Synthesis and Evaluation of Novel Carbohydrate-based Chiral Auxiliaries

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Dedication

To Andrew McAnulty McDougall

I would like to dedicate this thesis to the memory of my late father whose eternal spirit of love and encouragement walked with me constantly and drove me on with greater strength and determination to help me traverse the many difficult and wearisome steps I encountered during this long and strenuous journey.

Love Douglas

This thesis is also a tribute to my wife Margaret and daughter Sharon as well as my mum Agnes, brother Andrew and enduring friend John Donachie in recognition for their continuous and unwavering support.

Many Thanks

Acknowledgements

I take this opportunity to offer my heartfelt thanks to my supervisor Dr. Ian Gosney for providing me with the chance to do this PhD thesis and for giving me advice and moral support when it was most needed.

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In addition to the above, I would like to thank all of my research colleagues in the department and especially those in laboratory 64 for the warm spirit of friendship shown by them during my time spent there.

Finally I take the opportunity to express my sincere gratitude to my friend Keith Grant for the endless help he has given me from beginning to end of my PhD.

Courses Attended

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

Current Developments in Organic Chemistry, various speakers, Department of Chemistry, University of Edinburgh.

2D Nuclear Magnetic Resonance, Dr. R. L. Baxter and Dr. I. H. Sadler, Department of Chemistry, University of Edinburgh, 1993.

Smith Kline and French, Medicinal Chemistry Lectures, Department of Chemistry, University of Edinburgh, 1991.

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, ICI Pharmaceuticals, various speakers, Department of Chemistry, University of Edinburgh, 1992.

ABSTRACT

The work described in this thesis is primarily concerned with a series of asymmetric transformation reactions employing a newly developed (-)-D-fructose derived 1,3-oxazin-2-one (77) as a chiral derivatising agent. The synthetic route utilised the well-known but little used stereospecific nitrene insertion process.

The ability of the auxiliary to successfully participate in these reactions ranged from excellent, as was the case in aldol reactions, to disappointingly poor when failing to react at all, as was the case in alkylation reactions.

The auxiliary was also utilised in Lewis-acid catalysed Diels-Alder cycloaddition reactions in which contrasting results were achieved.

For α-bromination of the N-propionyl derivative, almost total asymmetric stereocontrol was obtained, whereas the performance of the auxiliary in asymmetric conjugate addition reactions of the corresponding N-acrylate compounds once again produced mixed results.

When employed in acylation reactions, Manders reagent (methyl cyanoformate) was required to promote the return of the desired product.

The performance of 77 as a resolving agent was highly favourable in the resolution of a racemic primary amine as well as a racemic acid halide.

In summation, the overall performance of this auxiliary was very promising. Although the reactions conducted have on occasion exposed ambiguous reactivity, any weaknesses present are now well-defined and most can be avoided or overcome.

Adequate diastereofacial differentiation is usually achieved and product separation is effected routinely and non-destructively by mild hydrolysis. Furthermore, a high incidence of crystallinity is found in products and intermediates which greatly facilitates product separation and identification.

Towards the end of the thesis a further auxiliary (147) derived from isosorbide is described. The synthesis of this 1,3-oxazolidin-2-one based auxiliary required selective protection procedures which resulted in an overall workable yield.

Initial studies showed that functionalisation of 147 at the oxazolidinone nitrogen is accomplished readily.

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INTRODUCTION

1 *AVANT - PROPOS*

The synthesis of optically active compounds is a subject with a long history dating back more than a hundred years to the seminal work of Louis Pasteur. The legendary Pasteur was the first person to recognise that optical activity is a result of molecular asymmetry and the first to separate a racemate into its diastereomers (in 1848)[1].

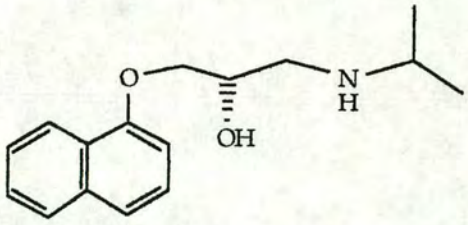
In recent years, interest in the synthesis of pure enantiomers has gained new impetus as a result of the increasing awareness of the importance of optical purity in the context of biological activity.

Enzymes, the organic catalysts produced by living cells, are actively involved in any biological processes which occur in the body. These enzymes have developed to such a sophisticated degree that they can actually discriminate between the isomers of a racemic mixture and can then react with each individual isomer in entirely different ways.

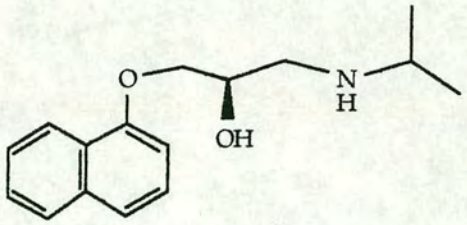
The products of these biological reactions are then of serious consequence. Whilst one reacting isomer (eutomer) will have the desired beneficial pharmacological effect, the other isomer (distomer) is either ineffective or can and often does react in a manner which results in serious side effects. There are many examples of commercially available compounds which illustrate the importance and the effect of optical purity on the biological properties of living systems.

For example, the 'tailor-made' synthetic drug (S)-propanolol (1), developed[2] specifically to block the action of the natural hormone adrenaline on the heart and blood vessels, is used in the treatment of high blood pressure.

In contrast, its analogous (R)-isomer **(2)** acts as a contraceptive.

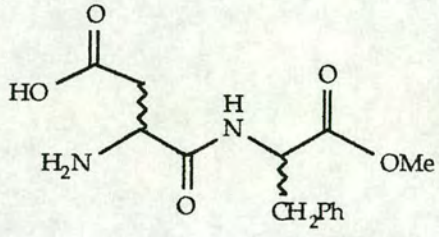


(1)
(S)-isomer
β-blocker

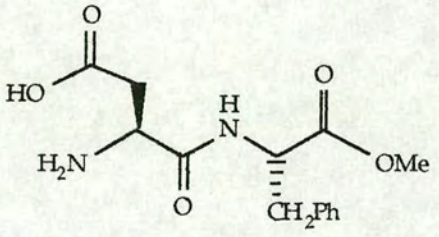


(2)
(R)-isomer
contraceptive

Of the four possible isomers of the illustrated structure **(3)**, only the isomer shown **(4)** known as the artificial dipeptide sweetener Aspartame is sweet tasting, each of the remaining three isomers bears a bitter taste.

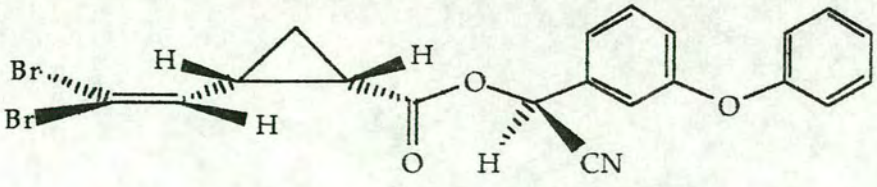


(3)



(4)
Nutrasweet
(Aspartame)

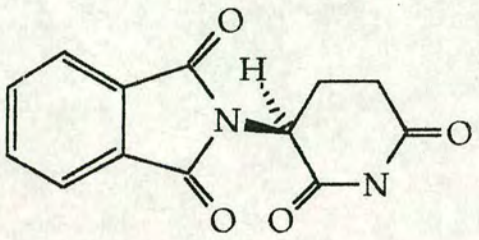
A striking example of the activity/inactivity of isomeric analogues is that of deltamethrin **(5)**. This particular isomer is used as an insecticide whereas the remaining seven isomers are completely inactive.



(5)
Deltamethrin (insecticide)

As well as being inactive, the distomer often has detrimental effects and probably the most tragic and poignant example of this is the case of the drug Thalidomide.

Prescribed as a sedative for morning sickness affecting pregnant women, the drug was sold as a racemate. Although both isomers acted as a sedative, the (S)-isomer **(6)** was teratogenic and was responsible for causing horrific foetal deformalities.



(6)

(S)-Thalidomide

The Thalidomide tragedy highlighted the need for the production and testing of individual isomers of all new candidate compounds (now stipulated by the Food and Drug Administration {FDA}).

Attention to the control of absolute stereochemistry is now of utmost importance in the fields of pharmaceutical and agricultural chemistry. The construction of individual isomers poses a great challenge, requiring a knowledge of methods, expertise and experimental dexterity and there now follows a review of the most common of these methods available in chemistry today.

2 Current Methodology for the Production of Optically Active Compounds

1 Chiral Auxiliaries

2 Resolution

3 Chiral Pool

4 Catalytic Asymmetric Synthesis

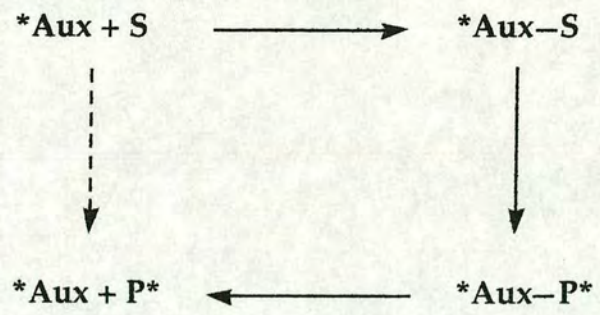
5 Bifunctional Chiral Auxiliary

2.1 Chiral Auxiliaries

Since the 1970's a class of compounds, known collectively as chiral auxiliaries, has supplied disciples of biosynthesis with a springboard in their quest to emulate the design concepts and architectural brilliance demonstrated by nature in the construction of complex organic molecules.

They have provided a fertile area of research which has experienced intense activity and which has resulted in a list of publications detailing varying degrees of success which are too numerous to mention here.

The basic function of a chiral auxiliary in an asymmetric transformation is to act as a stereodirector. This is done by attaching a prochiral substrate (S) to the auxiliary (*Aux), Scheme 1. Once appended, a reaction is carried out on the complex (*Aux-S) during which the auxiliary directs the course of the reaction and which results in the formation of a chiral product (*Aux-P*). The next stage involves the removal of the auxiliary to generate the chiral fragment (P*) together with the auxiliary (*Aux) which may be recycled.



Scheme 1

There are certain structural features which chiral auxiliaries must possess in order to successfully participate in asymmetric transformations. These features should ideally enable the chiral auxiliary to meet the following criteria:

a) it should be easily synthesised from readily available homochiral compounds.

b) it should be readily functionalised for ease of attachment to substrates.

c) it should induce highly stereoselective reactions.

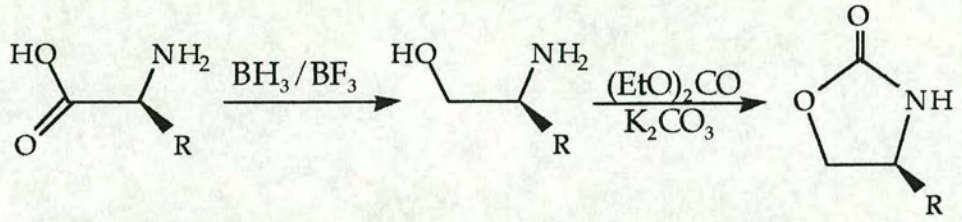
d) it should impart crystallinity to all intermediates and products.

e) it should be easily removable and in a form that can be recycled without compromising the stereochemical integrity of the product diastereomeric fragment.

Collectively this set of criteria presents a formidable challenge to a chiral system and in the following section there is a review of some of the most notable auxiliaries to date.

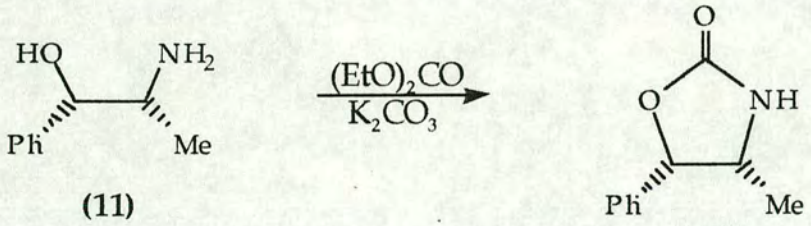
2.1(a) Evans' Oxazolidinones

The (S)-valine **(7)** and (S)-phenylalanine **(8)** derived auxiliaries **(9)** and **(10)** together with the (1S,2R)-norephedrine **(11)** derived auxiliary **(12)** all of which were devised by Evans[3,4] are the most illustrious and commonly encountered amino acid based auxiliaries in use today, Scheme 2.



(7): R=$CH(CH_3)_2$ **(9):** R=$CH(CH_3)_2$

(8): R=CH_2Ph **(10):** R=CH_2Ph

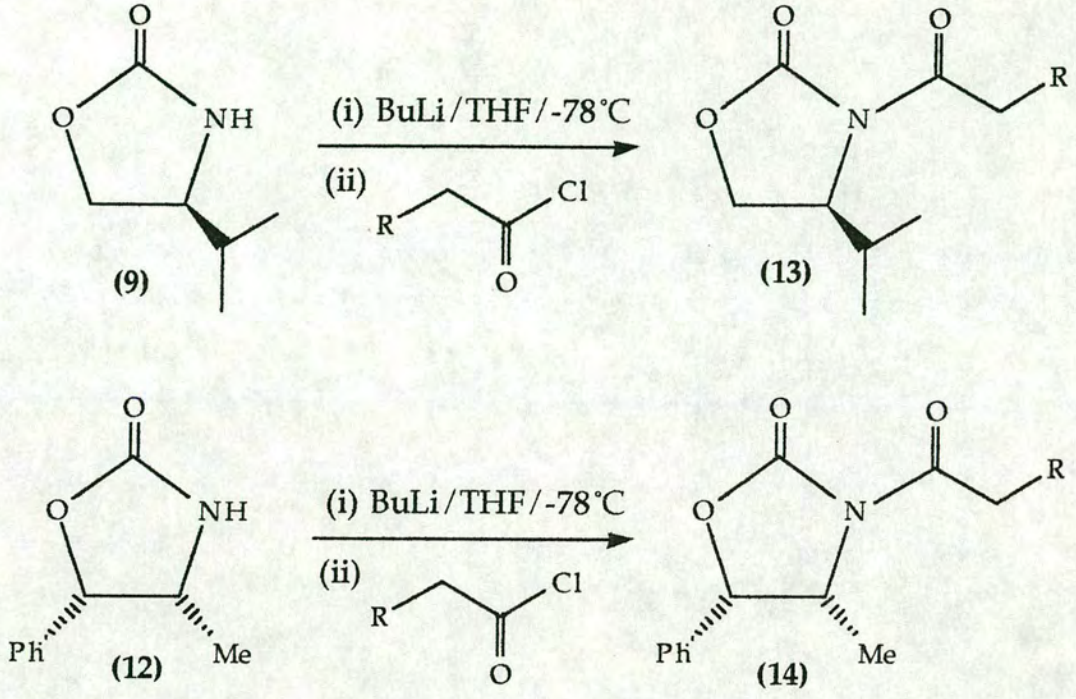


(11) **(12)**

Scheme 2

Upon appropriate functionalisation they have shown very high levels of asymmetric induction in a wide variety of reactions, including acylations[5], alkylations[6], oxygenations[7], α-brominations[8,9], aldol reactions[10-13] and Diels-Alder cycloadditions[14].

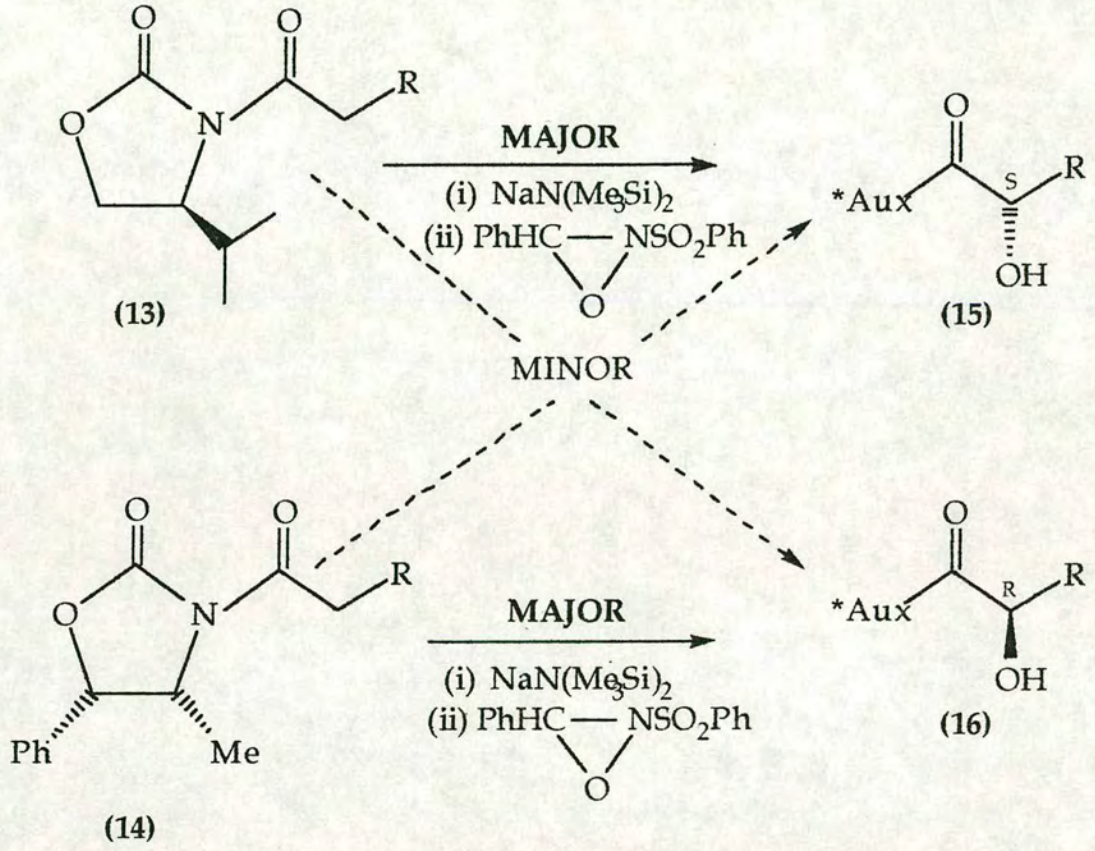
Each auxiliary is easily converted to its corresponding carboximide derivative by treatment with n-butyllithium and an acid chloride, Scheme 3.



Scheme 3

A typical example in which the newly functionalised auxiliary can be utilised is in the preparation of enantiomerically pure α-hydroxy carboxylic acid synthons[7].

By transforming each of the carboximides (13) and (14) into their corresponding Z-enolates, then treating with oxidant, oxaziridine, the α-hydroxy carboximides (15) and (16) were produced in high yield with exceptional asymmetric induction and opposite configuration, Scheme 4, Table 1.



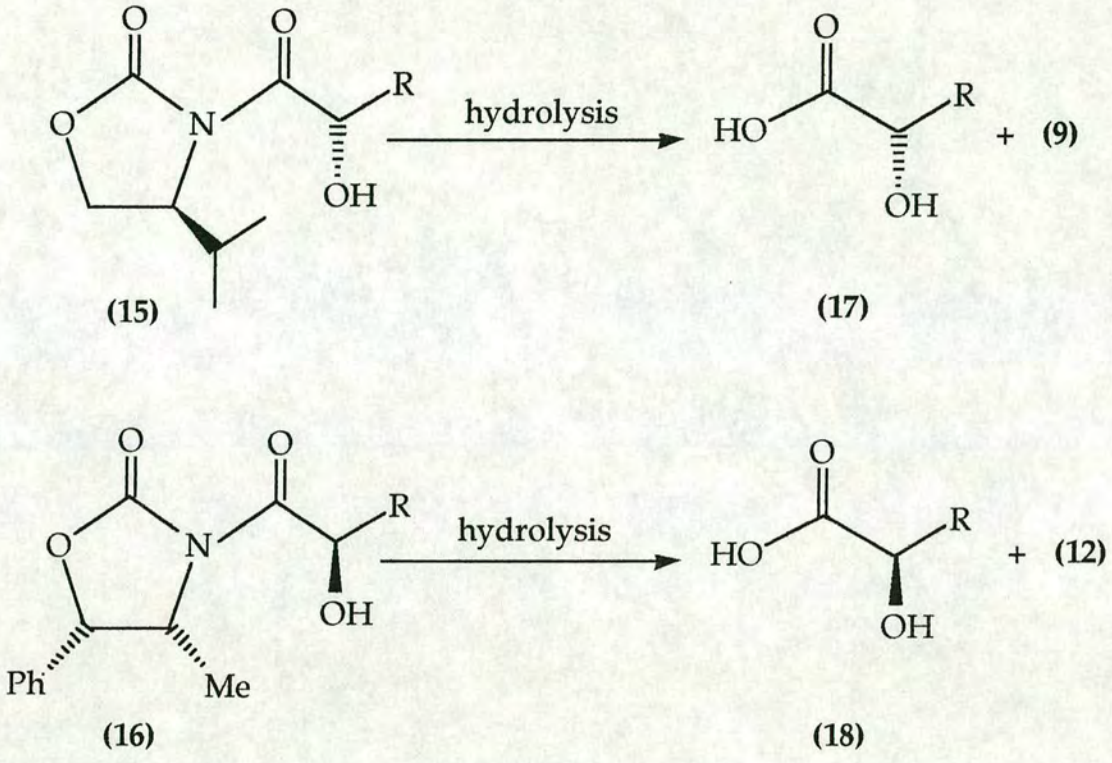
(13) (14) (15) (16)

Scheme 4

Imide	R =	R : S	% yield
(13)	CH_2Ph	5 : 95	85 (S)
(14)	CH_2Ph	94 : 6	86 (R)
(13)	*i*-C_3H_7	1 : 99	86 (S)
(14)	*i*-C_3H_7	99 : 1	94 (R)

Table 1

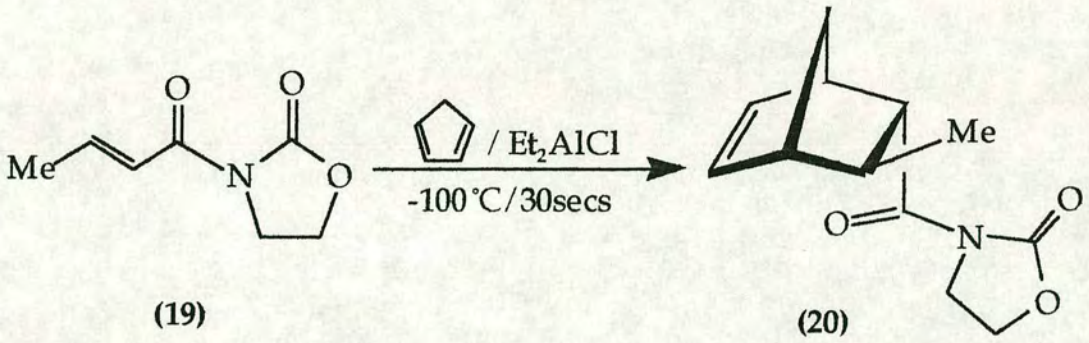
Mild hydrolysis of the acid derivatives (15) and (16) furnished the α-hydroxy carboxylic acids (17) and (18) in high yield with similarly high recovery of auxiliary, Scheme 5.



Scheme 5

Another example of the superb stereoselective quality offered by this range of auxiliaries is ably demonstrated by their conversion to the analogous α,β unsaturated carboximides.

These species are highly reactive dienophiles when employed in Lewis-acid catalysed Diels-Alder cycloaddition reactions[14]. For example, treatment of unsubstituted crotonyl oxazolidinone (19) with excess cyclopentadiene and diethylaluminium chloride at low temperature leads within seconds to a single cycloadduct (20) in quantitative yield, Scheme 6.



(19) (20)

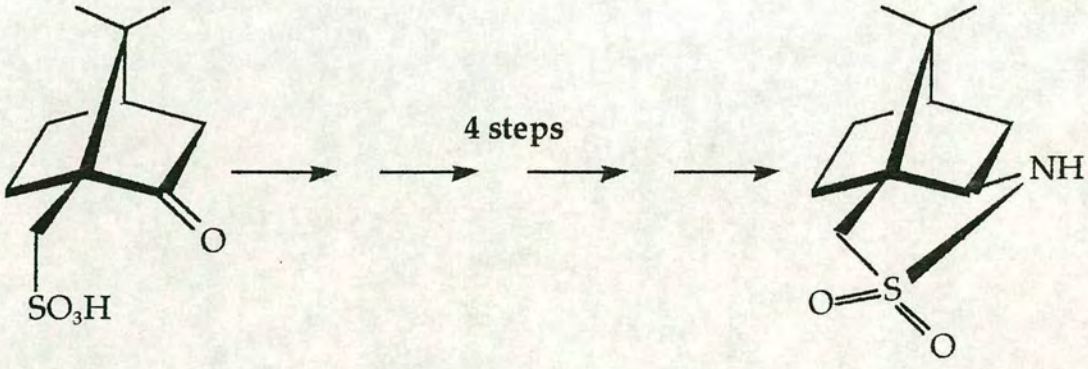
100% conversion

Scheme 6

2.1(b) Oppolzer's Chiral Sultam

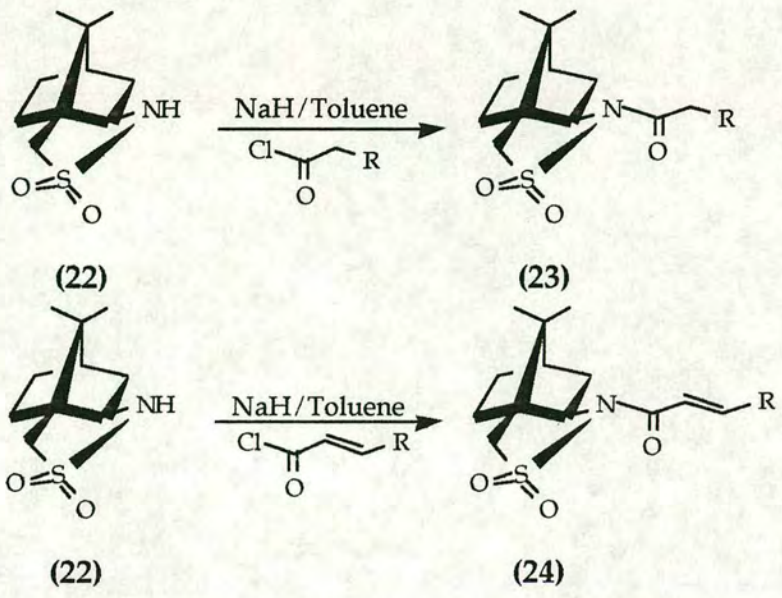
An auxiliary which has enjoyed unquestionable success by virtue of its excellent versatility and superb promotion of asymmetric induction is the bornane-ring derived Oppolzers sultam (22). It is synthesised in four steps[15] from (-)-camphor-10-sulphonic acid (21).

The enantiomeric analogue, prepared from (+)-camphor-10-sulphonic acid is also commercially available.



(21) (22)

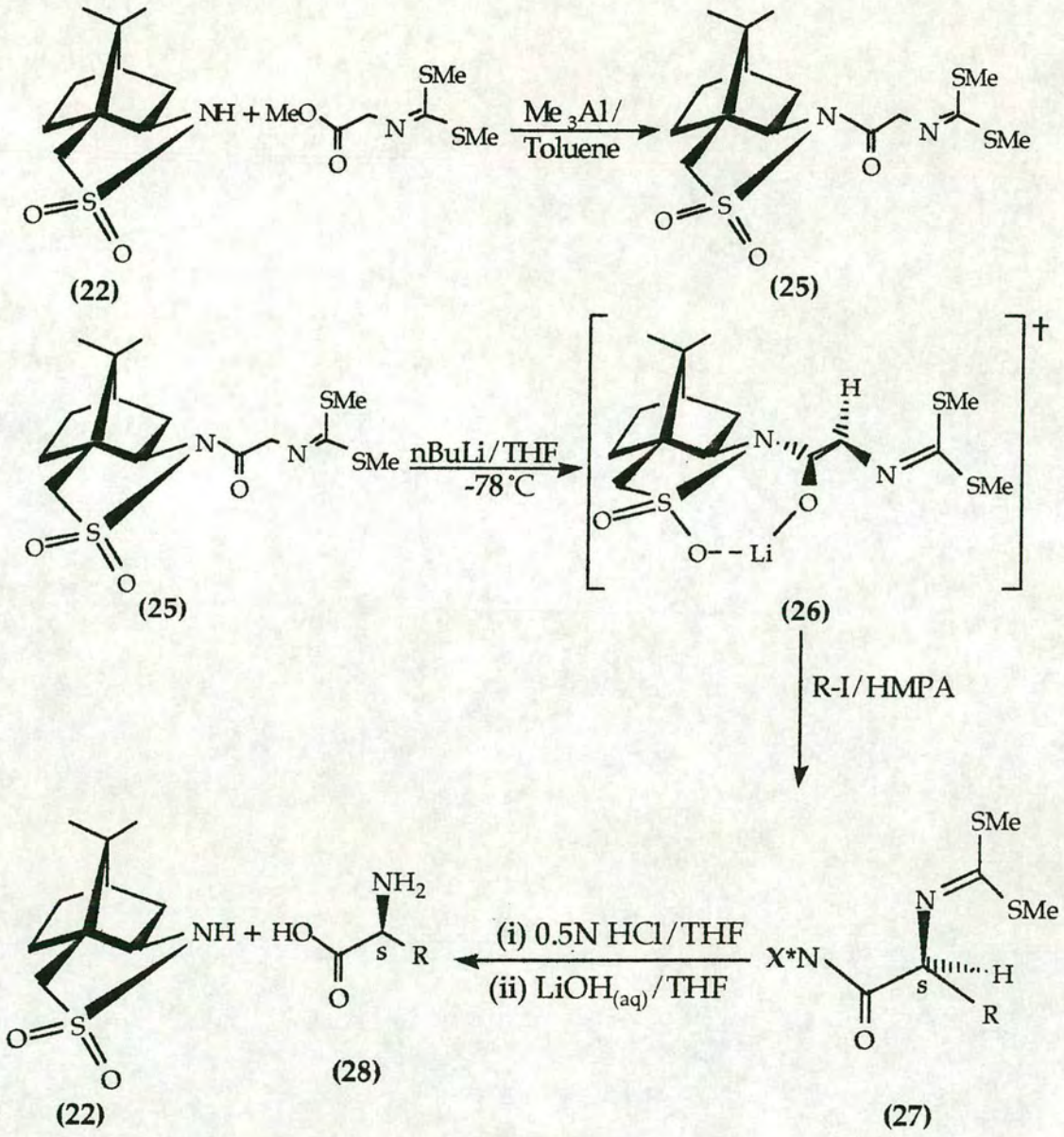
Functionalisation of the auxiliary is readily achieved *via* sodium hydride and acid chlorides to furnish saturated and unsaturated N-acyl derivatives (23) and (24) respectively, Scheme 7.



Scheme 7

Numerous successful applications utilising the auxiliary **(22)** have been carried out in asymmetric transformation reactions including the synthesis of α-amino acids[16,17], aldol reactions[18-20], hydrogenations[21], 1,3-dipolar cycloadditions[22,23] and Diels-Alder reactions[24,25].

An impressive example which typifies the versatility of Oppolzer's sultam is in the preparation of enantiomerically pure α-amino acids[16], Scheme 8. Conversion of auxiliary **(22)** to chiral glycine equivalent **(25)** is easily obtained in high yield (89%) *via* Me_3Al- mediated acylation. Deprotonation of glycinate **(25)** generates the glycine enolate intermediate **(26)** which is then alkylated with excellent π-face selectivity to give crystalline products **(27)**.



Scheme 8

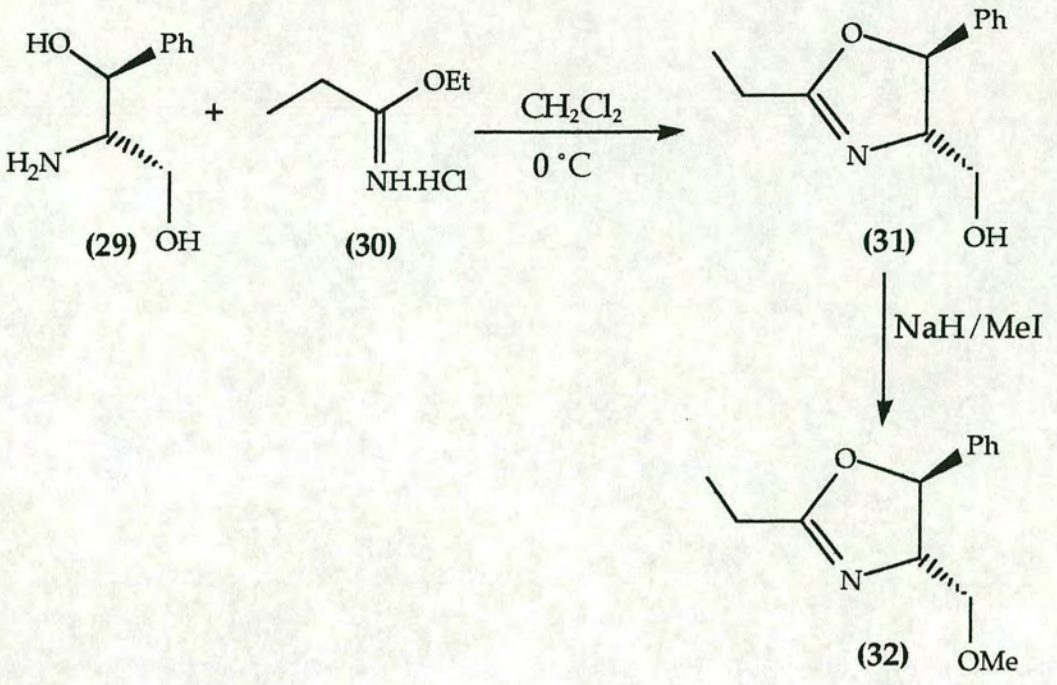
Mild hydrolysis of **(27)** leads to formation of α-amino acids **(28)** with almost absolute stereocontrol in high overall yield and with concomitant recovery of auxiliary **(22)**. This methodology has been carried out for a variety of alkyl groups and the excellent selectivity obtained for this series of reactions can be seen in Table 2.

R =	% yield (25) ⟶ (27)	% de (27)	% yield (27) ⟶ (28)	% ee (28)
$PhCH_2$	93	>99	>99	>99.8
n-C_4H_9	86	>99	>99	>99.8
Me	87	>99	>99	>99.8
Me_2CH-CH_2	85	>99	>99	99.5
Me_2CH	95	>99	84	>99.8
CH_2=CH-CH_2	87	>99	>99	>99.8

Table 2

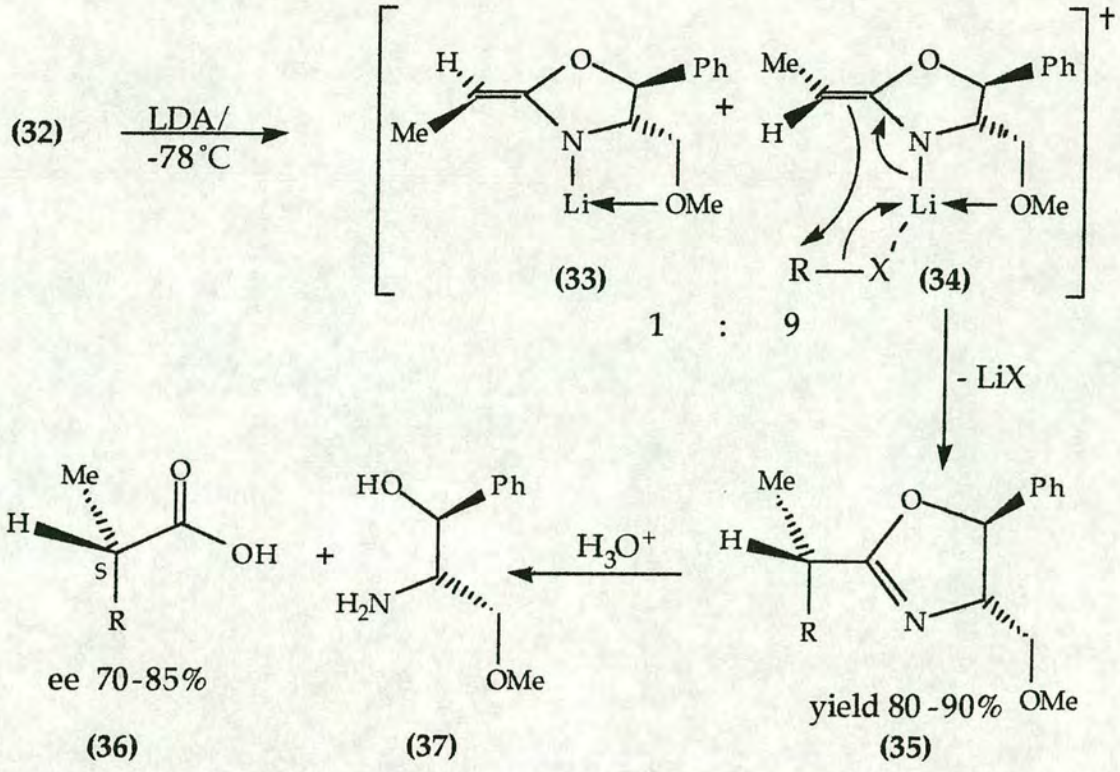
2.1(c) Meyers Chiral Oxazoline

Another superior example of a chiral auxiliary is the oxazoline **(32)** developed by Meyers[26,27]. Prepared from the reaction between the cheap amino diol **(29)** and the acidified imino-ether complex **(30)** to yield **(31)**, then by reacting with sodium hydride/methyl iodide to furnish the auxiliary **(32)**, it has principally been employed in the preparation of optically pure $C_{\alpha,\alpha}$-disubstituted carboxylic acids, Scheme 9.



Scheme 9

Initial treatment of the oxazoline **(32)** with lithium diisopropylamide (LDA) at low temperature generates the E : Z lithiated oxazolidines **(33)** and **(34)** respectively in a 1 : 9 ratio, Scheme 10. Subsequent reaction with various alkyl halides results in the formation of adducts **(35)** in 80-90% yield. Upon mild acid hydrolysis the $C_{\alpha,\alpha}$-disubstituted carboxylic acid products **(36)** are formed in 70-85% enantiomeric excess with simultaneous recovery of methoxylated starting alcohol **(37)** which can be recycled.



Scheme 10

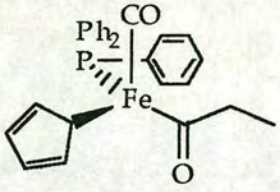
There are two distinguishing features of the auxiliary **(32)** which are crucial to its ability to function efficiently. Firstly, the methoxy substituent is an integral component for chelation to the lithium to form the rigid framework which leads to high asymmetric induction. Secondly, the bulkiness of the phenyl group on the top face provides steric hindrance which fosters π-facial selectivity and encourages attack from the sterically unprotected bottomside face. This theory has been affirmed by changing the methoxy group to a methyl group resulting in greatly reduced selectivity[28]. In addition, if the methoxymethyl group is replaced by a dimethylmethoxy group and the phenyl substituent is changed to a methyl or hydrogen, then the attack by the alkyl halide takes place at the topside face. This is due to the improved face-shielding of the now more sterically hindered bottomside face, leading to acids with opposite configuration.

2.1(d) Davies Chiral Organometallic Complex

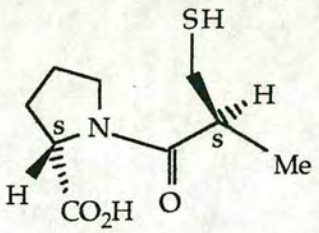
Although organometallic complexes have proved themselves to be of great service in organic synthesis, they have until recently remained an untapped source of potential in enantioselective synthesis.

However, organometallic complexes, in which the metal is a stereogenic centre, are presently making an impact and one illustrious example of this is the chiral iron complex **(38)** developed by S.G.Davies[29] which has been successfully utilised in the synthesis[30] of the angiotensin converting enzyme (ACE) inhibitor (-)-Captopril **(39)**.

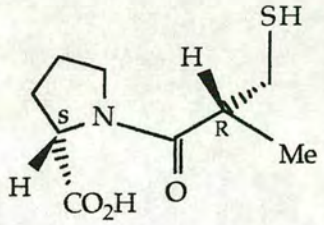
Previously, synthetic routes to Captopril have resulted in mixtures of **39** and its corresponding epimer **(40)** which require difficult separation. The (S,R) epimer **(40)** is known[31] to be 100 times less active than (S,S) Captopril **(39)**.



(38)
Iron complex

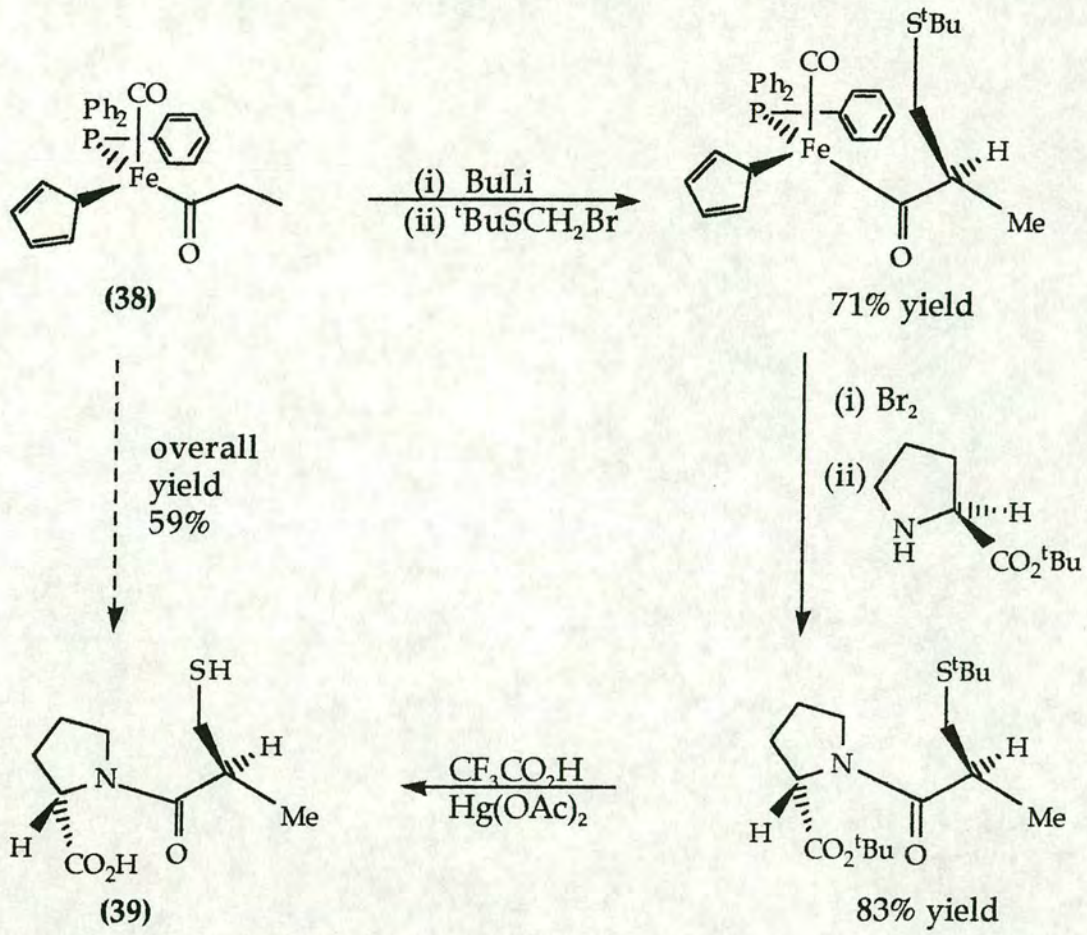


(39)
(-)-Captopril



(40)
(-)-epi-Captopril

However, using Davies chiral iron complex **(38)**, (-)-Captopril **(39)** can be produced with complete enantiomeric and diastereomeric purity in an overall yield of 59%, Scheme 11.



Scheme 11

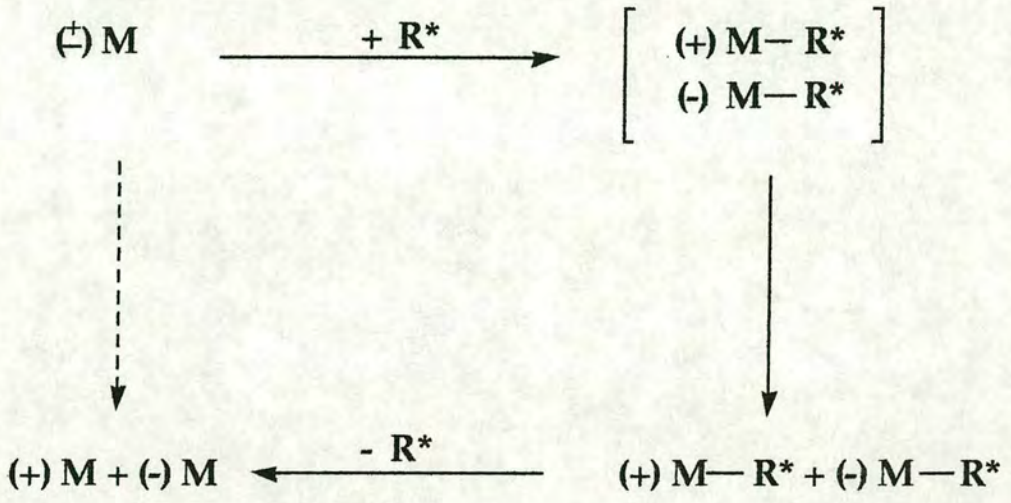
Mechanistic studies[32] have shown that the absolute stereochemical control is achieved *via* preferential stereoselective formation of the E-enolate with butyllithium and subsequent electrophilic addition of the alkylated sulphide species exclusively to the unhindered face.

2.2 Optical Purity By Resolution

Although the synthetic organic chemist of today has at his disposal a rich arsenal with which to prepare optically pure compounds, this has not always been the case.

The process known as resolution was the original approach by which compounds of chiral purity could be prepared and is a long standing and well established method which is still currently practised.

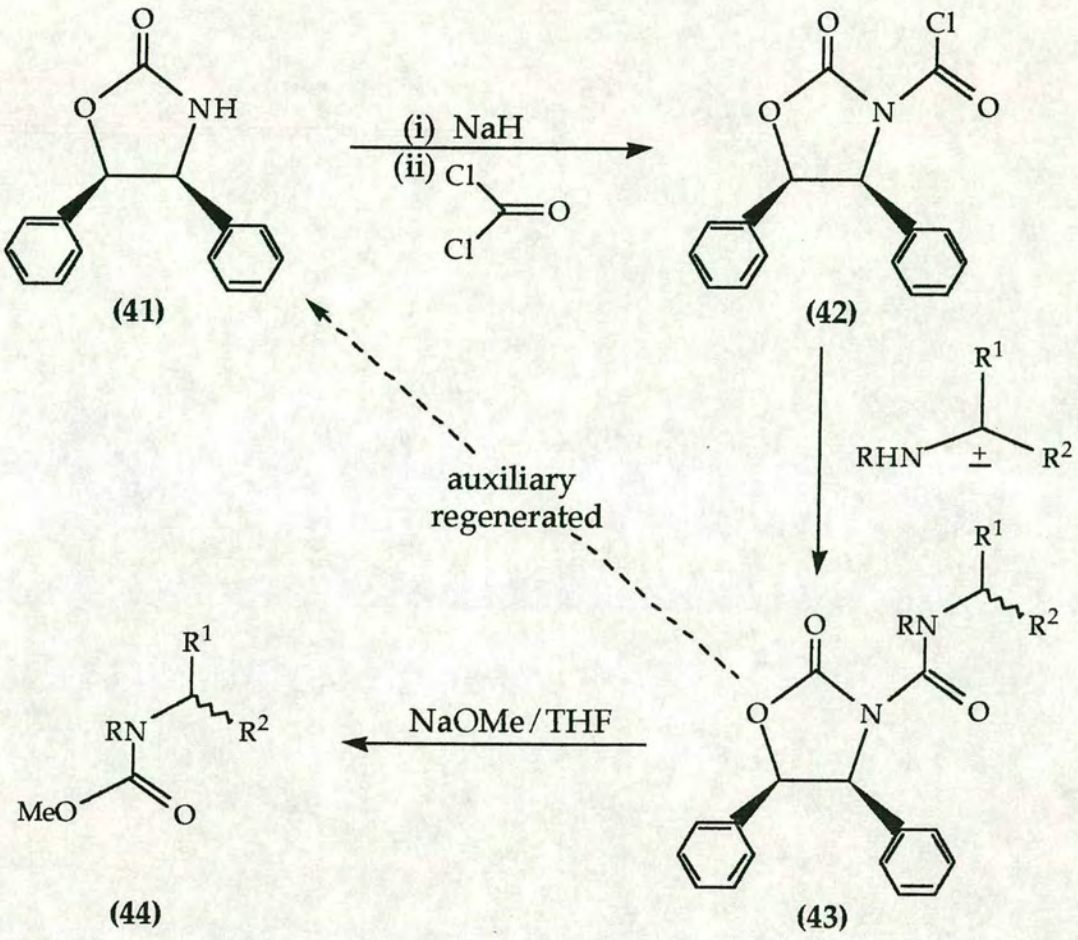
The technique basically involves appending an optically pure resolving agent (R*) to a racemic mixture (±M) to furnish a mixture of diastereomers. The individual diastereomers can then be separated from one another by exploiting their differing physical properties. Removal of the resolving agent from each exclusive diastereomer generates the unique products in enantiomerically pure form, Scheme 12.



Scheme 12

A noteworthy example of a resolving agent which has been successfully utilised in the field of resolution is the chiral *cis*-4,5-diphenyl oxazolidinone **(41)** prepared by Pirkle[33].

By converting auxiliary **(41)** to the corresponding carbamyl chloride **(42)** this compound has been used to derivatise various racemic primary and secondary amines. The resultant diastereomeric allophanates **(43)** can be separated readily by chromatographic techniques before chemically retrieving **(41)** together with the resolved substrate **(44)** *via* reaction with sodium methoxide, Scheme 13.



Scheme 13

The separability values (α) obtained from the chromatographic separation of diastereomeric allophanate pairs **(43)** show a marked contrast in relation to one another, Table 3.

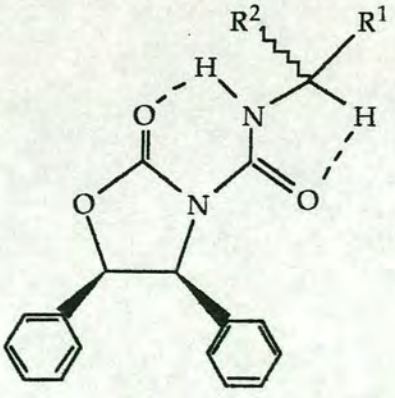
R	R^1	R^2	amine (1° or 2°)	α Value
H	methyl	ethyl	1°	1.32
H	methyl	hexyl	1°	2.50
H	methyl	phenyl	1°	2.69
H	pentyl	butyl	1°	1.17
H	methyl	t-butyl	1°	1.68
Me	methyl	phenyl	2°	1.24

Table 3

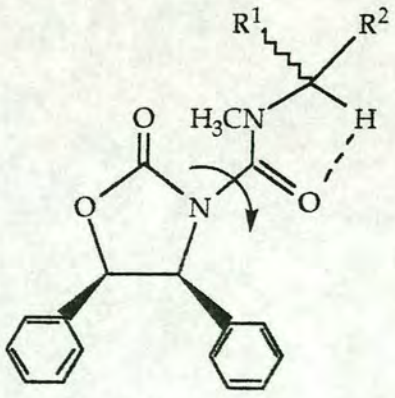
A study conducted by Pirkle[34] helps to explain the results shown in Table 3.

The results show that the separation of diastereomers carrying substituent groups of similar steric proportion (eg methyl vs ethyl) give rise to small separability values. In contrast where the substituent groups are more disparate in steric bulk (eg methyl vs phenyl) higher α values are obtained. Table 3 contains one entry from a secondary amine. The dramatic reduction in the separability value of this diastereomeric pair compared with the analogous primary amine (1.24 vs 2.69) is attributed to two factors. Firstly, in the diastereomeric allophanate pair **(43a)** pertaining to the primary amine, hydrogen bonding exists between the amidic proton and the carbonyl group on the oxazolidinone, this increases the conformational rigidity of the complex. In the corresponding allophanate pair **(43b)** relating to the secondary amine, the amidic hydrogen is absent and consequently there is no possibility of hydrogen bonding. Secondly, in addition to the loss of hydrogen bonding in allophanate pair **(43b)** there is freedom of rotation about the oxazolidinone nitrogen-carbonyl bond.

A consequence of these two factors is that the carbonyl groups in **43b** do not adopt an anti-periplanar arrangement as heavily as in **43a**. Overall this leads to a significant drop in conformational rigidity which is partly responsible for the α value.



(43a)



(43b)

These findings have been substantiated by Kreig[35,36] who has carried out IR and NMR studies on achiral allophanates very similar to **43** and concluded that they preferentially populate the conformation having the two carbonyls anti-periplanar with the amide hydrogen bonded to the ring carbonyl.

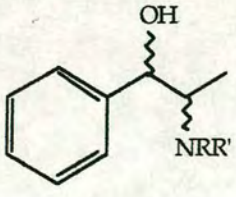
2.3 Chiral Pool

The group of compounds known collectively as the 'chiral pool' have for many years proved themselves to be highly efficient chiral agents for enantioselective synthesis.

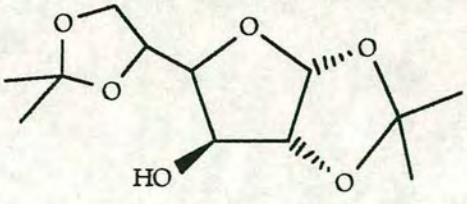
They are inexpensive, naturally occurring and are intrinsically chiral.

The group is comprised of five main classes: alkaloids, terpenes, hydroxy acids, carbohydrates and amino acids.

Each of these classes has undergone much examination and have participated in many highly successful enantioselective operations. For example, the ephedrine derived chiral reagent **(45)** has been employed in ketone reduction reactions with almost total asymmetric control[37]. The glucose derived auxiliary **(46)** is another excellent example which has been used in addition reactions to aldehydes resulting in very high enantioselection[38].



(45)



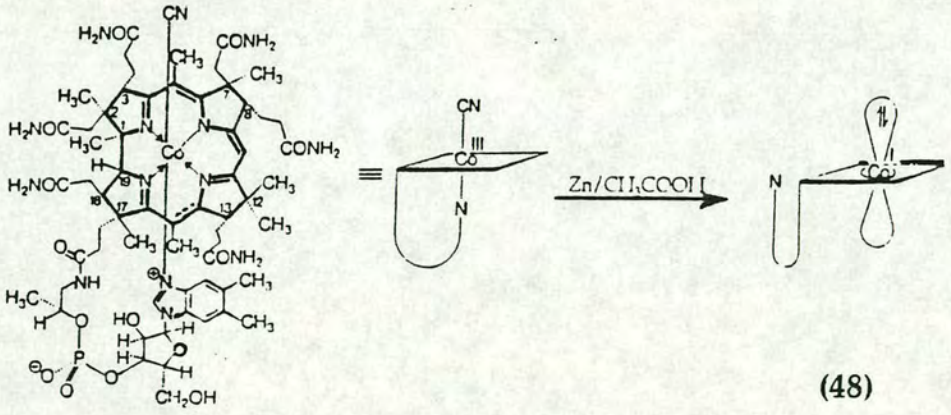
(46)

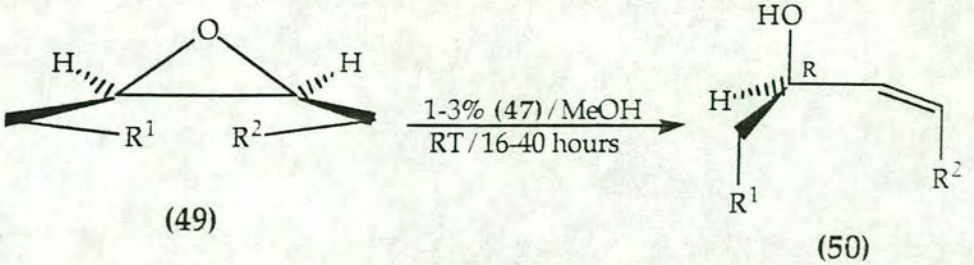
In addition to the main classes, there are a few miscellaneous sources of minor contribution to the chiral pool. One particularly enterprising example of these is the vitamin B_{12} **(47)** which has been used by Su *et al*[39] as an enantioselective catalyst in the isomerisation of epoxides **(49)** to generate optically active allylic alcohols **(50)** with highly acceptable enantiomeric excesses, Table 4, Scheme 14.

Epoxide	R^1 R^2	mol%(48)	Time(hrs)	%yield	%ee
a	$-(CH_2)-$	1	168	96	65
b	$-(CH_2)_2-$	3	16	80	42
c	H H	1	30	94	26

Table 4

The catalytically active species[40] is vitamin B_{12S} **(48)** obtained from vitamin B_{12} **(47)** by an *in-situ* two-electron reduction.





Scheme 14

For complete isomerisation, the reactions are carried out at room temperature under an inert atmosphere and on work-up the catalyst is easily regenerated and can be re-used without loss of catalytic activity.

2.4 Catalytic Asymmetric Synthesis

Such has been the progress enjoyed by the discipline of catalytic asymmetric synthesis, it is now one of the most promising methods of producing optically active compounds.

The concept involves the employment of a chiral metal catalyst to form a chelated complex with a prochiral substrate, which upon mutual secondary interaction, suppresses the degree of freedom in the transition state, leading to smooth control of the stereochemistry of the product.

The strategy has been successfully utilised in many areas of asymmetric transformations, among the most common of these are:

(a) asymmetric allylic alkylations

(b) Diels-Alder reactions

(c) Grignard cross-coupling reactions

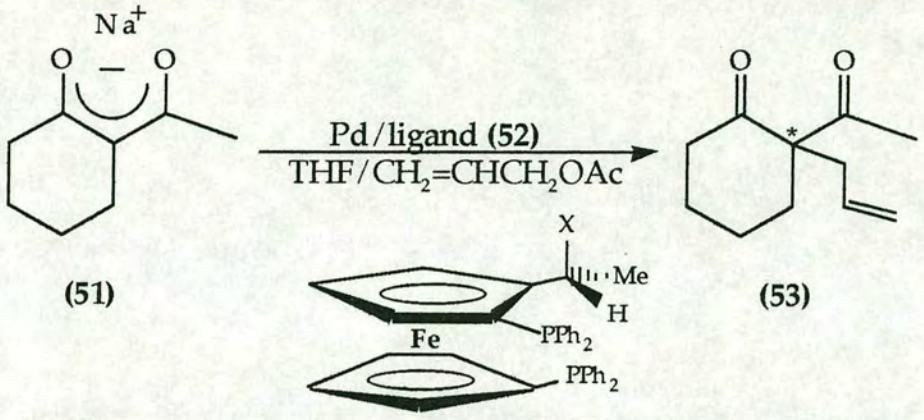
(d) hydroborations

(e) epoxidations

2.4(a) Asymmetric allylic alkylations

This discipline has been utilised to prepare optically active allylation products. For example, Hayashi *et al* [41,42] has carried out the asymmetric allylation of the sodium enolate of 2-acetylcyclohexanone **(51)** with allyl

acetate. The reaction is catalysed by palladium complexes carrying modified chiral ferrocenylphosphine ligands **(52)** and furnishes the asymmetric products **(53)**, Scheme 15.



(51) **(53)**

(52)

Scheme 15

The degree of selectivity and absolute configuration of the products are dependent upon the reaction temperature and the nature of the ligand substituent group X, Table 5.

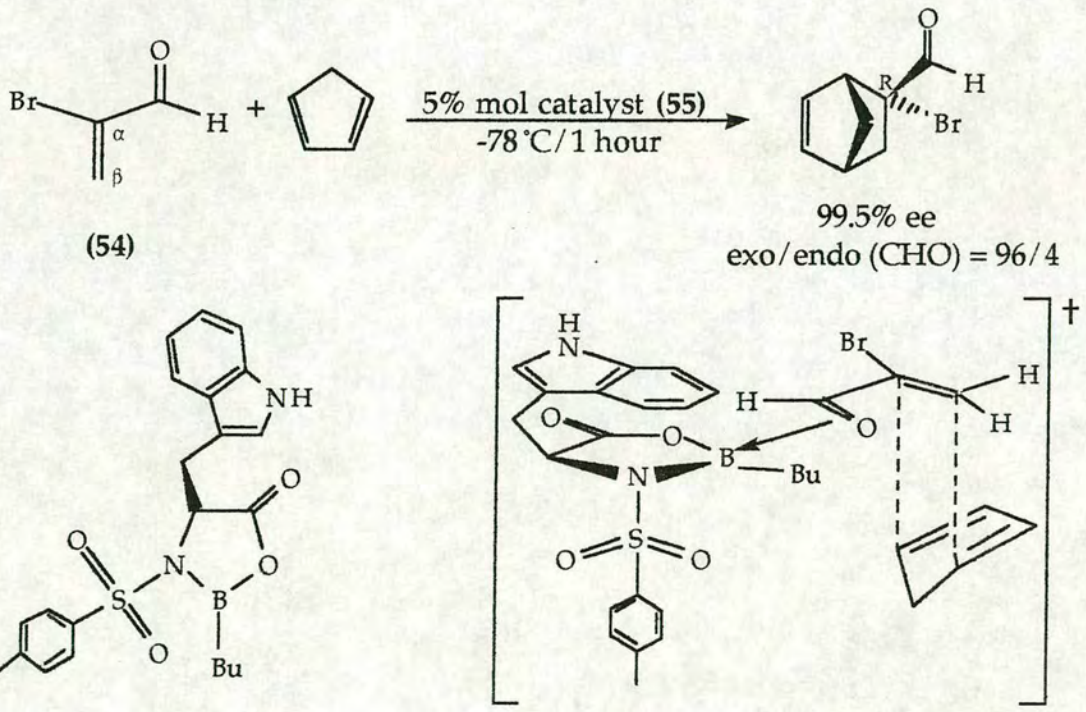
entry	X group (52)	T/°C	% ee
(a)	$NMeCH_2CH_2OH$	-50	73(S)
(b)	$NHCH_2C(CH_3)_2OH$	-50	31(S)
(c)	$NMeCH(CH_2OH)_2$	-50	49(S)
(d)	$NHCH_2CH_2OH$	-50	62(S)
(e)	$NH(CH_2)_3OH$	-50	46(S)
(f)	OH	-30	30(S)
(g)	$NMeCH_2CH_2NHMe$	-30	20(R)
(h)	$NHCH_2CH_2OMe$	-30	6(R)
(i)	NMe_2	-30	22(R)

Table 5

2.4(b) Catalytic Diels-Alder Reactions

An excellent enantioselective Diels-Alder reaction promoted by (S)-tryptophan derived oxazaborolidine catalyst **(55)** has been reported by Corey *et al*[43].

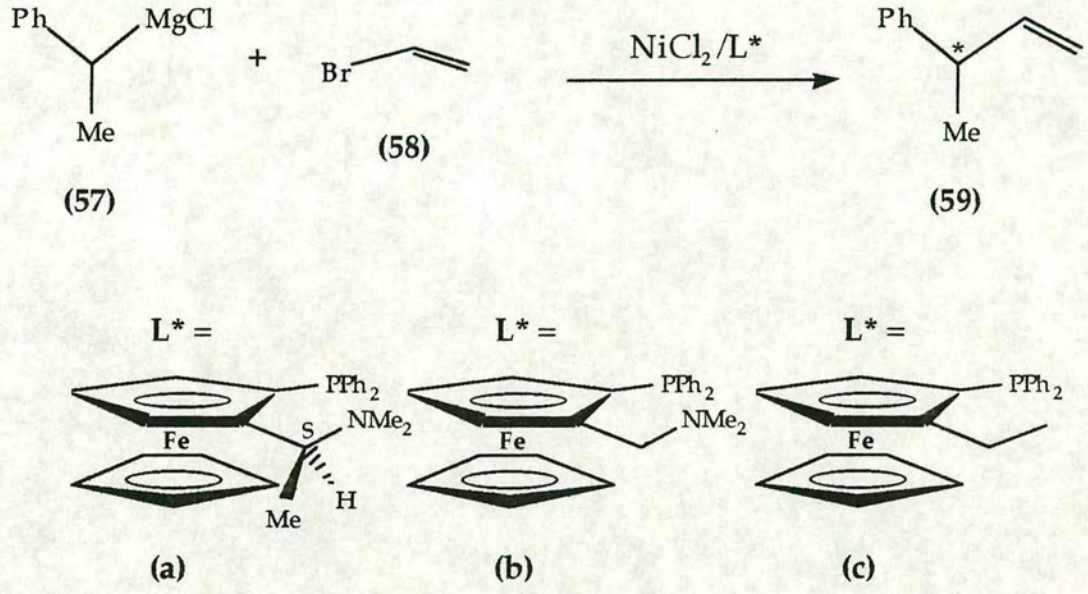
The reaction concerns the cycloaddition of an α,β unsaturated aldehyde **(54)** with cyclopentadiene, Scheme 16. The authors propose that the high stereoselectivity observed is due to an attractive donor/acceptor π-π interaction in the transition state **(56)** which favours coordination of the dienophile at the vacant coordination site of boron which is *cis* to the 3-indolymethyl substituent.



Scheme 16

2.4(c) Asymmetric Grignard Cross-Coupling

Kumada *et al*[44] have carried out asymmetric Grignard cross-coupling reactions using Grignard reagent **(57)** with vinyl bromide **(58)** to furnish coupling product **(59)**, Scheme 17.



Scheme 17

The reactions are nickel-catalysed and various chiral ferrocenylphosphine ligands (L*) have been examined to determine the effect on stereoselectivity by changing ligand substituent groups.

The importance of ligand group substituent can be seen from the dramatic diversity in degree of asymmetric induction, Table 6.

L*	% yield	% ee	configuration
(a)	99	59	R
(b)	98	60	S
(c)	86	4	S

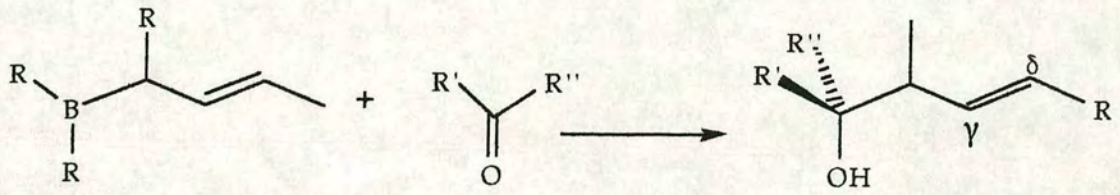
Table 6

Chiral ligand (b), which contains an amino group on the ferrocene side-chain, but lacks the central chirality possessed by (a), delivers coupling products **(59)** which exhibit almost the same degree of enantioselectivity as (a), but possess opposite configuration. In contrast, chiral ligand (c), which lacks both the central chirality and amino group, gives an almost racemic product.

These results indicate that the dimethylamino group on the chiral ferrocenylphosphine ligand side-chain is crucial to high stereoselectivity, whereas the sense of asymmetric induction is dependent upon both the presence and configuration* of the central chirality. {*The corresponding R-isomer of (a) gives rise to products with opposite configuration}.

2.4(d) Hydroborations

Yamaguchi and Mukaiyama[45] have reported a method for the regioselective and stereoselective synthesis of γ,δ unsaturated alcohols **(62)**. The process involves reacting hydroborating agents, allyldialkylboranes **(60)**, with aldehydes and ketones, Scheme 18.



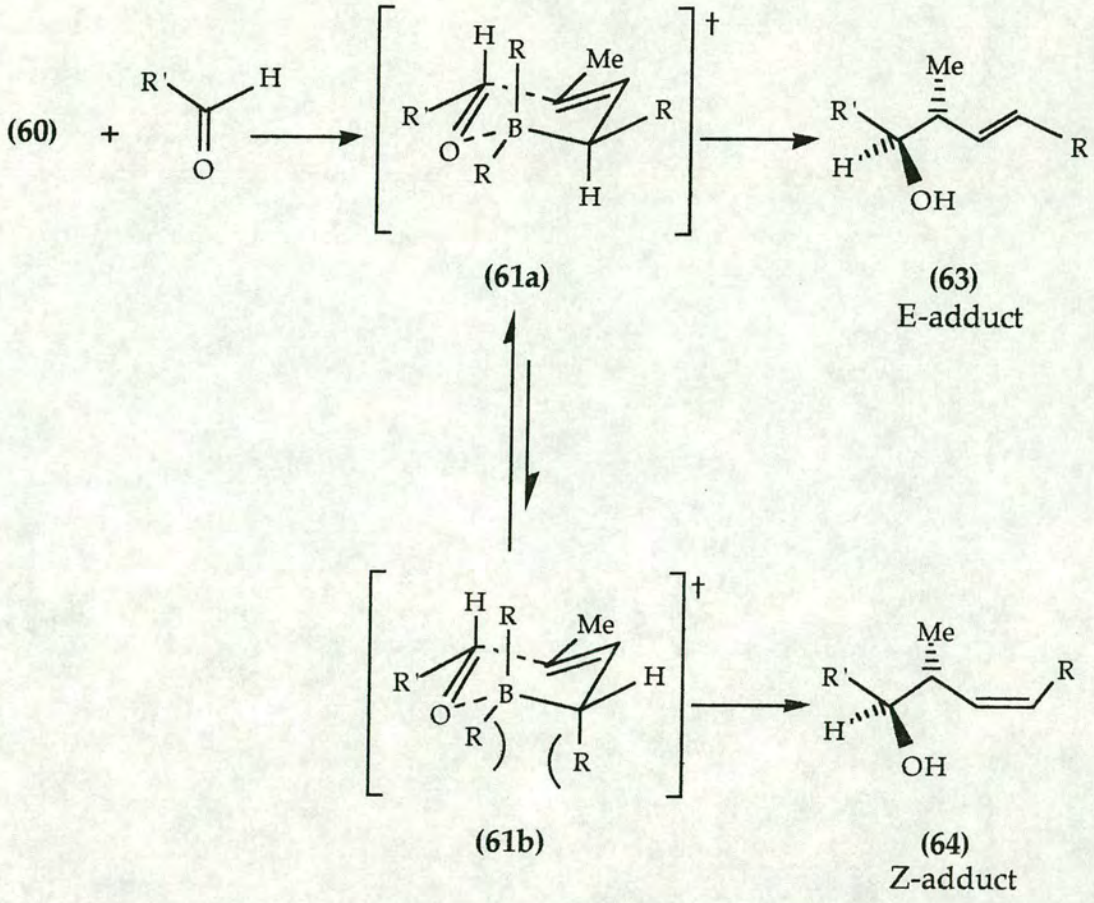
(60) (62)

Scheme 18

% yields	*erythro* : *threo*	E : Z
52 - 91	≥95 : ≤5	9 : 1

Table 7

Studies carried out by ApSimon and Collier[37] account for the high selectivities obtained in the reactions. The authors propose that the reaction of the allyldialkylborane **(60)** with aldehydes gives rise to two possible six membered transition states, **(61a)** and **(61b)**, Scheme 19. The transition states adopt chair conformations and the steric interaction between the adjacent equatorial/axial alkyl groups in **61b** causes **61a** to be more favourable and hence the preference in the formation of E-adduct **(63)** as opposed to Z-adduct **(64)**.



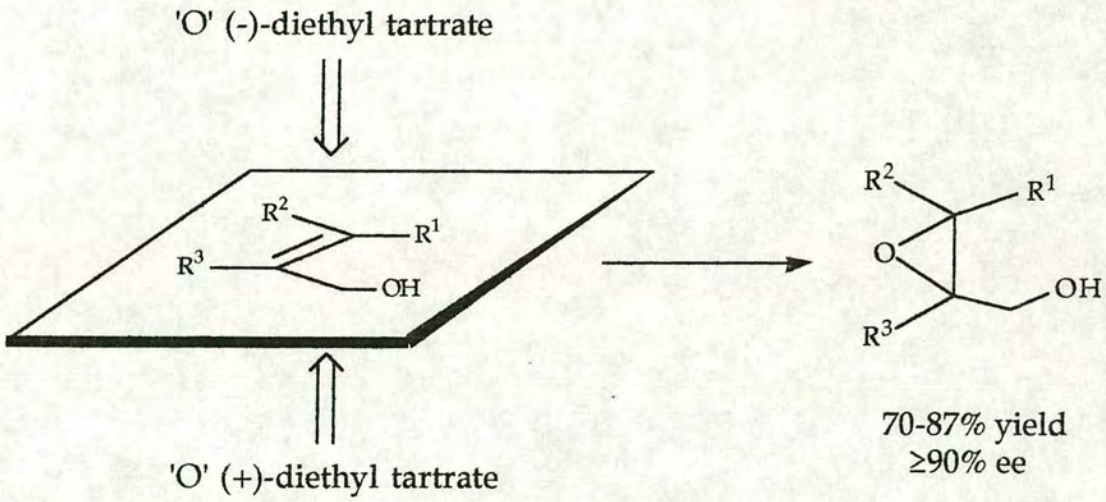
Scheme 19

2.4(e) Asymmetric Epoxidations

A highly proficient method for the metal-catalysed asymmetric epoxidation of allylic alcohols has been developed by Katsuki and Sharpless[46]. A favourable aspect of the reaction is that the process is straightforward and the necessary components are titanium tetraisopropoxide, *tert*-butyl hydroperoxide and (+)-diethyl tartrate or (-)-diethyl tartrate, all of which are available at low cost. There are two further features to this chiral epoxidation system which are attractive.

Firstly, the system can conduct uniformly high asymmetric inductions throughout a variety of substituents. Secondly, upon selection of one of the tartrate enantiomers and regardless of the substituent group, the system consistently delivers the epoxide oxygen from the same enantioface of the olefin.

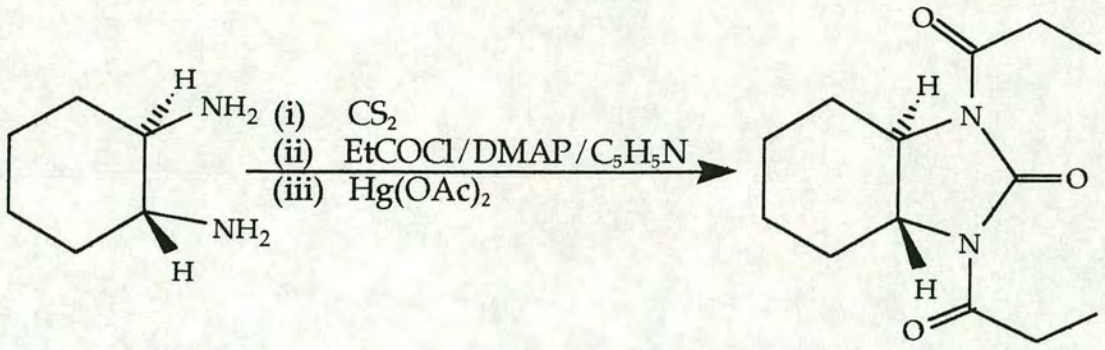
If, for example, addition of the epoxide oxygen is desired from the upper face, then (-)-diethyl tartrate is employed. Conversely, if the opposite enantiomer, (+)-diethyl tartrate is used, then the epoxide oxygen is delivered from the lower face, Scheme 20.



Scheme 20

2.5 Bifunctional Chiral Auxiliary

Davies and Mortlock[47] have developed and reported the bifunctional chiral auxiliary **(66)** prepared from trans-1,2-diaminocyclohexane **(65)**, Scheme 21.

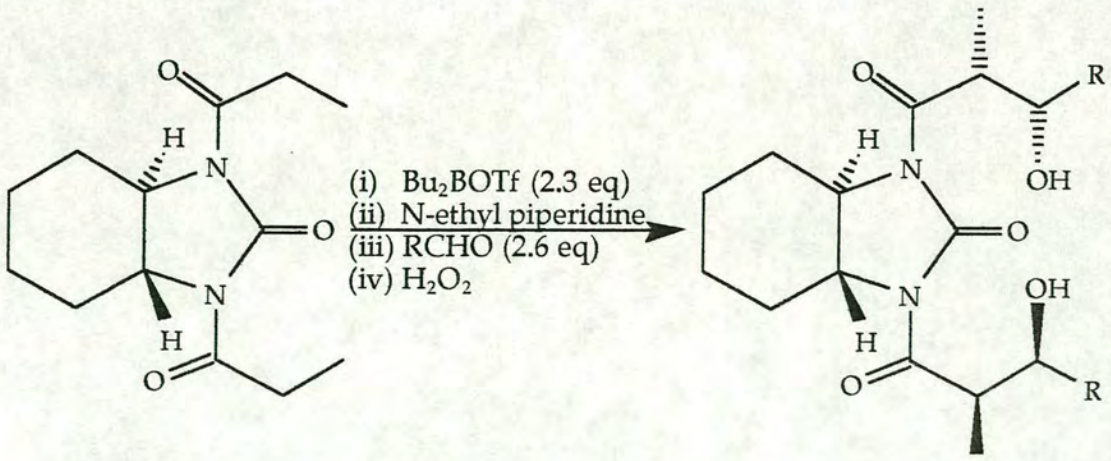


(65) (66)

Scheme 21

The authors claim that current methodology involving chiral auxiliaries in stereoselective synthesis has an inherent disadvantage in that the heavy chiral fragment has to be carried through a number of steps. Their aim therefore was to design a chiral propionate equivalent where the mass of the auxiliary was reduced as far as possible within the limits of maintaining high stereocontrol.

The bifunctional auxiliary **(66)** was utilised with a range of aldehydes to furnish β-hydroxy carbonyl products **(68)** in a series of very highly stereoselective dialdol reactions, Scheme 22, Table 8.



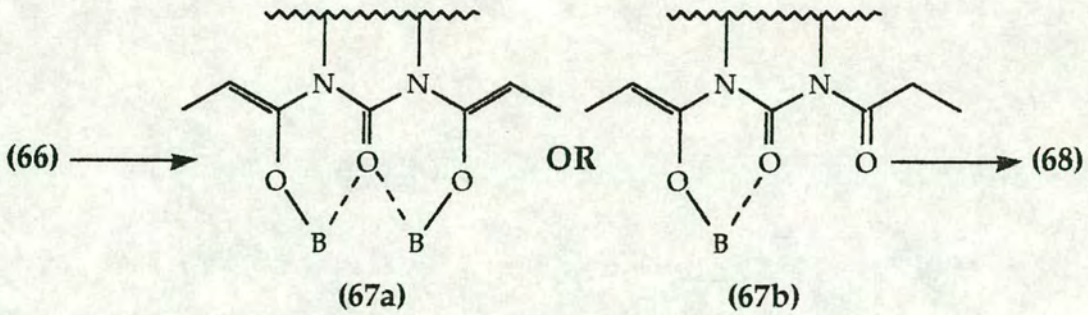
(66) (68)

Scheme 22

R	% yield	% de
Me	67	>96
Et	78	>96
n-Pr	71	>96
i-Pr	82	>96
Ph	89	>96

Table 8

The authors also relate preliminary findings based on mechanistic investigations performed by Heathcock[48] as to whether the reaction mechanism occurs by formation of a bis-enolate system **(67a)** or whether the process occurs sequentially **(67b)**, with the latter being predicted, Scheme 23.

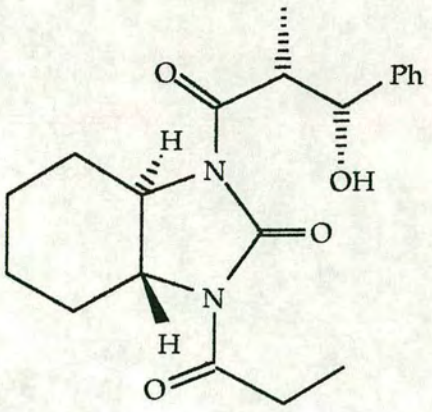


(67a) **(67b)**

Scheme 23

Examination of the ^1H NMR spectrum of the reaction mixture prior to addition of the aldehyde revealed signals corresponding to the presence of both an enolised side-chain and a non-enolised side-chain in a ratio consistent with a mono-enolate.

Furthermore, when the reactions were repeated using only single equivalents of dibutylboron triflate, 1-ethylpiperidine and the aldehyde, the mono-aldol product **(69)** was obtained cleanly.



(69)

The results suggest that the prediction of independent sequential mono-enolate systems **(67b)** is correct, or that if the formation of the bis-enolate **(67a)** does occur, then it must do so at a much slower rate than formation of the mono-enolate.

The authors are seeking further confirmative evidence of the postulation and intend to report this together with successful non-destructive methods of cleavage of the fragments.

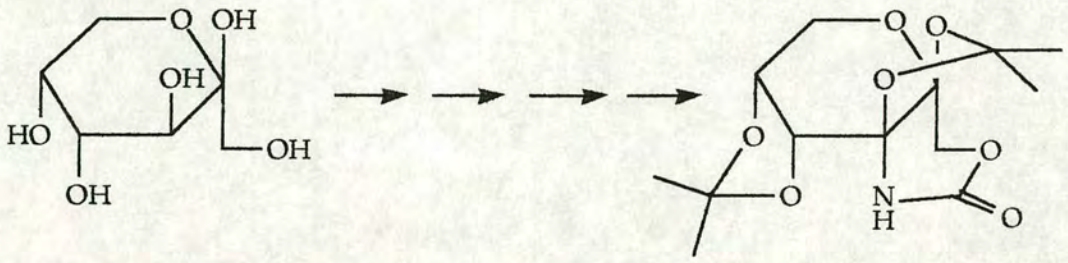
DISCUSSION

PREAMBLE

Programme of Research

Central to the programme of work involved in this thesis is the chiral oxazinone auxiliary (77) derived from (-)-D-fructose (72).

The synthesis of auxiliary (77) and subsequent exploration of its' stereodirective competence in a variety of asymmetric transformation reactions distinguishes it as the protagonist and dominant character of the work described herein.



(72) (77)

The series of reactions chosen to investigate the asymmetric inducting power of chiral auxiliary (77) largely reflects literature precedent in which many successful auxiliaries have been examined, this allows an accurate comparative appraisal to be carried out.

These included: aldol reactions, acylations, Diels-Alder reactions, alkylations, α-brominations and conjugate additions. The auxiliary (77) was also employed as a resolving agent in the resolution of racemic mixtures of a primary amine and an acid halide.

Chapter 1

Construction and Functionalisation of Auxiliary (77)

1.1 Strategy For Synthesis of Auxiliary (77)

Reported earlier in this thesis was the daunting list of criteria which any chiral auxiliary had to surmount to be successful.

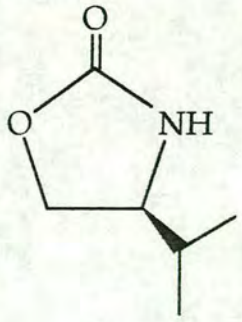
Certain pre-considered structural features incorporated into the design of a chiral auxiliary can help it to negotiate this list.

The following passage was taken from a report by Kunz[49].

"Carbohydrates are inexpensive, natural products which possess numerous functional groups and stereogenic centres. By directed regioselective and stereoselective formation of derivatives, they can be converted into efficient chiral auxiliaries for controlling asymmetric syntheses".

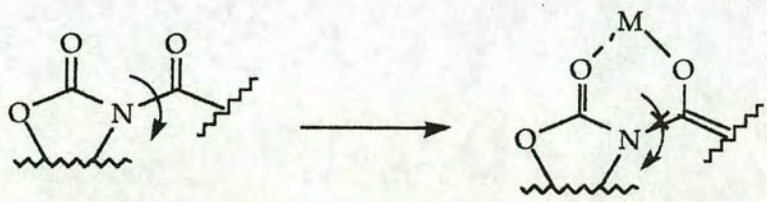
With regard to this, a carbohydrate based framework seemed a logical choice as a potential starting point in the construction of the auxiliary. Though a little care would have to be exercised, the selective shielding of groups could be readily achieved.

Examination of Evans' hailed auxiliary **(9)** reveals a nitrogen which can be easily functionalised for ensuing asymmetric reactions. Following these conversions the auxiliary can be recovered together with the product fragments by cleavage at the same nitrogen.



(9)
Evans Auxiliary

Also included in the design of auxiliary (9) is a carbonyl group which can be utilised as an integral part of a bidentate metal chelation centre. Addition of a second carbonyl group outside the oxazinone ring can be achieved *via* functionalisation at the nitrogen. Subsequent joint chelation of the two carbonyl groups to a central metal atom then restricts the various rotational degrees of freedom present and leads to stereochemical control and diastereofacial selectivity, Scheme 24.



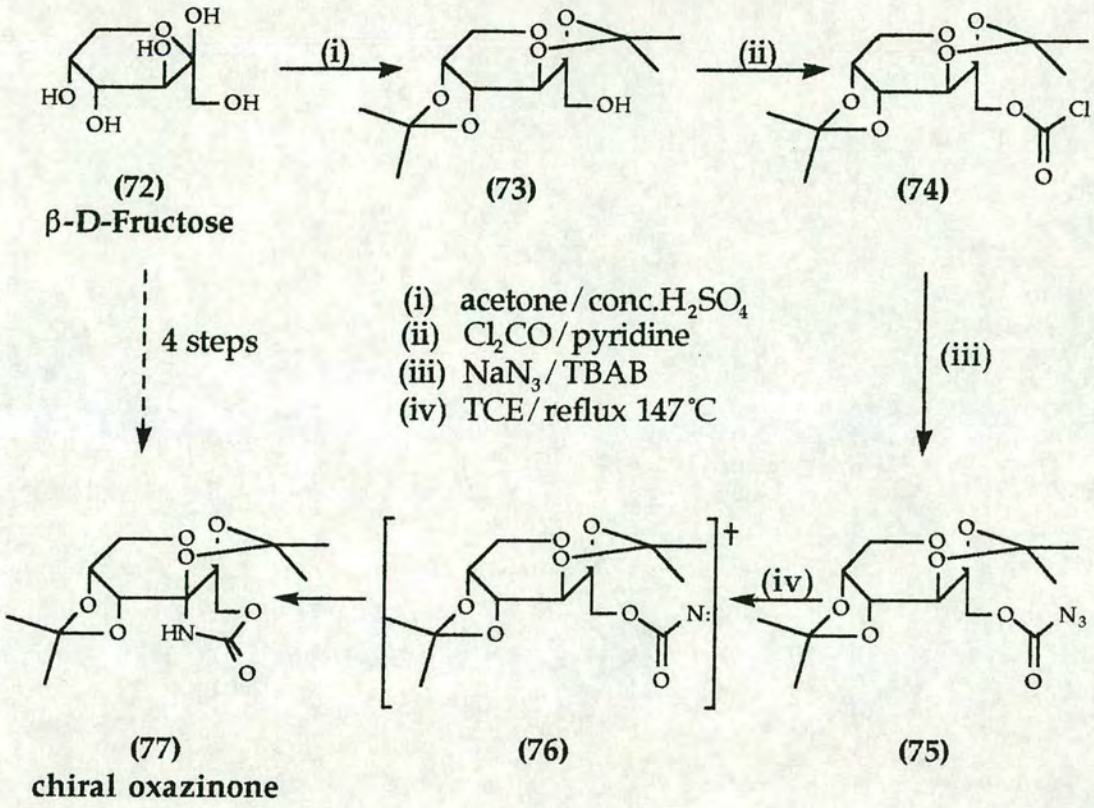
Scheme 24

These features are hallmarks of many auxiliaries and adoption of them was natural.

1.2 Synthesis of Auxiliary (77)

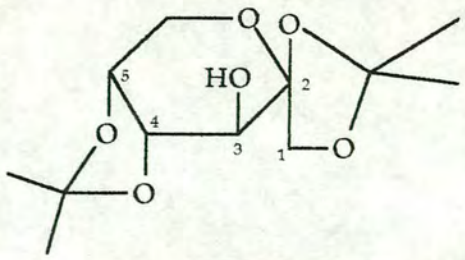
Previous research work conducted in Edinburgh by Banks *et al*[50] on the construction and cyclisation of five membered oxazolidinone rings from glucose had utilised the well known, but little used, nitrene insertion process. A similar strategy carried out on fructose as a chosen starting material would most likely result in a six membered oxazinone ring. It seemed reasonable to expect the nitrene insertion process to be just as successful in the formation of six membered oxazinone rings and indeed literature precedent[51] has shown that similar and often greater success is achieved in the formation of six membered oxazinone rings.

With this strategy in mind the synthesis of chiral auxiliary (77) was attempted and is comprehensively covered in Scheme 25.



Scheme 25

The synthesis is carried out in an overall four step process in which the first step involves condensation of the starting sugar β-D-fructose (72) with acetone in the presence of acid catalyst to give the *2,3:4,5* hydroxyl protected diisopropylidene derivative (73). The concentration of acid is important as at lower concentrations formation of the corresponding *1,2:4,5* hydroxyl protected isomer (78) is preponderant[52].



(78)

The second step involves conversion of protected alcohol **(73)** in quantitative yield into chloroformate **(74)** by reacting with phosgene in the presence of pyridine as base catalyst. The chloroformate **(74)** is then converted in similar high yield to the azidoformate derivative **(75)** by reacting with sodium azide under phase-transfer catalysis conditions, the phase-transfer catalyst used was tetrabutylammonium bromide (TBAB). The final step involves generation of the nitrene intermediate **(76)** which can then insert intramolecularly and stereospecifically to give the oxazinone chiral auxiliary **(77)**.

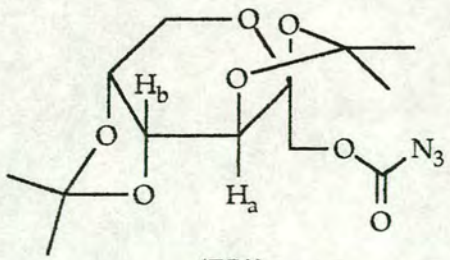
The methodology employed for the nitrene insertion process was solution thermolysis using *1,1,2,2*-tetrachloroethane (TCE) in which the nitreneoformate intermediate **(76)** is generated in a boiling solution. The choice of TCE as solvent was due to two reasons. Firstly, the boiling point of TCE is 147°C, this is sufficiently high to ensure the smooth decomposition of the azidoformate. Secondly, perusal of a literature report[53] had disclosed that polychlorinated solvents, especially those bearing two geminal chlorine atoms in their structures, are inert to nitrene attack. An obvious disadvantage encountered here however, is the extreme toxic nature of the solvent, it is widely recognized as a severe poison[54] which is readily absorbed through the skin. As such, all safety precautions required for using this solvent were adopted at all times. Nitrenes such as **(76)** are monovalent and the two non-bonded electrons can either be paired (singlet state) or unpaired (triplet state). The ground state of most nitrenes is the triplet state in which instance nitrenes will readily undergo hydrogen abstraction reactions with potential hydrogen donors.

It is the singlet state however, which is relevant to the insertion process required for cyclisation to form the oxazinone ring in (77). In this state, it is known[55] that the characteristic reactions of nitrenes is C-H bond insertion, with the order of preference being 3°>2°>1°.

Various concentrations of azidoformate (75) in TCE were tried to maximize the yield of auxiliary (77) and it was found that dropwise addition of the azide (75) at dilute concentrations between 1-2% acheived optimum results. Following purification *via* column chromatography, these conditions generally gave oxazinone auxiliary (77) in a yield of 55%.

Confirmation of the nitrene insertion was obtained from ^{1}H and ^{13}C nuclear magnetic resonance spectroscopy (NMR). From the ^{1}H NMR spectrum of the azidoformate (75) a doublet is observed at 4.2ppm. This doublet is due to spin-spin coupling of proton H_a with proton H_b, (75*).

However, in the ^{1}H NMR spectrum obtained from the auxiliary, the doublet at 4.2ppm is absent and is replaced by a broad singlet at 7.5ppm characteristic of an N-H signal. In the ^{13}C NMR spectrum of the auxiliary (77) there is one fewer C-H signal than in the corresponding spectrum obtained from the azidoformate, *ie* the C-H_a signal shown in the spectrum of (75*) is absent in the spectrum of (77).



(75*)

X-Ray Crystal Structure of Auxiliary (77)

The absolute stereochemistry of the auxiliary (77) can be seen from X-ray crystallographic studies which have determined that in the solid state, two conformations exist, Figure 1.

Mapping of the two conformations shows very little difference between the two, though this is hardly surprising when considering the near rigid arrangement of a tetracyclic structure with no appendant side chain groups.

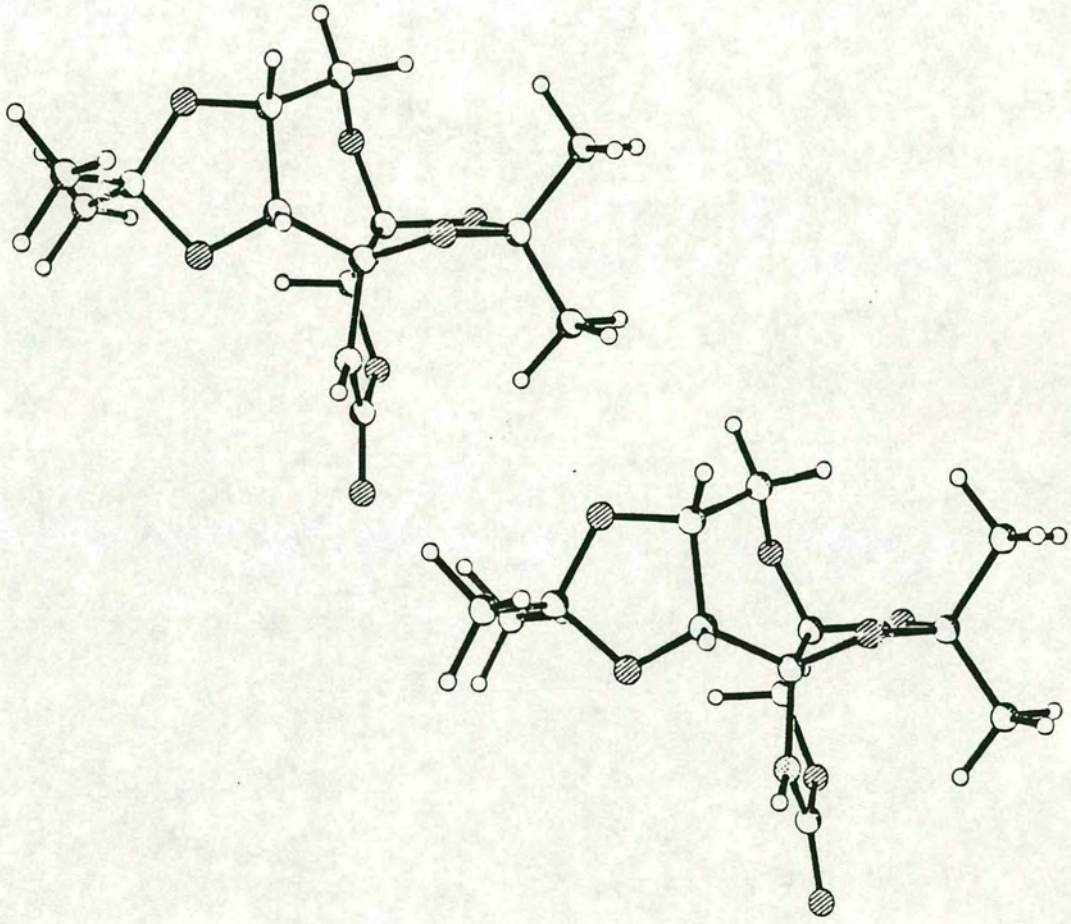


Figure 1

(X-Ray Crystal Structure of Auxiliary)

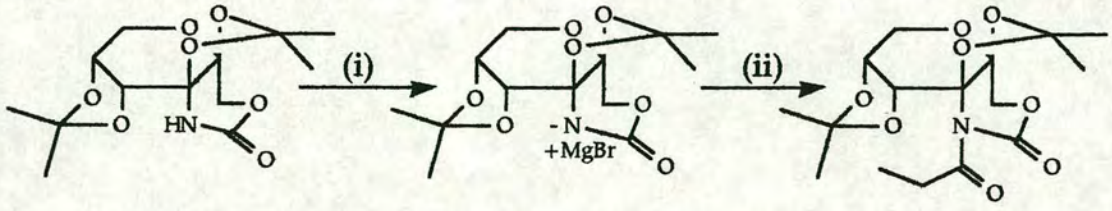
The auxiliary is a colourless, highly crystalline solid with a sharp melting point of 219°C.

Inspection of the X-ray crystal structures of auxiliary (77) show that the six membered parent sugar ring has adopted a distorted twist boat conformation, whilst the six membered oxazinone ring adopts a chair-like arrangement.

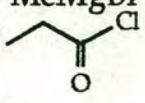
The steric imposition of the two five membered isopropylidene groups in relation to one face of the oxazinone ring looks highly favourable. If so, then the prospects for this auxiliary to successfully participate in asymmetric transformations look very promising.

1.3 Functionalisation of Oxazinone Auxiliary (77)

One important step *en route* to determining the competence of oxazinone (77) in promoting asymmetric induction, is by conversion to the corresponding N-acyl carboxymide derivative. This was achieved by reacting (77) with the Grignard reagent, methylmagnesium bromide, then treating the resulting N-bromomagnesium species (79) with propionyl chloride to afford the propionate (80) in quantitative yield, Scheme 26.



(77) (79) (80)

Reaction conditions: (i) MeMgBr
(ii) 

Scheme 26

Chapter 2

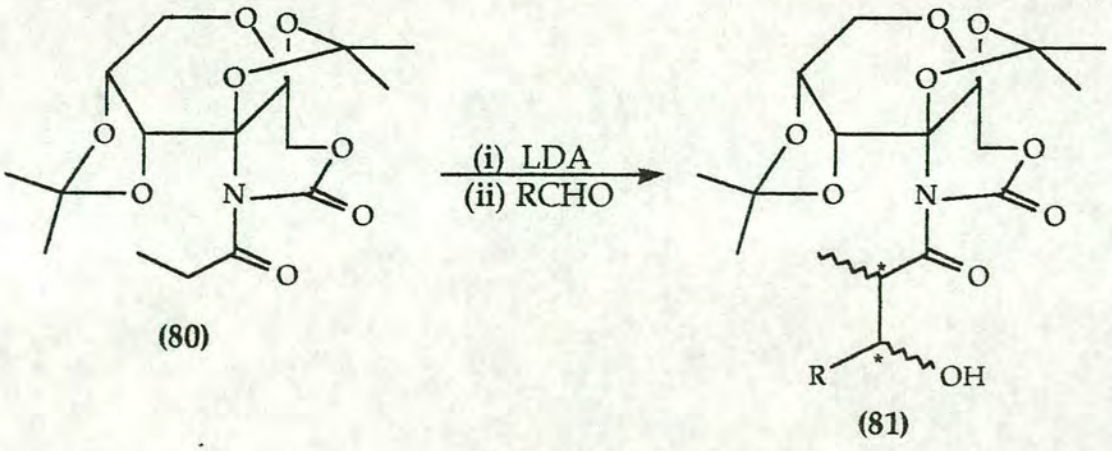
Asymmetric aldol transformation reactions using propionate (80)

2.1 Asymmetric aldol reactions *via* lithium enolate systems

Although the aldol addition reaction was first reported[56] as early as 1838, until the 1970's only occasional reference was paid to its stereochemistry. The last two decades however have witnessed a remarkable upsurge in stereochemical investigations of the aldol reaction. This has been due to two main developments, the advent of powerful analytical methods that are capable of analysing diastereomeric mixtures, particularly high field ^{1}H NMR and high performance liquid chromatography. The main factor though that has been responsible for the rebirth of the aldol reaction as a modern method of synthesis is the discovery that the stereochemistry can be controlled quite effectively through the use of preformed chiral enolates and in particular those of lithium. The stereochemistry of the aldol reaction has been dealt with in great detail by Heathcock[57,58].

2.1(a) Theory behind aldol reaction with propionate (80) *via* lithium enolate system

When propionate **(80)** is reacted with lithium diisopropylamide (LDA) and the resulting enolate system is treated with an aldehyde, the product **(81)** contains two new chiral centres, Scheme 27.



(80) **(81)**

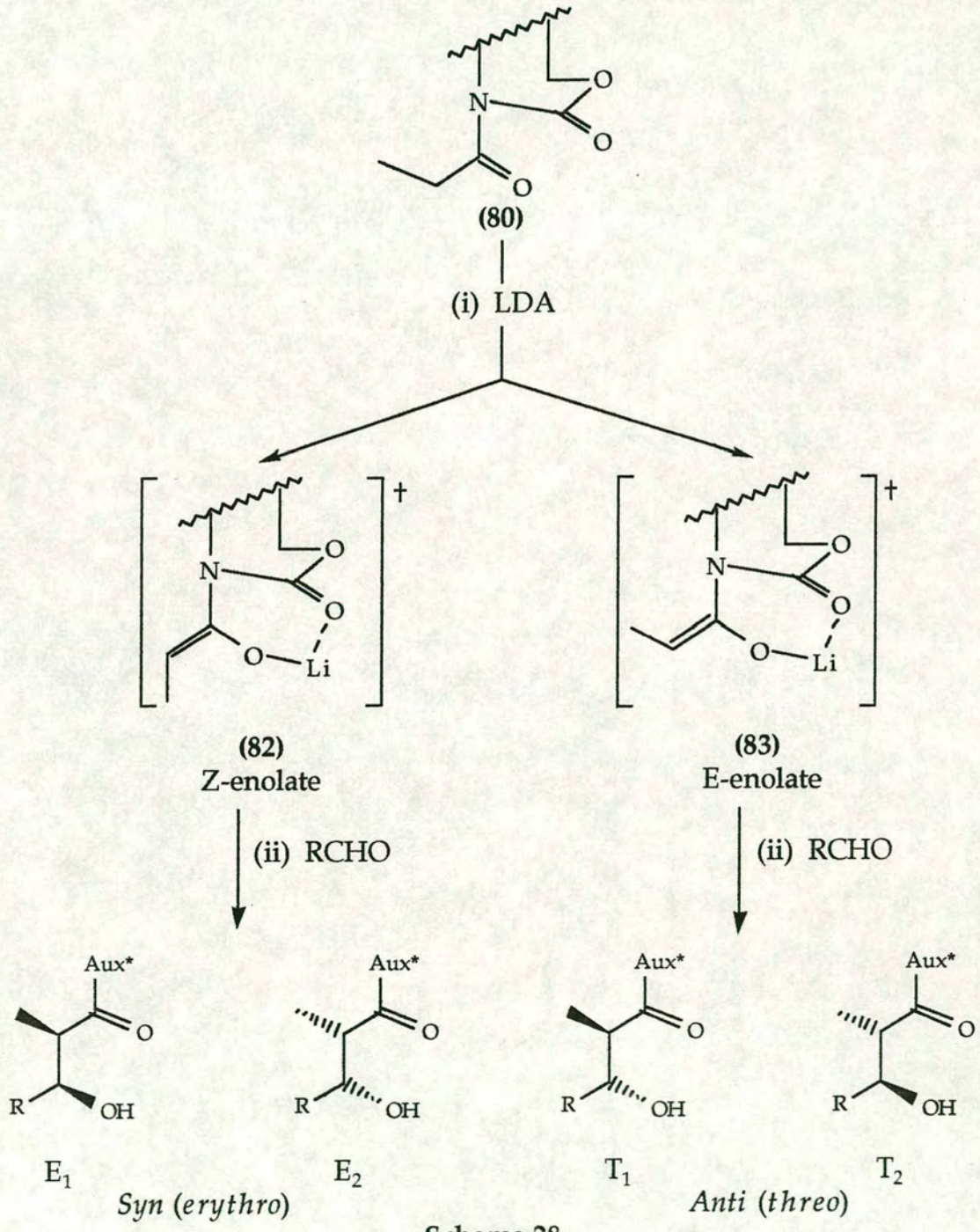
Scheme 27

This gives rise to four possible diastereomeric products, Scheme 28.

The configuration of the products is dependent upon two factors:

(i) the geometry of the enolate system.

(ii) the topological bias exerted by the auxiliary through steric influences.

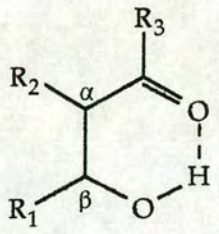


Scheme 28
(4 Products of Aldol Reaction)

In general, if the lithium mediated complex adopts the Z-enolate geometry **(82)**, then the relative configuration of the two possible products will be *syn* (also known as *erythro*) E_1,E_2. If, however, the geometry of the complex is that of the E-enolate **(83)**, then the relative configuration of the remaining two products will be *anti* (also known as *threo*) T_1,T_2.

Studies conducted by Heathcock[59] have shown that the relative configuration in an aldol product containing two asymmetric carbons can be determined by the use of NMR spectroscopy.

If there is a hydrogen present at both the α and β carbons relative to the carbonyl group **(84)**, and if intramolecular hydrogen bonding exists, then the vicinal coupling constant, J_{AB}, for the two protons can be used to predict the relative configuration as being *syn* or *anti*.

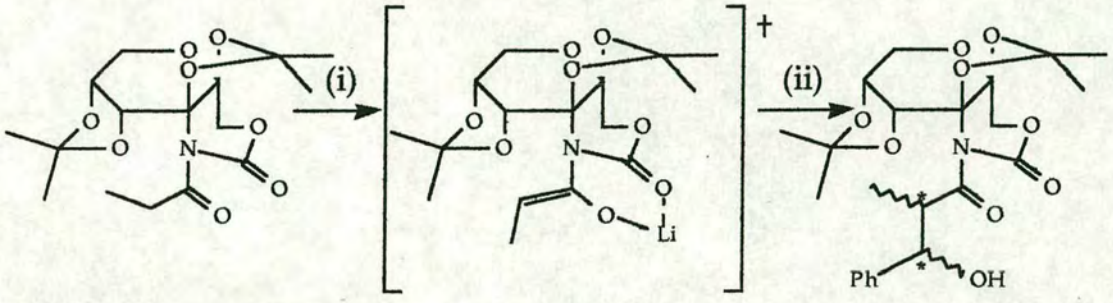


(84)

Typical values for products with *syn* configuration (E_1,E_2) are in the range, J_{AB} = 2 - 6 Hz, whereas the corresponding values of the products with *anti* configuration (T_1,T_2) are higher and in the range J_{AB} = 7 - 10 Hz.

2.1(b) Reaction of propionate (80) with benzaldehyde

The aldol reaction involving the propionate **(80)** was carried out by first generating the lithium enolate using LDA, then by adding benzaldehyde to furnish the adduct **(85)** in a mixture of two out of the four possible products in a yield of 85%, Scheme 29.

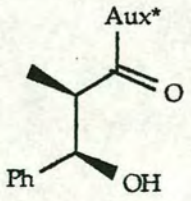


(80) **(82)** **(85)**

(i) LDA (ii) PhCHO

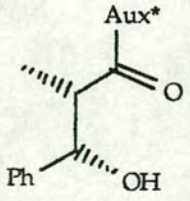
Scheme 29

Analysis of the 360MHz ^{1}H NMR spectrum revealed the presence of the vicinal protons in the region 3.4 - 4.1ppm with coupling constant values of J=3.2 Hz. These values fall into the range consistent with *syn* (*erythro*) configuration. This indicates that the lithium mediated complex adopts the Z-enolate geometry as shown in **(82)** which leads to the products **(86)** and **(87)**, Figure 2.



E_1 (*syn*)

(86)



E_2 (*syn*)

(87)

Figure 2

No signals could be detected in the spectrum for the product with *anti* (*threo*) configuration.

The ratio of the two products, **(86)** and **(87)**, was determined from integration of the resonance signals of the ^1H NMR spectrum and found to be 8 : 1, giving a diastereomeric excess of 78%, though at this stage it was not known which diastereomer was preponderant.

2.1(c) Cleavage of benzaldehyde aldol adduct (85)

Having carried out the asymmetric transformation leading to aldol adduct **(85)** and determined the relative configuration of each of the two product fragments as being *syn* (*erythro*), the next step involved determination of the absolute configuration which would ascertain which of the two *syn* products **(86** and **87)** was dominant.

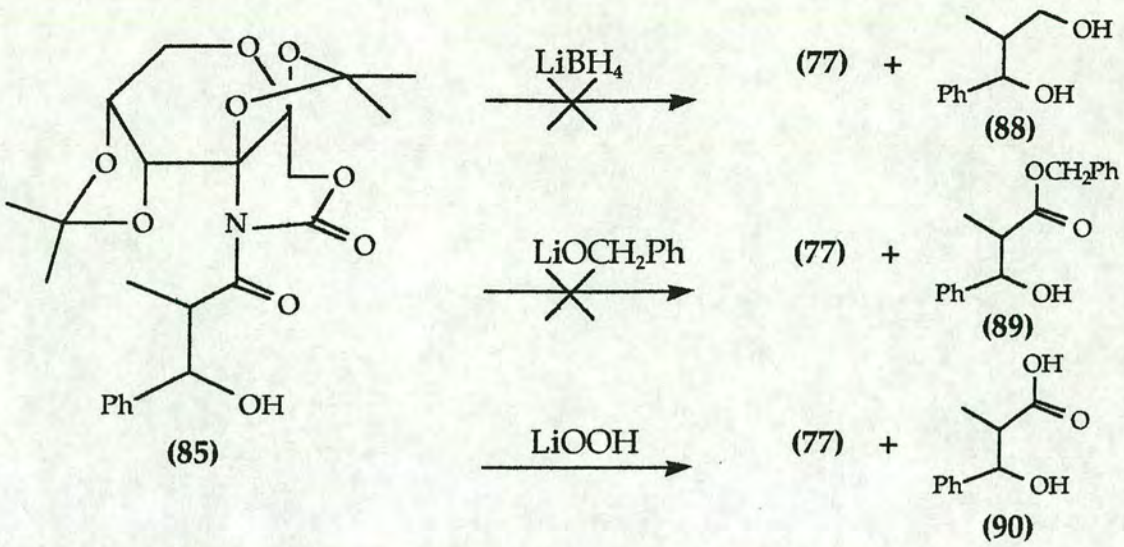
To achieve this, a method had to be employed which would result in non-destructive removal of the chiral auxiliary and without attendant racemisation of the newly-created centres of asymmetry. The cleaved fragment could then be analysed using optical rotation techniques and compared against literature values to verify absolute configuration.

Three different methods were tried, Scheme 30.

(1) reductive cleavage using lithium borohydride to yield the diol **(88)**.

(2) non-reductive cleavage using lithium benzyloxide to yield the benzyl ester **(89)**.

(3) hydrolysis using lithium hydroperoxide to yield the acid fragment **(90)**.

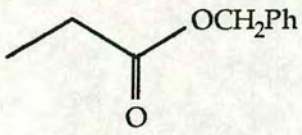


Scheme 30

The first method tried using lithium borohydride was in accordance with a much established protocol for the racemisation free removal of other auxiliaries[60]. The procedure of reductive cleavage to yield the diol (88) together with the recovered auxiliary was expected to occur quickly, however, monitoring by thin layer chromatography (TLC) showed very little, if anything at all, to be taking place. Constant supervision of the reaction mixture over the next two hours failed to detect any indication of cleavage taking place. This was surprising as it had previously been reported[61] that the active species involved, the hydroxyborohydride ion ($^{-}BH_3OH$), was a stable and powerful reducing agent. Despite this, after stirring for 48 hours the reaction simply did not proceed.

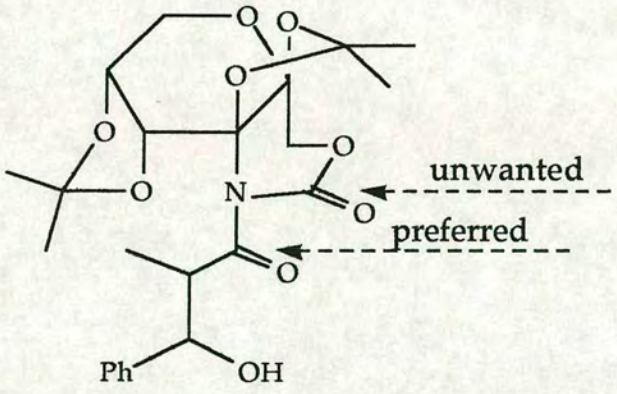
An alternative approach using lithium benzyloxide was then tried, this method had successfully been employed by Evans[62] in several reactions of this type. It was therefore anticipated that this non-reductive cleavage would succeed where the reductive cleavage had failed and would furnish the benzyl ester (89).

This time however, although the reaction did proceed, there were numerous products of which the most preponderant and only identifiable one was benzyl propanoate (91).



(91)

Examination of aldol adduct (85) shows that there are two carbonyl groups at which nucleophilic attack can take place, the oxazinone ring carbonyl (endocyclic) and the N-acyl carbonyl (exocyclic).



(85)

2 possible regions of nucleophilic attack by benzyloxide ion

For the operation to be a success, the nucleophilic benzyloxide ion ($^{-}OCH_2Ph$) must be regioselective and strike only at the exocyclic carbonyl group. In this instance, however, it appears that nucleophilic cleavage has occurred not only at the exocyclic carbonyl, but, because of the steric crowding in the immediate vicinity, reagent attack has also taken place at the endocyclic carbonyl.

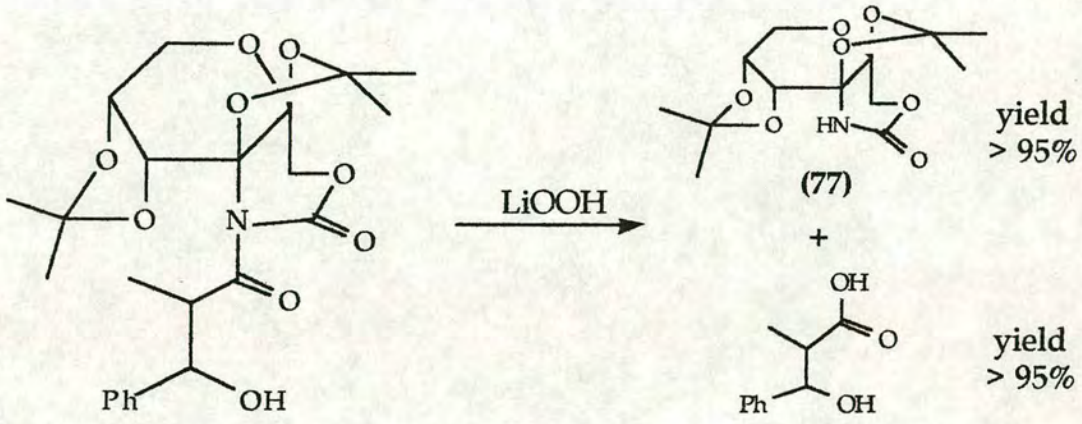
Another method was then sought, with fears mounting that although the auxiliary may be adept at inducing asymmetric transformations, it was

possible that non-destructive cleavage could not be achieved.

A literature search uncovered an alternative method of cleavage by Evans[63] *via* hydrolysis.

Accordingly a third method was tried, this time using lithium hydroperoxide which if successful, would afford the acid fragment **(90)** with concomitant recovery of auxiliary **(77)**, Scheme 31.

Once again there was the possibility of reagent attack at the endocyclic carbonyl.

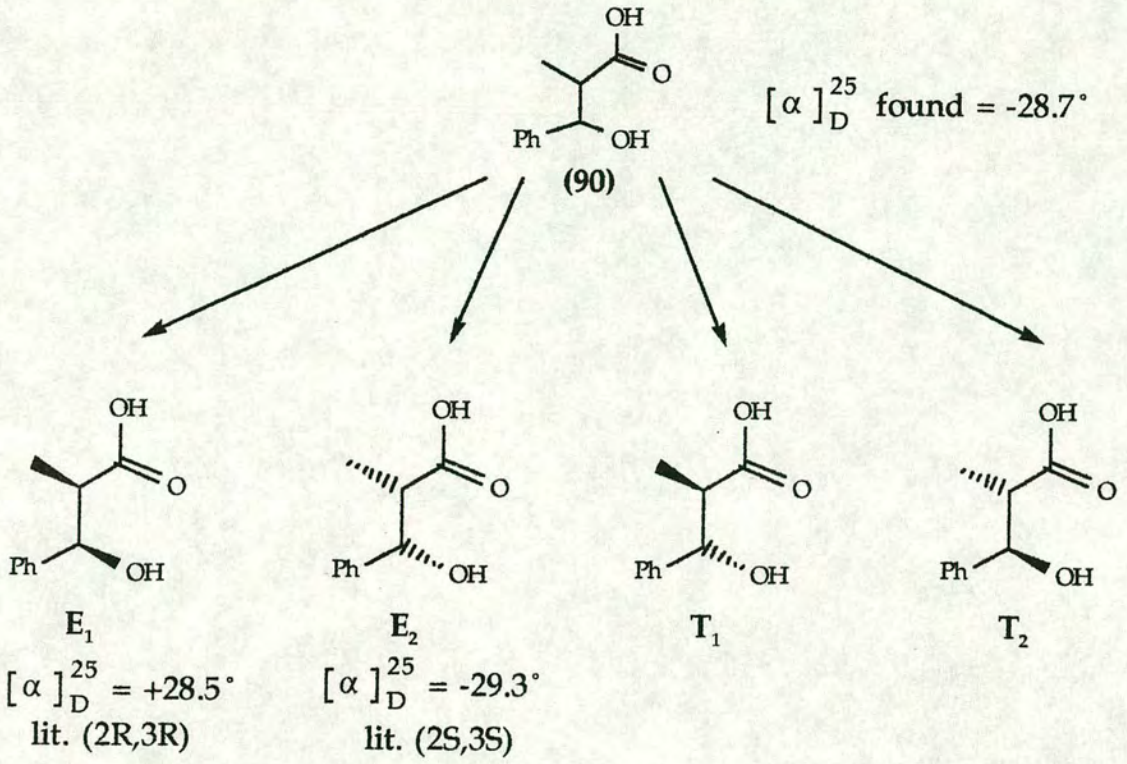


(85) **(77)** + **(90)**

Scheme 31

Despite this however, regioselective cleavage at the exocyclic carbonyl was absolute and both the carboxylic acid derivative **(90)** and the chiral oxazinone **(77)** were recovered in very high yield. The unwanted oxazinone ring cleavage reaction was not observed.

The chiral acid fragment **(90)** was obtained as a colourless liquid and inspected for its optical rotation value. This value was then compared with literature[64] values for all four diastereomers, Scheme 32.



Scheme 32

From the two diastereomers with relative configuration of *syn* stereochemistry predicted previously from coupling constants, the optical rotation value found compared very favourably with the literature value[64] for E_2 above and established the absolute configuration as (2S,3S).

Examination of the X-ray crystallograph of aldol adduct (87) confirms the absolute stereochemistry, Figure 3.

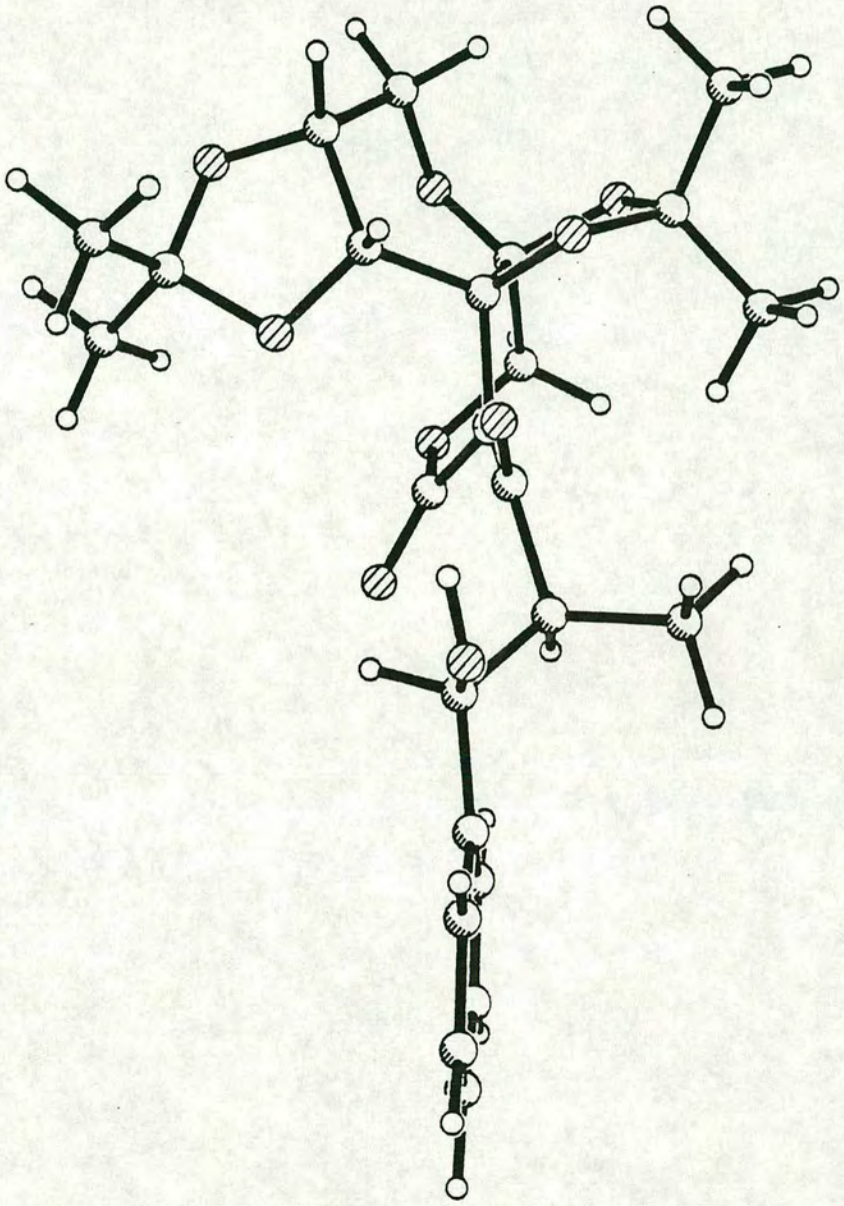
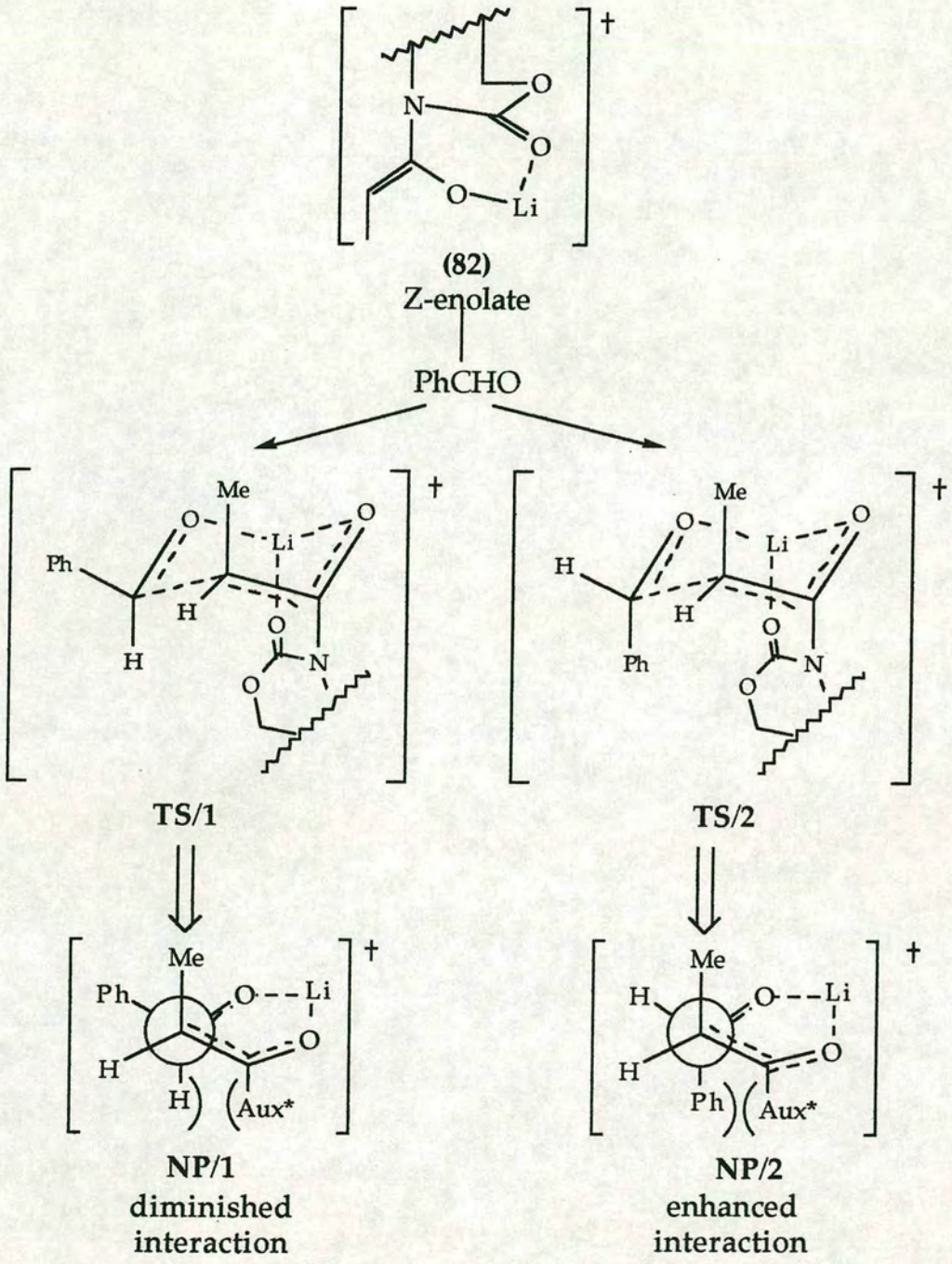


Figure 3

(X-ray Structure Benzaldehyde Aldol Adduct)

2.1(d) Transition State Hypothesis of Aldol Addition

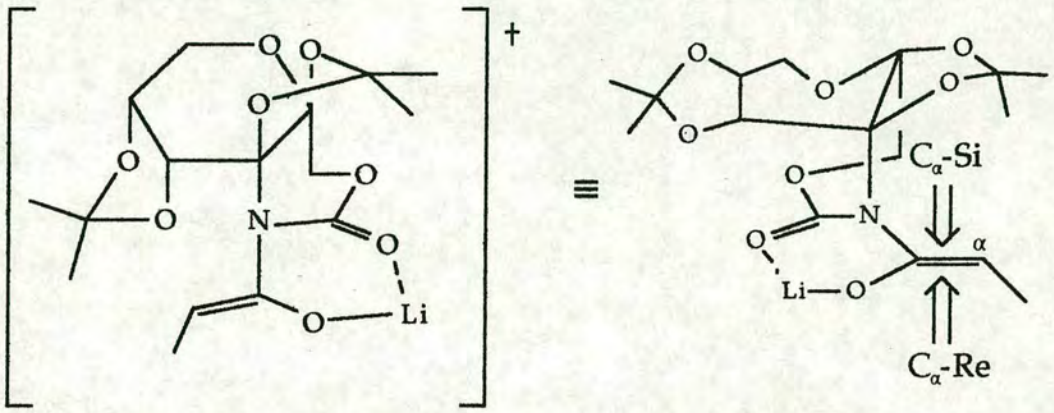
The stereochemical outcome of the process leading to products with relative configuration of *syn* only can be rationalised by the so-called 'closed transition state' theory proposed by Zimmerman and Traxler[65,66]. The authors advanced the theory that the six-membered intermediate species in the addition of the aldehyde to one face of the Z-enolate (82) can adopt either of two chair conformations TS/1 and TS/2, Scheme 33.
In both cases it can be seen upon examination of the transition states that the lithium is chelated to the aldehydic oxygen, the oxazinone oxygen and the enolate oxygen all at the same time. Further scrutiny reveals that in TS/2 there are 1,3 diaxial interactions between the phenyl group and the auxiliary. This compels the phenyl group to occupy the more stable equatorial position seen in TS/1 which leads to products with *syn* configuration. Inspection of the equivalent Newman projections NP/1 and NP/2 clearly shows why TS/2 is disfavoured due to the enhanced steric interactions between these two groups.



Scheme 33

Although this theory accounts for the absence of products with relative configuration of *anti* (*threo*), the issue of the predominance of one diastereomeric *syn* product over the other diastereomeric *syn* product remains to be quantified.

Examination of the enolate system (82) shows the co-planar orientation of the original two carbonyl groups upon intramolecular complexation to the lithium. Crystallographic studies have shown that a more realistic representation of the 3-D state of the complex is given in the equivalent diagram (82*), Figure 4.



(82) (82*)

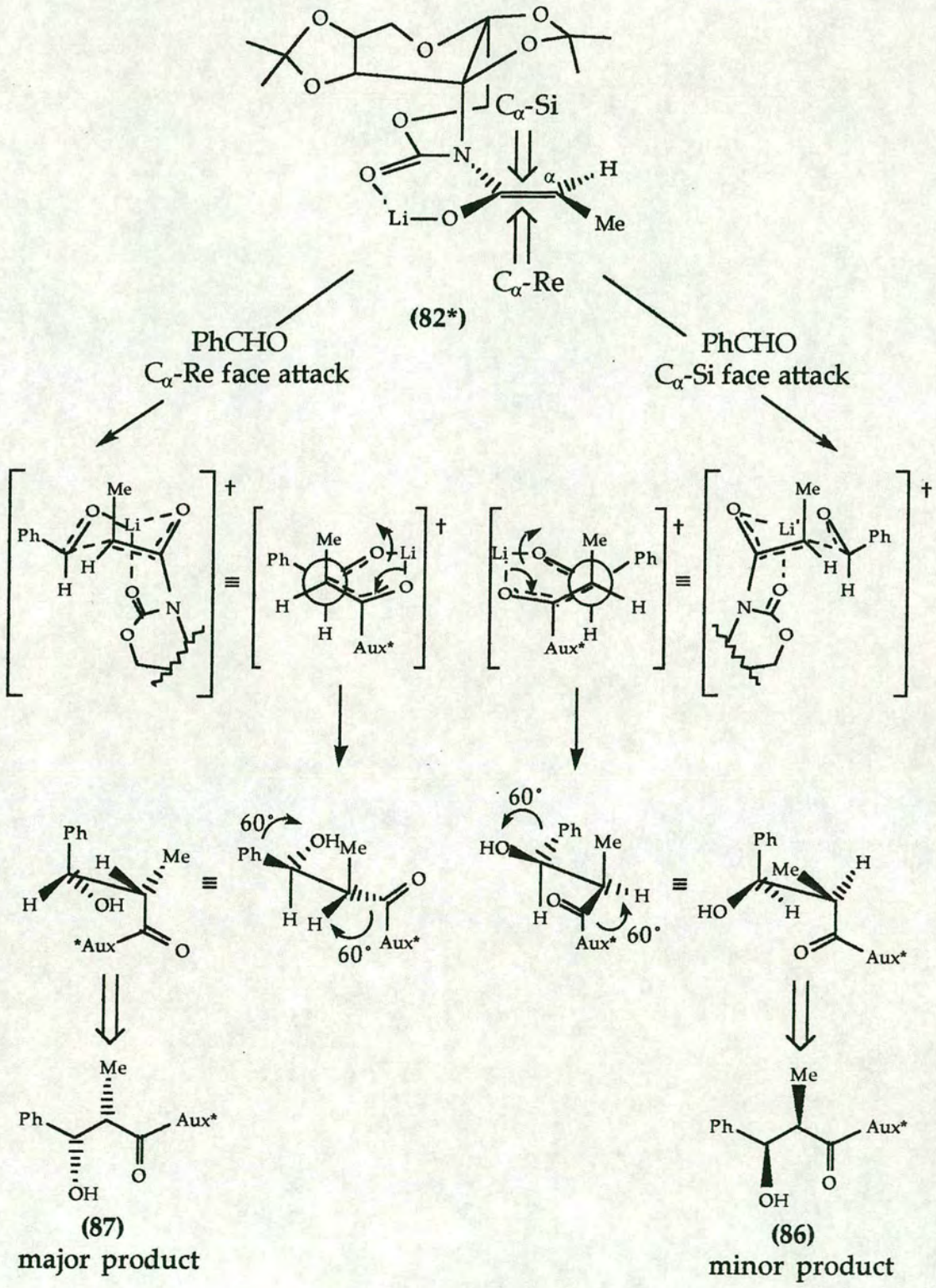
Figure 4

By inspection of the illustrated complex (82*) one can envisage the severe restrictions to one reacting face of the enolate system due to the considerable steric hindrance imposed by the auxiliary diisopropylidene groups. Thus the aldehyde can attack the complex with a topological bias for the relatively unshielded C_α-Re face as opposed to the sterically hindered C_α-Si face and a significant degree of dictated diastereofacial selectivity is obtained.

The preponderance of the major *syn* product (87) over the minor *syn* product (86) can therefore be explained by this difference in steric congestion at opposite faces of the enolate system. The C_α-Re face presents a more accessible avenue of approach to the attacking aldehyde

than the C_α-Si face and this creates a topological bias which favours attack at the C_α-Re face, Scheme 34.

The presence of the minor adduct (86) can be justified using the same rationale. Although the aldehyde has a propensity to approach the enolate system at the C_α-Re face which is sterically less imposing, it is not a unique route and diastereofacial competition does exist. The consequence of this is that an inferior population of the reacting aldehydic molecules 'disobey' the topological bias and attack the sterically more hindered C_α-Si face of the enolate system resulting in formation of the minor adduct, Scheme 34.


Cα-Si
Cα-Re
(82*)
PhCHO
Cα-Re face attack
PhCHO
Cα-Si face attack
(87)
major product
(86)
minor product

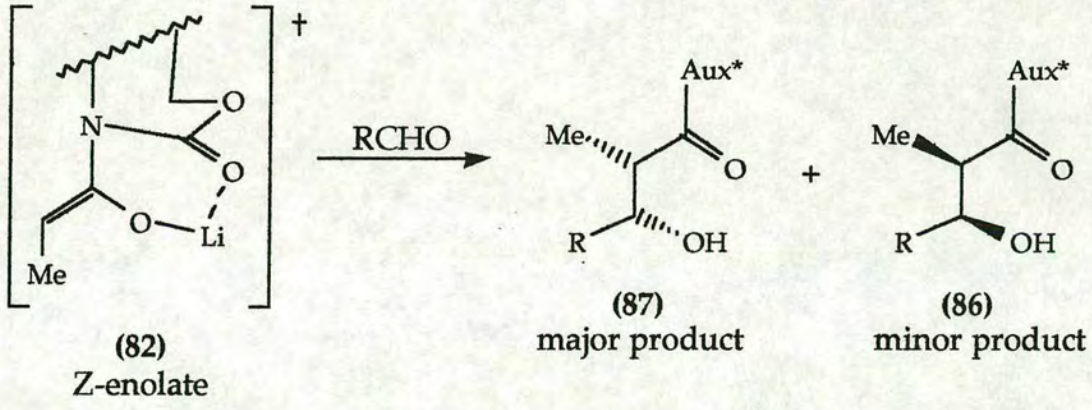
Scheme 34

2.1(e) Further lithium mediated aldol reactions of propionate (80) with acetaldehyde and isobutyraldehyde

Following the success of the aldol reaction using benzaldehyde it was decided to expand the investigation by repeating the experiment with other aldehydes.

By preparing the Z-enolate system (82) as before then reacting with aldehydes containing various alkyl groups, the asymmetric induction efficiency of the chiral system could be further examined.

The aldehydes chosen were isobutyraldehyde which in theory imposes slightly greater steric demand than benzaldehyde and acetaldehyde which should provide the least steric impediment of the three, Scheme 35.



(82)
Z-enolate

(87)
major product

(86)
minor product

Scheme 35

In each case the product was obtained in high yield (85-95%) and was accompanied by excellent diastereomeric selectivity, Table 9.

R	% yield	% de	configuration
Ph	85	78	(2S,3R)
$CH(CH_3)_2$	95	78	(2S,3R)
Me	85	single isomer	(2S,3R)

Table 9

The high diastereoselectivity seen for each reaction can be rationalised on a twofold basis. Firstly, as was seen in the transition states of the aldol reaction involving benzaldehyde, the alkyl group pertaining to the aldehyde occupies the more stable equatorial position **NP/3** which is sterically relaxed in comparison with **NP/4** in which the alkyl group occupies the axial position and as a consequence 1,3 diaxial interactions are evident, Figure 5. As a result of this no diastereomers with relative configuration of *anti* are obtained.

NP/3 **NP/4**
1,3 diaxial
interaction

Figure 5

Secondly, diastereofacial competition is once again in evidence and in each case greatly favours approach of the reacting aldehydic molecules to the C_α-Re face of the enolate system.

On the basis of previous conjecture regarding the presence of the minor adduct **(86)** from the benzaldehyde reaction, the result obtained for the reaction involving isobutyraldehyde is not unexpected. There are slight steric differences between the phenyl group and isopropyl group and a similar degree of selectivity is observed.

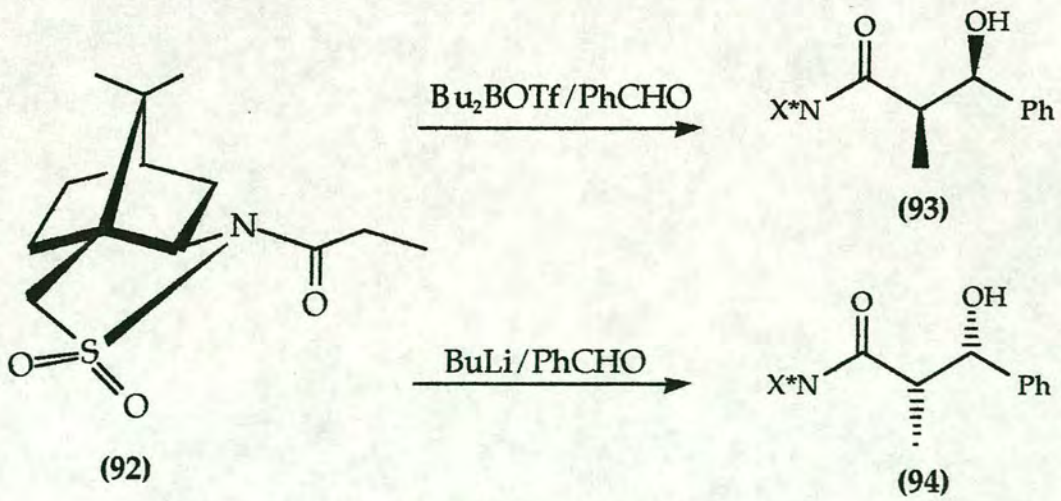
On the basis of steric imposition alone the absolute stereospecific control exhibited in the acetaldehyde reaction is somewhat surprising.

However, the result is more likely due to reactivity rather than steric reasons.

From a reactivity standpoint acetaldehyde is relatively unreactive in comparison with the other aldehydic reagents employed. As a consequence of this, the sluggish nature of acetaldehyde as the reagent in this reaction may be the determining factor in dictating which face of the enolate system the reaction occurs at, in this case the more accessible C_α-Re face, leading to absolute diastereomeric selectivity.

2.2 Aldol reactions *via* boron enolate systems

The use of boron mediated enolate systems in controlling the stereochemical outcome of aldol reactions is well documented. Oppolzer[19] has reported greatly improved selectivity when employing boron reagents as opposed to lithium. Rather intriguingly the increased diastereomeric purity is accompanied by a reversed sense of induction. For example, metal mediated aldol condensations carried out on the N-acyl bornane sultam **(92)**, clearly exhibit the contrast in results, Scheme 36, Table 10.



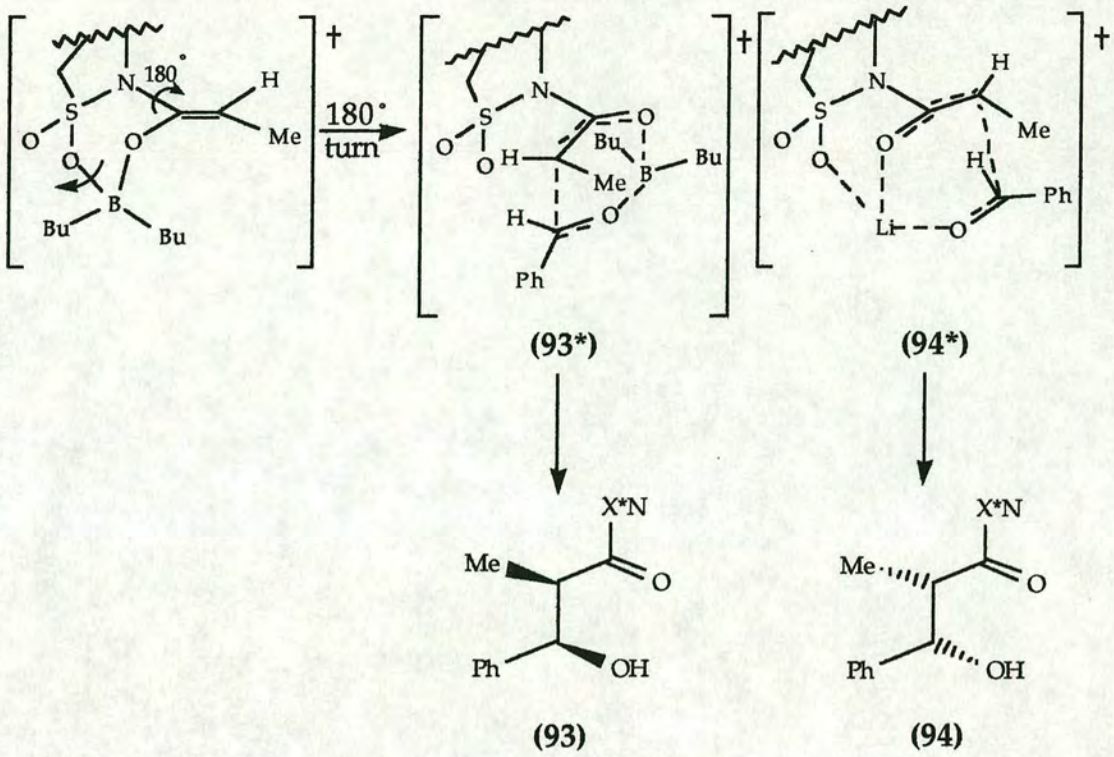
(92) **(93)** **(94)**

Scheme 36

Metal	% yield*	ratio (93) : (94)
boron	80	99 : 1
lithium	55	10 : 76
* after recrystallisation		

Table 10

Both the contradiction in stereochemistry and the amplified selectivity can be explained by interpretation of the transition states for the reactions. Firstly, studies[67] conducted on the metal-oxygen bond lengths in aldol condensation reactions have shown that the length of the lithium-oxygen bond (Li-O=1.92-2.00Å) is considerably longer than that of the boron-oxygen bond (B-O=1.36-1.47Å). This means that the transition state for the reaction of a boron enolate with an aldehyde is relatively more 'cramped' and hence steric interactions will be enhanced which leads to an increase in stereoselectivity. Secondly, the maximal coordination number of dialkylboron is four. This means that the boron cannot bind simultaneously to the three oxygens of the enolate, aldehyde and SO_2 group. This is in contrast to the analogous reaction involving lithium which possesses a higher coordination potential, see transition states **(93*)** and **(94*)**, Scheme 37.



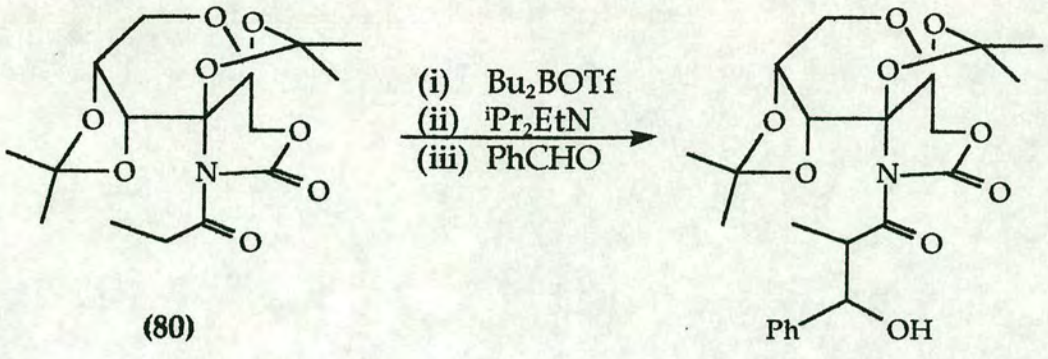
Scheme 37

To accommodate the aldehyde, the B-O bond pertaining to the SO_2 group of the sultam in **93*** is cleaved to 'free' the enolate system which undergoes a 180° rotation about the N-C bond to allow coordination between the boron and the oxygen of the aldehyde. In both cases the aldehyde approaches selectively from the bottom face opposite to the lone electron pair on the nitrogen and this leads to products **93** and **94** respectively.

This surmise is in accordance with that previously proposed by Grant[68] for similar operations involving aldolisation experiments conducted by Gallagher and Donohoe.

This sense of reversed selectivity has also been encountered by others[69,70] involved in these type of reactions.

The aldol reaction using dibutylboron triflate with benzaldehyde and propionate (80) was then attempted as depicted in Scheme 38.



(80)

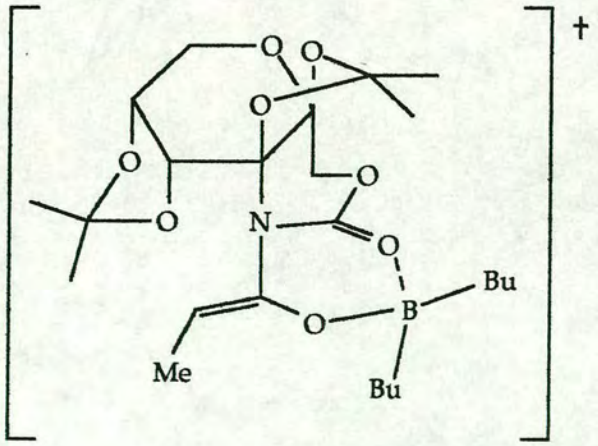
(85)

Scheme 38

Constant monitoring by TLC showed that the reaction failed to proceed. Quite why the reaction did not take place is not entirely clear, although problems associated with boron reagents, such as dibutylboron triflate in aldol condensations have previously been reported[71-73].

These problems are mainly based upon the extreme moisture sensitivity of the reagent and its' inclination towards rapid self-decomposition.

On an alternative vein of thought, the formation of the intermediate complex (95) may present its own difficulties.



(95)

In a review by Blaser[74] on the effect of structural elements in metal mediated complexes, the author describes that bulky ligand groups, such as butyl, can be advantageous in leading to better environments for asymmetric induction due to increased steric bulk. However, the author also indicates that too much bulk can decrease the accessibility to the central chelating atom thereby reducing its' activity. Bearing in mind that a B-O bond must cleave followed by rotation of the complex before coordination of the aldehyde can take place, it could be that the severe steric restrictions presented by the complex itself prevent the aldehyde from getting close enough to induce these changes. It should be noted that the above conclusions are at best tentative and the latter is offered as an issue for deliberation.

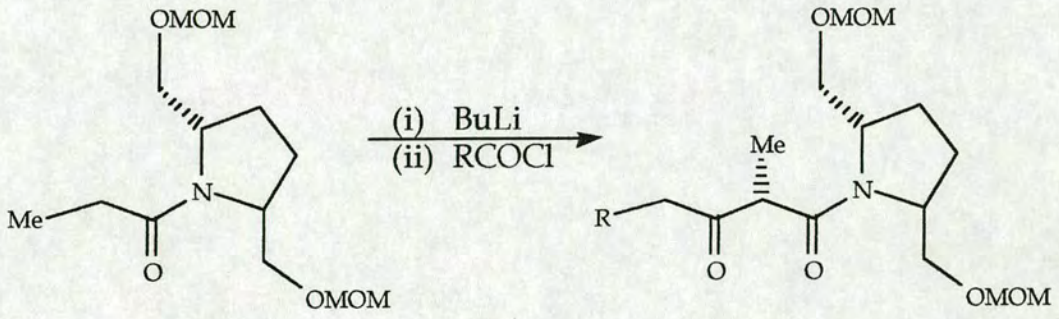
Whatever the reason though, boron reagents are highly expensive and it was decided to discontinue studies in this area.

Chapter 3

Asymmetric Acylation Reactions

The next area in which the chiral oxazinone auxiliary (77) was investigated was asymmetric acylation reactions carried out on the propionate derivative (80).

Previously, acylation experiments conducted by Ito[75] on the *trans*-2,5-bis(methoxymethoxymethyl) pyrrolidine moiety (96) with various acyl chlorides had resulted in consistently very high levels of asymmetric induction, Scheme 39, Table 11.



(96)

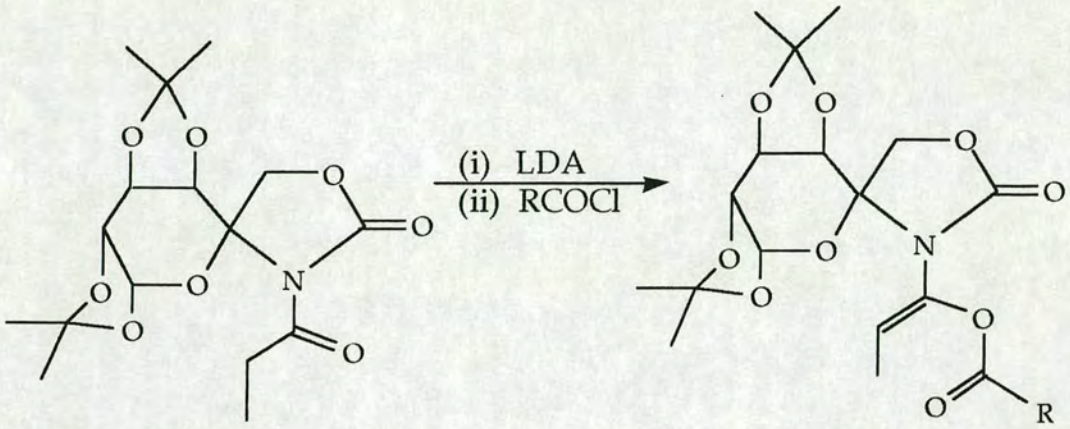
Scheme 39

R	% yield	% de
$CH(CH_3)_2$	95	98
$C(CH_3)_3$	80	98
Ph	90	98
$PhCH_2$	76	98

Table 11

Studies conducted by Evans[5] and Oppolzer[76] in similar work had also shown that the acylation reactions could be accomplished routinely with the products exhibiting a high degree of optical purity.

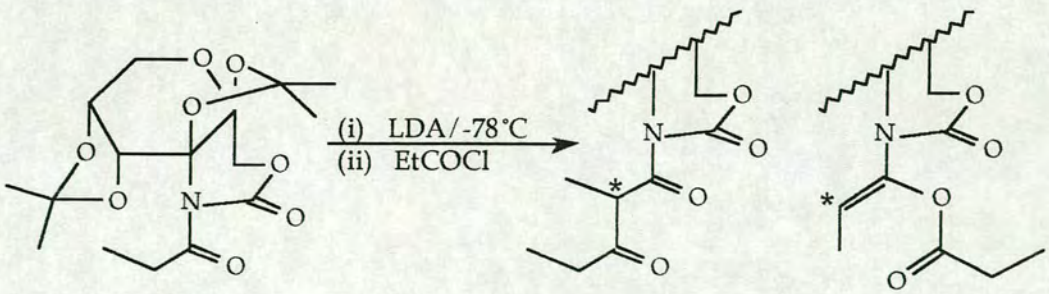
Contrary to this though other workers[72,77] had found the reactions to proceed in a less straightforward manner. For example, Gaur[72] had found that when acylation reactions were performed on the lithium enolate derivative of propionate **(97)** with various acyl chlorides, there was a propensity for the O-acylated product **(98)** to occur rather than the C-acylated, Scheme 40.



(97) **(98)**

Scheme 40

With this dichotomy in mind the acylation of carboximide **(80)** was carried out by generating the lithium enolate system using LDA then adding the acid chloride to furnish either or both the products **(99)** and **(100)**, with the C-acylated product **(99)** being desired, Scheme 41.



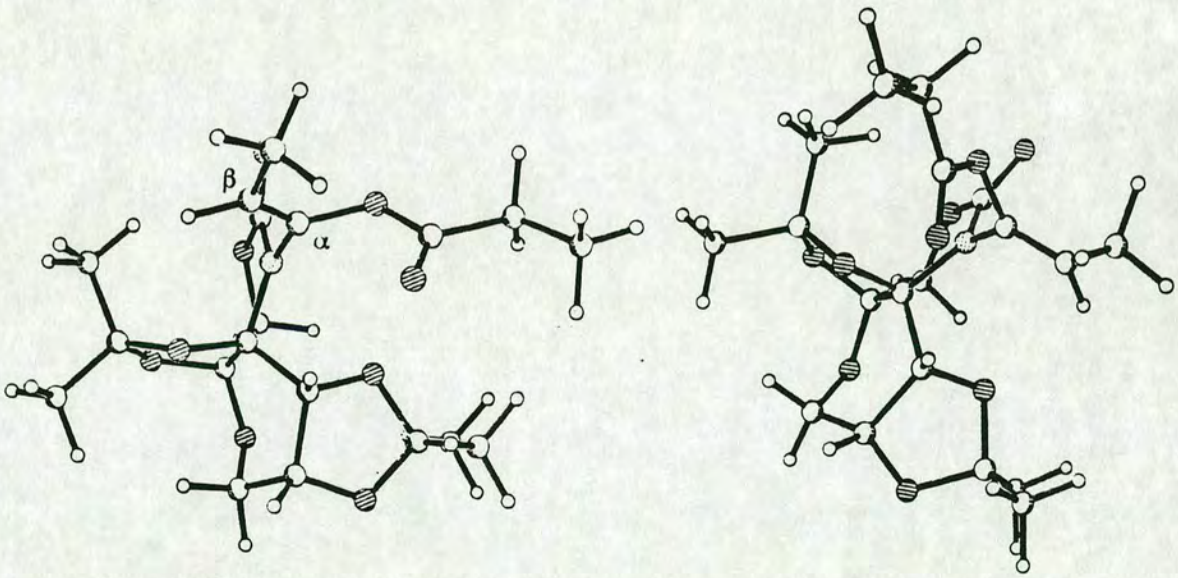
(80) **(99)** **(100)**

saturated *CH ≈ 30ppm

unsaturated *CH ≈ 120ppm

Scheme 41

The product of the reaction was highly crystalline and in excellent yield, however, examination of the ^{1}H and ^{13}C nuclear magnetic reasonance spectral values revealed the exclusive formation of the O-acylated product **(100)**. The identification of the product **(100)** was evident from the ^{13}C NMR value obtained for the *CH signal at approximately 120ppm which is characteristic of an unsaturated CH, rather than the expected[78] value of 30ppm for the corresponding saturated CH, (see **99** and **100**). The X-ray crystallographic structures obtained from crystals submitted for analysis support conclusively the interpretation of the spectra and the formation of the O-acylated product **(100)**, Figure 6.



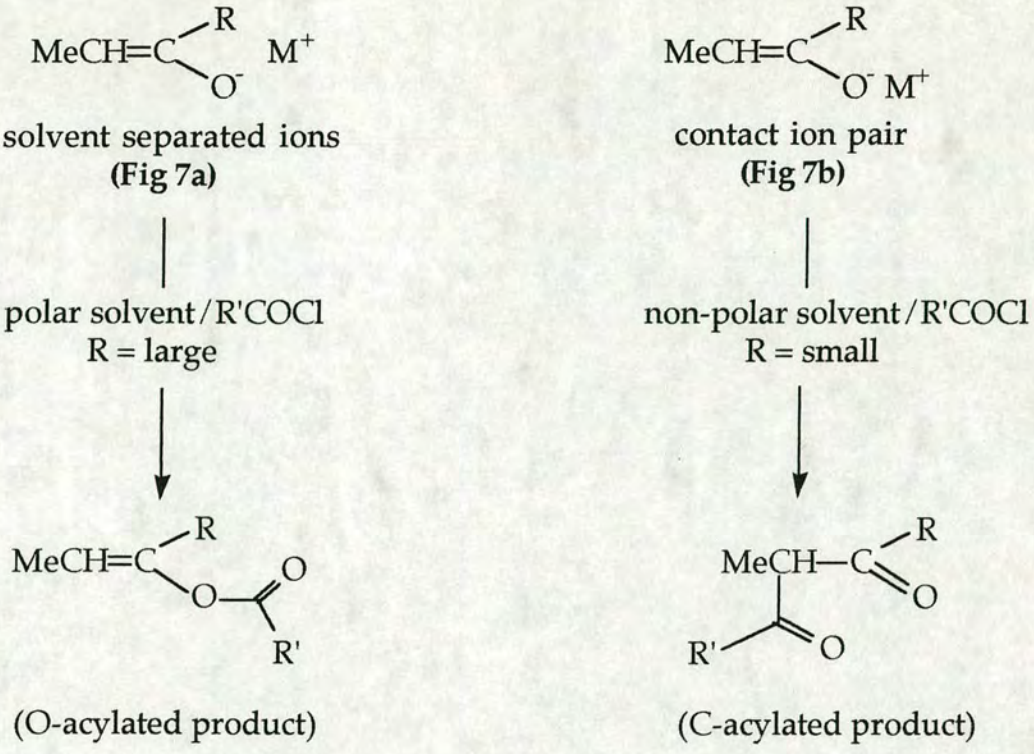
(100a) **(100b)**

Figure 6
(X-ray structure of O-acylated product)

Once again two conformations **(100a** and**100b)** are present in the solid state and although the inherent skeletal characteristics of each is the same, the O-acylated side chains have found relaxed modes which are significantly different.

One fortuitous feature exposed by the formation of this undesired product, is that it provides us with an unexpected, though matchless view of the N-functionalised α,β unsaturated system in which the geometry pertaining to the C_α-O and C_β-Me is easily seen in **100a**.

A review of the literature[79-81] revealed that the partition of products resulting from the competition between C- versus O- acylation in the reactions of metal enolates with acyl halides is dependent upon several considerations. These include: choice of solvent, stoichiometry, temperature of reaction, metal cation and steric congestion in the reagents. From the literature study[79] it was established that if a polar solvent is employed and if steric influences in the reagents are considerable, then the metal cation/enolate anion system adopts a solvent-separated ions structure (Figure 7a) which favours the formation of the O-acylated product. Conversely, when a non-polar solvent is used and when steric congestion in the reagents are minimal, then this results in a contact ion pair relationship (Figure 7b) which favours C-acylation, Scheme 42.



Scheme 42

Relating these findings to the acylation of carboximide **(80)** it is less than remarkable that the reaction resulted in the exclusive formation of the O-acylated product **(100)**. Furthermore, it presents a twofold dilemma with regard to the generation of the C-acylated product, **(99)**.

Firstly, the immense size of the carboximide **(80)** is the complete opposite of what is required and so is discordant with the formation of the desired product **(99)**. Secondly, the carboximide is also insoluble in non-polar solvents.

In an endeavour to encourage the reaction to undergo C-acylation these problems had to be addressed.

The first problem posed was incurable since the size of the carboximide could not be altered. However, a compromise could be reached with the second one. A polar/non-polar solvent mixture could be primed with

barely enough of the polar solvent to allow dissolution of the carboximide, **(80)**.

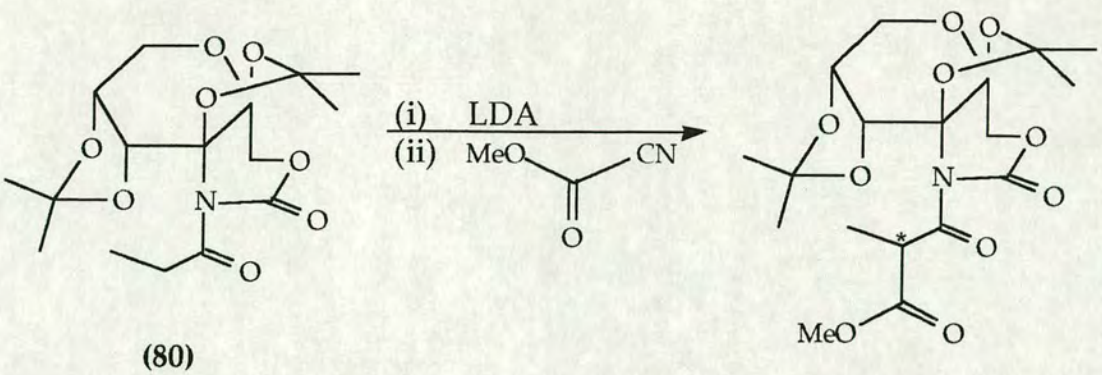
Thus a two solvent tetrahydrofuran/hexane mixture was prepared and the reaction was repeated, however, this only resulted in the formation of the O-acylated product as before and was accompanied by unreacted starting material.

Of the remaining dependent factors, those which favoured C-acylation were low temperature and stoichiometry.

The reactions were already being conducted at low temperature, however the literature[81] study had disclosed that the proportion of acylation occurring at the carbon atom could be increased if the enolate anion was always in excess. The reaction using the two solvent mixture was therefore repeated this time adding the propionyl chloride solution dropwise to the enolate solution. Disappointingly though, only the O-acylated product **(100)** was obtained again with still no indication of the presence of the target material, **(99)**.

A series of reactions carried out by Mander[82] using methyl cyanoformate as the acylating reagent with lithium enolates had shown the C-acylated product to be highly favoured.

Accordingly, the carboximide **(80)** was reacted with Mander's reagent in a last ditch bid to foster C-acylation which would result in product **(101)**, Scheme 43.



(80)

(101)

Scheme 43

This method proved to be highly successful and furnished the C-acylated product **(101)** exclusively in a yield of 85%.

The addition of the cyanoformate introduces chirality to the carbon atom at the point of reaction. From the resulting two diastereomers **(101a)** and **(101b)**, it was determined from ^{13}C NMR spectra that they had formed in an approximately 54 : 46 ratio such that little diastereomeric excess had been created, Figure 8. On the basis of previous work it is without question that a topographical bias was in place in the enolate system. However, the low stereoselectivity observed is probably a result of rapid racemisation at C_2 of the 1,3 dione unit resulting in an almost equal distribution of the two epimers.

(101a) (101b)

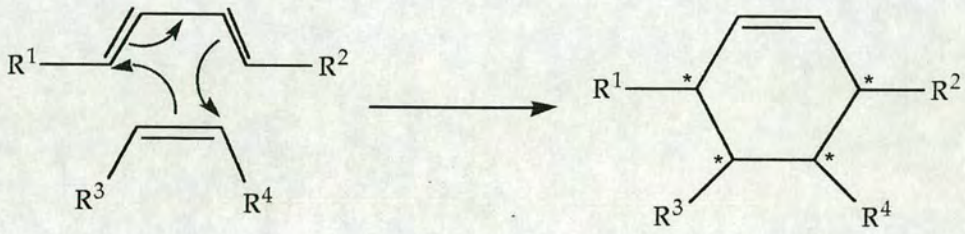
Figure 8

Chapter 4

Asymmetric Lewis-acid catalysed Diels-Alder cycloaddition reactions

The Diels-Alder reaction has a distinguished pedigree in the annals of organic chemistry. Many reviews are available[83-85] which exemplify the contribution it has made and which detail the versatility of this reaction in organic synthesis.

The fundamental nature of the reaction is that an electron rich diene reacts with a dienophile which results in the formation of a six membered ring which contains up to four contiguous asymmetric centres, Scheme 44.



Scheme 44

Widespread attention has broadened the scope of the reaction and one significant development has been the employment of Lewis-acid catalysts which not only increase the rate of the reaction, but also greatly amplify the regioselectivity and stereoselectivity.

The rate of the reaction depends largely upon the interaction between specific molecular orbitals of the reacting dienophile and diene.

Thus any reagent which intensifies the overlap between these molecular orbitals will in effect increase the rate of the reaction[86].

Lewis-acids are electron deficient and electron density withdrawal by the Lewis-acid from the alkene lowers the lowest unoccupied molecular orbital (LUMO) of the alkene such that overlap between the LUMO of the alkene and the highest occupied molecular orbital (HOMO) of the diene is enhanced and acceleration of the reaction ensues, Figure 9.

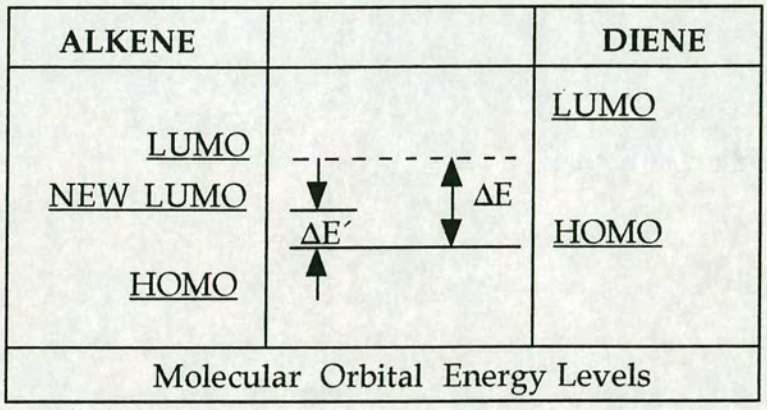
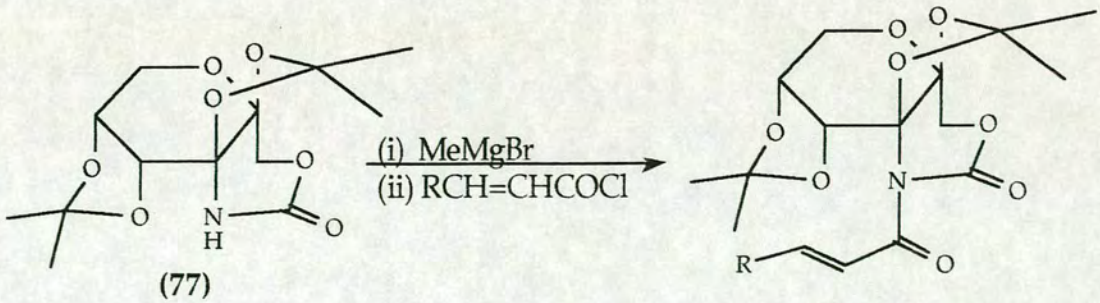


Figure 9

4.1 Preparation of α,β unsaturated carboximide dienophiles

Preparation of the selected dienophiles **(102-104)** was carried out in accordance with the method used for the N-acyl functionalisation of auxiliary **(77)** seen earlier, Scheme 45.



(77) **(102-104)**

R = H **(102)**, R = Me **(103)**, R = Ph **(104)**

Scheme 45

For continued evaluation of the asymmetric inducting powers of auxiliary (77) the dienophiles prepared conformed with those used in preceding research work which enabled direct comparisons to be made Table 12.

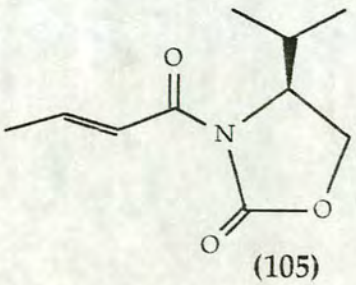
R	Name	% yield
H (102)	acrylate	22*
Me (103)	crotonate	90
Ph (104)	cinnamate	85
*all unreacted starting material recovered		

Table 12

From the dienophiles selected, although the crotonate (103) and cinnamate (104) were furnished in good yield, the acrylate (102) yield was very low. Despite attempts to heighten the yield by carrying out the reaction under alterations, a constant return of 22% was obtained.
As this was only a preliminary step *en route* to more weighty matters, it was decided to accept the poor yield and continue, since workable amounts could still be readily formed. Furthermore, similar problems with an associated reaction had previously been encountered and reported by Gaur[72], who had suggested that polymerisation of the product may occur.

4.2 Reactions of dienophiles (102-104) with cyclopentadiene

A study conducted by Evans[87] on Lewis-acid catalysed reactions between the α,β unsaturated N-acyl auxiliary (105) and cyclopentadiene has shown that hitherto, the most efficacious catalyst is diethylaluminium chloride.



(105)

The study has also concluded that Lewis-acid stoichiometry is a crucial factor in reaction stereoselectivity, Figure 10.

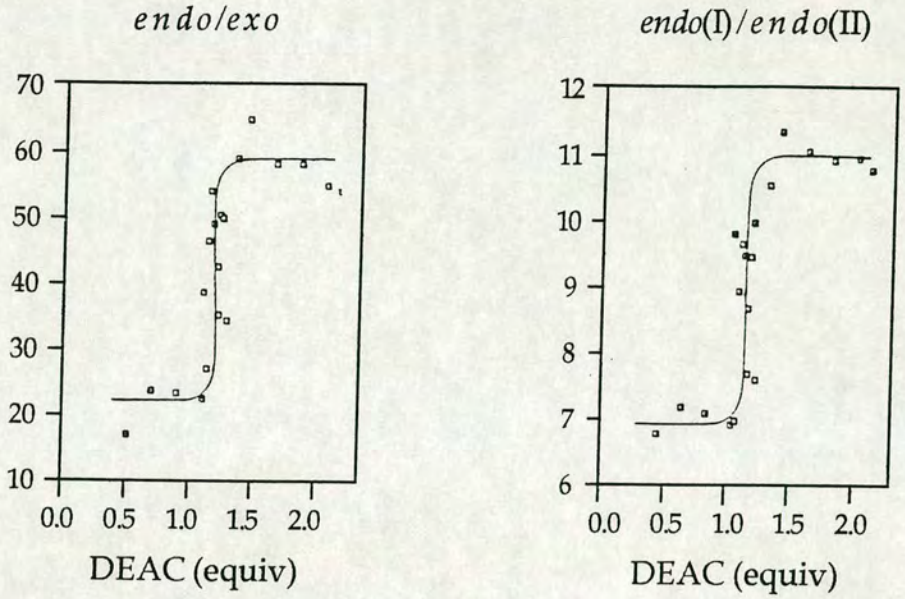
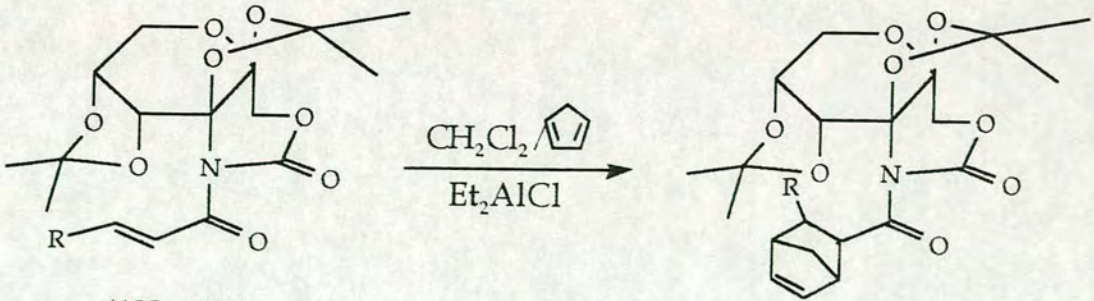


Figure 10

The results of the investigation revealed that stereoselectivity increases dramatically in the region of one equivalent of catalyst and that the optimum amount is 1.4 equivalents.

Accordingly, each of the three dienophiles (102-104) was reacted with a solution of diethylaluminium chloride (1.4 equivalents) in dichloromethane in the presence of a large excess of freshly cracked cyclopentadiene (avoids redimerisation) under the reaction conditions as depicted in Scheme 46, Table 13.



(102 - 104)

(106 - 108)

Scheme 46

R =	Reaction Conditions	
	Temp (°C)	Time (mins)
H (102)	-78	10
Me (103)	-78	60
Ph (104)	-20	40

Table 13

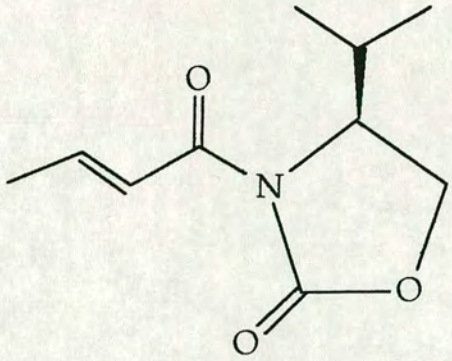
The progress of the reactions was monitored *via* colour changes until completion and upon work-up each of the crude products returned **(106-108)** was subjected to purification by flash chromatography. Analysis of the products, primarily by NMR spectroscopy, revealed a highly disparate outcome, Table 14.

R	*endo* :*exo*	*endo* de%
H	>95 : 5	87
Me	>95 : 5	20
Ph	4 : 1	63

Table 14

In the reactions involving the acrylate and crotonate no spectroscopic evidence of *exo* isomers could be detected. The substantial contrast was disappointing, but also deeply intriguing and clearly some rationalisation of the results was required.

Further information extracted from the study implemented by Evans[87] specified that the α,β unsaturated moiety **(105)** exists exclusively in the S-*cis* conformation.



(105)

Examination of the X-ray crystal structure of the analogous acrylate **(102)** concurs entirely with this postulation and also shows the two carbonyl groups to be in an anti-periplanar arrangement to one another, Figure 11.

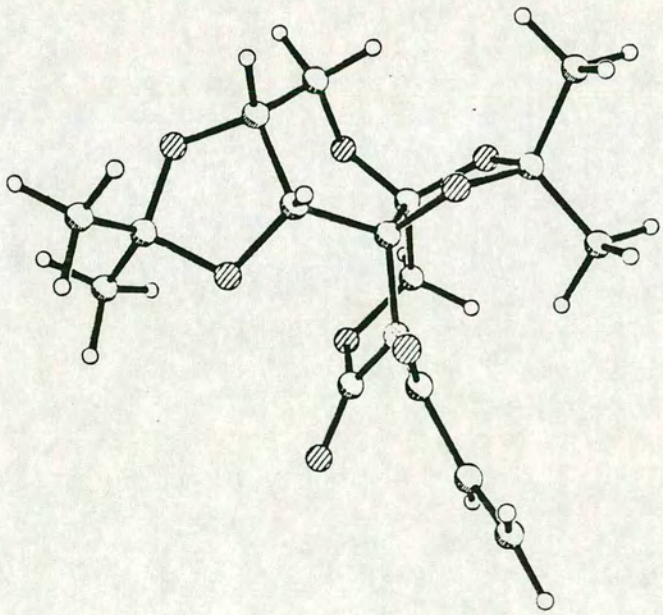
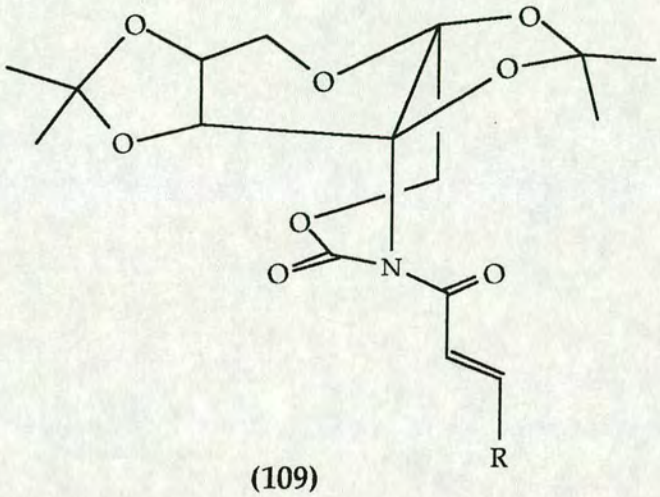


Figure 11
(X-ray crystal structure of acrylate)

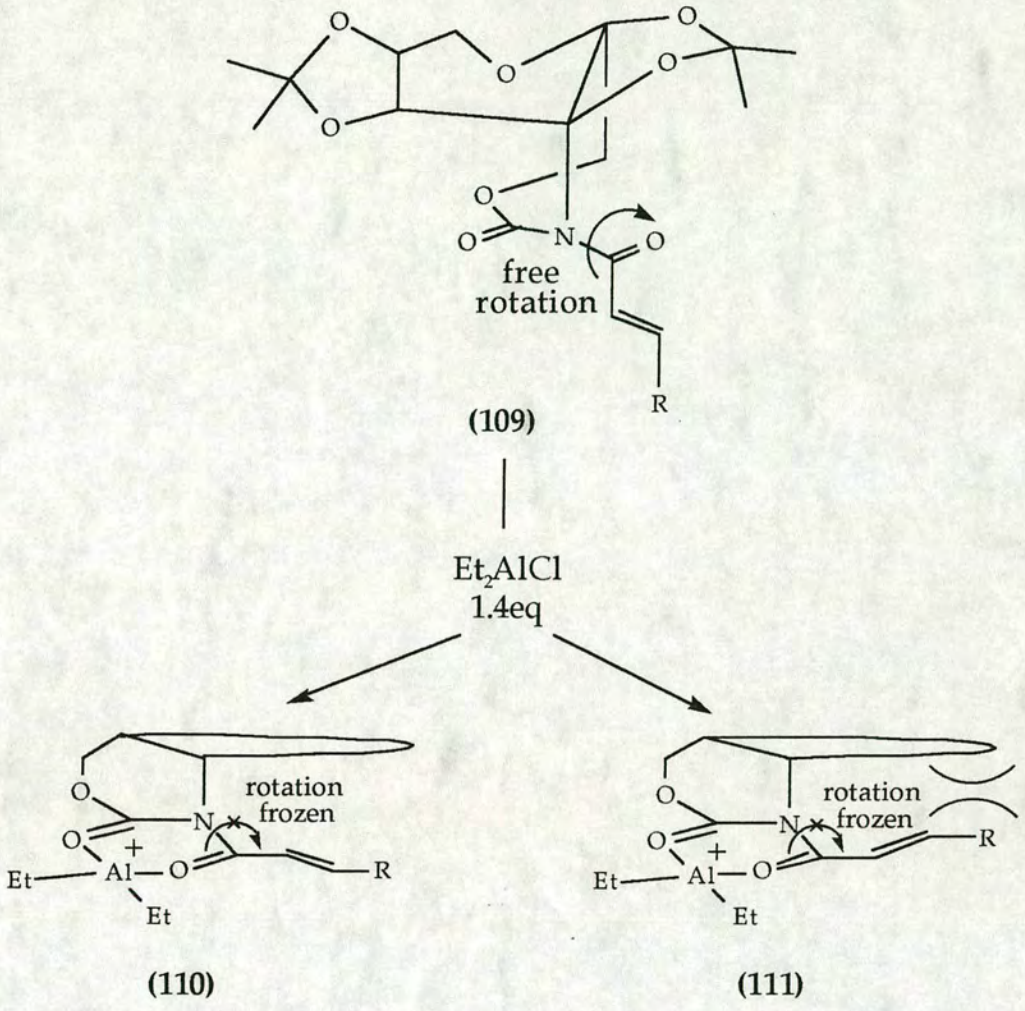
Assuming that the crotonate **(103)** and cinnamate **(104)** adopt a similar conformation, the three α,β unsaturated moieties can be represented by the general α,β unsaturated moiety **(109)** which enables us to elucidate the impact of the alkyl (R) group on steric interference, Figure 12.



(109)

Figure 12

Another issue which had to be considered, and a more decisive one, is the potential co-planar disposition adopted by the two carbonyl groups.
It was anticipated that improved diastereoselectivity would result if bidentate chelation could be achieved between the Lewis-acid promoter and both substrate carbonyl groups. Indeed, this bidentate theory is proposed by Evans[87] to be the reason for the sudden improvement in stereoselectivity obtained in parallel reactions. This proposal is supported by Lehmkuhl and Kobs[88] who have reported similar Lewis-acid behaviour in related work.
Engaging this theory to the particular studies in hand we find that upon chelation the N-C rotor previously present in the uncomplexed carboximide **(109)** is 'frozen', Scheme 47.



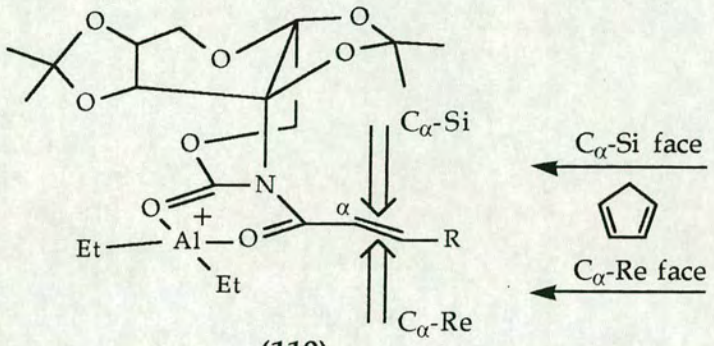
Scheme 47

From inspection of the two possible product conformations, **(110)** and **(111)**, it appears that *trans* conformer **(111)** is disfavoured due to the non-bonding steric interactions present between the olefinic alkyl group and the protecting isopropylidene group on the auxiliary.

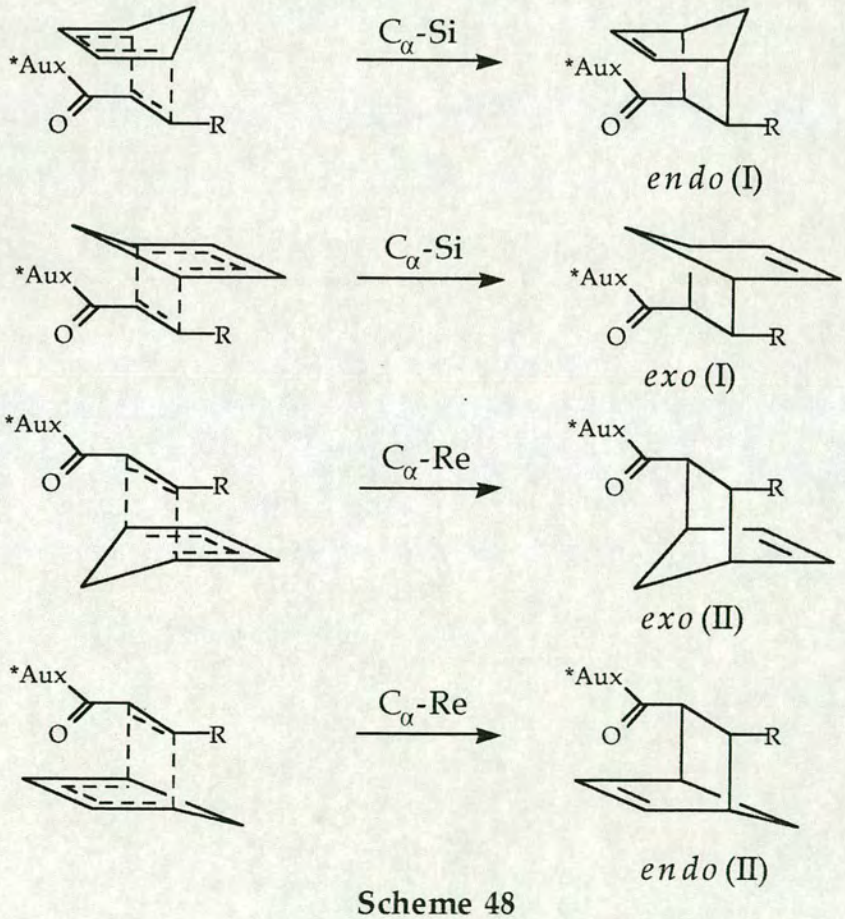
As a consequence of bidentate chelation in the Lewis-acid/dienophile complex **(110)**, a topographical difference arises.

The cycloaddition process between the cyclopentadiene and the olefin can occur at the C_α-Re face or the C_α-Si face of the olefin.

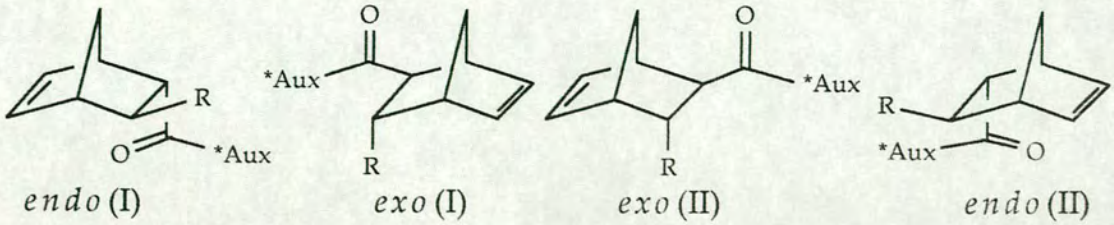
Attack at each of the two faces can lead to either the kinetically favoured *endo* product or the thermodynamically favoured *exo* product, so that there are four conceivable products in all, Scheme 48, Figure 13.



(110)



Scheme 48



Cα-Si face products Cα-Re face products

Figure 13

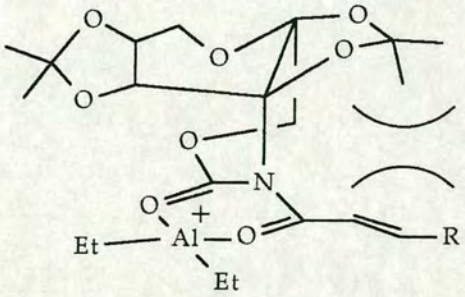
A retrospective look at Table 14 presents a more comprehensible set of results.

R	*endo* :*exo*	*endo* de%
H	>95 : 5	87
Me	>95 : 5	20
Ph	4 : 1	63

Table 14

At low reaction temperatures (-78°C), as in the case of the acrylate and crotonate, only the kinetically favoured *endo* products would be expected. The results in the table for the acrylate show that *endo* products are returned from cycloaddition reactions occurring at both the relatively unhindered C_α-Re face and relatively congested C_α-Si face.

This is perfectly feasible as scrutiny of Lewis-acid/dienophile complex **(110)** clearly shows that some of the steric imposition of the auxiliary is 'squandered' on account of being on the remote side of the reacting olefinic region, *ie* it presents no steric impediment to either face.



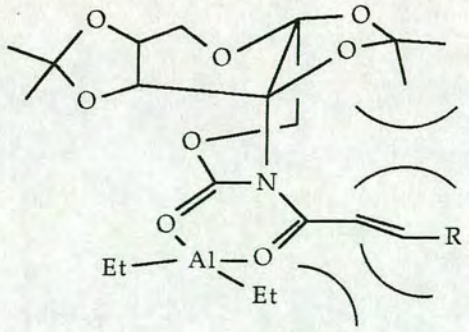
(110)

It would therefore be reasonable to assume that an inferior proportion of the reacting molecules would populate the C_α-Si face leading to the formation of the minor *endo* (I) adduct.

The greater selectivity of the acrylate (de 87%) over the crotonate (de 20%) is unexpected. On the basis of steric imposition the incorporation of the methyl group from the crotonate should intensify the interaction with the auxiliary isopropylidene group in the complex (110). This in turn would be expected to further influence the topographical distinction between the two faces of the reacting olefinic region in favour of the sterically relaxed bottomside C_α-Re face and lead to an increase in diastereoselectivity.

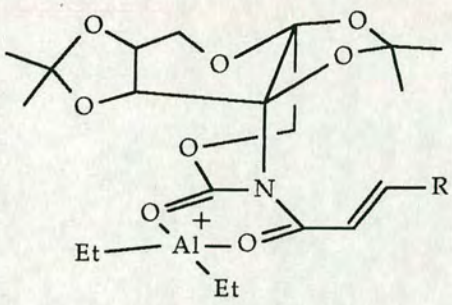
Clearly, however, this is not the case in this instance since a significant drop in selectivity is realized.

A possible explanation for the surprise outcome is that there may be ongoing competing steric inactions in the complex. As previously stated the most likely conformation of the metal centred chelated complex is that in which the alkyl group avoids congestion with the isopropylidene group of the auxiliary as seen in *cis* conformer (110). However, it may be that when the acrylate is changed to the crotonate, *i e* a hydrogen is replaced by a larger methyl substituent, steric competition may arise involving the methyl group interacting with either the isopropylidene group of the auxiliary or with the Lewis-acid ligand groups of the complex (110*).



(110*)

If this is so, then the complex can relieve the latter interaction by adopting the *trans* conformation **(111)**.



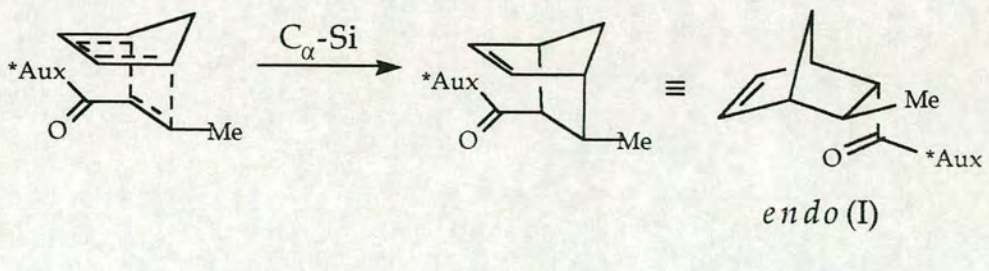
(111)

The narrow diastereoselectivity (de 20%) obtained for the reaction suggests there is little difference between the two interactions so that neither conformation is dominant, though the result indicates that there is preferential population of the *cis* conformer **(110)** and this is explained below.

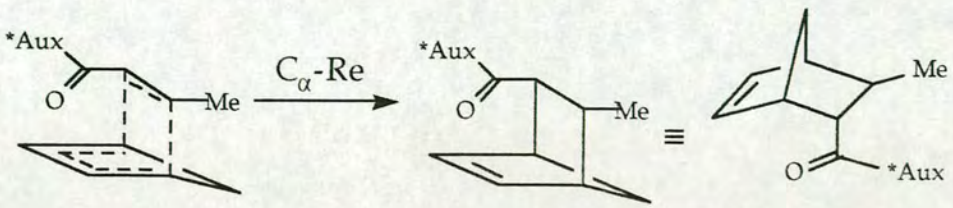
As in the case of the acrylate the reaction is carried out at low temperature (-78°C) and thus only kinetically favoured *endo* products are expected.

If *cis* conformer **(110)** operates in the cycloaddition reaction, approach of the cyclopentadiene can be expected at both the C_α-Re and C_α-Si faces with the sterically unencumbered C_α-Re face being favoured.

This leads to the preponderance of *endo* (II) adduct over *endo* (I) adduct.

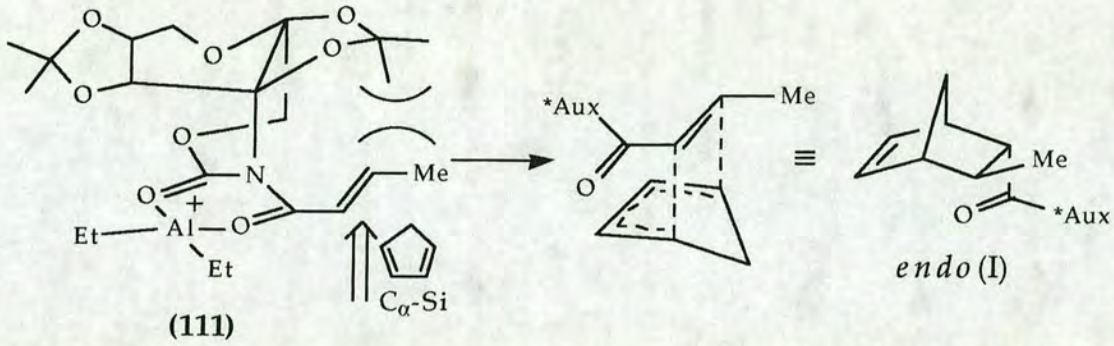


endo (I)



endo (II)

If however, *trans* conformer **(111)** is operational in the reaction then the increase in congestion at the topside face would hugely dictate a diastereofacial bias in favour of approach of the cyclopentadiene to the sterically relaxed bottomside face (now C_α-Si) which leads to formation of the *endo* (I) adduct.



(111)

Since there is an overall excess of the *endo* (II) adduct and it is proposed that this diastereomer can only be returned from reactions involving *cis* conformer **(110)** then it follows that this is the preferred conformation.

The deliberation above concerning the outcome of this reaction cannot be considered sure-fire. However, it is feasible and is supported by molecular models which show there is a fine distinction between the two conformations and relevant interactions.

The reaction involving the cinnamate **(104)** resulted in the formation of all four isomers in the following ratio:

endo (I) 15%, *exo* (I) 5% : *exo* (II) 15%, *endo* (II) 65%

With hindsight these results are not unusual since once again if *cis* conformer **(110)** is preferred, then reactions would be expected to occur at both the C_α-Re face and C_α-Si face leading to both *endo* products.

The existence of the thermodynamically favoured *exo* isomers is due to the increased reaction temperature (-20 °C) required for the less reactive cinnamate.

In general, the overall performance of auxiliary **(77)** in these asymmetric Diels-Alder cycloaddition reactions compared favourably against those carried out on Evans established auxiliary **(9)**, Table 15.

Comparison between Evans *Aux (9) and *Aux (77) in Lewis-acid catalysed Diels-Alder cycloaddition reactions with cyclopentadiene

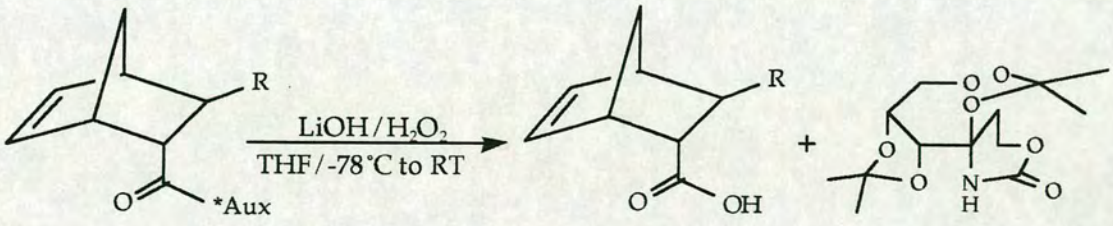
Aux	Evans *Aux (9)			D-Fructose *Aux (77)		
Dienophile	% yield	*endo:exo*	*endo* de%	% yield	*endo:exo*	*endo* de%
Acrylate	81	100:1	86	95	absolute	87
Crotonate	82	48:1	90	>90	absolute	20
Cinnamate	83	absolute	86	95	4:1	63

Table 15

Excellent *endo:exo* selectivity is achieved in each reaction and the *endo* diastereomeric excesses, although contrasting, are generally favourable.

4.3 Cleavage of Diels-Alder Cycloadducts (106-108)

Following the asymmetric conversions, each of the major cycloadducts from the products (106-108) was cleaved by hydrolysis to facilitate the diastereomerically pure acid fragments (112-114). The acid fragments were returned in quantitative yield with complementary recovery of auxiliary (77), Scheme 49.



(106 - 108)

R = H (106)
= Me (107)
= Ph (108)

(112 - 114)

R = H (112)
= Me (113)
= Ph (114)

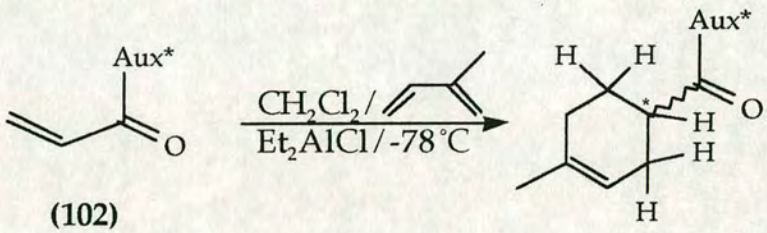
(77)

Scheme 49

4.4 Cycloaddition reaction of acrylate (102) with isoprene

In addition to the above set of Lewis-acid catalysed reactions a supplementary cycloaddition reaction employing an acyclic diene was carried out.

Accordingly, the acrylate **(102)** was matched with isoprene (acyclic diene) under identical conditions adopted for the reaction with cyclopentadiene, Scheme 50.



(102) **(115)**

Scheme 50

The resulting cycloadduct **(115)** possesses a new chiral centre. Perusal of the immediate locality of the chiral centre reveals two neighbouring protons on either side. Each of the four protons is in a distinct chemical environment and provided the four coupling constants to the chiral proton are explicit and unambiguous, then the ^{1}H NMR signal should result as a pattern of sixteen lines for each isomer, *i e* a doublet of doublets of doublets of doublets.

By close inspection of an expansion of the region pertaining to the chiral proton of the high resolution ^{1}H NMR spectrum obtained from the crude reaction product, one can interpret a pattern of exactly sixteen lines, Figure 14.

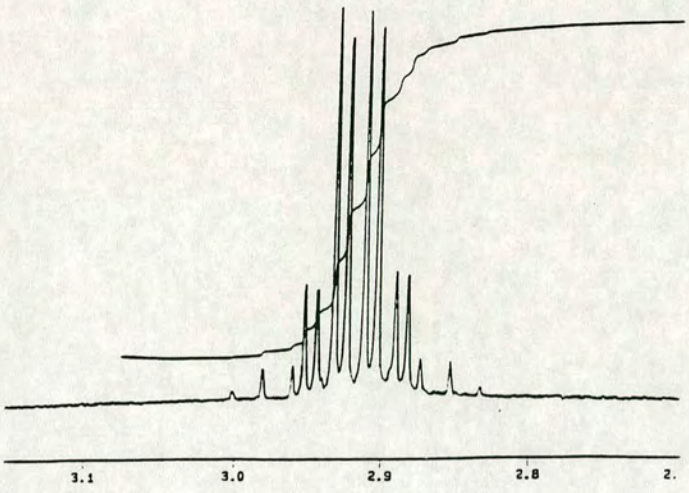
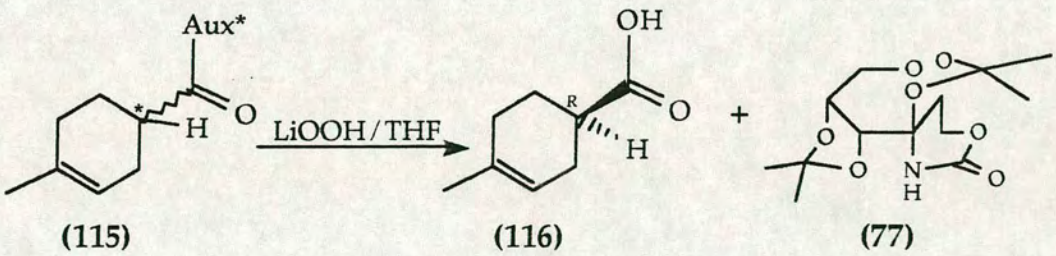


Figure 14

A less complicated region of the spectrum suggested the presence of both diastereomers formed by reaction on each face of the double bond and integration of these signals indicates a ratio of 7 : 1.

Isolation of the major cycloadduct was achieved by column flash chromatography and subsequent hydrolysis *via* now standard lithium hydroperoxide protocol yielded the acid fragment (116), Scheme 51.

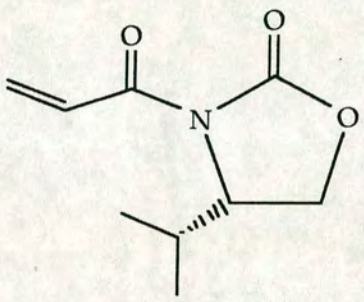


(115) (116) (77)

Scheme 51

Assignment of the configuration (R) of the isolated fragment **(116)** was based on diastereofacial preference consistent with C_α-Re attack, as was the case with the corresponding cyclopentadiene reaction.

The percentage return and diastereoselectivity offered by acrylate **(102)** in this cycloadduct reaction easily exceeds that obtained by Evans converted auxiliary **(117)** for the corresponding reaction, Table 16.



(117)

Aux	%yield	ratio
D-Fructose **(77)**	>95	7 : 1
Evans **(9)**	36*	5 : 1
* isolated yield of purified major cycloadduct		

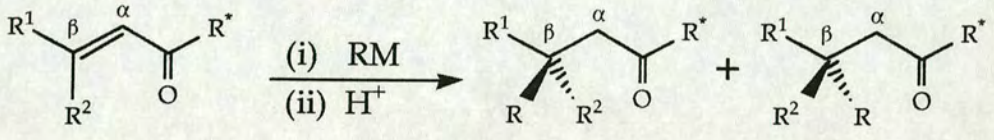
Table 16

Chapter 5

Asymmetric Conjugate Addition

The conjugate addition of organometallic reagents to α,β unsaturated organic substrates is an effective and well-established route to the construction of complex organic molecules.

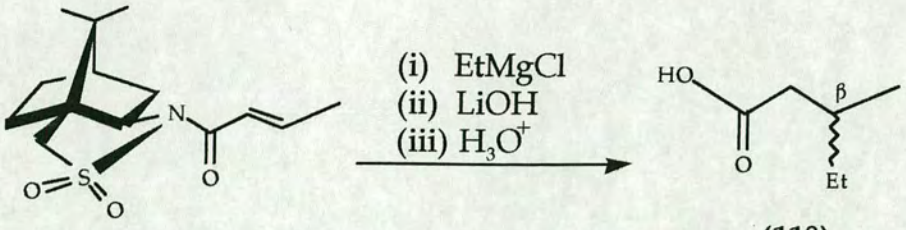
In these reactions the organic portion of an organometallic reagent (RM) adds to the β-carbon of an electron deficient diene which yields (*via* a stabilised carbanion and subsequent protonation) the β-substituted product, Scheme 52.



Scheme 52

Rossiter and Swingle[89] have compiled an excellent review based on universal studies in this field which is more often referred to as 1,4 conjugate addition.

Included in these deliberations is the diastereoselective conjugate addition of Grignard reagents to N-enoyl sultams **(117)** carried out by Oppolzer[90,91] to generate optically active β-alkyl substituted carboxylic acids **(118)**, Scheme 53.



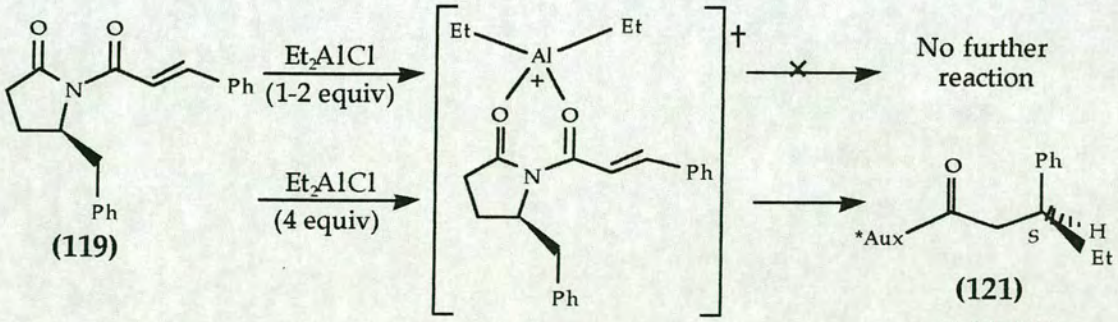
(117)

(118)
β-alkyl carboxylic acid
yield 80% de 89%
(configuration unspecified)

Scheme 53

Kunz[92] has also made use of the 1,4 conjugate addition methodology by reacting Evans auxiliary derived cinnamate **(119)** with a fourfold excess of diethylaluminium chloride (DEAC).

The resulting predominance of the (S) diastereomer **(121)** is in accordance with delivery of the ethyl nucleophile to the sterically unencumbered C_α-Re face (front face as drawn), Scheme 54.



(119)

(120)

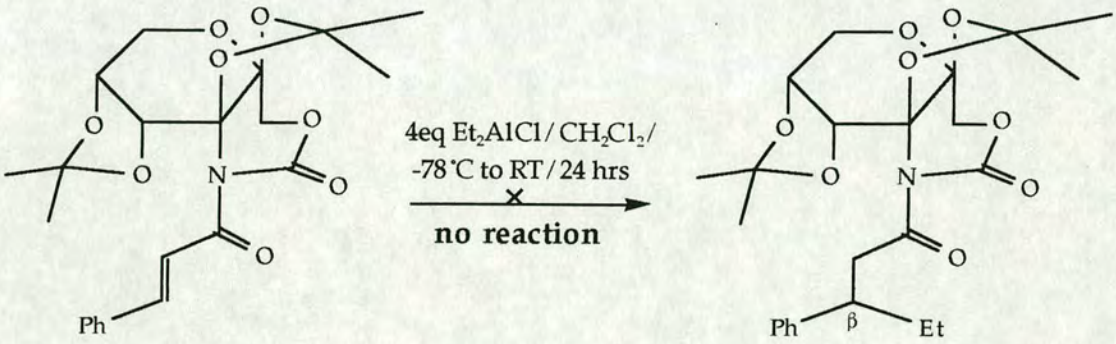
(121)
yield 98%
(S) : (R)
93 : 7

Scheme 54

The stoichiometry of the diethylaluminium chloride is decidedly important. Addition of between one and two equivalents leads only to

the formation of the complex (120) without further reaction. However, addition of more than two equivalents results in the ensuing reaction which affords the desired β-substituted product (121).

Accordingly, the cinnamate (104) was employed with diethylaluminium chloride in an attempted 1,4 conjugate addititon to furnish the C_β-ethylated product (122), Scheme 55.

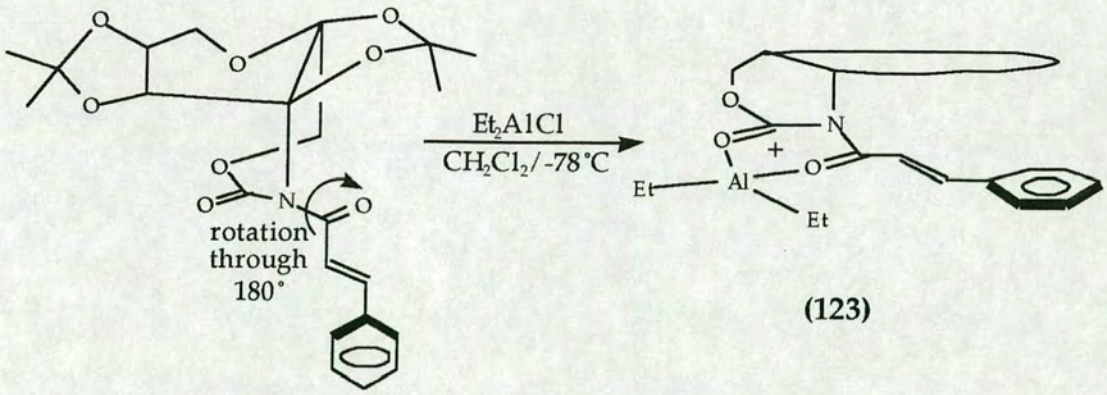


(104) (122)

Scheme 55

Most surprisingly the reaction failed to proceed. Although aware of the unreactive nature of the cinnamate (104), it was expected that progressive warming to room temperature combined with stirring overnight would have been sufficient to give life to the reaction.

Quite why the reaction did not go ahead is not fully understood. Since conditions used to generate the complex (123) were very similar to those employed in the Lewis-acid catalysed Diels-Alder cycloaddition reactions, it seems reasonable to assume that this stage of the reaction is achieved as before, Scheme 56.



(104) (123)

Scheme 56

It is the second stage therefore that is reluctant to progress. It was also established in the Diels-Alder cycloaddition reactions that the stereochemistry of the complex **(123)** allowed limited access for reagent attack at either face of the olefin.

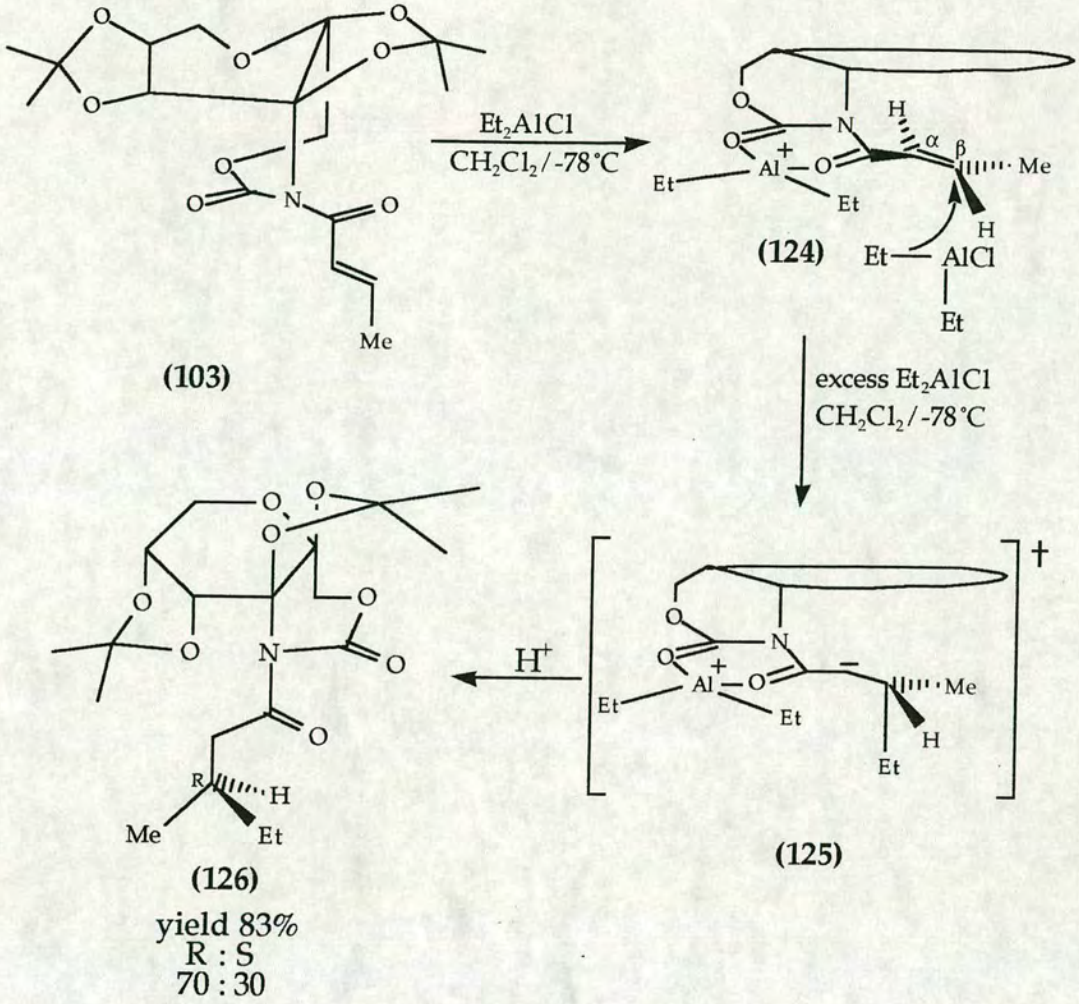
Tentatively therefore the reluctance of the reaction to proceed can be attributed to three main factors.

Firstly, the partial steric inhibition present in the complex **(123)**.

Secondly, the insubstantial nucleophilic character of the organometallic reagent and thirdly, the steadfast nature of the extended conjugate system exsisting in the complex due to reasonance stabilisation.

Of these the latter reason would be the greatest drawback to overcoming the reaction energy barrier.

Consequently the reaction was repeated using crotonate **(103)**, Scheme 57.



Scheme 57

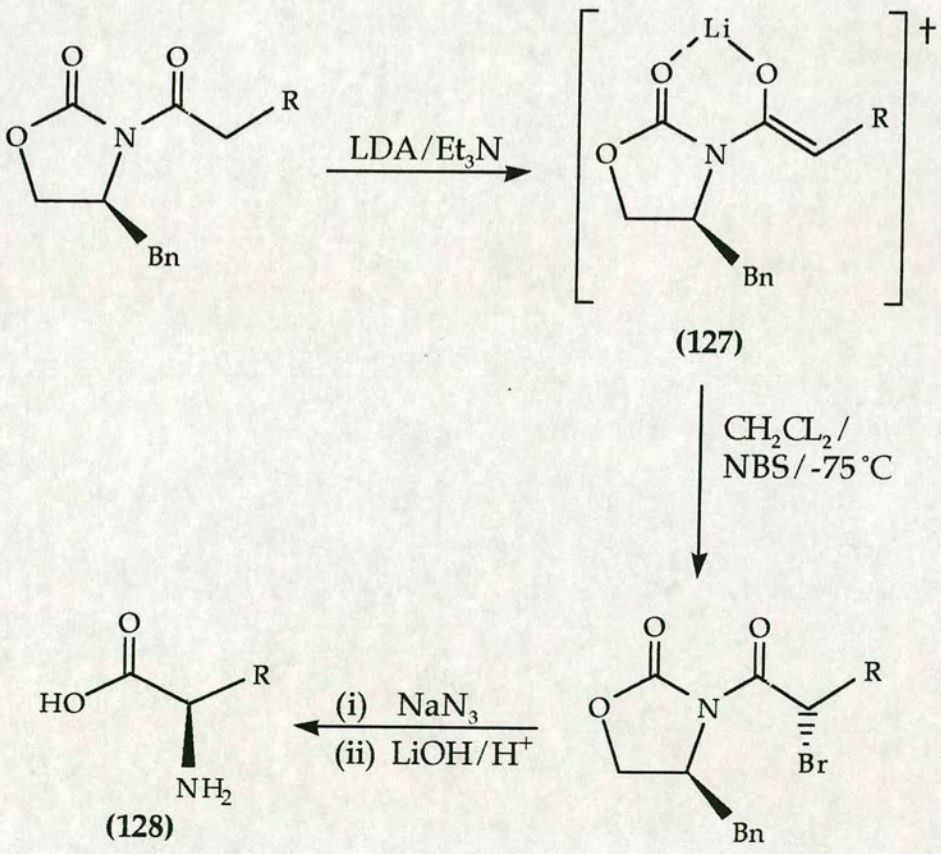
Generation of the aluminium mediated complex **(124)** was obtained and (in the presence of excess diethylaluminium chloride) was followed by creation of the intermediate carbanion **(125)** and subsequent protonation to furnish the diastereomeric C_β-ethylated product **(126)** in an overall yield of 83% and ratio of 70(R) : 30(S), Scheme 57.

The preponderance of the (R) isomer over the corresponding (S) isomer can be attributed to the diastereofacial preference shown by the reagent for the relatively unhindered C_α-Re face as was evident previously in the Diels-Alder reactions.

Chapter 6

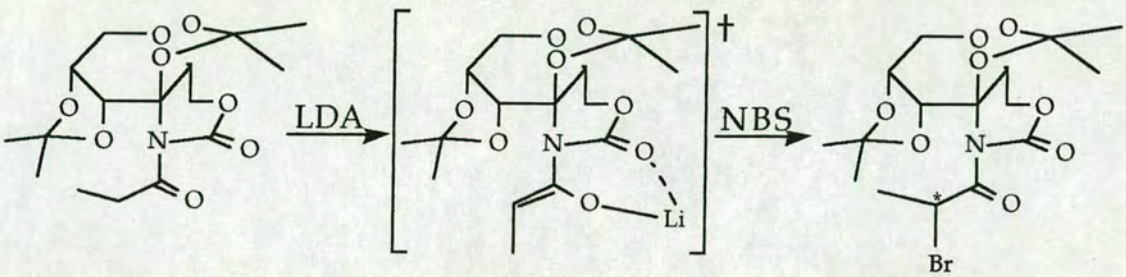
Diastereoselective α-bromination reaction of propionate (80) using N-bromosuccinimide

Evans[8] has devised a short sequence of reactions by which enantiomerically pure α-amino acids **(128)** can be prepared, Scheme 58. A pivotal step *en route* to deciding the stereochemistry of the product concerns the diastereoselective α-bromination of the intermediate lithium enolate complex **(127)** using N-bromosuccinimide (NBS).



Scheme 58

The propionate (80) was chosen to determine the stereospecificity of the α-bromination reaction by first developing the lithium mediated complex (82) using the same methodology exercised for the aldol reactions. Subsequent bromination with NBS returned the product (129) in quantitative yield, Scheme 59.



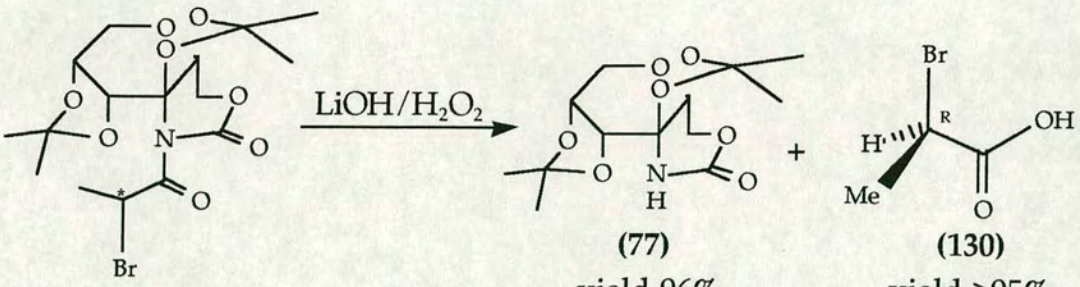
(80) (82) (129)

Scheme 59

Analysis of the 200MHz ^1H NMR spectrum of the crude reaction mixture intimated almost total asymmetric stereocontrol. However, there was a suggestion of the presence of a trace amount of the minor isomer and this was confirmed by examination of expansions of uncomplicated regions in the high field 360MHz ^1H NMR spectrum which unambiguously showed the existence of both isomers in a ratio of around 25:1.

Purification of the reaction mixture by flash chromatography using an elution ratio of hexane/ether (3:1) isolated the major diastereomer in an overall high yield of 90%.

Cleavage of the principal product of 129 by the familiar method using lithium hydroperoxide furnished the α-brominated carboxylic acid (130) in high yield with customary high return of auxiliary (77), Scheme 60.

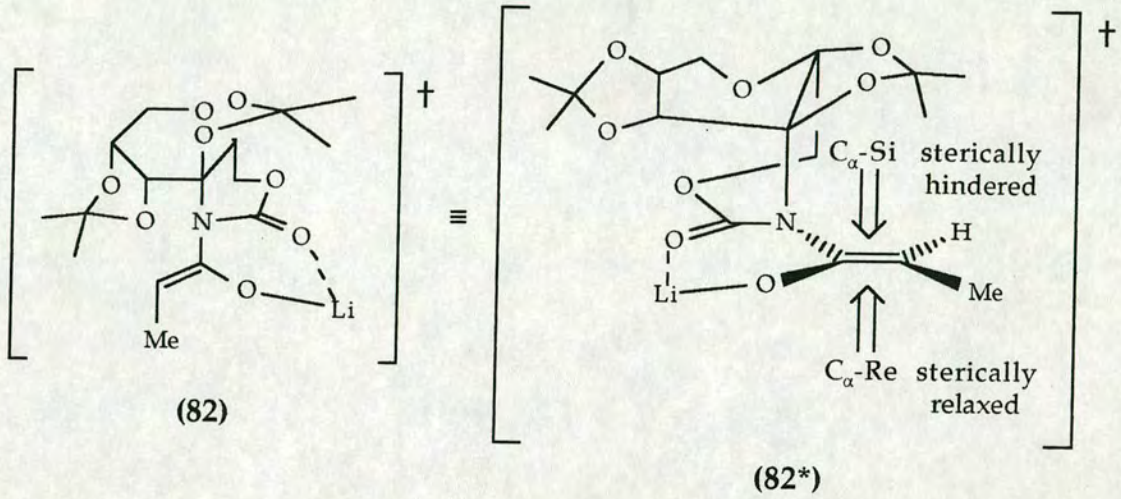


Scheme 60

Evaluation of the optical rotation value of 130 with literature[93] analogy determined the absolute configuration about the chiral carbon to be designated (R).

Stereochemical Interpretation

Previously it has been demonstrated that the lithium mediated intermediate complex **(82)** adopts the Z-enolate geometry as shown and that the 3-D state of the complex can be represented by the equivalent diagram **(82*)**, Figure 15.

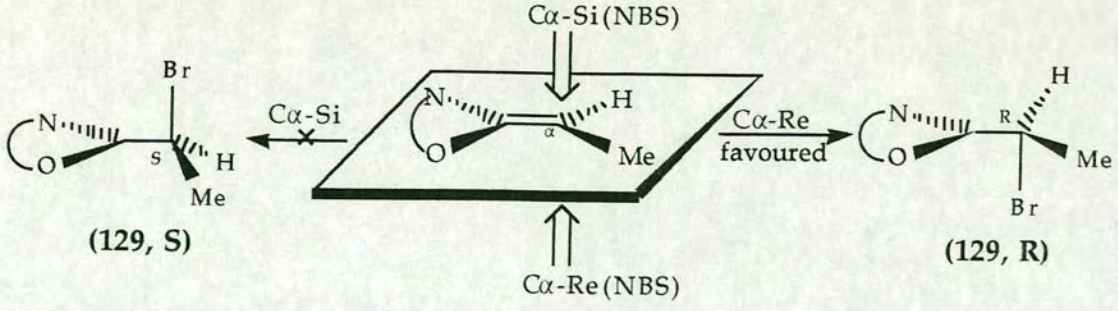


(82) **(82*)**

Figure 15

Scrutiny of the illustrated (Z) lithium enolate complex **(82*)** above shows there is a topographical bias in place. As a consequence of this, as in previous cases, the sense of asymmetric induction is consistent with electrophilic bromination of the sterically relaxed C_α-Re face.

This results in the near absolute diastereoselective preference for the R isomer **(129,R)**, Scheme 61.



Scheme 61

Chapter 7

Separation of Racemic Mixtures by Resolution

As part of the ongoing process in evaluating the competence of D-fructose derived auxilary (77) to promote intrinsic chirality, it was next utilised in the resolution of racemic mixtures.

The resolution of a racemic mixture is normally effected by chromatographic techniques and in particular HPLC, which, by virtue of its incomparable separating efficiency, makes it a hugely popular and resourceful methodology for qualitative analysis.

The principal consideration which determines the ease of separation of two components in a racemic mixture is a quantity named the separability factor, (α).

The magnitude of α is determined from the time taken for the elution of each component in the mixture measured against the elution time of a non-retained solute, Figure 16.

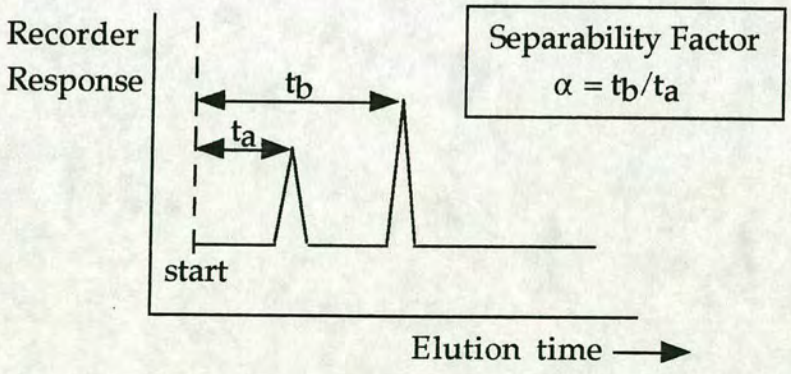


Figure 16

The times are presented as a fraction of the second time (t_b) over the first time (t_a) so that the value of α is always greater than one and a minimal value of 1.3 is necessary for successful baseline resolution[94].

The retention time for each component and thus the value of α depend largely upon chemical behaviour.

Strictly speaking, resolution and the separability factor (α) are two distinct considerations. Although the separability factor is dependent on chemical behaviour, it is independent of the particle size of adsorbent, column size, sample size (up to a point) or how well the column is packed.

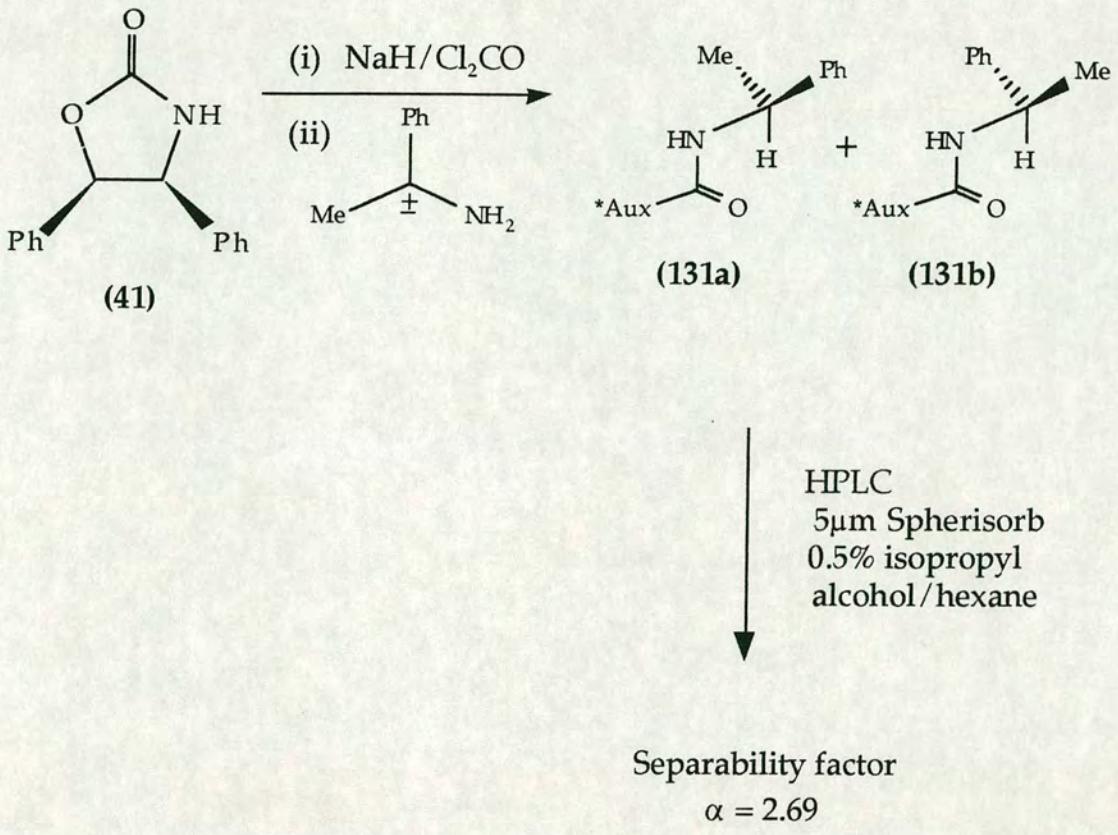
Resolution on the other hand is a measure of completeness of separation and depends not only on the magnitude of α, but, also upon all the aforementioned parameters.

An important consequence of the α value is with respect to the quantity of material which can be loaded onto any particular column. In general, the larger the value of α, the greater the quantity that can be loaded and separated, though once again parameters such as column size, particle size and packing are paramount in considerations carried out prior to loading.

7.1 Resolution of a racemic primary amine

During the introduction reference was made to the series of resolution reactions carried out by Pirkle[33] employing the *cis*-4,5-diphenyl substituted oxazolidinone **(41)** as the chiral derivatising agent.

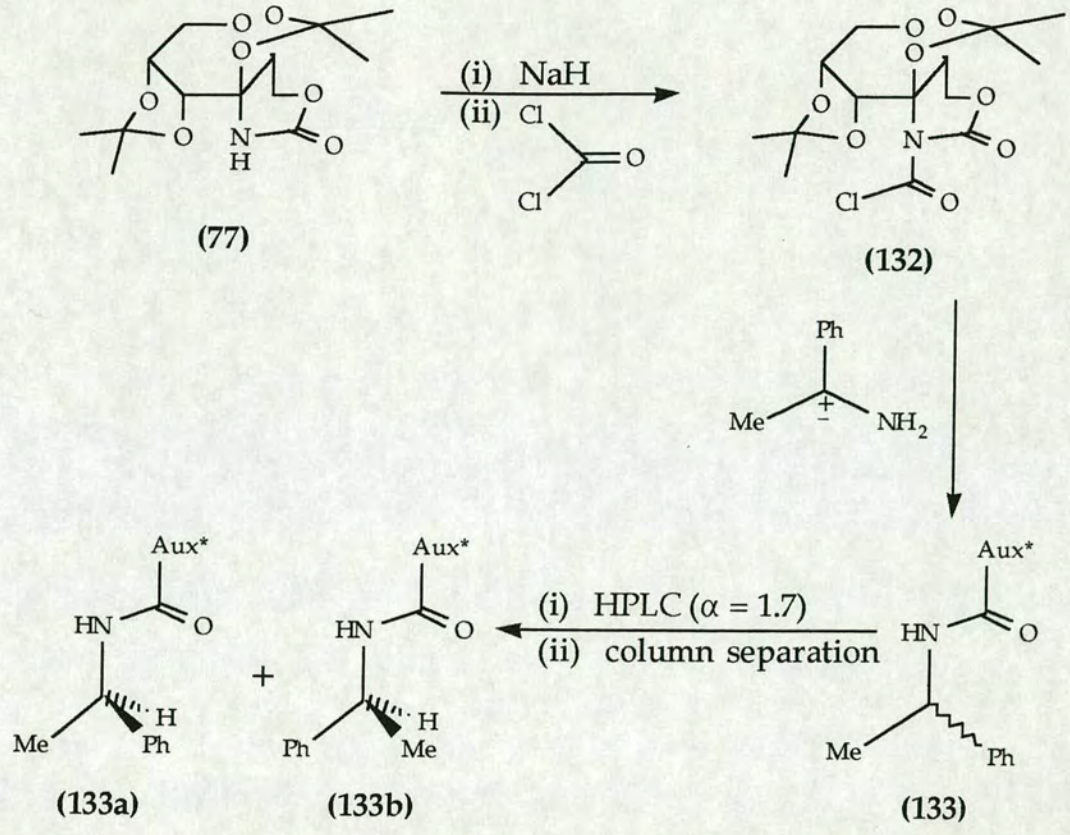
A selected example from that series of reactions was the resolution of a racemic mixture of (±)-2-phenylethylamine which resulted in the formation of the epimeric allophanate derivatives **(131a)** and **(131b)**, Scheme 62.



Scheme 62

Subsequent determination of the α value obtained on an analytical HPLC system using 5μm Spherisorb silica gel stationary phase and eluting with 0.5% isopropyl alcohol/hexane combination, led to a large separability factor (α) of 2.69.

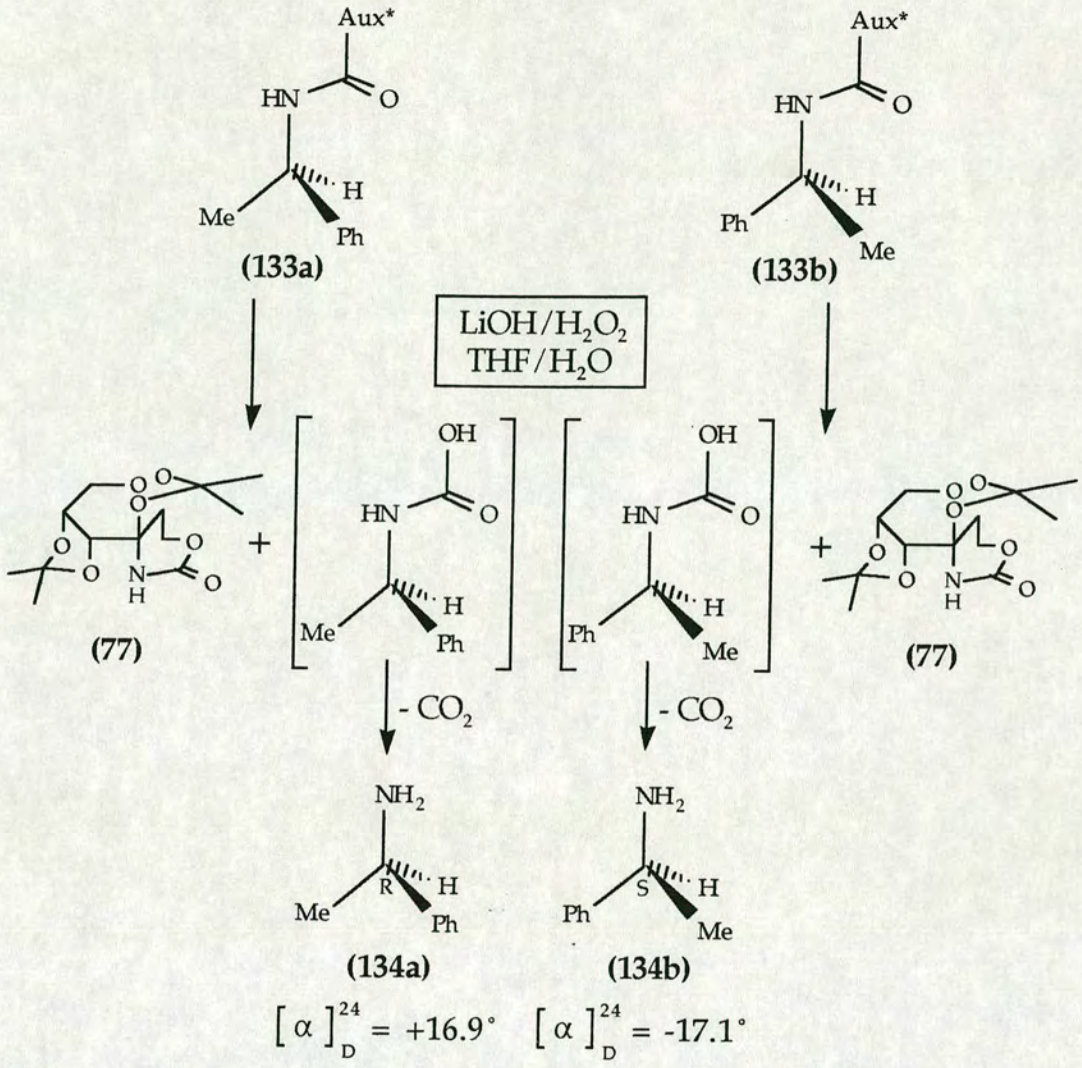
Following this protocol the efficacy of oxazinone **(77)** as a chiral resolving agent was examined by first converting it to the corresponding carbamyl chloride **(132)**, then by subsequently reacting with (±)-2-phenylethylamine to generate the diastereomeric allophanate pair **(133)**, Scheme 63.



Scheme 63

Chromatographic analysis of the trace obtained by HPLC gave a separability factor (α) of 1.7. The α value though small was well above the considered minimum (1.3) for effective resolution and although patience and care had to be exercised, the pair of diastereomers **(133a)** and **(133b)** were readily separated on the column.

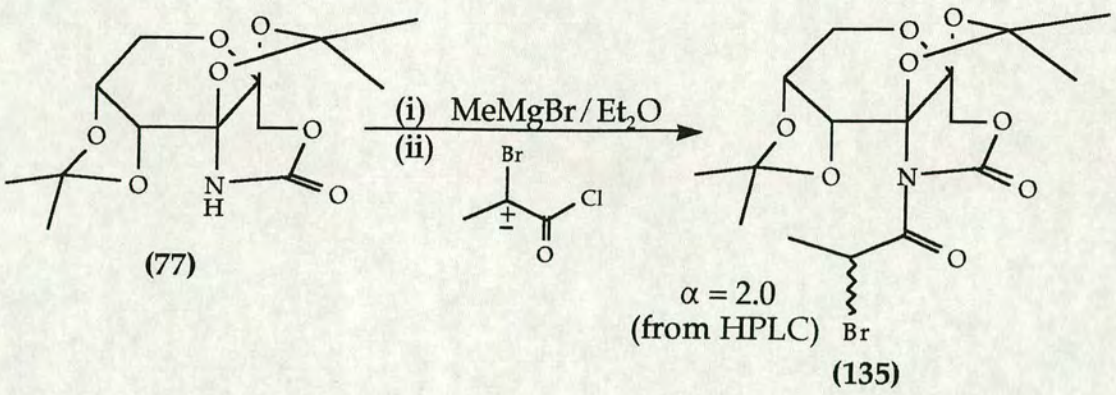
Cleavage of the pair of allophanates **(133a)** and **(133b)** by hydrolysis to furnish the amine fragments **(134a)** and **(134b)** *via in situ* decarboxylation of the corresponding carbamic acids was routinely achieved and comparison of their respective optical rotation values showed that they were of opposite configuration, Scheme 64.



Scheme 64

7.2 Resolution of a racemic acid halide

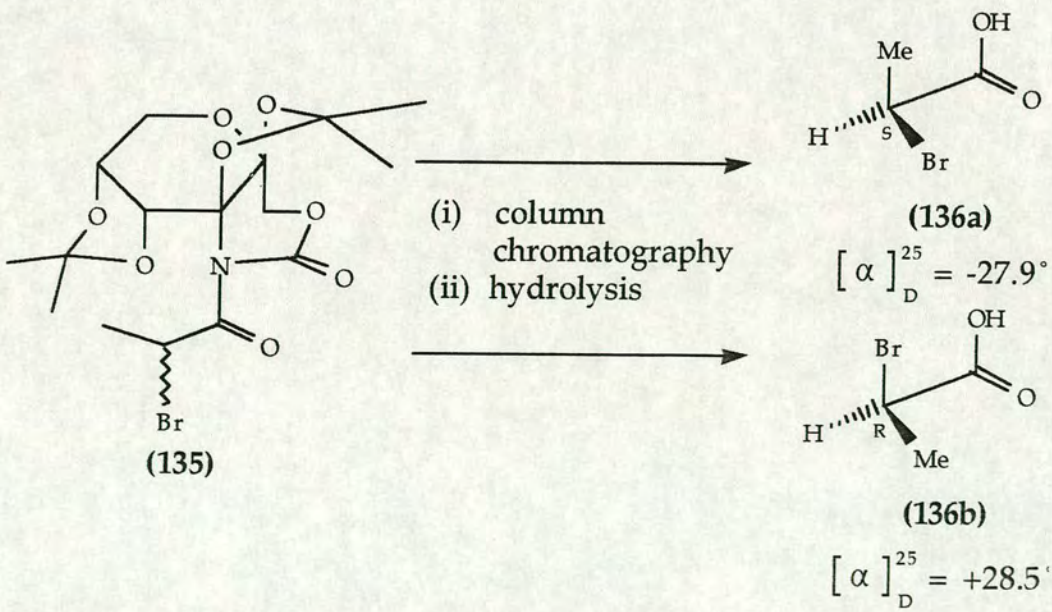
In addition to the above investigation, the resolution of a racemic combination of (±)-2-bromopropionyl chloride was conducted, Scheme 65. The operation was executed in part at low temperature by first generating the auxiliary anion *via* reaction with Grignard reagent followed by direct N-acylation with the bromo substituted acid chloride to furnish the diastereomeric mixture **(135)**, Scheme 65.



Scheme 65

Determination of the separability factor of the bromo substituted carboximide pair **(135)** by HPLC analysis led to the generous α value of 2.0. Ensuing disengagement of the chemical couple by flash chromatography was conducted cleanly.

As before, each of the separated products was fragmented by hydrolysis to furnish the α-brominated acids **(136a)** and **(136b)** and interpretation of the optical rotation values combined with literature[93] precedent established the absolute configurations, Scheme 66.



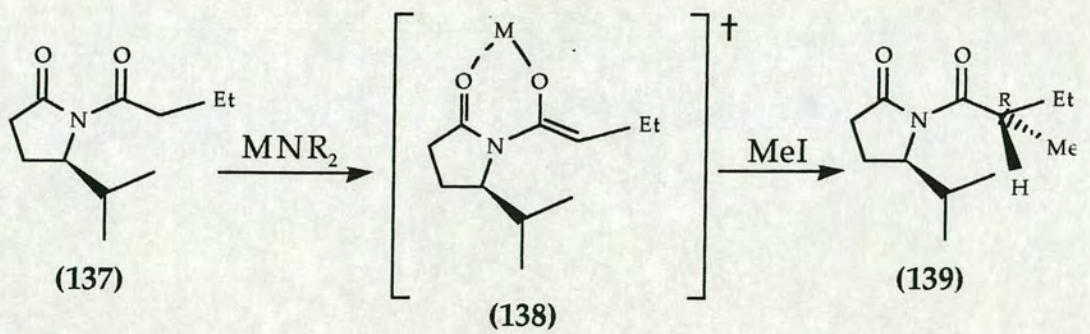
Scheme 66

Chapter 8

Asymmetric Alkylation Reactions

One department of asymmetric transformations which remained to be investigated was the alkylation reactions of chiral imide enolates. This particular area has been extensively researched by Evans who has demonstrated many hugely successful operations. An example of this is the superb diastereofacial selectivity obtained in the alkylation of carboximide **(137)** with methyl iodide, Scheme 67.

As with previous reactions involving this auxiliary, the intermediate metal enolate complex **(138)** adopts the Z-geometry as shown. This creates a diastereofacial bias for the alkylation process which favours electrophilic attack at the C_α-Si face and results in dominant formation of the (R) isomer **(139)**, Scheme 67.



(137) **(138)** **(139)**

Scheme 67

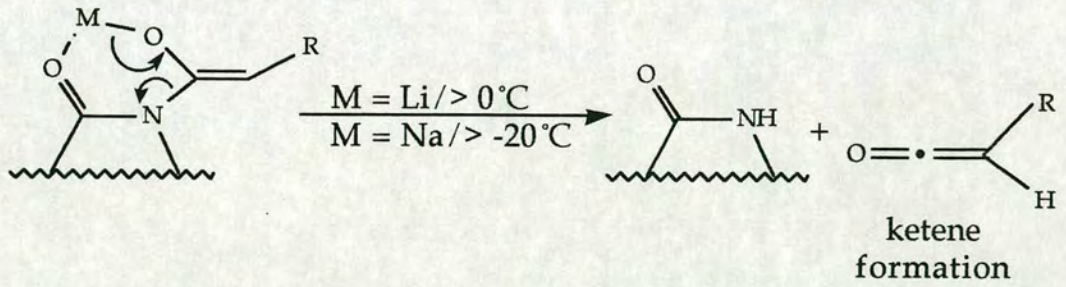
In these reactions Evans employed either lithium or sodium amide bases to generate the (Z)-metal enolate system.

In both cases excellent asymmetric induction was achieved with the latter being slightly superior, Table 17.

MNR_2	%Yield	Reaction ratio (R) : (S)	Purified ratio (R) : (S)
$LiN(i\text{-}C_3H_7)_2$	79	89 : 11	99 : 1
$NaN(SiMe_3)_2$	79	91 : 9	99 : 1

Table 17

Evans studies[6] also related that in surveying conditions for optimisation of the reaction, counteractive limitations were exposed.
It was established that the reactions would require to be carried out at temperatures ≤0 °C. This is because at temperatures above 0 °C, lithium enolate systems decompose via a ketene pathway, whilst the corresponding sodium enolates exhibit similar breakdown at temperatures above -20 °C, Scheme 68.

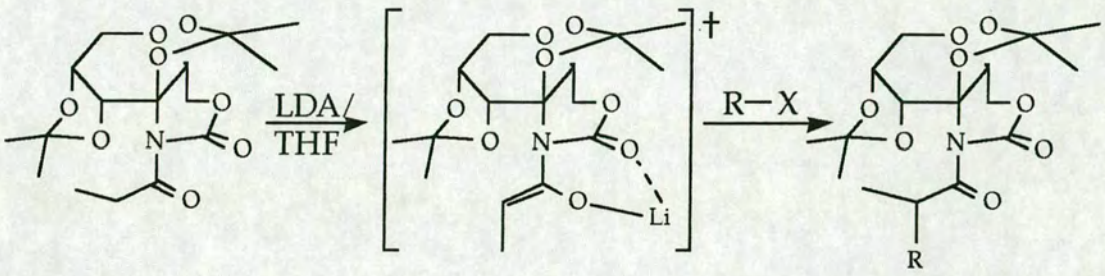


Scheme 68

It is also known that lithium enolates are poorer nucleophiles towards alkyl halides with respect to other enolate systems and require minimum reaction temperatures of between -10 °C and 0 °C. This leaves a very small

margin for success on temperature parameters alone.

The report by Evans[6] also disclosed that small alkyl halides are less stereoselective than their more sterically demanding counterparts. Primed with this knowledge the alkylation of the propionate **(80)** was initiated by generating the (Z)-lithium enolate complex **(82)** using lithium diisopropylamide at -78°C, Scheme 69.



(80) **(82)** **(140)**

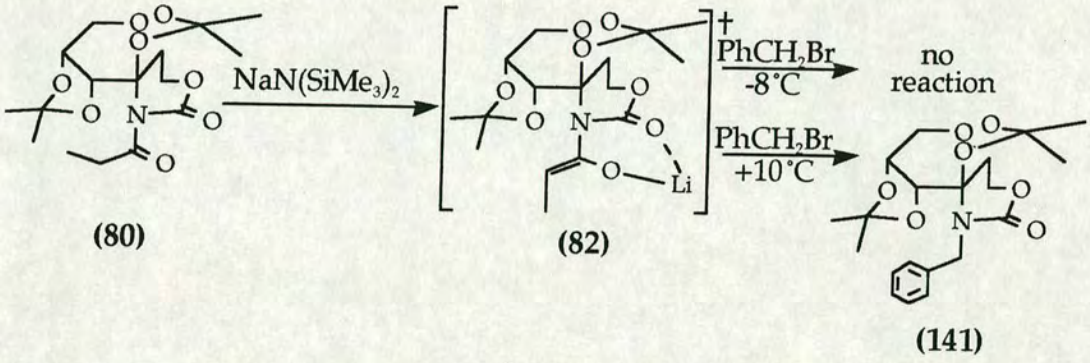
R-X	Temp (°C)
MeI	-8° no reaction
$PhCH_2Br$	0° no reaction

Scheme 69

Following formation of the precursor **(82)** the operation to furnish the alkylated product **(140)** was continued by treating the complex with methyl iodide at -8°C. The reaction temperature was then diligently controlled between -8°C and -4°C for several hours. However, careful monitoring of the chemical brew by thin layer chromatography failed to indicate any hint of reaction progress.

Judicious changes to reaction conditions such as gradually increasing the temperature to 0 °C and changing the alkylating agent to benzyl bromide failed to make any impression, Scheme 69.

Accepting the failure of the lithium amide base to promote alkylation, the more reactive sodium hexamethyldisilylazide was then employed. Benzyl bromide was again employed as the alkylating agent and the reaction was conducted at a temperature range between -8 °C and -4 °C as before, Scheme 70.



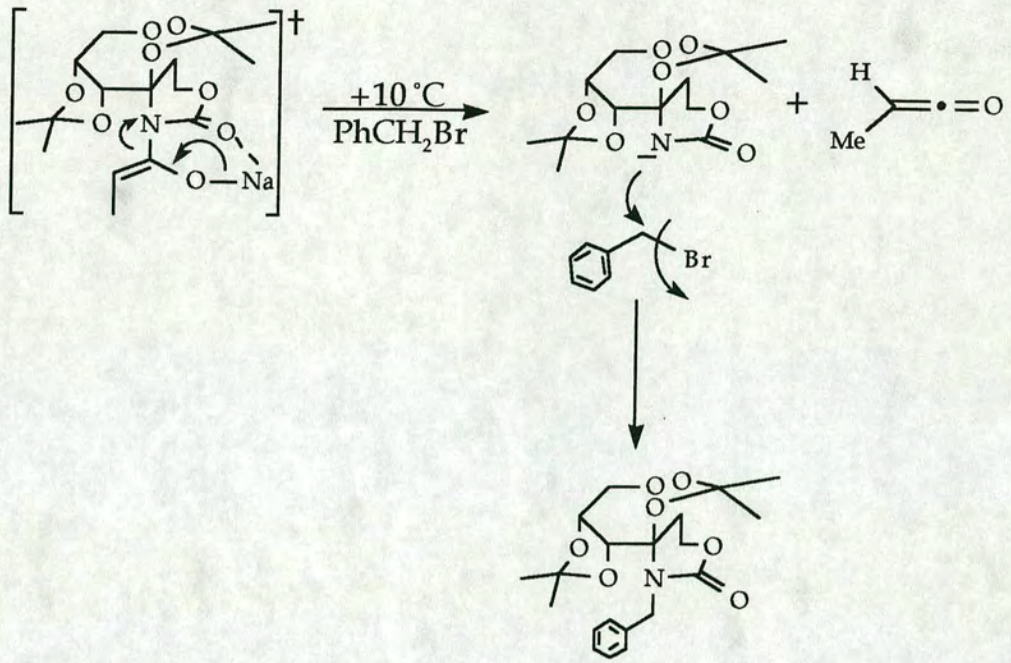
(80) (82) (141)

Scheme 70

Once again however, after supervising for several hours, no reaction occurred.

In a final bid to stimulate alkylation, the reaction was repeated at a temperature 'forbidden' +10 °C, Scheme 70.

However, although a reaction did occur this time, it only resulted in the formation of the N-benzylated product (141), presumably through the mechanistic pathway shown in Scheme 71.



(141)

Scheme 71

The lack of success in this particular reaction is not surprising. As indicated earlier, the tight temperature range combined with the poor electrophilic character of the alkyl halides towards the lithium enolate system in particular makes it an improbable reaction.

Also, there are reports from others in the literature[72,95] who have experienced similar difficulties in attempts to promote this reaction.

Chapter 9

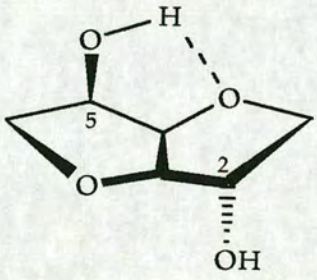
Construction and Functionalisation of Isosorbide derived Auxiliary (147) {Isosorbide=1,4:3,6-dianhydro-D-glucitol}

The synthesis of new auxiliary (147) proved to be a fascinating challenge requiring a high level of exacting patience and care.

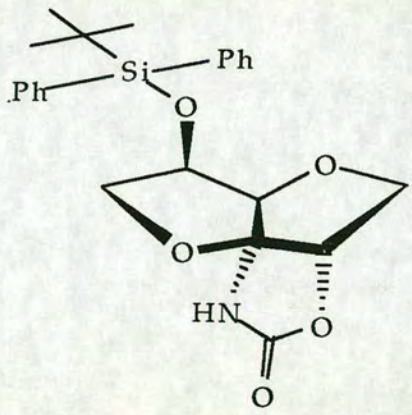
The starting material is the cheap and readily available carbohydrate 1,4:3,6-dianhydro-D-glucitol, otherwise known as isosorbide (142).

Isosorbide (142) has two nearly planar *cis*-fused five membered rings in the form of a 'V'.

The hydroxyl group at C-5 which lies inside the wedge is designated as *endo*, whereas the hydroxyl group at the C-2 position lying outside the wedge is designated *exo*.



(142)



(147)

Although the faces of the rings inside the 'V' are less accessible than the faces outside, single intramolecular hydrogen bonding at the C-5 position renders it to be the more reactive[96,97].

Both hydroxyl groups though are potential starting points for cyclisation and could feasibly be utilised together to synthesise a bifunctional chiral auxiliary such as was previously reported in this thesis, Figure 17.

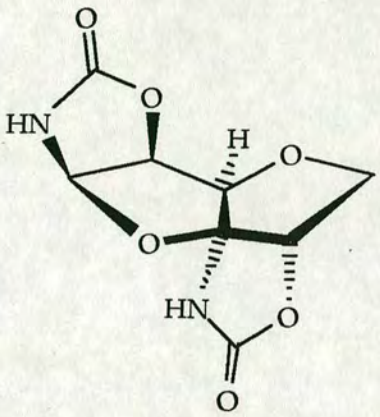


Figure 17

At this juncture though, a monofunctional chiral auxiliary was desired and molecular models suggested that formation of the oxazolidinone ring utilising the hydroxyl group at the C-2 position was the most promising. To attain this monofunctional auxiliary, selective protection of the hydroxyl functional group at the C-5 position is necessary to prevent interference in ensuing reactions.

In selecting any protecting group it is of paramount importance to know the reactivity of the resulting protected functionality towards various reagents and reaction conditions.

The two most convenient methods of protecting substituent hydroxyl groups is to convert them to their corresponding esters or ethers.

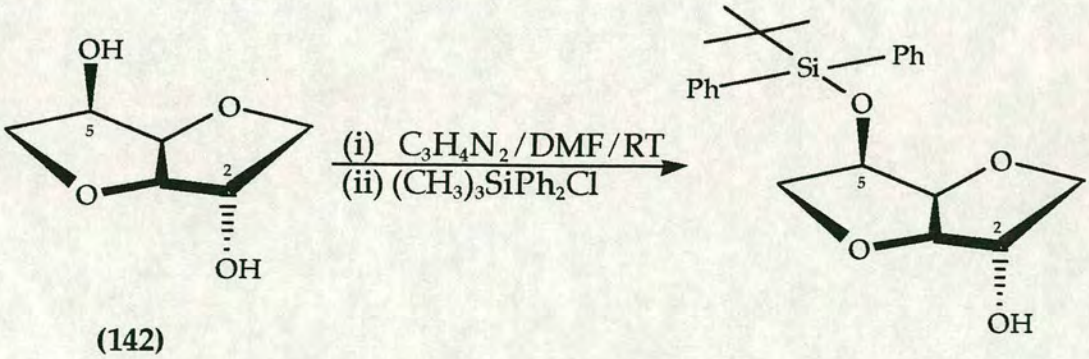
Of the two methods it seemed sensible to choose etherification since ethers are much more stable than their corresponding ester analogues.

A literature quest uncovered a report on extensive work conducted by Hanessian and Lavallee[98] on the protection of hydroxyl groups using alkylated silyl chlorides as the protecting agent.

From these it was decided to employ *tert*-butyldiphenylsilyl chloride on account of the excellent stability this reagent possesses. Furthermore, it was expected that the significant bulk of the combined substituent groups could be advantageous in providing a steric overload to one of the two reacting faces in the ensuing asymmetric reactions. This would create the topological bias necessary to dictate diastereofacial selectivity. Finally, the presence of the phenyl chromophore greatly facilitates the detection of products by ultra-violet and spectrophotometric methods.

9.1 Synthesis of Auxiliary (147)

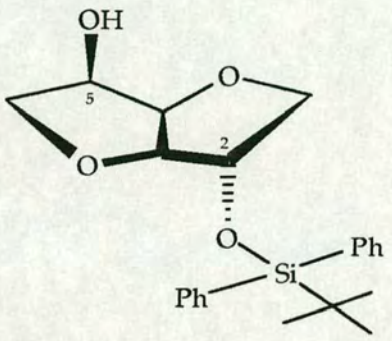
Accordingly, the protection of the more reactive *endo*-hydroxyl group of isosorbide **(142)** was carried out in the presence of 2.2 equivalents of imidazole[99] as catalyst in an attempt to furnish the mono-substituted product **(143)**, Scheme 72.



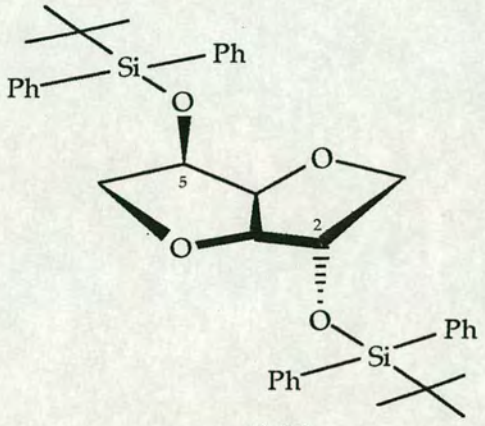
(142) **(143)**

Scheme 72

Unfortunately however, the C-5 *endo* protected product **(143)** was accompanied not only by the C-2 *exo* protected product **(144)**, but also by the disubstituted product **(145)**.



(144)



(145)

The enhanced stability of the *tert*-butyldiphenylsilyl chloride protecting group became a distinct disadvantage at this point since the removal of the group from the unwanted products requires harsh conditions and could not be facilitated without disruption of the favoured product **(143)**.

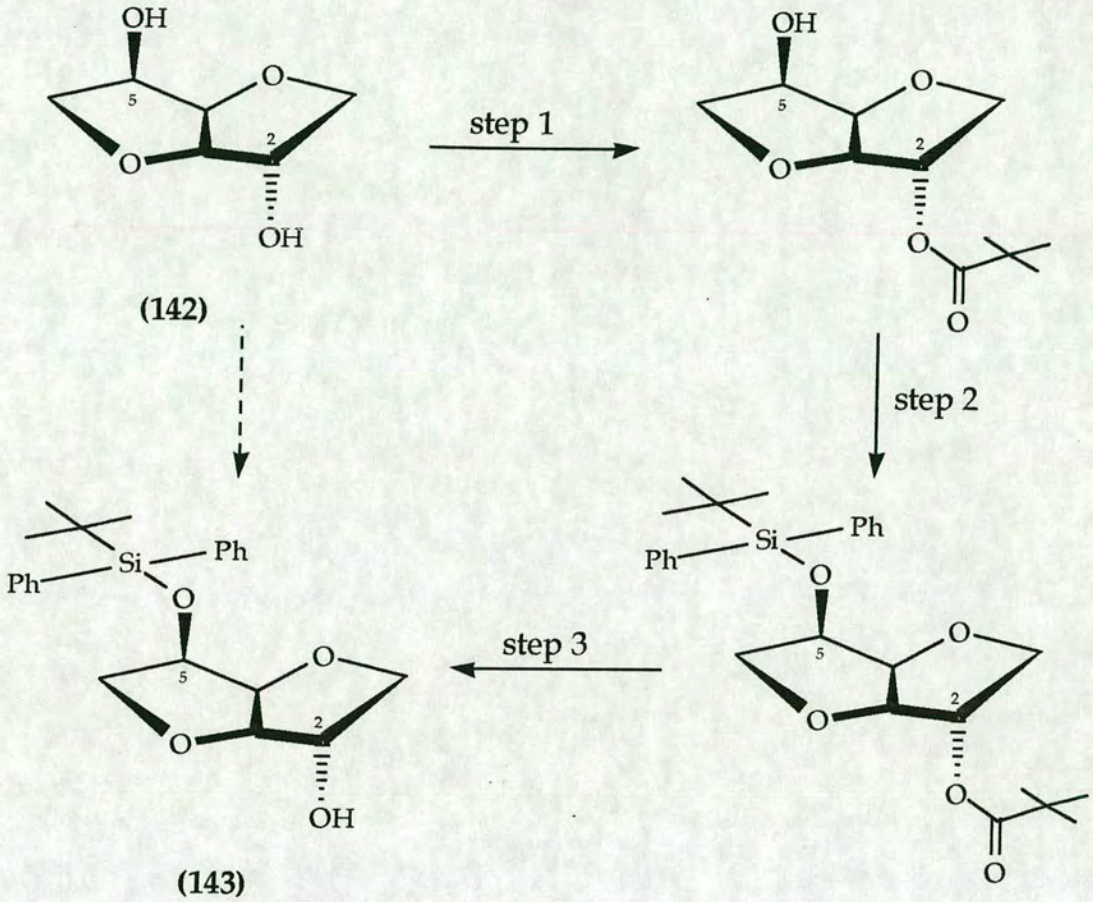
In addition to this problem, although the disubstituted product **(145)** could be separated routinely by chromatographic techniques, the almost identical chemical construction of the mono-protected products **(143)** and **(144)** made separation an extremely difficult task.

A review of the literature inspired an alternative strategy.

A series of esterification reactions performed by Cekovic and Tokic[100] on isosorbide **(142)** had shown that high levels of regioselective monoacylation could be achieved at the C-2 *exo* position under mild conditions.

The preference for esterification at the relatively unreactive C-2 *exo* position is not entirely surprising. As indicated earlier, although the C-5 *endo* hydroxyl group is more reactive due to intramolecular hydrogen bonding, it is also the more sterically hindered. Thus the employment of acylating agents carrying substituent groups of significant steric imposition encourage approach to the less hindered C-2 *exo* site.
By utilising this esterification methodology, the C-2 *exo* position could be temporarily protected as a preliminary step to permanent protection of the C-5 *endo* position by etherifying as before. Following the protection of the C-5 *endo* position, the temporary protecting group on the C-2 *exo* position could be readily removed to regenerate the original hydroxyl functional group thereby resulting in the intended target material (143).

Thus the calculated strategy to prepare the C-5 *endo* hydroxyl protected functionality **(143)** was executed in accordance with the steps detailed and tabulated in Scheme 73.



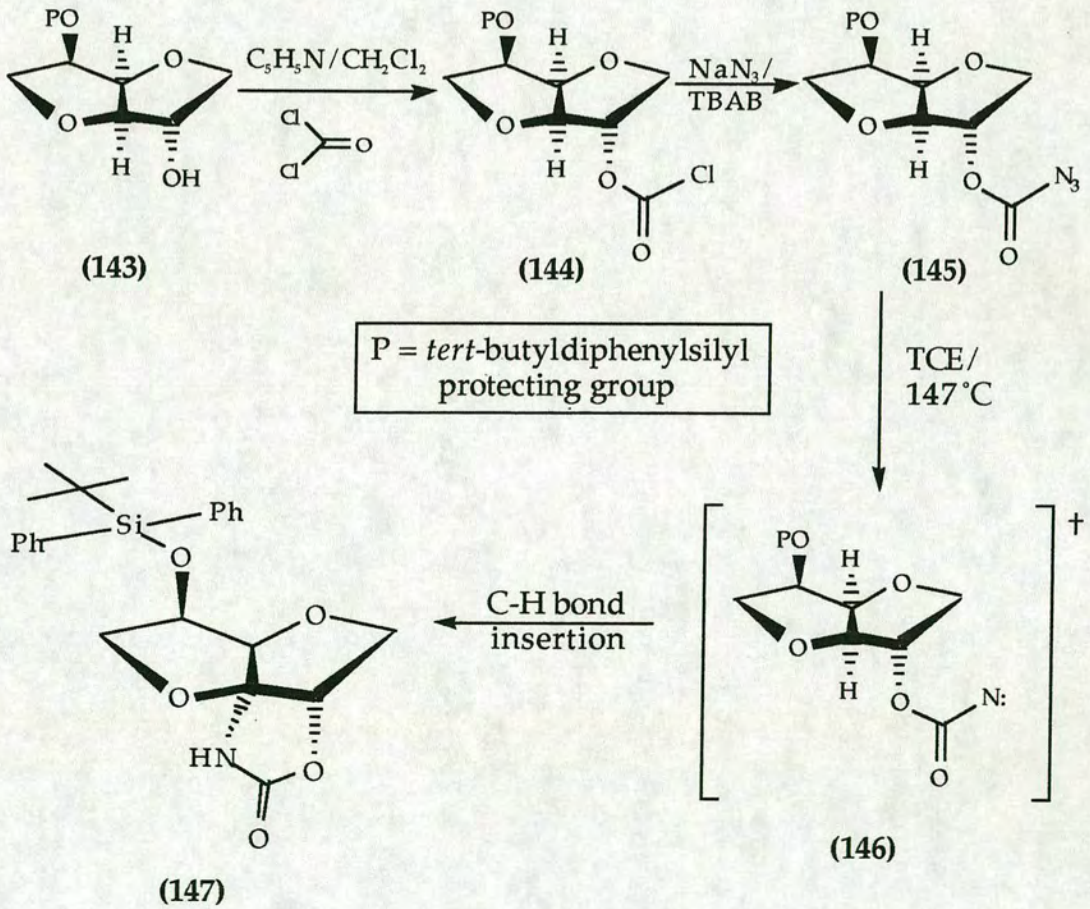
Scheme 73

Step	Operation	%Yield	Reaction Conditions
1	temporary protection of C-2 *exo* hydroxyl	65*	PvCl/CH_2Cl_2/DMAP/DCC @ RT/40hrs
2	permanent protection of C-5 *endo* hydroxyl	>95	(i) imidazole/DMF/@ RT (ii) t-BDPSiCl
3	deprotection of C-2 *exo* hydroxyl	>95	H_2O_2/LiOH.H_2O (mild acid hydrolysis)
* purified yield after flash chromatography and recrystallisation			

The overall payoff from this adventurous route to prepare the C-5 *endo* hydroxyl protected isosorbide (143) was a very acceptable and workable yield of 60%.

Having assembled the mono-protected isosorbide (143) such that the 'free' hydroxyl group lies at the C-2 *exo* position, the next steps were to incorporate a carbonyl group and a functionalisable nitrogen atom to complete an oxazolidinone ring system.

The pathway taken to achieve this is depicted in Scheme 74.



Scheme 74

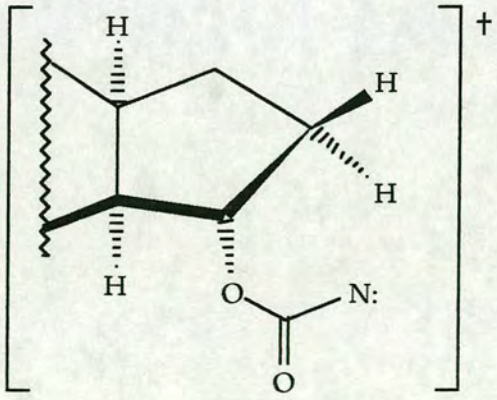
The mono-protected isosorbide **(143)** was converted in quantitative yield to its corresponding chloroformate derivative **(144)** by reaction in the presence of a pyridine base catalyst.

A similar quantitative yield of azidoformate derivative **(145)** was returned from the tetrabutylammonium bromide (TBAB) phase-transfer catalysed reaction of chloroformate **(144)** with a twofold excess of sodium azide.

The azidoformate **(145)** then underwent solution thermolysis in boiling tetrachloroethane *via* a nitrene intermediate to provide the desired five membered oxazolidinone auxiliary **(147)** in an overall 35% yield, Scheme 74.

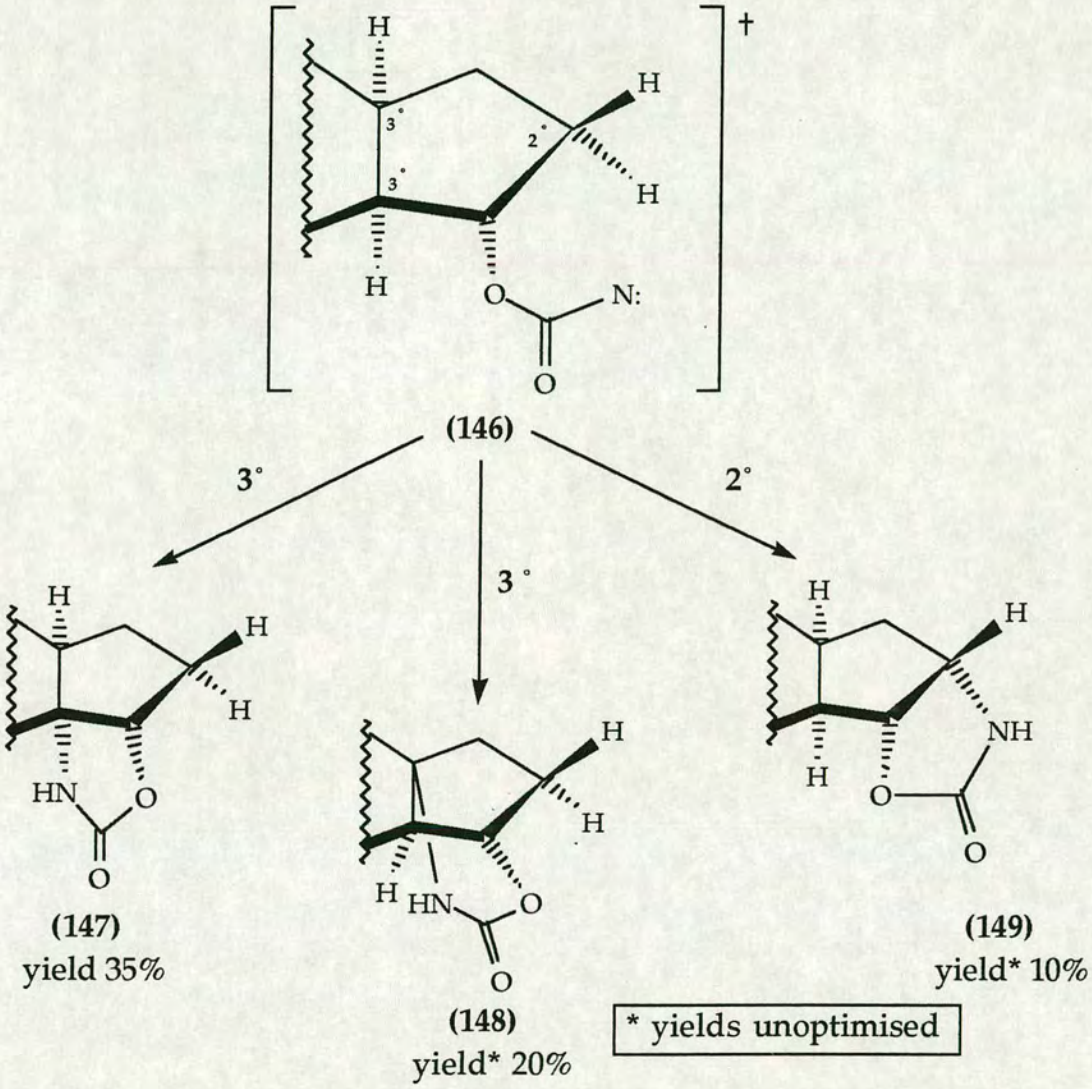
The low percentage yield of auxiliary **(147)** can be explained by examination of the nitrene intermediate **(146)** prior to C-H bond insertion, Scheme 75.

As was stated in the construction of the previous D-fructose auxiliary **(77)** the two non-bonded electrons present in the nitrene can either be paired (singlet state) or unpaired (triplet state). The singlet state is crucial to C-H bond insertion and the order of preference is $3^{\circ} > 2^{\circ} > 1^{\circ}$.



(146)

It can be seen by inspection of the nitrene intermediate (146) that there are three potential sites where C-H bond insertion can take place, Scheme 75.



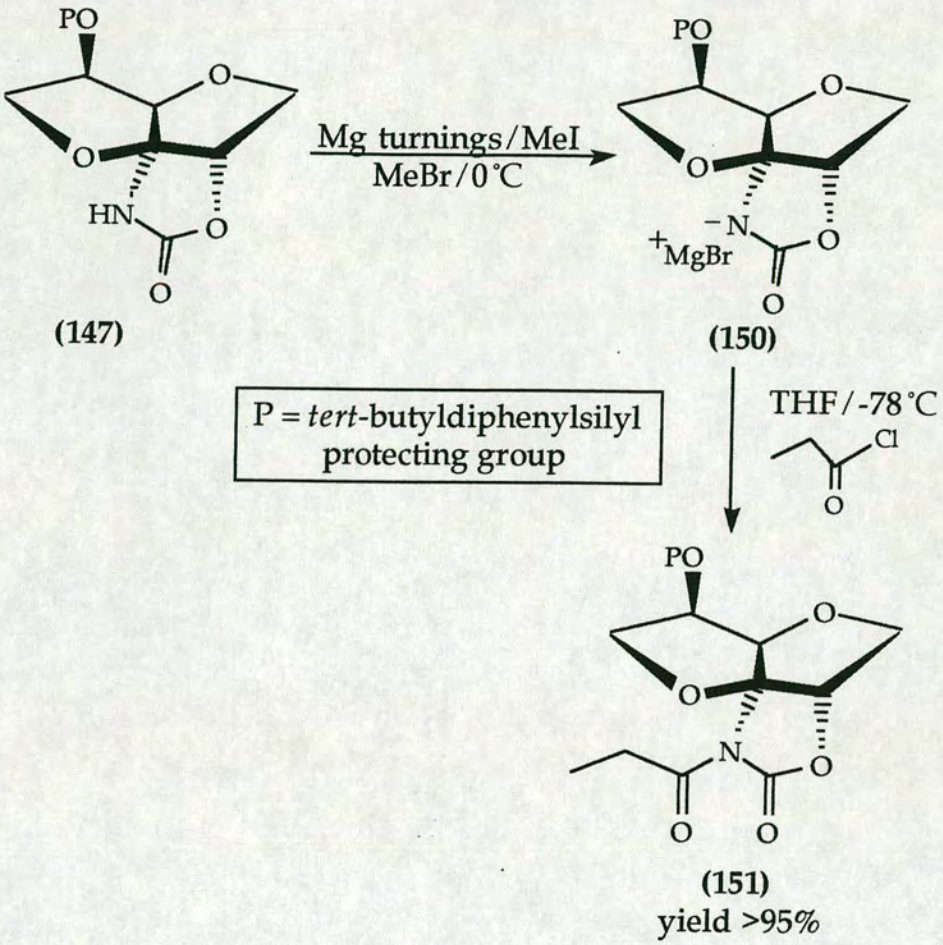
Scheme 75

Two of these involve preferential 3° C-H bond insertion with the first leading to the five-membered oxazolidinone ring based auxiliary (147). The other 3° position at which C-H bond insertion occurs leads to the six-membered oxazinone (148) in a lower yield of approximately 20%. The lower yield is attributed to the slight increase in steric strain in forming the six-membered ring as was evident in molecular models.

Finally, the remaining location at which bond insertion takes place is at the disfavoured 2° C-H site which leads to formation of the five membered oxazolidinone **(149)** in an even lower yield of around 10%. The above approximate percentage yields were determined from interpretation of ^{13}C NMR spectra and the desired product **(147)** was isolated by a single recrystallisation.

9.2 Functionalisation of auxiliary (147) to propionate derivative (151)

Following the construction of 1,4:3,6-dianhydro-D-glucitol derived auxiliary **(147)** it was necessary to functionalise the molecule as a precursor for participation in asymmetric transformations.
This was effected by following the protocol established previously, namely by employing Grignard reagent methylmagnesium bromide, Scheme 76.



Scheme 76

In this procedure the auxiliary **(147)** was added to an ice-cold *in situ* prepared solution of methylmagnesium bromide to generate the anionic species **(150)**. Upon cooling to -78°C, freshly distilled propionyl chloride was added to furnish the saturated carboximide **(151)** in a near quantitative yield.

EXPERIMENTAL

Symbols and Abbreviations

Å	*Angstroms* (10^{-10}m)
Ar	*aromatic*
[α]	*specific rotation*
bp	*boiling point*
br	*broad*
δ	*chemical shift*
DEAC	*diethylaluminium chloride*
DEPT	*distortionless enhancement by polarisation transfer*
DMAP	*4-dimethylaminopyridine*
DCC	*dicyclohexylcarbodiimide*
DMF	*dimethylformamide*
d	*doublet*
ei	*electron impact*
eq	*equivalents*
FAB	*fast atom bombardment*
FVP	*flash vacuum pyrolysis*
HPLC	*high performance liquid chromatography*
IR	*infra red*
J	*spin-spin coupling constant*
lit.	*literature value*
m	*multiplet*
M	*moles per litre*
M^+	*molecular ion*
mmol	*millimoles*

mol	*moles*
Mp	*melting point*
MS	*mass spectroscopy*
m/z	*mass to charge ratio*
NMR	*nuclear magnetic resonance*
ppm	*parts per million*
quat	*quaternary*
s	*singlet*
t	*triplet*
TBAB	*tetrabutylammonium bromide*
***t*-BDPSiCl**	*tert-butyldiphenylsilylchloride*
TCE	*1,1,2,2-tetrachloroethane*
THF	*tetrahydrofuran*
TLC	*thin layer chromatography*
TMS	*tetramethylsilane*
U.V.	*ultra-violet*
ν_{max}	*wave numbers at which absorbance is maximal*

1 Instrumentation and General Techniques

1 (a) NMR Spectroscopy

^{1}H NMR

Routine ^{1}H NMR spectra were obtained using a Joel PMX-60 spectrometer. High field spectra were obtained on a Bruker WP-200 spectrometer operating at 200.13 MHz and operated by Mr. J. Millar or Miss. H. Grant. Further high field spectra were obtained on a WH-360 spectrometer operating at 360.13 MHz and operated by Dr. D. Reed or Dr. I. Sadler.

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

^{13}C NMR

^{13}C NMR spectra were obtained on a WP-200 spectrometer operating at 50.32 MHz and operated by Mr. J. Miller or Miss H. Grant. Spectra for carbon-13 nuclei were also recorded at 90.56 MHz on a WH-360 spectrometer operated by Dr. D. Reed or Dr. I. Sadler.

Chemical shifts (δ) are reported in parts per million using TMS (δ 0.0) as a reference. DEPT ($\pi/2$ and $3\pi/4$) were used to interpret and assign signals.

1(b) Infra-red Spectroscopy

Infra-red spectra were recorded on a Perkin-Elmer 781 spectrometer. Liquid samples were examined as thin films and solid samples as nujol mulls, both on sodium chloride plates. Calibration was achieved by reference to the characteristic polystyrene peak at 1603 cm^{-1}.

1(c) **Mass Spectroscopy**

Low resolution mass spectra were recorded on a 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(d) **X-Ray Crystallography**

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

1(e) **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(f) **HPLC**

HPLC analyses of diastereomeric mixtures were conducted on a Gilson HPLC apparatus using a 5 μm spherisorb silica column and U.V. detection at 254 nm.

1(g) **Optical Rotations**

Optical rotations were measured on an Optical Activity AA 1000 polarimeter; readings were taken at 589 nm (sodium D-line) using a 10 cm polarimeter cell.

1(h) 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(i) 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 charring using a 10% sulphuric acid/ethanol solution.

1(j) Drying and Purification of Solvents

Toluene and DMF were dried by the addition of sodium wire to the analytical grade reagents. Methylene chloride and TCE were dried by distilling from calcium hydride under a nitrogen atmosphere. 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(k) Drying of Glassware and Inert Gases

Before conducting moisture sensitive reactions, reaction flasks were dried thoroughly either by leaving in oven overnight or by heating with a strong Bunsen flame whilst flushing and subsequently cooling with a strong pulse of argon.

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

2 Preparation and Functionalisation of Chiral Auxiliary (77)

2.1 Preparation of chiral auxiliary (77)

2.1.1 Preparation of *2,3:4,5-di-O-isopropylidene-D-fructopyranose* (73)

In accordance with the method described by Brady[52] D-fructose (36.0g, 0.20mol) was added in *ca* 6g proportions at regular intervals over 15 minutes to a stirring solution of acetone (700ml) and concentrated sulphuric acid (35ml) at 0 °C under a flushing inert argon atmosphere. The contents were allowed to warm with stirring to room temperature then vigorously stirred for a further 90 minutes. The solution was subsequently re-cooled to 0 °C before gradually adding an ice-cold solution of sodium hydroxide (110g, 2.75mol) in water (500ml). Following filtration of the reaction mixture, the acetone solvent was removed from the filtrate by *in vacuo* evaporation at the pump. The resultant pale yellow liquid layer was extracted into dichloromethane (3 x 100ml) and the combined organic extracts were then washed with water (100ml), dried ($MgSO_4$) and evaporated to yield a yellow crystalline solid which after recrystallisation from a diethyl ether (5ml/g) : n-pentane (5ml/g) mixture provided the target product as a colourless crystalline solid (46.8g, 90%).

Mp = 92 °C; **^{1}H NMR** (200.13MHz,$CDCl_3$) δ 4.57 (1H, dd, *J*=7.9, 2.6 Hz, C<u>H</u>), 4.30 (1H, d, *J*=2.6 Hz, C<u>H</u>), 4.19 (1H, ddd, *J*=7.9, 1.9, 1.1 Hz, C<u>H</u>), 3.87 (1H, dd, *J*=13.0, 1.1 Hz, C<u>H</u>), 3.71 (1H, dd, *J*=13.0, 1.1 Hz, C<u>H</u>), 3.63 (2H, s, C<u>H</u>$_2$), 2.60 (1H, broad s, O<u>H</u>), 1.50 (3H, s, C<u>H</u>$_3$), 1.43 (3H, s, C<u>H</u>$_3$), 1.35 (3H, s, C<u>H</u>$_3$), 1.30 (3H, s, C<u>H</u>$_3$) ppm; **^{13}C NMR** (50.3MHz,$CDCl_3$) δ 108.86 (quat C), 108.33 (quat C), 102.87 (quat C), 70.72 (CH), 70.58 (CH), 69.83 (CH), 65.21 (CH_2), 61.03 (CH_2), 26.26 (CH_3), 25.56 (CH_3), 25.14 (CH_3), 23.76 (CH_3) ppm; **IR** (thin film) ν_{max} 3290 (OH) cm^{-1}; **Accurate mass** (FAB), Found: 261.13381, ($C_{12}H_{21}O_6$) (M+H), Requires: 261.13382.

2.1.2 Preparation of *2,3:4,5-di-O-isopropylidene-D-fructopyranose-1-O-chloroformate* (74)

A solution of *2,3:4,5-di-O-isopropylidene-D-fructopyranose* **(73)** (28.0g, 0.108mol) and pyridine (9.30g, 0.117mol, 1.1eq) in dry diethyl ether (280ml) was added dropwise over 30 minutes to a rapidly stirred solution of phosgene (264ml, 20%w/v in toluene, 0.333mol, 3eq) under argon at 0 °C. Upon warming to ambient temperature the solution was stirred overnight then filtered. The resultant precipitate was washed thoroughly with dry ether and the combined filtrate and washings were evaporated to yield *2,3:4,5-di-O-isopropylidene-D-fructopyranose-1-O-chloroformate* as a yellow viscous oil (34.73g, 100%). **Note!** chloroformate hydrolyses readily and should therefore be used immediately for next stage.

^{1}H NMR (200.13MHz,$CDCl_3$) δ 4.60 (1H, dd, *J*=7.8, 2.7 Hz, C<u>H</u>), 4.56 (1H, d, *J*=11.2 Hz, C<u>H</u>), 4.31 (1H, d, *J*=2.7 Hz, C<u>H</u>), 4.21 (1H, dd, *J*=7.8, 1.8 Hz, C<u>H</u>), 4.19 (1H, d, *J*=11.2 Hz, C<u>H</u>), 3.89 (1H, dd, *J*=13.0, 1.8 Hz, C<u>H</u>), 3.74 (1H, d, *J*=13.0 Hz, C<u>H</u>), 1.53 (3H, s, C<u>H</u>$_3$), 1.45 (3H, s, C<u>H</u>$_3$), 1.40 (3H, s, C<u>H</u>$_3$), 1.32 (3H, s, C<u>H</u>$_3$) ppm; **^{13}C NMR** (50.3MHz,$CDCl_3$) δ 150.05 (C=O), 109.08 (quat C), 108.93 (quat C), 100.38 (quat C), 70.34 (CH), 70.30 (CH), 70.03 (CH), 69.60 (CH_2), 61.16 (CH_2), 26.23 (CH_3), 25.61 (CH_3), 24.80 (CH_3), 23.75 (CH_3) ppm; **IR** (thin film) ν_{max} 1780 (C=O) cm^{-1}; **MS** (ei) m/z 44 (base), 60 (62%), 113 (20%), 307 (48%, ^{35}Cl $(M-15)^+$), 309 (16%, ^{37}Cl $(M-15)^+$), 322 (96%, ^{35}Cl, M^+), 324 (32%, ^{37}Cl, M^+); **Accurate mass** (FAB), Found: 323.08973, ($C_{13}H_{20}{}^{35}ClO_7$) (M+H), Requires: 323.08974.

2.1.3 Preparation of *2,3:4,5-di-O-isopropylidene-D-fructopyranose-1-O-azidoformate* (75)

A solution of sodium azide (14.13g, 0.217mol) and tetrabutylammonium bromide, TBAB, (3g) in distilled water (500ml) was added in one aliquot to a rapidly stirred solution of *2,3:4,5-di-O-isopropylidene-D-fructopyranose-1-O-chloroformate* (74) (34.73g, 0.108mol) in dichloromethane (500ml). The reaction mixture was stirred vigorously for 4 hours, separated and the aqueous layer then extracted with dichloromethane (3 x 100ml). The combined organic layers were washed with water (100ml), dried with powdered $MgSO_4$, filtered and evaporated *in vacuo* to yield a brown viscous oil. The crude mixture was extracted with hot hexane to yield a brown viscous residue (*2,3:4,5-di-O-isopropylidene-D-fructopyranose-1-O-azidoformate*) (33.66g, 95%).

^{1}H NMR (200.13MHz, $CDCl_3$) δ 4.52 (1H, dd, *J*=7.9, 2.6 Hz, C<u>H</u>), 4.40 (1H, d, *J*=11.5 Hz, C<u>H</u>), 4.22 (1H, d, *J*=2.6 Hz, C<u>H</u>), 4.15 (1H, ddd, *J*=7.9, 1.8, 0.8 Hz, C<u>H</u>), 4.05 (1H, d, *J*=11.5 Hz, C<u>H</u>), 3.80 (1H, dd, *J*=13.0, 1.8 Hz, C<u>H</u>), 3.65 (1H, dd, *J*=13.0, 0.8 Hz, C<u>H</u>), 1.44 (3H, s, C<u>H</u>$_3$), 1.38 (3H, s, C<u>H</u>$_3$), 1.29 (3H, s, C<u>H</u>$_3$), 1.24 (3H, s, C<u>H</u>$_3$) ppm; **^{13}C NMR** (50.3MHz,$CDCl_3$) δ 157.03 (C=O), 108.80 (quat C), 108.70 (quat C), 100.70 (quat C), 70.34 (CH), 70.07 (CH), 69.92 (CH), 67.71 (CH_2), 60.99 (CH_2), 26.14 (CH_3), 25.49 (CH_3), 24.74 (CH_3), 23.70 (CH_3) ppm; **IR** (thin film) ν_{max} 2160 (N_3), 1740 (C=O) cm^{-1}; **MS** (ei) m/z 44 (base), 60 (70%), 70 (52%), 85 (36%), 113 (42%), 314 (79%, $(M-15)^+$), 330 (20%, M^+); **Accurate mass** (FAB), Found: 330.13012, ($C_{13}H_{20}N_3O_7$) (M+H), Requires: 330.13013.

2.1.4 Preparation of *(5S,10S)-4-aza-6,7:5,10-di-O-isopropylidene-2,9-dioxabicyclo-[4,4,0^{5,10}]-decan-3-one* (77) by solution thermolysis

(a) Using a 2% solution

A solution of *2,3:4,5-di-O-isopropylidene-D-fructopyranose-1-O-azidoformate* **(75)** (33.66g, 0.102mol) in dry *1,1,2,2*-tetrachloroethane, TCE, (100ml) was added dropwise *via* syringe pump over 20 minutes onto boiling dry 1,1,2,2-tetrachloroethane (bp=147°C) (1500ml) under a flushing argon atmosphere. Upon complete addition the contents were heated under reflux for a further 60 minutes at which point TLC analysis indicated all start material had been consumed. The solution was allowed to cool then removed of the reaction solvent by evaporation *in vacuo* (fume cupboard) to yield a thick viscous brown oil. The crude material was subjected to flash column chromatography using gradient elution (100% hexane to 100% ether) to yield after recrystallisation from ethyl acetate (5ml/g) the desired product *(5S,10S)-4-aza-6,7:5,10-di-O-isopropylidene-2,9-dioxabicyclo-[4,4,0^{5,10}]-decan-3-one* **(77)** as a colourless highly crystalline solid (16.9g, 55%).

Mp = 219°C; $[\alpha]_D^{26}$ = +57.1° (c=5.00, CH_2Cl_2); $_1$**H NMR** (200.13MHz,$CDCl_3$) δ 7.51 (1H, br s, NH), 4.46 (1H, d, *J*=7.9 Hz, CH), 4.25 (1H, dd, *J*=7.9, 1.8 Hz, CH), 4.18 (1H, d, *J*=11.7 Hz, CH), 4.16 (1H, d, *J*=11.7 Hz, CH), 3.92 (1H, dd, *J*=13.1, 1.8 Hz, CH), 3.75 (1H, d, *J*=13.1 Hz, CH), 1.44 (3H, s, CH_3), 1.38 (3H, s, CH_3), 1.29 (3H, s, CH_3), 1.25 (3H, s, CH_3) ppm; ^{13}**C NMR** (50.3MHz,$CDCl_3$) δ 153.87 (C=O), 111.12 (quat C), 109.46 (quat C), 98.16 (quat C), 85.68 (quat C), 71.84 (CH), 71.04 (CH), 67.83 (CH_2), 62.41 (CH_2), 28.25 (CH_3), 27.48 (CH_3), 25.86 (CH_3), 24.31 (CH_3) ppm; **IR** (thin film) ν_{max} 3300 (N-H), 1680 (C=O) cm^{-1}; **MS** (ei) m/z 32 (80%), 44 (base), 60 (90%), 186 (56%), 201 (95%), 244 (50%), 286 (61%, $(M\text{-}15)^+$), 302 (20%, M^+); **Accurate mass** (FAB), Found: 302.12395, ($C_{13}H_{20}NO_7$) (M+H), Requires: 302.12396;

X-ray (for X-ray structure and full crystal data see appendix A).

(b) Using a 10% solution

A solution of azidoformate (33.25g, 101.1mmol) in TCE (100ml) was added dropwise to boiling TCE (250ml) under an argon blanket over one hour. The solution was stirred at this temperature (>147°C) for a further 45 minutes after which it was allowed to cool and the reaction solvents removed *in vacuo* to yield a brown oily residue. The oil was taken up in hot ethyl acetate (50ml) then cooled and left over the weekend to yield a colourless crystalline solid. The remaining mother liquor was concentrated and cleaned up by flash chromatography then stood for a week to yield a second crop of crystals, (combined yields 9.7g, 32%). Spectroscopic analysis by ^{1}H and ^{13}C NMR confirmed the product as auxiliary **(77)**.

2.2 Functionalisation of Chiral Auxiliary (77)

2.2.1 Preparation of *N-propionyl-4-aza-6,7:5,10-di-O-isopropylidene-2,9-dioxabicyclo-[4,4,0^{5,10}]-decan-3-one* (80)

(a) *via* Grignard reagent (methylmagnesium bromide)

An ice-cold solution of auxiliary (77) (6g, 0.020mol) in dry tetrahydrofuran (60ml) was added over 10 minutes to a prepared solution* of magnesium turnings (0.67g, 0.028mol, 1.4eq) and bromomethane (1.6M, 25ml) in dry diethyl ether under argon. The reaction temperature was maintained at 0°C and the mixture stirred for 15 minutes before cooling to -78°C at which time a pre-cooled (-78°C) solution of freshly distilled propionyl chloride (2.6g, 0.028mol) in dry tetrahydrofuran (30ml) was added in small portions *via* syringe. Stirring was continued for 60 minutes then quenched by adding a saturated solution of aqueous ammonium chloride (50ml). After stirring vigorously for 10 minutes the reaction solvent was removed at the pump and the product extracted into dichloromethane (3 x 40ml). The combined organic extracts were washed with water (40ml), dried (powdered $MgSO_4$), filtered under gravity and evaporated to yield a pale yellow solid. The crude material was subjected to flash chromatography using gradient elution to return a colourless crystalline solid (6.87g, 97%).

*<u>Note</u> in previous laboratory use of Aldrich methylmagnesium bromide it was found that despite following recommended handling techniques the reagent was chemically inactive after only one use. It was therefore decided to prepare fresh quantities of the Grignard reagent as and when required.

This was effected by the following general procedure. Magnesium turnings were added to a reaction vessel and immersed under dry diethyl ether in an argon atmosphere. Following the addition of a few drops of

iodomethane (initiator) the contents were cooled to 10-15 °C whereupon bromomethane solution in dry diethyl ether (one small portion *via* syringe) was added. Hand warming of the reaction vessel and gentle agitation by tapping helps to start the reaction which is indicated by the production of bubbles. When underway the reaction is sustained by adding the remaining bromomethane in small portions until completion which is signified by cessation of bubble production. Excess halide was driven off from the reaction mixture **(fume cupboard!)** by heating the reaction vessel in warm water then the resulting solution was cooled to 0 °C in preparation for the addition of the auxiliary.

Mp = 130-131 °C; $[\alpha]_D^{24}$ = -16.6° (c=3.70, CH_2Cl_2); **^{1}H NMR** (200.13MHz, $CDCl_3$) δ 5.11 (1H, d, *J*=8.1 Hz, C<u>H</u>), 4.28 (1H, ddd, *J*=8.1, 1.8, 1.0 Hz, C<u>H</u>), 4.25 (1H, d, *J*=11.6 Hz, C<u>H</u>), 4.18 (1H, d, *J*=11.6 Hz, C<u>H</u>), 3.87 (1H, dd, *J*=13.2, 1.8 Hz, C<u>H</u>), 3.79 (1H, dd, *J*=13.2, 1.0 Hz, C<u>H</u>), 2.73 (2H, q, *J*=7.5 Hz, C<u>H</u>$_2$), 1.57 (3H, s, C<u>H</u>$_3$), 1.44 (3H, s, C<u>H</u>$_3$), 1.41 (3H, s, C<u>H</u>$_3$), 1.27 (3H, s, C<u>H</u>$_3$), 1.16 (3H, t, *J*=7.5 Hz, C<u>H</u>$_3$) ppm; **^{13}C NMR** (50.3MHz,$CDCl_3$) δ 179.09 (C=O), 152.29 (C=O), 111.88 (quat C), 109.11 (quat C), 101.04 (quat C), 89.82 (quat C), 70.54 (CH), 70.30 (CH), 68.41 (CH_2), 61.15 (CH_2), 32.52 (CH_2), 27.74 (CH_3), 27.30 (CH_3), 25.61 (CH_3), 23.94 (CH_3), 9.63 (CH_3) ppm; **IR** (thin film) ν_{max} 1760 (C=O), 1720 (C=O) cm^{-1}; **MS** (ei) m/z 31 (32%), 43 (76%), 57 (base), 244 (38%), 302 (95%), 342 (80%, $(M-15)^+$), 358 (75%, M^+) 414 (40%); **Accurate mass** (FAB), Found: 358.15019, ($C_{16}H_{24}NO_8$) (M+H), Requires: 358.15018.

(b) Attempted preparation of propionate (80) *via* sodium hydride

Sodium hydride* (0.05g) was added to an oven dried flask flushing with argon, (*present as an 80% dispersion in mineral oil). Dry diethyl ether was added (3 x 5ml portions) and the contents stirred for 5 minutes before decanting after each addition. The flask and its contents were cooled to 0 °C then an ice-cold solution of auxiliary (77) (0.5g, 1.66mmol) in dry THF (20ml) was added to the reaction vessel. The resulting solution was stirred for one hour before adding freshly distilled propionyl chloride (0.31g, 3.32mmol, 2.0eq) in dry diethyl ether and stirring at 0 °C for 15 minutes. The ice-bath was removed and the flask then allowed to warm to room temperature whereupon reaction progress was monitored at frequent intervals *via* TLC samples. Analysis by TLC indicated that the consumption of start material in the reaction had reached its maximum after 30 minutes. The mixture was diluted with ether (30ml) before quenching the reaction with aqueous ammonium chloride.

Following removal of reaction solvents by rotary evaporation at the pump, the aqueous layer was separated and extracted with dichloromethane (3 x 30ml). The organic extracts were combined then washed with aqueous sodium bicarbonate, dried with magnesium sulphate, filtered and evaporated to yield a yellow oil which following flash chromatography returned the target material as a colourless crystalline product in a 36% yield.

(c) Attempted preparation of propionate (80) *via* butyllithium

A solution of auxiliary (77) (1g, 3.32mmol) in dry THF (20ml) was added to an oven dried flask under a blanket of argon. Upon cooling to -78°C n-butyllithium (2.3ml, 1.6M, 3.65mmol, 1.1eq) was added dropwise *via* syringe. The solution was stirred for 30 minutes then freshly distilled propionyl chloride (0.62g, 6.64mmol, 2.0eq) in dry THF (5ml) was added dropwise *via* syringe over 5 minutes. After allowing to warm to room temperature the reaction mixture was stirred for 60 minutes with TLC sampling of reaction progress being conducted at 5 minute intervals. Excess acid chloride was hydrolysed by the addition of aqueous sodium carbonate solution and stirring vigorously. The THF reaction solvent was removed *in vacuo* then the mixture was extracted into diethyl ether (3 x 50ml). The combined organic extracts were washed with water (40ml), dried with powdered magnesium sulphate, filtered and then evaporated to yield a pale yellow oil. The oil was wet loaded onto a chromatographic column and passed down *via* an elution gradient to return a colourless and highly crystalline target product in a yield of 22%.

2.2.2 Preparation of α,β unsaturated carboximide dienophiles (102-104)

(a) Preparation of *N-acryloyl-4-aza-6,7:5,10-di-O-isopropylidene-2,9-dioxabicyclo-[4,4,0^{5,10}]-decan-3-one* (102)

An ice-cold solution of auxiliary (77) (1g, 3.32mmol) in dry THF (20ml) was added over 10 minutes to a prepared solution* of magnesium turnings (0.095g, 4.0mmol) and bromomethane (1.6M, 10ml) in dry diethyl ether under argon. The reaction temperature was maintained at 0 °C and the mixture stirred for 15 minutes before cooling to -78 °C at which time a pre-cooled (-78 °C) solution of freshly distilled acryloyl chloride (0.6g, 6.63mmol, 2.0eq) in dry tetrahydrofuran (30ml) was added in small portions *via* syringe. Stirring was continued for 60 minutes then quenched by adding a saturated solution of aqueous ammonium chloride (20ml). After stirring vigorously for 10 minutes the reaction solvent was removed at the pump and the product extracted into dichloromethane (3 x 30ml). The combined organic extracts were washed with water (30ml), dried (powdered $MgSO_4$), filtered under gravity and evaporated to yield a pale yellow solid. The crude material was subjected to flash chromatography using gradient elution of hexane (1) : ether (2) (500ml) to pure ether (500ml) to return a colourless crystalline solid (0.26g, 22%). All unreacted starting material of chiral auxiliary (77) recovered intact.
[*For method of preparation see part 2.2.1 (a) above].

^{1}H NMR (360.13MHz,$CDCl_3$) δ 6.44 (1H, dd, *J*=16.9, 9.7 Hz, C<u>H</u>), 6.34 (1H, dd, *J*=16.9, 1.8 Hz, C<u>H</u>), 5.70 (1H, dd, *J*=9.7, 1.8 Hz, C<u>H</u>), 5.11 (1H, d, *J*=8.1 Hz, C<u>H</u>), 4.26 (1H, dd, *J*=8.1, 1.8 Hz, C<u>H</u>), 4.24 (1H, d, *J*=11.7 Hz, C<u>H</u>), 4.18 (1H, d, *J*=11.7 Hz, C<u>H</u>), 3.82 (1H, dd, *J*=13.2, 1.8 Hz, C<u>H</u>), 3.76 (1H, d, *J*=13.2, Hz, C<u>H</u>), 1.56 (3H, s, C<u>H</u>$_3$), 1.42 (3H, s, C<u>H</u>$_3$), 1.39 (3H, s, C<u>H</u>$_3$), 1.24 (3H, s, C<u>H</u>$_3$) ppm;

^{13}C NMR (50.3MHz,$CDCl_3$) δ 168.74 (C=O), 152.23 (C=O), 131.20 (CH), 129.28 (CH_2), 112.10 (quat C), 109.35 (quat C), 101.28 (quat C), 89.97 (quat C), 70.79 (CH), 70.34 (CH), 68.92 (CH_2), 61.27 (CH_2), 27.66 (CH_3), 27.31 (CH_3), 25.60 (CH_3), 24.02 (CH_3) ppm; **MS** (ei) m/z 43 (36%), 55 (base), 103 (33%), 340 (28%, $(M-15)^+$), 356 (32%, M^+); **Accurate mass** (FAB), Found: 356.13452, ($C_{16}H_{22}NO_8$) (M+H), Requires: 356.13453;

X-ray (for X-ray structure and full crystal data see appendix C).

(b) Preparation of *N-crotonyl-4-aza-6,7:5,10-di-O-isopropylidene-2,9-dioxabicyclo-[4,4,$0^{5,10}$]-decan-3-one* (103)

An ice-cold solution of auxiliary **(77)** (0.3g, 1.00mmol) in dry THF (10ml) was added over 10 minutes to a prepared solution* of methylmagnesium bromide (4eq) in dry diethyl ether under argon. The reaction temperature was maintained at 0°C and the mixture stirred for 15 minutes before cooling to -78°C whereupon a pre-cooled (-78°C) solution of freshly distilled crotonyl chloride (0.13g, 1.24mmol, 1.3eq) in dry tetrahydrofuran (30ml) was added in small portions *via* syringe. Stirring was continued for 60 minutes then quenched by adding a saturated solution of aqueous ammonium chloride (20ml). Following removal of THF reaction solvent at the pump the crude mixture was extracted into diethyl ether (3 x 30ml). The extracts were combined, washed with water, dried with $MgSO_4$, filtered and evaporated to yield a fine oil which crystallised on standing. Subsequent recrystallisation from hexane/methylene chloride furnished a colourless highly crystalline product which was identified to be the target material of crotonate **(103)**.

[*For method of preparation see part 2.2.1 (a) above].

^1H NMR (360.13MHz,$CDCl_3$) δ 7.00 (1H, dq, *J*=15.1, 7.0 Hz, CH=C<u>H</u>), 6.20 (1H, d, *J*=15.1 Hz, CH=C<u>H</u>), 5.11 (1H, d, *J*=8.1 Hz, C<u>H</u>), 4.27 (1H, d, *J*=11.7

Hz, C<u>H</u>), 4.26 (1H, dd, *J*=8.1, 1.3 Hz, C<u>H</u>), 4.19 (1H, d, *J*=11.7 Hz, C<u>H</u>), 3.85 (1H, dd, *J*=13.2, 1.9 Hz, C<u>H</u>), 3.79 (1H, d, *J*=13.2, Hz, C<u>H</u>), 1.87 (3H, d, *J*=7.0 Hz, C<u>H</u>$_3$), 1.56 (3H, s, C<u>H</u>$_3$), 1.43 (3H, s, C<u>H</u>$_3$), 1.40 (3H, s, C<u>H</u>$_3$), 1.25 (3H, s, C<u>H</u>$_3$) ppm; **^{13}C NMR** (50.3MHz,$CDCl_3$) δ 168.49 (C=O), 152.27 (C=O), 144.03 (CH), 126.00 (CH), 111.80 (quat C), 109.16 (quat C), 101.48 (quat C), 89.80 (quat C), 71.03 (CH), 70.27 (CH), 68.90 (CH_2), 61.19 (CH_2), 27.49 (CH_3), 27.15 (CH_3), 25.49 (CH_3), 23.99 (CH_3), 17.89 (CH_3) ppm; **Accurate mass** (FAB), Found: 370.15023, ($C_{17}H_{24}NO_8$) (M+H), Requires: 370.15018.

(c) **Preparation of *N-cinnamoyl-4-aza-6,7:5,10-di-O-isopropylidene-2,9-dioxabicyclo-[4,4,0^{5,10}]-decan-3-one* (104)**

An ice-cold solution of auxiliary **(77)** (1.0g, 3.32mmol) in dry THF (30ml) was added over 10 minutes to a prepared solution* of methylmagnesium bromide (2eq) in dry diethyl ether under argon. The reaction temperature was maintained at 0°C and the mixture stirred for 30 minutes before lowering to -78°C whereupon a pre-cooled (-78°C) solution of freshly distilled cinnamoyl chloride (0.9g, 5.41mmol, 1.6eq) in dry THF (30ml) was added dropwise *via* syringe. Stirring was continued for 60 minutes then the reaction mixture was allowed to warm to room temperature and stirred overnight after which time the solution was quenched by adding a saturated solution of aqueous ammonium chloride (40ml). Following removal of THF reaction solvent at the pump the crude mixture was extracted into diethyl ether (3 x 40ml). The extracts were combined, washed with water, dried with $MgSO_4$, filtered and evaporated to yield a deep yellow oil. The crude product was refined by flash chromatography using a gradient elution ratio of hexane/ether (2:1, 1000ml) to (1:2, 500ml) to provide the cinnamate **(104)** as a colourless solid (1.3g, 90%).

[*For method of preparation see part 2.2.1 (a) above].

^{1}H NMR (360.13MHz,$CDCl_3$) δ 7.73 (1H, d, *J*=15.6 Hz, CH=C<u>H</u>), 7.54 (5H, m, Ph), 6.83 (1H, d, *J*=15.6 Hz, C<u>H</u>), 5.25 (1H, d, *J*=8.1 Hz, C<u>H</u>), 4.32 (1H, d, *J*=11.7 Hz, C<u>H</u>), 4.30 (1H, dd, *J*=8.1, 1.3 Hz, C<u>H</u>), 4.29 (1H, d, *J*=11.7 Hz, C<u>H</u>), 3.91 (1H, dd, *J*=13.2, 1.9 Hz, C<u>H</u>), 3.84 (1H, d, *J*=13.2, Hz, C<u>H</u>), 1.61 (3H, s, C<u>H</u>$_3$), 1.49 (3H, s, C<u>H</u>$_3$), 1.43 (3H, s, C<u>H</u>$_3$), 1.28 (3H, s, C<u>H</u>$_3$) ppm; **^{13}C NMR** (50.3MHz,$CDCl_3$) δ 168.74 (C=O), 152.33 (C=O), 143.78 (CH), 134.09 (quat C), 130.18 (CH), 128.52 (2xCH), 128.17 (2xCH), 121.29 (CH), 111.78 (quat C), 111.78 (quat C), 101.40 (quat C), 89.88 (quat C), 70.97 (CH), 70.19 (CH), 68.86 (CH_2), 61.09 (CH_2), 27.46 (CH_3), 27.09 (CH_3), 25.43 (CH_3), 23.89 (CH_3) ppm; **MS** (ei) m/z 43 (40%), 131 (base), 302 (60%), 374 (42%), 416 (64%, $(M-15)^+$), 432 (92%, M^+); **Accurate mass** (FAB), Found: 432.16585, ($C_{22}H_{26}NO_8$) (M+H), Requires: 432.16583.

3 Asymmetric applications involving N-propionyl functionalised auxiliary (80)

3.1 Asymmetric Aldol reactions *via* enolate-mediated systems

3.1A Aldol reactions *via* lithium enolates

3.1A (a) using benzaldehyde

To an ice-cold solution of diisopropylamine (0.93g, 1.1eq) in dry THF (15ml) was added butyllithium (6ml, 1.6M, 1.1eq) dropwise *via* syringe. After leaving the contents to stir for 20 minutes, the solution was cooled to -78°C whereupon a pre-cooled solution (-78°C) of the propionate **(80)** (3g, 8.4mmol) in dry THF (25ml) was added. The mixture was left to stir for 60 minutes then freshly distilled benzaldehyde (1g, 1.1eq) in dry THF (10ml) was added. After allowing stirring for 20 minutes the reaction mixture was quenched with a saturated aqueous ammonium chloride solution (15ml) then warmed to room temperature before removing the reaction solvent at the pump. Separation of the two layer mixture was followed by extraction with dichloromethane (3 x 40ml). The organic layer and extracts were combined, washed with water (40ml), dried with powdered magnesium sulphate, filtered and evaporated to yield the benzaldehyde product **(85)** as a pale yellow foam (3.3g, 85%).

Examination of the 360 MHz ^{1}H NMR spectrum revealed the presence of two diastereomers (both *erythro*) in the ratio of 8:1. The stereochemical assignment of the two diastereomers was determined from the coupling constant values obtained for the appropriate doublets of the PhC<u>H</u>OH and $CH_3C\underline{H}C{=}O$ vicinal protons (values were approximately 3.2 Hz).

From a single crystallisation (methylene chloride/hexane) the major diastereomer was isolated from which full spectroscopic data was obtained and is given below.

$[\alpha]_D^{25}$ = -18.2° (c=2.65, CH_2Cl_2); **^{1}H NMR** (360.13MHz,$CDCl_3$) δ 7.42-7.22 (5H, m, Ph), 5.26 (1H, d, *J*=8.1 Hz, C<u>H</u>), 4.37 (1H, dd, *J*=8.1, 1.2 Hz, C<u>H</u>), 4.28 (2H, s, 2xC<u>H</u>), 4.12 (1H, d, *J*=1.7 Hz, C<u>H</u>), 3.93 (1H, dd, *J*=13.3, 2.0 Hz, C<u>H</u>), 3.86 (1H, d, *J*=13.3 Hz, C<u>H</u>), 3.62 (1H, dq, *J*=6.9, 1.7 Hz, C<u>H</u>), 1.63 (3H, s, C<u>H</u>$_3$), 1.50 (3H, s, C<u>H</u>$_3$), 1.48 (3H, s, C<u>H</u>$_3$), 1.35 (3H, s, C<u>H</u>$_3$), 1.01 (3H, d, *J*=6.9 Hz, C<u>H</u>$_3$) ppm; **^{13}C NMR** (50.3MHz,$CDCl_3$) δ 181.35 (C=O), 152.10 (C=O), 141.07 (quat C), 127.71 (Phenyl CH), 126.69 (Phenyl CH), 125.33 (Phenyl CH), 112.02 (quat C), 109.29 (quat C), 100.79 (quat C), 90.25 (quat C), 72.14 (CH), 70.27 (CH), 70.25 (CH), 67.89 (CH_2), 60.89 (CH_2), 49.12 (CH), 27.87 (CH_3), 27.10 (CH_3), 25.38 (CH_3), 23.78 (CH_3), 8.57 (CH_3) ppm; **IR** (thin film) ν_{max} 3540 (OH), 1770 (C=O), 1720 (C=O) cm^{-1}; **MS** (ei) m/z 44 (64%), 58 (70%), 145 (base), 244 (44%), 286 (40%), 302 (86%); **Accurate mass** (FAB), Found: 464.19202, ($C_{23}H_{30}NO_9$) (M+H), Requires: 464.19203;

X-ray (for X-ray structure and full crystal data see appendix D).

3.1A (b) using isobutyraldehyde

Butyllithium (2.9ml, 1.6M, 1.1eq) was added dropwise *via* syringe to an ice-cold solution of diisopropylamine (0.47g, 1.1eq) in dry THF (15ml). Upon leaving the contents to stir for 20 minutes, the solution was cooled to -78°C at which time a pre-cooled solution (-78°C) of the propionate **(80)** (1.5g, 4.2mmol) in dry THF (20ml) was added. The mixture was left to stir for 60 minutes then freshly distilled isobutyraldehyde (1g, 1.1eq) in dry THF (10ml) was added. Stirring was continued for 20 minutes before quenching the reaction mixture with a saturated solution of aqueous ammonium chloride (15ml) at which time the reaction vessel was allowed to warm to room temperature. After removal of the reaction solvent at the pump, the two layer mixture was separated and the aqueous layer then extracted with methylene chloride (3 x 30ml).

The organic layer and extracts were combined, washed with water (30ml), dried with powdered magnesium sulphate, filtered and evaporated to yield the isobutyraldehyde product as a yellow/green viscous oil. Subsequent redissolution in dichloromethane (25ml) followed by high vacuum evaporation at the pump furnished the product as a white foam (1.71g, 95%).

^{1}H NMR (360.13MHz,$CDCl_3$) δ 5.12 (1H, d, *J*=8.1 Hz, C<u>H</u>), 4.27 (1H, dd, *J*=8.1, 1.4 Hz, C<u>H</u>), 4.15 (2H, s, 2xC<u>H</u>), 4.10 (1H, dd, *J*=6.6, 2.3 Hz, C<u>H</u>), 3.84 (1H, dd, *J*=13.2, 2.0 Hz, C<u>H</u>), 3.75 (1H, d, *J*=13.2 Hz, C<u>H</u>), 3.51 (1H, dq, *J*=6.8, 2.0 Hz, C<u>H</u>), 1.57 (1H, dq, *J*=6.6, 2.3 Hz, C<u>H</u>), 1.53 (3H, s, C<u>H</u>$_3$), 1.39 (3H, s, C<u>H</u>$_3$), 1.37 (3H, s, C<u>H</u>$_3$), 1.24 (3H, s, C<u>H</u>$_3$), 1.07 (3H, d, *J*=6.6 Hz, C<u>H</u>$_3$), 0.93 (3H, d, *J*=6.6 Hz, C<u>H</u>$_3$), 0.75 (3H, d, *J*=6.8 Hz, C<u>H</u>$_3$), ppm; **^{13}C NMR** (50.3MHz,$CDCl_3$) δ 182.04 (C=O), 151.99 (C=O), 112.17 (quat C), 109.31 (quat C), 100.34 (quat C), 90.31 (quat C), 76.90 (CH), 70.53 (CH), 69.81 (CH), 67.33 (CH_2), 61.10 (CH_2), 44.61 (CH), 30.33 (CH), 28.09 (CH_3), 27.33 (CH_3), 25.47 (CH_3), 23.78 (CH_3), 19.64 (CH_3), 18.56 (CH_3), 8.84 (CH_3) ppm;

IR (thin film) ν_{max} 3580 (OH), 1765 (C=O), 1735 (C=O) cm^{-1}; **MS** (ei) m/z 44 (90%), 60 (78%), 111 (74%), 244 (56%), 302 (78%), 342 (60%), 372 (32%), 414 (base, $(M-15)^+$), 430 (85%, M^+).

3.1A (c) using acetaldehyde

Neat butyllithium (1.4ml, 2.0M, 1.2eq) was added dropwise *via* syringe to an ice-cold solution of diisopropylamine (0.22g, 1.1eq) in dry THF (15ml). After leaving the contents to stir for 20 minutes, the solution was cooled to -78°C whereupon a pre-cooled solution (-78°C) of the propionate **(80)** (0.6g, 1.7mmol) in dry THF (20ml) was added. The mixture was left to stir for 60 minutes then freshly distilled acetaldehyde (0.4g, 5.0eq) was taken

up in dry THF (10ml) and added in a single aliquot. After allowing stirring for 40 minutes the reaction mixture was quenched with a saturated aqueous ammonium chloride solution (15ml) then warmed to room temperature before removing the reaction solvent at the pump. Separation of the two layer mixture was followed by extraction of the aqueous layer with dichloromethane (3 x 25ml). The organic layer and extracts were combined, washed with water (25ml), dried with powdered magnesium sulphate, filtered and evaporated to yield the aldol product as a yellow oil. The crude product was taken up in a hexane/methylene chloride (3:1) solution (20ml) which recrystallised upon standing to return the desired product in a yield of 85%.

^{1}H NMR (360.13MHz,$CDCl_3$) δ 5.22 (1H, d, *J*=8.0 Hz, C<u>H</u>), 4.32 (1H, dd, *J*=8.0, 1.9 Hz, C<u>H</u>), 4.21 (2H, s, 2xC<u>H</u>), 4.09 (1H, dq, *J*=6.5, 2.6 Hz, C<u>H</u>), 3.90 (1H, dd, *J*=13.2, 1.9 Hz, C<u>H</u>), 3.81 (1H, d, *J*=13.2 Hz, C<u>H</u>), 3.40 (1H, dq, *J*=6.9, 2.6 Hz, C<u>H</u>), 1.59 (3H, s, C<u>H</u>$_3$), 1.45 (3H, s, C<u>H</u>$_3$), 1.44 (3H, s, C<u>H</u>$_3$), 1.30 (3H, s, C<u>H</u>$_3$), 1.16 (3H, d, *J*=6.9 Hz, C<u>H</u>$_3$), 1.15 (3H, d, *J*=6.5 Hz, C<u>H</u>$_3$) ppm;

^{13}C NMR (50.3MHz,$CDCl_3$) δ 182.31 (C=O), 151.97 (C=O), 111.97 (quat C), 109.14 (quat C), 100.28 (quat C), 90.09 (quat C), 70.31 (CH), 69.55 (CH), 67.90 (CH), 67.11 (CH_2), 60.97 (CH_2), 47.90 (CH), 27.90 (CH_3), 27.10 (CH_3), 25.32 (CH_3), 23.66 (CH_3), 19.07 (CH_3), 10.17 (CH_3) ppm;

IR (thin film) ν_{max} 3520 (OH), 1750 (C=O), 1725 (C=O) cm^{-1};
MS (ei) m/z 43 (base), 57 (78%), 73 (45%), 85 (56%), 201 (40%), 228 (36%), 302 (40%), 386 (20%, $(M-15)^+$), 402 (35%, M^+).

3.1B Attempted aldol reaction *via* boron enolate

To an ice-cold solution of propionate **(80)** (0.5g, 1.4mmol) in dry methylene chloride (10ml) under argon was added dibutylboron triflate (1.5ml, 1.0M, 1.05eq) dropwise *via* syringe. This was succeeded by the addition of diisopropylethylamine (0.24g, 1.3eq) in dry methylene chloride (5ml). The resultant pale yellow mixture was stirred at 0 °C for 60 minutes before lowering to -78 °C and adding dropwise freshly distilled benzaldehyde (0.18g, 1.2eq). The temperature was maintained at -78 °C and the reaction mixture monitored by thin layer chromatography (TLC) over the next 2 hours, however, no hint of reaction progress was indicated. The reaction vessel was warmed to room temperature and stirring was allowed to continue overnight whereupon further TLC examination suggested the presence of start material only. The reaction mixture was then quenched by adding aqueous phosphate buffer solution (pH 7, 10ml) and methanol (15ml). Approximately 15ml of a 2:1 solution of methanol/hydrogen peroxide (30% aqueous) was then added dropwise *via* syringe and the mixture stirred for one hour at which point reaction volatiles were removed by rotary evaporation (@ 40 °C). The resultant slurry was then taken up in diethyl ether (50ml), separated and the aqueous layer extracted with diethyl ether (3 x 40ml). The organic layer and extracts were combined, washed with both sodium bicarbonate solution and brine, then dried with powdered magnesium sulphate, filtered and evaporated. Subsequent analysis by NMR (^{1}H and ^{13}C) confirmed the presence of propionate **(80)** starting material alone.

3.1C Cleavage Experiments on products of Aldol reactions

3.1C (a) Cleavage by hydrolysis using lithium hydroperoxide

3.1C (a) (i) Cleavage of aldol benzaldehyde product (87) to generate α-alkyl, β-hydroxy acid fragment (90)

To an ice-cold solution of the substrate **(87)** (0.90g, 1.94mmol) in tetrahydrofuran/water mixture (40ml, 3:1) was added hydrogen peroxide (1.47ml, 6.0eq, assay 27%) followed by hydrated lithium hydroperoxide (0.17g, 2.0eq). After allowing to warm to ambient temperature and stirring for 60 minutes, the excess peroxide was quenched with sodium sulphite solution (1.5M, 8ml, 1.1eq) and then buffered to pH 9-10 with saturated aqueous sodium bicarbonate. Upon removal of organic volatiles by rotary evaporation and subsequent work-up by separation and extraction from the aqueous layer with dichloromethane (3 x 30ml), the *auxiliary **(77)** was recovered as a white foam in high yield (0.56g, >95%). The aqueous phase was acidified to pH 1-2 by the dropwise addition of concentrated hydrochloric acid, extracted with ethyl acetate (3 x 30ml), then separated, dried ($MgSO_4$), filtered and evaporated to yield the carboxylic acid fragment **(90)** as a thin colourless oil (0.34g, >95%).

Spectral analysis of acid fragment **(90)**: (-)-(2*S*,3*S*)-3-hydroxy-2-methyl-3-phenyl-propanoic acid.

$[\alpha]_D^{25}$ = -28.7° (c=2.15, CH_2Cl_2); ^{1}**H NMR** (360.13MHz,$CDCl_3$) δ 7.30-7.22 (5H, m, Ph), 6.75 (1H, br s, OH), 5.16 (1H, d, *J*=3.9 Hz, PhC<u>H</u>OH), 2.82 (1H, dq, *J*=7.2, 3.9 Hz, CH_3C<u>H</u>), 1.13 (3H, d, *J*=7.2 Hz, C<u>H</u>$_3$) ppm; ^{13}**C NMR** (50.3MHz, $CDCl_3$) δ 180.50 (C=O), 140.93 (quat C), 128.21 (Phenyl CH), 127.50 (Phenyl CH), 125.82 (Phenyl CH), 73.24 (CHOH), 46.01 (CHC=O), 14.99 (CH_3) ppm.
*Analysis by ^{1}H and ^{13}C nuclear magnetic resonance confirmed the identity of the organic matrix as auxiliary **(77)**.

Following the success of the cleavage of fragment **(90)** by hydrolysis from the product of the benzaldehyde aldol reaction **(87)**, a similar protocol was adopted for the fragmentation of the products of the two other aldol reactions carried out involving isobutyraldehyde and acetaldehyde. Full spectral data for the carboxylic acid fragment obtained from each of the reactions is detailed below.

3.1C (a) (ii) Cleavage of aldol isobutyraldehyde product

Cleavage was carried out in accordance with the procedure detailed in part **3.1C (a) (i)** above.

Accordingly, a solution of the isobutyraldehyde aldol substrate (1.10g, 2.56mmol) in THF/H_2O was subjected to cleavage as before and furnished the acid fragment as a thin colourless oil (0.36g, >95%) with complementary high recovery of *auxiliary **(77)**.

*Analysis by ^1H and ^{13}C nuclear magnetic resonance confirmed the identity of the organic matrix as auxiliary **(77)**.

Spectral analysis of fragment: (-)-(*2S,3R*)-3-hydroxy-2,4-dimethyl-pentanoic acid.

$[\alpha]_D^{25}$ = -10.3° (c=1.90, CH_2Cl_2); **^1H NMR** (360.13MHz,$CDCl_3$) δ 7.28 (1H, br s, OH), 3.62 (1H, dd, *J*=8.1, 3.6 Hz, C<u>H</u>OH), 2.66 (1H, dq, *J*=7.1, 3.6 Hz, CH_3C<u>H</u>), 1.68 (1H, dd, *J*=8.1, 6.7 Hz, iPr-C<u>H</u>), 1.15 (3H, d, *J*=7.1 Hz, C<u>H</u>$_3$), 0.98 (3H, d, *J*=6.7 Hz, C<u>H</u>$_3$), 0.85 (3H, d, *J*=6.7 Hz, C<u>H</u>$_3$) ppm; **^{13}C NMR** (50.3MHz,$CDCl_3$) δ 181.12 (C=O), 76.63 (CHOH), 41.45 (CHC=O), 30.29 (iPrCH), 18.69 (iPrCH_3), 18.32 (iPrCH_3), 9.38 (CH_3) ppm; **MS** (ei) m/z 30 (35%), 43 (base), 70 (40%), 73 (35%), 135 (25%), 147 (85%, M^+).

3.1C (a) (iii) Cleavage reaction involving acetaldehyde aldol product

Cleavage was carried out in accordance with the procedure detailed in part **3.1C (a) (i)** above.

Accordingly, a solution of the acetaldehyde aldol adduct (1.38g, 3.44mmol) in THF/H_2O was subjected to cleavage as before and furnished the acid fragment as a thin colourless oil (0.39g, >95%) with complementary high recovery of *auxiliary **(77)**.

*Analysis by ^1H and ^{13}C nuclear magnetic resonance confirmed the identity of the organic matrix as auxiliary **(77)**.

Spectral analysis of acid fragment: (-)-(*2S,3R*)-3-hydroxy-2-methyl-butanoic acid.

$[\alpha]_D^{25}$ = -16.2° (c=2.35, CH_2Cl_2); **^1H NMR** (360.13MHz,$CDCl_3$) δ 7.12 (1H, br s, OH), 4.08 (1H, dq, *J*=6.5, 2.6 Hz, $CH_3C\underline{H}OH$), 3.40 (1H, dq, *J*=6.9, 2.6 Hz, $CH_3C\underline{H}$), 1.15 (3H, d, *J*=6.5 Hz, $C\underline{H}_3$), 1.16 (3H, d, *J*=6.9 Hz, $C\underline{H}_3$) ppm; **^{13}C NMR** (50.3MHz,$CDCl_3$) δ 180.73 (C=O), 75.86 (CHOH), 42.28 (CHC=O), 18.12 (CH_3), 11.46 (CH_3) ppm; **MS** (ei) m/z 27 (40%), 43 (base), 57 (84%), 73 (45%), 103 (60%, $(M-15)^+$), 119 (28%, M^+).

3.1C (b) Attempted reductive cleavage of aldol benzaldehyde product (87) using lithium borohydride to yield diol (88)

To a solution of the substrate **(87)** (1.62g, 3.50mmol) in THF (40ml) was added water (65µl, 3.61mmol). After cooling to 0°C a slight excess of solid lithium borohydride (0.08g, 3.67mmol) was added and the mixture stirred at 0°C while the progress was monitored. Constant TLC analysis of the contents of the reaction vessel over the next 2 hours failed to give hint of reaction headway. The solution was allowed to warm to room temperature and stirring and monitoring continued for a further 48 hours at which time the reaction was quenched by the dropwise addition of water (25ml) until the solution went clear. The reaction mixture was then poured onto methylene chloride/water (50ml, 1:1) and separated before extracting the aqueous layer with methylene chloride (3 x 30ml). The organic layer and extracts were combined, washed with water (30ml), dried with powdered magnesium sulphate, filtered and evaporated to yield an off white solid.

Subsequent interpretation of the ^{1}H and ^{13}C NMR spectra obtained from a sample of the solid returned revealed only the presence of the benzaldehyde starting material **(87)**.

3.1C (c) Attempted cleavage of aldol benzaldehyde product (87) using lithium benzyloxide to yield benzyl ester (89)

To a solution of benzyl alcohol (0.25g, 2eq) in dry THF (20ml) under flushing argon at -78°C was added dropwise *via* syringe butyllithium (1.1ml, 1.6M, 1.5eq). After stirring for 30 minutes a pre-cooled (-78°C) solution of the isobutyraldehyde adduct (0.54g, 1.17mmol) in dry THF (20ml) was added and stirring continued for a further 30 minutes.
A sample of the reaction solution was analysed by TLC and indicated mainly starting material remained, however, there was a faint suggestion of the presence of other substances, although it was unlikely that the target material was among them since there was no indication of the severed matrix auxiliary (77). The reaction vessel was warmed to 0°C then stirred again for 60 minutes in an effort to encourage the formation of the unidentified materials. Constant monitoring by TLC confirmed the presence of one major and several minor products though none corresponded to that of auxiliary (77). The reaction was then quenched by the addition of a saturated solution of ammonium chloride (40ml). Removal of the THF solvent by rotary evaporation at the pump was followed by separation and extraction of the aqueous layer into dichloromethane (3 x 30ml). Ensuing drying of the combined extracts and organic layer over magnesium sulphate followed by filtration and evaporation furnished the crude mixture as a brown viscous oil. The oil was then wet loaded onto a chromatographic column and subjected to flash chromatography using an elution combination of hexane/ether (500ml, 8:1). The major product was the first fraction eluted and was evaporated to yield a sticky sweet smelling oil which was later identified as benzyl propanoate. The second fraction eluted proved to be benzaldehyde adduct start material (87) and all subsequent fractions were either irretrievable or unidentifiable.

3.2 Asymmetric acylation reactions

3.2 (a) *via* Mander's reagent methyl cyanoformate to furnish C-acylated product (101)

To an ice-cold solution of diisopropylamine (0.1g, 1.0mmol, 1.2eq) in dry THF (10ml) under argon was added dropwise *via* syringe butyllithium (0.63ml, 1.6M, 1.2eq). After stirring for 20 minutes the reaction temperature was lowered to -78°C and a pre-cooled solution of the propionate **(80)** (0.3g, 0.84mmol) in dry THF (10ml) was added. Stirring was continued for a further 60 minutes whereupon Mander's reagent methyl cyanoformate (0.09g, 1.0mmol, 1.2eq) in dry THF (10ml) was added in a single aliquot. The contents of the reaction vessel were then stirred whilst maintaining the reaction temperature at -78°C for 30 minutes at which time the reaction mixture was quenched by the addition of dilute ammonium chloride (20ml). The reaction THF solvent was removed by rotary evaporation and the mixture then extracted into dichloromethane (3 x 25ml). The organic extracts were combined, washed with water (25ml), dried ($MgSO_4$), filtered and evaporated to yield a light oil. Preliminary inspection of a sample of the crude product on a TLC plate indicated some propionate starting material **(80)** still present, this was confirmed by analysis of a ^1H NMR spectrum from the same crude mixture. The crude material was therefore subjected to flash chromatographic separation using an eluant combination of hexane/ diethyl ether (3:1, 500ml) which upon individual standing crystallised to return the target C-acylated substance **(101)** in an 85% yield.

^{1}H NMR (200.13MHz,$CDCl_3$) δ 5.12 (1H, d, *J*=8.1 Hz, C<u>H</u>), 4.25 (1H, dd, *J*=8.1, 1.9 Hz, C<u>H</u>), 4.22 (1H, d, *J*=11.7 Hz, C<u>H</u>), 4.19 (1H, d, *J*=11.7 Hz, C<u>H</u>), 4.11 (1H, q, *J*=7.2 Hz, $CH_3C\underline{H}$), 3.89 (1H, dd, *J*=13.0, 1.9 Hz, C<u>H</u>), 3.89 (1H, d, *J*=13.0 Hz, C<u>H</u>), 3.68 (3H, s, $OC\underline{H}_3$), 1.56 (3H, s, $C\underline{H}_3$), 1.43 (3H, d, *J*=7.2 Hz, $CHC\underline{H}_3$), 1.42 (3H, s, $C\underline{H}_3$), 1.39 (3H, s, $C\underline{H}_3$), 1.25 (3H, s, $C\underline{H}_3$) ppm;

^{13}C NMR (50.3MHz,$CDCl_3$) δ 173.52 (C=O), 170.71 (C=O), 152.24 (C=O), 112.25 (quat C), 109.24 (quat C), 101.51 (quat C), 90.54 (quat C), 70.94 (CH), 70.27 (CH), 68.67 (CH_2), 61.44 (CH_2), 52.19 (OCH_3), 48.87 (CH), 27.93 (CH_3), 27.31 (CH_3), 25.75 (CH_3), 24.03 (CH_3), 14.86 (CH_3) ppm;

MS (ei) m/z 31 (20%), 43 (35%), 73 (60%), 244 (base), 302 (70%), 358 (40%), 400 (28%, $(M-15)^+$), 416 (65%, M^+); **Accurate mass** (FAB), Found: 416.15563, ($C_{18}H_{26}NO_{10}$) (M+H), Requires: 416.15564.

3.2 (b) Acylation reaction *via* propionyl chloride resulting in O-acylated product (100)

To an ice-cold solution of diisopropylamine (0.16g, 1.6mmol, 1.2eq) in dry THF (20ml) under argon was added dropwise *via* syringe butyllithium (0.63ml, 1.6M, 1.2eq). After stirring for 20 minutes the reaction temperature was lowered to -78°C and a pre-cooled solution of the propionate **(80)** (0.5g, 1.4mmol) in dry THF (30ml) was added. After stirring for 60 minutes, freshly distilled propionyl chloride (0.26g, 2.8mmol, 2eq) was taken up in dry THF (20ml) and added to the flask dropwise *via* syringe. Monitoring by TLC showed the reaction to be complete after only 4 minutes with no indication of any start material remaining. The mixture was immediately quenched by the addition of a saturated solution of ammonium chloride following which the THF reaction solvent was removed at the pump. The aqueous layer was then extracted with dichloromethane (3 x 30ml) and the extracts combined,

washed with water, dried with powdered magnesium sulphate, filtered and evaporated to yield a colourless, highly crystalline substance (0.55g, 95%) which was later identified to be the O-acylated product **(100)**.

Mp = 127-128 °C; $[\alpha]_D^{25}$ = +6.9 (c=1.80, CH_2Cl_2); **^{1}H NMR** (200.13MHz,$CDCl_3$) δ 5.71 (1H, q, *J*=7.1 Hz, $CH_3C\underline{H}$), 4.91 (1H, d, *J*=7.7 Hz, C<u>H</u>), 4.23 (1H, dd, *J*=7.7, 2.1 Hz, C<u>H</u>), 4.16 (2H, s, C<u>H_2</u>), 3.86 (1H, dd, *J*=13.1, 2.1 Hz, C<u>H</u>), 3.69 (1H, d, *J*=13.1 Hz, C<u>H</u>), 2.40 (2H, q, *J*=7.5 Hz, C<u>H_2</u>CH_3), 1.55 (3H, d, *J*=7.2 Hz, $CHC\underline{H_3}$), 1.55 (3H, s, C<u>H_3</u>), 1.46 (3H, s, C<u>H_3</u>), 1.40 (3H, s, C<u>H_3</u>), 1.26 (3H, s, C<u>H_3</u>), 1.16 (3H, d, *J*=7.5 Hz, $CH_2C\underline{H_3}$) ppm; **^{13}C NMR** (50.3MHz,$CDCl_3$) δ 169.88 (C=O), 152.26 (C=O), 135.23 (quat C), 118.64 (*CH), 111.51 (quat C), 109.16 (quat C), 98.93 (quat C), 89.52 (quat C), 71.14 (CH), 70.21 (CH), 66.87 (CH_2), 62.48 (CH_2), 28.18 (CH_3), 27.50 (CH_3), 27.08 (CH_3), 25.98 (CH_3), 24.42 (CH_3), 12.03 (CH_3), 8.73 (CH_3) ppm, (*CH = ethylenic CH=CH_2); **IR** (thin film) ν_{max} 2920 (aliphatic C-H), 1780 (C=O), 1740 (C=O), 1650 (C=C) cm^{-1}; **Accurate mass** (FAB), Found: 414.17641, ($C_{19}H_{28}NO_9$) (M+H), Requires: 414.17639;

X-ray (for X-ray structure and full crystal data see appendix E).

3.3 Attempted asymmetric alkylation reactions

3.3 (a) using methyl iodide *via* lithium enolate (temperature range -8°C to -4°C)

To an ice-cold solution of diisopropylamine (0.2g, 2.0mmol, 1.1eq) in dry THF (20ml) under argon was added dropwise *via* syringe butyllithium (1.4ml, 1.6M, 1.1eq). After stirring for 20 minutes the reaction temperature was lowered to -78°C and a pre-cooled solution of the propionate **(80)** (0.65g, 1.8mmol) in dry THF (20ml) was added. Stirring was continued for 60 minutes at which time freshly distilled methyl iodide (0.7g, 4.6mmol, 2.3eq) was taken up in dry THF (15ml) and added to the flask. The temperature was immediately adjusted to -8°C and then constantly maintained within a range of -8°C and -4°C throughout the course of the reaction. Monitoring of the reaction by TLC over the next 5 hours failed to provide any indication of reaction progress and the procedure was aborted by quenching with an aqueous solution of ammonium chloride.

3.3 (b) using benzyl bromide *via* lithium enolate (temperature held constant at 0°C)

A subsequent re-run of the reaction was then conducted employing benzyl bromide (0.8g, 4.7mmol, 2.5eq) as the alkylating agent and diligently controlling the temperature at 0°C throughout the course of the reaction.

The procedure was otherwise carried out in accordance with **3.3 (a)** above with all other reagents and quantities unchanged.

As before reaction progress was supervised by TLC, however, once again no progress was achieved and the procedure was terminated.

3.3 (c) using benzyl bromide *via* sodium enolate (temperature range -8°C to -4°C)

Following the failure of the lithium amide base to promote alkylation the more reactive sodium hexamethyldisilylazide (0.9g, 4.9mmol, 2.5eq) was employed.

The procedure was otherwise carried out in accordance with **3.3 (a)** above with all other reagents and quantities unchanged.

Once again the reaction mixture was constantly monitored by TLC for changes, however, as before no advancement was attained and the operation was discontinued by quenching with aqueous ammonium chloride.

3.3 (d) using benzyl bromide *via* sodium enolate (temperature increased to +10°C)

The experiment in **3.3 (c)** was repeated once again using sodium hexamethyldisilylazide (0.9g, 4.9mmol, 2.5eq) as the alkylating agent with the temperature increased to +10°C.

As before the procedure was otherwise carried out in accordance with **3.3 (a)** above with all other reagents and quantities unchanged.

Monitoring of the reaction progress was carried out by TLC and indicated the formation of a secondary substance almost immediately. The reaction was allowed to continue with stirring at +10°C until all of the starting propionate **(80)** material had been consumed. The reaction mixture was then quenched by the addition of a saturated solution of ammonium chloride. The THF reaction solvent was removed at the pump and the resulting aqueous layer extracted with diethyl ether (3 x 30ml). The organic extracts were combined, washed with water (30ml), dried and evaporated to yield a yellow oil. The crude mixture was passed down a

chromatographic column to remove excess benzyl bromide from the product of the reaction to yield a colourless thin oil.

The material recovered from the reaction was later identified as being N-benzylated product **(141)**, support data for which is given below.

^{1}H NMR (360.13MHz,$CDCl_3$) δ 7.27-7.21 (5H, m, Ph), 4.90 (1H, d, *J*=15.9 Hz, $PhC\underline{H}_2$), 4.48 (1H, d, *J*=7.6 Hz, C<u>H</u>), 4.37 (1H, d, *J*=15.9 Hz, $PhC\underline{H}_2$), 4.26 (1H, d, *J*=11.6 Hz, C<u>H</u>), 4.19 (1H, d, *J*=11.6 Hz, C<u>H</u>), 4.18 (1H, dd, *J*=7.6, 2.1 Hz, C<u>H</u>), 3.93 (1H, dd, *J*=13.1, 2.1 Hz, C<u>H</u>), 3.73 (1H, d, *J*=13.1 Hz, C<u>H</u>), 1.59 (3H, s, $C\underline{H}_3$), 1.39 (3H, s, $C\underline{H}_3$), 1.33 (3H, s, $C\underline{H}_3$), 0.88 (3H, s, $C\underline{H}_3$) ppm;

^{13}C NMR (50.3MHz,$CDCl_3$) δ 153.55 (C=O), 137.20 (C=O), 128.04 (Phenyl CH), 127.70 (Phenyl CH), 126.85 (Phenyl CH), 111.31 (quat C), 108.97 (quat C), 98.92 (quat C), 89.12 (quat C), 71.07 (CH), 70.42 (CH), 66.52 (CH_2), 62.30 (CH_2), 46.00 (CH_2), 27.59 (CH_3), 27.29 (CH_3), 25.62 (CH_3), 23.62 (CH_3) ppm;

MS (ei) m/z 43 (30%), 73 (base), 147 (25%), 207 (20%), 327 (35%), 376 (40%, $(M-15)^+$), 392 (95%, M^+).

3.4 Asymmetric α-Bromination reaction

3.4A α-Bromination of propionate (80) using NBS

Butyllithium (2.0ml, 1.6M, 1.1eq) was added dropwise *via* syringe to an ice-cold solution of diisopropylamine (0.31g, 1.1eq) in dry THF (15ml). Upon leaving the contents to stir for 20 minutes, the solution was cooled to -78°C at which time a pre-cooled solution (-78°C) of the propionate **(80)** (1.0g, 2.8mmol) in dry THF (20ml) was added. The mixture was left to stir for 60 minutes then a solution of N-bromosuccinimide (NBS, 1.00g, 5.6mmol, 2eq) in dry THF (25ml) was added dropwise. The temperature was maintained at -78°C and the reaction mixture allowed to stir whilst supervising reaction progress by TLC at regular 2 minute intervals. After a period of 12 minutes all starting material had been consumed and the reaction was immediately quenched by adding a saturated solution of aqueous ammonium chloride (40ml). The quenched solution was allowed to warm to room temperature whereupon the THF reaction solvent was removed *in vacuo* and the resultant aqueous layer extracted with diethyl ether (3 x 30ml). The extracts were combined, washed with water (30ml), dried with powdered $MgSO_4$, filtered and evaporated to return a pale yellow viscous oil in quantitative yield. The crude product was flushed down a chromatographic column with a mixture of hexane/ether (1:1) to remove reaction contaminants. A sample of the product returned **(129)** was analysed by high resolution ^1H NMR and revealed the existence of two isomers in a ratio of 25:1. The refined material was then subjected to flash chromatography using an elution ratio of hexane/ether (3:1, 1000ml) to separate the two isomers. The first fraction yielded an approximately 5-10% return of the minor isomer as a thin oil and the second fraction returned the major isomer as colourless crystals in an overall yield of 90%.

Spectral data relating to major isomer (second fraction **129f$_2$**):

Mp = 134-135°C; $[\alpha]_D^{25}$ = +46.6° (c=3.10, CH_2Cl_2); **^{1}H NMR** (360.13MHz, $CDCl_3$) δ 5.18 (1H, q, *J*=6.7 Hz, BrC<u>H</u>), 5.11 (1H, d, *J*=8.1 Hz, C<u>H</u>), 4.30 (1H, d, *J*=11.7 Hz, C<u>H</u>), 4.28 (1H, dd, *J*=8.1, 1.8 Hz, C<u>H</u>), 4.26 (1H, d, *J*=11.8 Hz, C<u>H</u>), 3.86 (1H, dd, *J*=13.2, 1.8 Hz, C<u>H</u>), 3.80 (1H, d, *J*=13.2 Hz, C<u>H</u>), 1.88 (3H, d, *J*=6.7 Hz, BrCHC<u>H</u>$_3$), 1.60 (3H, s, C<u>H</u>$_3$), 1.57 (3H, s, C<u>H</u>$_3$), 1.41 (3H, s, C<u>H</u>$_3$), 1.29 (3H, s, C<u>H</u>$_3$) ppm; **^{13}C NMR** (50.3MHz,$CDCl_3$) δ 173.86 (C=O), 152.83 (C=O), 112.38 (quat C), 109.41 (quat C), 103.73 (quat C), 90.67 (quat C), 72.93 (CH), 70.83 (CH_2), 69.93 (CH), 60.93 (CH_2), 43.30 (CH-Br), 28.23 (CH_3), 26.96 (CH_3), 25.29 (CH_3), 24.28 (CH_3), 21.41 (CH_3) ppm; **IR** (thin film) ν_{max} 1760 (C=O), 1700 (C=O) cm^{-1}; **MS** (ei) m/z 43 (85%), 57 (70%), 73 (40%), 244 (base), 302 (25%), 421 (40%, $(M-15)^+$), 437 (60%, M^+); **Accurate mass** (FAB), Found: 436.06078, ($C_{16}H_{23}{}^{79}BrNO_8$) (M+H), Requires: 436.06074, Found: 438.05880, ($C_{16}H_{23}{}^{81}BrNO_8$) (M+H), Requires: 438.05877.

Spectral data relating to minor isomer (first fraction **129f$_1$**):

Mp = 126-127°C; $[\alpha]_D^{25}$ = -16.8° (c=2.80, CH_2Cl_2); **^{1}H NMR** (360.13MHz, $CDCl_3$) δ 5.07 (1H, q, *J*=6.7 Hz, BrC<u>H</u>), 4.95 (1H, d, *J*=8.1 Hz, C<u>H</u>), 4.29 (1H, d, *J*=11.6 Hz, C<u>H</u>), 4.29 (1H, dd, *J*=7.9, 1.8 Hz, C<u>H</u>), 4.22 (1H, d, *J*=11.6Hz, C<u>H</u>), 3.90 (1H, d, *J*=13.2, 1.8 Hz, C<u>H</u>), 3.79 (1H, d, *J*=13.2 Hz, C<u>H</u>), 1.87 (3H, d, *J*=6.7 Hz, BrCHC<u>H</u>$_3$), 1.60 (3H, s, C<u>H</u>$_3$), 1.43 (3H, s, C<u>H</u>$_3$), 1.41 (3H, s, C<u>H</u>$_3$), 1.28 (3H, s, C<u>H</u>$_3$) ppm; **^{13}C NMR** (50.3MHz,$CDCl_3$) δ 175.12 (C=O), 151.98 (C=O), 112.42 (quat C), 109.40 (quat C), 102.98 (quat C), 90.73 (quat C), 70.58 (CH), 69.01 (CH), 67.24 (CH_2), 60.93 (CH_2), 43.09(CH-Br), 28.22 (CH_3), 27.50 (CH_3), 25.85 (CH_3), 23.93 (CH_3), 21.99 (CH_3) ppm; **IR** (thin film) ν_{max} 1780 (C=O), 1710 (C=O) cm^{-1}; **Accurate mass** (FAB), Found: 436.06076, ($C_{16}H_{23}{}^{79}BrNO_8$) (M+H), Requires: 436.06074, Found: 438.05878, ($C_{16}H_{23}{}^{81}BrNO_8$) (M+H), Requires: 438.05877.

3.4B Hydrolytic cleavage of major isomer of α-brominated product (129) using lithium hydroperoxide

To an ice-cold solution of the substrate (**129f$_2$**) (0.5g, 1.15mmol) in tetrahydrofuran/water mixture (40ml, 3:1) was added hydrogen peroxide (0.9ml, 6.0eq, assay 27%) followed by hydrated lithium hydroperoxide (0.10g, 2.0eq). After allowing to warm to ambient temperature and stirring for 60 minutes, the excess peroxide was quenched with sodium sulphite solution (1.5M, 6ml, 1.1eq) and then buffered to pH 9-10 with saturated aqueous sodium bicarbonate. Upon removal of organic volatiles by rotary evaporation and subsequent work-up by separation and extraction from the aqueous layer with dichloromethane (3 x 30ml), the auxiliary (**77**) was recovered as a white foam in high yield (0.33g, >95%). The aqueous phase was acidified to pH 1-2 by the dropwise addition of concentrated hydrochloric acid, extracted with ethyl acetate (3 x 30ml), then separated, dried ($MgSO_4$), filtered and evaporated to yield the carboxylic acid fragment as a thin colourless oil (0.16g, >90%). The absolute configuration of the fragment was later identified from literature analogy of its optical rotation value as being 2(R)-bromopropionic acid (**130**) in a yield of >85%.

$[\alpha]_D^{25}$ = +27.9° (c=4.30, CH_2Cl_2), {literature[93] value $[\alpha]^{25}$ = -27.6° (MeOH) for (2S) enantiomer}.

4 Asymmetric applications utilising α,β unsaturated carboximide dienophiles (102-104)

4.1 Lewis-acid catalysed Diels-Alder cycloaddition reactions

The procedures described in this category concern the use of a Lewis-acid catalyst in Diels-Alder cycloaddition reactions. The catalyst employed for each operation was diethylaluminium chloride in a stoichiometric excess of 1.4 equivalents, present as a 1.6M* solution in toluene.

4.1A Lewis-acid catalysed cycloaddition reactions of dienophiles (102-104) with cyclopentadiene

4.1A (a) Cycloaddition reaction of acrylate (102) with cyclopentadiene

To a solution of acrylate (102) (0.30g, 0.85mmol) in dry methylene chloride (20ml) at -78°C under argon was added a pre-cooled solution of freshly cracked cyclopentadiene (0.56g, 8.45mmol, 10eq) in dry methylene chloride (10ml). Diethylaluminium chloride (0.74ml, 1.6M*, 1.4eq) was promptly added *via* syringe and resulted in the transient appearance of a distinct yellow colour. The contents of the reaction vessel were stirred at -78°C for 10 minutes then quenched by the addition of a saturated solution of ammonium chloride (15ml) and allowed to warm to room temperature. The reaction mixture was poured onto a combination of methylene chloride/water (40ml, 1:1), then separated and the aqueous layer extracted with methylene chloride (3 x 30ml). The organic layer and extracts were combined, washed with both aqueous $NaHCO_3$ (30ml) and water (30ml), then dried $MgSO_4$, filtered and evaporated to yield a viscous oil. Excess cyclopentadiene was removed from the crude material by column chromatography (elution ratio: hexane/ether, 7:1, 500ml) to furnish the refined product which crystallised on standing as colourless crystals (0.34g, 95%).

Examination of the ^1H NMR spectrum of a sample of the purified product **(106)** revealed the presence of two isomers (both *endo*) in a ratio of 14:1 giving a diastereomeric excess of 87%. This value was determined by integration of the doublet signal obtained from an auxiliary proton which lies in the uncomplicated region of δ=5.07-5.03 ppm.

Spectral data relating to major isomer:

Mp = 134-135°C; **^1H NMR** (200.13MHz,$CDCl_3$) δ 6.15 (1H, dd, *J*=5.6, 3.1 Hz, CH=C<u>H</u>), 5.96 (1H, dd, *J*=5.6, 2.8 Hz, C<u>H</u>=CH), 5.05 (1H, d, *J*=8.1 Hz, C<u>H</u>), 4.29 (1H, d, *J*=11.6 Hz, C<u>H</u>), 4.26 (1H, ddd, *J*=8.0, 1.9, 0.8 Hz, C<u>H</u>), 4.15 (1H, d, *J*=11.6 Hz, C<u>H</u>), 3.87 (1H, dd, *J*=13.2, 1.9 Hz, C<u>H</u>), 3.78 (1H, dd, *J*=13.2, 0.8 Hz, C<u>H</u>), 3.68 (1H, ddd, *J*=9.3, 4.9, 3.3 Hz, C<u>H</u>C=O), 3.24 (1H, br s, bridgehead C<u>H</u>), 2.89 (1H, br s, bridgehead C<u>H</u>), 2.06 (1H, m, C<u>H</u>), 1.58 (1H, m, C<u>H</u>), 1.56 (3H, s, C<u>H</u>$_3$), 1.45 (3H, s, C<u>H</u>$_3$), 1.40 (3H, s, C<u>H</u>$_3$), 1.31 (3H, s, C<u>H</u>$_3$), 1.26 (1H, m, C<u>H</u>$_2$) ppm; **^{13}C NMR** (50.3MHz,$CDCl_3$) δ 179.62 (C=O), 152.57 (C=O), 137.35 (CH=CH), 132.89 (CH=CH), 111.92 (quat C), 109.26 (quat C), 101.74 (quat C), 90.11 (quat C), 71.04 (CH), 70.43 (CH), 68.69 (CH_2), 61.36 (CH_2), 49.48 (bridgehead CH_2), 47.79 (CH), 46.84 (CH), 42.66 (CH), 32.29 (CH_2), 28.02 (CH_3), 27.27 (CH_3), 25.69 (CH_3), 24.22 (CH_3) ppm; **IR** (thin film) ν_{max} 1760 (C=O), 1730 (C=O) cm^{-1}; **MS** (ei) m/z 32 (65%), 44 (base), 57 (60%), 73 (45%), 91 (70%), 121 (65%), 302 (70%), 396 (20%, $(M-15)^+$), 422 (30%, M^+); **Accurate mass** (FAB), Found: 422.18148, ($C_{21}H_{28}NO_8$) (M+H), Requires: 422.18147.

4.1A (b) Cycloaddition reaction of crotonate (103) with cyclopentadiene

To a solution of crotonate **(103)** (0.30g, 0.81mmol) in dry dichloromethane (20ml) at -78°C under argon was added a pre-cooled solution of freshly cracked cyclopentadiene (0.54g, 8.1mmol, 10eq) in dry methylene chloride (10ml). Diethylaluminium chloride (0.71ml, 1.6M*, 1.4eq) was promptly added *via* syringe and after stirring the contents of the reaction vessel at -78°C for 60 minutes, the reaction mixture was quenched by the addition of a saturated solution of ammonium chloride (15ml) and allowed to warm to room temperature. The mixture was poured onto a combination of methylene chloride/water (40ml, 1:1), then separated and the aqueous layer extracted with methylene chloride (3 x 30ml). The organic layer and extracts were combined, washed with both aqueous $NaHCO_3$ (30ml) and water (30ml), then dried $MgSO_4$, filtered and evaporated to yield a thin oil. Excess cyclopentadiene was removed from the crude material by column chromatography (elution ratio: hexane/ether, 3:1, 400ml) to furnish the refined product which crystallised on elution (0.32g, >90%), (*present as a 1.6M solution in toluene).

Examination of the 1H NMR spectrum obtained from a sample of the cleaned up product **(107)** once again revealed the presence of only two *endo* isomers, (no *exo* isomers indicated). The selectivity, however, was reduced to just 20%.

Spectral data relating to major isomer:

$[\alpha]_D^{25}$ = +2.2° (c=2.25, CH_2Cl_2); **^{1}H NMR** (200.13MHz,$CDCl_3$) δ 6.03 (1H, dd, *J*=5.6, 2.9 Hz, C<u>H</u>=CH), 5.89 (1H, dd, *J*=5.6, 2.8 Hz, CH=C<u>H</u>), 5.02 (1H, d, *J*=8.0 Hz, C<u>H</u>), 4.25 (1H, d, *J*=11.5 Hz, C<u>H</u>), 4.24 (1H, dd, *J*=8.0, 2.1 Hz, C<u>H</u>), 4.20 (1H, d, *J*=11.5 Hz, C<u>H</u>), 3.88 (1H, dd, *J*=13.2, 2.1 Hz, C<u>H</u>), 3.78 (1H, d, *J*=13.2 Hz, C<u>H</u>), 3.23 (1H, br s, bridgehead C<u>H</u>), 3.10 (1H, m, C<u>H</u>C=O), 3.09 (1H, m, C<u>H</u>), 2.93 (1H, m, C<u>H</u>), 2.47 (1H, br s, bridgehead C<u>H</u>), 1.75 (1H, m, C<u>H</u>CH_3), 1.57 (3H, s, C<u>H</u>$_3$), 1.47 (3H, s, C<u>H</u>$_3$), 1.43 (3H, d, *J*=6.7 Hz, CHC<u>H</u>$_3$), 1.32 (3H, s,

$C\underline{H}_3$), 1.23 (3H, s, $C\underline{H}_3$) ppm; **^{13}C NMR** (50.3MHz,$CDCl_3$) δ 180.45 (C=O), 152.65 (C=O), 138.11 (CH=CH), 133.09 (CH=CH), 112.09 (quat C), 109.26 (quat C), 100.86 (quat C), 90.10 (quat C), 70.72 (CH), 67.77 (CH_2), 61.63 (CH_2), 55.81 (CH), 49.86 (CH), 48.42 (CH), 46.63 (bridgehead CH_2), 43.06 (CH), 40.34 (CH), 28.36 (CH_3), 27.48 (CH_3), 25.89 (CH_3), 24.29 (CH_3), 20.78 (CH_3) ppm; **IR** (thin film) ν_{max} 1780 (C=O), 1720 (C=O) cm^{-1}; **Accurate mass** (FAB), Found: 436.19714, ($C_{22}H_{30}NO_8$) (M+H), Requires: 436.19712.

4.1A (c) Cycloaddition reaction of cinnamate (104) with cyclopentadiene

To a stirring solution of cinnamate (104) (0.30g, 0.70mmol) in dry dichloromethane (20ml) at -78°C under argon was added a pre-cooled solution of freshly cracked cyclopentadiene (0.46g, 6.97mmol, 10eq) in dry methylene chloride (10ml). Following the addition of the diethylaluminium chloride catalyst (0.61ml, 1.6M*, 1.4eq) in a single aliquot (*present as a 1.6M solution in toluene), the mixture was stirred for 5 minutes then warmed to -20°C (tetrachloromethane/dry ice combination) and the reaction progress monitored by thin layer chromatography (TLC). After stirring at this temperature for 40 minutes, TLC showed the reaction to be complete and the reaction mixture was quenched by the addition of a saturated solution of ammonium chloride (25ml) and allowed to warm to room temperature. Work up was effected by pouring the two layer mixture onto a combination of methylene chloride/water (40ml, 1:1). Separation of the two layers was followed by extraction of the aqueous layer with methylene chloride (3 x 30ml). The organic layer and extracts were combined, washed with both aqueous $NaHCO_3$ (30ml) and water (30ml), then dried $MgSO_4$, filtered and evaporated to yield a light oil. Subsequent removal of excess cyclopentadiene by flash chromatography (hexane/ether, 5:1, 500ml) returned the product in a yield of 95% from which a sample was submitted for analysis by proton nuclear magnetic resonance (^1H NMR). The spectrum revealed the presence of all four possible isomers with an *endo:exo* selectivity ratio of 4:1 and an *endo* diastereomeric excess of 63%.

Spectral data relating to major isomer:

$[\alpha]^{26} = -41.0^{\circ}$ (c=3.40, CH_2Cl_2); **^{1}H NMR** (360.13MHz,$CDCl_3$) δ 7.29-7.11 (5H, m, Phenyl C<u>H</u>), 6.40 (1H, dd, *J*=5.6, 3.1 Hz, C<u>H</u>=CH), 6.12 (1H, dd, *J*=5.5, 2.7 Hz, CH=C<u>H</u>), 5.09 (1H, d, *J*=8.1 Hz, C<u>H</u>), 4.26 (1H, dd, *J*=8.1, 1.7 Hz, C<u>H</u>), 4.23 (1H, d, *J*=11.6 Hz, C<u>H</u>), 4.07 (1H, d, *J*=11.6 Hz, C<u>H</u>), 3.88 (1H, dd, *J*=13.2, 2.1 Hz, C<u>H</u>), 3.87 (1H, d, *J*=13.2, 2.0 Hz, C<u>H</u>), 3.86 (1H, d, *J*=13.2 Hz, C<u>H</u>), 3.35 (1H, br s, bridgehead C<u>H</u>), 3.10 (1H, m, C<u>H</u>-CH=CH), 3.05 (1H, m, C<u>H</u>), 3.00 (1H, m, CH=CH-C<u>H</u>), 2.84 (1H, br s, bridgehead C<u>H</u>), 1.76 (1H, m, C<u>H</u>Ph), 1.52 (3H, s, C<u>H</u>$_3$), 1.46 (3H, s, C<u>H</u>$_3$), 1.32 (3H, s, C<u>H</u>$_3$), 1.24 (3H, s, C<u>H</u>$_3$) ppm; **^{13}C NMR** (50.3MHz,$CDCl_3$) δ 178.36 (C=O), 152.43 (C=O), 144.49 (Ar quat C), 139.26 (CH=CH), 133.10 (CH=CH), 129.72 (Phenyl CH), 128.61 (Phenyl CH), 127.73 (Phenyl CH), 112.11 (quat C), 109.35 (quat C), 100.81 (quat C), 90.14 (quat C), 70.76 (CH), 67.49 (CH_2), 61.88 (CH_2), 55.80 (CH), 49.90 (CHC=O), 48.56 (CHPh), 46.68 (bridgehead CH_2), 43.12 (CH), 40.36 (CH), 28.46 (CH_3), 27.62 (CH_3), 25.91 (CH_3), 24.35 (CH_3) ppm; **IR** (thin film) ν_{max} 1760 (C=O), 1710 (C=O) cm^{-1}; **Accurate mass** (FAB), Found: 498.21276, ($C_{27}H_{32}NO_8$) (M+H), Requires: 498.21277.

4.1B Hydrolytic cleavage of major isomers of cycloaddition products (106-108) using lithium hydroperoxide

4.1B (a) Cleavage of major cycloadduct of acrylate product (106)

To an ice-cold solution of the substrate **(106)** (0.82g, 1.95mmol) in tetrahydrofuran/water mixture (40ml, 3:1) was added hydrogen peroxide (1.47ml, 6.0eq, assay 27%) followed by hydrated lithium hydroperoxide (0.17g, 2.0eq). After allowing to warm to room temperature and stirring for 60 minutes, the excess peroxide was quenched with sodium sulphite solution (1.5M, 8ml, 1.1eq) and then buffered to pH 9-10 with saturated aqueous sodium bicarbonate. Upon removal of organic volatiles by rotary evaporation and subsequent work-up by separation and extraction from the aqueous layer with dichloromethane (3 x 30ml), the auxiliary* **(77)** was recovered as a white foam in high yield (0.56g, >95%). The aqueous phase was acidified to pH 1-2 by the dropwise addition of concentrated hydrochloric acid, extracted with ethyl acetate (3 x 30ml), then separated, dried ($MgSO_4$), filtered and evaporated to yield the carboxylic acid fragment **(112)** as a thin colourless oil (0.34g, >95%).

*Analysis by ^1H and ^{13}C nuclear magnetic resonance confirmed the identity of the organic matrix as auxiliary **(77)**.

Spectral analysis of acid fragment **(112)**:

^1H NMR (200.13MHz,$CDCl_3$) δ 7.11 (1H, br s, O<u>H</u>), 6.25 (1H, dd, *J*=5.6, 3.0 Hz, CH=C<u>H</u>), 6.04 (1H, dd, *J*=5.6, 3.0 Hz, C<u>H</u>=CH), 3.77 (1H, m, C<u>H</u>C=O), 3.32-3.24 (1H, br s, bridgehead C<u>H</u>), 2.96 (1H, br s, bridgehead C<u>H</u>), 2.17 (1H, m, CH<u>H</u>), 1.68 (1H, m, C<u>H</u>H), 1.33 (2H, m, C<u>H</u>$_2$) ppm;

^{13}C NMR (50.3MHz,$CDCl_3$) δ 179.46 (C=O), 137.30 (CH=CH), 132.82 (CH=CH), 49.76 (CH_2), 47.72 (CH), 46.78 (CH), 42.54 (CH), 32.16 (CH_2) ppm;

IR (thin film) ν_{max} 1750 (C=O), 1670 (C=C) cm^{-1}.

4.1B (b) Cleavage of major cycloadduct of crotonate product (107)

Cleavage was carried out in accordance with the procedure detailed in part **4.1B (a)** above.

Accordingly, crotonate **(107)** (1.0g, 2.30mmol) was subjected to cleavage as before and furnished the carboxylic acid fragment **(113)** as a colourless thin oil (0.34g, >97%) with complementary high recovery of *auxiliary **(77)**.

*Analysis by ^{1}H and ^{13}C nuclear magnetic resonance confirmed the identity of the organic matrix as auxiliary **(77)**.

Spectral analysis of acid fragment **(113)**:

^{1}H NMR (360.13MHz,$CDCl_3$) δ 7.02 (1H, br s, O<u>H</u>), 6.12 (1H, dd, *J*=5.6, 2.9 Hz, CH=C<u>H</u>), 5.98 (1H, dd, *J*=5.6, 2.8 Hz, C<u>H</u>=CH), 3.49 (1H, m, C<u>H</u>C=O), 3.30-3.20 (1H, br s, bridgehead C<u>H</u>), 2.55 (1H, br s, bridgehead C<u>H</u>), 1.84 (1H, m, C<u>H</u>CH_3), 1.50 (3H, d, *J*=7.0Hz, CHC<u>H</u>$_3$), 1.34 (2H, m, C<u>H</u>$_2$) ppm;

^{13}C NMR (50.3MHz,$CDCl_3$) δ 180.24 (C=O), 138.21 (CH=CH), 132.16 (CH=CH), 49.80 (CH), 48.48 (CH), 46.70 (CH_2), 43.13 (CH), 40.35 (CH), 22.61 (CH_3) ppm; **IR** (thin film) ν_{max} 1730 (C=O), 1650 (C=C) cm^{-1}.

4.1B (c) Cleavage of major cycloadduct of cinnamate product (108)

Cleavage was carried out in accordance with the procedure detailed in part **4.1B (a)** above.

Accordingly, cinnamate **(108)** (0.79g, 1.60mmol) was subjected to cleavage as before and furnished the carboxylic acid fragment **(114)** as a colourless oil (0.33g, >95%) with complementary high recovery of *auxiliary **(77)**.

*Analysis by ^{1}H and ^{13}C nuclear magnetic resonance confirmed the identity of the organic matrix as auxiliary **(77)**.

Spectral analysis of acid fragment **(114)**:

^{1}H NMR (360.13MHz,$CDCl_3$) δ 7.36-7.20 (5H, m, Phenyl C<u>H</u>), 6.90 (1H, br s, O<u>H</u>), 6.46 (1H, dd, *J*=5.6, 3.1 Hz, CH=C<u>H</u>), 6.20 (1H, dd, *J*=5.6, 2.8 Hz, C<u>H</u>=CH), 3.43 (1H, m, C<u>H</u>C=O), 3.23-3.11 (1H, br s, bridgehead C<u>H</u>), 3.06-2.92 (1H, br s, bridgehead C<u>H</u>), 2.82-2.70 (1H, m, C<u>H</u>Ph), 1.91-1.73 (2H, m, C<u>H</u>$_2$) ppm; **^{13}C NMR** (50.3MHz,$CDCl_3$) δ 179.73 (C=O), 144.61 (Ar quat C), 139.32 (CH=CH), 133.18 (CH=CH), 129.76 (Phenyl CH), 128.66 (Phenyl CH), 127.80 (Phenyl CH), 49.96 (CHC=O), 48.71 (CHPh), 46.66 (CH_2), 43.22 (CH), 40.49 (CH) ppm;

IR (thin film) ν_{max} 1730 (C=O), 1650 (C=C) cm^{-1}.

4.1C Cycloaddition reaction of acrylate (102) with isoprene

To a solution of acrylate **(102)** (0.30g, 0.85mmol) in dry methylene chloride (20ml) at -78 °C under argon was added a pre-cooled solution of freshly cracked isoprene (0.60g, 8.45mmol, 10eq) in dry methylene chloride (10ml). Diethylaluminium chloride (0.74ml, 1.6M*, 1.4eq) was promptly added *via* syringe and resulted in the transient appearance of a distinct yellow colour (*present as a 1.6M solution in toluene). The contents of the reaction vessel were stirred at -78 °C for 20 minutes then quenched by the addition of a saturated solution of ammonium chloride (15ml) and allowed to warm to room temperature. The reaction mixture was poured onto a combination of methylene chloride/water (40ml, 1:1), then separated and the aqueous layer extracted with methylene chloride (3 x 30ml). The organic layer and extracts were combined, washed with both aqueous $NaHCO_3$ (30ml) and water (30ml), then dried $MgSO_4$, filtered and evaporated to yield a viscous oil. Excess isoprene was removed from the crude material by column chromatography (elution ratio: hexane/ether, 6:1, 400ml) to furnish the refined product (0.34g, 95%). Examination of the ^1H NMR spectrum of a sample of the purified product **(115)** revealed the presence of two isomers in a ratio of 7:1 giving a diastereomeric excess of 75%.

Spectral data relating to major isomer:

^1H NMR (360.13MHz,$CDCl_3$) δ 5.35-5.33 (1H, br dd, *J*=3.4, 1.7 Hz, C<u>H</u>=CH_2), 5.09 (1H, d, *J*=8.0 Hz, C<u>H</u>), 4.28 (1H, dd, *J*=8.1, 1.7 Hz, C<u>H</u>), 4.21 (1H, d, *J*=11.6 Hz, C<u>H</u>), 4.18 (1H, d, *J*=11.6 Hz, C<u>H</u>), 3.88 (1H, dd, *J*=13.2, 2.1 Hz, C<u>H</u>), 3.80 (1H, d, *J*=13.2 Hz, C<u>H</u>), 3.08-3.00 (1H, symm m {dddd}, *J*=14.2, 11.6, 5.4, 2.3 Hz, C<u>H</u>C=O), 2.32-1.98 (6H, br m, 3C<u>H_2</u>), 1.62 (3H, s, C=CC<u>H_3</u>), 1.57 (3H, s, C<u>H_3</u>), 1.44 (3H, s, C<u>H_3</u>), 1.41 (3H, s, C<u>H_3</u>), 1.27 (3H, s, C<u>H_3</u>) ppm;

^{13}C NMR (50.3MHz,$CDCl_3$) δ 181.74 (C=O), 152.28 (C=O), 133.31 (quat C {C=C}), 119.01 (C<u>H</u>=C), 111.91 (quat C), 108.93 (quat C), 100.79 (quat C), 89.79 (quat C), 71.31 (CH), 70.89 (CH), 67.85 (CH_2), 61.30 (CH_2), 43.16 (C<u>H</u>C=O), 29.35 (CH_2), 29.15 (CH_2), 28.05 (CH_3), 27.26 (CH_3), 25.79 (CH_2), 25.64 (CH_3), 23.92 (CH_3) 23.07 (CH_3) ppm; **MS** (ei) m/z 43 (base), 57 (55%), 95 (90%), 123 (35%), 201 (30%), 244 (50%), 302 (75%), 422 (95%, M^+); **Accurate mass** (FAB), Found: 424.19709, ($C_{21}H_{30}NO_8$) (M+H), Requires: 424.19710.

4.1D Cleavage of major cycloadduct of acrylate product (115)

To an ice-cold solution of the substrate **(115)** (0.22g, 0.52mmol) in tetrahydrofuran/water mixture (20ml, 3:1) was added hydrogen peroxide (0.40ml, 6.0eq, assay 27%) followed by hydrated lithium hydroperoxide (0.05g, 2.0eq). After allowing to warm to room temperature and stirring for 60 minutes, the excess peroxide was quenched with sodium sulphite solution (1.5M, 2.3ml, 1.1eq) and then buffered to pH 9-10 with saturated aqueous sodium bicarbonate. Upon removal of organic volatiles by rotary evaporation and subsequent work-up by separation and extraction from the aqueous layer with dichloromethane (3 x 20ml), the *auxiliary **(77)** was recovered as a white foam in high yield (0.15g, >95%). The aqueous phase was acidified to pH 1-2 by the dropwise addition of concentrated hydrochloric acid, extracted with ethyl acetate (3 x 15ml), then separated, dried ($MgSO_4$), filtered and evaporated to yield the carboxylic acid fragment **(116)** as a thin colourless oil (0.10g, >95%).

*Analysis by ^{1}H and ^{13}C nuclear magnetic resonance confirmed the identity of the organic matrix as being that of the auxiliary **(77)**.

Spectral analysis of acid fragment **(116)**:

^{1}H NMR (200.13MHz,$CDCl_3$) δ 7.11 (1H, br s, O<u>H</u>), 5.91 (1H, m, C=C<u>H</u>), 3.44 (1H, m, C<u>H</u>C=O), 2.46 (2H, m, C<u>H</u>$_2$), 2.38 (2H, m, C<u>H</u>$_2$), 2.18 (2H, m, C<u>H</u>$_2$), 1.68 (3H, s, C<u>H</u>$_3$) ppm; **^{13}C NMR** (50.3MHz,$CDCl_3$) δ 180.58 (C=O), 134.20 (quat C=C), 119.22 (CH=), 42.69 (CH), 31.08 (CH_2), 27.83 (CH_2), 26.46 (CH_2), 23.54 (CH_3) ppm; **IR** (thin film) ν_{max} 1740 (C=O) cm^{-1}.

4.2 Asymmetric 1,4 conjugate addition reactions

4.2.A 1,4 conjugate addition of crotonate (103) with Et_2AlCl to furnish C_β-ethylated product (126)

To a stirring solution of crotonate **(103)** (0.30g, 0.81mmol) in dry CH_2Cl_2 (40ml) at -78°C under argon was added dropwise *via* syringe Et_2AlCl (1.8ml, 1.8M in toluene, 4eq). The resulting yellow solution was stirred at -78°C for 4 hours whilst conducting constant monitoring of the reaction progress by thin layer chromatography. Analysis by this method indicated the presence of a new product, however the rate of consumption of starting material appeared to be slow. The solution was therefore allowed to warm to room temperature and monitoring resumed. After overnight stirring at this temperature, TLC showed all starting material to be consumed and the reaction was quenched with a saturated solution of ammonium chloride (30ml). The mixture was poured onto a combination of CH_2Cl_2/H_2O (30ml), separation of the resultant two layers was followed by extraction of the aqueous layer into methylene chloride (3 x 30ml). The combined organic extracts were washed with aqueous $NaHCO_3$, then dried with powdered magnesium sulphate, filtered and evaporated to yield a colourless oil which crystallised on standing (0.27g, 83%). Examination and interpretation of the 360 MHz ^1H NMR spectrum of the crude product **(126)** showed the presence of two isomers in a diastereomeric ratio of 7(R) : 3(S). The ratio was determined from integration of the signal obtained for a sugar ring proton in the uncomplicated region of δ=5.15-5.18 ppm.

$[\alpha]_D^{25}$ = +45.4° (c=3.90, CH_2Cl_2); **^1H NMR** (360.13MHz,$CDCl_3$) δ 5.19 (1H, d, *J*=8.1 Hz, C<u>H</u>), 4.28 (1H, d, *J*=11.6 Hz, C<u>H</u>), 4.27 (1H, dd, *J*=8.0, 1.2 Hz, C<u>H</u>), 4.21 (1H, d, *J*=11.6 Hz, C<u>H</u>), 3.86 (1H, dd, *J*=13.2, 2.1 Hz, C<u>H</u>), 3.78 (1H, dd, *J*=13.2, 0.7 Hz, C<u>H</u>), 2.81 (1H, dd, *J*=16.2, 6.4 Hz, C<u>H</u>H), 2.73 (1H, dd, *J*=16.2, 5.0 Hz, C<u>H</u>H), 2.60-2.47 (1H, m, C<u>H</u>CH_3), 2.00-1.92 (2H, m, C<u>H</u>$_2CH_3$), 1.57 (3H, s, C<u>H</u>$_3$), 1.43 (3H, s, C<u>H</u>$_3$), 1.40 (3H, s, C<u>H</u>$_3$), 1.25 (3H, s, C<u>H</u>$_3$), 0.90 (3H,

J=6.8 Hz, $CHC\underline{H}_3$), 0.84 (3H, t, J=6.2 Hz, $CH_2C\underline{H}_3$) ppm; **^{13}C NMR** (50.3MHz, $CDCl_3$) δ 178.56 (C=O), 151.23 (C=O), 110.85 (quat C), 108.36 (quat C), 101.12 (quat C), 89.62 (quat C), 74.52 (CH), 70.96 (CH), 70.22 (CH), 68.11 (CH_2), 60.62 (CH_2), 32.19 (CH_2), 28.65 (CH_2), 27.64 (CH_3), 27.28 (CH_3), 25.45 (CH_3), 23.90 (CH_3), 12.62 (CH_3), 11.56 (CH_3) ppm; **IR** (thin film) ν_{max} 1740 (C=O), 1715 (C=O) cm^{-1}.

4.2.B Attempted 1,4 conjugate addition of cinnamate (104) with Et_2AlCl to furnish C_β-ethylated product (122)

To a stirring solution of crotonate **(104)** (0.20g, 0.464mmol) in dry CH_2Cl_2 (30ml) at -78 °C under argon was added dropwise *via* syringe Et_2AlCl (1.1ml, 1.8M in toluene, 4eq). The resulting yellow solution was stirred at -78 °C for 4 hours whilst conducting constant monitoring of the reaction progress by thin layer chromatography. Analysis by this method suggested little reaction progress so the solution was allowed to warm to room temperature and monitoring was resumed. After overnight stirring at this temperature, TLC showed only starting material to be present and the reaction was quenched with a saturated solution of ammonium chloride (30ml). The mixture was poured onto a combination of CH_2Cl_2/H_2O (30ml), separation of the resultant two layers was followed by extraction of the aqueous layer into methylene chloride (3 x 30ml). The combined organic extracts were washed with aqueous $NaHCO_3$, then dried with powdered magnesium sulphate, filtered and evaporated to yield an off-white solid. The crude mixture was cleaned up by column chromatography (hexane/ether 3:1, 500ml) and examination and interpretation of the 200 MHz ^{1}H NMR spectrum from a sample of the main product determined it to be start material **(104)**.

5 Separation of racemic mixtures by resolution

5.1 Resolution of racemic (±)-1-Phenylethylamine

To a stirring solution of oxazinone auxiliary (77) (1.00g, 3.32mmol) in dry THF (30ml) at -78°C under an inert argon atmosphere was added dropwise n-butyllithium (2.30ml, 1.6M, 1.1eq). After allowing to stir at -78°C for 40 minutes, the resultant anionic solution was transferred and added dropwise over 20 minutes to a vast excess of phosgene (40ml, 20% solution in toluene). Stirring was continued for 20 minutes then the solution was warmed to room temperature and allowed to stir for a further 60 minutes. Following this period, excess phosgene was removed (*via* evaporation) from the mixture by heating the reaction vessel in a warm water bath and flushing with a strong argon flow. Freshly distilled (±)-1-phenylethylamine (0.90g, 2eq) and triethylamine (0.32g, 3.32mmol) in dry THF (20ml) were then added dropwise over 15 minutes. The reaction mixture was left to stir at room temperature overnight whereupon water (30ml) was added. The THF reaction solvent was then removed *in vacuo* at the pump and the reaction mixture extracted with diethyl ether (3x30ml). The organic extracts were combined, washed with water (30ml), then dried with powdered $MgSO_4$, filtered and evaporated to yield the diastereomeric pair as a brown tacky oil (1.61g).

HPLC analysis of the diastereomeric mixture resulted in a separability factor (α) of 1.7 (spherisorb 5μm silica column, solvent elution ratio: hexane/ether 7 : 1, flow rate 2.0ml/min). The remainder of the crude product was subjected to careful separation by flash chromatography using an elution ratio of hexane/ether 5:1. This technique returned the two allophanates as individual fractions (133a and 133b), spectroscopic data for each is given below.

Spectral data relating to first fraction (133a):

^{1}H NMR (360.1MHz,$CDCl_3$) δ 7.42-7.30 (1H, br s, NH), 7.21-7.03 (5H, m, Ph), 5.22 (1H, d, *J*=8.1 Hz, CH), 4.29 (1H, dd, *J*=8.1, 2.0 Hz, CH), 4.28 (1H, d, *J*=11.6 Hz, CH), 4.23 (1H, d, *J*=11.6 Hz, CH), 3.90 (1H, dd, *J*=13.3, 2.0 Hz, CH), 3.86 (1H, d, *J*=13.3 Hz, CH), 2.76-2.62 (1H, m, $CHCH_3$), 1.63 (3H, s, CH_3), 1.50 (3H, s, CH_3), 1.48 (3H, s, CH_3), 1.35 (3H, s, CH_3), 0.95 (3H, d, *J*=6.9 Hz, CH_3) ppm; **^{13}C NMR** (50.3MHz,$CDCl_3$) δ 172.34 (C=O), 153.26 (C=O), 141.32 (quat C), 127.63 (Phenyl CH), 126.50 (Phenyl CH), 125.06 (Phenyl CH), 111.73 (quat C), 109.42 (quat C), 99.75 (quat C), 88.39 (quat C), 71.81 (CH), 70.98 (CH), 67.80 (CH_2), 62.39 (CH_2), 49.07 (CH), 27.82 (CH_3), 27.15 (CH_3), 25.34 (CH_3), 23.86 (CH_3), 11.60 (CH_3) ppm; **IR** (thin film) ν_{max} 3270 (NH), 1740 (C=O), 1710 (C=O) cm^{-1}.

Spectral data relating to second fraction (133b):

^{1}H NMR (360.1MHz,$CDCl_3$) δ 7.38-7.22 (1H, br s, NH), 7.24-7.10 (5H, m, Ph), 5.22 (1H, d, *J*=8.1 Hz, CH), 4.28 (1H, dd, *J*=8.1, 2.1 Hz, CH), 4.26 (1H, d, *J*=11.7 Hz, CH), 4.24 (1H, d, *J*=11.7 Hz, CH), 3.91 (1H, dd, *J*=13.2, 2.1 Hz, CH), 3.86 (1H, d, *J*=13.2 Hz, CH), 2.79-2.66 (1H, m, $CHCH_3$), 1.64 (3H, s, CH_3), 1.53 (3H, s, CH_3), 1.48 (3H, s, CH_3), 1.32 (3H, s, CH_3), 1.00 (3H, d, *J*=6.9 Hz, CH_3) ppm; **^{13}C NMR** (50.3MHz,$CDCl_3$) δ 172.39 (C=O), 153.40 (C=O), 141.32 (quat C), 127.66 (Phenyl CH), 126.55 (Phenyl CH), 124.98 (Phenyl CH), 111.70 (quat C), 109.41 (quat C), 99.79 (quat C), 88.38 (quat C), 71.78 (CH), 71.04 (CH), 67.82 (CH_2), 62.34 (CH_2), 49.13 (CH), 27.94 (CH_3), 27.12 (CH_3), 25.30 (CH_3), 23.81 (CH_3), 11.52 (CH_3) ppm;

IR (thin film) ν_{max} 3280 (NH), 1740 (C=O), 1710 (C=O) cm^{-1}.

5.2 Cleavage of individual allophanates

5.2 (i) Cleavage of isolated allophanate (133a)

To an ice-cold solution of the substrate **(133a)** (0.43g, 0.96mmol) in tetrahydrofuran/water mixture (20ml, 3:1) was added hydrogen peroxide (0.73ml, 6.0eq, assay 27%) followed by hydrated lithium hydroperoxide (0.085g, 2.0eq). After allowing to warm to room temperature and stirring for 60 minutes, the excess peroxide was quenched with sodium sulphite solution (1.5M, 4ml, 1.1eq) and then buffered to pH 9-10 with saturated aqueous sodium bicarbonate. Upon removal of organic volatiles by rotary evaporation and subsequent work-up by separation and extraction from the aqueous layer with dichloromethane (3 x 20ml), the auxiliary **(77)** was recovered as a white foam. The aqueous phase was acidified to pH 1-2 by the dropwise addition of concentrated hydrochloric acid, extracted with ethyl acetate (3 x 20ml), then separated, dried ($MgSO_4$), filtered and evaporated to yield the fragment **(134a)** as a colourless oil.

$[\alpha]^{24} = +16.9^{\circ}$ (R)-isomer.

5.2 (ii) Cleavage of isolated allophanate (133b)

The cleavage of allophanate **(133b)** was carried out in accordance with the procedure detailed in method **5.2(i)** given above.

Accordingly, allophanate **(133b)** (0.41g, 0.92mmol) was subjected to cleavage as before and furnished the fragment **(134b)** as a colourless thin oil.

$[\alpha]^{24} = -17.1^{\circ}$ (S)-isomer.

5.3 Resolution of racemic (±)-2-bromopropionyl chloride

Magnesium turnings (0.18g, 7.48mmol) were added to a reaction flask under an inert argon atmosphere and covered with dry diethyl ether. After adding a couple of drops of methyl iodide (as indicator), bromomethane (4.2ml, 2.0M, 1.7eq) was added slowly in small aliquots and reaction was allowed to continue until completion. At this point the temperature was lowered to 0 °C and a solution of the auxiliary **(77)** (1.5g, 4.98mmol) in dry THF (30ml) was added. Stirring was continued for 20 minutes before adjusting the temperature to -78 °C whereupon freshly distilled racemic 2-bromopropionyl chloride (1.70g, 2eq) was added dropwise over 10 minutes. The contents of the reaction vessel were stirred at -78 °C for a further 30 minutes then allowed to warm to room temperature and stirred again overnight. Analysis of a TLC sample suggested the reaction had reached completion and a saturated solution of ammonium chloride (30ml) was added to quench the reaction. The reaction volatiles were removed by rotary evaporation at the pump and the resulting aqueous layer was extracted with diethyl ether (3x50ml). The organic extracts were combined, washed with water, dried with magnesium sulphate, filtered and evaporated to return a purple light oil. HPLC analysis of the diastereomeric mixture resulted in a separability factor (α) of 2.0 (spherisorb 5µm silica column, solvent elution ratio: hexane/ether 7 : 1, flow rate 2.0ml/min). The remainder of the crude product was subjected to careful separation by flash chromatography using an elution ratio of hexane/ether 3:1. This technique separated the diastereomeric pair **(135)** as individual fractions which were subsequently hydrolysed to furnish the fragmented α-brominated acids **(136a)** and **(136b)**.

$[\alpha]^{25} = +28.5^{\circ}$ (R-isomer); $[\alpha]^{25} = -27.9^{\circ}$ (S-isomer).

6 Preparation and functionalisation of Isosorbide derived oxazolidinone auxiliary (147) *via* selective protection of C-2 *exo* hydroxyl group

{Isosorbide = 1,4:3,6-dianhydro-D-glucitol, also known as sorbitol}

6.1 Temporary protection of C-2 *exo* hydroxyl group of Isosorbide (142) (using pivaloyl chloride)

Isosorbide (12.0g, 0.082mol) and freshly distilled pivaloyl chloride (11.1ml, 1.1eq, 0.979 density) were added to dry methylene chloride (100ml) under argon and stirred to dissolution. Upon cooling to 0°C dicyclohexyl-carbodiimide (18.66g, 1.1eq) and 4-dimethylaminopyridine (0.1g) as catalyst were added and resulted in the immediate formation of a crystalline precipitate (N,N'-dicyclohexylurea). After allowing to warm to ambient temperature the reaction mixture was stirred and monitored at periodic intervals by thin layer chromatography. After 40 hours TLC analysis showed the presence of three products (1 major and 2 minor) and indicated reaction to be complete (all starting material was consumed). Following removal by filtration of the crystalline material from the reaction mixture, the filtrate was washed with both water (50ml) and ethanol (30ml), then dried with magnesium sulphate, filtered and evaporated to yield a yellow viscous oil. The crude material was subjected to flash chromatography (hexane/diethyl ether 3:1) to isolate the major product (R_f values: 2-acylates > 5-acylates > 2,5-diacylates) and the target substance (*1,4:3,6-dianhydro-D-glucitol-2-acylate*) was eluted as the first fraction which crystallised on standing as colourless flake-like crystals (12.3g, 65%).

$[\alpha]^{25}$ = +75.9°; **^{1}H NMR** (360.13MHz,$CDCl_3$) δ 5.04 (1H, dd, *J*=4.3, 1.4 Hz, C<u>H</u>), 4.81 (1H, dd, *J*=5.3, 4.7 Hz, C<u>H</u>), 4.32 (1H, d, *J*=4.7 Hz, C<u>H</u>), 4.25 (1H, d, *J*=4.3 Hz, C<u>H</u>), 3.84-3.74 (4H, m, 4xC<u>H</u>) 2.93 (1H, br s, O<u>H</u>), 1.18 (9H, s,

3xC<u>H</u>$_3$) ppm; ^{13}C **NMR** (50.3MHz,$CDCl_3$) δ 177.84 (C=O), 88.11 (CH), 80.13 (CH), 75.57 (CH), 74.85 (CH), 73.59 (CH_2), 70.60 (CH), 38.14 (quat C), 26.87 (3xCH_3) ppm; **IR** (thin film) ν_{max} 3440 (OH), 1730 (C=O) cm^{-1}; **MS** (ei) m/z 28 (30%), 40 (40%), 56 (base), 68 (30%), 85 (60%), 215 (25%, $(M-15)^+$), 231 (50%, M^+).

6.2 Permanent protection of C-5 *endo* hydroxyl group (using *tert*-butyldiphenylsilylchloride)

To a stirring solution of the *1,4:3,6-dianhydro-D-glucitol-2-acylate* (11.0g, 0.048mol) in dimethylformamide (100ml) at room temperature was imidazole (7.2g, 2.2eq) pre-dissolved in dimethylformamide (50ml). After stirring for 20 minutes *tert*-butyldiphenylsilylchloride (14.4g, 1.1eq) was added in one. Stirring was resumed and reaction progress was monitored by thin layer chromatography and after 4 hours indicated reaction had reached completion (all starting material consumed). At this point reaction solvent was removed under reduced pressure to yield a thick yellow paste. Dichloromethane (60ml) was added and the resultant inorganic salts were filtered off before evaporating the filtrate to yield a viscous yellow oil. The crude material was loaded onto a chromatographic column and flushed through with diethyl ether to return a pale yellow thin oil (21.5g, >95%).

^{1}**H NMR** (360.13MHz,$CDCl_3$) δ 7.70-7.66 (5H, m, Ph), 7.47-7.40 (5H, m, Ph), 4.72 (1H, dd, *J*=6.3, 4.5 Hz, C<u>H</u>), 4.44-4.39 (1H, m, 2xC<u>H</u>), 4.26 (1H, d, *J*=6.0 Hz, C<u>H</u>), 3.85 (1H, d, *J*=9.7 Hz, C<u>H</u>), 3.78 (1H, dd, *J*=9.2, 6.0 Hz, C<u>H</u>), 3.68 (1H, dd, *J*=9.7, 3.3 Hz, C<u>H</u>), 3.36 (1H, dd, *J*=9.2, 6.3 Hz, C<u>H</u>), 1.21 (9H, s, 3xC<u>H</u>$_3$), 1.08 (9H, s, 3xC<u>H</u>$_3$) ppm; ^{13}**C NMR** (50.3MHz,$CDCl_3$) δ 177.62 (C=O), 133.53 (Phenyl CH), 133.19 (quat C), 129.84 (Phenyl CH), 127.50 (Phenyl CH), 88.21

(CH), 81.42 (CH), 78.15 (CH), 75.82 (CH_2), 72.97 (CH_2), 72.32 (CH), 38.46 (quat C), 26.93 (3xCH_3), 26.85 (3xCH_3) ppm; **IR** (thin film) ν_{max} 3090 (Phenyl CH), 1730 (C=O) cm^{-1}; **MS** (ei) m/z 40 (55%), 56 (base), 68 (40%), 135 (50%), 199 (40%), 241 (35%), 369 (25%), 385 (70%).

6.3 Deprotection of C-2 *exo* hydroxyl group by mild hydrolysis (using butyllithium) to yield C-5 *endo* protected product (143)

Butyllithium (72ml, 1.6M, 3eq) was added dropwise over 30 minutes to a stirring solution of the substrate (18g, 0.038mol) in dry THF (80ml) under argon at -78°C. After stirring for 2 hours the reaction mixture was allowed to warm to room temperature and stirring continued for a further 72 hours with periodic monitoring by TLC. Upon completion of the reaction a saturated solution of ammonium chloride (60ml) was added and from the resulting two layer mixture the aqueous layer was extracted into diethyl ether (3x40ml). The organic layer and extracts were then combined, washed with water (50ml), dried with powdered magnesium sulphate, filtered and evaporated under reduced pressure to yield a pale yellow viscous oil. The crude material was loaded onto a chromatographic column and flushed through with diethyl ether to return the C-5 *endo* selectively protected product **(143)** as a colourless viscous oil (14.1g, >95%).

^{1}H NMR (360.13MHz,$CDCl_3$) δ 7.67-7.63 (5H, m, Ph), 7.44-7.39 (5H, m, Ph), 4.69 (1H, dd, *J*=6.5, 4.8 Hz, C<u>H</u>), 4.40-4.36 (1H, m, 2xC<u>H</u>), 4.26 (1H, d, *J*=6.1 Hz, C<u>H</u>), 3.89 (1H, d, *J*=9.7 Hz, C<u>H</u>), 3.80 (1H, dd, *J*=9.3, 6.1 Hz, C<u>H</u>), 3.67 (1H, dd, *J*=9.7, 3.2 Hz, C<u>H</u>), 3.41 (1H, dd, *J*=9.3, 6.3 Hz, C<u>H</u>), 2.70 (1H, br s, O<u>H</u>), 1.17 (9H, s, 3xC<u>H</u>$_3$) ppm; **^{13}C NMR** (50.3MHz,$CDCl_3$) δ 135.46 (Phenyl CH), 132.98 (quat C), 129.78 (Phenyl CH), 127.70 (Phenyl CH), 88.04 (CH), 81.58

(CH), 78.03 (CH), 75.66 (CH_2), 73.09 (CH_2), 72.25 (CH), 26.68 (3xCH_3), 18.96 (quat C) ppm; **IR** (thin film) ν_{max} 3360 (OH), 3070 (Phenyl CH) cm^{-1}; **MS** (ei) m/z 40 (50%), 56 (base), 68 (60%), 135 (60%), 199 (50%), 221 (30%), 369 (40%, $(M-15)^+$), 385 (50%, M^+).

6.4 Preparation of *1,4:3,6-dianhydro-D-glucitol-2-chloroformate* (144)

A solution of substrate **(143)** (8.0g, 0.021mol) and pyridine (1.8g, 0.023mol) in dry dichloromethane (120ml) was prepared and added carefully in 10ml aliquots to a stirring solution of phosgene (38ml, 1.93M, 3.5eq) in dichloromethane (80ml) at room temperature under argon. After leaving to stir overnight the by product precipitate (pyridinium chloride) was filtered off and washed with dry THF (3x30ml). The filtrate was then evaporated to remove the reaction solvent and excess phosgene (fume cupboard!) before combining with the washings and evaporating again to yield a light oil (9.3g, 100%), subsequently identified as target material **(144)**.

^{1}H NMR (200.13MHz,$CDCl_3$) δ 7.80-7.70 (5H, m, Ph), 7.51-7.43 (5H, m, Ph), 5.30 (1H, d, *J*=2.1 Hz, C<u>H</u>), 4.60-4.56 (2H, m, 2xC<u>H</u>), 4.34 (1H, dd, *J*=6.0, 4.8 Hz, C<u>H</u>), 4.19 (1H, d, *J*=2.1 Hz, C<u>H</u>), 3.72-3.64 (2H, m, 2xC<u>H</u>), 3.42 (1H, d, *J*=6.1 Hz, C<u>H</u>), 1.10 (9H, s, 3xC<u>H</u>$_3$) ppm; **^{13}C NMR** (50.3MHz,$CDCl_3$) δ 149.56 (C=O), 135.81 (Phenyl CH), 133.59 (quat C), 130.12 (Phenyl CH), 128.00 (Phenyl CH), 86.43 (CH), 84.91 (CH), 81.95 (CH), 74.21 (CH), 72.45 (CH_2), 72.43 (CH_2), 26.54 (3xCH_3), 19.07 (quat C) ppm; **IR** (thin film) ν_{max} 3070 (Phenyl CH), 1780 (C=O) cm^{-1}; **MS** (ei) m/z 44 (30%), 135 (base), 147 (40%), 186 (90%), 197 (50%), 350 (30%), 368 (35%), 431 (50%, ^{35}Cl $(M-15)^+$), 433 (10%, ^{37}Cl $(M-15)^+$), 446 (80%, $^{35}Cl, M^+$), 448 (25%, $^{37}Cl, M^+$).

6.5 Preparation of *1,4:3,6-dianhydro-D-glucitol-2-azidoformate* (145)

A solution of sodium azide (2.50g, 0.038mol) and tetrabutylammonium bromide, TBAB, (3g) in distilled water (150ml) was stirred at room temperature for 15 minutes before carefully adding in small aliquots a solution of chloroformate derivative **(144)** (8.6g, 0.019mol) in THF (60ml). The reaction vessel and contents were left to stir overnight whereupon the reaction solvent was removed *in vacuo* by rotary evaporation. The resulting aqueous solution was extracted into diethyl ether (3x40ml) and the organic extracts then combined, dried with powdered magnesium sulphate, filtered and evaporated to yield a light brown oil in quantitative yield, substance was later identified as being the target material *1,4:3,6-dianhydro-D-glucitol-2-azidoformate* **(145)**.

^{1}H NMR (200.13MHz,$CDCl_3$) δ 7.79-7.72 (5H, m, Ph), 7.50-7.43 (5H, m, Ph), 5.13 (1H, dd, *J*=3.3, 1.2 Hz, C<u>H</u>), 4.47 (1H, d, *J*=3.0 Hz, C<u>H</u>), 4.10 (1H, dd, *J*=3.3, 1.2 Hz, C<u>H</u>), 3.69 (1H, m, C<u>H</u>), 3.59-3.48 (4H, m, 4xC<u>H</u>), 1.07 (9H, s, 3xC<u>H</u>$_3$) ppm; **^{13}C NMR** (50.3MHz,$CDCl_3$) δ 156.60 (C=O), 135.61 (Phenyl CH), 133.43 (quat C), 129.99 (Phenyl CH), 127.84 (Phenyl CH), 85.07 (CH), 82.57 (CH), 81.76 (CH), 74.16 (CH), 72.57 (CH_2), 72.15 (CH_2), 26.54 (3xCH_3), 18.90 (quat C) ppm; **IR** (thin film) ν_{max} 2135 (N_3), 1735 (C=O) cm^{-1}; **MS** (ei) m/z 31 (30%), 40 (40%), 68 (80%), 91 (70%), 135 (base), 142 (70%), 184 (60%), 197 (70%), 242 (90%), 350 (20%), 376 (35%), 426 (50%, $M^+ - N_2$).

6.6 Solution thermolysis of azidoformate (144) in TCE to generate *1,3-oxazolidin-2-one* chiral auxiliary (147)

To a refluxing solution of dry 1,1,2,2-tetrachloroethane, TCE, (500ml) (bp=147°C) under argon was added dropwise by perfusion over 30 minutes a solution of substrate **(144)** (8.5g, 0.019mol) in TCE (20ml). The reflux was continued for a total of 90 minutes at which point TLC analysis indicated all start material had been consumed. The solution was allowed to cool then removed of the reaction solvent by *in vacuo* evaporation (fume cupboard) to yield a dark brown viscous oil. The crude material was subjected to flash chromatography using gradient elution and following recrystallisation upon standing, resulted in the isolation of the desired auxiliary **(147)** in a yield of 35%.

Mp = 201°C; **^{1}H NMR** (360.13MHz,$CDCl_3$) δ 7.64-7.60 (5H, m, Ph), 7.45-7.35 (5H, m, Ph), 6.63 (1H, br s, NH), 5.47 (1H, dd, *J*=6.1, 1.2 Hz, CH), 4.93-4.87 (2H, m, 2xCH), 4.41-4.37 (2H, m, 2xCH), 3.88-3.84 (2H, m, 2xCH), 1.06 (9H, s, 3xCH_3) ppm; **^{13}C NMR** (50.3MHz,$CDCl_3$) δ 157.69 (C=O), 135.35 (Phenyl CH), 132.81 (quat C), 129.80 (Phenyl CH), 127.65 (Phenyl CH), 88.71 (CH), 87.28 (CH), 80.39 (quat C), 79.70 (CH), 77.24 (CH_2), 77.12 (CH_2), 26.57 (3xCH_3), 18.86 (quat C) ppm; **IR** (thin film) ν_{max} 3360 (N-H), 1730 (C=O) cm^{-1}; **MS** (ei) m/z 44 (40%), 76 (50%), 105 (60%), 121 (40%), 135 (base), 163 (40%), 197 (80%), 350 (35%), 368 (25%), 410 (20%, $(M-15)^+$), 426 (70%, M^+).

6.7 Functionalisation of chiral 1,3-oxazolidin-2-one (147) to propionate derivative (151)

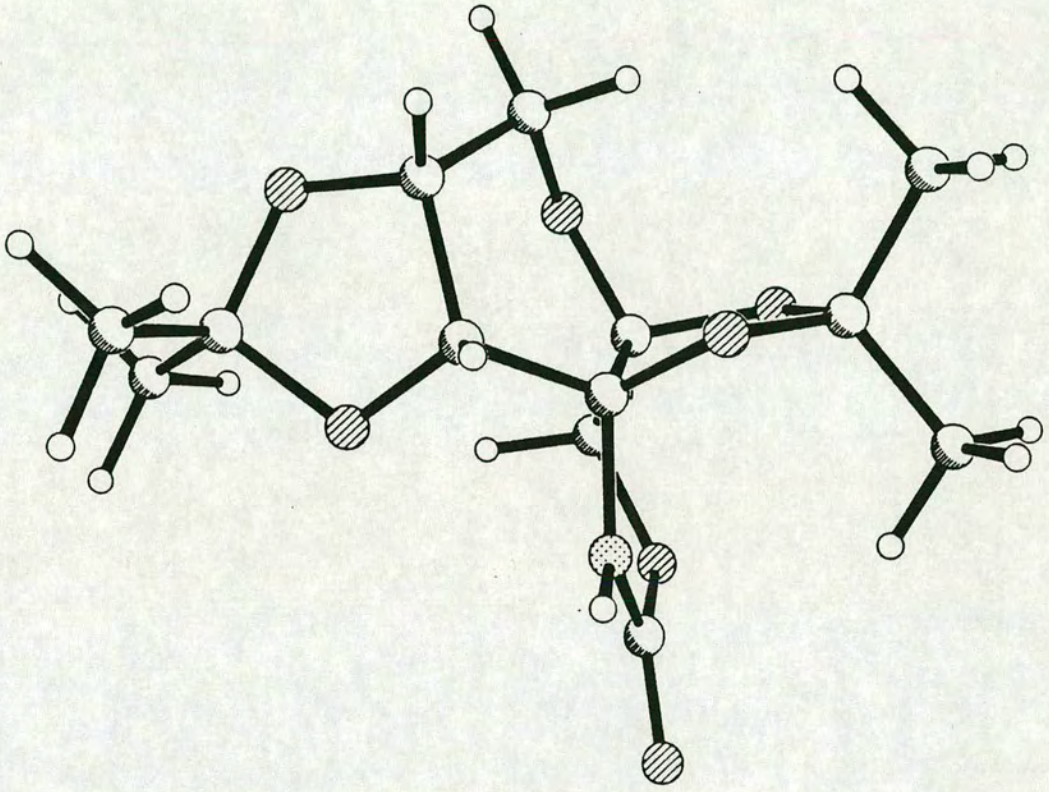
Magnesium turnings (0.14g, 5.65mmol) were added to a reaction flask under an inert argon atmosphere and covered with dry diethyl ether. After adding a couple of drops of methyl iodide (as indicator), bromomethane (2.0ml, 2.0M, 1.7eq) was added slowly in small aliquots and reaction was allowed to continue until completion. At this point the temperature was lowered to 0°C and a solution of the auxiliary (147) (2.0g, 4.71mmol) in dry THF (30ml) was added. Stirring was continued for 20 minutes before adjusting the temperature to -78°C whereupon freshly distilled propionyl chloride (2.61g, 6eq) was added dropwise over 10 minutes. The contents of the reaction vessel were stirred at -78°C for a further 30 minutes then allowed to warm to room temperature and stirred again overnight. Analysis of a TLC sample suggested reaction had reached completion and a saturated solution of ammonium chloride (30ml) was added to quench the reaction. The reaction volatiles were removed by rotary evaporation at the pump and the resulting aqueous layer was extracted with diethyl ether (3x30ml). The organic extracts were combined, washed with water, dried with magnesium sulphate, filtered and evaporated to return a colourless light oil which was later identified as propionate (151) (2.2g, >97%).

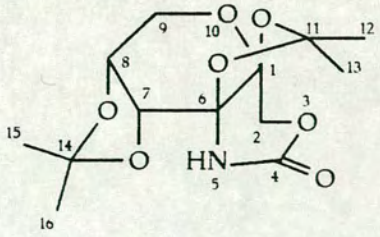
^{1}H NMR (360.13MHz,$CDCl_3$) δ 7.68-7.61 (5H, m, Ph), 7.41-7.35 (5H, m, Ph), 5.35-5.28 (2H, m, 2x C<u>H</u>), 4.10-4.05 (2H, m, 2xC<u>H</u>), 4.41-4.37 (2H, m, 2xC<u>H</u>), 3.19 (1H, d, *J*=5.9 Hz, C<u>H</u>), 2.30 (2H, q, *J*=7.7 Hz, C<u>H</u>$_2$), 1.11 (3H, t, *J*=7.6 Hz, C<u>H</u>$_3$), 1.04 (9H, s, 3xC<u>H</u>$_3$) ppm; **^{13}C NMR** (50.3MHz,$CDCl_3$) δ 178.42 (C=O), 158.34 (C=O), 135.64 (Phenyl CH), 133.02 (quat C), 129.62 (Phenyl CH), 127.72 (Phenyl CH), 88.80 (CH), 87.32 (CH), 80.46 (quat C), 79.77 (CH), 77.30 (CH_2), 77.14 (CH_2), 34.17 (CH_2), 26.61 (3xCH_3), 18.73 (quat C), 9.56 (CH_3) ppm; **IR** (thin film) ν_{max} 1760 (C=O), 1730 (C=O) cm^{-1}.

APPENDICES

Appendix A

X-Ray Crystal Structure of Auxiliary (77)





Appendix B

Stereoscopic view of Auxiliary (77)

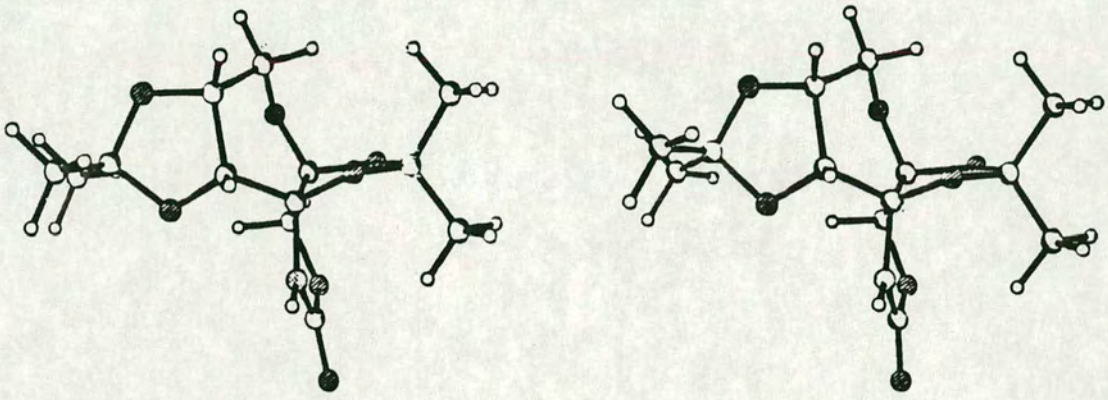


Table 1 Bond lengths (Å)

(with standard deviations)

C(1) - O(1)	1.428(7)	1.413(7)
C(1) - O(10)	1.394(7)	1.383(7)
C(1) - C(6)	1.511(7)	1.539(7)
C(1) - C(2)	1.496(8)	1.504(8)
O(1) - C(11)	1.437(7)	1.443(7)
O(10) - C(9)	1.438(7)	1.440(7)
C(9) - C(8)	1.504(8)	1.496(8)
C(8) - O(8)	1.423(7)	1.419(7)
C(8) - C(7)	1.533(8)	1.536(8)
O(8) - C(14)	1.423(7)	1.405(8)
C(7) - O(7)	1.423(6)	1.403(7)
C(7) - C(6)	1.525(7)	1.515(7)
O(7) - C(14)	1.445(7)	1.420(8)
C(6) - O(6)	1.415(6)	1.425(6)
C(6) - N(5)	1.453(7)	1.443(7)
O(6) - C(11)	1.434(7)	1.443(7)
N(5) - H(5)	0.99(5)	0.89(5)
N(5) - C(4)	1.360(8)	1.336(7)
C(4) - O(4)	1.200(8)	1.219(7)
C(4) - O(3)	1.348(8)	1.352(7)
O(3) - C(2)	1.432(7)	1.434(7)
C(11) - C(12)	1.500(9)	1.519(9)
C(11) - C(13)	1.503(9)	1.500(9)
C(14) - C(15)	1.499(9)	1.477(11)
C(14) - C(16)	1.516(8)	1.501(11)

Table 2 Bond angles (degrees)

(with standard deviations)

O(1) - C(1) - O(10)	109.0(4)	112.8(4)	
O(1) - C(1) - C(2)	110.5(4)	109.7(4)	
O(10) - C(1) - C(2)	105.1(4)	104.8(4)	
C(1) - O(1) - C(11)	110.6(4)	111.7(4)	
O(10) - C(9) - C(8)	110.4(5)	111.6(5)	
C(9) - C(8) - C(7)	113.1(5)	113.1(5)	
C(8) - O(8) - C(14)	108.7(4)	110.0(5)	
C(8) - C(7) - C(6)	114.7(4)	113.8(4)	
C(7) - O(7) - C(14)	107.3(4)	107.7(4)	
C(1) - C(6) - O(6)	103.8(4)	103.1(4)	
C(7) - C(6) - O(6)	107.1(4)	106.4(4)	
O(6) - C(6) - N(5)	111.7(4)	111.8(4)	
C(6) - N(5) - H(5)	112.0(30)	115.0(30)	
H(5) - N(5) - C(4)	118.0(30)	115.0(30)	
N(5) - C(4) - O(3)	116.3(5)	117.7(5)	
C(4) - O(3) - C(2)	117.3(5)	117.6(4)	
O(1) - C(11) - O(6)	104.4(4)	104.1(4)	
O(1) - C(11) - C(13)	110.0(5)	109.7(5)	
O(6) - C(11) - C(13)	111.7(5)	111.6(5)	
O(8) - C(14) - O(7)	103.0(4)	105.5(5)	
O(8) - C(14) - C(16)	112.0(5)	109.5(6)	
O(7) - C(14) - C(16)	110.7(5)	110.4(6)	
O(1) - C(1) - C(6)	103.9(4)	103.2(4)	
O(10) - C(1) - C(6)	115.5(4)	114.7(4)	
C(6) - C(1) - C(2)	112.8(5)	111.7(4)	
C(1) - O(10) - C(9)	116.1(4)	114.7(4)	
C(9) - C(8) - O(8)	108.0(4)	110.0(5)	
O(8) - C(8) - C(7)	104.6(4)	103.9(4)	
C(8) - C(7) - O(7)	104.3(4)	104.4(4)	
O(7) - C(7) - C(6)	107.5(4)	108.1(4)	
C(1) - C(6) - C(7)	115.0(4)	114.8(4)	
C(1) - C(6) - N(5)	109.9(4)	110.1(4)	
C(7) - C(6) - N(5)	109.3(4)	110.4(4)	
C(6) - O(6) - C(11)	108.8(4)	108.5(4)	
C(6) - N(5) - C(4)	128.4(5)	128.2(5)	
N(5) - C(4) - O(4)	123.3(6)	124.1(5)	
O(4) - C(4) - O(3)	120.4(6)	118.2(5)	
C(1) - C(2) - O(3)	110.8(5)	111.4(4)	
O(1) - C(11) - C(12)	110.6(5)	109.8(5)	
O(6) - C(11) - C(12)	108.0(5)	108.5(5)	
C(12) - C(11) - C(13)	111.9(5)	112.8(5)	
O(8) - C(14) - C(15)	109.0(5)	108.9(6)	
O(7) - C(14) - C(15)	108.0(5)	108.9(6)	
C(15) - C(14) - C(16)	113.5(5)	113.2(6)	

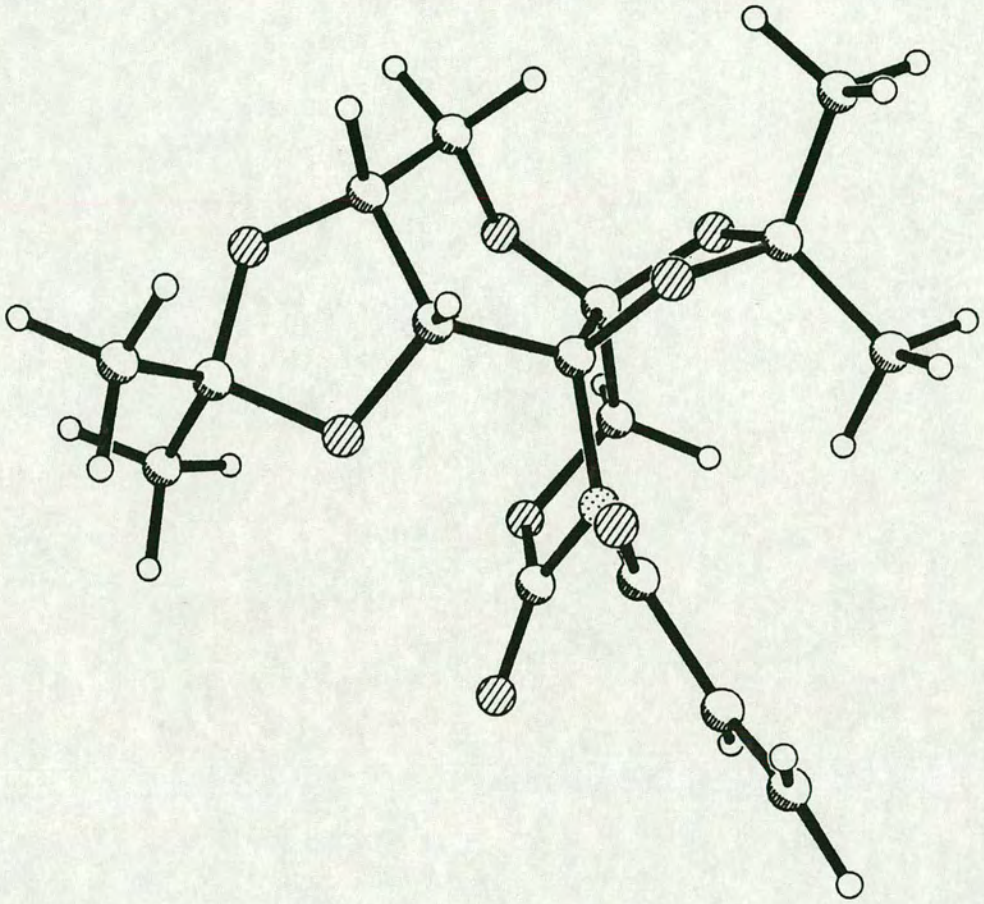
Table 3 Torsion angles (degrees)

(with standard deviations)

O(10) - C(1) - O(1) - C(11)	112.3(5)	110.9(6)	
C(2) - C(1) - O(1) -C(11)	-132.6(5)	-132.6(5)	
C(6) - C(1) - O(10) - C(9)	29.0(6)	34.3(6)	
O(1) - C(1) - C(6) - C(7)	141.4(4)	142.0(4)	
O(1) - C(1) - C(6) - N(5)	-94.8(5)	-92.7(5)	
O(10) - C(1) - C(6) - O(6)	-94.6(5)	-96.3(5)	
C(2) - C(1) - C(6) - C(7)	-98.9(5)	-100.2(5)	
C(2) - C(1) - C(6) - N(5)	24.9(6)	25.2(6)	
O(10) - C(1) - C(2) - O(3)	179.6(4)	-177.4(4)	
C(1) - O(1) - C(11) - O(6)	-6.2(6)	-5.0(6)	
C(1) - O(1) - C(11) - C(13)	113.8(5)	114.5(5)	
O(10) - C(9) - C(8) - O(8)	-71.2(5)	-76.2(6)	
C(9) - C(8) - O(8) - C(14)	138.4(5)	126.4(5)	
C(9) - C(8) - C(7) - O(7)	-113.1(5)	-106.2(5)	
O(8) - C(8) - C(7) - O(7)	4.1(5)	13.1(5)	
C(8) - O(8) - C(14) - O(7)	-32.5(5)	-21.3(6)	
C(8) - O(8) - C(14) - C(16)	86.5(5)	97.5(6)	
C(6) - C(7) - O(7) - C(14)	-146.2(4)	-148.0(4)	
C(8) - C(7) - C(6) - O(6)	77.0(5)	72.2(5)	
O(7) - C(7) - C(6) - C(1)	77.8(5)	74.4(5)	
O(7) - C(7) - C(6) - N(5)	-46.4(5)	-50.8(5)	
C(7) - O(7) - C(14) - C(15)	150.3(4)	146.9(5)	
C(1) - C(6) - O(6) - C(11)	-30.0(5)	-31.2(5)	
N(5) - C(6) - O(6) - C(11)	88.3(5)	87.0(5)	
C(7) - C(6) - N(5) - C(4)	133.8(6)	136.5(6)	
C(6) - O(6) - C(11) - O(1)	23.1(5)	23.4(5)	
C(6) - O(6) - C(11) - C(13)	-95.7(5)	-94.9(5)	
C(6) - N(5) - C(4) - O(3)	-9.5(9)	-15.1(8)	
O(4) - C(4) - O(3) - C(2)	159.2(6)	165.3(5)	
C(6) - C(1) - O(1) - C(11)	-11.4(5)	-13.4(5)	
O(1) - C(1) - O(1) - C(11)	-87.5(5)	-83.4(5)	
C(2) - C(1) - O(10) - C(9)	154.0(5)	157.2(4)	
O(1) - C(1) - C(6) - O(6)	24.8(5)	26.7(5)	
O(10) - C(1) - C(6) - C(7)	22.1(6)	18.9(6)	
O(10) -C(1) - C(6) - N(5)	145.9(4)	144.3(4)	
C(2) - C(1) - C(6) - O(6)	144.5(4)	144.6(4)	
O(1) - C(1) - C(2) - O(3)	62.1(6)	61.2(6)	
C(6) - C(1) - C(2) - O(3)	-53.7(6)	-52.7(6)	
C(1) - O(1) - C(11) - C(12)	-122.2(5)	-121.0(5)	
C(1) - O(10) - C(9) - C(8)	-64.1(6)	-66.2(6)	
O(10) - C(9) - C(8) - C(7)	44.0(6)	39.4(6)	
C(7) - C(8) - O(8) - C(14)	17.8(5)	5.1(6)	
C(9) - C(8) - C(7) - C(6)	4.2(6)	11.5(7)	
O(8) - C(8) - C(7) - C(6)	121.4(5)	130.7(5)	
C(8) - O(8) - C(14) - C(15)	-147.0(5)	-138.1(6)	
C(8) - C(7) - O(7) - C(14)	-24.1(5)	-26.5(5)	
C(8) - C(7) - C(6) - C(1)	-37.7(6)	-41.1(6)	
C(8) - C(7) - C(6) - N(5)	-161.8(4)	-166.3(4)	
O(7) - C(7) - C(6) - O(6)	-167.5(4)	-172.3(4)	
C(7) - O(7) - C(14) - O(8)	35.1(5)	30.2(6)	
C(7) - O(7) - C(14) - C(16)	-84.8(5)	-88.1(6)	
C(7) - C(6) - O(6) - C(11)	-152.0(4)	-152.4(4)	
C(1) - C(6) - N(5) - C(4)	6.7(7)	8.6(7)	
O(6) - C(6) - N(5) - C(4)	-107.9(6)	-105.3(6)	
C(6) - O(6) - C(11) - C(12)	140.9(5)	140.3(5)	
C(6) - N(5) - C(4) - O(4)	168.9(6)	163.7(5)	
N(5) - C(4) - O(3) - C(2)	-22.3(8)	-15.9(7)	
C(4) - O(3) - C(2) - C(1)	53.5(7)	49.3(6)	

Appendix C

X-Ray Crystal Structure of α,β unsaturated Acrylate (102)



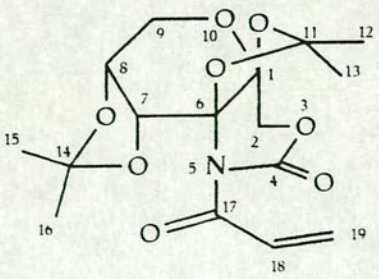


Table 1 Bond lengths (Å)

(with standard deviations)

C(1)-O(10)	1.392(10)	C(1')-O(10')	1.395(11)
C(1)-O(1)	1.395(10)	C(1')-O(1')	1.433(11)
C(1)-C(2)	1.515(12)	C(1')-C(2')	1.511(13)
C(1)-C(6)	1.565(11)	C(1')-C(6')	1.560(12)
O(1)-C(11)	1.416(10)	O(1')-C(11')	1.425(11)
C(2)-O(3)	1.443(10)	C(2')-O(3')	1.443(11)
O(3)-C(4)	1.354(10)	O(3')-C(4')	1.368(11)
C(4)-O(4)	1.196(11)	C(4')-O(4')	1.182(11)
C(4)-N(5)	1.388(11)	C(4')-N(5')	1.388(11)
N(5)-C(17)	1.432(10)	N(5')-C(17')	1.405(11)
N(5)-C(6)	1.476(10)	N(5')-C(6')	1.507(10)
C(6)-O(6)	1.416(9)	C(6')-O(6')	1.383(10)
C(6)-C(7)	1.542(11)	C(6')-C(7')	1.550(12)
O(6)-C(11)	1.445(9)	O(6')-C(11')	1.432(10)
C(7)-O(7)	1.429(9)	C(7')-O(7')	1.420(10)
C(7)-C(8)	1.532(11)	C(7')-C(8')	1.513(12)
O(7)-C(14)	1.433(11)	O(7')-C(14')	1.409(11)
C(8)-O(8)	1.439(10)	C(8')-O(8')	1.439(10)
C(8)-C(9)	1.492(12)	C(8')-C(9')	1.512(12)
O(8)-C(14)	1.421(12)	O(8')-C(14')	1.427(11)
C(9)-O(10)	1.424(11)	C(9')-O(10')	1.421(11)
C(11)-C(13)	1.518(13)	C(11')-C(13')	1.52(2)
C(11)-C(12)	1.530(13)	C(11')-C(12')	1.524(13)
C(14)-C(16)	1.48(2)	C(14')-C(16')	1.47(2)
C(14)-C(15)	1.48(2)	C(14')-C(15')	1.50(2)
C(17)-O(17)	1.211(10)	C(17')-O(17')	1.205(11)
C(17)-C(18)	1.477(12)	C(17')-C(18')	1.467(13)
C(18)-C(19)	1.266(14)	C(18')-C(19')	1.306(14)

Table 2 Bond angles (degrees)

O(10)-C(1)-O(1)	110.8(7)	O(10')-C(1')-O(1')	108.6(7)
O(10)-C(1)-C(2)	106.7(7)	O(10')-C(1')-C(2')	107.0(8)
O(1)-C(1)-C(2)	109.8(7)	O(1')-C(1')-C(2')	109.7(8)
O(10)-C(1)-C(6)	113.8(7)	O(10')-C(1')-C(6')	114.1(7)
O(1)-C(1)-C(6)	105.6(6)	O(1')-C(1')-C(6')	104.5(7)
C(2)-C(1)-C(6)	110.1(7)	C(2')-C(1')-C(6')	112.9(8)
C(1)-O(1)-C(11)	110.7(6)	C(11')-O(1')-C(1')	109.2(6)
O(3)-C(2)-C(1)	110.7(7)	O(3')-C(2')-C(1')	109.1(7)
C(4)-O(3)-C(2)	114.6(7)	C(4')-O(3')-C(2')	115.6(7)
O(4)-C(4)-O(3)	121.7(8)	O(4')-C(4')-O(3')	120.7(8)
O(4)-C(4)-N(5)	124.4(8)	O(4')-C(4')-N(5')	124.9(9)
O(3)-C(4)-N(5)	113.9(8)	O(3')-C(4')-N(5')	114.4(8)
C(4)-N(5)-C(17)	118.1(7)	C(4')-N(5')-C(17')	118.8(8)
C(4)-N(5)-C(6)	118.6(6)	C(4')-N(5')-C(6')	118.7(7)
C(17)-N(5)-C(6)	118.0(6)	C(17')-N(5')-C(6')	118.0(7)
O(6)-C(6)-N(5)	112.5(6)	O(6')-C(6')-N(5')	111.8(6)
O(6)-C(6)-C(7)	105.7(6)	O(6')-C(6')-C(7')	107.0(6)
N(5)-C(6)-C(7)	110.6(6)	N(5')-C(6')-C(7')	110.1(7)
O(6)-C(6)-C(1)	102.5(6)	O(6')-C(6')-C(1')	103.8(7)
N(5)-C(6)-C(1)	108.6(7)	N(5')-C(6')-C(1')	107.9(6)
C(7)-C(6)-C(1)	116.7(6)	C(7')-C(6')-C(1')	116.1(7)
C(6)-O(6)-C(11)	109.1(6)	C(6')-O(6')-C(11')	110.5(6)
O(7)-C(7)-C(8)	104.8(6)	O(7')-C(7')-C(8')	106.2(7)
O(7)-C(7)-C(6)	108.0(7)	O(7')-C(7')-C(6')	108.1(6)
C(8)-C(7)-C(6)	115.0(7)	C(8')-C(7')-C(6')	115.2(7)
C(7)-O(7)-C(14)	108.3(7)	C(14')-O(7')-C(7')	107.3(7)
O(8)-C(8)-C(9)	108.8(7)	O(8')-C(8')-C(9')	105.8(7)
O(8)-C(8)-C(7)	104.5(6)	O(8')-C(8')-C(7')	103.5(7)
C(9)-C(8)-C(7)	112.9(7)	C(9')-C(8')-C(7')	114.4(8)
C(14)-O(8)-C(8)	108.4(7)	C(14')-O(8')-C(8')	107.2(7)
O(10)-C(9)-C(8)	111.2(7)	O(10')-C(9')-C(8')	110.5(7)
C(1)-O(10)-C(9)	112.1(7)	C(1')-O(10')-C(9')	114.0(7)
O(1)-C(11)-O(6)	104.4(6)	O(1')-C(11')-O(6')	104.4(7)
O(1)-C(11)-C(13)	111.6(7)	O(1')-C(11')-C(13')	112.6(8)
O(6)-C(11)-C(13)	109.8(7)	O(6')-C(11')-C(13')	111.6(8)
O(1)-C(11)-C(12)	110.0(7)	O(1')-C(11')-C(12')	109.8(8)
O(6)-C(11)-C(12)	107.3(7)	O(6')-C(11')-C(12')	107.5(7)
C(13)-C(11)-C(12)	113.3(8)	C(13')-C(11')-C(12')	110.7(9)
O(8)-C(14)-O(7)	104.5(7)	O(7')-C(14')-O(8')	104.6(7)
O(8)-C(14)-C(16)	110.2(9)	O(8')-C(14')-C(16')	107.3(9)
O(7)-C(14)-C(16)	109.0(9)	O(7')-C(14')-C(16')	107.4(9)
O(8)-C(14)-C(15)	111.0(10)	O(8')-C(14')-C(15')	110.9(9)
O(7)-C(14)-C(15)	107.9(9)	O(7')-C(14')-C(15')	110.5(9)
C(16)-C(14)-C(15)	113.7(10)	C(16')-C(14')-C(15')	115.4(10)
O(17)-C(17)-N(5)	121.5(8)	O(17')-C(17')-N(5')	120.2(8)
O(17)-C(17)-C(18)	123.4(8)	O(17')-C(17')-C(18')	124.3(9)
N(5)-C(17)-C(18)	114.9(7)	N(5')-C(17')-C(18')	115.2(8)
C(19)-C(18)-C(17)	122.7(10)	C(19')-C(18')-C(17')	122.9(10)

Table 3 Torsion angles (degrees)

(with standard deviations)

O(10)-C(1)-O(1)-C(11)	130.7(7)	O(10')-C(1')-O(1')-C(11')	132.5(7)
C(2)-C(1)-O(1)-C(11)	-111.6(8)	C(2')-C(1')-O(1')-C(11')	-110.9(8)
C(6)-C(1)-O(1)-C(11)	7.1(9)	C(6')-C(1')-O(1')-C(11')	10.4(9)
O(10)-C(1)-C(2)-O(3)	-81.8(8)	O(10')-C(1')-C(2')-O(3')	-83.8(9)
O(1)-C(1)-C(2)-O(3)	158.0(6)	O(1')-C(1')-C(2')-O(3')	158.7(7)
C(6)-C(1)-C(2)-O(3)	42.2(9)	C(6')-C(1')-C(2')-O(3')	42.5(11)
C(1)-C(2)-O(3)-C(4)	-64.0(9)	C(1')-C(2')-O(3')-C(4')	-63.1(10)
C(2)-O(3)-C(4)-O(4)	-155.5(8)	C(2')-O(3')-C(4')-O(4')	-155.0(9)
C(2)-O(3)-C(4)-N(5)	23.5(9)	C(2')-O(3')-C(4')-N(5')	24.1(10)
O(4)-C(4)-N(5)-C(17)	9.3(12)	O(4')-C(4')-N(5')-C(17')	9.5(13)
O(3)-C(4)-N(5)-C(17	-169.7(7)	O(3')-C(4')-N(5')-C(17')	-169.7(7)
O(4)-C(4)-N(5)-C(6)	-144.5(8)	O(4')-C(4')-N(5')-C(6')	-146.2(9)
O(3)-C(4)-N(5)-C(6)	36.5(10)	O(3')-C(4')-N(5')-C(6')	34.6(10)
C(4)-N(5)-C(6)-O(6)	-165.1(7)	C(4')-N(5')-C(6')-O(6')	-162.6(7)
C(17)-N(5)-C(6)-O(6)	41.1(9)	C(17')-N(5')-C(6')-O(6')	41.5(9)
C(4)-N(5)-C(6)-C(7)	76.9(9)	C(17')-N(5')-C(6')-C(7')	-77.3(9)
C(4)-N(5)-C(6)-C(1)	-52.4(9)	C(4')-N(5')-C(6')-C(1')	-49.0(9)
C(17)-N(5)-C(6)-C(1)	153.8(7)	C(17')-N(5')-C(6')-C(1')	155.0(7)
O(10)-C(1)-C(6)-O(6)	-111.3(7)	O(10')-C(1')-C(6')-O(6')	-111.4(8)
O(1)-C(1)-C(6)-O(6)	10.5(8)	O(1')-C(1')-C(6')-O(6')	7.0(8)
C(2)-C(1)-C(6)-O(6)	128.9(7)	C(2')-C(1')-C(6')-O(6')	126.2(8)
O(10)-C(1)-C(6)-N(5)	129.5(7)	O(10')-C(1')-C(6')-N(5')	129.8(8)
O(1)-C(1)-C(6)-N(5)	-108.7(7)	O(1')-C(1')-C(6')-N(5')	-111.7(7)
C(2)-C(1)-C(6)-N(5)	9.7(9)	C(2')-C(1')-C(6')-N(5')	7.4(10)
O(10)-C(1)-C(6)-C(7)	3.7(11)	O(10')-C(1')-C(6')-C(7')	5.7(11)
O(1)-C(1)-C(6)-C(7)	125.5(7)	O(1')-C(1')-C(6')-C(7')	124.1(8)
C(2)-C(1)-C(6)-C(7)	-116.0(8)	C(2')-C(1')-C(6')-C(7')	-116.7(8)
N(5)-C(6)-O(6)-C(11)	92.4(8)	N(5')-C(6')-O(6')-C(11')	93.9(8)
C(7)-C(6)-O(6)-C(11)	-146.8(6)	C(7')-C(6')-O(6')-C(11')	-145.5(7)
C(1)-C(6)-O(6)-C(11)	-24.1(8)	C(1')-C(6')-O(6')-C(11')	-22.2(9)
O(6)-C(6)-C(7)-O(7)	-155.8(6)	O(6')-C(6')-C(7')-O(7')	-154.0(7)
N(5)-C(6)-C(7)-O(7)	-33.8(9)	N(5')-C(6')-C(7')-O(7')	-32.3(9)
C(1)-C(6)-C(7)-O(7)	91.0(8)	C(1')-C(6')-C(7')-O(7')	90.7(9)
O(6)-C(6)-C(7)-C(8)	87.6(8)	O(6')-C(6')-C(7')-C(8')	87.5(8)
N(5)-C(6)-C(7)-C(8)	-150.4(7)	N(5')-C(6')-C(7')-C(8')	-150.8(7)
C(1)-C(6)-C(7)-C(8)	-25.6(10)	C(1')-C(6')-C(7')-C(8')	-27.8(10)
C(8)-C(7)-O(7)-C(14)	-18.8(9)	C(8')-C(7')-O(7')-C(14')	-18.8(9)
C(6)-C(7)-O(7)-C(14)	-141.9(7)	C(6')-C(7')-O(7')-C(14')	-142.9(7)
O(7)-C(7)-C(8)-O(8)	0.2(9)	O(7')-C(7')-C(8')-O(8')	-1.6(9)
C(6)-C(7)-C(8)-O(8)	118.6(7)	C(6')-C(7')-C(8')-O(8')	117.9(8)
O(7)-C(7)-C(8)-C(9)	-117.8(8)	O(7')-C(7')-C(8')-C(9')	-116.1(8)
C(6)-C(7)-C(8)-C(9)	0.6(10)	C(6')-C(7')-C(8')-C(9')	3.4(10)
C(9)-C(8)-O(8)-C(14)	139.5(7)	C(9')-C(8')-O(8')-C(14')	141.7(8)
C(7)-C(8)-O(8)-C(14)	18.6(9)	C(7')-C(8')-O(8')-C(14')	21.2(9)
O(8)-C(8)-C(9)-O(10)	-68.7(9)	O(8')-C(8')-C(9')-O(10')	-70.1(9)
C(7)-C(8)-C(9)-O(10)	46.8(10)	C(7')-C(8')-C(9')-O(10')	43.1(11)
O(1)-C(1)-O(10)-C(9)	-74.2(9)	O(1')-C(1')-O(10')-C(9')	-72.8(9)
C(2)-C(1)-O(10)-C(9)	166.3(7)	C(2')-C(1')-O(10')-C(9')	168.9(7)
C(6)-C(1)-O(10)-C(9)	44.6(10)	C(6')-C(1')-O(10')-C(9')	43.2(10)

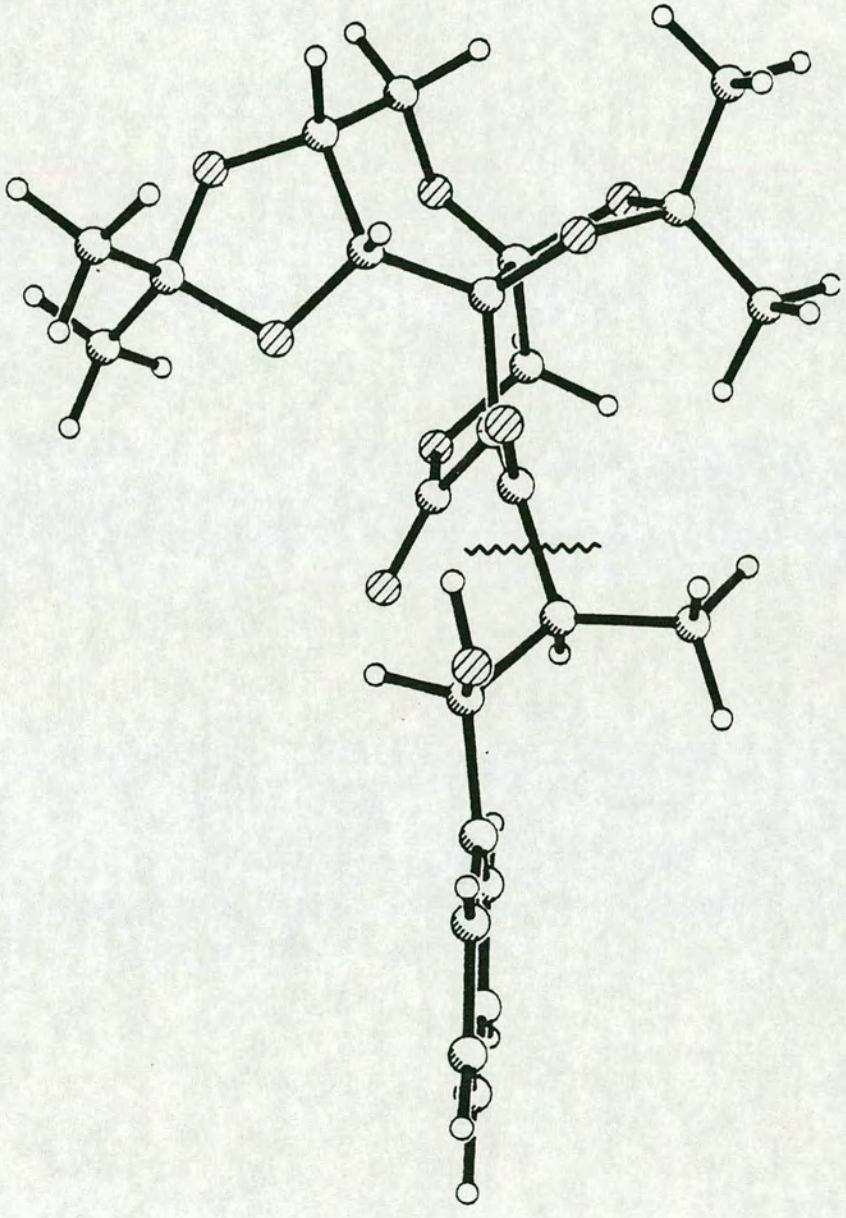
Table 3 Torsion angles (degrees) continued

(with standard deviations)

C(8)-C(9)-O(10)-C(1)	-73.3(9)	C(8')-C(9')-O(10')-C(1')	-70.0(10)
C(1)-O(1)-C(11)-O(6)	-21.7(9)	C(1')-O(1')-C(11')-O(6')	-23.5(9)
C(1)-O(1)-C(11)-C(13)	96.9(8)	C(1')-O(1')-C(11')-C(13')	97.7(9)
C(1)-O(1)-C(11)-C(12)	-136.5(7)	C(1')-O(1')-C(11')-C(12'	-138.5(8)
C(6)-O(6)-C(11)-O(1)	29.1(8)	C(6')-O(6')-C(11')-O(1')	29.2(9)
C(6)-O(6)-C(11)-C(13)	-90.7(8)	C(6')-O(6')-C(11')-C(13')	-92.7(9)
C(6)-O(6)-C(11)-C(12)	145.8(7)	C(6')-O(6')-C(11')-C(12')	145.7(8)
C(8)-O(8)-C(14)-O(7)	-30.4(10)	C(8')-O(8')-C(14')-O(7')	-33.4(10)
C(8)-O(8)-C(14)-C(16)	86.6(10)	C(8')-O(8')-C(14')-C(16')	-147.3(8)
C(8)-O(8)-C(14)-C(15)	-146.5(8)	C(8')-O(8')-C(14')-C(15')	85.8(10)
C(7)-O(7)-C(14)-O(8)	130.5(10)	C(7')-O(7')-C(14')-O(8')	32.1(9)
C(7)-O(7)-C(14)-C(16)	-87.3(9))	C(7')-O(7')-C(14')-C(16')	146.0(9)
C(7)-O(7)-C(14)-C(15)	148.7(9)	C(7')-O(7')-C(14')-C(15')	-87.3(9)
C(4)-N(5)-C(17)-O(17)	-133.0(9)	C(4')-N(5')-C(17')-O(17'	-134.6(9)
C(6)-N(5)-C(17)-O(17)	20.9(12)	C(6')-N(5')-C(17')-O(17')	21.3(12)
C(4)-N(5)-C(17)-C(18)	51.5(10)	C(4')-N(5')-C(17')-C(18')	50.6(10)
C(6)-N(5)-C(17)-C(18)	-154.6(7)	C(6')-N(5')-C(17')-C(18')	-153.5(7)
O(17)-C(17)-C(18)-C(19)	-5(2)	O(17')-C(17')-C(18')-C(19')	-5(2)
N(5)-C(17)-C(18)-C(19)	170.8(11)	N(5')-C(17')-C(18')-C(19')	169.9(11)

Appendix D

X-Ray Crystal Structure of Benzaldehyde Aldol Adduct (85)



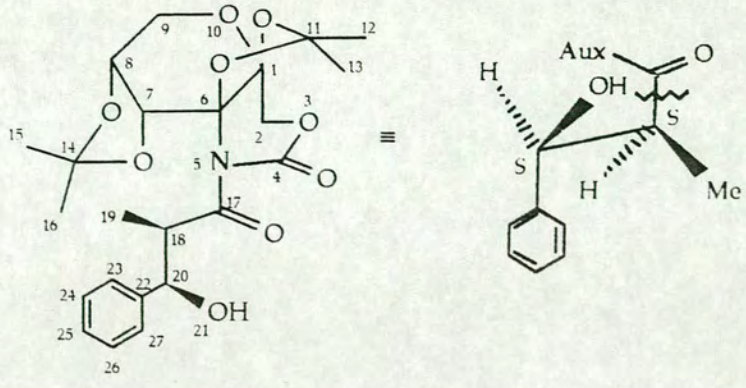


Table 1 Bond lengths (Å)

(with standard deviations)

C(13) - C(11)	1.5115	(0.0078)
C(12) - C(11)	1.5048	(0.0077)
C(11) - O(6)	1.4371	(0.0060)
C(11) - O(1)	1.4350	(0.0061)
O(6) - C(6)	1.3971	(0.0056)
C(6) - N(5)	1.5040	(0.0060)
C(6) - C(1)	1.5655	(0.0067)
C(6) - C(7)	1.5309	(0.0067)
N(5) - C(4)	1.4114	(0.0065)
N(5) - C(17)	1.4060	(0.0063)
C(4) - O(4)	1.2032	(0.0064)
C(4) - O(3)	1.3351	(0.0063)
O(3) - C(2)	1.4433	(0.0063)
C(2) - C(1)	1.5036	(0.0072)
C(1) - O(1)	1.4207	(0.0060)
C(1) - O(10)	1.3861	(0.0059)
O(10) - C(9)	1.4357	(0.0061)
C(9) - C(8)	1.5043	(0.0072)
C(7) - O(7)	1.4184	(0.0059)
C(7) - C(8)	1.5583	(0.0070)
O(7) - C(14)	1.4458	(0.0063)
C(14) - C(15)	1.4943	(0.0081)
C(14) - C(16)	1.5001	(0.0081)
C(14) - O(8)	1.4408	(0.0065)
O(8) - C(8)	1.4266	(0.0062)
C(17) - O(17)	1.2269	(0.0062)
C(17) - C(18)	1.5127	(0.0069)
C(18) - C(19)	1.5428	(0.0077)
C(18) - C(20)	1.5439	(0.0071)
C(20) - C(21)	1.4135	(0.0073)
C(20) - C(22)	1.5020	(0.0074)
C(22) - C(23)	1.3955	(0.0075)
C(22) - C(27)	1.3970	(0.0078)
C(23) - C(24)	1.3648	(0.0082)
C(24) - C(25)	1.3869	(0.0092)
C(25) - C(26)	1.3705	(0.0098)
C(26) - C(27)	1.3873	(0.0093)

Table 2 Bond angles (degrees)

(with standard deviations)

C(13) - C(11) - C(12) 112.980 (0.451)	C(13) - C(11) - O(6) 107.465 (0.410)
C(13) - C(11) - O(1) 109.207 (0.415)	C(12) - C(11) - O(6) 111.799 (0.418)
C(12) - C(11) - O(1) 111.184 (0.419)	O(6) - C(11) - O(1) 103.734 (0.371)
C(11) - O(6) - C(6) 110.650 (0.350)	O(6) - C(6) - N(5) 110.879 (0.358)
O(6) - C(6) - C(1) 104.146 (0.359)	O(6) - C(6) - C(7) 106.460 (0.367)
N(5) - C(6) - C(1) 107.534 (0.361)	N(5) - C(6) - C(7) 110.551 (0.369)
C(1) - C(6) - C(7) 117.071 (0.388)	C(6) - N(5) - C(4) 117.114 (0.377)
C(6) - N(5) - C(17) 118.746 (0.374)	C(4) - N(5) - C(15) 118.147 (0.399)
N(5) - C(4) - O(4) 123.957 (0.471)	N(5) - C(4) - O(3) 114.792 (0.428)
O(4) - C(4) - C(3) 121.249 (0.474)	C(4) - O(3) - C(2) 115.467 (0.392)
O(3) - C(2) - C(1) 109.303 (0.409)	C(6) - C(1) - C(2) 112.191 (0.403)
C(6) - C(1) - O(1) 104.168 (0.369)	C(6) - C(1) - O(10) 113.842 (0.388)
C(2) - C(1) - O(1) 109.528 (0.399)	C(2) - C(1) - O(10) 108.083 (0.400)
O(1) - C(1) - O(10) 108.898 (0.379)	C(11) - O(1) - C(1) 110.637 (0.360)
C(1) - O(10) - C(9) 112.734 (0.366)	O(10) - C(9) - C(8) 110.729 (0.406)
C(6) - C(7) - O(7) 108.615 (0.380)	C(6) - C(7) - C(8) 114.360 (0.397)
O(7) - C(7) - C(8) 104.251 (0.376)	C(7) - O(7) - C(14) 107.972 (0.360)
O(7) - C(14) - C(15) 109.041 (0.434)	O(7) - C(14) - C(16) 110.933 (0.436)
O(7) - C(14) - O(8) 102.846 (0.386)	C(15) - C(14) - C(16) 113.821 (0.478)
C(15) - C(14) - O(8) 108.705 (0.438)	C(16) - C(14) - O(8) 110.905 (0.441)
C(14) - O(8) - C(8) 108.227 (0.376)	C(9) - C(8) - C(7) 113.248 (0.412)
C(9) - C(8) - O(8) 107.741 (0.400)	C(7) - C(8) - O(8) 104.150 (0.382)
N(5) - C(17) - O(17) 119.301 (0.445)	N(5) - C(17) - C(18) 119.394 (0.415)
O(17) - C(17) - C(18) 121.227 (0.446)	C(17) - C(18) - C(19) 109.156 (0.413)
C(17) - C(18) - C(20) 107.432 (0.396)	C(19) - C(18) - C(20) 112.125 (0.419)
C(18) - C(20) - O(21) 111.287 (0.435)	C(18) - C(20) - C(22) 114.585 (0.430)
O(21) - C(20) - C(22) 109.417 (0.444)	C(20) - C(22) - C(23) 121.271 (0.466)
C(20) - C(22) - C(27) 119.759 (0.473)	C(23) - C(22) - C(27) 118.679 (0.490)
C(22) - C(23) - C(24) 121.014 (0.518)	C(23) - C(24) - C(25) 120.087 (0.573)
C(24) - C(25) - C(26) 119.790 (0.625)	C(25) - C(26) - C(27) 120.783 (0.636)
C(22) - C(27) - C(26) 119.607 (0.555)	

Table 3 Torsion angles (degrees)

(with standard deviations)

C(13)-C(11)-O(6)-C(6) 142.512 (0.405)
O(1)-C(11)-O(6)-C(6) 26.922 (0.464)
C(12)-C(11)-O(1)-C(1) 97.803 (0.471)
C(11)-C(6)-O(6)-N(5) 94.964 (0.420)
C(11)-O(6)-C(6)-C(7) -144.741 (0.377)
O(6)-C(6)-N(5)-C(17) 44.287 (0.531)
C(1)-C(6)-N(5)-C(17) 157.543 (0.399)
C(7)-C(6)-N(5)-C(17) -73.544 (0.506)
O(6)-C(6)-C(1)-O(1) 5.910 (0.450)
N(5)-C(6)-C(1)-C(2) 6.574 (0.524)
N(5)-C(6)-C(1)-O(10) 129.719 (0.396)
C(7)-C(6)-C(1)-O(1) 123.101 (0.418)
O(6)-C(6)-C(7)-O(7) -156.037 (0.356)
N(5)-C(6)-C(7)-O(7) -35.530 (0.493)
C(1)-C(6)-C(7)-O(7) 88.039 (0.476)
C(6)-N(5)-C(4)-O(4) -142.529 (0.495)
C(17)-N(5)-C(4)-O(4) 9.933 (0.736)
C(6)-N(5)-C(17)-O(17) 13.253 (0.661)
C(4)-N(5)-C(17)-O(17) -138.754 (0.485)
N(5)-C(4)-O(3)-C(2) 21.274 (0.602)
C(4)-O(3)-C(2)-C(1) -63.499 (0.535)
O(3)-C(2)-C(1)-O(1) 159.825 (0.375)
C(6)-C(1)-O(1)-C(11) 10.507 (0.475)
O(10)-C(1)-O(1)-C(11) 132.315 (0.391)
C(2)-C(1)-O(10)-C(9) 170.554 (0.390)
C(1)-O(10)-C(9)-C(8) -72.336 (0.497)
O(10)-C(9)-C(8)-O(8) -70.721 (0.489)
C(8)-C(7)-O(7)-C(14) -22.804 (0.468)
C(6)-C(7)-C(8)-O(8) 120.248 (0.422)
O(7)-C(7)-C(8)-O(8) 1.789 (0.469)
C(7)-O(7)-C(14)-C(16) -83.487 (0.494)
O(7)-C(14)-O(8)-C(8) -33.866 (0.471)
C(16)-C(14)-O(8)-C(8) 84.779 (0.502)
C(14)-O(8)-C(8)-C(7) 19.935 (0.482)
N(5)-C(17)-C(18)-C(20) -124.590 (0.462)
O(17)-C(17)-C(18)-C(20) 58.651 (0.600)
C(12)-C(11)-O(6)-C(6) -92.972 (0.472)
C(13)-C(11)-O(1)-C(1) -136.860 (0.422)
O(6)-C(11)-O(1)-C(1) -22.509 (0.473)
C(11)-O(6)-C(6)-C(1) -20.419 (0.461)
O(6)-C(6)-C(5)-N(4) -163.421 (0.387)
C(1)-C(6)-N(5)-C(4) -50.165 (0.510)
C(7)-C(6)-N(5)-C(4) 78.748 (0.496)
O(6)-C(6)-C(1)-C(2) 124.289 (0.416)
O(6)-C(6)-C(1)-O(10) -112.565 (0.414)
N(5)-C(6)-C(1)-O(1) -111.806 (0.385)
C(7)-C(6)-C(1)-C(2) -118.520 (0.464)
C(7)-C(6)-C(1)-O(10) 4.626 (0.588)
O(6)-C(6)-C(7)-C(8) 88.009 (0.460)
N(5)-C(6)-C(7)-C(8) -151.484 (0.387)
C(1)-C(6)-C(7)-C(8) -27.916 (0.582)
C(6)-N(5)-C(4)-O(3) 38.032 (0.592)
C(17)-N(5)-C(4)-O(3) -169.507 (0.416)
C(6)-N(5)-C(17)-C(18) -163.569 (0.403)
C(4)-N(5)-C(17)-C(18) 44.424 (0.620)
O(4)-C(4)-O(3)-C(2) -158.183 (0.476)
O(3)-C(2)-C(1)-C(6) 44.664 (0.534)
O(3)-C(2)-C(1)-O(10) -81.665 (0.473)
C(2)-C(1)-O(1)-C(11) -109.682 (0.438)
C(6)-C(1)-O(10)-C(9) 45.196 (0.518)
O(1)-C(1)-O(10)-C(9) -70.534 (0.469)
O(10)-C(9)-C(8)-C(7) 43.911 (0.552)
C(6)-C(7)-O(7)-C(14) -145.122 (0.386)
C(6)-C(7)-C(8)-C(9) 3.483 (0.591)
O(7)-C(7)-C(8)-C(9) -114.975 (0.437)
C(7)-O(7)-C(14)-C(15) 150.395 (0.425)
C(7)-O(7)-C(14)-O(8) 35.138 (0.463)
C(15)-C(14)-O(8)-C(8) -149.364 (0.431)
C(14)-O(8)-C(8)-C(9) 140.468 (0.411)
N(5)-C(17)-C(18)-C(19) 113.609 (0.495)
O(17)-C(17)-C(18)-C(19) -63.150 (0.613)
C(17)-C(18)-C(20)-O(21) -67.516 (0.526)

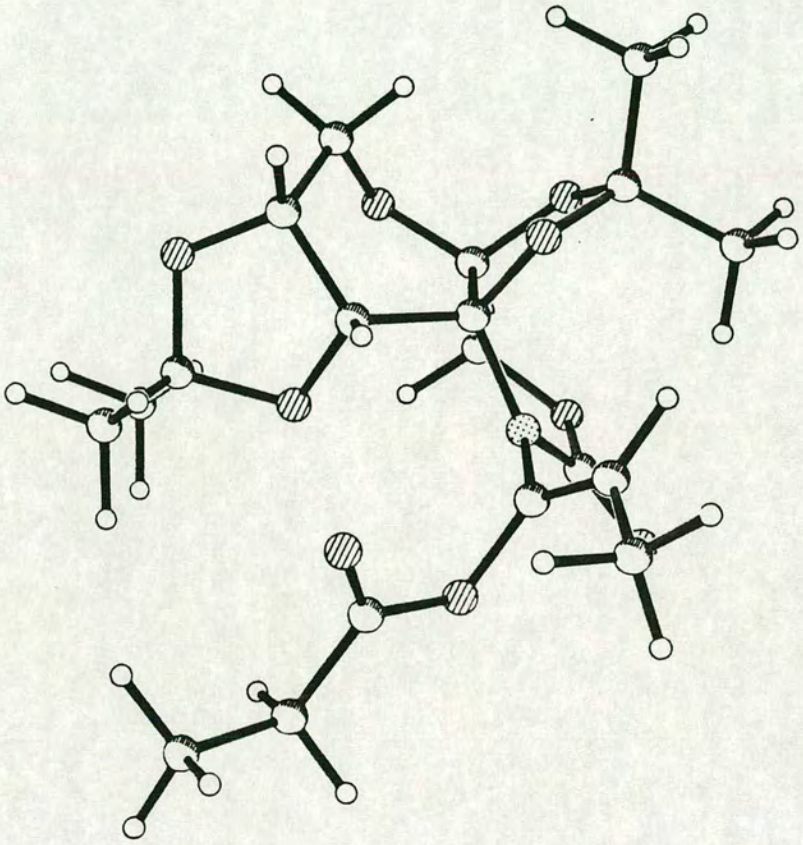
Table 3 Torsion angles (degrees) continued

(with standard deviations)

C(17)-C(18)-C(20)-C(22)	167.692 (0.423)	C(19)-C(18)-C(20)-O(21)	52.413 (0.578)
C(19)-C(18)-C(20)-C(22)	-72.379 (0.562)	C(18)-C(20)-C(22)-C(23)	-48.976 (0.674)
C(18)-C(20)-C(22)-C(27)	137.299 (0.509)	O(21)-C(20)-C(22)-C(23)	-174.749 (0.483)
O(21)-C(20)-C(22)-C(27)	11.526 (0.689)	C(20)-C(22)-C(23)-C(24)	-172.489 (0.524)
C(27)-C(22)-C(23)-C(24)	1.302 (0.822)	C(20)-C(22)-C(27)-C(26)	172.500 (0.549)
C(23)-C(22)-C(27)-C(26)	-1.388 (0.842)	C(22)-C(23)-C(24)-C(25)	0.327 (0.899)
C(23)-C(24)-C(25)-C(26)	-1.883 (0.979)	C(24)-C(25)-C(26)-C(27)	1.790 (1.034)
C(25)-C(26)-C(27)-C(22)	-0.145 (0.979)		

Appendix E

X-Ray Crystal Structure of O-acylated product (100)



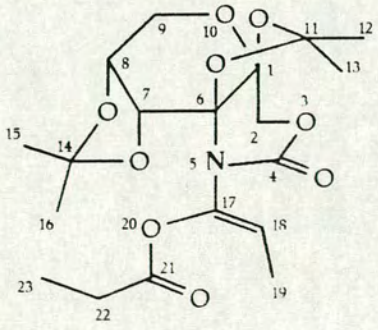


Table 1 Bond lengths (Å)

(with standard deviations)

C(1)-O(1)	1.395(10)	1.410(10)
C(1)-O(10)	1.418(11)	1.392(10)
C(1)-C(2)	1.504(12)	1.530(12)
C(1)-C(6)	1.527(13)	1.533(12)
O(1)-C(11)	1.413(12)	1.449(9)
C(2)-O(3)	1.440(11)	1.414(12)
O(3)-C(4)	1.327(11)	1.336(11)
C(4)-O(4)	1.201(11)	1.198(11)
C(4)-N(5)	1.371(11)	1.398(11)
N(5)-C(17)	1.410(11)	1.420(11)
N(5)-C(6)	1.482(10)	1.469(10)
C(6)-O(6)	1.430(9)	1.428(9)
C(6)-C(7)	1.530(12)	1.533(11)
O(6)-C(11)	1.423(11)	1.422(9)
C(7)-O(7)	1.420(10)	1.409(9)
C(7)-C(8)	1.537(12)	1.530(11)
O(7)-C(14)	1.423(11)	1.422(9)
C(8)-O(8)	1.413(11)	1.430(10)
C(8)-C(9)	1.51(2)	1.494(12)
O(8)-C(14)	1.437(13)	1.400(10)
C(9)-O(10)	1.424(12)	1.425(10)
C(11)-C(12)	1.515(14)	1.509(11)
C(11)-C(13)	1.523(14)	1.522(11)
C(14)-C(16)	1.47(2)	1.508(12)
C(14)-C(15)	1.49(2)	1.511(13)
C(17)-C(18)	1.316(13)	1.326(13)
C(17)-O(20)	1.405(11)	1.377(10)
C(18)-C(19)	1.501(14)	1.479(14)
O(20)-C(21)	1.362(12)	1.356(10)
C(21)-O(21)	1.197(11)	1.204(11)
C(21)-C(22)	1.49(2)	1.491(13)
C(22)-C(23)	1.45(2)	1.490(13)

Table 2 Bond angles (degrees)

C(4)-N(5)-C(17)	116.1(6)	115.6(7)
C(4)-N(5)-C(6)	124.6(7)	124.7(7)
C(17)-N(5)-C(6)	117.9(6)	118.8(6)
O(6)-C(6)-N(5)	111.4(6)	111.4(6)
O(6)-C(6)-C(1)	103.8(6)	102.5(6)
N(5)-C(6)-C(1)	110.9(7)	111.8(6)
O(6)-C(6)-C(7)	105.9(6)	107.8(6)
N(5)-C(6)-C(7)	109.3(6)	109.4(6)
C(1)-C(6)-C(7)	115.4(7)	113.7(6)
C(11)-O(6)-C(6)	107.7(6)	109.5(5)
O(7)-C(7)-C(6)	106.7(6)	106.7(6)
O(7)-C(7)-C(8)	102.9(7)	105.5(6)
C(6)-C(7)-C(8)	114.0(8)	113.6(6)
C(7)-O(7)-C(14)	108.1(6)	107.2(6)
O(8)-C(8)-C(9)	110.0(9)	109.1(7)
O(8)-C(8)-C(7)	104.3(7)	103.0(6)
C(9)-C(8)-C(7)	113.2(8)	112.6(6)
C(8)-O(8)-C(14)	110.5(7)	110.8(6)
O(10)-C(9)-C(8)	110.7(8)	110.5(7)
C(1)-O(10)-C(9)	114.2(7)	113.2(6)
O(1)-C(11)-O(6)	106.1(7)	104.5(5)
O(1)-C(11)-C(12)	110.0(9)	110.3(6)
O(6)-C(11)-C(12)	108.2(9)	109.0(7)
O(1)-C(11)-C(13)	109.4(10)	108.1(6)
O(6)-C(11)-C(13)	112.2(9)	113.6(7)
C(12)-C(11)-C(13)	110.8(9)	111.2(7)
O(7)-C(14)-O(8)	103.3(8)	106.2(6)
O(7)-C(14)-C(16)	108.2(9)	110.5(7)
O(8)-C(14)-C(16)	109.6(10)	110.2(7)
O(7)-C(14)-C(15)	111.3(10)	108.4(7)
O(8)-C(14)-C(15)	110.5(10)	109.2(7)
C(16)-C(14)-C(15)	113.4(10)	112.1(8)
C(18)-C(17)-O(20)	122.6(8)	124.8(8)
C(18)-C(17)-N(5)	123.9(8)	122.2(8)
O(20)-C(17)-N(5)	113.3(7)	112.7(7)
C(17)-C(18)-C(19)	125.0(11)	126.0(10)
C(21)-O(20)-C(17)	119.5(7)	119.3(7)
O(21)-C(21)-O(20)	122.9(9)	123.3(8)
O(21)-C(21)-C(22)	127.0(10)	124.9(8)
O(20)-C(21)-C(22)	110.1(9)	111.7(8)
C(23)-C(22)-C(21)	115.7(11)	115.6(9)
O(1)-C(1)-O(10)	110.9(7)	112.1(6)
O(1)-C(1)-C(2)	113.2(8)	109.6(7)
O(10)-C(1)-C(2)	102.7(7)	105.4(7)
O(1)-C(1)-C(6)	104.6(7)	104.8(6)
O(10)-C(1)-C(6)	113.4(8)	114.0(7)
C(2)-C(1)-C(6)	112.4(7)	111.0(7)
C(1)-O(1)-C(11)	111.3(7)	110.6(6)
O(3)-C(2)-C(1)	109.6(8)	110.9(7)
C(4)-O(3)-C(2)	118.0(7)	118.1(7)
O(4)-C(4)-O(3)	119.9(9)	120.1(8)
O(4)-C(4)-N(5)	121.9(9)	122.4(8)
O(3)-C(4)-N(5)	118.2(7)	117.4(8)

Table 3 Torsion angles (degrees)

(with standard deviations)

C(2)-O(3)-C(4)-O(4)	160.6(9)	163.4(8)
C(2)-O(3)-C(4)-N(5)	-19.3(13)	-19.8(11)
O(4)-C(4)-N(5)-C(17)	-1.9(13)	-8.2(12)
O(3)-C(4)-N(5)-C(17)	178.0(8)	175.1(7)
O(4)-C(4)-N(5)-C(6)	164.1(8)	160.8(8)
O(3)-C(4)-N(5)-C(6)	-16.1(12)	-15.9(11)
C(4)-N(5)-C(6)-O(6)	-102.5(9)	-101.5(8)
C(17)-N(5)-C(6)-O(6)	63.2(9)	67.2(8)
C(4)-N(5)-C(6)-C(1)	12.5(10)	12.5(10)
C(17)-N(5)-C(6)-C(1)	178.2(7)	-178.8(7)
C(4)-N(5)-C(6)-C(7)	140.8(8)	139.4(7)
C(17)-N(5)-C(6)-C(7)	-53.5(9)	-52.0(9)
O(1)-C(1)-C(6)-O(6)	19.4(8)	22.9(7)
O(10)-C(1)-C(6)-O(6)	-101.6(7)	-100.0(7)
C(2)-C(1)-C(6)-O(6)	142.6(7)	141.2(7)
O(1)-C(1)-C(6)-N(5)	-100.3(7)	-96.5(7)
O(10)-C(1)-C(6)-N(5)	138.7(6)	140.6(7)
C(2)-C(1)-C(6)-N(5)	22.9(10)	21.8(10)
O(1)-C(1)-C(6)-C(7)	134.7(7)	139.0(7)
O(10)-C(1)-C(6)-C(7)	13.8(9)	16.1(9)
C(2)-C(1)-C(6)-C(7)	-102.1(8)	-102.7(8)
N(5)-C(6)-O(6)-C(11)	93.6(8)	90.5(7)
C(1)-C(6)-O(6)-C(11)	-25.8(8)	-29.2(7)
C(7)-C(6)-O(6)-C(11)	-147.7(7)	-149.4(6)
O(6)-C(6)-C(7)-O(7)	-172.9(6)	-173.8(6)
N(5)-C(6)-C(7)-O(7)	-52.7(9)	-52.5(8)
C(1)-C(6)-C(7)-O(7)	73.0(8)	73.3(8)
O(6)-C(6)-C(7)-C(8)	74.3(9)	70.4(8)
N(5)-C(6)-C(7)-C(8)	-165.6(7)	-168.3(6)
C(1)-C(6)-C(7)-C(8)	-39.8(9)	-42.5(9)
C(6)-C(7)-O(7)-C(14)	-152.0(8)	-147.1(6)
C(8)-C(7)-O(7)-C(14)	-31.7(10)	-26.0(8)
O(7)-C(7)-C(8)-O(8)	17.8(10)	15.1(8)
C(6)-C(7)-C(8)-O(8)	132.8(9)	131.6(6)
O(7)-C(7)-C(8)-C(9)	-101.8(9)	-102.3(7)
C(6)-C(7)-C(8)-C(9)	13.3(11)	14.2(10)
C(9)-C(8)-O(8)-C(14)	123.6(10)	121.1(7)
C(7)-C(8)-O(8)-C(14)	1.9(12)	1.4(8)
O(8)-C(8)-C(9)-O(10)	-78.3(9)	-74.2(8)
C(7)-C(8)-C(9)-O(10)	37.9(11)	39.5(9)
O(1)-C(1)-O(10)-C(9)	-76.6(10)	-78.9(8)
C(2)-C(1)-O(10)-C(9)	162.2(8)	161.9(7)
C(6)-C(1)-O(10)-C(9)	40.7(10)	40.0(9)
C(8)-C(9)-O(10)-C(1)	-69.0(10)	-71.0(8)
C(1)-O(1)-C(11)-O(6)	-9.7(10)	-8.1(8)
C(1)-O(1)-C(11)-C(12)	-126.6(9)	-125.0(7)
C(1)-O(1)-C(11)-C(13)	111.5(9)	113.2(7)
C(6)-O(6)-C(11)-O(1)	22.6(9)	24.0(7)
C(6)-O(6)-C(11)-C(12)	140.7(8)	141.9(6)

Table 3 Torsion angles (degrees) continued

(with standard deviations)

O(10)-C(1)-O(1)-C(11)	116.5(9)	114.8(7)
C(2)-C(1)-O(1)-C(11)	-128.8(8)	-128.5(7)
C(6)-C(1)-O(1)-C(11)	-6.1(9)	-9.4(8)
O(1)-C(1)-C(2)-O(3)	64.4(10)	61.5(9)
O(10)-C(1)-C(2)-O(3)	-176.0(7)	-177.6(6)
C(6)-C(1)-C(2)-O(3)	-53.9(10)	-53.8(10)
C(1)-C(2)-O(3)-C(4)	54.0(11)	54.8(10)
C(6)-O(6)-C(11)-C(13)	-96.7(9)	-93.6(7)
C(7)-O(7)-C(14)-O(8)	33.1(11)	27.1(8)
C(7)-O(7)-C(14)-C(16)	149.2(9)	-92.4(8)
C(7)-O(7)-C(14)-C(15)	-85.5(11)	144.4(7)
C(8)-O(8)-C(14)-O(7)	-20.9(12)	-17.2(8)
C(8)-O(8)-C(14)-C(16)	-136.0(10)	102.5(8)
C(8)-O(8)-C(14)-C(15)	98.3(11)	-134.0(7)
C(4)-N(5)-C(17)-C(18)	-96.8(11)	98.7(10)
C(6)-N(5)-C(17)-C(18)	96.3(10)	-70.9(11)
C(4)-N(5)-C(17)-O(20)	78.5(8)	-76.0(9)
C(6)-N(5)-C(17)-O(20)	-88.4(8)	114.4(8)
O(20)-C(17)-C(18)-C(19)	4.(2)	-4.(2)
N(5)-C(17)-C(18)-C(19)	179.0(9)	-178.2(11)
C(18)-C(17)-O(20)-C(21)	-69.8(11)	69.5(11)
N(5)-C(17)-O(20)-C(21)	114.8(8)	-116.0(8)
C(17)-O(20)-C(21)-O(21)	0.3(12)	-6.8(12)
C(17)-O(20)-C(21)-C(22)	178.6(8)	172.2(8)
O(21)-C(21)-C(22)-C(23)	6.(2)	-6.(2)
O(20)-C(21)-C(22)-C(23)	-172.6(11)	175.1(8)

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