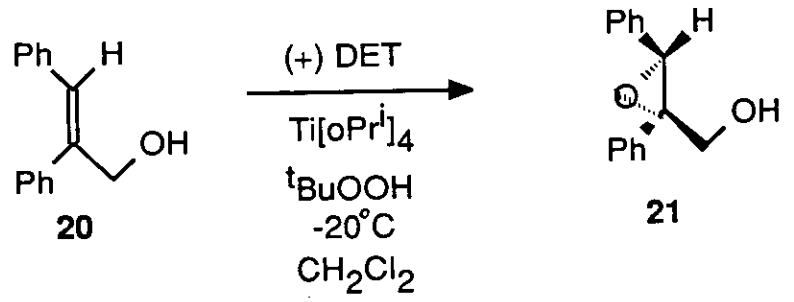


Scheme 4

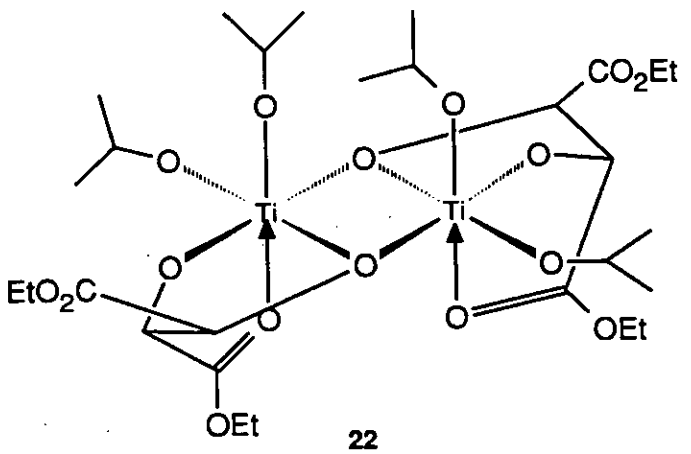
1.4.6 Asymmetric epoxidations

In 1980,Sharpless *et al*[19] reported a method for the epoxidation of allylic alcohols in good yield with excellent enantiomeric excesses. For example, alcohol **20** can be epoxidised in the presence of tert-butyl hydroperoxide,

L-(+)-diethyl tartrate and titanium tetraisopropoxide yielding the epoxide **21** in 87% chemical yield and >95% ee.



The major catalytic species in this reaction is the binuclear titanium complex **22** which undergoes successive displacement of isopropoxy groups from one titanium by the hydroperoxide and the allylic hydroxy function. Epoxidation then occurs between these two species in the highly asymmetric environment[20].



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1.5 Chiral auxiliaries

In recent years the growth in the area of asymmetric synthesis has snowballed by the study and use of chiral auxiliaries. It would not be possible or practical to record here each and every example of a chiral auxiliary; indeed, it is hard to open a journal on asymmetric synthesis without finding a new chiral auxiliary which claims to induce very high diastereomeric excesses. Therefore, one is bound to discuss the auxiliaries which have made the most impact in the literature. However, before

embarking upon such a discussion, it is worth summarising the features of a chiral auxiliary and the guiding principles involved in the design and use of such a molecule.

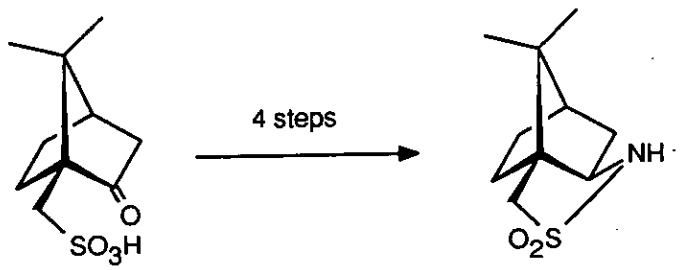
A chiral auxiliary is a compound of high optical purity for use in asymmetric transformations. Therefore:-

1. An auxiliary should be easily synthesised from readily available homochiral compounds (*e.g.* the "Chiral Pool" (see section **1.2**)).
2. It should be readily functionalised with the prochiral,reactive handle.
3. It should provide a stereochemical bias such that chemical as well as optical yields are high. In addition it is desirable that the auxiliary possesses a U.V. chromophore so that the diastereomers formed can be detected conveniently by HPLC.
4.The newly created chiral moiety should be able to be cleaved under mild conditions so that the chiral integrity of the sp^3 centres is not compromised.
5. The auxiliary should be recoverable in high yield and recycled.

When considered in their fullness, these requirements assume a great deal of a chiral system and only a few auxiliaries have achieved such distinction.

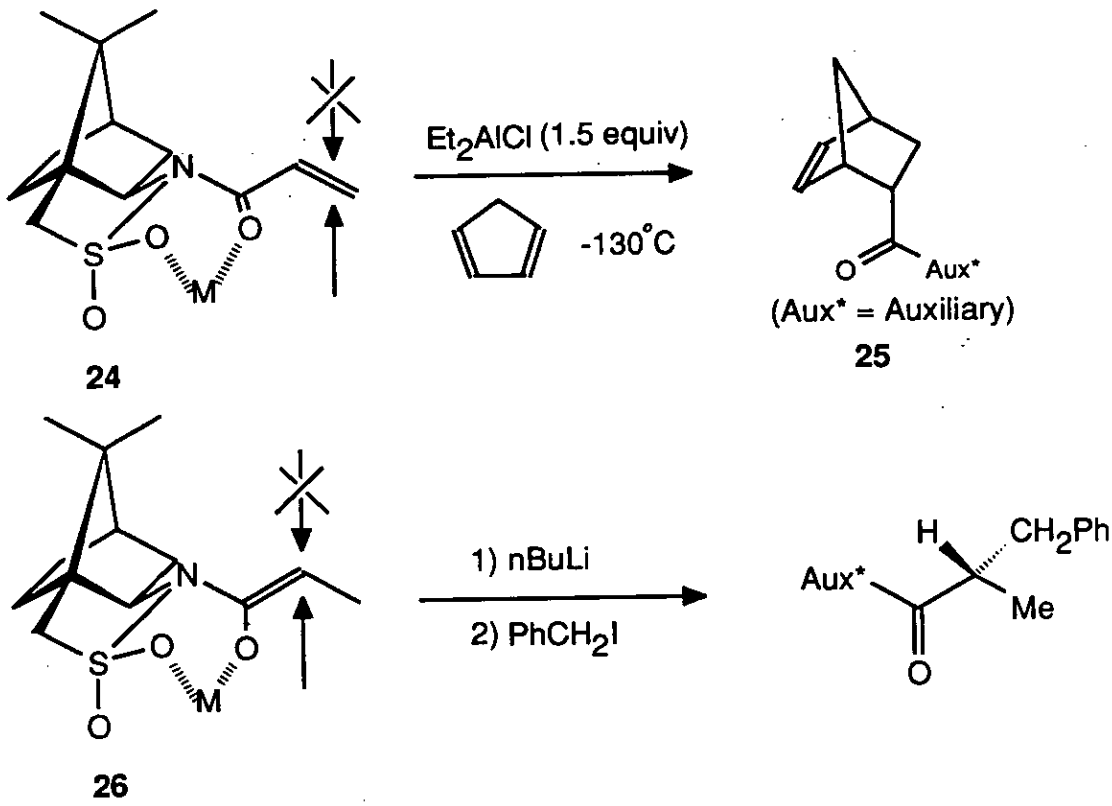
1.5.1 Oppolzer's chiral sultam (13)

By far, this is the most celebrated and widely used bornane-ring derived auxiliary. It is prepared in four steps[8] from camphor-10-sulphonic acid **23**.Also, since both antipodes of camphor are commercially available, it is accessible in both mirror image forms.The reagent is easily functionalised using saturated or unsaturated acid chlorides and derivatives have been successfully used to attain very high levels of induction in asymmetric Diels-Alder reactions[21,22], 1,3-dipolar cycloadditions[23,24], aldol



23 13

reactions[25-27], 1,4 Michael addition/enolate trapping reactions[28], the synthesis of α-amino acids[29,30] and enantiomerically pure C(α,α)-disubstituted carboxylic acid derivatives[31] , cyclopropanation reactions[32], dihydroxylations[33] and hydrogenations[34]. For example,dienophile **24** undergoes a Diels-Alder reaction with cyclopentadiene in the presence of Et_2AlCl catalyst to furnish, almost exclusively,the *endo* adduct **25** in 93% de; enolate **26** undergoes alkylation with benzyl iodide with 97% de (Scheme 5).

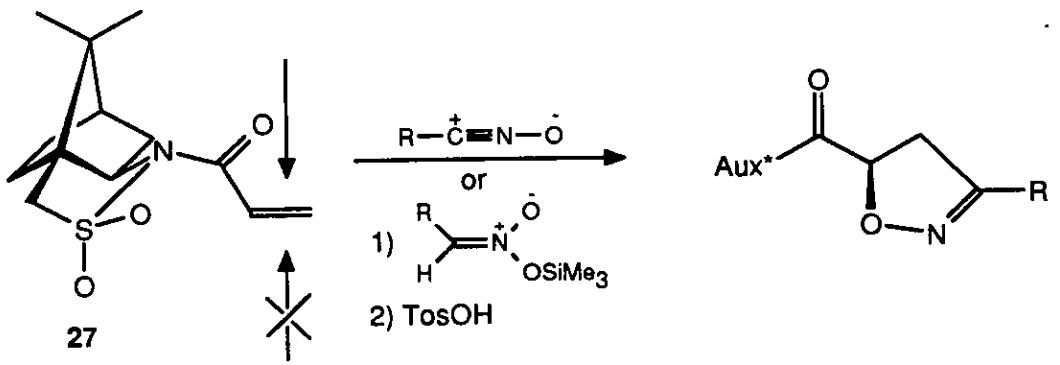


24 25

26

Scheme 5

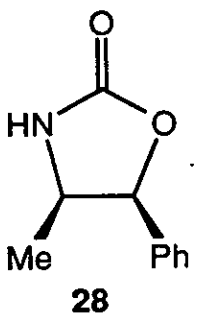
In all cases the C_α-si face of **24** or C_α-si face of **26** (the "upper faces") are hindered by the auxiliary and the respective "lower" C_α-re faces are open to attack by the incoming reactants. Only one exception to this general rule exists; in the reaction of **24** in the absence of Lewis acid with 1,3 dipoles, conformation **27** is favoured and the upper C_α-re face is accessible. It would seem in these cases that the axial S-O bond exerts a stereoelectronic effect on the incoming dienophile and causes it to react at the "top" face[23] (Scheme 6).



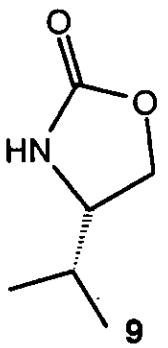
Scheme 6

1.5.2 Evans' Oxazolidinones

These are the most renowned of the amino-acid derived auxiliaries. One is the (1*S*,2*R*)-norephedrine derived molecule **28**, but by far the most commonly encountered are the (*S*)-valine and (*S*)-phenylalanine derived auxiliaries, **9** and **29** respectively.



28



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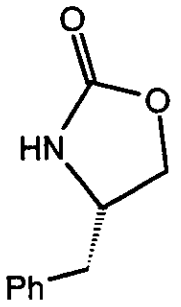
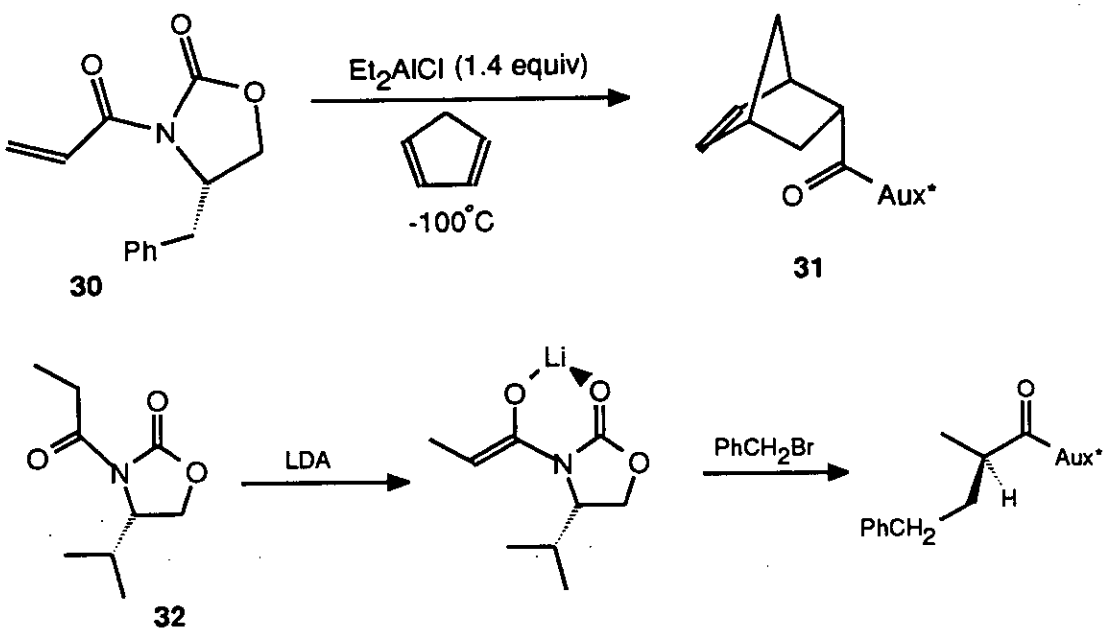


29

Between them **9** and **29** have shown high levels of asymmetric induction in α-brominations[35], α-hydroxy carboxylic acid synthesis[36], alkylations[37], acylations[38], conjugate additions of allyltrimethylsilanes[39], direct α-azidation[40], aldol reactions[41-45] and Diels-Alder reactions[46]. For example, imide **30** undergoes a Diels-Alder reaction with cyclopentadiene in the presence of Et_2AlCl to yield predominantly **31** with 89% de; imide **32** undergoes alkylation with benzyl bromide with 98% de (Scheme 7).



Scheme 7

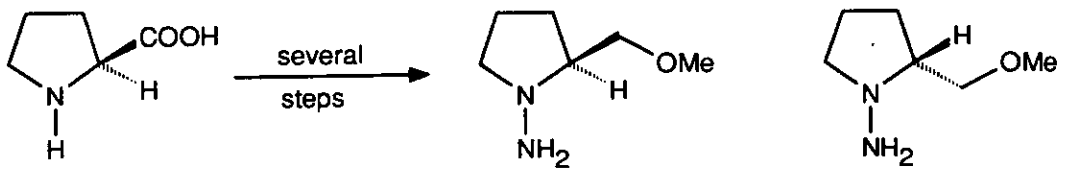
The function of the auxiliary is almost self-explanatory; the group on the carbon α to the nitrogen blocks the "bottom" C_α-re faces of the alkene and enolate, allowing only the "top" face to be open to attack. It has been demonstrated by Evans *et al*[47] that there is no Corey π-donor/acceptor type complex in the unsaturated imide systems such as **30**, there is only a Van der Waals or dipole-dipole type attraction between the phenyl ring of the benzyl group and the dienophile.

Both Evans' and Oppolzer's adducts can be readily cleaved under mild conditions to yield esters,acids or alcohols, whilst maintaining the chiral

integrity, and allowing direct recyclability of the auxiliaries (*i.e.* without any further chemical manipulation).

1.5.3 Enders' SAMP and RAMP

Other amino acid derived auxiliaries are those of Enders, namely (*S*)-1-amino-2-methoxymethylpyrrolidine (SAMP) **33** and its enantiomer RAMP **34**. The former is derived from (*S*)-proline **35**, which, after several manipulations[48], furnishes **33** in 55% overall yield (Scheme 8).



35 **33** **34**

SAMP **RAMP**

Scheme 8

However, this method suffers from the draw-back that the precursor to **33** is a nitrosamine and therefore undesirable as an intermediate. An alternative synthesis[49] avoids this problem by the use of a Hofmann degradation reaction to obtain the *N*-amine function.

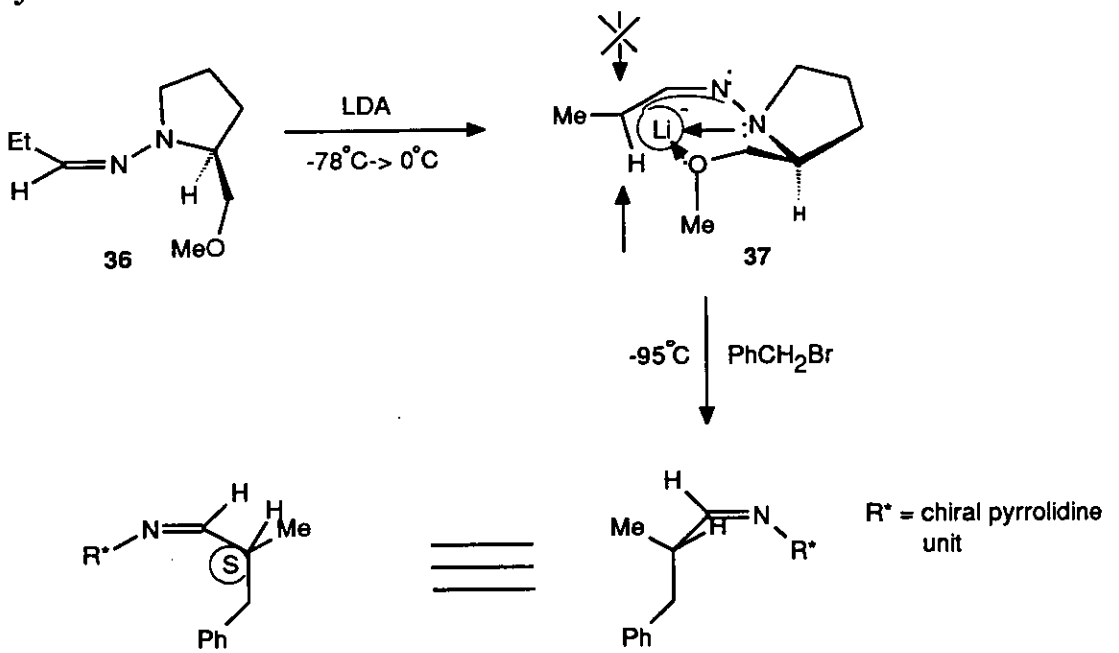
Hydrazones formed from **33** and **34** have been used in a variety of asymmetric reactions including α-alkylations of aldehydes[50] and ketones[48,51], aldol reactions[52] and Michael reactions to α,β unsaturated esters[53]. For instance, the reaction of propanal derived SAMP hydrazone **36** with LDA at -78^{0}C produces anion **37** which undergoes alkylation with benzyl bromide at -95^{0}C forming predominantly the (*S*)-adduct with 82% de (Scheme 9).

MISCELLANEOUS AUXILIARIES

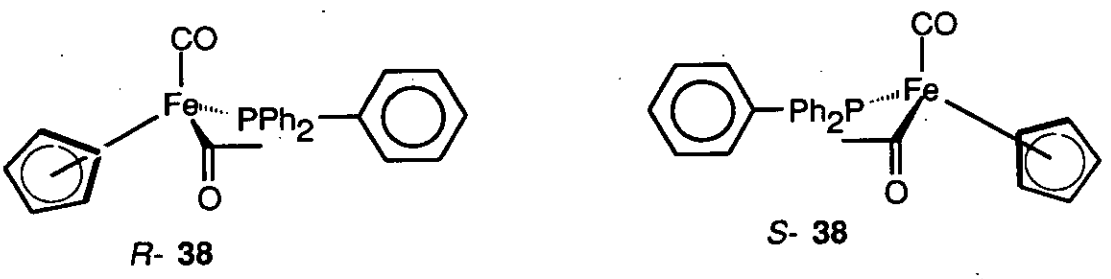
1.5.4 Davies' auxiliary

Davies' chiral iron complex (*R*)-**38** and its antipode (*S*)-**38** is a good example of an organometallic species which has been used as a chiral

auxiliary and has exploited the asymmetric alkylation reaction in the synthesis of the ACE inhibitor Captopril **39**[54] in addition to the asymmetric aldol reaction [55].

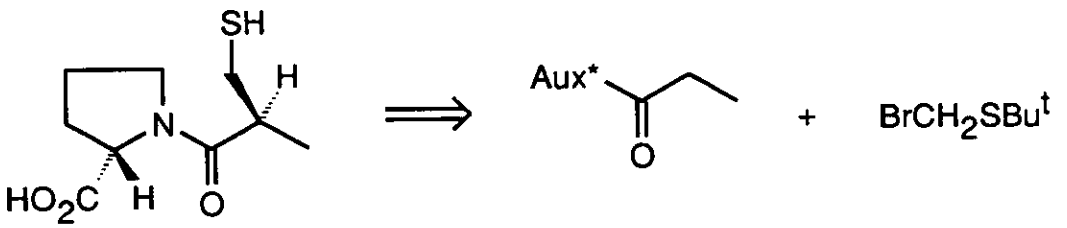


Scheme 9



R- **38**

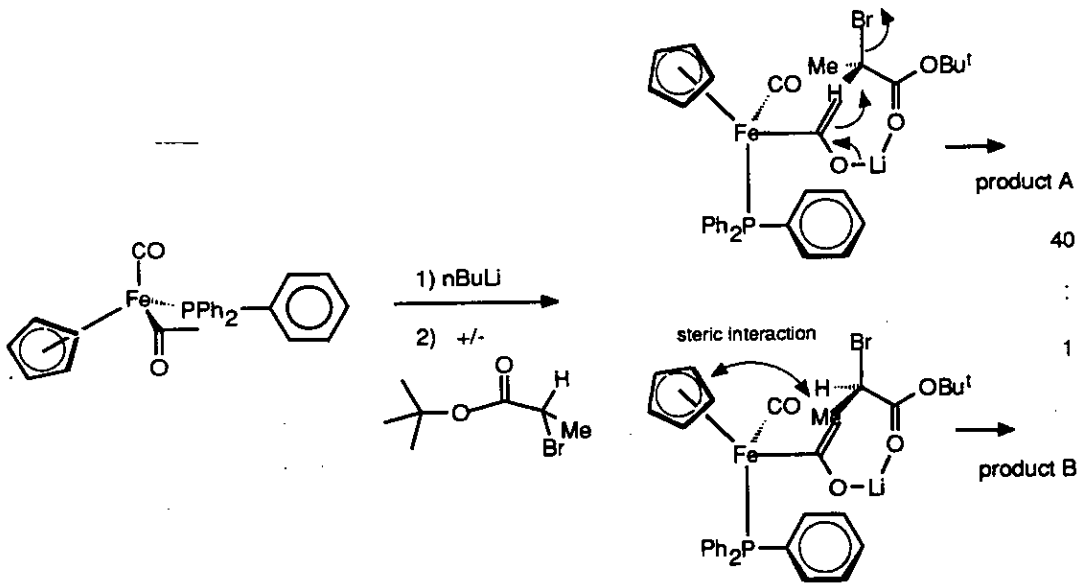
S- **38**



39

Here, one of the phenyl groups of the triphenylphosphine ligand at any one time blocks one face of the acyl group. However, the most interesting concept which is borne out in practice by this system is that of "chiral

recognition[56]", the phenomenon of the auxiliary reacting with (or "recognising") one enantiomer faster than its antipode. In the reaction of the lithium enolate of (*R*)-**38** with racemic ^{t}butyl-2-bromopropionate, the (*R*)-form reacts forty times faster than the (*S*)-form,due to the energy differences in the diastereomeric transition states (Scheme 10). This effect has already been seen in the Sharpless' epoxidation of racemic alcohols (see section **1.1**). Despite the fact that the auxiliary is available in both enantiomeric forms, it possess a dissuadingly high molecular weight. In addition to this disadvantage, cleavage of the chiral moieties

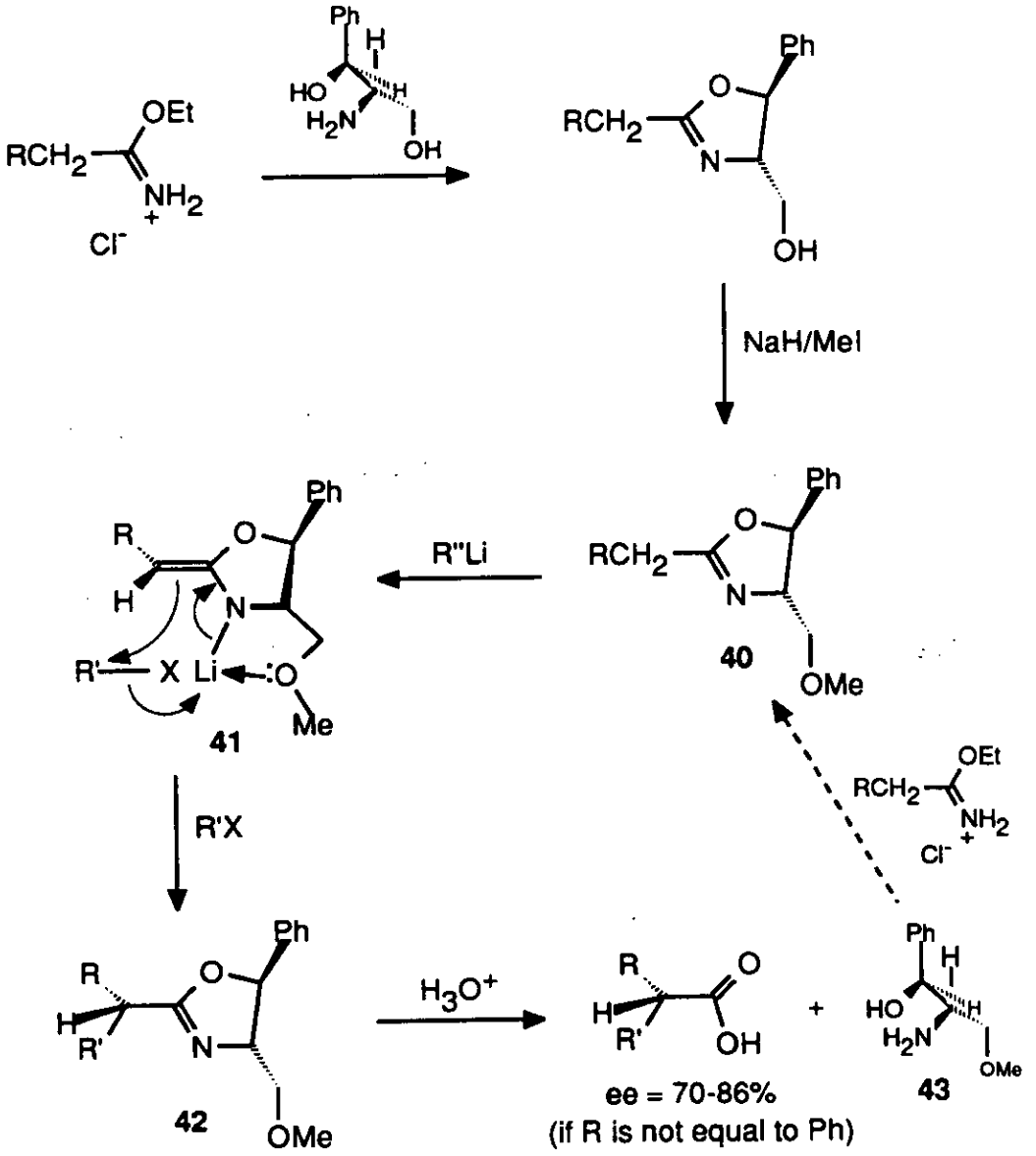


Scheme 10

causes destruction of the auxiliary, which needs to be regenerated and the resulting enantiomers require resolution.

1.5.5 Meyer's Oxazolines

This is an example of an established auxiliary whose function is well understood. The most famous example of the use of **40** regards the synthesis of C(α,α) disubstituted carboxylic acids of high optical purity in some cases[57]. Treatment of **40** with an alkyllithium generates, predominantly, the *Z*-lithiooxazole **41** which undergoes reaction with alkyl halides to form adducts **42** which hydrolyse with acid, and form the required acids in high e.e.'s with regeneration of the starting methoxy-amino alcohol **43** for re-use (Scheme 11).

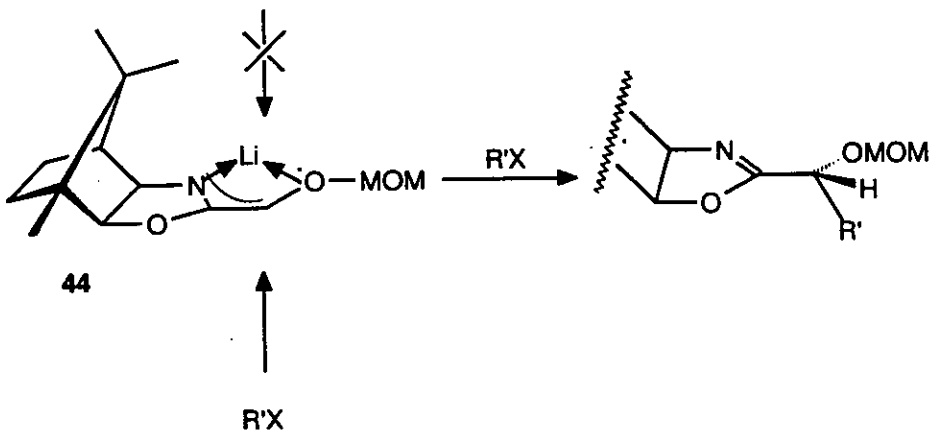


Scheme 11

Changing the order that R and R' are introduced into the cycle inverts the final stereochemistry exhibited by the acid. Two features of this auxiliary are important in achieving good selectivity. Firstly, the phenyl group is important; changing this to methyl or hydrogen drastically reduces the enantiomeric excesses observed[58]. Secondly, the methoxy group is essential for chelation to the lithium; changing the methoxy to methyl also drastically reduces the selectivity. In addition,changing the methoxymethyl to dimethylmethoxy and changing phenyl to hydrogen reverses the selectivity observed, as the bottom face of the enolate is now blocked by the bulky chelate group.

In addition to alkylation reactions, the auxiliary has been used for the synthesis of β-hydroxy esters *via* the aldol reaction[59], it has been exploited as a chiral reducing agent[60] and also has been used in kinetic resolution experiments using the chiral recognition phenomenon[61] in addition to the furnishment of C(β,β) disubstituted carboxylic acids, *via* the Michael reaction, in excellent optical yields[62].

Kelly *et al*[63] have used Meyers' chemistry in a rigid camphor-derived system **44** to obtain carboxylic acids in good to excellent enantiomeric excesses. The high degree of asymmetric induction here is attributable to the methyl group of the bornane skeleton which shields the β-face of the anion.

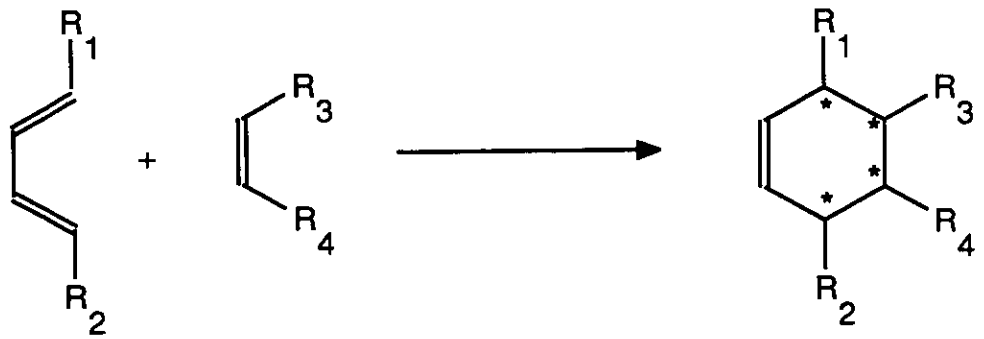


1.6 The importance of various types of asymmetric reactions

During the course of this thesis, several different types of reaction will be discussed in detail. However, it is important to realise that these reactions are not just academic curiosities but find their place in practical asymmetric synthetic situations.

1.6.1 The Diels-Alder reaction

Since its discovery in 1928[64a], the Diels-Alder reaction has become a very powerful tool in organic synthesis. Its great importance is based on the creation of a six membered ring in one step with the simultaneous generation of up to four chiral centres (Scheme 12).

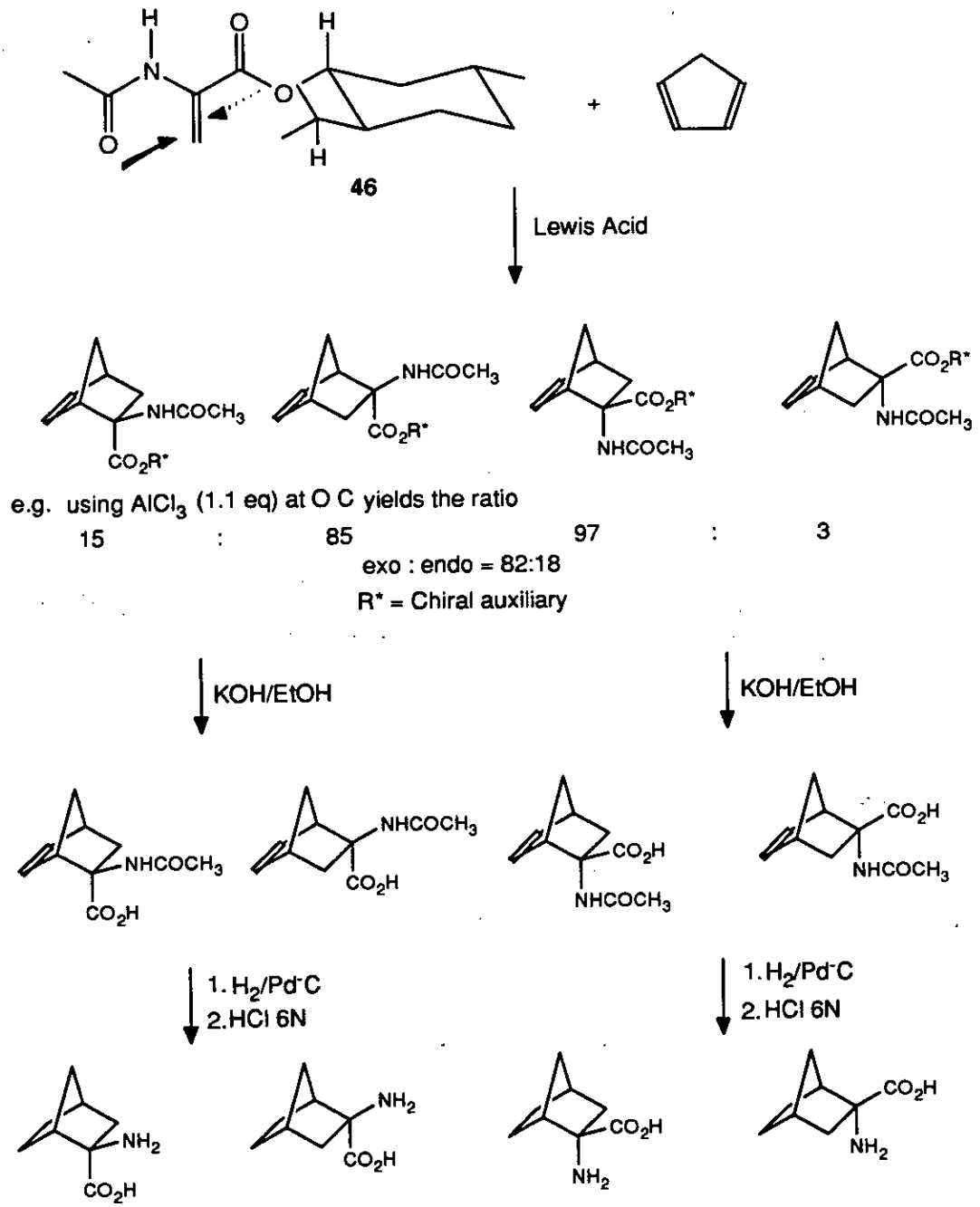


Scheme 12

A full discussion of the stereochemical aspects of the reaction will be given later in chapter 1. It is suffice to point out that there are four possible isomers which can form in this reaction, the two *endo* and two *exo* isomers. However, only one *endo* and one *exo* isomer can form from each face of the alkene.

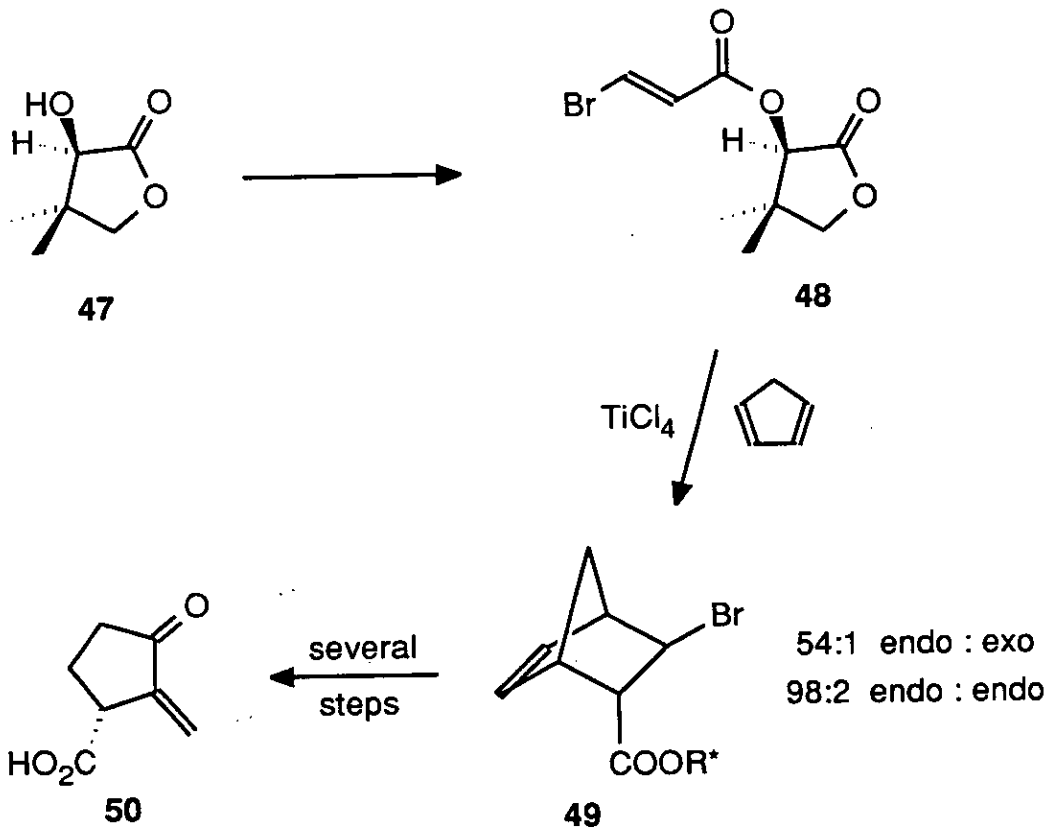
During the last few years a flood of papers on the use of this reaction in asymmetric synthesis have been published and this topic (in regard to chiral auxiliaries) has been reviewed by Oppolzer[64b]. For this reason, it would be best to concentrate on a few well chosen examples of asymmetric Diels-Alder reactions in which the synthesis of key intermediates of biological interest has been achieved.

(i) 2-Aminonorbornane-2-carboxylic acids **45** (Scheme 13) are of biological interest as far as the transport through membranes is concerned[65]. The problem of an asymmetric synthesis of these amino acids has been addressed by Cativiela *et al*[66] who used a menthol derived auxiliary **46** to effect the stereocontrol in a Lewis acid-mediated Diels-Alder reaction.



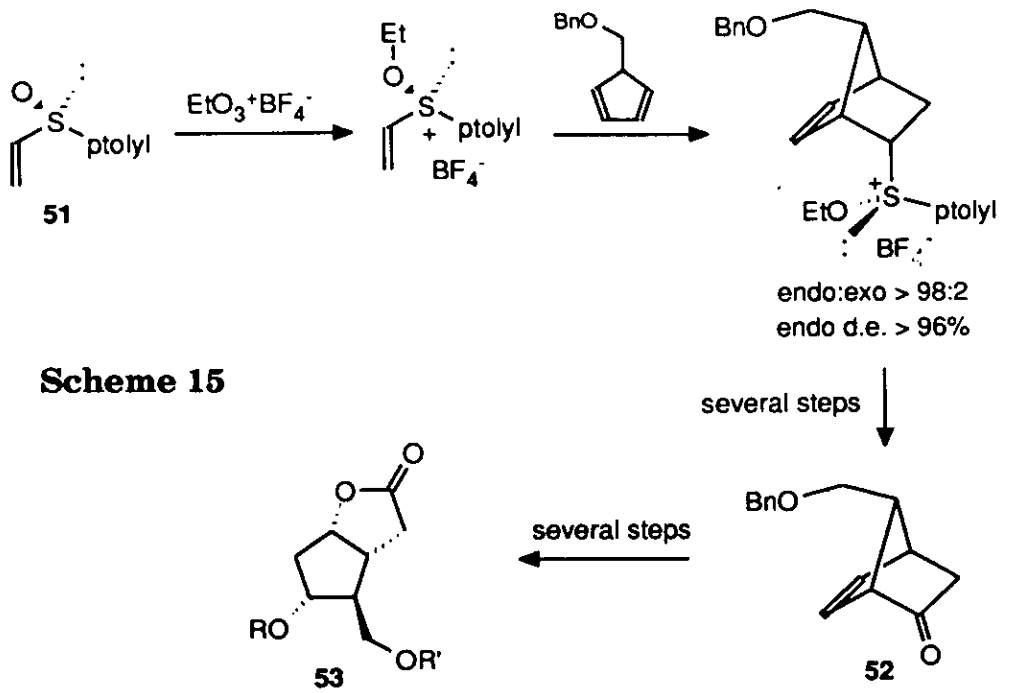
Scheme 13

(ii) Helmchem *et al*[67] have employed an (*R*)-pantolactone auxiliary **47** in the Diels-Alder reaction of (*E*)-β-bromoacrylic ester **48** with cyclopentadiene to furnish the cycloadduct **49** with very high diastereoselectivity. This is a key intermediate in the synthesis of the antitumour agent Sarkomycin **50** (Scheme 14).



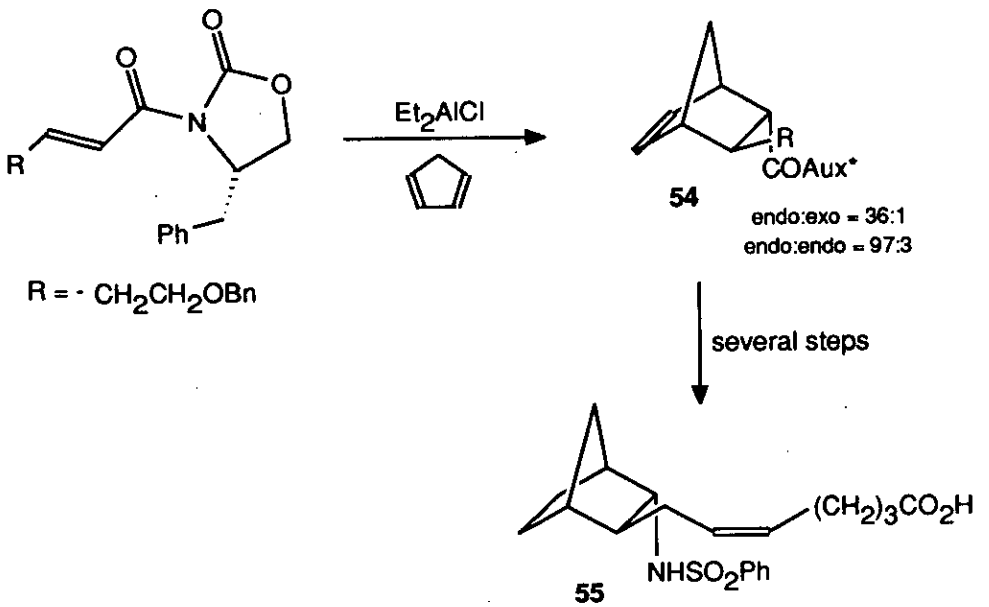
Scheme 14

(iii) Kagan *et al*[68] have used a chiral vinyl sulphoxide **51** to synthesise the key Corey intermediate **52**, used to make lactones **53** which are key entities in prostaglandin synthesis[69] (Scheme 15).



Scheme 15

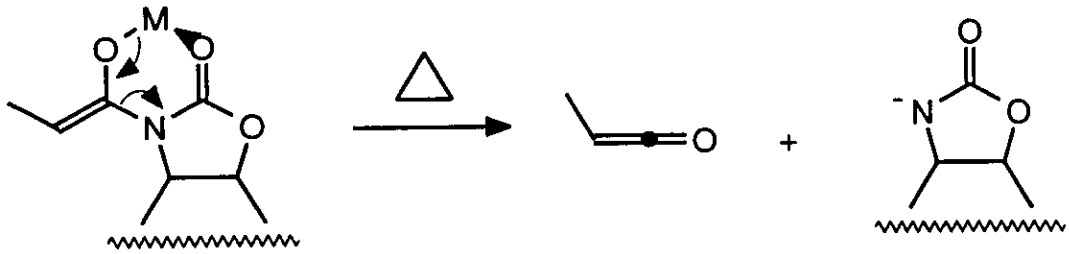
(iv) Martinelli[70] has employed Evans' (*S*)-phenylalanine derived auxiliary **29** to make the cycloadduct **54** with high *endo/exo* and high *endo/endo* selectivity (Scheme 16). The intermediate **54** was then modified to the target molecule of (+)-*S*-145 **55** which is a potent Thromboxane A_2 receptor antagonist, used in the treatment of diseases such as asthma, angina pectoris and thrombosis.



Scheme 16

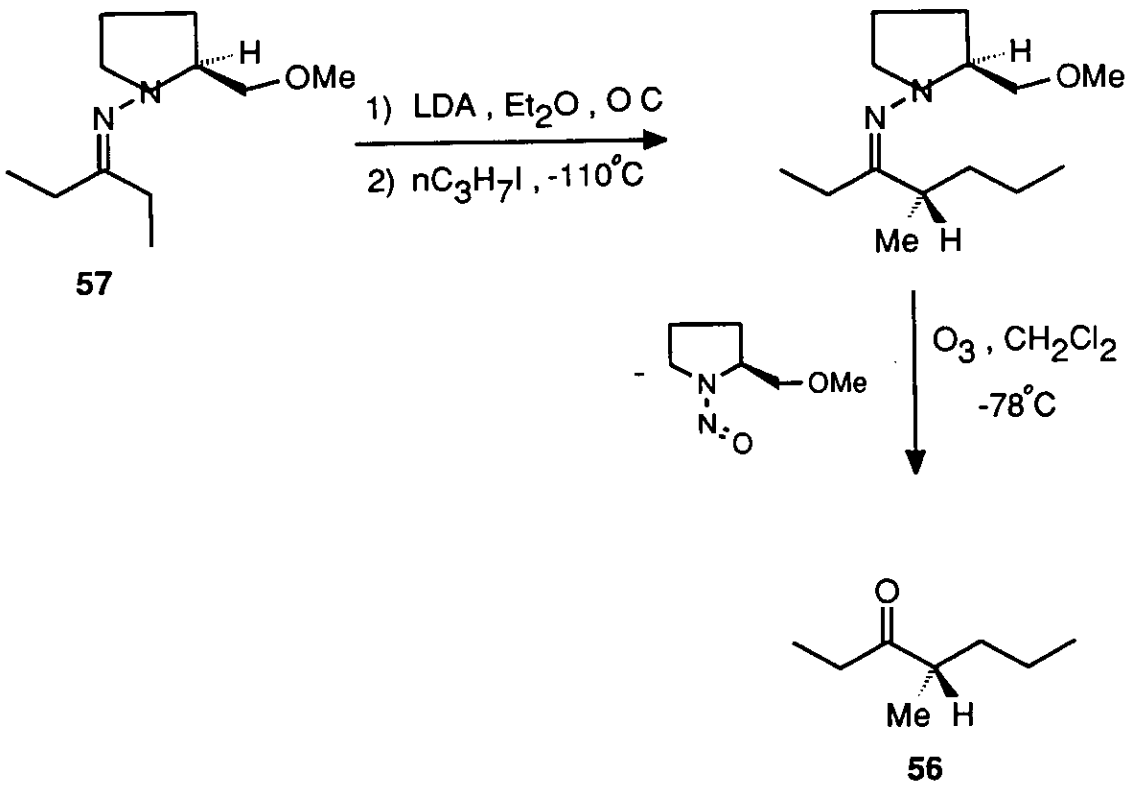
1.6.2 The alkylation reaction

Despite the versatility of the Evans'-type auxiliary,lithium and sodium derived enolates display a poor propensity to reaction towards alkyl halides[4]. In addition, by raising the temperature above 0^0C the lithium enolate decomposes *via* the ketene[37] (Scheme 17). (Sodium enolates display similar behaviour above -20^0C). However, this problem is not encountered in the use of other auxiliaries, for example Meyers' isoxazolines smoothly alkylate at -100^0C[57].



Scheme 17

As mentioned earlier,Davies' iron-acyl complex has been utilised in the synthesis of the ACE inhibitor Captopril **39**, the key step being the asymmetric alkylation reaction with bromomethyl-^{t}butyl sulphide (see section **1.5.4**). Another elegant synthesis involving an alkylation reaction is that of **56** (Scheme 18),which has been indentified as the alarm pheromone in four ant species, as a component of the defensive secretion of the "daddy longlegs" and is produced by the elm bark beetles *Scolytus scolytus (F)* and *S.multistriatus*. The molecule **56** is 400 times more active than its antipode and a synthesis has been achieved by Enders *et al*[71]. Using the SAMP-derived pentanone hydrazone **57**, treatment with LDA followed by alkylation with n-propyl iodide at -110^0C furnished the desired product,following ozonolysis, with >=97% ee.



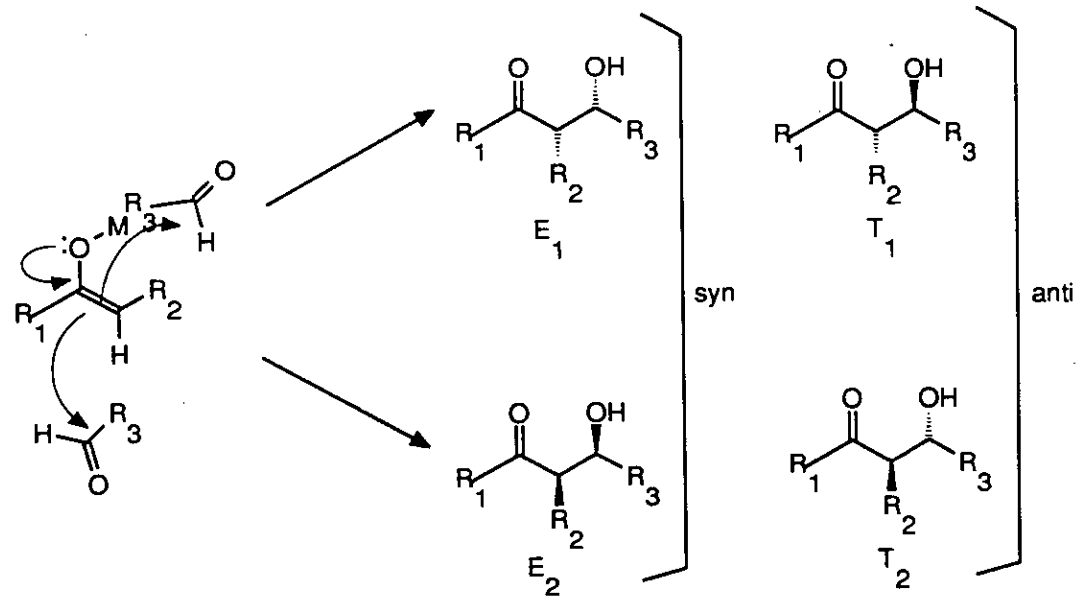
57

56

Scheme 18

1.6.3 The aldol reaction

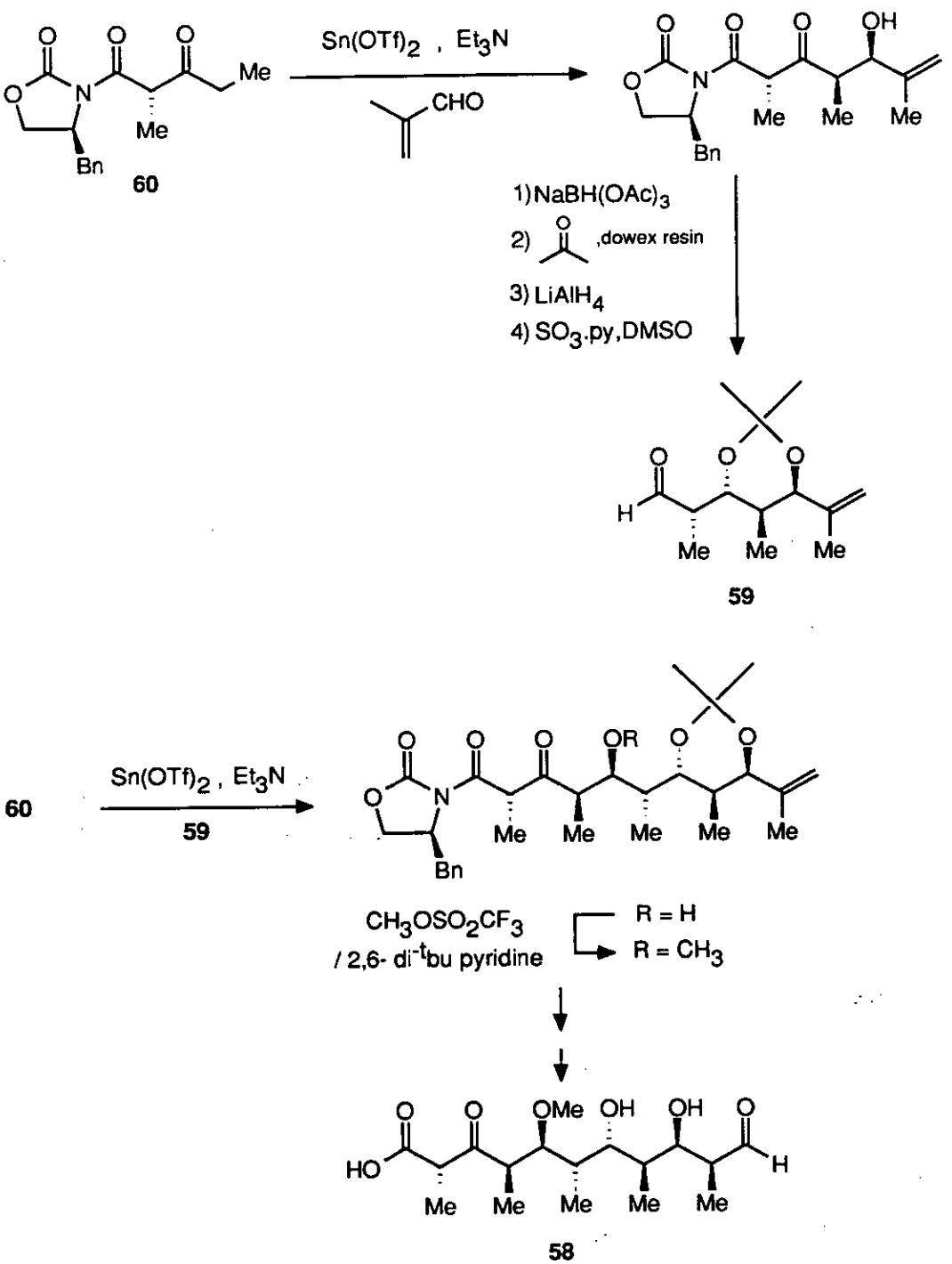
The aldol reaction has developed into one of the most powerful and selective carbon-carbon bond forming reactions in synthetic organic chemistry[72]. The reaction is used to make β-hydroxy carbonyl compounds with the simultaneous generation of two new chiral centres; one from the α-carbon of the imide keto function and one from the aldehydic or ketonic electrophile. The aldol reaction can yield a possible four products; there are two erythro (E) ("syn") isomers and two threo (T) ("anti") isomers possible (Scheme 19). However, only one syn and one anti isomer can be formed from each face of an enolate if this enolate exhibits a fixed geometry. For these reasons, the aldol reaction is akin to the Diels-Alder reaction, but the similarities between the two reactions at this point finish.



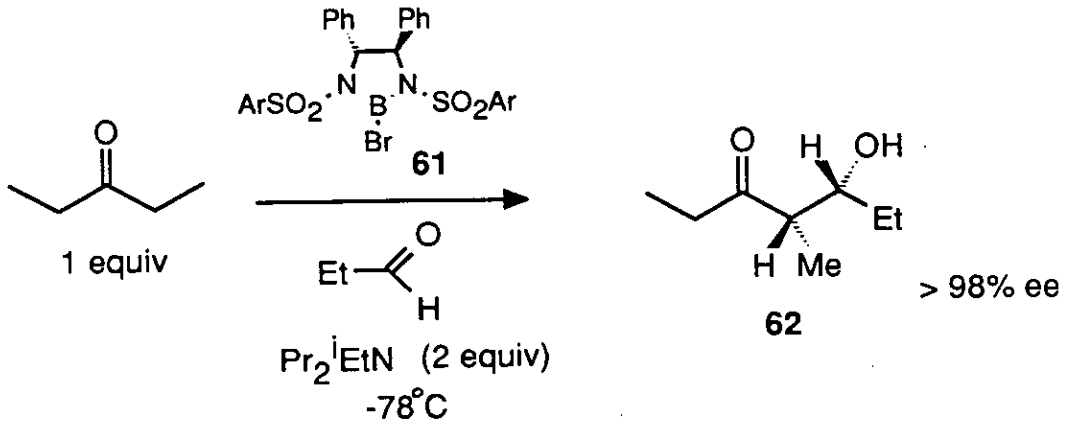
Scheme 19

The aldol reaction is of paramount importance in the construction of polyketide systems[4,73]. For example,the C_1-C_{11} synthon **58** of the antibiotic Lonomycin has been synthesised by a convergent route, *via* **59**, by two tin enolate-mediated reactions[73] (Scheme 20). The starting imide **60** is synthesised from the lithium enolate of the propionate of **28** in an acylation reaction with propionyl chloride[38].

Corey *et al*[74] have employed a benzil-derived boron chiral catalyst **61** in the synthesis of the rice and corn weevil aggregation pheromone Sitophilure **62**[75] (Scheme 21). An aluminium analogue of **61** has also been used by Corey for the enantioselective synthesis of the prostaglandin intermediate **52**[74].


Sn(OTf)2 , Et3N
CHO
Me
Bn
60
OH
Me
Me
Me
1) NaBH(OAc)3
2) ,dowex resin
3) LiAlH4
4) SO3.py,DMSO
H
59
60
Sn(OTf)2 , Et3N
59
OR
CH3OSO2CF3
/ 2,6- di-tbu pyridine
R = H
R = CH3
OMe
OH
HO
58

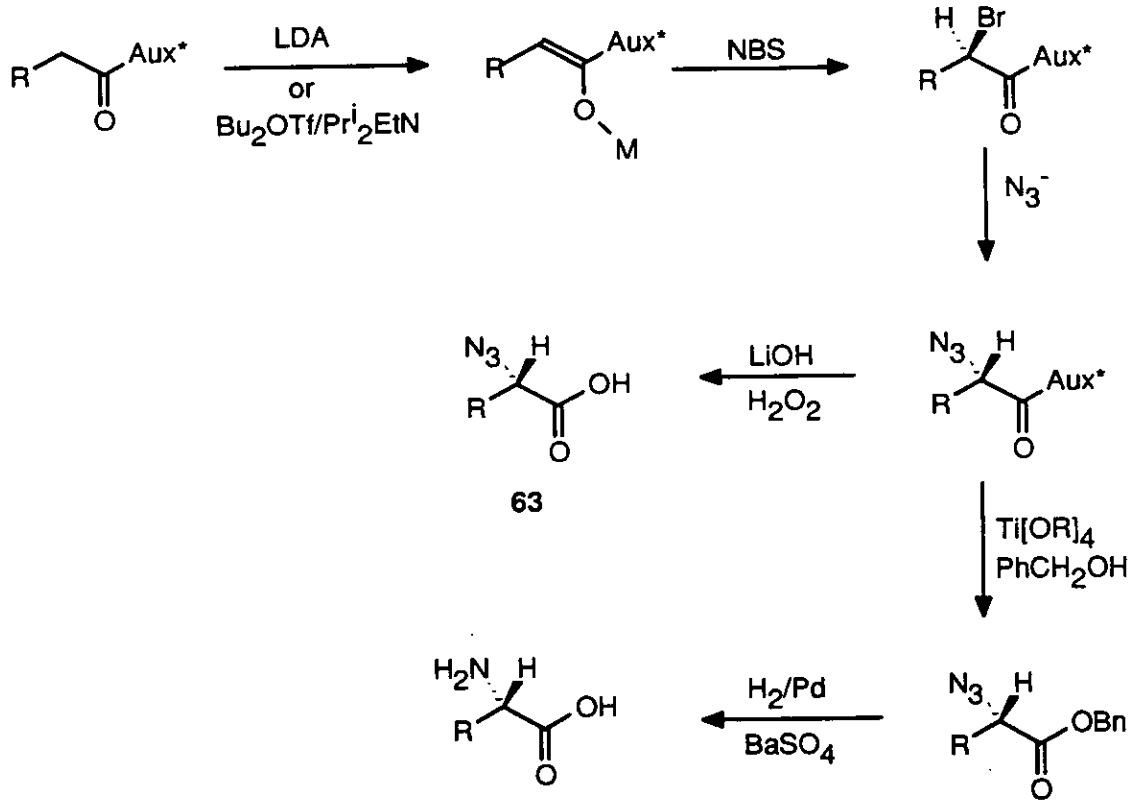
Scheme 20



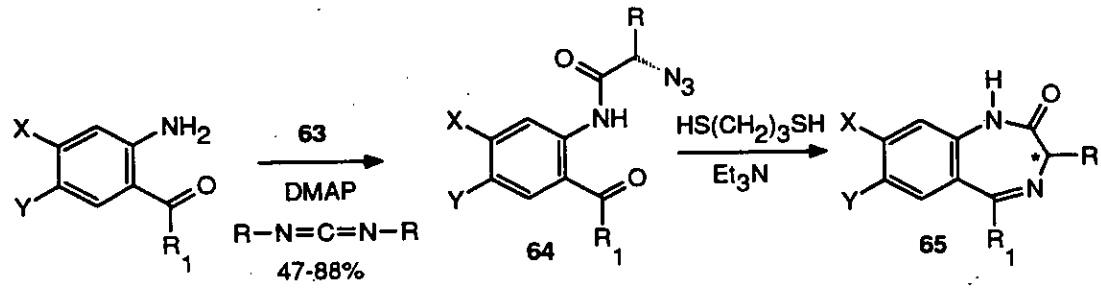
Scheme 21

1.6.4 The α-halogenation reaction

This is a reaction of key importance in the asymmetric synthesis of α-amino acids, exploited mainly by the enolate chemistry of Evans[35] and Oppolzer[76]. The essential features of the synthesis are the asymmetric α-halogenation reaction with NCS or NBS, followed by displacement with azide (Scheme 22). The azido keto function is then cleaved off to form the α-azido ester which undergoes hydrogenolysis to yield the α-amino acid. Of interest is the use of this synthesis in the creation of unnatural D-amino acids, which can be incorporated into peptides[77]. Of added value is the utility of α-azido acids **63** in the synthesis of CCK antagonists. Goldstein *et al*[78] have recently reported the coupling of 2-amino benzophenones with α-azido acids; the resulting anilides **64** were reductively cyclised to yield 3-substituted 2*H*-1,4-benzodiazepin-2-ones **65** (Scheme 23) using propanedithiol and triethylamine.



Scheme 22

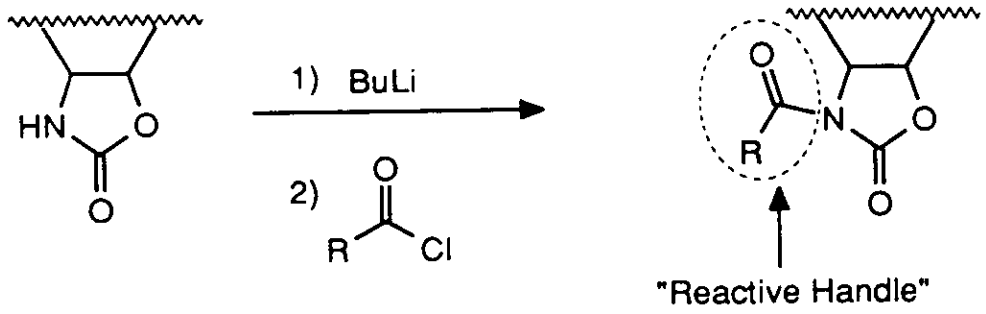


Scheme 23

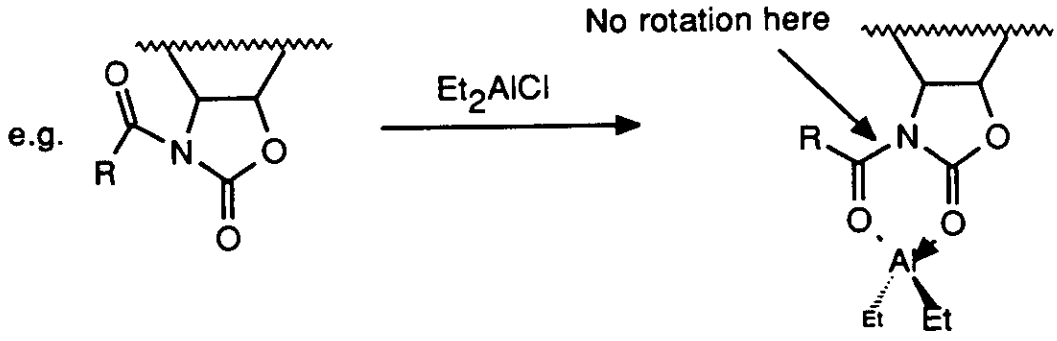
1.7 The utility of the oxazolidin-2-one ring as a template for chiral auxiliaries

The oxazolidin-2-one ring is a very useful system to incorporate into an auxiliary for three reasons:-

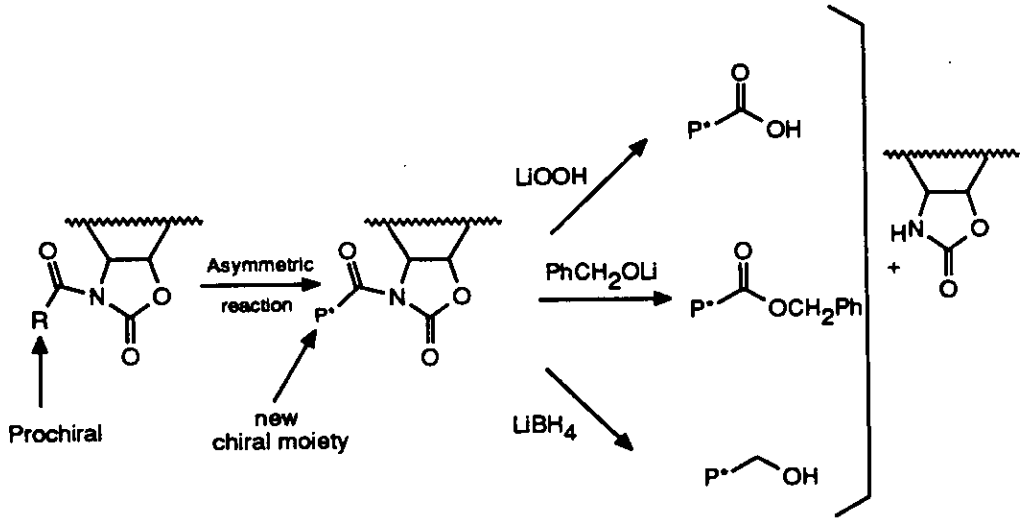
(i) The ring can be easily functionalised in high yield by the use of a strong base (*e.g.* *n*butyllithium) and the appropriate acid chloride.



(ii) The conformation adopted by the reactive handle can be controlled by chelation[4] in enolate mediated reactions and in enoate reactions by the use of metal-containing reagents *e.g.* LDA, Et_2AlCl; this provides a rigid framework upon which asymmetric reactions can occur.



(iii) The newly created chiral moiety can be removed from the auxiliary by methods which maintain the chiral integrity. These include lithium hydroperoxide[79] to furnish acids, lithium benzyl oxide[46] to furnish benzyl esters and lithium borohydride[4] to furnish alcohols (Scheme 24). In addition, the auxiliary can be recylced for re-use.

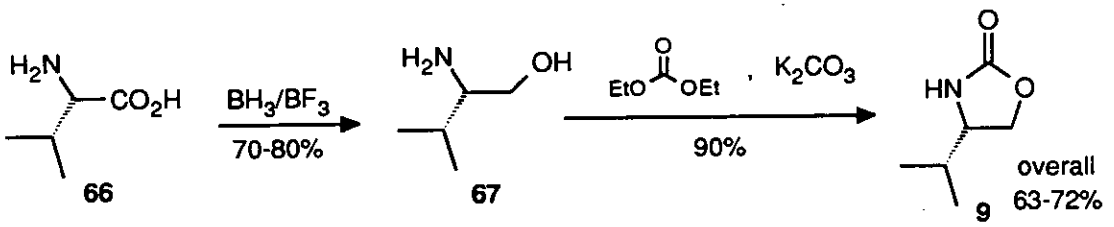


Scheme 24

1.8 Methods of synthesising oxazolidin-2-one rings

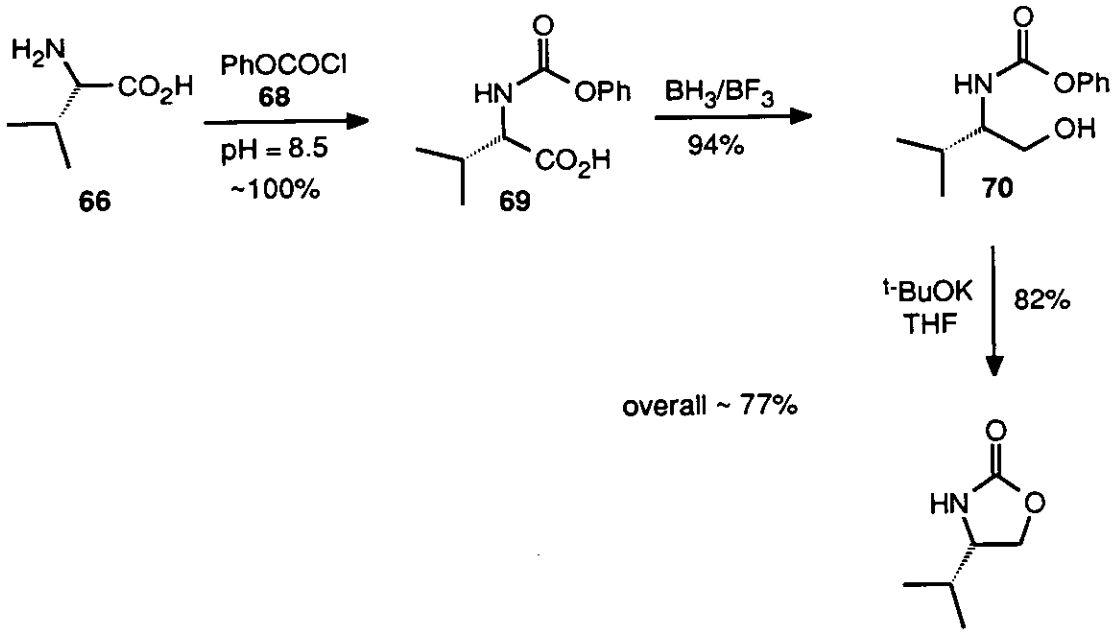
(i) From β-amino alcohols

This is the most widely used method and the common step is the cyclocarbamation reaction[80] after which resolution of the isomers may be required or the β-amino alcohol may be obtained from homochiral amino acids. For example (*S*)-valine **66** is reduced to (*S*)-valinol **67** and subsequent treatment with diethyl carbonate yields an Evans' auxiliary **9**[4] (Scheme 25).



Scheme 25

An improved synthesis of this auxiliary is reported by Wuts *et al*[81] in which **66** is first *N*-acylated with phenyl carbonochloridate **68** to yield **69** which undergoes reduction to yield the phenoxycarbonylamino butanol **70** (Scheme 26). This intermediate does not suffer the water soluble problems of **67** and makes a large scale synthesis more practical. Ring closure to form the final product is then achieved using a catalytic amount of potassium tert-butoxide. A second advantage is that the yield is a few percent higher; this is quite significant if performed on an industrial scale!

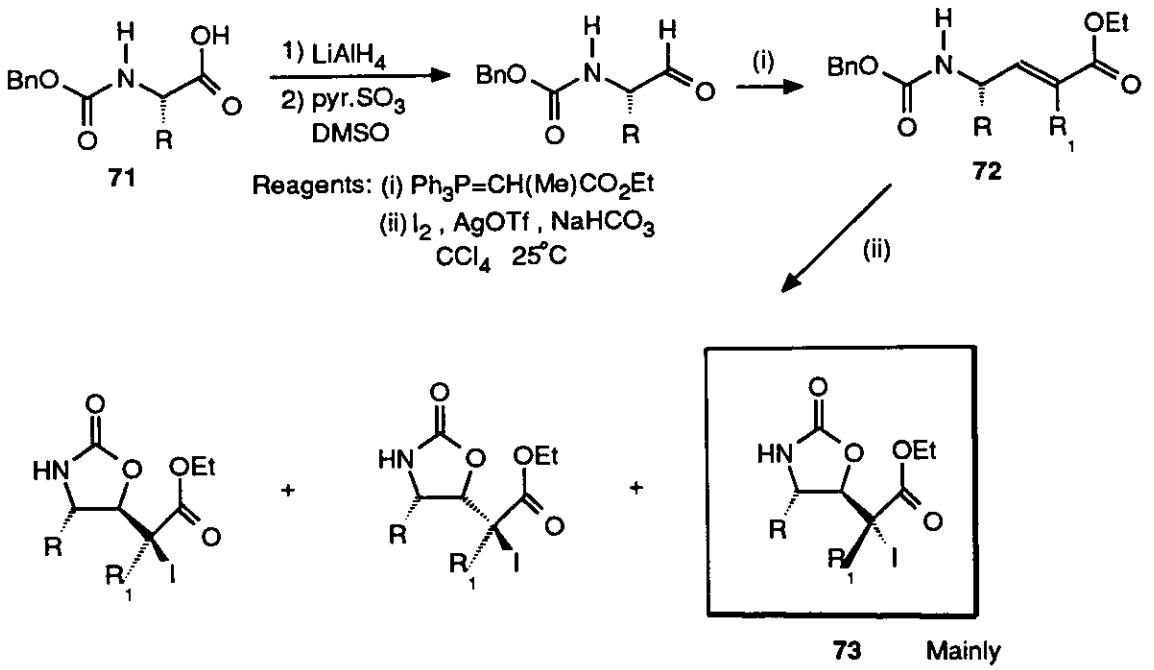


Scheme 26

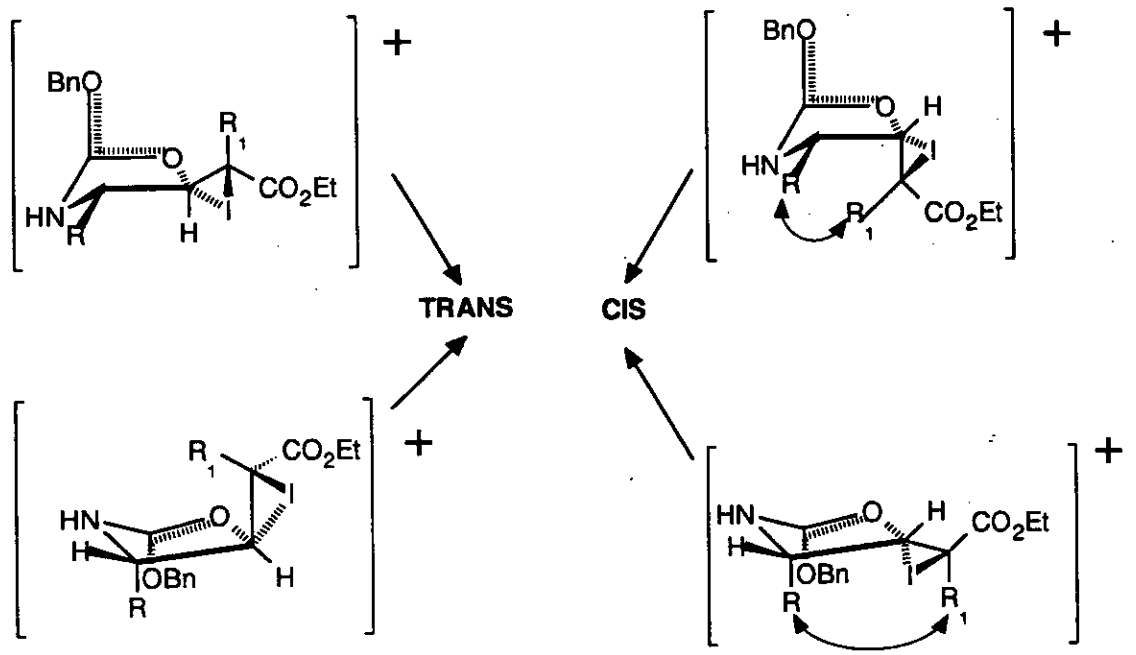
(ii) By iodocyclisation of α-amino acid derivatives

A recent and elaborate synthesis of a more highly substituted oxazolidinone ring is that reported by Guindon *et al*[82]. In this work, a protected amino acid **71** is converted in several steps into the enone **72** which undergoes the key iodocyclisation step using iodine, silver triflate and sodium bicarbonate in carbon tetrachloride to form the product **73** (Scheme 27).

The reaction is highly stereoselective when R_1=Me, which avoids 1,3 allylic strain in the transition state to the product, giving rise to a *trans* relationship between the substituents at the 2 and 3 positions of the oxazolidinone ring (Scheme 28).



Scheme 27

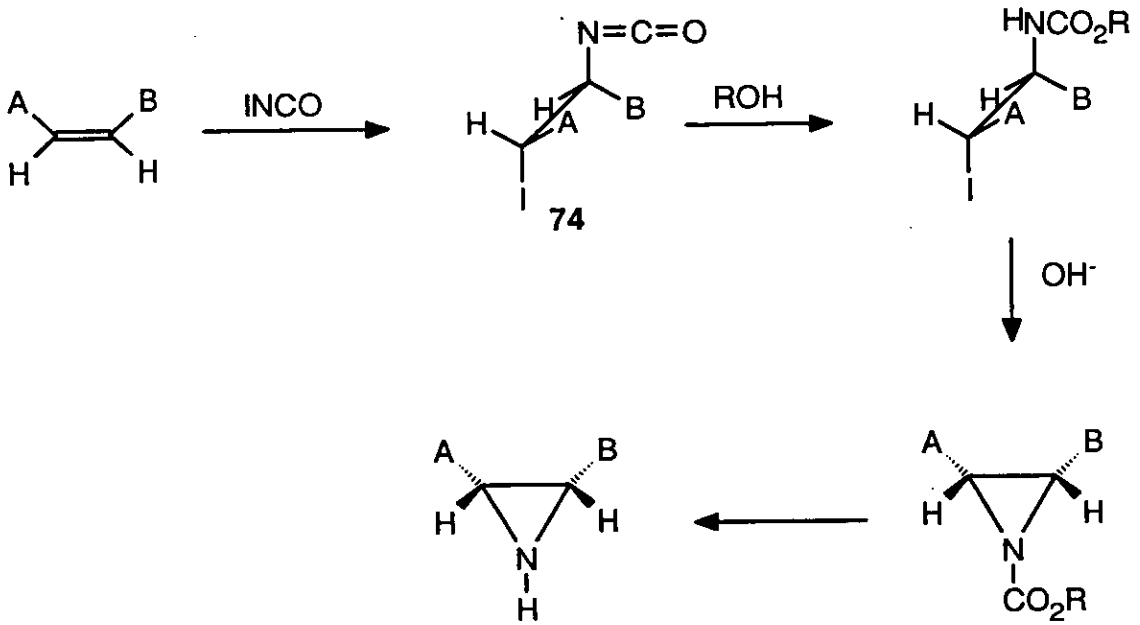


Scheme 28

1.9 Chiral aziridines

Unlike the chiral epoxidation of alkenes,the corresponding process for aziridines has received little attention.The classical method of synthesising aziridines is that of Hassner *et al*[83] whereby an alkene is

treated with iodine isocyanate (generated from iodine and silver cyanate); the electrophile adds regiospecifically to the olefin (Scheme 29)

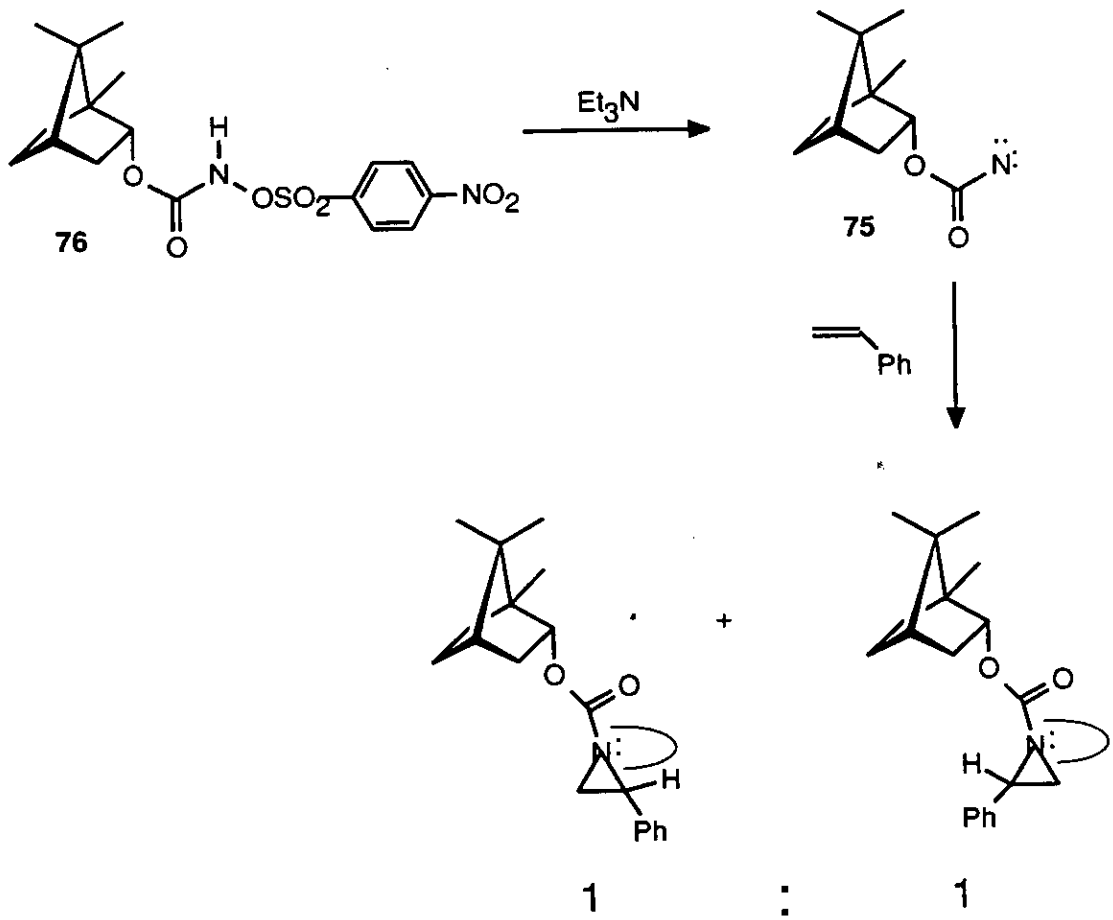


Scheme 29

The β-iodoisocyanate **74**, upon treatment with an alcohol, yields the β-iodocarbamate which undergoes cyclisation and hydrolysis to furnish the chiral aziridine. Fujita[84] have modified this to include the chiral alcohol (-)-menthol and the resulting aziridines were separated by resolution.

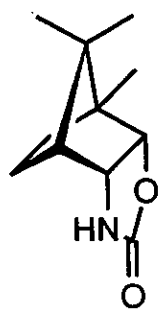
1.9.5 The Edinburgh route to Chiral Oxazolidinones-a serendipitous discovery

In an attempt to synthesise chiral aziridines by a previously untried route whereby a chiral nitrene is reacted with a prochiral alkene (styrene), Thomson[85] perceived that the use of the nitrenoformate **75**, generated from the Lwowski derivative of (1*S*)-*endo*-borneol **76**, furnished the desired aziridine but with no discernable asymmetric induction (Scheme 30). Upon subsequent re-investigation into this reaction, it was noted that a very small amount of a side product had formed. Repeating the experiment in the absence of styrene yielded three products,which were shown to be derived directly from **75** and the



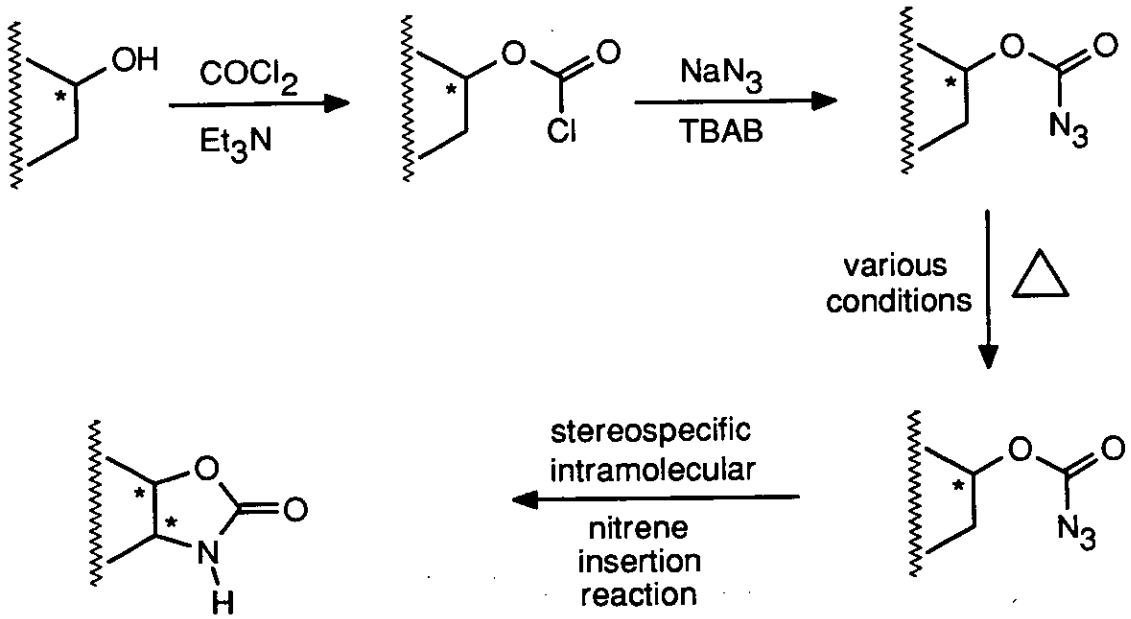
Scheme 30

material in largest quantity was the side-product formed in the original styrene reaction[86]. This was isolated from the other products and proven to be the five-membered ring compound **77**, later to be called Chirabornox-*N* or Chirabornox for short. The name derives from the fact that it is chiral, it is derived from *endo* - borneol and it possesses the oxazolidinone ring system.



77

Chirabornox is a crystalline stable solid (melting point 162-163^{0}C) whose ring system is characteristic of all Evans'-type auxiliaries (*vide supra*). It was soon realised that this route to oxazolidinones was a general one (see Scheme 31 below) and could be applied to other homochiral systems which have a free hydroxyl group, in particular terpene-derived alcohols and suitably protected carbohydrates.



Scheme 31

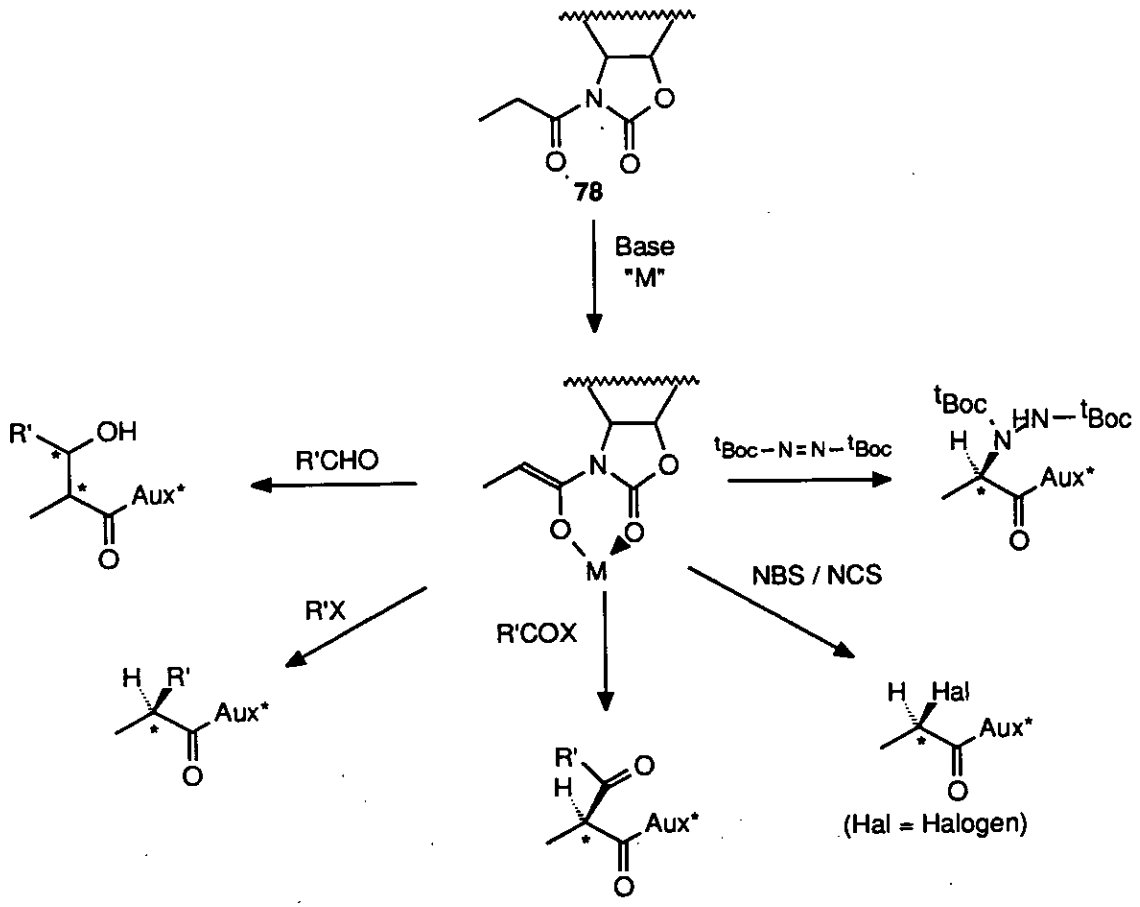
2 Programme of research

The utility of Chirabornox as a chiral auxiliary

At the time of the synthesis and characterisation of **77**, no terpenoid-derived oxazolidinone had ever been reported in the literature for use as a chiral auxiliary. The potential therefore existed to exploit the chemistry of the oxazolidinone ring[4] whilst simultaneously utilising the rigid asymmetric template provided by the bornane ring.

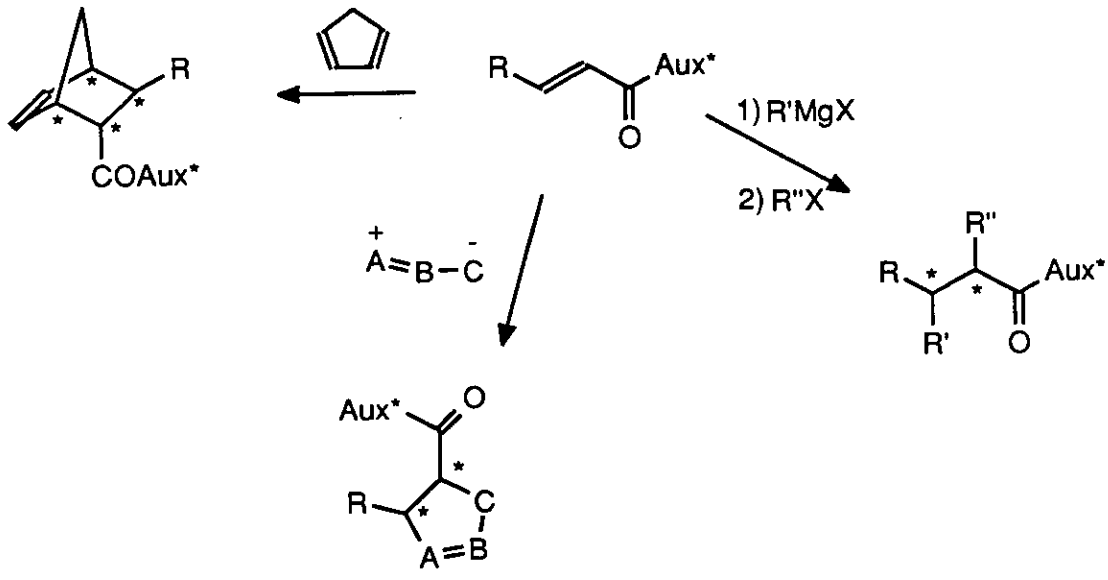
By converting Chirabornox into its *N*-propionyl derivative **78** the auxiliary is expected to be able to undergo a variety of asymmetric transformations of the type exemplified in Scheme 32, and the levels of

induction would give a measure of the degree of topological bias exhibited by the auxiliary in such transformations.



Scheme 32

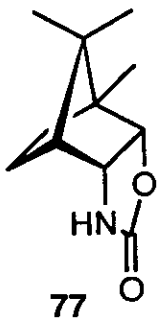
Similarly, the unsaturated carboximides are anticipated to undergo the asymmetric transformations outlined in Scheme 33. In addition, it was envisaged that the molecule could be used for the resolution of racemic mixtures of amines, carboxylic acids and alcohols. It was foreseen that the auxiliary could be cleaved from the newly created *N*-acyl chiral appendages under mild conditions and the oxazolidinone recycled.



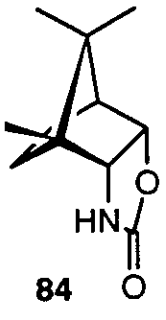
Scheme 33

DISCUSSION

The work in this thesis primarily describes the stereochemical investigations conducted upon Chirabornox **77**, a chiral auxiliary derived from [(1*S*)-*endo*]-(-)-borneol. Also included is a much smaller section on the attempted synthesis of **84**, the so-called "transfigomer" of **77**.



77



84

The discussion is divided into four main sections. These are :-

(i) The work conducted on the α,β-unsaturated carboximides of **77**, in particular the Diels-Alder reactions of the acrylate with cyclopentadiene and isoprene under a variety of conditions.

(ii) The work carried out on the propionate of **77**, namely alkylation, acylation, aldol and α-bromination reactions.

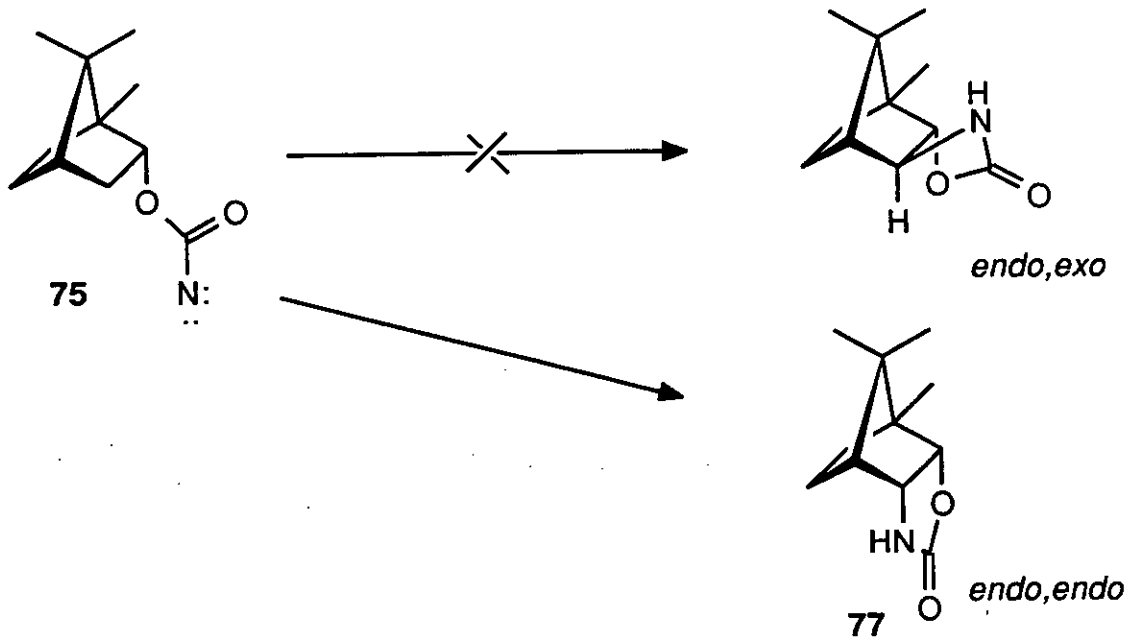
(iii) The work conducted with (+/-) 1-phenyl ethanol and (+/-) trans-2-methyl cyclohexanol with regard to their resolution.

(iv) The attempted synthesis of the transfigomer of Chirabornox, **84**, including the NOE study of an unexpected intermediate product.

Preamble

Optimisation of the reaction conditions for the formation of (77)

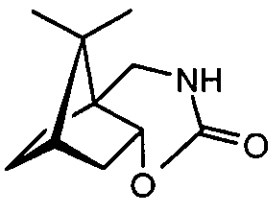
The work of Banks and Dawson[86] sought to optimise the conditions for the formation of the nitrenoformate **75**, and hence **77**, by the key step of stereospecific nitrene insertion[87], the resultant stereochemistry of which is inherent in the chirality in the parent alcohol. In the case of **77**, the nitrene is conformationally restricted to insert in an *endo* fashion into the adjacent methylene (Scheme 34).



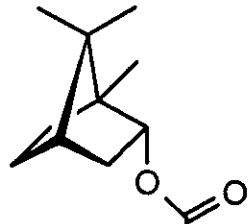
Scheme 34

In the reaction of *p*-nitrobenzenesulphonoxycarbamate **76** with sodium bicarbonate in the presence of a phase-transfer catalyst, two other products are formed; the first is the oxazinone **79** formed by insertion of the nitrene into the bridgehead methyl group, and the second is the carbamate **80** which is formed by proton abstraction. By converting *endo*-borneol into the azidoformate **81** *via* the chloroformate **82**, one has a

precursor which can lose nitrogen by a variety of conditions to yield **75** (Scheme 35).

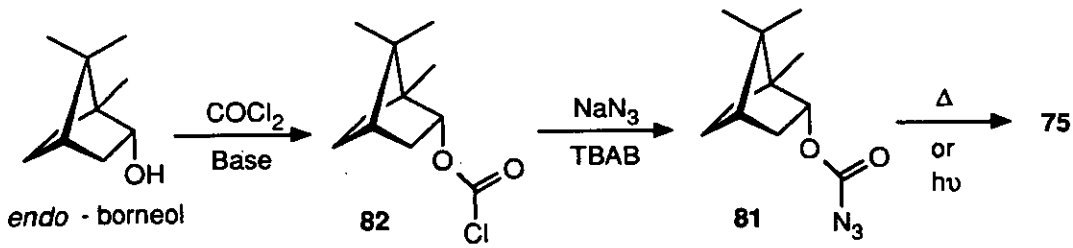


79



80

In Scheme 35, Δ represents a variety of thermolytic methods including flash vacuum pyrolysis (FVP), spray pyrolysis or solution thermolysis. All of these techniques can be used to generate nitrenes and a short description of each is now justified.



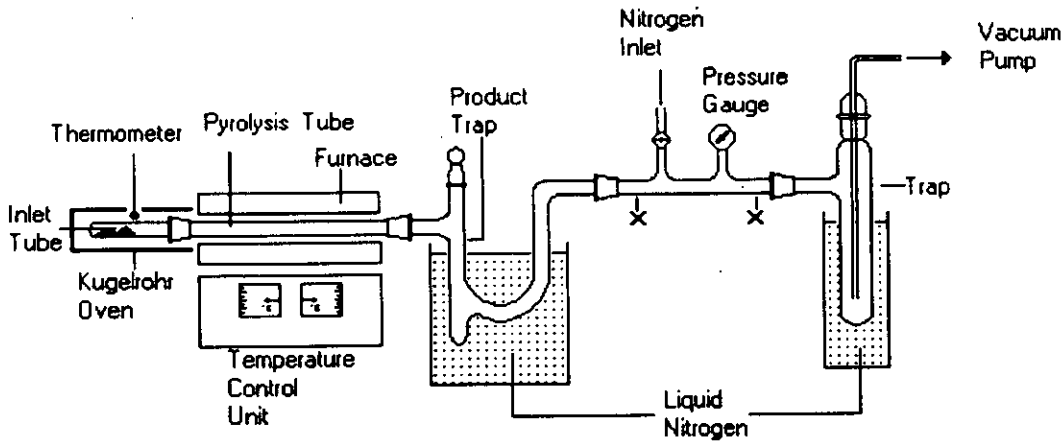
endo - borneol **82** **81**

Scheme 35

(a) Flash vacuum pyrolysis (FVP)

The basic principle lying behind this technique is that a volatilisable sample is very rapidly pulled through a hot tube (*ca* several hundred ^{0}C). under a vacuum typically of 10^{-1} to 10^{-2} torr. During this time the transient species is generated, but, due to the low concentration situation it finds itself in, it can only react with itself *i.e.* the apparatus is ideal for promoting intramolecular reactions. The contact time is only *ca* 1/1000th second and the product is rapidly condensed into a trap which is held at

liquid nitrogen temperature (see below).Fuller details regarding this technique can be found in the literature[88a].



Schematic representation of FVP apparatus

(b) Spray Pyrolysis

This is a modification of FVP developed by Meth-Cohn[87a], in which an oil or low melting solid precursor is sprayed by a stream of nitrogen into a vertical furnace.This technique is reported to give higher yields than thermolysis,but cannot be used for thermally involatile starting materials.

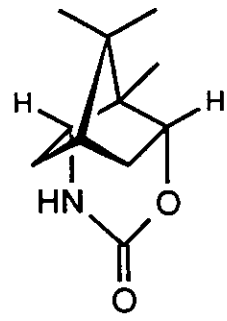
(c) Solution thermolysis

In this technique, the nitrene is generated in a solvent which is inert to nitrene insertion and boils at a temperature sufficiently high enough to decompose the precursor azide. For this reason, 1,1,2,2-tetrachloroethane (TCE), which boils at 147^{0}C, is ideal.In essence a TCE solution of the azide is dripped into boiling TCE and the dilution is high enough for only intramolecular reactions to occur.

(d) Photolysis

The nitrene is generated in a photolytic reactor in which the azide, dissolved in an inert solvent (for example methylene chloride), is exposed to ultraviolet radiation. For example, a medium pressure mercury lamp operates at a wavelength of 365-366 nm. The apparatus required for photolysis is described in the literature[88b].

Banks and Dawson employed all of the techniques except for solution thermolysis.In all cases except photolysis a third tricylic compound was formed in addition to **79** and **80**; this was identified as the oxazinone **83** which results from nitrene insertion into the C-6 methylene group.

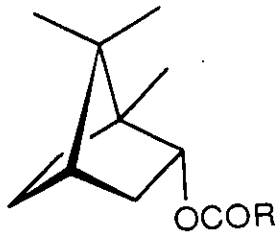


83

Table 1 (overleaf) shows the various ratios of **79**,**80** and **83** obtained by the two authors *vide supra* upon employment of the different techniques.

Chirabornox **77** is always the main isomer to be formed no matter which technique was employed. Interestingly, when comparing the primary (expected to minor) insertion product relative to the secondary (**79** vs **83**), the primary insertion product is always present in larger quantities, except for spray pyrolysis. Presumably this is due to the fact that the bridgehead methyl is more accessible to the nitrene than the much more sterically crowded CH_2. Also, amide **80** is only present in significant amounts when photolysis is employed,which could be explained by the

Table 1. Ratios of the four products obtained under a variety of conditions of generation of the nitrenoformate **75**

	**77** /%	**79** /%	**80** /%	**83** /%
R =				
$NHOSO_2C_6H_4NO_2$				
Conditions				
$NaHCO_3$ / $PhCH_2NEt_3Cl$	43	36	14	-
$R = N_3$				
Conditions				
FVP / 300^0C	46	23	-	23
SP / 300^0C	57	17	-	25
Photolysis	39	25	35	-

fact that some of the nitrene molecules can undergo intersystem crossing and relax into the triplet state T_1 before reacting in an abstractive fashion instead of inserting (in the S_1 singlet state).

Solution thermolysis experiments

To add to the work of Banks and Dawson,the nitrenoformate **75** was generated in boiling TCE by two methods : (1) dropwise addition of a TCE solution of the azide into the boiling solvent from a separating funnel, such that the overall concentration was less than 1% (10g of azide in 1500ml of TCE) ; (2) a solution of the azide was added dropwise *via* syringe pump to the boiling solvent but in a much higher overall concentration (10%).In both cases the crude reaction mixtures were analysed by 200MHz ^{1}H NMR and gave the results shown in Table 2

Table 2. Variation of product ratios with concentration of **75**

	77 /%	**79** /%	**80** /%	**83** /%
0.7% solution	46.5	32	6.5	15
10% solution	37	29	25.5	8.5

Two points are particularly noteworthy when comparing these results. The first is that an increase in concentration significantly lowers the yield of **77** with concomitant increased formation of carbamate **80**. Contrary to prediction, it would appear that the increase in concentration *encourages* the formation of the triplet nitrene; this could be brought about by the nitrenoformate molecules being able to relax each other. The second point concerns the primary insertion product **79** and the secondary insertion product **83**. By increasing the concentration significantly it was noted that the ratio of the primary to secondary insertion products increases, with a notable associated reduction of **83**.

Banks and Dawson had shown that separation of the two oxazinone isomers **79** and **83** was not readily effected; these products were in addition less attractive candidates for chiral auxiliaries than Chirabornox **77** as it was anticipated that they would possess less rigid six membered rings than that of the five membered ring of **77**.
In contrast, Chirabornox **77** was easily separated from the two six membered ring products **79** and **83** by flash column chromatography. The auxiliary is highly crystalline, with a melting point of 162-163^{0}C and it was anticpated that the bornane moiety would impart crystallinity to all of its derivatives, in addition to providing a rigid, asymmetric bias. For these reasons it was anticipated that Chirabornox **77** would make an excellent candidate for a chiral auxiliary.

X-RAY CRYSTAL STRUCTURE OF CHIRABORNOX (77)

Initial examination of the X-ray crystal structure of the auxiliary (Appendix 1) revealed a number of intriguing features.Firstly,the oxazolidin-2-one ring is planar which is to be expected on the basis of resonance and the possible canonical forms of the system, and due to conformational restrictions imposed by the bornane ring.Secondly, if one functionalises the nitrogen with an acyl reactive handle and thereby freeze the rotation about the N-C bond by bidentate chelation of the carbonyl groups, one can envisage an alkene or the formation of an enolate in which the unsaturated moiety exists in the same plane as the oxazolidinone ring.

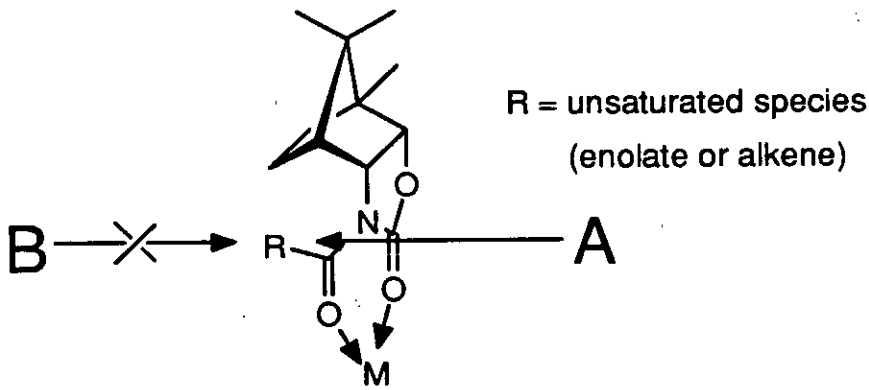


Figure 1

With reference to Figure 1 and Appendix 1, one can envisage that upon approach A by an incoming reactant, this face of the π-system is completely unhindered and allows easy access. Conversely, upon approach B to the π-system, the reactant encounters the steric control elements, *i.e.* the methyl and methylenes of the bornane ring which hinder its path. Thus, a very clear π-topological bias can be seen, inherent in the bornane skeleton.

Chapter 1

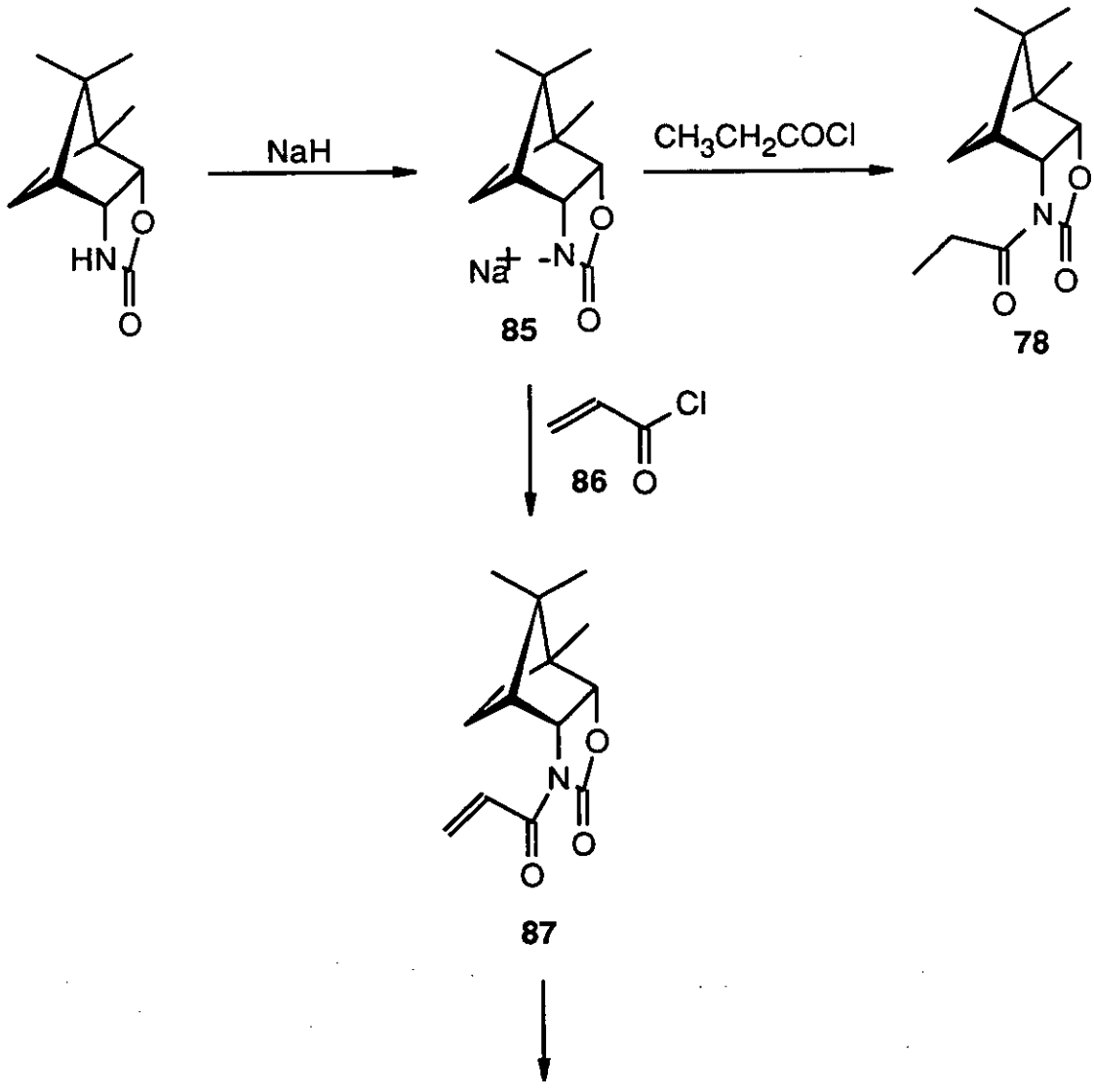
The α,β-unsaturated carboximides of Chirabornox (77) : 1. Preparation of the acrylate (87) and its Diels-Alder reactions with cyclopentadiene.

(i) Problems with the preparation of the acrylate of (77)

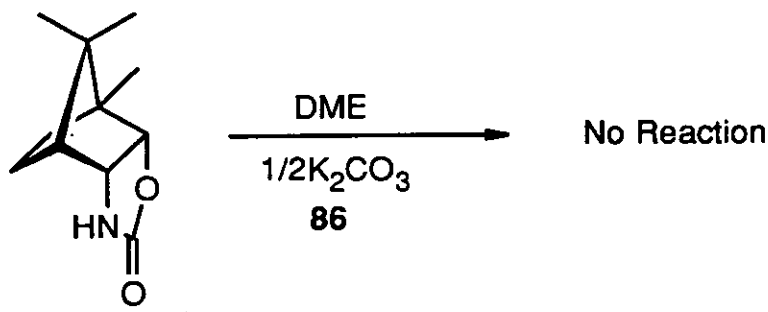
The propionate **78** of Chirabornox had previously[86] been prepared by treating the oxazolidinone with sodium hydride,to form an isolable hydroscopic sodium salt intermediate **85** which underwent reaction with propionyl chloride to yield the product **78** in 95% yield. Accordingly, synthesis of the analogous α,β-unsaturated moiety was thought to be best achievable by the same method; indeed this is the method of choice for the functionalisation of Oppolzer's auxiliary[8].Thus,treatment of **85** with acryloyl chloride (2-propenoyl chloride) **86** in dry diethyl ether yielded the desired product **87**, but this subsequently polymerised on attempted purification by Kugelrohr distillation (Scheme 36).

As a result of this setback, methods were tried to form the desired product without concomitant polymerisation. Initially, **77** and acryloyl chloride were introduced together in the presence of potassium carbonate in DME which made the salt soluble, giving a homogeneous reaction mixture. However, despite a protracted period at ambient temperature and a further period at 50^{0}C under an argon atmosphere, thin layer chromatography revealed that only a trace of product had formed (Scheme 37).

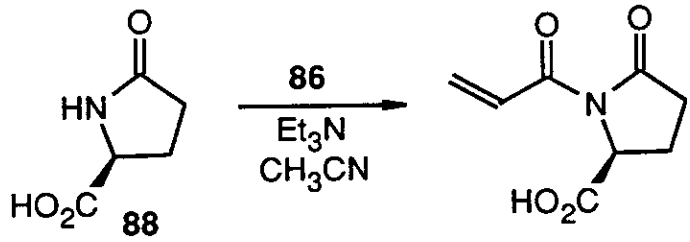
Stimulated by a literature finding of the work of Sempuku[89] in which pyroglutamine **88** was *N*-acryloylated,**77** and acryloyl chloride together with triethylamine in acetonitrile were accordingly introduced together, but with the same negative result (Scheme 38).



Scheme 36



Scheme 37

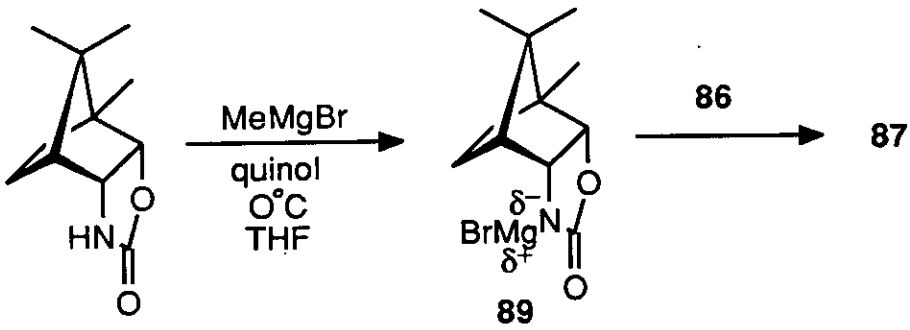


Scheme 38

Further investigations of the literature revealed[90] that *N*-acryloylation could be achieved by reaction of acryloyl chloride with the *N*-bromomagnesium derivative of **77**. Thus, if a method for *N*-bromination of Chirabornox could be found, the Grignard type moiety ought to be generated and solve the problem. Such a method was found[91] and involved treating an aqueous solution of the oxazolidinone with bromine,using sodium hydroxide to keep the pH alkaline. However, despite adaptation of the literature procedure,attempts to *N*-brominate the auxiliary failed.

At this point it was thought that the origin of the polymerisation could be free-radical in nature, the source being peroxides in the ether. In order to avoid this possibility the sodium salt **85** was reacted with acryloyl chloride in DME as before, but this time a trace of the free-radical inhibitor galvinoxyl[92] was added to the solution. However, polymerisation was still observed to occur. DME was then treated for peroxides as described in the literature[93], in case it was producing radicals at a concentration greater than could be dealt with by galvinoxyl, but the same result was observed. Indeed, the same reaction performed in dry methylene chloride still yielded polymer. These findings suggested a different form of polymerisation was occurring, possibly anionic in nature, whereby the sodium salt itself is the initiator, forming plausible resonance stabilised carbanions with the initially formed acrylate.

Adoption of a relatively inaccessible literature procedure[90] (found in a subsequent publication[46]) in which the acrylate was obtained in good yield without polymerisation was undertaken. Thus,treatment of **77** in THF with methylmagnesium bromide afforded the *N*-bromomagnesium species **89** which smoothly reacted with acryloyl chloride to furnish **87** in 75% yield (Scheme 39). Quinol was used in addition to prevent free radical polymerisation of the product.



Scheme 39

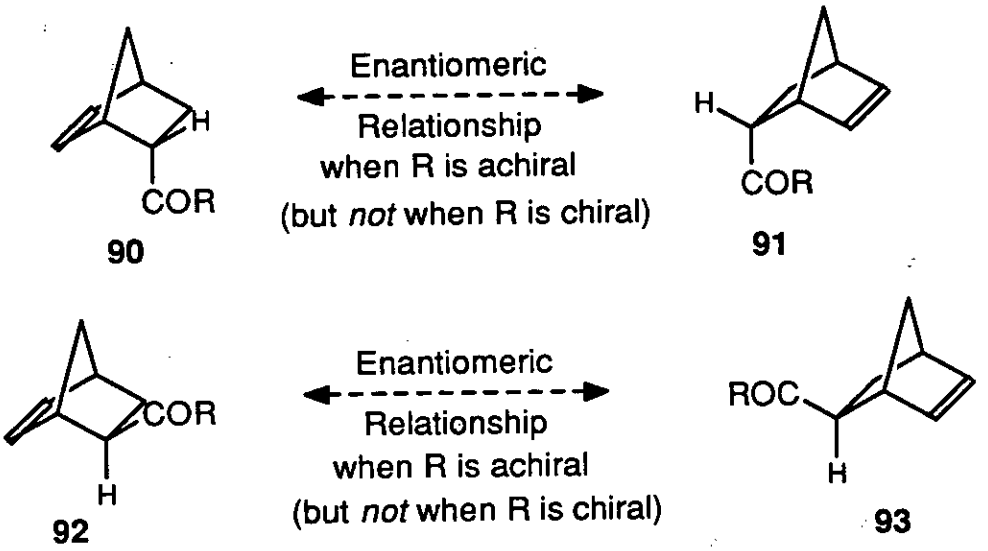
This method possesses the key feature that no formal charges are present in the starting material, or indeed in the Grignard species **89**, thereby preventing anionic polymerisation. The oxazolidinone is also soluble in the solvent used, which is an added advantage over using a suspension of sodium salt in ether, giving an entirely homogeneous mixture.

A final method of acrylate synthesis was then attempted, which involved generation of the lithiated oxazolidinone using *n*-butyllithium and subsequent *N*-acylation.This technique had not been attempted at an earlier stage as Evans had reported[90,46] the propensity of oxazolidinone acrylates towards polymerisation under these conditions.However, when attempted, the method furnished the desired product albeit in low yield (48%) but with no concomitant polymerisation. Lack of polymerisation as

observed could be attributed to the predominance of covalent character in the N-Li bond compared to that of the N-Na bond, and presumably this holds true for the N-MgBr bond compared with that of the N-Na bond. In conclusion, it is necessary to activate the nitrogen of the oxazolidinone ring to electrophilic attack and in this connection weak bases do not suffice, but "over-activation" with very strong bases can cause subsequent polymerisation of the product through a possible anionic mechanism.

(ii) The use of titanium catalysts in the Diels-Alder reaction of the acrylate (87) with cyclopentadiene : initial studies

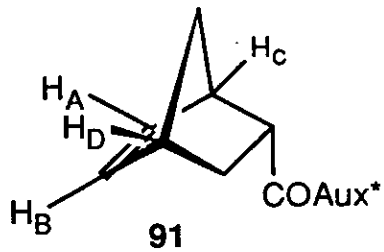
When an acrylate reacts with cyclopentadiene,the formation of four isomers is possible. These are the two kinetically favoured *endo* adducts **90** and **91** and the two thermodynamically favoured *exo* adducts **92** and **93** (Scheme 40).



Scheme 40

Because the auxiliary is homochiral, the two *endo* isomers are not mirror images of each other. This is also true for the two *exo* isomers. Hence all four isomers are diastereomers of each other. Thus, all of the signals in

the ^1H NMR spectrum of the mixture will not necessarily have the same chemical shift (but can have) and this fact can be used to determine the ratio of the isomers formed. For example, consider one of the diastereomers, **91** (below).It can be expected that olefinic proton H_A will couple with H_B to give a doublet which is split by the proton H_C. H_B, on



91

the other hand will be split by H_A and H_D.Hence,the one isomer shown will yield two sets of doublets of doublets.Therefore,if all four isomers depicted in Scheme 40 are formed, the olefinic region of the ^1H NMR spectrum will show eight sets of doublets of doublets.

In the absence of Lewis acid,there are four possible conformations of the acrylate (A) to (D) (Figure 2).

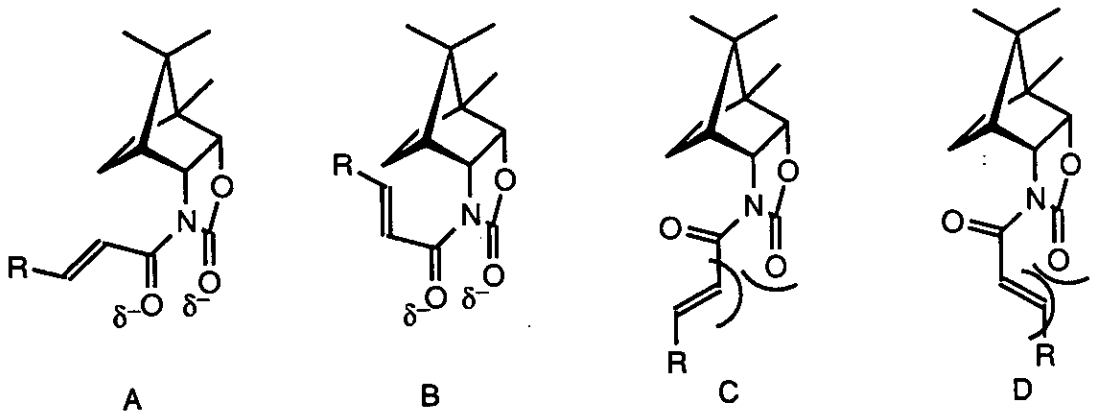
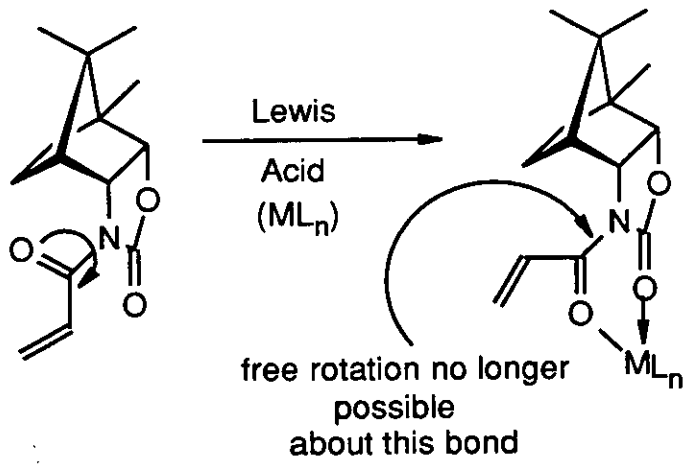


Figure 2

Conformations (A) and (B) are disfavoured due to dipole-dipole repulsions. On the other hand, conformation (D) is disfavoured over (C) due to steric repulsion between the unsaturated methylene and the

carbonyl of the auxiliary.These assumptions are adopted from literature considerations by Curran *et al*[23].

In Chirabornox **77**, a key feature for any *N*-acyl derivative, and not just the acrylate, is the possible coplanar deposition of the two carbonyl groups by chelation to a metal centre, *i.e.* a Lewis acid. The N-C bond in the *N*-acyl portion is free to rotate, unless co-ordination takes place (Scheme 41).



Scheme 41

The metal catalyst, M, therefore serves a dual purpose : firstly, it provides a more rigid π-framework for the attacking diene to "lock-into". Secondly, it withdraws electron density from the acrylate carbonyl, making the 2π system even more reactive towards the diene, giving a more kinetically accessible pathway (Figure 3).

Thus, the larger the value of ΔE-ΔE', the faster will be the Diels-Alder reaction (the reader is directed towards the latter part of this chapter in which the use of aluminium catalyst is discussed fully).

The protocol followed for this reaction using titanium Lewis acids closely matched literature procedures and, in particular, work by Oppolzer *et al*[9].

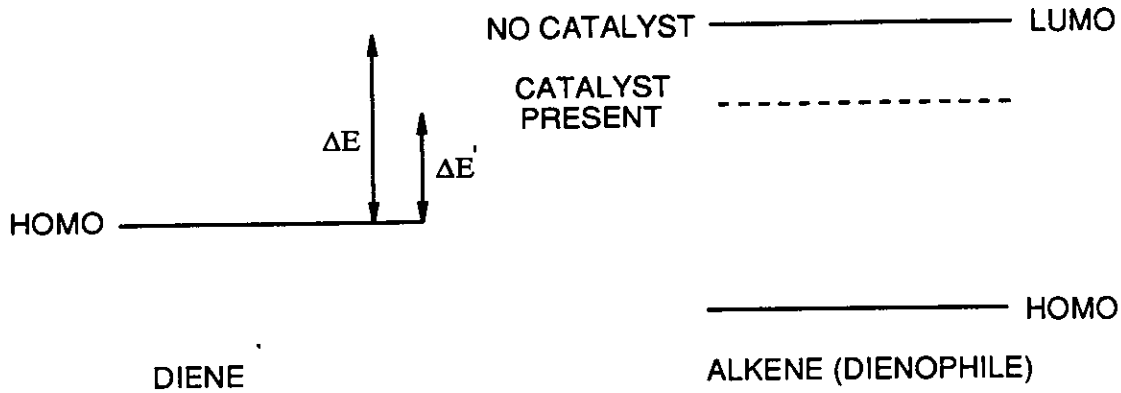


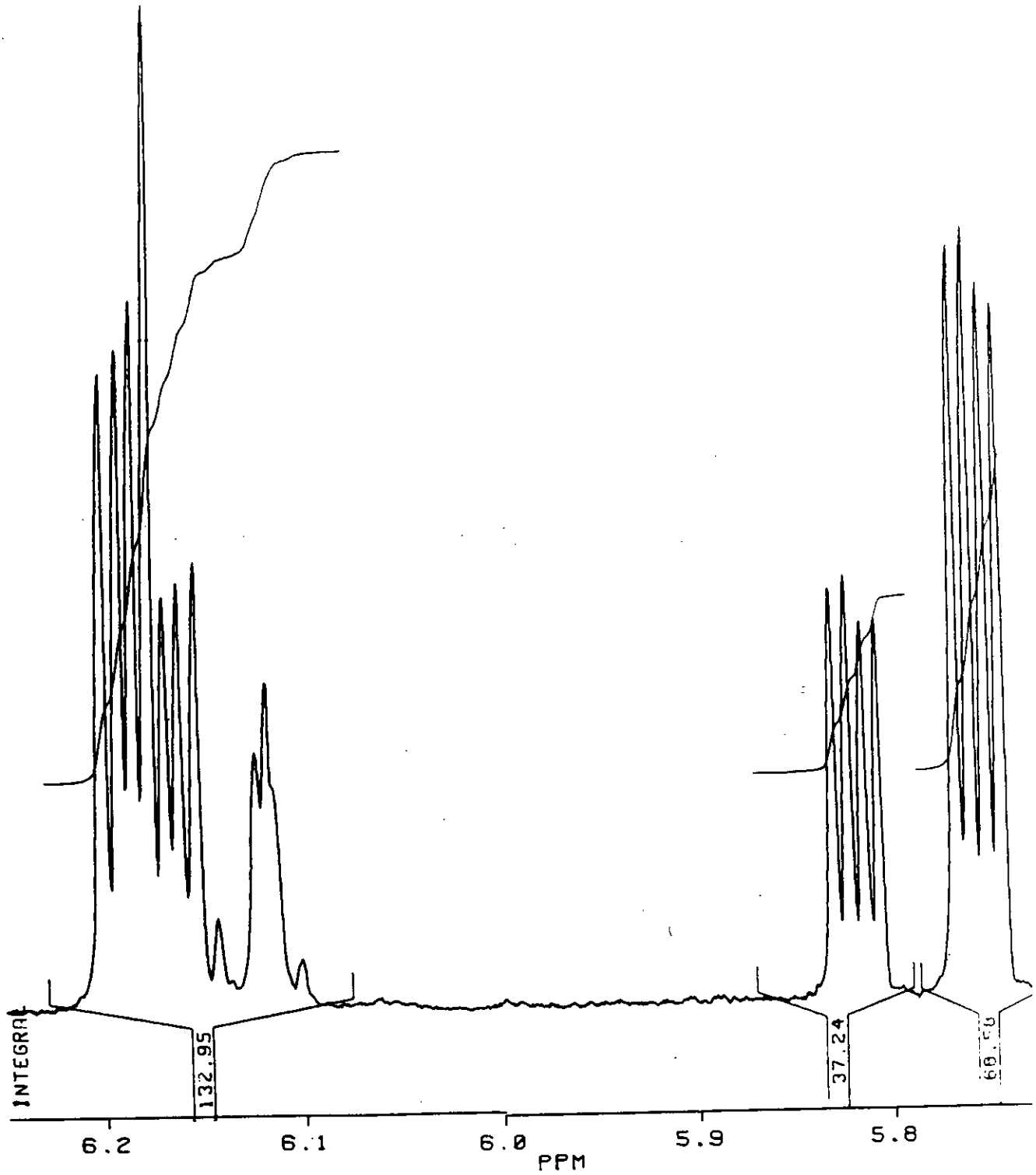
Figure 3

Initially,the catalyst chosen was $TiCl_2(OPr^i)_2$, a mild Lewis acid which does not induce polymerisation of cyclopentadiene, a problem encountered with $TiCl_4$[94]. The ratio of catalyst to substrate chosen was 2:1 as Oppolzer *et al* had commented[21] on the finding that it was advantageous to employ more than one equivalent of catalyst for improved chemical and optical yields; indeed in the case of the $TiCl_2(OPr^i)_2$ catalyst, the author had used three equivalents.

Unfortunately, and only with hindsight, the conditions of the reaction were not repeated identically; rather naively titanium tetrachloride was added to a cooled solution of acrylate before titanium tetraisopropoxide was added, in contrast to adding the acrylate to a pre-prepared solution of $TiCl_2(OPr^i)_2$ (made from $TiCl_4$ and $Ti(OPr^i)_4$ in a 1:1 mixture).The resulting solution was held at -16^0C before freshly cracked cyclopentadiene was added.After monitoring the reaction by thin layer chromatography for ten hours the reaction was quenched and, following literature work-up,chromatography on silica yielded a white solid which was examined by high field ^1H NMR.

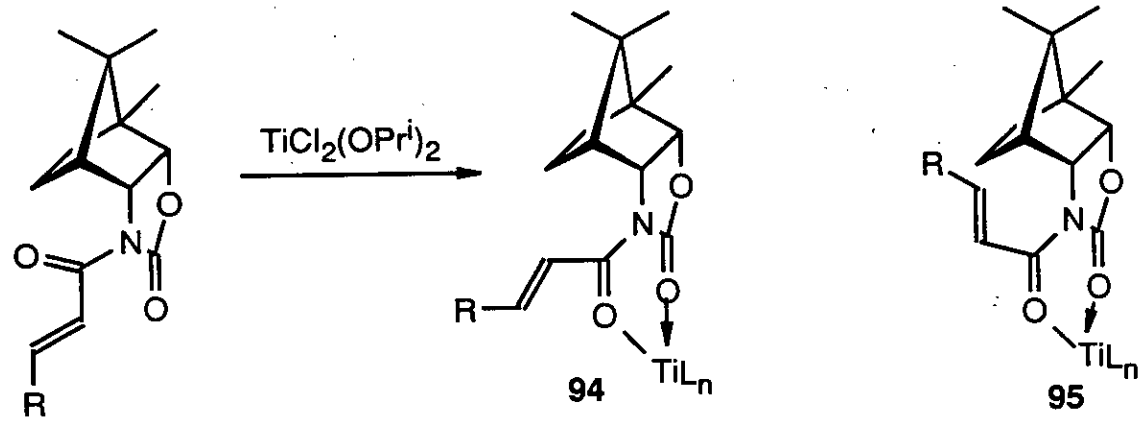
The olefinic region of the 360 MHz ^1H NMR spectrum (shown overleaf) clearly shows that four sets of resonances are present, *i.e.* two isomers had been formed. In addition, the ratio of the major to minor isomer is

Olefinic region of 360 MHz ^1H NMR spectrum of the product of the "$TiCl_2(OPr^i)_2$" catalysed reaction, between the acrylate **87** and cyclopentadiene.



approximately 2:1. This result posed a number of intriguing questions. Firstly, what were the identities of these isomers? Secondly, why was the selectivity so poor? Thirdly, could the selectivity be improved by changing the reaction variables such as temperature, amount of catalyst and type of catalyst? In order to answer the first question, one needs to consider the most likely conformation of the acrylate in its complexed form, and the relative transition state energies of "above" and "below" attack of the alkene.

Firstly, co-ordination of the two carbonyls to the titanium metal centre yields the rigid π-deficient reactive species **94**.The model for this complex is consistent with octahedral co-ordination observed for other titanium (IV) complexes[21,95]. Chelation therefore alters the conformer preference, with (A) rather than (C) (Figure 2 and Scheme 42) now being the more stable.



Scheme 42

Evans *et al*[46] state that the α,β-unsaturated carboximide is assumed to exist exclusively in its s-*cis* conformation as depicted in **94**; the s-*trans* rotamer **95** undergoes steric, non-bonding interactions with the auxiliary, particularly if one changes the functionality (*i.e.* if R is not equal to H). Having controlled both the N-C rotor by chelation and the C=O-C_α rotor

by the auxiliary, π-face discrimination can now come into operation. Thus, if approach of the diene to the C_α-si face is severly restricted by steric interactions, only the C_α-re face is open to reaction (Figure 4).

Hence this would be compelling evidence that the two isomers formed are the *endo* and *exo* isomers, shown below ,as only one *endo* and one *exo* isomer can form from one face of the alkene (Scheme 43).

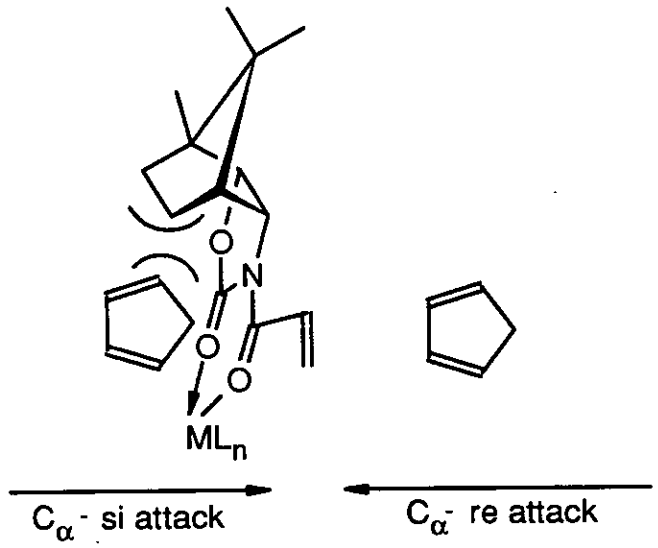
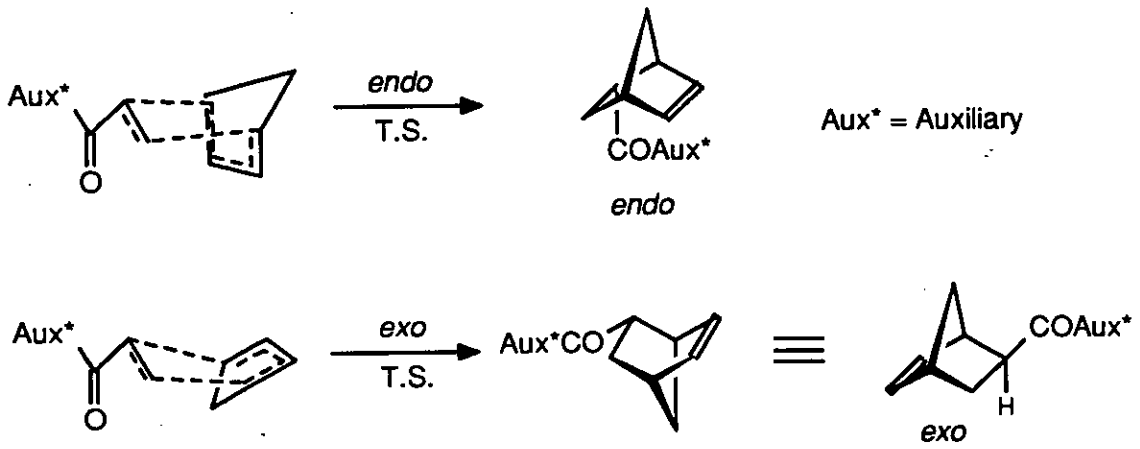


Figure 4



Scheme 43

With this assumption in mind, it was thought that the *endo/exo* selectivity could be improved by lowering the temperature, since *endo*

isomers are kinetically favoured due to secondary orbital overlap interactions[96]. However, upon repeating the reaction albeit at -78^{0}C with the use of four equivalents of catalyst only improved the ratio marginally (Table 3). This was rather puzzling in view of the proposed indentities of the isomers, coupled to the fact that separation of these isomers was not a trivial task, and required the use of TLC grade silica and elution with 40:1 *n*hexane : diethyl ether. These are extreme conditions for two isomers which do not even have an enantiomeric relationship to each other, *i.e.* they are distinctly stereochemically different. The major isomer crystallised in a suitable form and was examined by X-ray crystallography (see Figure 5). The result was very pleasing; not only did it show that this isomer is *endo* in nature but it exhibits the stereochemistry predicted it would have.

Unfortunately, the minor isomer formed in the same reaction did not crystallise in the desired form so readily but eventually crystals were grown in an NMR tube. The X-ray crystal structure provided a surprise as it clearly showed that this was *endo* in nature (Figure 6). This observation is contrary to the expected situation in which the diene is prevented from attacking the C_α-si face due to steric repulsions with the auxiliary. The only explanation for this situation is that the assumption that the acrylate exists only in the s-*cis* conformation is false. Indeed, an examination of "ball and stick" models leads immediately to the conclusion that the auxiliary does not possess sufficient steric interaction with the unsaturated portion of the *N*-acyl function to prevent the s-*trans* conformation occurring to a significant extent. Hence, as shown in Scheme 44, an *endo*-transition state with the s-*trans* conformation of the

Figure 5. X-Ray crystal structure of major cycloadduct

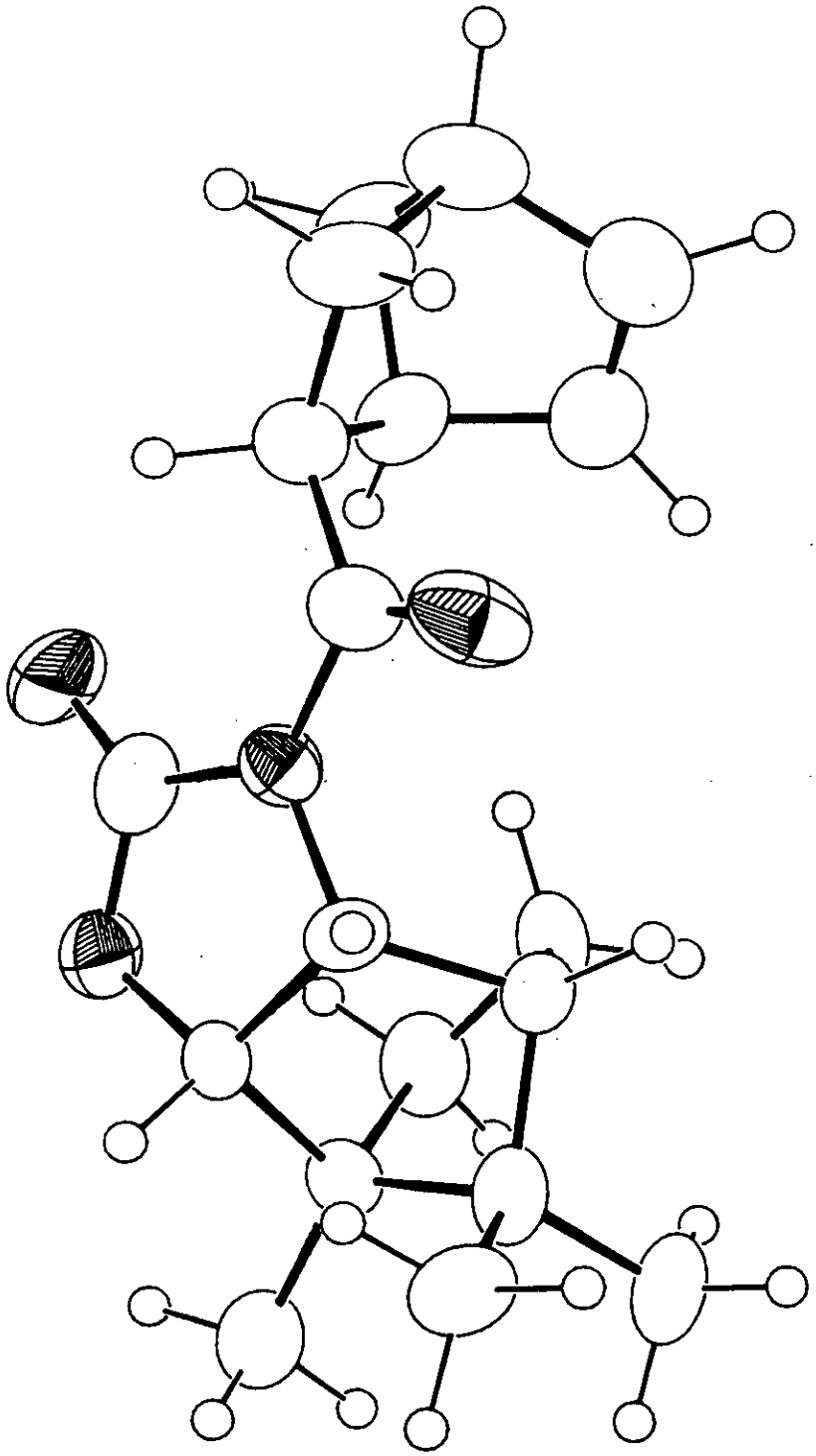
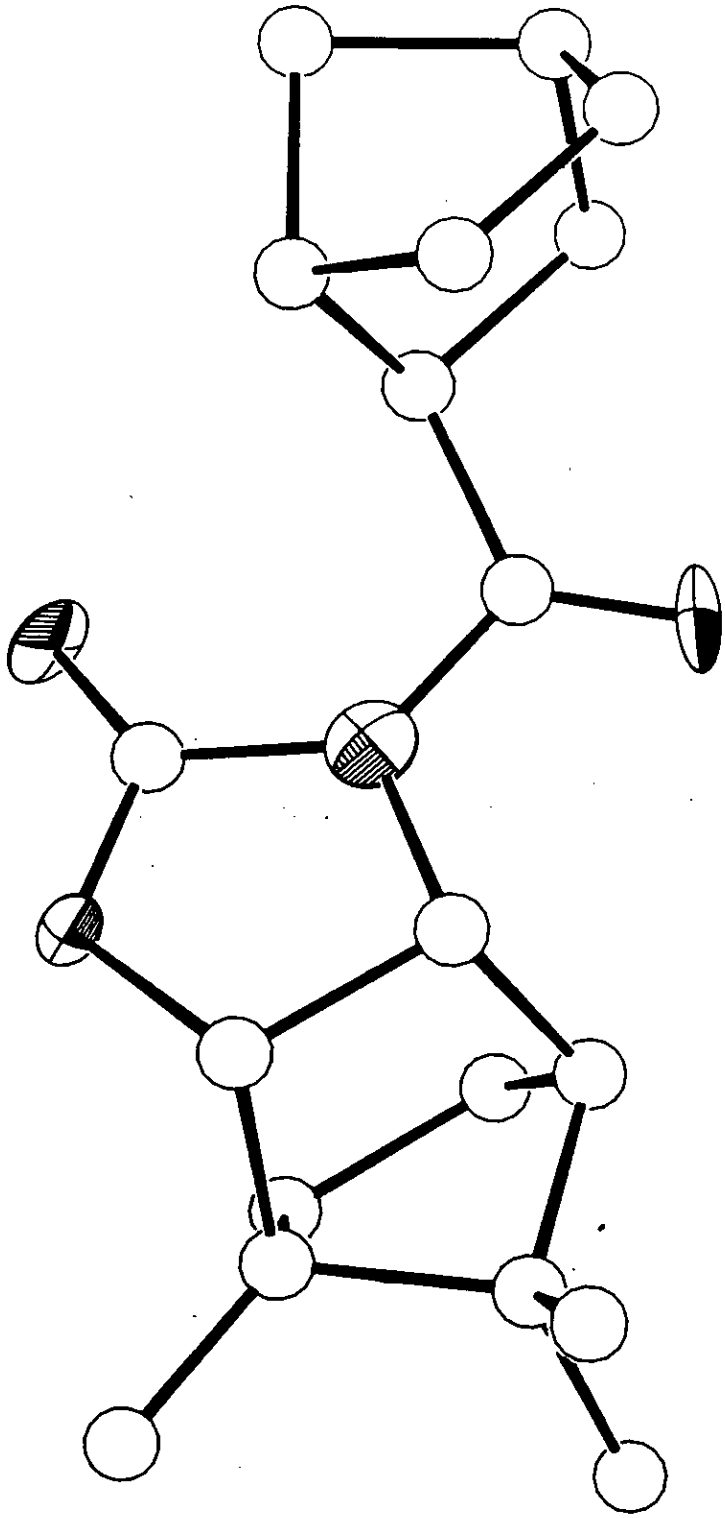
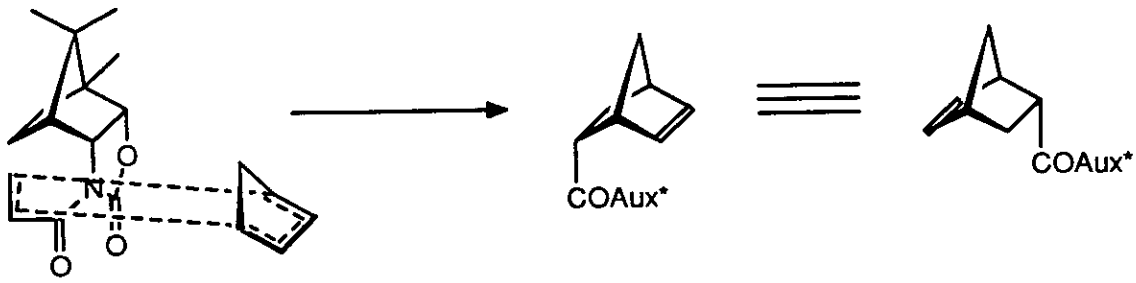


Figure 6. X-Ray crystal structure of minor cycloadduct





endo T.S.

Scheme 44

acrylate, and reaction from the least hindered side of the auxiliary, leads to the other *endo* isomer.

The fact that both isomers are *endo* in nature would explain the ineffective use of lower temperature to promote greater *endo/endo* stereoselectivity and the difficulty in the separation of the isomers. *Endo/endo* selectivity is generally a function of, and most sensitive to, the auxiliary and catalyst used and not the temperature. Re-examination of the ^1H NMR spectrum of the crude reaction mixture from the reaction reaction carried out at -16^{0}C does actually reveal an *exo* isomer present, albeit in a small quantity, from the appearance of an extra broad singlet at *ca.* δ 3.2, due to the cycloadduct bridgehead proton nearest the carbonyl. This was observed in addition to the corresponding broad singlets pertaining to the two major isomers.

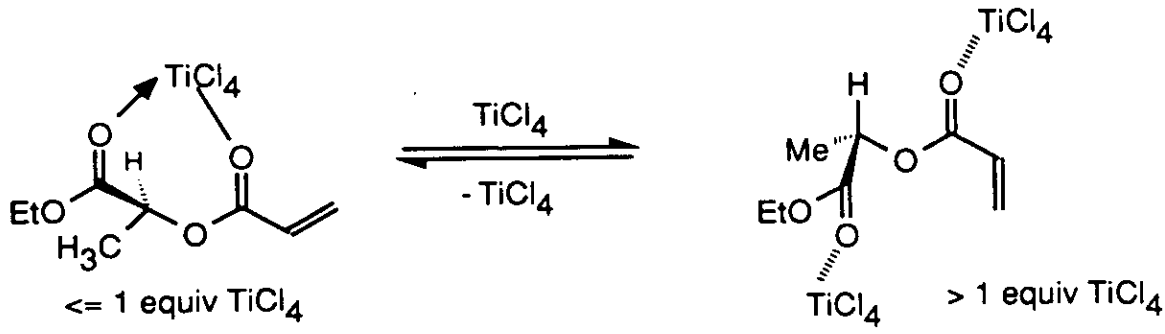
It was therefore of interest to attempt to improve the diastereoselection observed. Initially it was thought best to perform the Diels-Alder reaction again but to use the "proper" order of addition *i.e.* to synthesise the $TiCl_2(OPr^i)_2$ catalyst first from $TiCl_4$ and $Ti(OPr^i)_4$ and add the acrylate afterwards.This order of addition could affect the selectivity, assuming a different catalytic species was present, compared with that of the first set of conditions. Indeed, at -78^{0}C, employment of this catalyst yielded the same two isomers but in a 1:1 mixture, *i.e.* no diastereoselectivity

whatsoever! (Table 3).Poor diastereoselection with the use of $TiCl_2(OPr^i)_2$ catalyst has also been observed by Helmchen *et al*[97].Of additional interest was the use of Evans' valine-derived oxazolidinone acrylate with this catalyst which gave an *endo/endo* ratio of *ca* 1.6 : 1 together with significant amounts of both *exo* isomers (Table 3).

Helmchen *et al*[98] reported very high levels of stereoselectivity with simple lactates,the source of this high induction being the participation of one of the chlorines of the titanium catalyst within the complex which shields one of the faces of the alkene.This effect has also been observed by Helmchen *et al*[99] in the use of (*S*)-malic acid and (*R*)-pantolactone-derived auxiliaries,and Waldmann's (*S*)-proline benzyl ester[100].

Helmchen also pointed out, in contrast to Oppolzer's general findings[21], that use of more than one equivalent of titanium tetrachloride catalyst diminished the selectivity. This is attributed to the possiblity of competing complexes which expose the opposite face of the alkene to attack (Scheme 45).Thus, Chirabornox acrylate was treated with half an equivalent of $TiCl_4$ and cyclopentadiene at -78^{0}C in the hope of excluding competing complexes and thereby increasing the selectivity observed. However under these conditions,a slight preference for the original *minor* isomer was observed (with a corresponding ratio of 0.85:1), *i.e.* a reversal of selectivity occurred. Use of Oppolzer's auxiliary (**13**)-derived acrylate under the same conditions showed complete *endo* selectivity and very good *endo/exo* selectivity (Table 3).

This disappointing result with Chirabornox-acrylate can be explained by applying Helmchen's theory to the Chirabornox system. If the titanium tetrachloride undergoes bidentate chelation, one of the chlorine atoms can in theory shield the C_α-re face (the face normally open to attack).It



Scheme 45

would be expected that the acrylate prefers to exist to a significantly greater extent in the s-*cis* conformer than the s-*trans* conformer, especially since the $TiCl_4$ is a smaller Lewis acid than $TiCl_2(OPr^i)_2$ (due to the fact that OPr^i is larger than Cl) (Figure 7). Thus,both faces of the alkene are significantly shielded; one face by the chlorine of the Lewis acid and the other face by the bornane skeleton. In this case it would appear that the less accessible C_α-si face in the $TiCl_2(OPr^i)_2$ promoted reaction is now slightly more open to attack.

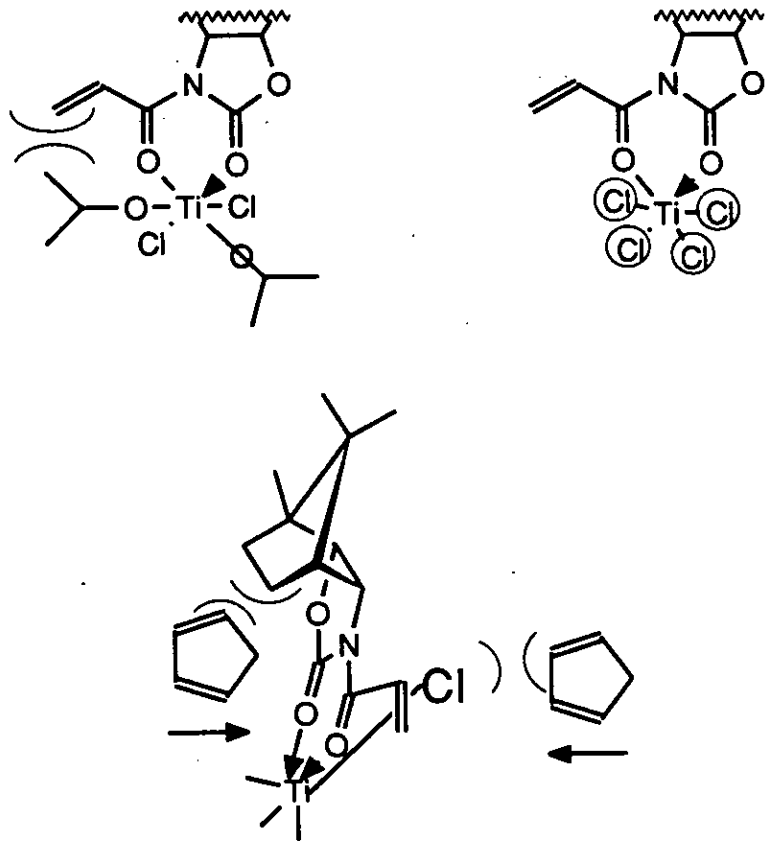


Figure 7

The question of why the selectivity changes from 2:1 to 1:1 depending on the order of addition of the catalysts has not been addressed.It would appear that at least two different types of Lewis acid complex are operating, to give the two different selectivities observed. A useful study therefore, would be to study as similar a system as possible in which the stoichiometry and temperature are altered and the resulting complex probed spectroscopically to observe any changes taking place. Waldmann has already shown in his (*S*)-proline benzyl ester-derived system[100] that both $TiCl_4$ and $SnCl_4$ undergo bidentate chelation, but $ZnCl_2$,BF_3 and $EtAlCl_2$ prefer monodentate chelation, which explains the reversal of selectivity observed in his researches.Hence,it would appear that similarities exist between the type of chelation enjoyed by $TiCl_4$ and $SnCl_4$.Thus,if one could study the complexes of $SnCl_4$,it might be possible to apply these conclusions to titanium systems.Such a study has been conducted by Castellino[101] in which Evans' (*S*)-valine derived crotonyl oxazolidinone was treated with various amounts of $SnCl_4$ at various temperatures and the resulting complexes studied by ^{119}Sn NMR.^{119}Sn is a convenient nucleus to study as it has spin 1/2 and possesses an absolute sensitivity of more than twice that of a ^{13}C nucleus,which is studied routinely.

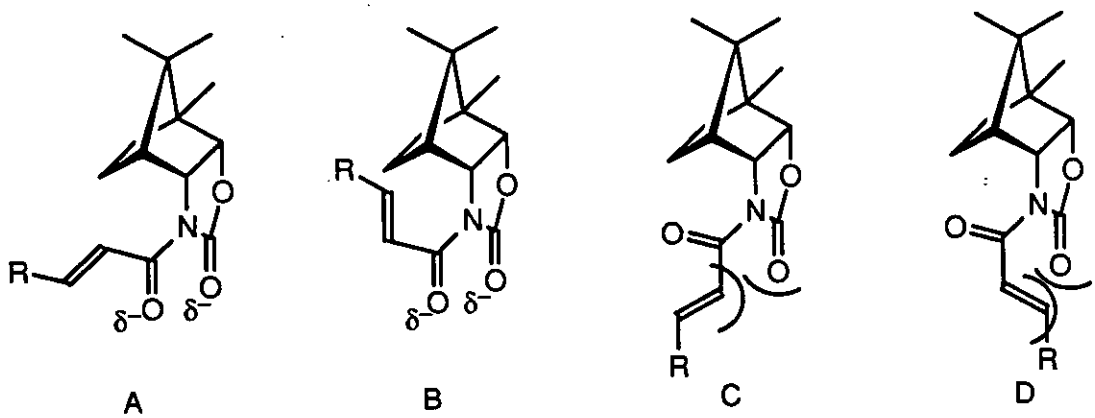
In his study,Castellino did not find any evidence for any other complexes other than the bidentate ("1:1") complex, for which the broadness of the signal due to the ^{119}Sn nuclei changed by varying the temperature. Thus, no "2:1" complexes are observed with $SnCl_4$. Presumably these cannot form due to the steric influence of one chiral appendage upon the other. One cannot say that is the case for $TiCl_4$ and other titanium species since Helmchen *et al* noted dramatic decreases in selectivity when using more

than one equivalent of $TiCl_4$. Thus it would seem that titanium does not enjoy the simplistic co-ordination that tin appears to exhibit, but undergoes competing complexation to diminish selectivity. One possibility is that the initial complex of acrylate **87** with $TiCl_4$ then undergoes reaction with $Ti(OPr^i)_4$ to produce some other complex, possibly a dimer, which is stereochemically different. For example, a complex with a titanium dimer nucleus has been proposed as the intermediate in the Sharpless epoxidation reaction of allylic alcohols[20] (see section **1.4.6** of the introduction). The fact that $SnCl_4$ does not form a 2:1 complex with Evans' *N*-acyl oxazolidinone does not rule out the possibility of titanium being able to.

Avenoza *et al*[102] have also conducted $TiCl_4$ mediated Diels-Alder reactions of *N*-acryloyl-*N*-methyl-L-alanine methyl ester with cyclopentadiene. They observed that the ratio of isomers obtained changed with varying reaction times and with varying ratio of catalyst to substrate used. They attribute this variation to the reversibity of the reaction. Such a supposition is certainly questionable, as the retro-Diels-Alder reaction normally requires extreme conditions to bring about cleavage of the thermodynamically stable adducts, *e.g.* high temperatures to overcome the large activation enthalpy and therefore acid-catalysed retro-Diels-Alder reactions are rare.Recently, Hondrogiannis *et al*[103] reported the reversibility of the Diels-Alder reaction between methyl acrylate and cyclopentadiene with activated alumina at 50^0C. However, the reversibility of the Diels-Alder reaction between an oxazolidinone-derived dienophile and diene has not been reported, and so a time-dependent selectivity does not seem likely in the case of Chirabornox acrylate.

The reaction of the acrylate with cyclopentadiene in the absence of Lewis acid was of interest,as it would indicate the dependence of the system on the use of a metal centre to control the various degrees of freedom. The reaction was conducted at 0^0C to slow down redimerisation of the cyclopentadiene and to help promote any observable selectivity. Indeed, the resultant ratio was 1.2:1 in favour of the major isomer of the original $TiCl_4$ and $Ti(OPr^i)_4$ reaction. Another notable feature of the reaction was the almost complete absence of *exo* adducts.

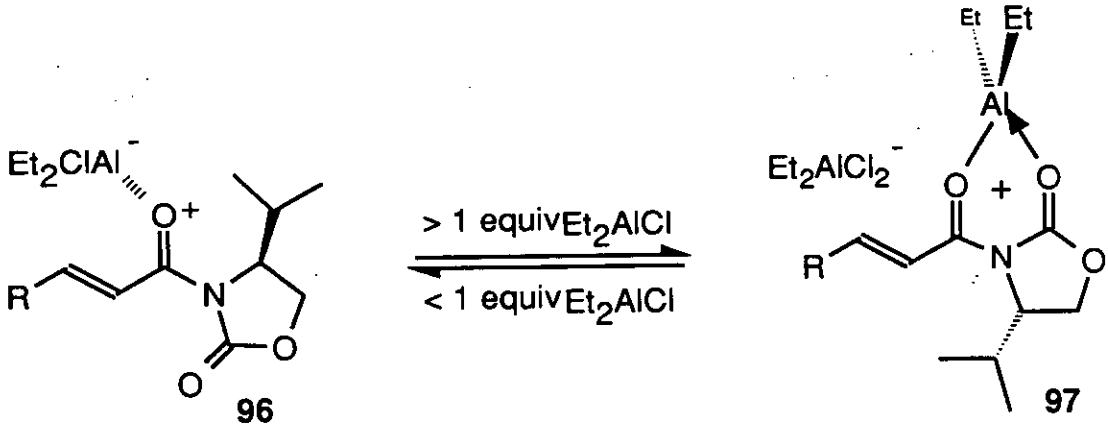
The foregoing demonstration of some *endo* diastereoselection, albeit only *ca* 7%, points to the greater stability of conformer (D) over conformer (C) (below), assuming that the other conformers are too unstable due to dipole/dipole interactions. The stability of certain conformations in *N*-enoyl systems in the absence of Lewis acids has also been observed by Oppolzer *et al*[104]. Interestingly though, one would expect (C) to be more stable than (D) for reasons already stated.This apparent discrepancy is not understood on the basis of these stereoelectronic arguments.



(iii) The use of Et_2AlCl in the Diels-Alder reaction of the acrylate with cyclopentadiene.

Evans *et al* reported[46] the study of various Lewis acids in the Diels-Alder reaction and noted that Et_2AlCl is the most effective in this respect.Also pointed out was the fact that with the use of more than one equivalent of catalyst the selectivity of the reaction improves markedly, which is explained by the proposition that the complex changes from a monodentate system **96** to a rigid, ionic, highly dienophilic bidentate complex **97** (Scheme 46).The reason for the formation of **97** is the possibility that the catalyst provides itself with a counterion when there is surplus catalyst present.

Accordingly, Chirabornox acrylate was treated with 1.4 equivalents of diethylaluminium chloride at -78^{0}C, followed by cyclopentadiene.



Scheme 46

Unfortunately, polymerisation was observed to occur using this Lewis acid. The polymerisation is presumed to stem from the fact that the acrylate is acting as a Michael acceptor and the ethyl group of the catalyst undergoes conjugate addition, leading to chain polymerisation.

Loss of the double bond character could be seen on repeating the reaction, whereby the initial bright yellow solution began to fade with time prior to addition of the diene. In addition, the ^1H NMR spectrum of the crude product clearly showed the absence of any olefinic resonances belonging either to the starting material or expected products, thus establishing that the loss of conjugation is complete before addition of the diene.This mechanism is reasonable on the grounds that Et_2AlCl is known to undergo 1,4 Michael additions to α,β unsaturated carboximides in synthetically useful situations[105,106] (the reader is directed to the relevant section in chapter 2).

Martinelli's paper[70] stated that the order of addition of Et_2AlCl and diene can be critical in some cases due to the nature of the dienophile, and mentioned that Et_2AlCl formed an adduct with electron deficient alkenes.As a result,the cyclopentadiene was added to Chirabornox acrylate first, before addition of the catalyst.The initially formed yellow complex instantly faded and,upon work-up, yielded a mixture of the same *endo* isomers in a corresponding ratio of 4:1. Another interesting feature was the virtual absence of any *exo* isomers.The increase in *endo/endo* selectivity is presumably accounted for by the highly dienophilic nature of the aluminium complex which magnifies the difference in the energies of the diastereomeric *endo* transition states leading to the two products. This exaggerated effect exerted by the catalyst also accounts for the fact that essentially no *exo* isomers are observed (Table 3); here the increased electron deficient nature of the aluminium catalyst increases the coefficient of the carbonyl carbon's LUMO, thereby increasing the secondary overlap, and making the *endo* isomers even more kinetically favoured in relation to the *exo* isomers (Figure 8)[107].

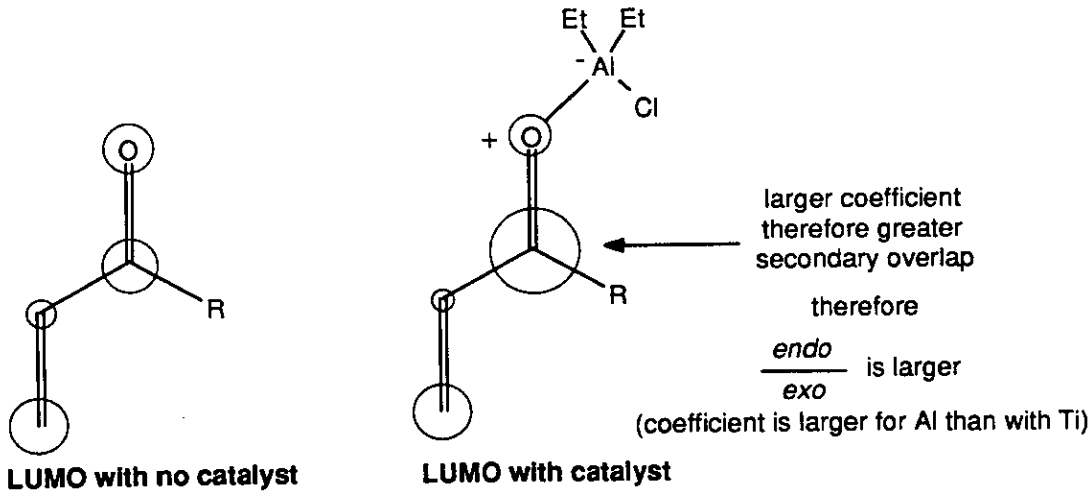


Figure 8. Relative orbital sizes of the LUMO of the dienophile bound and unbound to Lewis acid.

Table 3. Diels-Alder reactions of the acrlyate (87) with cyclopentadiene.

Temp /^{0}C	Catalyst (order of addition) (equiv)	*Endo/endo* ratio	*Endo/exo* ratio	d.e. /%
-16	1 acrylate 2. A , 3. B (2)	1.84 : 1	15 : 1	19 (30*)
-78	1. acrylate 2. A , 3. B (2)	2.06 : 1	no exo observed	35*
O	No catalyst	1.16 : 1	24 : 1	3 (7*)
-78	1. A , 2. B (4) 3. acrylate	1 : 1	57 : 1	O
-78	1. A (O.5) 2. acrylate	O.85 : 1	no exo observed	8*
-78 Evans' auxiliary **9**	1. A , 2. B (4) 3. acrylate	1.63 : 1	unmeasur--able from spectrum	24*
-78 Oppolzer's auxiliary **13**	1. A (O.5) 2. acrylate	*Endo* selective	16 : 1	88 (100*)
-78	1. acrylate 2. cyclopentadiene 3. C (1.3)	3.87 : 1	26 : 1	53 (59*)
-78 Evans' auxiliary **9**	1. acrylate 2. cyclopentadiene 3. C (1.5)	8.6 : 1	41 : 1	75 (79*)

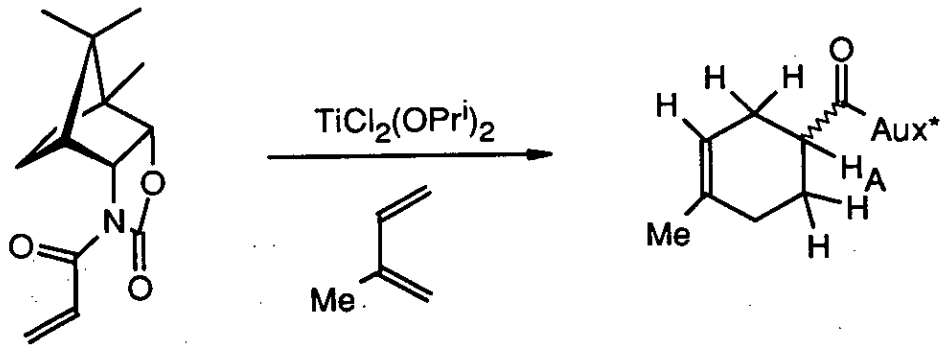
KEY :A = $TiCl_4$; B = $Ti(OPr^i)_4$;C = Et_2AlCl * *Endo* diastereomeric excess only

Chapter 2

Diels-Alder reactions of the acrylate (87) with isoprene and the crotonate (101) and cinnamate (102) with cyclopentadiene.

(i) Lewis acid-mediated Diels-Alder reactions of the acrylate (87) with isoprene.

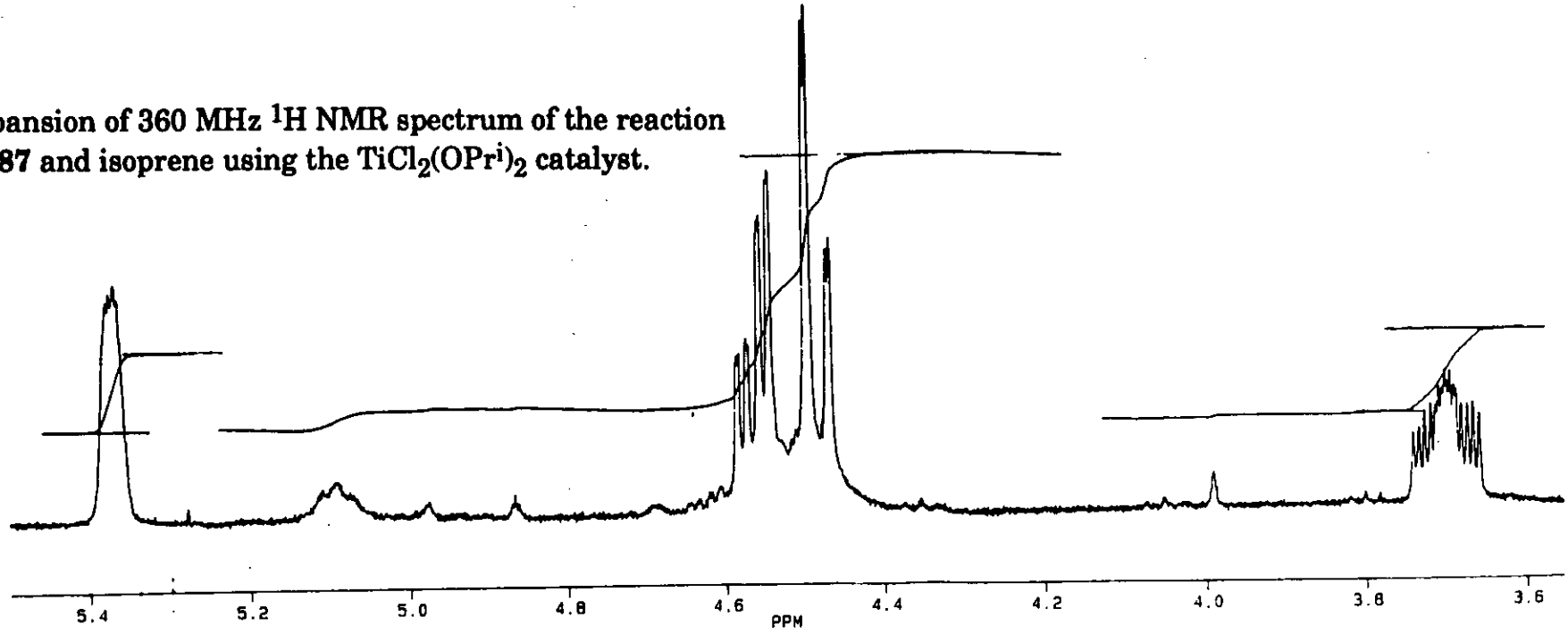
To further extend the scope of the acrylate reactions it was considered desirable to use a second diene, namely isoprene, which had been employed by Evans[46] and Koga *et al*[108] in Lewis acid-mediated Diels-Alder reactions.Thus,the acrylate was added to preformed $TiCl_2(OPr^i)_2$ catalyst at -78^{0}C and isoprene was then added (Scheme 47). Analysis of

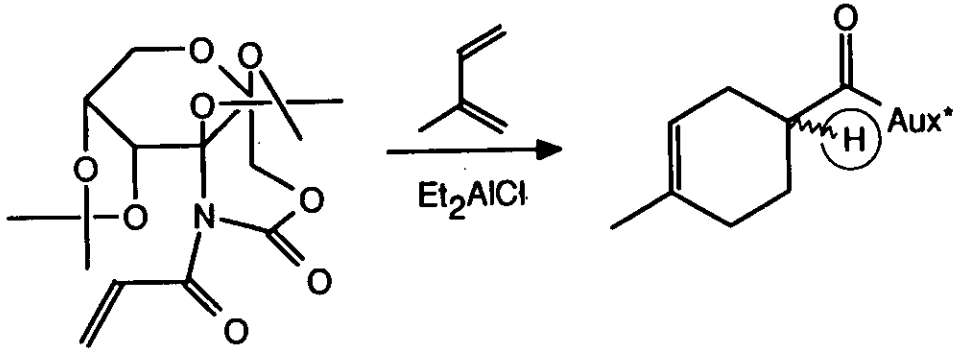


Scheme 47

the crude reaction mixture by high field ^{1}H NMR spectroscopy looked very promising in that the expanded region containing the alkenic resonance and the chiral proton resonance appeared to show that only one isomer was present (Figure 9). Indeed, one could be persuaded that the chiral centre proton, H_A, consisted of sixteen lines,the number expected if coupling to the four adjacent protons yielded four separate coupling constants, *i.e.* a doublet of doublets of doublets of doublets, as all four protons are in different environments. This is not an unreasonable hypothesis since the same reaction conducted with a fructose-derived

Figure 9. Expansion of 360 MHz ^1H NMR spectrum of the reaction between **87** and isoprene using the $TiCl_2(OPr^i)_2$ catalyst.





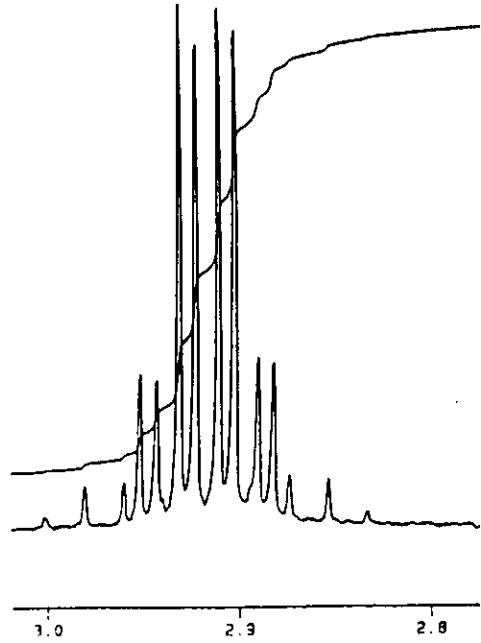
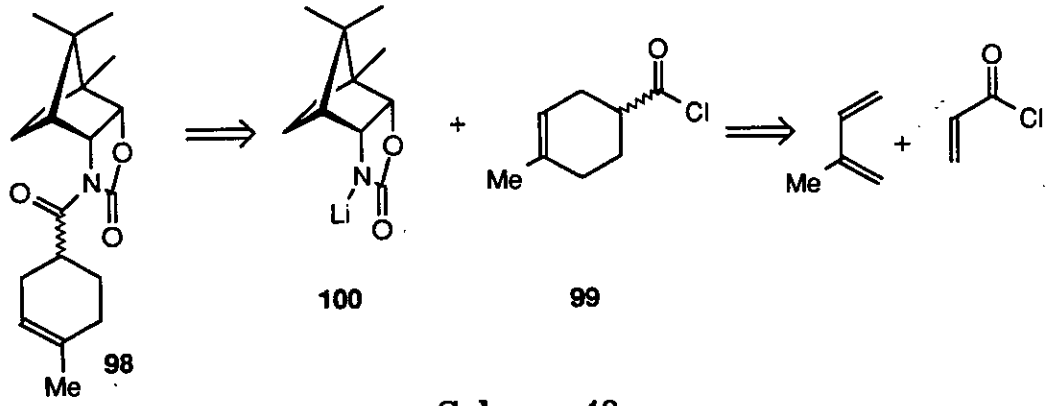


Figure 10. Reaction of an oxazin-2-one based acrylate (derived from fructose), with isoprene in the presence of Et_2AlCl and the corresponding spectrum of the product.

auxiliary (shown in Figure 10), which had been developed in the same laboratory and contained a 1,3-oxazin-2-one ring, also yielded an adduct with isoprene which displays sixteen lines in the corresponding spectrum (Figure 10). The $^{13}C\{^1H\}$ and ^{13}C DEPT spectra of the mixture were rather inconlusive, due to the poor quality of the sample which was contaminated with a very fine, unfilterable titanium salt. It was therefore necessary to be able to show that one isomer was present,and if not,to determine the ratio of the isomers present.

Two approaches were considered; the first was to synthesise an authentic racemic mixture of the two possible epimers and to compare the resultant spectra. The second was to employ a chiral shift reagent in an attempt to separate the isomer peaks and thus obtain a ratio for the diastereomeric adducts.

In order to synthesise the desired racemic mixture of the cycloadducts **98** it was decided to prepare **99**, which could be made from isoprene and acryloyl chloride, and couple it to the lithiated oxazolidinone **100** (Scheme 48).



Scheme 48

Due to the unreactive nature of isoprene compared with that of cyclopentadiene, in the absence of a Lewis acid, the initial cycloaddition reaction was effected in a sealed tube. Examination of the high field ^1H

NMR spectrum of the crude reaction mixture of the acid chloride **99** showed that only one regioisomer was apparently present. This racemic acid chloride was then coupled to the auxiliary at -78^{0}C (*vide supra*) and studied by both 360 and 600 MHz ^{1}H NMR spectroscopy. Analysis of the same region of the spectrum as in the original isoprene and Chirabornox acrylate reaction revealed the appearance of an extra set of resonances next to the original chiral centre peaks (Figure 11). At first it was thought that these two sets of peaks belonged to the two epimers, but this

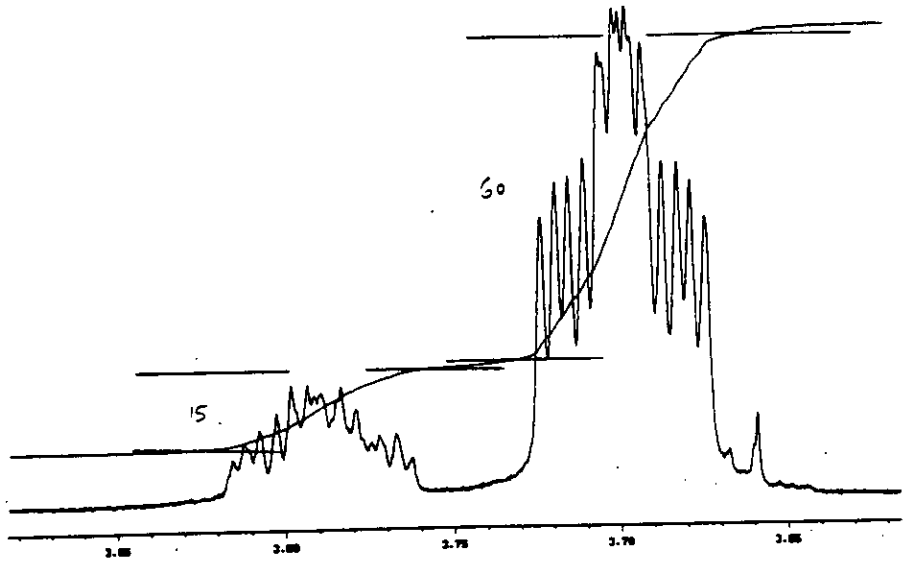
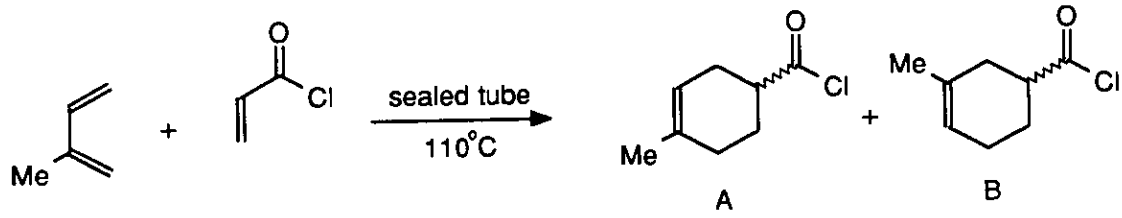


Figure 11. 600 MHz ^{1}H NMR spectrum - chiral centre region.

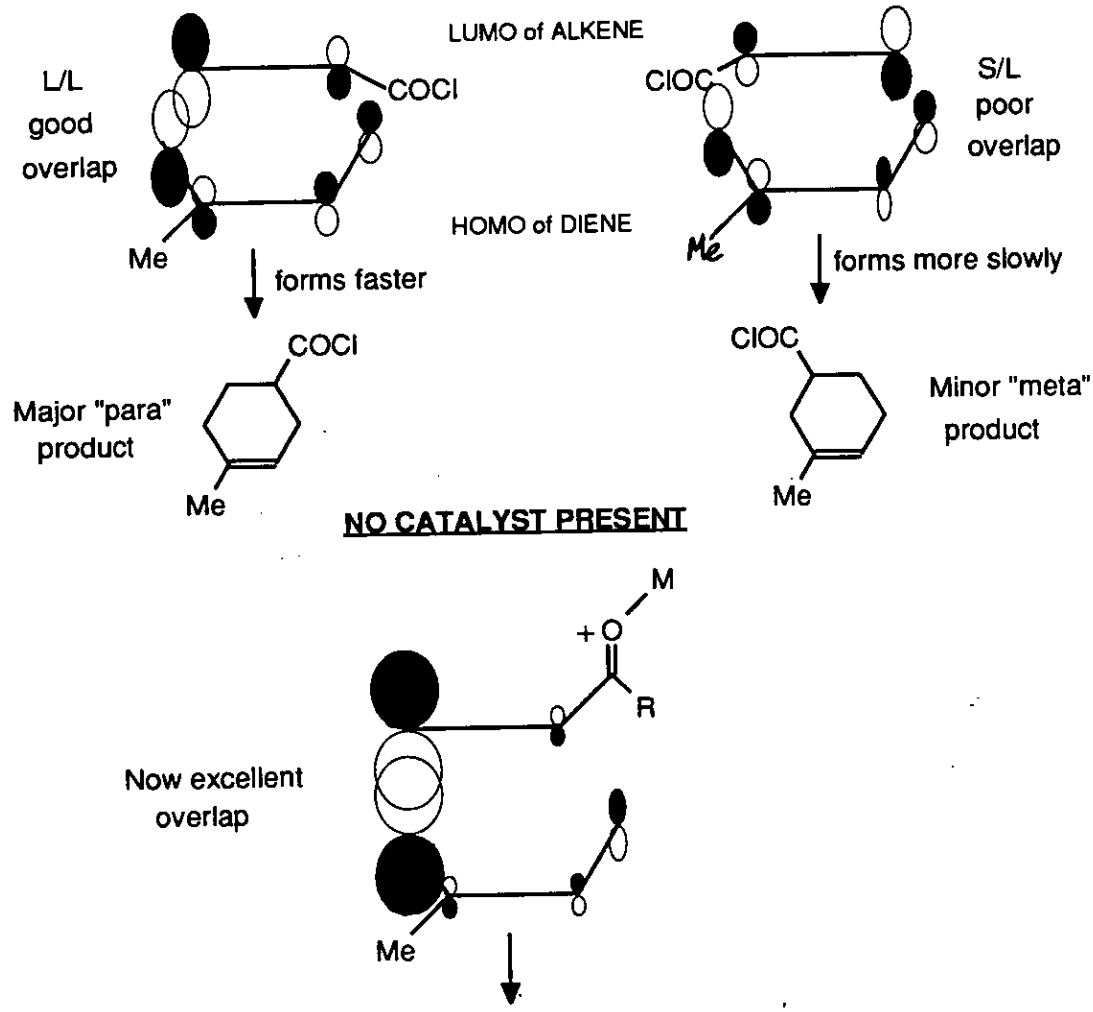
seemed unlikely due to the fact that they were present in the ratio of *ca.* 4 : 1, and the unequal distribution of products could not be sensibly attributed to some chiral recognition exerted by the auxiliary, for such a facile reaction. Therefore this 4 : 1 ratio was thought to stem from the formation of the two possible regioisomers in the original thermal Diels-Alder reaction (A and B) respectively (Scheme 49).

It can be argued that regioisomer A is formed in preference to B due to the "large/large" and "small/small" frontier orbital sizes of the respective HOMO and LUMO of the diene and alkene mix to form A faster than B



Scheme 49

(Scheme 50). The effect of a Lewis acid is to exaggerate the differences in the sizes of the orbital coefficients[107], which explains why the minor regioisomer is not observed in the reaction of Chirabornox acrylate **87** and isoprene in the presence of a titanium catalyst.



Scheme 50

The mixture of regioisomers did demonstrate where the minor regioisomer resonates in the ^1H NMR spectrum, and served some useful purpose in showing that it does not form in the titanium catalysed reaction.

The problem of determining whether a single epimer had been formed in the original catalysed reaction still remained, and consequently a europium chiral shift reagent was used in a series of ^1H NMR experiments to decide the matter.

The basic spectrum (bottom spectrum, Figure 13a) shows four sets of resonances; the first at *ca.* δ 5.4 is the olefinic resonance, the doublet of doublets of doublets at *ca.* δ 4.55 is the proton geminal to the nitrogen of the oxazolidinone ring, the doublet of doublets at δ 4.5 is that geminal to the oxygen. Finally, the resonance at δ 3.7, as seen previously, is the proton at the chiral centre; the most important feature of this resonance is the basic triplet shape it possessess. Addition of 4 mol% of europium (III) chiral shift reagent caused the resonances of the chiral centre proton to shift *ca.* 0.1 ppm downfield; in addition the fine structure observed in the coupling was lost, and only the broad triplet shape remained. The structure and shift of the resonance of the proton geminal to the oxygen were virtually unaffected. In contrast, the resonances of the proton geminal to the nitrogen shifted and broadened significantly. By comparison, the olefinic resonance at δ 5.4 showed almost no change. The relative changes in shift are consistent with the McConnell and Robertson equation[109] which states that the change in shift is proportional to the cube of the reciprocal of the distance from the europium to the proton under study.Therefore, a small increase in distance has a large effect upon the observed change in shift. Since the

olefinic proton is furthest away, r is larger and hence $\Delta\delta$ is much smaller (Figure 12)

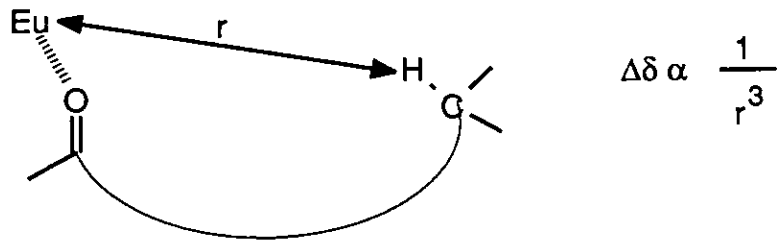
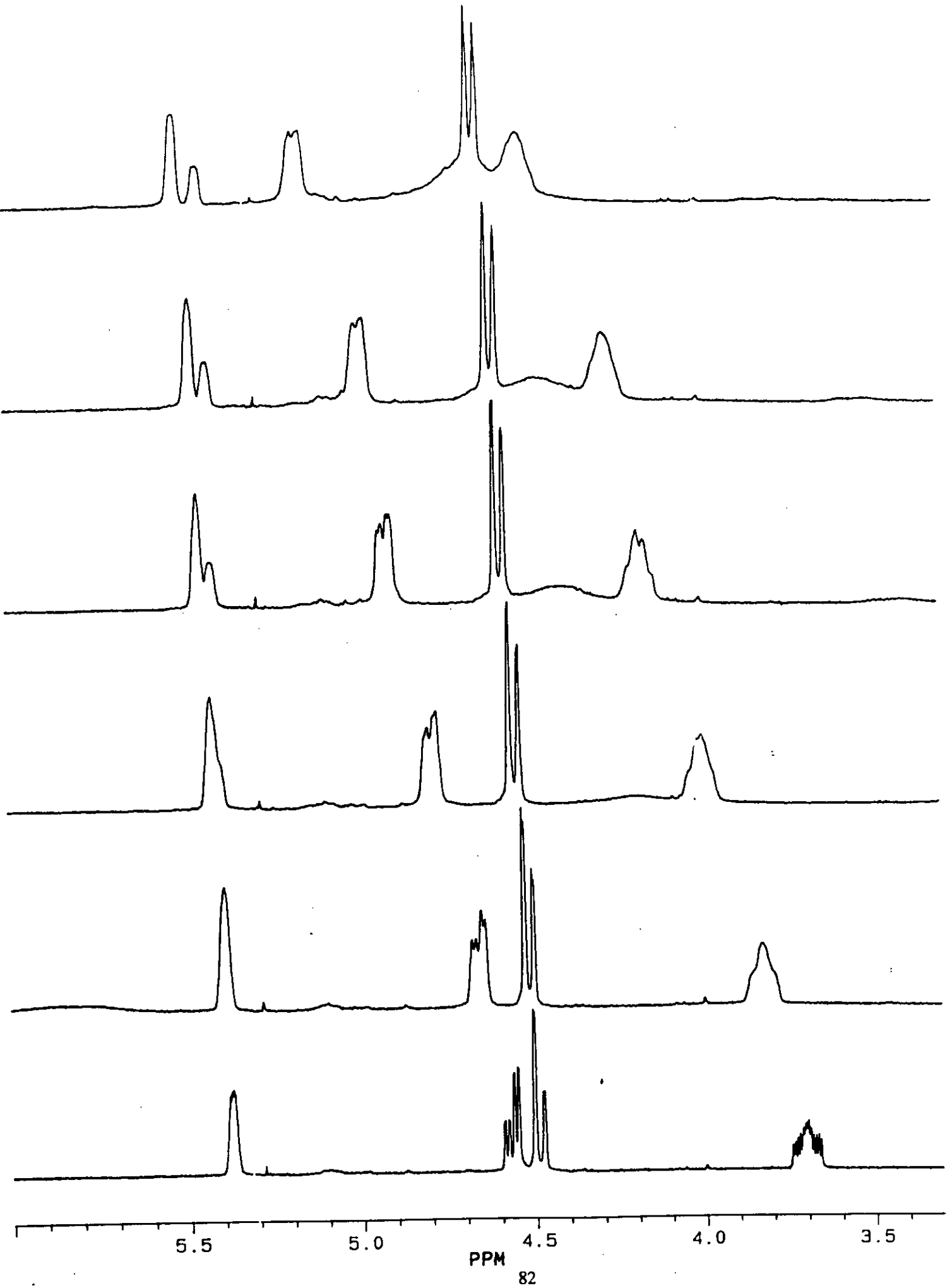


Figure 12

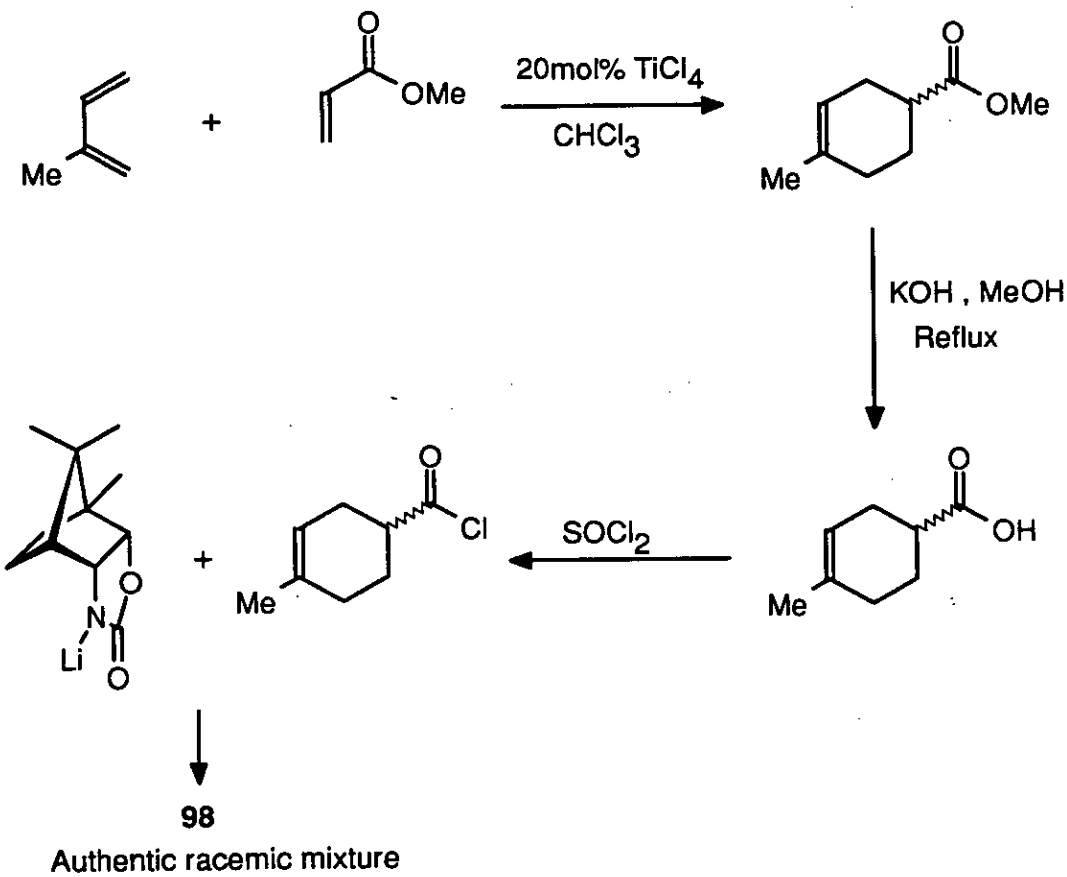
Addition of a further 4 mol% of shift reagent caused further broadening and shifting of the chiral centre proton resonances and also those of the proton geminal to nitrogen, but the most interesting feature was the shoulder which began to appear on the olefinic resonance. Further additions of europium reagent lead to a clear split of this shouldered peak into two distinct resonances, assumed to be the two isomers of interest, which were in the ratio of *ca*.2 : 1.

To be confident that the two separated signals were authentic epimers, it was deemed necessary to synthesise a truly authentic mixture of the diastereomeric epimers and perform the same chiral shift experiment.To achieve this, the same strategy as before was adopted, but on this occasion, it was necessary to form just one regioisomer of the isoprene/acryloyl chloride adduct before continuing the synthesis. Literature investigations revealed[110] that the Diels-Alder reaction between isoprene and methyl acrylate in the presence of titanium tetrachloride at room temperature furnished an excellent yield of the desired cycloadduct with high concomitant regioselectivity. This finding was of great interest as the ester formed could be hydrolysed to the acid which could then be purified by recrystallisation to remove the small

Figure 13a Europium chiral shift experiments conducted upon the product of **87** and isoprene in the presence of $TiCl_2(OPr^i)_2$ catalyst.



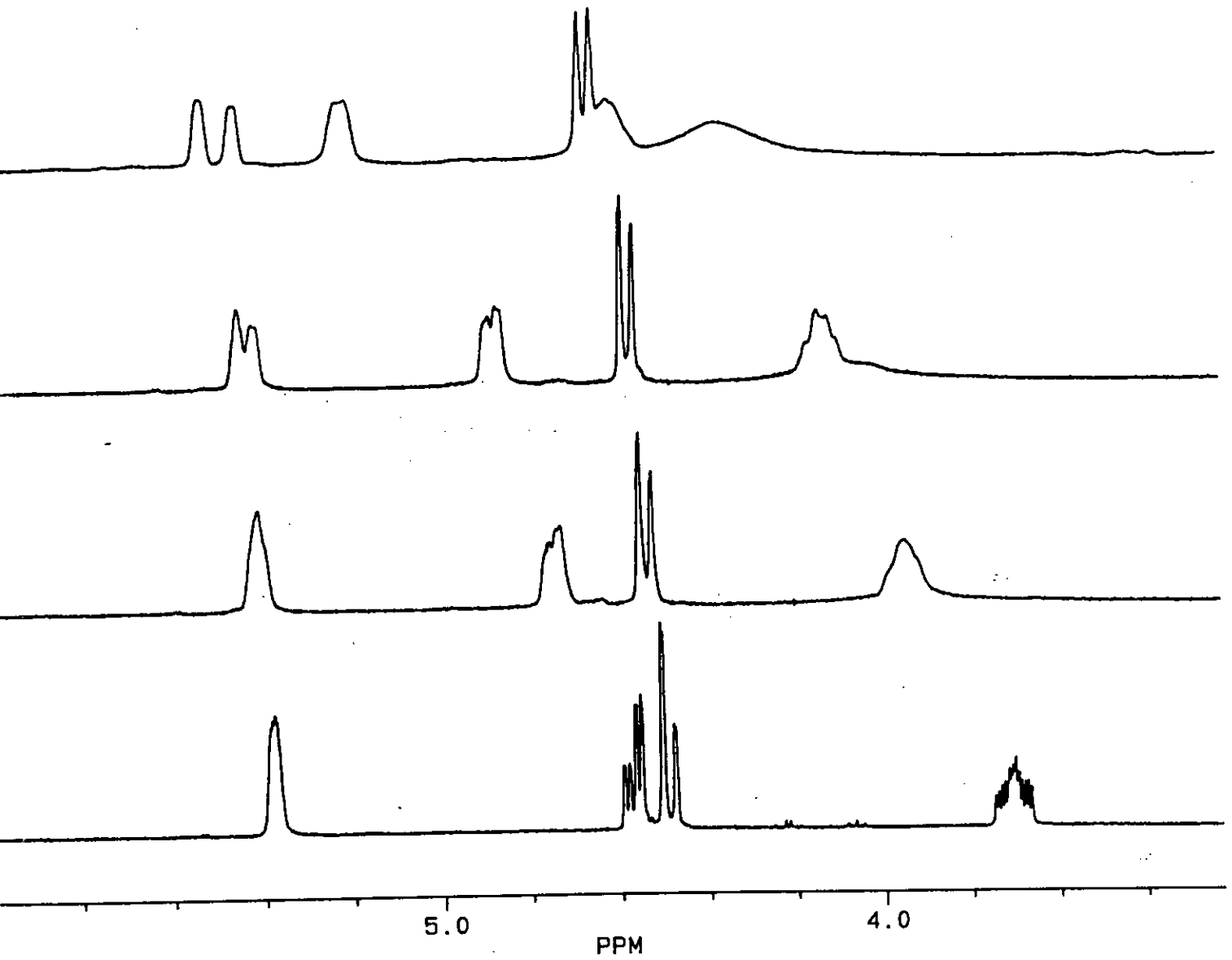
amount of the minor "meta" regioisomer. Thus the methyl ester was synthesised as depicted in Scheme 51, and subsequently hydrolysed in alkali. Three recrystallisations of the resulting acid from hexane yielded a colourless solid which, on examination by ^{13}C NMR spectroscopy showed that the adduct was regiochemically pure. Subsequent treatment of the racemic acid with thionyl chloride, followed by coupling with the lithiated oxazolidinone **100** yielded the authentic racemic cycloadduct mixture **98**



98
Authentic racemic mixture

Scheme 51

Figure 13b Europium chiral shift experiments conducted upon the racemate



The mixture was subjected to the same chiral shift reagent study as before and the same two peaks appeared, albeit in a ratio of 1.1 :1, after addition of the necessary amounts of europium shift reagent (Figure 13b). The fact that the ratio was not exactly 1 :1 is attributed to a limited amount of true chiral recognition whereby the chiral lithiated oxazolidinone **100** reacted slightly faster with one isomer than the other. Employment of 1.45 equivalents of the Et_2AlCl catalyst to the Chirabornox acrylate/isoprene reaction caused an instantaneous reaction to occur. In this instance the same europium chiral shift experiment showed that the two isomers were present with an improved ratio of 5.4 : 1. A summary of these Diels-Alder results is presented in Table 4.

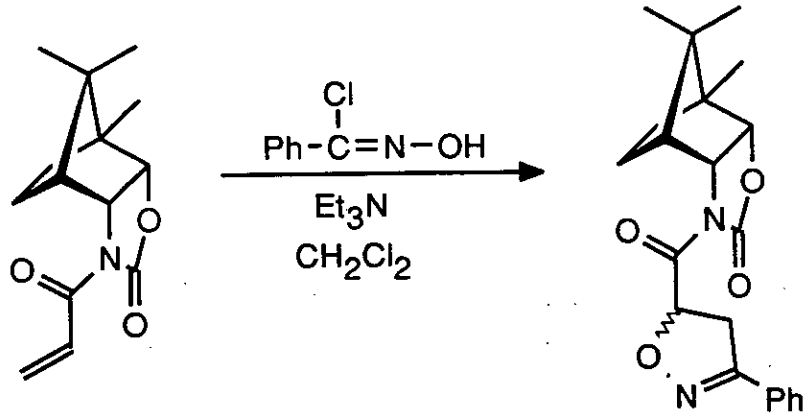
Table 4. Diels-Alder reactions of the acrylate with isoprene

Temp /^{0}C	Catalyst (order of addition) (equiv)	*Endo/endo* ratio	*Endo/exo* ratio	d.e. /%
-78	1: A , 2. B (4) 3. acrylate 4. isoprene	2 : 1	-	33
-78	1. acrylate 2. isoprene 3. C (1.45)	5.4 : 1	-	69

KEY :A = $TiCl_4$; B = $Ti(OPr^i)_4$;C = Et_2AlCl

Reaction of acrylate (87) with benzonitrile oxide

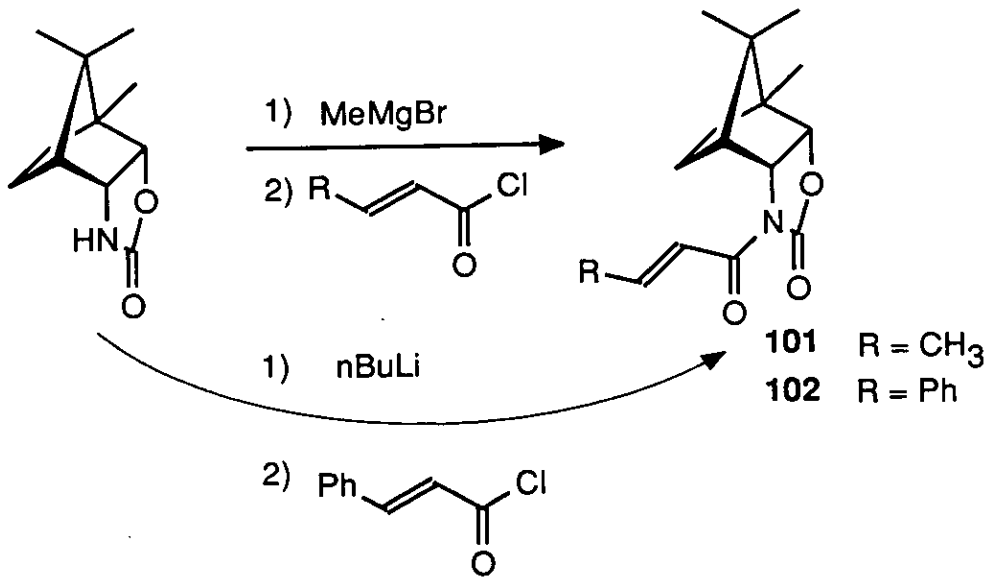
A solution of the acrylate in methylene chloride was also treated with benzonitrile oxide, generated from the chlorooxime with slow addition of triethylamine (Scheme 52).No Lewis acid was used in this reaction as the 1,3 dipole is Lewis basic.Not surprisingly,on the basis of the result of cyclopentadiene with the acrylate in the absence of Lewis acid,the ratio of isomers was found to be only 3 : 2,determined by high field ^1H NMR.The result compared unfavourably with a value of 4 : 1 obtained by Curran *et al*[23] with Oppolzer's sultam using 2,2-dimethylpropane nitrile oxide in the same solvent,and 95 : 5 for benzonitrile oxide in hexane; this latter solvent was not used in the case of the acrylate due to its low solubility.



Scheme 52

(i) Preparation of crotonyl (101) and cinnamoyl (102) derivatives of Chirabornox

On the basis of experience acquired in attempts to functionalise the auxiliary with acryloyl chloride, the crotonate (**101**, R = CH_3 , Scheme 53) and the cinnamate (**102**, R = Ph) were obtained in 85% and 81% yield, respectively by using the Grignard method described earlier. The cinnamate was also synthesised by using the butyllithium method, but the yield obtained was only a moderate 60%. This drop in yield is



Scheme 53

consistent with that observed in the preparation of the acrylate **87** when employing this base.

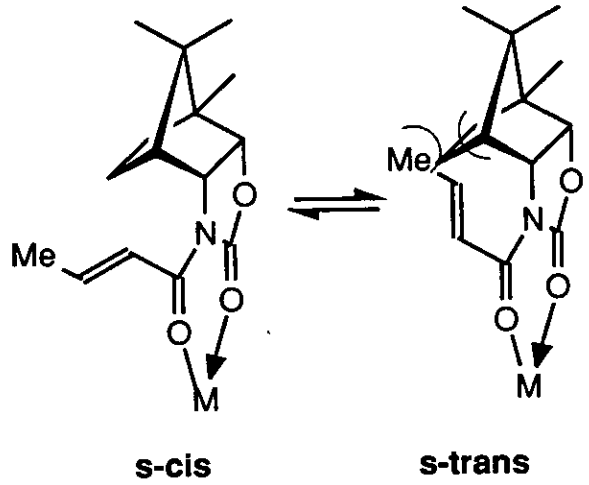
The *trans* nature of the two dienophiles was confirmed by 200 MHz ^1H NMR spectroscopy, the olefinic protons in the crotonate having a coupling constant of 15.3 Hz and that of the cinnamate being 15.7 Hz.

(ii) Diels-Alder reactions of the crotonate (101) with cyclopentadiene using titanium and aluminium catalysts.

(a) With titanium catalysts

The experiments conducted with this dienophile closely matched those employed for the acrylate in order that the results could be compared.The first reaction chosen was that of the crotonate with the "true" $TiCl_2(OPr^i)_2$ catalyst at -78^{0}C. Here, a 3 : 2 ratio of *endo/endo* isomers was obtained, an improvement on the diastereoselection obtained in the case of the acrylate under identical conditions. However, larger amounts of *exo* isomers were also observed (Table 5). Repetition of the reaction, but adding the catalysts in a different order, *i.e.* crotonate before $TiCl_4$ and then adding $Ti(OPr^i)_4$ did improve the *endo/endo* ratio to 3 : 1, a result

consistent with the acrylate system. The *endo/exo* selectivity was also doubled from *ca.* 6 : 1 to *ca.* 11 : 1. The *endo/endo* selectivity improvement for the crotonate over the acrylate using these catalysts can be accounted for by a greater proportion of molecules being in the more stable s-*cis* conformation compared to s-*trans* (Figure 14); this difference is due to increased steric interaction of the auxiliary with the unsaturated *N*-acyl moiety which now carries the methyl group.



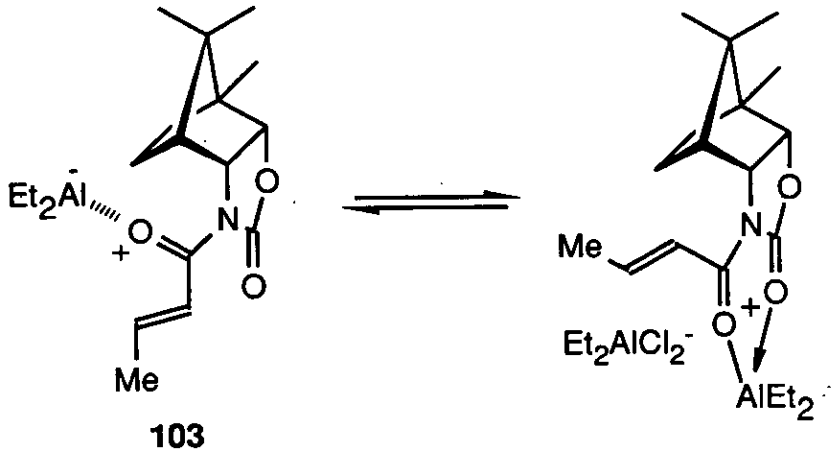
s-cis **s-trans**

Figure 14

(b) With Et_2AlCl catalyst

Employment of Et_2AlCl catalyst and its' addition before that of the diene, raised the *endo/endo* selectivity to 4 : 1 (which is no better than the acrylate) but smaller amounts of *exo* isomers were formed. On the other hand, adding the catalyst after the diene improved the *endo/endo* ratio to 6 : 1, and led to reduced quantities of *exo* isomers (virtually unmeasurable by high field ^1H NMR spectroscopy). The other difference observed concerned the fact that the former reaction was allowed to run for *ca.* one hour before quenching, in order to ensure complete consumption of alkene, whereas the latter reaction was quenched almost

immediately since it was known to be complete by an instantaneous colour change. The fact that a difference in selectivity was observed depending on the order of addition of the catalyst is readily explained upon closer examination of the ^1H NMR spectrum of the reaction in which the catalyst is added first. This spectrum revealed that *ca.* 45% of the reaction mixture was the 1,4 Michael addition adduct (the reader is directed to the end of this chapter which concerns this reaction). This means that nearly half of the catalyst had been consumed prior to the addition of the diene. Therefore, less than one equivalent of catalyst was present at the time the diene was added, and hence the more weakly dienophilic complex **103** (Figure 15) (referred to in chapter 1) is more likely to be operating, and give rise to larger quantities of the less favoured *endo* isomer, by attack from the opposite face of the alkene.

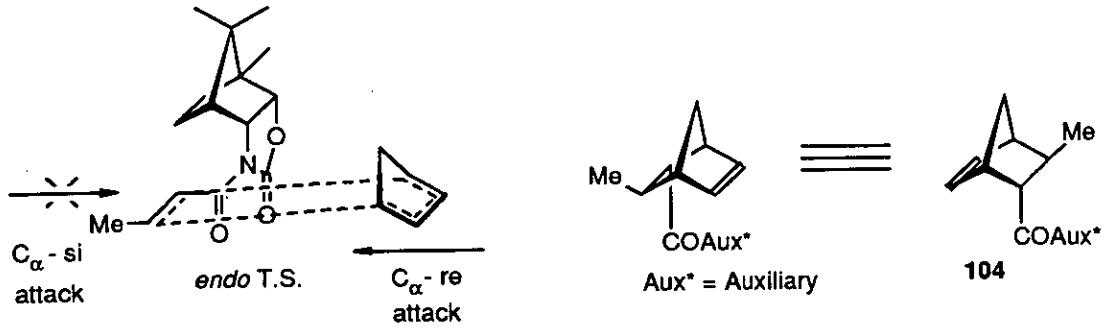


103

Figure 15

The major isomer could not be isolated in a pure form due to difficulties in the separation of the compounds, but by using the information gleaned from the acrylate work, one can say with a high degree of certainty that it is isomer **104** (Scheme 54). This assumption relies on the diene having easier access to the C_α-re face of the alkene than that of the C_α-si face (shown in Scheme 54), as this was the case for the acrylate. Further

evidence to sustain this assumption is gained from the stereochemistry obtained in the reaction of the cinnamate with cyclopentadiene (*vide infra*).



Scheme 54

It was of interest to examine the dependence of this dienophile upon a Lewis acid for the control of the various degrees of freedom available in this dienophile. To achieve this goal, the reaction of the crotonate **101** with cyclopentadiene in the absence of a Lewis acid was undertaken. In contrast to the behaviour of the acrylate which undergoes a facile Diels-Alder reaction with cyclopentadiene without the aid of a Lewis acid, the corresponding crotonate reaction was only *ca.* 10% complete after 24 hours. The poorer reactivity of crotonate dienophiles over the acrylate analogues has been remarked upon by Oppolzer[21] and is the result of the crotonate possessing a LUMO of higher energy than the acrylate,due to the influence of the methyl group which "feeds" electron density into the frontier molecular orbitals. Thus the amount of overlap between the HOMO of cyclopentadiene and the LUMO of the crotonate is smaller and a slower reaction will result (Figure 16).

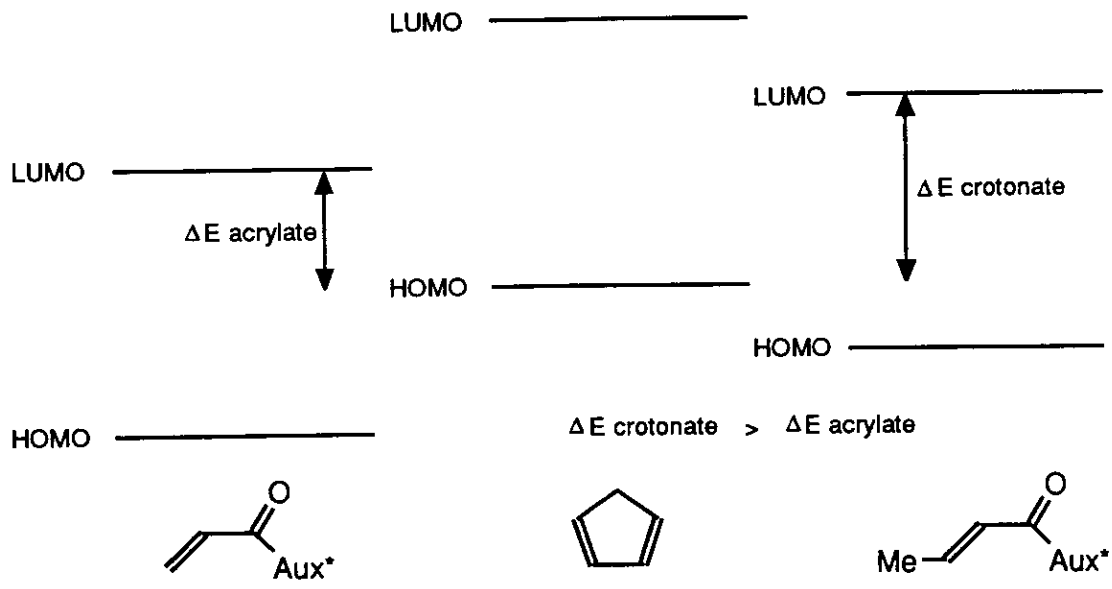
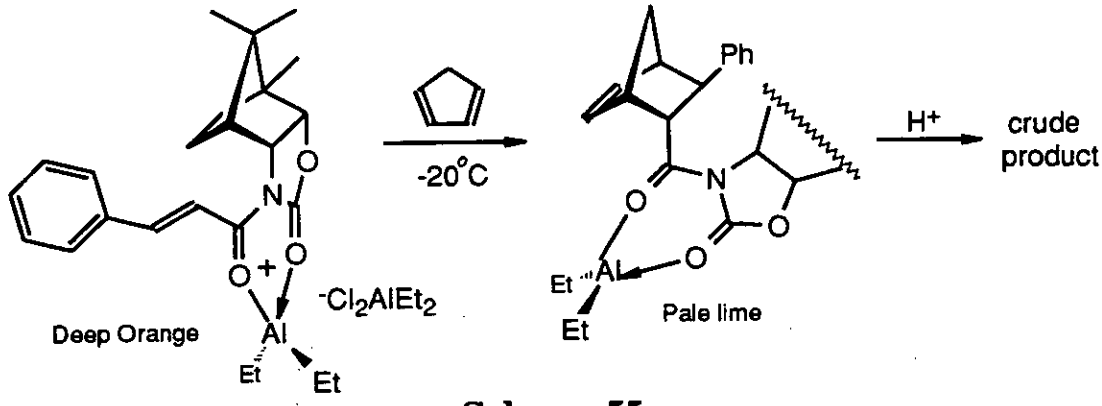


Figure 16

(iii) Diels-Alder reaction of the cinnamate (102) with cyclopentadiene using titanium and aluminium catalysts.

With $TiCl_2(OPr^i)_2$ as catalyst, the reaction of the cinnamate **102** with cyclopentadiene was carried out at -78^{0}C. As anticipated from the aforementioned comparison of reactivities, this reaction was extremely slow and was only *ca.* 20% complete after three days (*cf.* the acrylate and crotonate where reaction takes place in *ca.* 12 hours or less). This occurred despite addition of excess freshly cracked cyclopentadiene, so as to ensure that the reason for the sluggishness of the reaction was not lack of diene caused by re-dimerisation, during this long reaction period. Et_2AlCl was then employed as catalyst, and with 1.75 equivalents of this Lewis acid, a deep orange colouration was formed upon addition to the dienophile; due to the conjugation present in the system (Scheme 55). However, unlike the behaviour of the first two dienophiles which reacted instantaneously upon addition of the diene, the cinnamate-aluminium complex shown in Scheme 55 refused to react at -78^{0}C, as indicated by

the persistance of the deep orange colouration. This change reflects the significant energy increase of the LUMO of the olefin due to the conjugative electron donating quality of the phenyl group. However, upon raising the temperature to -20^{0}C, the deep orange colouration rapidly faded to yellow and finally to a pale lime colour, all of which occurred within one minute. The fading of the solution demonstrated the fact that the conjugation was being "drained out" of the system; the reaction in this case is therefore self-titrating and the pale lime colour marked the end of the reaction at which point the cycloadduct is bound to the aluminium centre as depicted in Scheme 55.

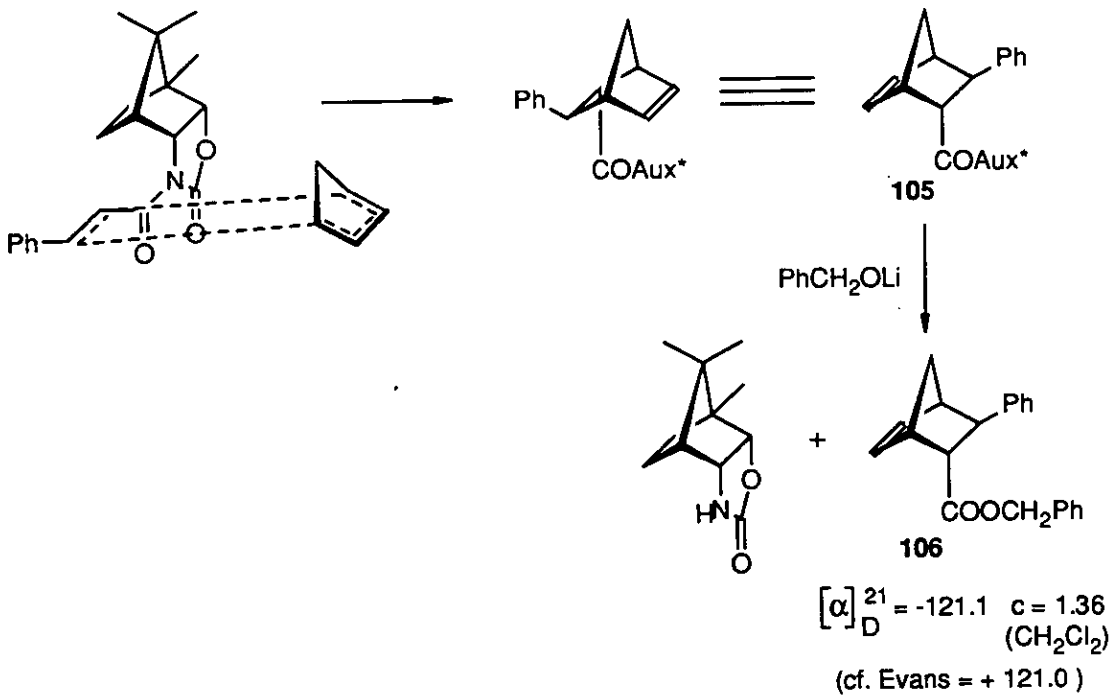


Scheme 55

The forgoing observations underline the fact that the ionic, highly dienophilic complex shown in Scheme 55 is in a different reactivity range from the titanium complexes encountered earlier. Examination of the ^{1}H NMR spectrum of the reaction mixture after column chromatography showed that the reaction is virtually stereospecific.

The resulting product **105** (Scheme 56) is assumed to have formed from reaction on the less hindered C_α-re face of the alkene. This was confirmed by one recrystallisation from a di-isopropyl ether/hexane mixture, followed by cleavage with lithium benzyloxide[46]; the 4'*R*, 5'*R*

stereochemistry of the resulting product **106** was equal but of opposite sign to that obtained by Evans[46] (Scheme 56).



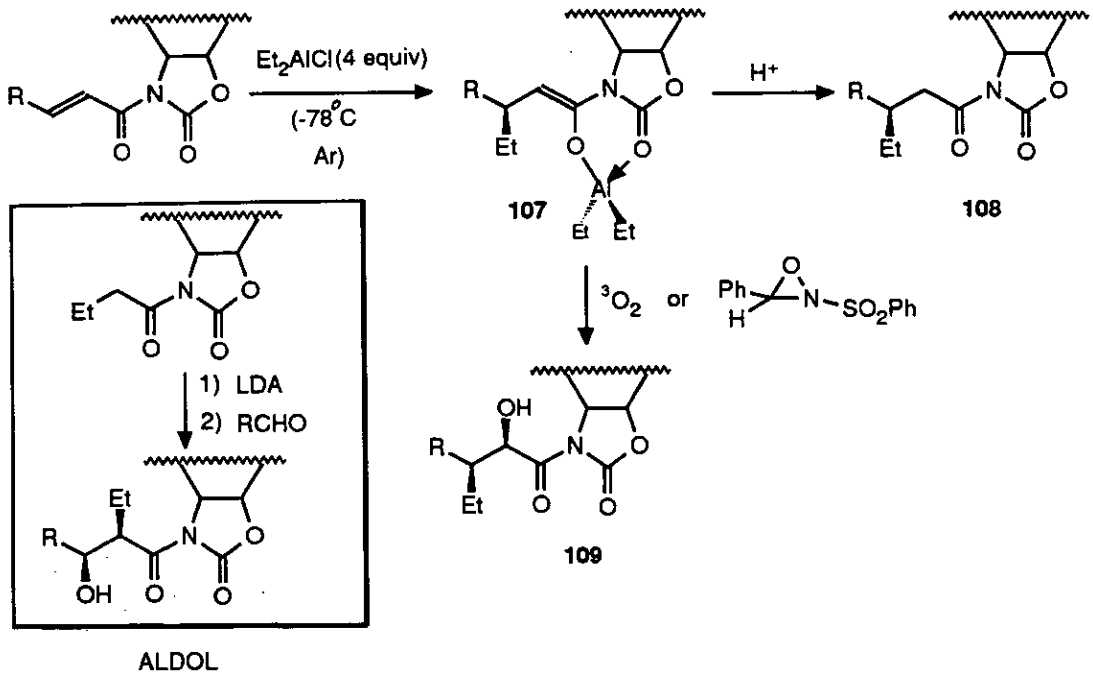
Scheme 56

Since the stereochemistry of the cinnamate adduct **105** and that of the major isomer of the acrylate (shown in Figure 5) are the same, it can be argued that the stereochemistry of the major crotonate adduct exhibits that which is depicted in **104**.

1,4 Michael reactions of the crotonate (101) and cinnamate (102) in the presence of Et_2AlCl

The Michael reactions as depicted in Scheme 57 were of synthetic interest because of the possibility of functionalising the β-carbon of the unsaturated carboximide *via*. nucleophilic attack, with an alkyl group and the α-carbon with an oxygen, by reaction with triplet oxygen or *N*-sulphonoxy oxaziridine[36]. These reactions result in the formation of

products which possess a substitution pattern opposite to that obtained in an aldol reaction[106] (Scheme 57). The first step involved a 1,4 Michael addition reaction of the nucleophilic ethyl group (from the Lewis acid) to form the aluminium enolate **107** which may be quenched with acid to yield the β-alkyl compound **108**, or trapped with triplet oxygen or *N*-sulphonoxy oxaziridine to yield the β-ethyl-α-hydroxy carboximide **109**.



Scheme 57

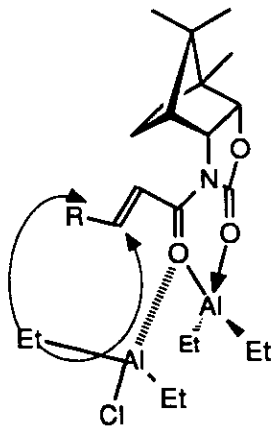
Initially it was decided to perform the Michael reaction and quench it with acid to discern the degree of asymmetric induction for the first step. Once this was established and provided it was good enough, the reactions could be repeated, but quenched with the hydroxylating agent.
Thus, the crotonate was treated with four equivalents of Et_2AlCl at -78^0C and after *ca.* 1.5 hr the deep yellow colour faded completely to a pale lime colour, indicating that the reaction had reached completion. Acidic work-up yielded the diastereomeric Michael adducts which were

Table 5. Diels-Alder reactions of the crotonate and cinnamate with cyclopentadiene

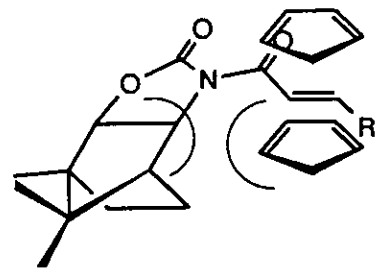
Temp /^{0}C	Catalyst (order of additon) (equiv)	*Endo/endo* ratio	*Endo/exo* ratio	d.e. /%
Crotonate				
-78	1. A ; 2. B (4) 3. crotonate	1.48 : 1	5.8 : 1	2 (19*)
-78	1. crotonate 2. A ; 2. B (4)	3.05 : 1	11.4 : 1	38 (51*)
-78	1. crotonate 2. Et_2AlCl (1.4) 3. cyclopentadiene	3.89 : 1	21 : 1[a]	52 (59*)
-78	1. crotonate 2. cyclopentadiene 3. Et_2AlCl (1.4)	5.93 : 1	104 : 1	69.5 (71*)
O	No catalyst	[b]	[b]	
Cinnamate				
-78	1. A 2. B (4) 3. cinnamate	[c]	[c]	
-20	1. cinnamate 2. Et_2AlCl (1.75)	147 : 2	-	97

KEY : A = $TiCl_4$; B = $Ti(OPr^i)_4$.* Endo diastereomeric excess only. [a] With associated 1,4 Michael addition product. [b] *ca.* 10% reaction took place. [c] Reaction formed a small (*ca.* 20%) of product and peaks too small to obtain accurate ratios.

analysed by both ^{1}H and ^{13}C NMR spectroscopy. Even at high field, the ^{1}H NMR spectrum was too complex to interpret in as far as determination of ratios was concerned. Instead, the $^{13}C\{^{1}H\}$ spectrum was used for this purpose, although in general the relative intensities of the signals should not be used as a good indicator of the relative amounts of diastereomers present. However, experience has shown that the relative signal intensities in the $^{13}C\{^{1}H\}$ spectrum are a good reflection of isomer ratios when the bornane moiety is present in the molecule. Disappointingly, the approximate ratio obtained by this method was 5 : 4 *i.e.* very little asymmetric induction had occurred in the reaction. By comparison, the reaction of the cinnamate substrate **102** took several hours to complete, apparently due to the increased steric hindrance between the phenyl group and the ethyl groups, of the Michael donor. Moreover, conjugation with the phenyl group is likely to lead to a lowering in the electrophilic nature of the β-carbon and hence reduced reactivity. The ratio obtained in this instance was marginally better at 7.5 : 3, although the poor diastereoselectivity observed in both reactions reflects the fact that the β-prochiral centre and the incoming reactant are too remote from the auxiliary.



relatively "loose" transition state



relatively sterically demanding transition state

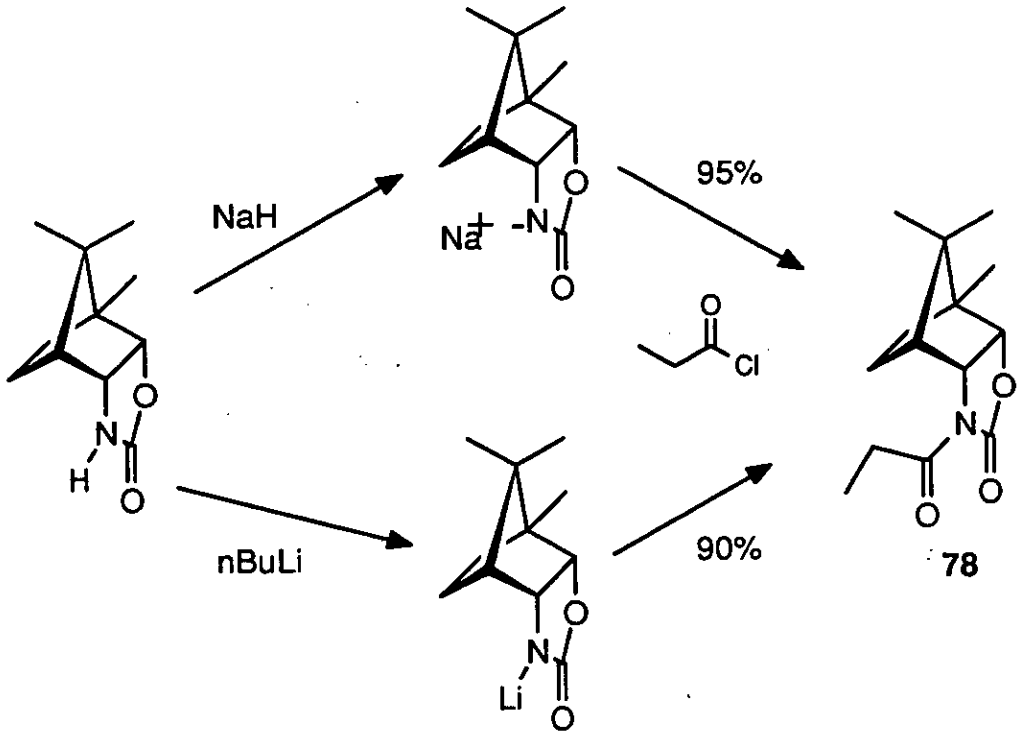
Scheme 58

In summary, the diastereoselectivity obtained in the 1,4 Michael addition reactions is poorer than that of the Diels-Alder reactions. This is explained by the fact that the site of attack in the former reaction is too remote from the chiral auxiliary to be influenced. By contrast in the Diels-Alder reaction the diene necessitates a well defined reaction environment with a sterically demanding transition state in which the auxiliary can exert its powerful topological bias (Scheme 58).

Chapter 3

The propionyl derivative (78) of Chirabornox :- Preparation and asymmetric alkylation and acylation reactions

The propionyl derivative **78** of Chirabornox proved to be a readily accessible starting material which could be synthesised in two ways. It had been shown previously by Banks *et al*[86] that treatment of the sodium salt of **77** or its lithiated analogue **100** with propionyl chloride readily formed the desired product **78** in excellent yield (Scheme 59).



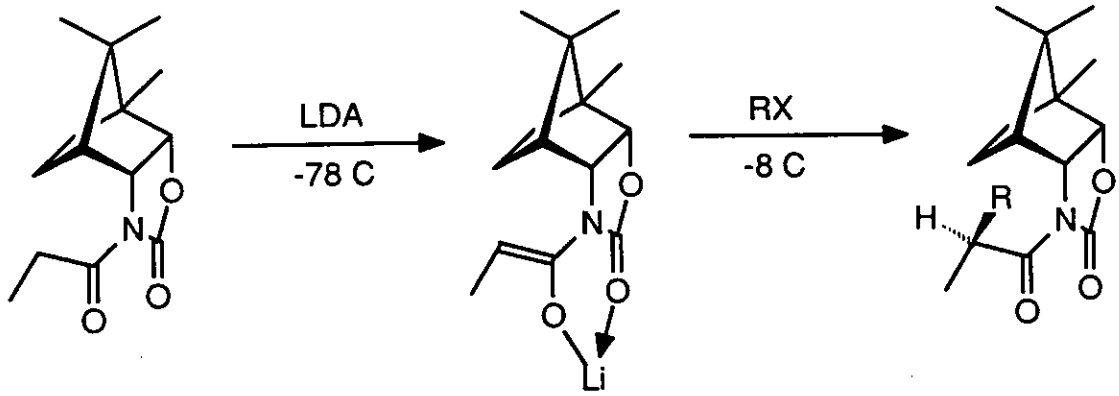
Scheme 59

Enolate reactions

1. Asymmetric alkylation reactions

Some preliminary experiments conducted by Gallagher and Donohoe[111] using the procedure of Evans *et al*[37], showed that the lithium enolate of

78, *viz.* **110** underwent reactions using alkyl halides with very high levels of asymmetric induction (the minor epimers were not detected by high field ^{1}H NMR) (Scheme 60, Table 6). However, whilst the yield obtained with allyl bromide was acceptable (70%) the benzyl bromide yield was disappointing low and that of the ethyl iodide adduct was appallingly bad.



110

Scheme 60

Table 6. Summary of the alkylation reactions performed by Gallagher and Donohoe.

Electrophile (RX)	Yield /%	diastereomer ratio
allyl bromide	70	> 10 : 1
benzyl bromide	42	only one isomer detected
ethyl iodide	6	only one isomer detected

In addition, the stereochemistry of the adducts had not been determined and it was necessary to firmly establish its outcome. Optimisation of the

reaction conditions and an understanding of the mechanism of the reaction were also thought to be desirable goals in this area of study. In initial experiments, the benzyl bromide reaction was repeated in order to optimise the yield for the stated conditions,these being reaction at -8^{0}C for several hours in THF solvent, and a more acceptable yield of 62% was obtained.

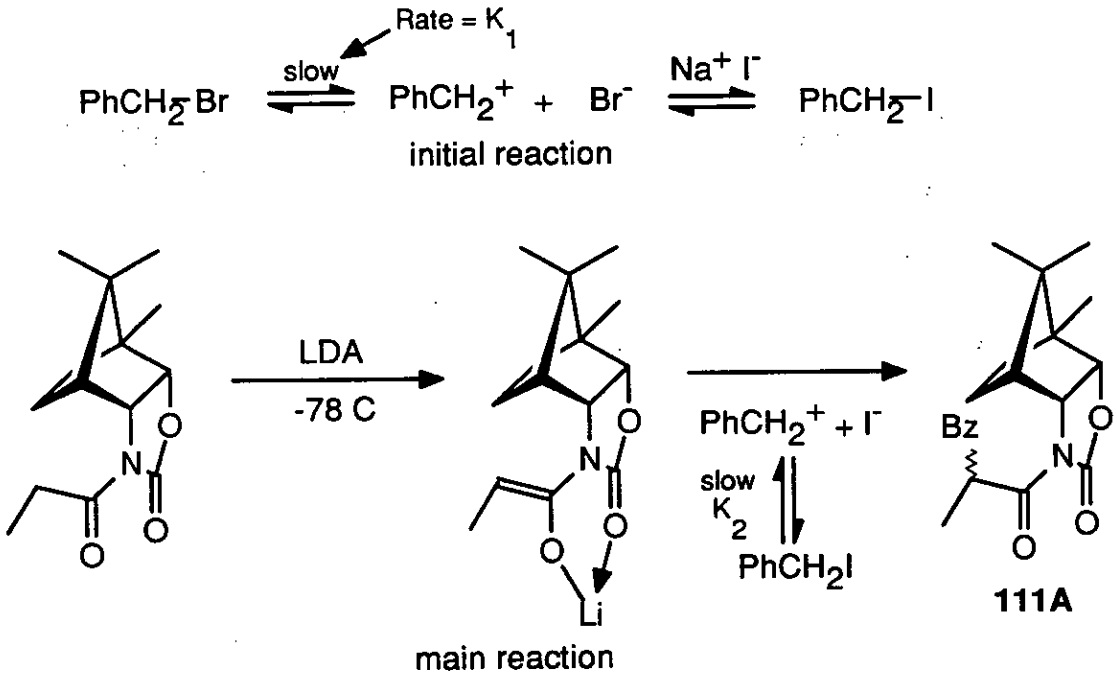
As mentioned in the introduction, oxazolidinone-derived enolates are poor nucleophiles towards alkyl halides[4], a problem also coupled to the associated problem of lithium enolate decomposition above 0^{0}C (or above -20^{0}C in the case of sodium analogues). This meant that an optimum temperature of *ca.* -10^{0}C was required in the case of lithium enolates in order for reaction to occur without significant decomposition.

A curious feature of the initial studies was the significant difference in the yield obtained with allyl bromide and that obtained with ethyl iodide. The reason for this cannot be steric in origin, nor can it be accounted for in terms of leaving group superiority. The only plausible reason is that the reaction is operating at the S_N1 end of the nucleophilic scale, *i.e.* it is overwhelmingly favoured by electrophiles with an alkyl/aryl group which can stabilise the intermediate carbocation by resonance. This dichotomy between ethyl iodide and its π-Huckel analogues, in regard to alkylation reactions, has been observed in other imide-derived systems[37,112-114].

In order to investigate this hypothesis further, two experiments needed to be conducted. If the reaction is truly S_N1 in nature, then adding NaI would form a species with a better leaving group and hence a faster reaction would occur (Scheme 61). As a result, more product would form before the enolate decomposed. Thus, if the rate-determining step is the

cleavage of the benzyl-halide bond, a faster reaction should occur as $K_1 < K_2$. Thus, the benzylation reaction was repeated in the presence of pre-dried NaI, and after work-up and chromatography, an 80% yield of product **111A** was isolated. Analysis of **111A** by 200 MHz ^{1}H NMR spectroscopy showed that it contained *ca.* 10% of **78**, which presumibly formed by hydrolysis of the enolate, by traces of water in the NaI or by incomplete enolisation of **78** with LDA. However, it still represents a significant rise in yield, thereby supporting this mechanism.

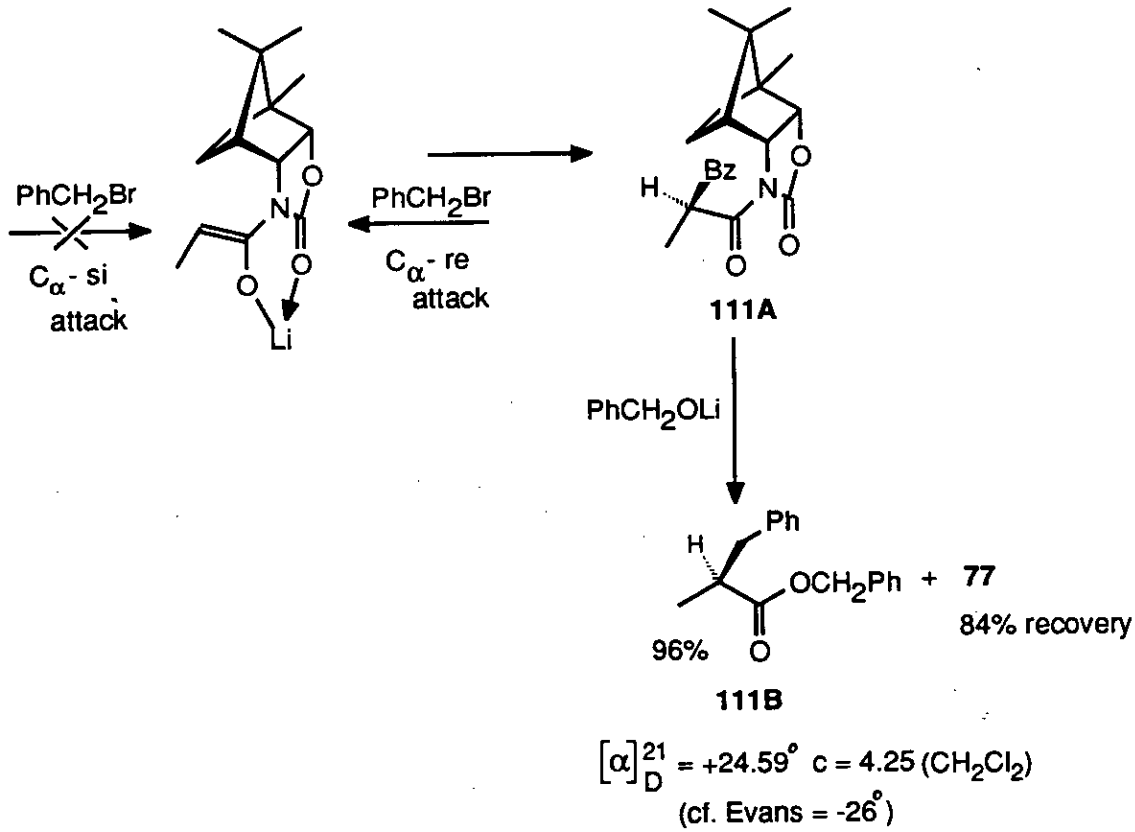
A second experiment was also conducted to try to improve the yield of the ethylation product. Treatment of the enolate **110** with ethyl tosylate (which possesses an excellent resonance-stabilised leaving group) yielded no product whatsoever. One cannot conclude from these results that the reaction is S_N2 in nature.



Scheme 61

The question of the stereochemistry of these adducts still remained. Cleavage of the benzylated adduct with lithium benzyloxide furnished

the desired ester **111B** in excellent yield (96%) with an optical rotation close in magnitude but of opposite sign to that obtained by Evans[37], together with an excellent recovery of auxiliary (Scheme 62). In addition, crystals of the original adduct were grown and an X-ray crystal structure obtained (Figure 17) which clearly demonstrates that the absolute configuration of the 2' centre is *S*. These results were in agreement and showed that the electrophile attacked the less hindered C_α-re face of the enolate.



Scheme 62

This result is also in agreement with the selectivity obtained in the Diels-Alder reactions, where the same side of the oxazolidinone plane is open to attack (*vide infra*).

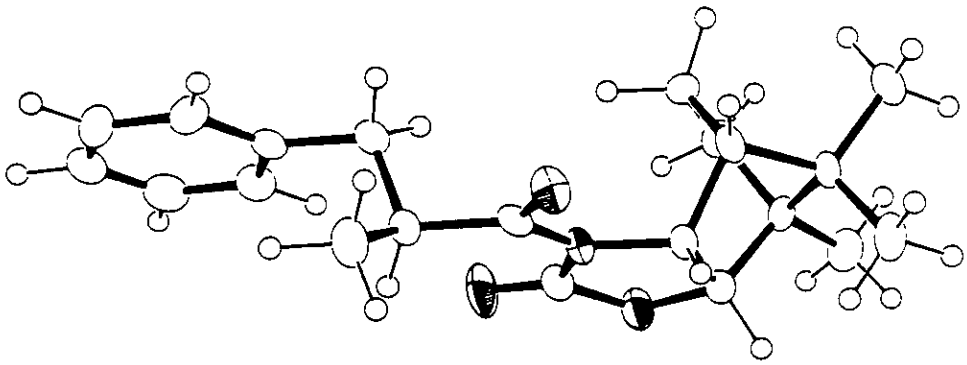


Figure 17. X-ray crystal structure of the benzylated adduct **111A**.

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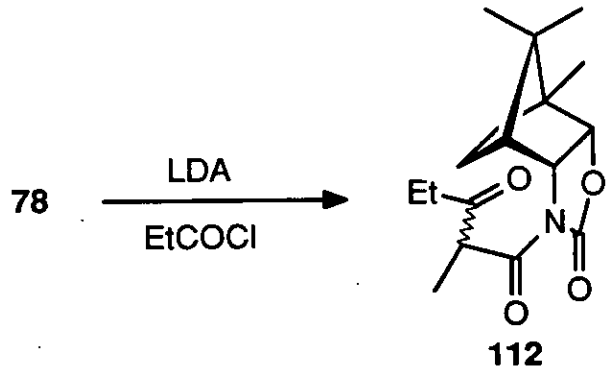
2. Asymmetric acylation reactions

In stark contrast to the alkylation reaction, the acylation of carboximide derived lithium enolates was found by Evans *et al*[38] to be a facile process at -78^{0}C. Indeed, in the case of the valine and norephedrine derived systems (**9** and **28** respectively) the reaction was quenched immediately after the addition of reagents was complete.

In accordance with this literature precedent, the lithium enolate **110** was prepared in the same way as for the alkylation reactions, before being treated with a THF solution of the freshly distilled acid chloride under study. For the first experiment, the acid chloride chosen was propionyl chloride which was allowed to react with the enolate for one minute before quenching the solution. In these reactions, a delicate balance between a sufficient time for complete consumption of the enolate, and the ensuing problem with racemisation of the newly created chiral centre by residual LDA, needed to be attained.

A high field ^{1}H NMR spectrum of the crude reaction mixture was then obtained, the analysis of which revealed a complex spectrum (Figure 18) of three compounds. One of these was starting material, **78**, whilst the second was the required product **112** (Scheme 63) which was identified from the quartet at *ca.*δ 4.5 ppm slightly masked by the auxiliary signals. The third compound was represented by a quartet of smaller area at *ca.* δ 5.1. Initially, this was thought to be the minor isomer, *i.e.* the epimer of the expected product. However, taking into account the similarity observed in spectra obtained of other diastereomers with Chirabornox (see page 82), it seems unlikely that signals which are 0.6 ppm apart can be attributed to the epimers of **112**.

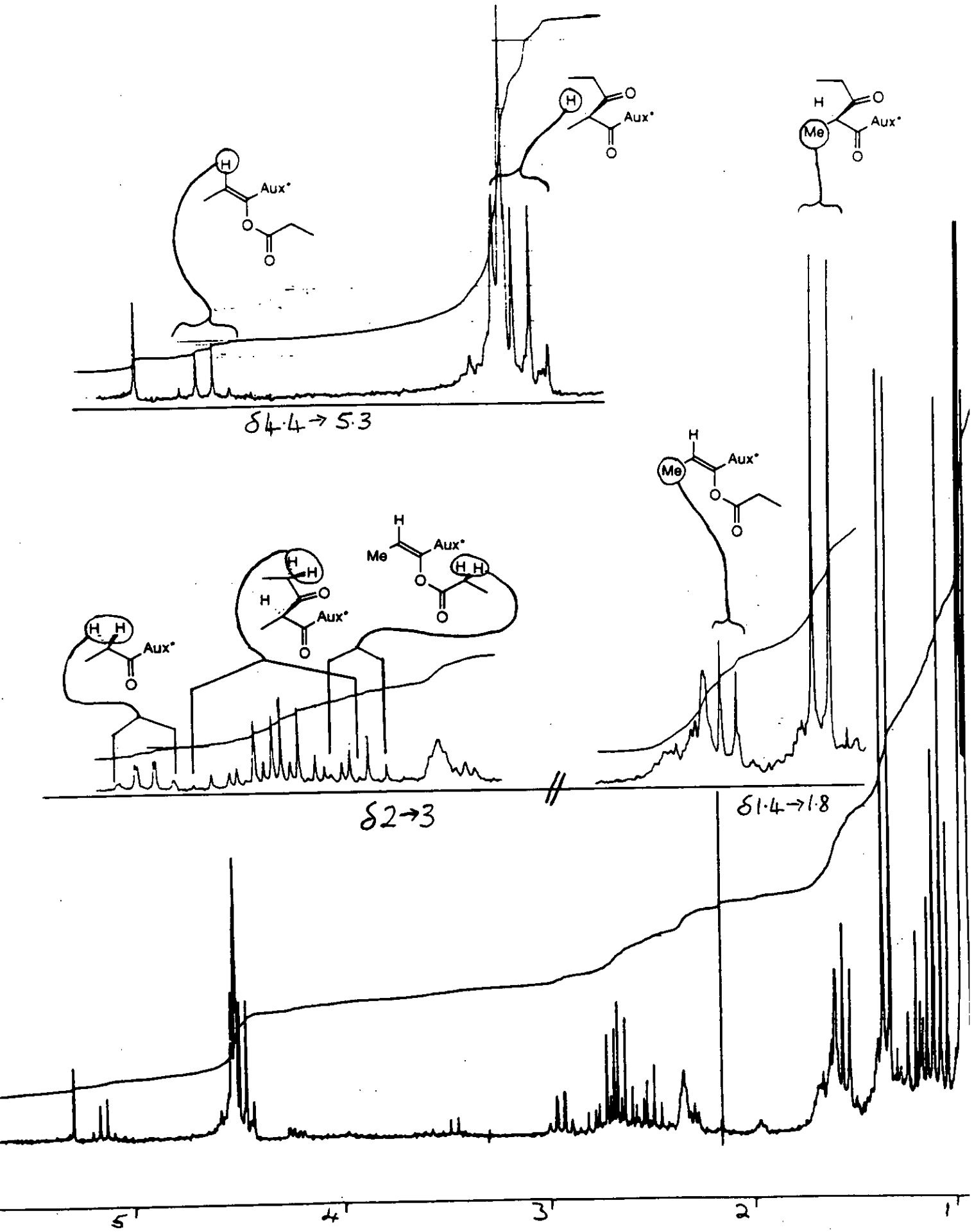


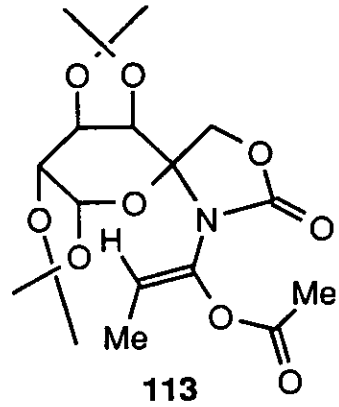
112

Scheme 63

The work by Gaur[5] in the study of the corresponding acylation reactions with Chiragalox **10** showed the sole products to be formed were the *O*-acylated derivatives, *e.g.* **113** as established by X-ray crystallography. The ^{1}H NMR spectra of these *O*-acylated derivatives showed an olefinic resonance at *ca.* δ 5.6 ppm, in addition to the observation of an olefinic signal in its ^{13}C{^{1}H} spectrum. On this basis, and a similar observations in the laboratory, the quartet in the Chirabornox-derived system at δ 5.1 ppm was assigned to *O*-acylated product **114** (Scheme 64). The question of *O* vs *C*-acylation in the realms of asymmetric synthesis appears not to

Figure 18. ^{1}H NMR spectrum of the crude reaction product between the lithium enolate **110** and propionyl chloride.



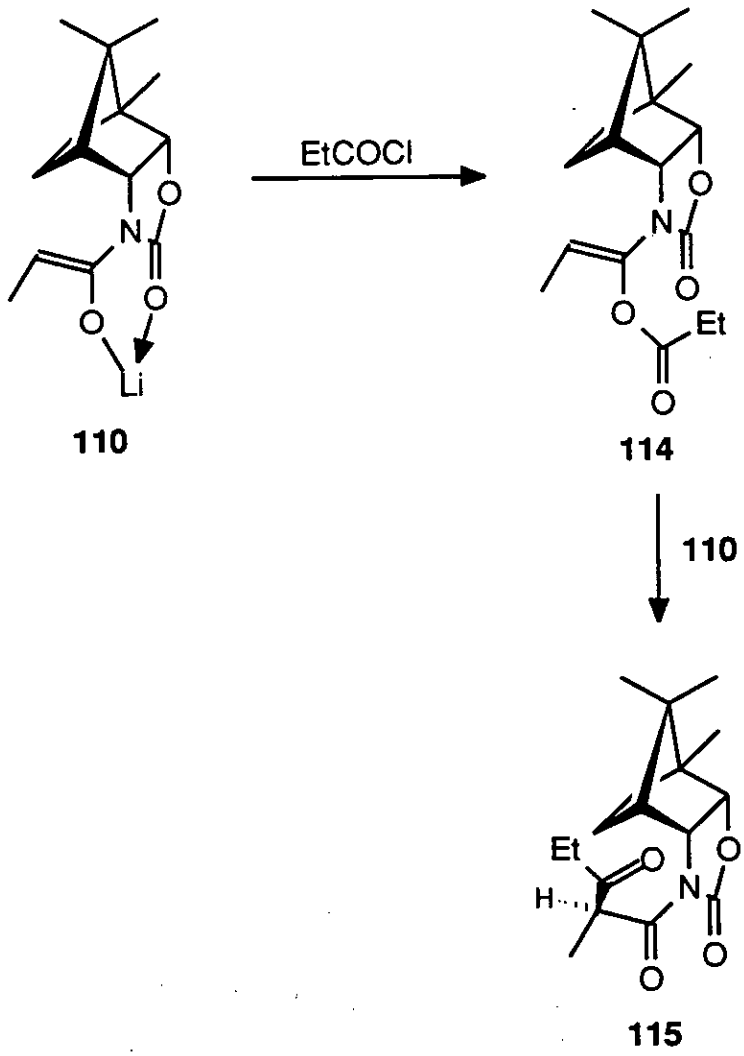


113

arise and is not a difficulty encountered with the auxiliaries of either Evans[38] or Oppolzer[114]. The problem of controlling *C* vs *O* acylation is a complex one and can depend on several factors such as the temperature, the nature of the electrophile, the amount of steric conjestion present in the substrate, the counterion of the enolate, the solvent and the stoichiometry of the reaction[115].

A possible mechanism for this reaction is the initial formation of the *O*-acylated product **114**, which then reacts with more lithium enolate to produce the desired *C*-acylated product **115** (Scheme 64), as is the case for ketone enolates with acid chlorides or anhydrides[115].

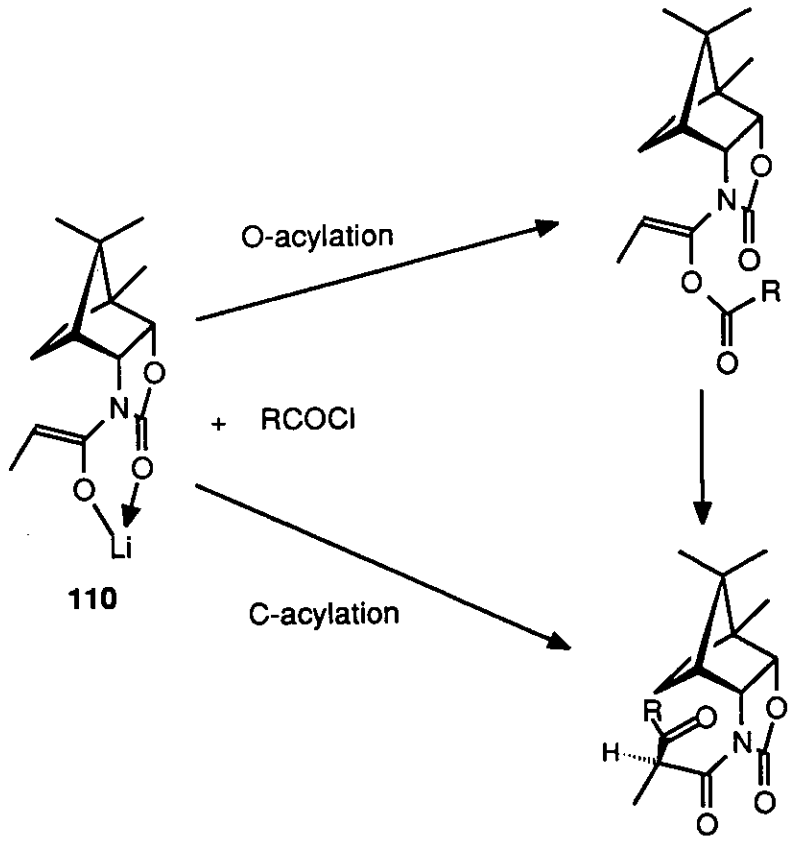
Thus, for *C*-acylation, the most fruitful conditions are the dropwise addition of a solution of the acid chloride to ensure that the enolate is always in excess, or else a substantial proportion of *O*-acylated product will survive. The more sterically crowded the enolate, the more the *O*-acylated product will predominate as the transferral reaction of the acyl group from oxygen to carbon is slowed down. This is an explanation for the sole formation of *O*-acylated products in the case of Gaur's sterically hindered auxiliary **10**.



Scheme 64

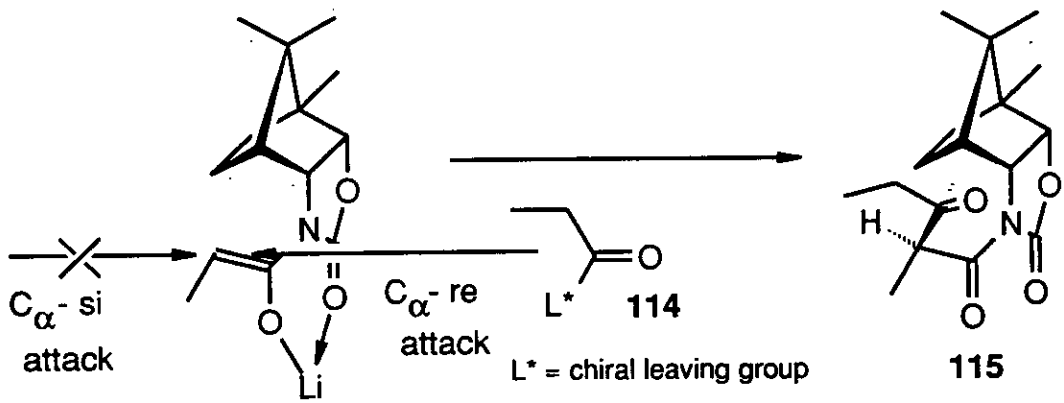
Alternatively, it is possible that in the case of the carboximide-derived enolate system, the acylating agent has a choice of whether to react at oxygen or carbon. The initial *C* : *O* ratio will then increase as more enolate reacts with the *O*-acylated species (Scheme 65). The ratio of initially formed *C* : *O* products will then be a function of the steric demand imposed by the auxiliary on the acylating agent, amongst other factors.

Further analysis of the ^{1}H NMR spectrum of the crude reaction mixture from the propionyl chloride reaction also showed that only one isomer could be detected, out of the two possible *C*-acylated products (Table 7),



Scheme 65

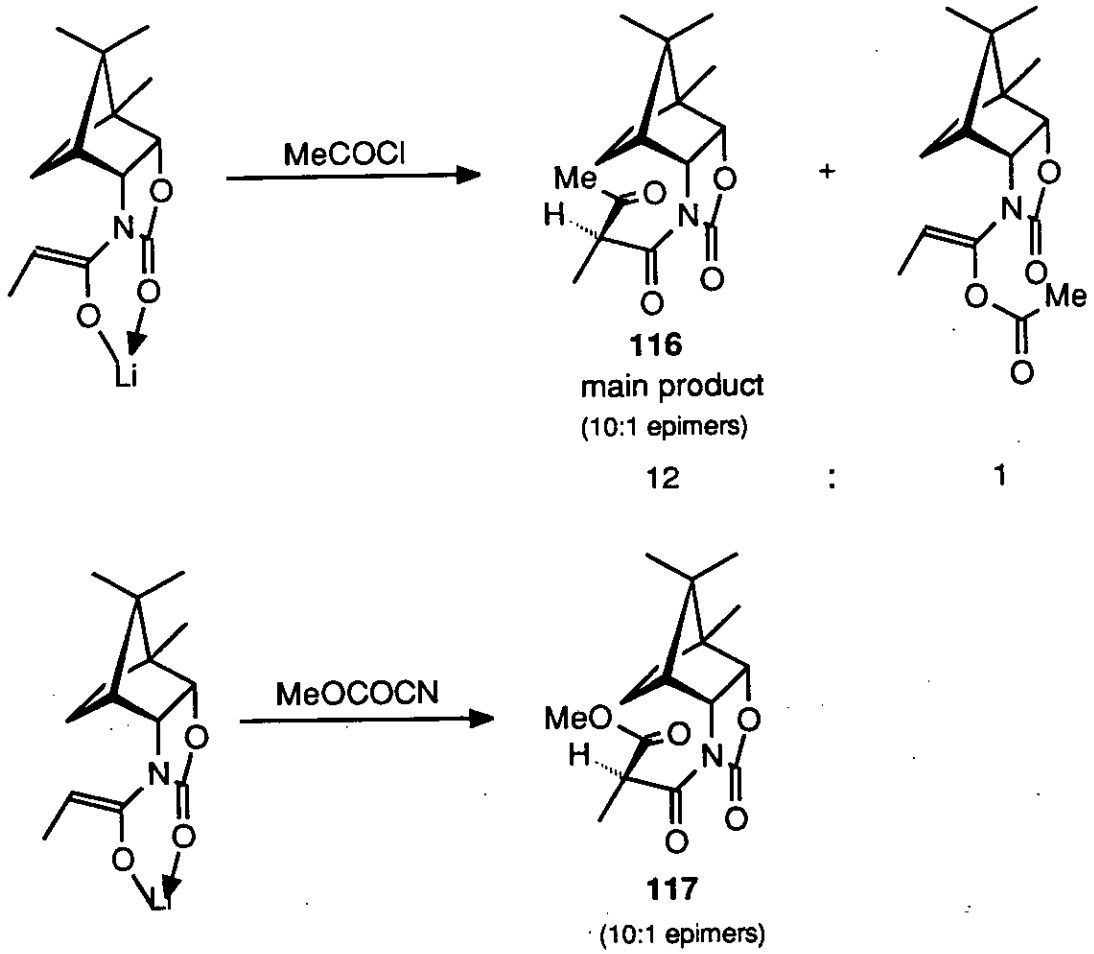
The stereochemistry of this isomer is believed to be that of **115** (Scheme 66), formed by acylation at the C_α-re face of the enolate.



Scheme 66

The reaction was repeated using acetyl chloride and quenched after 45 seconds (a shorter reaction time was allowed since acetyl chloride is a smaller acid chloride and was thought therefore to be more reactive). The resultant mixture was conservatively estimated to contain a ratio of *ca.*

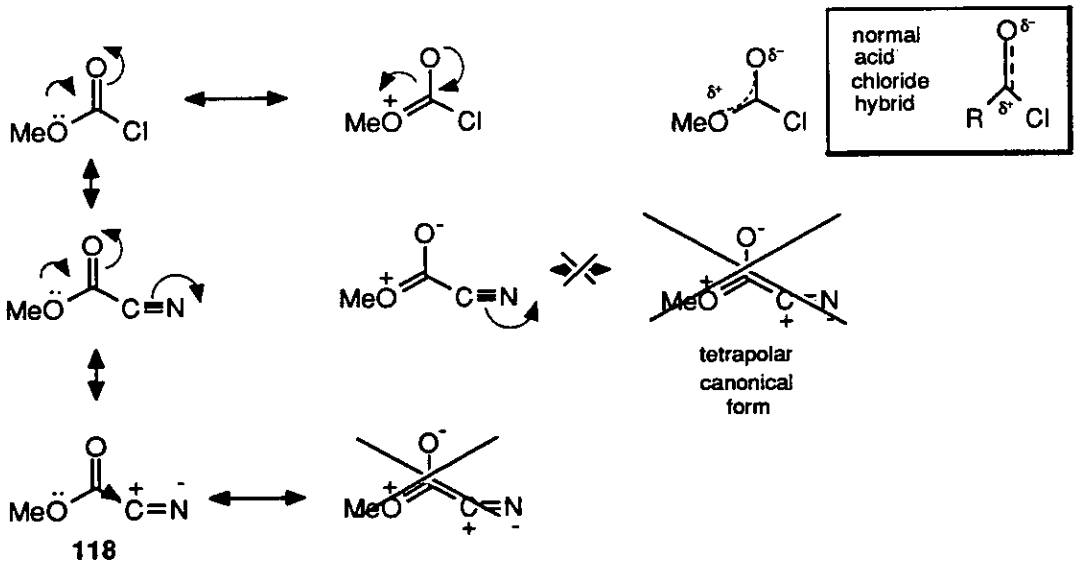
12:1 *C*:*O* products with a selectivity of 10 : 1 of the epimers **116** (Scheme 67). Employment of Mander's reagent (methyl cyanoformate), a reagent reported[116] to undergo *C*-acylation in cases where *O*-acylation is a major problem, yielded exclusively the *C*-acylated products **117** in a ratio of 10 : 1.



Scheme 67

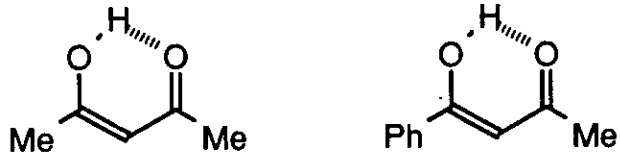
Interestingly, the lithium enolate **110** failed to undergo any reaction with methyl chloroformate after one minute. This reflects the contribution made through resonance by the methoxy oxygen to deactivate the carbonyl to nucleophilic attack. In the case of Mander's reagent, the nitrile group competes for the electron density of the carbonyl, negating the contribution from the methoxy, otherwise a highly unstable

tetrapolar form will develop, as depicted in Scheme 68. Furthermore, the nitrile activates the carbonyl to nucleophilic attack by its canonical structure **118**.



Scheme 68

A more interesting acylation reaction was then attempted, involving the use of benzoyl chloride which invited the possibility of observing racemisation through enolisation, the driving force being the attainment of conjugation with the phenyl group. For example, 2,4-pentandione **119A** exists 76.4% in the enol form, in the liquid state, whereas 1-benzoylacetone **119B** exists 89.2% in its enol form, showing a significant contribution made from conjugation with the phenyl group to the stabilisation of this form[117].



119A **119B**

Evans *et al*[38] have argued against racemisation by enolisation, postulating that acidification of the α-proton by its adjacent carbonyl

would cause unfavourable allylic strain interactions between either the phenyl or the hydroxyl of the acyl substituent and the auxiliary (Figure 19).

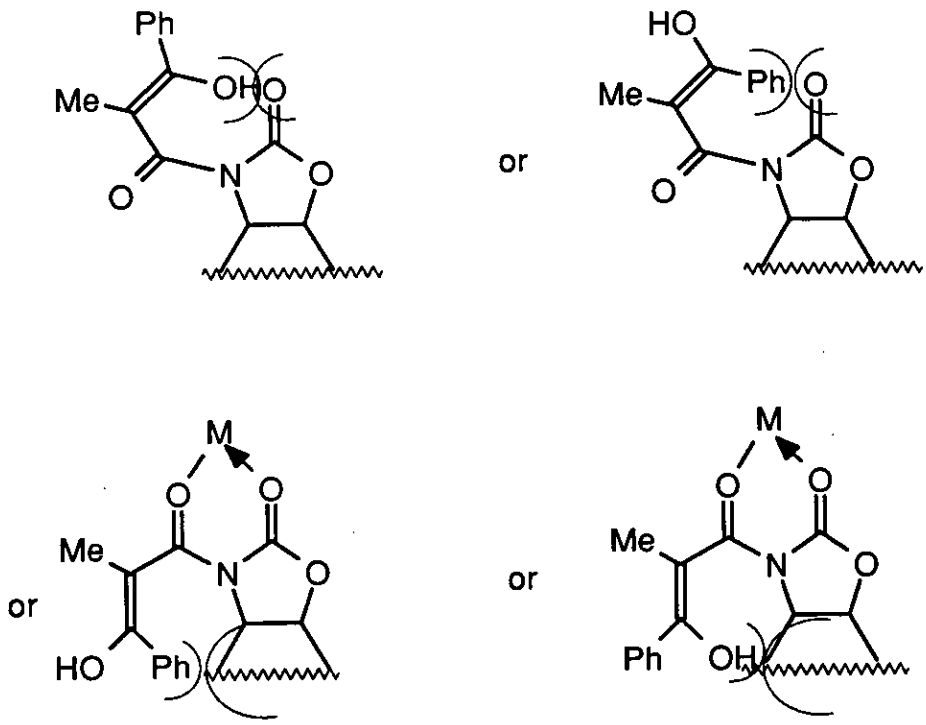
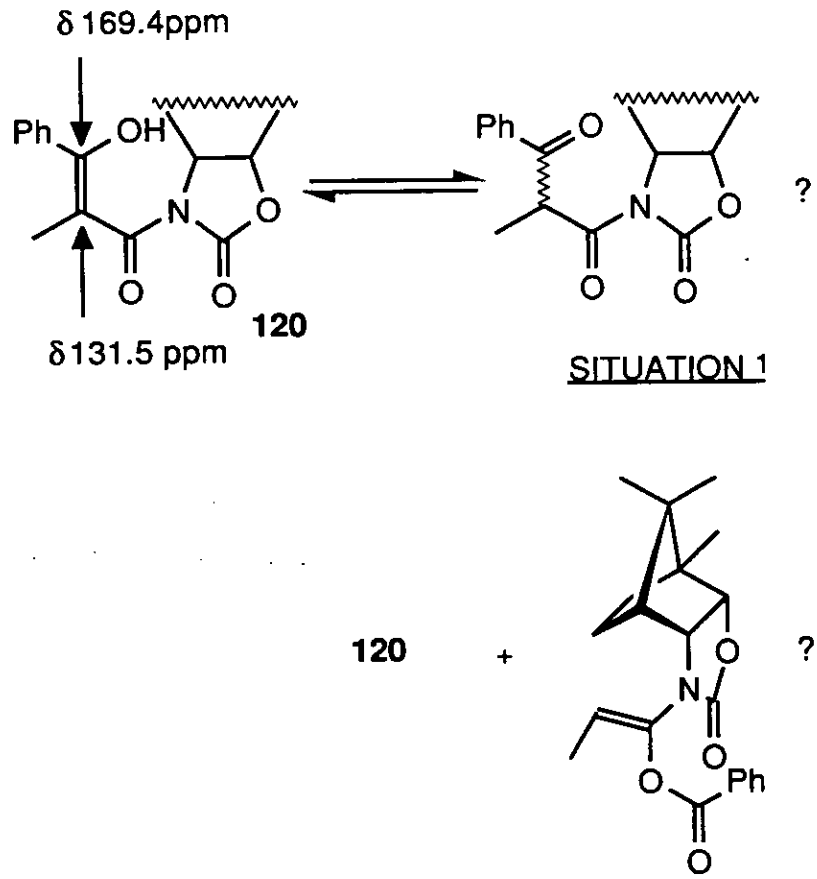


Figure 19

Anticipating that this reaction would be marginally slower due to steric reasons, the benzoyl chloride was allowed to react with the lithium enolate **110** for a period of two minutes before quenching. Following work-up, analysis of the high field ^{1}H NMR spectrum of the crude product revealed the presence of a doublet at δ 1.5 and a quartet at δ 5.4 ppm. This quartet need not be due to *O*-acylated material but could be *C*-acylated product, as one would expect a deshielded chiral centre proton relative to the acetyl and propionyl cases, due to the influence of the phenyl group. In addition to these signals, two broad singlets were visible at δ 6.0 and 6.2 ppm indicating the presence of enolic protons. Coupled with this finding, the $^{13}C\{^{1}H\}$ spectrum showed a larger than expected number of signals in the olefinic region and an extra signal at δ 169 ppm.

These findings and the observation of hydroxyl and olefinic absorbances in the infrared spectrum, in addition to carbonyl absorbances, confirmed the fact that some enol compound was present in the reaction mixture (Scheme 69). One of two possible situations were thought possible ; situation 1 in which the enol **120** is in equilibrium with its keto tautomer, or situation 2 in which the enol is a separate entity from the *O*-acylated product, shown in Scheme 69.



Scheme 69

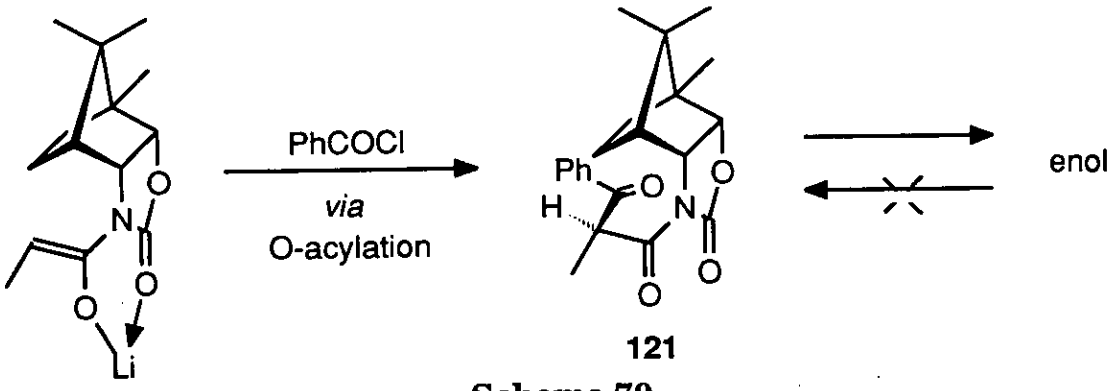
Recrystallisation of the material from methanol yielded a crystalline product, which upon analysis of its spectra, showed the enol component to be missing as established by the absence of enol peaks at δ 6.0 and 6.2 ppm in the ^{1}H NMR spectrum. Moreover, the simplification of the olefinic

and carbonyl region at δ 170 ppm in the $^{13}C\{^{1}H\}$ spectrum were clear indicators of this finding. However, no peaks in the region *ca.* δ 200 ppm were found for the *C*-acyl carbon, which would have confirmed its identity as *C*- rather than *O*- acylated product. Fourier-transform infrared spectroscopy of the recrystallised material showed the presence of three absorbances at 1786, 1705 and 1676 cm^{-1}. Whilst the first two are clearly carbonyls, the other absorbance is questionably a carbonyl, as the olefinic stretch in enol esters, enol ethers and enamines appears between 1630-1690 cm^{-1}.[118] A further determination of the $^{13}C\{^{1}H\}$ spectrum did in fact reveal the presence of a previously missed quarternary peak at δ 198 ppm, in addtion to two others, one at δ 170 ppm and the other at δ 154 ppm, thus proving beyond all doubt that the crystalline material was the *C*-acylated compound **121**, shown in Scheme 70. Furthermore, re-examination of the ^{1}H NMR spectrum of the crude material showed that no other isomers were present. However, the amount of required product to enol form was in the ratio of 1.3 : 1.

It would appear that these enol forms are thermodynamically stable since they can be separated from the keto tautomer as stable entities in their own right. During the reaction, it seems that after initial formation of the *C*-acylated product **121** the enol can then form; the lack of observation of any *O*-acylated product would appear to indicate that the driving force for *C*-acylation (possibly *via* *O*-acylated material) is the creation of the thermodynamically stable resonance stabilised enol structure, as depicted in Scheme 70.

The absence of any racemisation would indicate that the keto to enol conversion is not a reversible process. The postulated structure of the two

enol forms are the hydrogen-bonded (A) and its unbound version (B) (Figure 20).



121

Scheme 70

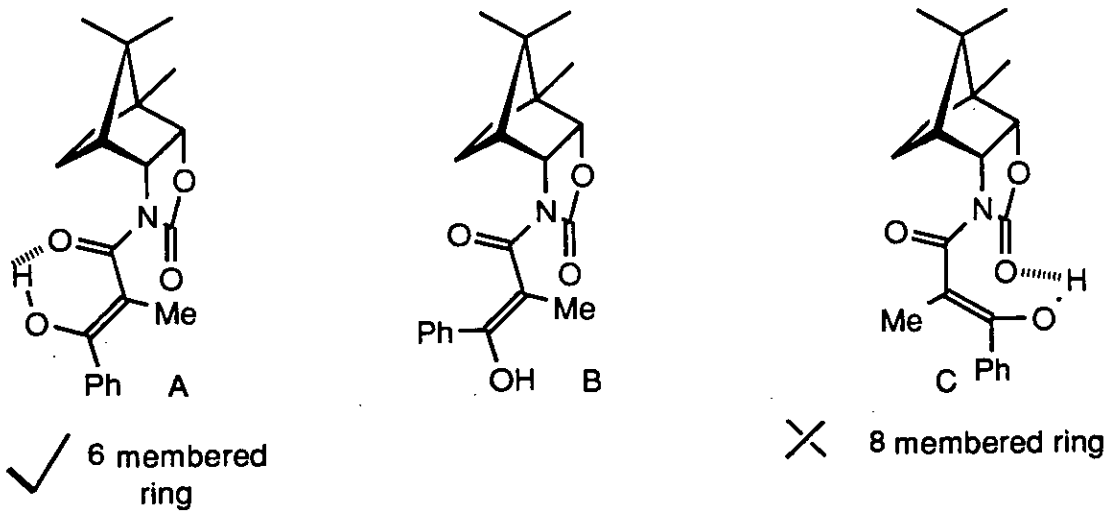


Figure 20

A further structure (C) is unlikely due to the formation of the unstable eight membered ring.

In further experiments, addition of the benzoyl chloride more quickly led to *O*-acylation, giving a near 50:50 ratio of *C*:*O* products. This would be expected if the enolate is not in excess for the majority of the reaction, allowing significant quantities of *O*-acylated product to be made. Adding the benzoyl chloride more slowly but quenching more quickly yielded starting material, *C*-acylated product and enol only, indicating that *O*-

acylated material is not the favoured product when the enolate is in excess. It may also be that benzoyl chloride is more reactive than expected (compare the reactivity of an aromatic aldehyde with that of its non-aromatic counterpart) and so the *O*- to *C*- benzoylation reaction is quicker. This would explain why *O*-acylation is not usually observed. This therefore demonstrates the limited synthetic utility of acylating agents possessing α-aromatic functionality, in contrast to their non-aromatic counterparts which do not suffer the associated problem of enolisation.

Table 7. Asymmetric acylation reactions

Acyl electrophile	Reaction time before quenching /seconds	*C* : *O* ratio	d.e.* /%
EtCOCl	60	6 : 1	> 95
MeCOCl	45	12 : 1	82
MeCOCN	90	(*C* acylation only)	82
MeCOCl	60	No reaction	-
PhCOCl	120	(*C* acylation only	>95 [a]

* By high field ^{1}H NMR spectroscopy.

[a] (*C* : enol ratio = 1.3 : 1)

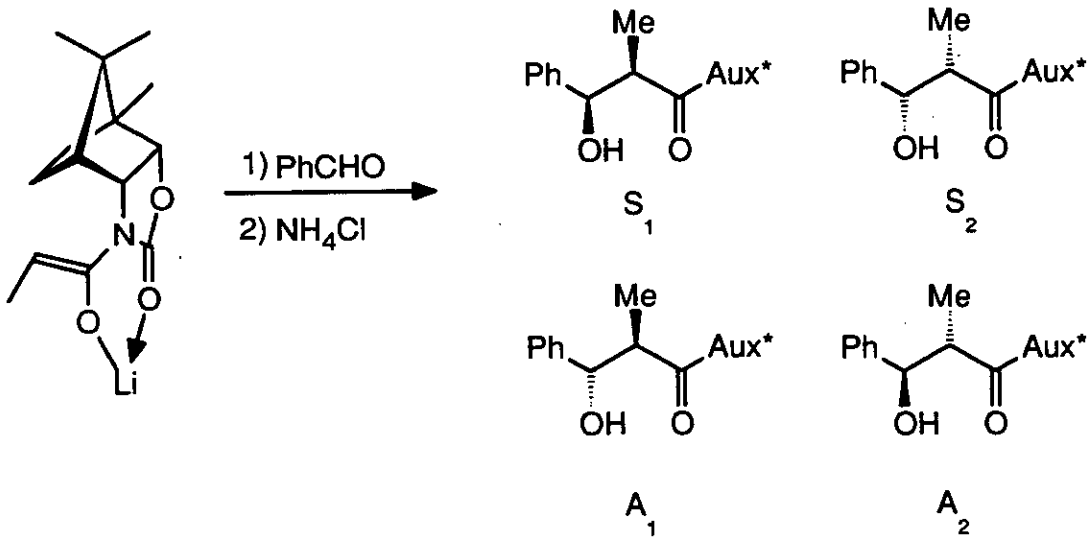
Chapter 4

Asymmetric aldol reactions with the propionyl derivative (78) of Chirabornox

The work concerning this reaction is divided into four sections corresponding to the four types of Chirabornox propionate-derived enolates studied, namely the lithium enolate, boron enolate, chlorotitanium enolate and zinc enolate reactions. Although most of the boron enolate chemistry had already been investigated by Gallagher and Donohoe[111], no rationalisation of the observed stereochemistry had been proposed and the scope of the reaction needed to be increased.

(a) Lithium enolate chemistry

An initial study in our laboratory by Banks and Dawson showed that reaction of the lithium enolate **110** with benzaldehyde with quenching after thirty seconds yielded a colourless crystalline solid which was shown by high field ^1H NMR spectroscopy to be a mixture of the four possible aldol products (Scheme 71) in a ratio of 55.4 : 28.7 : 10.3 : 5.7 (giving a d.e. of 11%); these components were not assigned to the four

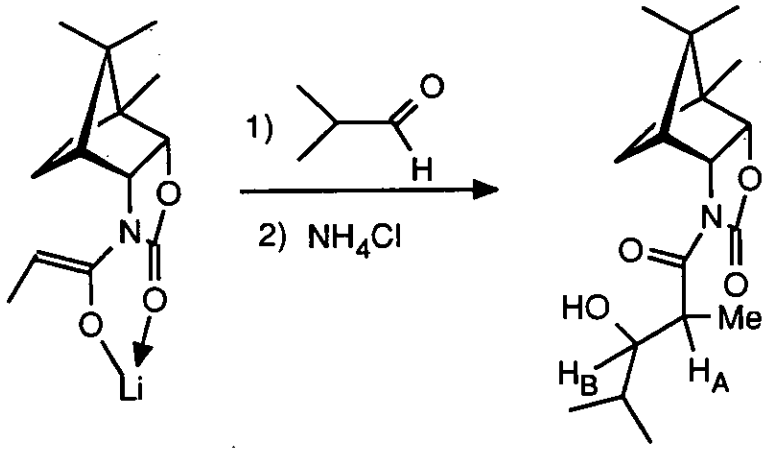


Scheme 71

possible structures.

The poor level of diastereoselection attained with lithium enolates in this reaction has been noted by other groups[25,43,119,120] and can be attributed to a less "tight" transition state compared to other enolate systems (*e.g.* those of boron) due to the relatively long Li-O bond lengths[121]. In addition, lithium does not possess true ligands (*i.e.* ligands other than those of solvent, for example, alkyl groups), which would make steric interactions in the aldol transition state greater[122]. (The reader is directed to the section on boron enolate chemistry).

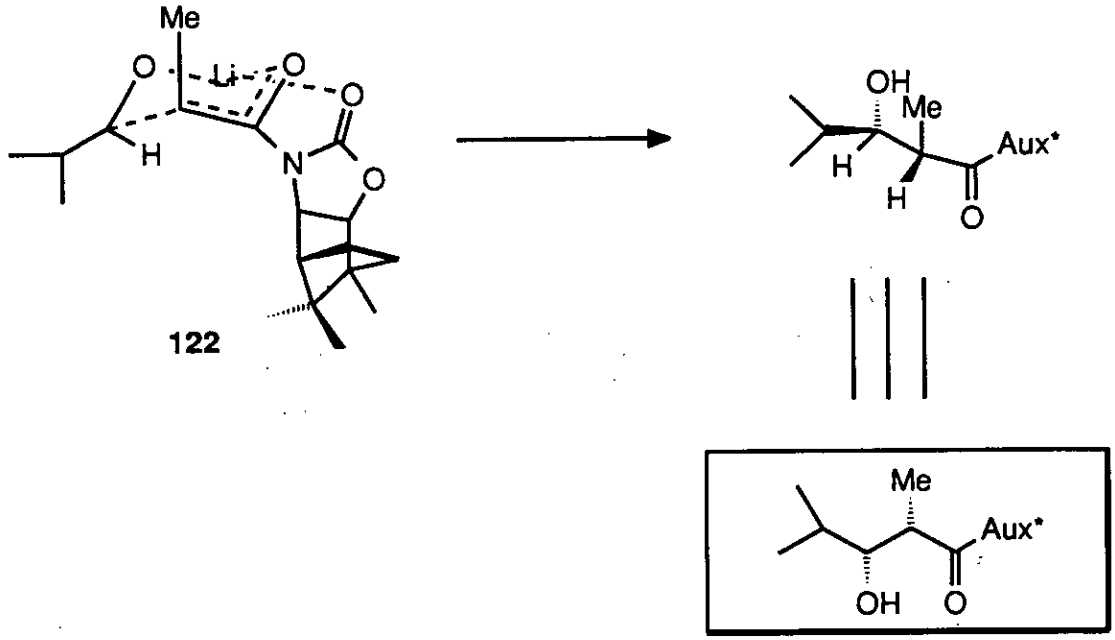
To increase the scope of these lithium enolate-mediated aldol condensations, the aldehydes chosen in addition to benzaldehyde were isobutyraldehye and acetaldehyde. Thus, reaction of **110** with isobutyraldehye with quenching after two minutes yielded a colourless crystalline solid (Scheme 72). A longer reaction time was allowed as one



Scheme 72

anticipated that this aldehyde would be less reactive because of the poorer electrophilic quality of the carbonyl group compared to that of benzaldehyde. This is due to the absence of the α-aromatic group, as well as the increased steric demand imposed by the isopropyl function. Analysis of the crude reaction mixture by high field ^{1}H NMR

spectroscopy revealed the presence of one major product and three minor ones in the ratio 74.0: 9.5 : 8.5 : 8.0, giving an improved d.e. of 48% (Table 8) compared to the benzaldehyde reaction. The major isomer was identified as being an erythro ("syn") isomer by its small vicinal coupling constant, J_{AB} = 2.7 Hz[123]. However, this isomer was not isolated and its identity is therefore unknown but, on the basis of the alkylation work which confirmed that a *Z*-enolate was being formed, combined with a previous understanding of the preferred mode of attack (C_α-re face), and assuming a "closed" Zimmerman-Traxler transition state **122**[124], one can predict that this isomer has the stereochemistry depicted in Scheme 73.



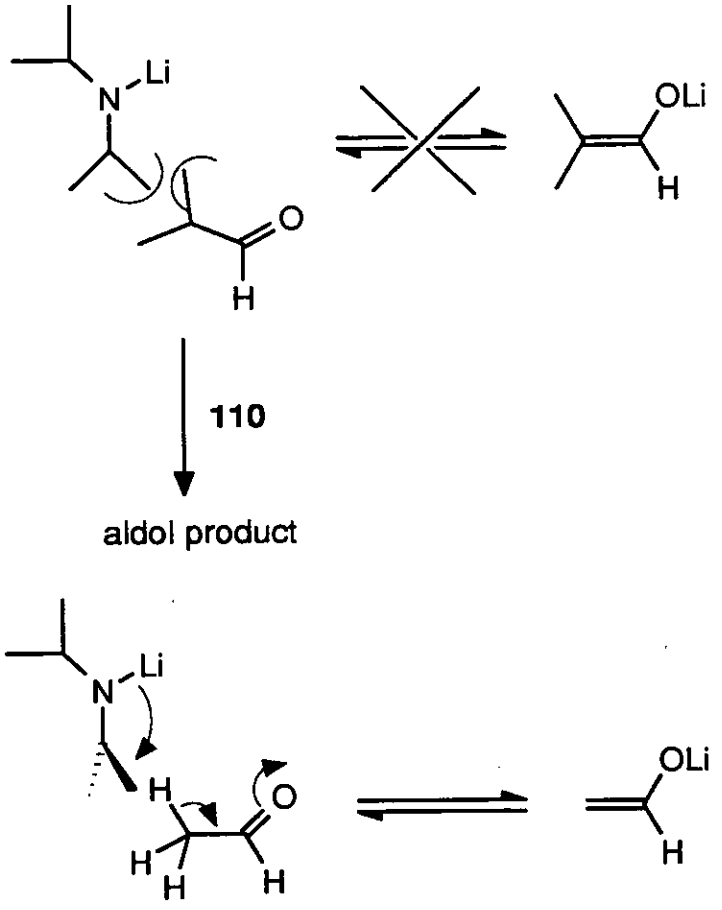
Scheme 73

This prediction is also reasonable when compared to the result obtained with the corresponding boron enolate by Gallagher and Donohoe (*vide infra*).

Treatment of the lithium enolate with acetaldehyde, allowing the reaction to proceed for ninety seconds for this sterically less hindered system, gave the surprising result that about one third of the starting

material remained. Repeating the reaction and allowing it to proceed for three minutes before quenching made no change to the ratio of unreacted to reacted material. This reluctance of acetaldehyde to react with the lithium enolate was a curious observation considering that one could not account for it on the basis of steric arguments, although it could be argued that the enolisation of the aldehyde by the LDA suppresses the aldol reaction. Enolisation is less likely to occur in the case of isobutyraldehye due to steric interactions between the isopropyl groups of the aldehyde and the LDA which inhibit this process (Scheme 74). This enolisation is obviously not a problem in the benzaldehyde case, as it has no enolisable proton and hence it reacts readily. Such a hypothesis has been put forward by Gaur[5] to explain the unreactive nature of aldehydes with α-hydrogens.

Allowing the reaction with acetaldehyde to proceed for one and three quarter hours caused essentially complete consumption of the enolate, as monitored by thin-layer chromatography. Direct comparison of the ^1H NMR spectra of the ninety second and one and three quarter hour reaction mixtures revealed no major difference between the two with the presence of both *syn* isomers in a ratio of 2:1 in each case. A small amount of *anti* isomer (4%) was also present in the one and three quarter hour reaction mixture in addition to dehydration products. The corresponding amount of minor isomers in the ninety second reaction mixture could not be determined due to the complexity of the spectrum.



Scheme 74

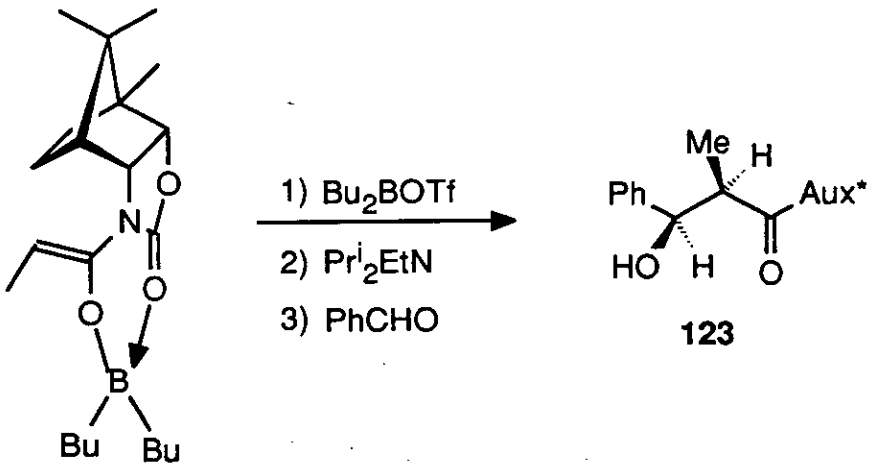
Table 8. Reaction of lithium enolate (110) with representative aldehydes.

RCHO	Reaction time /s	product ratio	d.e. /%
PhCHO	30	55.4 : 28.7 : 10.3 : 5.7	11
isobutyraldehye	120	74.0 : 9.5 : 8.5 : 8.0	48
acetaldehyde	90	31.5 : 15.25[a]	-
acetaldehyde	1.75 hr	64.5 : 31.5 : 4[b]	29

[a] syn isomers only. [b] accompanied by some degradation.

(b) Boron enolate chemistry

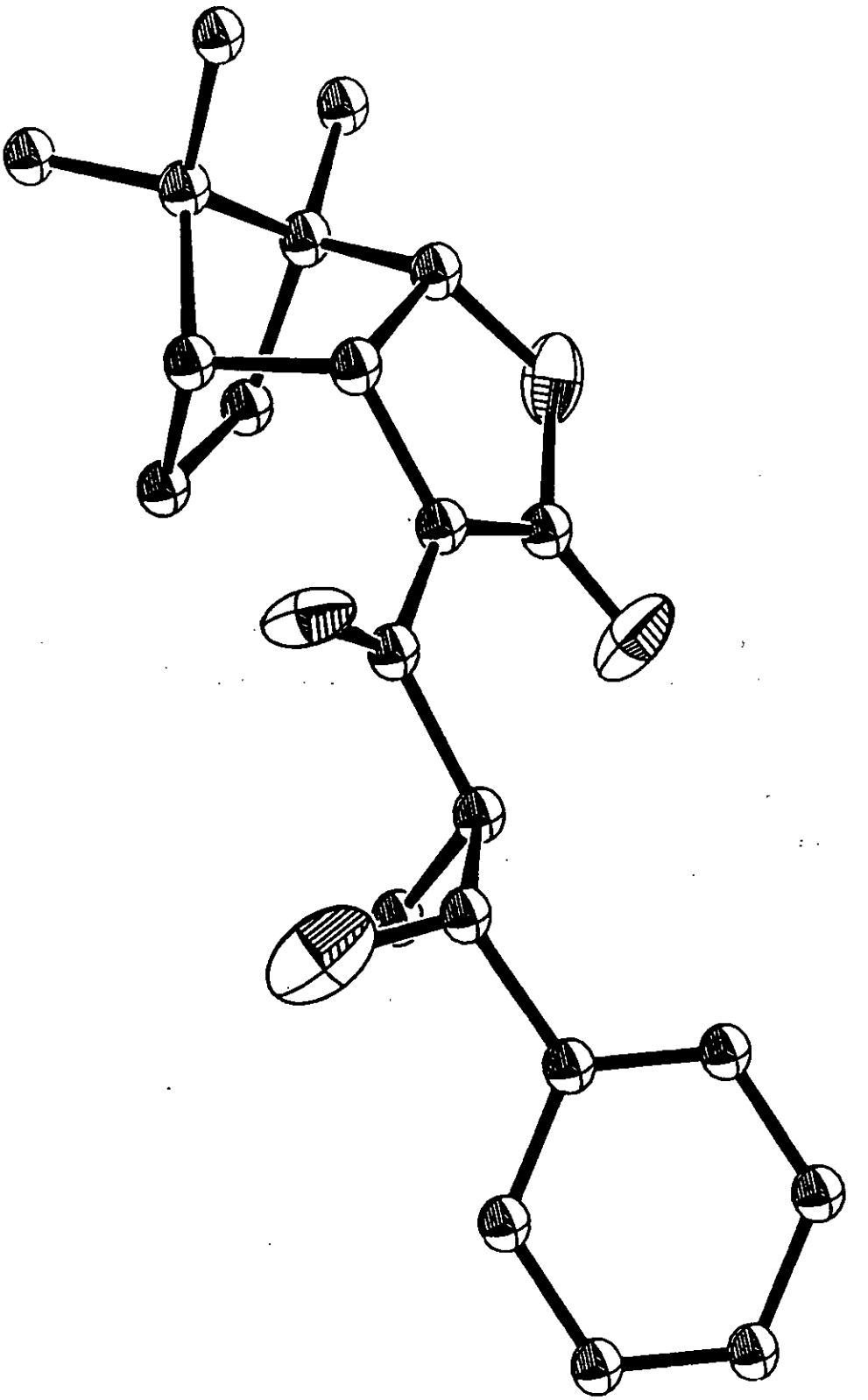
To circumvent the problem of poor selectivity observed with the lithium enolate **110**, Gallagher and Donohoe employed the boron enolate of **78**, generated using dibutylboryl triflate and di-isopropyl ethylamine. Reaction of this enolate with benzaldehyde for thirty minutes at -78^{0}C and one and three quarter hours at room temperature yielded the crude product, which upon purification by flash chromatography, furnished a crystalline single isomer as shown by high field ^{1}H NMR spectroscopy.



Scheme 75

Gallagher and Donohoe obtained an X-ray crystal structure of the product (Figure 21) and confirmed it to exhibit the *syn* structure **123** as depicted in Scheme 75. In addition, these workers treated the boron enolate with isobutyraldehyde, and again high field ^{1}H NMR spectroscopy established that a single isomer had been obtained, the structure of which was not determined, but its *syn* nature could be assumed from the size of the vicinal coupling constant (2.5 Hz) and the α-Me shift in the ^{13}C{^{1}H} spectrum of 10.22 ppm, typical of a *syn* β-hydroxy carbonyl compound[123]. It is not unreasonable to assume that this isomer exhibits the same stereochemistry as the adduct **123**. However, no explanation had been given to account for the observed stereochemistry

Figure 21 X-Ray crystal structure of the benzaldehyde adduct obtained by Gallagher *et al*



and a rationale was required for this purpose.

Rationalisation of stereochemistry of the benzaldehyde adduct **123**

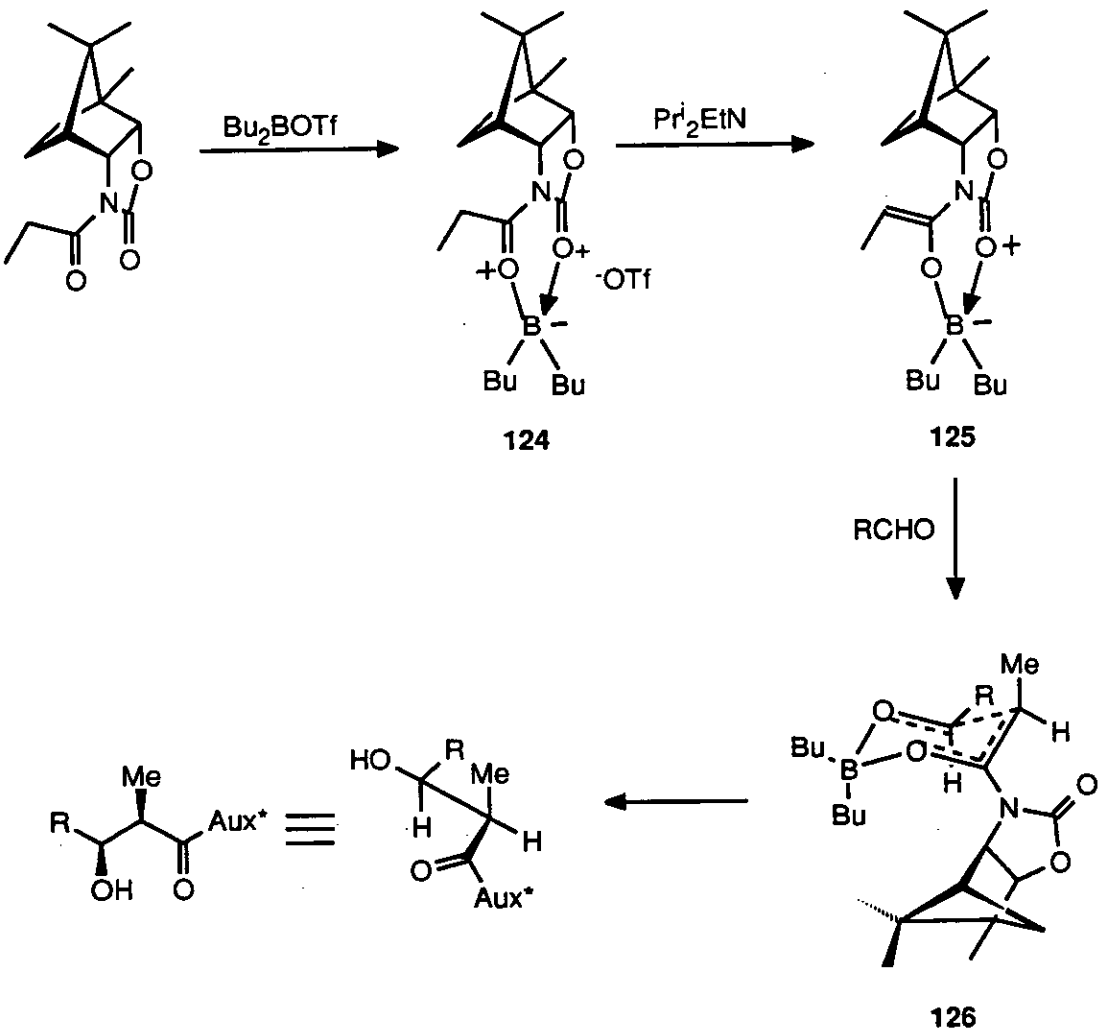
When the di-butylboryl triflate is added to **78**, the boron initially co-ordinates to the oxazolidinone and *N*-acyl carbonyls in a tetrahedral fashion giving complex **124**[125]. Subsequent treatment of **124** with Pr^i_2EtN then forms the boron enolate **125** (Scheme 76) in direct analogy to the lithium enolate, with concomitant formation of di-isopropyl ethyl ammonium hydrogen triflate. Upon addition of the aldehyde, the B-O bond pertaining to the oxazolidinone is cleaved and the auxiliary is free to rotate 180^0 about the N-C bond, to allow the boron to co-ordinate to the oxygen belonging to the carbonyl of the incoming aldehyde. The Zimmerman-Traxler transition state **126** then proceeds, except this time the opposite C_α-si face is open to attack, as the C_α-re face is blocked by the auxiliary.

There are two reasons for the dramatic increase in selectivity :

(i) the fact that the B-O bond is much shorter than the Li-O bond[121] (as stated before) and this makes the transition state "tighter" and increases the steric interactions, especially between the R group of the aldehyde and the auxiliary. As a consequence, the R group is forced to reside in an equatorial position in the chair form shown in Scheme 76; (ii) boron, unlike lithium, carries alkyl ligands which makes the possibility of the aldehydic R group to exist in a stable chair-like transition state in an axial position even more unlikely due to 1,3 diaxial interactions with the axial butyl group of the boron.

Thus, the assumption made earlier which stated that the major adduct from the reaction of **110** with isobutraldehyde is as shown in Scheme 73 is a reasonable one, because the other *syn* isomer would be expected to

form if the opposite face of the enolate is open to attack. Such a reversal of selectivity has also been noted by Thornton *et al*[122] and Yan *et al*[119].



Scheme 76

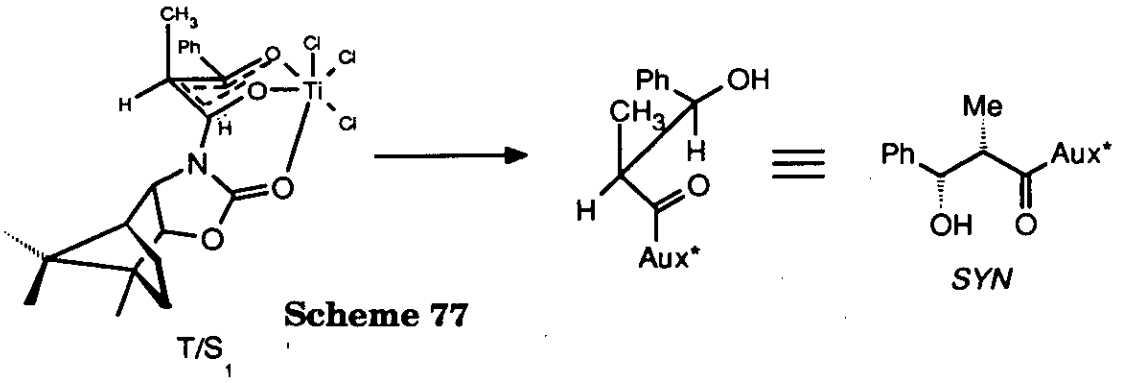
The reaction of acetaldehyde with the boron enolate was then attempted but no product formed, despite a prolonged period of stirring at room temperature. This result is in accordance with the observations made regarding the lithium enolate, the more reactive of the two nucleophiles.

(c) Titanium enolate chemistry

An interesting variation in the aldol reaction is the use of titanium enolates which have been demonstrated to show enhanced selectivities over lithium enolates[122] and importantly avoid the use of relatively expensive dibutylboryl triflate which also cannot be stored for extensive periods without significant decomposition.

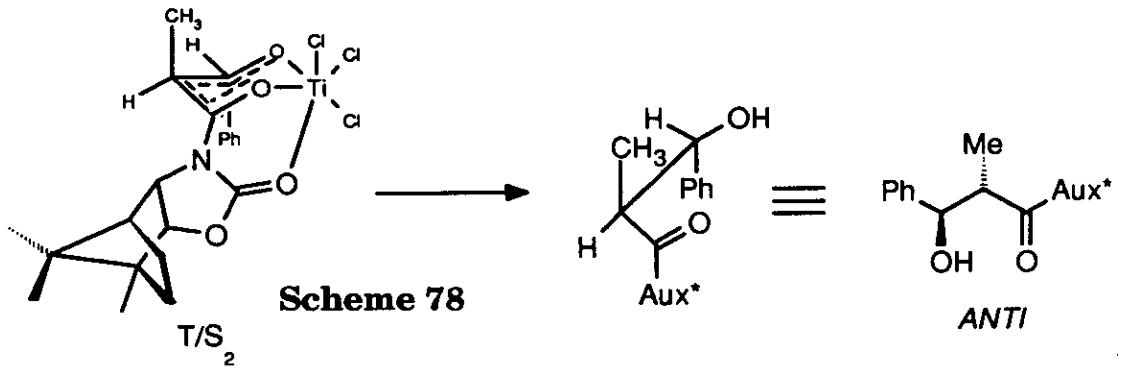
Initially the protocol adopted followed that of Evans *et al*[126] whereby a methylene chloride solution of **78** was treated with titanium tetrachloride (1.1 equivalents), followed by dropwise addition of triethylamine (1.35 equivalents). Upon addition of the base, the solution turned from a light yellow to an intensely deep purple, in contrast to the deep red solution reported by Evans[126]. This change in colour indicated the advent of a charge-transfer complex (the chlorotitanium enolate), in which the intense colour can be attributed to a ligand to metal $\pi \rightarrow \pi^*$ transition[127]. After addition of freshly distilled benzaldehyde at -78^{0}C the purple colour persisted for five minutes before it gradually changed to a brown colour. After *ca.* three quarters of an hour the solution had faded to a light brown colour and was examined by thin layer chromatography, which revealed that some propionate still remained. After three hours at -78^{0}C no more propionate appeared to have been consumed, whereupon the reaction was quenched and the resultant crude sticky crystalline material was analysed by high field ^{1}H NMR spectroscopy. This gave the very interesting result that only two isomers were present and these could be identified as *anti* and *syn* in the ratio 6 : 5 by their respective vicinal coupling constants of 8.0 and 4.2 Hz. The observation of the formation of excess of the *anti* adduct is also significant since this is contrary to theory if one proposes a "closed" Zimmerman-Traxler transition state with

chelation control[120], depicted in Schemes 77 and 78, as was the case for the lithium enolate system. One can conclude that although one face of the enolate is sterically shielded by a combination of the auxiliary and



Scheme 77

T/S$_1$



Scheme 78

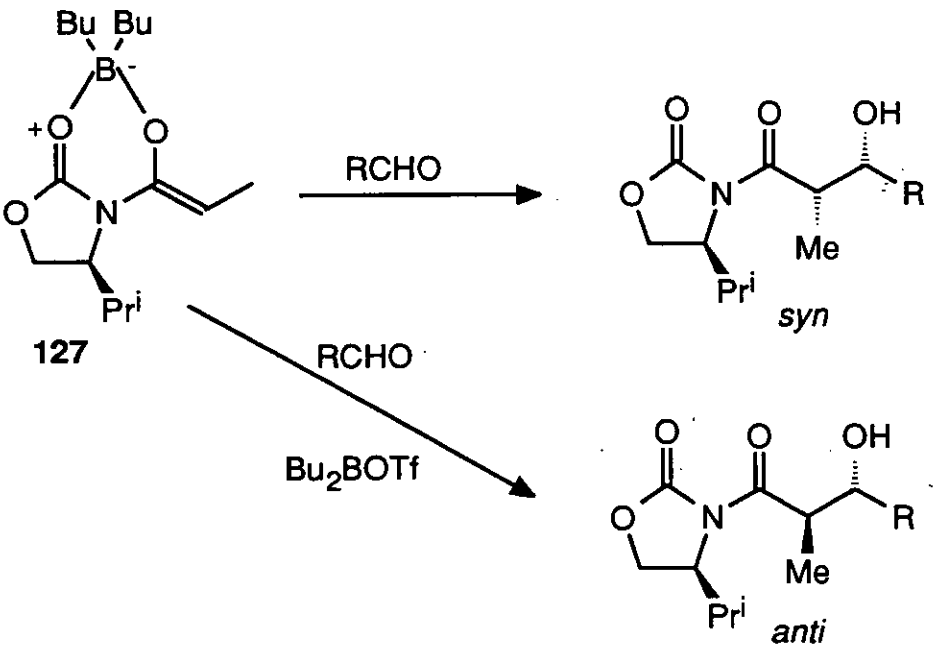
T/S$_2$

chlorine ligands, the other face is open to attack, but the difference in the diastereomeric transition states T/S$_1$ (Scheme 77) and T/S$_2$ (Scheme 78) is small because there is no significant preference for either. One could argue that there is a slight excess of *anti* isomer because of 1,3 axial/equatorial strain present in the T/S$_1$ transition state between the phenyl and methyl group causing the T/S$_2$ transition state to be favoured.

In the case of the boron enolate chemistry the transition state is tighter, and the axial phenyl shown in T/S$_2$ would have much more serious interactions with the auxiliary and metal ligands, favouring the formation of the *syn* isomer.

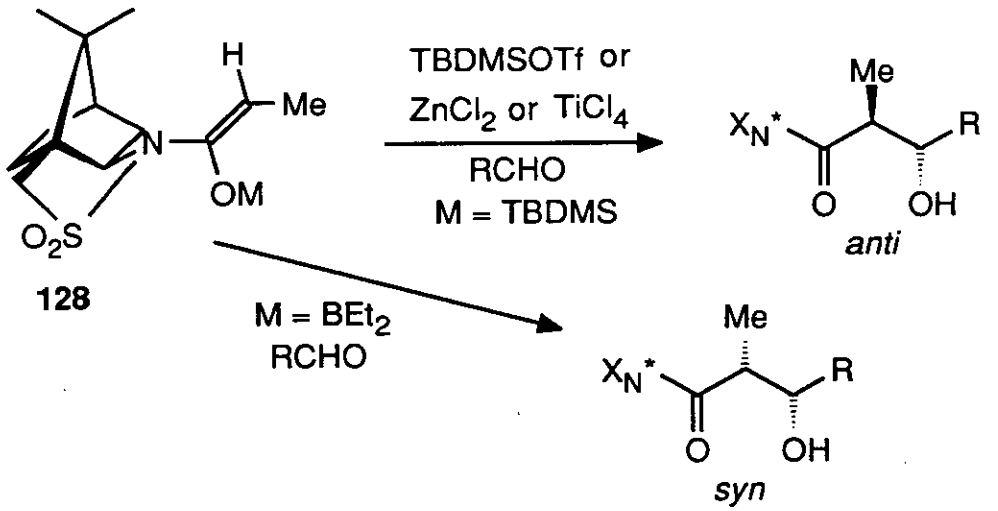
In an attempt to improve the selectivity, the reaction conditions were altered. Use of *ca.* five equivalents of titanium tetrachloride with

triethylamine as base caused a very sluggish reaction to ensue. The reaction was then allowed to warm to room temperature and stirred for a protracted period of time due to significant quantities of starting material which remained. Even so, a considerable amount was still unreacted and the reaction was quenched and studied by high field ^{1}H NMR spectroscopy which revealed that the reaction had gone to *ca.* 30% completion. However, the most striking feature was the predominant formation of two *threo* adducts (J = 11 and 7 Hz for the carbinol resonances) in the ratio 4 : 1. Reference to the literature showed that this is not unexpected for example, Danda *et al*[125] reported that Evans' boron enolate-derived system **127** (Scheme 79) gives *syn* adducts in the absence of Lewis acid, but in the presence of excess Bu_2BOTf furnishes *anti* aldol products. Similarly, Oppolzer *et al*[26,27] found that Lewis acid-mediated aldol reactions of the TBDMS enol ether **128** gave *anti* aldol products (Scheme 80). Analogous observations have been made by Walker and Heathcock[128] and Xiang *et al*[129].



Scheme 79

The generally accepted reason for this change in selectivity appears to be a switch from the closed Zimmerman-Traxler transition state to an open one; this is brought about by the excess of Lewis acid which co-ordinates to the aldehyde. The system can then react *via* either transition state A

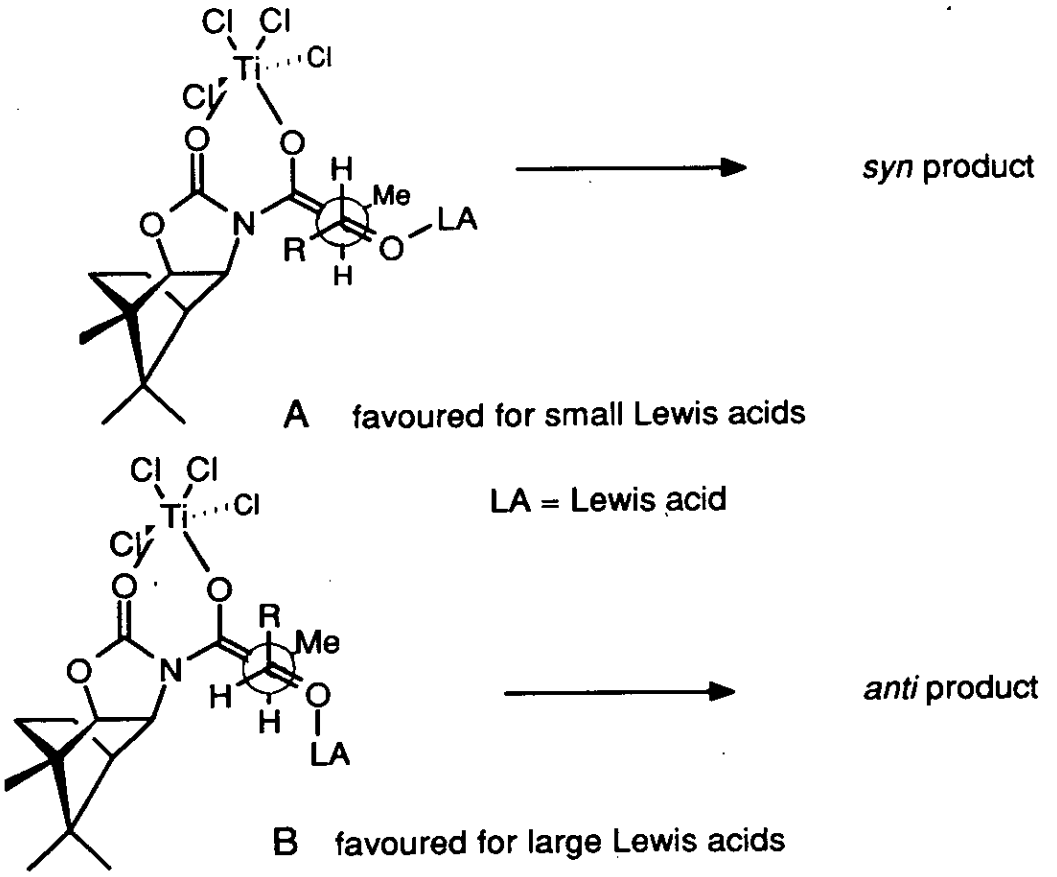


Scheme 80

or B as depicted in Scheme 81. In A, the gauche interactions about the ends of the forming bond are minimised, together with minimisation of interactions between the Lewis acid and the R group of the aldehyde[128]. However, if the Lewis acid is large enough, the Lewis acid-methyl interaction becomes important and transition state B predominates, giving rise to *anti* products.

It would appear that B is favoured in this case, possibly aided by the fact that the hexadentate titanium carries chlorine ligands which interact with the chlorine ligands of the Lewis acid attached to the aldehyde. This would disfavour transition state A, making transition state B more likely to occur.

In addition to the use of excess titanium tetrachloride, the base was changed to di-isopropylethylamine, an alternative to triethylamine[126],

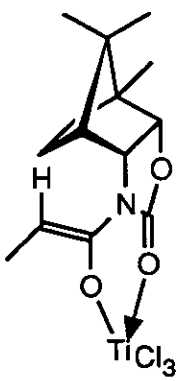


Scheme 81

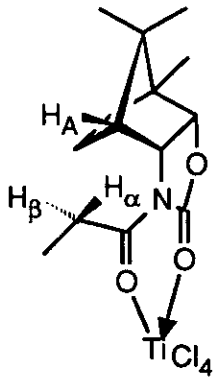
which has been shown by Danda *et al*[125] to dramatically change the *syn/anti* selectivity compared to that obtained with Et_3N in analogous boron enolate mediated reactions[125]. Use of this base also caused the advent of a deep purple colouration, but despite a prolonged time at ambient temperature, the reaction yielded no product. This was unexpected since some product formation was observed with triethylamine as base. In order to explain this result the chemical nature of the reactants prior to the addition of the aldehyde were studied by high field ^1H NMR spectroscopy.

The enolate was generated using Pr^i_2EtN and excess titanium tetrachloride but in deuteriated chloroform, instead of methylene chloride, and the purple colour was observed to form as before. On warming the solution to room temperature, the purple colour changed to

dark brown and a precipitate of di-isopropylethylamine hydrogen chloride was formed. The filtered solution was then studied by 360 MHz ^{1}H NMR spectroscopy, which revealed the absence of the expected olefinic quartet for enolate species **129** (Figure 22) (*cf.* the acylation work with Chirabornox, page 104).



129

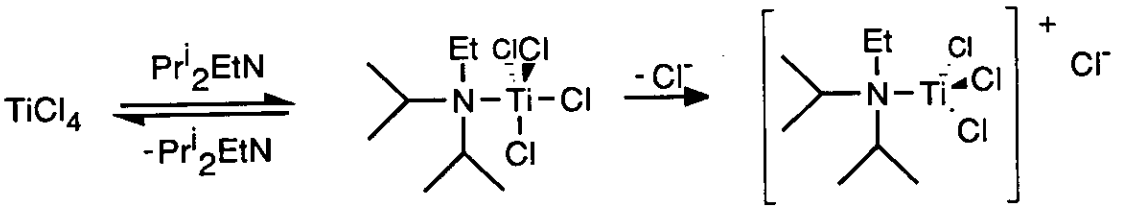


130

figure 22

Instead, it was found that complex **130** was present; this was apparent for two reasons: firstly, the diastereotopic protons H_α and H_β had very distinct chemical shifts and each appeared as a doublet of quartets due to coupling to both the geminal proton and methyl group. This indicated that the *N*-acyl function had adopted a "frozen" conformation, as depicted in **130**. Indeed, the diastereotopic protons H_α and H_β have almost the same chemical shift in the freely rotating system (*i.e.* with no Lewis acid present) and each shows a quartet which are distinguished only by the effect of the local chiral environment due to the bornane moiety. Secondly, in NOE studies, irradiation of the bridgehead proton H_A in **130** caused a 2.5% enhancement of the signal due to H_β, but negligible enhancement of the H_α signal, confirming the "locked" conformation of the complex. In addition to these findings, the signals of the complex were shifted downfield relative to the spectrum of the free propionate, indicative of electron donation to the titanium.

In conclusion, it would appear that the lack of product formation is due to the interaction of the base with the titanium tetrachloride; all of the di-isopropylethylamine appears to have been consumed by the Lewis acid as shown in Scheme 82. Such a hypothesis has already been put forward to



Scheme 82

explain why a conjugate base releases the chlorine ligand so readily in Co^{III} amine systems[130]. Thus, only a small amount of enolate is required to produce an intense purple colour; this would be produced by the small amount of amine that had not been consumed by the Lewis acid. One can only assume that in the case of triethylamine, expulsion of chloride occurs less readily due to less steric interaction to be relieved in a triethylamine/titanium tetrachloride system when compared to that of the corresponding diisopropyl ethylamine system. A further assumption is that the initial base/titanium tetrachloride reaction is reversible, as depicted in Scheme 82.

It was of interest to test the hypothesis that the excess base consumed the excess titanium tetrachloride. If this were so then the outcome of the original experiment, in which there was no excess of Lewis acid, would be repeated. In fact, use of excess titanium tetrachloride (2.3 equivalents) with an excess of triethylamine (2.5 equivalents) gave the same result in that the *anti* ($J_{vicinal}$ = 8 Hz) and *syn* ($J_{vicinal}$ = 4.2 Hz) products had formed, and their respective ratio was exactly the same (6 : 5). Since one reaction had been quenched at -78^{0}C and the other at ambient

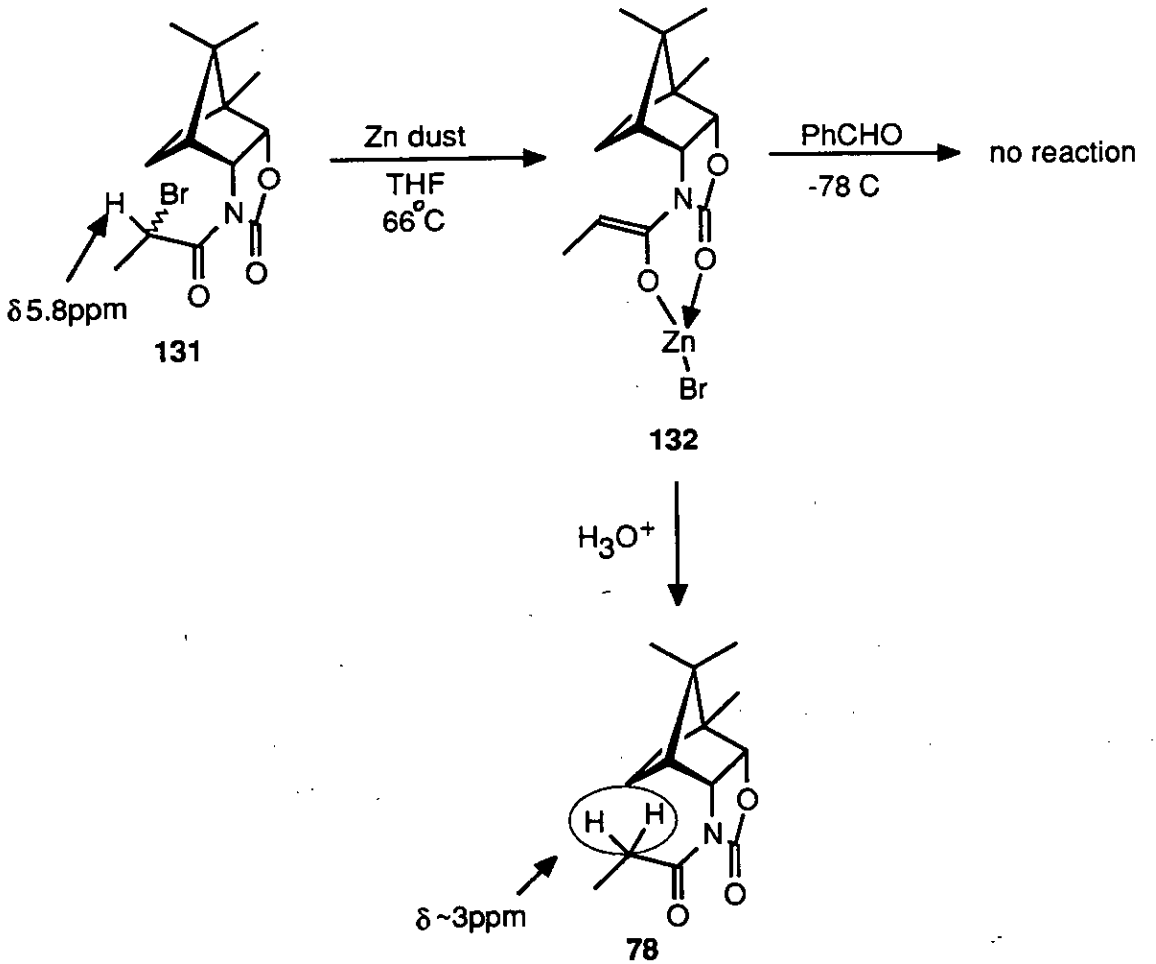
temperature, one could not say that *syn/anti* equilibration[131] had occurred since the ratio remained unchanged. Furthermore, the *anti* product with $J_{vicinal}$ = 11 Hz was not formed by equilibration with excess triethylamine and consequently must be produced directly in the reaction.

Three coupling constants of greater than or equal to 7 Hz had been found, and the structures pertaining to these couplings had all been assigned the *anti* configuration. Of course only two *anti* isomers are possible and it is not understood why there are three distinct couplings.

(d) Zinc enolate chemistry

In contrast to the lithium, boron and titanium enolate chemistry, zinc enolates have received scant attention in relation to oxazolidinone-derived carboximides. Ito and Terashima[132] have employed a number of 3-(2-bromopropionyl)-2-oxazolidinone derivatives for aldol reactions over a temperature range of -78^{0}C to +67^{0}C. Zinc enolates are attractive candidates for study, since they appear to function at higher temperatures and consequently open up the possibility of carrying out alkylation reactions with less reactive alkyl halides. This is a situation which was not possible with the corresponding lithium enolate **110**. Accordingly, the racemic 2-bromopropionate **131** was synthesised from (+/-)-2-bromopropionyl bromide and the lithiated oxazolidinone **100**. The zinc enolate **132** was generated by the dropwise addition of a THF solution of **131** into a heated suspension of freshly activated[133] zinc powder in dry THF, which had been pre-treated with ultrasound[134]. After boiling for *ca.* one hour, the solution was cooled to -78^{0}C whereupon freshly distilled benzaldehyde was added. Quenching after several

minutes and subsequent work-up provided an oily solid which was shown by 60 MHz ^{1}H NMR spectroscopy to be the propionate **78** by the absence of the characteristic quartet at δ 5.8 ppm and the appearance of another quartet at δ 3ppm (Scheme 83).



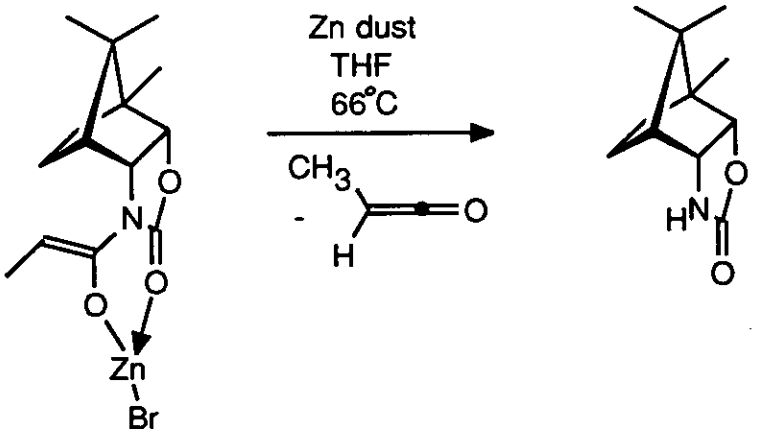
Scheme 83

The reaction was repeated under different conditions, including ultrasound treatment and prolonged boiling in THF. Disappointingly no aldol reaction occurred under any of these conditions, except the generation of auxiliary **77** when the solution was boiled.

The formation of **77** can only be attributed to the zinc enolate **132** undergoing cleavage *via* the ketene, as depicted in Scheme 84, which is the analogous process for the lithium enolate system, except that it occurs

at elevated temperatures. No other route to Chirabornox is possible, since it is known that **78** and **131** are thermally stable at temperatures in excess of 150^{0}C. Therefore the enolate must have formed or no cleavage product would have been observed.

In conclusion, it can be stated that the zinc enolate **132** shows no reactivity towards benzaldehyde at temperatures below that at which the enolate is readily cleaved.



132

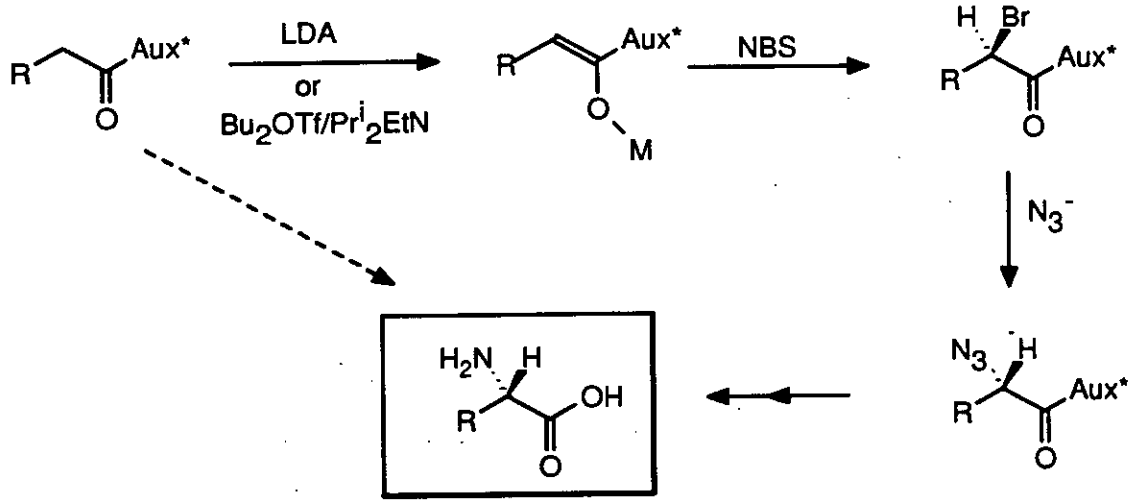
Scheme 84

In an attempt to overcome this problem, the zinc enolate was added to the benzaldehyde which had been pre-complexed with diethylaluminium chloride. Unfortunately, no aldol products could be detected despite extended stirring at ambient temperature.

Chapter 5

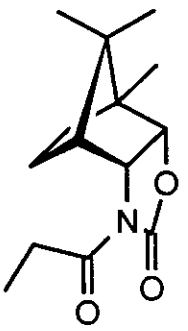
Asymmetric α-bromination reactions of enolates derived from the propionate (78) of Chirabornox

Following the efforts of Evans and Oppolzer to carry out α-bromination reactions from boron enolates[35] and *O*-silyl ketene acetals[76] with N-bromosuccinimide (NBS), similar methodology was explored using the propionate **78** as starting material. This reaction is of key importance in the synthesis of α-amino acids (Scheme 85).

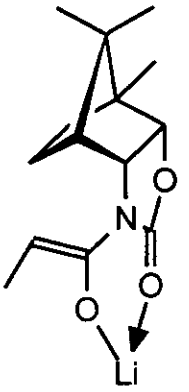


Scheme 85

Initial studies began with the lithium enolate **110** and the examination of the selectivity of its reaction with NBS. This served as a platform for the attempted synthesis of the model amino acid system (L)-(+)-alanine. Treatment of **110** with NBS at -78^{0}C for forty minutes and subsequent analysis by thin-layer chromatography showed that both possible epimers from attack by bromine at different faces of the enolate (Scheme 86) had formed, although significant amounts of starting material still remained. After a total of three hours reaction, no apparent change could be

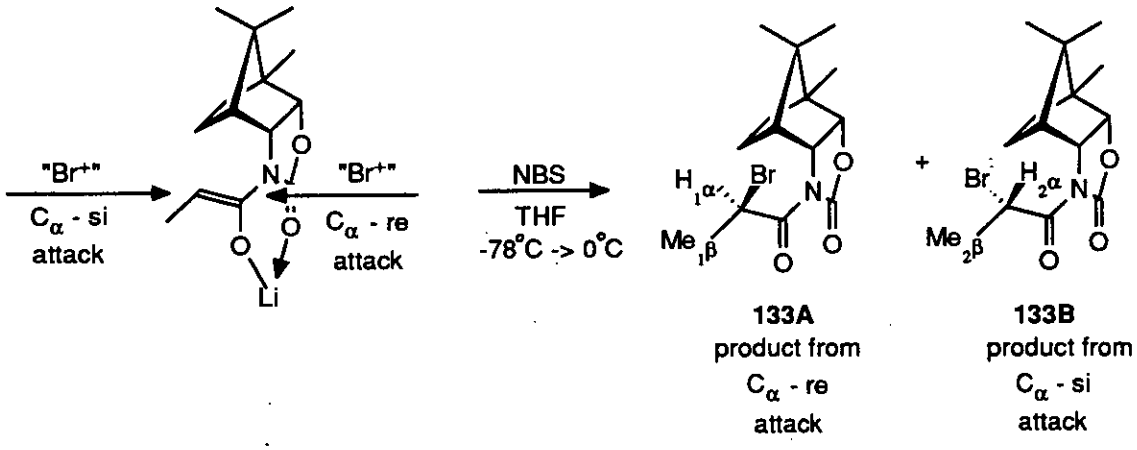


78



110

detected and the reaction was allowed to warm to -8^{0}C with stirring overnight. Quenching of the reaction and subsequent analysis by ^{1}H NMR spectroscopy showed that only small amounts of starting material (20%) remained, together with the two products. According to thin-layer chromatography, the spot with the higher R_f value was the fainter of the two and well separated from the slower running more intense spot. The minor isomer was easily separated from the mixture by flash chromatography on silica, although the major isomer could not be separated from unreacted **78**.



Scheme 86

The ratio of epimers **133A** and **133B** could not be determined by analysis of their ^{1}H NMR spectrum due to overlap of the signal due to $H_{1\alpha}$ and $H_{2\alpha}$ (Scheme 86). To overcome this problem, the pair of doublets due to

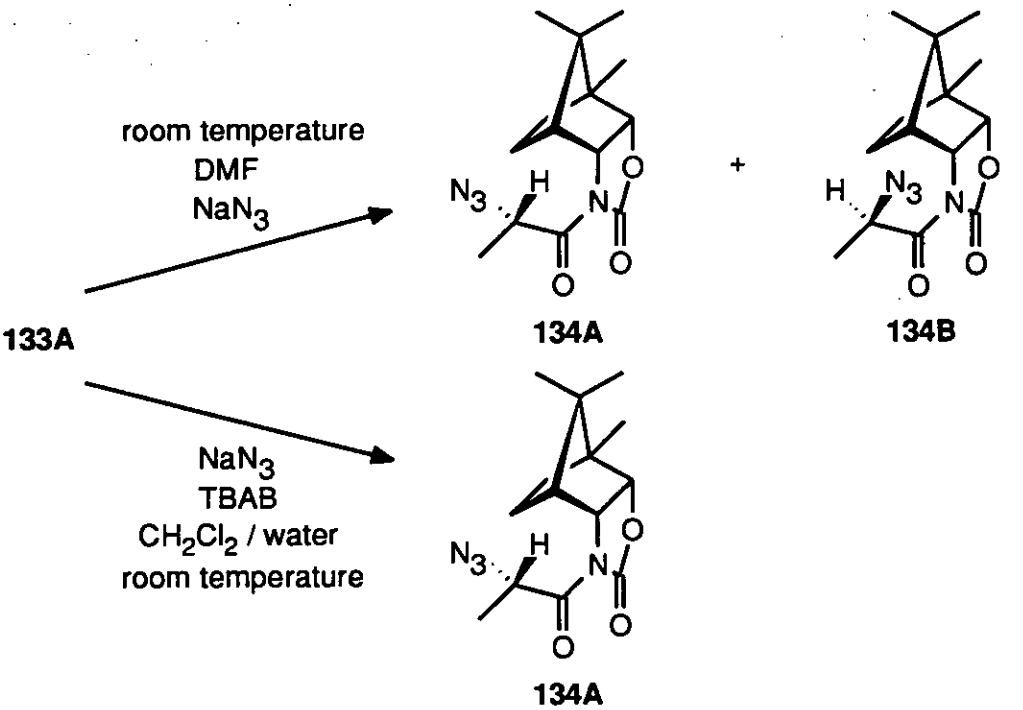
the vicinal methyl groups $Me_{1\beta}$ and $Me_{2\beta}$ were decoupled in order to make the said methine protons collapse to separated singlets. This technique yielded an isomer ratio for the two products depicted in Scheme 86 of 6 : 1. This selectivity is poorer than that obtained for the corresponding alkylation reactions of **110** (see chapter 3) but the superior electrophilic qualities of NBS over alkyl halides is evident from the facile nature of the reaction.

In sharp contrast, employment of the boron analogue of enolate **110**, synthesised under the conditions described in chapter 4, and reaction with NBS led to a dramatic increase in the ratio to approximately 60:1, *i.e.* the reaction was essentially stereospecific.

From consideration of a model of the enolate **110** it is evident that electrophilic attack can occur from both faces, although it can be expected that the C_α-re face is the preferred mode of attack by "Br^+" (Scheme 86). On this basis one would predict **133A** to be the configuration of the major epimer. In order to substantiate this prediction, it is worth noting that the corresponding α-chloro isomers of **133** had been synthesised previously by Banks and Dawson[135] and the isomer with the higher R_f value was proven to be the chlorine analogue of **133B** by X-ray crystallography. The ^1H NMR spectrum of this isomer revealed that the protons geminal to the nitrogen and oxygen of the oxazolidin-2-one ring had very similar chemical shifts, in contrast to its epimer which had distinctly different chemical shifts for these protons. The ^1H NMR spectrum of the minor α-bromo isomer showed the oxazolidinone protons to have a very similar spectral pattern to the faster running α-chloro isomer, but the ^1H NMR spectrum of the major α-bromo isomer had distinctly different chemical shifts and a pattern in keeping with its analogous slower running α-chloro isomer. These findings are consistent

with the prediction that the major α-bromo isomer has the (2'*R*) configuration as depicted in **133A**. Further evidence to support this claim followed treatment of **133A** with sodium azide and subsequent removal of the auxiliary by transesterification as the following describes.

The second stage in the attempted synthesis of L-(+)-alanine concerned the nucleophilic displacement of bromide by azide ion. Thus, treatment of chirally pure **133A** with sodium azide in DMF at room temperature for a prolonged period of time yielded the required α-azido product **134** as evidenced by the loss of the quartet at δ 5.8 ppm and the appearance of another at δ 5.0 ppm. Examination of this compound by high field ^{1}H NMR spectroscopy revealed that *ca.* 30% racemisation had taken place, as shown by the doubling of peaks at δ 1.55 ppm for the methyl group adjacent to the azide. It is not known whether this racemisation occurred due to warming of the reaction mixture to remove DMF (under high vacuum), or was produced by the action of azide ion (Scheme 87).



Scheme 87

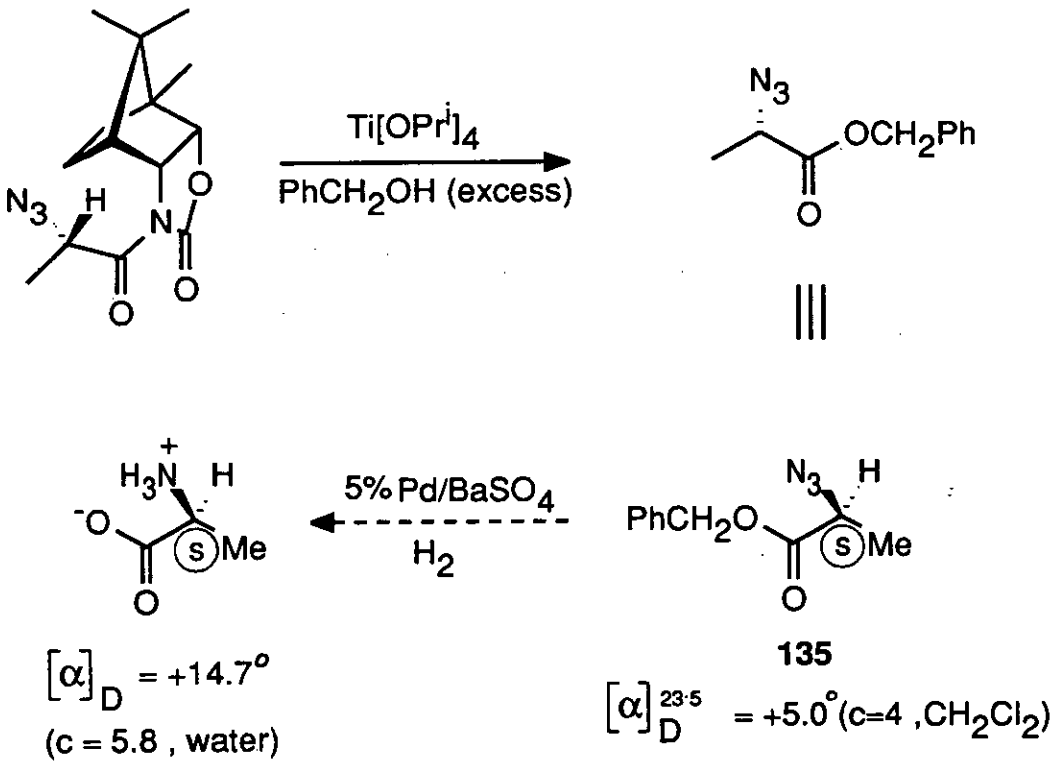
In an attempt to overcome the problem of racemisation, the reaction was carried out under phase-transfer conditions (CH_2Cl_2 / H_2O) in the presence of tetrabutylammonium bromide as catalyst. Under these conditions the azido compound **134A** was formed in 75% yield and did not appear to have undergone racemisation to any extent that could be detected by high field ^1H NMR spectroscopy.

During attempts to purify the bromo derivative **133A** it was found that it could be isolated in an optically pure state by column chromatography, but that further purification by recrystallisation from diisopropyl ether induced a small amount of epimerisation, as shown by thin-layer chromatography. This discovery was serendipitous, as it provided a sample with a known initial ratio of α-bromo isomers, which could be subjected to the S_N2 reaction with azide. The ratio of α-azido products **134A** and **134B** would then indicate any deviation from the initial ratio of the α-bromo epimers. Accordingly, a specific α-bromo sample which had been shown to contain both **133A** and **133B** in the ratio of 85 : 15 was allowed to undergo nucleophilic displacement with azide under phase-transfer conditions. Isolation of the crude product gave a corresponding ratio of 87.5 : 12.5 which established unequivocally that epimerisation had not taken place during the reaction.

Removal of the appended auxiliary with titanium tetraisopropoxide and benzyl alcohol under the extremely mild conditions prescribed by Seebach *et al*[136] yielded, after chromatography, the α-azido benzyl ester **135** only in moderate yield (38%) (Scheme 88). This low yield of product may be due to the poor quality of the titanium tetraisoproxide used, but unfortunately the reaction could not be repeated due to the small quantities of material in hand and a lack of time. In fact, the final step of hydrogenolysis to reduce the azide function to amine and ester to acid

could not be carried out for the same reason, but the sign of the optical rotation of **135** was found to be positive ($+5.0^0$).

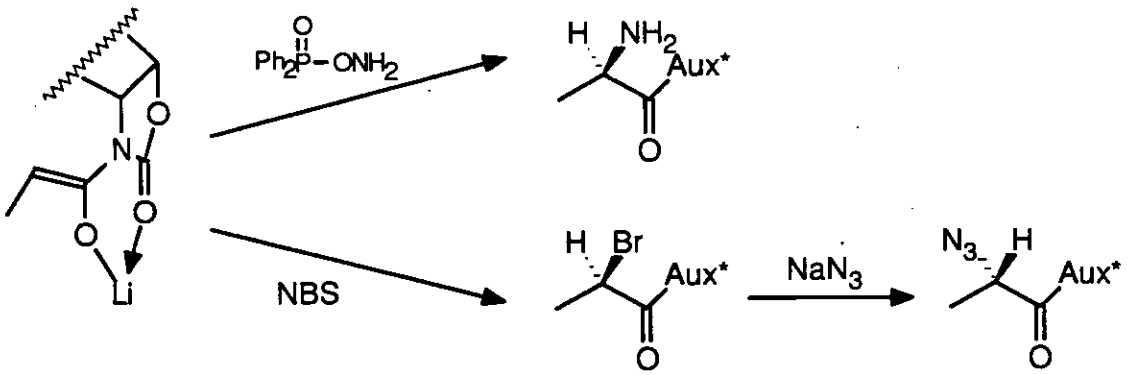
Despite the fact that **135** does not represent the final target molecule (L-(+)-alanine), all of the necessary groupings are directly attached to the chiral centre and it is difficult to imagine that the conversion of azide into amine and $COOCH_2Ph$ into COOH would lead to any inversion in the sign. Hence, when compared to the value of $+14.7^0$ for the optical rotation of authentic L-(+)-alanine (*S* isomer), it can be safely concluded that the stereochemistry of the ester **135** is as shown in Scheme 88. This result also provides further proof that the stereochemistry of the α-bromo carboximide **133A** is (2'*R*).



Scheme 88

It is of course possible to aminate the enolate **110** directly, without resorting to the extra step of azide reduction, by using the reagent *O*-(diphenylphosphinyl) hydroxylamine[137] as a source of "electrophilic

amine". This would also be a route to non-proteinogenic amino acids by direct amination of the C_α-re face of the enolate, since it avoids the S_N2 displacement step (Scheme 89). However, attempts to carry out the reaction under various conditions failed.



Scheme 89

Finally, in an attempt to understand the epimerisation of **133A** to **133B**, reference to the X-ray crystal structure of the previously mentioned α-chloro isomer (Figure 23) showed how in the crystal the chlorine group avoids interactions with the auxiliary by allowing the propionyl methyl group to point towards the bornane ring. Also, dipole-dipole interactions between the carbonyl groups are avoided in this conformation. In the other epimer the halide now points unfavourably towards the oxazolidinone ring (compare Figure 24a with Figure 24b). When **133A** is considered (Figure 24c), these interactions are even more severe due to the increase in size of bromine relative to chlorine. Raising the temperature, *i.e.* during recrystallisation, are likely to make these interactions even more unfavourable and promote epimerisation, presumably through enolisation. In fact, allowing a solution of the α-bromo carboximide to stir over silica did not induce epimerisation, showing that heat was necessary to bring about this process.

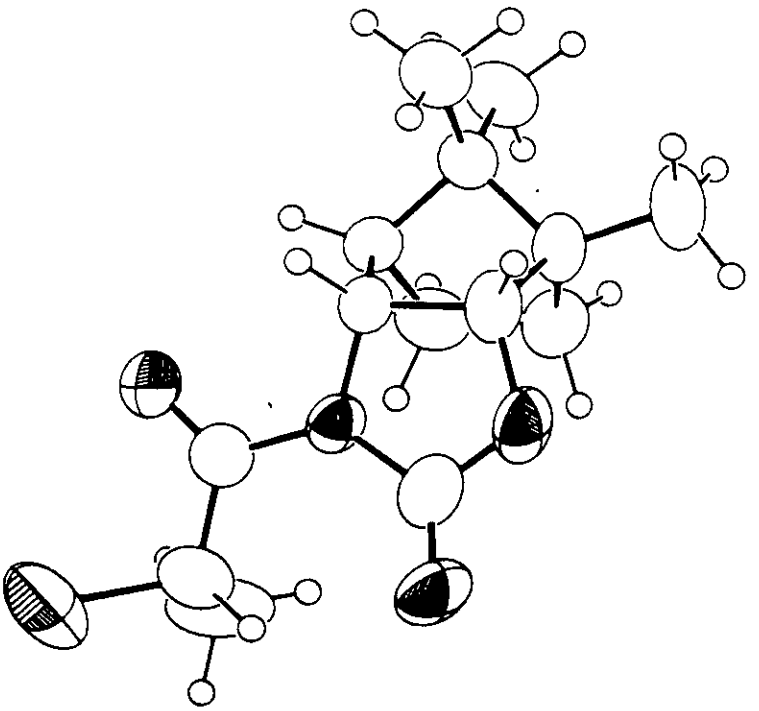
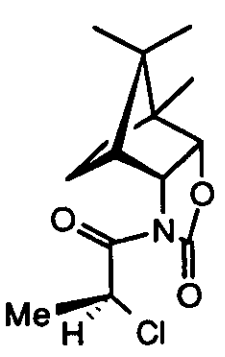
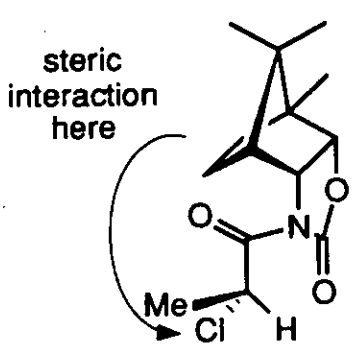


Figure 23. X-ray crystal structure of the α-chloro isomer with the higher R_f value



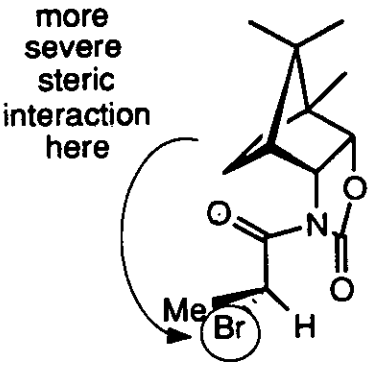
chlorine analogue
of **133B**
(as X-ray)

Figure 24a



chlorine analogue
of **133A**

24b



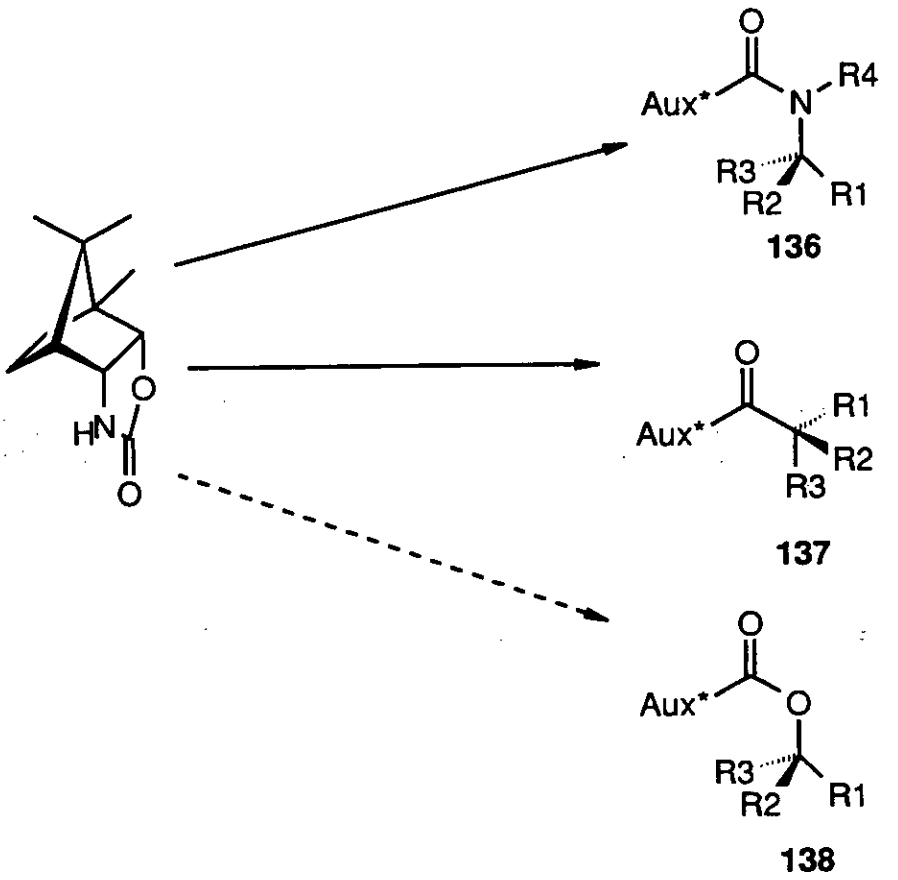
133A

24c

Chapter 6

The resolution of racemic alcohols using Chirabornox

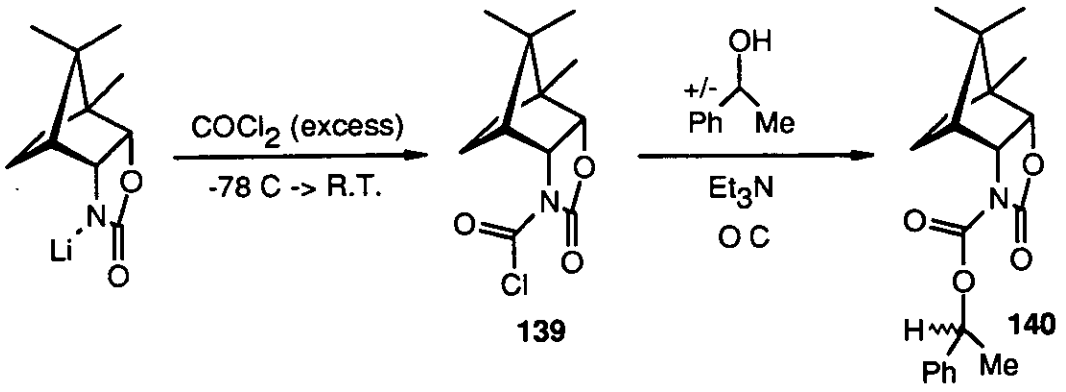
In earlier work in the laboratory by Banks *et al*[135], Chirabornox **77** had been shown to be an effective reagent for the resolution of racemic mixtures of amines *via* the diastereomeric allophanates **136** (Scheme 90) and of carboxylic acids *via* the diastereomeric carboximides **137**. However, the resolution of alcohols *via* the diastereomeric carbamates **138** had not been examined.



Scheme 90

The oxygen analogue of racemic 1-phenylethylamine, 1-phenyl ethanol was thought to be the most desirable alcohol to study as it is readily available and possesses an aromatic group to allow detection by U.V.

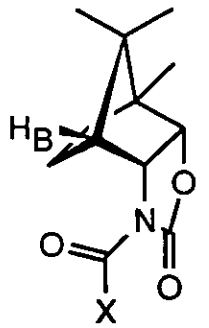
spectroscopy, desirable for HPLC analysis. In order to prepare the required diastereomeric carbamates from this alcohol and **77**, the same protocol as used for the allophanate synthesis was adopted, whereby the carbamyl chloride **139** (Scheme 91) was prepared from lithiated oxazolidinone **100** and phosgene. Subsequent treatment of 1-phenyl ethanol by dropwise addition of a methylene chloride solution of **139** at 0^0C using triethylamine as base, furnished a light brown oil after stirring overnight.



Scheme 91

Following work-up, analysis of the crude reaction mixture by high field ^{1}H NMR spectroscopy showed that the product **140** and unreacted auxiliary were present in a respective ratio of 20:17. In an attempt to improve the yield of the diastereomeric carbamates **140**, the reaction was repeated but with the use of of 4-dimethylaminopyridine (DMAP) as catalyst. The solution was heated under reflux in THF for a prolonged period since it was observed that stirring at room temperature for *ca.* 18 hours produced only traces of product. High field ^{1}H NMR examination of the reaction showed that very little auxiliary remained, but the yield of desired product was correspondingly low. Moreover, close examination of the spectrum revealed that the auxiliary was now functionalised by a different species, of the structural type **141** (Figure 25); this was

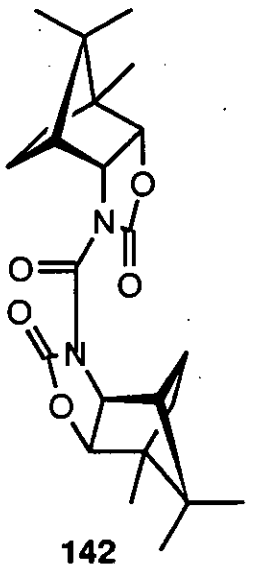
indicated by the shift of the bridgehead proton, H_B, which occurred at over 2ppm whereas in the parent unfunctionalised molecule **77**, H_B resonates below 2ppm.



141

Figure 25

Chromatography of the reaction mixture afforded an almost quantitative yield (*ca.* 90%) of a colourless crystalline solid, shown by FAB-mass spectrometry to have the formula $C_{23}H_{32}N_2O_5$, therefore identifying it as the dimer **142** shown in Figure 26. The question of its formation was of

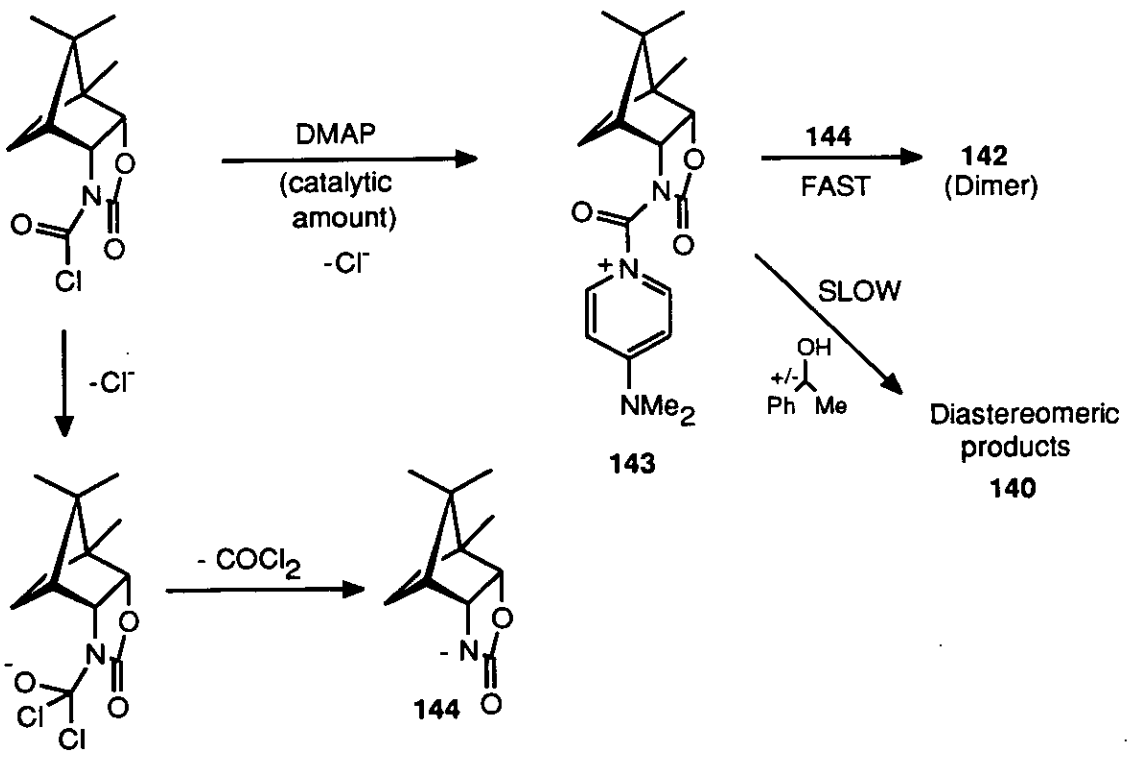


142

Figure 26

interest; it was initially difficult to imagine how two carbamyl chloride molecules **139** could combine to give **142**. However, consideration of the

mechanism of action of DMAP[138] led one to the conclusion that its formation must proceed *via* the intermediate species **143** (Scheme 92),

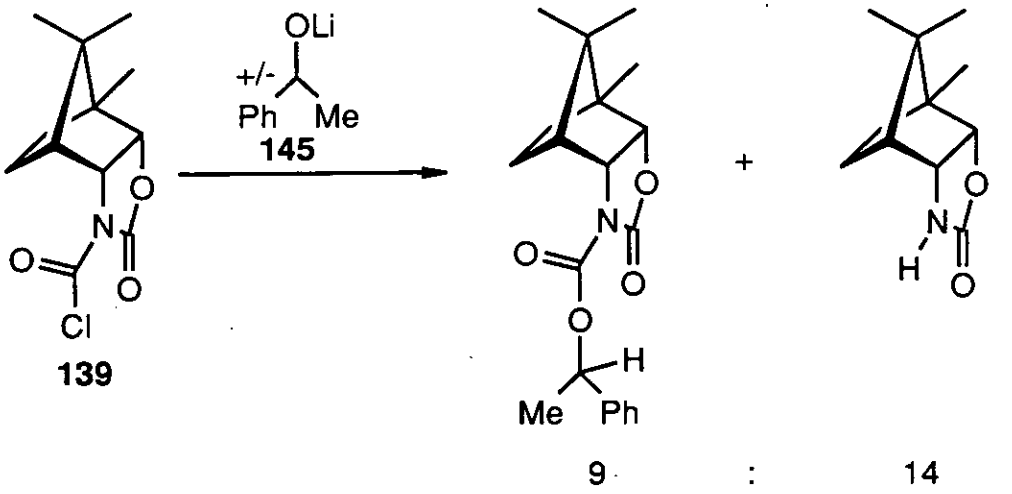


Scheme 92

which can then undergo reaction either with the alcohol to form **140**, or condense with the anion **144** to give dimer **142**. The former is presumably generated as shown in Scheme 92 by cleavage of the *N*-acyl group with expelled chloride ion, which generates phosgene. It would appear that reaction of **143** with the newly released Chirabornox anion **144** is more favourable than with the secondary alcohol. In addition, the presence of the dimer is proof that the carbamyl chloride intermediate is forming in the initial reaction.

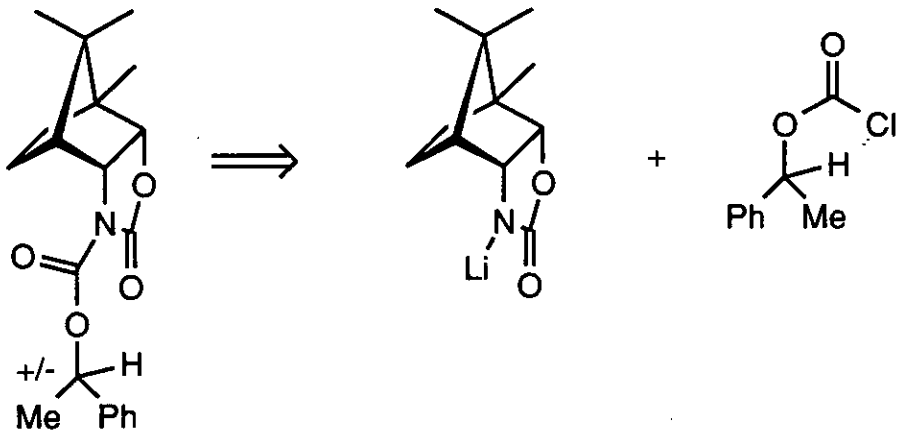
In a further attempt to improve the reactivity of the alcohol, it was pre-treated with *n*butyllithium to form the lithium oxide **145**, before being added to **139** (Scheme 93). The resulting solution was allowed to warm to room temperature and then heated under reflux for several hours, but

even under these conditions, analysis of the crude product by ^{1}H NMR spectroscopy showed that the ratio of product-to-unreacted auxiliary was *ca.* 9:14.



Scheme 93

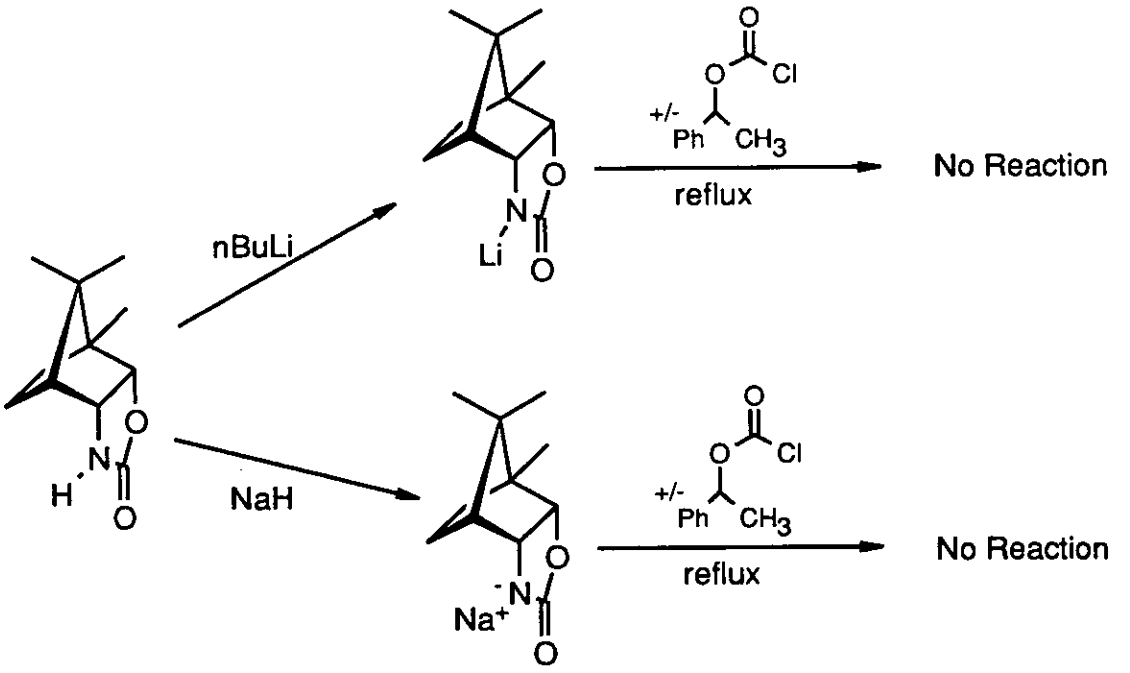
In an attempt to circumvent this poor reactivity, a different bond disconnection was chosen in which product formation could be achieved *via* the lithiated oxazolidinone **100** and the chloroformate of the alcohol (Scheme 94).



Scheme 94

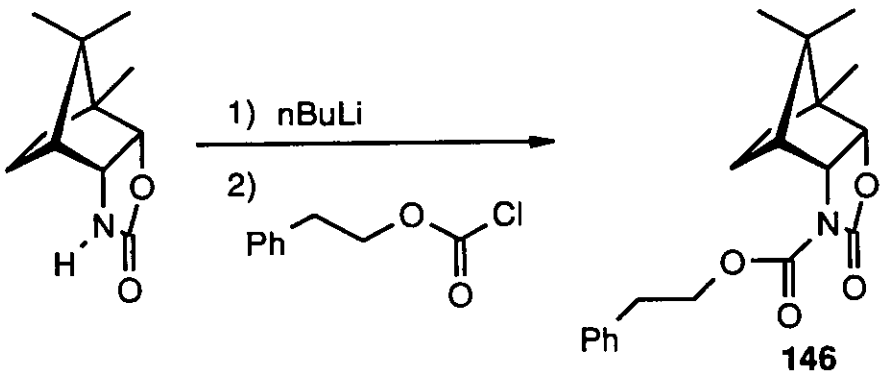
However, use of this method which involved the reaction being stirred at room temperature for a prolonged period, and then heated under reflux for two hours, disappointingly yielded only recovered auxilary (Scheme

95). The same result was also obtained with the sodium salt **85** after a protracted period of boiling.



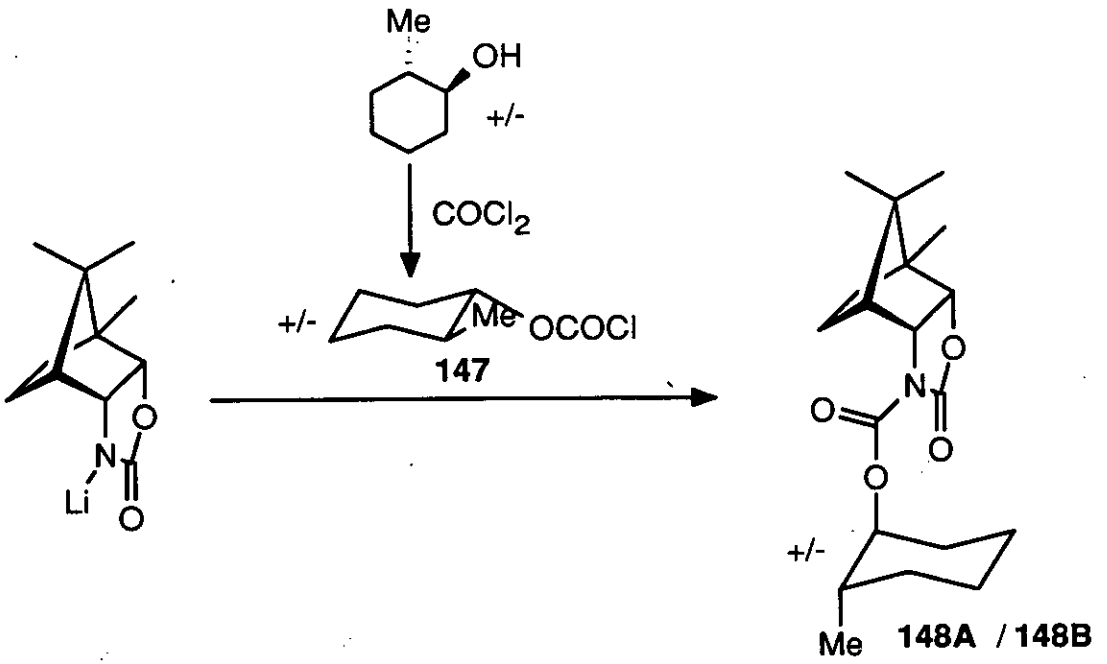
Scheme 95

Believing the reluctant reactivity of this alcohol to be steric in origin, the chloroformate of the structural isomer of 1-phenylethanol, namely 2-phenylethanol, was prepared and found to react readily with **100** on warming the reaction from -78^{0}C to room temperature, to furnish the desired carbamate **146** in excellent yield (Scheme 96).



Scheme 96

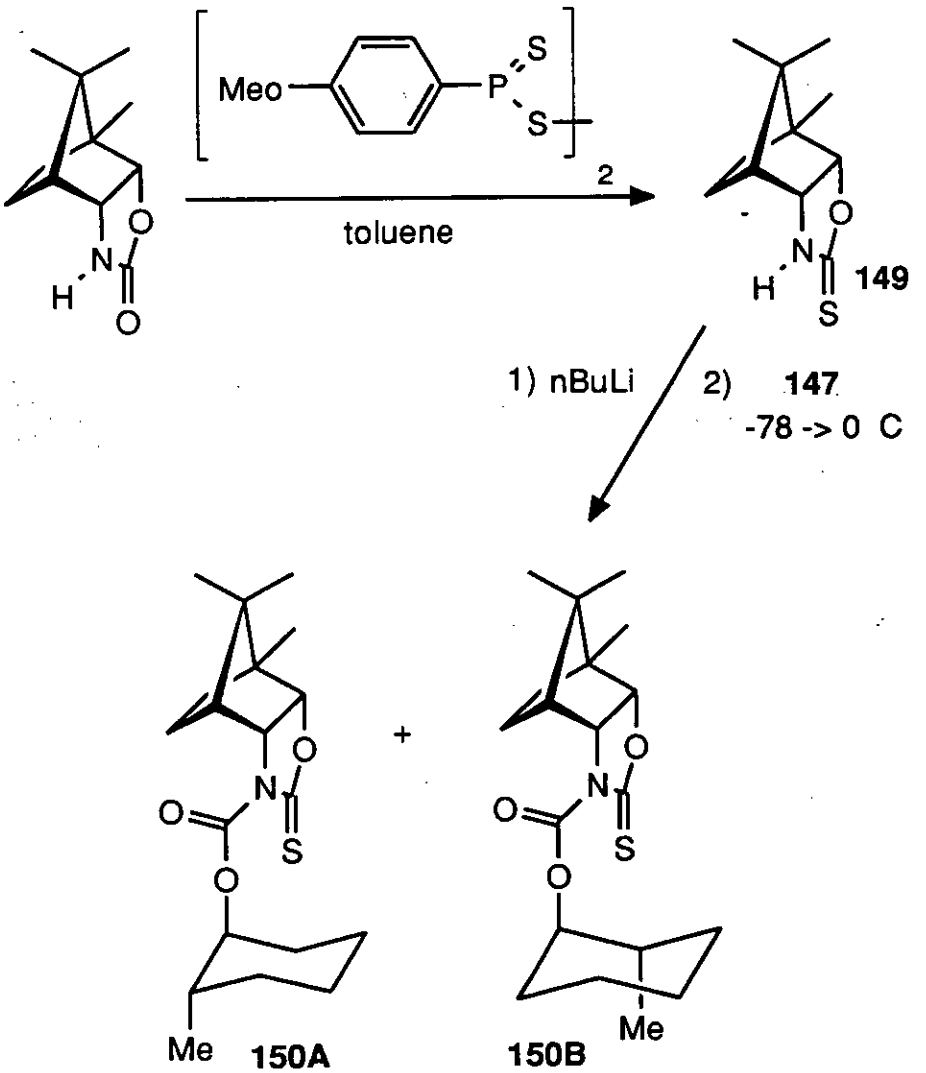
Due to the unsatisfactory results obtained with 1-phenylethanol, an alternative alcohol, (+/-)-*trans*-2-methyl cyclohexanol, was chosen and following conversion into its chloroformate **147**, found to react quantitatively with the lithiated oxazolidinone (Scheme 97). Unfortunately, due to the lack of a strong U.V. chromophore possessed



Scheme 97

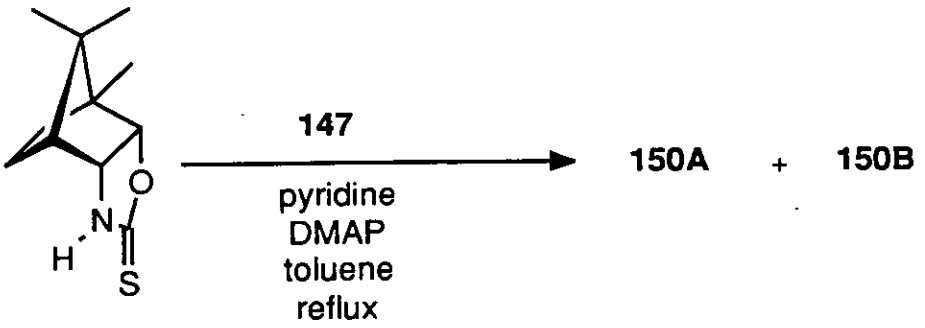
by Chirabornox, it was not possible to detect the diastereomers **148A** and **148B** with a simple HPLC apparatus (which possesses a detector working at 258 nm). In order to overcome this problem, the thione analogue **149** of Chirabornox was used, which had been prepared previously from **77** by Gaur[5] using Lawessons reagent. Compound **149** has an ε_{max} of 28,000 compared with 160 for **77** and provides the necessary λ_{max} shift from 227nm to 247 nm. Thus, treatment of the lithiated oxazolidinethione with the chloroformyl derivative **147** yielded quantitiatively the diastereomeric adducts **150A** and **150B** (Scheme 98) which could be easily detected by HPLC analysis. The separability factor (α) is a reliable guide to the ease of separation of two components. It is the ratio of the

retention time of one eluent (realtive to a non-retained solute) to that of the other. α-values are not affected by the particle size of the column or the way it is packed or the sample size (up to a point). Therefore, this is a universal value for a pair of diastereomers. For the adducts **150A** and **150B**, a separability factor (α) of 1.34 was obtained[135]. The ratio of the area under the lower R_f peak to that of the faster moving isomer was also noted to be 1.85:1. These isomers were also prepared, albeit in lower yield, from **149** and the chloroformyl derivative **147** using pyridine and DMAP (Scheme 99). HPLC analysis gave the same α value of 1.35, but



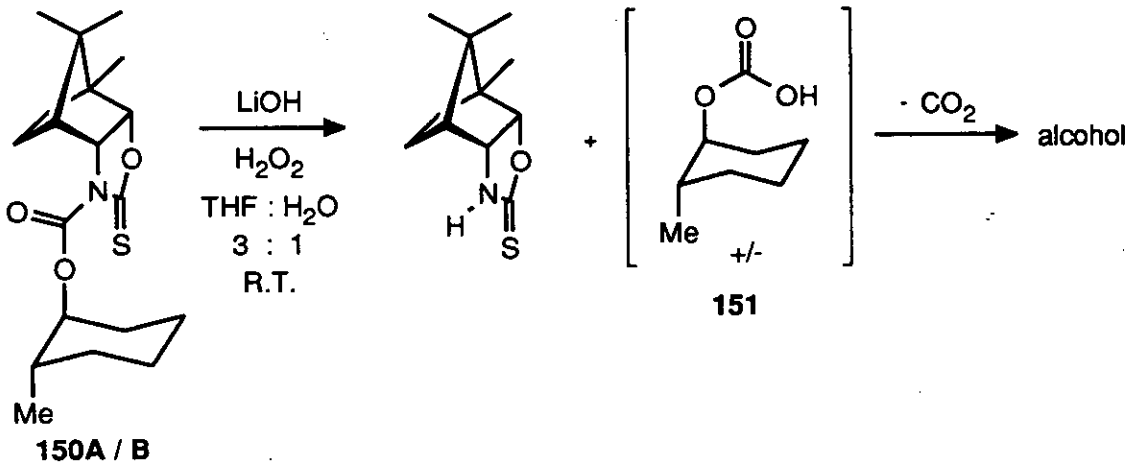
Scheme 98

the corresponding ratio was 0.88:1. This drop in ratio presumably reflects the difference in the reaction temperatures, the latter ratio being the thermodynamic product distribution whilst the former ratio represents the kinetic distribution.



Scheme 99

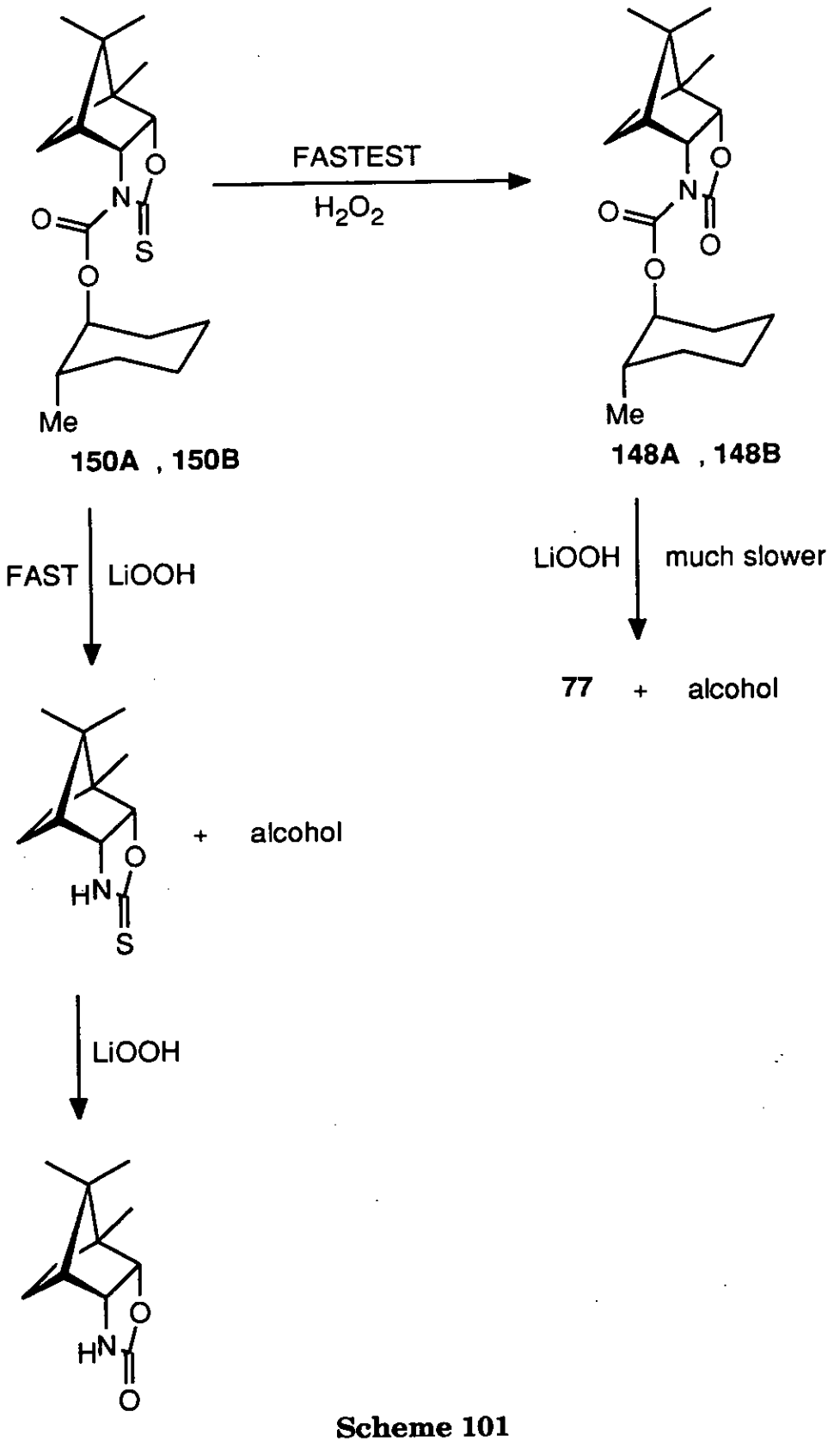
Although these isomers were not separated on a preparative scale, it was still important to demonstrate that both could be cleaved from the chiral auxiliary and thereby complete the chiral resolution. The method chosen was to use lithium hydroperoxide[79] to generate the alcohol *via* the unstable carbonate **151**, as shown in Scheme 100. After a reaction time of



Scheme 100

one hour at room temperature, thin-layer chromatography established that the spot corresponding to the thione diastereomers **150A** and **150B** had essentially gone and been replaced by a slower running spot, due to

trans-2-methyl cyclohexanol. Quenching of the reaction with sodium sulphite solution and subsequent analysis of the reaction mixture by high field ^{1}H NMR specroscopy showed that the alcohol had been generated, but surprisingly from the pattern of signals in the spectrum it was obvious that the parent Chirabornox **77** had been formed, with only traces of the thione **149** present in the mixture. Moreover the reaction was only 55% complete, with all of the thione adducts **150A** and **150B** completely oxidised to the carbonyl adducts **148A** and **148B**. This indicated that the faster reaction is the hydrogen peroxide oxidation of **150A** and **150B**, with attack of lithium hydroperoxide at the exocyclic carbonyl function being the slower reaction (Scheme 101). In addition, the conversion into **148A** and **148B** was likely to reduce nucleophilic attack at the exocylic carbonyl and hence slow down the remaining cleavage of the adducts to the alcohol. Finally, in order to complete cleavage of the adducts **148A** and **148B**, fresh excess lithium hydroxide monohydrate and hydrogen peroxide were added and the reaction mixture allowed to stir at room temperature for a further five hours. Quenching and subsequent flash chromatography yielded two fractions; the first contained mainly the alcohol, but, with concomitant uncleaved adducts **148A** and **148B**, the second fraction was **77**. Based on the yield of **77** recovered, the reaction was deemed to be *ca.* 80% complete, showing that adducts **148A** and **148B** are indeed strongly deactivated to exocyclic nucleophilic attack relative to **150A** and **150B**.


FASTEST
H_2O_2
Me
150A , 150B
148A , 148B
FAST
LiOOH
LiOOH
much slower
77
+
alcohol
+
alcohol
LiOOH

Scheme 101

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

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

J.Bredt and W.H.Perkin, jun,
J.Chem.Soc, 1913, 2183.

Chapter 7

The attempted synthesis of the structural isomer of Chirabornox (84) *via* (-)-epicamphor (154)

As discussed previously in Chapter 1, the poor levels of asymmetric induction exhibited by Chirabornox **77** in the Diels-Alder reaction stem from a lack of steric interaction between the unsaturated *N*-acyl moiety and the parent auxiliary, resulting in a poor population difference between the s-*cis* and s-*trans* conformations. An intriguing question to be answered is why does Evans' (*S*)-valine derived auxiliary **9** perform so much better than Chirabornox in these reactions? The answer appears to derive from the fact that **9** possesses a *rotatable* isopropyl grouping, in sharp contrast to the fixed, rigid bornane cage of Chirabornox. This "propeller effect" makes the isopropyl grouping highly effective not only in providing steric shielding of one face of the π-system, but also in forcing the alkene to adopt the more stable s-*cis* conformation, for in the s-*trans* it would incur relatively severe steric interactions as highlighted in Figure 27.

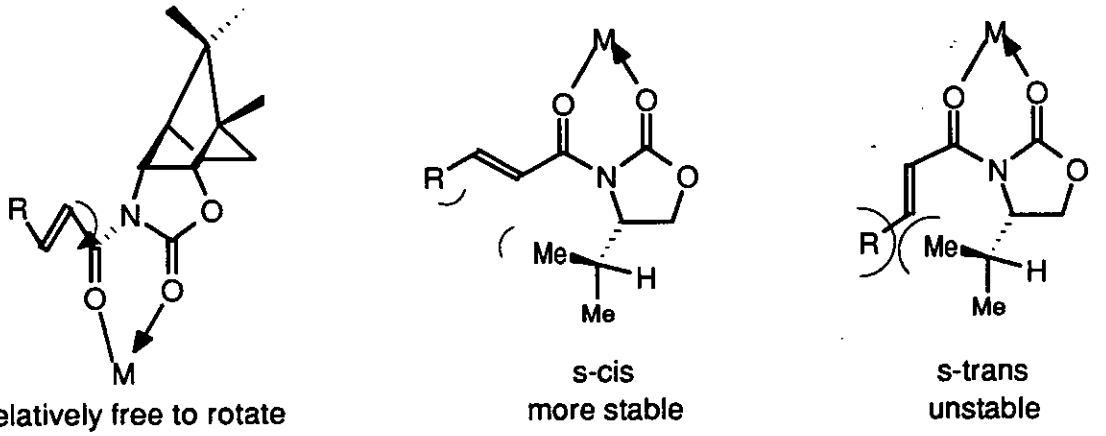


Figure 27

In order to increase the effective steric bulk exhibited by auxiliary **77**, one requires a group of greater size than hydrogen at the bridgehead carbon, *i.e.* vicinal to the nitrogen. Inspection of the structure of Chirabornox shows that whilst it possesses a bridgehead methyl on the opposite side of the bornane ring, this group serves no useful purpose as far as providing an effective shielding group in the immediate reaction sphere. From this point of view, it would therefore be highly desirable to "move" this dormant methyl from the rear to the front of the bornane ring and closer to the reaction zone, as depicted in Figure 28, to create a new chiral auxiliary that is essentially a "transfigomer" of **77**, *viz* **84**.

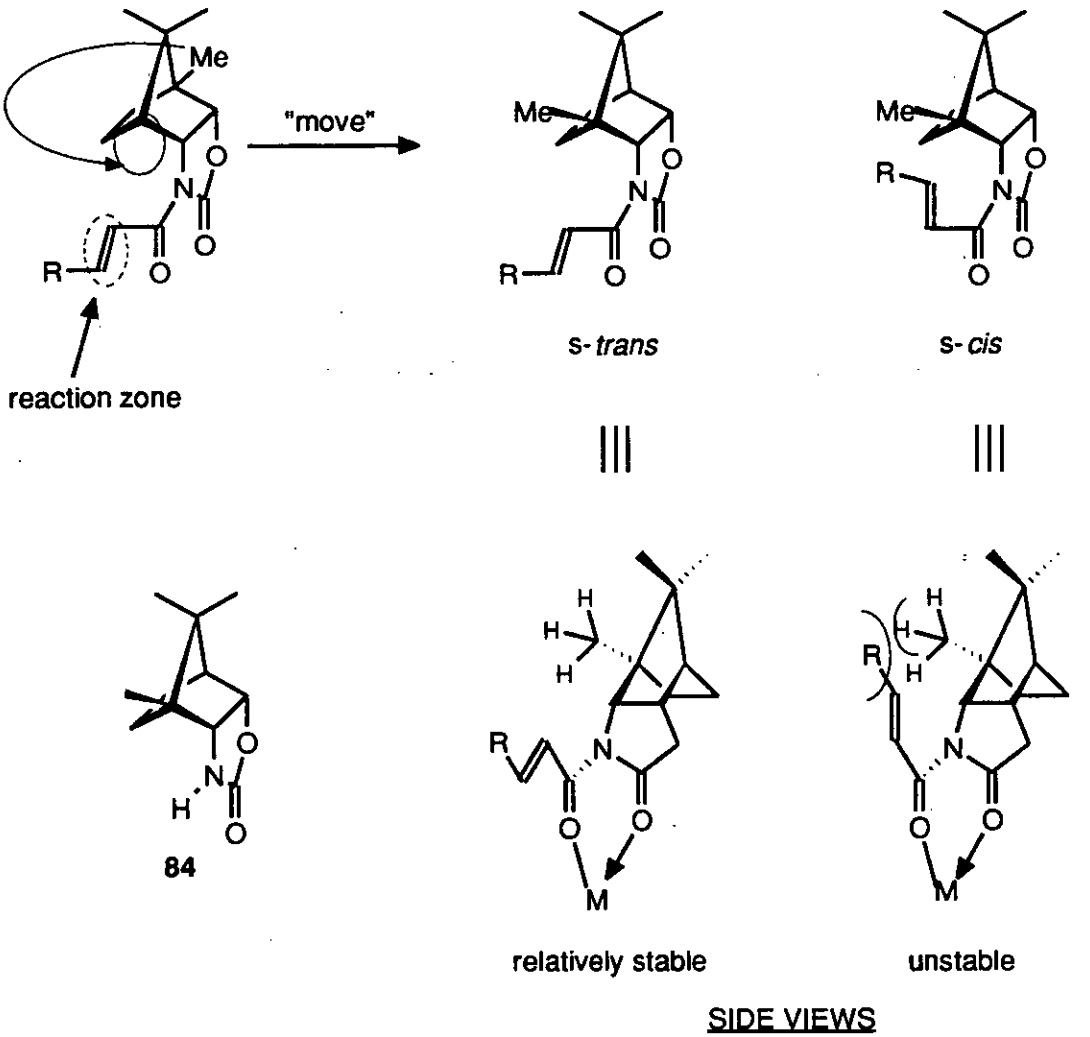
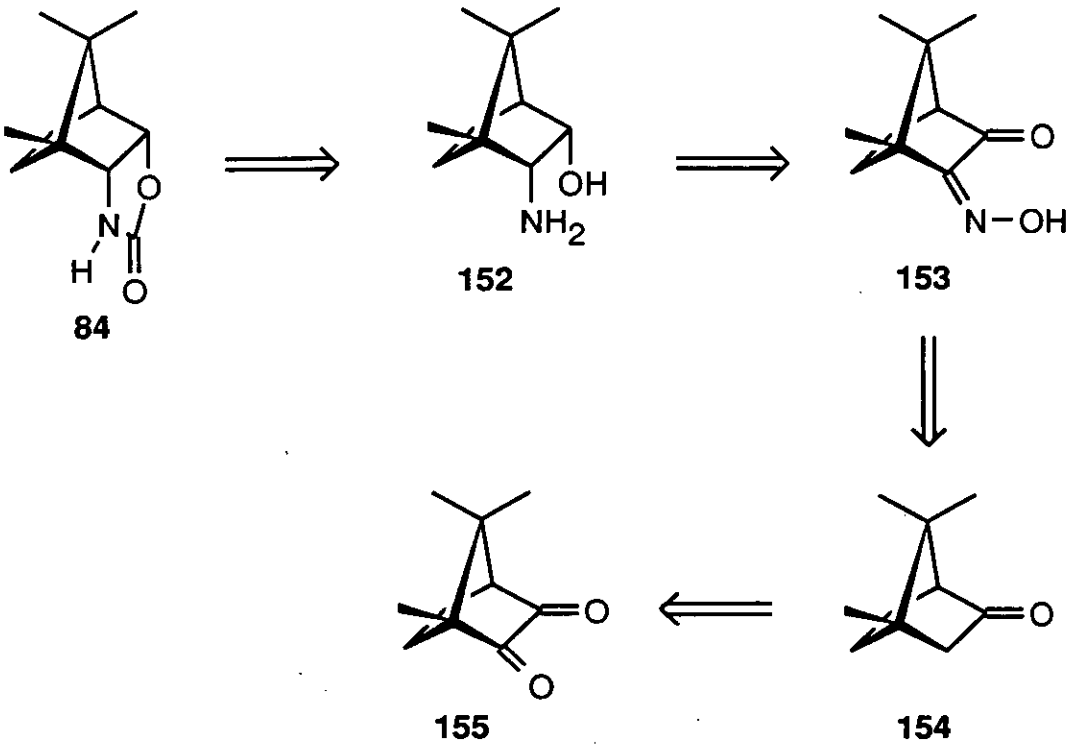


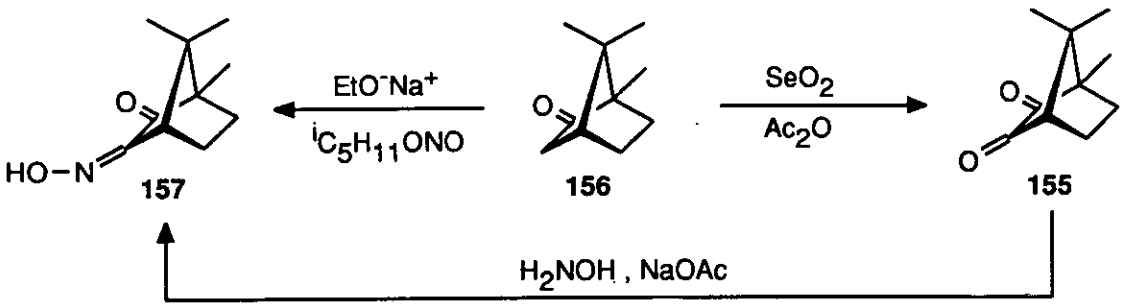
Figure 28

Scheme 102 depicts a retro-synthetic pathway to the potential auxiliary **84**, disconnection generating a number of key intermediates, namely *endo,endo* - 2-amino-3-hydroxybornane **152**, 2-hydroximinoepicamphor **153**, epicamphor **154** and camphorquinone **155**.



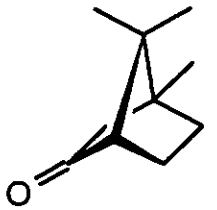
Scheme 102

The appeal of this route is strengthened by the work of Claisen *et al*[139] who showed that when camphor **156** is treated with isoamylnitrite in the presence of sodium ethoxide it furnished 3-hydroxyiminocamphor **157**



Scheme 103

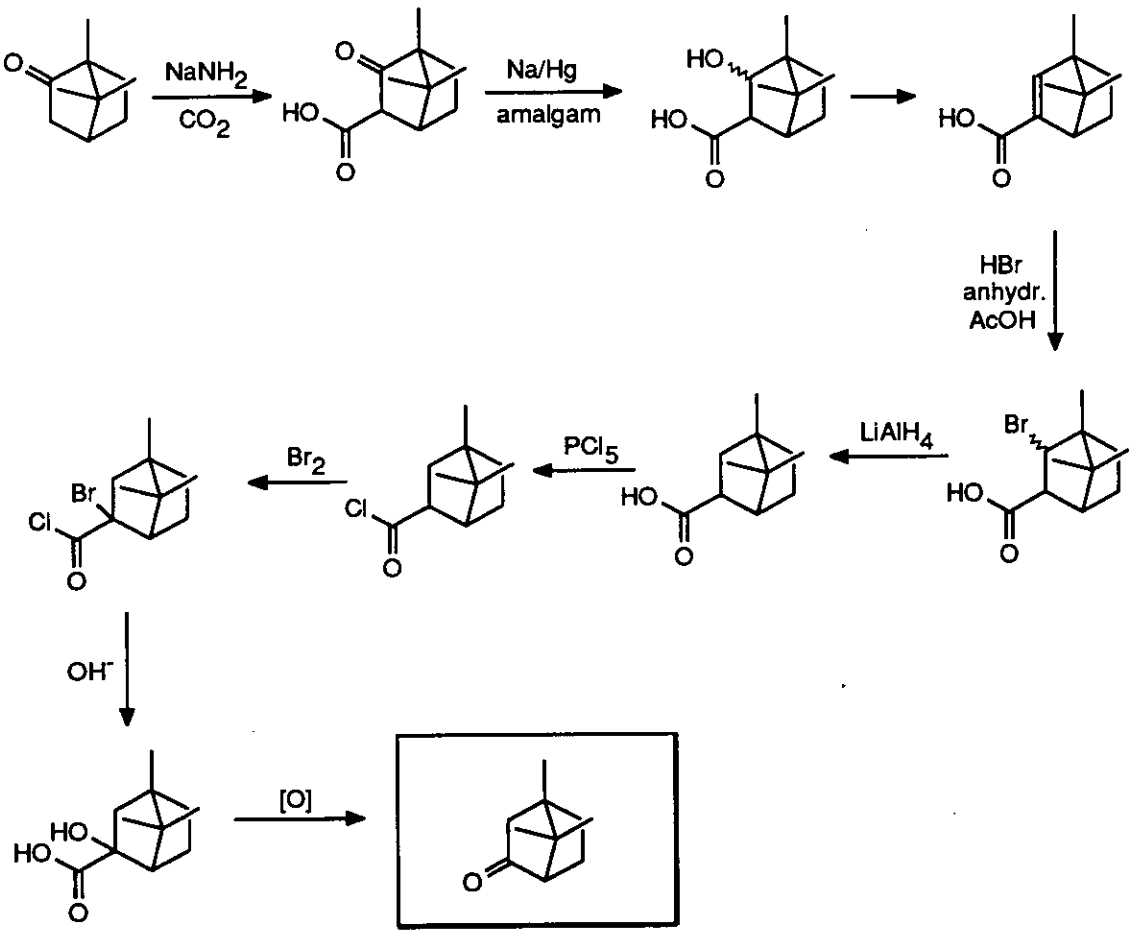
(Scheme 103), *i.e.* the α-position of camphor can be directly aminated. The acidic nature of the α-methylene of camphor is also demonstrated by the fact that it can be oxidised by selenium dioxide to camphorquinone **155** as shown by Evans *et al*[140]. Interestingly, **157** can be obtained directly from **155** by hydroximination of the 3-keto function[141]. Obviously the key intermediate in the synthesis of **84** is epicamphor **154**, the isomeride of camphor which has not been found in nature[142].



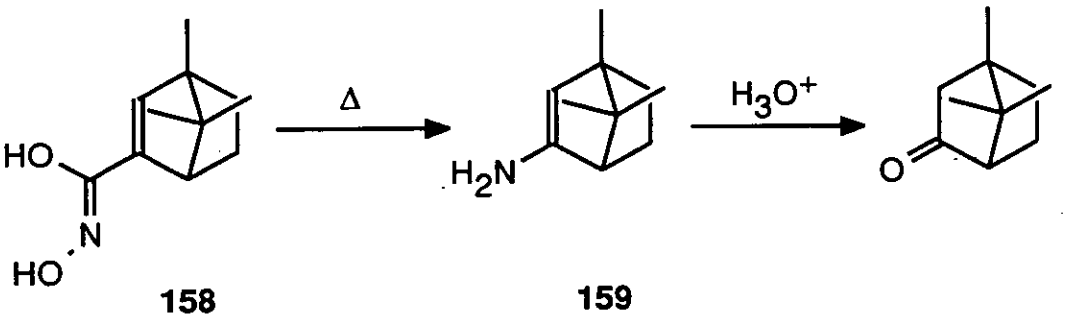
154

The potential of epicamphor in synthesis, and indeed asymmetric synthesis, had only begun to be realised in 1913 when Bredt and Perkin made their prohetic statement, shown at the beginning of this chapter. The synthesis of the chiral auxiliary **84** offered an opportunity to further realise this goal and demonstrate the synthetic utility of epicamphor in the ever-growing sphere of asymmetric synthesis.

Epicamphor is chemically derived from camphor, but it is not entirely straightforward to synthesise; indeed, an earlier route used nine steps in the elaborate synthesis outlined in Scheme 104. Another route uses the hydroxamic acid **158** derived from methyl bornene-3-carboxylate which, upon heating above its melting point, affords enamine **159** (Scheme 105). Subsequent hydrolysis of this intermediate yields epicamphor[142].



Scheme 104

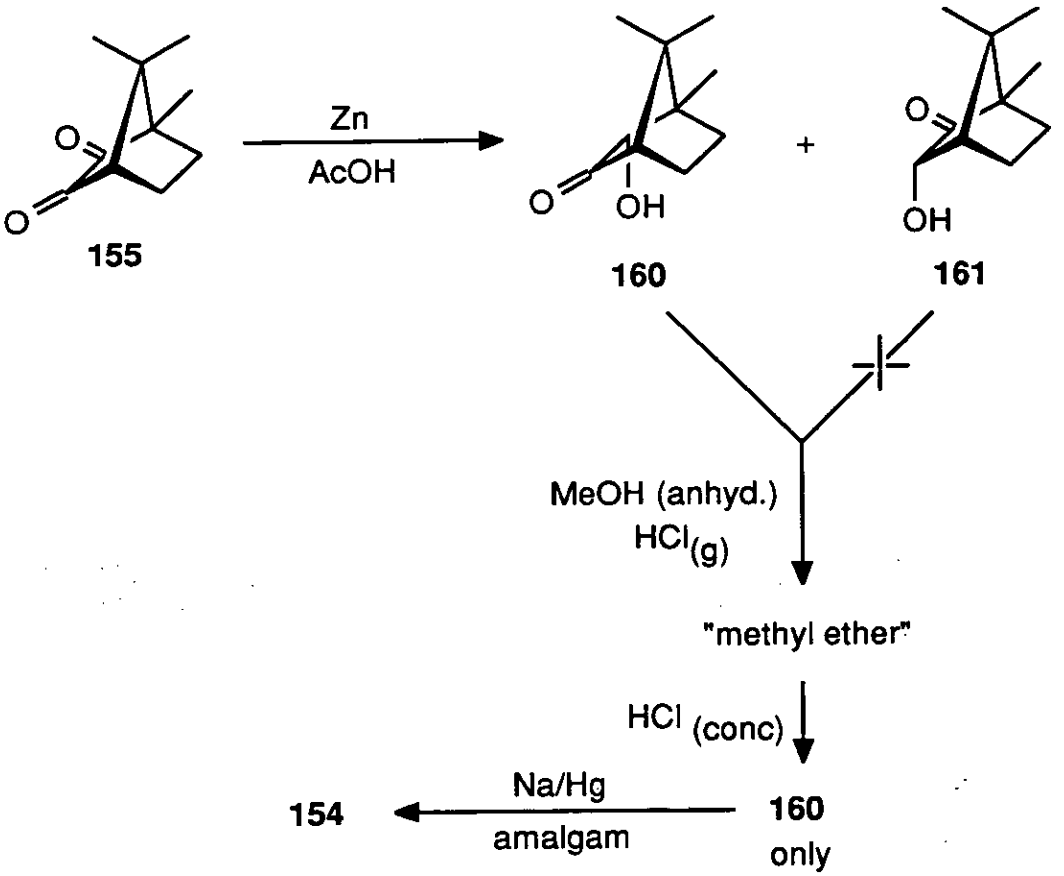


158 **159**

Scheme 105

The best procedure for producing **154** in bulk quantities is that used by Huckel and Fechtig[143] and was the method chosen for the current study. The synthesis is outlined in Scheme 106 and begins with the preparation of camphorquinone **155** which is then reduced by zinc in acetic acid,

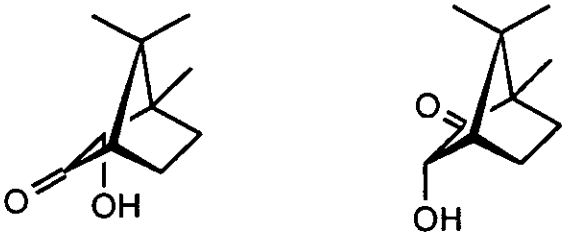
yielding a mixture of *endo* 2-hydroxyepicamphor **160** and *endo* 3-hydroxycamphor **161**. Separation of these intermediates is achieved by a reaction which produces what is described as a "methyl ether" (*vide infra*) and allows **160** to be produced in pure form. Reduction using a Na/Hg amalgam then affords epicamphor in a reasonable yield.



Scheme 106

In the present work, (1*R*)-(+)-camphor was oxidised in high yield to camphorquinone (83%) which was then reduced with zinc in acetic acid to furnish **160** and **161** in excellent yield; their identity was confirmed by the presence of hydroxyl and carbonyl absorbances in the infrared spectrum, together with the high resolution electron impact mass spectrum which established the molecular formula to be $C_{10}H_{16}O_2$.

Interestingly, the reduction furnished selectively the *endo* isomers (as shown in Figure 29) compared to other methods[144] which produced *exo* isomers as well in varying amounts. In this mixture, isomer **161** could be detected in the low field ^{1}H NMR spectrum by the appearance of a doublet at *ca.* δ 4.2 ppm for the proton geminal to the hydroxy grouping, arisen from coupling with proton at the bridgehead.



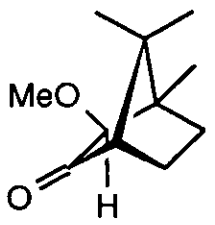
160 **161**

Figure 29

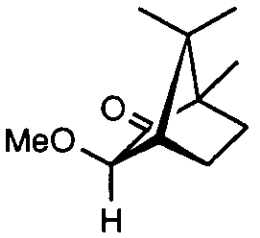
The method used for the separation of **160** from **161** is that of Huckel *et al* ,who adopted the procedure of Bredt and Ahrens[145], who in turn used the experiment original report by Manasse[146] in 1902. In their account, Huckel *et al* state that **160** undergoes a reaction in anhydrous methanol using dry hydrogen chloride gas to form a "methyl ether" which crystallises out of solution. The crystals are filtered off, to leave unreacted **161** still dissolved in the methanol.

Employment of this method yielded colourless crystals with identical melting point and optical rotation to literature values[145], indicating that the same compound had been formed. Examination of these crystals by low field ^{1}H NMR spectroscopy showed that the doublet at δ 4.2 ppm had now disappeared, in keeping with the loss of **161** from the mixture. Instead the presence of an OMe signal at δ 3.3 ppm was clearly visible. Huckel *et al* did not characterise the product and described it as the "methyl ether of 2-hydroxyepicamphor". Naively it was assumed that the

product had the structure of **162** (Figure 30). although doubts began to grow when curiously it was realised that **161** did not react in the same way to furnish the corresponding ether **163**



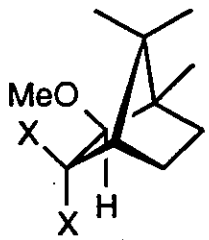
162



163

Figure 30

In order to establish unequivocally the structure of the "methyl ether" $^{13}C\{^1H\}$ spectrum was obtained, in addition to the high field ^1H NMR spectrum. The former showed eleven environments, which initially indicated that it had the proposed structure, **162**. However, no signal corresponding to a carbonyl could be detected; indeed the peak with the highest shift was a quaternary at δ 102.0 ppm (Figure 31). The infrared spectrum confirmed the absence of any carbonyl absorbance, but in addition it also showed an absence of a hydroxyl absorbance thus discounting **162** as a possible structure. These observations, coupled with the fact that the ^1H NMR spectrum displayed all the characteristics necessary for a structure such as **162**, suggested a revised structure, *viz.* **164**, in which X cannot be oxygen.



164

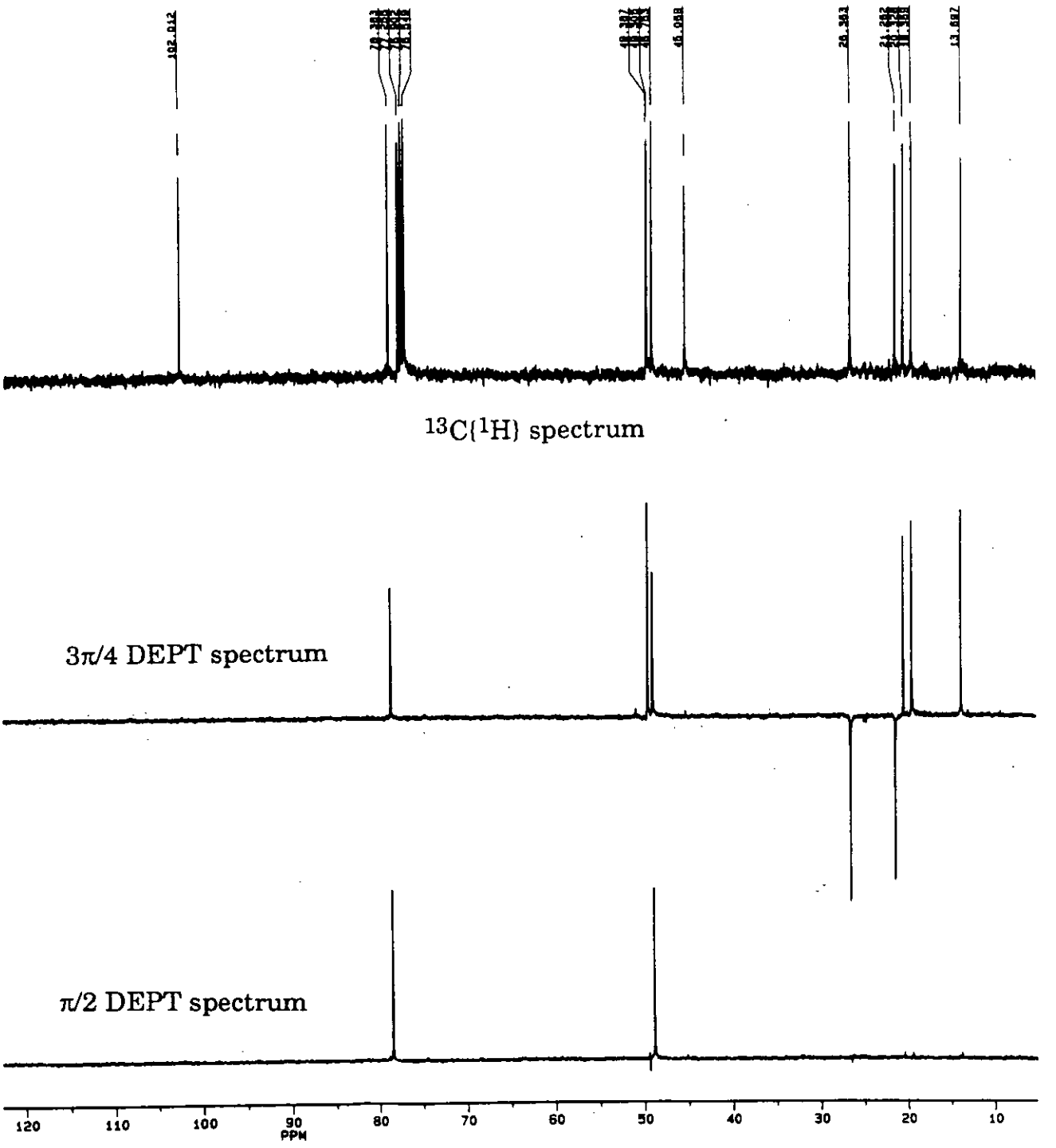
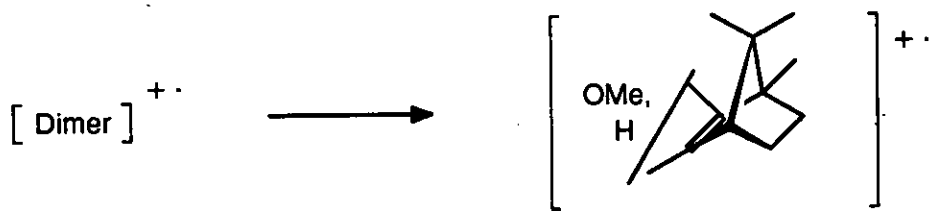


Figure 31 ^{13}C spectra of the dimer

It was conceivable that X could be chlorine arising from the use of HCl gas but a sodium fusion test showed without any doubt that no chlorine was present in the molecule. Low resolution electron impact mass spectrometry showed two main peaks; the base peak at 166 a.m.u. and one at 364 a.m.u. which is exactly *twice* that of the mass-to-charge ratio expected for the originally proposed structure **162**. High resolution mass spectrometry confirmed the compound to be a dimer of formula $C_{22}H_{36}O_4$, in addition to showing that the break-down peak at 166 had the formula $C_{11}H_{18}O$ (Figure 32). From this evidence it would appear that Manasse[146], who originally formed the dimer, had determined the correct empirical formula, $C_{11}H_{18}O_2$ by combustion analysis, but did not realise its true formula. The molecule in question must be symmetrical since only eleven discrete environments are present in the $^{13}C\{^1H\}$ spectrum of this dimer of 22 carbons.

Closer examination of the literature revealed that Bredt *et al*[145] had correctly determined the relative molecular mass of the molecule by density measurements and given a plausible mechanism for its



$C_{22}H_{36}O_4$ requires : 364·26134
found : 364·2594
deviation 5.3ppm

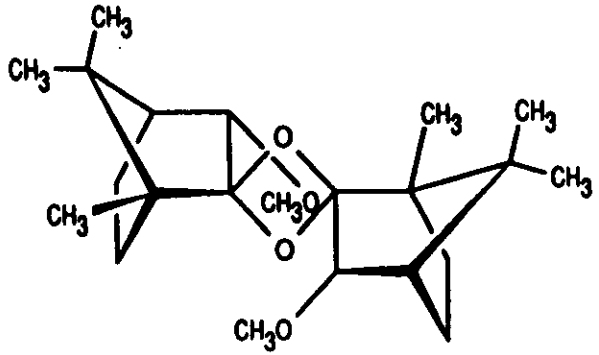
$C_{11}H_{18}O$ requires : 166·13576
found : 166·1371
deviation 8.2ppm

Figure 32

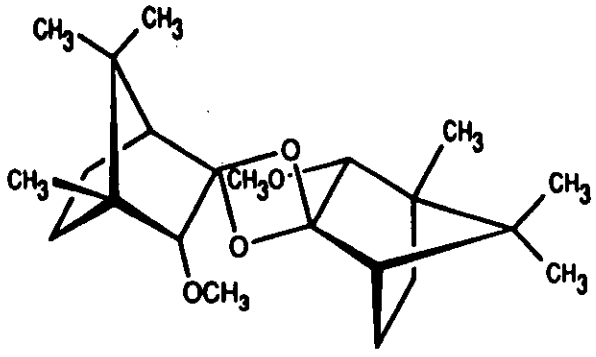
formation. Much later, Theoren[147] had attempted to elucidate the dimer's structure on the basis of stereochemical considerations and minimal ^1H

NMR data, but the results were inconclusive. The peak at δ 102.0 ppm in the $^{13}C\{^{1}H\}$ spectrum is consistent with a gem dialkoxy grouping. For example, the C-1 carbon in α-glucose resonates at 97ppm[148]. This information coupled with the fact that the dimer has two methylene and two methinic carbons *per* bornane ring suggest four possible structures, **I-IV** as shown in Figure 33 (overleaf). The *anti* forms of **III** and **IV**, *i.e.* **V** and **VI** can be ruled out on the basis that that **160** and its antipode are required for their formation. Of the remaining proposed structures, pair **I** and **II** are unlikely from a mechanistic point of view, and the strain inherent in the 1,3 dioxetan ring, since the dimer is a stable, highly crystalline solid. Structure **IV** is also unlikely as the overall mechanism of formation requires a hydrogen atom to move from carbon 2 to carbon 3. Nevertheless, all four structures would be expected to exhibit similar detail in both the ^{1}H and ^{13}C NMR spectra.The decision was made to elucidate, if possible, the true identity of the dimer using high field ^{1}H NOE difference spectroscopy and this became the subject of a recent publication[149].

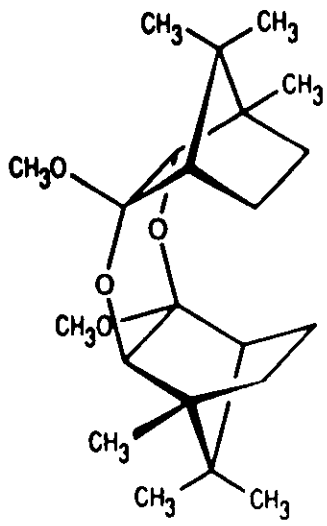
The ^{1}H NMR in Figure 34 comprises of ten different resonances, labelled A to J. Peak A can be assigned unequivocally to the methinic proton geminal to oxygen; peak B to the methoxy protons and peak C to the bridgehead proton of the bornane skeleton. Irradiation of B caused an 8% enhancement at C and a 3% enhancement of the triplet A. This lead to the conclusion that the methinic proton A is adjacent to the methoxy group and must also be adjacent to C; this leads one to the only conclusion that the methoxy group resides at the 9a position, *i.e.* α to C and A. This excluded structures **II** and **IV**. In addition, an 8% enhancement of C is consistent with the methoxy group being in an *exo*



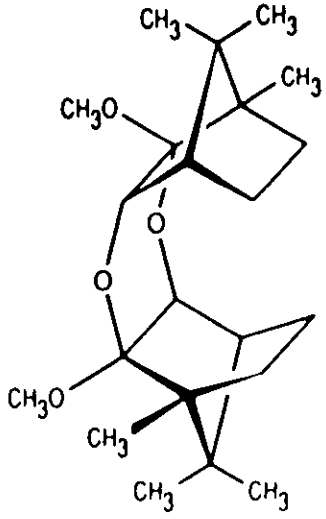
I



II

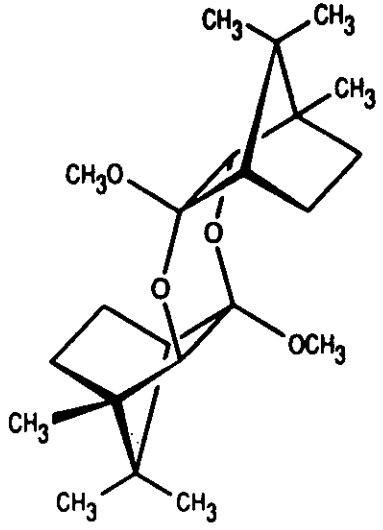


III

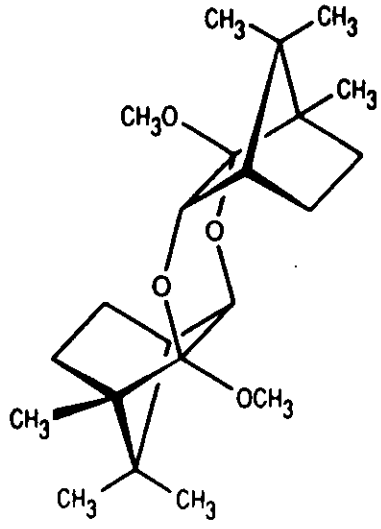


IV

Figure 33 Possible structures **I** to **IV** for the dimer together with the *anti* forms **V** and **VI**



V



VI

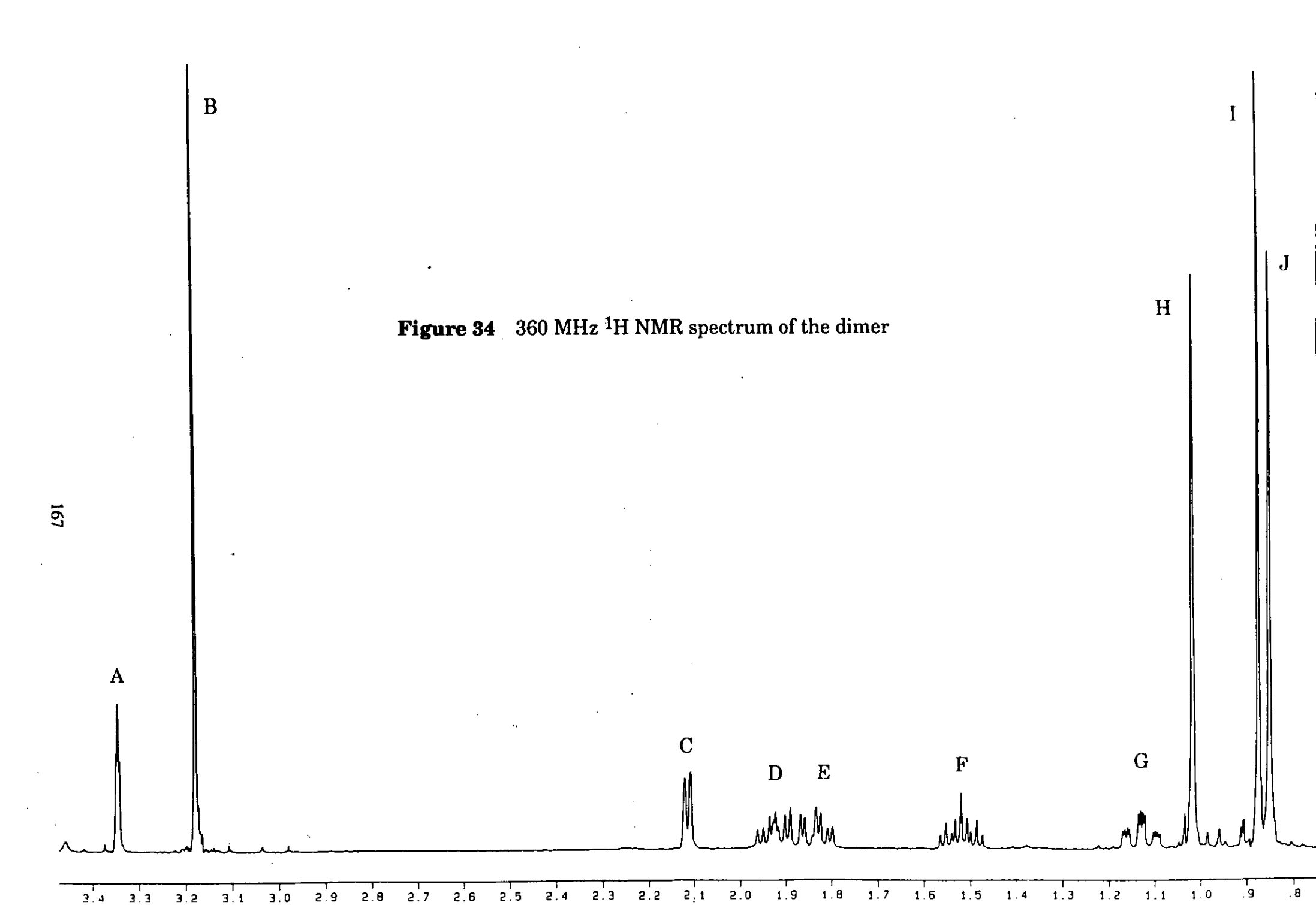
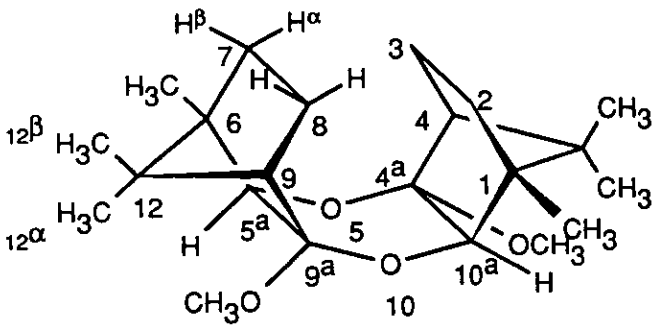


Figure 34 360 MHz ^{1}H NMR spectrum of the dimer

position and makes structure **I** also unlikely. This left structure **III**, which was wholly consistent with the remaining NOE difference experiments as the most likely structure for the dimer **165** (see Figure 35).



165 (structure III)

Figure 35

Irradiation of the methyl signal J caused 5% enhancements to both F and G and a 4% enhancement to C. Thus J is consistent with being the C-12β methyl group, with F and G being H-7β and H-8β or *vice-versa*. Saturation of I resulted in an 8% enhancement of A and a 3% enhancement of G. Thus I can be assigned to the bridgehead methyl at C-6, with G being the signal from H-7β. Irradiation of H confirmed this as the C-12α methyl group, giving a 15% enhancement at A (H-5a) and a 3% enhancement at C. Irradiation of C enhanced F by 2% and even the methoxy protons by 2%, consistent with its assignment as H-9. Finally, irradiation of G (H-7β) enhanced D by 20%,consistent with D being H-7α. F (H-8β) is also enhanced by 3%; this leaves E as H-8α. Figure 36 shows the NOE difference spectra, the irradiation points being marked with arrows.

Table 9 summarises the results and the assignments for the proton resonances of the dimer **165** from the NOE experiments and Table 10

Figure 36

Results of NOE difference experiments conducted upon dimer

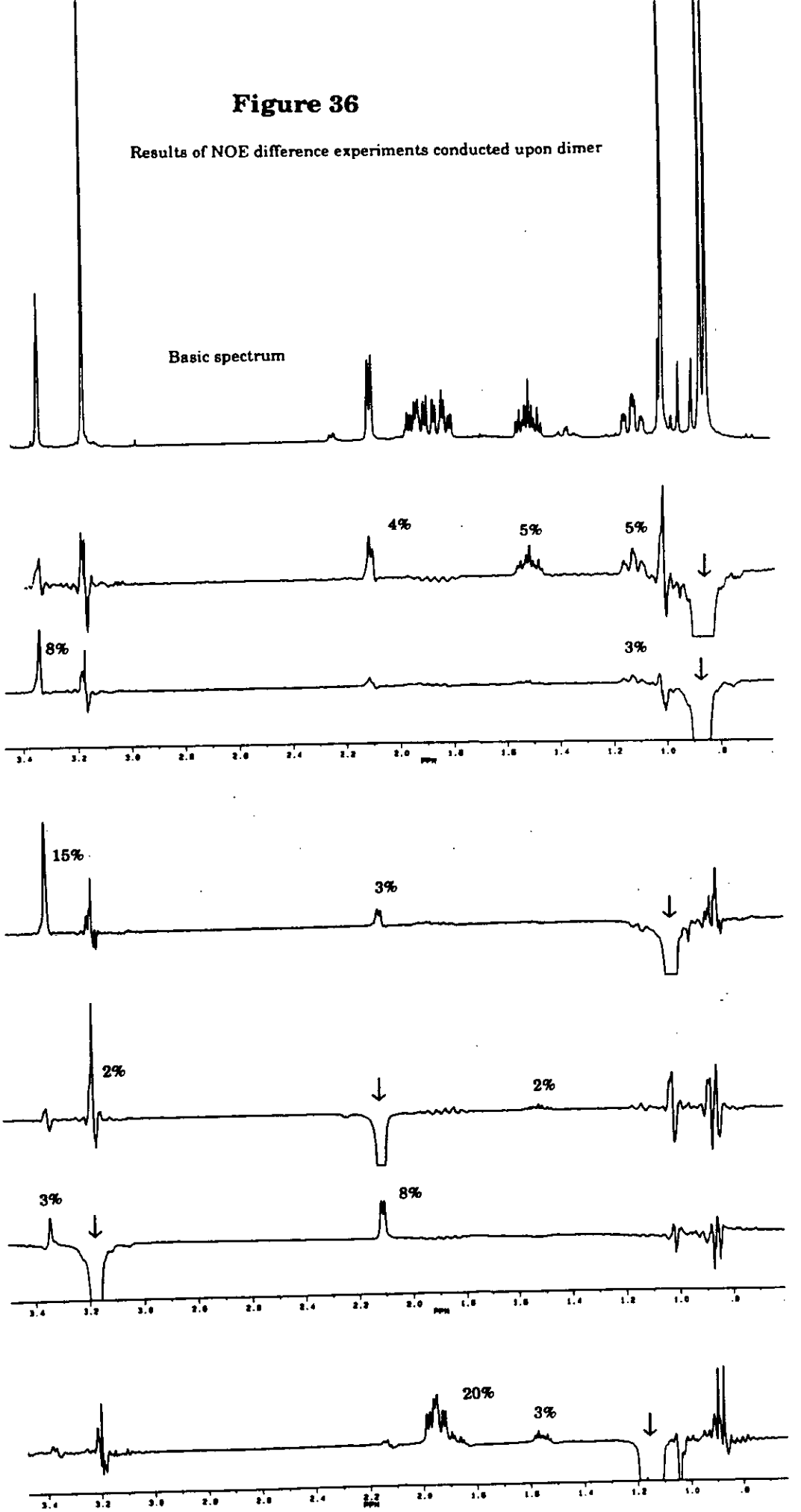
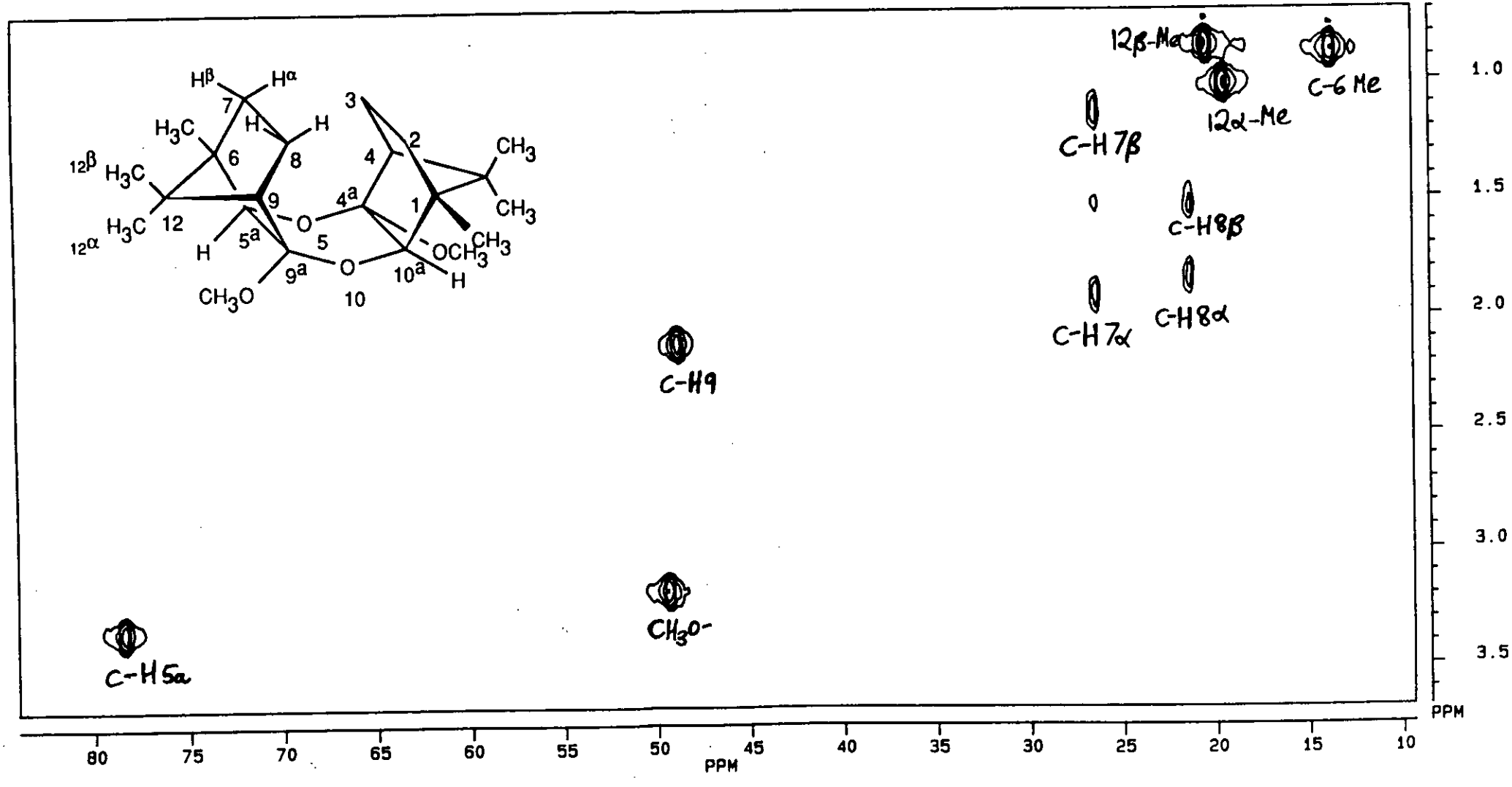


Figure 37 ^{1}H-^{13}C correlated spectrum



contains the fully assigned ^{1}H NMR data. The ^{1}H-^{13}C correlated spectrum is shown in Figure 37, and the summarised ^{13}C data in Table 11.

Table 9. Results of proton-proton NOE difference experiments upon dimer (165) (structure III)

Irradiated proton	proton observed	NOE /%
$C\underline{H}_3$-O	9	8
	5a	3
12β	8β	5
	7β	5
	9	4
6-$C\underline{H}_3$	7β	3
	5a	8
12α	5a	15
	9	3
9	8β	2
	$C\underline{H}_3$-O	2
7β	7α	20
	8β	3

Table 10. ^{1}H NMR spectral data for the dimer (165) in $CDCl_3$.

Label	δ (ppm)	Multiplicity, *J*(Hz)	assignment
J	0.85	s	12β-C<u>H</u>$_3$
I	0.88	s	6-C<u>H</u>$_3$
H	1.02	s	12α-C<u>H</u>$_3$
G	1.13	t,d,d (2x12.0,3.4,1.6)	7β
F	1.52	t,t (2x12.0,4.6x2)	8β
E	1.83	d,d,d (12.0,9.5,3.4)	8α
D	1.92	d,d,d (12.0,9.5,4.6)	7α
C	2.11	d,d (4.5,1.5)	9
B	3.18	s	9a (OC<u>H</u>$_3$)
A	3.35	t (1.5)	5a

Table 11. ^{13}C chemical shifts for the dimer (165).

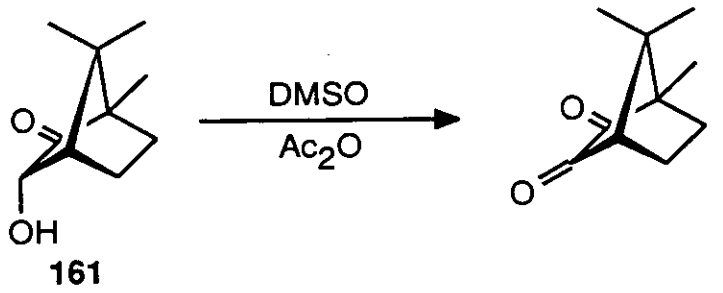
Carbon	δC (ppm)	Carbon	δC (ppm)
5a	78.4	9a	102.0
6	49.4	9a-OC<u>H</u>$_3$	49.3
6-C<u>H</u>$_3$	13.7	12	45.1
7	26.4	12α-<u>C</u>H$_3$	19.4
8	21.3	12β-<u>C</u>H$_3$	20.3
9	48.8		

Interestingly, in addition to these experiments, decoupling of the finely coupled triplet corresponding to proton H-5a caused simplification of the signals due to the H-7β proton. This long range 2-*exo* to 6-*exo* coupling of 1.5 Hz was first observed by Anet[150] in the ^{1}H NMR study of camphane-2,3-diols. Decoupling the H-5a triplet also caused simplification of the H-9 proton signals, showing a four-bond coupling is present with this proton also.

The HCl gas in methanol experiment was conducted on a racemic mixture of **160** and **161** which furnished a crystalline product, having a melting point close to the literature value of 133-134^{0}C[145], compared to the chirally pure compound which has a melting point of 149-150^{0}C. However, the former gave rise to identical ^{1}H and ^{13}C NMR spectra, indicating the same material (although racemic) had formed. The difference in the melting point of the two samples is intriguing and can only be accounted for by the different stacking of the isomers in the crystal, resulting from different interactions. One would expect that structure **V** (Figure 33) would form, but this cannot be the case since no changes occurred in the spectra.

Decomposition of the dimer was readily effected in concentrated hydrochloric acid to regenerate **160**, which was deemed to be pure enough for the next stage of the synthesis on the basis of melting point and high field ^{1}H and ^{13}C NMR spectra. The unwanted 3-hydroxycamphor was re-oxidised to camphorquinone (Scheme 107) using DMSO in acetic anhydride, in order to re-cycle the material.

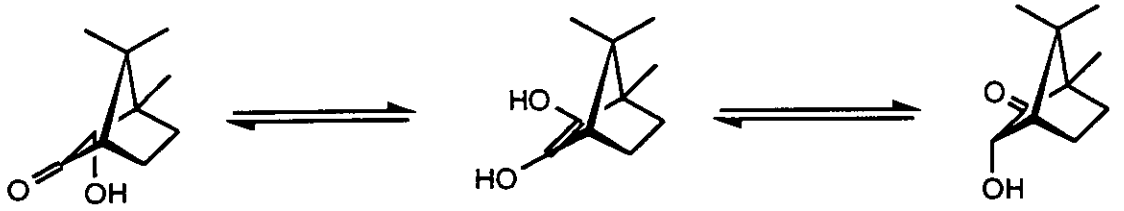
Reduction of **160** using Na/Hg amalgam suffers the complication that under alkaline conditions, significant amounts of camphor are formed



161

Scheme 107

during the reaction[147]. This is attributed to the fact that, under these conditions **160** undergoes enolisation *via* the diolene **166** to **161**[151]

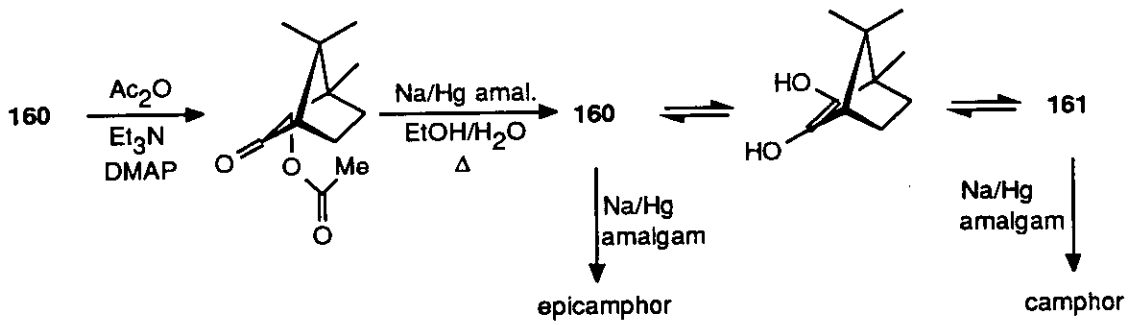


160 **166** **161**

Scheme 108

(Scheme 108). To prevent this process, Theoren formed the acetate of **160** and showed that almost pure epicamphor could be obtained[147]. Acetylation of **160** was achieved quantitatively using acetic anhydride and triethylamine in the presence of a catalytic amount of DMAP (Scheme 109). However, use of the sodium to mercury ratio prescribed by Theoren furnished a solid amalgam which needed to be heated in order to melt it and mix efficiently with the acetate of **160**. Following work-up, it was quite obvious from ^{1}H and ^{13}C NMR spectra that the crude reaction mixture consisted predominantly of camphor and epicamphor in a ratio of 58:42. This disappointing result appeared to arise from the fact that under the aqueous reaction conditions employed, akin to those used by Holleman[152], hydrolysis of the acetate must have occurred, allowing the enolisation mechanism to come into play (Scheme 109). The technique described by Huckel *et al* for the separation of these compounds[143] uses

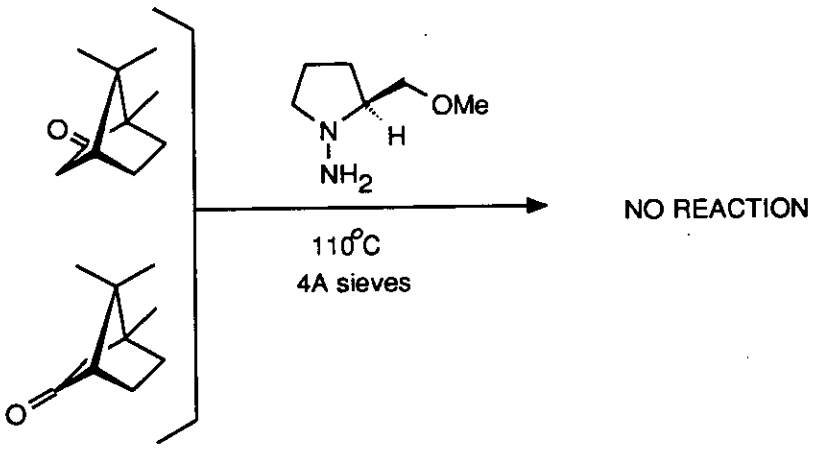
the fact that the semicarbazone of epicamphor forms faster than that of camphor. This procedure is unattractive due to the low yields of pure



Scheme 109

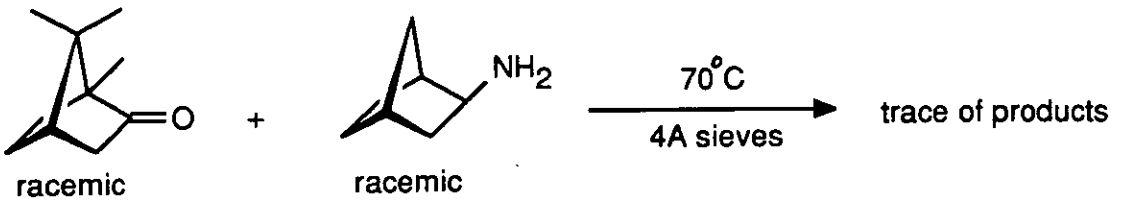
epicamphor obtained. It was thought that the separation of the camphor and epicamphor so-formed could be achieved by analytical reverse-phase HPLC. However this proved to be an unsuccessful method. In a further attempt to separate the isomerides, it was thought that the difference in their physical properties could be exaggerated by the formation of SAMP hydrazones (Scheme 110). However, negligible change was observed by thin-layer chromatography despite overnight boiling in benzene using a Dean-Stark trap to remove water and force the reaction to completion. Removal of the benzene and replacement with toluene, together with the use of 4A molecular seives, did not bring about any noticable reaction despite heating at 110^0C for four days. Column chromatography yielded unreacted camphor and epicamphor with 85% recovery.

In order to substantiate this finding, a test reaction was carried out in which the steric interactions were similar to those in the system just described. Racemic camphor was heated at 70^0C with racemic *exo*-2-aminonorbornane in the presence of 4A molecular sieves for *ca.* one day (Scheme 111). Column chromatography furnished a fraction in which



Scheme 110

high resolution electron impact mass spectrometry indicated that the desired products were present, but only in trace amounts.

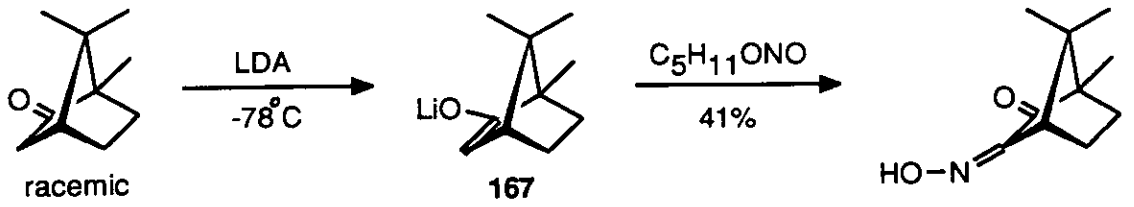


Scheme 111

The final investigation concerned the α-hydroximination of camphor, which had been shown to occur in poor (*ca.* 40%) yields by treatment of camphor with sodium ethoxide in the presence of isoamyl nitrite[139,153]. In an attempt to improve this yield, the lithium enolate of camphor **167** (Scheme 112) was prepared by treatment of camphor with LDA, followed by the addition of a THF solution of amyl nitrite. However, following flash chromatography, the desired product was formed in the same poor yield.

Despite these failures, work has continued on this problem, and the synthesis of pure epicamphor has been successfully achieved. Further

steps are now in hand and it is hoped that that the "transfigomer" **84** will be synthesised shortly.



Scheme 112

"I do not understand what I do.For what I want to do I do not do, but what I hate I do"

Romans chapter 7 verse 15.

EXPERIMENTAL

Abbreviations

ABq	an AB quartet
Ar	aromatic
$[\alpha]_D$	specific rotation
BP	boiling point
b	broad
cm	complex multiplet
d	doublet
DAMP	4-dimethylaminopyridine
δ	chemical shift (ppm) (relative to tetramethylsilane)
DME	dimethoxyethane
DMSO	dimethylsulphoxide
ei	electron impact
eq	equivalents
FAB	fast atom bombardment
HPLC	high performance liquid chromatography
IR	infrared
J	spin-spin coupling constant
lit	literature value
M^+	molecular ion
mmol	millimoles
MP	melting point
MS	mass spectrometry
m	multiplet
NMR	nuclear magnetic resonance spectroscopy
ppm	parts per million
s	singlet
symm	symmetrical
TBAB	tetrabutylammonium bromide
TCE	1,1,2,2-tetrachloroethane
THF	tetrahydrofuran
TLC	thin layer chromatography
t	triplet
q	quartet
quat	quaternary
ν_{max}	wave numbers pertaining to maximum absorbance

1. Instrumentation and General Techniques

1.10 NMR Spectroscopy

Routine continuous wave ^{1}H NMR spectra were obtained using a Joel PMX-60 spectrometer. High field fourier transform spectra were obtained on a Bruker WP-80 operating at 80.13 MHz for protons, operated by Miss H. Grant or on a WP-200 spectrometer operating at 200.13 MHz for protons and 50.32 MHz for carbon-13 nuclei, operated by Mr. J.R.A. Millar and Miss H. Grant or on a Bruker WH-360 MHz spectrometer operating at 360.13 MHz for protons and 90.56 MHz for carbon-13 nuclei operated by Dr D. Reed or on a Varian VXR-600 spectrometer operating at 599.96 MHz for protons operated by Dr. I. Sadler.

Chemical shifts (δ) are reported in parts per million using tetramethylsilane (δ 0.0) as a reference for protons and the centre line of the triplet of $CDCl_3$ (δ 76.9) as a reference for ^{13}C spectra. DEPT $\pi/2$ and $3\pi/4$ spectra were used to assign all of the signals in the $^{13}C\{^{1}H\}$ spectra.

1.15 Infrared Spectroscopy

Infrared spectra were recorded either on a Perkin-Elmer 781 spectrometer or on a Biorad FTS-7 spectrometer. Liquid samples were recorded as thin films and solid samples as Nujol mulls, both on sodium chloride plates. Calibration for the former instrument was achieved by reference to the characteristic polystyrene peak at 1603 cm^{-1}.

1.20 Mass Spectrometry

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

1.25 Elemental Analysis

Elemental analysis for carbon, hydrogen and nitrogen were carried out on a Carbo-Erba elemental analyser, model 1106, operated by Mrs. E. MacDougall, or on a Perkin-Elmer 2400 CHN elemental analyser, operated by Miss E. Stevenson.

1.30 X-Ray Crystallography

X-ray crystal structures were determined on a Stoe STADI-4, four circle diffractometer by Dr. A. Blake.

1.35 Melting Points and Boiling points

Melting points were measured on a digital Gallenkamp capillary tube apparatus and are uncorrected. Boiling points were measured using a Buchi Kugelrohr distillation apparatus.

1.40 HPLC

HPLC analysis of diastereomeric mixtures were conducted on a Gilson HPLC apparatus using a 5 mm spherisorb silica column and U.V. detection at 254 nm. Attempted separation of epicamphor from camphor was conducted on an Applied Biosystems 1406A instrument with an Applied Biosystems RP18 column, using U.V. detection at 214 nm.

1.45 Optical Rotations

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

1.50 Flash Column Chromatography

Flash column chromatography was carried out routinely using Fluka 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 solvent elution.

1.55 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-in-ethanol solution, followed by gentle flaming.

1.60 Drying and Purification of Solvents

Toluene and DME were dried by the addition of sodium wire to the analytical grade reagents, or by standing over finely divided calcium hydride overnight. Methylene chloride and TCE were dried by distilling from calcium hydride and stored over calcium hydride. THF and diethyl ether were dried by distilling from sodium and benzophenone, under a nitrogen atmosphere; these solvents were collected when the deep purple colour, due to sodium benzophenone ketyl, had formed.

1.65 Drying of Glassware and Inert gases.

Before conducting moisture sensitive reactions, reaction flasks were scrupulously dried by heating with a strong Bunsen flame whilst flushing with a strong pulse of dry argon, and allowing to cool under this strong pulse of gas.

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

1.70 Determination of isomer ratios in Diels-Alder reactions with cyclopentadiene

This was routinely done by examination of the olefinic region (δ 5.5-6.5) of the high field ^{1}H NMR spectrum (200 or 360 MHz) and integration of the doublets of doublets pertaining to each isomer.

2. Preparation of starting materials.

2.1 Preparation of *[(1S)-endo]-1,7,7-trimethylbicyclo [2.2.1.] heptane-2-chloroformate* (82)

Following the method of Banks *et al*[86],a solution of [(1*S*)-*endo*]-(-)-borneol (100g,648mmol) in methylene chloride (*ca*. 500ml) was added dropwise to a rapidly stirred solution of phosgene (20% w/v in toluene, 1000ml, 1.93m,3eq) under argon at 0^0C.The resulting solution was stirred at ambient temperature for 164 hours before the solvents and excess phosgene were removed *in vacuo* to yield a pale yellow oil (139.75g, 99.5%).The infrared spectrum was identical to that of an authentic sample of **82** ; IR (neat) ν_{max} 2960,1770 (C=O),1173,1154,1148 cm^{-1}.

2.1.1 Preparation of *[(1S)-endo]-1,7,7-trimethylbicyclo [2.2.1] heptane-2-azidoformate* (81)

Following the method of Banks *et al*,chloroformate **82** (70.25g,324mmol), in dry methylene chloride (*ca*. 300ml) was added in portions to a rapidly stirred solution of sodium azide (42.14g,648mmol,2eq) and TBAB (*ca*. 0.1g) in water (*ca*. 300ml) at room temperature.The resulting mixture was stirred at ambient temperature for *ca*. 18 hours,separated and the aqueous layer extracted with methylene chloride (4 x *ca*. 100ml).The combined organic layers were washed with water (*ca*. 20ml),dried over magnesium sulphate,filtered and the solvent removed *in vacuo* to yield a yellow oil (70.72g,98%).The infrared spectrum was identical to that of an authentic sample of **81** ; IR(neat) 2980,2138(N_3),1730 (C=O),1240(b) cm^{-1}.

2.1.2 Preparation of *[(2R,6S)-endo]-5-aza-1,10,10-trimethyl-3-oxatricyclo [5.2.1.$0^{2,6}$] decan-4-one* (77) by solution thermolysis

(a) Using a 10% solution

A solution of azidoformate (25g,112mmol) in dry TCE (*ca*. 20ml) (giving a total volume of *ca*. 50ml) was added *via*. syringe pump to boiling dry TCE (*ca*. 250ml) under an argon atmosphere over *ca*. 45 minutes after which time *ca*. 20ml had been added.The rate of addition was then increased such that the remaining 30ml was added over 30 minutes.The resulting golden brown solution was allowed to cool and analysed by TLC which

revealed the presence of a small amount of unreacted azide.The solution was then boiled for a further 15 minutes before being allowed to cool,and subsequent removal of the TCE yielded a brown oil.Analysis of the crude reaction mixture by high field ^{1}H NMR showed that **77** and the six membered ring products **79** and **83** and amide **80** were present in a ratio 37 : 29 : 8.5 : 25.5.The mixture was subjected to flash chromatography (400g SiO_2) (eluting with *n*hexane (700ml) followed by pure diethyl ether) yielded the desired compound **77** as an off-white solid (8.00g,37%),which was identical in all respects to that obtained by Banks *et al*[86]; **MP** = 162-163^{0}C (from ethyl acetate); **^{1}H NMR** (360MHz,$CDCl_3$) δ 6.55 (1H,bs,NH), 4.56-4.53 (1H,dd,*J* = 9.9 and 1.8 Hz,CHO),4.15-4.11 (1H,ddt,*J* = 9.9,4.5 and 1.2 Hz,CHN),1.85-1.83 (1H,t,*J* = 4.3 Hz, bridgehead CH),1.59-1.46 (3H,cm),1.32-1.23 (1H,tdd,*J* = 13.2,4.9 and 1.9 Hz,CHH),0.92 (3H,s,CH_3), 0.91 (3H,s,CH_3),0.87 (3H,s,CH_3) ppm; **^{13}C NMR** (50.3MHz,$CDCl_3$) δ 160.78(C=O),85.34(CH),54.61(CH),48.75 (quat C),48.13(CH /quat C),26.12(CH_2),19.74(CH_3),19.50(CH_2),17.57 (CH_3),13.81(CH_3) ppm; **IR** (Nujol) ν_{max} 3300 (NH),1755,1715(C=O),1242, 1110,1085,1048(d) cm^{-1}.See Appendix 1 for X-Ray crystal structure.

(b) Using a 0.7% solution

A solution of azidoformate (10.09g,45mmol) in dry TCE (*ca*. 50ml) was added dropwise from a pressure-equalising separating funnel to boiling TCE (*ca*. 1500ml) over 15 minutes under an argon atmosphere.The resulting solution was heated under reflux for a further 25 minutes before a sample of the solution was taken and the excess TCE removed under high vacuum.An infrared spectrum revealed that azide was no longer present and the solution was allowed to cool.Analysis of the crude reaction mixture by high field ^{1}H NMR showed the same four products as in section 2.1.2 (a) in a corresponding ratio of 50 : 34 : 16 : 7.

Note :- Reactions of **77** with all acid chlorides were monitered by TLC using *n*hexane : ethyl acetate (1:1).

2.1.3 Attempted syntheses of the Chirabornox derived acrylate (87).

Preparation of the sodium salt of Chirabornox (85)

This was prepared using the method of Banks *et al*[155].

To an ice-cooled,stirred suspension of sodium hydride (2.50g,104mmol, 1eq) in dry diethyl ether (*ca.* 100ml) under argon,was added *dropwise* a solution of **77** (20.20g,104mmol,1eq) in dry methylene chloride (*ca.* 100ml) (*CAUTION* :-vigourous evolution of hydrogen gas).The resulting solution was allowed to stir overnight before being filtered under suction with the aid of a funnel suspended above the filter funnel through which argon streamed to prevent hydrolysis of the salt.The product was washed with diethyl ether to remove any unreacted auxiliary before being crushed into a powder and dried under high vacuum,yielding a colourless powder (19.33g,86%).

Attempted synthesis of (87) using the sodium salt (85)

(a) Using diethyl ether as solvent

To an ice-cooled suspension of **85** (0.5g,2.3mmol) in dry diethyl ether (*ca.* 40ml) was added dropwise neat redistilled acryloyl chloride (0.21g, 2.32mmol,1eq).The resulting mixture was allowed to warm to ambient temperature and stirred for *ca.* one hour before the sodium chloride was filtered off and washed with a little ether (*ca.* 10ml).The ether was then removed *in vacuo* to yield an oil (0.53g,93%).Attempted purification by Kugelrohr or flash chromatography resulted in sustantial polymerisation of the product.The same result was observed using DME as solvent in the presence of galvinoxyl; the DME had been pre-treated for peroxides as described in the literature[93] in which the DME was stirred overnight over potassium hydroxide.After decantation,the solvent was stirred over sodium borohydride,with the exclusion of light, for *ca.* one day before being distilled.

(b) Using methylene chloride as solvent

To an ice-cooled stirred suspension of **85** (0.5g,2.3mmol) in dry methylene chloride (*ca.* 50ml) (to which galvinoxyl (*ca.* 10mg) had been added) under argon,was added neat,redistilled acryloyl chloride (0.23g,2.54mmol, 1.1eq).The resulting solution was allowed to warm to ambient temperature and stirred for *ca.* one day during which time polymeric material could be seen to form.

2.1.4 Attempted *N*-bromination of (77)

Following the method of Dockx *et al*[91], to a solution of **77** (1g,5.13mmol) in distilled water (*ca.* 60ml) was added bromine (0.819g,0.264ml, 5.1mmol,1eq) in small portions over *ca.* 15minutes, whilst keeping the pH of the solution between 8 and 11 throughout by the addition of sodium hydroxide solution.The resulting solution was stirred for *ca.* 30 minutes at ambient temperature before the solution was filtered and the green precipitate which had formed was washed with water (*ca.* 20ml) and dried (0.98g). The infrared and ^{1}H NMR spectra were shown to be identical with those of **77**.Extraction of the aqueous layer yielded a further crop,shown to be **77** also.The residue was dissolved in methylene chloride (*ca.* 50ml) and bromine (1.1g,0.36ml,7mmol,1.35eq) was added dropwise at alkaline pH and stirred overnight in an alkaline condition and extracted with methylene chloride (3 x *ca.* 20ml).The combined organic layers were dried over magnesium sulphate, filtered and solvents removed *in vacuo* to yield 1.36g.However the infrared spectrum revealed that only starting material was present.

2.1.5 Attempted synthesis of (87) using potassium carbonate as base.

To a solution of **77** (0.5g,2.56mmol) in dry DME (*ca.* 50ml) under argon at room temperature,was added dropwise neat, redistilled acryloyl chloride (0.24g, 2.56mmol,1.05eq) followed by potassium carbonate (0.18g, 1.30mmol,0.5eq).The resulting solution was then allowed to stir for *ca.* 70 hours before TLC revealed that essentially starting material was present. Galvinoxyl (*ca.* 10mg) was then added to the reaction mixture which was then heated at 50^{0}C for a prelonged period afterwhich time TLC showed that no change had taken place.

2.1.6 Attempted synthesis of (87) using triethylamine as base.

This reaction was conducted according to the procedure of Sempuku *et al*[89].

To a solution of **77** (0.5g,2.56mmol) and triethylamine (0.52g,5.15mmol, 2eq) in dry acetonitrile at 0^{0}C under an argon atmosphere,was added dropwise neat,redistilled acryloyl chloride (0.23g,2.54mmol,1eq).The resulting solution was stirred at 0^{0}C for two hours before stirring at room temperature for 19 hours.A trace of galvinoxyl was added and the

acetonitrile removed under high vacuum.The residue was dissolved in methylene chloride (*ca.* 20ml) and water (*ca.* 10ml) was added.The layers were separated and the aqueous layer was extracted with methylene chloride (2 x *ca.* 20ml).The combined organic extracts were dried over magnesium sulphate,filtered and evaporated to yield an oil which was shown by infrared spectroscopy to be unreacted auxiliary.

2.1.7 Synthesis of (87) using methylmagnesium bromide as base

This was conducted by the method of Evans *et al*[46].

To an ice-cooled solution of **77** (0.5g,2.56mmol) and quinol (*ca.* 10mg) in freshly distilled THF (*ca.* 40ml),under argon,was added dropwise methylmagnesium bromide (3M in diethyl ether(Aldrich),0.9ml,2.7mmol, 1.05eq).The resulting solution was stirred at 0^0C for 10 minutes before the temperature was lowered to -78^0C .Neat redistilled acryloyl chloride (0.30g,3.3mmol,1.3eq) was then added and the resulting mixture stirred at -78^0C for 10 minutes before being warmed to 0^0C and stirred for a further 75 minutes, and then at room temperature for 15 minutes,by which time TLC revealed that no more starting material had been consumed.The reaction mixture was quenched with saturated ammonium chloride solution (*ca.* 10ml),diluted with diethyl ether (*ca.* 120ml) and the layers were separated.The aqueous layer was extracted with diethyl ether (2 x *ca.* 75ml),the combined layers dried over magnesium sulphate and evaporated to yield an oil which was purified by flash chromatography using *n*hexane : ethyl acetate (7:1) as the elution solvent to furnish *[(2R,6S)-endo]-N-Acryloyl-5-aza-1,10,10-trimethyl-3-oxatricyclo [5.2.1.$0^{2,6}$] decan-4-one* **87** as colourless crystals (0.48g,75%); **MP** = 47-50^0C; $[\alpha]_D^{22}$ = -156.9^0 (c = 2.58,CH_2Cl_2); **^{1}H NMR** (360 MHz,$CDCl_3$) δ7.58-7.50 (1H,dd,*J* = 17.0 and 10.5 Hz (trans and cis coupling), HHC=C<u>H</u>-), 6.50-6.45 (1H,dd,*J* = 17.0 and 1.9 Hz (trans and geminal coupling), <u>H</u>HC=CH-),5.85-5.82 (1H,dd,*J* = 10.5 and 1.9 Hz (cis and geminal coupling), H<u>H</u>C=CH-), 4.63-4.58 (1H,ddd,*J* = 9.8,4.5 and 1.4 Hz,C<u>H</u>N), 4.52-4.49 (1H,dd,*J* = 9.7 and 1.7 Hz,C<u>H</u>O), 2.31-2.29 (1H,t,*J* = 4.3 Hz,bridgehead C<u>H</u>), 1.66-1.52 (2H,cm), 1.39-1.30 (1H,cm),1.22-1.12 (1H,cm), 0.96 (3H,s,C<u>H</u>$_3$), 0.95 (3H,s,C<u>H</u>$_3$), 0.94 (3H,s,C<u>H</u>$_3$) ppm ; **^{13}C NMR** (50.3 MHz,$CDCl_3$) δ 164.96 (C=O),154.04 (C=O),131.39 (<u>C</u>H_2=), 127.19 (CH_2=<u>C</u>H),82.63 (CH),57.82(CH),49.33(quat C),48.44 (quat C), 47.68(CH),26.18(CH_2),19.76(CH_3),19.66(CH_2),17.92(CH_3),13.68(CH_3)

ppm; **IR** (Nujol) ν_{max} 1786,1770 (C=O),1688 (C=O),1620 (C=C),1412, 1326,1258,1212(d) cm^{-1}; **MS** (ei) m/z 250 (14%, $^{12}C_{13}{}^{13}CH_{19}NO_3{}^+$), 249(92,$M^+$),205(17),190(36),162(14),135(85),134(63),119(28),109(18), 108(9),95(56),79(10),67(12),55(base,$H_2C{=}CHCO^+$),41(33); **Accurate mass** (ei),Found : 249.1371; $C_{14}H_{19}NO_3$ requires 249.13648.

Note :- It was found that after <u>one</u> use of Aldrich methylmagnesium bromide,despite the use of recommended procedures for the handling of air and water sensitive reagents,the Grignard was discovered to be chemically inactive towards the oxazolidinone upon attempted use thereafter.As a result,it was found desirable to freshly synthesise the Grignard,and this was routinely achieved on a 6 mmol scale by the following general procedure :-
Magnesium turnings (0.151g,6.3mmol) and freshly distilled diethyl ether (*ca.* 30ml) were subjected to sonication for 15 minutes under an argon atmosphere.The solution was allowed to cool to ambient temperature (more ether is added if required) and a little bromomethane solution (2M in diethyl ether,excess) is added.After several minutes little bubbles formed (warming with the heat of the hand and also occasional gentle tapping of the reaction flask helps).When the bubble production was strong enough,the reaction mixture was *gently* stirred and bromomethane added at such a rate to keep the reaction progressing.The reaction was complete within a few minutes (total consumption of the magnesium) and the solution heated with warm water for a few seconds to remove the excess halide (CARE! : FUMECUPBOARD).The solution was then cooled to 0^0C ready for the dropwise addition of the auxiliary in dry THF.

2.1.7.5 Preparation of (87) using *n*butyllithium as base

The protocol followed for this reaction also followed that of Evans *et al*[46]. To a solution of **77** (1g,5.13mmol) in dry,freshly distilled THF at -78^{0}C under an argon atmosphere,was added dropwise nbutyllithium (1.6M in hexanes,4ml,6.4mmol,1.2eq).The resulting solution was then stirred at -78^{0}C for one hour before neat redistilled acryloyl chloride (0.56g, 6.19mmol,1.2eq) was added dropwise.The resulting mixture was then stirred at -78^{0}C for 30 minutes before being allowed to warm to room temperature.At this point TLC showed that the reaction was complete whereupon it was quenched with saturated aqueous ammonium chloride (*ca.* 100ml).The mixture was concentrated *in vacuo* and diluted with diethyl ether.The layers were separated and the organic layer washed successively with saturated aqueous sodium bicarbonbate and saturated aqueous sodium chloride.Filtration and evaporation yielded an oil (0.56g,46%) which was identified by 60 MHz ^{1}H NMR spectroscopy to be the desired product.Further extractions of the aqueous layer did not furnish any more product.

2.1.8 Preparation of the crotonate (101) of Chirabornox

To an ice-cooled solution of freshly prepared methylmagnesium bromide (made according to the general procedure) (0.73g,6.15mmol,1.2eq) in dry freshly distilled diethyl ether (*ca.* 30ml) under an argon atmosphere,a solution of **77** (1g,5.13mmol) in dry,freshly distilled THF (*ca.* 30ml) was added dropwise.The resulting solution was allowed to stir at 0^{0}C for 20 minutes before being cooled to -78^{0}C.Neat redistilled crotonyl chloride (0.65g,6.22mmol,1.2eq) was added dropwise and the resulting solution stirred at -78^{0}C for 20 minutes before being warmed to 0^{0}C and stirred for one hour.TLC showed that some starting material remained and as a result the reaction was warmed to room temperature and stirred overnight.After this period virtually all of the starting material had been consumed,whereupon the reaction was quenched with aqueous ammonium chloride and stirred for 5 minutes to destroy excess acid chloride.The layers were separated and the aqueous layer extracted with diethyl ether (3 x *ca.* 50ml).The combined organic extracts were washed with saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride,dried over magnesium sulphate,filtered and evaporated to yield a pale yellow solid (1.34g,99%) which was purified by flash

chromatography (50g SiO_2, using *n*hexane : ethyl acetate (7:1) as the elution solvent) to yield *[(2R,6S)-endo]-N-Crotonoyl-5-aza-1,10,10-trimethyl-3-oxatricyclo [5.2.1.0^{2,6}] decan-4-one* **101** as colourless crystals (1.15g,85%); **MP** = 121.5-123^{0}C (from di-isopropyl ether); $[\alpha]_D^{21.5}$ = -173.9^0 (c = 4.94,CH_2Cl_2); **^{1}H NMR** (200 MHz,$CDCl_3$) δ 7.32-7.22 (1H,dq, *J* = 15.3 and 1.5 Hz,MeHC=C<u>H</u>-), 7.14-6.96 (1H,dq,*J* = 15.3 and 6.6 Hz, Me<u>H</u>C=CH-), 4.60-4.52 (1H,ddd,*J* = 9.8,4.3 and 1.2Hz,C<u>H</u>N),4.48-4.42 (1H,ddd,*J* = 9.8,1.7 and 0.6 Hz,C<u>H</u>O),2.26-2.22 (1H,t,*J* = 4.2 Hz, bridgehead C<u>H</u>), 1.90-1.86(3H,dd,*J* = 6.7 and 1.4 Hz,C<u>H</u>$_3$HC=O), 1.62-1.09 (4H,m), 0.91-0.90 (9H,2 x s,3 x C<u>H</u>$_3$) ppm; **^{13}C NMR** (90.56 MHz, $CDCl_3$) δ 164.95 (C=O),154.05 (C=O),146.17(=<u>C</u>HCO),121.65 (Me<u>C</u>H=), 82.34 (CH),57.76(CH),49.25(quat C),48.30 (quat C),47.78 (CH),26.17 (CH_2),19.71(CH_3),19.59(CH_2)18.19(<u>C</u>H$_3$CH=),17.85(CH_3),13.60(CH_3) ppm; **IR** (Nujol) ν_{max} 1763 (C=O),1682 (C=O),1635 (C=C),1375,1210,1055 cm^{-1}; **MS** (ei) 265 (10%,$^{12}C_{14}{}^{13}CH_{21}NO_3^+$),264(53,M$^+$),248(8),204(15), 136(12),135(45),134(27),119(12),109(8),95(20),93(8),79(9), 69 (base,MeCH=CHCO$^+$); **Accurate mass** (ei), Found : 263.1521; $C_{15}H_{21}NO_3$ requires 263.15213; **Elemental analysis**, Found : 68.0% C,7.89% H,5.35% N, $C_{15}H_{21}NO_3$ requires 68.4% C,8.04% H,5.32% N.

2.1.9 Preparation of the cinnamate (102) of Chirabornox

This was carried out using the procedure described in section 2.1.8 using **77** (0.624g,3.2mmol) and methylmagnesium bromide (0.38g, 3.2mmol) and cinnamoyl chloride (0.55g,3.3mmol,1eq) in dry THF (*ca.* 5ml).After quenching and concentration of the reaction mixture *in vacuo* the aqueous layer was extracted with methylene chloride (3 x *ca.* 60ml).The combined layers were washed successively with saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride, dried over magnesium sulphate,filtered and evaporated to yield an oily solid.This was purified by flash chromatography (50g SiO_2, using *n*hexane : ethyl acetate as the elution solvent) to yield *[(2R,6S)-endo]-N-Cinnamoyl-5-aza-1,10,10-trimethyl-3-oxatricyclo [5.2.1.0^{2,6}] decan-4-one* **102** as colourless crystals (0.843g,81%); **MP** = 169.5-170.5^{0}C (from ethyl acetate); $[\alpha]_D^{23.5}$ = -133.0^0 (c = 4.22,CH_2Cl_2); **^{1}H NMR** (200 MHz,$CDCl_3$) δ 8.04-7.96 (1H,d,*J* = 15.7 Hz,PhCH=C<u>H</u>-),7.84-7.77 (1H,d,*J* = 15.7 Hz, PhC<u>H</u>=CH-),7.63-7.58 (2H,cm,Ph C<u>H</u>),7.39-7.34 (3H,cm,Ph C<u>H</u>),4.67-4.64 (1H,ddd,*J* = 9.8,4.4 and 1.3 Hz,C<u>H</u>N),4.56-4.50 (1H,dd,*J* = 9.7 and 1.40

Hz,CHO),2.37-2.33 (1H,t,J = 4.3 Hz,bridgehead CH),1.67-1.22 (4H,cm), 0.98-0.97 (9H,2 x s,3 x CH_3) ppm; **^{13}C NMR** (90.56 MHz,$CDCl_3$) δ 165.16 (C=O),154.15(C=O),145.80(PhCH=CH-),134.46 (Ph quat C),130.33 (Ph CH),128.63(Ph CH),128.37(Ph CH),116.90(PhCH=CH-),82.43(CH), 57.94(CH),49.29(quat C),48.35(quat C),47.82(CH),26.20(CH_2), 19.73 (CH_3),19.66(CH_2),17.88(CH_3),13.62(CH_3) ppm; **IR** (Nujol) ν_{max} 1762 (C=O),1682 (C=O),1618 (C=C),1372,1348,1212,1050 cm^{-1}; **MS** (ei) 326(3%,$^{12}C_{19}{}^{13}CH_{23}NO_3^+$),325(15,$M^+$),281(3),266(2),143(2),136(3),131(4, $PhCH=CHCO^+$),119(2),108(2),103(13,$PhCH=CH^+$),102(2),95(2),77(7,Ph^+), 69(base),51(11),43(3); **Accurate mass** (ei), Found : 325.1674; $C_{20}H_{23}NO_3$ requires 325.16778; **Elemental analysis**, Found : 73.8% C, 7.25% H, 4.36% N, $C_{20}H_{23}NO_3$ requires 73.8% C,7.12% H,4.30% N.

2.1.9.5 Preparation of (102) using *n*butyllithium as base

The reaction was conducted as for the acrylate in section 2.1.7.5 using **77** (1g,5.13mmol) in dry THF (*ca.* 50ml) and cinnamoyl chloride (0.92g, 5.52mmol,1.1eq) in dry THF (*ca.* 10ml).Following work-up and purification by flash chromatography, **102** was formed in reduced yield (1.01g,60%); the product was identical by 60 MHz ^{1}H NMR spectroscopy to that obtained for the material isolated in section 2.1.9.

3 Diels-Alder reactions

A. Using titanium catalysts

3.1.1 Reaction of (87) with cyclopentadiene at -16^{0}C using titanium tetrachloride and titanium tetraisopropoxide

Method A

To a solution of **87** (0.54g,2.17mmol) in dry methylene chloride (*ca.* 50ml) at -16^{0}C ($CCl_4/CO_{2(s)}$) under argon, was added titanium tetrachloride (0.82g,4.32mmol,2eq) followed by titanium tetraisopropoxide (1.23g, 4.33mmol,2eq).To the resulting brown complex neat, freshly cracked cyclopentadiene (0.57g,8.64mmol) was added dropwise and the resulting solution stirred at -16^{0}C for 10 hours.The reaction mixture was then poured onto crushed ice and after separation of the layers, the aqueous

fraction was extracted with methylene chloride (3 x *ca.* 50ml).The combined organic layers were washed successively with saturated aqueous sodium bicarbonate solution,saturated aqueous sodium chloride solution and dried over magnesium sulphate.Filtration and evaporation yielded an oily residue (0.79g) which was shown by 200 MHz ^{1}H NMR spectroscopy to contain two major (*endo*) isomers in the ratio 1.84 : 1 and an *endo/exo* ratio of 15:1. Purification of this residue by flash chromatograpy (50g SiO_2) using *n*hexane : ethyl acetate (7:1) as elution solvent yielded a crystalline solid (0.52g,76%) which was shown to contain only the major (*endo*) isomers in the same ratio.These could not be separated using silica of 30A pore size with *n*hexane : diethyl ether (40:1) as elution solvent. Some separation was achieved using TLC grade silica (70g) with *n*hexane : diethyl ether (40:1) as elution solvent.The first isomer to be eluted was the minor isomer *[(2R,6S)-endo]-N-(3'R,4'R,6'R)-Bicyclo [2.2.1] heptene-4'-carbonyl-5-aza-1,10,10-trimethyl-3-oxatricyclo [5.2.1.0^{2,6}] decan-4-one* as colourless crystals; **MP** = 143.5-145.5^{0}C (from *n*hexane : diisopropyl ether); $[\alpha]_D^{23}$ = -25.1^0 (c = 1.95,CH_2Cl_2); **^{1}H NMR** (360 MHz,$CDCl_3$) δ 6.21-6.19 (1H,dd,*J* = 5.6 and 3.1 Hz,HC=CH),5.87-5.84 (1H,dd,*J* = 5.6 and 2.8 Hz,HC=CH), 4.49-4.48 (2H,cm,CHO and CHN),4.05-4.00 (1H,ddd,*J* = 9.0,4.4 and 3.5 Hz,CH-CO),3.28 (1H,bs, cycloadduct brigdehead CH),2.92-2.91 (1H,bs, cycloadduct bridgehead CH),2.25-2.23 (1H,t,*J* = 4.2 Hz,bridgehead (auxiliary) CH), 2.00-1.93 (1H,ddd,*J* = 12.8,9.1 and 3.7 Hz,CHH-CO), 1.68-1.15 (6H,cm), 1.14-1.06 (1H,ddd,*J* = 13.0,9.0 and 3.8 Hz), 0.96 (3H,s,CH_3), 0.94 (3H,s, CH_3), 0.92 (3H,s,CH_3) ppm; **^{13}C NMR** (50.3 MHz,$CDCl_3$) δ174.51(C=O),153.93 (C=O),137.65 (HC=CH),131.50(HC=CH),82.26(CH),58.07(CH),49.93 (CH_2),49.23(quat C),48.18 (quat C),47.76(CH),46.12(CH),43.09(CH),42.68 (CH),29.42 (CH_2),26.16(CH_2),19.55(CH_3),19.44(CH_2),17.82(CH_3),13.65 (CH_3) ppm; **IR** (Nujol) ν_{max} 1765 (d,C=O)1696 (C=O),1340,1283,1222, 1212 cm^{-1}; **MS** (ei) 316 (8%,$^{12}C_{18}{}^{13}CH_{25}NO_3^+$),315(36,$M^+$)251(18), 250(base),249(11), 131(10),120(14),119(11),109(6),95(13),77(16),69(26),66 (62),55(45); **Accurate mass** (ei), Found : 315.1839; $C_{19}H_{25}NO_3$ requires 315.18343; **Elemental analysis**, Found : 72.0% C,7.87% H,4.34% N, $C_{19}H_{25}NO_3$ requires 72.4% C,8.00% H,4.44% N.See Appendix 3 for X-Ray crystal structure.

The second (major) isomer to be eluted was *[(2R,6S)-endo]-N-(3'S,4'S,6'S) -Bicyclo [2.2.1] heptene-4'-carbonyl-5-aza-1,10,10-trimethyl-3-oxatricyclo*

[5.2.1.0^{2,6}] decan-4-one as colourless crystals; **MP** = 155-157^{0}C (from *n*hexane : diisopropyl ether); $[\alpha]_D^{22}$ = -287.5^0 (c = 3.08,CH_2Cl_2); **^{1}H NMR** (360 MHz,$CDCl_3$) δ 6.21-6.19 (1H,dd,*J* = 5.6 and 3.1 Hz,HC=CH),5.78-5.76(1H,dd,*J* = 5.7 and 2.8 Hz,HC=CH),4.53-4.49 (1H,ddd,*J* = 9.9,4.2 and 1.2 Hz,CHN),4.47-4.44 (1H,dd,*J* = 9.4 and 1.3 Hz,CHO),4.05-4.00 (1H, ddd,9.0,4.4 and 3.4 Hz,CH-CO),3.36 (1H,bs, cycloadduct bridgehead CH),2.90 (1H,bs,cycloadduct bridgehead CH), 2.21-2.18 (1H,t,*J* = 4.1 Hz,bridgehead (auxiliary) CH),1.90-1.83 (1H,ddd, *J* = 12.6,9.0 and 3.7 Hz,CHH-CH-CO), 1.70-1.20 (6H,cm),1.18-1.10 (1H, ddd,*J* = 12.6,8.5 and 3.3 Hz),0.95 (3H,s, CH_3), 0.93 (3H,s, CH_3), 0.90 (3H, s,CH_3) ppm; **^{13}C NMR** (50.3 MHz, $CDCl_3$) δ174.31(C=O),153.89(C=O), 137.88(HC=CH),130.95(HC=CH), 82.17(CH), 57.62(CH),50.01(CH_2),49.18 (quat C),48.18(quat C),47.53(CH), 46.26(CH),42.79(CH), 42.63(CH),28.80 (CH_2),26.14(CH_2),19.60(CH_3),19.35(CH_2),17.73(CH_3),13.55(CH_3) ppm; **IR**(Nujol) ν_{max} 1782(d,C=O),1690 (C=O),1288,1215(d),1050 cm^{-1}; **MS** (ei) 316(8%,$^{12}C_{18}{}^{13}CH_{25}NO_3^+$), 315(37,$M^+$),251(11),250(69), 249(8),135(29), 120(29),93(15),91(10),69(base),67(7),66(56),55(47); **Accurate mass** (ei), Found : 315.1823; $C_{19}H_{25}NO_3$ requires 315.18343; **Elemental analysis**, Found : 72.5% C,8.05% H,4.72% N, $C_{19}H_{25}NO_3$ requires 72.3% C, 8.00% H,4.4% N.See Appendix 2 for X-ray crystal structure.

The reaction was repeated at -78^{0}C under otherwise identical conditions giving a sparingly improved *endo*:*endo* ratio of 2.06:1.No *exo* isomers could be detected.

3.1.2 Reaction of (87) with cyclopentadiene at -78^{0}C using titanium tetrachloride and titanium tetraisopropoxide

METHOD B

To a solution of titanium tetrachloride (0.345g,1.82mmol,4eq) in dry methylene chloride (*ca*. 2ml) at 0^{0}C under argon was added titanium tetraisopropoxide (0.483g,1.7mmol,4eq).The resulting mixture was cooled to -78^{0}C and diluted with dry methylene chloride (*ca*. 2ml) due to the highly viscous nature of the catalyst mixture.A solution of acrylate (0.1g, 0.4mmol) in dry methylene chloride (*ca*. 4ml) was added.to the resulting light brown complex,neat freshly cracked cyclopentadiene (0.27g, 4.1mmol,1eq) was added.The resulting solution was stirred at -78^{0}C for 18 hours before the reaction mixture was poured onto ice (*ca*. 25ml).The layers were separated and the aqueous layer extracted with methylene

chloride (3 x *ca.* 25ml).The combined organic layers were washed successively with saturated aqueous sodium bicarbonate solution and saturated sodium chloride solution,dried over magnesium sulphate, filtered and evaporated to yield an oil which was purified by flash chromatography (20g SiO_2) using gradient elution with *n*hexane : diethyl ether as elution solvents (100:0 to 0:100) to yield a white solid (0.112g, 88%).This was shown by high field ^1H NMR spectroscopy to contain the same *endo* isomers in a corresponding ratio of 1:1,with an *endo:exo* ratio of 57:1.

3.1.3 Reaction of (87) with isoprene using titanium tetrachloride and titanium tetraisopropoxide.

Using method B as described in section 3.1.2, titanium tetrachloride (0.24g,1.27mmol,4eq) and titanium tetraisopropoxide (0.36g,1.24mmol, 4eq) were mixed at -78^{0}C before a solution of **87** (78mg,0.313mmol) in dry methylene chloride (*ca.* 4ml) was added,followed by isoprene (0.21g, 3.1mmol,10eq).After 45.5 hours,the reaction was quenched and work-up provided an oil (80mg,80%) which was studied by high field ^1H NMR spectroscopy using the chiral shift reagent Tris[3(heptafluoropropyl hydroxymethylene)-d-camphorato] europium (III),Eu(hfc)$_3$.Use of 17mg of the product dissolved in $CDCl_3$ (0.3ml) and addition of Eu(hfc)$_3$ (15.8mg in total,1.32 x10^{-2}mmol,25mol%) in portions of 2.8mg,2.7mg,2.8mg,2.6mg and 4.9mg gave satisfactory peak separation,showing the ratio of the two possible isomers formed in this reaction, namely *[(2R,6S)-endo]-N-((4'R) and (4'S)-1'-methylcylohexene-4'-carbonyl)-5-aza-1,10,10-trimethyl-3-oxatricyclo [5.2.1.0^{2,6}] decan-4-one,* to be 2:1; **^{1}H NMR** (360MHz,$CDCl_3$) δ 5.38 (1H,bm, HC=C),4.59-4.54 (1H,ddd,*J* = 9.8,4.4 and 1.1Hz,CHN),4.50-4.47 (1H,dd,*J* = 9.8 and 1.5 Hz,CHO),3.74-3.66 (1H,symm m,CH-CO),2.28-1.87(6H,m), 1.78-1.51 (6H,m),1.40-1.24 (1H,m),1.22-1.08 (1H,m),0.96 (3H,s,CH_3),0.95 (3H,s, CH_3),0.94 (3H,s,CH_3) ppm; **^{13}C NMR** (50.3 MHz,$CDCl_3$) (both isomers) δ 176.59 (C=O),153.77 (C=O),133.58 (quat C,major isomer), 133.37(quat C,minor isomer),119.00 (HC=C,minor isomer),118.87 (HC=C, major isomer),82.25(CH),57.72(CH),49.29(quat C), 48.31(quat C),47.63 (CH),38.20(CH_3-C=),29.43(CH_2,minor isomer),29.26 (CH_2,major isomer), 27.76(CH_2,major isomer),26.89(CH_2,minor isomer), 26.16(CH_2),25.29(CH_2),23.26(CH),19.74(CH_3),19.51(CH_2),17.87(CH_3),

13.68(CH_3) ppm; **Accurate mass** (ei), Found : 317.1977; $C_{19}H_{27}NO_3$ requires 317.19908.

3.1.4 Preparation of an authentic racemic mixture of adducts of (87) and isoprene (one regioisomer only).

This was prepared in the following three steps :-

3.1.4.1 Preparation of (+/-)-Methyl-1-methylcyclohexene-4-carboxylate.

This was conducted by the method of Brown and Hall[110].

To an ice-cooled solution of methyl acrylate (5g,58mmol) in dry methylene chloride (*ca.* 25ml) under argon,was added titanium tetrachloride (2.79g, 1.61ml,15mmol,0.25eq).The resulting orange solution was allowed to warm to room temperature whereupon isoprene (5.47g,80.3mmol,1.58eq) was added.The resulting exothermic reaction required cooling and was then stirred at room temperature overnight before being quenched with dilute hydrochloric acid and stirred vigourously for 5 minutes.The layers were separated and the aqueous layer extracted with methylene chloride (3 x *ca.* 30ml) and the combined organic layers were washed successively with saturated aqueous sodium bicarbonate solution (2 x *ca.* 50ml) and saturated sodium chloride solution ,dried over magnesium sulphate, filtered and evaporated to yield a cloudy oil which was purified by kugelrohr distillation to yield predominantly the title regioisomer as a colourless oil (7.77g,87%); **BP** = 30^{0}C/0.2mmHg; lit[110] (90-95^{0}C/ 30mmHg); **^{1}H NMR** (200 MHz,$CDCl_3$) δ 5.34-5.29 (1H,symm m,$\underline{H}$C=C), 3.63-3.60 (1H,m,C$\underline{H}$-$COCH_3$) superimposed on 3.62 (3H,s,$OC\underline{H}_3$),2.51-2.36 (1H,m),2.21-2.11(2H,m), 2.00-1.70(3H,m),1.69-1.60 (1H,cm),1.61-1.52 (3H,m,C$\underline{H}_3$-C=) ppm;**^{13}C NMR** (50.3 MHz,$CDCl_3$) δ 176.15(C=O), 133.40(quat C),118.97(CH),51.28(CH_2),38.87(CH),29.01(O$\underline{C}H_3$),27.42 (CH_2),25.21(CH_2),23.19(CH_3) ppm; **Accurate mass**, Found : 154.0987; $C_9H_{14}O_2$ requires 154.09937.

3.1.4.2 Alkali hydrolysis to (+/-)-1-methylcyclohexene-4-carboxylic acid.

The ester from 3.1.4.1 (3g,19.5mmol) was dissolved in methanol (*ca.* 100ml) and a solution of potassium hydroxide (1.25g,22.3mmol,1.14eq) in aqueous methanol (75%,*ca.*10ml) was added.The resulting solution was heated under reflux for three hours before being allowed to cool and a white solid was seen to precipitate out of the methanolic solution.The

methanol was removed under reduced pressure and methylene chloride (*ca.* 20ml) was added.Dilute hydrochloric acid was added to the rapidly stirred solution until the pH was less than 2.The layers were separated and the aqueous layer extracted with methylene chloride (3 x *ca.* 30ml). The combined organic extracts were washed with water (*ca.* 10ml),dried over magnesium sulphate,filtered and evaporated to yield a white solid (2.43g,89%).This was recrystallised three times from the minimum quantity of *n*hexane to remove the minor regioisomer, yielding the title compound which was shown by ^{13}C NMR spectroscopy to be regiochemically pure;**^{1}H NMR** (200 MHz,$CDCl_3$) δ 11.92 (1H,bs,COO<u>H</u>), 5.35 (1H,bs,<u>H</u>C=C), 2.58-2.44 (1H,m),2.23-2.16 (2H,bm),2.07-1.99 (3H, bm),1.80-1.67 (1H,cm), 1.63 (3H,s,C<u>H</u>$_3$) ppm; **^{13}C NMR** (50.3MHz,$CDCl_3$) δ 182.82(C=O),133.61(quatC),118.86(H<u>C</u>=),38.93(CH),28.96(CH_2),27.21 (CH_2),25.03(CH_2),23.28 (CH_3) ppm; **Accurate mass** (ei), Found : 140.0838; $C_8H_{12}O_2$ requires 140.08372.

The racemic product was then converted to the corresponding acid chloride by boiling in excess thionyl chloride.The unreacted thionyl chloride was removed *in vacuo* yielding the crude product which was purified by kugelrohr distillation (30^{0}C/0.25mmHg) immediately prior to use.

3.1.4.3 Coupling of racemic 1-methylcyclohexene-4-carboxylic acid chloride to lithiated Chirabornox (100).

To a stirred solution of **77** (0.201g,1.03mmol) in dry THF (*ca.* 20ml) at -78^{0}C under argon,butyllithium (1.6M in hexanes,0.71ml,1.13mmol, 1.1eq) was added.The resulting solution was stirred at -78^{0}C for *ca.* one hour before freshly distilled racemic acid chloride from 3.1.4.2 (0.27g, 1.70mmol,1.65eq) in dry THF (*ca.* 30ml) was added.This mixture was stirred at -78^{0}C for 10 minutes before being allowed to warm to 0^{0}C and stirred for a further 10 minutes.TLC revealed that all of the starting material had been consumed and the reaction was quenched with saturated aqueous sodium bicarbonate solution and the mixture was stirred at room temperature for 15 minutes to destroy the excess acid chloride.The mixture was concentrated *in vacuo* and the aqueous layer was extracted with diethyl ether (3 x *ca.*100ml),the organic layers were combined,washed with water (*ca.* 10ml),dried over magnesium sulphate,filtered and evaporated to yield an oil still contaminated with a trace of acid chloride (0.351g,107%).This was shown to have an identical

high field ^1H NMR spectrum to that obtained in section 3.1.3 (for the reaction of **87** and isoprene in the presence of $TiCl_2(OPr^i)_2$ catalyst).The same chiral shift experiment (as for 3.1.3) was conducted and a gave a corresponding ratio of 1.1:1; **^{13}C NMR** (50.3 MHz,$CDCl_3$) δ 176.28 (C=O,isomer #1),176.20 (C=O,isomer #2),153.54(C=O),133.31(quat C, isomer #1),133.10(quat C,isomer #2),118.87(HC=C,isomer #2),118.73 (HC=C,isomer #1),82.02(CH),57.49(CH),49.08(quat C),48.11(quat C), 47.46(CH),37.98(CH_3C=),29.25(CH_2,isomer #1),29.08(CH_2,isomer #2), 27.58(CH_2,isomer #1),26.67(CH_2,isomer #2),25.98(CH_2),25.08(CH_2), 23.10(CH),19.56(CH_3),19.33(CH_2),17.67(CH_3),13.49(CH_3) ppm; **Accurate mass** (ei), Found : 317.1982; $C_{19}H_{27}NO_3$ requires 317.19908.

3.1.5 Preparation of an authentic mixture of the adducts of (87) and isoprene and also their regioisomers.

This was carried out in two steps.

3.1.5.1 Reaction of acryloyl chloride and isoprene using a sealed tube.

To freshly distilled acryloyl chloride (1.28g,14mmol) under argon in a tube suitable for sealing,isoprene (1.06g,16mmol,1.1eq) was added.The resulting mixture was then sealed in the tube and heated at 105^{0}C for 22 hours before being allowed to cool.The product was then distilled by kugelrohr immediately prior to use (196^{0}C,760mmHg) to yield a colourless liquid (1.45g,65%).

3.1.5.2 Coupling of the regiomeric acid chlorides from 3.1.5.1 to Chirabornox.

To an ice-cooled solution of methylmagnesium bromide (prepared by the general procedure) (0.73g,6.15mmol,1.2eq) in dry diethyl ether (*ca.* 20ml) under argon,was added dropwise a solution of **77** (1g,5.13mmol) in dry THF (*ca.* 50ml).The resulting solution was stirred at 0^{0}C for 15 minutes before being cooled to -78^{0}C.Freshly distilled regiomeric acid chlorides (from 3.1.5.1) (0.98g,6.18mmol,1.2eq) was then added and the resulting solution stirred at -78^{0}C for 20 minutes before being allowed to warm to 0^{0}C and stirred for a further 40 minutes.TLC revealed that some starting material was present and the reaction was allowed to warm to room temperature and stirred overnight.The mixture was quenched with saturated aqueous ammonium chloride and extracted with diethyl ether (3 x *ca.* 50ml).The combined organic extracts were dried over magnesium

sulphate,filtered and evaporated.Purification by flash chromatography (50g SiO_2) using *n*hexane : diethyl ether (2:1) as the elution solvent yielded a colourless solid (1.45g,89%).Examination of the product by high field ^1H NMR spectroscopy showed the presence of two regioisomers in the ratio 4:1.Repeating the reaction and adding the acid chloride at 0^0C did not change this 4:1 ratio,indicating that the ratio of "para" to "meta" regioisomers formed in the original isoprene/acryloyl chloride reaction is indeed 4:1.

3.1.6 Comparison of the performance of Evans' (*S*)-valinol derived auxiliary (9) and Oppolzer's chiral sultam (13) with (77) under identical conditions.

Preparation of starting materials

3.1.6.1 Preparation of the acrylate of (9)

This was achieved by the method described in section 2.1.7 using methylmagnesium bromide (0.91g,7.66mmol,1.1eq) and **9** (0.9g, 6.97mmol) and acryloyl chloride (0.82g,9.1mmol,1.3eq).TLC using U.V. detection revealed that the reaction was complete after 50 minutes. Following work-up,the crude orange oil was purified by flash chromatography (50g SiO_2) using gradient elution (*n*hexane : diethyl ether 100:0 to 0:100) yielding *(4S)-N-acryloyl-4-(isopropyl)-2-oxazolidinone* as colourless crystals (0.5g,39%); **^1H NMR** (200 MHz,$CDCl_3$) δ 7.41-7.28 (1H,dd,*J* = 17.0 and 10.4 Hz (trans and cis coupling),CH_2=C<u>H</u>CO),6.39-6.30 (1H,dd,*J* = 17.0 and 1.9 Hz (trans and geminal coupling), <u>H</u>HC=CHCO),5.75-5.69 (1H,dd,*J* = 10.4 and 1.9 Hz (cis and geminal coupling), H<u>H</u>C=CHCO), 4.38-4.31 (1H,cm,chiral centre CH),4.22-4.05(2H,cm,C<u>H</u>$_2$),2.29-2.20 (1H,symm m,$(CH_3)_2$C<u>H</u>-),0.80-0.71 (6H,2 x d,*J* = 7.1 Hz,2 x CH_3) ppm; **^{13}C NMR** (50.3 MHz,$CDCl_3$) δ 164.21 (C=O),153.46(C=O),130.77(<u>C</u>H_2=),127.06(=<u>C</u>H),63.05(CH_2),58.01(CH), 27.94(CH),17.40(CH_3),14.17(CH_3) ppm.Further elution with ethyl acetate yielded recovered oxazolidinone (0.21g).

3.1.6.2 Preparation of the acrylate (24) of Oppolzer's sultam

Following the literature procedure of Oppolzer *et al*[21], a solution of **13** (1g,4.65mmol) in dry toluene (*ca.* 50ml) was added dropwise to an ice-cooled suspension of oil-free sodium hydride (0.13g,5.42mmol,1.15eq) in

dry toluene (*ca.* 20ml) under an argon atmosphere.The resulting solution was allowed to warm to room temperature and stirred for one hour before neat,redistilled acryloyl chloride (0.51g,5.63mmol,1.2eq) was added dropwise with cooling.The resulting solution was stirred overnight at room temperature before examination by TLC showed that starting material **13** was still present.Excess acryloyl chloride was added (0.5g,5.52mmol,1.2eq) and the reaction mixture was stirred for a further 24 hours.The reaction was then quenched with aqueous ammonium chloride solution (10%,*ca.* 50ml) and the layers were separated.The aqueous layer was extracted with methylene chloride (2 x *ca.* 20ml) and the combined organic layers were dried over magnesium sulphate,filtered and evaporated to yield an off-white solid which was purified by flash chromatography (50g SiO_2) using *n*hexane : ethyl acetate (4:1) as the elution solvent yielded the first fraction identified as *(7R)-N-acryloyl-10,10-Dimethyl-5-thia-4-azatricyclo [5.2.1.0^{3,7}] decan-5,5-dioxide* **24** as a colourless solid (0.6g,48%); **^{1}H NMR** (200 MHz,$CDCl_3$) δ 6.88-6.74 (1H,dd,*J* = 16.7 and 10.3 Hz (trans and cis coupling),CH_2=C<u>H</u>CO), 6.47-6.38 (1H,dd,*J* = 16.7 and 1.7 Hz (trans and geminal coupling), <u>H</u>HC=CHCO), 5.82-5.76 (1H,dd,*J* = 10.3 and 1.7 Hz (cis and geminal coupling),H<u>H</u>C=CHCO),3.89-3.85 (1H,dd,*J* = 7.2 and 1.6 Hz,C<u>H</u>N),3.53-3.36 (2H,ABq,*J* = 13.8 Hz,C<u>H$_2$</u>SO_2),2.08-2.04 (2H,cm),1.86-1.82 (3H,cm), 1.34 (2H,cm),1.11 (3H,s,CH_3),0.92 (3H,s,CH_3) ppm; **^{13}C NMR** (50.3 MHz, $CDCl_3$) δ 163.5 (C=O),130.88(CH_2=),127.62(=CH),64.83(CH), 52.81(CH_2), 48.32(quat C),47.52(quat C),44.45(CH),38.16(CH_2),32.57 (CH_2),26.20 (CH_2),20.58(CH_3),19.62(CH_3) ppm.Further elution yielded a second fraction identified by 60 MHz ^{1}H NMR spectroscopy as recovered auxiliary.A third fraction was also isolated which was not the desired product or starting material; this was tentatively assigned as ring opened product.

3.1.7 Diels-Alder reaction between Evans' acrylate and cyclopentadiene using $TiCl_4$ and $Ti(OPr^i)_4$ catalysts.

This was conducted using method B as described in section 3.1.2 with titanium tetrachloride (0.41g,2.16mmol,4eq) and titanium tetraisopropoxide (0.62g,2.18mmol,4eq) mixed at -78^{0}C,then acrylate (0.099g,0.541mmol) followed by cyclopentadiene (0.36g,5.45mmol,10eq) was added.After 18.5 hours the reaction was quenched and work-up

yielded an oil which contained dicylcopentadiene (0.27g,200%).Analysis of this crude reaction mixture by high field ^{1}H NMR spectroscopy showed the *endo* : *endo* ratio to be 1.63 : 1.The *endo* : *exo* ratio was not obtainable due to the complexity of the spectrum.This compares with no measurable asymmetric induction obtained when the same conditions were employed with **87**, and is in stark contrast to the result obtained using diethylaluminium chloride as catalyst (see section 3.5.2).

3.1.8 Diels-Alder reaction between (87) and cyclopentadiene using 0.5 equivalents of $TiCl_4$ catalyst.

The conditions for this reaction closely resembled those of Oppolzer *et al*[21].

To a solution of titanium tetrachloride (0.05g,0.234mmol,0.5eq) in dry methylene chloride (*ca.* 2ml) under argon at -78^{0}C, was added a solution of **87** (0.118g,0.474mmol) in dry methylene chloride (*ca.* 2ml).Freshly cracked,neat cyclopentadiene (0.313g,4.74mmol.10eq) was added and the resulting solution was stirred at -78^{0}C for 19 hours.The reaction mixture was quenched by pouring onto ice,and filtered to remove the polymeric material which had formed as a result of use of this catalyst[94]. The layers were separated and the aqueous layer was extracted with methylene chloride (3 x *ca.* 30ml) and the combined organic extracts were dried over magnesium sulphate,filtered and evaporated to yield an oil which was subjected to purification by two dry flash columns (50g SiO_2) using gradient elution with *n*hexane : diethyl ether 100:0 to 0:100 yielding an oily solid (0.09g,60%).This was shown by high field ^{1}H NMR spectroscopy to contain the same *endo* isomers as section 3.1.1 but in a corresponding ratio of 0.85 : 1.

3.1.9 Diels-Alder reaction between Oppolzer's acrylate (24) and cyclopentadiene using 0.5 equivalents of $TiCl_4$ catalyst.

This was performed under identical conditions to those described in section 3.1.8 using titanium tetrachloride (0.04g,0.21mmol,0.5eq) and **24** (0.109g,0.41mmol) and cyclopentadiene (0.27g,4.1mmol,10eq),yielding after purification by column chromatography a solid (0.07g,50%).This reaction was shown by high field ^{1}H NMR spectroscopy to be completely *endo* selective with an *endo* : *exo* selectivity of 16:1, giving an overall d.e. of 88% which is better than that reported[21] of 66%.

3.2 Reaction of (87) with cyclopentadiene in the absence of catalyst.

Freshly cracked cyclopentadiene (1.50g,22.7mmol,12eq) was added to an ice-cooled solution of acrylate (0.48g,1.93mmol) in dry methylene chloride (*ca.* 50ml) under argon.The reaction mixture was stirred at 0^0C for 23 hours before the excess cyclopentadiene and solvent were removed *in vacuo* and residue purified by flash chromatography to yield a colourless solid (0.42g,69%).Analysis of the product by high field ^{1}H NMR spectroscopy showed that the *endo* isomers described in section 3.1.1 were formed in a corresponding ratio of 1.16 : 1 with an *endo* : *exo* ratio of 24 : 1.

3.3.1 Reaction of Chirabornox derived crotonate (101) with cyclopentadiene at -78^{0}C using $TiCl_4$ and $Ti(OPr^i)_4$ - method B.

This was carried out using the method described in 3.1.2 with titanium tetrachloride (0.29g,1.53mmol,4eq),titanium tetraisopropoxide (0.43g, 1.51mmol,4eq),a solution of crotonate (0.1g,0.38mmol) and cyclopentadiene (0.25g,3.79mmol,10eq),which were reacted for 20 hours.Following work-up,purification by dry flash chromatography (50g SiO_2) using gradient elution (*n*hexane : diethyl ether 100:0 to 0:100) yielded a colourless solid (0.115g,92%),which was shown by high field ^{1}H NMR spectroscopy to contain all four possible isomers,*endo* 1 : *endo* 2 : *exo* 1 : *exo* 2 in a ratio 51:34:11:4 giving an *endo* : *endo* ratio of 3:2 and an *endo* : *exo* ratio of 5.8:1 (overall d.e = 2%); **Accurate mass**, Found : 329.1995; $C_{20}H_{27}NO_3$ requires 329.19908.

3.3.2 Reaction of (101) with cyclopentadiene at -78^{0}C using $TiCl_4$ and $Ti(OPr^i)_4$ - method A.

This was conducted using the method described in section 3.1.1 with titanium tetrachloride (0.30g,1.6mmol,4eq) added to a solution of crotonate (0.105g,0.399mmol) at -78^{0}C,followed by a solution of titanium tetraisopropoxide (0.45g,1.58mmol,4eq) in dry methylene chloride.Under argon.Cyclopentadiene (0.26g,3.99mmol,10eq) was finally added to the resulting light-orange complex and the reaction was stirred at -78^{0}C for *ca.* 55 hours in total before work-up and purification by dry flash chromatography yielded a colurless solid (0.124g,95%).Examination of

the mixture by high field ^1H NMR spectroscopy gave a corresponding ratio to that in section 3.3.1 of 62.25 : 20.5 : 5.75 : 1.5 ,giving an improved *endo* : *endo* ratio of 3.05 : 1 and an *endo* : *exo* ratio of 11.4 : 1 (overall d.e. = 38%). These improvements are in accordance with those observed using the dienophile **87**.

3.3.3 Attempted reaction of the crotonate with cyclopentadiene in the absence of catalyst

This was conducted as for the acrylate (section 3.2) using 20 equivalents of diene.However, high field ^1H NMR spectrum revealed that the reaction was only *ca.* 10% complete.

3.4 Attempted reaction of Chirabornox cinnamate (102) with cyclopentadiene using $TiCl_4$ and $Ti(OPr^i)_4$ - method B.

Using the method described in section 3.1.2,titanium tetrachloride (0.25g, 1.32mmol,4eq),titanium tetraisopropoxide (0.37g,1.30mmol) and a solution of cinnamate (0.105g,0.323mmol) in dry methylene chloride (*ca.* 4ml) gave a bright yellow complex to which cyclopentadiene (0.22g,3.33mmol,10eq) was added.After 45 hours at -78^{0}C, TLC revealed that a significant amount of starting material was present and excess freshly cracked cyclopentadiene (*ca.* 1g) was added.After a total of *ca.* 3 days the reaction was quenched and,following work-up,high field ^1H NMR spectroscopy showed that the reaction was only *ca.* 20% complete.

B. Use of diethylaluminium chloride as catalyst in the Diels-Alder reactions

3.5.1 Reaction of the acrylate with cyclopentadiene at -78^{0}C using Et_2AlCl.

To a solution of **87** (0.102g,0.41mmol) in dry methylene chloride (*ca.* 2ml) at -78^{0}C under argon was added dropwise freshly cracked cyclopentadiene (0.27g,4.1mmol,10eq).To this resulting solution was added diethylaluminium chloride (1.8M in toluene,0.3ml,0.065g, 0.54mmol,1.3eq).The bright yellow colour which formed faded instantly and the reaction mixture was diluted with methylene chloride (*ca.* 50ml) and quenched with dilute hydrochloric acid (2M,*ca.* 5ml).The reaction

mixture was allowed to warm to room temperature and the layers were separated.The aqueous layer was extracted with methylene chloride (3 x *ca.* 10ml) and the combined organic extracts were washed successively with saturated aqueous sodium bicarbonate solution and saturated aqueuous sodium chloride solution,dried over magnesium sulphate, filtered and evaporated to yield a colourless solid (0.130g,100%).This was shown by high field ^{1}H NMR spectroscopy to be a mixture of the same (*endo*) isomers as for section 3.1.1 with a corresponding improved ratio of 3.9:1, and an *endo* : *exo* ratio of 26:1,giving an overall d.e. of 53%.Adding the catalyst *before* the diene caused polymerisation of the dienophile and the loss of conjugation could be monitered by the fading of the bright yellow colour,in addition to the loss of olefinic resonances in the ^{1}H NMR spectrum.

3.5.2 Comparison of the performance of Evans' acrylate at -78^{0}C using Et_2AlCl.

This was conducted using acrylate (0.109g,0.595mmol) in dry methylene chloride (*ca.* 5ml) and Et_2AlCl (1.8M in toluene,0.5ml,0.9mmol,1.5eq) under otherwise identical conditions to those described for **87** in section 3.5.1.Work-up and dry flash chromatography yielded a colourless solid (0.13g,88%) which was shown by high field ^{1}H NMR spectroscopy to contain two *endo* isomers and one detectable *exo* isomer in the ratio 14.6 : 1.7 : 0.4 giving an overall d.e. of 75%,with an *endo* : *endo* ratio of 8.6:1 and an *endo* : *exo* ratio of 41:1.

3.5.3 Reaction of (87) with isoprene at -78^{0}C using Et_2AlCl.

This was conducted according to the procedure described in section 3.5.1, using **87** (0.200g,0.803mmol) and isoprene (0.55g,8.07mmol,10eq) and diethylaluminium chloride (1.8M in toluene,0.65ml,0.254g,1.17mmol, 1.46eq) to yield,following work-up,a "sticky" solid (0.256g,100%).The ^{13}C NMR spectrum showed the presence of both isomers; the same chiral shift experiment was carried out on the sample, as conducted in section 3.1.3,which showed the presence of both isomers in an improved corresponding ratio of 5.4:1 (d.e. = 69%).

3.5.4 Reaction of the crotonate (101) with cyclopentadiene at -78^{0}C using Et_2AlCl.

(a) Addition of the catalyst before the diene

This was done according to the procedure given in section 3.5.1 using a solution of crotonate (0.1g,0.38mmol),diethylaluminium chloride (1.8M in toluene,0.3ml,0.54mmol,1.4eq) before the addition of cyclopentadiene (1g,15mmol,40eq).After stirring at -78^{0}C for 75 minutes the reaction was quenched,and following work-up,analysis by high field ^{1}H NMR spectrum showed that *ca.* 45% of the reaction mixture was 1,4 Michael addition product (compared with authentic product).Of the other 55%,this was shown to be Diels-Alder cycloadducts with an *endo* 1 : *endo* 2 : *exo* 1 : *exo* 2 ratio (corresponding to that in section 3.3.1) of 76 : 20 : 4 : 0, giving an *endo* : *endo* ratio of 3.9 : 1 and an *endo* : *exo* ratio of 24 : 1 (overall d.e. = 52%).

(b) Addition of the catalyst after the diene

This was done according to the preocedure given in section 3.5.1 using a solution of crotonate (0.198g,0.753mmol) and cyclopentadiene (0.198g, 7.58mmol,10eq) at -78^{0}C followed by diethylaluminium chloride (1.8M in toluene,0.6ml,1.08mmol,1.4eq).Work-up and dry flash chromatography yielded a colourless solid (0.196g,79%) which was shown by high field ^{1}H NMR spectroscopy to contain the isomers as described in section 3.3.1 in a corresponding ratio of 89 : 15 : 1 : 0, giving an *endo* : *endo* ratio of 5.9 : 1 and an *endo* : *exo* ratio of 104 : 1 (overall d.e. = 69.5 %).Recrystallisation from diisopropyl ether / methylene chloride did not effect separation of these isomers.Spectral data for the major isomer is as follows : **^{1}H NMR** (360 MHz,$CDCl_3$) δ 6.30-6.29 (1H,dd,*J* = 5.7 and 3.2 Hz,HC=CH), 5.66-5.64 (1H,dd,*J* = 5.7 and 2.7 Hz,HC=CH), 4.52-4.48 (1H,dd,*J* = 9.9 and 4.3 Hz,CHN),4.45-4.42 (1H,dd,*J* = 9.8 and 1.4 Hz,CHO),3.52-3.50 (1H,cm, HCMe),3.30 (1H,bs,cycloadduct CH),2.45 (1H,bs,cycloadduct bridgehead CH),2.16-2.14 (1H,t,*J* = 4.1 Hz,auxiliary bridgehead CH),2.03-1.98 (1H, cm),1.67-1.49 (4H,cm),1.41-1.29 (2H,cm), 1.05-1.03 (3H,d,*J* = 7.1 Hz, CH_3CH),0.92 (3H,s,CH_3),0.90 (3H,s,CH_3),0.88 (3H,s,CH_3) ppm; **^{13}C NMR** (90.56 MHz,$CDCl_3$) δ 173.93 (C=O),153.95 (C=O),139.52 (HC=CH),130.54(HC=CH),82.10(CH),57.60(CH),51.24(CH),49.24(CH/ quat C),48.24(quat C),47.51(CH),47.29(CH),46.97(CH_2),35.64(CH),26.16 (CH_2),20.15(CH_3),19.67(CH_3),19.34(CH_2),17.79(CH_3),13.61(CH_3) ppm.

3.5.5 Reaction of the cinnamate (102) with cyclopentadiene at -20^{0}C using Et_2AlCl.

To a stirred solution of cinnamate (0.101g,0.311mmol) in dry methylene chloride (*ca.* 2ml) at -78^{0}C under argon,was added Et_2AlCl (1.8M in toluene,0.3ml,0.54mmol,1.75eq).To the resulting deep yellow/orange complex was added pre-cooled, freshly cracked cyclopentadiene (1g,15mmol,48eq) *via* cannula.The resulting solution did not change colour after stirring at this temperature for several minutes and was warmed to -20^{0}C and within one minute the colour of the solution faded to bright yellow and finally to a pale lime colour.The reaction was diluted with methylene chloride (*ca.* 50ml) and quenched with dilute hydrochloric acid (2M,*ca.* 10ml) and allowed to warm to room temperature with stirring. The layers were separated and the aqueous layer extracted with methylene chloride (3 x *ca.* 20ml).The combined organic layers were washed successively with saturated aqueous sodium bicarbonate solution,saturated aqueous sodium chloride solution,dried over magnesium sulphate, filtered and evaporated to yield a white solid (0.22g) which was purified by dry flash chromatography (50g,SiO_2),using gradient elution (*n*hexane : diethyl ether 100:0 to 0:100) to furnish a colourless crystalline compound (0.11g,92%).High field ^{1}H NMR spectroscopy showed that the *endo* : *endo* ratio was 147:2, giving a d.e. of 97%.Recrystallisation from *n*hexane : diisopropyl ether (4:1) yielded pure*[(2R,6S)-endo]-N-((3'S,4'R,5'R,6'S)-5-phenylbicyclo [2.2.1] heptene-4'-carbonyl)-5-aza-1,10,10-trimethyl-3-oxatricyclo [5.2.1.0^{2,6}] decan-4-one* **105** as colourless crystals; **MP** = 131-134^{0}C (from *n*hexane : diisopropyl ether (4:1)); $[\alpha]_D^{21}$ = -263.6^0 (c = 2.54, CH_2Cl_2); **^{1}H NMR** (360MHz, $CDCl_3$) δ 7.30-7.14 (5H,cm,Ph),6.53-6.51 (1H,dd,*J* = 5.6 and 3.2 Hz, HC=CH),5.88-5.86 (1H,*J* = 5.6 and 2.7 Hz,HC=CH),4.59-4.55 (1H,ddd,*J* = 9.9,4.5 and 1.2 Hz,CHN),4.49-4.46 (1H,dd,*J* = 9.8 and 1.6 Hz,CHO),4.23-4.21 (1H,dd,*J* = 5.3 and 3.3 Hz, CHCO),3.56 (1H,bs,cycloadduct bridgehead CH),3.35-3.32 (1H,dd,*J* = 5.3 and 1.7 Hz,CHPh),3.00-2.99 (1H,bd,*J* = 1.5Hz,cycloadduct bridgehead CH),2.26-2.24 (1H,t,*J* = 4.2 Hz,auxiliary bridgehead CH), 1.99-1.96 (1H,bd,*J* = 8.7Hz),1.73-1.58 (2H,cm) superimposed on 1.61-1.58 (1H,dd,*J* = 8.7 and 1.7 Hz),1.45-1.37 (1H,cm),1.25-1.14 (1H,cm),0.98(3H, s,CH_3), 0.97 (3H,s,CH_3),0.94 (3H,s, CH_3) ppm; **^{13}C NMR** (50.3 MHz, $CDCl_3$) δ 173.54 (C=O),153.91 (C=O),143.63(Ar,quat C),140.08 (HC=CH), 131.86(HC=CH),128.24

(Ar CH),127.34 (Ar CH),125.85 (Ar CH),82.24 (CH),57.66(CH),50.53(CH), 49.24(CH),48.31(quat C),48.09(CH_2),47.51 (CH/quatC),47.31(CH),46.12 (CH),26.18(CH_2),19.71(CH_3),19.44(CH_2),17.83(CH_3),13.64(CH_3) ppm; **IR** (nujol) ν_{max} 1776(bs,2 x C=O), 1648 (C=C),1338,1277,1240(d),1220(d), 1088,1060,1040(d) cm^{-1}; **MS** (ei) 392(1%,$^{12}C_{24}{}^{13}CH_{29}NO_3^+$),391(4,$M^+$), 327(22),326(base),325(18, dienophile (M-66)$^+$),135(23),132(10),131(97, PhCH=CHCO$^+$),103(21), 91(8),77(9,Ph^+),66(15); **Accurate mass** (ei), Found : 391.2149; $C_{25}H_{29}NO_3$ requires 391.21473; **Elemental analysis**, Found : 76.4% C, 7.64% H,3.64% N, $C_{25}H_{29}NO_3$ requires 76.7% C, 7.47% H,3.58% N.

3.5.6 Cleavage of the cinnamate cycloadduct formed in section 3.5.5 using lithium benzyloxide.

This was carried out according to the procedure described by Evans *et al*[46].

To a solution of benzyl alcohol (0.272g,2.56mmol,2eq) in dry THF (*ca.* 5ml) at -78^{0}C under argon,was added nbutyllithium (1.6M in hexanes, 1ml,1.6mmol,1.2 eq).The resulting solution was stirred at -78^{0}C for 30 minutes before a solution of the cinnamate adduct (0.5g,1.28mmol) in dry THF (*ca.* 5ml) was added dropwise.The resulting mixture was allowed to warm to 0^{0}C and stirred for 30 minutes before TLC analysis (using *n*hexane : diethyl ether 1:1 as elution solvent) revealed that a significant amount of starting material remained.The reaction mixture was then allowed to warm to room temperature and stirred for a further 3 hours before TLC showed that complete consumption of the adduct had taken place.The reaction was then quenched with aqueous ammonium chloride solution and concentrated *in vacuo*.Water (*ca.* 40ml) was added to the residue and this was extracted with methylene chloride (4 x *ca.* 60ml). The combined organic extracts were washed successively with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution,dried over magnesium sulphate,filtered and evaporated to yield an oil (0.71g) which was subjected to purification by flash chromatography (60g SiO_2) using gradient elution with *n*hexane : diethyl ether (100:0 to 90:10) to yield the chirally pure ester *benzyl (3S,4S,5R,6S)-5-phenylbicyclo [2.2.1.] heptene-4-carboxylate* **106** as a colourless oil (0.333g,86%); $[\alpha]_D^{22}$ =-121.1^0 (c = 1.36,CH_2Cl_2) (lit[46] = +121.0^0 (c = 1.33,$CHCl_3$) (antipode));**^{1}H NMR** (200 MHz,$CDCl_3$) δ 7.47-

7.25 (10H,cm,2 x Ph),6.53-6.49 (1H,dd, J = 5.6 and 3.2 Hz,HC=CH),6.19-6.14 (1H,dd,J = 5.7 and 2.8 Hz,HC=CH), 5.29-5.14 (2H,ABq,J = 12.4 Hz,COOCH_2Ph),3.41 (1H,bs,CH-CO),3.29-3.26 (1H,bd,J = 4.8 Hz),3.20-3.12 (2H,cm),1.90-1.86 (1H,bd,J = 8.3 Hz),1.69-1.64 (1H,bdd,J = 8.7 and 1.8 Hz) ppm; **^{13}C NMR** (50.3 MHz,$CDCl_3$) δ 173.76 (C=O),143.93 (Ar quat C),138.89(HC=CH),135.98(Ar quat C), 134.17 (HC=CH),128.23 (Ar CH),127.83(Ar CH),127.76(Ar CH),127.20(Ar CH),125.79(Ar CH), 65.95 (OCH$_2$),51.99(CH),48.02(CH),47.18(CH), 46.95(CH$_2$),46.11(CH) ppm; **IR** (Thin film) ν_{max} 2990,1732 (C=O),1500,1457,1335,1260,1170, 1112,1015 cm^{-1}.

Further elution with *n*hexane : diethyl ether (7:3) yielded unreacted benzyl alcohol,followed by recovered auxiliary (0.142g,57%) using a 1:4 mixture of the same solvents.

3.6 Reaction of (87) with benzonitrile oxide.

To a rapidly stirred solution of **87** (0.350g,1.41mmol) and benzohydroximoyl chloride (0.221g,1.42mmol,1eq) in methylene chloride (*ca.* 35ml) at room temperature was added,*via* syringe pump,a solution of triethylamine (0.156g,1.54mmol,1.1eq) in dry diethyl ether (*ca.* 16ml) over a period of *ca.* 24 hours.The reaction was concentrated *in vacuo* and water (*ca.* 10ml) was added.The residue was extracted with methylene chloride (3 x *ca.* 25ml) and the combined extracts were washed successively with water and saturated aqueous sodium chloride solution, dried over magnesium sulphate,filtered and evaporated to yield a glassy solid (0.490g,95%).This was purified by flash chromatography (50g SiO_2) using *n*hexane : diethyl ether (4:1) as elution solvent to yield an oil (0.354g,68%).High field ^{1}H NMR spectroscopy showed that two isomers were present in a ratio of 3:2; **Accurate mass** (ei), Found : 368.1741; $C_{21}H_{24}N_2O_4$ requires 368.17359.

3.7 1,4 Michael Addition reactions using Et_2AlCl as nucleophile.

These experiments were conducted as described by Ruck *et al*[106].

3.7.1 Reaction of the crotonate (101) with Et_2AlCl

To a solution of **101** (0.103g,0.392mmol) in dry methylene chloride (*ca.* 5ml) at -78^{0}C under argon, was added diethylaluminium chloride (1.8M in toluene,0.9ml,1.62mmol,4.1eq).The resulting bright yellow solution was stirred at -78^{0}C for 1.5 hours by which time the colour had faded completely.The reaction was quenched after a total of 2 hours with aqueous ammonium chloride solution, and after separation of the layers, the aqueous layer was extracted with methylene chloride (3 x *ca.* 30ml).The combined organic extracts were washed successively with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution,dried over magnesium sulphate,filtered and evaporated to yield a mixture of *[(2R,6S)-endo]-N-(3'(R) -methylpentanoyl)-5-aza-1,10,10-trimethyl-3-oxatricyclo [5.2.1.0^{2,6}] decan-4-one* and *[(2R,6S)-endo]-N-(3'(S) -methylpentanoyl)-5-aza-1,10,10-trimethyl-3-oxatricyclo [5.2.1.0^{2,6}] decan-4-one* as a colourless crystalline solid (0.119g,100%).Analysis of the $^{13}C\{^1H\}$ spectrum yielded an estimate of the isomer ratio of 5:4; **^{1}H NMR** (200 MHz,$CDCl_3$) (both isomers) δ 4.56-4.49 (1H,ddd,*J* = 9.8,4.1 and 1.2 Hz,C<u>H</u>N),4.47-4.42 (1H,dd,*J* = 9.8 and 1.4 Hz,C<u>H</u>O),2.97-2.59 (2H,symm m,C<u>H$_2$</u>CO),2.26-2.22 (1H,t,*J* = 4.1 Hz,bridgehead CH),1.99-1.83 (1H, symm m,C<u>H</u>MeEt),1.65-1.43 (2H,cm),1.42-1.01 (4H,cm),0.92-0.83 (15H,9 x s,5 x C<u>H$_3$</u> (both diastereomers)) ppm; **^{13}C NMR** (50.3 MHz, $CDCl_3$) δ 172.82 (C=O),154.06 (C=O),82.24(CH),57.63(CH,minor isomer), 57.57(CH,major isomer),49.21(quat C),48.25(quat C),47.61(CH),41.84 (<u>C</u>H$_2$CO),30.84 (CH),29.23(<u>C</u>H$_2$CH$_3$,major isomer),29.03(<u>C</u>H$_2$CH$_3$,minor isomer),26.12 (CH_2),19.68(CH_3),19.54(CH_2),19.07(CH_3,minor isomer),18.94 (CH_3,major isomer),17.83(CH_3),13.61(CH_3),11.07(CH_3) ppm; **MS** (ei) 294 (1%, $^{12}C_{16}{}^{13}CH_{27}NO_3^+$),293(3,M$^+$),278(3,M-15$^+$),265(5),264(30,M-29$^+$), 249(4),239(2),238(15),237(base,M-56$^+$ (M^{c}Lafferty product)),196(4), 193(6),178(4),152(3),151(5),150(3),136(6),135(39),134(25); **Accurate mass** (ei), Found : 293.1987; $C_{17}H_{27}NO_3$ requires 293.19908.

3.7.2 Reaction of the cinnamate (102) with Et_2AlCl

This was conducted as for experiment 3.7.1 using a solution of **102** (0.178g,0.548mmol) in dry methylene chloride (*ca.* 5ml) and diethylaluminium chloride (1.8M in toluene,1.22ml,2.20mmol,4eq) at -78^{0}C under argon.The reaction required an extended period for complete consumption of the Michael acceptor (compared to **101**) and needed to be stirred overnight before the strong orange/yellow complex had faded to a light lime colour.Work-up provided *[(2R,6S)-endo]-N-(3'(R) -phenylpentanoyl)-5-aza-1,10,10-trimethyl-3-oxatricyclo [5.2.1.0^{2,6}] decan-4-one* and *[(2R,6S)-endo]-N-(3'(S) -phenylpentanoyl)-5-aza-1,10,10-trimethyl-3-oxatricyclo [5.2.1.0^{2,6}] decan-4-one*as a colourless oil which crystallised on standing (0.174g,90%).The ratio of the two isomers was estimated to be 7.5:3 from the $^{13}C\{^1H\}$ spectrum; **^{1}H NMR** (200 MHz,$CDCl_3$) (both isomers) δ 7.29-7.09 (5H,cm,Ph),4.46-4.36(2H,cm,C<u>H</u>O and C<u>H</u>N),3.50-3.36 (1H,cm),3.22-3.05 (2H,cm),2.31-2.12 (1H,cm),1.71-1.04 (6H,cm),0.93-0.86 (9H,5 x s,3 x C<u>H</u>$_3$ (both isomers)),0.81-0.73 (3H,t,*J* = 7.3 Hz,CH_3) ppm; **^{13}C NMR** (50.3 MHz,$CDCl_3$) δ 171.92 (C=O),154.04 (C=O), 143.88(quat C,Ph,major isomer),128.01(Ph CH),127.49(Ph CH), 125.99 (Ph CH),82.27(CH,major isomer),82.15(CH,minor isomer),57.55 (CH), 49.14(quat C,major isomer),49.07(quat C,minor isomer),48.19 (quat C), 47.50(CH,major isomer),47.37(CH,minor isomer),43.24(CH, minor isomer),42.72(CH,major isomer),41.43(CH_2,major isomer),41.00 (CH_2,minor isomer),29.23(CH_2,major isomer),29.09(CH_2,minor isomer), 26.09(CH_2,major isomer),25.99(CH_2,minor isomer),19.62(CH_3),19.55 (CH_2,major isomer),18.94(CH_2,minor isomer),17.76(CH_3),13.56(CH_3), 11.78(CH_3) ppm; **MS** (ei) 356(8%,$^{12}C_{21}{}^{13}CH_{29}NO_3^+$),355(33,$M^+$), 326(24,M29$^+$),,237(40),196(18),178(6),177(7),160(11), 136(7),135(26), 134(15),133(6),132(30),131(38),119(42),118(6),117(10),109(8),104(10), 103(13),100(7),95(15),93(12),92(9),91(base); **Accurate mass**, Found : 355.2149; $C_{22}H_{29}NO_3$ requires 355.21473.

4. Preparation, alkylation and acylation reactions of the propionate of Chirabornox.

4.1 Preparation of the propionate (78)

This was synthesised according to the procedure of Evans *et al*[43].
To a solution of **77** (1.5g,7.69mmol) in dry THF (*ca.* 10ml) at -78^{0}C under argon, was added nbutyllithium (1.6M in hexanes,5.3ml,8.48mmol,1.1eq). The resulting solution was stirred at -78^{0}C for *ca.* 20 minutes before freshly distilled propionyl chloride (1.07g,12mmol,1.56eq) in dry THF (*ca.* 2ml) was added dropwise.The resulting solution was stirred at -78^{0}C for 5 minutes before being allowed to warm to room temperature.TLC analysis revealed that the reaction was complete and quenching was effected with sodium carbonate solution.After stirring for *ca.* 10 minutes at room temperature, the layers were separated and the aqueous layer extracted with methylene chloride (3 x *ca.* 40ml).The combined organic extracts were washed successively with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution,dried over magnesium sulphate,filtered and evaporated to yield a pale yellow oil which was purified by flash chromatography (50g SiO_2) using *n*hexane : diethyl ether (4:1) as elution solvent,followed by Kugelrohr distillation to yield a colourless oil (1.73g,90%); **BP** = 150^{0}C/0.1mmHg; **^{1}H NMR** (200MHz,$CDCl_3$) δ 4.59-4.46 (2H,cm,C<u>H</u>O and C<u>H</u>N),2.99-2.87 ((2H,2 x q, *J* = 7.5 Hz,C<u>H</u>$_2$CH$_3$),2.29-2.25 (1H,t,*J* = 4.1 Hz,bridgehead CH),1.66-1.51 (2H,cm),1.41-1.04 (2H,cm) superimposed on 1.16-1.09 (3H,t,*J* = 7.3 Hz,CH$_2$C<u>H</u>$_3$),0.95 (3H,s,CH$_3$),0.94 (3H,s,CH$_3$),0.93 (3H,s,CH$_3$) ppm; **^{13}C NMR** (50.3 MHz,$CDCl_3$) δ 170.04 (C=O),154.17 (C=O),82.44(CH), 57.55(CH),49.23(quat C),48.26(quat C),47.60(CH),28.79(CH_2), 26.13 (CH_2),19.67(CH_3),19.61(CH_2),17.82(CH_3),13.61(CH_3),8.16(CH_3) ppm.

4.1.1 General procedure for the preparation of lithium diisopropylamide (LDA) and subsequent enolate generation (suitable for 0.1g of propionate).

To a solution of dry diisopropylamine (0.050g,0.495mmol,1.2eq) in dry THF (*ca.* 2ml) at 0^{0}C under argon, was added nbutyllithium (1.6M in hexanes,0.30ml,0.48mmol,1.15eq).The resulting solution was allowed to stir at 0^{0}C for *ca.* 15 minutes before being cooled to -78^{0}C and allowed to thoroughly cool at this temperature.A solution of propionate **78** (0.104g, 0.414mmol) in dry THF (*ca.* 7ml) was added <u>*dropwise*</u> over a period of *ca.*

5 minutes.The resulting solution was then stirred at -78^{0}C for one hour before being ready for the appropriate lithium enolate-mediated reaction.

4.2 ASYMMETRIC ALKYLATION REACTIONS

4.2.1 Reaction of the lithium enolate (110) with benzyl bromide in the absence of sodium iodide.

To a solution of freshly prepared lithium enolate made from propionate (0.202g,0.797mmol) and LDA (0.11g,0.891mmol,1.1eq) as described in section 4.1.1 at -78^{0}C under argon, was added freshly distilled benzyl bromide (0.50g,3.95mmol,5eq) in dry THF (*ca.* 5ml).The reaction temperature was then raised to -8^{0}C ($KCl/H_2O_{(s)}$) and stirred at that temperature for *ca.* 8 hours and was allowed to warm overnight to room temperature before being quenched with aqueous ammonium chloride solution.The reaction mixture was concentrated *in vacuo* and the aqueous layer was extracted with diethyl ether (4 x *ca.* 40ml).The combined organic extracts were washed successively with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution,dried over magnesium sulphate,filtered and evaporated to yield an oil which was purified by fry flash chromatography (50g SiO_2), using gradient elution with *n*hexane : diethyl ether 100:0 to 50:50 yielding *[(2R,6S)-endo]-N-((2'S)-Phenylmethylpropionyl)-5-aza-1,10,10-trimethyl-3-oxatricyclo [5.2.1.0^{2,6}] decan-4-one* **111A** as a yellow oil which crystallised on standing (0.169g,62%).This had the same spectral characteristics as those reported by Donohoe[111]; **MP** = 100.5-101.5^0 (from methanol);$[\alpha]_D^{21}$ = -63.4^0 (c = 2.12,CH_2Cl_2); **^{1}H NMR** (200 MHz,$CDCl_3$) δ 7.30-7.12 (5H,cm,Ph),4.58-4.51(1H,bdd,*J* = 9.9 and 4.3 Hz,C<u>H</u>N),4.47-4.42 (1H,bd,*J* = 9.6 Hz,C<u>H</u>O),4.23-4.06 (1H,symm m,C<u>H</u>CH_2),3.17-3.07 (1H,dd,*J* = 13.2 and 7.2 Hz,C<u>H</u>H),2.62-2.51 (1H,dd,*J* = 13.2 and 7.8 Hz,CH<u>H</u>),2.19-2.15 (1H,t,*J* = 4.2 Hz,bridgehead CH),1.52-1.45 (1H,dd,*J* = 11.6 and 2.9 Hz, bornane ring C<u>H</u>H),1.34-1.24 (3H,cm),1.15-1.11 (3H,d,*J* = 6.8 Hz, $C\underline{H}_3CH$),0.93-091 (9H,2 x s,3 x CH_3) ppm; **^{13}C NMR** (50.3 MHz,$CDCl_3$) δ176.38 (C=O),153.76 (C=O),139.10 (Ph quat C),129.04(Ph CH),128.06(Ph CH),126.04(Ph CH),82.16(CH),57.75(CH),49.16(quat C),48.23(quat C),47.47(CH),39.53($\underline{C}H_2Ph$),39.40($\underline{C}HCH_2$),26.05(CH_2), 19.69(CH_3),19.01(CH_2),17.83(CH_3),16.47(CH_3),13.64(CH_3) ppm. See Appendix 4 for X-Ray crystal structure.

The reaction was repeated with the further addition of sodium iodide (0.146g,0.974mmol,1.2eq).This lead,following purification by column chromatography to the same product (0.218g,80%).High field ^{1}H NMR spectroscopy showed that of this 80%, 8% was unreacted propionate (formed presumibly by hydrolysis of the lithium enolate by traces of water in the NaI).However,72% still represents a significant yield increase of 10%.

4.2.2 Attempted improvement in the α-ethylation reaction using ethyl tosylate as electrophile.

To a freshly prepared solution of propionate-derived lithium enolate (0.797mmol) (made according to the procedure described in section 4.1.1) at -78^{0}C under argon,was added a solution of ethyl tosylate (0.48g, 2.40mmol,3eq) in dry THF (*ca.* 5ml).The resulting mixture was warmed to -8^{0}C ($KCl/H_2O_{(s)}$) and stirred at that temperature for *ca.* 10 hours before being warmed to +10^{0}C overnight.Following work-up,column chromatography furnished unreacted propionate.None of the desired product could be detected.

4.2.3 Cleavage of the benzylated adduct (111A) from the auxiliary

Using the same protocol as described in section 3.5.6, benzyl alcohol (0.0753g,0.696mmol,2eq) and nbutyllithium (1.6M in hexanes,0.33ml, 1.5eq) were reacted together and a solution of benzyl adduct **111A** (0.119g,0.394mmol) in dry THF (*ca.* 6ml) was added.After stirring at -78^{0}C for 15 minutes and at room temperature for 1.5 hours,the reaction was deemed to be complete bt TLC whereupon it was worked-up and purified by flash chromatography (25g SiO_2) using gradient elution with *n*hexane : diethyl ether (100:0 to 95:5).This yielded *(2S)-phenylmethylbenzyl propionate* **111B** as a waxy solid (0.085g,96%); $[\alpha]_D^{22}$ = +24.59^0 (c = 4.25,CH_2Cl_2) (lit[37] = -26.9^0 (c = 6.12) (antipode));**^{1}H NMR** (200MHz,$CDCl_3$) δ 7.34-7.12 (10H,cm,2 x Ph),5.07 (2H,s,$OC\underline{H}_2$), 3.08-2.99 (1H,dd,*J* = 12.4 and 6.3 Hz,$C\underline{H}_3$,$C\underline{H}H$-$CHCH_3$),2.89-2.64 (2H,cm,$CH\underline{H}$,-$CHCH_3$ and CHH-$C\underline{H}CH_3$),1.19-1.16 (3H,d,*J* = 6.7 Hz, $C\underline{H}_3$) ppm; **^{13}C NMR** (50.3 MHz,$CDCl_3$) δ 175.77 (C=O), 139.14(Ph #1 quat C), 135.92(Ph #2 quat C),128.89(Ph CH),128.39(Ph CH),128.27(Ph CH),127.98(Ph CH),126.22(Ph CH),66.02($O\underline{C}H_2$),41.41(CH),39.64 ($\underline{C}H_2Ph$),16.73(CH_3) ppm.Further elution (*n*hexane : diethyl ether 95:5 to

80:20) yielded unreacted benzyl alcohol.Finally,elution with pure diethyl ether yielded recovered auxiliary (0.057g,84%).

4.3 ASYMMETRIC ACYLATION REACTIONS

4.3.1 Reaction of propionyl chloride with the lithium enolate (110).

To a freshly prepared solution of lithium enolate (0.797mmol) (made using the general procedure described in section 4.1.1) in dry THF (*ca.* 7ml) under argon,a solution of freshly distilled propionyl chloride (0.118g, 1.27mmol,1.6eq) in dry THF (*ca.* 2ml) was added.The resulting solution was stirred at -78^{0}C for one minute before being quenched with saturated aqueous ammonium chloride solution.The mixture was allowed to warm to room temperature and concentrated *in vacuo*.Water (*ca.* 100ml) was added and this residue was extracted with methylene chloride (3 x *ca.* 60ml).The combined organic extracts were washed with saturated aqueous sodium chloride solution (*NOT* sodium bicarbonate solution, to prevent racemisation),dried over magnesium sulphate,filtered and evaporated to yield a light brown oil (0.248g).High field ^{1}H NMR spectroscopy revealed that only one epimer could be detected giving a d.e. of >95%, in addition to some *O*-acylated product with a *C*:*O* ratio of 6:1 and a little unreacted starting material.Purification by dry flash chromatography yielded an oil (0.217g,89%) which was shown to be contaminated still by *O*-acylated product and starting material. Recrystallisation from methanol yielded the major product *[(2R,6S)-endo]-N-((2'S)-methyl-3-oxopentanoyl)-5-aza-1,10,10-trimethyl-3-oxatricyclo [5.2.1.0^{2,6}] decan-4-one* **115** as colourless crystals (0.062g,26%); **MP** = 120-121^{0}C (from methanol); $[\alpha]_D^{22}$ = -53.3^0 (c = 3; CH_2Cl_2); **^{1}H NMR** (200 MHz,$CDCl_3$) δ 4.50-4.42 (2H,cm,C<u>H</u>O and C<u>H</u>N) superimposed 4.49-4.38 (1H,q,*J* = 7.3Hz,C<u>H</u>CH_3) ,2.77-2.46 (2H,q of ABq, *J* = 10.8 and 7.3 Hz,C<u>H</u>$_2$$CH_3$),2.29 (1H,bs, bridgehead CH),1.62-1.16 (4H,cm) superimposed on 1.32-1.28 (3H,d,*J* = 7.3 Hz,C<u>H</u>$_3$CH),1.06-0.99 (3H,t,*J* = 7.2 Hz,C<u>H</u>$_3$$CH_2$),0.92 (3H,s,$CH_3$),0.91 (3H,s,$CH_3$),0.89 (3H,s, CH_3) ppm; **^{13}C NMR** (50.3 MHz,$CDCl_3$) δ 208.09 (C=O), 170.00 (C=O), 154.36 (C=O),83.05(CH),57.79(CH),52.46(<u>C</u>HCH_3), 49.25(quat C),48.42 (quat C),47.82(CH),33.68(<u>C</u>H$_2$$CH_3$),26.15($CH_2$),19.69($CH_3$),18.89($CH_2$),

17.88(CH_3),13.65(CH_3),12.58(CH_3),7.39(CH_3) ppm; **IR** (nujol) ν_{max} 1765 (C=O),1717 (C=O),1702 (C=O),1360,1218(d),1150,1084, 1054,1038 cm^{-1}; **MS** (ei) 308(1%,$^{12}C_{16}{}^{13}CH_{25}NO_4^+$),307(3,$M^+$),278(5),252 (17),196(8),178 (7),136(13),135(47),134(18),119(11),113(7),109(7),108(8), 95(26),93(20), 91(8),81(7),79(9),77(7),69 (12),67(12),57(base,$EtCO^+$); **Accurate mass**, Found : 307.1785; $C_{17}H_{25}NO_4$ requires 307.17835; **Elemental analysis**, Found : 66.26% C,7.93% H,4.57% N; $C_{17}H_{25}NO_4$ requires 66.43% C, 8.20% H,4.56% N.

4.3.2 Reaction of acetyl chloride with (110).

This was conducted adopting the same procedure described in section 4.3.1, using **78** (0.797mmol) in dry THF (*ca.* 12ml) and adding acetyl chloride (0.1g,1.27mmol,1.6eq) in dry THF (*ca.* 2ml).The reaction was quenched after 45 seconds,and work-up yielded an oil (0.204g).This was analysed by high field ^1H NMR spectroscopy which revealed the presence of two epimers in the ratio 10:1 in addition to *O*-acylated product, with a *C*:*O* ratio estimated to be 12:1.Recrystallisation from methanol yielded the major product *[(2R,6S)-endo]-N-((2'S)-methyl-3-oxobutanoyl)-5-aza-1,10,10-trimethyl-3-oxatricyclo [5.2.1.$0^{2,6}$] decan-4-one* **116** as a colourless crystalline solid (0.076g,33%); **MP** = 139-140.5^{0}C (from methanol); $[\alpha]_D^{23}$ = -51.1^0 (c = 3.75, CH_2Cl_2); **^{1}H NMR** (200 MHz,$CDCl_3$) δ 4.51-4.44 (2H,cm,C<u>H</u>O and C<u>H</u>N) superimposed on (1H,q,*J* = 7.3 Hz,C<u>H</u>CH_3),2.29-2.27 (1H,bs,bridgehead CH) superimposed on 2.28 (3H,s,C<u>H</u>$_3$CO),1.58-1.30 (4H,cm) superimposed on 1.33-1.30 (3H,d,*J* = 7.3 Hz,C<u>H</u>$_3$CH),0.93 (3H,s,CH_3),0.92 (3H,s,CH_3),0.90 (3H,s,CH_3) ppm; **^{13}C NMR** (50.3 MHz,$CDCl_3$) δ 205.46 (C=O),169.75 (C=O),154.42 (C=O),83.10(CH),57.74 (CH),53.05(<u>C</u>HCH_3),49.28(quat C),48.44(quat C), 47.81(CH),28.19(<u>C</u>H_3CO),26.12(CH_2),19.69(CH_3),18.84 (CH_2),17.89 (CH_3),13.67(CH_3), 12.20(<u>C</u>H_3CH), ppm; **IR** (nujol) ν_{max} 1778 (C=O),1721 (C=O),1701 (C=O), 1310,1291,1220(d),1163,1148,1055 cm^{-1}; **MS** (ei) 293 (1%,M^+),252(9),251 (60,McLaffertyproduct),136(10),135(35), 134(10),119(12),109(8),99(11),95(27),93(13),67(8),55(11),43(base, CH_3CO^+); **Accurate mass**, Found : 293.1617; $C_{16}H_{23}NO_4$ requires 293.16270; **Elemental analysis**, Found : 65.15% C,7.94% H,4.80% N; $C_{16}H_{23}NO_4$ requires 65.51% C,7.90% H, 4.77%, N.

4.3.3 Reaction of methyl cyanoformate (Mander's reagent[116]) with (110).

To a solution of **110** (0.41mmol) was added methyl cyanoformate (0.41g, 0.482mmol,1.2eq) in dry THF (*ca.*4ml).The reaction was quenched after 1.5 minutes and worked-up to yield a white crystalline solid (0.126g, 99%). Analysis of the crude reaction mixture by high field ^{1}H NMR spectroscopy showed that no *O*-acylated product was present and the epimeric ratio was 10:1. Recrystallisation from methanol yielded *[(2R,6S)-endo]-N-((2'R)-methylformylpropionyl)-5-aza-1,10,10-trimethyl-3-oxatricyclo [5.2.1.0^{2,6}] decan-4-one* **117** as colourless crystals (0.081g,64%); **MP** = 103-104.5^{0}C (from methanol); $[\alpha]_D^{21}$ = -96.99^0 (c = 4.05, CH_2Cl_2); **^{1}H NMR** (200 MHz, $CDCl_3$) δ 4.50-4.42 (2H,cm,C<u>H</u>O and C<u>H</u>N) superimposed on 4.45-4.35 (1H,q,*J* = 7.3 Hz,C<u>H</u>CH_3),3.64 (3H,s,O$C\underline{H}_3$), 2.27 (1H,bs,bridgehead CH), 1.58-1.29 (4H,cm) superimposed on 1.37-1.33 (3H,d,*J* = 7.3 Hz,$C\underline{H}_3$CH), 0.91-0.89 (9H,2 x s,3 x CH_3) ppm; **^{13}C NMR** (50.3 MHz,$CDCl_3$) δ 170.78 (C=O),169.18 (C=O),154.02(C=O),82.85 (CH),57.79(CH),52.08($CH_3\underline{C}H$), 49.19(quat C),48.34(quat C),47.69(CH), 45.32($\underline{C}H_3CO$),26.04(CH_2),19.60 (CH_3), 18.76(CH_2),17.79(CH_3),13.57 (CH_3),12.91($\underline{C}H_3CH$) ppm; **IR** (nujol) ν_{max} 1770 (C=O),1738 (C=O),1699 (C=O),1300,1282,1262,1217(d),1147, 1084,1055,1041 cm^{-1}; **MS** (ei) 309 (2%,M$^+$),278(7,(M-MeO)$^+$),265(40, M^{c}Lafferty product$^+$),250(22, (M^{c}Lafferty productCH_3)$^+$),150(19),137(10), 135(94),134(83),132(19),119(39),115(34),109(16),108(19),107(10),,96(9),95 (88),93(21),91(15),87(10),86(10),82(13),81(17),79(15),77(14),67(25),59(87, MeOCO$^+$),41(base); **Accurate mass**, Found : 309.1575; $C_{16}H_{23}NO_5$ requires 309.15761; **Elemental analysis**, Found : 62.04% C,7.45% H,4.52% N; $C_{16}H_{23}NO_5$ requires 62.12% C,7.49% H,4.53% N.

Repeating the above reaction but substituting Mander's reagent for methyl chloroformate and quenching after one minute did not produce any product as evident by 60 MHz ^{1}H NMR spectroscopy.

4.3.4 Reaction of benzoyl chloride with (110).

To a solution of freshly generated **110** (0.793mmol) at -78^{0}C under argon, benzoyl chloride (0.17g,1.21mmol,1.5eq) in dry THF (*ca.* 4ml) was added. The reaction was quenched after 2 minutes and following work-up yielded a yellow solid (0.331g,118%).This crude product was shown by

high field ^{1}H NMR spectroscopy to contain only one detectable isomer,but significant amounts of enol product was also evident from this spectrum, in addition to O-H and C=C stretches in the infrared spectrum.
Recrystallisation from methanol yielded *[(2R,6S)-endo]-N-((2'S)-benzoylpropionyl)-5-aza-1,10,10-trimethyl-3-oxatricyclo [5.2.1.0^{2,6}] decan-4-one* **121** as a colourless crystalline solid (0.16g,56%); **MP** = 133.1-133.3^{0}C; $[\alpha]_D^{22.5}$ = +1.75^0 (c = 0.8, CH_2Cl_2); **^{1}H NMR** (200 MHz,$CDCl_3$) δ 7.99-7.93 (2H,cm,Ph),7.57-7.37 (3h,cm,Ph),5.41-5.30 (1H,q,*J* = 7.3 Hz,$CH_3C\underline{H}$), 4.62-4.55 (1H,bdd,*J* = 9.8 and 4.2 Hz,C$\underline{H}$N),4.52-4.47 (1H,bd,*J* = 9.8 Hz, C$\underline{H}$O),2.37-2.33 (1H,t,*J* = 3.9 Hz,bridgehead CH),1.69-1.23 (4H,cm) superimposed on 1.41-1.38 (3H,d,*J* = 7.3 Hz,$C\underline{H}_3$CH),0.95-0.92 (9H,2 x s,3 x CH_3) ppm; **^{13}C NMR** (50.3 MHz,$CDCl_3$) δ 197.83 (C=O),170.38 (C=O),154.36 (C=O),135.07(Ph quat C),132.99(Ph CH), 128.51(Ph CH), 83.16(CH),57.82(CH),49.33(quat C),48.54(quatC/CH), 47.88(CH),26.16(CH_2),19.73(CH_3),18.90(CH_2),17.93(CH_3),13.69(CH_3), 13.49(CH_3) ppm; **IR** (nujol) ν_{max} 1786 (C=O),1705 (C=O),1676 (C=O) cm^{-1}; **MS** (ei) 355(6%,M$^+$),135(5),106(16),105(base,PhCO$^+$),95(5), 77 (23,Ph$^+$),32(11); **Accurate mass**, Found : 355.1776; $C_{21}H_{25}NO_4$ requires 355.17835.
Adding the benzoyl chloride much more quickly caused *O*-acylation to be observed with a *C*:*O* ratio of 1:1.Adding the benzoyl chloride more slowly but quenching after *ca*. one minute caused only *C*-acylation (as in the initial experiment) but also significant amounts of unreacted starting material were present,in addition to the enolic compounds observed in the first experiment.

5 ASYMMETRIC ALDOL REACTIONS

5.1 Lithium enolate-mediated aldol reactions

5.1.1 Using isobutyraldehyde

To a solution of lithium enolate (0.793mmol) (made according to the procedure described in section 4.1.1) at -78^{0}C under argon,was added freshly distilled isobutyraldehyde (0.122g,1.69mmol,2.1eq) in dry THF (*ca.* 2ml).After 2 minutes the reaction was quenched with aqueous ammonium chloride solution and concentrated *in vacuo*.Water (*ca.* 50ml) was added and the product was extracted with methylene chloride (3 x *ca.* 25ml).The combined organic extracts were washed thoroughly with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution,dried over magnesium sulphate,filtered and evaporated to yield an oil (0.225g,88%) which crystallised on standing. This was shown by high field ^{1}H NMR spectroscopy to contain a mixture of all four possible isomers with a *syn* 1 : *syn* 2 : *anti* 1 : *anti* 2 ratio of 74 : 8.5 : 9.5 : 8, giving a d.e. of 48%.(These values were determined by measuring the ratio of the doublets of doublets for the carbinol resonances which resonate at δ 3-3.8; the major isomer has $J_{vicinal}$ = 2.7 Hz; **Accurate mass** (FAB), Found : 324.21748; $C_{18}H_{30}NO_4$ (M+H) requires 324.21747.In addition, the ratio of reacted:unreacted material was 95:5 with some cleaved auxiliary present.

5.1.2 Using acetaldehyde

This was conducted as for the isobutraldehyde reaction using acetaldehyde (10eq) and allowed to react in the first instance for 90 seconds before quenching.High field ^{1}H NMR spectroscopy showed that *ca.* one third of the starting material remained.Of the reacted material,two *erythro* (*syn*) isomers were detected by the carbinol resonances between δ 3.7 and 3.9 which showed vicinal couplings of 3.35 and 3.06 Hz.The ratio of *syn* 1 : *syn* 2 was *ca.* 2:1.The complexity of the spectrum did not allow measurement of the amount of unreacted to reacted material.The reaction was therefore repeated and,using propionate (0.150g,0.598mmol) and acetaldehyde (30 eq), was determined to be complete by TLC after a total of 1.75 hours,yielding a brown solid (0.176g).As well as cleavage product and small amounts of dehydration product,the high field ^{1}H NMR spectrum showed the same two *erythro*

products in the same 2:1 ratio,in addition to a *threo* isomer with J = 10.5 Hz, giving a *syn* 1 :*syn* 2 : *anti* 1 ratio of 64.5 : 31.5 : 4 and an overall d.e. of 29%; **Accurate mass** (FAB), Found : 296.186173; $C_{16}H_{26}NO_4$ (M+H) requires 296.18617.

5.2 Formation of the boron enolate of (78) and subsequent attempted reaction with acetaldehyde.

This was conducted as decribed in the literature by Danda *et al*[125].
To solution of propionate (0.200g,0.797mmol) in dry methylene chloride (*ca*. 5ml) at 0^0C under argon,was added dibutylboryltriflate (1M in CH_2Cl_2,0.96ml,1.2eq),followed by diisopropylethylamine (0.134g, 0.104mmol,1.3eq) in dry methylene chloride (*ca*. 5ml).The resulting pale yellow solution was stirred at 0^0C for one hour before being cooled to -78^0C.Freshly distilled,neat acetaldehyde (1g,22.7mmol,30eq) was then added and the resulting solution stirred at -78^0C for 2 hours before TLC showed that essentially starting material only was present.The reaction was allowed to warm to room temperature and stirred for a further 18 hours and further analysis by TLC showed that no significant change had taken place and the reaction was quenched with pH 7 phosphate buffer and stirred for several minutes.The reaction mixture was extracted into methylene chloride (3 x *ca*. 20ml) and the combined extracts were concentrated *in vacuo*.To the residue was added methanol (*ca*. 10ml) and after cooling to 0^0C,hydrogen peroxide (100 volumes,3ml) was added.The resulting mixture was stirred at 0^0C for *ca*. one hour before being diluted with water (*ca*. 20ml) and the product extracted into methylene chloride (4 x *ca*. 20ml).The combined extracts were washed successively with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution,dried over magnesium sulphate,filtered and evaporated to yield an oil which was shown by 60MHz ^{1}H NMR spectroscopy to be only starting material.

5.3 Formation of the chlorotitanium enolate and subsequent aldol reactions with benzaldehyde.

This was initially conducted according to the protocal of Evans *et al*[126].

5.3.1 Using $TiCl_4$ (1.14eq) and Et_3N (1.35eq).

To a solution of **78** (0.201g,0.801mmol) in dry methylene chloride (*ca.* 5ml) at -78^{0}C under argon, was added a solution of titanium tetrachloride (0.1ml),0.91mmol,1.14eq).After a few minutes, a solution of triethylamine (0.109g,1.08mmol,1.35eq) in dry methylene chloride (*ca.* 5ml) was added dropwise.The resulting deep purple solution was stirred at -78^{0}C for 80 minutes before freshly distilled benzaldehyde (0.106g,1mmol,1.25eq) in dry methylene chloride (*ca.* 5ml) was added.The resulting solution was stirred at -78^{0}C for 45 minutes by which time the purple colour had completely faded to a light brown colour.TLC analysis revealed that a small amount of starting material still remained and so stirring was continued at -78^{0}C for a futher 2.25 hours afterwhich time TLC showed no futher change in the reaction.After quenching with saturated ammonium chloride solution, the aqueous layer was extracted with methylene chloride (3 x *ca.* 30ml) and the combined extracts were washed successively with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution,dried over magnesium sulphate,filtered and evaporated to yield a sticky crystalline solid (0.272g,95%).This was shown by 200 MHz ^{1}H NMR spectroscopy to contain one *anti* and one *syn* isomer in a respective ratio of 6:5; **Accurate mass** (FAB), Found : 358.20184; $C_{21}H_{28}NO_4$ (M+H) requires 358.20182.

5.3.2 Using $TiCl_4$ (5.8eq) and Et_3N (1.2eq)

The reaction described in the previous section was repeated with the change that excess titanium tetrachloride (5.8eq) and triethylamine (1.2eq) were employed.Despite stirring at room temperature for a protracted period of time,upon work-up,subsequent analysis showed that the reaction was only *ca.* 30% complete.However, it also showed the presence of two *anti* isomers ($J_{vicinal}$ = 11 Hz and 7 Hz) in a respective ratio of 4:1.

Repeating the reaction under identical conditions but employing diisopropylethylamine in place of triethylamine did not furnish any product whatsoever.High field ^{1}H NMR spectroscopy of this mixture prior to the addtion of aldehyde showed that no enolate had formed.

5.3.3 Using $TiCl_4$ (2.28eq) and Et_3N (2.50eq)

The reaction was repeated but with the use of titanium tetrachloride (2.28eq) and excess triethylamine (2.50eq).After stirring for a protracted period at ambient temperature,following work-up,the high field ^1H NMR spectrum of the crude product gave a spectrum identical to that of 5.3.1 with the same *anti* and *syn* isomers in the same ratio of 6:5.

5.4 The zinc enolate of (78)

5.4.1 Preparation of racemic *[(2R,6S)-endo]-N-((2')-bromopropionyl)-5-aza-1,10,10-trimethyl-3-oxatricyclo [5.2.1.$0^{2,6}$] decan-4-one.*

To a solution of **77** (1g,5.13mmol) in dry THF (*ca.* 20ml) at -78^{0}C under argon, was added nbutyllithium (1.6M in hexanes,3.5ml,5.6mmol,1.1eq). The resulting solution was stirred at -78^{0}C for 45 minutes before freshly distilled racemic 2-bromopropionyl bromide (1.22g,5.65mmol,1.1eq) in dry THF (*ca.* 4ml) was added.The resulting solution was stirred at -78^{0}C for 10 minutes before being allowed to warm to 0^{0}C .The reaction was then stirred at this temperature for a further 40 minutes before being quenched with saturated aqueous sodium bicarbonate solution and stirred for 20 minutes at ambient temperature.The reaction mixture was then concentrated *in vacuo* and extracted with methylene chloride (3 x *ca.* 50ml).The combined organic extracts were washed with saturated aqueous ammonium chloride,dried over magnesium sulphate,filtered and evaporated to yield a "sticky" yellow solid (1.63g,96%).This was recrystallised from ethanol and purified further by sublimation onto a "cold finger" condenser (150^{0}C/0.1mmHg) yielding the title racemate **131** as colourless crystals (0.628g,37%).This had the same spectral charateristics in the ^1H NMR spectrum as previously reported by Banks[154]; **^1H NMR** (200 MHz,$CDCl_3$) (both isomers) δ 5.78-5.68 (1H,q,*J* = 6.7 Hz,C<u>H</u>CH_3), 4.65-4.51 (2H,cm,C<u>H</u>O and C<u>H</u>N),2.34-2.31 (1H,t,*J* = 3.8 Hz,bridgehead CH),1.82-1.79 (3H,d,*J* = 6.8 Hz,CHC<u>H</u>$_3$),1.70-1.37 (4H,cm),0.98 (3H,s, CH_3),0.97 (3H,s,CH_3),0.95 (3H,s,CH_3) ppm.

5.4.2 Preparation of the zinc enolate (132) of the propionate and subsequent attempted Reformatsky reaction.

Pre-activated[133] zinc dust (0.201g,3.07mmol,5eq) under THF (*ca.* 20ml) and an argon atmosphere was treated with ultrasonic waves[134] for 15-20 minutes.A solution of racemic α-bromopropionate **131** (0.200g, 0.606mmol) in dry THF (*ca.* 5ml) was added in small portions to the pre-heated (*ca.* 50^{0}C) zinc suspension, using a catalytic amount of mercuric chloride as initiator.After the addition of **131** was complete,the resulting solution was heated under reflux for one hour before TLC indicated that both α-bromo isomers had been consumed and enolate had formed.The resulting solution was cooled to -78^{0}C and freshly distilled benzaldehyde (0.079g,0.745mmol,1.2eq) in dry THF (*ca.* 2ml) was added.This mixture was stirred at -78^{0}C for ten minutes before the reaction was quenched with saturated aqueous ammonium chloride solution.Following filtration (to remove the zinc),the mixture was concentrated *in vacuo* and water (*ca.* 20ml) was added.The product was extracted with methylene chloride (3 x *ca.* 70ml) and the combined organic extracts were washed successively with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution, dried over magnesium sulphate, filtered and evaporated to yield an oil which was shown by 60 MHz ^{1}H NMR spectroscopy to be propionate **78**.

The reaction was repeated, but the mixture was allowed to warm to ambient temperature and stirred for a protracted period.TLC analysis after this time showed that no product had formed and, following ultrasonic treatment for 2.5 hours, further analysis showed that a small amount of relatively polar material had formed.The mixture was then heated under reflux for *ca.* 60 hours and, following work-up, analysis by 80 MHz ^{1}H NMR spectroscopy showed that auxiliary had formed.

5.4.3 Attempted Reformatsky reaction using pre-complexed (activated) benzaldehyde.

The zinc enolate **132** was prepared as described in section 5.4.2 and cooled to -78^{0}C .To this enolate was added pre-cooled (-78^{0}C),pre-complexed benzaldehyde (1.1eq) with diethylaluminium chloride (1.8M in toluene,0.3ml,1.2eq) in dry methylene chloride (*ca.* 10ml).The reaction was allowed to warm to 0^{0}C and stirred overnight at that temperature, before being raised to ambient temperature and stirred for a protracted

period.Following work-up, analysis by 80 MHz ^{1}H NMR spectroscopy showed that other than substantial amounts of propionate and cleaved auxiliary, there were no detectable products.

6.1 ASYMMETRIC α-BROMINATION REACTIONS OF THE PROPIONATE WITH *N*-BROMOSUCCINIMIDE.

6.1.1 Reaction of the lithium enolate (110) with NBS at -78^{0}C.

To a freshly prepared solution of **110** (0.797mmol) in dry THF (*ca.* 13ml) under argon (as described in section 4.1.1) was added a solution of NBS (0.286g,1.6mmol,2eq) in dry THF (*ca.* 11ml).The resulting solution was stirred at -78^{0}C for 40 minutes before TLC showed that some product had formed.After a total of *ca.* 3.5 hours no further progress in the reaction was apparent and the mixture was allowed to warm to -7^{0}C and stirred for *ca.* 6 hours before being allowed to warm to +7.5^{0}C overnight.After quenching with saturated aqueous ammonium chloride,the mixture was concentrated *in vacuo*.The product was extracted with methylene chloride (3 x *ca* 70ml) and the combined organic extracts were washed successively with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution, dried over magnesium sulphate,filtered and evaporated to yield an oil which was analysed by high field ^{1}H NMR spectroscopy.This showed that the reaction was *ca.* 75% complete and by decoupling the doublet at δ 1.8, the epimer ratio was found to be 6:1.

The reaction was conducted again using propionate (0.5g). Following flash chromatography (70g SiO_2) using gradient elution with *n*hexane : diethyl ether (100:0 to 0:100) the minor isomer was isolated and assigned as *[(2R,6S)-endo]-N-((2'S)-bromopropionyl)-5-aza-1,10,10-trimethyl-3-oxatricyclo [5.2.1.0^{2,6}] decan-4-one* as a light green solid (30mg,4.5%), whose ^{1}H NMR data was in agreement to that obtained by Banks[154]; **^{1}H NMR** δ 5.82-5.72 (1H,q,*J* = 6.8 Hz,C<u>H</u>CH$_3$),4.58-4.56 (2H,2 x s,C<u>H</u>O and C<u>H</u>N),2.34-2.30 (1H,m,bridghead CH),1.85-1.81 (3H,d,*J* = 6.8 Hz,C<u>H</u>$_3$CH),1.70-1.02·(4H,cm),0.99 (3H,s,CH$_3$),0.97 (3H,s,CH$_3$),0.96 (3H,s,CH$_3$) ppm.

6.1.2 Reaction of the boron enolate of (78) with NBS at -78^{0}C

The boron enolate of **78** (1.2mmol) was prepared as described in section 5.2 (N.B. *the dibutylboryltriflate was not fresh*).The light yellow solution was diluted to *ca.* 50ml with dry methylene chloride and added *via cannula* to a slurry of NBS (1.32mmol,1.1eq).The resulting solution was stirred at -78^{0}C for 75 minutes before being examined by TLC which showed the presence of both isomers including some starting material. Stirring was continued for a further 1 hour and 40 minutes afterwhich time no change in the reaction situation could be detected.The reaction was allowed to warm to 0^{0}C and stirred overnight at this temperature. The reaction was then quenched and worked-up as described in section 5.2 to yield an oily solid (0.340g,86%).Examination by high field ^{1}H NMR spectroscopy showed that the reaction was *ca.* 52% complete.The same decoupling experiment as that described in the preceeding section showed that the corresponding isomer ratio was 58:1 *i.e.* essentially stereospecific. Repeating the reaction using fresh dibutylboryltriflate and propionate (1.816g,7.24mmol),yielded,after flash chromatography ((100g SiO_2) using gradient elution with *n*hexane : diethyl ether (20:1 to 2:1)) the major isomer *[(2R,6S)-endo]-N-((2'R)-bromopropionyl)-5-aza-1,10,10-trimethyl-3-oxatricyclo [5.2.1.0^{2,6}] decan-4-one* **133** as a colourless solid (1.506g,63%); **MP** = 151-153^{0}C (from diisopropyl ether); $[\alpha]_D^{21}$ = -132.8^0 (c = 5; CH_2Cl_2); **^{1}H NMR** (200 MHz,$CDCl_3$) δ 5.78-5.68 (1H,q,*J* = 6.8 Hz, C<u>H</u>CH_3),4.64-4.55 (1H,ddd,*J* = 9.8,4.2 and 1.1 Hz,C<u>H</u>N),4.55-4.50 (1H,dd, *J* = 9.1 and 1.5 Hz,C<u>H</u>O),2.34-2.30 (1H,t,*J* = 4.0 Hz,bridgehead CH),1.81-1.78 (3H,d,*J* = 6.8 Hz,C<u>H</u>$_3$CH),1.71-1.35 (4H,cm),0.97 (3H,s,CH_3) 0.96 (3H,s,CH_3),0.95 (3H,s,CH_3) ppm; **^{13}C NMR** (50.3 MHz,$CDCl_3$) δ 169.48 (C=O),153.10 (C=O),82.72(CH),57.44(CH),49.37(quat C),48.59(quat C), 47.55(CH),38.19(<u>C</u>HBr),26.04(CH_2),20.18(<u>C</u>H_3CH),19.67(CH_3),19.19 (CH_2),17.87(CH_3)13.65(CH_3) ppm; **IR** (nujol) ν_{max} 1770 (C=O),1704 (C=O), 1262,1218(d),1149,1041 cm^{-1}; **MS** (ei) 331 (47%,$C_{14}H_{20}{}^{81}BrNO_3$), 329 (47, $C_{14}H_{20}{}^{79}BrNO_3$),272(19),270(19),250(22,(M-$^{79/81}$Br$^+$)),206(base), 150(9),136(15),135(93),134(67),119(25),109(15),106(15),95(77),93(22),91 (12),81(12),79(13),77(11),69(18),67(20); **Accurate mass**,Found : 329.0636; $C_{14}H_{20}{}^{79}BrNO_3$ requires 329.06270; **Elemental analysis**, Found : 51.0% C,5.87% H,4.41% N; $C_{14}H_{20}{}^{79}BrNO_3$ requires 50.92% C, 6.10% H,4.24% N.

6.2 Reaction of (133A) with sodium azide

(a) In DMF

To a solution of **133A** (0.043g,0.13mmol) in DMF (*ca.* 2ml), a solution of sodium azide (0.088g,0.135mmol,1eq) in DMF (*ca.* 10ml) was added (***NB*** NaN_3 is *sparingly* soluble in DMF).The resulting solution was stirred at room temperature for 97 hours before the DMF was removed *in vacuo* (*NB* this required some heating).The residue was dissolved in methylene chloride (*ca.* 7ml) and water (*ca.* 3ml) was added.The layers were separated and the aqueous layer extracted further with methylene chloride (2 x *ca.* 10ml).The combined organic extracts were washed with water (*ca.* 5ml) and saturated aqueous sodium chloride solution,dried over magnesium sulphate,filtered and evaporated to yield a "sticky" solid (0.044g).Analysis of this solid by high field ^1H NMR spectroscopy revealed that although all of the starting material had been consumed, apparent from complete dissappearance of the quartet at δ 5.8 and the appearance of a new one at δ 5.0, significant racemisation (*ca.* 30%) had occurred.

(b) Under phase transfer conditions

To a solution of **133A** (0.253g,0.767mmol) in methylene chloride (*ca.* 10ml) was added sodium azide (0.100g,1.54mmol,2eq) and TBAB (catalytic amount) in water (*ca.* 20ml).The resulting solution was stirred rapidly at room temperature overnight before the layers were separated and the aqueous layer extracted with methylene chloride (2 x *ca.* 30ml).The combined organic layers were dried over magnesium sulphate,filtered and evaporated to yield a "sticky" crystalline solid (0.222g,99%) which was purified by flash chromatography (60g SiO_2) using gradient elution with *n*hexane : diethyl ether 100:0 to 0:100 which yielded *[(2R,6S)-endo]-N-((2'S)-azidopropionyl)-5-aza-1,10,10-trimethyl-3-oxatricyclo [5.2.1.$0^{2,6}$] decan-4-one* **134A** as a colourless crystalline solid (0.168g,75%); **MP** = 102-103^{0}C; $[\alpha]_D^{24.5}$ = -113.00^0 (c = 2.6,CH_2Cl_2); **^{1}H NMR** (200MHz, $CDCl_3$) δ 5.01-4.90 (1H,q,*J* = 6.9 Hz,C<u>H</u>CH_3),4.57-4.56 (2H,cm,C<u>H</u>O and C<u>H</u>N), 2.28-2.25 (1H,bt,*J* = 3.4 Hz,bridgehead CH),1.62-0.99 (4H,cm) superimposed on 1.55-1.51 (3H,d,*J* = 6.9 Hz, $C\underline{H}_3CH$),0.941 (3H,s,CH_3), 0.935 (3H,s,CH_3),0.92 (3H,s,CH_3) ppm; **^{13}C NMR** (50.3 MHz,$CDCl_3$) δ 171.55 (C=O),153.42 (C=O),83.18(CH),57.46 (CH),55.72(<u>C</u>HN_3),49.29 (quat C),48.41(quat C),47.24(CH),25.99(CH_2), 19.60(CH_3),19.47(CH_2), 17.74(CH_3),16.59(CH_3),13.52(CH_3) ppm; **IR**

(nujol) ν_{max} 2115 (N_3),1782 (C=O),1707 (C=O),1240,1218(d) cm^{-1}; **Accurate mass** (FAB), Found : 293.16134; $C_{14}H_{21}N_4O_3$ (M+H) requires 293.16135.

Starting with a 85:15 mixture of α-Br isomers yielded a mixture of the α-azido isomers in a ratio of 87.5:12.5,indicating that no detectable racemisation is occurring in the reaction (outside the limits of ^1H NMR spectroscopy).

6.3 Cleavage of the α-azidopropionate (134A) using $Ti(OPr^i)_4$ and benzyl alcohol.

This was achieved using the method of Seebach *et al*[136].
To benzyl alcohol (12.65ml,100eq),pre-oxygenated using a strong pulse of argon with stirring,was added titanium tetraisopropoxide (0.33g,0.34ml, 1eq).To this resultant mixture was added α-azidocarboximide (0.342g, 1.17mmol) and the solution was heated under an argon atmosphere at 130^0C for 21 hours by which time TLC showed that all of the starting material had been consumed.The reaction was allowed to cool and quenched with dilute hydrochloric acid (1M,*ca.* 5ml).The mixture was stirred vigorously and diluted with water (*ca.* 20ml), before being extracted with methylene chloride (4 x *ca.* 60ml).The combined organic extracts were washed successively with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution, dried over magnesium sulphate,filtered and evaporated.The resultant oil was purified by flash chromatography (200g,SiO_2) using gradient elution with *n*hexane : diethyl ether 100:0 to 5:1 to yield *Benzyl (2S)-azidopropionate* **135** as a pale yellow oil (0.090g,38%); $[\alpha]_D^{23.5} = +4.95^0$ (c = 4, CH_2Cl_2); **^1H NMR** (200MHz,$CDCl_3$) δ 7.40-7.33 (5H,Ph),5.22 (2H, s,$OC\underline{H}_2$),4.03-3.92 (1H,q,*J* = 7.2 Hz,$C\underline{H}CH_3$),1.50-1.46 (3H,2 x d,*J* = 7.2 Hz,$C\underline{H}_3CH$) ppm; **^{13}C NMR** (50.3 MHz,$CDCl_3$) δ 170.65 (C=O),134.93 (Ph, quat C),128.49(Ph CH),128.38(Ph CH),128.13(Ph CH),67.24 ($O\underline{C}H_2$), 57.14($\underline{C}HN_3$),16.55($\underline{C}H_3CH$) ppm; **IR** (thin film) ν_{max} 3010(cm),2118 (N_3),1760(C=O),1470,1400,1275,1202,1103(d) cm^{-1}.

6.4 Preparation of *O-(Diphenylphosphinyl) hydroxylamine*

This was prepared by the method of Colvin *et al*[137].
To a rapidly stirred solution of hydroxylamine hydrochloride (8.10g, 117mmol,2.8eq) in a mixture of aqueous sodium hydroxide solution (2M,

60ml,120mmol,3eq) and dioxane (*ca.* 50ml) at 0^0C was added a solution of diphenylphosphinyl chloride (10g,42mmol) in dioxane (*ca.* 40ml) in one portion.The resulting thick white suspension was diluted with water (*ca.* 100ml) and after *ca.* 10-20 minutes stirring at 0^0C,the solid was filtered off. This was resuspended in aqueous sodium hydroxide solution (0.2M, 100ml,20mmol) and stirred at 0^0C for *ca.* 50 minutes by which time the solution turned red litmus paper purple.The reaction mixture was filtered off and the residue washed with water (*ca.* 100ml).The resulting sticky white paste was dried ina high vacuum oven at 50^0C for 17-18 hours,before being dried for a further 24 hours at 60^0C to yield the title compound as a white powder (3.64g,37%); **MP** = 120^0C (lit[155] = 130-135^0C); ^{31}**P NMR** (36.23 MHz,$CDCl_3$) δ 28.13 ppm; (81.02 MHz,d_6-DMSO (reaction takes place)) δ 20.56 ppm; **IR** (nujol) ν_{max} 3268(d,NH), 3170 (NH),1207(P=O),1130,895 cm^{-1}; **MS** (ei) (no M^+),219(5%),217(3),202 (12), 201(93,(M-ONH_2^+)),133(62),77(base,Ph^+).

6.5 Attempted direct α-amination of (110).

Following the method of Colvin *et al*[137], a solution of freshly prepared enolate **110** (0.916mmol) in dry THF (17ml) (prepared according to the general procedure described in section 4.1.1) at -78^0C under argon was added *O*-(diphenylphosphinyl) hydroxylamine (0.254g,0.966mmol, 1.05eq). The resulting creamy-white mixture was stirred at -78^0C for 2.5 hours afterwhich time TLC analysis revealed that no reaction had taken place.The reaction was warmed to -8^0C and stirred for *ca.* 6 hours before being allowed to warm to +10^0C overnight.The reaction was quenched with pH 7 phosphate buffer and extracted with methylene chloride (3 x *ca.* 30ml).The combined organic extracts were washed with saturated aqueous sodium chloride solution ,dried over magnesium sulphate, filtered and evaporated to yield a yellow oil which crystallised on standing.Analysis of the crude mixture by 80 MHz ^{1}H NMR spectroscopy revealed significant amounts of cleaved auxiliary to be present,in addition to propionate,formed by hydrolysis of the lithium enolate with traces of water in the phosphorus compound.No quartet corresponding to the expected product could be detected though.

7.1 Preparation of *[(2R,6S)-endo]-N-(chlorocarbonyl)-5-aza-1,10,10-trimethyl-3-oxatricyclo [5.2.1.$0^{2,6}$] decan-4-one* (139) and subsequent attempted resolution with racemic 1-phenylethanol.

The carbamyl chloride was prepared using an analogous synthesis of this molecule,achieved by Banks *et al*[154].

To a solution of **77** (0.5g,2.56mmol) in dry THF (*ca.* 20ml) at -78^{0}C under argon,was added nbutyllithium (1.6M in hexanes,1.7ml,2.72mmol, 1.05eq).The resulting solution was stirred at -78^{0}C for 30 minutes before being added dropwise *via cannula* into a solution of phosgene (1.93M in toluene,5.5ml,10.6mmol,4eq) at -78^{0}C.The resulting mixture was allowed to warm to room temperature and stirred for a further one hour.The excess phosgene and solvents were removed *in vacuo* before the residue was dissolved in dry methylene chloride (*ca.* 20ml) (*NOTE*: the lithium chloride formed did not dissolve in this solvent).This solution was added *via* syringe pump over *ca.* 3.5 hours to an ice-cooled solution of racemic 1-phenylethanol (0.63g,5.164mmol,2eq) and triethylamine (0.26g, 2.57mmol,1eq) in dry methylene chloride (*ca.* 20ml).The reaction mixture was allowed to stir overnight and was quenched with aqueous ammonium chloride solution.The reaction mixture was stirred for 10 minutes and the layers were separated.The aqueous layer was extracted with methylene chloride (2 x *ca.* 60ml) and the combined extracts were washed successively with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution,dried over magnesium sulphate,filtered and evaporated to yield a brown oil (0.586g).High field ^{1}H NMR spectroscopy showed this mixture to contain product : unreacted auxiliary in a ratio of 20:17.

7.2 Attempted resolution of 1-phenylethanol using (139) and triethylamine in the presence of DMAP.

The carbamyl chloride **139** (0.57g,2.56mmol) was prepared as described in the previous section and dissolved in dry THF (*ca.* 20ml) under argon, and a solution of freshly distilled racemic 1-phenylethanol (0.312g, 2.56mmol,1eq) in dry THF (*ca.* 5ml) followed by dry triethylamine (0.26g, 2.57mmol,1eq) in dry THF (*ca.* 5ml) and DMAP (0.0508g,0.416mmol, 0.16eq) was added.The resulting solution was stirred at room temperature overnight before TLC analysis showed that only a trace of

product had formed.The reaction was then heated under reflux for 22.5 hours before quenching with dilute hydrochloric acid.The reaction mixture was then concentrated *in vacuo* and water (*ca.* 20ml) was added.The aqueous layer was extracted with methylene chloride (3 x *ca.* 60ml) and the combined extracts were washed successively with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution,dried over magnesium sulphate,filtered and evaporated to yield an oil (0.62g).Examination of this product by high field ^1H NMR spectroscopy showed that the desired material to unreacted auxiliary were in a ratio of 1 : 1.9, but both were present in very small amounts. The crude product was purified by column chromatography (60g,SiO_2), using gradient elution with *n*hexane : diethyl ether (100:0 to 1:1) to yield a white crystalline solid (0.472g,89%),shown to be auxiliary dimer, $(Aux)_2C{=}O$.**Accurate mass** (FAB), Found : 417.23891; $C_{23}H_{33}N_2O_5$ (M+H) requires 417.23893.

7.3 Attempted resolution of 1-phenylethanol using (139) and lithiated alcohol.

A solution of freshly prepared **139** (0.57g,2.56mmol) in dry DME (*ca.* 10ml) at -78^{0}C under argon, was added *via cannula* to a solution of freshly prepared lithiated 1-phenylethanol (made from racemic 1-phenylethanol (0.312g,2.56mmol,1eq) and nbutyllithium (1.6M in hexanes,1.75ml,1.1eq) at 0^{0}C).The resulting mixture was allowed to warm to room temperature and stirred overnight,afterwhich time TLC revealed that a significant amount of starting material remained.The reaction mixture was then heated under reflux under an argon atmosphere for *ca.* 1.5 hours before being allowed to cool and quenched with water (*ca.* 20ml).The mixture was concentrated *in vacuo* and the aqueous layer extracted with methylene chloride (4 x *ca.* 50ml).The combined organic extracts were washed successively with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution,dried over magnesium sulphate,filtered and evaporated to yield a "sticky" solid (0.80g).^1H NMR spectroscopy showed that the desired product to unreacted auxiliary were present in a ratio of 9:14.

7.4 Attempted resolution of 1-phenylethanol by reaction of the chloroformyl derivative of the alcohol with the lithiated auxiliary (100).

To a solution of **77** (0.5g,2.56mmol) in dry THF (*ca.* 20ml) at -78^{0}C under argon,was added nbutyllithium (1.6M in hexanes,1.7ml,2.72mmol, 1.05eq).The resulting solution was stirred at -78^{0}C for 30 minutes before freshly distilled racemic 1-phenylethanol chloroformate (0.472g, 2.56mmol,1eq) in dry THF (*ca.* 5ml) was added dropwise.The resulting solution was stirred at -78^{0}C for 15 minutes before being allowed to warm to ambient temperature and stirred for 20 minutes before TLC revealed that essentially no reaction had occurred.Stirring at room temperature was continued overnight and no change in the state of the reaction could be observed.The reaction was then heated under reflux under an argon atmosphere for 2.5 hours before being allowed to cool.The mixture was concentrated *in vacuo* and the residue diluted with water (*ca.* 20ml).The aqueous layer was extracted into methylene chloride (3 x *ca.* 60ml) and the combined extracts were washed successively with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution,dried over magnesium sulphate, filtered and evaporated to yield a solid (0.54g),which was shown by ^{1}H NMR spectroscopy to be only unreacted auxiliary.

The sodium salt of the auxiliary **85** was prepared *in situ* (using sodium hydride as described in section 2.1.3) but showed the same complete lack of propensity to react with the chloroformate despite prolonged heating under reflux in THF under an argon atmosphere.

7.5.1 Preparation of 2-phenylethanol chloroformate.

To an ice-cooled,rapidly stirred solution of phosgene (1.93M in toluene, 75ml,0.145m,3.5eq) under argon,was added dropwise a solution of 2-phenylethanol (5g,41mmol) and triethylamine (4.14g,41mmol,1eq) in dry diethyl ether (*ca.* 100ml).The resulting solution was allowed to warm to room temperature and stirred for *ca.* 4 hours.The hydrochloride salt was then filtered off,the precipitate washed thoroughly with dry diethyl ether (*ca.* 50ml) and the excess phosgene and solvents removed *in vacuo* to yield an oil which was purified by Kugelrohr distillation (120^{0}C/ 2mmHg) to yield a colourless oil (6.47g,86%).This had an infrared

spectrum identical to that obtained by Gaur[156]; **IR** (thin film) ν_{max} 3032,1775 (C=O),1497,1455,1147,846,824,749,698 cm^{-1}.

7.5.2 Reaction of 2-phenylethanol chloroformate with (100).
To a solution of **77** (0.203g,1.04mmol) in dry THF (*ca.* 10ml) at -78^{0}C under argon,was added nbutyllithium (1.6M in hexanes,0.71ml, 1.14mmol,1.1eq).The resulting solution was stirred at -78^{0}C for 45 minutes before freshly distilled 2-phenylethanol chloroformate (0.216g, 1.17mmol,1.1eq) in dry THF (*ca.* 5ml) was added.The resulting solution was allowed to warm to room temperature and stirred for a further 10 minutes before TLC revealed that a small amount of starting material remained.The reaction mixture was then stirred overnight before further TLC analysis showed that only a trace of auxiliary remained unreacted. The reaction was then quenched with aqueous ammonium chloride solution and extracted with methylene chloride (4 x *ca.* 40ml). The combined extracts were washed successively with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution,dried over magnesium sulphate,filtered and evaporated to yield a cloudy oil (0.376g).The product was shown to be unstable on both silica and neutral alumina,upon attempted purification,and was purified without decomposition by crystallisation from diethyl ether : *n*hexane : diisopropyl ether (excess : 3 : 1) furnishing *[(2R,6S)-endo]-N-((2'-phenylethanoformyl)-5-aza-1,10,10-trimethyl-3-oxatricyclo [5.2.1.0^{2,6}] decan-4-one* **146** as colourless,fluffy crystals (0.219g,61%); **MP** = 72-74^{0}C; $[\alpha]_D^{20}$ = -104.4^0 (c = 2.5,CH_2Cl_2); **^{1}H NMR** (200 MHz,$CDCl_3$) δ 7.27-7.18 (5H,cm,Ph),4.46-4.35 (4H,cm,C<u>H</u>O,C<u>H</u>N and $CH_2C\underline{H}_2O$),3.01-2.94 (2H,t, *J* = 6.9 Hz,$C\underline{H}_2CH_2O$),1.92-1.88 (1H,t,*J* = 3.8 Hz,bridgehead CH),1.68-1.09 (4H,cm),0.91 (3H,s,CH_3),0.89 (3H,s,CH_3),0.87(3H,s,CH_3) ppm; **^{13}C NMR** (50.3 MHz,$CDCl_3$) δ 152.45 (C=O),150.53 (C=O),136.89(Ph quat C),128.63(Ph CH),128.23(Ph CH),126.39(Ph CH),81.71(CH),66.84 ($\underline{C}H_2O$),57.68(CH),49.09(quat C),47.87(quat C/CH),34.62($\underline{C}H_2CH_2O$), 25.94(CH_2),19.58(CH_3),19.41(CH_2),17.70(CH_3),13.56(CH_3) ppm; **IR** (nujol) ν_{max} 1844(C=O),1730(C=O),1400,1332,1300,1280,1082 cm^{-1}; **Accurate mass** (FAB), Found : 344.18615; $C_{20}H_{26}NO_4$ (M+H) requires 344.18617; **Elemental analysis**, Found : 69.71% C,7.37% H,4.17% N; $C_{20}H_{25}NO_4$ requires 69.95% C,7.34% H,4.08% N.

7.6.1 Preparation of racemic *trans*-2-methylcyclohexanol chloroformate (147).

This was prepared using according to the procedure described in section 7.5.1 using phosgene (1.93M in toluene,27ml,0.052m,3eq),racemic *trans*-2-methylcyclohexanol (2g,0.0175m) and triethylamine (1.77g,0.0175m, 1eq).After allowing the mixture to react at room temperature overnight,the mixture was work-up to yield an oil which was purified by Kugelrohr distillation,giving the title compound as a colourless oil (2.02g,65%); **BP** = 80^0C/10mmHg; **^{1}H NMR** (200 MHz,$CDCl_3$) δ 4.52-4.40 (1H,distorted td,*J* = 10.2 and 4.4 Hz,HCOCOCl),2.16-2.07 (1H,cm, $HCCH_3$),1.83-1.72 (2H,cm),1.70-1.58 (2H,cm),1.56-0.96 (4H,cm) superimposed on 0.99-0.96 (3H,d,*J* = 6.4 Hz,$HCCH_3$) ppm; **^{13}C NMR** (50.3 MHz,$CDCl_3$) δ 149.80 (C=O),87.94(CHO),36.90($CHCH_3$),33.05 (CH_2),30.93(CH_2),24.67(CH_2),24.34(CH_2),18.00(CH_3) ppm; **IR** (thin film) ν_{max} 2960,2878,1789 (C=O),1463,1182,1160,980,915,888,858,830,785,700 cm^{-1}; **MS** (ei) (no M^+),119(1%),84(4),97(53),96(94),95(8),82(9),81(base), 79(4),70(11); FAB (no $(M+H)^+$ or $(M-H)^+$).

7.6.2 Reaction of (100) with racemic *trans*-2-methylcyclohexanol chloroformate (147)

This was done using the procedure described in section 7.5.2 with **77** (0.200g,1.03mmol),nbutyllithium (1.6M in hexanes,0.71ml,1.1eq) and freshly distilled chloroformate (0.203g,1.15mmol,1.1eq) being employed.The reaction mixture was stirred at room temperature for 1.75 hours before quenching.Work-up yielded a cloudy oil (0.349g,100%) which crystallised on standing.This crude product was recrystallised from *n*hexane : diisopropyl ether (3:1) to yield racemic *[(2R,6S)-endo]-N-(2'-methylcyclohexyl-1'-oxycarbonyl)-5-aza-1,10,10-trimethyl-3-oxatricyclo [5.2.1.$0^{2,6}$] decan-4-one* as colourless crystals (0.225g,66%);**^{1}H NMR** (360 MHz, $CDCl_3$) (both isomers) δ 4.50-4.42 (3H,cm,CHN,CHO and HCCO),2.17-2.15 (1H,cm,$HCCH_3$),2.06-2.01 (1H,cm,bridgehead CH),1.85-1.71 (2H,cm),1.70-1.58 (4H,cm),1.39-1.01 (6H,cm),0.97-0.89 (12H,6 x s,4 x CH_3 (both isomers)) ppm; **^{13}C NMR** (50.3 MHz,$CDCl_3$) (both isomers) δ 152.65 (C=O),152.56 (C=O),150.49 (C=O),150.40 (C=O),81.56(CH),81.27 (CH),57.78(CH),49.15(quat C),48.36(CH),47.99(quat C),36.84(CH),36.67 (CH),33.09(CH_2),33.00(CH_2),31.37(CH_2),31.19(CH_2),26.01(CH_2),24.80(C H_2),24.31(CH_2),19.71(CH_3),19.55(CH_3),19.44(CH_2),18.15(CH_3),

17.82 (CH_3), 13.61(CH_3) ppm; **Accurate mass** (FAB), Found : 336.21745; $C_{19}H_{30}NO_4$ (M+H) requires 336.21747.These isomers could not be detected at 258nm, the detection wavelength of the instrument, and therefore no α-value could be obtained.

7.6.3 Reaction of the thione derivative (149) of Chirabornox with (147).

(a) Using nbutyllithium as base

This was done according to the procedure described in section 7.5.2, using Chirabornox-derived oxazolidinethione **149** (0.092g,0.436mmol), nbutyllithium (1.6M in hexanes,0.3ml,0.48mmol,1.1eq) and freshly distilled chloroformate (0.085g,0.481mmol,1.1eq).This reaction was quenched after TLC revealed that all of the thione had been consumed once the reaction temperature had reached ambient.Work-up yielded racemic *[(2R,6S)-endo]-N-(2'-methylcyclohexyl-1'-oxycarbonyl)-5-aza-1,10,10-trimethyl-3-oxatricyclo [5.2.1.$0^{2,6}$] decan-4-thione* as an oil (0.157g,100%); **^{1}H NMR** (200 MHz,$CDCl_3$) (both isomers) δ 4.69-4.66 (2H,cm,C<u>H</u>O and C<u>H</u>N),4.47-4.42 (1H,symm m,<u>H</u>CCO),2.15-2.12 (1H,m,<u>H</u>CCH_3),2.02-1.98 (1H,m,bridgehead CH),1.74-1.52 (6H,cm),1.39-1.05 (6H,cm),0.94-0.92 (9H,2 x s,3 x CH_3 (both isomers)),0.87-0.84(3H,d,*J* = 6.4 Hz,HC<u>C</u>H_3) ppm; **^{13}C NMR** (50.3 MHz,$CDCl_3$) δ 185.01(C=S), 150.48 (C=O),88.35(CH),82.01 (CH),81.89(CH),62.78(CH),49.80 (quat C),48.98(CH),48.87(quat C),36.69(CH),36.48(CH),32.97(CH_2),32.86 (CH_2),31.27(CH_2),31.05(CH_2),26.54(CH_2),24.65(CH_2),24.20(CH_2),19.87 (CH_3),19.77(CH_3),19.54(CH_2),18.18(CH_3),18.09(CH_3),13.52(CH_3) ppm; **IR** (nujol) ν_{max} 1763 (C=O),1054 (C=S),1030 cm^{-1}; **Accurate mass** (ei), Found : 351.1889; $C_{19}H_{29}NO_3S$ requires 351.18680.

The isomers were studied by normal phase HPLC analysis using 3:1 *n*hexane : diethyl ether as elution solvent and the α-value obtained was 1.35.The ratio of the area under the slower to the faster moving eluent was estimated to be 1.85:1.

(b) Using pyridine as base in the presence of DMAP

To a solution of **149** (0.100g,0.474mmol) and dry pyridine (0.041g, 0.519mmol,1.1eq) in dry toluene (*ca.* 20ml) at room temperature under argon, was added freshly distilled chloroformate (0.092g,0.521mmol, 1.1eq) in dry toluene (*ca.* 50ml).The resulting solution was stirred at room temperature overnight afterwhich time TLC showed that a

significant amount of starting material was still present.The mixture was then heated under reflux under an argon atmosphere for 29 hours by which time TLC showed that no further change had occurred.The mixture was allowed to cool and quenched with dilute hydrochloric acid and concentrated *in vacuo*.The residue was diluted with water (*ca.* 15ml) and extracted with methylene chloride (3 x *ca.* 30ml).The combined organic exctracts were washed successively with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution,dried over magnesium sulphate,filtered and evaporated to yield a "sticky" white solid.This was purified by flash chromatography (20g SiO_2) eluting with *n*hexane : diethyl ether (4:1) to yield a colourless oil (0.059g,36%) which gave the same α-value by HPLC of 1.34 and a corresponding thermodynamic ratio of 0.88:1.

7.7 Cleavage of the alcohol from the thione adducts (150A/B).
This was conducted according to the protocol used by Evans *et al*[79].
To a solution of **150A/B** (0.153g,0.436mmol) in a solution of THF:water (3:1) (*ca.* 12ml) at 0^0C, was added hydrogen peroxide (100 volumes,1ml, 8.1mmol,19eq),followed by lithium hydroxide monohydrate (0.04g, 0.953mmol,2.2eq).The resulting solution was stirred at room temperature for one hour before TLC analysis revealed that the adduct had been essentially all consumed.The reaction was quenched with sodium sulphite solution (*CAUTION* : the reaction became warm) and left to stir for *ca.* 50 minutes.The mixture was extracted with methylene chloride (4 x *ca.* 20ml) and the combined layers were dried over sodium sulphate, filtered and evaporated to yield an oil (0.138g).Analysis of the crude product by high field ^{1}H NMR spectroscopy showed that the cleavage reaction was 55% complete with only a trace of thione auxiliary present.The remainder was oxidised adduct (*i.e.* **148A/B** had formed) in addition to **77** (formed by oxidation of **149**).The mixture was redissolved in THF:water (3:1) (*ca.* 12ml) and hydrogen peroxide (*ca.*1ml,19eq) and lithium hydroxide monohydrate (0.045g,0.953mmol,2.2eq) was added.The reaction was stirred at room temperature for five hours before the reaction was quenched.Work-up as before yield an oil which was purified by dry flash chromatography (60g SiO_2) using *n*hexane : diethyl ether (100:0 to 1:1) yielded an oil (0.042g) which was shown by ^{1}H NMR spectroscopy to be the desired alcohol,but with *ca.* 20% unreacted

Chirabornox adduct **148A/B**.Further elution with pure diethyl ether yielded a colourless solid, shown by ^{1}H NMR to be Chirabornox **77** (0.067g,79%).Based on the yield of recovered auxiliary,the reaction was estimated to be *ca.* 80% complete.

8.1 Oxidation of (1*R*)-(+)-Camphor to Camphorquinone (155).

This was achieved by the method of Evans *et al*[140].

To a suspension of (1*R*)-(+)-Camphor (100g,0.657m) in acetic anhydride (*ca.* 80ml) was added selenium dioxide (80g,0.721m).The resulting stirred suspension was heated under gentle reflux for *ca.* two hours before being allowed to cool and further selenium dioxide (20g,0.180m) was added. Boiling was continued for a further two hours before a final portion of selenium dioxide (17g,0.153m) was added and the resulting mixture heated under reflux for 3-4 hours.The solution was allowed to cool and neutralised with sodium hydroxide solution (30%,*ca.* 200ml) and brought to pH 8.The solution was filtered through celite and the celite washed thoroughly with diethyl ether (*ca.* 2.5 litres) until it ran clear.The layers were separated and the aqueous layer extracted further with diethyl ether (2 x *ca.* 300ml).The combined organic extracts were concentrated *in vacuo* to yield a yellow/orange residue which contained insoluble impurities.The residue was stirred over magnesium sulphate in boiling ethanol and hot filtered; the filtrate was washed with methylene chloride and the solvents removed *in vacuo*.The dark-yellow residue was recrystallised from ethanol to yield yellow crystals of camphorquinone (85.89,79%). Recrystallisation of the mother liquors yielded a further 4.48g (total yield 90.37g,83%); **MP** = 196.4-201.7^{0}C (lit[144] = 198-199^{0}C).It was subsequently discovered that camphorquinone could be purified by use of a crude dry flash silica column,using diethyl ether as elution solvent,which removed the polar selenium residues.

8.2 Reduction of Camphorquinone using zinc in acetic acid.

The protocol for this reaction followed the modification by Huckel and Fechtig[143] of Bredt and Ahrens method[145].

(1*R*)-(+)-Camphorquinone (90.37g,0.554m) was dissolved in the minimum amount of hot acetic acid (*ca.*50ml) and hot (65^{0}C) water (*ca.* 750ml) was added.The resultant mixture was heated to 90-100^{0}C, with mechanical stirring, and activated[133] zinc dust was added in portions

until the yellow solution had faded completely (*ca.* 400g in total). The reaction mixture was quickly filtered through celite, and hot water (*ca.* 2 litres) used to wash the compound out of the zinc and celite.The aqueous layer was saturated with sodium chloride and extracted into methylene chloride (4 x *ca.* 500ml).The combined organic layers were neutralised with saturated aqueous sodium bicarbonate solution (*ca.* 50ml) when universal indicator showed that the solution was slightly alkaline.The organic layer was dried over sodium sulphate,filtered and evaporated to yield a white solid (54.7g,60%).Further product was obtained by stirring the crushed up zinc in refluxing methylene chloride (*ca.* 1 litre) and washing the filtrate with more hot methylene chloride (*ca.* 500ml).The combined organic layers were neutralised and dried as before to yield a further 29.49g (total yield 85.32g (93%)); **MP** = 202-205^{0}C (lit[145] = 203-205^{0}C); **Accurate mass** (ei), Found : 168.1165; $C_{10}H_{16}O_2$ requires 168.11502; **IR** (nujol) ν_{max} 3420 (OH),1745 (C=O) cm^{-1}.

8.3 Separation of *endo*-2-hydroxyepicamphor (160) from *endo*-3-hydroxycamphor (161) *via* the formation of Manasse's dimer.

Following the method of Manasse[146], hydrogen chloride gas (freshly generated from concentrated sulphuric acid and ammonium chloride) (115mmol,1eq) was bubbled into a solution of **160** and **161** (19.35g, 115mmol) in dry methanol (*ca.* 50ml) assisted by a stream of argon.The resulting solution was allowed to stand at room temperature for several days,over which time crystals of the dimer formed.These were filtered off and the methanol was allowed to evaporate to yield a second crop.The combined crops were washed with a little cold pentane to furnish *[(1R,4S,4aS,5aR,6R,9S,9aS,10aR)] 1,4 : 6,9 - diisopropano - 4a,9a - dimethoxy - 1,6 - dimethylperhydrodibenzodioxin* **165** as colourless crystals (8.64g,41%); **MP** = 149-150^{0}C (lit[145] = 149-150^{0}C); $[\alpha]_D^{22}$ = +178.0^0 (c = 5.06, EtOH:CH_2Cl_2 (8:1)) (lit[145] = +174.2^0); **^{1}H NMR** (360 MHz,$CDCl_3$) δ 3.35-3.34 (1H,t,*J* = 1.2 Hz,HCO),3.18 (3H,s,OCH_3),2.12-2.11 (1H,dd,*J* = 4.5 and 1.5 Hz,bridgehead CH),1.96-1.89 (1H,ddd,*J* = 11.8,9.5 and 4.6 Hz),1.87-1.80 (1H,ddd,*J* = 12.1,9.7 and 3.3 Hz),1.56-1.47 (1H,tt,*J* = 11.7 and 4.3 Hz),1.17-1.09 (1H,tdd,*J* = 12.2,3.7 and 1.5 Hz), 1.02 (3H,s,CH_3), 0.88 (3H,s,CH_3), 0.85 (3H,s,CH_3) ppm; **^{13}C NMR** (90.56 MHz,$CDCl_3$) δ 102.01(quat C),78.38(CHO),49.39(quatC),49.31(OCH_3), 48.75(CH),45.07 (quatC),26.36(CH_2),21.26(CH_2),20.33(CH_3),19.37(CH_3),

13.70(CH_3) ppm; **IR** (nujol) ν_{max}1462,1394,1352,1335,1310,1245,1205, 1115,1052 cm^{-1}; **MS** (ei) 364(2%,M^+),166(base),151(23),138(59),123(21); **Accurate mass**, Found : 364.2594; $C_{22}H_{36}O_4$ requires 364.26134; Found : 166.1371; $C_{11}H_{18}O$ requires 166.13576.For full assignments of ^1H and ^{13}C spectra (including HETCOR spectrum) see Chapter 7.

The experiment was repeated with racemic *endo*-2-hydroxyepicamphor (3.4g,20mmol), which furnished a crystalline solid (1.41g,38%) shown to have identical ^1H and ^{13}C NMR spectra to the chirally pure molecule; **MP** = 127-133^{0}C (lit[145] = 133-134^{0}C); $[\alpha]_D^{21}$ = +0.22^0 (*i.e.* racemic) (c = 5,EtOH:CH_2Cl_2 (8:1)).

8.4 Regeneration of (160) from Manasse's dimer (165)

To Manasse's dimer (10g,27.5mmol) was added concentrated hydrochloric acid (*ca.* 15ml,5eq).The resulting suspension was stirred gently at room temperature for 2.5 hours before a further portion of concentrated hydrochloric acid (7.5ml,2.5eq) was added and the mixture was stirred overnight.After this period,the dimer had completely dissolved and the solution was neutralised and raised to pH 8 by the *careful* (copious carbon dioxide gas evolved) addition of powdered sodium carbonate, with stirring.The solution was saturated with sodium chloride and extracted with methylene chloride (3 x *ca.* 150ml).The combined extracts were dried over sodium sulphate,filtered and evaporated to yield **160** as a foamy solid (9.14g,99%); **MP** = 219^{0}C (from *n*hexane (lit[143] = 221^{0}C)); **^1H NMR** (200 MHz,$CDCl_3$) δ 3.83 (1H,bs,OH),3.10 (1H,bs,C<u>H</u>OH),2.26-2.23 (1H, dd,*J* = 4.1 and 1.0 Hz,bridgehead CH),2.05-1.88 (2H,cm),1.46-1.28 (2H, cm),1.02 (3H,s,CH_3),0.95 (3H,s,CH_3),0.90 (3H,s,CH_3) ppm; **^{13}C NMR** (50.3 MHz,$CDCl_3$) δ 219.60 (C=O),78.43(<u>C</u>HOH),59.29(CH),50.05(quat C), 42.84(quat C),24.84(CH_2),24.36(CH_2),19.12(CH_3),17.67(CH_3),12.68(CH_3) ppm; **IR** (nujol) ν_{max} 3430 (OH),1745(C=O),1284,1170,1084 cm^{-1}; **MS** (ei) 169(4%,$^{12}C_9{}^{13}CH_{16}O_2^+$),168(31,$M^+$),154(8),153(9),136(8),109(14),108(12), 97(8),95(32),84(19),83(38),82(8),70(base),69(45),55(42)43(82),41(84); **Accurate mass**, Found : 168.1153; $C_{10}H_{16}O_2$ requires 168.11502.

8.4.5 Re-oxidation of (161) to camphorquinone.

This was achieved by adopting the method of Szarek *et al*[157].

To a solution of **161** (5.47g,33mmol) in DMSO (*ca.* 25ml) was added acetic anhydride (*ca.* 30ml).The resulting mixture was heated at 120^{0}C for *ca.*

3 $^{3}/_{4}$ hours whereupon thin layer chromatography (1:1 *n*hexane : diethyl ether) showed that no starting material was present.Water (*ca.* 30ml) was added and the mixture extracted with ethyl acetate (2 x *ca.* 70ml).The combined extracts were washed with water (*ca.* 30ml),dried for an extended period over magnesium sulphate,filtered and the dimethyl sulphide and solvents were removed *in vacuo*, to yield camphorquinone (5.47g,quantitative).The reaction was repeated on a 42.28g scale and the combined products from both reactions were recrystallised from ethanol, yielding a yellow crystalline solid (31.67g,67%).

8.5 Acylation of *endo*-2-hydroxyepicamphor with acetic anhydride in the presence of DMAP.

This was achieved by adopting the literature conditions of Wilson and Price[158].To a solution of **160** (5g,30mmol) in methylene chloride (*ca.* 20ml) was added acetic anhydride (5.69ml,6.14g,60mmol,2eq) and triethylamine (8.38ml,6.08g,60mmol,2eq) at room temperature.To the resulting mixture was added DMAP (0.37g,3.03mmol,0.1eq) which caused an exothermic reaction to occur.Stirring was continued at room temperature for a further 3.5 hours before the reaction was quenched with dilute hydrochloric acid (*ca.* 0.1M,*ca.* 10ml).The mixture was allowed to stir for *ca.* 10 minutes before being extracted with methylene chloride (3 x *ca.* 75ml).The combined organic extracts were washed with saturated aqueous sodium bicarbonate solution,dried over sodium sulphate,filtered and evaporated to yield *endo 2-acetoxyepicamphor* as a yellow oil which crystallised on standing (6.30g,100%); **MP** = 58.5-59.5^{0}C (lit[147] = 61-62^{0}C); **^{1}H NMR** (200 MHz,$CDCl_3$) δ 5.19-5.18 (1H,d,*J* = 0.9 Hz, C<u>H</u>OCOCH$_3$),2.30-2.27 (1H,d,*J* = 4.8 Hz,bridgehead CH),2.19-1.81 (2H,cm) superimposed on 2.12 (3H,s,C<u>H</u>$_3$CO),1.52-1.37 (2H,cm),0.99-0.96 (9H,2 x s,3 x CH_3) ppm; **^{13}C NMR** (50.3 MHz,$CDCl_3$) δ 212.54 (C=O), 170.10 (C=O),78.48(H<u>C</u>OCOCH$_3$),59.21(CH),49.81(quat C),43.13(quat C), 26.05(CH_2),23.84(CH_2),20.44(<u>C</u>H$_3$CO),19.21(CH_3),17.51(CH_3),12.77(CH_3) ppm; **IR** (nujol) ν_{max} 1760(b,2 x C=O),1370,1228,1062,1015 cm^{-1}; **MS** (ei) 211(3%,$^{12}C_{11}{}^{13}CH_{18}O_3^+$),210(15,$M^+$),168(26),153(7),123(25),122(11), 113(11),107(7),95(9),81(16),71(17),70(21),69(16),55(8),43(base,CH_3CO^+), 41(17); **Accurate mass**, Found : 210.1256; $C_{12}H_{18}O_3$ requires 210.12559.

8.5.5 Preparation of the Na/Hg amalgam.

This used the amounts specified by Theoren[147].

A glove bag, which contained a conical flask filled with mercury metal (1546g,7.71moles,3.9eq) and also a vessel which contained freshly washed sodium metal (*ca.* 45g,1.96moles),was evacuated and purged with nitrogen several times.SMALL pieces of sodium metal were added (*CAUTION*: a latent period occurs,afterwhich a violent exothermic reaction occurs) with gentle swirling; pauses were required to allow the sodium to react before more was added.As the sodium reacted, the mercury vapour which formed needed to be removed by high vacuum pump, followed by a nitrogen purge.The sodium took *ca.* 30 minutes to add in total,during which time the flask became *very* hot (*ca.* 200-300^{0}C) but the sodium could be added in larger amounts and more frequently as the reaction proceeded.The amalgam was then allowed to cool under a nitrogen atmosphere.The resulting solid amalgam was then stored under an argon atmosphere in a glove box.

8.6 Attempted formation of epicamphor (154) by reduction of *endo* 2-acetoxyepicamphor with Na/Hg amalgam.

This was achieved by adaptation of the literature procedures of Bredt *et* al[159] and Holleman[152].

A solution of *endo* 2-acetoxyepicamphor (4.87g,23mmol) in ethanol (95%, *ca.*100ml) was added to Na/Hg amalgam (prepared in section 8.5.5) (187.31g,838mmol,36eq).Heating with a hot plate and bunsen burner was required to melt the amalgam,then a large stirrer bar was added to stir the solution above the amalgam.Water (2 x *ca.* 20ml) was added and the the vigourous stirring was continued (using hot plate heating to keep the amalgam molten) for five hours.The solution was then allowed to cool and stood overnight.TLC analysis showed that the starting material had all been consumed, but a more polar material was present.The aqueous ethanolic solution was decanted and the mercury residue washed with several portions of ethanol.The combined ethanolic extracts were concentrated *in vacuo* and extracted with methylene chloride (3 x *ca.* 80ml).The combined layers were washed with saturated aqueous sodium chloride solution,dried over magnesium sulphate,filtered and evaporated to yield a white,camphor smelling solid (2.36g,67%).60 MHz ^{1}H NMR

spectroscopy revealed that all of the acetate group had been consumed, with only traces of hydroxy compound remaining.
The reaction was repeated on a 38.60g scale,which yielded a further 27.94g, giving a combined yield of 30.3g.The combined crude material was purified by flash chromatography (350g SiO_2) using *n*hexane : diethyl ether (4:1) as elution solvent and yielded a white camphor smelling solid which could not be detected by U.V. or charring (16.40g,52%).Analysis by ^1H NMR spectroscopy showed that both camphor and epicamphor were present in a respective ratio of 58:42.Further elution using *n*hexane : diethyl ether yielded a white solid (5.50g) which was shown to be unreacted 3-hydroxy camphor.Elution with *n*hexane : diethyl ether (1:1 to 0:100) yielded a third fraction (2.14g) tentatively assigned as the 2,3 diol.The camphor and epicamphor so-formed could not be separated by analytical reverse phase HPLC using gradient elution with water (including 0.1% trifluoroacetic acid) : acetonitrile as the solvent system.

8.6.5 Attempted formation of the (1S)-amino-2-methoxymethylpyrrolidine (SAMP) imines of camphor and epicamphor.

This was conducted using the literature procedures of Enders *et al*[51,160].
To a solution of SAMP (0.97g,7.45mmol) in benzene (*ca.* 10ml) was added a solution of a mixture of camphor and epicamphor (1.19g,7.83mmol, 1.05eq) in benzene (*ca.* 10ml).The resulting solution was heated at *ca.* 65^0C for 19 hours afterwhich time TLC showed that only unreacted epicamphor and SAMP were present amongst traces of other products. The mixture was heated under reflux using a Dean-Stark apparatus for 41 hours,Before dry 4A molecular sieves were added and boiling was continued overnight.No change in the TLC chromatograph could be detected and the benzene was removed *in vacuo* and toluene (*ca.* 40 ml) was added.The mixture was heated to,and maintained at,110^0C for 4 days before being filtered through celite.The mixture was concentrated *in vacuo* and purified by flash chromatography (80g SiO_2) using *n*hexane : diethyl ether (95:5) as elution solvent to yield unreacted starting material (1.01g,85% recovery).

8.7 Attempted reaction of racemic camphor with racemic *exo*-2-aminonorbornane.

To a solution of racemic camphor (1g,6.58mmol) in toluene (*ca.* 30ml) was added racemic *exo*-2-aminonorbornane (0.696g,6.27mmol) in toluene (*ca.* 5ml).The resulting mixture was stirred at room temperature for 1 hour 40 minutes before TLC revealed that no product had formed.The mixture was then heated at 70^0C for 19 hours before TLC showed that only a trace of compund had formed.Dry 4A molecular sieves were added to the reaction and heating was continued for *ca.* 1 day before the mixture was filtered through celite.The toluene was removed *in vacuo* and water (*ca.*. 20ml) was added.The aqueous layer was extracted with methylene chloride (3 x *ca.* 40ml) and the combined extracts were dried over magnesium sulphate,filtered and evaporated to yield a yellow oil (1.65g). The residue was purified by column chromatography (80g SiO_2) (using *n*hexane : diethyl ether and gradient elution 100:0 to 35:15),yielding an orange oil (0.012g,0.7%); high field electron impact mass spectrometry suggested that the product could be in this oil, Found : 245.2143; $C_{17}H_{27}N$ requires 245.21434.

8.8 α-hydroximination of racemic camphor.

To a solution of freshly prepared LDA (0.969g,7.88mmol,1.2eq) (prepared according to the general procedure described in section 4.1.1) in dry THF (*ca.* 10ml) at -78^0C under argon, was added dropwise a solution of racemic camphor (1g,6.57mmol) in dry THF (*ca.* 10ml).The resulting solution was stirred at -78^0C for 45 minutes before amyl nitrite (90%, 0.77g,6.58mmol,1eq) in dry THF (*ca.* 10ml) was added.The resulting deep yellow solution was stirred at -78^0C for 20 minutes before being warmed to 0^0C and stirred for a further 55 minutes.TLC analysis showed that some product had formed and the reaction was allowed to warm to room temperature and stirred overnight.The reaction was quenched with pH 7 phosphate buffer, and dilute acetic acid was used to lower the pH from 14 to 7.The mixture was extracted with methylene chloride (3 x *ca.* 50ml) and the combined extracts were washed with saturated aqueous sodium chloride solution,dried over magnesium sulphate,filtered and evaporated to yield a yellow oil (2.13g).The excess of the amyl alcohol formed was removed by kugelrohr distillation (100^0C/10mmHg) but the product could not be crystallised from a mixture of methylene chloride : diisopropyl

ether. Purification by column chromatography (80g SiO_2) using *n*hexane : diethyl ether with gradient elution (100:0 to 3:1) yielded *3-hydroximinocamphor* as a colourless solid (0.478g,41%); **MP** = 118-134^{0}C (*syn* and *anti* isomers); **^{1}H NMR** (200 MHz,$CDCl_3$) δ 10.25 (1H,bs, C=N-O<u>H</u>),3.20-3.18 (1H,d,*J* = 4.4 Hz,bridgehead CH),2.02-1.89 (1H, cm),1.75-1.71 (1H,t,*J* = 9.0 Hz),1.54-1.40 (2H,ABq,*J* = 8.8 Hz),0.93 (3H,s,CH_3),0.92 (3H,s,CH_3),0.79 (3H,s,CH_3) ppm; **^{13}C NMR** (50.3 MHz, $CDCl_3$) δ 204.26 (C=O),159.19 (C=N),58.20(quat C),46.30(CH),44.61 (quat C),30.35(CH_2),23.42(CH_2),20.36(CH_3),17.30(CH_3),8.60(CH_3) ppm; **IR** (nujol) ν_{max} 3419 (OH),1741 (C=N),1642 (C=O),1000,927,885 cm^{-1}; **Accurate mass** (FAB), Found : 182.11809; $C_{10}H_{16}NO_2$ (M+H) requires 182.11810.

APPENDICES

Appendix 1

X-Ray Crystal Structure of Chirabornox

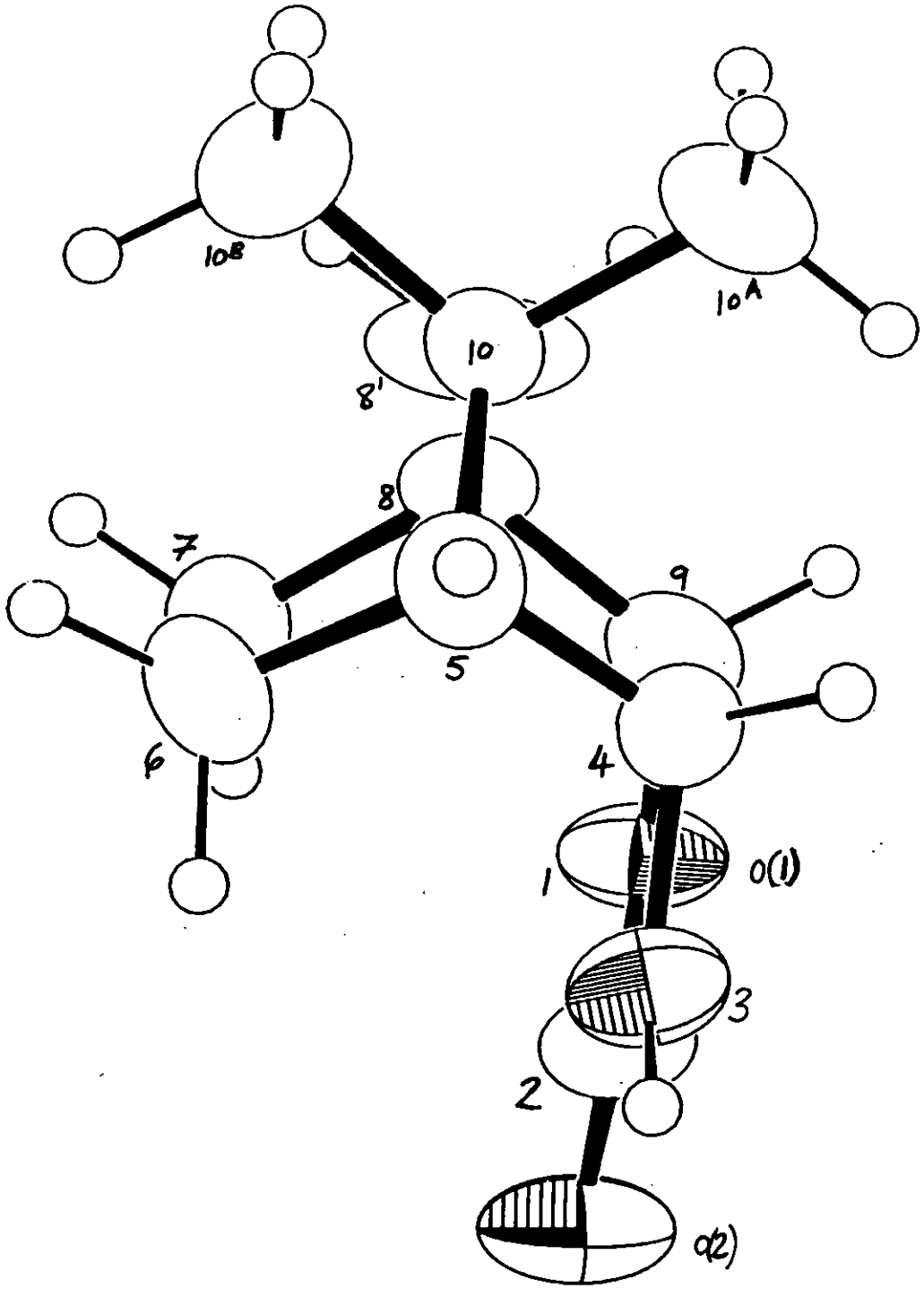


Table 1. Bond Lengths(Å), angles(degrees) and torsion angles(degrees) with standard deviations

O(1) - C(2)	1.369(8)	C(5) -C(10)	1.561(8)
O(1) - C(9)	1.443(8)	C(6) - C(7)	1.552(9)
C(2) - O(2)	1.211(9)	C(7) - C(8)	1.548(9)
C(2) - N(3)	1.330(9)	C(8) -C(8A)	1.535(9)
N(3) - C(4)	1.470(8)	C(8) - C(9)	1.525(8)
C(4) - C(5)	1.520(8)	C(8) -C(10)	1.568(8)
C(4) - C(9)	1.535(8)	C(10) -C(10A)	1.551(9)
C(5) - C(6)	1.540(9)	C(10) -C(10B)	1.517(9)

C(2) - O(1) - C(9)	109.2(5)	C(7) - C(8) - C(9)	107.2(5)
O(1) - C(2) - O(2)	120.4(6)	C(7) - C(8) -C(10)	100.9(5)
O(1) - C(2) - N(3)	109.8(6)	C(8A) - C(8) - C(9)	115.4(5)
O(2) - C(2) - N(3)	129.7(7)	C(8A) - C(8) -C(10)	116.4(5)
C(2) - N(3) - C(4)	113.9(6)	C(9) - C(8) -C(10)	100.4(5)
N(3) - C(4) - C(5)	118.0(5)	O(1) - C(9) - C(4)	106.9(5)
N(3) - C(4) - C(9)	99.9(5)	O(1) - C(9) - C(8)	114.4(5)
C(5) - C(4) - C(9)	103.4(5)	C(4) - C(9) - C(8)	104.5(5)
C(4) - C(5) - C(6)	109.3(5)	C(5) -C(10) - C(8)	93.0(4)
C(4) - C(5) -C(10)	101.4(5)	C(5) -C(10) -C(10A)	113.9(5)
C(6) - C(5) -C(10)	102.8(5)	C(5) -C(10) -C(10B)	114.5(5)
C(5) - C(6) - C(7)	101.6(5)	C(8) -C(10) -C(10A)	113.8(5)
C(6) - C(7) - C(8)	105.2(5)	C(8) -C(10) -C(10B)	114.7(5)
C(7) - C(8) -C(8A)	114.7(5)	C(10A)-C(10) -C(10B)	106.8(5)

C(9) - O(1) - C(2) - O(2)	175.4(6)	C(6) - C(5) -C(10) -C(10A)	-174.6(5)
C(9) - O(1) - C(2) - N(3)	-4.3(7)	C(6) - C(5) -C(10) -C(10B)	62.1(6)
C(2) - O(1) - C(9) - C(4)	2.4(6)	C(5) - C(6) - C(7) - C(8)	-1.7(6)
C(2) - O(1) - C(9) - C(8)	-112.7(6)	C(6) - C(7) - C(8) -C(8A)	-160.0(5)
O(1) - C(2) - N(3) - C(4)	4.6(8)	C(6) - C(7) - C(8) - C(9)	70.6(6)
O(2) - C(2) - N(3) - C(4)	-175.1(7)	C(6) - C(7) - C(8) -C(10)	-34.0(6)
C(2) - N(3) - C(4) - C(5)	108.3(7)	C(7) - C(8) - C(9) - O(1)	47.7(6)
C(2) - N(3) - C(4) - C(9)	-2.8(7)	C(7) - C(8) - C(9) - C(4)	-68.8(6)
N(3) - C(4) - C(5) - C(6)	-36.9(7)	C(8A) - C(8) - C(9) - O(1)	-81.3(7)
N(3) - C(4) - C(5) -C(10)	-145.0(5)	C(8A) - C(8) - C(9) - C(4)	162.1(5)
C(9) - C(4) - C(5) - C(6)	72.2(6)	C(10) - C(8) - C(9) - O(1)	152.7(5)
C(9) - C(4) - C(5) -C(10)	-35.9(5)	C(10) - C(8) - C(9) - C(4)	36.1(5)
N(3) - C(4) - C(9) - O(1)	0.1(6)	C(7) - C(8) -C(10) - C(5)	54.2(5)
N(3) - C(4) - C(9) - C(8)	121.7(5)	C(7) - C(8) -C(10) -C(10A)	172.0(5)
C(5) - C(4) - C(9) - O(1)	-122.0(5)	C(7) - C(8) -C(10) -C(10B)	-64.6(6)
C(5) - C(4) - C(9) - C(8)	-0.4(6)	C(8A) - C(8) -C(10) - C(5)	179.0(5)
C(4) - C(5) - C(6) - C(7)	-69.7(6)	C(8A) - C(8) -C(10) -C(10A)	-63.2(7)
C(10) - C(5) - C(6) - C(7)	37.4(6)	C(8A) - C(8) -C(10) -C(10B)	60.2(7)
C(4) - C(5) -C(10) - C(8)	56.2(5)	C(9) - C(8) -C(10) - C(5)	-55.8(5)
C(4) - C(5) -C(10) -C(10A)	-61.6(6)	C(9) - C(8) -C(10) -C(10A)	62.0(6)
C(4) - C(5) -C(10) -C(10B)	175.1(5)	C(9) - C(8) -C(10) -C(10B)	-174.5(5)
C(6) - C(5) -C(10) - C(8)	-56.9(5)		

Appendix 2

X-Ray Crystal Structure of the Major Acrylate/Cyclopentadiene Adduct

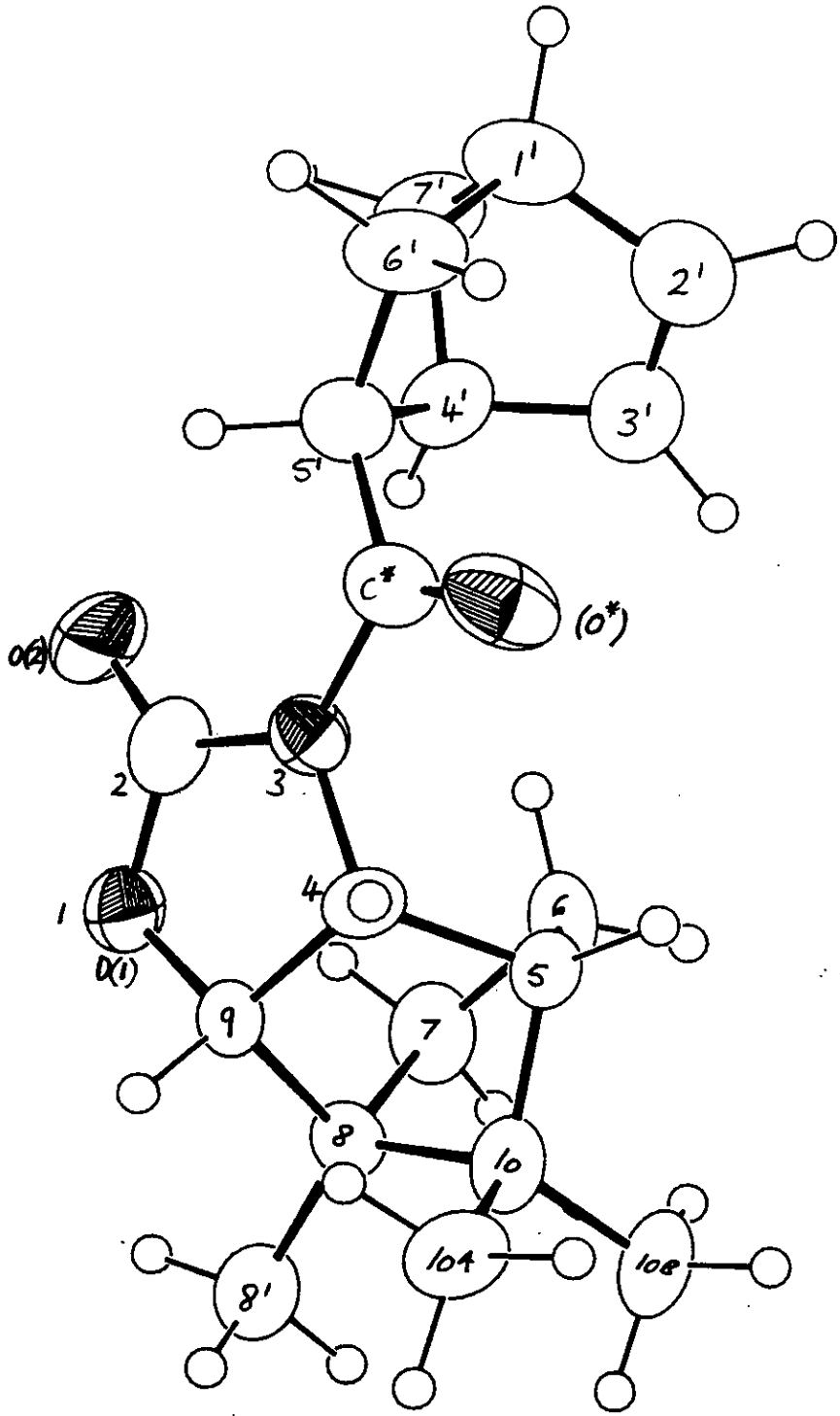


Table 1. Bond Lengths(Å) with standard deviations

O(1)	- C(2)	1.362(7)	O(1*)	-C(2*)	1.344(8)
O(1)	- C(9)	1.427(7)	O(1*)	-C(9*)	1.454(7)
C(2)	- O(2)	1.189(8)	C(2*)	-O(2*)	1.179(8)
C(2)	- N(3)	1.399(8)	C(2*)	-N(3*)	1.406(8)
N(3)	- C(4)	1.449(7)	N(3*)	-C(4*)	1.455(7)
N(3)	- C	1.407(8)	N(3*)	- C(*)	1.395(8)
C(4)	- C(5)	1.546(8)	C(4*)	-C(5*)	1.523(8)
C(4)	- C(9)	1.531(8)	C(4*)	-C(9*)	1.542(8)
C(5)	- C(6)	1.532(8)	C(5*)	-C(6*)	1.532(9)
C(5)	-C(10)	1.559(8)	C(5*)	-C(10*)	1.574(9)
C(6)	- C(7)	1.559(9)	C(6*)	-C(7*)	1.549(9)
C(7)	- C(8)	1.560(8)	C(7*)	-C(8*)	1.548(8)
C(8)	-C(8M)	1.500(8)	C(8*)	-C(8M*)	1.535(9)
C(8)	- C(9)	1.539(8)	C(8*)	-C(9*)	1.534(8)
C(8)	-C(10)	1.565(8)	C(8*)	-C(10*)	1.569(8)
C(10)	-C(10A)	1.531(9)	C(10*)	-C(0A*)	1.526(10)
C(10)	-C(10B)	1.533(9)	C(10*)	-C(0B*)	1.535(9)
C	- O	1.206(7)	C(*)	- O(*)	1.226(7)
C	-C(5')	1.495(8)	C(*)	-C(5'*)	1.501(8)
C(1')	-C(2')	1.517(10)	C(1'*)	-C(2'*)	1.512(10)
C(1')	-C(6')	1.553(9)	C(1'*)	-C(6'*)	1.544(9)
C(1')	-C(7')	1.525(9)	C(1'*)	-C(7'*)	1.531(10)
C(2')	-C(3')	1.304(10)	C(2'*)	-C(3'*)	1.329(10)
C(3')	-C(4')	1.504(9)	C(3'*)	-C(4'*)	1.506(9)
C(4')	-C(5')	1.576(9)	C(4'*)	-C(5'*)	1.570(9)
C(4')	-C(7')	1.545(9)	C(4'*)	-C(7'*)	1.508(9)
C(5')	-C(6')	1.557(8)	C(5'*)	-C(6'*)	1.583(9)

Table 2. Angles(°) with standard deviations

C(2)	- O(1) - C(9)	111.0(4)	C(2*)	-O(1*)	-C(9*)	112.8(5)
O(1)	- C(2) - O(2)	122.5(6)	O(1*)	-C(2*)	-O(2*)	122.9(6)
O(1)	- C(2) - N(3)	108.6(5)	O(1*)	-C(2*)	-N(3*)	107.8(5)
O(2)	- C(2) - N(3)	129.0(6)	O(2*)	-C(2*)	-N(3*)	129.3(6)
C(2)	- N(3) - C(4)	111.8(5)	C(2*)	-N(3*)	-C(4*)	112.5(5)
C(2)	- N(3) - C	128.1(5)	C(2*)	-N(3*)	- C(*)	127.3(5)
C(4)	- N(3) - C	119.9(5)	C(4*)	-N(3*)	- C(*)	120.2(5)
N(3)	- C(4) - C(5)	117.3(5)	N(3*)	-C(4*)	-C(5*)	117.3(5)
N(3)	- C(4) - C(9)	102.2(4)	N(3*)	-C(4*)	-C(9*)	102.3(4)
C(5)	- C(4) - C(9)	103.6(4)	C(5*)	-C(4*)	-C(9*)	103.2(5)
C(4)	- C(5) - C(6)	108.5(5)	C(4*)	-C(5*)	-C(6*)	109.4(5)
C(4)	- C(5) -C(10)	99.8(4)	C(4*)	-C(5*)	-C(10*)	100.9(5)
C(6)	- C(5) -C(10)	103.6(5)	C(6*)	-C(5*)	-C(10*)	102.8(5)
C(5)	- C(6) - C(7)	102.3(5)	C(5*)	-C(6*)	-C(7*)	103.4(5)
C(6)	- C(7) - C(8)	105.1(5)	C(6*)	-C(7*)	-C(8*)	103.5(5)
C(7)	- C(8) -C(8M)	114.7(5)	C(7*)	-C(8*)	-C(8M*)	115.8(5)
C(7)	- C(8) - C(9)	106.1(4)	C(7*)	-C(8*)	-C(9*)	109.0(5)
C(7)	- C(8) -C(10)	100.7(4)	C(7*)	-C(8*)	-C(10*)	102.6(5)
C(8M)	- C(8) - C(9)	115.1(5)	C(8M*)	-C(8*)	-C(9*)	112.0(5)
C(8M)	- C(8) -C(10)	118.2(5)	C(8M*)	-C(8*)	-C(10*)	116.4(5)
C(9)	- C(8) -C(10)	100.0(4)	C(9*)	-C(8*)	-C(10*)	99.5(4)
O(1)	- C(9) - C(4)	106.5(4)	O(1*)	-C(9*)	-C(4*)	104.7(4)
O(1)	- C(9) - C(8)	114.8(4)	O(1*)	-C(9*)	-C(8*)	113.7(5)
C(4)	- C(9) - C(8)	104.9(4)	C(4*)	-C(9*)	-C(8*)	104.1(5)
C(5)	-C(10) - C(8)	94.3(4)	C(5*)	-C(10*)	-C(8*)	92.2(4)
C(5)	-C(10) -C(10A)	114.8(5)	C(5*)	-C(10*)	-C(0A*)	112.8(5)
C(5)	-C(10) -C(10B)	113.2(5)	C(5*)	-C(10*)	-C(0B*)	114.3(5)
C(8)	-C(10) -C(10A)	112.4(5)	C(8*)	-C(10*)	-C(0A*)	114.2(5)
C(8)	-C(10) -C(10B)	113.2(5)	C(8*)	-C(10*)	-C(0B*)	114.3(5)
C(10A)	-C(10) -C(10B)	108.6(5)	C(0A*)	-C(10*)	-C(0B*)	108.5(5)
N(3)	- C - O	117.2(5)	N(3*)	- C(*)	- O(*)	115.5(5)
N(3)	- C -C(5')	118.2(5)	N(3*)	- C(*)	-C(5'*)	119.4(5)
O	- C -C(5')	124.5(5)	O(*)	- C(*)	-C(5'*)	125.0(5)
C(2')	-C(1') -C(6')	105.6(5)	C(2'*)	-C(1'*)	-C(6'*)	104.9(5)
C(2')	-C(1') -C(7')	98.7(5)	C(2'*)	-C(1'*)	-C(7'*)	99.0(5)
C(6')	-C(1') -C(7')	101.2(5)	C(6'*)	-C(1'*)	-C(7'*)	101.1(5)
C(1')	-C(2') -C(3')	108.7(6)	C(1'*)	-C(2'*)	-C(3'*)	108.9(6)
C(2')	-C(3') -C(4')	107.9(6)	C(2'*)	-C(3'*)	-C(4'*)	106.7(6)
C(3')	-C(4') -C(5')	107.2(5)	C(3'*)	-C(4'*)	-C(5'*)	105.7(5)
C(3')	-C(4') -C(7')	99.2(5)	C(3'*)	-C(4'*)	-C(7'*)	101.6(5)
C(5')	-C(4') -C(7')	99.4(5)	C(5'*)	-C(4'*)	-C(7'*)	97.9(5)
C	-C(5') -C(4')	112.4(5)	C(*)	-C(5'*)	-C(4'*)	115.1(5)
C	-C(5') -C(6')	114.7(5)	C(*)	-C(5'*)	-C(6'*)	112.2(5)
C(4')	-C(5') -C(6')	102.4(5)	C(4'*)	-C(5'*)	-C(6'*)	103.1(5)
C(1')	-C(6') -C(5')	103.2(5)	C(1'*)	-C(6'*)	-C(5'*)	101.7(5)
C(1')	-C(7') -C(4')	94.3(5)	C(1'*)	-C(7'*)	-C(4'*)	95.7(5)

Table 3. Torsion angles(degrees) with standard deviations

C(9)	O(1)	C(2)	O(2)	-179.0(6)	C(6')	C(1')	C(2')	C(3')	70.6(7)
C(9)	O(1)	C(2)	N(3)	1.2(6)	C(7')	C(1')	C(2')	C(3')	-33.7(7)
C(2)	O(1)	C(9)	C(4)	-2.1(6)	C(2')	C(1')	C(6')	C(5')	-67.8(6)
C(2)	O(1)	C(9)	C(8)	-117.6(5)	C(7')	C(1')	C(6')	C(5')	34.7(6)
O(1)	C(2)	N(3)	C(4)	0.2(6)	C(2')	C(1')	C(7')	C(4')	50.1(5)
O(1)	C(2)	N(3)	C	-174.8(5)	C(6')	C(1')	C(7')	C(4')	-57.8(5)
O(2)	C(2)	N(3)	C(4)	-179.6(6)	C(1')	C(2')	C(3')	C(4')	0.0(8)
O(2)	C(2)	N(3)	C	5.5(10)	C(2')	C(3')	C(4')	C(5')	-69.6(7)
C(2)	N(3)	C(4)	C(5)	111.0(6)	C(2')	C(3')	C(4')	C(7')	33.3(7)
C(2)	N(3)	C(4)	C(9)	-1.4(6)	C(3')	C(4')	C(5')	C	-58.8(6)
C	N(3)	C(4)	C(5)	-73.5(7)	C(3')	C(4')	C(5')	C(6')	64.8(6)
C	N(3)	C(4)	C(9)	174.1(5)	C(7')	C(4')	C(5')	C	-161.6(5)
C(2)	N(3)	C	O	171.1(6)	C(7')	C(4')	C(5')	C(6')	-38.0(5)
C(2)	N(3)	C	C(5')	-12.7(9)	C(3')	C(4')	C(7')	C(1')	-50.7(5)
C(4)	N(3)	C	O	-3.5(8)	C(5')	C(4')	C(7')	C(1')	58.6(5)
C(4)	N(3)	C	C(5')	172.7(5)	C	C(5')	C(6')	C(1')	124.5(5)
N(3)	C(4)	C(5)	C(6)	-40.8(6)	C(4')	C(5')	C(6')	C(1')	2.4(6)
N(3)	C(4)	C(5)	C(10)	-148.8(5)	C(9*)	O(1*)	C(2*)	O(2*)	-179.0(6)
C(9)	C(4)	C(5)	C(6)	70.8(5)	C(9*)	O(1*)	C(2*)	N(3*)	-0.1(7)
C(9)	C(4)	C(5)	C(10)	-37.2(5)	C(2*)	O(1*)	C(9*)	C(4*)	-0.7(6)
N(3)	C(4)	C(9)	O(1)	2.0(5)	C(2*)	O(1*)	C(9*)	C(8*)	-113.7(6)
N(3)	C(4)	C(9)	C(8)	124.0(4)	O(1*)	C(2*)	N(3*)	C(4*)	1.0(7)
C(5)	C(4)	C(9)	O(1)	-120.3(5)	O(1*)	C(2*)	N(3*)	C(*)	-176.5(5)
C(5)	C(4)	C(9)	C(8)	1.7(5)	O(2*)	C(2*)	N(3*)	C(4*)	179.8(6)
C(4)	C(5)	C(6)	C(7)	-70.6(5)	O(2*)	C(2*)	N(3*)	C(*)	2.3(11)
C(10)	C(5)	C(6)	C(7)	34.8(5)	C(2*)	N(3*)	C(4*)	C(5*)	110.7(6)
C(4)	C(5)	C(10)	C(8)	56.9(5)	C(2*)	N(3*)	C(4*)	C(9*)	-1.3(6)
C(4)	C(5)	C(10)	C(10A)	-60.2(6)	C(*)	N(3*)	C(4*)	C(5*)	-71.6(7)
C(4)	C(5)	C(10)	C(10B)	174.4(5)	C(*)	N(3*)	C(4*)	C(9*)	176.4(5)
C(6)	C(5)	C(10)	C(8)	-55.0(5)	C(2*)	N(3*)	C(*)	O(*)	176.1(6)
C(6)	C(5)	C(10)	C(10A)	-172.1(5)	C(2*)	N(3*)	C(*)	C(5'*)	-7.8(9)
C(6)	C(5)	C(10)	C(10B)	62.5(6)	C(4*)	N(3*)	C(*)	O(*)	-1.2(8)
C(5)	C(6)	C(7)	C(8)	0.0(6)	C(4*)	N(3*)	C(*)	C(5'*)	174.8(5)
C(6)	C(7)	C(8)	C(8M)	-162.2(5)	N(3*)	C(4*)	C(5*)	C(6*)	-39.7(7)
C(6)	C(7)	C(8)	C(9)	69.6(5)	N(3*)	C(4*)	C(5*)	C(10*)	-147.5(5)
C(6)	C(7)	C(8)	C(10)	-34.2(5)	C(9*)	C(4*)	C(5*)	C(6*)	71.9(6)
C(7)	C(8)	C(9)	O(1)	46.3(6)	C(9*)	C(4*)	C(5*)	C(10*)	-36.0(5)
C(7)	C(8)	C(9)	C(4)	-70.2(5)	N(3*)	C(4*)	C(9*)	O(1*)	1.2(5)
C(8M)	C(8)	C(9)	O(1)	-81.7(6)	N(3*)	C(4*)	C(9*)	C(8*)	120.8(5)
C(8M)	C(8)	C(9)	C(4)	161.9(5)	C(5*)	C(4*)	C(9*)	O(1*)	-121.0(5)
C(10)	C(8)	C(9)	O(1)	150.6(5)	C(5*)	C(4*)	C(9*)	C(8*)	-1.4(6)
C(10)	C(8)	C(9)	C(4)	34.2(5)	C(4*)	C(5*)	C(6*)	C(7*)	-70.2(6)
C(7)	C(8)	C(10)	C(5)	53.0(5)	C(10*)	C(5*)	C(6*)	C(7*)	36.4(6)
C(7)	C(8)	C(10)	C(10A)	172.1(5)	C(4*)	C(5*)	C(10*)	C(8*)	57.7(5)
C(7)	C(8)	C(10)	C(10B)	-64.5(6)	C(4*)	C(5*)	C(10*)	C(0A*)	175.2(5)
C(8M)	C(8)	C(10)	C(5)	178.8(5)	C(4*)	C(5*)	C(10*)	C(0B*)	-60.2(6)
C(8M)	C(8)	C(10)	C(10A)	-62.2(7)	C(6*)	C(5*)	C(10*)	C(8*)	-55.3(5)
C(8M)	C(8)	C(10)	C(10B)	61.3(7)	C(6*)	C(5*)	C(10*)	C(0A*)	62.2(6)
C(9)	C(8)	C(10)	C(5)	-55.6(5)	C(6*)	C(5*)	C(10*)	C(0B*)	-173.2(5)
C(9)	C(8)	C(10)	C(10A)	63.4(6)	C(5*)	C(6*)	C(7*)	C(8*)	-1.0(6)
C(9)	C(8)	C(10)	C(10B)	-173.1(5)	C(6*)	C(7*)	C(8*)	C(8M*)	-162.6(5)
N(3)	C	C(5')	C(4')	-77.3(7)	C(6*)	C(7*)	C(8*)	C(9*)	70.0(6)
N(3)	C	C(5')	C(6')	166.2(5)	C(6*)	C(7*)	C(8*)	C(10*)	-34.8(6)
O	C	C(5')	C(4')	98.5(7)	C(7*)	C(8*)	C(9*)	O(1*)	44.7(6)
O	C	C(5')	C(6')	-18.0(8)	C(7*)	C(8*)	C(9*)	C(4*)	-68.6(6)
C(8M*)	C(8*)	C(9*)	O(1*)	-84.8(6)	C(6'*)	C(1'*)	C(2'*)	C(3'*)	70.5(7)
C(8M*)	C(8*)	C(9*)	C(4*)	161.9(5)	C(7'*)	C(1'*)	C(2'*)	C(3'*)	-33.6(7)
C(10*)	C(8*)	C(9*)	O(1*)	151.6(5)	C(2'*)	C(1'*)	C(6'*)	C(5'*)	-70.0(6)
C(10*)	C(8*)	C(9*)	C(4*)	38.3(5)	C(7'*)	C(1'*)	C(6'*)	C(5'*)	32.5(6)
C(7*)	C(8*)	C(10*)	C(5*)	54.2(5)	C(2'*)	C(1'*)	C(7'*)	C(4'*)	48.5(6)
C(7*)	C(8*)	C(10*)	C(0A*)	-62.0(6)	C(6'*)	C(1'*)	C(7'*)	C(4'*)	-58.6(6)
C(7*)	C(8*)	C(10*)	C(0B*)	172.2(5)	C(1'*)	C(2'*)	C(3'*)	C(4'*)	2.7(8)
C(8M*)	C(8*)	C(10*)	C(5*)	-178.3(5)	C(2'*)	C(3'*)	C(4'*)	C(5'*)	-71.7(7)
C(8M*)	C(8*)	C(10*)	C(0A*)	65.4(7)	C(2'*)	C(3'*)	C(4'*)	C(7'*)	30.0(7)
C(8M*)	C(8*)	C(10*)	C(0B*)	-60.4(7)	C(3'*)	C(4'*)	C(5'*)	C(*)	-58.0(7)
C(9*)	C(8*)	C(10*)	C(5*)	-57.8(5)	C(3'*)	C(4'*)	C(5'*)	C(6'*)	64.6(6)
C(9*)	C(8*)	C(10*)	C(0A*)	-174.1(5)	C(7'*)	C(4'*)	C(5'*)	C(*)	-162.4(5)
C(9*)	C(8*)	C(10*)	C(0B*)	60.1(6)	C(7'*)	C(4'*)	C(5'*)	C(6'*)	-39.8(6)
N(3*)	C(*)	C(5'*)	C(4'*)	-75.8(7,	C(3'*)	C(4'*)	C(7'*)	C(1'*)	-48.2(6)
N(3*)	C(*)	C(5'*)	C(6'*)	166.6(5)	C(5'*)	C(4'*)	C(7'*)	C(1'*)	59.8(5)
O(*)	C(*)	C(5'*)	C(4'*)	99.8(7)	C(*)	C(5'*)	C(6'*)	C(1'*)	128.7(5)
O(*)	C(*)	C(5'*)	C(6'*)	-17.7(8)	C(4'*)	C(5'*)	C(6'*)	C(1'*)	4.2(6)

Appendix 3

X-Ray Crystal Structure of the Minor Acrylate/Cyclopentadiene Adduct

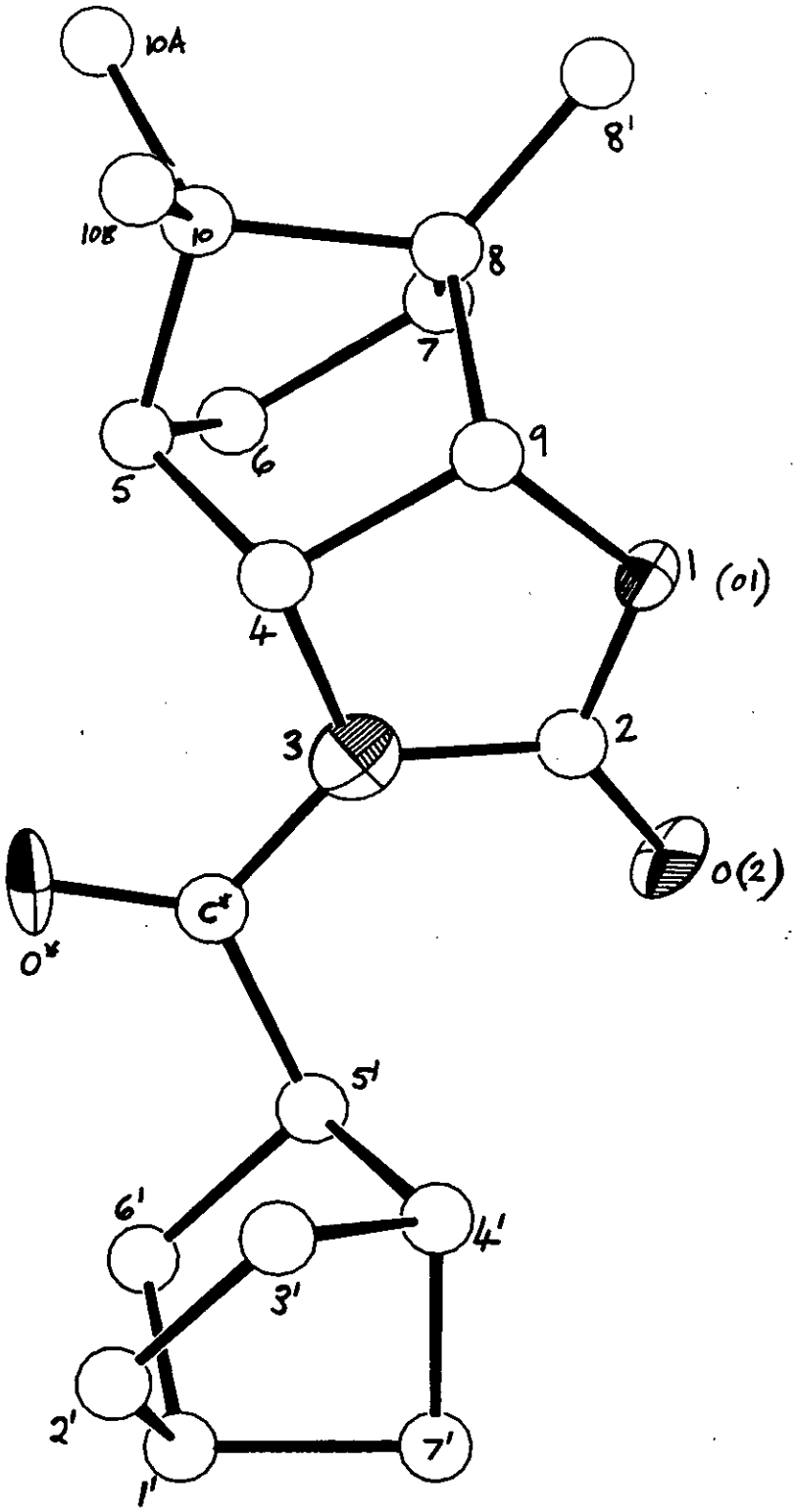


Table 1. Bond Lengths(Å) with standard deviations

O(1) - C(2)	1.341(6)	O(1*) -C(2*)	1.342(6)
O(1) - C(9)	1.448(5)	O(1*) -C(9*)	1.444(6)
C(2) - O(2)	1.207(6)	C(2*) -O(2*)	1.206(7)
C(2) - N(3)	1.379(5)	C(2*) -N(3*)	1.389(6)
N(3) - C(4)	1.464(5)	N(3*) -C(4*)	1.457(6)
N(3) - C	1.407(5)	N(3*) - C(*)	1.410(6)
C(4) - C(5)	1.535(6)	C(4*) -C(5*)	1.547(6)
C(4) - C(9)	1.520(6)	C(4*) -C(9*)	1.533(7)
C(5) - C(6)	1.534(7)	C(5*) -C(6*)	1.531(7)
C(5) -C(10)	1.541(7)	C(5*) -C(10*)	1.554(7)
C(6) - C(7)	1.533(8)	C(6*) -C(7*)	1.536(7)
C(7) - C(8)	1.550(7)	C(7*) -C(8*)	1.528(7)
C(8) -C(8M)	1.524(8)	C(8*) -C(8M*)	1.508(7)
C(8) - C(9)	1.537(6)	C(8*) -C(9*)	1.545(7)
C(8) -C(10)	1.563(7)	C(8*) -C(10*)	1.558(7)
C(10) -C(10A)	1.524(7)	C(10*)-C(0A*)	1.534(8)
C(10) -C(10B)	1.545(8)	C(10*)-C(0B*)	1.543(7)
C - O	1.215(6)	C(*) - O(*)	1.194(7)
C -C(5')	1.495(7)	C(*) -C(5'*)	1.507(7)
C(1') -C(2')	1.492(10)	C(1'*)-C(2'*)	1.497(8)
C(1') -C(6')	1.559(9)	C(1'*)-C(6'*)	1.549(8)
C(1') -C(7')	1.518(10)	C(1'*)-C(7'*)	1.519(8)
C(2') -C(3')	1.304(10)	C(2'*)-C(3'*)	1.305(8)
C(3') -C(4')	1.523(9)	C(3'*)-C(4'*)	1.504(7)
C(4') -C(5')	1.552(7)	C(4'*)-C(5'*)	1.569(7)
C(4') -C(7')	1.535(9)	C(4'*)-C(7'*)	1.506(7)
C(5') -C(6')	1.543(7)	C(5'*)-C(6'*)	1.546(7)

Table 2. Angles(°) with standard deviations

C(2)	- O(1) - C(9)	110.9(3)	C(2*)	-O(1*)	-C(9*)	111.5(4)
O(1)	- C(2) - O(2)	122.1(4)	O(1*)	-C(2*)	-O(2*)	122.6(5)
O(1)	- C(2) - N(3)	109.3(4)	O(1*)	-C(2*)	-N(3*)	108.9(4)
O(2)	- C(2) - N(3)	128.7(4)	O(2*)	-C(2*)	-N(3*)	128.4(5)
C(2)	- N(3) - C(4)	111.9(3)	C(2*)	-N(3*)	-C(4*)	111.8(4)
C(2)	- N(3) - C	128.2(3)	C(2*)	-N(3*)	- C(*)	128.2(4)
C(4)	- N(3) - C	119.8(3)	C(4*)	-N(3*)	- C(*)	119.9(4)
N(3)	- C(4) - C(5)	118.5(3)	N(3*)	-C(4*)	-C(5*)	118.8(4)
N(3)	- C(4) - C(9)	101.7(3)	N(3*)	-C(4*)	-C(9*)	101.9(4)
C(5)	- C(4) - C(9)	103.4(3)	C(5*)	-C(4*)	-C(9*)	104.0(4)
C(4)	- C(5) - C(6)	108.7(4)	C(4*)	-C(5*)	-C(6*)	107.6(4)
C(4)	- C(5) -C(10)	99.9(4)	C(4*)	-C(5*)	-C(10*)	99.0(4)
C(6)	- C(5) -C(10)	102.9(4)	C(6*)	-C(5*)	-C(10*)	101.9(4)
C(5)	- C(6) - C(7)	103.2(4)	C(5*)	-C(6*)	-C(7*)	104.3(4)
C(6)	- C(7) - C(8)	104.7(4)	C(6*)	-C(7*)	-C(8*)	104.4(4)
C(7)	- C(8) -C(8M)	115.4(4)	C(7*)	-C(8*)	-C(8M*)	115.3(4)
C(7)	- C(8) - C(9)	106.8(4)	C(7*)	-C(8*)	-C(9*)	107.4(4)
C(7)	- C(8) -C(10)	101.0(4)	C(7*)	-C(8*)	-C(10*)	101.4(4)
C(8M)	- C(8) - C(9)	114.8(4)	C(8M*)	-C(8*)	-C(9*)	113.3(4)
C(8M)	- C(8) -C(10)	117.6(4)	C(8M*)	-C(8*)	-C(10*)	118.2(4)
C(9)	- C(8) -C(10)	99.0(3)	C(9*)	-C(8*)	-C(10*)	99.4(4)
O(1)	- C(9) - C(4)	106.0(3)	O(1*)	-C(9*)	-C(4*)	105.5(4)
O(1)	- C(9) - C(8)	114.1(4)	O(1*)	-C(9*)	-C(8*)	113.8(4)
C(4)	- C(9) - C(8)	105.1(3)	C(4*)	-C(9*)	-C(8*)	104.4(4)
C(5)	-C(10) - C(8)	94.4(4)	C(5*)	-C(10*)	-C(8*)	94.9(4)
C(5)	-C(10) -C(10A)	114.7(4)	C(5*)	-C(10*)	-C(0A*)	113.4(4)
C(5)	-C(10) -C(10B)	113.0(4)	C(5*)	-C(10*)	-C(0B*)	113.9(4)
C(8)	-C(10) -C(10A)	114.6(4)	C(8*)	-C(10*)	-C(0A*)	113.0(4)
C(8)	-C(10) -C(10B)	113.5(4)	C(8*)	-C(10*)	-C(0B*)	115.2(4)
C(10A)	-C(10) -C(10B)	106.7(4)	C(0A*)	-C(10*)	-C(0B*)	106.3(4)
N(3)	- C - O	116.6(4)	N(3*)	- C(*)	- O(*)	117.2(5)
N(3)	- C -C(5')	118.3(4)	N(3*)	- C(*)	-C(5'*)	118.7(4)
O	- C -C(5')	124.9(4)	O(*)	- C(*)	-C(5'*)	124.0(5)
C(2')	-C(1') -C(6')	105.7(6)	C(2'*)	-C(1'*)	-C(6'*)	105.8(4)
C(2')	-C(1') -C(7')	100.4(6)	C(2'*)	-C(1'*)	-C(7'*)	99.9(4)
C(6')	-C(1') -C(7')	101.2(5)	C(6'*)	-C(1'*)	-C(7'*)	100.2(4)
C(1')	-C(2') -C(3')	107.9(6)	C(1'*)	-C(2'*)	-C(3'*)	108.5(5)
C(2')	-C(3') -C(4')	107.8(6)	C(2'*)	-C(3'*)	-C(4'*)	106.8(5)
C(3')	-C(4') -C(5')	105.3(4)	C(3'*)	-C(4'*)	-C(5'*)	106.2(4)
C(3')	-C(4') -C(7')	98.6(5)	C(3'*)	-C(4'*)	-C(7'*)	100.6(4)
C(5')	-C(4') -C(7')	101.2(4)	C(5'*)	-C(4'*)	-C(7'*)	100.5(4)
C	-C(5') -C(4')	111.8(4)	C(*)	-C(5'*)	-C(4'*)	112.9(4)
C	-C(5') -C(6')	112.2(4)	C(*)	-C(5'*)	-C(6'*)	113.1(4)
C(4')	-C(5') -C(6')	102.8(4)	C(4'*)	-C(5'*)	-C(6'*)	101.6(4)
C(1')	-C(6') -C(5')	102.6(5)	C(1'*)	-C(6'*)	-C(5'*)	103.2(4)
C(1')	-C(7') -C(4')	93.7(5)	C(1'*)	-C(7'*)	-C(4'*)	94.1(4)

Table 3. Torsion angles(degrees) with standard deviations

C(9) - O(1) - C(2) - O(2)	177.3(4)	C(6') -C(1') -C(2') -C(3')	-71.3(7)
C(9) - O(1) - C(2) - N(3)	-1.3(5)	C(7') -C(1') -C(2') -C(3')	33.6(8)
C(2) - O(1) - C(9) - C(4)	-1.7(5)	C(2') -C(1') -C(6') -C(5')	67.5(6)
C(2) - O(1) - C(9) - C(8)	-116.8(4)	C(7') -C(1') -C(6') -C(5')	-36.7(6)
O(1) - C(2) - N(3) - C(4)	3.9(5)	C(2') -C(1') -C(7') -C(4')	-51.1(6)
O(1) - C(2) - N(3) - C	-172.0(3)	C(6') -C(1') -C(7') -C(4')	57.4(5)
O(2) - C(2) - N(3) - C(4)	-174.5(5)	C(1') -C(2') -C(3') -C(4')	0.6(8)
O(2) - C(2) - N(3) - C	9.6(7)	C(2') -C(3') -C(4') -C(5')	70.3(6)
C(2) - N(3) - C(4) - C(5)	107.8(4)	C(2') -C(3') -C(4') -C(7')	-34.0(7)
C(2) - N(3) - C(4) - C(9)	-4.7(4)	C(3') -C(4') -C(5') - C	53.9(5)
C - N(3) - C(4) - C(5)	-75.9(5)	C(3') -C(4') -C(5') -C(6')	-66.7(5)
C - N(3) - C(4) - C(9)	171.6(3)	C(7') -C(4') -C(5') - C	156.1(4)
C(2) - N(3) - C - O	-173.7(4)	C(7') -C(4') -C(5') -C(6')	35.5(5)
C(2) - N(3) - C -C(5')	11.0(6)	C(3') -C(4') -C(7') -C(1')	50.4(5)
C(4) - N(3) - C - O	10.6(6)	C(5') -C(4') -C(7') -C(1')	-57.2(5)
C(4) - N(3) - C -C(5')	-164.7(4)	C -C(5') -C(6') -C(1')	-119.8(5)
N(3) - C(4) - C(5) - C(6)	-41.6(5)	C(4') -C(5') -C(6') -C(1')	0.4(5)
N(3) - C(4) - C(5) -C(10)	-149.0(3)	C(9*) -O(1*) -C(2*) -O(2*)	178.5(5)
C(9) - C(4) - C(5) - C(6)	69.9(4)	C(9*) -O(1*) -C(2*) -N(3*)	0.2(5)
C(9) - C(4) - C(5) -C(10)	-37.5(4)	C(2*) -O(1*) -C(9*) -C(4*)	-3.8(5)
N(3) - C(4) - C(9) - O(1)	3.7(4)	C(2*) -O(1*) -C(9*) -C(8*)	-117.7(4)
N(3) - C(4) - C(9) - C(8)	124.8(3)	O(1*) -C(2*) -N(3*) -C(4*)	3.8(5)
C(5) - C(4) - C(9) - O(1)	-119.7(4)	O(1*) -C(2*) -N(3*) - C(*)	-172.4(4)
C(5) - C(4) - C(9) - C(8)	1.4(4)	O(2*) -C(2*) -N(3*) -C(4*)	-174.3(5)
C(4) - C(5) - C(6) - C(7)	-70.5(5)	O(2*) -C(2*) -N(3*) - C(*)	9.4(9)
C(10) - C(5) - C(6) - C(7)	34.8(5)	C(2*) -N(3*) -C(4*) -C(5*)	107.7(5)
C(4) - C(5) -C(10) - C(8)	57.6(4)	C(2*) -N(3*) -C(4*) -C(9*)	-5.8(5)
C(4) - C(5) -C(10) -C(10A)	-62.0(5)	C(*) -N(3*) -C(4*) -C(5*)	-75.7(5)
C(4) - C(5) -C(10) -C(10B)	175.4(4)	C(*) -N(3*) -C(4*) -C(9*)	170.8(4)
C(6) - C(5) -C(10) - C(8)	-54.4(4)	C(2*) -N(3*) - C(*) - O(*)	-172.9(5)
C(6) - C(5) -C(10) -C(10A)	-174.0(4)	C(2*) -N(3*) - C(*) -C(5'*)	10.5(7)
C(6) - C(5) -C(10) -C(10B)	63.5(5)	C(4*) -N(3*) - C(*) - O(*)	11.1(7)
C(5) - C(6) - C(7) - C(8)	0.0(5)	C(4*) -N(3*) - C(*) -C(5'*)	-165.4(4)
C(6) - C(7) - C(8) -C(8M)	-161.9(4)	N(3*) -C(4*) -C(5*) -C(6*)	-43.9(5)
C(6) - C(7) - C(8) - C(9)	69.1(5)	N(3*) -C(4*) -C(5*) -C(10*)	-149.5(4)
C(6) - C(7) - C(8) -C(10)	-34.0(5)	C(9*) -C(4*) -C(5*) -C(6*)	68.4(4)
C(7) - C(8) - C(9) - O(1)	45.6(5)	C(9*) -C(4*) -C(5*) -C(10*)	-37.3(4)
C(7) - C(8) - C(9) - C(4)	-70.1(4)	N(3*) -C(4*) -C(9*) -O(1*)	5.6(4)
C(8M) - C(8) - C(9) - O(1)	-83.8(5)	N(3*) -C(4*) -C(9*) -C(8*)	125.8(4)
C(8M) - C(8) - C(9) - C(4)	160.6(4)	C(5*) -C(4*) -C(9*) -O(1*)	-118.5(4)
C(10) - C(8) - C(9) - O(1)	150.1(4)	C(5*) -C(4*) -C(9*) -C(8*)	1.8(4)
C(10) - C(8) - C(9) - C(4)	34.4(4)	C(4*) -C(5*) -C(6*) -C(7*)	-70.8(4)
C(7) - C(8) -C(10) - C(5)	53.2(4)	C(10*)-C(5*) -C(6*) -C(7*)	32.8(5)
C(7) - C(8) -C(10) -C(10A)	172.9(4)	C(4*) -C(5*) -C(10*)-C(8*)	57.5(4)
C(7) - C(8) -C(10) -C(10B)	-64.2(5)	C(4*) -C(5*) -C(10*)-C(0A*)	175.3(4)
C(8M) - C(8) -C(10) - C(5)	179.7(4)	C(4*) -C(5*) -C(10*)-C(0B*)	-62.9(5)
C(8M) - C(8) -C(10) -C(10A)	-60.6(6)	C(6*) -C(5*) -C(10*)-C(8*)	-52.7(4)
C(8M) - C(8) -C(10) -C(10B)	62.3(6)	C(6*) -C(5*) -C(10*)-C(0A*)	65.0(5)
C(9) - C(8) -C(10) - C(5)	-56.0(4)	C(6*) -C(5*) -C(10*)-C(0B*)	-173.2(4)
C(9) - C(8) -C(10) -C(10A)	63.6(5)	C(5*) -C(6*) -C(7*) -C(8*)	1.6(5)
C(9) - C(8) -C(10) -C(10B)	-173.4(4)	C(6*) -C(7*) -C(8*) -C(8M*)	-164.1(4)
N(3) - C -C(5') -C(4')	70.0(5)	C(6*) -C(7*) -C(8*) -C(9*)	68.6(4)
N(3) - C -C(5') -C(6')	-175.1(4)	C(6*) -C(7*) -C(8*) -C(10*)	-35.2(4)
O - C -C(5') -C(4')	-104.9(5)	C(7*) -C(8*) -C(9*) -O(1*)	43.6(5)
O - C -C(5') -C(6')	10.0(7)	C(7*) -C(8*) -C(9*) -C(4*)	-70.9(4)
C(8M*)-C(8*) -C(9*) -O(1*)	-84.8(5)	C(6'*)-C(1'*)-C(2'*)-C(3'*)	-71.0(6)
C(8M*)-C(8*) -C(9*) -C(4*)	160.7(4)	C(7'*)-C(1'*)-C(2'*)-C(3'*)	32.6(6)
C(10*)-C(8*) -C(9*) -O(1*)	148.8(4)	C(2'*)-C(1'*)-C(6'*)-C(5'*)	66.9(5)
C(10*)-C(8*) -C(9*) -C(4*)	34.3(4)	C(7'*)-C(1'*)-C(6'*)-C(5'*)	-36.5(5)
C(7*) -C(8*) -C(10*)-C(5*)	53.6(4)	C(2'*)-C(1'*)-C(7'*)-C(4'*)	-49.4(5)
C(7*) -C(8*) -C(10*)-C(0A*)	-64.5(5)	C(6'*)-C(1'*)-C(7'*)-C(4'*)	58.8(4)
C(7*) -C(8*) -C(10*)-C(0B*)	173.0(4)	C(1'*)-C(2'*)-C(3'*)-C(4'*)	0.3(6)
C(8M*)-C(8*) -C(10*)-C(5*)	-179.4(4)	C(2'*)-C(3'*)-C(4'*)-C(5'*)	70.9(5)
C(8M*)-C(8*) -C(10*)-C(0A*)	62.6(6)	C(2'*)-C(3'*)-C(4'*)-C(7'*)	-33.4(6)
C(8M*)-C(8*) -C(10*)-C(0B*)	-60.0(6)	C(3'*)-C(4'*)-C(5'*)- C(*)	53.8(5)
C(9*) -C(8*) -C(10*)-C(5*)	-56.4(4)	C(3'*)-C(4'*)-C(5'*)-C(6'*)	-67.7(5)
C(9*) -C(8*) -C(10*)-C(0A*)	-174.5(4)	C(7'*)-C(4'*)-C(5'*)- C(*)	158.2(4)
C(9*) -C(8*) -C(10*)-C(0B*)	62.9(5)	C(7'*)-C(4'*)-C(5'*)-C(6'*)	36.8(5)
N(3*) - C(*) -C(5'*)-C(4'*)	67.5(6)	C(3'*)-C(4'*)-C(7'*)-C(1'*)	50.0(5)
N(3*) - C(*) -C(5'*)-C(6'*)	-177.9(4)	C(5'*)-C(4'*)-C(7'*)-C(1'*)	-58.9(4)
O(*) - C(*) -C(5'*)-C(4'*)	-108.8(6)	C(*) -C(5'*)-C(6'*)-C(1'*)	-121.2(4)
O(*) - C(*) -C(5'*)-C(6'*)	5.8(7)	C(4'*)-C(5'*)-C(6'*)-C(1'*)	0.1(5)

Appendix 4

X-Ray Crystal Structure of the Benzyl Adduct (111A)

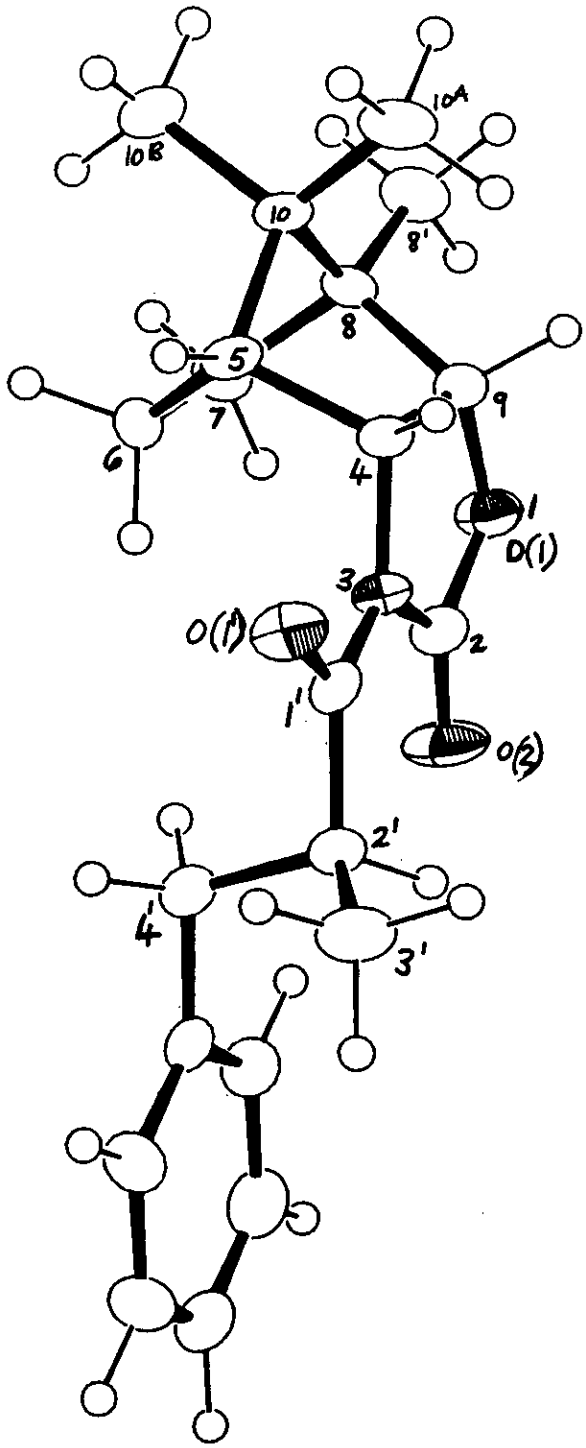


Table 1. Bond Lengths(Å) with standard deviations

O(1) - C(2)	1.362(4)	C(7) - C(8)	1.536(4)
O(1) - C(9)	1.459(4)	C(8) -C(8')	1.507(5)
C(2) - O(2)	1.199(4)	C(8) - C(9)	1.534(4)
C(2) - N(3)	1.384(4)	C(8) -C(10)	1.550(4)
N(3) - C(4)	1.460(4)	C(10) -C(10A)	1.542(5)
N(3) -C(1')	1.392(4)	C(10) -C(10B)	1.534(5)
C(4) - C(5)	1.540(4)	C(1') -O(1')	1.216(4)
C(4) - C(9)	1.534(4)	C(1') -C(2')	1.518(4)
C(5) - C(6)	1.533(4)	C(2') -C(3')	1.527(5)
C(5) -C(10)	1.562(4)	C(2') -C(4')	1.552(4)
C(6) - C(7)	1.557(4)	C(4') -C(1P)	1.518(4)

Table 2. Angles(degrees) with standard deviations

C(2) - O(1) - C(9)	110.40(22)	C(9) - C(8) -C(10)	99.20(22)
O(1) - C(2) - O(2)	121.6(3)	O(1) - C(9) - C(4)	105.74(22)
O(1) - C(2) - N(3)	109.43(24)	O(1) - C(9) - C(8)	114.24(23)
O(2) - C(2) - N(3)	129.0(3)	C(4) - C(9) - C(8)	105.10(22)
C(2) - N(3) - C(4)	112.02(23)	C(5) -C(10) - C(8)	94.02(22)
C(2) - N(3) -C(1')	128.12(24)	C(5) -C(10) -C(10A)	113.1(3)
C(4) - N(3) -C(1')	119.59(23)	C(5) -C(10) -C(10B)	114.3(3)
N(3) - C(4) - C(5)	116.83(23)	C(8) -C(10) -C(10A)	113.6(3)
N(3) - C(4) - C(9)	102.31(21)	C(8) -C(10) -C(10B)	114.8(3)
C(5) - C(4) - C(9)	102.88(22)	C(10A)-C(10) -C(10B)	106.9(3)
C(4) - C(5) - C(6)	109.07(23)	N(3) -C(1') -O(1')	117.7(3)
C(4) - C(5) -C(10)	99.89(23)	N(3) -C(1') -C(2')	120.03(24)
C(6) - C(5) -C(10)	102.43(23)	O(1') -C(1') -C(2')	122.3(3)
C(5) - C(6) - C(7)	103.03(23)	C(1') -C(2') -C(3')	108.79(24)
C(6) - C(7) - C(8)	104.09(24)	C(1') -C(2') -C(4')	108.38(23)
C(7) - C(8) -C(8')	114.7(3)	C(3') -C(2') -C(4')	112.32(25)
C(7) - C(8) - C(9)	107.28(23)	C(2') -C(4') -C(1P)	112.77(23)
C(7) - C(8) -C(10)	102.54(23)	C(4') -C(1P) -C(2P)	121.08(18)
C(8') - C(8) - C(9)	114.16(25)	C(4') -C(1P) -C(6P)	118.88(18)
C(8') - C(8) -C(10)	117.2(3)		

Table 3. Torsion angles(degrees) with standard deviations

C(9)	O(1)	C(2)	O(2)	176.4(3)	C(6)	C(5)	-C(10)	-C(10B)	-174.04(25)
C(9)	O(1)	C(2)	N(3)	-2.8(3)	C(5)	C(6)	C(7)	C(8)	-1.5(3)
C(2)	O(1)	C(9)	C(4)	1.3(3)	C(6)	C(7)	C(8)	-C(8')	-161.5(3)
C(2)	O(1)	C(9)	C(8)	-113.8(3)	C(6)	C(7)	C(8)	C(9)	70.6(3)
O(1)	C(2)	N(3)	C(4)	3.3(3)	C(6)	C(7)	C(8)	-C(10)	-33.4(3)
O(1)	C(2)	N(3)	-C(1')	-170.6(3)	C(7)	C(8)	C(9)	O(1)	45.3(3)
O(2)	C(2)	N(3)	C(4)	-175.9(3)	C(7)	C(8)	C(9)	C(4)	-70.1(3)
O(2)	C(2)	N(3)	-C(1')	10.2(5)	C(8')	C(8)	C(9)	O(1)	-83.0(3)
C(2)	N(3)	C(4)	C(5)	109.1(3)	C(8')	C(8)	C(9)	C(4)	161.61(25)
C(2)	N(3)	C(4)	C(9)	-2.3(3)	C(10)	C(8)	C(9)	O(1)	151.64(23)
C(1')	N(3)	C(4)	C(5)	-76.3(3)	C(10)	C(8)	C(9)	C(4)	36.2(3)
C(1')	N(3)	C(4)	C(9)	172.18(23)	C(7)	C(8)	-C(10)	C(5)	53.2(3)
C(2)	N(3)	-C(1')	-O(1')	177.5(3)	C(7)	C(8)	-C(10)	-C(10A)	-64.1(3)
C(2)	N(3)	-C(1')	-C(2')	-4.5(4)	C(7)	C(8)	-C(10)	-C(10B)	172.4(3)
C(4)	N(3)	-C(1')	-O(1')	4.0(4)	C(8')	C(8)	-C(10)	C(5)	179.8(3)
C(4)	N(3)	-C(1')	-C(2')	-177.99(24)	C(8')	C(8)	-C(10)	-C(10A)	62.4(4)
N(3)	C(4)	C(5)	C(6)	-40.5(3)	C(8')	C(8)	-C(10)	-C(10B)	-61.0(4)
N(3)	C(4)	C(5)	-C(10)	-147.48(24)	C(9)	C(8)	-C(10)	C(5)	-56.93(24)
C(9)	C(4)	C(5)	C(6)	70.6(3)	C(9)	C(8)	-C(10)	-C(10A)	-174.3(3)
C(9)	C(4)	C(5)	-C(10)	-36.3(3)	C(9)	C(8)	-C(10)	-C(10B)	62.2(3)
N(3)	C(4)	C(9)	O(1)	0.6(3)	N(3)	-C(1')	-C(2')	-C(3')	153.7(3)
N(3)	C(4)	C(9)	C(8)	121.81(23)	N(3)	-C(1')	-C(2')	-C(4')	-83.9(3)
C(5)	C(4)	C(9)	O(1)	-120.97(23)	O(1')	-C(1')	-C(2')	-C(3')	-28.4(4)
C(5)	C(4)	C(9)	C(8)	0.2(3)	O(1')	-C(1')	-C(2')	-C(4')	94.0(3)
C(4)	C(5)	C(6)	C(7)	-69.6(3)	C(1')	-C(2')	-C(4')	-C(1P)	171.06(22)
C(10)	C(5)	C(6)	C(7)	35.6(3)	C(3')	-C(2')	-C(4')	-C(1P)	-68.7(3)
C(4)	C(5)	-C(10)	C(8)	57.73(24)	C(2')	-C(4')	-C(1P)	-C(2P)	89.9(3)
C(4)	C(5)	-C(10)	-C(10A)	175.49(25)	C(2')	-C(4')	-C(1P)	-C(6P)	-87.8(3)
C(4)	C(5)	-C(10)	-C(10B)	-61.8(3)	C(4')	-C(1P)	-C(2P)	-C(3P)	-177.68(19)
C(6)	C(5)	-C(10)	C(8)	-54.48(25)	C(4')	-C(1P)	-C(6P)	-C(5P)	177.73(19)
C(6)	C(5)	-C(10)	-C(10A)	63.3(3)					

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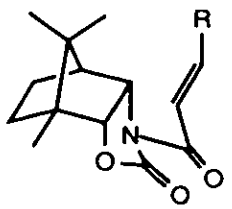
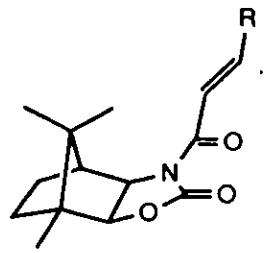
POSTSCRIPT

During the final stages of the preparation of this thesis, a paper appeared by Tanaka *et al*[161] which described the use of the antipode of Chirabornox in a number of Diels-Alder reactions using a variety of catalysts. The diastereomeric excesses are comparable to those reported in this thesis when methylene chloride was employed as solvent. However, these excesses rise dramatically when toluene is used instead. The results obtained by Tanaka *et al* and those of the *exo* analogue are recorded below for the readers' interest.



Endo-1a : R = Me
Endo-1b : R = Ph



Exo-4a : R = Me
Exo-4b : R = Ph

Asymmetric Diels-Alder reactions of *endo*-oxazolidinone-1 or *exo*-oxazolidinone-4 with cyclopentadiene.[a]

dieno-phile	Lewis acid	equiv.	temp. (°C)	time (h)	yield of adduct	*endo*/*exo* ratio	% ee of *endo*-product
1a	$EtAlCl_2$	0.2	0	18	97	79/21	69 (**3a**)
1a	$EtAlCl_2$	0.2	0	4	94	82/18	48 (**3a**)[b]
1a	$EtAlCl_2$	1	0	18	96	80/20	68 (**3a**)
1a	$TiCl_2(O\text{-}i\text{-}Pr)_2$	0.2	0	5	82	90/10	71 (**3a**)
1a	$TiCl_2(O\text{-}i\text{-}Pr)_2$	1	0	5	78	88/12	84 (**3a**)
1a	$TiCl_2(O\text{-}i\text{-}Pr)_2$	1	0	5	98	87/13	47 (**3a**)[b]
1a	$TiCl_2(O\text{-}i\text{-}Pr)_2$	1	-30	10	78	94/6	87 (**3a**)
1a	$BF_3{\cdot}OEt_2$	0.2	0 ~ r.t.	18	52	94/6	57 (**3a**)
1a	$SnCl_4$	0.2	0	18	99	88/12	51 (**6a**)
1b	$TiCl_2(O\text{-}i\text{-}Pr)_2$	1	0	10	97	90/10	100 (**3b**)
1b	$TiCl_2(O\text{-}i\text{-}Pr)_2$	0.05	0	10	8	87/13	93 (**3b**)
1b	$SnCl_4$	1	0	10	24	95/5	50 (**3b**)
4a	$TiCl_2(O\text{-}i\text{-}Pr)_2$	1	-40 ~ -10	18	94	87/13	68 (**6a**)
4a	$TiCl_2(O\text{-}i\text{-}Pr)_2$	1	-40 ~ -10	18	40	84/16	37 (**6a**)[b]
4a	$SnCl_4$	1	0	18	96	93/7	27 (**3a**)
4b	$TiCl_2(O\text{-}i\text{-}Pr)_2$	1	0	10	71	85/15	100 (**6b**)
4b	$SnCl_4$	1	0	10	79	91/9	93 (**6b**)

[a] Toluene was used as solvent. [b] Dichloromethane was used.

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Enantiospecific Preparation of [(2R, 6S)-*endo*]-5-Aza-1,10,10-trimethyl-3-oxatricyclo[5.2.1.$0^{2,6}$]decan-4-one by a Nitrene-mediated Route from [(1S)-*endo*]-(-)-Borneol and its Utility as a Chiral Auxiliary in Some Asymmetric Transformations

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(*Received in USA* 3 *August* 1992)

Abstract: Attempted chiral aziridination of styrene by addition of optically-active alkoxycarbonylnitrene **5** derived from [(1S)-*endo*]-(-)-bornyl *p*-nitrobenzenesulphonoxycarbonate **4** is reported. No measurable asymmetric induction is observed under the various conditions employed, but in the absence of alkene, a tricyclic oxazolidin-2-one **8** is formed to which preparatively simpler access can be gained by thermal decomposition of azidoformate **7**, either in 1,1,2,2-tetrachloroethane (50%) or by spray pyrolysis (58%). The oxazolidin-2-one **8** is demonstrated to be a successful chiral auxiliary by contemporary standards in a variety of asymmetric transformations, including alkylation, acylation, and aldol reactions for which high levels of asymmetric induction are observed. Diethylaluminium chloride-catalysed Diels-Alder reactions exhibit poorer selectivity except for the cinnamoyl derivative **23** which is stereospecific.

Introduction

Compared to the chiral epoxidation of alkenes[1] the corresponding process for aziridination has received scant attention, although Nozaki *et al*[2] have succeeded, albeit with resolution, by using a chiral modification of Hassner's classical method *via* β-iodocarbamates[3]. More recently, Atkinson and co-workers[4] have achieved modest-to-exclusive stereoselectivities by the oxidation of an *N*-aminobenzimidazole and *N*-aminoquinazolones in the presence of prochiral alkenes. Recent evidence[5] indicates that such aziridinations involve electrophilic addition of intermediate *N*-acetoxyaminoquinazolone and not a free nitrene or nitrenium ion. Chiral aziridination by addition of optically-active nitrenes to prochiral alkenes has, to the best of our knowledge, not been used. We now report the generation of the optically-active alkoxycarbonyl nitrene **5**, and the outcome of its potentially enantioselective addition to styrene. Furthermore, we wish to relate the serendipitous discovery of a new chiral

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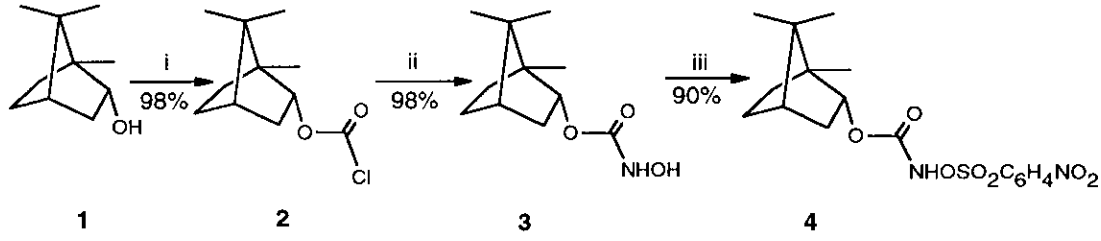
We dedicate this paper to Professor Charles Rees, FRS not only for his outstanding contribution to chemistry and encouragement of others, but for his perspicacious wit and friendship.

oxazolidin-2-one **8**, which was found amongst the minor products during these initial studies, and subsequently isolated in bulk quantities, to further bolster the existing armoury of chiral auxiliaries based on this nucleus and used in a range of asymmetric manipulations.

1. Attempted chiral nitrene-mediated aziridination

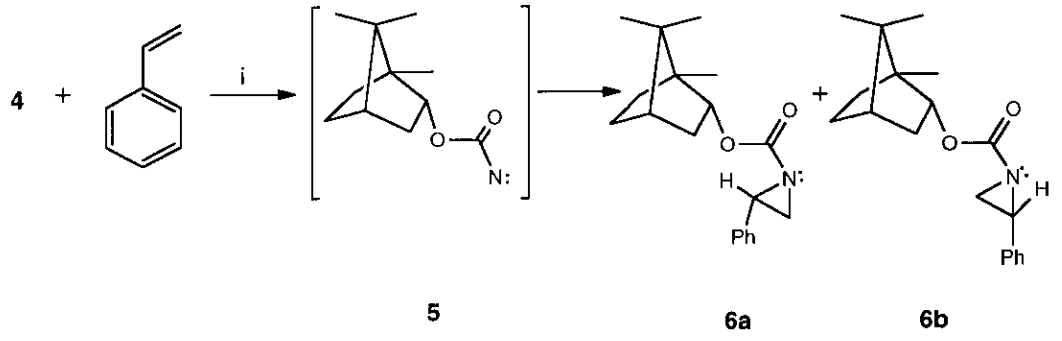
Our choice of precursor for nitrene **5** was [(1S)-*endo*]-1,7,7-trimethylbicyclo[2.2.1]heptan-2-*p*-nitrobenzenesulphonoxycarbamate **4** hereafter called [(1S)-*endo*]-(-)-bornyl *p*-nitrobenzenesulphonoxycarbamate, which is easily prepared as shown in Scheme 1 by a similar route to that originally used for Lwowski's reagent[6].Thus, chloroformylation of optically pure [(1S)-*endo*]-(-)-borneol **1** with phosgene followed by *N*-hydroxycarbamation with hydroxylamine and subsequent esterification with *p*-nitrobenzenesulphonyl chloride gave the desired reagent **4** in 85% overall yield.



Scheme 1. *Reagents and conditions:* (i), phosgene, triethylamine, toluene-ether, 0°C, 4h; (ii), hydroxylamine hydrochloride, sodium hydrogen carbonate, ether, 25°C, 12h; (iii), *p*-nitrobenzenesulphonyl chloride, triethylamine, ether, 25°C.

The optically-active nitrene **5** was generated from **4** as depicted in Scheme 2 in a two-phase system[7] and trapped with the prochiral alkene styrene to give 1-([(1S)-*endo*]-(-)-bornoxycarbonyl)-2-phenylaziridine **6** as its *trans*-invertomer (21%). The enantioselectivity of the reaction was determined by proton-decoupled ^{13}C NMR. spectroscopy since the ^{1}H chemical shifts of the aziridine ring protons in the two diastereomeric products **6a** and **6b** were unresolvable even at high field (360 MHz). No difference in the relative proportions of the two diastereomers could be detected. Indeed, the ^{13}C NMR spectrum of the crude reaction mixture was identical to that for an authentic 1:1 mixture of both diastereomers prepared from the reaction of racemic 2-phenylaziridine with [(1S)-*endo*]-(-)-bornylchloroformate **2**. In particular, two pairs of resonances of equal intensity were observed for the aziridine carbons at δ39.11 and δ38.87, and δ34.37 and δ33.94 in both cases. Attempts to promote some selectivity by lowering the temperature were equally frustrated by the failure of the reagent **4**, to react with the generating base (triethylamine) at temperatures below -5°C. Use of *n*-butyl lithium as base gave decomposition products.

From these results it is evident that the use of the [(1S)-*endo*]-(-)-bornyl moiety as the chiral auxiliary in an alkoxycarbonylnitrene does not lead to any discernable enantiomeric excess in aziridine formation under the conditions employed. Apparently, the bornyl moiety is



Scheme 2. *Reagents and conditions:* (i), benzyltriethylammonium chloride, sodium hydrogen carbonate, dichloromethane-water, 25°C.

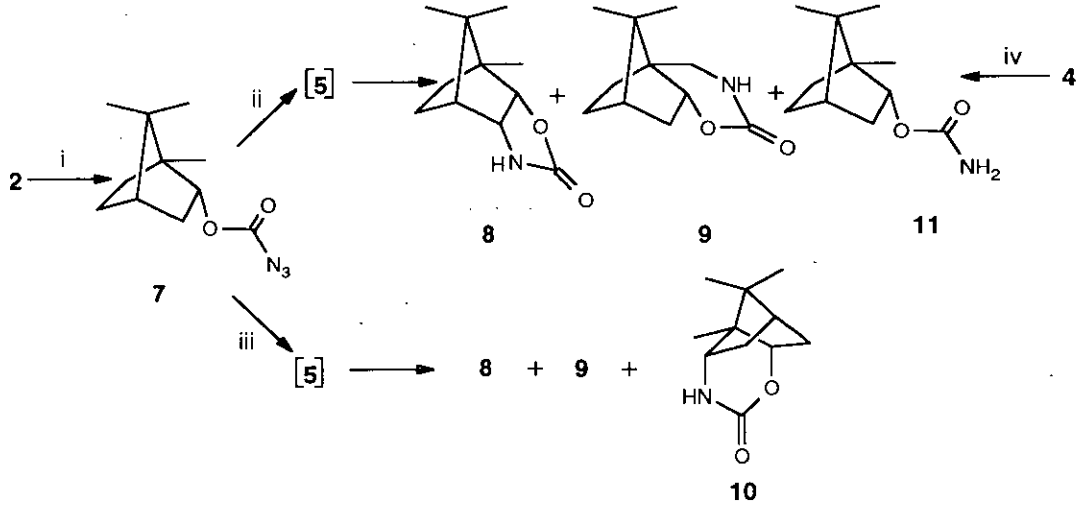
too remote from the bond-making centre to allow for any discrimination in the activation energies of the different transition states leading to the two possible diastereomers **6a** and **6b**. Further to these experiments, it is worth noting that no measurable asymmetric induction took place during aziridine formation between styrene or 1-methylcyclohexene and carboethoxynitrene (EtO_2C-N:) when the latter was generated in a two-phase system[8] using (-)-*N*-benzylcinchonidinium chloride as a chiral phase-transfer catalyst, or in a homogenous system[6] by the action of (S,S)-(+)-2,3-dimethoxy-1,4-bis(dimethylamino)butane as a chiral base.

In spite of the futility of our efforts to induce chirality in the foregoing aziridination reactions, we had occasion to examine in detail the outcome of the benzyltriethylammonium chloride-catalysed reaction in the absence of styrene (Scheme 3). In this scenario, analysis of the crude reaction mixture revealed the presence of three products which were shown to be derived directly from nitrene **5**. These were isolated by flash chromatography and identified as the tricyclic oxazolidin-2-one **8** (43%), the six-membered tetrahydro-1,3-oxazin-2-one **9** (36%) and carbamate **11** (14%). Mindful of the seminal work by Evans in the development of chiral oxazolidin-2-ones similar to **8** as effective chiral auxiliaries for the elaboration of stereogenic centres *via* acyl derivatives[9], we sought to suppress the formation of co-products **9** and **11** and improve the synthetic yield of **8** in enantiomerically pure form by exploring alternative methods of generating the precursor nitrene **5**. Herein we describe the optimum conditions for the synthesis of **8** and its utilisation as a chiral auxiliary in an array of asymmetric reactions.

2. Preparation of [(1s)-*endo*]-(-)-borneol-derived oxazolidin-2-one 8

Current methodology for access to preparatively useful chiral oxazolidin-2-ones, whether as reagents for stereoregulated aldol condensations[10] or resolution of racemic amines[11], employ direct cyclocarbamation of relatively expensive optically pure β-amino alcohols, or resort to the more tedious separation of similarly prepared racemic analogues[12]. For the improved preparation of the new chiral reagent **8** in an optically pure state we undertook a *de novo*

study of both thermolytic and photolytic methods of generating nitrene intermediate **5** from the azidoformate **7** by loss of nitrogen (Scheme 3). We envisaged the use of the device of intramolecular nitrene delivery[13], coupled with the conformational rigidity offered by the bornyl moiety, would ensure transfer of chirality from the existing chiral centre at C(2) to the nascent centre at C(3), by preferential insertion of **5** into the secondary *endo*-C-H bond. Various conditions were employed including neat thermolysis (**8**,48%), solution thermolysis in either boiling chlorobenzene (47%) or 1,1,2,2-tetrachloroethane (50%), flash vacuum pyrolysis (fvp) at 300°C (46%), and photolysis in CH_2Cl_2 (39%). Spray vacuum pyrolysis[14] using a modified apparatus and a vertical furnace was found to be the optimal method producing **8** in 58% yield (Scheme 3).



Scheme 3. *Reagents and conditions:* (i), sodium azide, tetrabutylammonium bromide, dichloromethane-water, 25°C, 4h; (ii), photolysis, 400W, dichloromethane, 30°C, 160m; (iii), spray pyrolysis, 300°C, 0.1-0.5 mmHg, or fvp, 300°C, 0.01-0.005 mmHg, or solution thermolysis in 1,1,2,2-tetrachloroethane, 147°C; (iv), benzyltriethylammonium chloride, sodium hydrogen carbonate, dichloromethane-water, 25°C.

Pyrolytic methods yielded the tricyclic oxazolidin-2-one **8** admixed with easily separated (by flash chromatography on silica using cyclohexane:ethyl acetate as eluent) six-membered tetrahydro-1,3-oxazin-2-one **9** and isomeric **10**, whose structure was determined by X-ray crystallography (Fig. 1a), in the ratio of *ca.* 2:1:1. Non-pyrolytic methods such as photolysis or Lwowski-type reactions did not produce compound **10**, but instead gave rise to carbamate **11** from hydrogen abstraction by the nitrene **5**. The preferred formation of **8** over **9** and **10** presumably reflects the bias towards 5- *vs.* 6-membered ring formation, coupled with the propensity by the nitrenoformate intermediate **5** for secondary H-insertion relative to primary in a cyclic system. Further crystallisation from di-*iso*-propyl ether or ethyl acetate: n-

hexane furnished well-formed crystals of the chiral oxazolidin-2-one **8** (m.p. 163-163.5°C; $[\alpha]^{21.5}$ -73.4°, c=5.1, ethanol); its structure was confirmed by microanalysis, mass spectral (including parent molecular ion by electron impact),and NMR data. X-Ray diffraction analysis confirmed the stereochemical integrity of **8** and has shown that the absolute configuration of the chiral centres at C(2) and C(6) is (2R, 6S), (Fig. 1b).

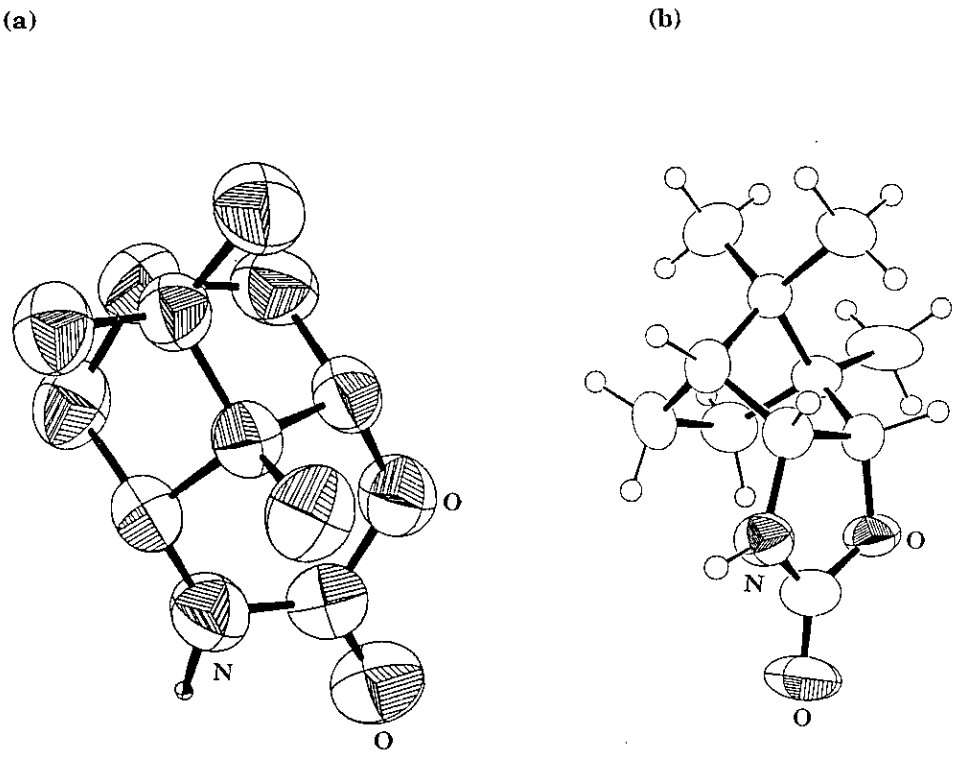


Figure 1. (a) Molecular structure of 1,3-oxazin-2-one **10**, and (b) of oxazolidin-2-one **8**.

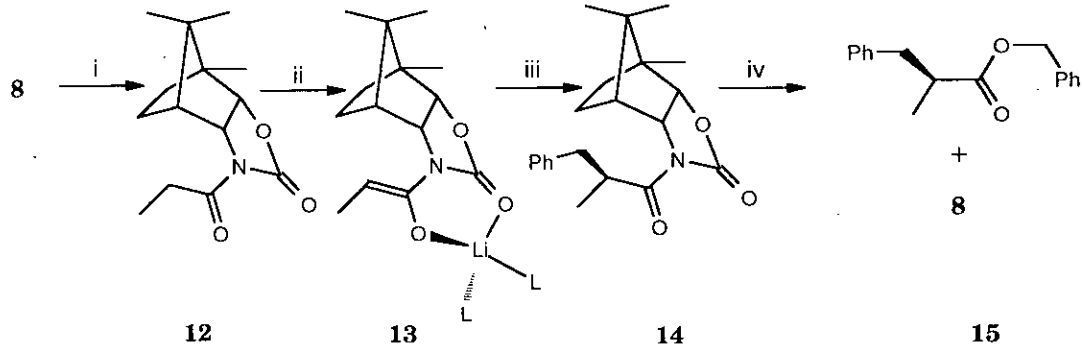
3. Utility of chiral auxiliary 8 in asymmetric transformations

Chiral oxazolidin-2-ones have been used extensively for substrate-controlled asymmetric synthesis, especially in the context of their *N*-acyl derivatives as precursors to chiral imide enolate synthons in carbon-carbon bond-forming reactions. In this connection, the bornyl-based oxazolidinone **8** was felt to be a promising candidate as a chiral auxiliary for the following reasons: (i) optically pure **8** can be readily prepared in multi-gram quantities in three simple steps from inexpensive *endo*-(-)-borneol; (ii) the highly crystalline nature of **8** imparts good crystallinity to derivatives, and consequently aids its synthetic utility in preparing optically pure products; (iii) the rigidity of the bornyl moiety attached to the oxazolidinone should dictate excellent π-topological bias as enjoyed by other camphor-based

auxiliaries[15,16,17]; (iv) the expected ease of non-destructive removal of the chiral auxiliary from the desired chiral synthon without racemization, and its propitious recyclability. On these grounds, we now report our observations on the stereochemical control imparted by **8** in diastereoselective alkylation, acylation and aldol processes with the respective enolate derived from the *N*-propionyl analogue **12**, and the level of chiral induction attainable with **8** bearing acryloyl substituents in Diels-Alder reactions.

(i) Alkylation and acylation reactions

Acylation of oxazolidinone **8** with *N*-propionyl chloride in the presence of sodium hydride or *n*-butyl lithium led to an almost quantitative yield of the *N*-propionyl imide **12** (Scheme 4). For the alkylation studies reported in Table 1, the lithium enolate **13** was generated by treatment of **12** with lithium di-*iso*-propylamide in tetrahydrofuran at -78°C. At this temperature the imide enolate **13** failed to alkylate, even with the more reactive benzyl bromide, but reaction did ensue at a convenient rate upon raising the temperature to -10°C. At temperatures >0°C the lithium enolate **13** decomposed, apparently *via* a ketene pathway[18].



Scheme 4. *Reagents and conditions:* (i), sodium hydride, toluene, 110°C, 1h then propionyl chloride, 25°C, 1h; or *n*-butyl lithium, tetrahydrofuran, -78°C, 30m, then propionyl chloride, 1h, 25°C; (ii), lithium di-*iso*-propylamide, tetrahydrofuran, -78°C, 30m; (iii). benzyl bromide, sodium iodide, tetrahydrofuran, -8°C, 18h; (iv). benzyl alcohol, *n*-butyl lithium, tetrahydrofuran, -78°C, 45m.

The diastereomeric composition of the crude alkylated product was determined by 400 MHz ^{1}H NMR spectral analysis and the results in Table 1 reflect the superb diastereofacial selection dictated by **8** for all alkylations, even with the less sterically demanding ethyl iodide (entry c), although this result was marred by the very poor yield. Attempts to improve the latter by replacing ethyl iodide with ethyl tosylate proved futile. On the other hand, an improvement in the yield with benzyl bromide from 62 to 80% was achieved by the judicious addition of sodium iodide to the reaction (entry d).

The absolute stereochemical configuration for the benzylated product **14** was determined by X-ray crystallography (Fig. 2), and also by adoption of Evan's transesterification method for racemisation-free removal of the oxazolidinone auxiliary with lithium benzyloxide[18]. As shown in Scheme 4, this procedure transformed **14** into the (*S*)-benzyl ester **15** in 96% yield ([α] +24.6°) in good agreement with the rotation (-26.9°) for the (R)-enantiomer[18]. The sense of diastereofacial bias is readily rationalised in terms of attack by the alkylating agent at the C_α-*re* face of the lithium-chelated (**Z**)-enolate **13**.

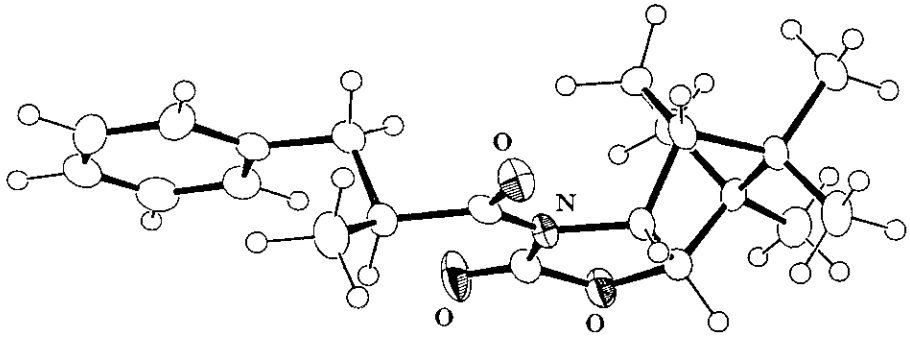


Figure 2. Molecular structure of benzylated derivative 14.

These results demonstrate the viability of **8** as a chiral auxiliary for the asymmetric alkylation of acyl derivatives, although it is recognised that enolate formation with lithium di-*iso*-propylamide can lead to severely reduced yields, albeit with good selectivity. This limitation has been recognised by others in the development of effective auxiliary-mediated asymmetric enolate alkylation[16,18,19] and for this reason, further studies are under way to probe the effect of counterion (Na *vs.* Li) and reaction conditions, particularly temperature, on yields without adversely affecting the selectivity. In contrast to the foregoing alkylation processes, acylation reagents reacted rapidly with the chelated (**Z**)-enolate **13** even at -78°C to afford the desired β-keto imides (entries e-h, Table 1). In order to preserve the integrity of the newly created chiral centre under the highly basic conditions employed, the reactions had to be quenched almost immediately with a saturated solution of aqueous ammonium chloride. In all but one case (entry g), the kinetic diastereoselection was found to be very good-to-excellent, although both acetylation (entry e) and propionylation (entry f) were marred by the formation of small amounts of *O*-acylated products. This problem was avoided in the former

case by employing Mander's reagent (entry h),which yielded only *C*-substitution[20]. Despite immediate quenching, the β-dicarbonyl adduct obtained from benzoylation (entry g) underwent rapid epimerization *via* enol formation as evidenced by the appearance of strong hydroxy absorptions in both IR and NMR spectra. This outcome contrasts strikingly with the low kinetic acidity exhibited by the corresponding β-keto imide derived from Evan's valinol-based oxazolidin-2-one[21] for which propitious steric effects negate the influence of the exocyclic imide carbonyl toward acidification of the acyclic methine hydrogen.

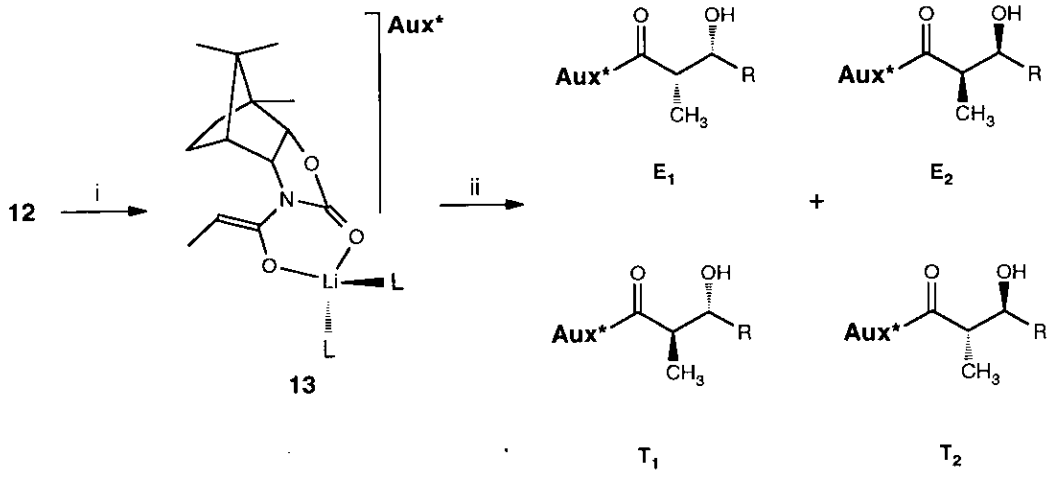
Table 1. Stereoselectivity of alkylation and acylation reactions of the lithium enolate **13** derived from *N*-propionyl imide **12** (Scheme 4)

entry	electrophilic reagent	reaction time	C *vs.*O selection (%)	isolated yield (%)	de (%)
a	benzyl bromide	18h	-	62	>99
b	allyl bromide	18h	-	70	>99
c	ethyl iodide	4h	-	6	>99
d	benzyl bromide/sodium iodide	18h	-	80	>99
e	acetyl chloride	45s	85:15	88	82
f	propionyl chloride	60s	85:15	89	>99
g	benzoyl chloride	120s	100:0	95	a
h	methyl cyanoformate	90s	100:0	99	82

a. enolisation occurred to cause racemisation.

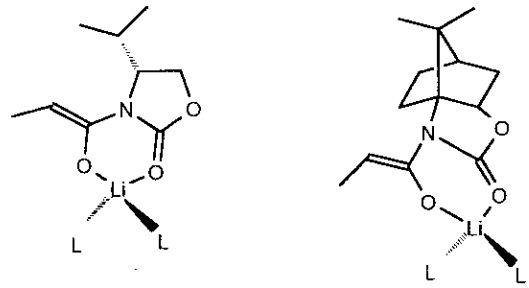
(ii) Aldol diastereoselection *via* chiral enolates derived from *N*-propionyl imide 12

The demand for enantiomerically pure β-hydroxycarbonyl-containing compounds has led to a rapidly growing interest in chiral metal-mediated enolates which can achieve exceptionally high diastereoselectivity[22]. Of these, use of optically pure oxazolidin-2-ones as recyclable chiral auxiliaries has emerged as an attractive option for aldol condensations[23]. With access to the aforementioned *N*-propionyloxazolidinone **12** in hand, our investigation commenced with the lithium-chelated (*Z*)-enolate **13**, generated under kinetic conditions (*vide supra*) and reacted with freshly distilled benzaldehyde (R=Ph). After 30s, the reaction was quenched with saturated ammonium chloride solution to afford all four possible diastereomeric adducts (E_1, E_2, T_1, T_2) (Scheme 5) in the ratio 55.4:28.7:10.3:5.7 by consideration of the carbinol resonances in the 360 MHz ^{1}H NMR spectrum. An equally low level of stereoregulation was found for the lithium-enolate condensation of **13** with isobutyraldehyde (R=Me_2CH), for which HPLC analysis gave a product distribution for the four aldol stereoisomers of 64.7:22.5:7.9:4.9. This poor quality of aldol diastereoselection is akin to that reported with Evan's (S)-valinol-based oxazolidin-2-one for which the analogous condensation of the corresponding lithium enolate **16**, the observed diastereomer ratios were 10.6:11.0:71.4:7.0[10]. Likewise, the diastereoselectivity of the corresponding aldol reactions with the (+)-camphor-based imide lithium enolate **17** is equally moderate[16].



Scheme 5. *Reagents and conditions:* (i),lithium di-*iso*-propylamide, tetrahydrofuran, -78°C; (ii), RCHO.

Much greater diastereoselectivity is achieved in both these cases by use of boron-chelated enolates. Indeed, aldol condensations from the boron enolate analogous to **16** exhibited complete *erythro*-stereoselection and absolute stereochemical control, and in the case of that corresponding to **17**[16], the combined *threo*-adduct contaminants never exceeded 0.9%. The same behaviour gratifyingly occurred with the boron enolate generated from **12**. Subsequent condensation with both benzaldehyde and isobutyraldehyde furnished single diastereomerically pure *erythro*-adducts whose assignment was confirmed from low J-values for the carbinol resonances (J=<6 Hz), and in the case of benzaldehyde adduct **18**, by X-ray crystallography.



16 **17**

The ORTEP diagram shown in Fig. 3 confirms the absolute stereochemistry of the two newly formed chiral centres to be *erythro* (**E_2**). This sense of diastereofacial selectivity is opposite to that reported above for the boron enolate corresponding to **16**, but is the same as that

obtained from the oxazolidin-2-one prepared from (1S,2R)-norephredrine[10], and the (+)-camphor-based boron enolate corresponding to **17** (*vide supra*)[16].

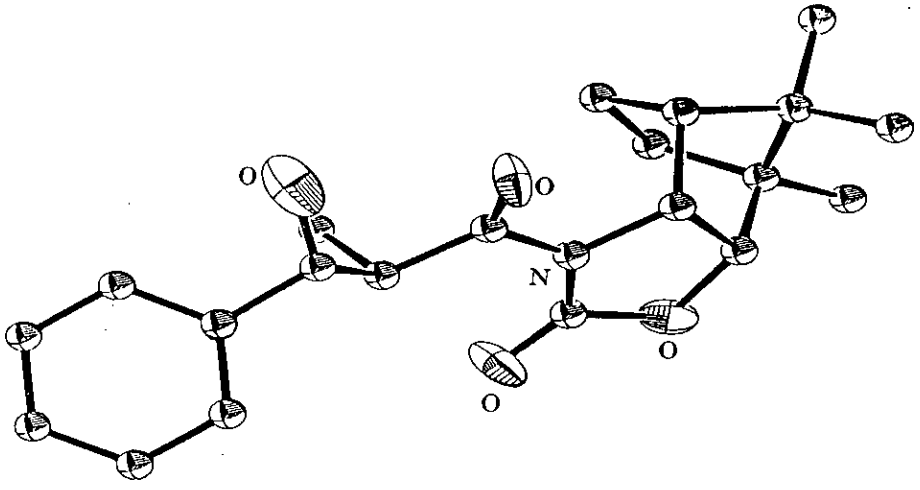
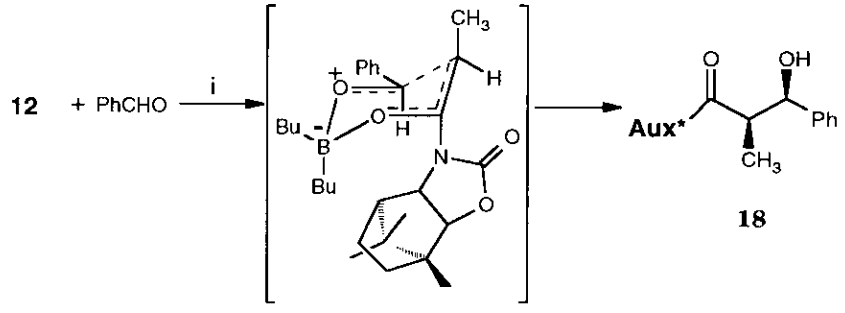


Figure 3. View of the X-ray structure of aldol-adduct 18.

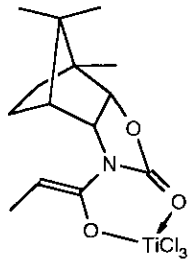
The origin of the remarkable stereospecificity in these boron enolate-mediated reactions and the *erythro*-stereochemistry of the adducts can be rationalised in terms of the preferred chair-like transition state shown in Scheme 6, given the reasonable postulate that the aldol condensation proceeds *via* a pericyclic process [10] , and that chelation with the carbonyl group in the auxiliary is absent (*cf.* corresponding lithium enolate **13**).



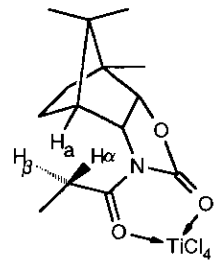
Scheme 6. *Reagents and conditions:*(i), di-*n*-butylboron triflate, di-*iso*-propylethylamine, tetrahydrofuran, 0°C, 10m, then -78°C, 30m; (ii), benzaldehyde.

Despite these successes neither the lithium- or boron-enolates derived from **12** condensed with acetaldehyde readily. In the former case, total consumption required approx. 1.5h and led to dehydration products as well as cleavage of the auxiliary. A similar reluctance to react was also observed for the corresponding titanium enolate **19**, even with benzaldehyde. In initial studies, attempts to form the latter, by treatment with titanium tetrachloride, failed

despite the advent of a deep purple coloration. Instead, high-field NMR spectroscopy revealed the presence of the bidentate complex **20** as evidenced by the observation of the distinctive pair of quartets for each of the diastereotopic protons H_α and H_β arising from the immobilisation of the *N*-acyl function. Moreover, irradiation of the bridgehead proton H_a enhanced H_β by 3%, but caused no change to H_α thereby confirming the 'locked' structure as depicted in **20**.



19



20

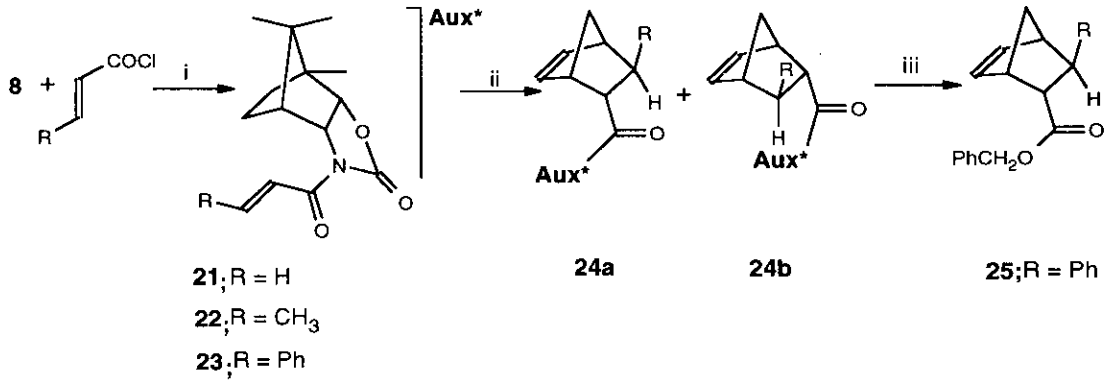
It was found that reaction did occur, albeit to 40% completion, by changing the base to triethylamine, and only after a prolonged reaction period (48h) at room temperature. Despite its sluggishness, this condensation is notable in the antithetical formation of only the *threo*-adducts (T_1, R=Ph) and (T_2, R=Ph), the stereochemical assignments being made from carbinol proton coupling constants (J=9 and 11 Hz), in the ratio of 13:1. At this stage it is not proven which is the major diastereomer, but irrespective of this fact, the sole formation of *'anti'* adducts is noteworthy, especially when compared to the stereochemical control of the titanium(IV) enolate derived from the *exo*-analogue of **12**[17] which affords predominant amounts of the *erythro*-diastereomer (E_1), the product predicted from chelation control. This dichotomy is under further investigation, coupled with attempts to force the reaction to completion.

(iii) Diels-Alder cycloadditions

Our initial attempts to prepare chiral acrylate derivatives as dienophiles in Diels-Alder cycloaddition reactions as a route to optically-active cyclohexenes involved the reaction of an ethereal solution of the sodium salt of **8** with the appropriate α,β-unsaturated acid chloride. However, in the case of acryloyl chloride the procedure was frustrated by polymerisation, which is believed to be anionic in nature. The problem was circumvented by use of Evan's elegant method[24] whereby the oxazolidinone **8** was successively treated with methylmagnesium bromide and the acid chloride under carefully defined conditions to afford the desired dienophile **21** in 75% isolated yield. The same procedure also yielded the crotonoyl- and cinnamoyl dienophiles **22** (85%) and **23** (81%) respectively in a pure and crystalline state without the problem of polymerisation (Scheme 7).

It is well established in Diels-Alder cycloaddition reactions with chiral unsaturated carboximides such as **21-23**, that the rotameric preference must be controlled in order to

observe high diastereoselectivity. In the absence of Lewis acid promoters four planar conformers, *e.g.* **A-D** are possible (Fig. 4), although a combination of dipole-dipole interactions and steric destabilization favours only the S-*cis* conformer **C**[25].Chelation alters this



Scheme 7. Diels-Alder cycloadditions. *Reagents and conditions:* (i), methylmagnesium bromide, tetrahydrofuran, 0°C, then cooled to -78°C, acryloyl chloride, (ii), cyclopentadiene, catalyst, (iii) benzyl alcohol, *n*-butyl lithium, tetrahydrofuran, -78°C for 30m then 25°C, 3h.

conformer preference and in Lewis acid promoted reactions, rotameric preference is directed towards S-*cis* conformer **A** rather than S-*trans* **B** due to steric constraints in the latter (see Fig. 4).The bias depends on the temperature used and also the nature of the Lewis acid catalyst, but in essence, bidentate chelation by the promoter to both carbonyl groups freezes the *N-C* rotor and allows π-face discrimination, although the direction of attack depends upon the topological bias provided by the auxiliary.

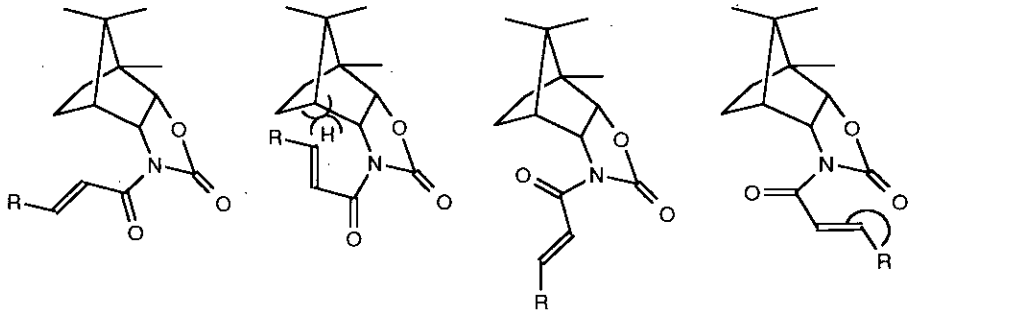


Figure 4. Conformations adopted by *N*-substituted acryloyl derivatives of **8**.

Our results with auxiliary **8** proved disappointing. The cycloaddition of acryloyl imide **21** with excess cyclopentadiene employing $TiCl_2(OPr^i)_2$ (4 equiv.) in dichloromethane at -78°C afforded only *endo*-adducts **24a** and **24b** , albeit in the ratio of 2:1, and derived respectively from conformers **A** (R=H) and **B** (R=H). Use of an excess of Et_2AlCl (1.4 equiv.) as the promoter under identical conditions led to a modest improvement of the ratio to 4:1. The results are summarised in Table 2, together with *endo*-diastereoselectivities obtained for crotonoyl imide **22** and cinnamoyl imide **23** in the same reaction. A surprising feature is the loss of selectivity on going from the acryloyl imide **21** (entry b) to the crotonoyl dienophile **22** (entry g) which also gives rise to small amounts of otherwise unobserved *exo*-adducts; use of Et_2AlCl as catalyst failed to enhance the diastereoselection. The level of reactivity for the uncatalysed crotonoyl reaction is also diminished (entry f) when compared to the acryloyl dienophile **21** (entry a), and after 24h it is recovered virtually unchanged. Dienophile reactivity is markedly improved in the presence of Et_2AlCl (entry h), but the diastereoselectivity remains unchanged compared to the corresponding acryloyl reaction (entry c). The cinnamoyl dienophile **23** is the least reactive yet thus far the most diastereoselective, and even after three days and the addition of more cyclopentadiene, led to only a 22% yield of a single adduct (entry i). Change of Lewis acid promoter from $TiCl_2(OPr^i)_2$ to Et_2AlCl improved reactivity considerably (entry j), and even at -20°C afforded within 1m an excellent yield of distereomerically pure cycloadduct **24a** (R=Ph) (92%). The sense of asymmetric induction in the latter reaction was established by removal of the chiral auxiliary from the adduct by treatment with lithium benzyloxide in tetrahydrofuran (0°C, 3h). Comparison of the literature value for the optical rotation of the isolated benzyl ester **25** ($[\alpha] = -121.1^{\circ}$) confirmed its optical purity and opposite sense to that obtained by Evans *et al*[24] with their (S)-valinol-derived oxazolidinone (antipode $[\alpha] = +121.0^{\circ}$).

Table 2. Lewis acid promoted reactions of dienophiles **21-23** with cyclopentadiene (and isoprene)

entry	R	catalyst/temp(°C)	diene	isolated yield (%)	ratio	de (%)
a	H	none,0°C	cyclopentadiene	69	1.1:1	
b	H	$TiCl_2(OPr^i)_2$, -78°C	cyclopentadiene	83	2:1	33
c	H	Et_2AlCl, -78°C	cyclopentadiene	98	4:1	60
d	H	$TiCl_2(OPr^i)_2$, -78°C	isoprene	80	2:1	33
e	H	Et_2AlCl, -78°C	isoprene	94	5:1	69
f	CH_3	none,0°C	cyclopentadiene	10	a	a
g	CH_3	$TiCl_2(OPr^i)_2$, -78°C	cyclopentadiene	92	3:2	20
h	CH_3	Et_2AlCl, -78°C	cyclopentadiene	96	4:1	60
i	Ph	$TiCl_2(OPr^i)_2$, -78°C	cyclopentadiene	22	a	a
j	Ph	Et_2AlCl, -20°C	cyclopentadiene	92	>99:1	99

a. reaction is very slow and only a small amount of product was formed after 24h.

As expected on the basis of the foregoing results, only the acryloyl dienophile **21** underwent cycloaddition with the much less reactive acyclic diene isoprene. Once again, Et_2AlCl-catalysed reaction produced a significantly better level of diastereoselection (5:1) (entry e) than the corresponding reaction (entry d) with $TiCl_2(OPr^i)_2$ (2:1). In both cases, the ratios could only be determined by ^1H 360 Mz NMR with the aid of a europium chiral shift reagent.

From these results it is evident that auxiliary **8** induces consistently low levels of diastereofacial differentiation in Lewis acid mediated asymmetric Diels-Alder reactions of cyclopentadiene (and isoprene), apart from with the cinnamoyl imide **23**. Although in all cases investigated, *endo/exo* ratios are extremely high, *endo*-diastereoface selectivity never exceeds 67%, except for the cycloaddition with the relatively less reactive cinnamoyl dienophile (entry j) which is stereospecific. The reason for the poor diastereoselection is probably steric in origin and reflects the inability of **8** to provide the necessary topological bias in Diels-Alder reactions and establish significant population differences between the chelated S-*cis* and S-*trans* conformers **A** and **B**, respectively (Fig. 3). We are currently investigating other likewise terpenoid-based oxazolidinones with the necessary control element to improve π-face discrimination.

Acknowledgements
We are grateful to Dr T. C. Gallagher and Tim Donohoe for their helpful contributions during a British Petroleum Vacation Scholarship (T. D.).

EXPERIMENTAL

Melting points are uncorrected. ^1H and ^{13}C NMR spectra were obtained on a Brucker-270 operating at 270 MHz or 50.3 MHz respectively, or a Brucker-270 operating at 270 MHz or 67.9 MHz, or a Brucker WH-360 operating at 360 MHz or 90.56 MHz, or a Brucker 400 operating at 400 MHz or 100.57 MHz. IR spectra were recorded on a Perkin-Elmer 781 spectrometer and accurate mass measurements determined on a Kratos MS 50TC mass spectrometer. Elemental analyses were determined on a Carlo-Erba 1106 analyser and polarimetry measurements were carried out on an Optical Activity Ltd. instrument using sodium light. UV spectra were obtained on a SP 800A spectrophotometer. Tetrahydrofuran and ether were distilled prior to use from sodium/benzophenone ketyl and dichloromethane was distilled from finely divided (Fisons) calcium hydride. Thin layer chromatography was carried out on silica gel 60 F_{254} 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). For all X-ray structures reported, atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.

[(1S)-*endo*]-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-chloroformate (2). A solution of [(1S)-*endo*]-(-)-borneol (9.0g, 58 mmol) and dry pyridine (4.61g, 58 mmol) in anhydrous ether (200 ml) was added dropwise to a rapidly stirred solution of phosgene (20% w/v in toluene, 86

ml, 174 mmol) under argon at 0°C. After the addition was complete the reaction mixture was stirred at room temperature for 4h and filtered. The precipitate was washed well with anhydrous ether. The ether fractions were combined and evaporated *in vacuo* to yield **2** as a pale yellow oil (12.1g, 97%); $bp_{0.7}$ 85°C (Kugelrohr); $[\alpha]^{21.5}$ = -36.5°, c = 5.1 (ethanol); M^+ 216.0917 $C_{11}H_{17}ClO_2$ requires 216.0917; ν_{max} (thin film) 1780 (s, C=O) cm^{-1};^{1}H NMR (200 MHz, $CDCl_3$) δ 0.8-0.9 (3s, 9H, 3xCH_3), 1.0-2.5 (m, 7H), 5.0 (ddd, 1H, C*H*O).

[(1S)-*endo*]-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-*N*-hydroxycarbamate (3). Chloroformate **2** (7.0g, 35 mmol) in ether (10 ml) was added dropwise to a stirred mixture of finely ground hydroxylamine hydrochloride (2.5g, 35 mmol) and potassium carbonate (4.4g, 32 mmol)in ether containing water (0.5 ml) at 0°C. The mixture was stirred at room temperature for 12h, filtered and evaporated *in vacuo* to give **3** as a colourless crystalline solid (6.74g, 98%); mp 85°C; M^+ 213.1366 $C_{11}H_{19}NO_3$ requires 213.1365; ν_{max} (mull) 3280 (br. s -OH), 1690 (s, C=O) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.82 (s, 3H, CH_3), 0.84 (s, 3H, CH_3), 0.87(s, 3H, CH_3), 0.7-2.5 (m, 7H), 4.0 (br. s, 1H), 4.85 (m, 1H,C*H*O), 7.0 (br. s, 1H).

[(1S)-*endo*]-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-*p*-nitrobenzenesulphonoxycarbamate (4). p-Nitrobenzenesulphonyl chloride (4.65g, 21 mmol) was added gradually to an ice-cold stirred solution of *N*-hydroxycarbamate in ether (150 ml). Concurrently triethylamine (1.81g, 18 mmol) in ether (25 ml) was added dropwise, ensuring that the reaction mixture was acidic at all times. The mixture was stirred at room temperature for 48h, filtered and the filtrate evaporated *in vacuo* to give **4** as a yellow solid (7.63g, 90%) which was recrystallised from chloroform/*n*-hexane to give fine cream needles; mp 138-139°C; $[\alpha]^{22}$ = -16.3°, c = 5.0 (ethanol); (Found: C, 51.5; H 5.63; N 7.04%. $C_{17}H_{22}N_2O_7S$ requires C, 51.3; H, 5.6; N, 7.0%); M^+ 398 $C_{17}H_{22}N_2O_7S$ requires 398; ν_{max} (mull) 3240, 3200, 1750 (s, C=O), 1535, 1195 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.6-2.4 (m, 16H), 4.75 (m, 1H, C*H*O), 8.27 (m, 4H), 9.6 (br. s 1H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 155.85, 157.17, 139.15, 130.71, 123.98, 83.75, 48.79, 47.74, 44.47, 35.94, 27.65, 26.64, 19.37, 18.47, 12.97.

Addition of [(1S)-*endo*]-1,7,7-trimethylbicyclo[2.2.1]heptan-2-oxycarbonylnitrene (5) to styrene. Benzyltriethylammonium chloride (0.07g, 0.3 mmol) was added to a stirred mixture of **4** (0.5g, 1.25 mmol) and styrene (0.5g, 4.3 mmol) in aquous sodium hydrogen carbonate solution (1M, 10 ml) and dichloromethane (6 ml). The mixture was stirred vigorously for 5h at ambient temperature following which dichloromethane (50 ml) was added and the two fractions separated. The organic fraction was washed with water (3x50 ml), dried (magnesium sulphate), and the solvent removed *in vacuo* to give a yellow oil. Residual styrene was removed under high vacuum at room temperature to give a viscous yellow oil containing equal amounts of the diastereomers of 1-([(1S)-*endo*]-1,7,7-trimethylbicyclo[2.2.1]heptan-2-oxycarbonyl)-2-phenylaziridine **6a** and **6b** (20%, as determined by ^{1}H NMR integral) as shown by spectral comparison with an authentic sample (*vide infra*).

1-([(1S)-*endo*]-1,7,7-trimethylbicyclo[2.2.1]heptan-2-oxycarbonyl)-2-(R,S)-phenylaziridine (6a and 6b). [(1S)-*endo*]-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-chloroformate **2** (0.36g, 1.66 mmol) in anhydrous ether (4 ml) was added dropwise to an ice

cold stirred solution of 2-phenylaziridine[3] (0.198g, 1.66 mmol) and triethylamine (0.336g, 3.33 mmol) in anhydrous ether (10 ml). The mixture was stirred at room temperature for 1h, filtered, and the solvent removed *in vacuo* to yield **6a** and **6b** as a colourless oil (0.49g, 96%); $[\alpha]^{24} = -23.3^{o}$, c = 4.0 (ethanol); M^+ 299.1880 $C_{19}H_{25}NO_2$ requires 299.18852; ν_{max} (thin film) 1720 (s, C=O) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.8-2.0 (m, 16H), 2.33 (m, 1H, H-1_b), 2.67 (dd, 1H, J=1.0, 6.0 Hz, H-1_a), 3.56 (m, 1H, H-3), 4.85 (br. d, 1H, C*H*O), 7.31 (s, 5H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 163.0, 136.65, 136.48, 128.07, 127.43, 125.99, 81.59, 48.43, 47.43, 44.37, 39.11, 38.87, 36.28, 36.09, 34.37, 33.94, 27.60, 26.53, 19.28, 18.40, 13.14.

Reaction of [(1S)-*endo*]-1,7,7-trimethylbicyclo[2.2.1]heptan-2-*p*-nitrobenzenesulphonoxycarbamate (4) with benzyltriethylammonium chloride. Benzyltriethylammonium chloride (0.1g, 4.39 mmol) was added to a stirred mixture of **4** (3.5g, 8.79 mmol) in aqueous sodium hydrogen carbonate solution (1M, 50 ml) and dichloromethane (180 ml). The reaction mixture was stirred vigorously overnight at room temperature, following which dichloromethane (100 ml) was added and the mixture washed with water (3x50 ml). The organic phase was dried (magnesium sulphate), evaporated *in vacuo*, and the product subjected to flash chromatography (silica, gradient elution 10/90 v/v-100/0 v/v ethyl acetate-*n*-hexane). Three fractions were collected in the following order:-

[(1S)-*endo*]-1,7,7-trimethylbicyclo[2.2.1]heptan-2-carbamate (11) (0.234g, 14%); mp 124-126°C; $[\alpha]^{22} = -34.4^{o}$, c = 4.96 (ethanol); M^+ 197.1425 $C_{11}H_{19}NO_2$ requires 197.1421; ν_{max} (KBr) 3480, 3340 (br. d, NH_2), 1700, 1605 (s, $CO.NH_2$) cm^{-1}; ^1H NMR (200 MHz,$CDCl_3$) δ 0.83 (s, 3H, CH_3), 0.84 (s, 3H, CH_3), 0.88 (s, 3H, CH_3), 0.97 (dd, 1H, J=13.7, 3.4 Hz), 1.19 (m, 2H), 1.61 (m, 2H), 1.84 (m, 1H), 2.24 (m, 1H), 4.74 (ddd, 1H, J=9.9, 3.3, 2 Hz, C*H*O), 5.11 (br. s, 2H, NH_2); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 157.5, 80.4, 48.6, 47.7, 44.7, 36.5, 27.8, 26.7, 19.5, 18.6, 13.3;

[(2R, 6S)-*endo*]-5-aza-1,10,10-trimethyl-3-oxatricyclo[5.2.1.$0^{2,6}$]decan-4-one (8) (0.74g,43%); mp 163-163.5°C; $[\alpha]^{21.5} = -73.4^{o}$, c = 5.1 (ethanol); (Found: C, 67.6; H, 9.0; N, 7.2%. $C_{11}H_{17}NO_2$ requires C, 67.7; H, 8.8; N, 7.2%); ν_{max} (KBr) 3300 (br. s, NH), 1755 (s, C=O), 1715 (s, NH) cm^{-1}; ^1H NMR (200 MHz,$CDCl_3$) δ 0.90 (s, 3H, CH_3), 0.94 (s, 6H, 2xCH_3), 1.30 (m, 2H, CH_2), 1.65 (m, 2H, CH_2), 1.87 (m, 1H, CH), 4.16 (dd, 1H, J=9.82, 4.68 Hz, C*H*N), 4.60 (dd, 1H, J=9.94, 1.68 Hz, C*H*O), 5.56 (br. s, 1H, NH); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 160.5, 85.71, 54.66, 49.04, 48.44, 29.51, 26.34, 19.97, 19.71, 17.82, 14.00;

[(6S)-*endo*)]-3-aza-11,11-dimethyl-5-oxatricyclo[6.2.1.$0^{1,6}$]undecan-4-one (9)(0.62g, 36%); mp 170-171°C; $[\alpha]^{23} = +72.1^{o}$, c = 5.1 (ethanol); (Found: C, 67.5; H, 8.8; N, 7.1%. $C_{11}H_{17}NO_2$ requires C, 67.7; H, 8.8; N, 7.2%); ν_{max} (KBr) 3345 (br. s, NH), 1713 (s, C=O), 1668 (s, NH) cm^{-1}; ^1H NMR (200 MHz,$CDCl_3$) δ 0.94 (s, 3H, CH_3), 0.95 (s, 3H, CH_3), 1.37 (m, 3H), 1.80 (m, 2H, CH_2), 2.95 (dd, 1H, J=10.7, 3.9 Hz, CH_bN), 3.3 (d, 1H, J=10.7 Hz, CH_aN), 4.51 (ddd, 1H, J=10.1, 4.4, 2.0 Hz, C*H*O), 6.25 (br. s, NH); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 155.92, 80.24, 46.16, 45.86, 44.48, 43.50, 32.75, 27.36, 24.50, 19.72, 18.42.

[(1S)-*endo*]-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-azidoformate (7). Chloroformate **2** (10g, 46 mmol) in dichloromethane (50 ml) was added over 10 m to a rapidly stirred solution of sodium azide (6.0g, 92 mmol) and tetrabutylammonium bromide (0.2g) in water (50 ml). The reaction mixture was stirred for 4h, separated and the aqueous fraction was extracted

with dichloromethane (2x20 ml). The organic fractions were combined, washed with water (x1), dried (magnesium sulphate), and evaporated *in vacuo* to yield **7** as a slightly yellow oil (10.1g, 98%);$bp_{0.15}$ 85°C; $[\alpha]^{22.5}$ = -42°, c = 4.9 (ethanol); M^+ 223.13207 $C_{11}H_{17}N_3O_2$ requires 223.1321; ν_{max} (thin film) 2150, 2115 (s, N_3), 1720 (s, C=O) cm^{-1}; ^1H NMR (200 MHz,$CDCl_3$) δ 0.86 (s, 3H, CH_3), 0.87 (s, 3H, CH_3), 0.89 (s, 3H, CH_3), 1.08 (dd, 1H, J=13.96, 3.42 Hz, CH), 1.28 (m, 2H, CH_2), 1.78 (m, 3H), 2.39 (m, 1H, CH), 4.89 (m, 1H, C*H*O); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 157.42, 84.58, 48.83, 47.77, 44.53, 63.10, 27.65, 26.56, 19.39, 18.53, 13.14.

Pyrolysis of azidoformate 7. The azidoformate **7** (20g, 89.6 mmol) was passed through a vertical spray pyrolysis apparatus at 300°C with a vacuum of 0.1-0.5 mmHg. The products were collected in a vessel cooled with dry-ice (16.08g, 92%) and purified by flash chromatography (silica, gradient elution 10/90 v/v-100/0 v/v ethyl acetate-*n*-hexane). Three products were eluted in the following order:- **[(2R, 6S)-*endo*]-5-aza-1,10,10-trimethyl-3-oxatricyclo[5.2.1.$0^{2,6}$]decan-4-one (8)** (9.96g, 57%); and a mixture of **[(6S)-*endo*)]-3-aza-11,11-dimethyl-5-oxatricyclo[6.2.1.$0^{1,6}$]undecan-4-one (9)** (2.97g, 17%) and **[(4R,8S)-*endo*]-6-aza-1,10,10-trimethyl-3-oxa-tricyclo[6.1.1.1]decan-4-one (10)** (4.37g, 25%); mp 170°C; (Found: C, 67.4; H, 9.0; N, 7.2%. $C_{11}H_{17}NO_2$ requires C, 67.7; H, 8.8; N, 7.2%); ^1H NMR (200 MHz,$CDCl_3$) δ 3.45 (m, 1H, C*H*N), 4.5 (m, 1H, C*H*O), 7.1 (br. NH); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 152.31, 82.69, 54.24, 48.58, 46.10, 41.28, 39.22, 36.63, 19.24, 18.64, 11.07. In addition azidoformate **7** was pyrolysed in a FVP apparatus at 300°C to give **8** (46%), **9** (23%), and **10** (23%).

Solution pyrolysis of 7. A solution of **7** (25g, 112 mmol) in 1,1,2,2-tetrachloroethane (TCE) (20ml) was added over 90m *(via* a syringe pump) to TCE (250 ml) at reflux under an argon atmosphere. The solvent was removed *in vacuo* and the brown oil obtained (21.8g, 99%) was subjected to flash chromatography (silica, eluted with ether) to yield **8** (8.00g, 37%). ^1H NMR (200 MHz) of crude reaction mixture prior to chromatography showed a product distribution of **8** (50%), **9** (39%), **10** (11%). Trace amounts of unreacted **7** and **11** were recovered during chromatography, the order of elution being **7**, **11**, and **8**, **9** and **10** were eluted together.

Photolysis of 7. A solution of **7** (5.28g, 23.6 mmol) in anhydrous dichloromethane (700 ml) was irradiated with uv light (400 W) for 160m and evaporated *in vacuo* to yield a brown oil (4.61 g, 100%).^1H NMR (200 MHz) analysis of the crude oil showed a product distribution of **8** (39%), **9** (25%), and **11** (35%). The oil was purified by flash chromatography (silica, *n*-hexane:ethyl acetate) which gave **11** (1.6g, 34%), **8** (1.7g, 36%), and **9** (1.1g, 25%).

[(2R, 6S)-*endo*]-*N*-Propionyl-5-aza-1,10,10-trimethyl-3-oxatricyclo[5.2.1.$0^{2,6}$]decan-4-one (12). A solution of **8** (2g, 10.2 mmol) in anhydrous toluene (100 ml) was added to a stirred suspension of oil-free sodium hydride (0.27g, 11.2 mmol) in toluene (30 ml) under argon. The reaction mixture was heated under reflux for 1h, cooled to room temperature and treated dropwise with propionyl chloride (1.0g, 10.8 mmol) in toluene (3 ml). The mixture was stirred for a further 1h, poured into saturated sodium hydrogen carbonate solution and the two fractions were separated. The organic fraction was washed with water, dried (magnesium sulphate) and evaporated *in vacuo* to give a colourless oil (2.62g) which was purified by

Kugelrohr distillation (2.42g, 95%); $bp_{0.25}$ 165°C; $[\alpha]^{26}$ = -150.6°, c = 5.0 (ethanol); M^+ 251.1524 $C_{14}H_{21}NO_3$ requires 251.1521; ν_{max} (thin film) 1780 (s, C=O), 1700 (s, C=O) cm^{-1}; ^1H NMR (200 MHz,$CDCl_3$) δ 0.90 (s, 3H, CH_3), 0.91 (s, 3H, CH_3), 0.93 (s, 3H, CH_3), 1.09 (t, 3H,CH_3, J=7.34 Hz), 1.1-1.7 (m, 4H), 2.24 (t, 1H, CH, J=4.0 Hz), 2.90 (dq, 2H, CH_2, J=7.73, 7.29 Hz), 4.45-4.6 (m, 2H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 174.0, 154.2, 82.4, 57.5, 49.2, 48.3, 47.6, 28.8, 26.1, 19.7, 17.8, 13.6, 8.1.

Preparation of 12 using *n*-butyl lithium. A solution of **8** (3.99g, 20 mmol) in anhydrous tetrahydrofuran (40 ml) at -78°C under argon was treated with *n*-butyl lithium (1.6M, 15.53 ml, 1.2 eq) and stirred for 30m, treated with freshly distilled propionyl chloride (2.74g, 30 mmol, 1.49 eq.), stirred for another 60m then allowed to come to ambient temperature. The reaction mixture was quenched with sodium carbonate solution, concentrated *in vacuo* and extracted with dichloromethane (4x40 ml). The combined organic extracts were washed successively with water (20 ml) and brine, dried (magnesium sulphate), filtered and evaporated to yield a pale yellow oil which was purified by flash chromatography (silica, ether:*n*-hexane, 2:1) or by distillation ($bp_{0.25}$ 165°C) gave **12** as a colourless oil (4.42g, 90%).

ASYMMETRIC TRANSFORMATIONS

Lithium enolate 13. A solution of lithium diisopropylamide (2.18 mmol, 1.1 eq.) was prepared by the dropwise addition of 1.6M butyl lithium (1.36 ml) to a solution of anhydrous diisopropylamine (0.221g, 2.18 mmol, 1.1 eq.) in dry tetrahydrofuran (30 ml) at 0°C under argon. The solution was stirred at 0°C for 30m, cooled to -78°C and treated with a solution of **12** (0.498g, 1.98 mmol, 1 eq.) in tetrahydrofuran (5 ml). The reaction mixture was stirred at this temperature for a further 30m before being treated with a range of substrates.

(i) Alkyl halides- General procedure:

(a) Benzyl bromide in the presence of sodium iodide. To a freshly prepared solution of LDA (0.11g, 8.94 mmol) *vide supra* in dry tetrahydrofuran (5 ml) at -78°C under argon, was added dropwise a solution of **12** (0.20g, 0.79 mmol) in dry tetrahydrofuran (8 ml). The reaction mixture was stirred at -78°C for 1h and treated with freshly distilled benzyl bromide (0.513g, 4.06 mmol, 5 eq.) followed by sodium iodide (pre-dried in a vacuum oven, 0.146g, 0.97 mmol, 1.2 eq.). The reaction mixture was warmed to -8°C (KCl, ice) and stirred overnight, quenched with ammonium chloride solution and concentrated *in vacuo*. The oil so obtained was treated with water (30 ml) and extracted with dichloromethane (4x60 ml). The combined organic extracts were washed successively with saturated sodium hydrogen carbonate, brine and dried (magnesium sulphate). Filtration and evaporation *in vacuo* gave an oil which was subjected to flash chromatography (silica, gradient elution *n*-hexane:ether 100:0 - 0:100) to give a colourless solid **[(2R,6S)]-*N*-((2'S)-benzylpropionyl)-5-aza-1,10,10-trimethyl-3-oxatricyclo[5.2.1.$0^{2,6}$]decan-4-one 14** which was recrystallised from methanol (0.218g, 80%); mp 100.5-101.5°C; $[\alpha]^{21}$ = -63.4°, c = 2.12 (dichloromethane); (Found: C, 74.0; H, 8.16; N, 4.12%. $C_{21}H_{27}NO_3$ requires C, 73.87; H, 7.97; N,4.10%); ν_{max} (thin film) 1760 (s, C=O), 1680 (s, C=O) cm^{-1}; ^1H NMR (200 MHz,$CDCl_3$) δ 0.91-0.93 (2xs, 9H, 3xCH_3), 1.11-1.52 (d, J=6.76 Hz, 3H, CH_3 superimposed on cm, 4H, 2xCH_2), 2.17 (t, 1H, CH,

J=4.18 Hz), 2.57 (dd, 1H, CH_2, J=13.19, 7.76 Hz), 3.12 (dd, 1H, CH_2, J=13.18, 7.23 Hz), 4.14 (m, 1H), 4.38 (dd, 1H,C*H*O J=9.64, 1.0 Hz), 4.55 (ddd, 1H, C*H*N, J=9.85, 4.27, 1.0 Hz), 7.12-7.30 (cm, 5H, aromatic H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 176.38, 153.76, 139.10, 129.04, 128.06, 126.04, 82.16, 57.75, 49.16, 48.23, 47.47, 39.53, 39.41, 26.05, 19.69, 19.01, 17.83, 16.47, 13.64. This was the only isomer detected.

(b) Ethyl iodide. This reaction was carried out as described for benzyl bromide *vide supra* to give **[(2R,6S)]-*N*-((2'S)-methylbutanoyl)-5-aza-1,10,10-trimethyl-3-oxatricyclo[5.2.1.$0^{2,6}$]decan-4-one** as a colourless solid (17 mg,6%) ; M^+ 279.182, $C_{16}H_{25}NO_3$ requires 279.183; ^1H NMR (200 MHz,$CDCl_3$) δ 0.93 (t, 3H, CH_3, J=7 Hz), 0.95 (s, 3H, CH_3), 0.96 (s, 3H, CH_3), 0.97 (s, 3H, CH_3), 1.15 (d, 3H, J=7Hz), 1.20-1.85 (m. 6H), 2.3 (t, 1H, J=4 Hz), 3.69 (sextet, 1H, J=7 Hz), 4.45-4.63 (m, 2H, C*H*O, C*H*N).

(c) Allyl bromide. This reaction was carried out as described above but with the exclusion of sodium iodide and quenched after 4h. The product was purified by flash chromatography and yielded **[(2R,6S)]-*N*-(2'S)-methylbut-3-enoyl)-5-aza-1,10,10-trimethyl-3-oxatricyclo[5.2.1.$0^{2,6}$]decan-4-one** as a colourless solid which was crystallised from aqueous methanol (70%); mp 79-80°C; (Found: C, 69.7; H, 8.71; N, 4.73%. $C_{17}H_{25}NO_3$ requires C, 70.07; H, 8.65; N,4.81%); ^1H NMR (200 MHz,$CDCl_3$) δ 0.96 (s, 3H, CH_3), 0.97 (s, 3H, CH_3), 0.98 (s, 3H, CH_3), 1.15 (d, 3H, J=6Hz), 1.20 (m, 1H), 1.39 (m, 1H), 1.55-1.70 (m, 2H), 2.15 (m, 1H), 2.27 (m, 1H), 2.51 (m 1H), 3.88 (m, 1H), 4.49-4.60 (m, 2H), 4.96-5.12 (m, 2H), 5.79 (m, 1H).

(d) Cleavage of benzyl adduct (14) with lithium benzyloxide. A stirred solution of benzyl alcohol (0.07g, 0.69 mmol) in anhydrous tetrahydrofuran (4 ml) at 0°C under argon was treated dropwise with *n*-butyl lithium (1.6M, 0.33 ml, 1.5 eq.). The mixture was stirred at 0°C for 15m then cooled to -78°C and treated dropwise with a solution of **14** (0.119g, 0.349 mmol) in anhydrous tetrahydrofuran (6 ml). The reaction mixture was stirred at -78°C for 15m, warmed to room temperature and stirred for a further 30m, quenched with saturated ammonium chloride solution (5 ml) and concentrated *in vacuo*. Water (15 ml) was added and the reaction products were extracted into dichloromethane (3x20 ml). The combined organic extracts were washed with saturated sodium hydrogen carbonate solution, brine, dried (magnesium sulphate), filtered and evaporated *in vacuo* to yield an oily solid (0.17g) which was purified by flash chromatography (silica, gradient elution *n*-hexane:ether 100:0 - 0:100) to yield **(2S)-phenylmethylbenzyl propionate** as a colourless waxy solid (0.085g, 96%), further elution gave the cleaved auxiliary **8** (0.057g, 84%). The ester had the following physical properties:- $[\alpha]^{21} = +24.59°$, c = 4.25 (dichloromethane) cf. lit. value of antipode -26° c = 6.12 (dichloromethane)[18]; ^1H NMR (200 MHz,$CDCl_3$) δ 1.16-1.19 (d, 3H, CH_3, J=6.67 Hz), 2.64-2.89 (cm, 2H, CH_2), 2.99-3.08 (cm, 1H, CH), 5.07 (s, 2H, O-CH_2), 7.12-7.34 (cm, 10H, aromatic H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 175.77, 139.14, 135.92, 128.89, 128.39, 128.27, 127.98, 126.22, 66.02, 41.41, 39.64, 29.62, 16.73.

(ii) Acyl halides- General procedure:

(a) Acetyl chloride. A stirred solution of the enolate of **12** (0.2g,0.791 mmol) in anhydrous tetrahydrofuran (12 ml) at -78°C under argon was treated rapidly with freshly distilled acetyl chloride (0.1g, 1.27 mmol, 1.6 eq.) in anhydrous tetrahydrofuran (2 ml). The reaction

mixture was stirred for 45s, quenched with ammonium chloride solution, concentrated *in vacuo* and the residue was extracted with dichloromethane (4x25 ml). The organic fractions were combined, washed with brine, dried (magnesium sulphate), filtered and evaporated *in vacuo* to yield **[(2R,6S)]-*N*-((2'S)-methyl-3-oxobutanoyl)-5-aza-1,10,10-trimethyl-3-oxatricyclo[5.2.1.0^{2,6}]decan-4-one** as an oil (0.204, 88%). Crystallisation from methanol gave a colourless solid (major product) (76 mg, 33%); mp 139-140.5°C; $[\alpha]^{23}$ =-51.1°, c = 3 (dichloromethane); M$^+$ (EI) 293.1617 $C_{16}H_{23}NO_4$ requires 293.1627; ν_{max} (mull) 2915, 1780 (s,C=O), 1722 (s,C=O), 1701 (s,C=O), 1362, 1292, 1225 cm^{-1}; ^{1}H NMR (200 MHz,$CDCl_3$) δ 0.90 (s, 3H, CH_3), 0.92 (s, 3H, CH_3), 0.93 (s, 3H, CH_3), 1.30-1.33 (d, 3H, CH_3, J=7.33 Hz), 1.30-1.58 (cm, 4H, 2xCH_2), 2.28 (s, 3H, CH_3CO), 4.49-4.51 (cm, 2H,C*H*O, C*H*N, superimposed on q, 1H, J=7.5 Hz); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 205.46, 169.75, 154.42, 83.10, 57.74, 53.05, 49.28, 48.44, 47.81, 28.19, 26.12, 19.69, 18.84, 17.89, 13.67, 12.20.

The reaction was repeated with the following substrates:-

(b)Propionyl chloride. The reaction was carried out as described above but was quenched after 1m to yield **[(2R,6S)-*N*-((2'S)-methyl-3-oxopentanoyl)-5-Aza-1,10,10-trimethyl-3-oxatricyclo[5.2.1.0^{2,6}]decan-4-one** as an oil (89%). Crystallisation from methanol gave the major product as a colourless solid (62 mg, 26%);; mp 120-121°C; $[\alpha]^{22}$ =-53.3°, c = 3 (dichloromethane);M$^+$ (EI) 307.1785 $C_{17}H_{25}NO_4$ requires 307.17835; ν_{max} (mull) 2922, 1765 (s,C=O), 1718 (s, C=O), 1705 (s, C=O), 1360, 1223, 1215 cm^{-1};^{1}H NMR (200 MHz,$CDCl_3$) δ 0.89 (s, 3H, CH_3), 0.91 (s, 3H, CH_3), 0.92 (s, 3H, CH_3), 0.99-1.06 (t, 3H, CH_3,J=7.24Hz), 1.28-1.32 (d, 3H, CH_3, J=7.28Hz, superimposed 1.16-1.62 cm, 4H, 2xCH_2), 2.11-2.29 (bs, 1H,), 2.46-2.80 (2xdq, 2H,CH_2, J=18.13, 7.33 Hz), 4.50-4.80 (cm, 2H, C*H*O, C*H*N, superimposed on q, 1H, J=7.29 Hz, CH); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 208.09, 170.00, 154.36, 83.05, 57.79, 52.46, 49.25, 48.42, 47.82, 33.68, 26.15, 19.69, 18.89, 17.88, 13.65, 12.58, 7.39.

(c)Benzoyl bromide. The reaction was quenched after after 2m and crystallisation from methanol gave **[(2R,6S)]-*N*-((2'S)-benzoylpropionyl)-5-aza-1,10,10-trimethyl-3-oxatricyclo[5.2.1.0^{2,6}]decan-4-one** as a colourless solid (126 mg, 48%); mp 133°C; $[\alpha]^{21}$ =+1.75°; c = 0.8 (dichloromethane); M$^+$ (EI) 355.1776 $C_{21}H_{25}NO_4$ requires 355.17835; ν_{max} (mull) 3365 (br. s, enol O-H), 2965, 1770 (s, C=O), 1705 (s, C=O), 1680 (s, C=O), 1600 (enol, C=C), 1215, 975 cm^{-1};^{1}H NMR (200 MHz,$CDCl_3$) δ 0.94 (2xs, 6H, 2xCH_3), 0.97 (s, 3H, CH_3), 1.44-1.44 (d, 3H, CH_3, J=7.26 Hz), superimposed on 1.16-1.71 (cm, 4H, 2xCH_2), 2.36-2.39 (t, 1H, J=4.21 Hz), 4.49-4.54 (d, 1H,C*H*O, J=10.23 Hz), 4.57-4.64 (dd, 1H, C*H*N, J=9.81, 4.24 Hz), 5.31-5.42 (q, 1H, J=7.27 Hz), 7.38-7.60 (cm, 3H, aromatic H), 7.78-7.99 (dd, 2H, aromatic H, J=6.82, 1.67 Hz); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 170.29, 169.39, 154.29, 134.94, 132.94, 131.57, 129.61, 128.43, 128.23, 127.50, 127.15, 83.07, 57.73, 49.22, 48.46, 48.39, 47.78, 26.07, 19.64, 18.82, 17.83, 13.60, 13.42.

(d)Methyl cyanoformate (Manders reagent)[20]. The reaction was quenched after 1.5m to yield **[(2R,6S)]-*N*-((2'S)-methylformylpropionyl)-5-aza-1,10,10-trimethyl-3-oxatricyclo[5.2.1.0^{2,6}]decan-4-one** as a colourless solid (81mg, 99%); mp 103-104.5°C; $[\alpha]^{21}$ = -96.99°, c = 4.05 (dichloromethane); M$^+$ (EI) 309.1575 $C_{16}H_{23}NO_5$ requires 309.15761; ν_{max} (mull) 2923, 1770 (s, C=O), 1740 (s, C=O), 1698 (s, C=O),1358, 1223, 1213 766 cm^{-1}; ^{1}H NMR (200 MHz,$CDCl_3$) δ 0.89 (s, 3H, CH_3), 0.91 (2xs, 6H, 2xCH_3), 1.33-1.37

(d, 3H, CH_3, J=7.29 Hz), 1.11-1.58 (cm, 4H, 2xCH_2), 2.27 (bs, 1H), 3.64 (s, 3H, OCH_3), 4.44-4.50 (cm, 2H, C*H*O, C*H*N), superimposed on 4.35-4.45 (q, 1H, J=7.29 Hz, CH); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 170.78, 169.18, 154.02, 82.85, 57.79, 52.08, 49.19, 48.34, 47.69, 45.32, 26.04, 19.60, 18.76, 17.79, 13.57, 12.91.

(iii) Aldehydes (the aldol reaction)- General procedure using metal-enolates of 12:

(a) Benzaldehyde. Neat freshly distilled benzaldehyde (0.21g, 1.98 mmol, 1eq.) was added rapidly to a freshly prepared solution of lithium enolate of **12** *vide supra* (1.98 mmol, 1 eq.) at -78°C and the reaction mixture was quenched after 30s with saturated ammonium chloride solution (5 ml). Water (50 ml) was added and the reaction products were extracted into ether (3x20 ml). The organic fractions were combined, dried (magnesium sulphate), filtered and evaporated to dryness *in vacuo* to give a colourless crystalline mass of the aldol products (0.69g, 97%); ^1H NMR (360 MHz, $CDCl_3$) showed that all four possible diastereomeric aldol products were present in a ratio of 55.4:28.7:10.3:5.7.

(b) *iso*-Butyraldehyde. The reaction was carried out using freshly distilled *iso*-butyraldehyde (0.122g, 1.69 mmol, 2.1 eq.) and lithium enolate of **12** (0.79 mmol). The reaction was quenched after 2m and the products isolated (*vide supra*) (0.225, 88%) as an oil which solidified on standing. HPLC analysis (silica, spherisorb 5μ, *n*-hexane:ether, 5:1) gave a product distribution of 64.7:22.5:7.9:4.9 cf. EVANS 71.4:11.0:10.6:7.0.[10].

(c) Acetaldehyde. The reaction was conducted for 90s and 180s before quenching but starting material was still present. The reaction was then conducted for 1.75h. To freshly prepared lithium enolate **13** (0.598 mmol) in anhydrous tetrahydrofuran (10 ml) at -78°C under argon, freshly distilled acetaldehyde (1 ml, 0.78g, 17.8 mmol, 30 eq.) in anhydrous tetrahydrofuran (5 ml) was added and stirred for 1.75h, quenched with saturated ammonium chloride solution and extracted with dichloromethane (3x40 ml). The combined organic extracts were washed with saturated sodium hydrogen carbonate solution, brine, dried (magnesium sulphate), filtered and evaporated *in vacuo* to yield a brown oil (0.18g, 100%) which was analysed by ^1H NMR. FAB-MS (thioglycerol) showed not only aldol products but dehydrated products as well as cleaved auxiliary **8** to be present.

(d)Using the boron enolate 18 of 12. To a solution of **12** (0.3g, 1.2 mmol) in anhydrous dichloromethane (5 ml) at 0°C under argon was added di-*n*-butylboron triflate (1M in dichloromethane, 1.31 ml, 1.31 mmol, 1.1 eq.) followed by di-*iso*-propylethylamine (0.18g,1.43 mmol,1.2 eq.). The mixture was stirred for 30m then cooled to -78°C and treated with a variety of substrates.

(e) Aldehydes- General procedure:

A solution of aldehyde (1.31 mmol) in tetrahydrofuran (1 ml) was added dropwise to the boron enolate solution *vide supra* at -78°C and stirred for 30m, the temperature was allowed to rise to 20°C and the mixture stirred for a further 1.5h, quenched with a pH7 phosphate buffer (50 ml) and the organic phase separated. The aqueous phase was extracted with dichloromethane (3x30 ml). The organic fractions were combined and evaporated *in vacuo*. The resultant oil was treated with 30% w/v hydrogen peroxide solution (2 ml) at 0°C for 1h and then thoroughly extracted with ether. The ether extracts were combined, dried (sodium

sulphate) and evaporated. The products were isolated following purification by flash chromatography.

(f) *iso*-Butyraldehyde. The protocol just described was followed and a single product **[(2R,6S)]-*N*-((3'R)-hydroxy-(2'R)-methyl-4'-methylpentanoyl)-5-aza-1,10,10-trimethyl-3-oxatricyclo[5.2.1.0^{2,6}]decan-4-one** was isolated as a colourless solid which was recrystallised from ethyl acetate-petroleum ether (86%); mp 161-162°C; (Found: C, 66.8; H, 9.32; N, 4.44%. $C_{18}H_{29}NO_4$ requires C,66.84; H,9.04; N,4.33%); ν_{max} (mull) 1770, 1660 cm^{1}; m/z (CI) 324 (M^++1, 20%), 306 (100%), 252 (95%), 196 (80%); ^{1}H NMR (200 MHz,$CDCl_3$) δ 0.90 (d, 3H, J=7Hz), 0.97 (s, 3H, CH_3), 0.98 (s, 3H, CH_3), 0.99 (s, 3H, CH_3), 1.02 (d, 3H, J=7 Hz, CH_3), 1.15 (m, 1H), 1.23 (d, 3H, J=8Hz), 1.40 (m, 1H), 1.58-1.75 (m, 3H), 2.30 (t, 1H, J=4Hz), 2.87 (br, 1H, OH), 3.52 (dd, 1H, J=8.0, 2.5 Hz), 4.02 (qd, 1H, J=6.0, 2.5 Hz), 4.4-4.64 (cm, 2H).

(g)Benzaldehyde. [(2R,6S)]-*N*-((3'R)-hydroxy-(2'R)methyl-3'-phenylpropionyl)-5-aza-1,10,10-trimethyl-3-oxatricyclo[5.2.1.0^{2,6}]decan-4-one 18 was isolated as a single product by following the method described above and was recrystallised from ethyl acetate-petroleum ether (52%); mp 136-137°C; ν_{max} (mull) 1770, 1658cm^{-1} ; ^{1}H NMR (200 MHz,$CDCl_3$) δ 0.95 (s, 3H, CH_3), 0.98 (br. s, 6H, 2xCH_3),1.17 (d, 3H, J=7Hz), 1.05-1.44 (m, 2H), 1.55-1.73 (m, 2H), 2.30 (t, 1H, J=4Hz), 3.00 (br, 1H, OH), 4.14 (qd, 1H, J=7.0, 3.5 Hz), 4.45-4.58 (m, 2H), 5.12 (d, 1H, J=3.5 Hz), 7.21-7.45 (m, 5H, aromatic H).

(h) Procedure for the generation of titanium(IV)enolate 19 and subsequent aldol reaction with benzaldehyde: To a stirred solution of **12** (0.200g, 7.97 mmol) in anhydrous dichloromethane (4 ml) at -78°C under argon was added titanium tetrachloride (0.51 ml, 8.8 mmol, 1.1 eq.). The resulting solution was stirred for 10m and treated dropwise with triethylamine (0.1g, 9.88 mmol, 1.2 eq.) in dichloromethane (2 ml). Stirring was continued at -78°C for a further 90m before freshly distilled benzaldehyde (0.108g,1.02 mmol, 1.2 eq.) in dichloromethane (4 ml) was added dropwise. The reaction mixture was stirred for 48h at room temperature, quenched with saturated ammonium chloride solution and extracted with dichloromethane (3x40 ml). The combined organic extracts were washed with saturated sodium hydrogen carbonate solution, brine, dried (magnesium sulphate), filtered and evaporated *in vacuo* to yield a yellow oil (0.312g, 109%) which was analysed by ^{1}H (200 MHz)NMR. The analysis revealed that as well as contamination with benzaldehyde and benzoic acid there was only two isomers present. The main features in the spectrum were two carbinol resonances at δ 5.09-5.14 (d, 1H, J=10.94 Hz, PhC.OH.*H*) (major isomer) and δ 5.15-5.5.19 (d, 1H, J=9.0 Hz, PhC.OH.*H*) (minor isomer), and an α-methine resonance at δ 4.68-4.80 (dq, 1H, J=10.92,6.92 Hz, PhC.OH.H-C*H*.CH_3.CO.) (major isomer).

(v) Diels-Alder reactions:

(a) Preparation of [(2R, 6S)-*endo*]-*N*-Acryloyl-5-aza-1,10,10-trimethyl-3-oxatricyclo[5.2.1.0^{2,6}]decan-4-one (21). To a solution of oxazolidinone **8** (0.5g, 2.56 mmol) in anhydrous tetrahydrofuran (40 ml) under argon at 0°C methyl magnesium bromide (3.0 M in ether, 0.9 ml,2.7 mmol, 1.05 eq.) was added and stirred for 10m. The temperature was lowered to -78°C and the reaction mixture was treated with freshly distilled acryloyl chloride (0.3g, 3.3 mmol, 1.3 eq.), stirred for 10m, and the temperature was raised to 0°C. The mixture

was stirred for 75m quenched with aqueous ammonium chloride and extracted into ether (3x75 ml). The combined organic extracts were washed with saturated sodium hydrogen carbonate solution, brine, dried (magnesium sulphate), filtered and evaporated *in vacuo* to yield a colourless solid which was subjected to flash chromatography (silica, *n*-hexane:ethyl acetate 7:1) (0.48g, 75%); mp 47-50°C; $[\alpha]^{21.5}$ = -156.9°, c = 2.58 (dichloromethane); M^+ 249.1371 $C_{14}H_{19}NO_3$ requires 249.136475; ν_{max} (mull) 2930, 1770 (s, C=O), 1690 (s, C=O), 1620, 1460, 1415, 1380 cm^{-1}; ^1H NMR (200 MHz,$CDCl_3$) δ 0.95 (s, 3H, CH_3), 0.96 (s, 3H, CH_3), 0.97 (s, 3H, CH_3), 1.09-1.7 (m, 4H, 2x CH_2), 2.31 (t, 1H, J=4.2Hz), 4.49-4.66 (cm, 2H, C*H*O, C*H*N), 5.85 (dd, 1H, J=10.45, 1.86Hz), 6.50 (dd, 1H, J=17, 1.92Hz), 7.55 (dd, 1H, J=17, 10.48 Hz); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 164.96, 154.04, 131.39, 127.19, 82.63, 57.82, 49.33, 48.44, 47.68, 26.18, 19.76, 19.66, 17.92, 13.67.

(b) Preparation of [(2R, 6S)-*endo*]-*N*-Crotonoyl-5-aza-1,10,10-trimethyl-3-oxatricyclo[5.2.1.$0^{2,6}$]decan-4-one (22). A solution of oxazolidinone **8** (1.0g, 5.13 mmol) in anhydrous tetrahydrofuran (30 ml) was added to a freshly prepared solution of methyl magnesium bromide (0.73g, 6.15 mmol, 1.2 eq.) in anhydrous ether (30 ml) at 0°C under argon and stirred for 20m before the temperature was lowered to -78°C. Freshly distilled crotonoyl chloride (0.65g, 6.22 mmol, 1.2 eq.) was added and the mixture stirred for 20m and the temperature raised to 0°C. The reaction mixture was stirred at this temperature for 1h then at ambient temperature overnight. Thin layer chromatography on silica (*n*-hexane:ethyl acetate) revealed a trace of starting material. The reaction mixture was quenched with ammonium chloride solution and extracted with ether (3x50 ml). The combined organic extracts were washed with saturated sodium hydrogen carbonate solution, brine, dried (magnesium sulphate), filtered and evaporated *in vacuo* to yield a pale yellow solid which was subjected to flash chromatography (silica, *n*-hexane:ethyl acetate 7:1) (1.15g, 85%); mp 117-121°C; $[\alpha]^{21.5}$ = -173.9°, c = 4.94 (dichloromethane); M^+ 263.1521 $C_{15}H_{21}NO_3$ requires 263.152125; ν_{max} (mull) 2920, 1763(s, C=O), 1682 (s, C=O), 1635, 1375, 1208, 1050 cm^{-1}; ^1H NMR (200 MHz,$CDCl_3$) δ 0.90-0.91 (2xs, 9H, 3xCH_3), 1.08-1.61 (cm, 4H,2xCH_2), 1.88 (dd,3H, CH_3, J=6.69, 1.44 Hz), 2.24 (t, 1H, CH, J=4.2 Hz), 4.45 (ddd, 1H, C*H*O, J=9.78, 2.2, 0.6 Hz), 4.56 (ddd, 1H, C*H*N, J=9.8, 4.3, 1.22 Hz), 7.05 (dq, 1H, CH_3CH=CH, J=15.26, 6.56 Hz), 7.27 (dq, 1H, CH=C*H*CO), J=15.25, 1.50 Hz); ^{13}C NMR (90.56 MHz, $CDCl_3$) δ 164.95, 154.05, 146.17, 121.65, 82.34, 57.76, 49.25, 48.30, 47.78, 26.17, 19.71, 19.59, 18.19, 17.85, 13.60.

(c) Preparation of [(2R, 6S)-*endo*]-*N*-Cinnamoyl-5-aza-1,10,10-trimethyl-3-oxatricyclo[5.2.1.$0^{2,6}$]decan-4-one (23). A solution of oxazolidinone **8** (0.624g, 3.2 mmol) in anhydrous tetrahydrofuran (40 ml) was added to a freshly prepared solution of methyl magnesium bromide (0.73g, 6.15 mmol, 1.2 eq.) in anhydrous ether (30 ml) at 0°C under argon and stirred for 10m before the temperature was lowered to -78°C. Freshly distilled cinnamoyl chloride (0.64g, 3.84 mmol, 1.2 eq.) in anhydrous tetrahydrofuran (5 ml) was added and the mixture stirred for 20m and then warmed to room temperature and stirred overnight. The reaction mixture was quenched with ammonium chloride solution concentrated *in vacuo* taken up in water (20 ml) and extracted with dichloromethane (3x60 ml). The combined organic extracts were washed with saturated sodium hydrogen carbonate solution, brine, dried (magnesium sulphate), filtered and evaporated *in vacuo* to yield a solid

which was subjected to flash chromatography (silica, *n*-hexane:ethyl acetate 7:1) (0.84g, 81%); mp 169.5-170.5°C (*n*-hexane:di-*iso*-propylether); $[\alpha]^{23.5}$ = -133.0°, c = 4.22 (dichloromethane); M+325.1674 $C_{20}H_{23}NO_3$ requires 325.167775; ν_{max} (mull) 2920, 1760 (s, C=O), 1680 (s, C=O), 1615 (C=C), 1378, 1368, 1210, 1048 cm^{-1}; ^1H NMR (200 MHz,$CDCl_3$) δ 0.97-0.98 (2xs, 9H, 3xCH_3), 1.09-1.67 (cm, 4H,2xCH_2), 2.35 (t, 1H,CH, J=8.41 Hz), 4.53 (dd, 1H, C*H*O, J=11.1, 1.42 Hz), 4.64 (ddd, 1H, C*H*N, J=11.1, 4.50, 1.33 Hz), 7.34-7.39 (cm, 3H, aromatic H), 7.58-7.63 (cm, 2H, aromatic H), 7.81 (d, 1H, PhC*H*=CH-, J=15.74Hz), 8.00 (d, 1H,CH=C*H*CO, J=15.73 Hz); ^{13}C NMR (90.56 MHz, $CDCl_3$) δ 165.16, 154.15, 145.80, 134.46, 130.33, 128.63, 128.37, 116.90, 82.43, 57.94, 49.29, 48.35, 47.82, 26.20, 19.73, 19.66, 17.88, 13.62.

(d) Diels-Alder reaction between acryloyl compound (21) and cyclopentadiene at -78°C.

Without the use of a catalyst. Freshly cracked cyclopentadiene (1.50g, 22.7 mmol, 12 eq.) was added to a solution of **21** (0.48g, 1.93 mmol) in anhydrous dichloromethane (50 ml) at 0°C under argon. The reaction mixture was stirred at 0°C for 23h evaporated *in vacuo* and subjected to flash chromatography to yield a colourless solid (0.42g, 69%). High-field ^1H NMR (360 MHz) analysis showed the presence of two isomers in the ratio of 1.1:1.

Using $TiCl_2(OPr^i)_2$ as a catalyst[15]. A solution of **21** (0.162g, 0.651 mmol) in anhydrous dichloromethane (3 ml) at -78°C under argon was treated with titanium(IV) chloride (0.52g, 2.74 mmol 4eq.) followed by titanium(IV) *iso*-propoxide (0.74g, 2.60 mmol, 4 eq.). Freshly cracked cyclopentadiene (0.43g, 7.17 mmol, 11 eq.) was added and the reaction mixture was stirred for 22h, poured onto crushed ice and extracted with dichloromethane (3x20 ml). The combined organic fractions were washed with saturated sodium hydrogen carbonate solution, brine, dried (magnesium sulphate), filtered and evaporated *in vacuo* to yield a solid which was subjected to flash chromatography (silica, gradient elution *n*-hexane:ether 100:0-50:50) to give a colourless solid (0.17g, 83%). The solid consisted of a mixture of two *endo*-isomers in a ratio of 2:1, which were separated by column chromatography (TLC silica (70g), *n*-hexane:ether 40:1). **[(2R,6S)]-*N*-((3'R,4'R,6'R)-Bicyclo[2.2.1]heptene-4'-carbonyl)-5-aza-1,10,10-trimethyl-3-oxatricyclo[5.2.1.$0^{2,6}$]decan-4-one** (minor isomer):-mp 143-145.5°C (*n*-hexane:di-*iso*-propylether); $[\alpha]^{23}$ =-25.1°, c = 1.95 (dichloromethane); M+315.1839 $C_{19}H_{25}NO_3$ requires 315.183425; ν_{max} (mull) 2924, 1770 (s, C=O), 1755 (s, C=O), 1695 (C=C), 1280, 1220, 1040 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 0.92 (s, 3H, CH_3), 0.94 (s, 3H, CH_3), 0.96 (s, 3H, CH_3), 1.06-1.68 (cm, 7H), 1.97 (ddd, 1H, J=12.77, 9.09, 3.74 Hz), 2.15-2.27 (cm, 1H), 2.91 (bs, 1H, CH), 3.28 (bs, 1H), 4.00-4.05 (ddd, 1H,J=9.11, 4.42, 3.47Hz), 4.48-4.49 (cm, 2H, C*H*N, C*H*N), 5.85 (dd, 1H, =C*H*, J=5.64, 2.85 Hz), 6.20 (dd, 1H, =C*H*, J=5.64, 3.08 Hz);^{13}C NMR (50.3 MHz, $CDCl_3$) δ 174.51, 153.93, 137.65, 131.50, 82.26, 58.07, 49.93, 49.23, 48.18, 47.76, 46.12, 43.09, 42.68, 29.42, 26.16, 19.55, 19.30, 17.83, 13.65. **[(2R,6S)]-*N*-((3'S,4'S,6'S)-Bicyclo[2.2.1]heptene-4'-carbonyl)-5-aza-1,10,10-trimethyl-3-oxatricyclo[5.2.1.$0^{2,6}$]decan-4-one** (major isomer):- mp 155-157.5°C ; $[\alpha]^{22}$ = -287.5°, c = 3.08 (dichloromethane); (Found: C, 72.3; H, 8.0; N, 4.4%. $C_{19}H_{25}NO_3$ requires C,72.5; H,8.05; N,4.72%); M+315.1823 $C_{19}H_{25}NO_3$ requires 315.183425; ν_{max} (mull) 2920, 1790 (s, C=O), 1775 (s, C=O), 1640 (C=C), 1460, 1380 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 0.90 (s, 3H,

CH_3), 0.93 (s, 3H, CH_3), 0.95 (s, 3H, CH_3), 1.08-1.70 (cm, 7H), 1.86 (ddd, 1H, J=12.6, 9.0, 4.7 Hz), 2.19 (t, 1H, J=4.0Hz), 2.90 (bs, 1H), 3.36 (bs, 1H), 4.03 (ddd, 1H, J=9.0, 4.4, 3.4Hz), 4.45 (dd, 1H, J=9.3, 1.3 Hz), 4.51 (ddd, 1H, J=9.9,4.2, 1.2 Hz), 5.77 (dd, 1H, =C*H*, J=5.6, 2.8 Hz), 6.20 (dd, 1H, =C*H*,J=5.6, 3.0 Hz); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 174.31, 153.89, 137.88, 130.95, 82.17, 57.62, 50.00, 49.18, 48.19, 47.53, 46.26, 42.79, 42.63, 28.80, 26.14, 19.60, 19.35, 17.73, 13.55.

Using Et_2AlCl as a catalyst. To a rapidly stirred solution of **21** (0.102g, 0.41 mmol) in anhydrous dichloromethane (2 ml) under argon at -78°C was added freshly cracked cyclopentadiene (0.27g, 4.1 mmol, 10 eq.) followed by diethylaluminium chloride (1.8M in toluene, 0.3 ml, 0.54 mmol, 1.4 eq.). After 3m the reaction was quenched with hydrochloric acid (2M, 5ml) and stirred for 5m. The two fractions were separated and the aqueous fraction was extracted with dichloromethane (3x10 ml). The combined organic fractions were washed with saturated sodium hydrogen carbonate solution, brine, dried (magnesium sulphate), filtered and evaporated *in vacuo* to yield a solid which was subjected to flash chromatography (silica, gradient elution *n*-hexane:ether 100:0-50:50) to give a colourless solid (0.124g, 98%). The solid consisted of a mixture of the same two *endo*-isomers (*vide supra*) but in a ratio of 4:1.

(f)Diels-Alder reaction between acryloyl compound (21) and isoprene at -78°C.

Using $TiCl_2(OPr^i)_2$ as a catalyst. The same protocol as for cyclopentadiene (*vide supra*) the reaction was conducted for 46h before quenching. Work-up provided a colourless oil (0.08g, 80%) which crystallised on standing. ^1H NMR (360 MHz) using a europium chiral shift reagent (tris[3-(heptafluoropropylhydroxymethylene)-d-camphorato]europium(III)) revealed that the two *endo*-isomers were present in a ratio of 2:1.

Using Et_2AlCl as a catalyst. Adopting the same procedure as above work-up yielded a colourless solid (0.24g, 94%) which contained the *endo*-isomers in a ratio of 5:1.

(g)Diels-Alder reaction between crotonoyl compound (22) and cyclopentadiene at -78°C.

Using $TiCl_2(OPr^i)_2$ as a catalyst. To a stirred solution of titanium(IV) chloride (0.29g, 1.53 mmol, 4 eq.) and titanium(IV) *iso*-propoxide (0.43g, 1.51 mmol, 4 eq.) in anhydrous dichloromethane (2 ml) at -78°C under argon was added a solution of **22** (0.1g, 0.38 mmol) in anhydrous dichloromethane (3 ml). Freshly cracked cyclopentadiene (0.25g, 3.79 mmol) was added and the mixture stirred for 20h, poured onto crushed ice and extracted with dichloromethane (3x20 ml). The combined organic fractions were washed with saturated sodium hydrogen carbonate solution, brine, dried (magnesium sulphate), filtered and evaporated *in vacuo* to yield the product which was subjected to flash chromatography(silica, gradient elution *n*-hexane:ether 100:0-50:50) to give a colourless solid (0.115g, 92%). The product was analysed by ^1H NMR (360 MHz) and was shown to contain four isomers in the ratio of 51:34:11:4. Major isomers were not characterised due to difficulty in separation of these compounds.

Using Et_2AlCl as a catalyst. To a stirred solution of **22** (0.1g, 3.8 mmol) in anhydrous dichloromethane (2 ml) at -78°C under argon was added diethylaluminium chloride (1.8M in toluene, 0.3 ml, 0.539 mmol, 1.4 eq.) which produced a bright yellow complex. This complex

was treated rapidly *via* a canula with pre-cooled freshly cracked cyclopentadiene (1.0g, 15 mmol, 40 eq.). After 5m the colour had faded and the reaction mixture was diluted with dichloromethane (50 ml) and quenched with dilute hydrochloric acid (2M, 10 ml). The organic layer was separated and the aqueous fraction extracted with ether (3x30 ml). The combined organic fractions were washed with saturated sodium hydrogen carbonate solution, brine, dried (magnesium sulphate), filtered and evaporated *in vacuo* to yield the product which was subjected to flash chromatography (silica, gradient elution *n*-hexane:ether 100:0-50:50) to give a colourless solid (0.12g, 96%). Analysis of the product revealed the same four isomers in the ratio 67:15:3:15.

(h) Diels-Alder reaction between cinnamoyl compound (23) and cyclopentadiene at -78°C.

Using Et_2AlCl as a catalyst. To a stirred solution of **23** (0.101g, 0.311 mmol) in anhydrous dichloromethane (2 ml) at -78°C under argon was added diethylaluminium chloride (1.8M in toluene, 1.0 ml, 0.568 mmol, 1.8 eq.) which produced a deep yellow/orange complex. This complex was treated rapidly *via* a canula with pre-cooled freshly cracked cyclopentadiene (1.0g, 15 mmol, 48 eq.). The reaction mixture was warmed to -20°C and within 1m the colour had faded to pale yellow/green, it was diluted with dichloromethane (50 ml) and quenched with dilute hydrochloric acid (2M, 10 ml). The organic layer was separated and the aqueous fraction extracted with dichloromethane (3x30 ml). The combined organic fractions were washed with saturated sodium hydrogen carbonate solution, brine, dried (magnesium sulphate), filtered and evaporated *in vacuo* to yield the product which was subjected to flash chromatography (silica, gradient elution *n*-hexane:ether 100:0-0:100) to give **[(2R,6S)]-*N*-((3'S,4'R,5'R,6'S)-5'-phenylbicyclo[2.2.1] heptene-4'-carbonyl)-5-aza-1,10,10-trimethyl-3-oxatricyclo[5.2.1.$0^{2,6}$]decan-4-one 24** as a colourless solid (0.11g, 92%). Analysis of the product by ^1H NMR (360 MHz) revealed only one isomer; mp 131-134°C (*n*-hexane:di-*iso*-propylether); $[\alpha]^{21}$ = -263.6°, c = 2.54 (dichloromethane); M^+391.2149 $C_{25}H_{29}NO_3$ requires 391.214725; ν_{max} (mull) 2930, 1778 (s, 2xC=O), 1700 (C=C), 1338, 1225, 1212, 1060 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 0.94 (s, 3H, CH_3), 0.97 (s, 3H, CH_3), 0.98 (s, 3H, CH_3), 1.14-1.25 (cm, 1H), 1.39-1.45 (m, 1H), 1.58-1.73 (dd, 1H, J=8.69, 1.69 Hz, superimposed on cm, 2H), 1.98 (bd, 1H, J=8.72 Hz),2.25 (t, 1H, CH, J=4.22 Hz), 2.99-3.01 (cm, 1H, CH), 3.34 (dd, 1H, CH, J=5.26, 1.68 Hz), 3.56 (bs, 1H, CH), 4.22 (dd, 1H, CH, J=5.27, 3.35 Hz), 4.48 (dd, 1H, C*H*O, J=9.78, 1.59 Hz), 4.57 (ddd, 1H, C*H*N, J=9.89, 4.47, 1.18 Hz), 5.87 (dd, 1H, =CH, J=5.63, 2.75Hz), 6.52 (dd, 1H, =CH, J=5.63, 3.19 Hz),7.14-7.29 (cm, 5H, aromatic H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 173.54, 153.91, 143.63, 140.08,131.86, 128.24, 127.34, 125.85, 82.24, 57.66, 50.33, 49.24, 48.31, 48.09, 47.51, 47.31, 46.12, 26.18, 19.71, 19.43, 17.83, 13.64.

(i)Cleavage of the cycloadduct 24 formed in the reaction between 17 and cyclopentadiene : chiral ester formation. *n*-Butyl lithium (1.6M, 1 ml, 1.6 mmol, 1.2 eq.) was added to a solution of benzyl alcohol (0.272g, 2.52 mmol, 2 eq.) in anhydrous tetrahydrofuran (5 ml) at -78°C under argon and the mixture was stirred for 30m, then treated with cinnamate adduct **24** (0.5g, 1.28 mmol) in anhydrous tetrahydrofuran (5 ml). The mixture was warmed to 0°C and stirred for 75m and then at ambient temperature for 3h, quenched with ammonium chloride solution and concentrated *in vacuo*. Water (40 ml) was

added and the reaction products were extracted into dichloromethane (4x60 ml). The combined organic fractions were washed with saturated sodium hydrogen carbonate solution, brine, dried (magnesium sulphate), filtered and evaporated *in vacuo* to yield an oil which was subjected to flash chromatography (silica, gradient elution *n*-hexane:ether 19:1-7:3) to give chirally pure **benzyl(3S,4S,5R,6R)-5-phenylbicyclo[2.2.1] heptene-4-carboxylate 25** (0.333g, 86%). Further elution (*n*-hexane:ether 1:4) yielded the recovered chiral auxiliary **8** (0.142g, 57%). Physical data for the ester: $[\alpha]^{21} = -121.1^{o}$,cf. lit value of antipode $+121.0^{o}$, c = 1.36 (dichloromethane)[24]; M^{+}391.2149 $C_{25}H_{29}NO_3$ requires 391.214725; ν_{max} (thin film) 2980, 1735 (s, C=O), 1502, 1458, 1335, 1260, 11701338, 1220 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.64-1.70 (dd, 1H, CH_2, J=8.67, 1.76 Hz), 1.88 (bd, 1H, CH_2, J=8.33 Hz), 3.12-3.14 (cm, 2H), 3.15 (bd, 1H,CH_2, J=3.63Hz), 3.34 (bs, 1H, CH), 5.17 (d, 1H, CH_2, J=12.42 Hz), 5.26 (d, 1H, CH_2, J=12.40 Hz), 6.17 (dd, 1H, =CH, J=5.65, 2.75 Hz), 6.51 (dd, 1H, =CH, J= 5.65, 3.21 Hz), 7.25-7.47 (cm, 10H, 2x aromatic H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 173.76, 143.93, 138.89, 135.98, 134.17, 128.23, 127.83, 127.76, 127.20, 125.79, 65.95, 51.99, 48.02, 47.18, 46.95, 46.11.

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Structure of Manasse's Dimer from *endo*-2-Hydroxyepicamphor by NOE Difference Spectroscopy

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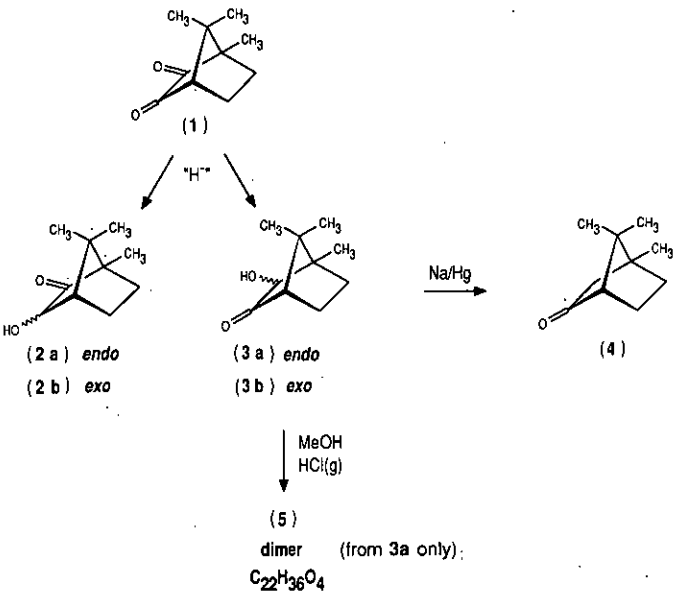
Reduction of (1*R*)-(+)-camphorquinone by zinc in acetic acid yields a mixture of *endo*-2-hydroxyepicamphor and 3-hydroxycamphor. The former undergoes reaction in anhydrous methanol with HCl gas to furnish a stable crystalline solid, first reported in 1902. High-resolution electron impact mass spectrometry showed the solid to be a dimer of formula $C_{22}H_{36}O_4$. The $^{13}C\{^1H\}$ spectrum showed 11 discrete environments, in keeping with a symmetrical dimer. High-field ^1H NOE difference experiments were used to determine not only the connectivity but also the stereochemistry of the system. All of the NOE experiments are consistent with only one structure, that of the symmetrical dimer. In addition, 2D carbon–proton correlation experiments (HETCOR) were used to assign unambiguously its $^{13}C\{^1H\}$ spectrum.

KEY WORDS 2-Hydroxyepicamphor 3-Methoxy dimer ^1H NOE difference spectroscopy ^{13}C–^1H

INTRODUCTION

(1*R*)-(+)-Camphorquinone (**1**) can be reduced by a variety of methods[1] to obtain a mixture of β-hydroxycamphor [3-hydroxycamphor (**2**)] and α-hydroxycamphor [2-hydroxyepicamphor (**3**)] in both *endo* and *exo* forms with varying degrees of selectivity. Notably, only reduction by zinc in acetic acid yields selectively the *endo* isomers, *viz.* **2a** and **3a**. Subsequent treatment of 2-hydroxyepicamphor (**3**) in both its *exo* and *endo* forms with Na–Hg amalgam yields epicamphor (**4**), which is not found in nature. Because the latter is a potentially valuable starting material in asymmetric synthesis,[2] it is important to achieve efficient separation of **2** from **3**. One such method, first reported by Manasse in 1902,[3] employs the reaction of an anhydrous methanolic solution of a mixture of **2a** and **3a** with HCl gas. The resulting dimer (**5**), incorrectly postulated later by Bredt and Ahrens[4] to be formed from *endo*-3-hydroxycamphor (**2a**), but which is actually formed from *endo*-2-hydroxyepicamphor (**3a**), can be easily separated from unreacted **2a** on the basis of differing solubilities. Regeneration of **3a** can then be effected by dissolving the dimer in concentrated hydrochloric acid.



In their previous work, Bredt and Ahrens[4] (see above) had correctly determined the relative molecular mass of the dimer **5** by density measurements, but did not study it further. Much later, Hückel and Fechtig[5] had employed the aforementioned separation technique, but failed to characterize the intermediate dimer. Only Theoren[6] attempted to elucidate its structure on the basis of stereochemical considerations and minimal ^1H

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NMR data, but the results were inconclusive. We therefore decided to elucidate the true identity of **5** using high-field ^{1}H NOE difference spectroscopy.

RESULTS AND DISCUSSION

The dimer formed is a colourless, stable, highly crystalline solid (m.p. 149–150 °C) which is optically active $\{[\alpha]_D = +178°, c = 5.06[EtOH–CH_2Cl_2(8:1)\}$. The IR spectrum shows no hydroxyl or carbonyl absorptions. High-resolution electron-impact mass spectrometry confirmed the dimer to have the formula $C_{22}H_{36}O_4$.

The 90.56 MHz $^{13}C\{^1H\}$ NMR spectrum of the compound shows 11 discrete environments, in keeping with a symmetrical structure. In addition, a quaternary signal at δ 102.0 ppm is consistent with a *gem*-dialkoxy grouping (e.g. C-1 in glucose resonates at 97 ppm[7]). These data, coupled with resonances for two methylenic carbons and two methinic carbons, suggest four possible structures, **I**–**IV**, shown in Fig. 1 for the dimer **5**. The *anti* forms of **III** and **IV** (**V** and **VI**, respectively) can be ruled out on the basis of the mechanism of formation, which would require combination of **3a** and its antipode.

Of these proposed structures, the diastereomeric pair **I** and **II** are less likely both from the mechanistic point of view of their formation and the strain inherent in the 1,3-dioxetane ring, especially under the acidic conditions of the reaction. Nonetheless, all four structures would be expected to exhibit similar detail in both the ^{1}H and ^{13}C NMR spectra. The former is shown in Fig. 2 and consists of 10 different resonances, labelled A–J. Peak B can be assigned unequivocally to the methoxy protons and peak C to the bridgehead proton in the bornane skeletal structure. Further assignment of the resonances, and the determination of the structure of the dimer, was effected by the use of NOE difference experiments.

Irradiation of B causes an 8% enhancement at C and a 3% enhancement of the triplet A. This leads to the conclusion that A is the methinic proton adjacent to the methoxy group which resides at the 9a-position, i.e. α to C. This excludes structures **I** and **IV**. In addition, an 8% enhancement of C is consistent with the methoxy group being in an equatorial ('*exo*') position on the molecule and makes structure **II** also unlikely. This leaves structure **III**, which is wholly consistent with the remaining NOE difference measurements.

Irradiation of the methyl signal J causes 5% enhancements to both F and G and a 4% enhancement to C. Thus J is consistent with the C-12β methyl group, with F and G being H-7β and H-8β or vice versa. Saturation of I results in an 8% enhancement of A and a 3% enhancement of G. Thus I can be assigned to the bridgehead methyl at C-6, with G being the signal from H-7β. Irradiation of H confirms this as the C-12α methyl group, giving a 15% enhancement at A (H-5a) and a 3% enhancement at C. Irradiation of C enhances F by 2% and B by 2%, consistent with its assignment as H-9. Finally, irradiation of G (H-7β) enhances D by 20%, consistent with D being H-7α. F (H-8β) is also enhanced by 3%; this leaves E as H-8α.

Table 1 summarizes the results and the assignments for the proton resonances of dimer **5** from the NOE experiments and Table 2 contains the fully assigned ^{1}H NMR spectral data. The assigned stereochemical structure **III** of dimer **5** is shown in Fig. 3.

The ^{13}C NMR data for dimer **5** are summarized in Table 3. The δ values and multiplicities of the ^{13}C signals were obtained from $^{13}C\{^1H\}$ and ^{13}C DEPT spectra. The assignments were confirmed by carrying out a 2D carbon–proton correlation experiment (HETCOR).

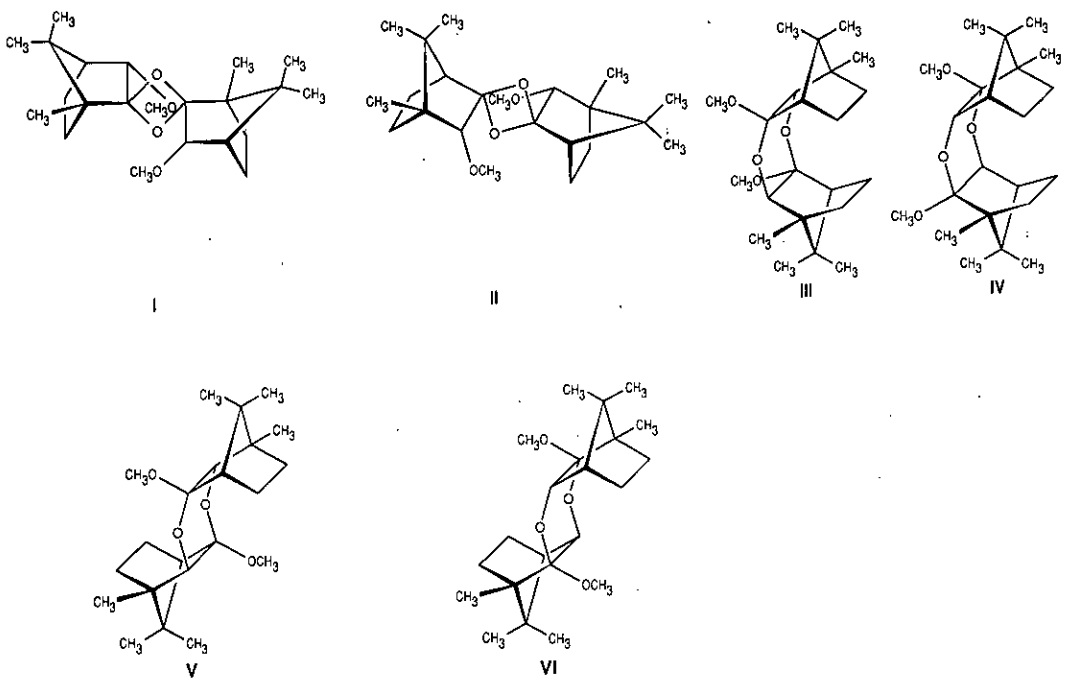

Figure 1. Possible stereochemical structures **I**–**IV** of dimer **5**, together with the *anti* forms **V** and **VI**.

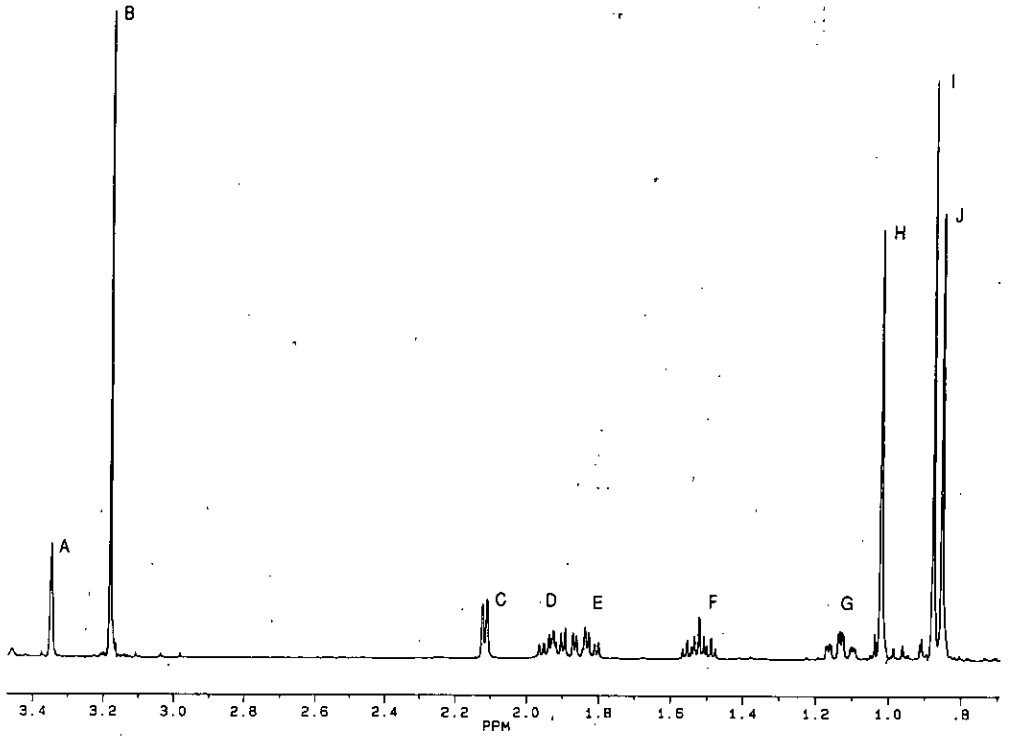

Figure 2. ^{1}H NMR spectrum of dimer **5**.

Table 1. Results of proton–proton 1D NOE difference experiments on dimer 5

Irradiated proton	Progon observed	NOE (%)
CH_3—O	9	8
	5a	3
12β	8β	5
	7β	5
	9	4
6-CH_3	7β	3
	5a	8
12α	5a	15
	9	3
9	8β	2
	CH_3—O	2
7β	7α	20
	8β	3

Table 2. ^{1}H NMR spectral data for the dimer 5 in $CDCl_3$

Label	δ (ppm)	Multiplicity, J (Hz)	Assignment
J	0.85	s	12β
I	0.88	s	6-CH_3
H	1.02	s	12α-CH_3
G	1.13	t, d, d (2 × 12.0, 3.4, 1.6)	7β
F	1.52	t, t (2 × 12.0, 4.6 × 2)	8β
E	1.83	d, d, d (12.0, 9.5, 3.4)	8α
D	1.92	d, d, d (12.0, 9.5, 4.6)	7α
C	2.11	d, d (4.6, 1.5)	9
B	3.18	s	9a (OCH_3)
A	3.35	t (1.5)	5a

Table 3. ^{13}C chemical shifts (ppm) for dimer 5

Carbon	δC	Carbon	δC
5a	78.4	9a	102.0
6	45.1	9a-OCH_3	49.3
6-CH_3	13.7	12	49.4
7	26.4	12α	19.4
8	21.3	12β	20.3
9	48.8		

EXPERIMENTAL

Spectroscopy

Spectra were recorded at 298 K on a Bruker WH360 spectrometer operating at 360.13 MHz for protons and 90.56 MHz for ^{13}C nuclei. Standard ^{1}H NMR spectra were acquired in $CDCl_3$ using 32K data points over a spectral width of 4000 Hz, giving rise to an acquisition time of 4.1 s. Proton NOE experiments were obtained using 8K data points over a spectral width of 1736 Hz. Secondary irradiation of 51 dB below 0.2 W was applied for 7 s, followed by spin excitation using a 90° pulse. Blocks of 16 scans preceded by two dummy scans were accumulated for each irradiation site, to give a total of 144 scans per site. Two control spectra were acquired by irradiation at δ 4.47 and −0.3. Line broadening of 1 Hz was applied prior to Fourier transformation. Consistent results were obtained, regardless of which control spectrum was subtracted. Proton chemical shifts are quoted relative to TMS.

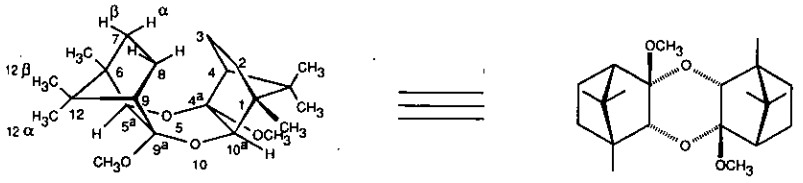

Figure 3. Assigned stereochemical structure of dimer **5**.

Carbon-13 data were obtained on a 100 mg sample dissolved in $CDCl_3$. The spectra were acquired over 20000 Hz and referenced to the solvent at δ 76.9. The two-dimensional carbon–proton correlation experiment was carried out using the XHCORRD.AU program provided by Bruker Spectrospin. The sequence is $D1$–90(H)–$t_{1/2}$–90(H)–$D3$–180(H), 180(C)–$D3$–90(H)–$t_{1/2}$–$D3$–90(H)–D4–AQ(^{13}C), where $D1$ is a relaxation delay of 3.0 s, $D3$ and $D4$ are fixed delays of 0.0037 and 0.0019 s, respectively, and t_1 is the incremented delay. Other experimental parameters used were $SW(^{13}C) = 9804$ Hz, $SW(^{1}H) = 800$ Hz, with 1024K data points for the ^{13}C dimension and 92 FIDs each of 16 scans. Proton composite pulse decoupling was applied only during the acquisition (AQ) period. The data were processed using a shifted sine-bell squared function ($Q/2$) in the F_1 (^{13}C) dimension and a sine-bell squared function (Q) in the F_1 (^{1}H) dimension. The F_1 dimension was zero filled to 512 data points.

Synthesis

Dimer **5** was prepared in two steps, as follows.

Reduction of (1*R*)-(+)-camphorquinone (1). The procedure adopted followed that of Hückel and Fechtig.[5] To a stirred solution of **1** (90.37 g, 0.554 mol) in acetic acid (*ca.* 50 ml) was added hot water (*ca.* 750 ml). The resulting mixture was heated to 90–100 °C and freshly activated Zn (*ca.* 15 g) was added in portions until the yellow colour of the solution had faded completely. The solution was quickly filtered through a Celite pad and washed thoroughly with hot water. The aqueous medium was saturated with NaCl and extracted into methylene chloride. The organic phase was dried over Na_2SO_4, filtered and evaporated to yield a mixture of **2a** and **3a** (85.32 g, 93%), m.p. 202–204.5 °C (lit.[4] m.p., 203–205 °C). IR (Nujol): 3420 cm^{-1} (νOH), 1745 cm^{-1} (νCO). Mass spectrum (electron impact): m/z, found 168.1165; $C_{10}H_{16}O_2$ requires 168.11502.

Reaction of 3a with MeOH and HCl gas. Following the method of Manasse,[3] HCl gas (freshly generated from H_2SO_4 and NH_4Cl, 0.254 mol, 0.5 equiv.) was bubbled into a solution of **2a** and **3a** (85.32 g, 0.507 mol) in dry methanol. The resulting solution was allowed to stand at room temperature for several days, during which period crystals of the dimer formed. These were filtered off and washed with a small volume of cold pentane to yield **5** (31.34 g, 34%), m.p. 149–150 °C (lit.[4] m.p., 149–150 °C), $[\alpha]_D^{22} = +178.0°$, $c = 5.06$ [EtOH–CH_2Cl_2(8:1)] (lit.[4] +174.2°). IR (Nujol): 1465 cm^{-1}. Mass spectrum (electron impact): m/z, found 364.2594; $C_{22}H_{36}O_4$ requires 364.26134.

CONCLUSIONS

1D NOE experiments have been used both to determine the connectivity and to firmly establish the stereochemistry of the dimer **5**. These experiments also allowed the unambiguous assignment of all the resonances in the ^{1}H NMR spectrum. In addition, a 2D carbon–proton correlation experiment allowed unambiguous assignment of its ^{13}C spectrum.

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Chromatographic Resolution of Racemic Amines, Carboxylic Acids, and Alcohols by a New Homochiral Reagent Derived from *endo*-Borneol

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Key Words

Column liquid chromatography
Diastereomer separation
Chiral derivatizing agent
Chiral oxazolidin-2-one

Summary

Chromatographic separation of racemic amines, carboxylic acids and alcohols can be achieved with excellent resolution as measured in terms of the chromatographic separation factor α by derivatization with a homochiral oxazolidin-2-one easily prepared in three steps from *endo*-borneol. The resolved materials can be isolated in excellent yields by cleavage of the resultant diastereomers using conventional methods, which also allow recovery of the chiral resolving agent for re-use.

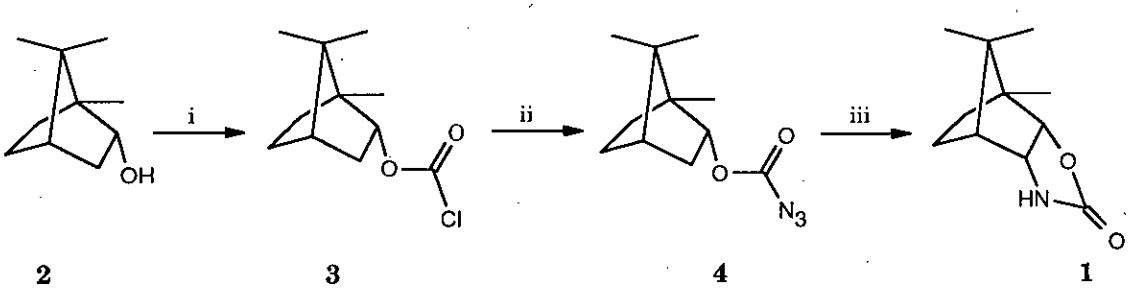
Introduction

Interest in chiral separation has grown enormously over the last decade [1]. Derivatization of enantiomers with optically active reagents and separation of the resulting diastereomers on achiral columns is a widely used method as exemplified by FLEC [(+)-1-(9-fluorenyl)-ethyl chloroformate] which offers favourable chromatographic properties for chiral separations using reverse-phase liquid chromatography [2]. Pirkle has employed chiral oxazolidin-2-ones for the resolution of racemic amines [3], although access to these reagents required either cyclocarbamation of relatively expensive optically pure β-amino alcohols, or the more tedious separation of similarly prepared racemic analogues [4]. We now report a new reagent **1**, readily prepared in bulk quantities by three simple steps from inexpensive [(1S)-*endo*]-(−)-borneol **2**, wherein the easily functionalized oxazolidin-2-one moiety is enriched by the powerful topological bias inherent in the bornane skeleton. The practical value of **1** as a cheap chiral derivatizing agent (CDA) for the normally difficult resolution of optically active amines, carboxylic acids, and alcohols is illustrated here.

Experimental

Homochiral Resolving Agent

For the preparation of the new homochiral reagent **1** we employed the simple, albeit little used, device of intramolecular nitrene delivery [5] coupled with the conformational rigidity offered by the bornyl moiety. This process, outlined in Figure 1, was achieved starting from *endo*-(−)-borneol **2** with optical purity in > 98 % (Aldrich) by



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

Figure 1
Preparation of homochiral oxazolidin-2-one **1**: (i) phosgene, NEt_3, toluene-ether, 0 °C, 4 h, (97 %; (ii) NaN_3, TBAB, CH_2Cl_2-H_2O, 25 °C, 4 h, (98 %); (iii) solution thermolysis in 1,1,2,2-tetrachloroethane (b.p. 147 °C), (50 %).

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conversion into the azidoformate **4** *via* chloroformate **3** and subsequent thermolysis in boiling 1,1,2,2-tetrachloroethane.

By this procedure we obtained the CDA **1** which was purified by flash chromatography on silica using cyclohexane:ethyl acetate as eluent. Further crystallisation from di-*iso*-propylether or ethyl acetate:*n*-hexane furnished well-formed crystals of the oxazolidinone (**1**; m.p. 163–163.5 °C; $[\alpha]_D^{21.5}$–73.4°, c = 5.1, ethanol); its structure was confirmed by microanalysis, ^{1}H NMR and MS (including parent molecular ion by electron impact) measurement. X-Ray diffraction analysis also confirmed the stereochemical integrity of **1** and has shown that the absolute configuration of the chiral centres at C(2) and C(6) is (2R, 6S).

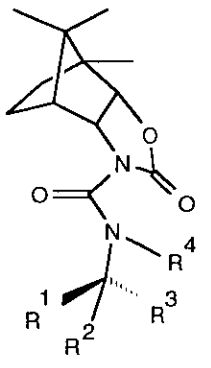
Preparation of Diastereomers

The following examples illustrate the efficacy of **1** as a homochiral derivatizing agent for the normally difficult chromatographic resolution of (i) chiral amines *via* diastereomeric ureas, e.g. **5–8**, (ii) carboxylic acids as the corresponding amides, e.g. **9–14**, and (iii) alcohols with no UV chromophore as the equivalent oxazolidinethione carbamate, e.g. **16**. In each case the resultant diastereomers are stable and are formed quantitatively within a few minutes.

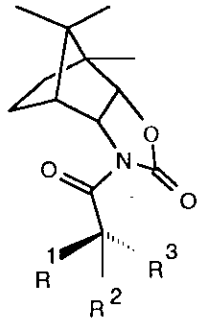
(i) Racemic Amines: In a typical procedure oxazolidinone **1** was converted into its lithio-derivative by treatment of an ethereal solution with of 1.6 M *n*-butyl lithium (1.1 equivs.) and added to an ice cold 20 % phosgene solution in toluene (3 equivs.) which had been pre-treated with finely divided calcium hydride (0.02 equivs.). After 1 hour the reaction mixture was filtered and evaporated *in vacuo* to produce, in quantitative yield, the *N*-chloroformyl derivative. Dropwise treatment of a solution of racemic 1-phenylethylamine (1 equiv.) and triethylamine (1 equiv.) in CH_2Cl_2 with a solution of *N*-chloroformyl derivative (1 equiv.) (CH_2Cl_2) produced a 1:1 mixture (98 %) of the diastereomeric ureas **5** and **6** (98 %). Application to the more difficult to separate secondary amine, *N*-methyl-2-phenylethylamine, produced a pair of diastereomeric derivatives **7** and **8** in a 95 % yield.

(ii) Racemic Carboxylic Acids: A different approach was adopted in that the racemic acid was utilized as an acid halide (1 equiv.) and added to a stirred solution of lithiated CDA **1** (1 equiv.) in THF at –78 °C. Diastereomeric amides **9** and **10** were isolated in 94 % yield from racemic 2-bromopropionyl bromide, whilst reaction with 2-chloropropionyl chloride and 2-phenylpropionyl chloride gave diastereomers **11** and **12** (84 %), and **13** and **14** (97 %), respectively.

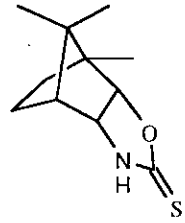
(iii) Racemic Alcohols (with no UV chromophore): For this purpose the oxazolidinethione **15** was prepared from CDA **1** (1 equiv.) in 65 % yield by treatment with Lawesson's reagent (0.6 equivs.) in toluene at reflux. The thione group was chosen because it provides both the necessary bathochromic shift and absorbs more strongly in the UV (**15** λ_{max}247 nm, $\varepsilon_{max}2.8 \times 10^4$ cf. **1** λ_{max}227 nm, $\varepsilon_{max}1.6 \times 10^2$). In a procedure reverse to the resolution of amines, the chloroformate of the alcohol, e.g. racemic *trans*-2-methylcyclohexan-1-ol (1 equiv.) was added to the lithio-derivative of **15** (1 equiv.) in DME at –78 °C, to afford equal amounts of carbamate (S,S)-**16** and its (R,R)-**17** diastereomer in 88 %.



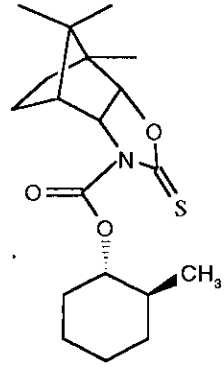
5-8



9-14



15



(S,S)-**16** [and (R,R)-**17**]

	R^1	R^2	R^3	R^4
5	Me	H	Ph	H
6	H	Me	Ph	H
7	Me	H	Ph	Me
8	H	Me	Ph	Me

	R^1	R^2	R^3
9	Br	Me	H
10	H	Me	Br
11	Cl	Me	H
12	H	Me	Cl
13	Ph	Me	H
14	H	Me	Ph

Figure 2
Structures of diastereomeric ureas **5–8**, amides **9–14**, and carbamates **16–17**.

Analysis of Diastereomers

Analysis of crude reaction mixtures was by HPLC on a Gilson system consisting of a Model 802 manometric module, a Model 302 piston pump to deliver the mobile phase (2 ml/min), a Model 112 variable wavelength UV-vis detector set at 258 nm, and a Gallenkamp Datascan recorder. Injections were made on Spherisorb 5 μm SiO_2-S5W-250A column, 25 × 0.46 cm. The mobile phases used were mixtures of *n*-hexane-ether (3:1 v/v) to analyse the amine- and alcohol- derived diastereomers and a 4:1 v/v mixture to analyse the carboxylic acid diastereomers.

Cleavage of Diastereomers and Recovery of Resolved Material and Auxiliary

After chromatographic separation, both the CDA **1** and the resolved substrate can be recovered by the following appropriate procedures:

(i) Amines: the ureas were successfully cleaved in high yields with sodium methoxide in anhydrous THF [4] and the CDA **1** recovered in almost quantitative yield (m.p. 162–163 °C).

(ii) Acids: typically, cleavage of a diastereomer **11** was achieved using lithium hydroperoxide [6] following which **1** was recovered in 96 % yield and the resolved acid in 89 % yield by an acid/base extraction process.

(iii) Alcohols: the same procedure was adopted as used for the acid-derived diastereomer **11** (*vide-supra*), but for a longer period of time (24 h). Cleavage of the diastereomeric pair **16** and **17** occurred quantitatively and noteworthly, the CDA was recovered in its oxidized form, *viz.* **1** following dry flash silica chromatography.

Results and Discussion

Under the conditions mentioned above, the diastereomeric pairs are very well separated. Table I illustrates the high degree of separation as measured in terms of chromatographic separation factor α conferred on the resultant diastereomers by CDA **1** through their differential absorbtion by the stationary phase. The magnitude of α in each case is such as to facilitate straightforward effective resolution of sizeable quantities of material on silica columns. For example, the diastereomeric ureas **5** and **6** are easily separated on a millimolar scale by flash chromatography (Fluka GF 254 SiO_2, gradient elution, *n*-hexane:ether). This approach was developed further by carrying out a kinetic resolution of **5** and **6** which afforded a diastereomeric excess of 3:1 (lower R_f: higher R_f material). The kinetic resolution experiment consisted of the slow addition of *N*-chloroformyl derivative of **1** (1 equiv.) to an ice cold solution of racemic 1-phenylethylamine (2 equivs.) and triethylamine (1 equiv.) in CH_2Cl_2 (4 h).

Normally, diastereomers derived from secondary amines can be observed to separate, but with much diminished α values. In the case of the diastereomeric ureas **7** and **8**, an α value of 1.20 is found, well in excess of the value (1.09) reported for the corresponding secondary amine derived from FLEC [(+)-1-(9-fluorenyl)-ethyl chloroformate] [2]. Differing combinations of hydrogen bonding, dipolar repulsion and carbinyl hydrogen bonding effects, together with the greater conformational rigidity of **1** may account for this improved separation.

Table I. Separation factors (α) for resolution of amines, carboxylic acids and alcohols.

Racemate	Diastereomers	α-Value
1-phenylethylamine	**5:6**	2.01
N-methyl-2-phenylethylamine	**7:8**	1.20
2-bromopropionic acid	**9:10**	2.10
2-chloropropionic acid	**11:12**	2.10
2-phenylpropionic acid	**13:14**	2.08
trans-2-methylcyclohexan-1-ol	**16:17**	1.34

This same conformational rigidity also appears to play a large role in promoting the high chromatographic separability observed for the corresponding diastereomeric amides derived from carboxylic acids. Table I shows the magnitude of the α values are all in excess of 2.0 and such as to ensure large-scale chromatographic resolutions of all pairs of diastereomers on silica (gradient elution 1:2 to 1:1 v/v ether:*n*-hexane).

The broad spectrum of chromatographic separability conferred by CDA **1** is further reflected in the α value of 1.34 for the alcohol-derived carbamate diastereomers **16** and **17** which is more than adequate for facile preparative separation on silica columns with gradient elution (ether:*n*-hexane, 1:5).

Conclusion

In conclusion we can state that the present method allows a rapid and effective means for the chromatographic resolution of racemic amines, carboxylic acids, and alcohols on normal-phase silica. The CDA **1** is an easy to prepare, inexpensive, crystalline, stable and odourless compound with an enantiomeric purity not less than 99.9 %. These characteristics, coupled with the stability of the resultant diastereomers, should ensure that **1** becomes a powerful addition to the CDAs available to the organic chemist. We also note that the highly crystalline nature of these diastereomeric derivatives also offers as a bonus the opportunity for separation by the classical approach of fractional crystallization.

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