ASYMMETRIC TRANSITION METAL CATALYSTS BASED ON CARBOHYDRATES

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of Doctor of Philosophy

By

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DEDICATED TO MY PARENTS

Unless otherwise stated, the work described in this thesis is that of the author and no portion of the work has been submitted in support of an application for another degree or qualification in this or any other university or institute of learning.

The author received a Bachelor of Science degree in Chemistry from the King Saud University, Riyadh, Saudia Arabia, in 1983. During 1985/1986 he joined the Diploma Course in Education from Um-Alqura University, Saudi Arabia. From 1989-1991 he studied in the Chemistry Department at UMIST and graduated in April 1991 with a Master of Science. Between May 1991 and February 1994 the author carried out the research described in this thesis in the Department of Chemistry (UMIST), under the supervision of Dr. B.L. Booth Ph.D., D.Sc., F.R.S.C.

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Contents

ABBREVIATION

Ac	Acetyl
Å	Angstrom
Ar	Aromatic
BINAP	2,2'-bis(diphenylphosphino)-1,1'binaphthyl
b.p.	boiling point
Bn	Benzyl
br.	broad
Bu	Butyl
CHIRAPHOS	2,3-bis(diphenylphosphino)butane
CI	Chemical Ionization
cod	cyclooctadiene
conc.	concentrated
DEAD	Diethyl azodicarboxylate
DIOP	2,3-*O*- isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)ethane
d	doublet
dd	doublet of doublet
Dept	Distortionless Enhancement by Polarization Transfer
DCFC	Dry Column Flash Chromatography
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
e.e.	enantiomeric excess
EI	Electron Impact
Eqn.	Equation
equiv.	equivalent
Et	Ethyl

FAB	Fast Atom Bombardment
h	hour
H	Hertz
IR	Infrared
^{i}Pr	Isopropyl
J	coupling constant
m	medium (in the IR spectrum)
m	multiplet (in the ^{1}H NMR)
m- CPBA	*m*- Chloroperoxybenzoic acid
m.p.	melting point
Me	Methyl
min	minute
MS	molecular sieve
M.W.	Molecular Weight
Mes	Mesyl
NMR	Nuclear Magnetic Resonance
α	optical rotation
Ph	Phenyl
ppm	parts per million
q	quartet
Rf	Retention factor
r.t.	room temperature
sec.	secondary
s	strong (in the IR spectrum)
s	singlet (in the ^{1}H NMR)
str.	stretch

THF	Tetrahydrofuran
tert.	tertiary
TLC	Thin Layer Chromatography
Ts	Tosylate
TMS	Trimethylsilyl
t	triplet
vs	very strong
ν	wave number (cm^{-1})
vib.	vibration
w	weak

ABSTRACT

Starting from D-mannitol, the successful synthesis of the new novel ligands (+)-4-N,N-(dimethylamino)-3-hydroxy-1,2:5,6-di-*O*- isopropylidene-D-mannitol and its dibutyl analogue have been achieved in 9 and 6 steps respectively. Other ligands based on D-mannitol such as the 3,4-bis-*O*- (diphenylphosphinito)-1,2:5,6-di-*O*- isopropylidene-D-mannitol and 4-*O*- diphenylphosphinito-3-hydroxy-1,2:5,6-di-*O*- isopropylidene-D-mannitol are also described. The preparation of the 3,4-diazido-1,2: 5,6- di-*O*- isopropylidene-D-mannitol was unsuccessful. Both β-amino alcohols were employed as catalysts in the enantioselective addition of diethylzinc to benzaldehyde to afford 1-phenylpropanol in low to moderate enantiomeric excesses (22 to 66%) respectively.

Starting from the Feist's acid the new ligands (2R,3R)-(-)-bis(diphenylmethanol)-1-methylenecyclopropane and its enantiomer (2S,3S)-(+)-diol have been prepared successfully. The titanium complexes of both enantiomers have been prepared *in situ* using $TiCl_4$ and used as catalysts in the addition of the diethylzinc to benzaldehyde to afford 0.0 and 30% **e.e.**of the chiral alcohol respectively. The spirotitanate complex of (2R,3R)-(-)-diol was isolated as stable solid and attempets to use it as catalyst in the same reaction were unsuccessful. The *trans*- (±)-2,3-bis(aminomethyl)-1-methylenecyclopropane was prepared in 10 steps, but all attempts to isolate it in a pure state were unsuccessful. Similarly, the preparation of other ligands based on Feist's acid [e.g. *trans*- (±)-2,3-bis(diphenylphosphino)-1-methylenecyclopropane and its bis(thiomethyl) analogue] were unsuccessful.

All the intermediates and new compounds have been fully characterized by $[\alpha]^t$, IR, ^1H, ^{13}C and ^{31}P NMR spectroscopy in addition to microanalysis and mass spectroscopy.

I. INTRODUCTION

Chapter 1

I.1.1 Asymmetric Synthesis and Chirality

Asymmetric synthesis can be defined as a process which converts a prochiral unit into a chiral unit so that unequal amounts of stereoisomeric products result.[1,2,3] An object is said to be chiral if it cannot be superimposed upon its mirror image. Any compound may be obtained in two different forms in which the molecular structures are constitutionally identical but differ in the three-dimensional arrangements of the atoms such that they are related as mirror images. In such cases, the two possible forms are called enantiomers. **(Fig.1).**

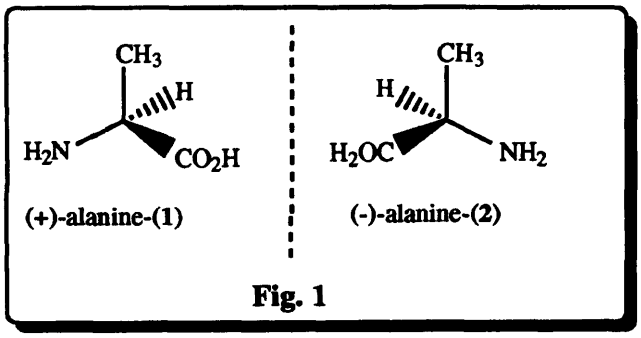


Fig. 1

If there are "**n**" stereogenic units there can be up to 2^n stereoisomers. Two possibilities arise, either they are mirror images of each other (i.e. enantiomers), or they are not in which case they are called diastereomers **(Fig.2).**

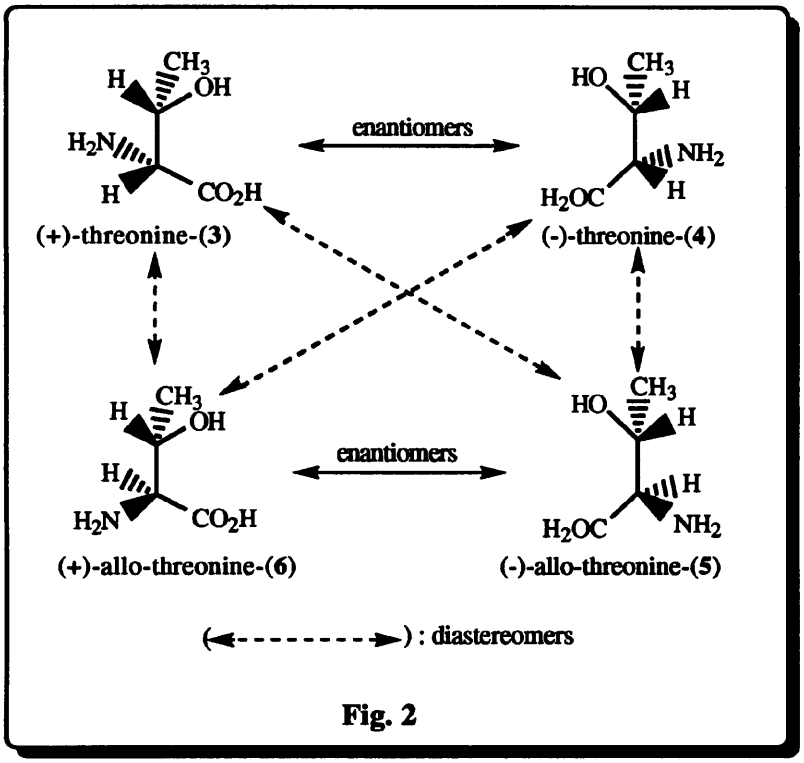


Fig. 2

While a pair of enantiomers have identical chemical and physical properties and equal and opposite optical rotation values, a pair of diastereomers have completely different chemical and physical properties and optical rotations to each other.[1]

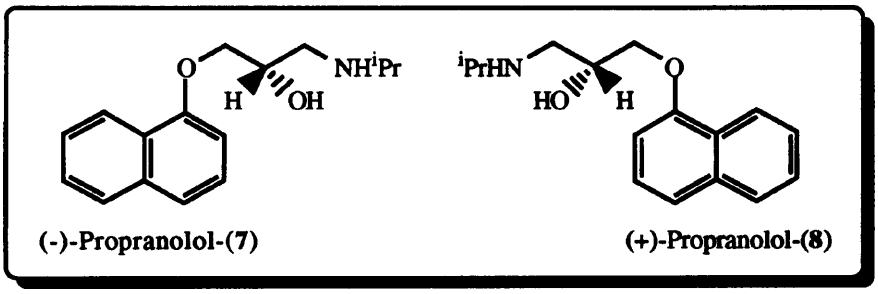
I.1.2 The Need for Asymmetric Synthesis

Asymmetric synthesis is a very attractive option because, unlike classical resolution, the yield of a desired enantiomer can, in principle, be 100%. Additionally, the synthesis of an enantiomerically pure compound (**EPC**) is becoming increasingly important for research and development in industry.[3]

The importance of obtaining enantiomerically pure compounds arises from the fact that all biological systems interact differently with chiral molecules and their mirror images. Thus, for all applications of chemicals in fragrants, cosmetics, nutrients, agricultural pesticides, vitamins and pharmaceutical drugs it is essential to have access to either

enantiomer.[4]

When, for instance, a biologically active chiral compound such as a drug interacts with its chiral receptor site, it should come as no surprise that the two enantiomers of the drug interact differentially and may lead to different effects. For example, the pure enantiomer (-)-propranolol (**7**) was introduced in the 1960's as a β-blocker for the treatment of heart disease, but the (+)-enantiomer (**8**) acts as a contraceptive so enantiomeric purity was obviously essential for clinical use.[2,5]



(-)-Propranolol-(7) (+)-Propranolol-(8)

I.1.3 Measurement of Enantioselectivity

Enantioselectivity can be achieved if one of the two enantiomers is formed preferentially. The degree of enantioselectivity can be measured by the most commonly used enantiomeric excess (**e.e.**) (**Eqn. 1**).

$$\% \text{ e.e.} = \frac{\text{moles R - moles S}}{\text{moles R + moles S}} \times 100 \qquad \textbf{Eqn. 1}$$

where R and S are enantiomers and R is in excess over S.

The degree of asymmetric induction is often specified by reference to the percentage optically purity of the product (**Eqn. 2**).

$$\% \text{ Optical Purity} = \frac{[\alpha] \text{ enantiomeric mixture}}{[\alpha] \text{ pure enantiomer}} \times 100 \qquad \textbf{Eqn. 2}$$

Where [α] = specific rotation at a certain temperature, concentration and wavelength.

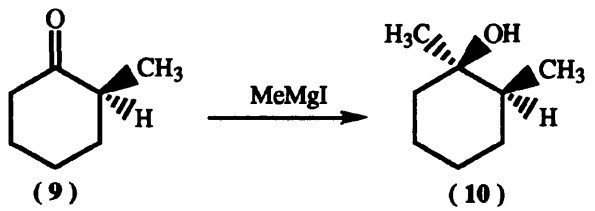
The determination of the enantiomeric purity on the basis of optical rotation measurements should be confirmed by an independent method before assigning absolute rotations [e.g. chiral gas chromatography (GC), high performance liquid chromatography (HPLC)].[2]

I.1.4 Some Methods of Asymmetric Synthesis

Asymmetric synthesis falls into the category of kinetically-controlled asymmetric transformations. The known methods can be conveniently divided into three major classes.

A) Substrate-Controlled Method

The formation of the new chiral centre most often occurs by reaction with an achiral reagent at a diastereotopic site controlled by a nearby stereogenic unit, as shown in (Eqn. 3):

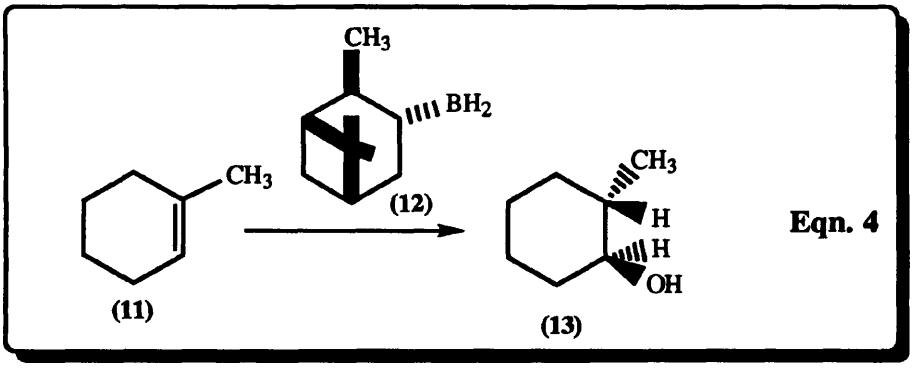


(9) (10) **Eqn. 3**

Unless the desired substrate is readily available this method is of limited value.[2]

B) Reagent-Controlled Method

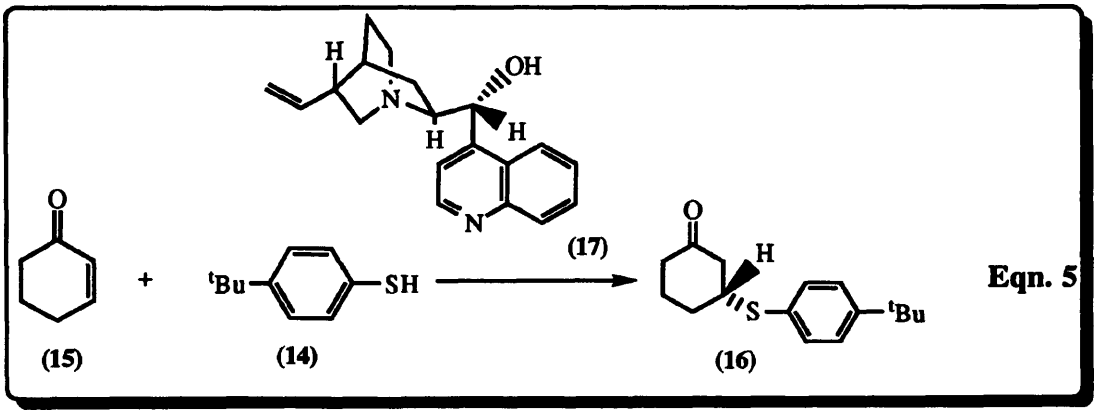
An achiral substrate can be converted into a chiral product by using a chiral reagent. For example the chiral alcohol **(13)** is formed in the hydroboration of 1-methylcyclohexene **(11)** using the chiral reagent (+)-isopinocamphenylborane **(12)** **(Eqn. 4)**[6].



Eqn. 4

C) Catalyst-Controlled Method

In this method a chiral catalyst is used to direct the conversion of an achiral substrate directly to a chiral product with an achiral reagent. An example is the asymmetric conjugate addition of thiophenol **(14)** to cyclohexenone **(15)** to give **(16)** catalyzed by the chiral alkaloid cinchonidine **(17)** **(Eqn. 5)**.[7]



Eqn. 5

I.1.5 Criteria for Evaluating an Asymmetric Synthesis

Asymmetric induction refers to the creation of a new chiral unit in which one configuration is produced in excess over the other. Criteria for an efficient asymmetric synthesis have been summarized by Eliel as follows.[8]

1. The desired enantiomer (or diastereomer) should be formed with high stereoselectivity.[9]
2. The chiral product must be readily separable from the chiral auxiliary reagent employed in the synthesis.
3. The chiral auxiliary reagent must be recovered in good yield and with no loss of enantiomeric purity .[4]

In addition, a good chiral ligand should meet several conditions.[10]

(i) It must be coordinated to a metal during the step in which the chiral centre on the substrate is created.

(ii) The catalytic activity when the chiral ligand is present should be reasonably good relative to that of the achiral catalysts.

(iii) The structure of the ligand should allow for various chemical modifications to be made in order to permit the synthesis of variants.

(iv) The synthesis of the ligands must be relatively easy. Resolution is to be avoided and the starting material should be an inexpensive one taken from the chiral pool.[11]

(v) It is desirable to be able to get both antipodes of the ligand.

I.1.6 C_2 -Symmetry and Asymmetric Inductions

In the majority of scenarios for absolute stereochemical control, the presence of a C_2 axis of symmetry within the chiral auxiliary can reduce the number of possible competing diastereomeric transition states dramatically and provide higher levels of absolute stereochemical control.[12] Thus, when the rotation axis is of first order (C_1 or C_2)

changing the direction of rotation makes no difference, because the same equivalent orientation of the molecule is arrived at in either case, for example borane trifluoride (BF_3) contains three C_2 axes, which are in the plane of the molecule and are perpendicular to the C_3 axes.**(Fig.3)**.[13,14]

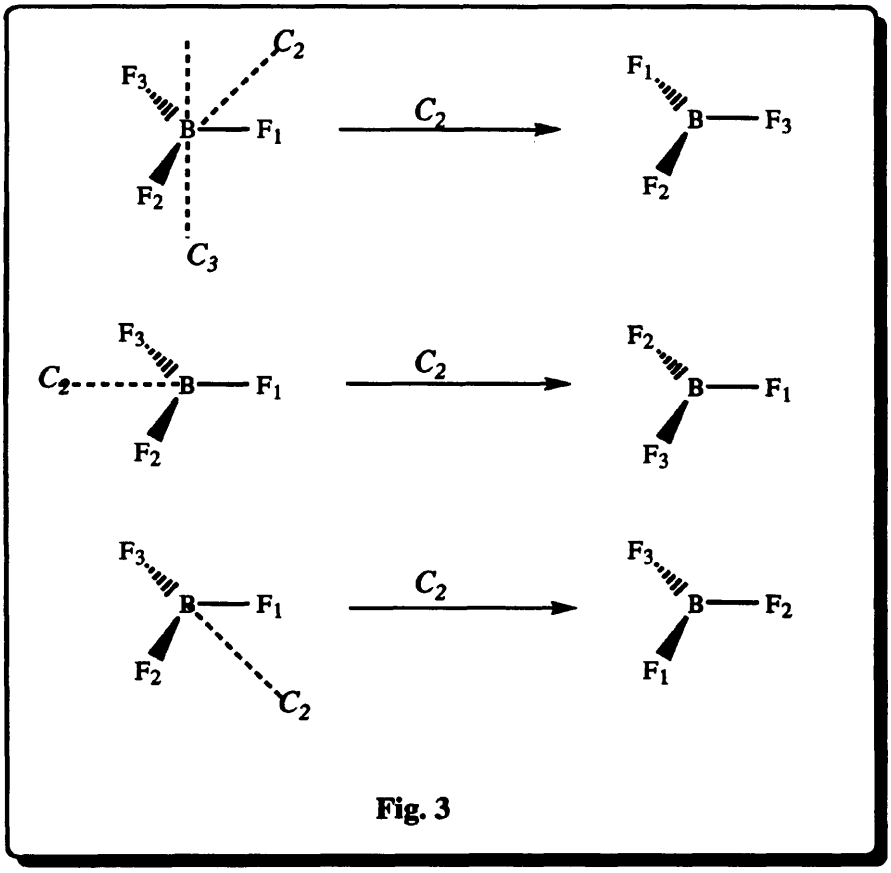
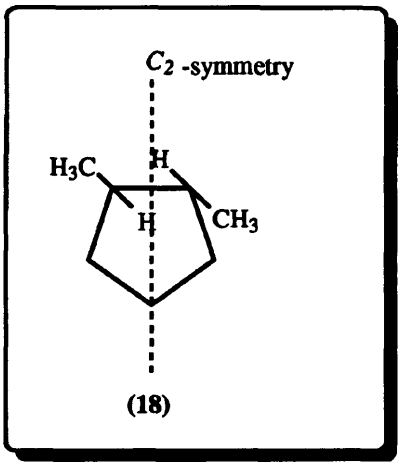


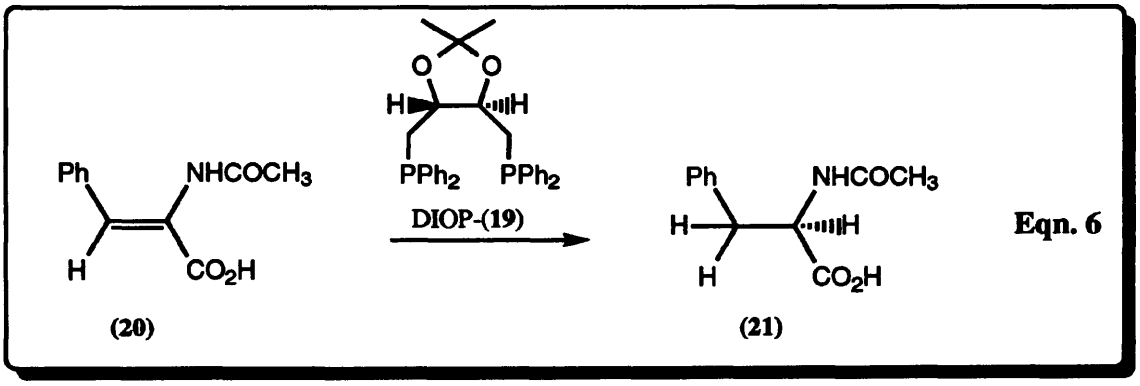
Fig. 3

An example of a simple two-fold axis of symmetry (C_2 axis) can be seen in planar 1,2-dimethylcyclopentane **(18)**, which can be brought to an indistinguishable position by a 180° rotation around this axis.



(18)

The first C_2 chiral auxiliary ligand was the DIOP ligand **(19)** used by Kagan[15] to catalyse the asymmetric hydrogenation of olefins (e.g. **20**) in the presence of a Rh(I)-complex to give **(21)** in 70% **e.e. (Eqn. 6)**.



(20) (21) **Eqn. 6**

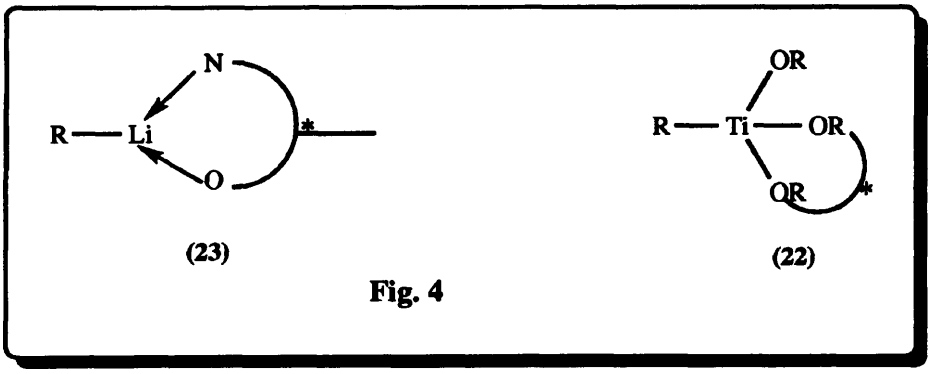
Chapter 2

I.2 Synthesis and Application of Chiral Diol Ligands Based on Titanium Lewis Acids

I.2.1 Importance of Organotitanium Reagents

Many titanium compounds are commercially available and all of them are easily prepared on a large scale. Unlike most other transition metal reagents the titanium derivations can be employed stoichiometrically, not only are they inexpensive, but also non-toxic [e.g. $TiCl_4$, $Ti(O^iPr)_4$, $Ti(NMe_2)_4$, and $Ti(NEt_2)_4$].[16]

Organotitanium derivatives of type **(22)** are expected to give higher enantioface-differentiations than the classical organometallic compounds such as RLi **(23)** and RMgBr, **(Fig.4)**.



(23) **(22)**

Fig. 4

The high reactivity of these organolithium and Grignard reagents are often accompanied with disadvantages, for example, the need to protect other carbonyl and carboxy groups in the compound, and their incompatibility with the presence of groups such as CN, NO_2, and I.[16,17]

I.2.2 Preparation of Some Organotitanium Reagents

The actual reagent is often generated *in situ* and may be derived from lower-valent titanium complexes. Some titanium reagents, which have been mentioned earlier, can be prepared in one step as illustrated in the following equations **(Eqns. 7-10).**

$$TiCl_4 + 3\,Ti(OR)_4 \longrightarrow 4\,ClTi(OR)_3 \qquad \textbf{Eqn. 7}$$

$$ClTi(OR)_3 + R'Li \longrightarrow R'\text{-}Ti(OR)_3 + Li\,Cl \qquad \textbf{Eqn. 8}$$

$$TiCl_4 + 2\,ROH \longrightarrow Cl_2Ti(OR)_2 + 2HCl \qquad \textbf{Eqn. 9}$$

$$TiCl_4 + 4\,LiNEt_2 \longrightarrow Ti(NEt_2)_4 + 4LiCl \qquad \textbf{Eqn. 10}$$

Duthaler and Hafner have summarized the general principles of obtaining chiral titanium complexes as shown in **scheme (1).**[18]

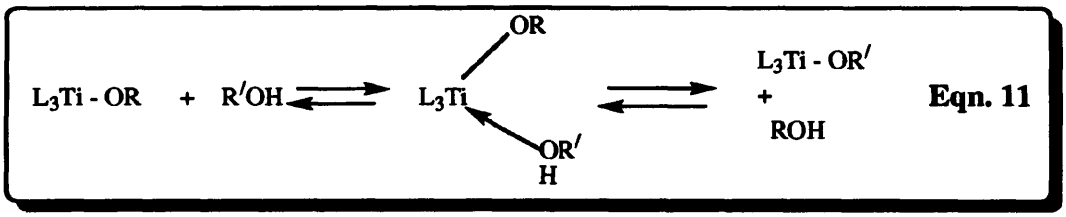
$$R_3Ti\text{-}Cl + LM \longrightarrow R_3Ti\text{-}L + MCl$$

$$R_3Ti\text{-}Cl + LSiMe_3 \longrightarrow R_3Ti\text{-}L + Me_3SiCl$$

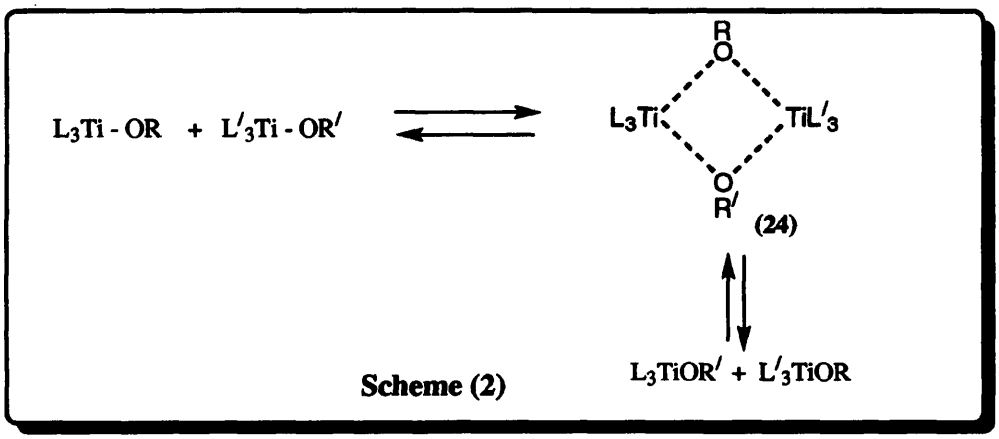
$$R_3Ti\text{-}Cl + L\text{-}H \longrightarrow R_3Ti\text{-}L + HCl_g \xrightarrow{Et_3N} Et_3N^+HCl^-$$

Scheme (1)

A very efficient method of synthesizing titanium alkoxides is the transesterification with a free alcohol **(Eqn. 11).**



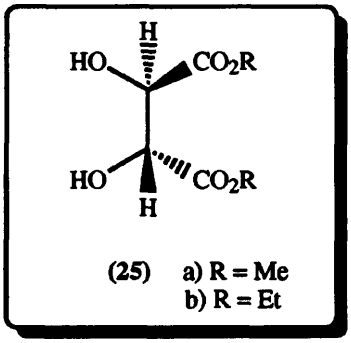
Alkoxide ligand can also be interchanged via bridged dimers **(24) scheme (2).**



However, the idea of using bidentate chiral ligands originates from the expectation that chelate rings stabilize such complexes and that the rigidity gained improves the stereoselectivity of the corresponding reagents.[18]

I.2.3 Tartaric Acid-based Ligands

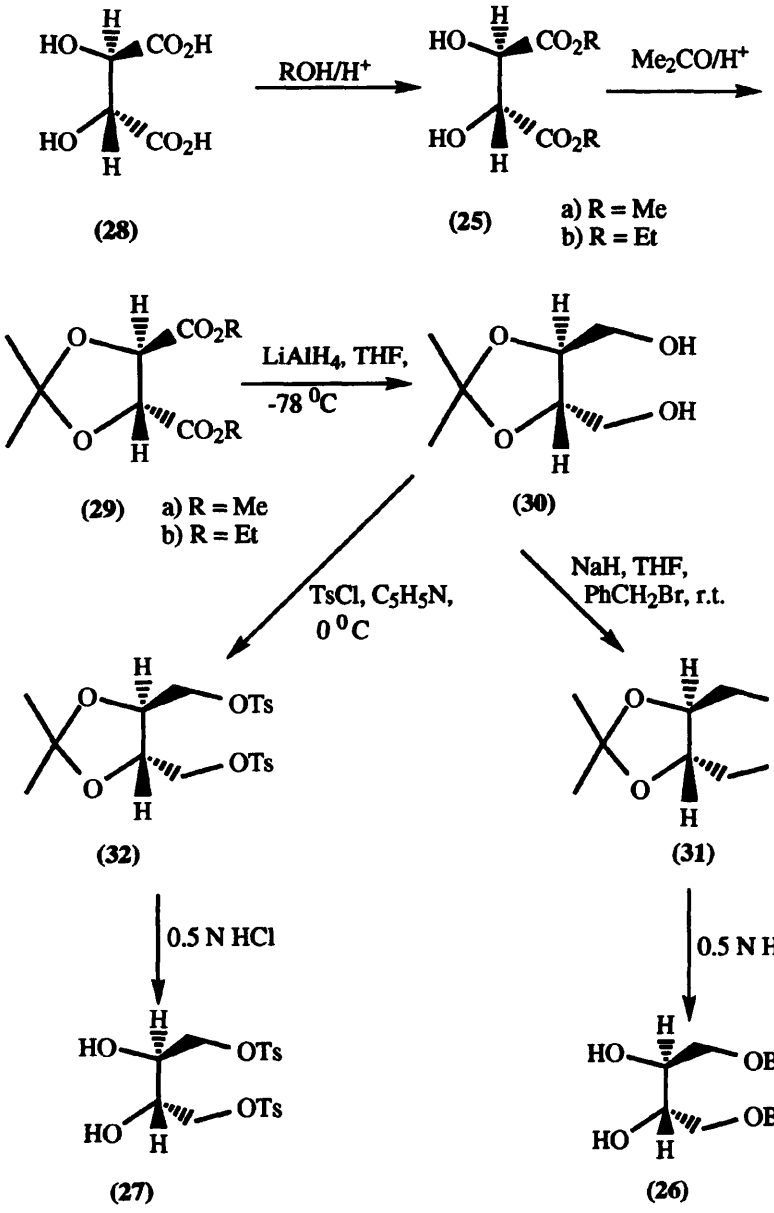
There are several catalytic systems which involve alcohols as ligands. The most useful classes of catalysts are those based on 1,2-diols. One spectacular chiral catalyst has been devised by Sharpless *et al.* and is obtained from a dialkyltartrate **(25)** and titanium tetraisopropoxide, $Ti(O^iPr)_4$.[19,20]



(25) a) R = Me
b) R = Et

(i) Synthesis of Threitol Ligands

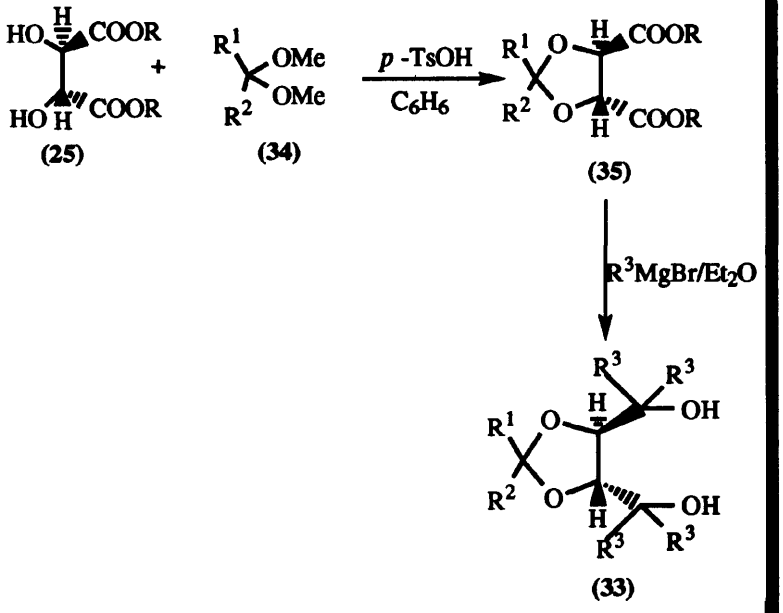
Early reported examples of chiral diols as ligands were the syntheses of 1,4-di-*O*-benzyl and 1,4-di-*O* -tosyl-threitols **(26)** and **(27)** respectively from the readily available (R,R)-(+)-tartaric acid **(28)** as shown in **scheme (3)**.[21-25]


ROH/H+
Me2CO/H+
(28)
(25)
a) R = Me
b) R = Et
LiAlH4, THF,
-78 0C
(29)
a) R = Me
b) R = Et
(30)
TsCl, C5H5N,
0 0C
NaH, THF,
PhCH2Br, r.t.
(32)
(31)
0.5 N HCl
0.5 N HCl
(27)
(26)
Bn = PhCH2
Ts = p - CH3C6H4SO2-

Scheme (3)

(ii) Synthesis of TADDOL Ligands

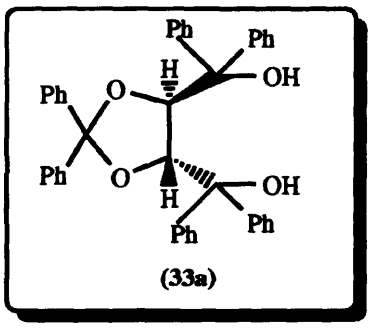
Important and commonly used chiral 1,4-diol ligands have been prepared from L-(+)-tartaric acid derivatives **(25)**. Thus, tetraaryldioxolanedimethanol (TADDOLs) **(33a-i)**[17,26-40] and hexamethyldioxolanedimethanol (HMDDOL) **(33j)**[17,27,28,39] have been obtained from L-(+)-tartrate **(28)** as illustrated in **scheme (4)**.



a) $R^1 = R^2 = R^3 = Ph$	ref. (26, 27)
b) $R^1 = R^2 = Me$, $R^3 = Ph$	" (26, 27, 31-35, 39)
c) $R^1 = R^3 = Ph$, $R^2 = Me$	" (27, 31, 39)
d) $R^1 = H$, $R^2 = R^3 = Ph$	" (27, 30, 37, 38)
e) $R^1 = R^2 = Me$, $R^3 = 2,5\text{-}(Me)_2C_6H_3$-	" (27, 40)
f) $R^1 = R^2 = Et$, $R^3 = 2,5\text{-}(Me)_2C_6H_3$-	" (27, 38, 40)
g) $R^1 = R^2 = Me$, $R^3 = 1,1'$ - naphthyl-	" (36, 37, 39)
h) $R^1 = H$, $R^2 = Me$, $R^3 = Ph$	" (40)
i) $R^1 = H$, $R^2 = {}^t Bu$, $R^3 = Ph$	" (27)
j) $R^1 = R^2 = R^3 = Me$	" (17, 27, 28)

Scheme (4)

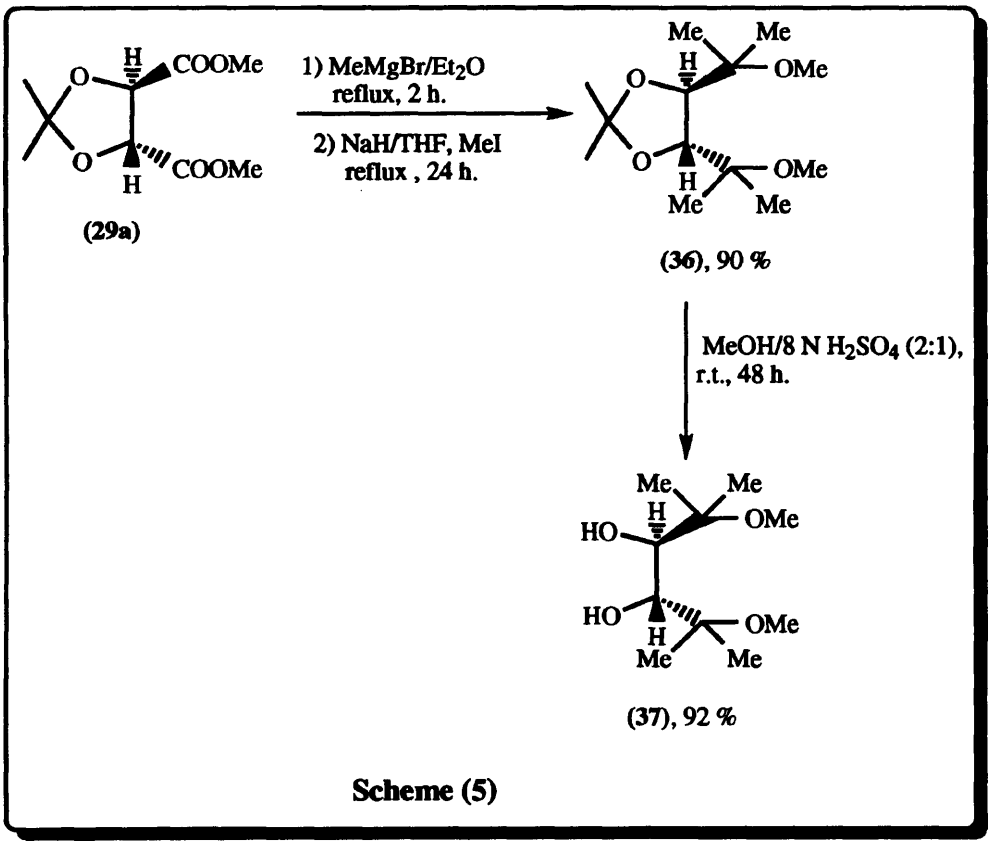
By following this synthetic **scheme (4)** Irurre and Alija[41] synthesized **(33a)** by transacetalization of the dimethylacetal of benzophenone (**34**, $R^1 = R^2 = Ph$) with commercial dimethyl L-tartrate (**25**, $R = CH_3$) to provide the dioxolane **(35)** in 82% yield.[41,42] Treatment of **(35)** with an excess of phenylmagnesium bromide gave the desired 1,4-chiral diol **(33a)** in 65% yield and 98% **e.e.**[41]



(33a)

(iii) Other Ligands

Other chiral diols as ligands derived from (R,R)-(+)-dimethyl tartrate **(29a)**[43] and possessing C_2-symmetry have been described by Hope. 2,5-Dimethoxyhexane-3,4-diol **(37)**, (S,S)-1,4-bis(dimethylamino)butane-2,3-diol **(38a)** and 1,4-bis(methylpiperidino) butane-2,3-diol **(38b)** were synthesized as described in the synthetic **schemes (5)** and **(6)** respectively.[44,45]

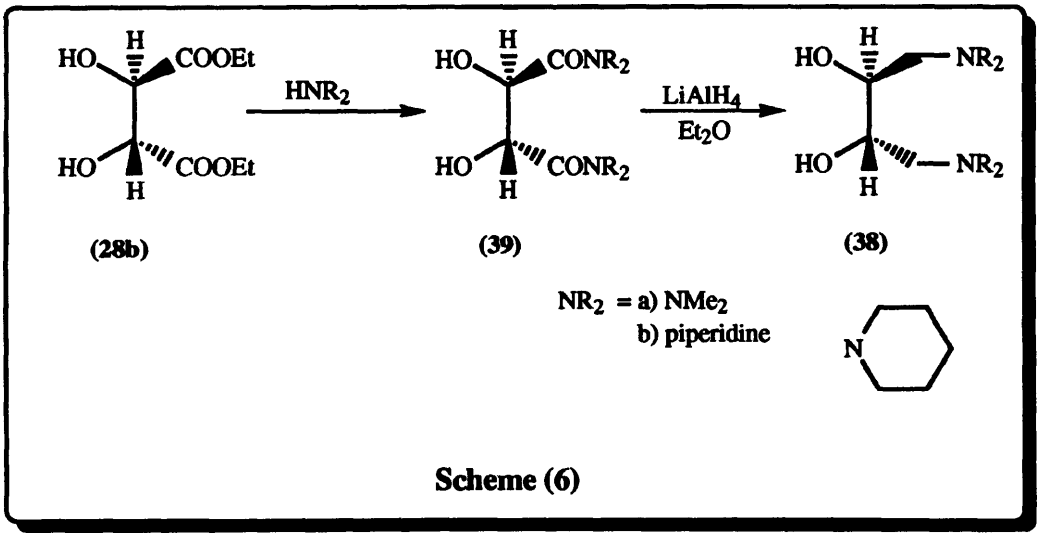


(29a)

(36), 90 %

(37), 92 %

Scheme (5)



(28b)

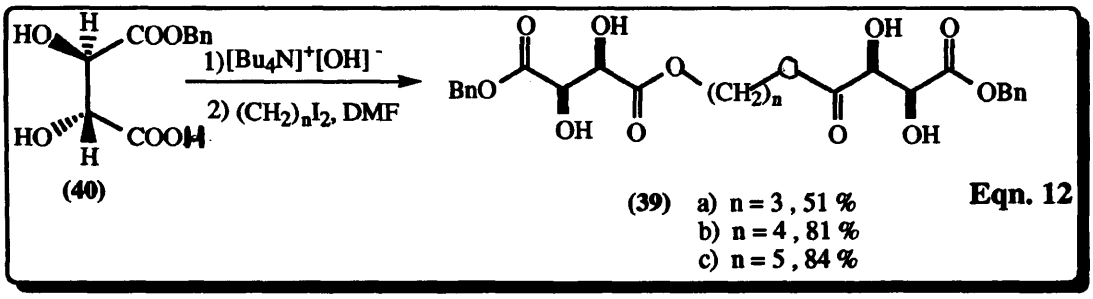
(39)

(38)

Scheme (6)

These chiral diols were found by Chapuis and Jutczak to be very useful ligands in asymmetric Diels-Alder reactions.[46]

In 1989 Sharpless and Carlier described the synthesis of the linked bistartrate ester ligand **(39)** formed by alkylation of monobenzyltartaric acid **(40)**, **(Eqn. 12)**.[47-49]

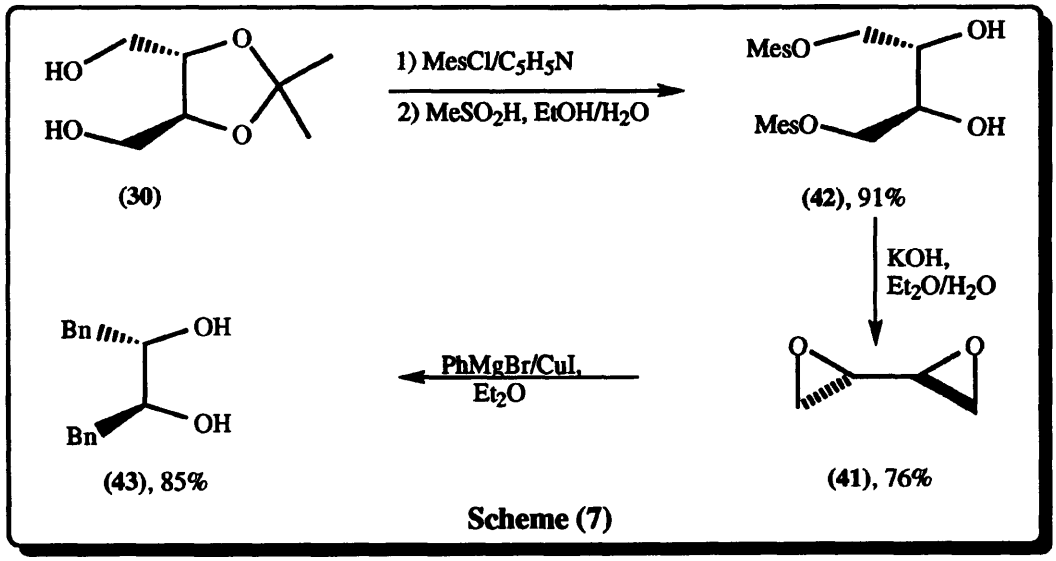


(40)

(39) a) n = 3 , 51 %
b) n = 4 , 81 %
c) n = 5 , 84 %

Eqn. 12

As part of their study of Lewis acid-catalyzed asymmetric Diels-Alder reactions Devine and Oh[50] have described the synthesis of (R,R)-1,2-dibenzylethane-1,2-diol **(43)** starting from (R,R)-dimethyl tartrate [21,23,51] as shown in **scheme (7)**.



(30)

(42), 91%

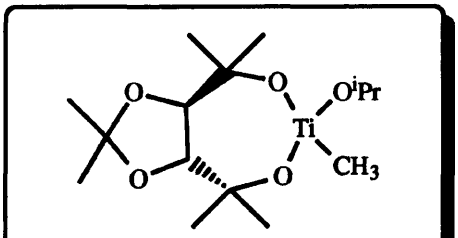
(43), 85%

(41), 76%

Scheme (7)

I.2.3.1 Reactions of Chiral Titanium Diol Complexes Derived from Tartaric Acid

Chiral 1,4-diols [e.g. **(33)**] are useful ligands for the formation of chiral titanium complexes. For instance **(44)** can be prepared from the reaction of the diol **(33j)** with chlorotitanium triisopropoxide $ClTi(^{i}OPr)_3$ followed by the reaction with methyl magnesium bromide.[16,17]

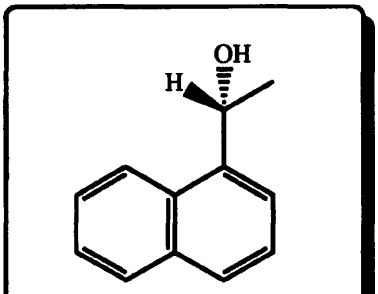


(R,R)-(44)

These titanium complexes can be used either stoichiometrically or catalytically in the enantioselective reactions.[16,38]

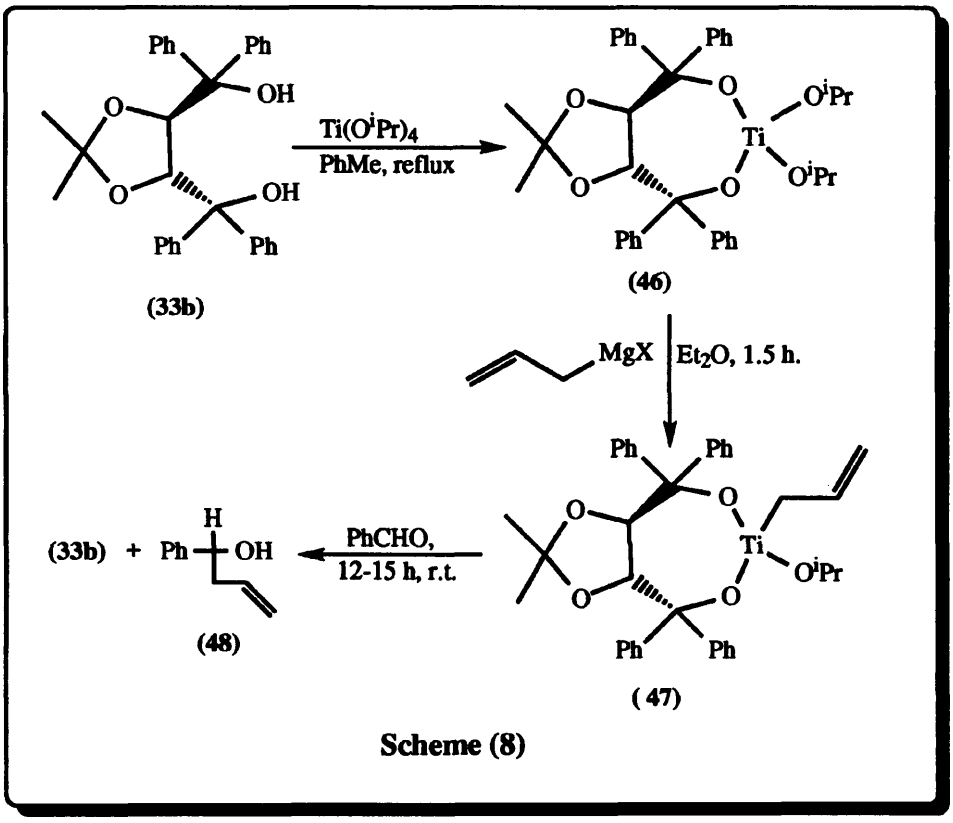
A. Alkylation

In 1980 Seebach reported that the chiral titanium complex **(44)** was an effective reagent for the enantioselective alkylation of aldehydes (e.g. naphthaldehyde) to afford the chiral alcohol (R)-**(45)** in 50% **e.e.**[17,27,28]



(R)-(45)

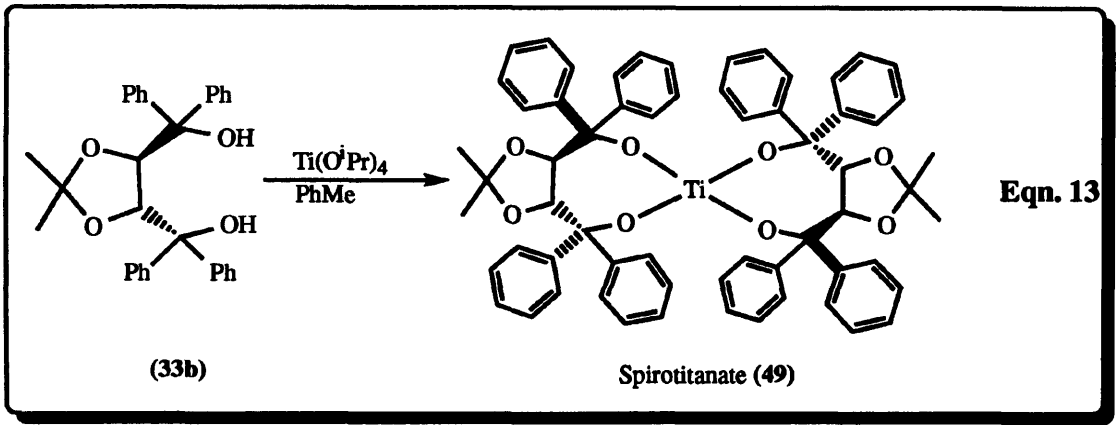
Takahashi *et al.* have pointed out that the TADDOL **(33b)** was a moderately effective reagent (2 equiv.) for the enantioselective reaction of aldehydes with chiral alkyltitanate complexes. Diol **(33b)** was reacted with titanium tetraisopropoxide to form **(46)** which was converted into the alkyltitanate-complex **(47)** by reacting an equimolar amount of alkylmagnesium halide. This chiral complex reacted with benzaldehyde to afford the alcohol **(48)** in a moderate enantiomeric excess (54% **e.e.**)[a] in 68% yield, **scheme (8)**.[33]



Scheme (8)

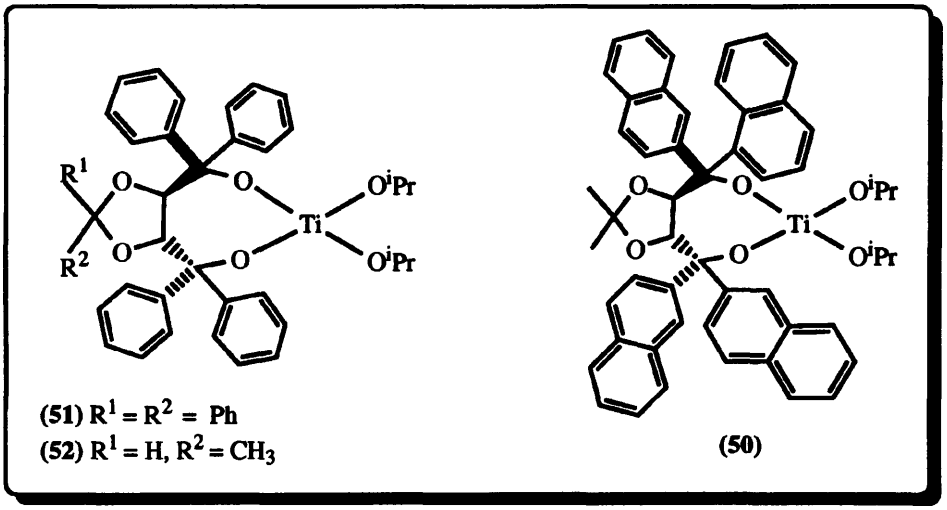
(a) : the absolute configuration is unknown.

Several important chiral titanium complexes have been described by Seebach and co-workers. The spirotitanate **(49)** has proved to be a useful asymmetric catalyst[34-37,40] It is easily prepared from the TADDOL compounds **(33a-i)** as shown in **(Eqn. 13)**, and is obtained as a stable colourless crystalline material.[35]



Eqn. 13

Other chiral titanium complexes such as the β-naphthyl-substituted titanate **(50)**[36,37], the pentaphenyltitanate **(51)**[37,40] and tetraphenyltitanate complexes **(52)** were also prepared from TADDOLs.[37,40]

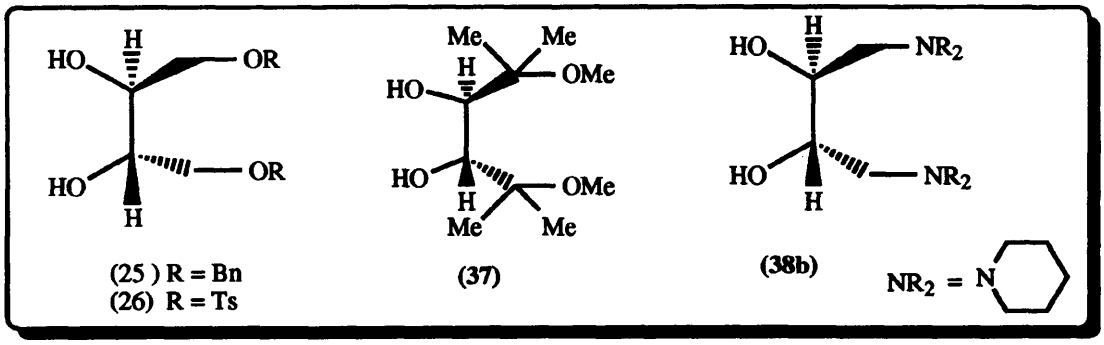


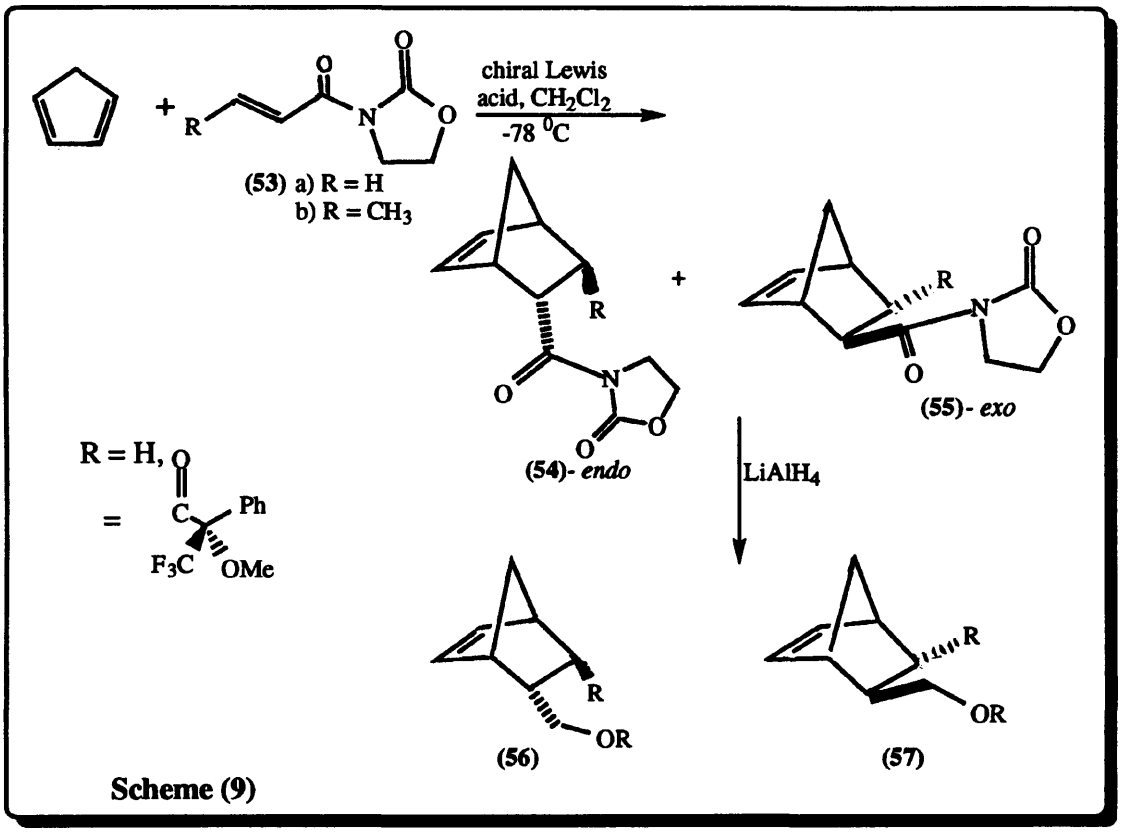
Seebach has shown that all these chiral, rigid titanium complexes **(49-52)** are useful reagents either catalytically (0.025-0.1 equiv) or stoichiometrically, in the enantioselective addition of diethylzinc to aliphatic or aromatic aldehydes and ketones to afford chiral alcohols (S-configuration in most cases) in very high enantiomeric excesses (98 to 99%) and moderate to high yields.

B. Diels-Alder Reaction

The Diels-Alder reaction has long been recognized as one of the most important methods for the construction of cyclohexane derivatives. Due to the concerted and secondary orbital controlled reaction pathway highly predictable stereoselectivity can be realized, making this reaction particularly useful in the stereoselective synthesis of various synthetic intermediates.[30]

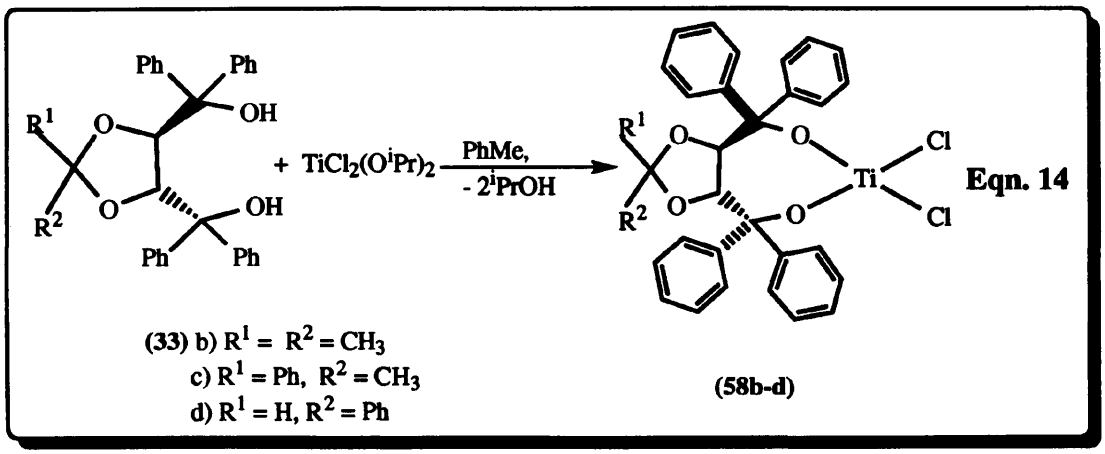
Thus, Chapius *et al.* have carried out the asymmetric Diels Alder reaction of cyclopentadiene with two bidentate dienophiles, 3-crotonoyl-**(53a)** and 3-acryloyl-4,4-dimethyl-1,3-oxazolidin-2-one **(53b)**, using stoichiometric amounts of various chiral diol ligands **(25, 26, 37** and **38b)** and titanium tetraisopropoxide to afford the *exo*-cyclo-adduct **(55)** with high diasteromeric excess (89-97% **d.s**) as described in **scheme (9)**.[46]





Scheme (9)

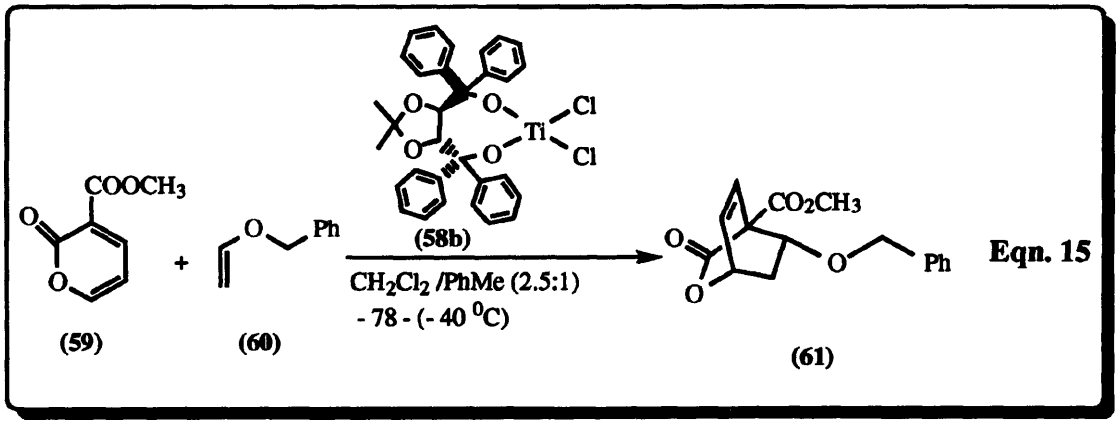
Other useful chiral titanium catalysts **(58b-d)** prepared *in situ* from dichlorotitanium diisopropoxide and TADDOLs **(33b-d)** are shown in **(Eqn. 14)**.



Eqn. 14

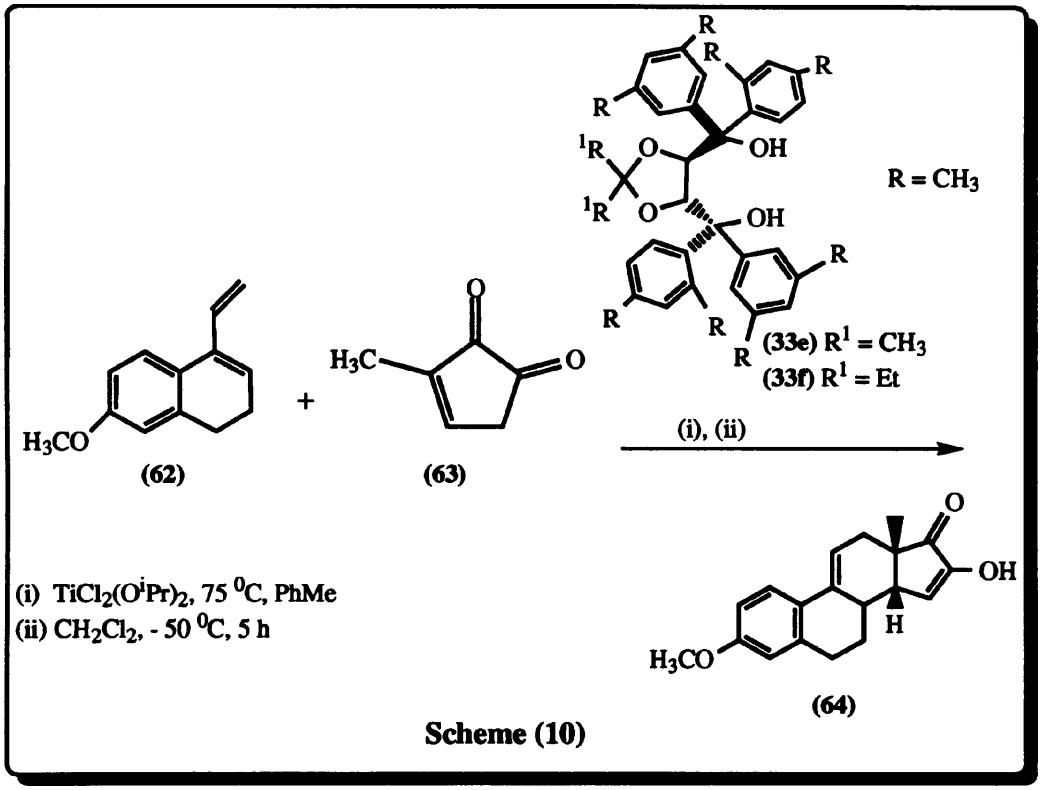
These were employed by Narasaka and Corey to catalyze asymmetric Diels-Alder reactions (0.4-1.0 equiv., **scheme 9**, p.23) in toluene at -15 °C as shown previously. High enantiomeric excesses of 94 to 96% **e.e.** and chemical yields of 93% were obtained.[31,38,52]

Posner *et al.*[32] have recently reported that 3-methoxycarbonyl-2-pyrone **(59)** reacts with allyl vinyl ether **(60)** catalyzed by the same chiral titanium complex **(58b)** to give a moderate enantiomeric excess (55% **e.e.**) and 63% yield of the *endo*-bicyclo lactone **(61) (Eqn. 15).**[32]



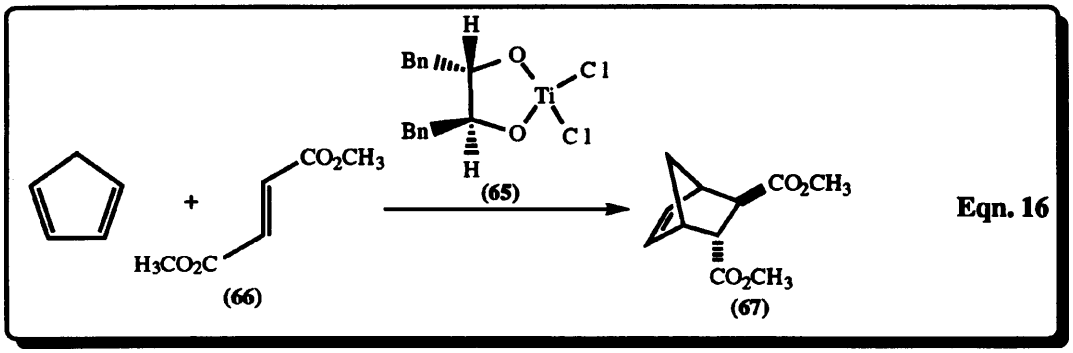
Eqn. 15

Quinkert *et al.* [39] used chiral titanium complexes of TADDOLs **(33e-f**, 2-2.20 equiv.) for the asymmetric Diels-Alder reaction of diene **(62)** and dienophile **(63)** to afford cycloadduct **(64)**, a steroid precursor[53], in good yield (77%) and 79% **e.e.** **scheme (10).**[39]



Scheme (10)

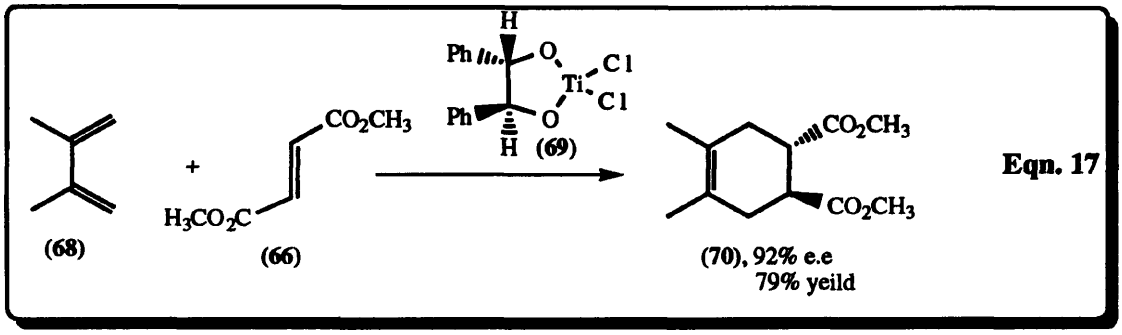
Additionally, bidentate diol ligand **(43)** was reacted with titanium tetrachloride ($TiCl_4$) to form the chiral modified Lewis acid **(65)**. This catalyzed the asymmetric DAR of cyclopentadiene with dimethyl formate **(66)**[54] to give an 86% yield of the cycloadduct **(67)** with moderate to high enantioselectivity of 48-80% **e.e., (Eqn. 16).**[55]



Eqn. 16

An improvement in the enantioselectivity was observed when an acyclic diene

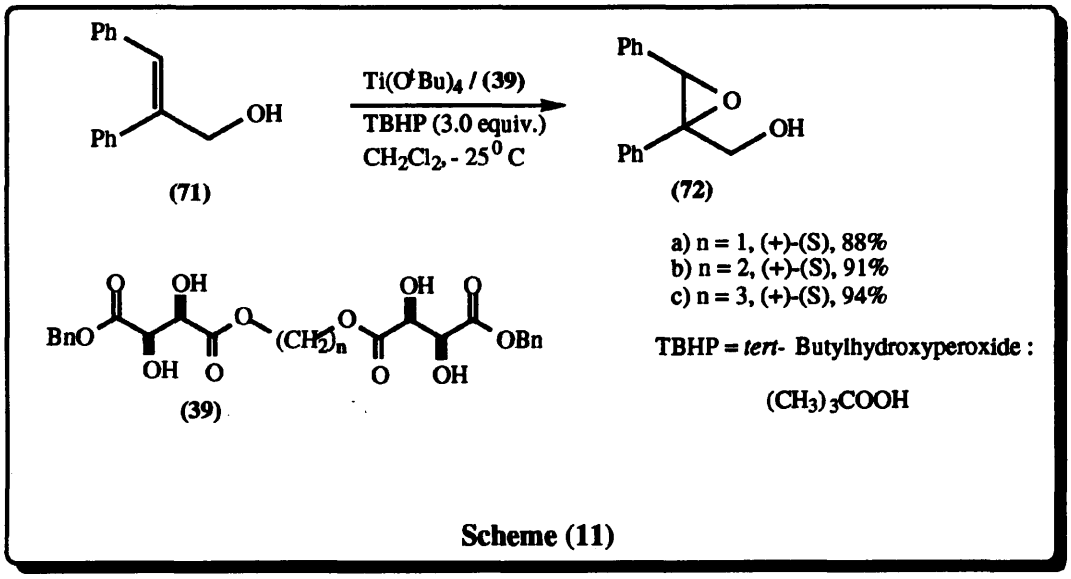
(68) was used instead of cyclopentadiene in the presence of the chiral diphenylethane-1,2-diol titanium dichloride complex **(69)** as shown in **(Eqn. 17)**.[55]



Eqn. 17

C. Asymmetric Epoxidation

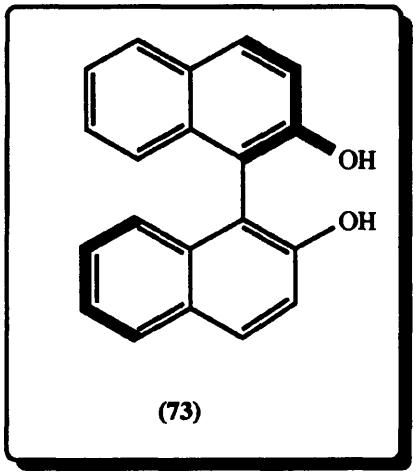
Chiral titanium complexes of the ligands **(39a-c)** were used as catalysts (1.0 equiv.) in the asymmetric epoxidation of the allylic alcohol **(71)** and gave a high enantiomeric excess up to 94% of the epoxy alcohol **(72) scheme (11)**.[47]



Scheme (11)

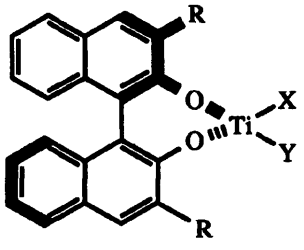
I.2.4 Binaphthol-based Ligands

Axially dissymmetric 1,1'-binaphthyl derivatives have proved to be highly effective ligands because of their structural rigidity, simplicity, resistance to racemization and above all, effectiveness of chiral recognition.[56-59]



(73)

1,1'-Binaphthol **(73)** is a rigid chiral 1,4-diol which can form seven-membered ring complexes of titanium, such as **(74a-h)**.[18]



(74)

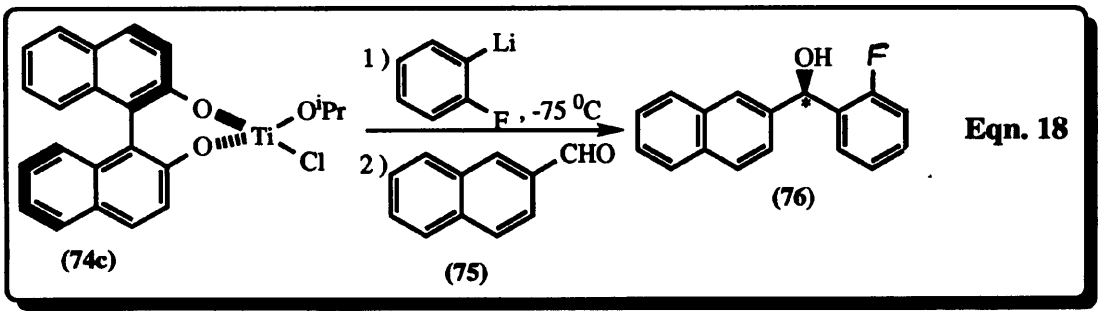
a) R = H, X = O^{i}Pr, Y = Ph	ref. 11,28, 59
b) R = H, X = Me, Y = O^{i}Pr	" 17, 27
c) R = H, X = Cl, Y = O^{i}Pr	" 29 ,28,60
d) R = H, X = Y = O^{i}Pr	" 29 , 59 61
e) R = Ph, X = Y = Cl	" 46
f) R = H, X = O^{i}Pr, Y = 1,1'- naphthyl	" 17 , 58
g) R = H , X = Y = Cl	" 61- 63
h) R = H , X = Y = C_5H_5	" 63

Thus,1,1'-binaphthol **(73)** was found to be useful in a variety of asymmetric syntheses.

A. Alkylation

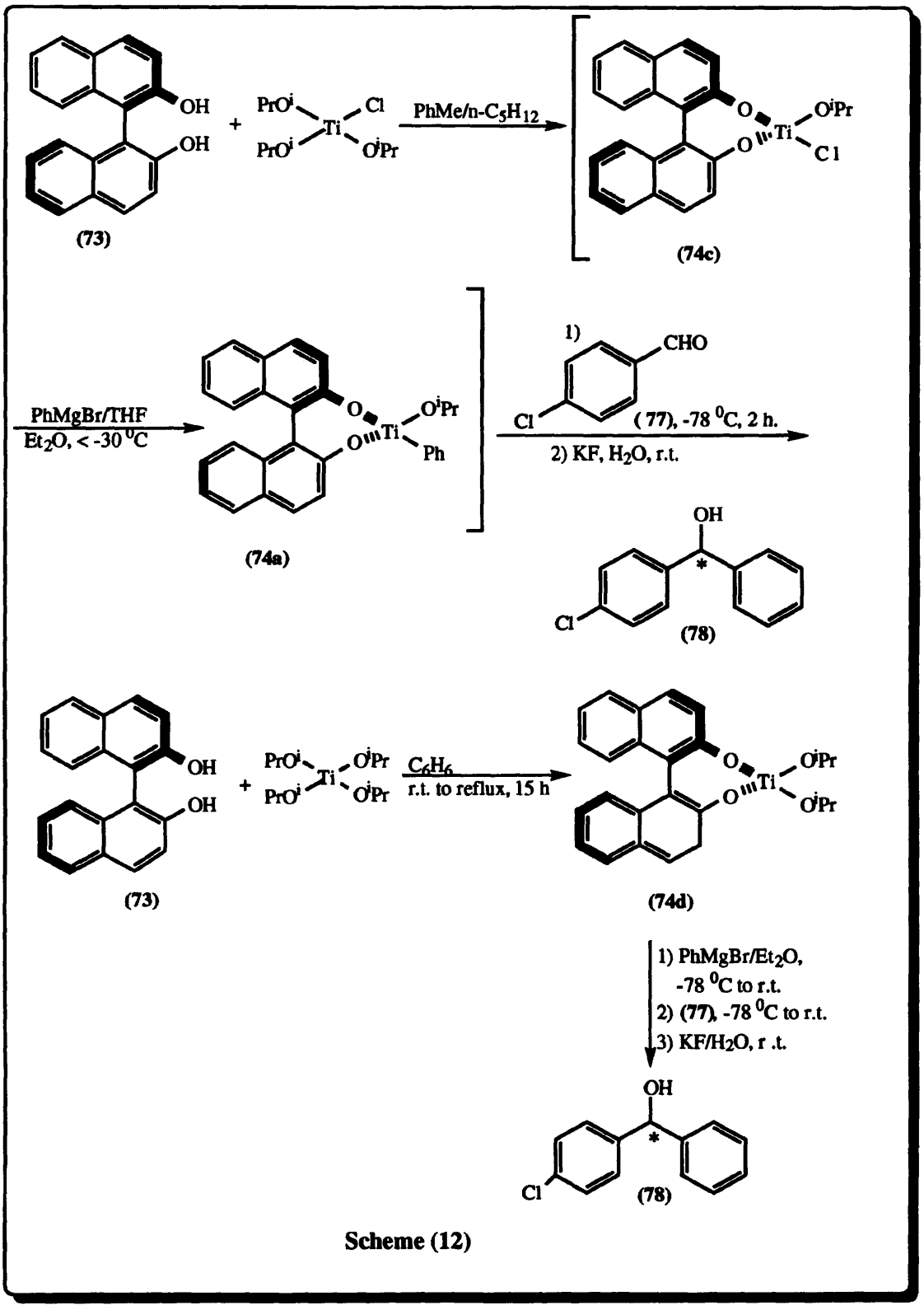
In 1981 Seebach reacted **(73)** with $ClTi(OR`)_3$ followed by reaction with phenyl magnesium bromide to obtain the titanium complex **(74a)** which was used in the enantioselective addition of the phenyl group of **(74a)** to various aromatic aldehydes and up to 88% **e.e.** of the chiral alcohols were achieved.[17,59]

A very high enantiomeric excess (98% **e.e.**) was also achieved using **(74a)** as the reagent in the addition of a phenyl group to naphthaldehyde. However, only a low enantiomeric excess (48%) was obtained when complex **(74b)** was used as the reagent with benzaldehyde. The other complex **(74c)** was generated *in situ* starting from the binaphthol **(73)**. This intermediate complex **(74c)** transfers an aryl group to naphthaldehyde **(75)** to afford alcohol **(76)** in 89% **e.e.** as shown in **(Eqn. 18)**.[29]



Eqn. 18

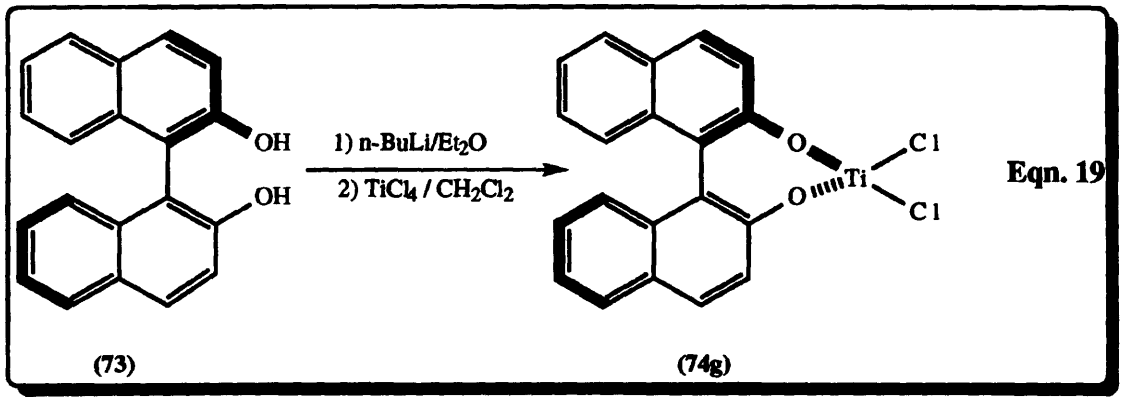
Other impressive results were achieved by Wang. Up to 100% **e.e.** was obtained by using the chiral titanium complexes **(74c** and **74d)** (prepared *in situ*) in the asymmetric addition of phenylmagnesium bromide to 4-chlorobenzaldehyde **(77)** as described in **scheme (12)**.[59]


OH
OH
(73)
PrO^i
PrO^i
Ti
Cl
O^{i}Pr
PhMe/n-C$_5$H$_{12}$
O
O
Ti
O^{i}Pr
Cl
(74c)
PhMgBr/THF
Et$_2$O, < -30 ^{0}C
O
O
Ti
O^{i}Pr
Ph
(74a)
1)
CHO
Cl
(77), -78 ^{0}C, 2 h.
2) KF, H$_2$O, r.t.
OH
*
Cl
(78)
OH
OH
(73)
PrO^i
PrO^i
Ti
O^{i}Pr
O^{i}Pr
C$_6$H$_6$
r.t. to reflux, 15 h
O
O
Ti
O^{i}Pr
O^{i}Pr
(74d)
1) PhMgBr/Et$_2$O,
-78 ^{0}C to r.t.
2) (77), -78 ^{0}C to r.t.
3) KF/H$_2$O, r .t.
OH
*
Cl
(78)

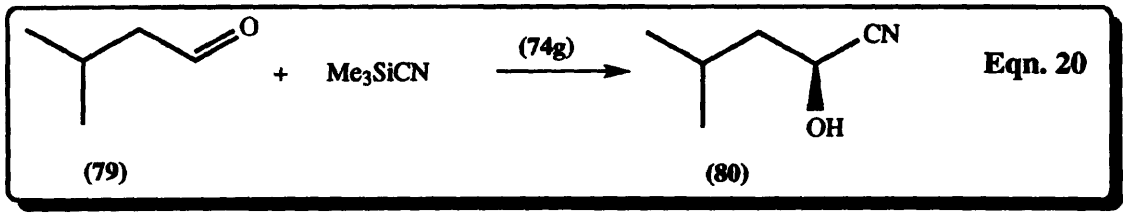
Scheme (12)

B. Other Asymmetric Inductions

Reetz has described the preparation of the complex **(74g)**, **(Eqn. 19)**. When **(74g)** was employed in cyanohydrin formation a high enantiomeric excess was achieved (82% e.e. and 85% chemical yield) (**Eqn. 20**).[62,63]

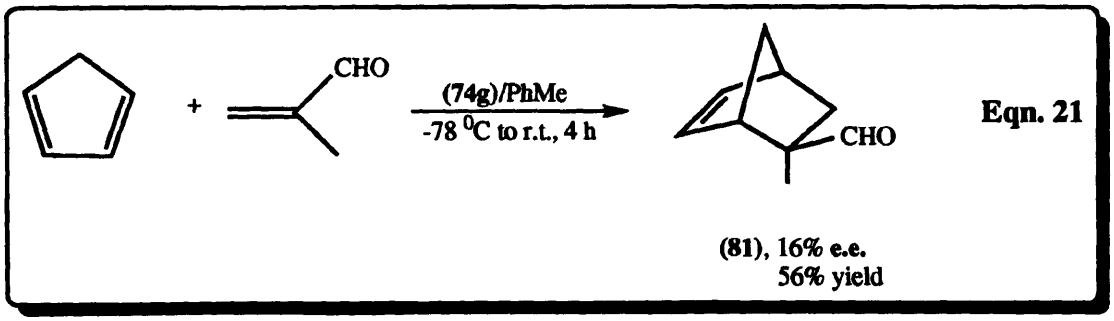


Eqn. 19



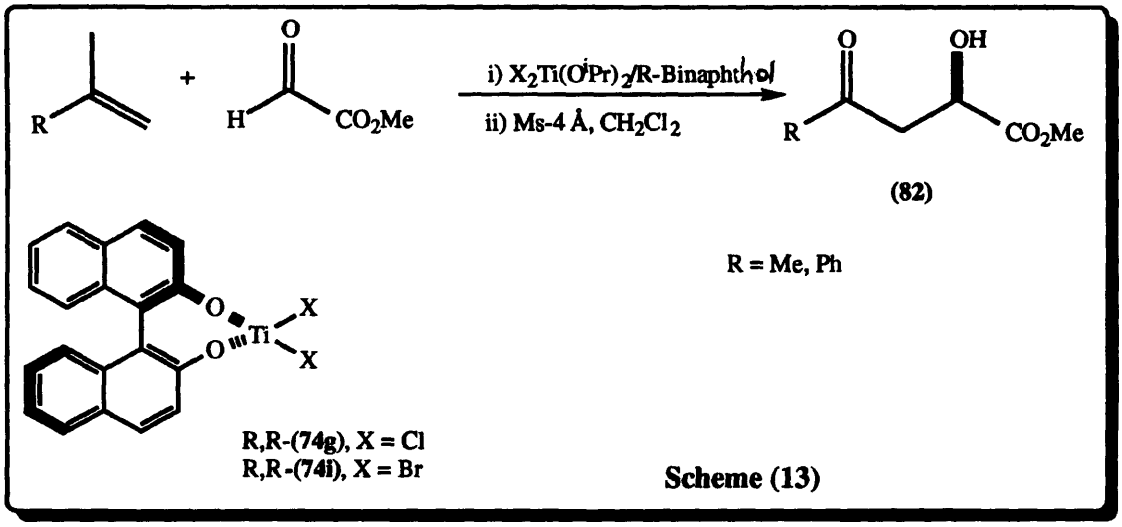
Eqn. 20

The complex **(74g)** has also been used as a catalyst for Diels-Alder reactions, but only a low enantiomeric excess was observed, **(Eqn. 21)**.[62]



Eqn. 21

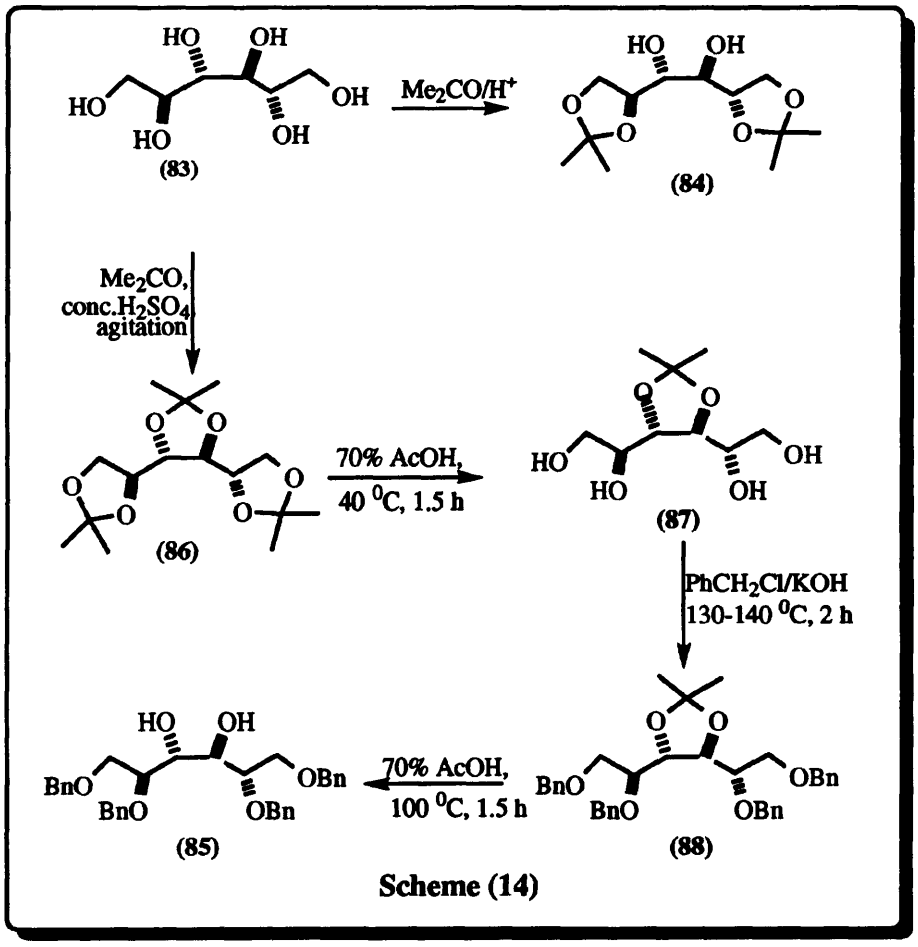
Complexes (**74g** and **74i**) were also used as catalysts (~ 0.1 equiv.) in the asymmetric glyoxylate-ene reaction, **scheme (13)**.[64-66] Excellent enantiomeric excesses (97%) and chemical yields (97%) were achieved.



Scheme (13)

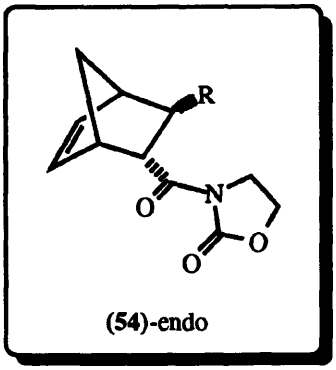
I.2.5 D-Mannitol-based Ligands

Other chiral diol ligands which possess C_2-symmetry, such as D-mannitol derivatives (**84**) and (**85**), were prepared according to **scheme (14)**.[67-69]



Scheme (14)

When both complexes (**84** and **85**) were used as catalysts (stoichiometric amount) in the asymmetric Diels-Alder reaction of cyclopentadiene, (**scheme 9**, p.23) high diastereomeric excesses (94% and 92% **d.s.** respectively) of the ***endo***-cycloadduct (**54**) were obtained in good yields, 89-92%.[46]



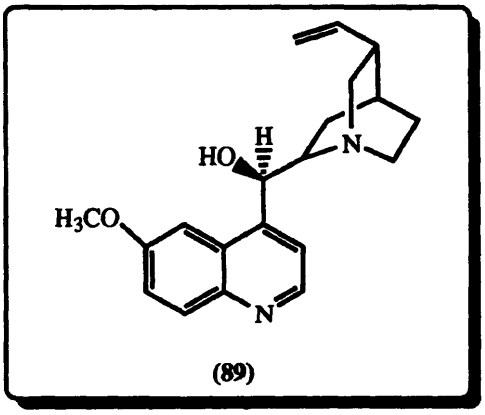
(**54**)-endo

Chapter I.3

Synthesis and Applications of Chiral Amino Alcohol Ligands in Asymmetric Synthesis

I.3.1 Introduction

Recent interest has been centred increasingly on homogeneously catalyzed asymmetric induction reactions which involve β-amino alcohols as catalyst precursors. Such compounds have been used not only in general asymmetric synthesis, for instance, the synthesis of insecticidal compounds[70], but also for the resolution of racemic mixtures[71] e.g. L-(-)-quinine-**89**).[72]



(89)

The chiral 2-amino-1-alcohols are in general much more effective and give much higher optical yields than chiral diamines and diols.[73] For instance, the addition reaction of diethylzinc reagents to aldehydes are usually very slow, but a β-amino alcohol alone catalyses the addition process[74,75] and many excellent amino alcohol ligands have so far been developed for this purpose.

For the purpose of our survey, chiral amino alcohol ligands can be classified as follows:

I.3.2 Ephedrine-based Ligands

I.3.3 Aminoborneol-based Ligands

I.3.4 Pyrrolidinyl Methanol (PMPM)-based Ligands

I.3.5 Isoquinolinyl Methanol-based Ligands

I.3.6 Oxazolidinone and Oxazoline-based Ligands

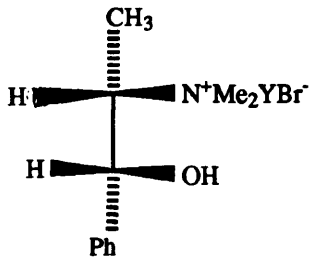
I.3.7 Amino Sugar-based Ligands

I.3.8 Miscellaneous Chiral Amino Alcohols

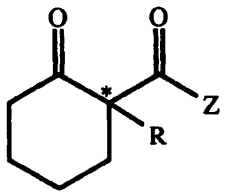
I.3.2 Ephedrine-based ligands

One of the advantages of the use of ephedrine and norephedrine as chiral sources in asymmetic synthesis is that both enantiomers are readily available. Thus both enantiomers of the chiral catalysts can be obtained.[76]

Among the earliest examples of a chiral amino alcohol is (2S, 3S)-(-)-N-benzyl-N-methylephedrine bromide **(90)** which was synthesized by Fiaud in 1975 and used as a catalyst in the enantioselective alkylation of cyclic β-keto esters and ketones to obtain **(91)**.[77]

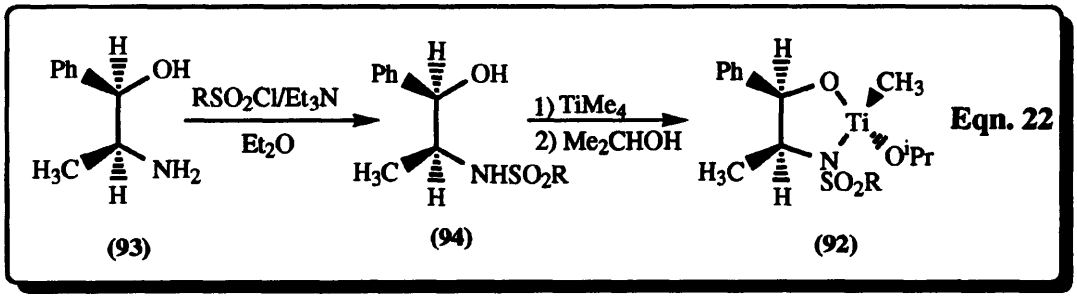


(2S,3S)-(-)-(**90**)
a) Y = CH_2Ph
b) Y = CH_3



(**91**), R = CH_3, -CH=CH_2, -$H_2CC{\equiv}CH$
Z = OEt, OMe, Me

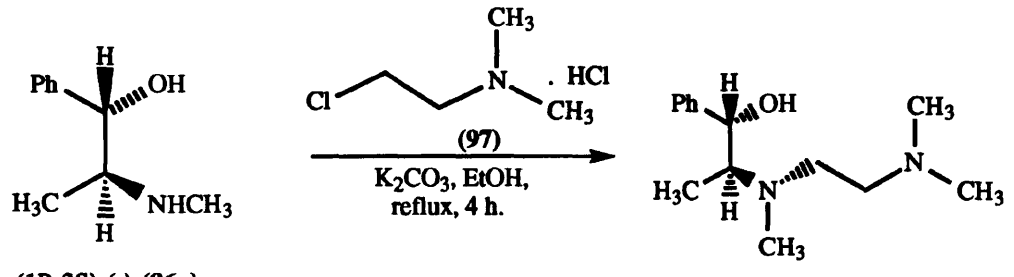
Reetz and co-workers have synthesized an excellent ligand **(92)** based on the readily available norephedrine **(93)** as described in **(Eqn. 22).**[78,79]



(93) **(94)** **(92)** **Eqn. 22**

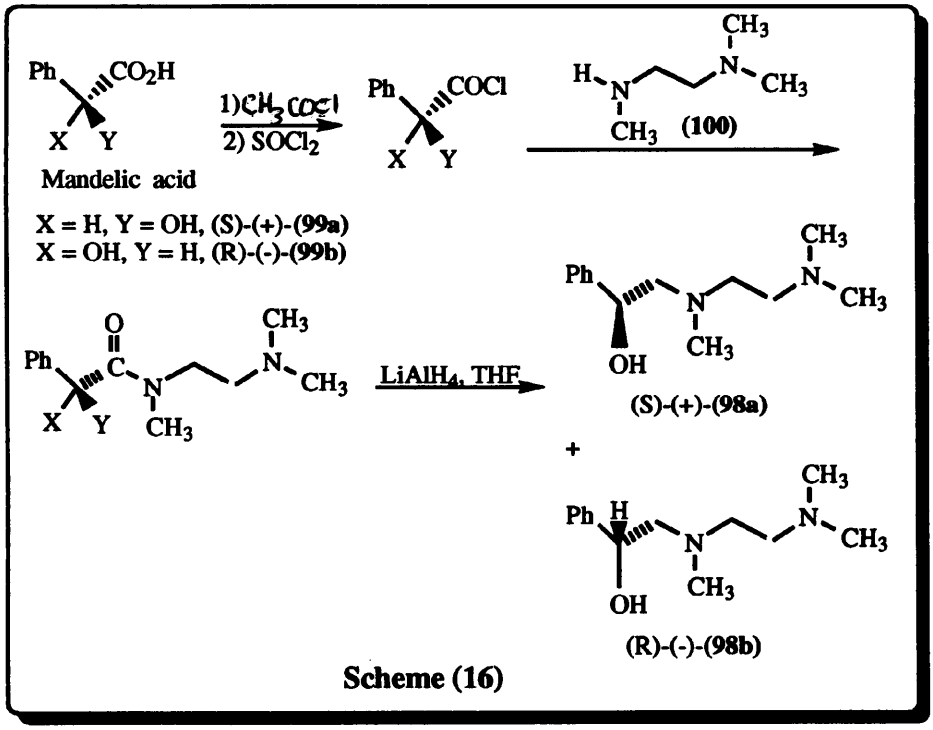
The titanium complex **(92)** was used by the authors as a reagent in the enantioselective addition of the methyl group of the titanium complex **(92)** to various aromatic aldehydes to form (R)-carbinols in up to 92% yield and 90% **e.e.**[78]

Corey and co-workers have described many useful chiral β-amino alcohol ligands based on ephedrine **(96).**[80-82] Thus (1R,2S)-(**95**),[80] and (1R)-(-)-(**98a**) and its enantiomers (1S)-(**98b**) were synthesized as pure ligands starting from (1R,2S)-(-)-ephedrine **(96a)** and mandelic acid **(99a** and **99b)** according to the synthetic **schemes (15)** and **(16)** respectively.[80]



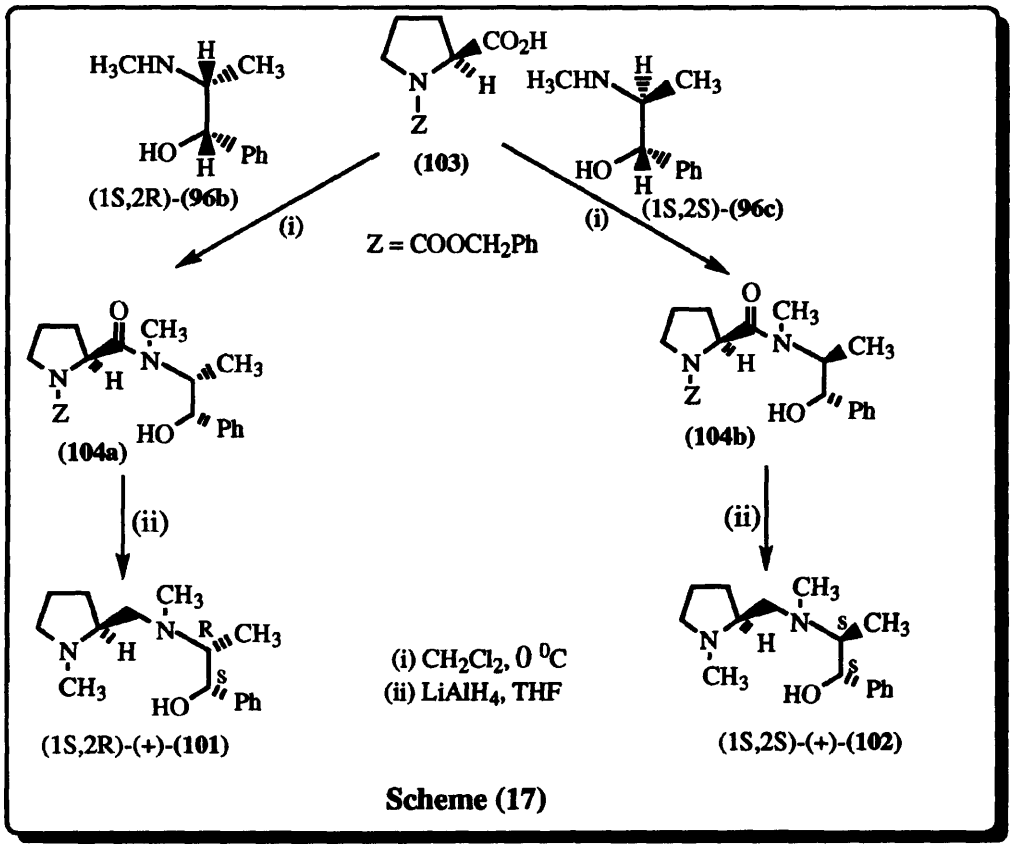
(1R,2S)-(-)-(**96a**) (1R,2S)-(**95**)

Scheme (15)



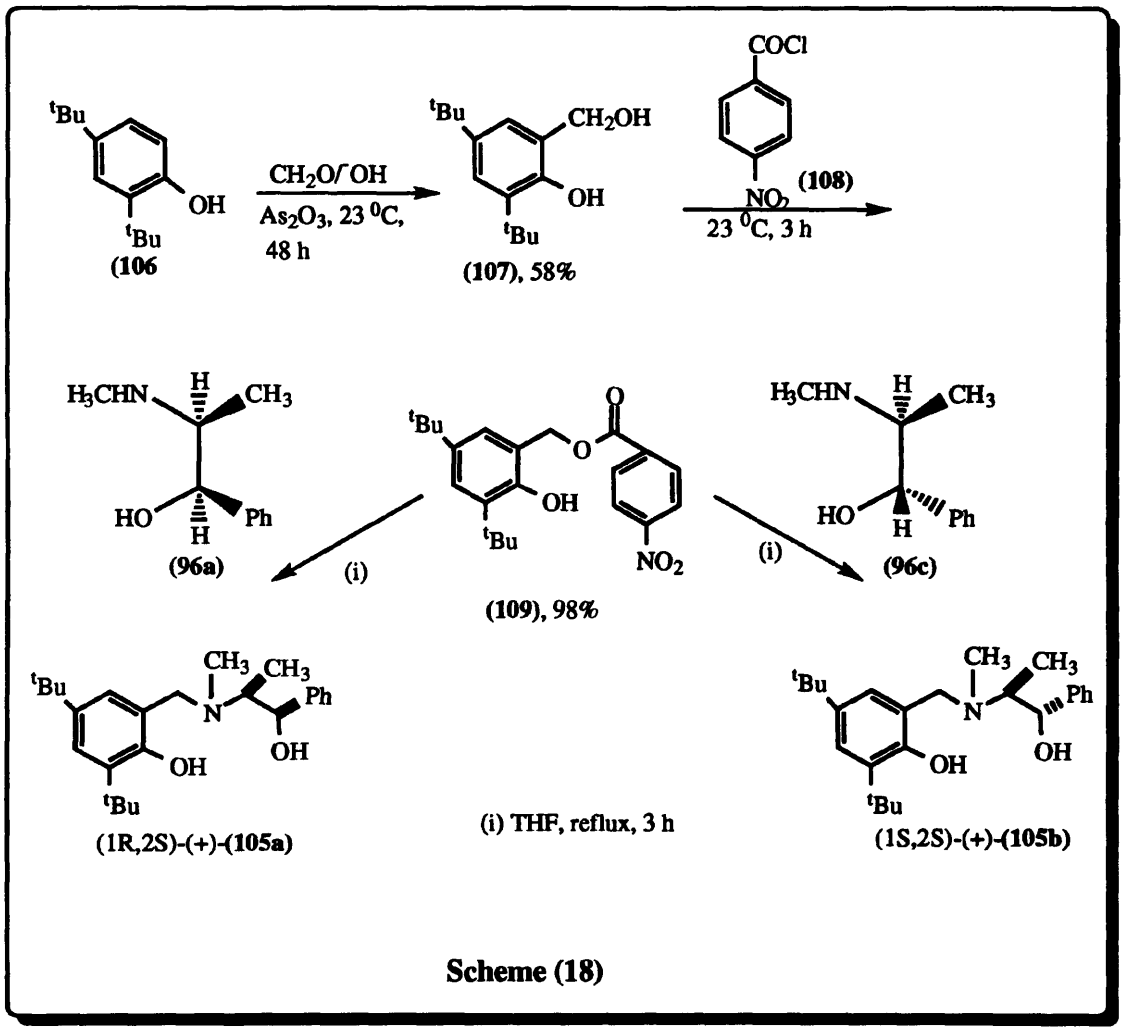
Scheme (16)

Chiral β-amino alcohols (+)-(1S, 2R)-**(101)** and (+)-(1S, 2S)-**(102)** were also synthesized by the same authors from the reaction of N-benzyloxycarbonyl-(S)-proline **(103)** and (1S,2R)-(+)-ephedrine **(96b)** and (1S,2S)-(+)-pseudo-ephedrine **(96c)** respectively as described in **scheme (17)**[81]



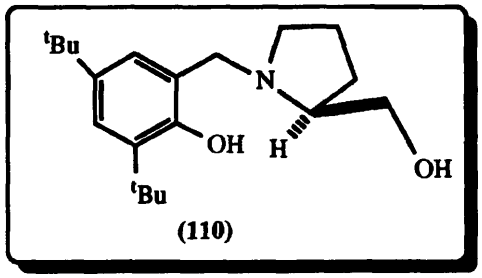
Scheme (17)

Corey and Hannon have also reported the preparation of the tridentate β-amino diol ligands **(105a)** and **(105b)** from 2,4-di-t-butylphenol **(106)** using (1R,2S)-(-)-ephedrine **(96a)** and (1S,2S)-(+)-pseudoephedrine **(96c)** respectively as shown in **scheme (18)**.[82]



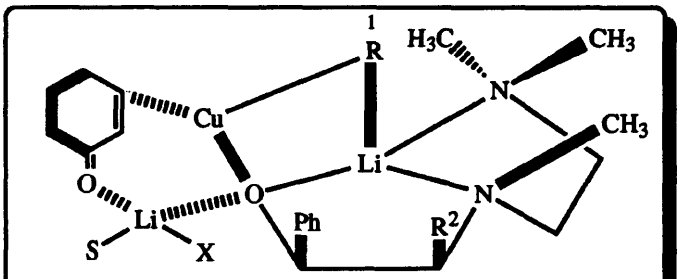
Scheme (18)

They have also prepared the tridentate β-amino diol ligand **(110)** using a similar approach.



The β-amino alcohol ligands **(95, 98a** and **98b)** have been employed in the enantioselective reduction of 2-cyclohexenone derivatives in the presence of cuprous iodide

and alkyl lithium **(111)**, **(Fig.5)**, to afford **(112)** in 95% **e.e.**, (66% yield) and 90% **e.e.** (60% yield), respectively).[80]

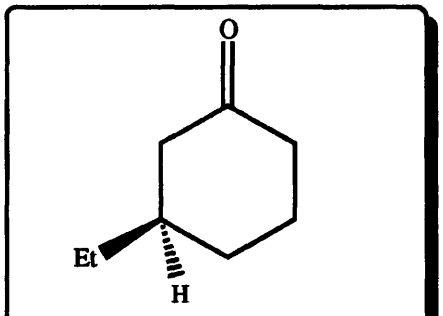


(111)

a) R^1 = Et, R^2 = Me
b) R^1 = Me, R^2 = H

X = I^-, THF
S = THF

Fig. 5



(R)-(+)-(112)

The ligands **(101, 102, 105a, 105b** and **110)** have also been used for enantioselective addition of diethylzinc to benzaldehyde giving enantiomeric excess values in the range 70-95% **e.e.**[80-82]

Corey and Hannon proposed the mechanistic model shown in **(Fig.6)** to predict correctly the predominant (S)-configuration of the product resulting from the ligand **(105b)**.[82]

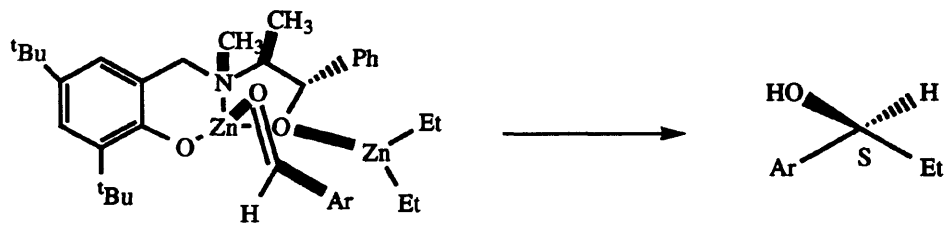
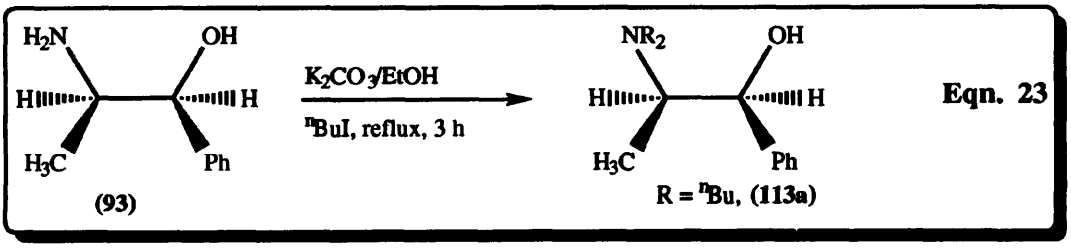


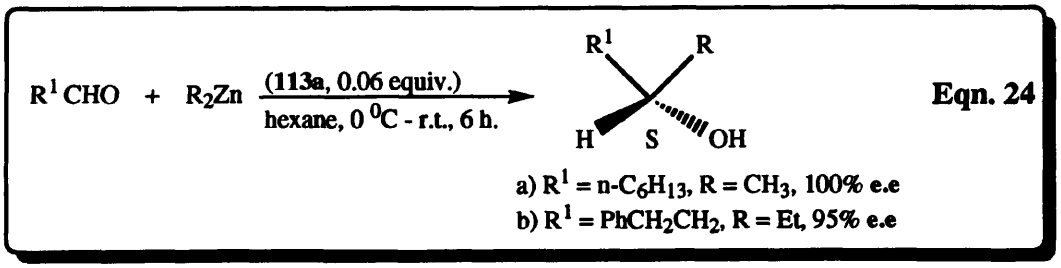
Fig. 6

Soci *et al.* have synthesized in 38% yield an important chiral amino alcohol ligand **(113)**. Thus (1S,2R)-(-)-2-N,N-(dibutylamino)-1-phenylpropan-1-ol-(DBNE)-**(113a)** was prepared from the reaction of (1S,2R)-(+)-norephedrine **(93)** and 1-iodobutane as shown in **(Eqn. 23)**.[83]



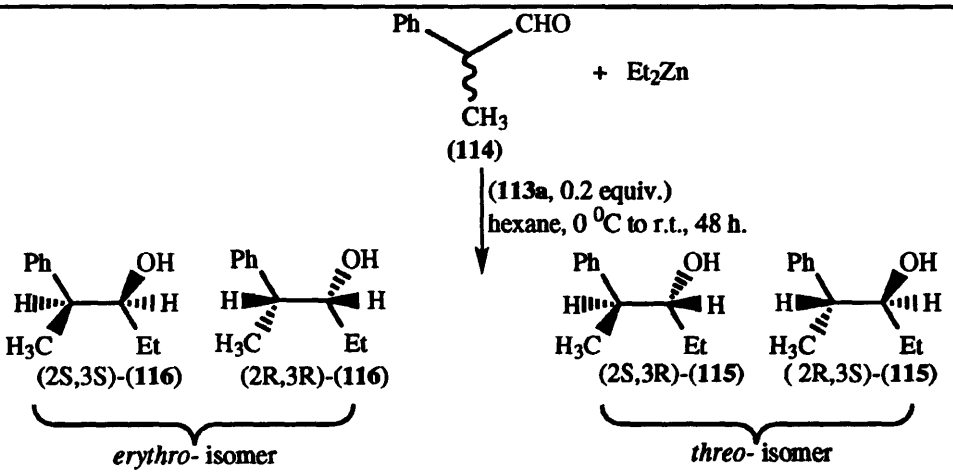
Eqn. 23

Ligand **(113a)** was found to be a very useful catalyst for the enantioselective addition of diethylzinc to various aliphatic aldehydes. It afforded optically active secondary alcohols in excellent enantiomeric excesses (95-100%) and 70-94% yields **(Eqn. 24)**.[83]



Eqn. 24

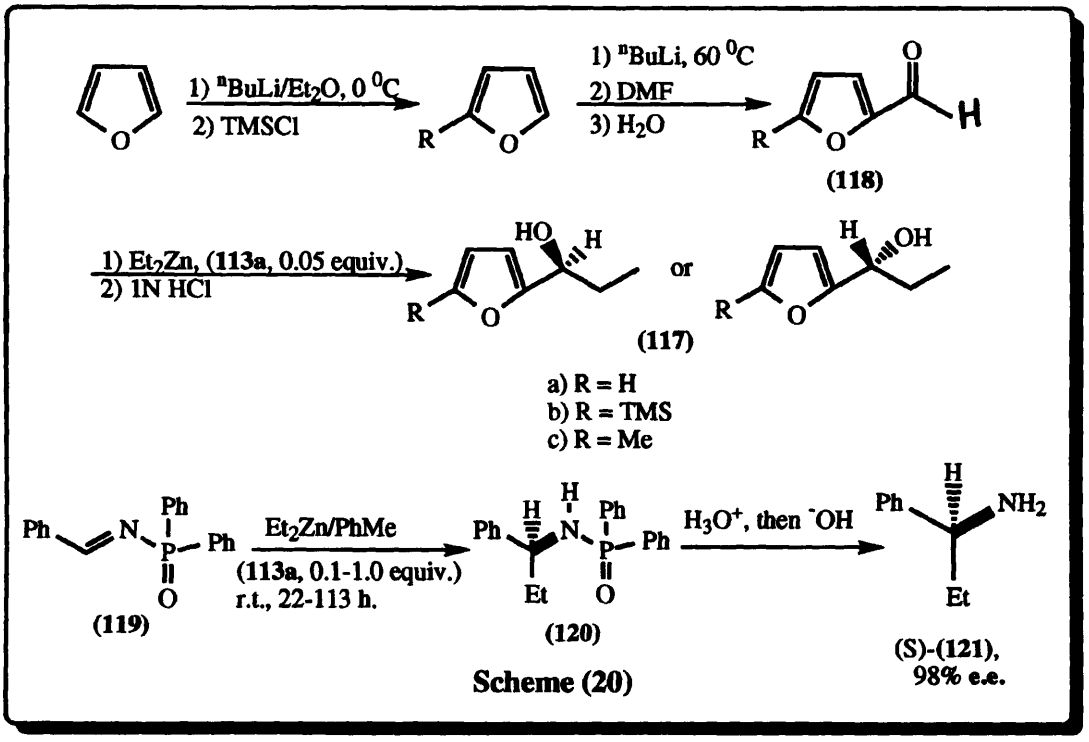
DBNE (**113a**) was also found to be a good catalyst in the enantioselective addition of diethylzinc to aldehydes containing two chiral centres affording the *threo-* isomer of chiral secondary alcohols (**115** and **116**) in 95% **e.e.** as shown in **scheme (19).**[84,85]



time(min.)	yield[%]	*erythro* (116)	*threo* (115)	e.e. % (115)	e.e. % (116)
3	66	29	71	95	75

Scheme (19)

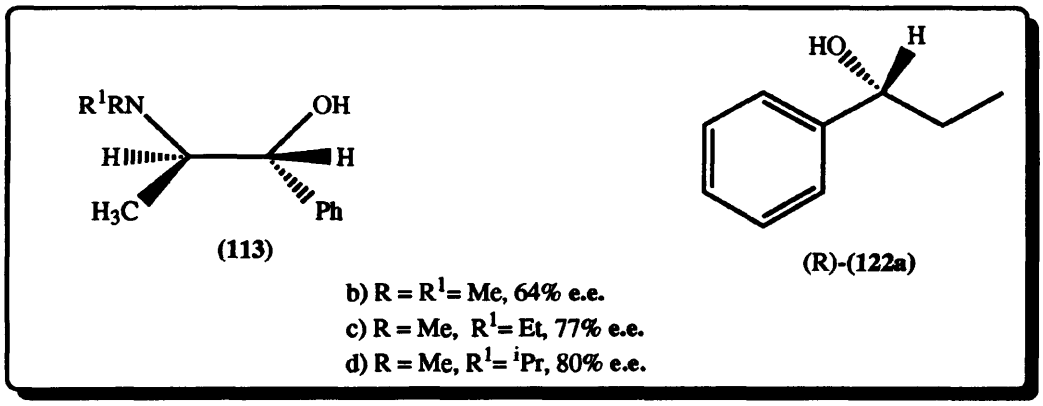
Ligand (**113a**) was also found to be a useful catalyst in the enantioselective synthesis of furyl alcohol (**117**) from furaldehyde (**118**)[86,87] and in the alkylation of imines (**119**)[88] to obtain amine (**121**) in high yields and high **e.e.** values **scheme (20).**[89]



Scheme (20)

The same author has also reported that the dibutylamino group in DBNE, **(113a)**, is essential for the achievement of high enantioselectivities with aliphatic aldehydes.[83] Dialkylzinc may be chelated to form a five-membered ring with the nitrogen and oxygen atoms from the zinc alkoxide.[85]

Chaloner and coworkers[91,92] have described their own results in the alkylation of benzaldehyde using ephedrine derivatives **(113)**[93] as catalysts to give 77-80% **e.e.** of (R)-(+)-1-phenylpropanol **(122a)** in moderate yield.[91,92]



Katsuki *et al.*, have used other ephedrine derivatives, such as the amino alcohol ligands **(123-126)**, modified by titanium, to catalyze the enantioselective addition of diethylzinc to benzaldehyde affording high enantiomeric excesses of 81-97% **(Fig.7)**.[94]

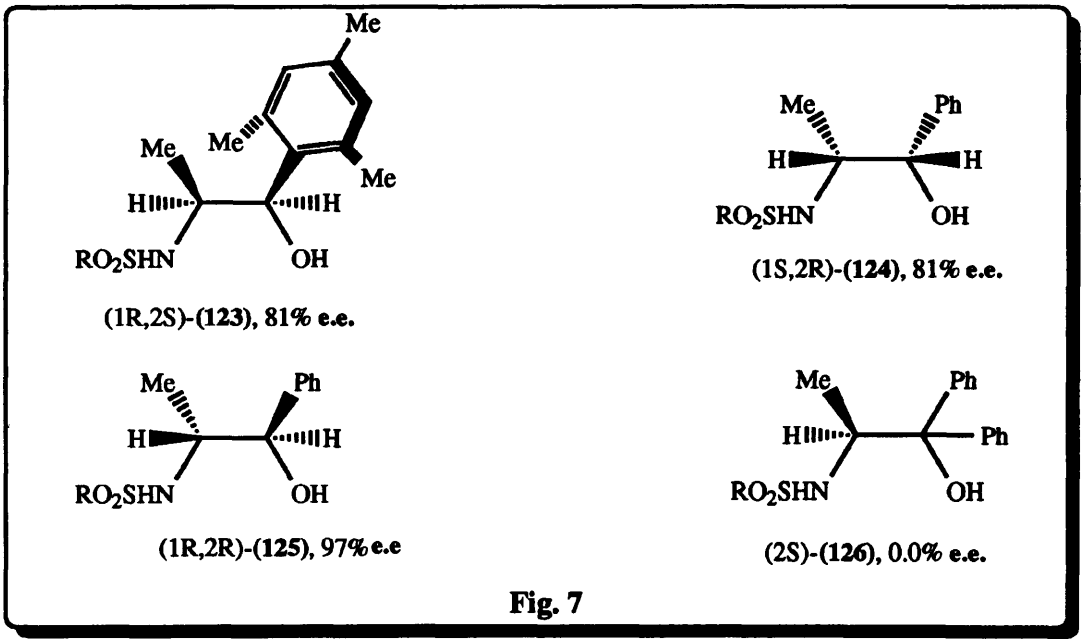
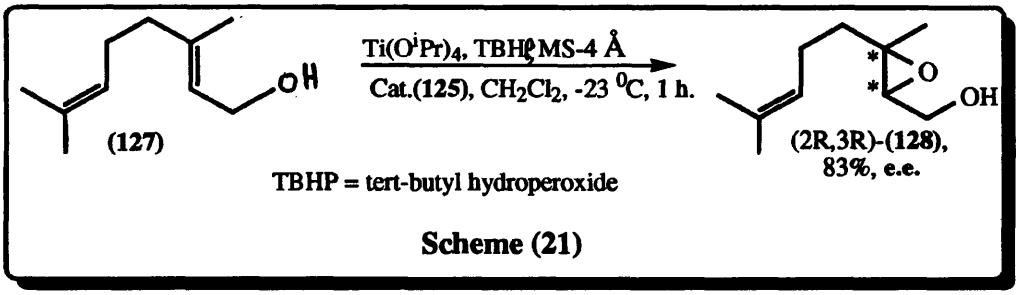


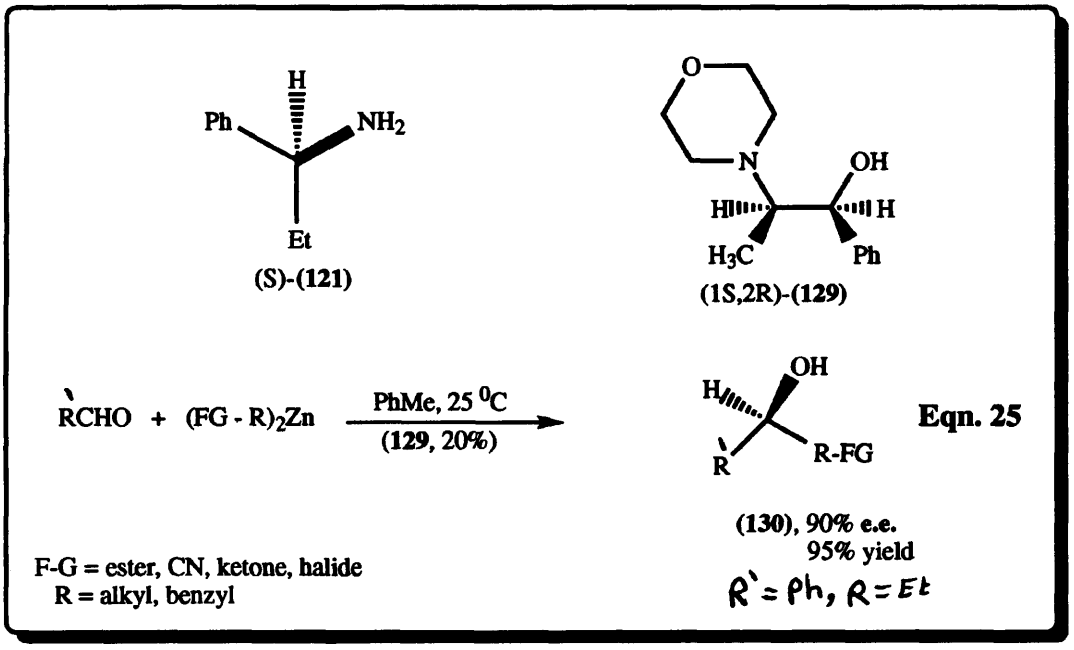
Fig. 7

When C-1 was achiral as in compound **(126)** no asymmetric alkylation was observed. Ligand **(125)** was found to be a useful chiral catalyst (1.0 equiv.) for the titanium-mediated asymmetric epoxidation of geraniol **(127)** to obtain 2,3-epoxy alcohol **(128)** in good enantiomeric excesses (74%) **(scheme 21)**.[95]



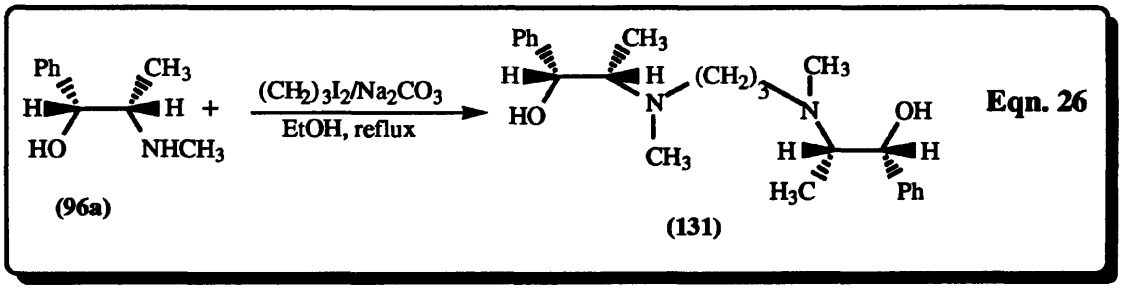
Scheme (21)

A new chiral amino alcohol ligand (1S,2R)-1-phenyl-2-morpholine-propan-1-ol **(129)** has also been used as a catalyst. In the enantioselective addition of polyfunctional diorganozincs and diethylzinc to aldehydes **(Eqn. 25)**[96] and imines **(scheme 20, p.42)**. Moderate to high enantiomeric excesses **(e.e.)** of chiral alcohol **(130)** and chiral amine **(121)** up to 75 and 90 % **e.e.**'s were obtained respectively.[90,96]

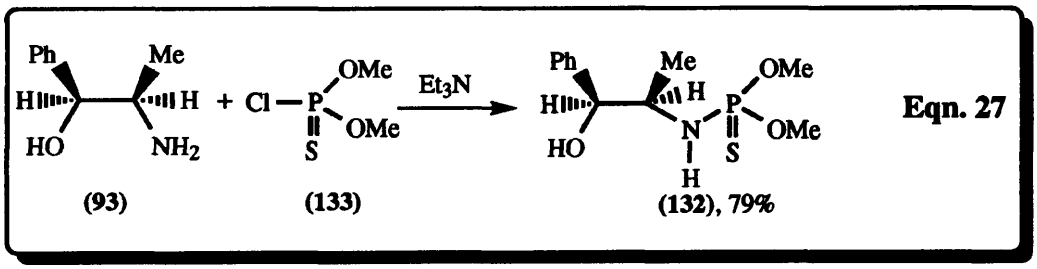


Lithium salts of the dimeric (C_2-symmetric) β-amino alcohol ligand **(131)** derived from (1R,2S)-(-)-ephedrine **(96a)**, **(Eqn. 26)**, has been found to be a good catalyst (4%

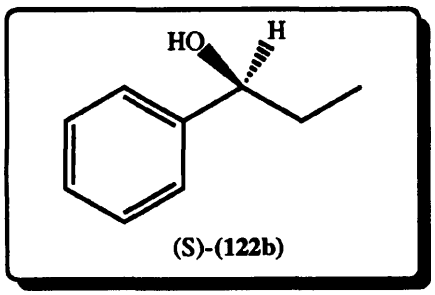
equiv.) for the addition of diethylzinc to aldehydes to give 85% **e.e.** of the (R)-secondary alcohols.[97]



Recently, a quite useful ligand (1R,2R)-(+)-N-dimethoxyphosphinothioyl norephedrine **(132)** was prepared by Soai in 79% yield from dimethylchlorothiophosphate **(133)** and (1S,2R)-(+)-norephedrine **(93)** in the presence of triethylamine, **(Eqn. 27)**.

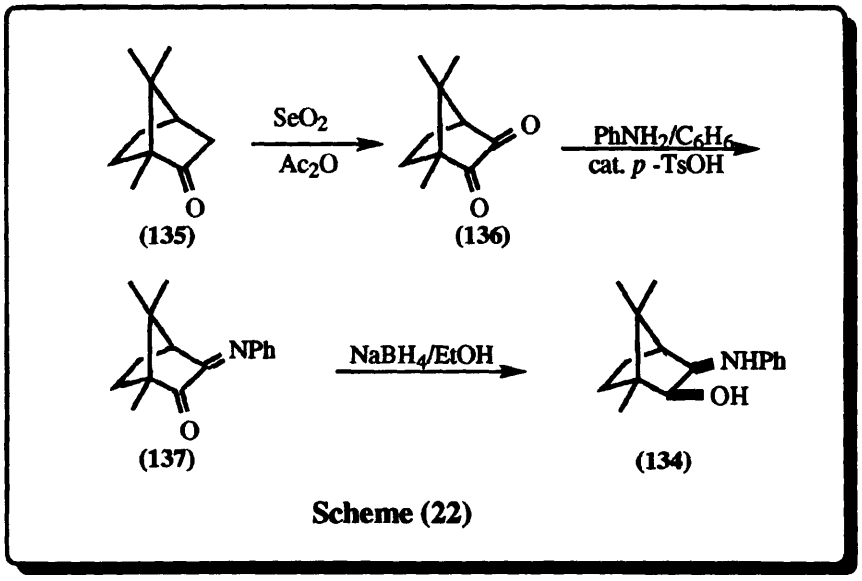


This ligand was found to be highly effective for the addition of diethylzinc to benzaldehyde in the presence of titanium tetraisopropoxide, the secondary alcohol (1S)-**(122b)** being obtained in up to 97% **e.e.** and 93% yield.[98]



I.3.3 Amino Borneol-based Ligand

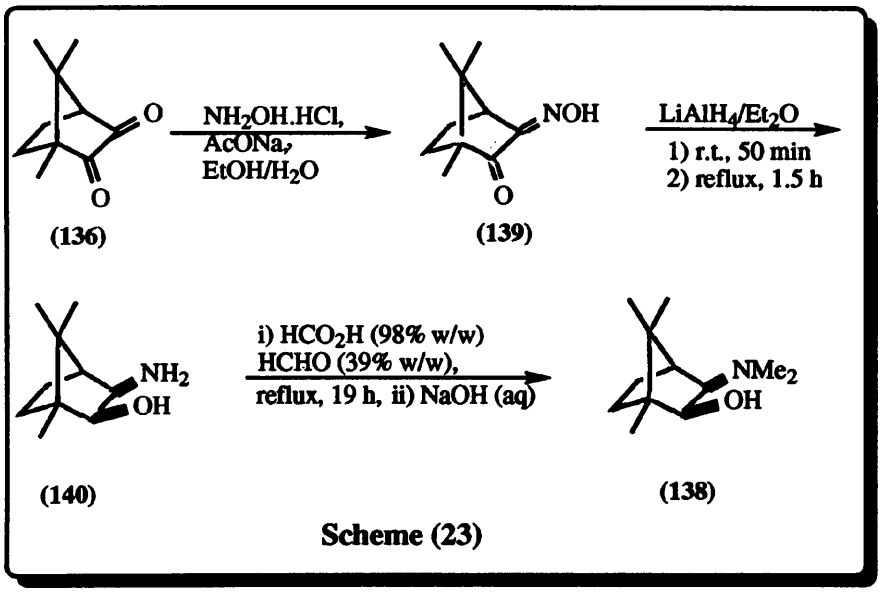
One of the earliest examples of the use of a chiral β-amino alcohols in asymmetric synthesis is (+)-(1R,4S)-3-*exo*-anilino-2-*exo*- hydroxybornane **(134)**. It is synthesized in three steps from commercially available (+)-camphor **(135)** in moderate yield, see **scheme (22)**.[99-101]



Scheme (22)

This gave a moderate enantiomeric excess of 43% in the reduction of acetophenone by lithium hydride.

The camphor-derived homochiral amino alcohol (-)-3-*exo*-(dimethylamino) isoborneol, DAIB **(138)**, has been prepared by Noyori from camphor **(136)** see **scheme (23)**. This is an excellent chiral auxiliary for the enantioselective addition of diethylzinc (2.0 equiv.) to aldehydes to give 99% **e.e.** of (S) chiral alcohols in high chemical yield (98%).[102-106]



Scheme (23)

Noyori demonstrated that for a successful reaction the ratio R_2Zn:DAIB must be greater than 1. A complex formed from equimolar amount of R_2Zn and DAIB could not ethylate benzaldehyde, but instead slowly gave benzyl alcohol. The studies concluded that two Zn atoms per aldehyde are necessary for the alkylation reaction.[102,103] It was also demonstrated that the (S)-Zn alkoxide is derived consistently from the dinuclear intermediate **(141)** possessing the (S)-configurated Zn and O atoms at the angular positions, whereas, the corresponding (R)-configuration around the Zn and O atoms in structure **(142)** leads to the (R)-enantiomers shown in **(Fig.8)**.[102-104]

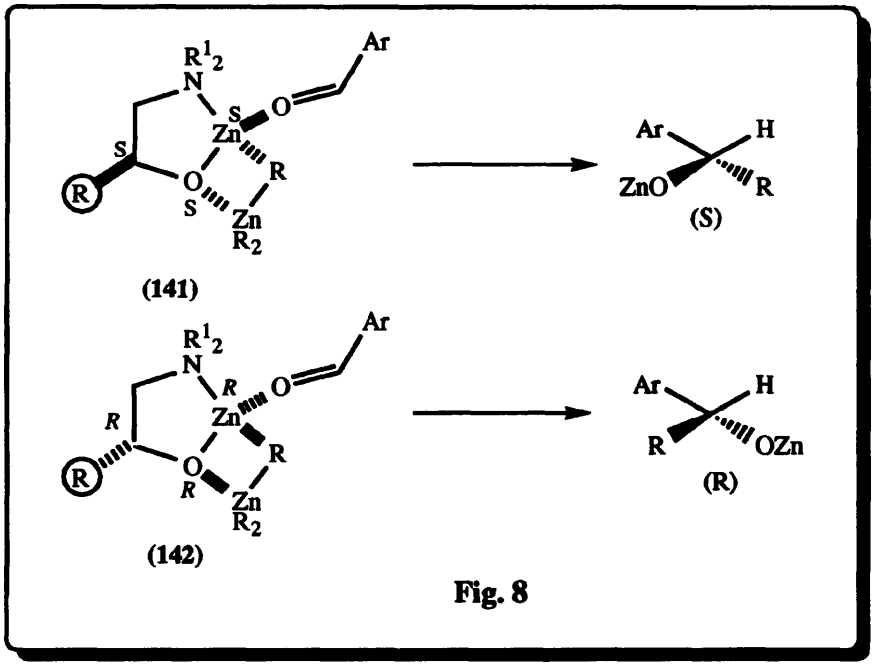
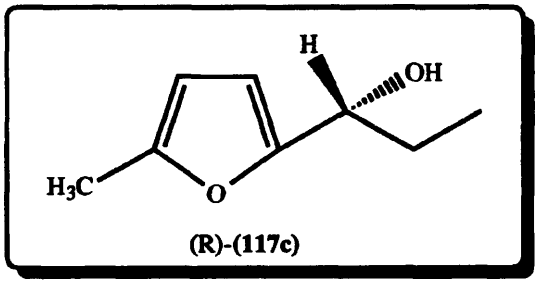


Fig. 8

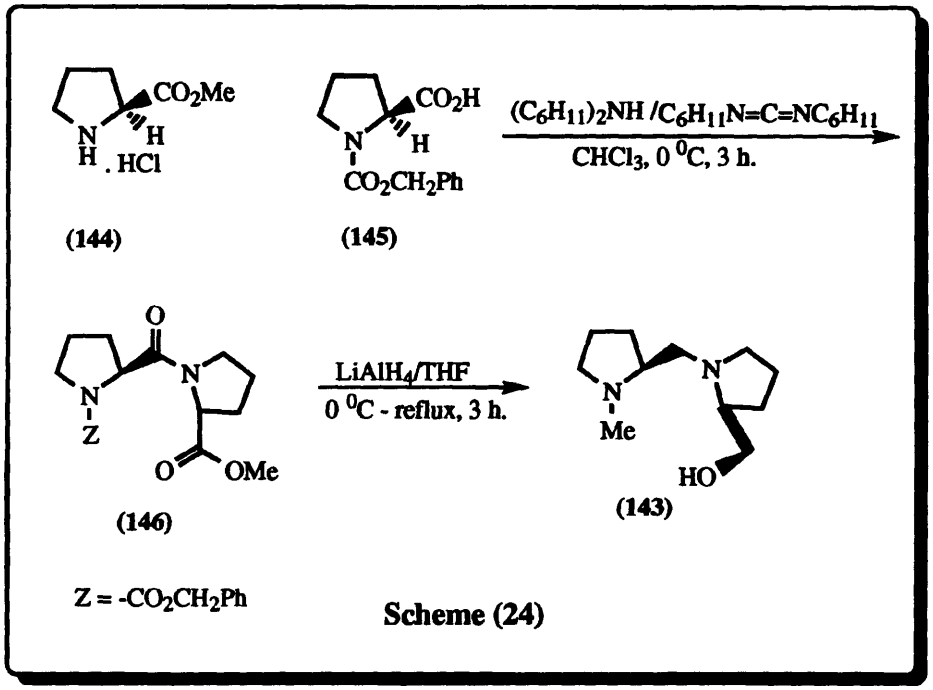
The ligand (-)-DAIB **(138)** was also found to be effective in the enantioselective addition of diethylzinc to 5-methyl-2-furaldehyde **(118c)** to give the resulting furyl alcohol **(117c)** in 97% **e.e.**, see **(scheme 20**, p.42).[89]



I.3.4 Pyrrolidinyl Methanol (PMPM)-based Ligands

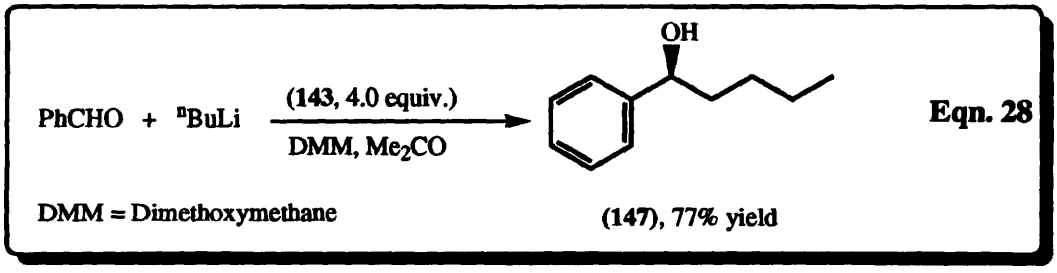
The first example of this type of chiral β-amino alcohol was described by Mukayama and co-workers.[106-110] They prepared (2S, 2'S)-2-hydroxymethyl-1-[(1-

methylpyrrolidin-2-yl)methyl]pyrrolidine (**143**) starting from 5-proline methyl ester hydrochloride (**144**) and the dicyclohexylamine salt of (S)-N-benzyloxycarbonyl proline (**145**) in the presence of dicyclohexylcarbodiimide, **scheme (24)**.[106-110]



Scheme (24)

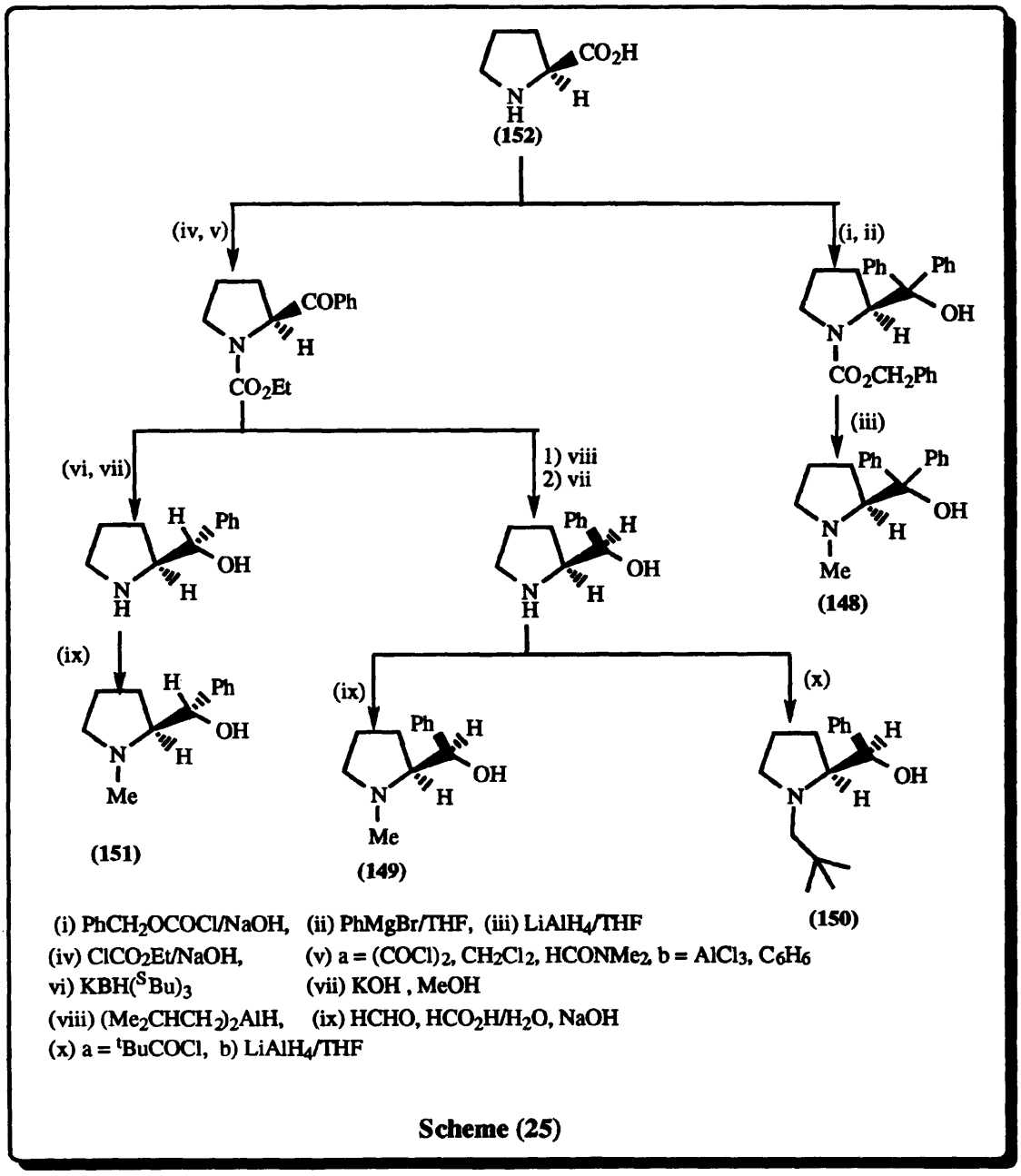
Compound (**143**) was found to be an efficient stoichiometric reagent for the asymmetric addition of n-butyllithium to benzaldehyde to give (S)-1-phenylpentanol (**147**) with 95% optical purity in 77% yield, **(Eqn. 28)**.



Eqn. 28

Soai and co-workers have synthesized a series of chiral β-amino alcohol ligands

based on pyrrolidinyl alcohol. Thus, (2S)-(+)-diphenyl(1-methylpyrrolidin-2-yl)methanol (DPMPM, **148**); (1R,2`S)-phenyl-(1-methylpyrrolidin-2-yl)methanol (**149**, *erythro*-PMPM); (1R, 2`S)-(-)-phenyl-(1-neopentylpyrrolidin-2-yl)methanol (**150**, *erythro*-PNPM) and (*threo*- PMPM, **151**) were prepared from (S)-proline **(152)** according to **scheme (25).**[111,112]

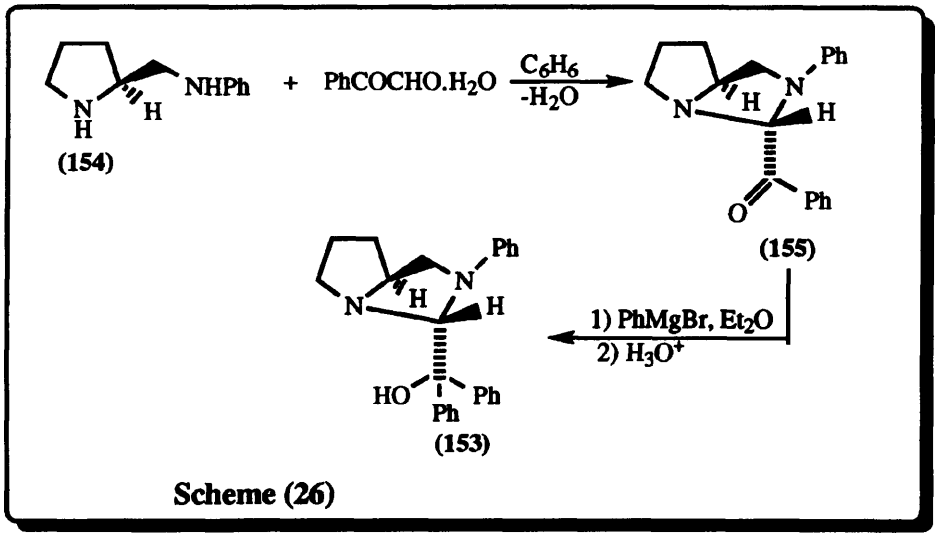


Scheme (25)

Optimum enantiomeric excesses (up to 100%) and chemical yields (100%) of sec. alcohols were achieved by using the chiral ligands DPMPM **(148)** and *erythro*- PNPM **(150)** in the enantioselective addition of diethylzinc to benzaldehyde. Threo-PMPM **(151)** and *erythro*- PMPM **(149)** were less successful and gave only low to moderate enantiomeric excesses.

One of the reasons for the high asymmetric induction may be the co-ordination of the alkoxide of **(148)** and **(150)** with the zinc atom of Et_2Zn, thus inducing chirality in the ethylating reagents.[111] Additionally, (S)-(+)-DPMPM **(148)** has been employed as a catalyst for the enantioselective addition of diethylzinc to the racemic aldehyde **(114)** containing more than one chiral centre **(scheme 19,** p.41) giving 94% yield and 68% **e.e.** of the *threo*- isomer (2S,3R)-**(115)**.[85]

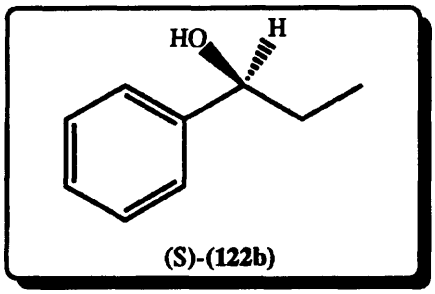
Another chiral-β-amino alcohol derived from pyrrolidine has been described by Asami and Inoue. Compound (2R,5S)-2-(diphenylhydroxymethyl)-3-phenyl-1,3-diaza-bicyclo[3.3.0]octane **(153)** was synthesized from (S)-2-(anilinomethyl)pyrrolidine **(154)** as shown in **scheme (26)**.[113,114]



(154) (155) (153)

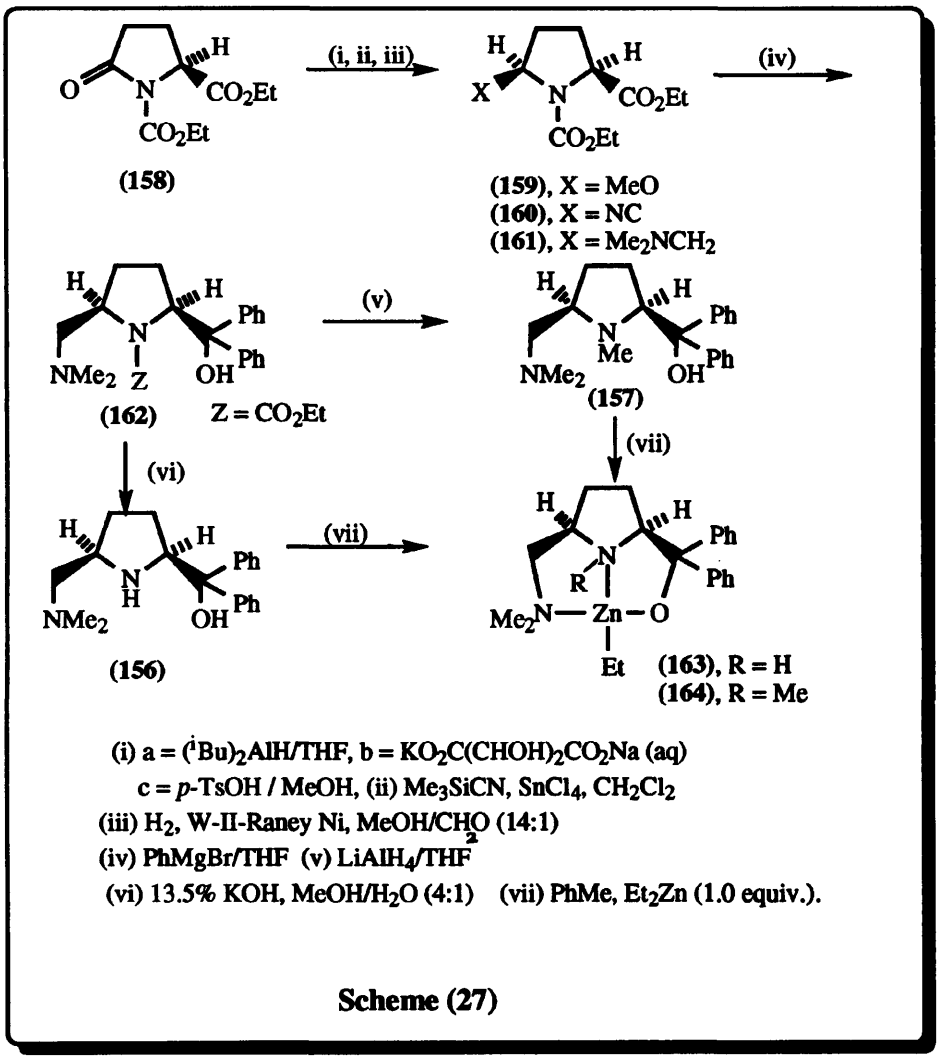
Scheme (26)

The chiral ligand **(153)** has proven to be an efficient catalyst in the enantioselective addition of diethylzinc to benzaldehyde to give 96% **e.e.** and 93% yield of the (S)-alcohol **(122b)**.



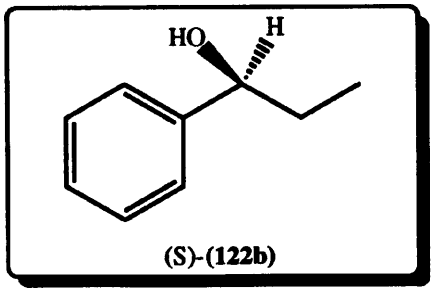
(S)-(122b)

Corey has reported the preparation of another family of chiral pyrrolidine alcohol ligands, namely (2S,5R)-(-)-2-(hydroxydiphenylmethyl)-5-dimethylaminopyrrolidine derivatives **(156)** and **(157)** starting from ethyl (S)-N-(ethoxycarbonyl)pyroglutamate **(158)** as described in **scheme (27)**.[115,116]



Scheme (27)

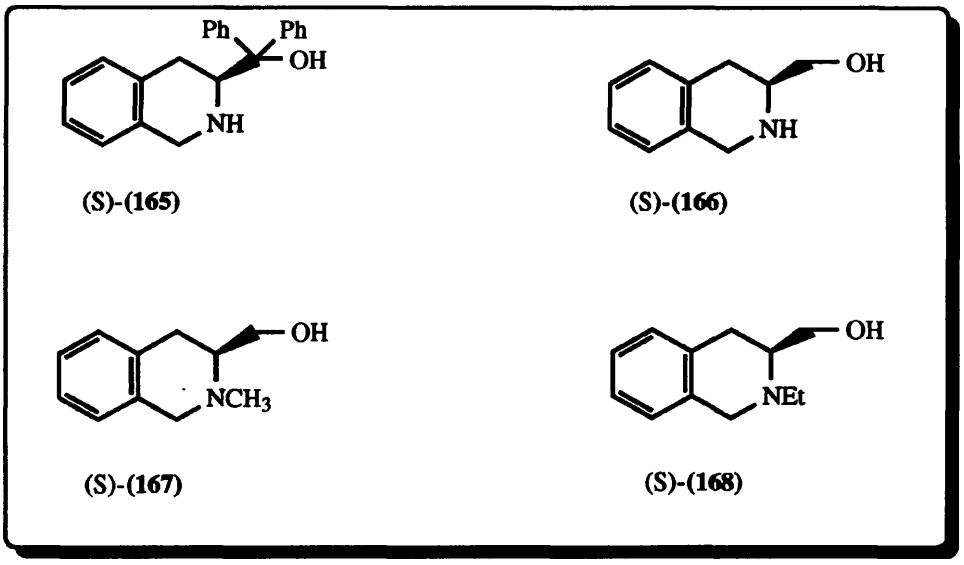
With diethylzinc and benzaldehyde the ligands **(163)** and **(164)** were highly effective and gave (S)-1-phenylpropanol **(122b)** in 93-95% **e.e.** and 94-100% yield. These ligands were recovered unchanged after the reaction.



(S)-(122b)

I.3.5 Isoquinoline Methanol-based Ligands

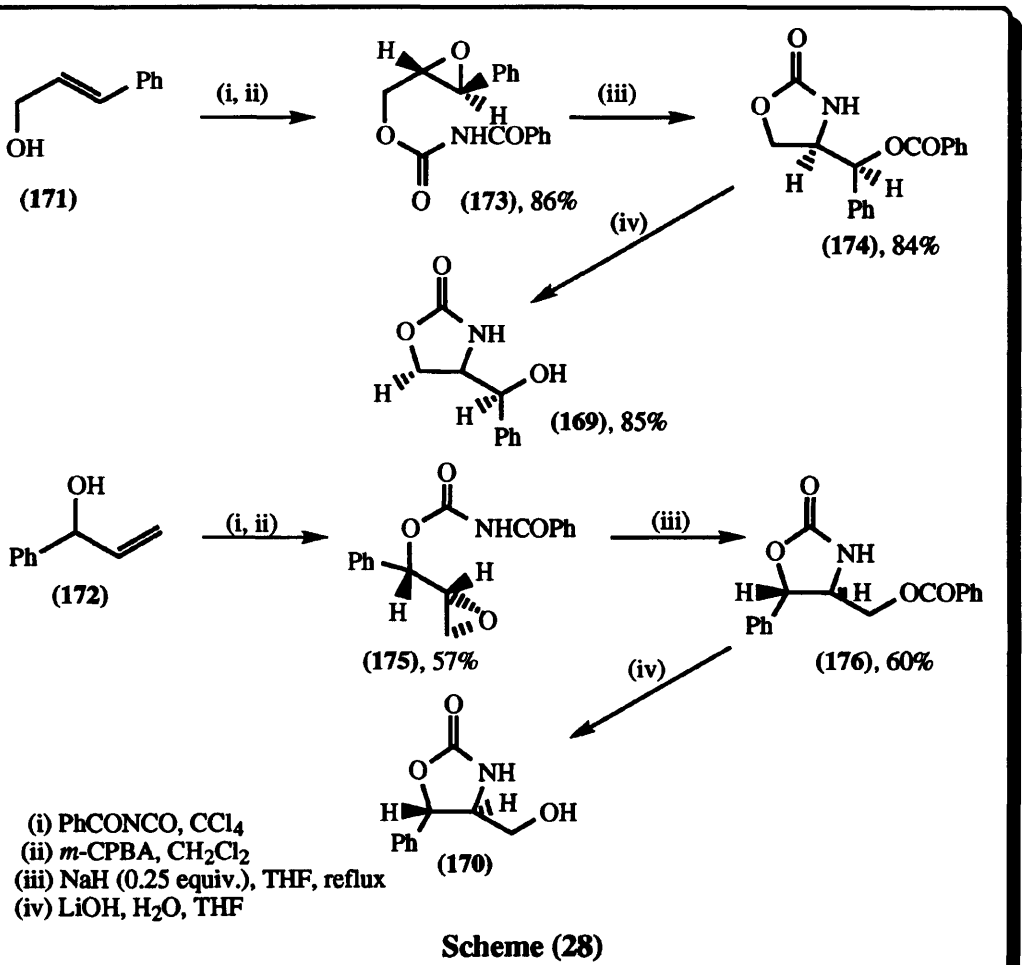
Stingle has described the synthesis of other chiral β-amino alcohols of the type **(165-168)** derived from (S)-porretine.[117-119]



Only low enantiomeric excesses (up to 35%) were obtained when using a catalytic amount (10% mol) of these isoquinoline ligands for the addition of diethylzinc to aromatic aldehydes[118] and similar low to moderate enantiomeric excesses were found upon reduction of ketones (32-71% **e.e.**).[117]

I.3.6 Oxazolidinone and Oxazolines-based Ligands

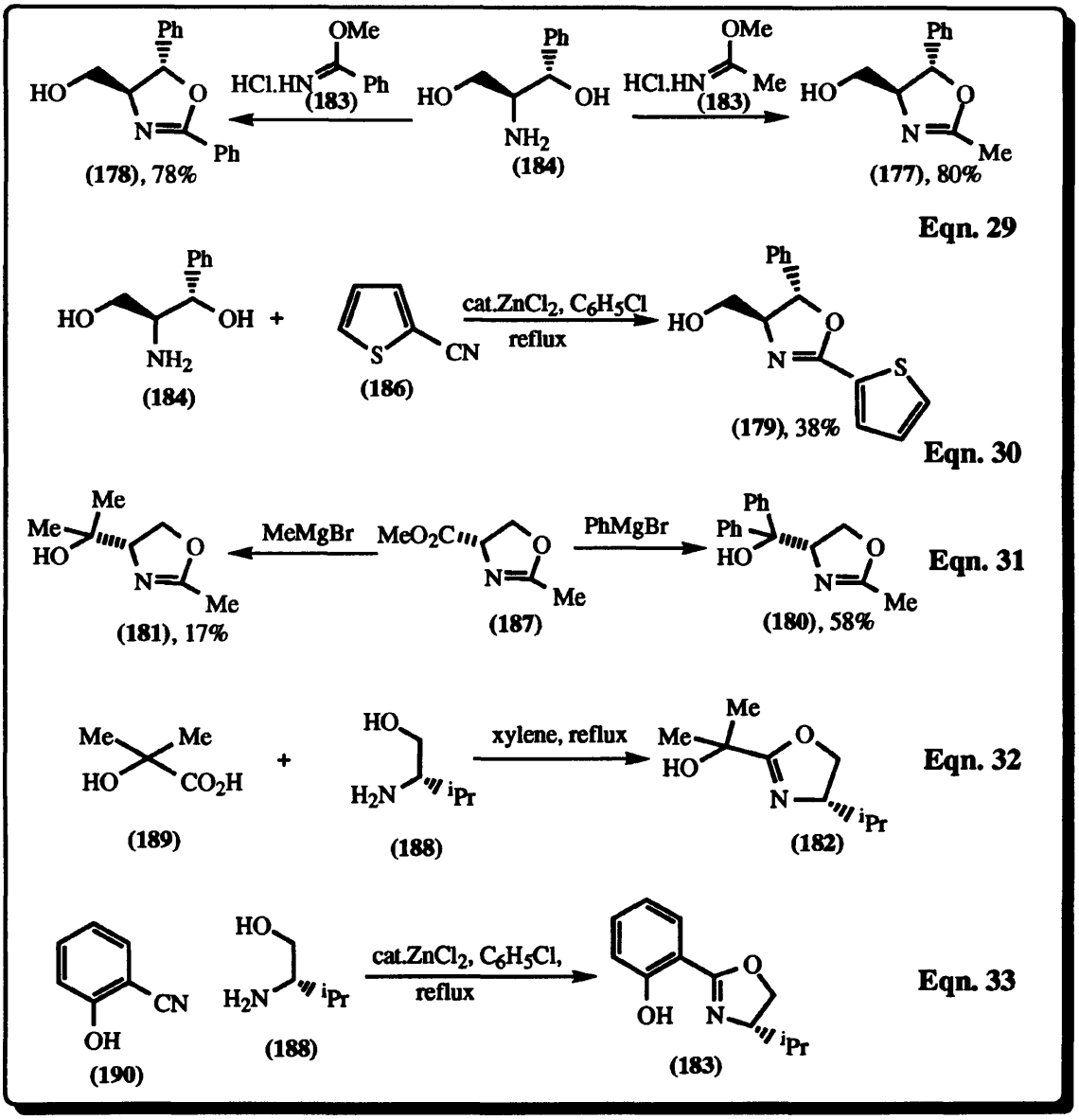
Knapp and co-workers have described the synthesis of the oxazolidinone ligands **(169)** and **(170)** from cinnamyl alcohol **(171)** and phenylvinylmethanol **(172)** respectively according to the synthetic **scheme (28)**.[120]



Scheme (28)

To our knowledge no applications have been reported using these hydroxy oxazolidinone ligands (**167** and **168**) as catalysts in asymmetric induction reactions.

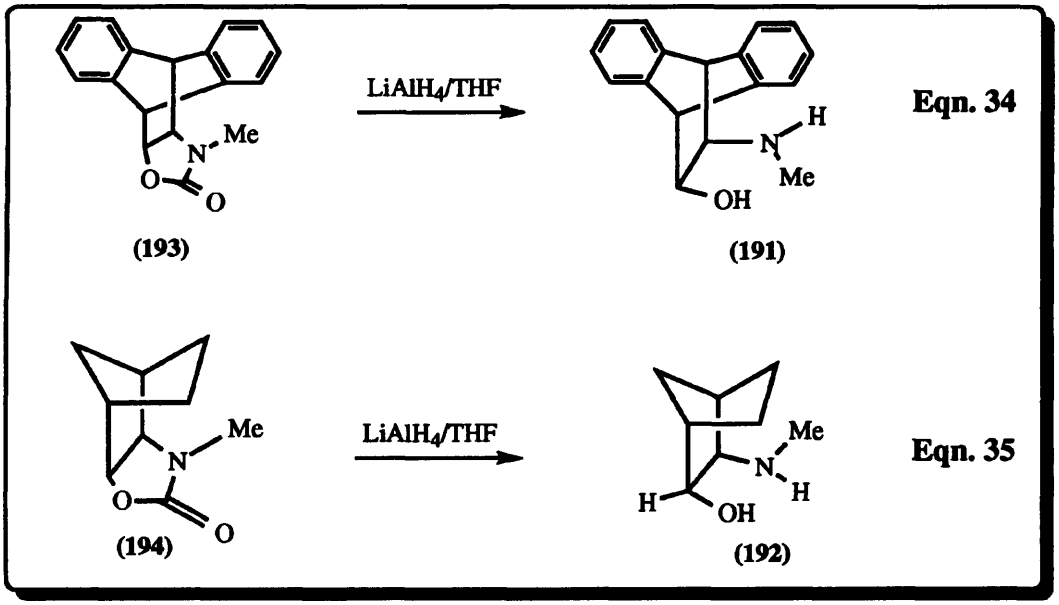
More recently Williams *et al.* [121,122] have outlined the preparation of other useful hydroxymethyloxazolidine ligands (**177-183**) in one step from readily available starting materials[123-126] as described in (**Eqns. 29-33**) respectively.



These enantiomerically pure oxazolines **(177-183)** have been successfully employed as ligands for the rhodium-catalyzed hydrosilylation of alkenes (99% **e.e.**, 93% yield)[127], copper-catalyzed cyclopropanation of alkenes (99% **e.e.**, 77% yield)[128], catalytic-Diels-Alder reactions (91% **e.e.**)[129] and palladium-catalyzed allylic substitution reactions (95% **e.e.**, 94% yield).[130]

The same ligands **(177-183)** have also been used for the addition of diethylzinc to aromatic aldehydes to afford low to moderate enantiomeric excesses [67% (S), 59% (S), 57% (S), 30% (R), 14% (R), 25% (S) and 23% (S) respectively].[121,122].

Other chiral β-amino alcohols, such as N-Methyl-1,2-(9,10,-dihydro-9,10-anthraceno)-(**191**) and N-Methyl-1,2-(1,3-cyclopentano)-2-aminoethanols (**192**) are readily obtainable from the chiral 4,5-disubstituted 2-oxazolidinones, (**193**) and (**194**) as shown in equations (**34**) and (**35**) respectively.[131]

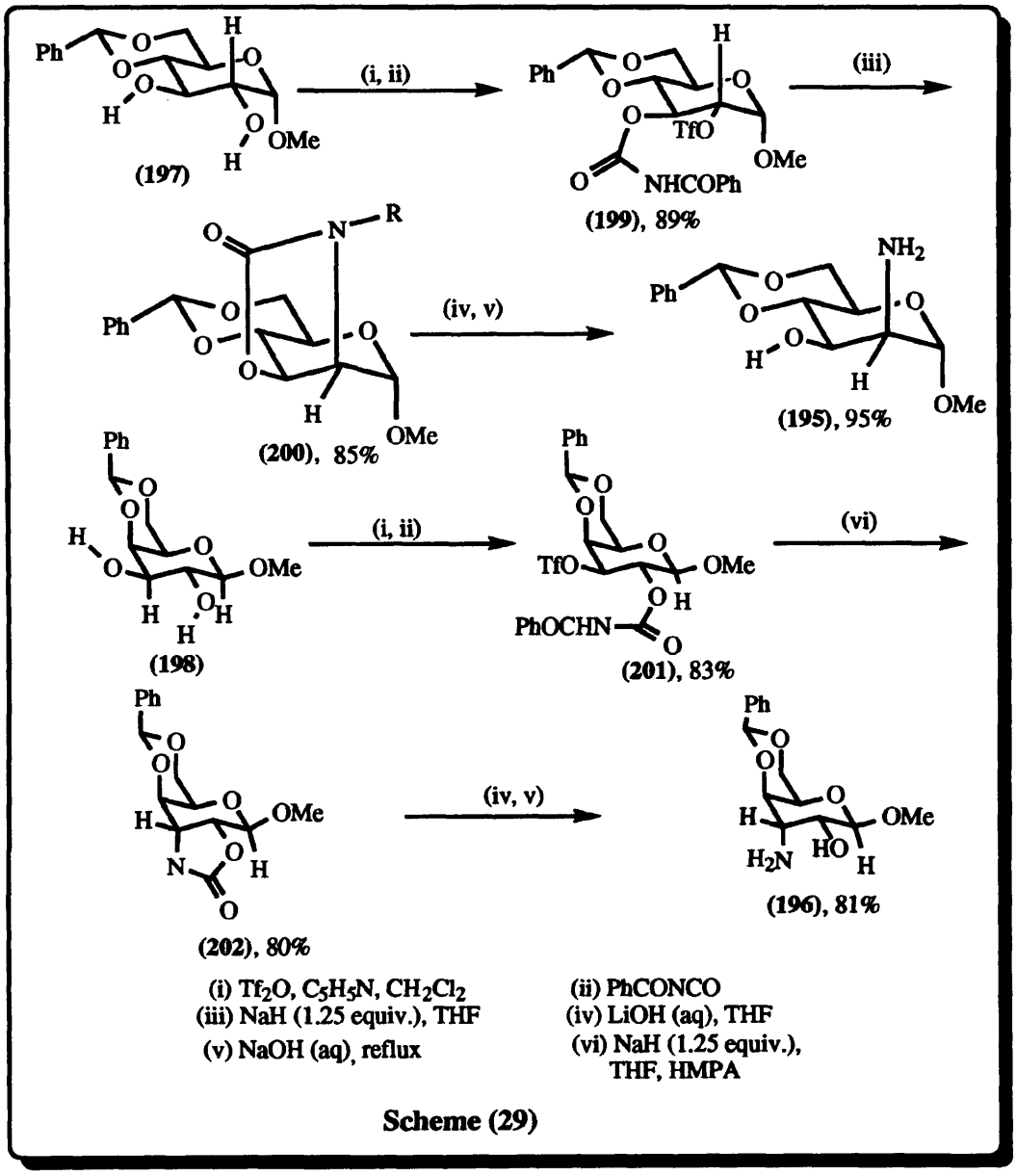


High enantioselectivities were achieved [~ 97% **e.e.** (S) and 98% **e.e.** (S)] when ligands (**191**) and (**192**) were employed in the reaction of benzaldehyde with diethylzinc.

I.3.7 Amino Sugar-based Ligands

Many amino sugars have been synthesized from carbohydrates by nucleophilic displacement reactions of *p* -toluenesulfonate, or, better, trifluoromethanesulfonate (triflate) derivatives. Thus, methyl-2-amino-2-deoxymannopyranoside (**195**) and 3-amino-1-methyl-4,6-*O* -(phenylmethylene)-β-D-glucose (**196**) have been prepared from 4,6-*O* -(phenylmethylene)-α-D-glucopyranoside (**197**) and methyl-4,6-*O* -(phenylmethylene)-β-

galactopyranoside (**198**) respectively as described in **scheme (29)**.[120,132,133]

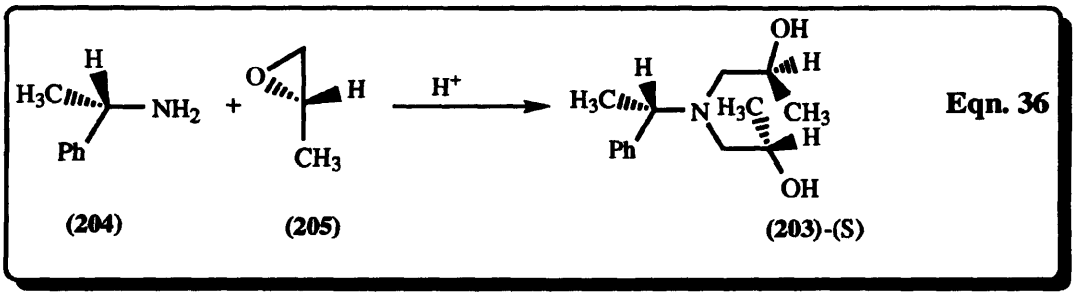


Scheme (29)

To our knowledge these compounds have not yet been used as ligands in asymmetric synthesis.[120]

I.3.8 Miscellaneous Chiral-Amino Alcohols

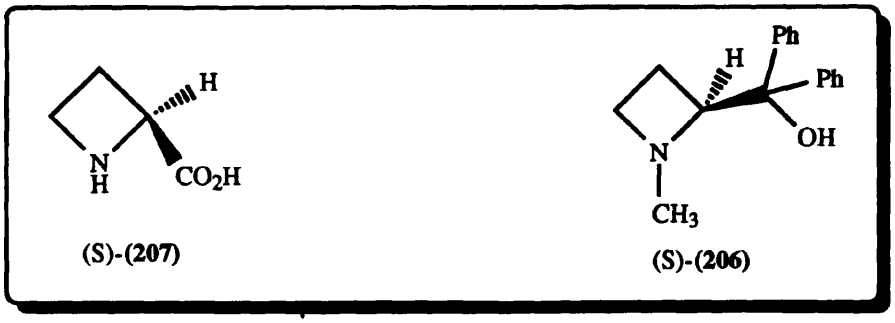
In 1981, Morrison and *et al.* reported the preparation of chiral amino diol ligand **(203)** from the reaction of the appropriate primary amine **(204)** with two equivalents of (S)-(-)-propylene oxide **(205)** as described in **(Eqn. 36)**.[134,135]



(204) (205) (203)-(S) **Eqn. 36**

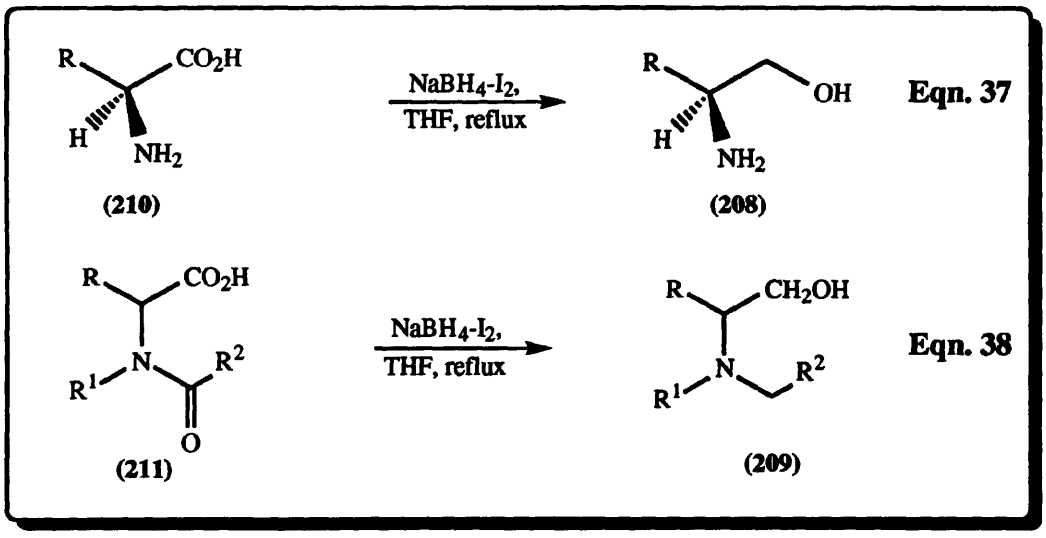
This ligand **(203)** was found to be an efficient reagent, when used in more than stoichiometric amount, for the enantioselective reduction of ketones using lithium aluminium hydride giving the corresponding chiral alcohol in up to 82% **e.e.** (R) and 98% yield.[134]

The new optically active amino alcohol (S)-1-methyl-2-(diphenylhydroxymethyl)-azetidine **(206)** derived from (S)-azetidinecarboxylic acid **(207)**[136] has been shown to catalyze the enantioselective addition of diethylzinc to *p* -chloro and *p* -methoxybenzaldehyde with up to 100% **e.e.** and 90% yield.[137]



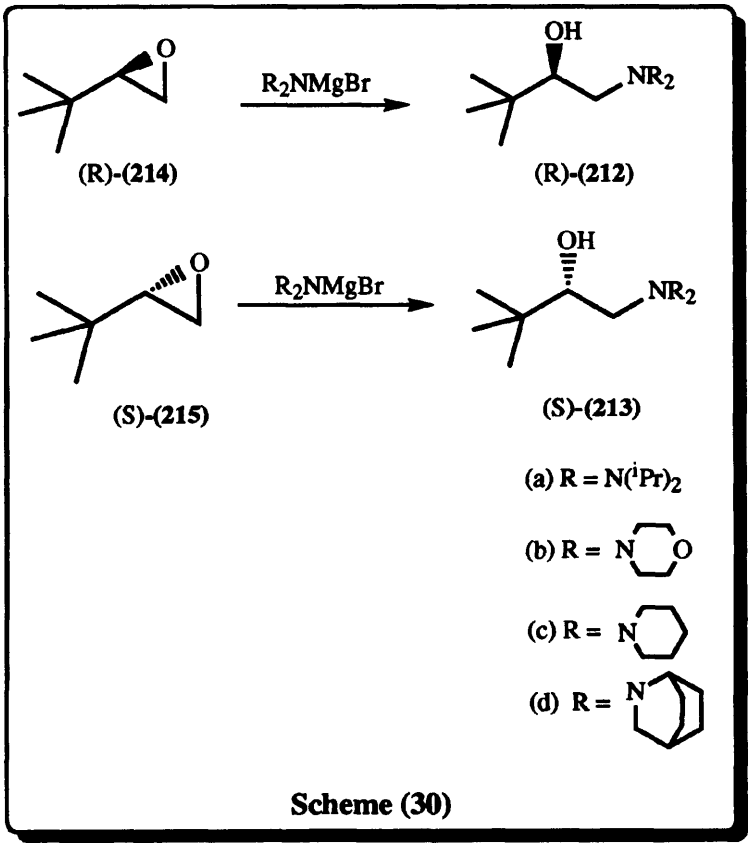
(S)-(207) (S)-(206)

Recently, other chiral β-amino alcohols **(208)** and **(209)** have been prepared by the reduction of α-amino acids **(210)** and N-acetyl-α-amino acids **(211)** using sodium borohydride-iodine in up to 94% and 83% yields respectively as shown in equations **(37** and **38)**.



According to the literature no asymmetric induction reactions have been carried out using these ligands.[138]

Finally, other types of chiral β-amino alcohols (R)-**(212)** and (S)-**(213)** based on t-butyloxirane have been prepared by the ring opening of (R) and (S)-t-butyloxirane **(214)** and **(215)** respectively as described in **scheme (30)**.[139,140]



Scheme (30)

While (R)-isomers of **(212a)** and **(212b)** were found to be an effective catalysts in the enantioselective addition of diethylzinc to aldehydes giving 85-90.6% **e.e's** of the (S)-alcohols.[105] Other ligands **(213b)**, **(213c)** and **(213d)** showed poor enantioselectivities for this reaction.[141,142]

I.4 Summary

In view of the current interest in the synthesis of the chiral β-amino alcohol and chiral diol ligands based on titanium Lewis acids, this project will be concerned mainly with the synthesis of new chiral dimethyl and dibutyl amino alcohol ligands based on D-mannitol, as well as the synthesis of chiral diol and diamine ligands based on Feist's acid. The use of these as catalysts in asymmetric induction reactions (e.g. alkylative reduction of dialkylzincs to racemic aldehydes) has been explored. The methodology and the proposed target ligands will be discussed in the next chapters.

II. DISCUSSION AND RESULTS

Chapter 4

II.4.1 Objectives of the Study

Within the last decades researchers in the field of asymmetric synthesis have prepared a wide range of catalytically-active transition metal complexes containing phosphine (R_3P), phosphite [$(RO)_3P$], cyano, amino, isocyanide and thiol ligands. For example, complexes containing trivalent phosphorus groups have been shown to be catalysts for the hydroformylation, hydrogenation, isomerization and oligomerization of olefins.[143] When monodentate ligands are used in these complexes, metal leaching into solution is a major problem during catalysis and this can cause corrosion problems as well as separation difficulties.[144,145] This has led researchers to explore the use of bidentate ligands rather than monodentate ligands in the preparation of the asymmetric catalysts.

It is expected that such ligands will chelate to metal complexes and this, in effect, is supposed to prevent the dissociation of metal during the course of reactions.

The main objective of this work is to prepare new chiral chelating diamines, diphosphines, thiophosphine and diphosphinite ligands based on inexpensive carbohydrate substrates.[146]

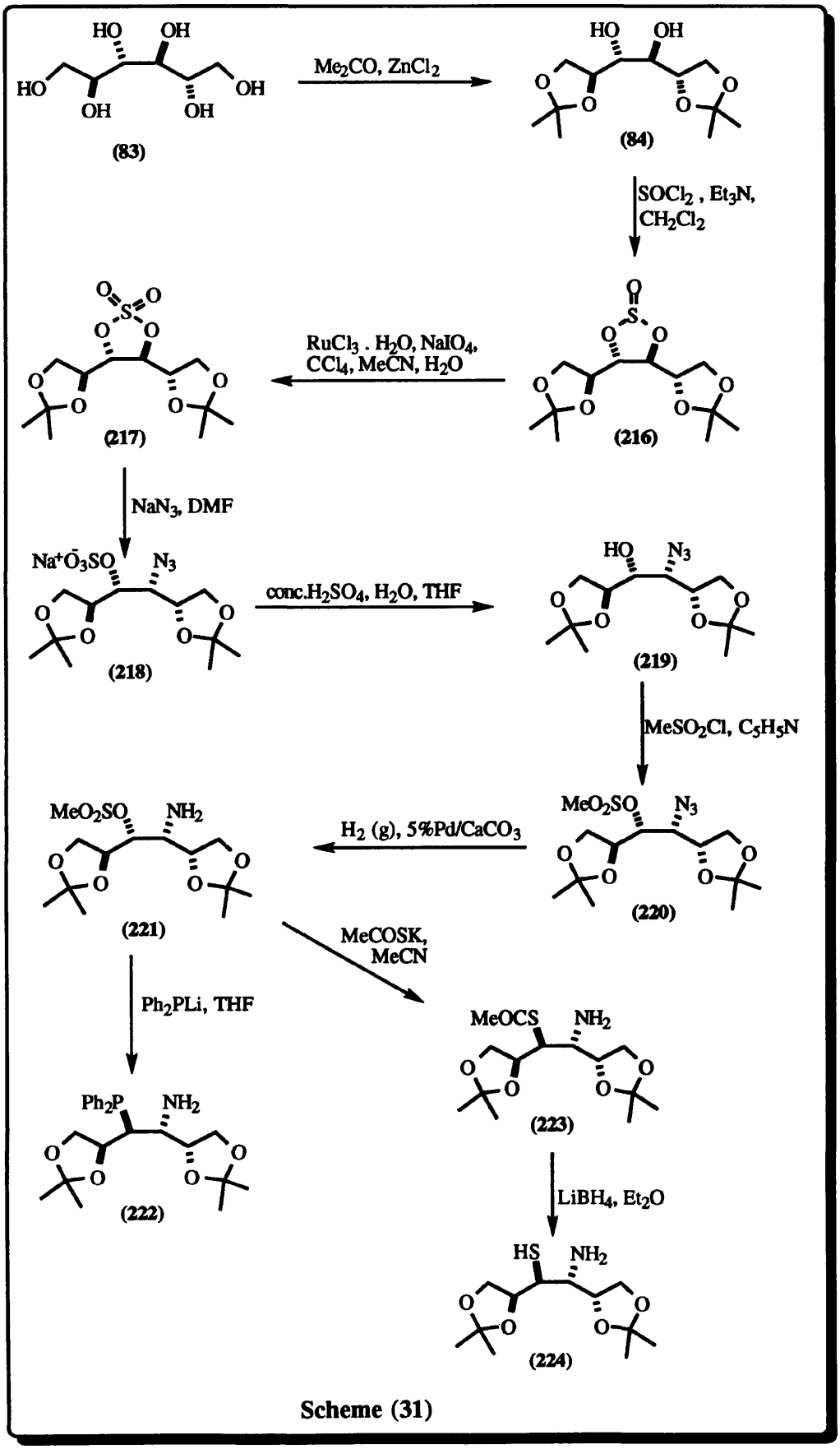
There is also a great deal of interest in the use of chiral alcohols as ligands for the metal-catalyzed addition of Grignard reagents to carbonyl compounds[147,148] and the enantioselective addition of diethylzinc to aldehydes catalyzed by chiral β-amino alcohols, particularly chiral titanate complexes.[34,78,102,115,149,150] These asymmetric bidentate ligands should be capable of forming five-membered, or less desirably, seven-membered, conformationally rigid complexes of rhodium, palladium, or titanium that may be able to exert high chiral preference in asymmetric catalytic reactions.

II.4.2 D-Mannitol-based Ligands

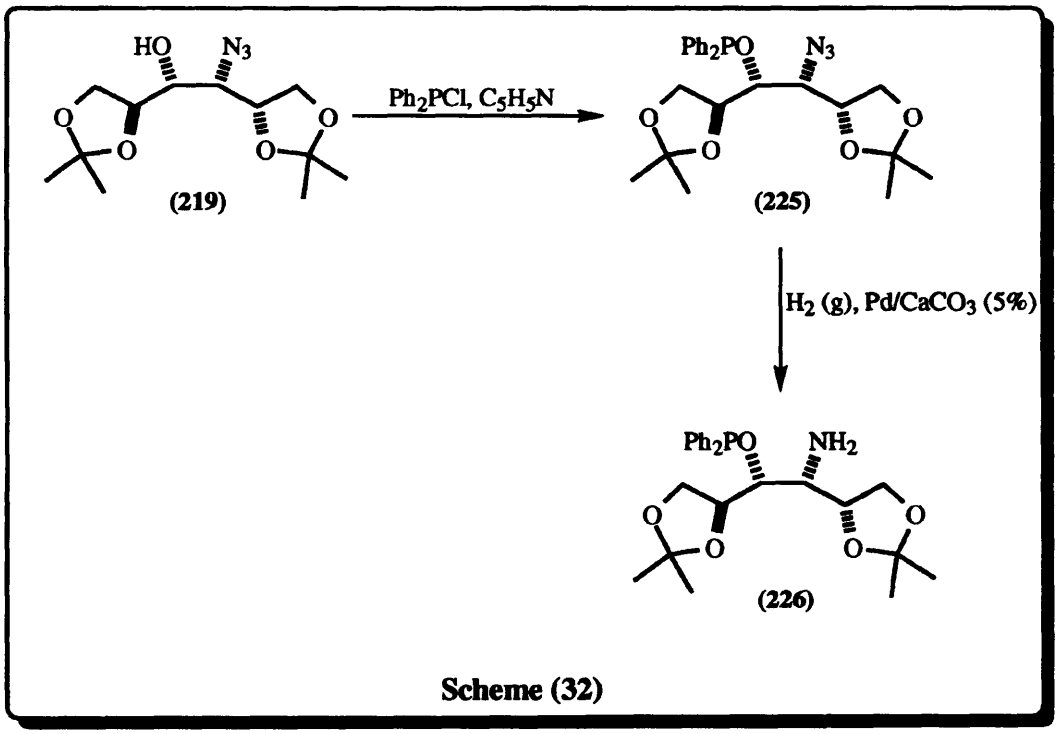
In order to prepare a bidentate ligand (e.g. diamine, diphosphine) an inexpensive starting material, which is easy to prepare, had to be sought.

The compound should have chiral centres and functionalities that could be protected and deprotected easily. The synthetic sequence had to be short and hence inexpensive. All these features were found in 1,2:5,6-di-*O* -isopropylidene-D-mannitol **(84)**[68,151-155] which had already been used in the department by Booth's group[152,153] and by Stille's group[151] in the USA.

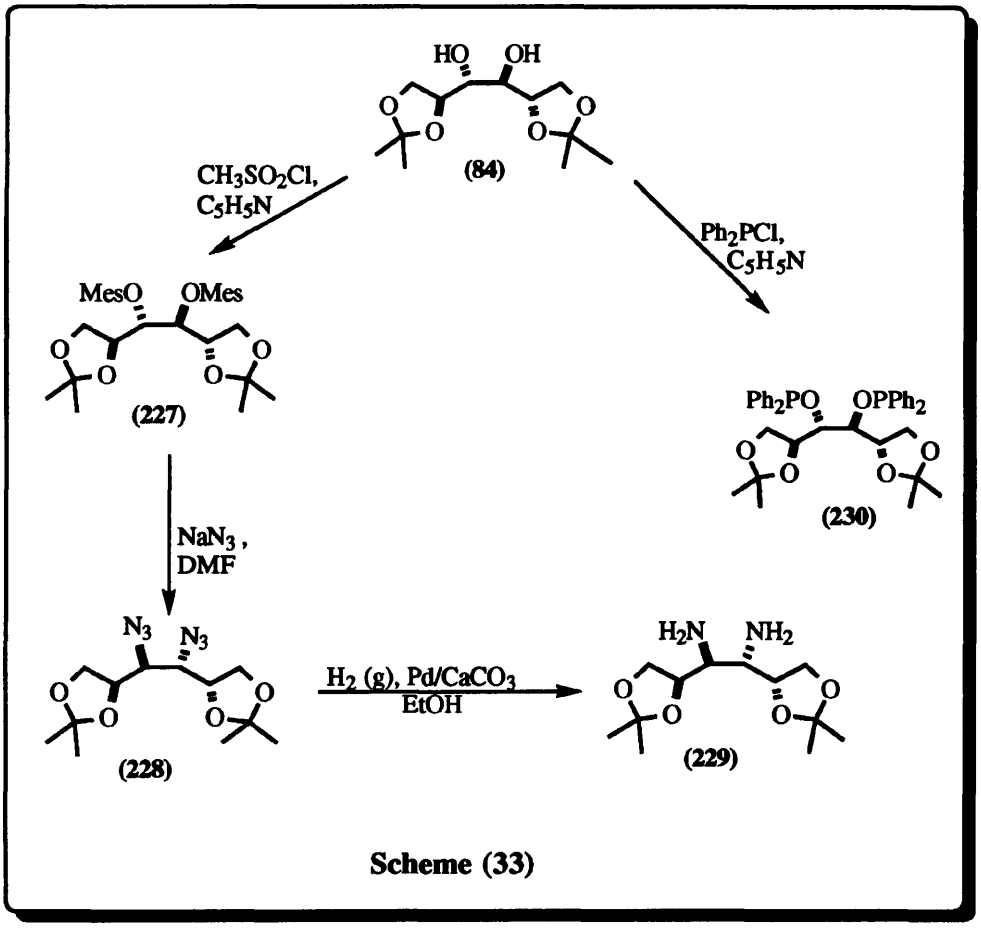
At the beginning of this project, the following synthetic sequences to prepare new chiral 1,2-diphosphinite, diamine, amino phosphinite and thioamine ligands were proposed as shown in **schemes (31), (32),** and **(33).**


HO
OH
HO
OH
OH
OH
(83)
Me2CO, ZnCl2
HO
OH
(84)
SOCl2 , Et3N,
CH2Cl2
RuCl3 . H2O, NaIO4,
CCl4, MeCN, H2O
(217)
(216)
NaN3, DMF
Na+O3SO
N3
(218)
conc.H2SO4, H2O, THF
HO
N3
(219)
MeSO2Cl, C5H5N
MeO2SO
N3
(220)
H2 (g), 5%Pd/CaCO3
MeO2SO
NH2
(221)
MeCOSK,
MeCN
Ph2PLi, THF
Ph2P
NH2
(222)
MeOCS
NH2
(223)
LiBH4, Et2O
HS
NH2
(224)

Scheme (31)

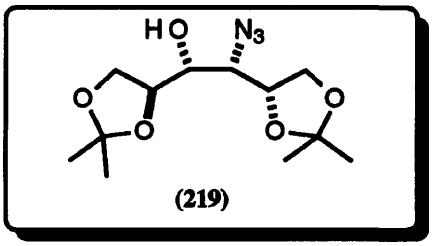

HO
N3
Ph2PCl, C5H5N
Ph2PO
N3
(219)
(225)
H2 (g), Pd/CaCO3 (5%)
Ph2PO
NH2
(226)

Scheme (32)



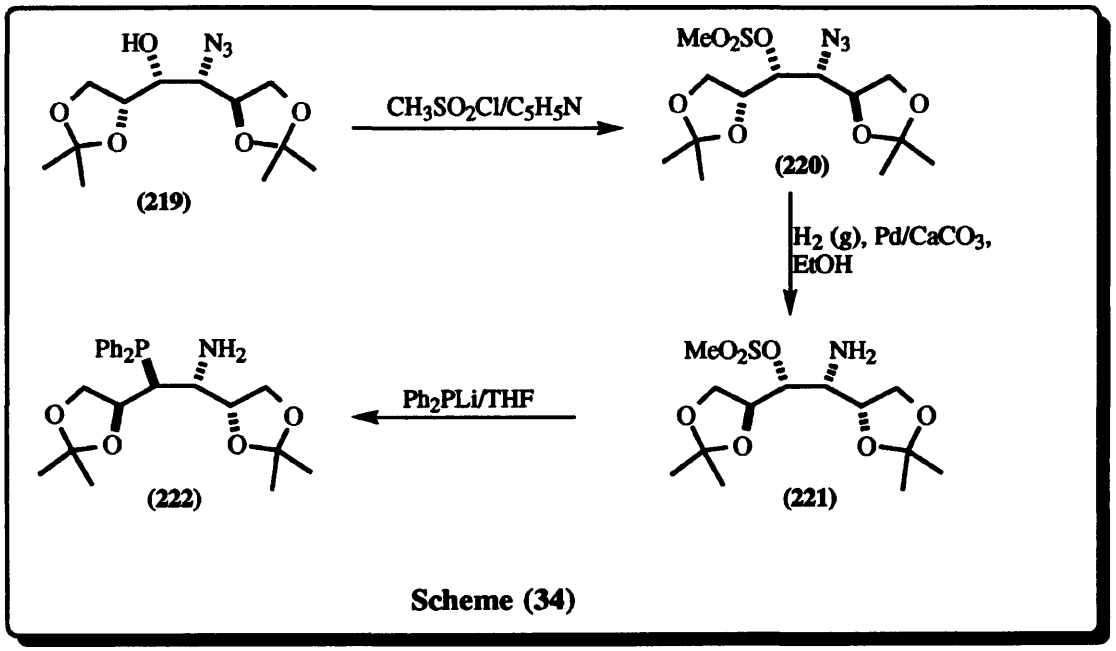
Scheme (33)

The intermediate **(84)** is, of course, well-known and also the key compounds **(216-219)** have been described by Sharpless[156] and repeated in our department by Lutfi (in addition to **220**),[153] but to our knowledge, the other compounds have not been reported previously. Starting from 1,2:5,6-di-*O*- isopropylidene-D-mannitol **(84)**, Sharpless prepared the cyclic sulfate **(217)** in an excellent yield (94%) via the formation of the cyclic sulfite **(216)** in the presence of base and oxidation of the sulfite **(216)** using a catalytic amount of $RuCl_3$. H_2O. Reaction of this cyclic sulfate with a nucelophile such as azide ion provides an intermediate azido sulfate **(218)** which can be successfully hydrolyzed using a catalytic amount of concentrated H_2SO_4 and 0.5-1.0 equivalent of H_2O in THF, to afford the azido alcohol **(219)** in good yield (91%).[156]



(219)

Lutfi[153] extended Sharpless's work as a part of his Ph.D. study and he attempted to prepare a chiral amino phosphine ligand **(222)** using the reactions shown in **scheme (34)**.



Scheme (34)

Lutfi isolated the azido alcohol **(219)** as a viscous yellow oil in 83% yield. Then he treated this compound **(219)** with mesyl chloride in the presence of pyridine to afford azido mesylate **(220)** as a yellow oil in 86% yield.[153]

On a small scale (0.1 g), compound **(220)** was hydrogenated using 5% Pd/C as a catalyst[157] in dry ethyl acetate for 16 hours at room temperature in an effort to prepare

compound **(221)**. This compound was isolated as a yellow viscous oil in 73% yield, but he could not obtain the product pure and it was only characterized by IR spectroscopy.

When he tried to hydrogenate the azido mesylate **(220)** on a large scale (4.0 g) at room temperature, no reduction of the azide occurred, even when the time of reaction was extended to five days. It was not clear why this reaction failed on a large scale, but, perhaps, the amine **(221)** acted as a catalyst poison.

It was decided to carry on this work further to prepare the various chiral bidentate ligands (i.e. **222**, **224**, **226**, **229**, and **230**) shown in **(Fig.9)**.

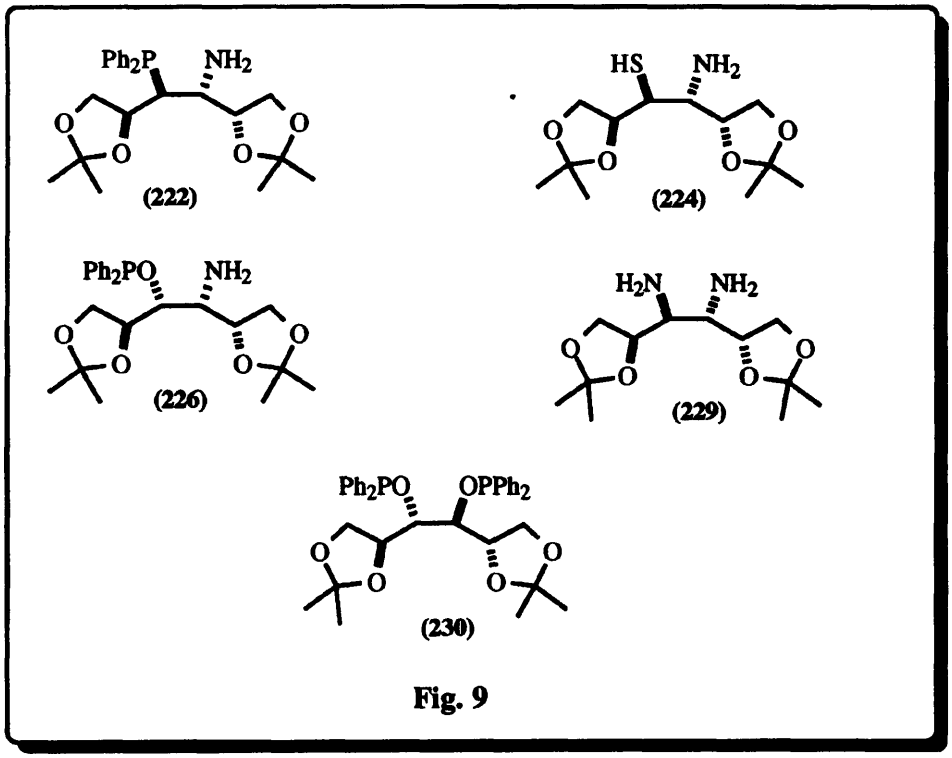
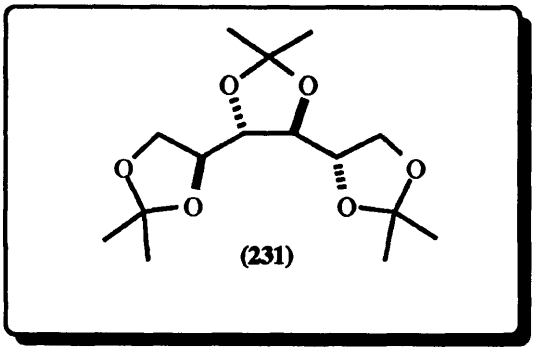


Fig. 9

The synthesis utilized inexpensive, readily available D-mannitol which was first converted to 1,2:5,6-di-*O* -isopropylidene-D-mannitol **(84)** in 50% yield by reaction with dry acetone in the presence of zinc chloride. Baer,[68] in his preparation, reported that the

yield of (**84**) depended largely on the efficiency of mixing, the temperature of reaction (19 to 20 ^{0}C), and the duration of reaction. With a temperature above 20 °C and a reaction time exceeding 2 hours, formation of triisopropylidene-D-mannitol (**231**) is favoured.[68,154]

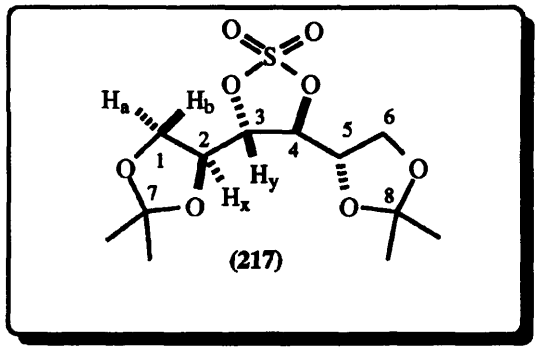


(231)

In our attempt to improve the yield, compound (**84**) was obtained in 57% yield (lit.,[155] 55%) when the reaction was carried out at 18 °C for 3 hours. 1,2:5,6-di-*O*-Isopropylidene-D-mannitol (**84**) was treated with thionyl chloride in the presence of triethylamine in dichloromethane to give the cyclic sulfite (**216**) as a beige coloured solid in 89% yield. The IR spectrum of the isolated compound (**216**) showed a band at 1175 cm^{-1} representing the (ν S=O) vibration. Compound (**216**) was then oxidized with a catalytic amount of ruthenium trichloride and aqueous sodium periodate in 1:1 mixture of carbon tetrachloride and acetonitrile to give the cyclic sulfate (**217**) in 69% yield (lit.,[156] 94%). Both the m.p. 117-119 °C (lit.[156], 124-126 °C) and the optical rotation $[\alpha]_D^{23}$ +26.9 (c 2.9, $CHCl_3$) [lit.,[156] $[\alpha]_D^{23}$ +28.7 (c 2.9, $CHCl_3$] agreed with that expected, and the microanalysis showed that the compound had the molecular formula $C_{12}H_{20}O_8S$. The IR spectrum in $CHBr_3$ was in agreement with that reported for this compound.[156] It showed the characteristic bands of the sulfate group at 1380 [ν $S(=0)_2$ asym. str. vib.], 1205 [ν $S(=0)_2$ sym. str. vib.] and various bands in the range of 1050-680 (ν S-O-C)

cm^{-1}.

The ^1H NMR spectrum showed the four methyl groups as two singlets at δ 1.28 and δ 1.40 ppm. The other aliphatic hydrogens appeared as an ABX pattern with J_{AB} 9.6 Hz; J_{AX} 3.5 Hz, and J_{BX} 6.1 Hz.



(217)

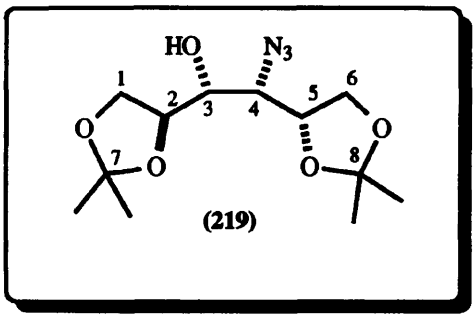
The ^{13}C NMR spectrum showed the presence of the four carbon atoms of the methyl groups at δ 24.7 and 26.6 ppm, and the five other peaks at δ 66.0 (C-1 and C-6), 73.2 (C-2 and C-5), 82.3 (C-3 and C-4) and 110.9 (C-7 and C-8) ppm.

For the next stage, the nucleophilic ring opening of the cyclic sulfate **(217)** with azide ion, Sharpless[156] used lithium azide in DMF. We used sodium azide in the same solvent rather than lithium azide as the latter was not commercially available.

Sharpless has reported that the hydrolysis of the azide sulfate **(218)** in THF using a catalytic amount of concentrated sulfuric acid in the presence of 0.5-1.0 equivalent of water is very selective and in a series of similar compounds examined by coworkers, only the sulfate group was hydrolyzed to the alcohol. The isopropylidene protecting groups were unaffected using this technique. This is a vital step in the synthetic sequence as, of course, any deprotection of the terminal diol moieties would lead to a mixture and a lack of regioselectivity in the subsequent transformations.

Although sodium azide[158,159] showed low reactivity the ring opening step appeared to take place smoothly. The hydrolysis step was carried out directly without isolation of **(218)** by treatment of the residue with a catalytic amount of concentrated sulfuric acid and water in THF.

When this reaction was first carried out, difficulties were experienced with the hydrolysis and the isolated yields of the azido alcohol were poor. After many attempts it was found that the hydrolysis could be achieved in good yield using an excess of sodium bicarbonate at 17-18 °C, followed by concentration of the mixture to half its volume, and addition of diethyl ether. Using this procedure, compound **(219)** was isolated as a viscous yellow oil in 82% yield (lit.,[156] 91% yield). It was fully characterized by microanalysis, ^{1}H, ^{13}C NMR spectroscopy and mass spectrometry. Microanalysis gave correct values for the expected molecular formula $C_{12}H_{21}N_3O_5$.



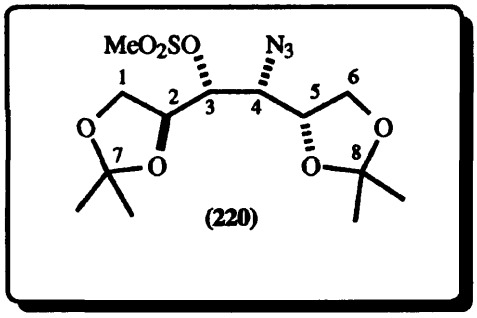
(219)

The IR spectrum (neat film) showed a broad band at 3450 cm^{-1} [ν OH] characteristic of alcohols and a strong sharp band at 2110 cm^{-1} characteristic of an azide group.

More evidence comes from the ^{1}H NMR spectrum which showed the methyl groups as four singlets at δ 1.35, 1.38, 1.42, and 1.50 ppm confirming that deprotection of the terminal diols had not occurred. The (OH) hydrogen was observed as a doublet at δ 2.75 ppm with *J* 6.1 Hz. The mass spectrum (CI) showed an m/z value at 305 due to

$[M+NH_4]^+$. The (EI) spectrum showed fragments at 272 due to loss of CH_3 (42%), at 214 due to loss of CH_3 and N_2 (64.1%) and the most important fragment at 43.0 representing $[N_3 + H]^+$, and (FAB), m/z: 288 due to $[M+H]^+$, 100%.

The azido alcohol **(219)** was then mesylated using standard procedures either in anhydrous pyridine at 0 °C,[153] or using triethylamine and dichloromethane at -5 °C,[160] to afford **(220)** as a pale yellow oil in very high yields of 98% and 94% respectively (lit.,[153] 86%). The microanalysis results confirmed the expected molecular formula $C_{13}H_{23}O_7N_3S$. The IR spectrum of the azido mesylate **(220)** showed the absence of the hydroxyl group at 3450 cm^{-1} and the presence of an azide group at 2110 cm^{-1}. The two characteristic bands of the mesylate group appeared at 1370 [ν $S(=0)_2$ asym. str.] and 1220 [ν $S(=0)_2$ sym. str.] cm^{-1} respectively.



(220)

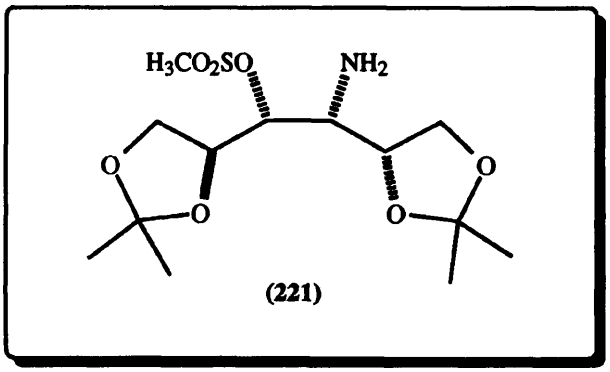
The singlet for the hydroxyl group at δ 2.75 ppm was absent from the ^1H NMR spectrum and a new singlet (3H) was observed at δ 3.07 ppm due to the methyl of the mesylate group. The ^{13}C NMR spectrum supported the assigned structure and showed four peaks at δ 25.0, 25.1, 26.1 and 26.30 ppm representing the four methyl groups of the isopropylidene moieties, and a peak at δ 38.6 ppm representing the methyl group of the mesylate group.

The mass spectum (EI) showed m/z bands at 366 $(M+H)^+$, 9.2%, 350 $(M-Me)^+$, 13.8% and 43 $(N_3+H)^+$, 100%.

As mentioned earlier, it was thought that the difficulties experienced by Lutfi[153] in reducing the azido mesylate **(220)** to the pure amine **(221)** on a large scale using Pd/C (5%), could be caused by poisoning of the catalyst by the amine formed during the initial stages of the reaction. This did not appear to happen when the reaction was carried out on a small scale probably because a much higher ratio of catalyst to azide was used. To test this hypothesis, it was decided to use palladium hydroxide on carbon (20%) as the hydrogenation catalyst which is possibly less susceptible to poisoning by amines.

The palladium hydroxide on carbon [$Pd(OH)_2/C$] was prepared from the reaction of palladium chloride with lithium hydroxide monohydrate in the presence of carbon (Darco G-60) and water.[153] The azide **(220)** was hydrogenated using this catalyst in ethyl acetate at room temperature to give a yellow viscous, impure product. This crude product was purified by dry flash column chromatography (EtOAc-hexane, 1:3) to give mainly starting material and only a low yield of an amine. From IR and ^1H NMR spectroscopy it was immediately apparent that the mesylate group had been cleaved during the reaction presumably by the hydroxide ion. An attempt was made to reduce the azido mesylate **(220)** using $LiAlH_4$ in THF but this also resulted in cleavage of the mesylate group.

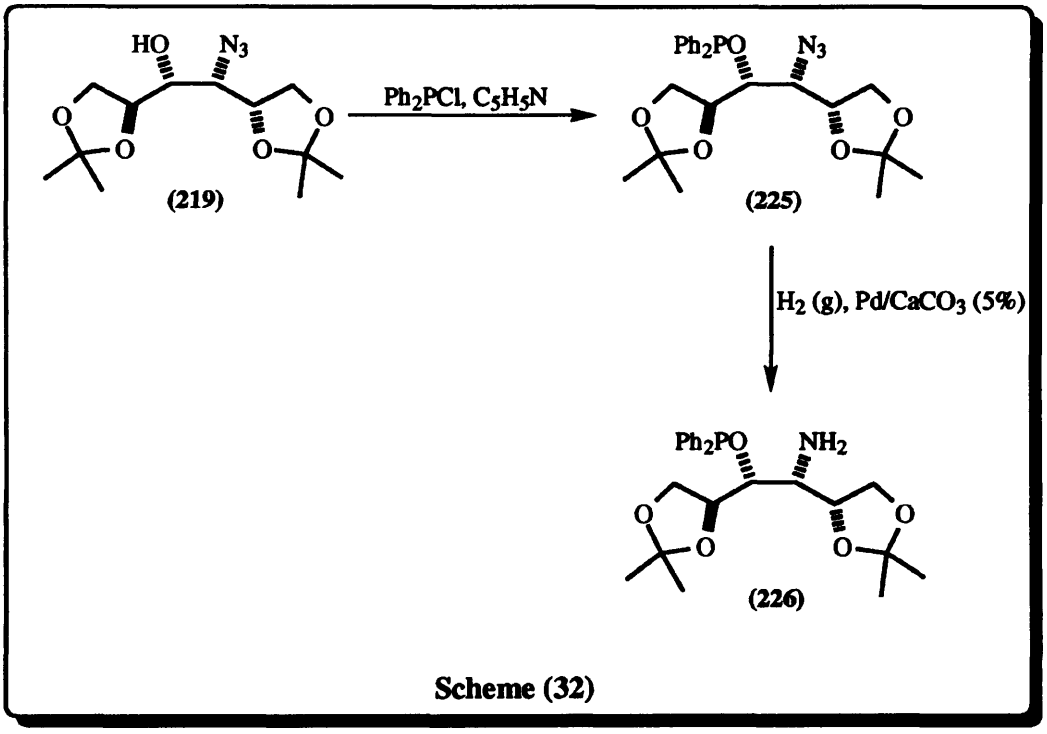
It was then decided to use Lindlar catalyst (5% $Pd/CaCO_3$)[161,162] in dry ethanol under 1 atm of hydrogen pressure and this gave the desired product **(221)** as a white crystalline solid in high yield (89%), (m.p. 167-168 °C). Microanalysis results agreed with the calculated molecular formula; $C_{13}H_{25}NO_7S$.



(221)

The strong sharp azide band at 2110 cm^{-1} was absent from the IR spectrum and the spectrum showed two weak bands at 3265, 3230 and a third band at 1620 cm^{-1} characteristic of a primary amine. The ^1H NMR spectrum showed a singlet for the SCH_3 group at δ 3.09 ppm and another singlet (2H) at δ 5.22 ppm for the NH_2 protons. This encouraging result was achieved on a small scale reaction (0.50 g), but when the reaction was scaled up to 3.0 g of substrate no reduction of the azide occurred at room temperature, even when the reaction time was extended to 2 weeks. TLC showed no evidence for amine formation. The use of Lindlar catalyst[162] is a standard method for the reduction of azides to primary amines under mild conditions and we have no satisfactory explanation why this reaction failed on large scale in this particular case, unless the product is able to bind strongly (perhaps *via* a chelate complex) to the active sites on the palladium. A stock of **(221)** could be prepared by carrying out the reduction of **(220)** on 0.50 g scale and putting on 4-6 reactions simultaneously, but this is not a desirable alternative.

Starting from the intermediate azide alcohol **(219)**, we attempted to prepare the chiral aminophosphinite **(226)** by conversion of **(219)** to the azide diphenylphosphinite **(225)** using chlorodiphenylphosphine with anhydrous pyridine. Compound **(225)** could then be hydrogenated to afford the amino phosphinite **(226) scheme (32).**

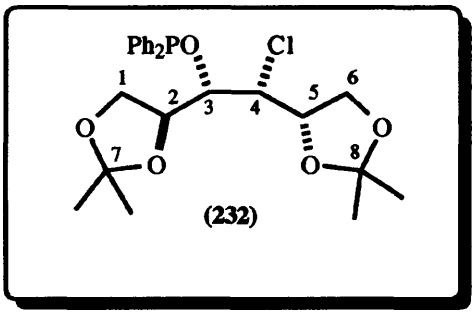


Scheme (32)

When the azido alcohol **(219)** was treated with chlorodiphenyl phosphine using anhydrous pyridine, and stirred at room temperature for five days, an impure glassy solid was obtained. This was purified by recrystallization from ethanol followed by dry flash column chromatography (DCFC) to afford a white solid, m.p. 164-165 °C in 50% yield contaminated with a small amount of chlorodiphenyl phosphine.

Spectroscopic analysis of this product identified the product obtained as compound **(232)** by giving band at m/z (FAB) 465 $(M+H)^+$, 12.6%. There was no evidence for the expected product (**225**, MW 471). Moreover, the mass spectrum (EI) of **(232)** gave bands at m/z 422 $[M_{(232)}\text{-}Me_2C]^+$ (42%) and a strong band at m/z 201 (100%) confirming the presence of $OPPh_2$ group.

The IR spectrum showed no OH group and the strong sharp band of the azide group at ν 2110 cm^{-1} was no longer present. Bands at 1140 (m), 725 (m), 700 (w) representing ν (P-Ph str.) and 850 w, ν (asym. C-OP str.) cm^{-1} were present and confirmed that the compound contained the $OPPh_2$ group.



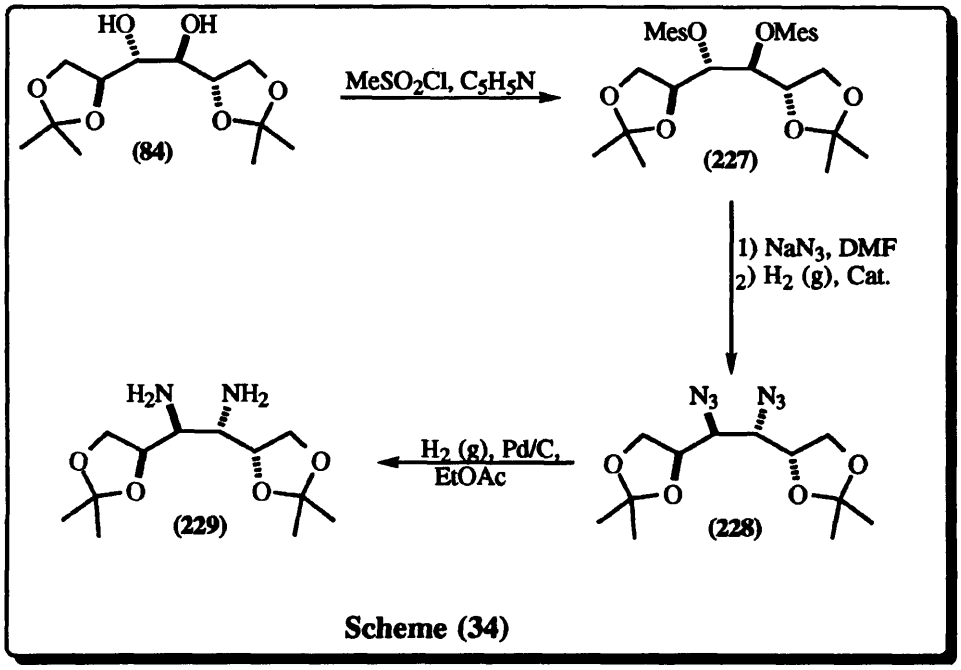
(232)

The ^{1}H NMR spectrum showed four singlets for the methyl groups of the acetals at δ 1.13, 1.19, 1.24, and 1.28 ppm. The other aliphatic protons were observed at δ 4.00 ppm, while other aromatic protons could be seen at δ 7.43-7.83 ppm.

The ^{13}C NMR spectrum showed the four methyl groups of the acetal moieties at δ 25.2, 25.4, 26.4, and 26.5 ppm. The remaining aliphatic carbon atoms were shown at δ 67.1 (C-6), 68.1 (C-1), 73.5 (C-5), 73.5 (C-2), 76.1 (C-4), 76.7 (C-3), 109.8 (C-7 or C-8) and 110 (C-7 or C-8) ppm, while the aromatic carbons appeared between δ 127.7 to 133.2 ppm.

The ^{31}P NMR spectrum showed a single peak at δ +23.10 ppm representing a C-OP moiety.

Due to our inability to obtaine the azido phosphinite **(225)**, it was decided to prepare chiral diamine **(229)**. In order to prepare the diamine **(229)** ligand from the diol **(84)**, it was necessary to obtain the dimesylate **(227)** and then convert the mesylate to the diamine **(229)**[159,161] via formation of the diazide **(228)** as illustrated in **scheme (34)**.



Scheme (34)

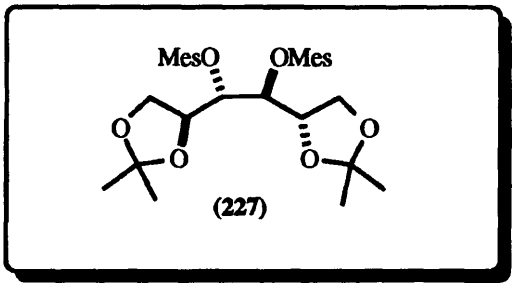
The diol (**84**) was treated with mesyl chloride in anhydrous pyridine at 0 °C to afford the dimesylate (**227**) as a white crystalline solid in 88% yield, m.p. 129-130 °C. Microanalysis gave the required values for a molecular formula of $C_{14}H_{26}O_{10}S_2$.

The IR spectrum ($CHBr_3$, mull) showed no broad OH peak and the presence of bands at 1370 and 1220 cm^{-1} for the ν (S=O) stretching vibrations and various bands at 940, 910, 865, 760 cm^{-1} for the mesylate group.

The ^1H NMR spectrum showed a singlet at δ 3.16 ppm for the two methyl groups of the mesylates and the other four methyl groups of the isopropylidene moiety at δ 1.35 and 1.48 ppm.

The ^{13}C NMR spectrum showed two peaks at δ 25.0 and 26.4 ppm corresponding to the four methyl groups of the isopropylidene moieties and the SCH_3 carbon atom at δ 38.8. Four other peaks were observed at δ 66.3, 73.3, 78.8 and 110.1 ppm representing

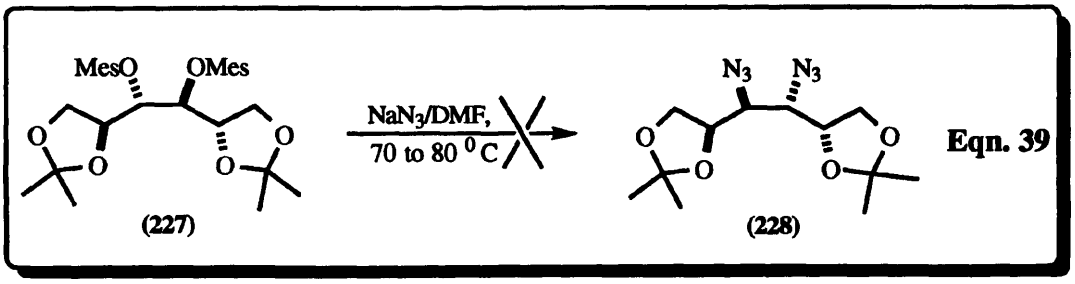
the remaining four carbon atoms.



(227)

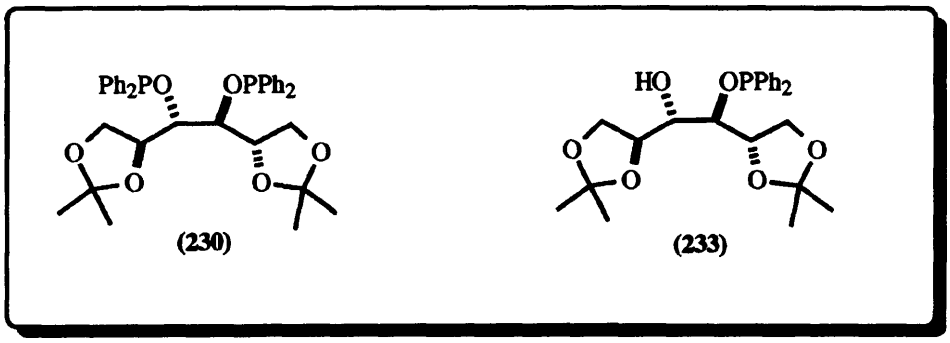
The mass spectrum (FAB) confirmed the molecular weight at m/z 419 $(M+H)^+$, 100% and additional bands at 403 $(M-CH_3)$, 24% and 837 $(2M+H)^+$, 5%.

The displacement of a sulfonate leaving group by azide ion is an important route to organic azides. The most commonly employed sulfonate leaving group is the methane-sulfonate (mesyl) group.[160] Thus, the 3,4-dimesylate of di-isopropylidene-D-mannitol **(227)** was heated at 70-80 °C with sodium azide in anhydrous DMF[159] for 5 days. Unfortunately, TLC showed no evidence that the starting material was converted to the azide **(228)** **(Eqn. 39)**. The IR, ^1H and ^{13}C NMR spectroscopic data further confirmed that this reaction had not taken place.



(227) (228) **Eqn. 39**

Another chiral phosphinite ligand (**230**) could be obtained by the reaction of the same diol (**84**) with chlorodiphenylphosphine (3 equiv.) in the presence of anhydrous pyridine at room temperature under an argon atmosphere. However, the reaction time was very long (~two weeks) and the resulting product was not a single compound. Three compounds were observed on TLC (EtOAc-hexane, 2:1). The mixture was separated by flash column chromatography to give the starting material (50% recovered) plus two impure compounds. These two compounds were purified further by recrystallization from ethanol to afford bis-*O* -diphenylphosphinite (**230**) in 16.6% yield, m.p. 150 - 155 °C and the monodiphenylphosphinite (**233**) in 29.4% yield, m.p. 145 °C.



(230) (233)

Microanalysis gave values which were close to those expected for the mono-diphenylphosphinite (**233**), while the analysis results for the bis-*O* -diphenylphosphinite (**230**) were poor. The IR spectrum ($CHBr_3$ mull) for both products confirmed the presence of diphenylphosphinite bands at 3010 (m) cm^{-1} and 1600 (s) cm^{-1} representing the phenyl rings. Other bands at 1140 (m) and 860 cm^{-1} characterized the P-Ph and P-OC stretches respectively.

The ^{1}H and ^{13}C NMR spectra showed the presence of aromatic protons, but unfortunately, the spectra were of poor quality since the compounds were of low purity.

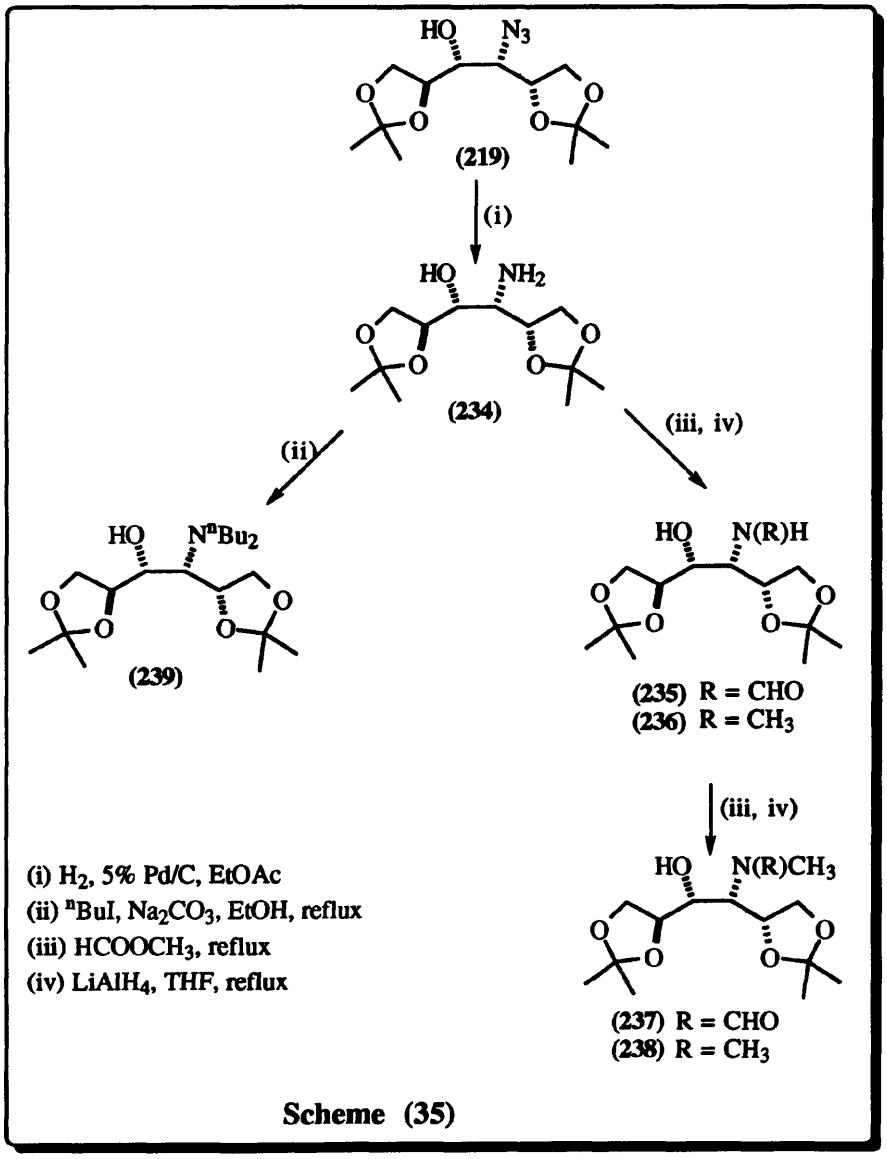
The mass spectrum (FAB, EI, CI) of the monodiphenylphosphinite **(233)** gave a strong band at m/z 201 for the ion $[Ph_2PO]^+$ and an $(M+H)^+$ ion at m/z 447, 13%.

The mass spectrum (FAB) of the bis-*O* -diphenyl phosphinite **(230)** did not show the expected molecular ion at m/z 630 $(M+H)^+$. Instead, a strong signal at m/z 623 (70%) was observed.

It was concluded that the disubstitution of diphenylphosphine had taken place. However the product was contaminated with chlorodiphenylphosphine and further attempts at purification have not been successfull.

II.4.3 Exploration of Some Methods of Preparing Other Homogeneous Asymmetric Ligands Based on D-Mannitol

As a result of the preliminary unsuccessful efforts in obtaining pure ligands, it was thought that other chiral ligands based on D-mannitol such as β-dialkylamino alcohols (**238** and **239**) might be useful as asymmetric catalysts in the reactions involving the addition of dialkylzinc to aldehydes or ketones and Diels-Alder reactions (DAR). Their syntheses are described in **scheme (35)**.



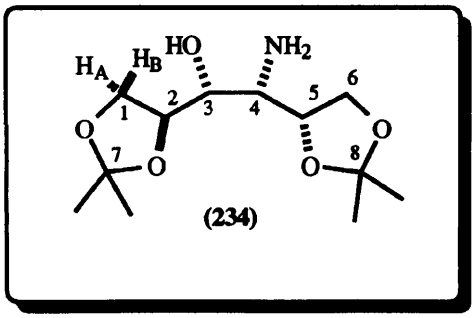
Scheme (35)

When the azido alcohol **(219)** was hydrogenated using Pd/C (5%) at room temperature for 48 hours, the amino alcohol **(234)** was obtained as a crystalline solid product in high yield (88%), m.p 83 ^{0}C. $[\alpha]_D$ -9.7^0 (c 2.0, $CHCl_3$).

The IR spectrum indicated the azido group (at 2110 cm^{-1}) had been substituted, and showed two bands at 3280 and 3060 cm^{-1} representing the stretching vibrations of the NH_2 group.

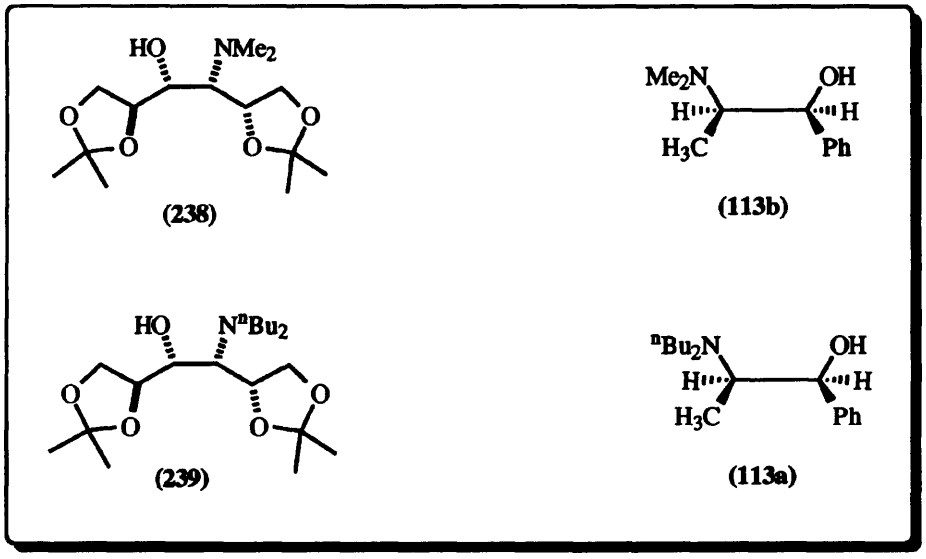
The ^{1}H NMR spectrum showed the four singlets of the four methyl groups, which were slightly shifted towards high field at δ 1.25, 1.26, 1.29 and 1.30 ppm, compared to the spectrum of the starting material. The hydroxyl group was observed as a doublet in the ^{1}H NMR of the starting material **(219)**, whereas in the spectrum of the product **(234)** it was a triplet with *J* 5 Hz at δ 2.84 ppm. Two multiplets appeared between δ 3.69-4.13 ppm (6H); 2H (H_2 and H_5) at δ 3.69 and 4H (H_A and H_B) at δ 4.13 ppm. The NH_2 protons were not seen in the spectrum, presumably due to an exchange process. The remaining two hydrogens appeared at δ 3.65 as a triplet and δ 4.30 as a quartet characteristic of H_4 and H_3 respectively. The ^{13}C NMR spectrum showed the expected 12 peaks.

The elemental analysis and mass spectrum (FAB) agreed with the expected molecular formula.

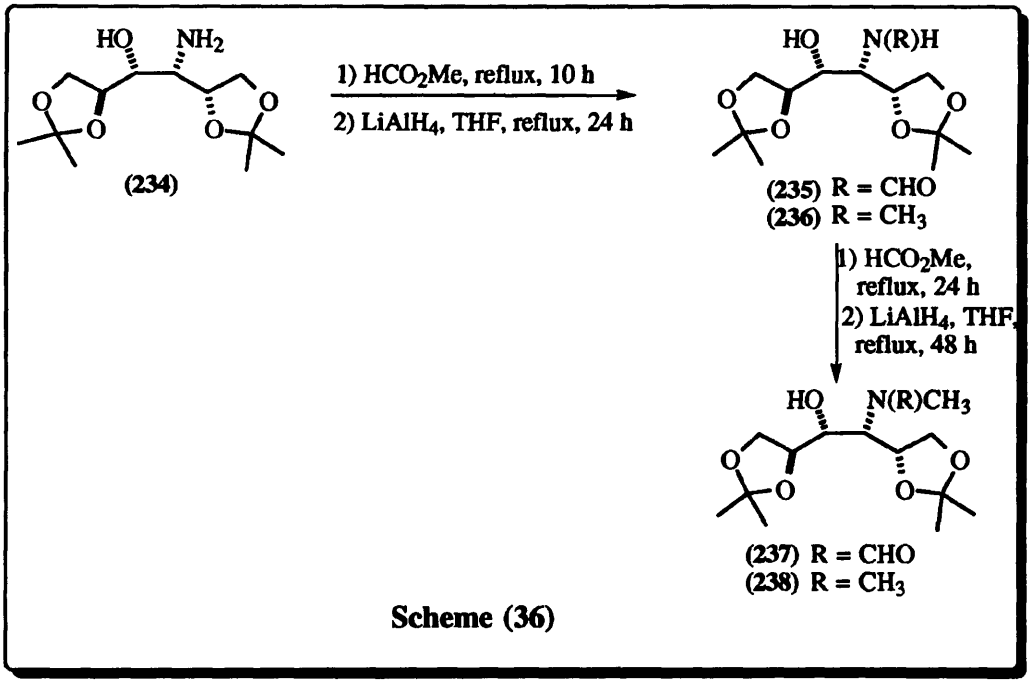


(234)

The β-amino alcohol **(234)** is a useful starting material for the preparation of chiral β-tertiary amino alcohols **(238)** and **(239)** which are similar to the earlier reported ligands DMNE **(113b)** and DBNE **(113a)**[83] respectively.



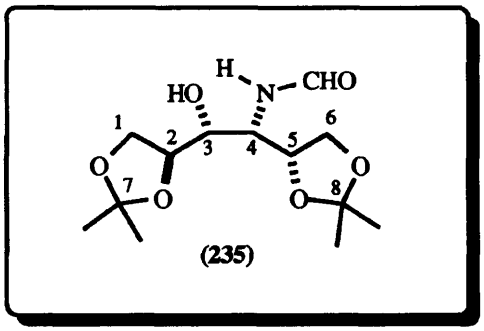
As mentioned earlier, these types of ligands could be useful in catalytic asymmetric induction reactions particularly asymmetric alkylation of carbonyl compounds and Diels-Alder reactions. Thus, it was decided first to carry out the preparation of the dimethyl derivative **(238)** as shown in the synthetic **scheme (36)**.



Scheme (36)

Thus, when the optically active β-amino alcohol **(234)** was treated with an excess of methyl formate under reflux conditions for 12 hours the 3-N-formylamino alcohol **(235)** resulted as a white solid in good yield (90%),$[\alpha]_D^{25}$ +44.8^0 (c 2.0, $CHCl_3$). No diformylated adduct was produced despite the long reaction time.

Microanalysis and mass spectroscopy confirmed that compound **(235)** had the expected molecular formula and molecular weight. The IR spectrum showed the presence of an N-H band at 3400 cm^{-1} and a weak broad OH band was observed at 3370 cm^{-1}. A strong absorption for the carbonyl group of the amide was observed at 1650 cm^{-1}.



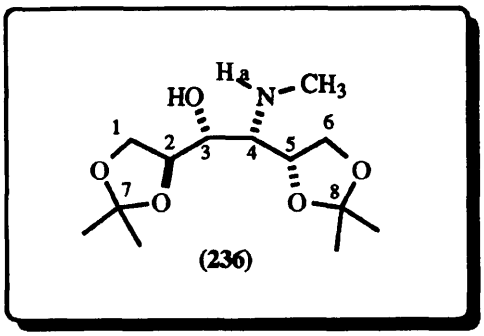
(235)

The ^{1}H NMR spectrum was consistent with the assigned structure and showed the N-H proton at δ 6.16 as a doublet with J 8 Hz and the proton of the CHO group at δ 8.30 ppm.

The ^{13}C NMR spectrum showed the required 13 peaks and the amino carbonyl carbon appeared at δ 161.2 ppm.

This intermediate compound **(235)** was then reduced by lithium aluminium hydride in THF under reflux for 12 hours. Purification using dry column flash

chromatography followed by Kügelröhr bulb-to-bulb distillation under reduced pressure afforded the optically active methyl amino alcohol **(236)** as a pure, colourless oily product in a moderate yield (40%), $[\alpha]_D^{25}$ + 8.6^0 (c 2.0, $CHCl_3$).



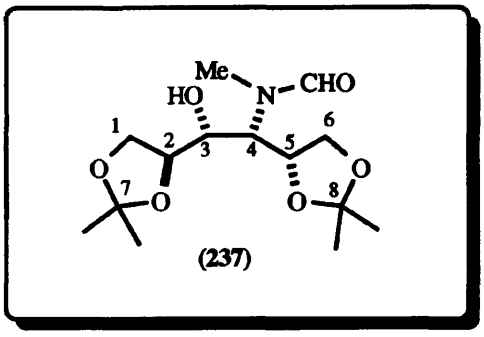
(236)

Microanalysis and mass spectroscopy supported the proposed molecular formula. The IR spectrum showed no carbonyl absorption. All other bands were characteristic of the structure.

The ^{1}H NMR spectrum showed four singlets for the methyl groups of the isopropylidene moieties at δ 1.25, 1.39, 1.42 and 1.46 ppm, and the N-methyl group ($N\text{-}CH_3$) as a singlet at δ 2.40 ppm. The hydroxyl group was observed at high field, compared with the N-formyl analogue, at δ 2.63 ppm. The position of H_a was observed as quartet at δ 4.37 ppm with *J* 6.5 Hz. The remaining seven hydrogens appeared as multiplets at δ 3.66 (1H) and δ 3.85-4.15 ppm (6H) as is usual in these compounds.

The ^{13}C NMR spectrum showed the required 13 peaks. No carbonyl signal was apparent in the spectrum, indicating complete reaction had taken place.

By following the same route, namely treatment of the methyl amino alcohol **(236)** with an excess of methyl formate, the 3-N-formyl methylamino alcohol **(237)** was obtained in 88% yield as an oil, (see **scheme 36**, p.86).



(237)

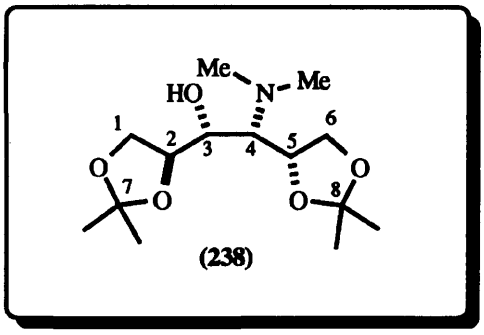
This compound gave an optical rotation of $[\alpha]_D^{25}$ -26.3° (c 0.44, $CHCl_3$) with an opposite sign to that of starting material **(236)**. IR spectroscopy confirmed the presence of the carbonyl group by a strong (C=O) absorption at 1655 cm^{-1}. The mass spectrum (FAB)

showed m/z 304 $(M+H)^+$ (64% intensity), corresponding to the expected structure.

The ^1H NMR spectrum agreed with the assigned structure. The presence of the formyl group was confirmed by the singlet peak observed at δ 8.10 ppm respectively.

The ^{13}C NMR spectrum showed 14 peaks, one of which was present in the carbonyl carbon region of the spectrum at δ 164.0 ppm.

When **(237)** was reduced by $LiAlH_4$ in THF under reflux for 48 hours, i.e. a longer time than that used for the reduction of **(235)**, the desired β-dimethylamino alcohol ligand **(238)** was obtained as an oil in 75% yield. This was purified twice by dry column flash chromatography and also by Kügelröhr bulb-to-bulb distillation under reduced pressure. The pure 4-N,N-(dimethylamino)-3-hydroxy-1,2:5,6-di-*O* -isopropylidene-D-mannitol **(238)** was obtained in moderate yield (60%).



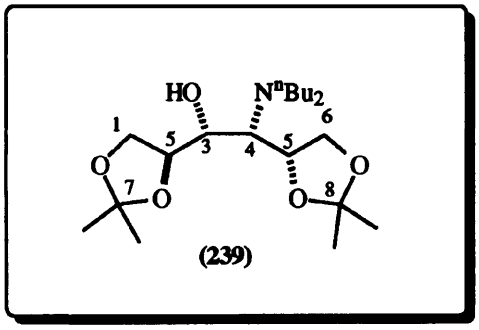
(238)

The spectroscopic data supported the assigned structure. The product was shown to have an optical rotation of $[\alpha]_D^{25}$ + 25.10 ° (c 0.44, $CHCl_3$) and microanalysis confirmed that the compound had a molecular formula of $C_{14}H_{27}NO_5$.

The mass spectrum (FAB) also confirmed the molecular mass, m/z = 290 $(M+H)^+$, 100%.

The IR and ^1H NMR spectra confirmed that reduction of the amide had occurred.

The more bulky β-dibutylamino alcohol (**239**) was prepared in a one step reaction by treating the primary amino alcohol (**234**) with two equivalents of 1-iodobutane in ethanol. No reaction was observed at room temperature, but, on heating the reaction mixture at reflux temperature for 10 hours, an impure product resulted which was purified twice by dry column flash chromatography, followed by further purification by Kugelröhr bulb-to-bulb distillation under reduced pressure to afford the β-dibutylamino alcohol (**239**) in 26% yield as a pure, colourless oil.

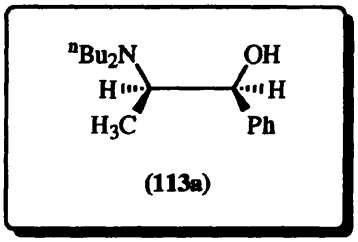


(239)

Mass spectrum and microanalytical data confirmed that the compound (**239**) had the molecular formula $C_{20}H_{39}O_5N$.

The ^1H NMR spectrum was consistent with the assigned structure and showed the 18 hydrogen atoms of the two butyl groups were observed at 0.85 (m, 5H), 1.37 (m, 7H), 1.52 (m, 3 H), 2.60 (t, *J* 7 Hz, 2H) and 3.42 (q, *J* 7 Hz, 1H). It was not possible to obtain a clear ^{13}C NMR spectrum.

Attempts to improve the yield either by use of an excess of 1-iodobutane or by a longer reaction time was unsuccessful. A low yield has also been reported in the synthesis of the ligand (**113a**), and this has been attributed to the steric hinderance.[83] Finally the compound (**239**) has been shown to be an optically active compound.

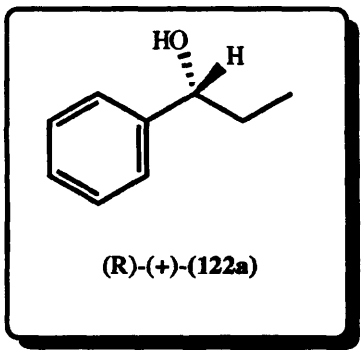


(113a)

The two novel β-amino alcohol ligands **(238)** and **(239)** have been used as homogeneous catalysts in the asymmetric alkylation of benzaldehyde and will be discussed in the next section **II.4.4.**

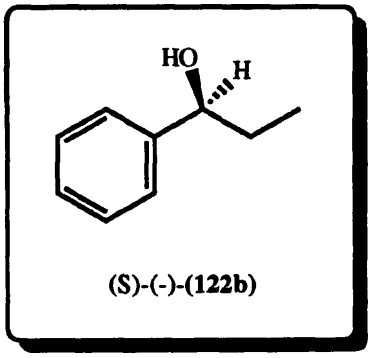
II.4.4 Enantioselective Addition of Diethylzinc to Benzaldehyde Using the Chiral β-Tertiaryamino Alcohols as Catalysts.

The reaction was carried out using diethylzinc (2.23 equivalents) and benzaldehyde (1 equivalent) with a catalytic amount (2.34%) of the (2*S*,3*S*,4R,5*S*)-(+)-4-N,N-(dimethylamino)-3-hydroxy-D-mannitol **(238)** in toluene at 0 ^{0}C at room temperature under argon. The reaction mixture was followed by TLC (EtOAc-hexane, 1:5) which indicated complete reaction after 2 days. After the standard work up, 80% yield of the crude 1-phenylpropanol **(122)** was obtained. After purification by column chromatography followed by Kügelröhr bulb-to-bulb distillation the pure product was isolated in 60% yield. The product had a low specific optical rotation of $[\alpha]_D^{23}$ + 10.0^{0}, c 0.2, $CHCl_3$, indicating an optical purity of only ca. 22% by comparison with the reported optical purity of (R)-(+)-1-phenylpropanol **(122a)** of ($[\alpha]_D$ -45.45^{0} c 5.15, $CHCl_3$).[163]



(R)-(+)-(122a)

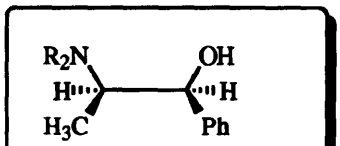
Under similar reaction conditions the use of the N,N-dibutyl analogue **(239)** as a catalyst for the addition of diethylzinc to benzaldehyde gave crude (S)-(-)-1-phenylpropanol **(122b)** in 58% yield after 48 hours and the same workup procedure. The optical purity of the purified product **(122)** had increased to 66% ($[\alpha]_D^{23}$ -30.0°, c 0.2, $CHCl_3$) and the product had the (S)-configuration, i.e. the opposite configuration to that found with the dimethyl analogue **(238)**. This supports the view that bulky groups on the nitrogen atom of these amino alcohol ligands was essential for high asymmetric induction.[83]



(S)-(-)-(122b)

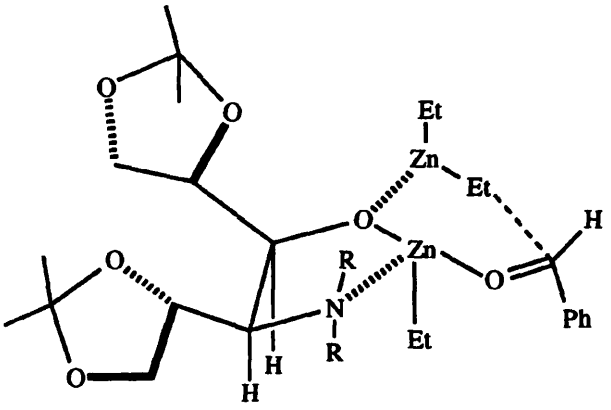
It has been noted previously[83] in the ephedrine-based ligand **(113)**, that a change from the $-NBu_2$ groups to $-NMe_2$ groups results in loss of optical purity (of approximately

40%) in the ethylation of n-heptanal ($C_6H_{13}CHO$), our results on the D-mannitol-based ligands gave 22% **e.e.** of (R)-1-phenyl-propanol **(122a)** which followed a similar trend.



(113) a) R = ^{n}Bu
b) R = Me

The low **e.e.** value may be due to the fact that in the transition state the phenyl group could have the opposite orientation to that assumed with other amino alcohol ligands.[115] **(Fig.10)**.

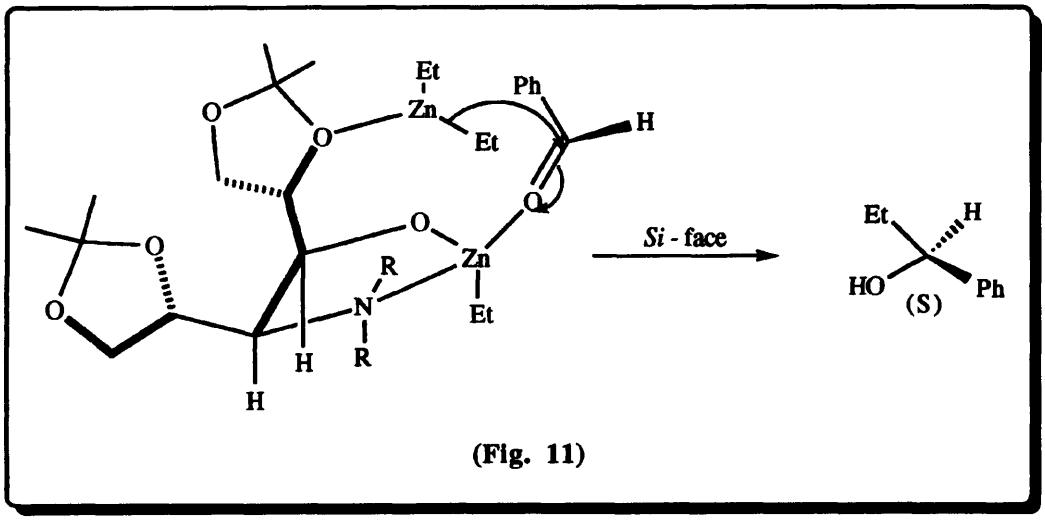


R = ^{n}Bu

(Fig. 10)

This would lead to a 1,3-diaxial interaction with the ethyl group on the zinc atom.

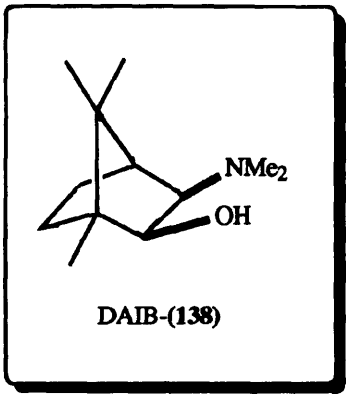
Another possibility is that the second zinc atom may coordinate to the oxygen atom of the isopropylidene group. This would be a 9-membered transition state (T.S.) which is less favoured than 6-membered T.S., leading to the (S)-enantiomer. However, the steric requirements are not as severe and could lead to either the (R) or (S)-enantiomer. If the phenyl group is in an axial position as shown **(Fig.11)**, this would give the (S)-enantiomer and if the phenyl group is equatorial it would give the (R)-enantiomer.



(Fig. 11)

This is a possible explanation for the poor enantiomeric excess **(e.e.)**. It would only require *ca.* 18% of the (R)-enantiomer to be formed by this competing reaction to give the 66% **e.e.** observed in the case of the dibutylamino alcohol ligand **(239)**.

It has been noted previously[89,105] that aliphatic aldehydes which have a side chain heteroatom leads to racemization. For example in the enantioselective addition of diethylzinc to aldehydes catalyzed by DAIB **(138)**.



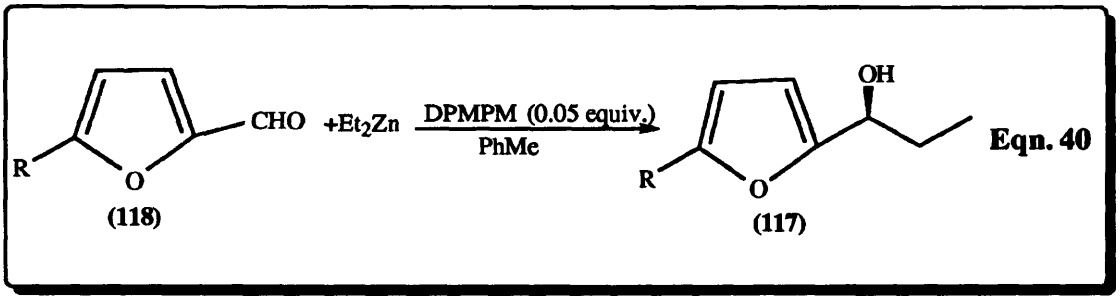
DAIB-(138)

It was found that no enantioselective reaction occured (0.0% **e.e.**) when the benzyloxymethyl aldehyde (**240**) was employed (**Table 1**).

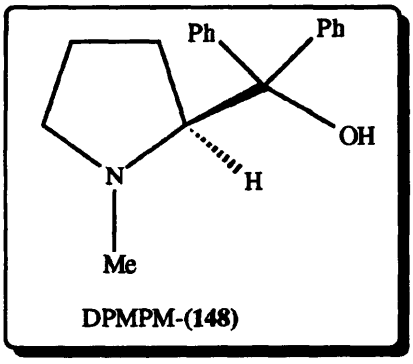
(Table 1)

Aldehyde	Time (h)	Yield (%)	**e.e.** (%)
PhCHO	6	97	98 (S)
p- ClC_6H_4CHO	12	86	93 (S)
$PhCH_2OCH_2CHO$ (**240**)	5	80	0.0

More evidence comes from the asymmetric addition of diethyl zinc to 2-furaldehyde (**118**) catalyzed by DPMPM (**148**). When the R-group of (**118**) at position-5 is a dioxolane ring the **e.e.** value dropped considerably. (**Eqn. 40**), (**Table 2**).



Eqn. 40



DPMPM-(148)

(Table 2)

Aldehyde (118) (R) =	Yield (%)	e.e. (%) (S)
H	68	65
CH_3	90.50	97
dioxolane	56	46
Si $(CH_3)_3$	78	89

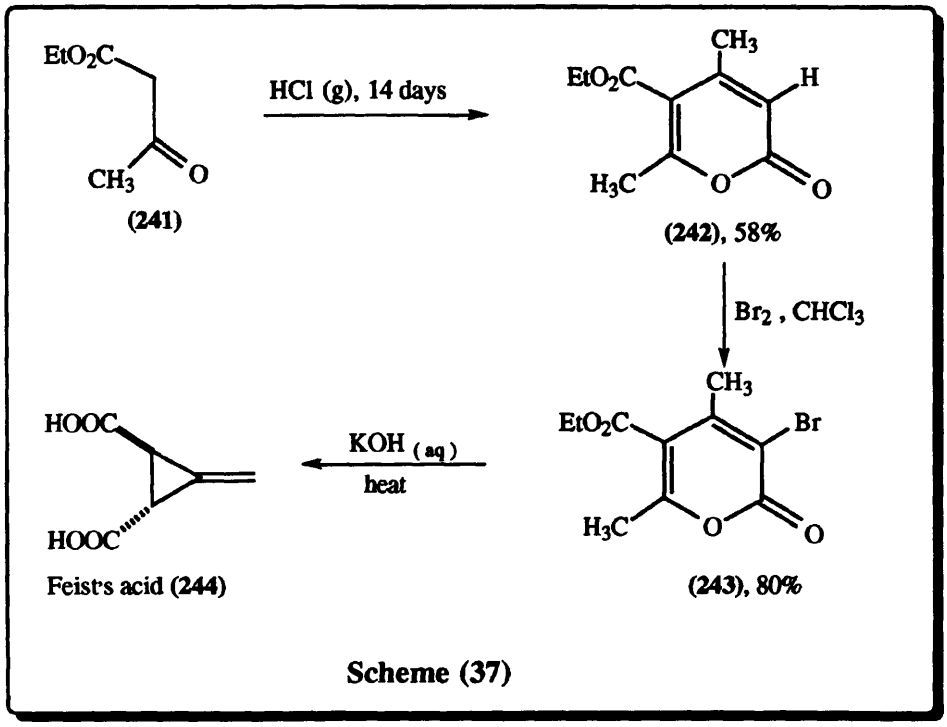
The explanation given in this report[105] was that the "O" atom coordinates to the zinc, thus facilitating the uncatalyzed achiral pathway.

Chapter 5

II.5 Exploration of New Asymmetric Ligands Based on Feist's Acid

II.5.1 Introduction

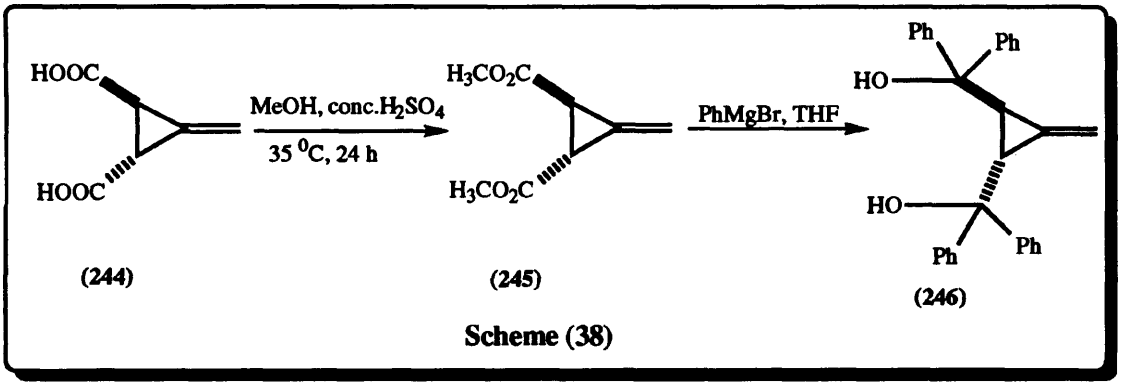
In view of the unsatisfactory results obtained using D-mannitol as the precursor to chiral ligands, we decided to investigate other starting materials to obtain various homogeneous asymmetric ligands. Thus, *trans*-1-methylenecyclopropane-2,3-dicarboxylic acid (Feist's acid) **(244)**[71,164-169] was envisaged as an available alternative intermediate to prepare various chiral ligands, and **(244)** was synthesized according to the **scheme (37).**



Scheme (37)

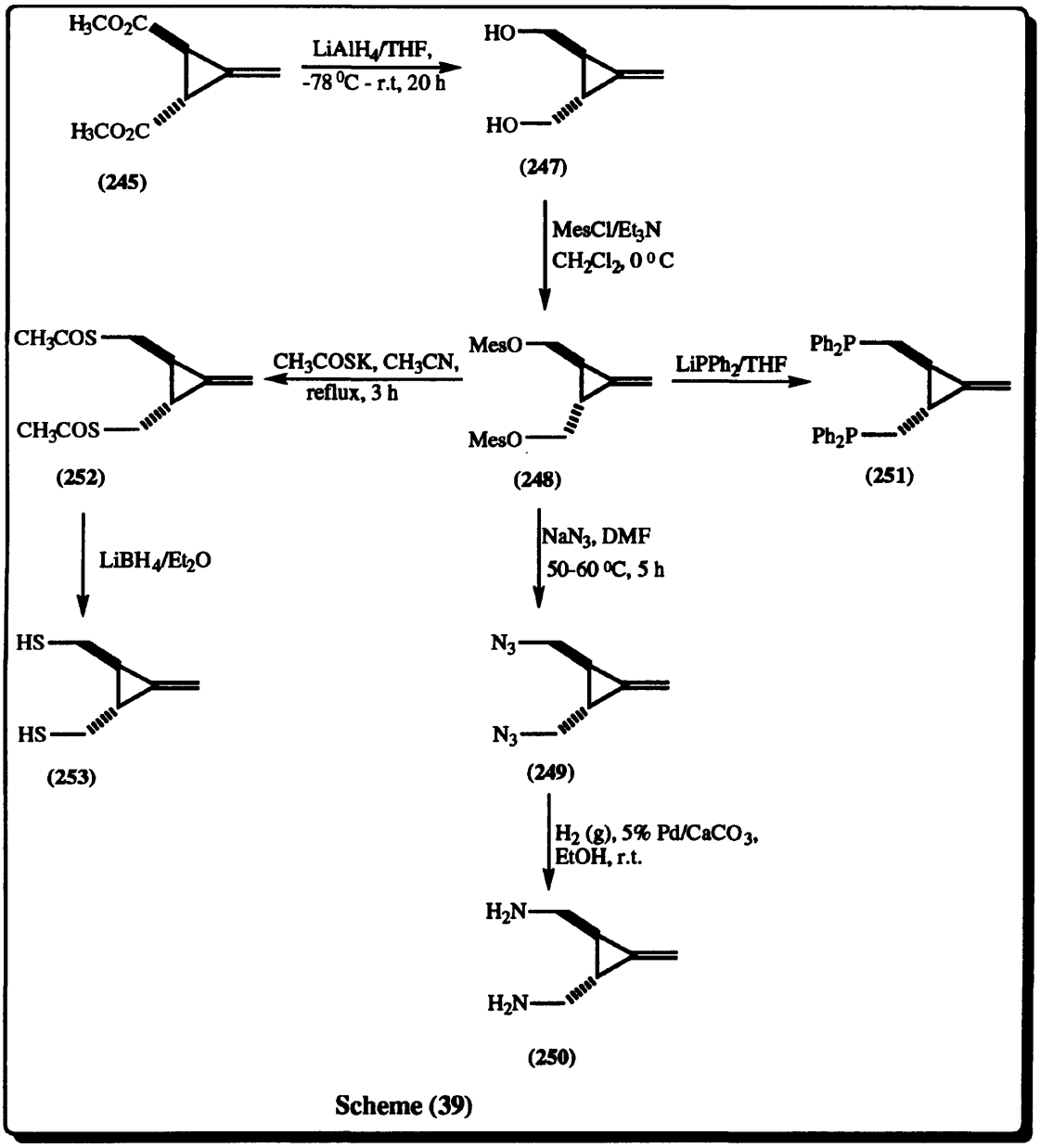
This Feist's acid **(244)** was racemic and needed to be resolved (prior to use in later reactions) using a suitable chiral reagent (e.g. L-(-)-quinine, **89**).[72]

The chiral *trans*-2,3-bis(diphenylmethanol)-1-methylenecyclopropane **(246)** can be prepared starting from Feist's acid **(244)** as shown in **scheme (38)**.



Scheme (38)

The two pure enantiomers of the 1,4-diol **(246)** can be modified by Lewis acids [e.g. $TiCl_4$, $Ti(O^iPr)_4$] and might be useful in the asymmetric addition of dialkylzinc to aldehydes. The dimethyl ester **(245)** could be useful as a starting material to prepare chiral bidentate ligands e.g. diamine **(250)**, diphosphine **(251)**, and dithiol **(253)** as shown in the synthetic sequences in **scheme (39)**.

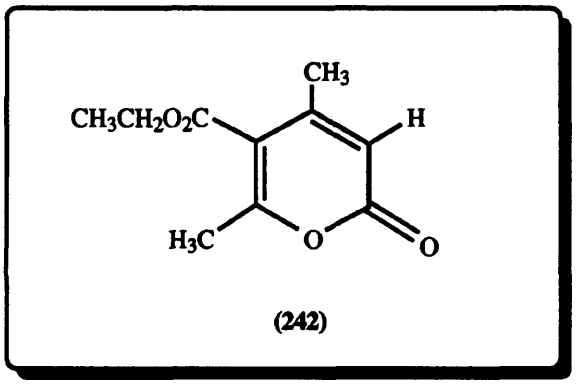


Scheme (39)

These chiral bidentate ligands **(250, 251,** and **253)** could be used to bind suitable rhodium complexes e.g. [Rh(Cl)cod], hence use them as chiral homogeneous catalysts to induce asymmetric hydrogenation of olefins.

II.5.2 Preparation of Feist's Acid (244)

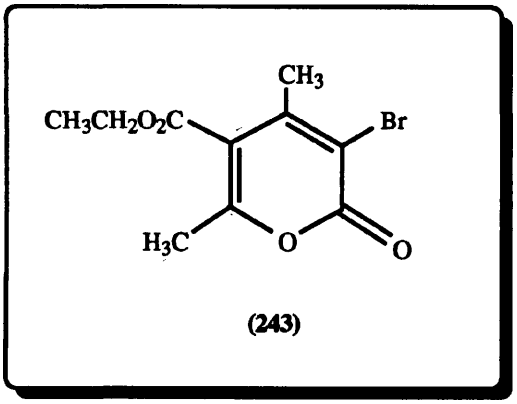
The preparation of Feist's acid (**244**) from ethyl acetoacetate (**241**) was carried out using essentially the procedure as that described by Goss *et al.* [165] and modified by Blomquist.[166] According to this procedure ethyl acetoacetate (**241**) was treated with hydrogen chloride gas to afford the pyrone (**242**) in 58% yield. The IR spectrum of (**242**) confirmed the presence of two carbonyl stretching bands at 1720 and 1630 cm^{-1}. The microanalysis and mass spectroscopic (FAB) data were consistent with the structure.



(242)

The ^{1}H NMR spectrum the pyrone (**242**) showed two distinct singlets representing the two non-equivalent methyl groups at δ 2.20 and 2.35 ppm, an additional singlet for the olefinic hydrogen was observed at δ 6.0 ppm. The ethyl group was confirmed by a triplet at δ 1.35 (CH_3) and a quartet at δ 4.30 (CH_2) with a coupling constant of ^{3}J 7.5 Hz. The ^{13}C NMR spectrum showed the expected 10 peaks, corresponding to 10 non-equivalent carbon atoms.

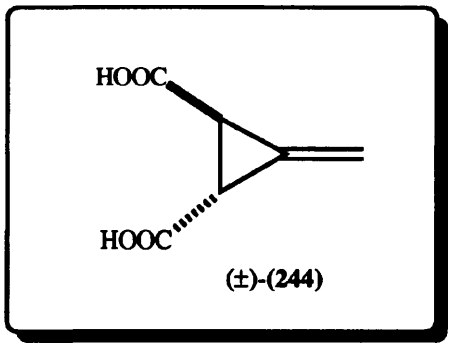
Bromination of the pyrone (**242**) at the 3-position gave the corresponding bromo compound (**243**) as a pale yellow solid in 80% yield.



(**243**)

The spectroscopic data for this product (**243**) was similar to those of the starting material (**242**), but, as expected, the olefinic proton was no longer present in the ^{1}H NMR spectrum. The two methyl groups now had the same chemical shift, i.e., overlapped at δ 2.25 ppm.

Treatment of the bromopyrone (**243**) with boiling aqueous potassium hydroxide solution gave the ring closure product, Feist's acid (**244**), in 55% yield. The ^{1}H NMR spectrum of the product (**244**) showed both olefinic protons at δ 5.9 and the ring protons at δ 2.85 ppm appeared as second order triplets. The carboxylic acid protons appeared at low field (δ 13.00 ppm) as a broad singlet.



(±)-(244)

The ^{13}C NMR spectrum showed the terminal olefinic carbon atom at δ 110.0. The internal olefinic atom and the carbon atom of the carboxylic acid groups were downfield at δ 133.5 and 174.0 ppm respectively.

II.5.3 Resolution of the Feist's Acid

Introduction

Resolution is one of the key unit processes utilized by organic chemists, whether their interests are synthetic, mechanistic, or structural.[170,171] The important practical methods for the production of enantiomeric compounds are:

1. spontaneous resolution by recrystallization.[171,172]
2. resolution via diastereomer formation.[173-175]
3. enzymatic optical activation.[176-177]
4. kinetic resolution.[178,179]
5. chromatographic resolution.[180,181]
6. asymmetric Synthesis.[182,183]

Conversion of mixtures of enantiomers into diastereomers by reaction with a chiral reagent constitutes the principal conventional, classical, and practical resolution methods. Equilibrium typified by **Eqn. 41** describes resolution via diastereomer salt formation.

$$\begin{bmatrix} (+)\ \text{Acid}_A \\ (-)\ \text{Acid}_B \end{bmatrix} + (+)\ \text{Base} \rightleftharpoons \begin{bmatrix} (+)\ (+)\text{-Salt}_A \\ (-)\ (+)\text{-Salt}_B \end{bmatrix} \qquad \textbf{Eqn. 41}$$

Principal desirable features of conventional resolutions of the type shown in **Eqn. 41** are:

(i) availability and stability of the resolving agent (low cost, stability of supply and under conditions of use and storage)[170];

(ii) complete and preferably rapid reaction under mild conditions;

(iii) facile, complete separation of the diastereomeric product mixture in high yield;

(iv) easy isolation of the product mixture with minimal loss;

(v) facile and complete reversal of the equilibrium to the desired optical active compound under conditions minimizing racemization;

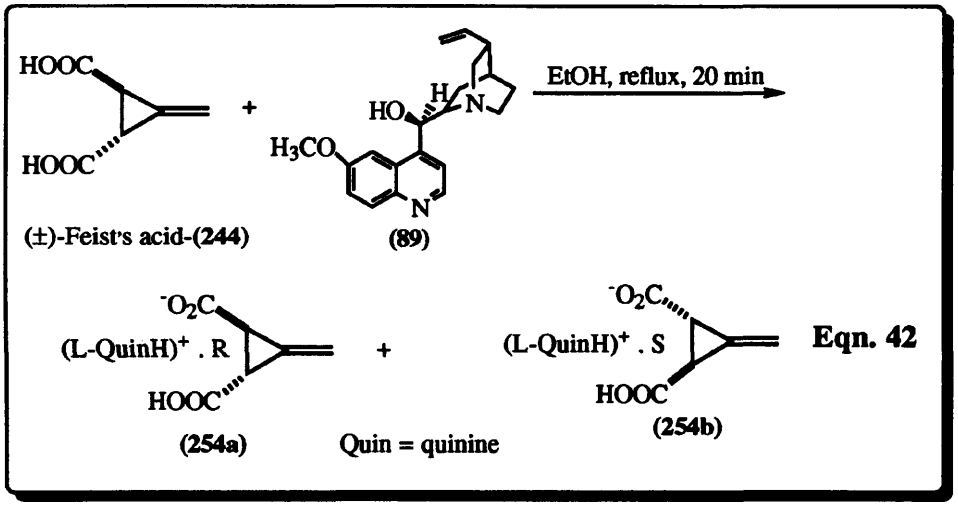
(vi) isolation of both enantiomers, each optically pure; and

(vii) recovery in high yield and re-use of the resolving agent should be facile.

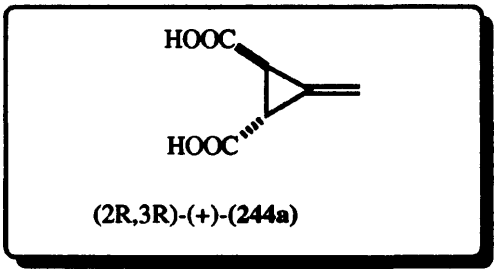
However, rarely do resolutions meet even a majority of these criteria. Many attempts have been carried out to resolve the racemic Feist's acids **(244)** via diastereomer formation using chiral reagent and are outlined below.

(i) Via L-(-)-quinine (89)[72]

Racemic Feist's acid **(244)** was treated with L-(-)-quinine **(89)** (1:1 mole equivalents) and after heating at reflux for 20 minutes in absolute ethanol two diastereomeric salts **(254a, 254b)** were formed as shown in **(Eqn. 42)**.



The first salt was collected in 60% yield and a fractional crystallization was carried out using dry ethanol to afford (2R, 3R)-(Feist's acid)-L-quinine salt **(254a)** as a crystalline product in 43% yield, with an optical rotation of $[\alpha]_{546}$ -145° (c 0.4, EtOH), which is close to the reported value,[72] $[\alpha]_{546}^{23}$ -139.7° (c 0.7, EtOH). The melting point, however, differed from that reported, m.p. 183-184 °C (lit.[72] 146-147 °C). The salt **(254a)** was then hydrolyzed using 10% H_2SO_4 in diethyl ether to afford (+)-1-methylene-cyclopropane-(2R,3R)-dicarboxylic acid **(244a)** in 84% yield (lit.,[72] 80%), m.p. 207 °C (lit.,[72] 203-205 °C).

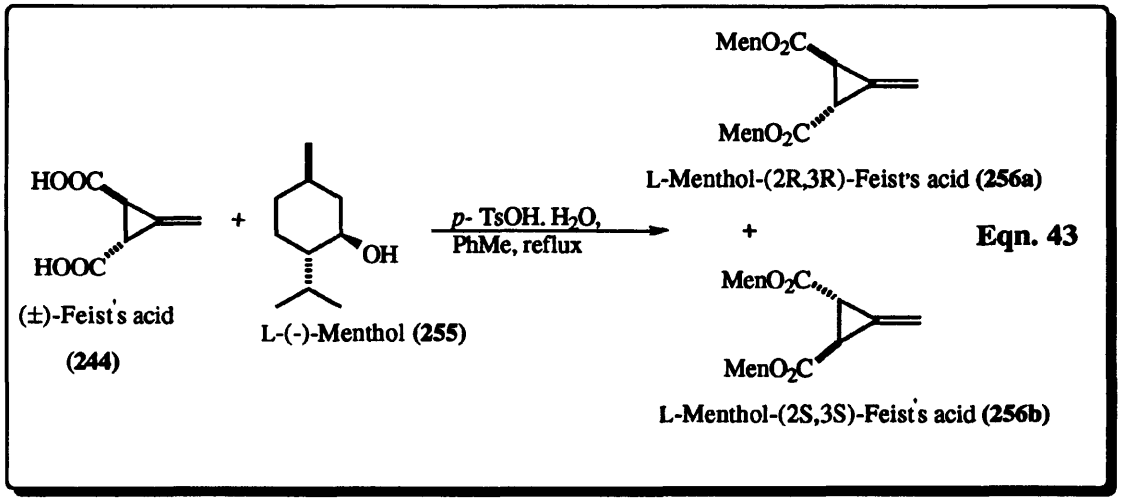


The optical rotation $[\alpha]_{546}^{23}$ $+116.0^0$ was lower than that reported by Doering

($[\alpha]_{546}$ +176.0^0)[72] and if his value is accurate, then the product obtained in our work has an optical purity of only 65%. This procedure has been repeated twice, but no improvement in the optical purity was observed.

(ii) Via L-(-)-Menthol (255)[184]

The unsuccessful outcome of the resolution of (±)-Feist's acid **(244)** by L-(-)-quinine **(89)**, led us to find an alternative route to isolate Fiest's acid **(244)** in high optical purity. The racemic acid **(244)** was treated with 2 equivalents of L-(-)-menthol **(255)** and refluxed in toluene for 48 hours to afford a hygroscopic solid (73% yield), which was a mixture of the two diastereomeric esters **(256a** and **256b)**, as given below in **(Eqn. 43)**.

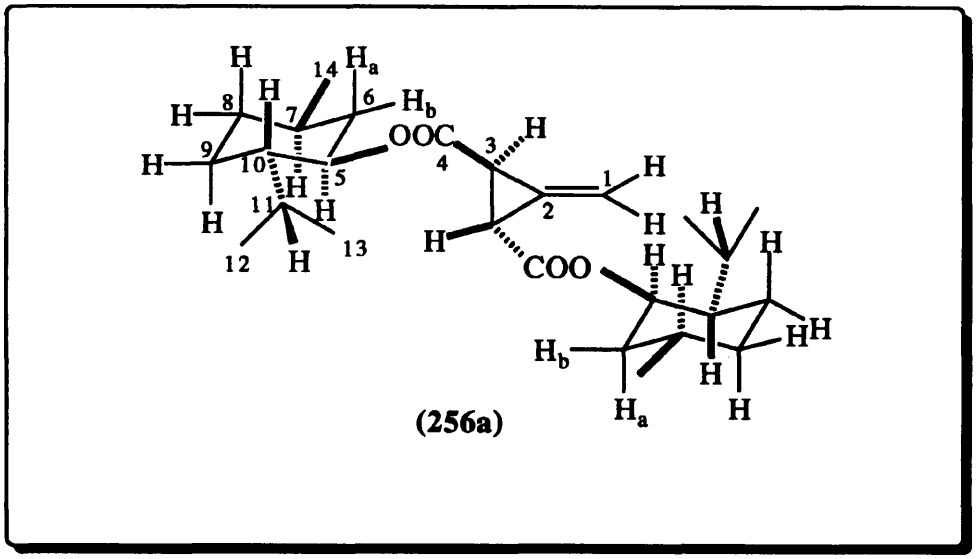


The mixture was then purified repeatedly by column chromatography using (EtOAc-hexane, 1:40) as eluant. Further purification has been carried out by recrystallization from dry methanol to afford a pure crystalline product of dimenthyl (2R,3R)-(-)-1-methylenecyclopropane-2,3-dicarboxylate **(256a)** in moderate yield (59%). The purity was monitored by TLC (EtOAc-hexane, 1:40) and ^{13}C NMR spectroscopy. This ester

(256a) showed an optically rotation of $[\alpha]_D^{25}$ -122° (c 0.47, $CHCl_3$) and was fully characterized by spectroscopic techniques.

Microanalysis and mass spectrometry were in full agreement with the expected molecular formula. In the IR spectrum, the broad OH absorptions at 3000-3700 cm^{-1} of Feist's acid **(244)** and menthol **(255)** were absent, but a strong sharp band at 1730 cm^{-1}, characteristic of the carbonyl group was observed.

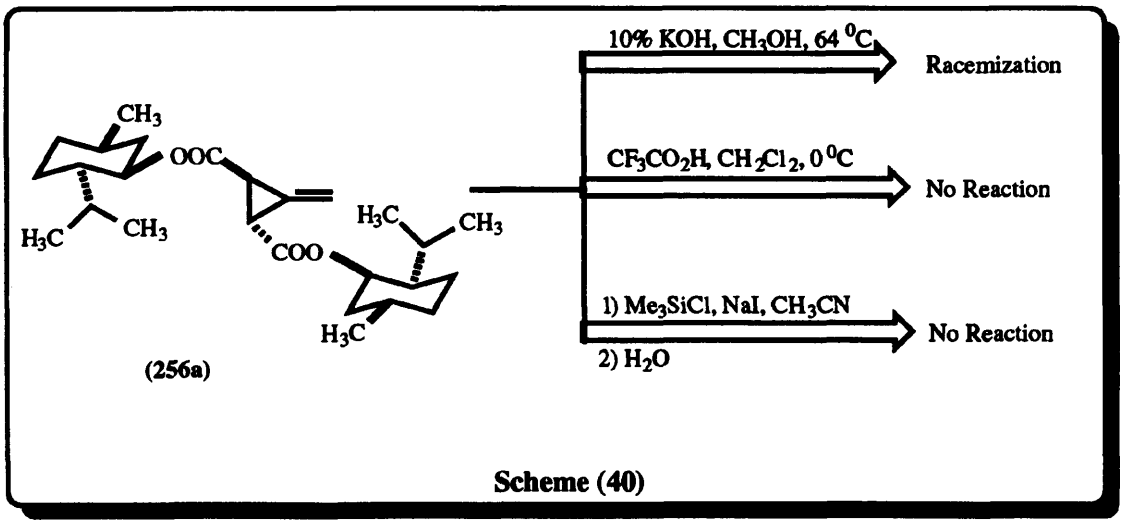
The ^1H NMR spectrum showed the two methyl groups (H_{12} & H_{13}) of the menthol moiety at δ 0.80 ppm as a doublet which coupled with H_{11} at ^2J 6.75 Hz. The other methyl group of the menthol (H_{14}) was observed as a singlet at δ 0.90 ppm. The remainder of the menthol protons (except H_5) appeared as a complex multiplet in the region of δ 0.93 -1.95 ppm with a small coupling constant, ^3J 2.5 Hz. The H_5 proton of the menthol appeared at δ 4.69 ppm and was seen as a doublet of triplets due to coupling to (H_{10}), H_a and H_b with ^3J 11 Hz and ^3J 4.5 Hz respectively. The proton H_3 on the Feist's acid moiety was observed as a triplet at δ 2.85 ppm. The two olefinic protons (H_1) appeared as a complex multiplet at δ 5.69 ppm.



(256a)

The ^{13}C NMR spectrum showed the expected 14 peaks, including the characteristic band at δ 163.7 ppm for the carbonyl group.

An attempt was made to hydrolyze the pure ester **(256a)** using aqueous potassium hydroxide solution (10% w/w KOH) but unfortunately racemization of the ester took place via the enolate, **scheme (40).**

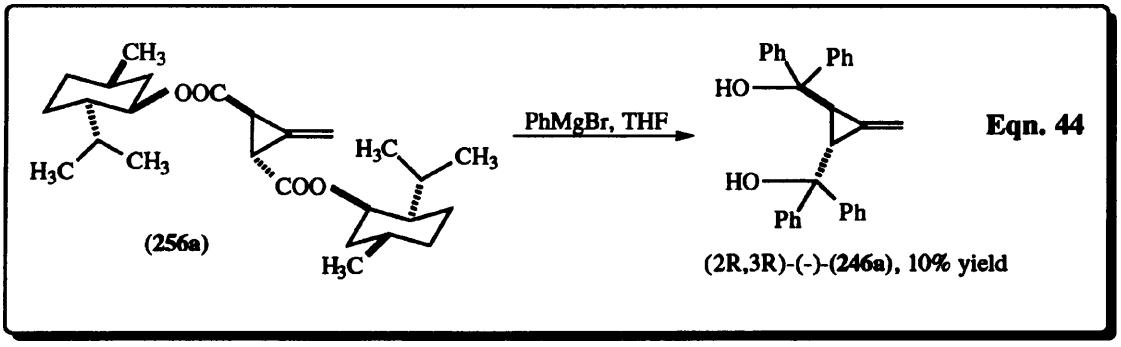


Scheme (40)

Another attempt was carried out using acidic conditions [using either trifluoroacetic acid

(TFA)[185] or trimethylsilylchloride[186]]. However, no reaction occurred in either case. An attempt to reduce the ester **(256a)**, using $LiAlH_4$ also failed.

It was decided to react the ester **(256a)** directly with a Grignard reagent (PhMgBr) in THF to give the tetraphenyl diol **(246a)**, but a low yield (5-10%) was obtained **(Eqn. 44)**



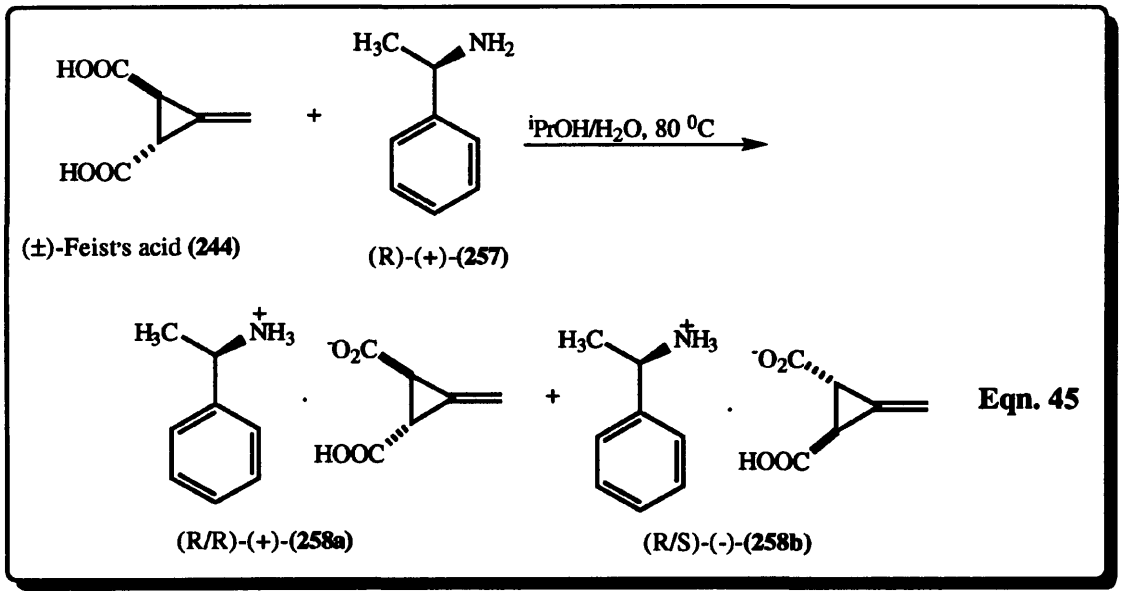
Eqn. 44

These results suggest that the menthyl group is too bulky and hindered attack at the ester carbonyl. These unsuccessful efforts provide evidence for this steric hinderance at the ester carbonyl.

Failure to isolate Feist's acid **(244)** in high optical purity was an unexpected set back which took up a great deal of time (~ six months) and meant that furher stocks of the starting material had to be re-prepared.

(iii) Via (R)-(+)-α-methylbenzylamine (257)[169]

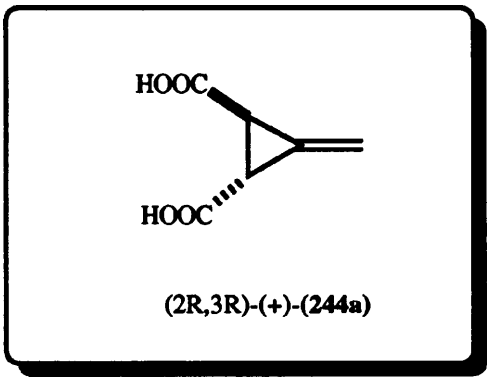
The last attempt to resolve Feist's acid **(244)** was by reaction of the racemate with one equivalent of (R)-(+)-α-methylbenzylamine **(257)** contained in a mixture of iso-propanol and water (9:1). This gave the crude ammonium salt containing two diastereomers **(258a** and **258b)** in good yield (89%) (lit.,[169] 89%), **(Eqn. 45).**



Eqn. 45

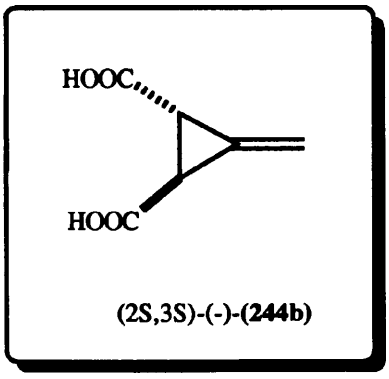
Fractional recrystallization from iso-propanol/water (3:1) was carried out to afford (R)-α-methylbenzylammonium salt of (2R,3R)-(+)-1-methylenecyclopropane-2,3-dicarboxylic acid (1:1) **(258a)** in 73% yield (lit.,[169] 71%). The melting points and optical rotations were close to those reported by Godfrey [169] m.p. 221-224° (lit.,[169] 218-223 °C); $[\alpha]_D^{25}$ + 102.46° (H_2O), [lit.,[169] $[\alpha]_{546}$ + 112.6° $[\alpha]_D^{25}$ +94.7°(H_2O)]. Microanalysis and mass spectra were in agreement with the (1:1) salt **(258a).**

The diastereomer salt **(258a)** was then hydrolyzed using 1N HCl in ethyl acetate to afford the pure free acid (2R,3R)-(+)-Feist's acid **(244a)** as a white solid in high yield 92%. The (R)-enantiomer obtained **(244a)** was reasonably pure and gave an optical rotation close to that reported, $[\alpha]_{546}^{23}$ +155.5° (lit.,[72] $[\alpha]_{546}$ + 176.0°; c 0.76; EtOH).



(2R,3R)-(+)-(**244a**)

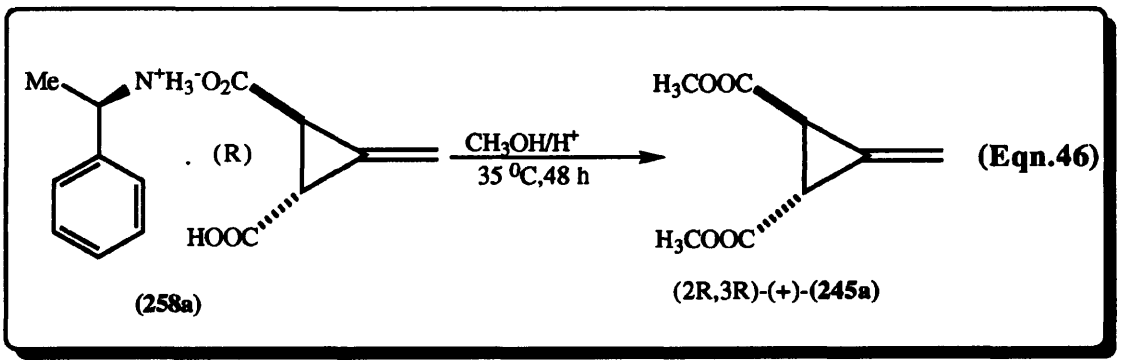
The mother liquor obtained from the resolution of (2R,3R)-Feist's acid **(244a)** was hydrolyzed by 1N HCl to afford the other enantiomer (2S,3S)-(-)-Feist's acid **(244b)** in high yield (96%). Measurement of its optical rotation ($[\alpha]_{546}^{23}$ -95.3°) showed that it had a moderate optical purity. (lit.,[169] $[\alpha]_{546}$ - 131.3° ; c 0.81; EtOH).



(2S,3S)-(-)-(**244b**)

II.5.4 Preparation of pure enantiomers of dimethyl 1-methylenecyclo-propane-2,3-dicarboxylate (245)

When the salt (R,R)-(+)- (**258a**) was reacted directly with methanol in the presence of a catalytic amount of the concentrated sulfuric acid at 35 °C for 48 hours the dimethyl ester (**245a**) was obtained in 71% yield as a single enantiomer as shown in **(Eqn. 46)**.

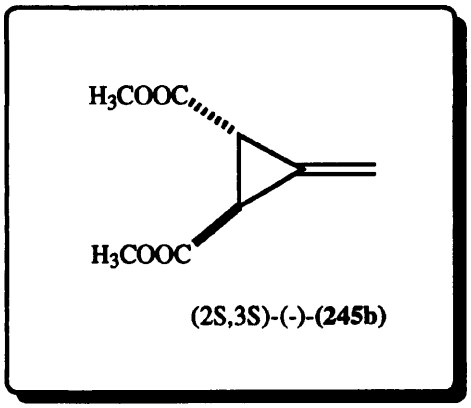


But when the free acid (2R,3R)-(+) (**244a**) was employed instead of the salt (**258a**) the dimethyl ester (**245a**) was obtained as a crystalline product in good yield (89%) in a shorter period of time (24 h). This compound was shown to have a rotation of $[\alpha]_D^{25}$ +123.3° (c 0.76, CCl_4) which is close to the reported value (lit.,[169] $[\alpha]_D^{25}$ +124.8°, (c 0.76, CCl_4).

The IR spectrum showed that the broad band for the carboxylic hydroxy group at 3500-2500 cm^{-1} was no longer present. This is indicative of ester formation.

The ^1H NMR spectrum showed a singlet at δ 3.72 ppm corresponding to two methyl groups confirming that the esterification had taken place. In addition, a second order triplet for the olefinic and ring protons appeared at δ 5.60 and 2.82 ppm respectively. All the other data were consistent with the suggested structure (**245a**).

By following the same method, the (2S,3S)-(-)-dimethyl ester **(245b)** was prepared from the analogous (2S,3S)-(-)-Feist's acid **(244b)** in good yield (85%).

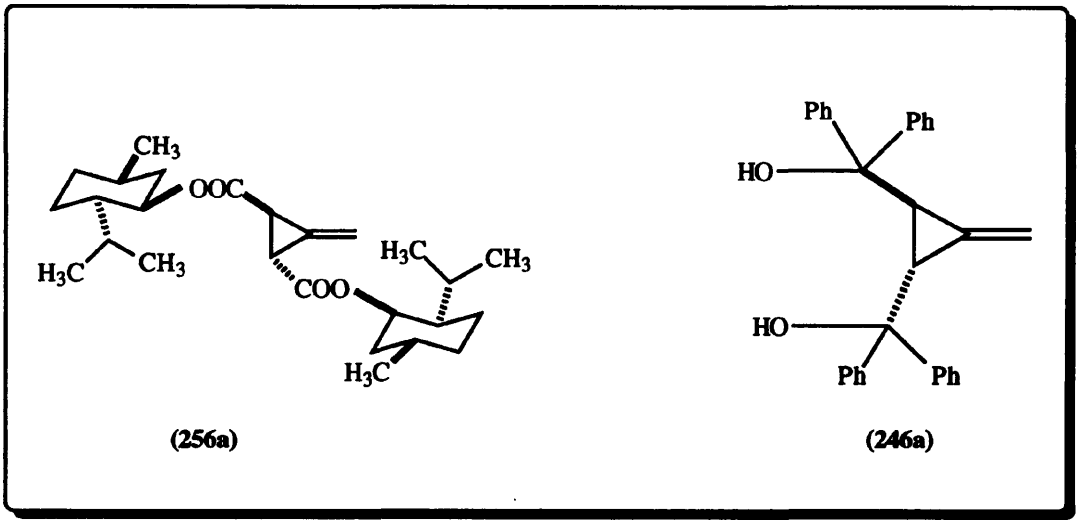


(2S,3S)-(-)-**(245b)**

However, as the acid starting material was not enantiomerically pure the optical purity was only *ca.* 57%, ($[\alpha]_D^{25}$ -70.8°, c 0.83, CCl_4).

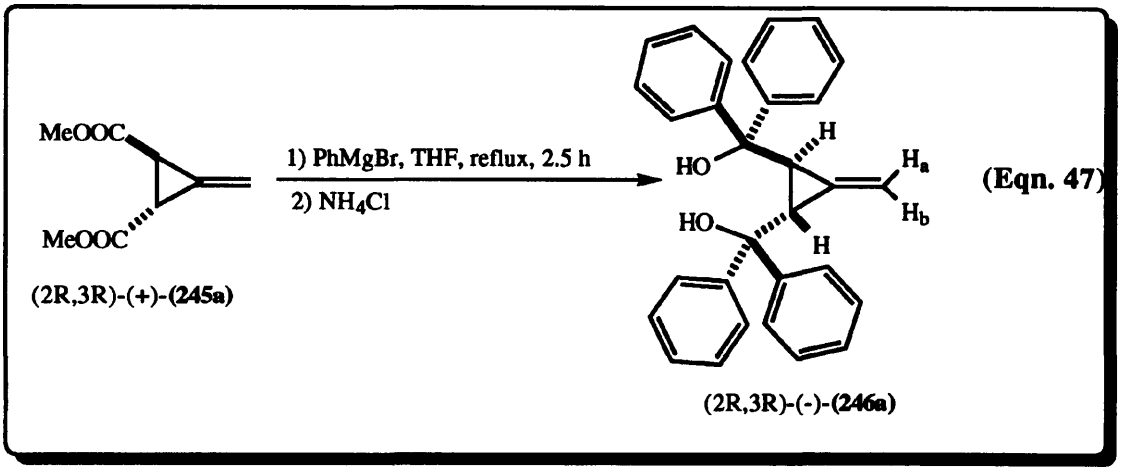
II.5.5 Synthetic Progress Toward the Desired Diol Ligands Based on Feist's Acid.

It has been mentioned that attempts to prepare the enantiomerically pure novel ligand **(246a)** by reaction of the menthol derivative **(256a)** of Feist's acid with phenylmagnesium bromide gave only a poor yield (*ca.* 5-10%) of the desired diol ligand **(246a)**.



(256a) **(246a)**

This was attributed to steric hinderance due to the menthol group. Consequently, the reaction was repeated on the dimethyl ester **(245a)** using diethyl ether to afford (2R,3R)-(-)-bis-(diphenylmethanol)-1-methylenecyclopropane **(246a)**. The crude product was decolourized and recrystallized several times from diethyl ether to give the desired diol **(246a)** as a pure white, crystalline product in 30% yield. When this reaction was repeated in THF and chromatographed (EtOAc-hexane, 1:4 as eluant) followed by recrystallization from a mixture of ethyl acetate and hexane (1:1) the yield improved to 58% **(Eqn. 47)**.



(2R,3R)-(+)-(245a)

(2R,3R)-(-)-(246a)

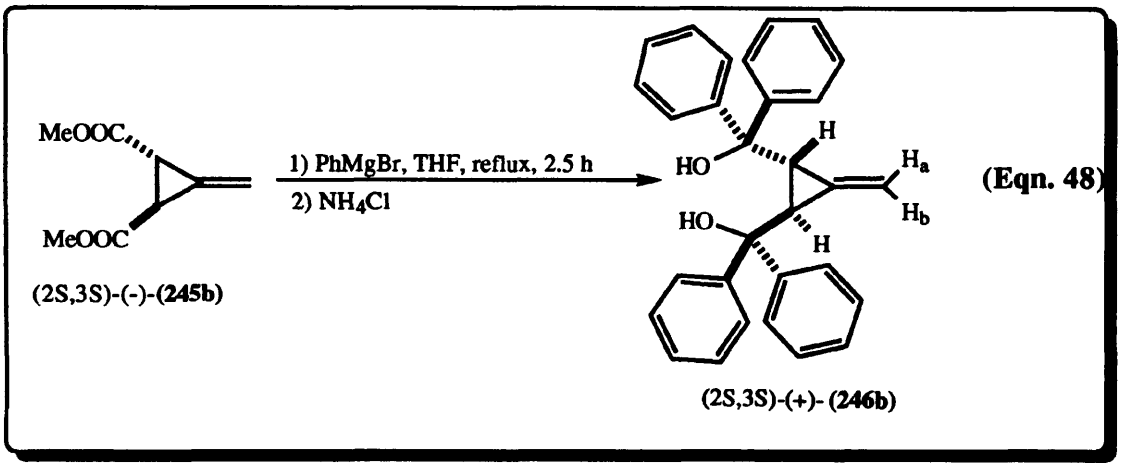
(Eqn. 47)

The product **(246a)** showed an optical rotation of $[\alpha]_D^{25}$ -276.0° (c 0.25, CCl_4), with the opposite sign to that of the starting dimethyl ester **(245a)**. Microanalysis and mass spectroscopic data were in full agreement with the assigned structure.

The IR spectrum showed a strong band at 3600-3100 cm^{-1} confirming the presence of a hydroxy group, and a band at 3000 cm^{-1} representing the aromatic C-H, stretching vibrations. The ester carbonyl group (at 1740 cm^{-1}) was no longer present in the spectrum.

The ^1H NMR spectrum showed complex multiplets for both the olefinic and ring protons at δ 5.43 and δ 2.38 ppm respectively, and a singlet at δ 1.78 ppm for the CH protons. The aromatic protons appeared as a complex multiplet in the range δ 7.08-7.22 ppm.

The other enantiomer **(246b)** was also prepared in 51% yield from the reaction of (2S,3S)-(-)-dimethyl ester **(245b)** with the Grignard reagent (PhMgBr) in THF, but, as expected, the purity was low, $[\alpha]_D^{25}$ +50° (c 0.25, CCl_4), **(Eqn. 48)**



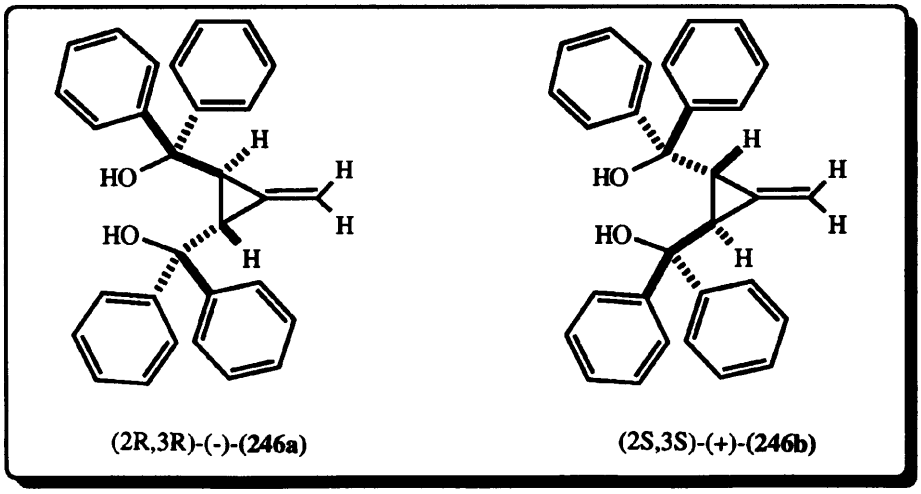
(Eqn. 48)

All data for the novel **(246b)** were in full agreement with the (2R,3R)-(-)-diol **(246a)**.

II.5.6 Enantioselective Addition of Diethylzinc to Benzaldehyde Catalyzed by Chiral Diol Ligands and Modified by Titanium Lewis Acids.

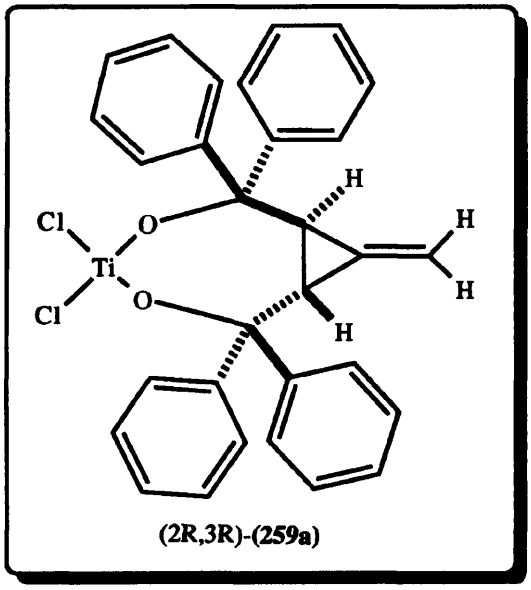
It has been noted previously that titanium complexes derived from chiral diol ligands are highly enantioselective catalysts in various asymmetric induction reactions, particularly in the enantioselective addition of dialkylzincs to aldehydes.[18,149] These titanate complexes can be used in both stoichiometric or catalytic amounts. In many cases, formation of the complex is achieved by mixing a diol with $TiCl_4$ in a solvent (e.g. dichloromehane, diethyl ether) and the resulting solution is used without isolation or identification of the species formed.[54,55] It is found that the enantioselectivities and the reactivities of these diethylzinc addition reactions are dependent on the donor-acceptor properties of the solvent used.[76,149]

In our work we have examined the efficiency of the two enantiomers (2R,3R)-(-)-**(246a)** and (2S,3S)-(+)-**(246b)** of 2,3-bis(diphenylmethanol)-1-methylenecyclopropane-**(246)** catalysts in the enantioselective addition of diethylzinc to aldehydes in the presence of titanium Lewis acids [e.g. $TiCl_4$, $Ti(^iOPr)_4$].



(2R,3R)-(-)-**(246a)** (2S,3S)-(+)-**(246b)**

The pure (2R,3R)-(-)-diol ligand **(246a)** was reacted with n-butyl lithium in diethyl ether, followed by addition of a solution of $TiCl_4$ (1M, 1.5 equivalent) in dichloromethane. The reaction was carried out under an inert atmosphere of argon at room temperature and a red solution resulted. This was assumed to be the titanium dichloride complex of ligand **(246a)**. TLC (hexane-EtOAc, 4:1) showed no starting material was present indicating that the titanium complex **(259a)** was formed. The stock solution in dichloromethane was used immediately without isolation of the titanium(IV) complex **(259a)**.

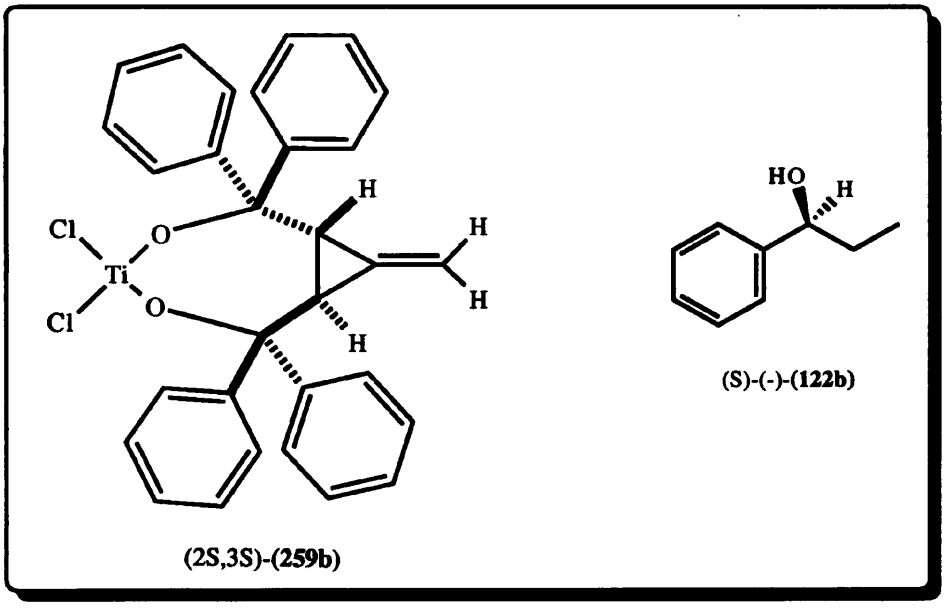


(2R,3R)-(259a)

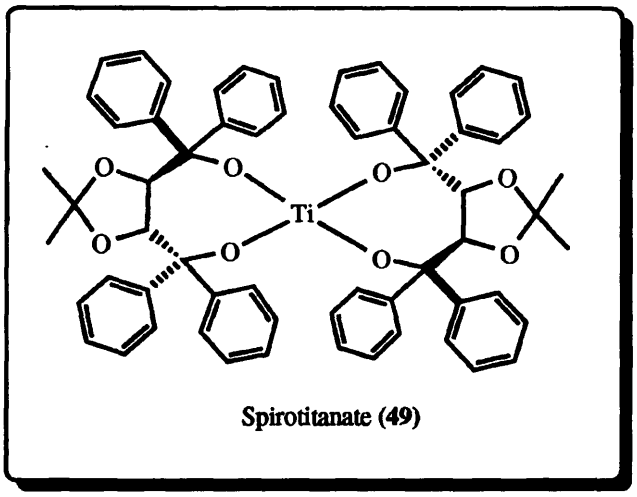
The red stock solution of the chiral titanium complex **(259a)** was mixed with benzaldehyde and diethylzinc (1.1M, 2 equiv.) in toluene at room temperature under an inert atmosphere of argon for 48 hours. TLC showed that the benzaldehyde was still present and the reaction was allowed to stir further for 24 hours, but benzaldehyde was still observed by TLC. After the standard work up the product mixture was separated by column chromatography. One fraction was identified as the titanium complex **(259a)**, the two other fractions isolated were a mixture of benzaldehyde and some impurities. These slight

impurities were removed by Kügelröhr bulb-to-bulb distillation under reduced pressure to give eventually a 70% recovery of benzaldehyde. No chiral alcohol was obtained.

When the chiral titanium complex **(259b)** of the partially resolved enantiomeric (2S,3S)-(+)-diol ligand **(246b)** was prepared following the same procedure and used as a catalyst for the diethylzinc addition to benzaldehyde, (S)-1-phenylpropanol **(122b)** was obtained in low yield (31%) and only 34% **e.e.**, $[\alpha]_D^{25}$ -15.3^0, c 1.8 $CHCl_3$, (lit.,[163] $[\alpha]_D^{25}$ -45.45^0, c 5.5, $CHCl_3$).

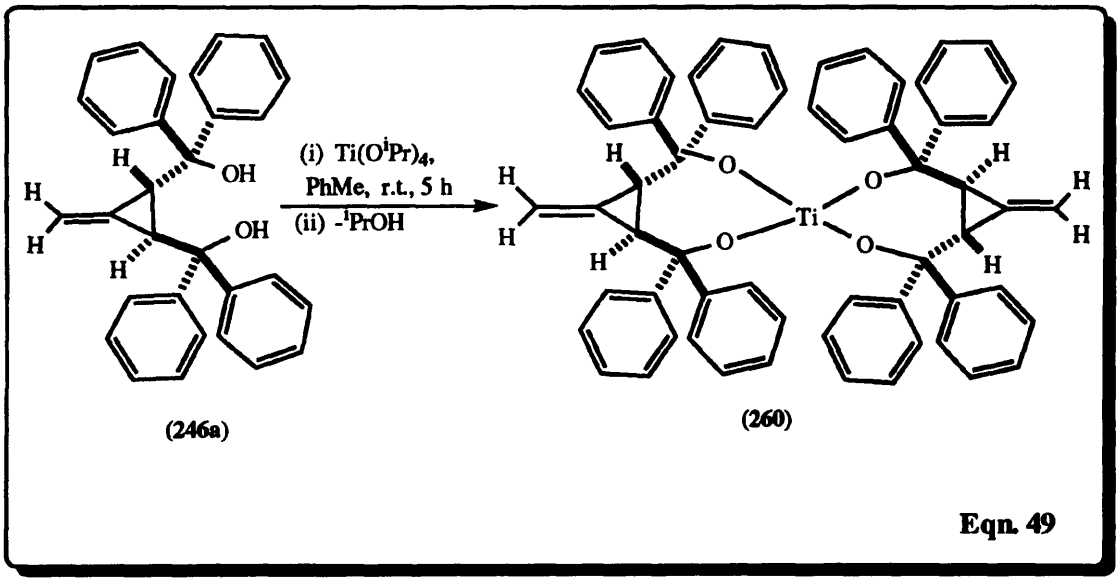


In a second attempt titanium tetraisopropoxide $Ti(^iOPr)_4$ was use instead of titanium tetrachloride. Thus, the chiral orthotitanate complex **(260)** was prepared. This has similarities to the spirotitanate complex **(49)** prepared by Seebach and coworkers[27,34-37,40] and found to be highly effective for the addition of diethylzinc to benzaldehyde.



Spirotitanate (49)

The reaction of ligand (**246a**) with titanium tetraisopropoxide in toluene was carried out by azeotropic removal of isopropanol under reduced pressure (**Eqn. 49**).



(246a) (260)

Eqn. 49

The titanium complex (**260**) was isolated as a white solid in moderate yield (60%). Microanalysis (except the Ti percentage which was not determined due to the lack of material), and mass spectrum (FAB) confirmed that the product had the molecular formula $(C_{30}H_{24}O_2)_2Ti$.

The IR spectrum showed that the strong broad band of the hydroxy group at 3500 cm^{-1} was not present, indicating a reaction had taken place. The ^{1}H NMR spectrum showed that the singlet peak at δ 1.78 ppm which characterized the hydroxy group was no longer present. The ^{13}C NMR spectrum showed the required 12 peaks of the symmetrical titanium complex **(260)**.

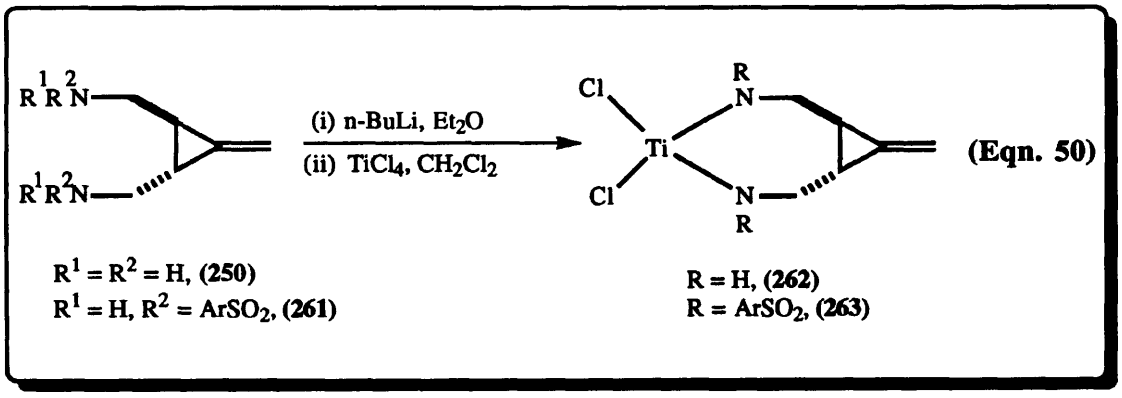
Benzaldehyde was caused to react with diethylzinc (2.0 equiv.) in the presence of the chiral titanate complex **(260)** in toluene at room temperature under an inert atmosphere of argon for 24 hours. TLC (hexane-EtOAc, 5:1) showed that no reaction occurred. Consequently, benzaaldehyde (80%) and the complex **(260)** were recovered.

The results confirmed that titanium complexes based on Fiest's acid derivatives could be formed. However, these complexes, particularly those derived from (2R,3R)-diol **(246a)**, were of limited value.

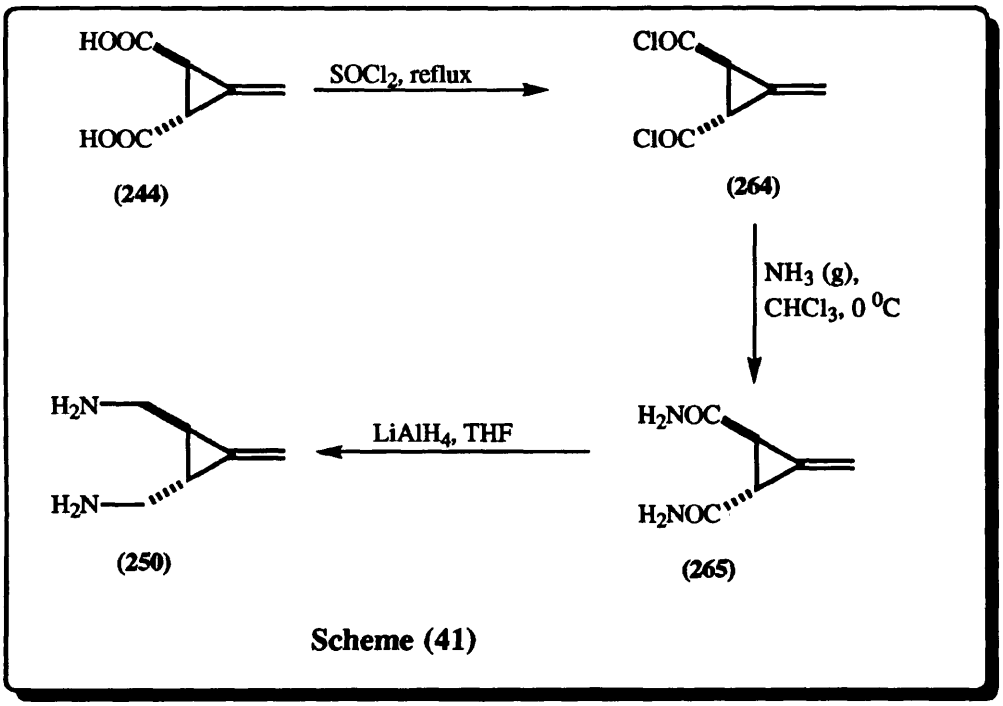
We believe that the problem could be due to the highly strained cyclopropane ring which has less flexibility than a five-membered isopropylidene ring.

II.5.7 Synthesis Progress Towards the Desired Diamine Based on Feist's Acid

Chiral diamines have been utilized with some success in the presence of rhodium complexes (e.g. $[RhCl(cod)]_2$) for the asymmetric hydrogenation of alkenes.[10,55] but they are hard ligand compared with phosphines. They have also been used in the presence of a Lewis acid, such as $TiCl_4$, to catalyze carbon-carbon bond forming reactions, such as the addition of diethylzinc to the aromatic aldehydes[149,87-189]. For this reason, an attempt has been made to form chiral diamine ligands of the type **(250)** and **(261)**[149,188], and to complex them with $TiCl_4$ to provide derivatives, such as **(262** and **263)**, **(Eqn. 50)**.



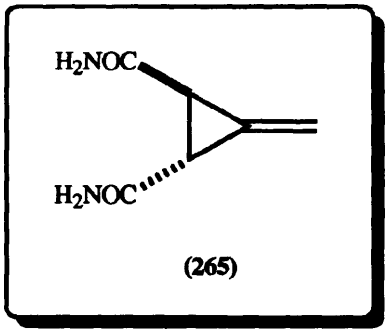
In order to prepare the diamine **(250)** the following synthetic **scheme (41)** was proposed.



Scheme (41)

Feist's acid (**244**) was refluxed with thionyl chloride for 1.5 hour according to the procedure reported by Blomquist and Longone[166] to afford the diacid chloride (**264**) in 79% yield (lit.,[166] 93%) as a dark green oil. The IR spectrum showed a strong band at 1800 cm^{-1} representing the carbonyl of the acid chloride, and the strong broad OH band at 3500 cm^{-1} for the carboxylic acid was no longer present in the spectrum. The crude acid chloride (**264**) is extremely hygroscopic and is treated immediately with ammonia gas in chloroform at 0 °C for 1.5 hour to afford the diamide (**265**) as an off-white solid in almost quantitative yield, m.p. 230 °C. The molecular formula was confirmed by mass spectrometry and elemental analysis.

The IR spectrum showed that carbonyl group absorption was shifted from 1800 cm^{-1} to 1700 cm^{-1} confirming that conversion to the amide (**265**) had taken place. Two other weak bands appeared at 3370 cm^{-1} and 3310 cm^{-1} representing the stretching vibrations of the NH_2 group of the amide.

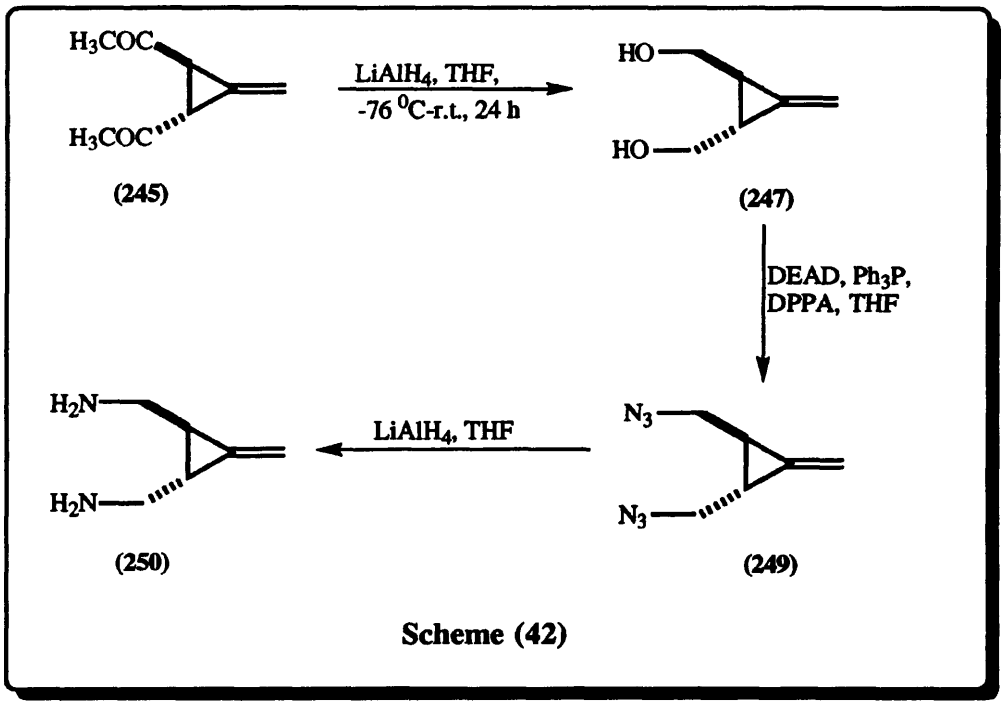


(265)

The ^{1}H NMR spectrum showed a singlet at δ 7.70 ppm representing the NH_2 group of the amide. The ring and olefinic protons appeared as complex multiplets at δ 2.40 and 5.35 ppm respectively. The ^{13}C NMR showed the expected four peaks of the C_2 -symmetrical molecule.

Reduction of **(265)** to the diamine **(250)** was attempted, thus, the diamide **(265)** as a suspension in THF, was refluxed with lithium aluminium hydride for 24 hours and the reaction was monitored by IR spectroscopy. No reaction was observed during this period and even after a further 30 hours at reflux there was no evidence that the reaction had taken place. This lack of reaction was attributed to the low solubility in the solvent. Attempts to find a suitable solvent were unsuccessful, the amide being insoluble in all common organic solvents.

Thus, it was decided to use a different route to the desired diamine **(250)** using Mitsonobu methodology[190-192] starting from the dimethyl ester **(245)** as shown in **scheme (42)**.



Scheme (42)

The dimethyl ester (**245**) was reduced by lithium aluminium hydride ($LiAlH_4$) in dry THF at -76 °C to give the diol (**247**) as an extremely hygroscopic white solid in 82% yield (lit.,[167] 85%); m.p. 39-40 °C (lit.,[167] 38-39 °C); $[\alpha]_D^{25}$ -108.5° (c o.24, CCl_4) [lit.,[167] $[\alpha]_D^{25}$ -116.3° (c 1.75, $CHCl_3$)]. The IR spectrum showed a strong broad band at 3300 cm^{-1} for the hydroxyl stretching vibration.

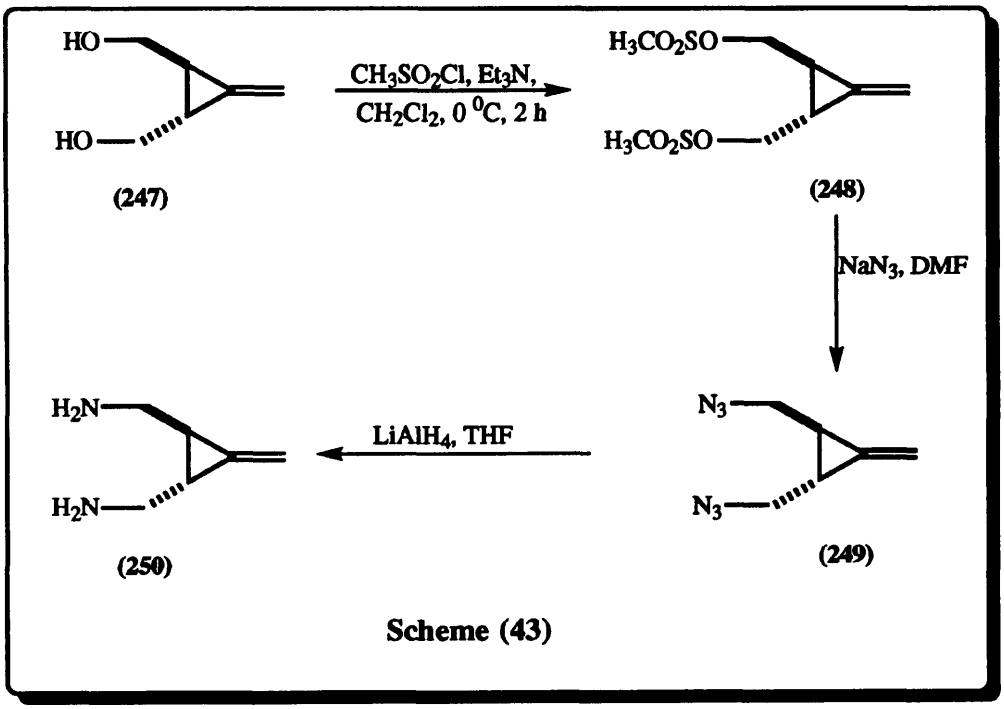
The olefinic protons in the ^1H NMR spectrum again appeared as the characteristic second order triplets at δ 5.45 ppm, while the ring protons now become multiplets due to additional coupling to the neighbouring methylene groups at C-2. The methylene groups had a distinctive doublet of doublets ABX splitting pattern at δ 3.20 and 3.90 ppm. All analytical data supported the structure.

The alcohol (**247**) was reacted with 2.2 equivalents of diphenylphosphoryl azide (DPPA) in the presence of 2.2 equivalents of diethyl azodicarboxylate (DEAD) and

triphenylphosphine in THF. After 15 hours at room temperature[192], TLC (hexane-EtOAc, 1:1) showed no reaction had occurred. The mixture was then refluxed for 7 hours

when TLC showed that no starting material was present, but the reaction mixture showed at least five closely running products. Attempts to separate these by chromatography were unsuccessful.

In a final effort to obtain the diamine **(250)** the classical synthetic **scheme (43)** was followed.



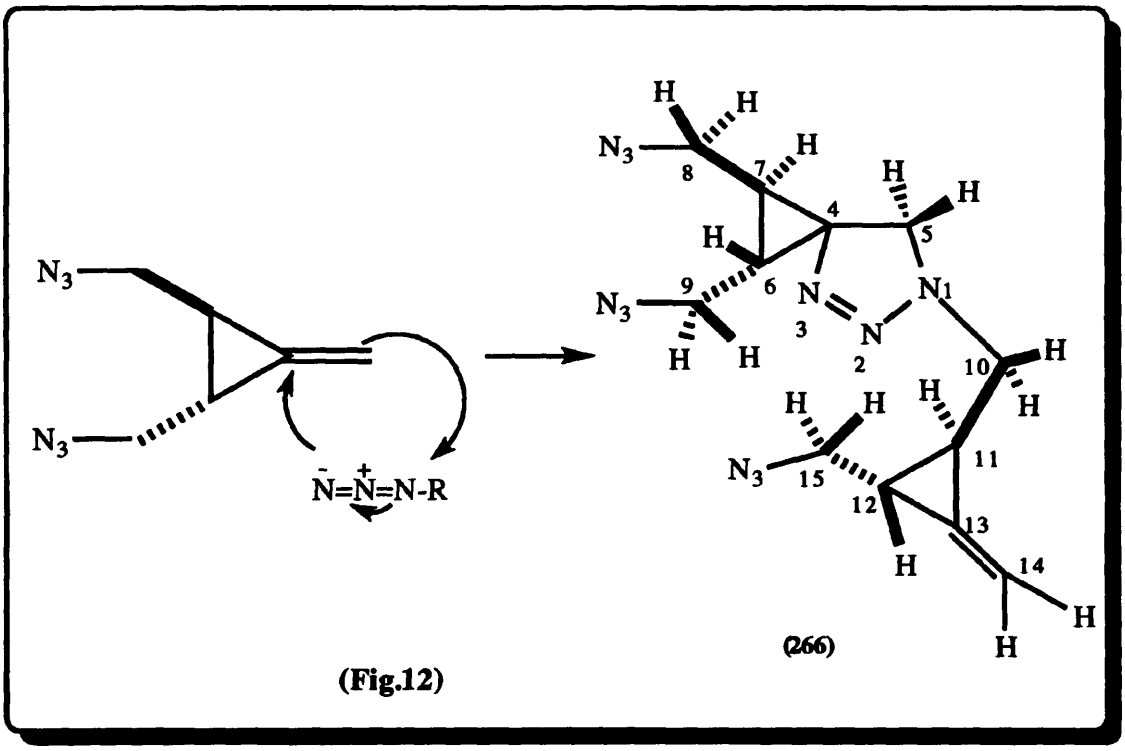
Scheme (43)

The diol **(247)** was treated with methanesulfonyl chloride (3.0 equiv.) in dry triethylamine and dichloromethane at 0 °C for 2 hours to afford the dimesylate **(248)** in an excellent yield of 96%; m.p. 70-71 ^{0}C, with no change in the sign of the optical rotation

$[[\alpha]_D^{25}$ -21.63^0 (c 1.55^0, CCl_4].

Microanalysis and mass spectrum (FAB) data were in full agreement with the assigned structure. The IR spectrum showed that the strong broad hydroxy band was no longer present and showed two strong bands at 1380 cm^{-1} and 1230 cm^{-1} (v SO_2) for the mesylate groups. The ^1H NMR spectrum showed no longer had a signal at δ 2.85 ppm for the OH proton, but showed a new singlet (6H) at δ 3.00 ppm for the two methyl groups of the mesylate moiety. The olefinic and ring protons were again observed as multiplets at δ 1.90 and 5.60 ppm respectively, and the non-equivalent hydrogens (H_a and H_b) of the methylene groups were observed at δ 4.00 and 4.30 ppm respectively as a doublet of doublets. The ^{13}C NMR spectrum showed the expected 5 signals.

The dimesylate (**248**) was then reacted with sodium azide in DMF at 100 °C for 10 hours. These vigorous conditions were necessary due to the low reactivity of NaN_3.[158] Somewhat unexpectedly compound (**266**) was obtained as the major product in 62% yield **(Fig.12)**.



(Fig.12)

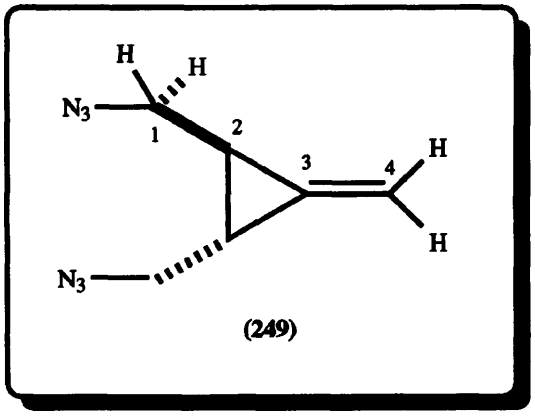
It is clear that this arose by the expected S_N2 displacement of the mesylate groups by the azide, but under the vigorous reaction conditions employed the azide group of one molecule is undergoing a 1,3-dipolar addition across the double bond of the second molecule to give the interesting 4-spirotriazole (**266**) rather than the C_2-symmetrical diazide (**249**).

The proposed structure (**266**) was confirmed by mass spectroscopy which showed an $(M+H)^+$ peak at the expected value of 329 with 100% intensity. Additionally, the ^1H NMR spectrum showed the one of the 4-ring protons as a quartet at δ 1.46 (*J* 14 Hz) and the other 3-ring protons as multiplets at δ 1.68 (2H) and 1.96 (1H) ppm. The 10 aliphatic protons for the diastereotopic methylene groups in the region of δ 3.43 - 3.70 ppm as complicated multiplets. The remaining two olefinic protons were also observed as a multiplet at δ 5.61 ppm.

The 4-spirotriazole (**266**) was also confirmed by ^{13}C NMR (Dept 135°) spectroscopy which showed five methylene carbon atoms at δ_C 20.7 (C-8), 21.0 (C-9), 27.2 (C-15), 29.8 (C-10) and 30.4 (C-5) ppm. The four ring carbon atoms appeared at δ_C 47.8 (C-7), 48.0 (C-6), 50.0 (C-11) and 52.7 (C-12) ppm. The tetra substituted carbon atom (C-4) was observed at δ 65.1 ppm. While the terminal olefinic carbon atom (C-14) appeared at δ 107.5 ppm the internal olefinic carbon atom (C-13 appeared down field at δ 133.9 ppm.

To avoid this 1,3-dipolar addition the reaction was repeated under milder conditions (60 °C, 6 h) and the desired diazide (**249**) was obtained in 84% yield as a yellow oil.

IR spectroscopy showed a strong sharp band at 2110 cm^{-1} confirming the presence of the azide group. The diazide (**249**) was purified by dry column flash chromatography and was pure by TLC and spectroscopic analysis, but a satisfactory microanalysis could not be obtained despite repeated re-purification. An accurate RMM measurement of 165.0699 (100% intensity) was obtained by mass spectrometry.



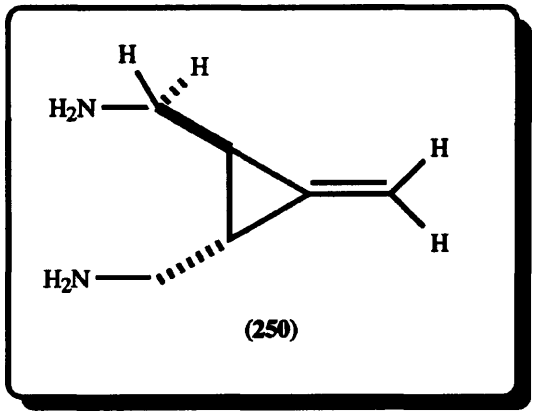
(**249**)

The ^1H NMR spectrum showed the ring protons as multiplets at δ 1.75 and the two

methylene groups as doublets ($^3J_{1,2}$ 6.5 Hz) at δ 3.25 ppm. The olefinic protons were seen as a clear triplet (^2J 4 Hz) at δ 5.65 ppm.

The ^{13}C NMR showed four peaks at δ_C 21.1 (C-1), 52.7 (C-2), 107.9 (C-4) and 133.0 (C-3) ppm as expected for this C_2-symmetrical compound.

The diazide **(249)** was hydrogenated in the presence of Lindlar catalyst (5% $Pd/CaCO_3$) in ethanol to afford the crude, unstable, diamine **(250)** as an oily product in moderate yield (*ca.* 60%). The IR spectrum showed the expected stretching vibration at 3320 w and 3260 m for the NH_2 groups. The strong band at 2110 cm^{-1} for the azide group was no longer present.

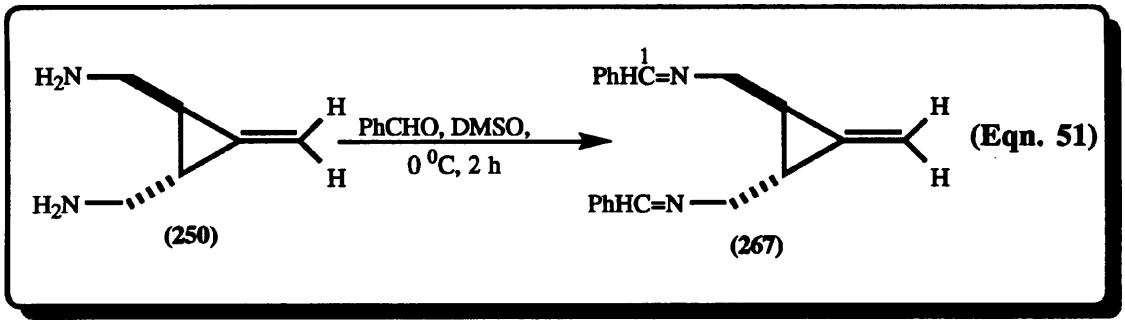


(250)

The ^1H NMR spectrum showed a broad singlet for the amine protons at δ 8.33 ppm (~ 4H) confirming that the azide groups had been hydrogenated. The amine is not very stable and all attempts to purify the crude product further by chromatography failed and led to reduce amounts of the amine. An attempt to convert the diamine **(250)** to its hydrochloride salt was also unsuccessful.

The amount of diamine **(250)** available was now small. An attempt was made to

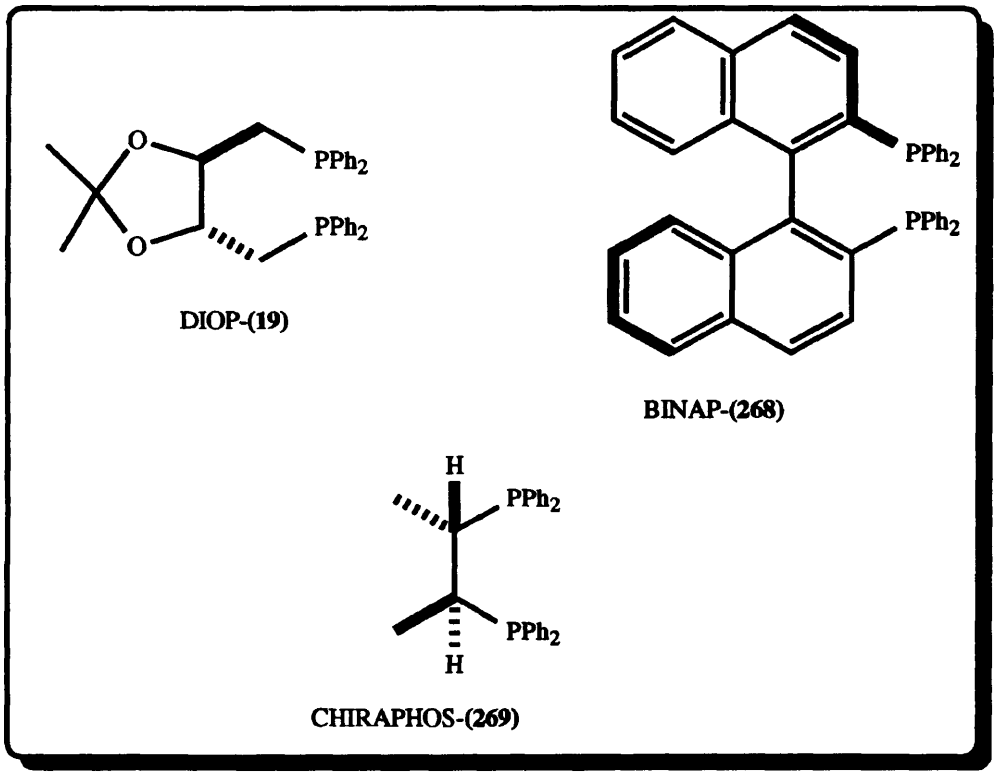
convert (**250**) to an imine by reaction with benzaldehyde[192] in dimethylsulfoxide (DMSO) in the presence of a catalytic amount of concentrated H_2SO_4 at 0 °C. This gave the Schiff base (**267**) as an impure oily product (**Eqn. 51**), but there was insufficient material to make the purification worthwhile.



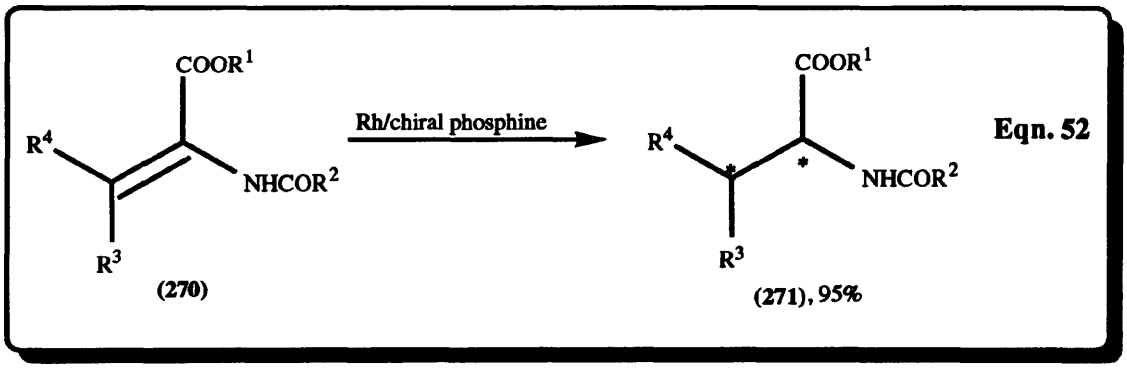
However, by analyzing the ^1H NMR spectrum it was clear the imine product (**267**) was obtained, since the spectrum showed a signal at δ 8.05 ppm indicative of the proton at C-1, and the aromatic protons appeared as a complex multiplet at δ 7.20 ppm. The Schiff base (**267**) appears to be a mixture of the four possible E/Z isomers since the spectrum shows 4 bands in the region of δ 8.05 ppm.

II.5.8 Synthetic Progress Towards the Diphosphine and Dithiol Ligands Based on Feist's Acid.

Asymmetric hydrogenation creating new chiral centres is obviously one of the most fundamental reactions in organic synthesis[10,143,194]. Many of the efficient chiral ligands used are diphosphines possessing a C_2 axis of symmetry [e.g., DIOP **(19)**[15,195], BINAP **(268)**[196] and CHIRAPHOS **(269)**[197]].

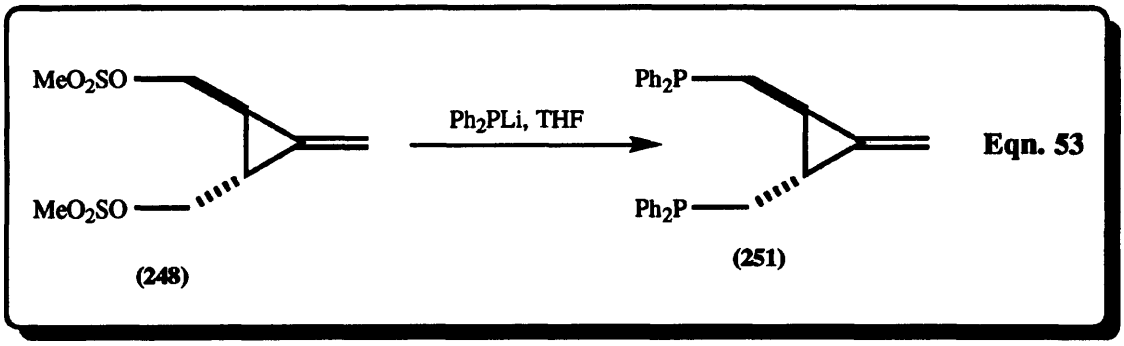


These are excellent catalysts for the asymmetric hydrogenation of α-(acylamino)acrylic acids or esters **(270)**. High enantiomeric excesses (> 95% **e.e.**) have been reported using these diphosphines in the presence of rhodium(I) complexes **(Eqn. 52)**[144,195].



Eqn. 52

It was, therefore, of interest to study the behaviour of the previously unreported diphosphine ligand **(251)** derived from Feist's acid. This can be prepared from the dimesylate **(248)**, **(Eqn. 53)**.

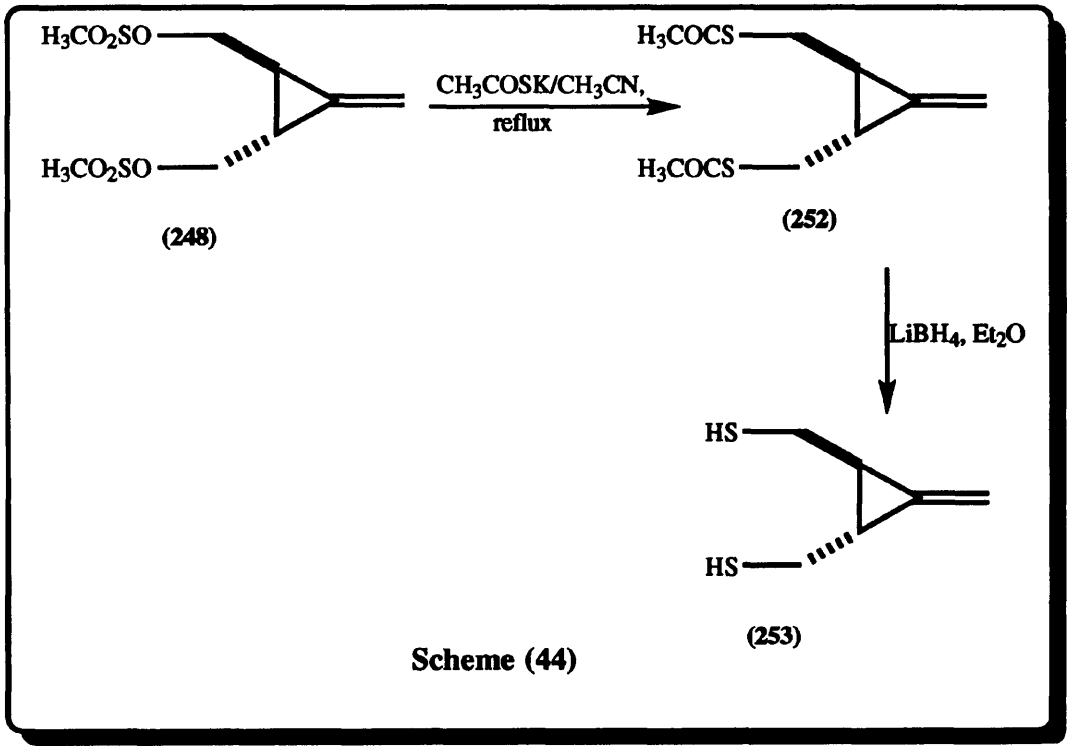


Eqn. 53

Thus, lithium diphenylphosphide was prepared *in situ* from the reaction of freshly-distilled chlorodiphenyl phosphine with finely-cut strips of beaten lithium metal (4.12 equiv.) in THF. The reaction was carried out under anhydrous conditions in an inert atmosphere of argon at room temperature for 20 hours followed by refluxing for an additional 3 hours. An orange-red colour was observed indicative of formation of the desired $LiPPh_2$ compound. This reagent was used immediately in the reaction with the dimesylate **(248)** in THF at -40 ^{0}C under argon, then stirred at room temperature for 20 hours. After work up, ca. 75% of the starting material was recovered plus 25% of the desired diphosphine **(251)** contaminated with an amount of diphenyl phosphine. An attempt to purify the

product by recrystallization under argon was unsuccessful. This reaction was repeated twice but we were unable to obtain the diphosphine **(251)** in a pure form.

However, the dimesylate **(248)** was found to be a good starting material for the preparation of the dithiol ligand **(253)** as shown in **scheme (44)**.



Scheme (44)

The dimesylate **(248)** was allowed to react with potassium thioacetate (2.5 equiv.) in acetonitrile under reflux for 3 hours. The S_N2 substitution of the mesylate group by the thioacetate occurred smoothly and the dithioacetate **(252)** was obtained as a light brown oil in 90% yield.

The microanalysis and mass spectrum (FAB) confirmed that the product has the expected molecular formula $C_{10}H_{14}O_2S_2$.

The ^{1}H NMR spectrum showed that all the characteristic signals were present, but showed a small upfield shift when compared to the chemical shifts of the corresponding peaks in the starting material. While the olefinic protons in the dimesylate **(248)** appeared as a multiplet at δ 5.60 ppm, in the dithioacetate they appeared as a triplet (with a small coupling constant *J* 2 Hz) at δ 5.40 ppm. The ^{13}C NMR spectrum showed the expected six signals including the characteristic band for the carbonyl group at δ 195.1 ppm.

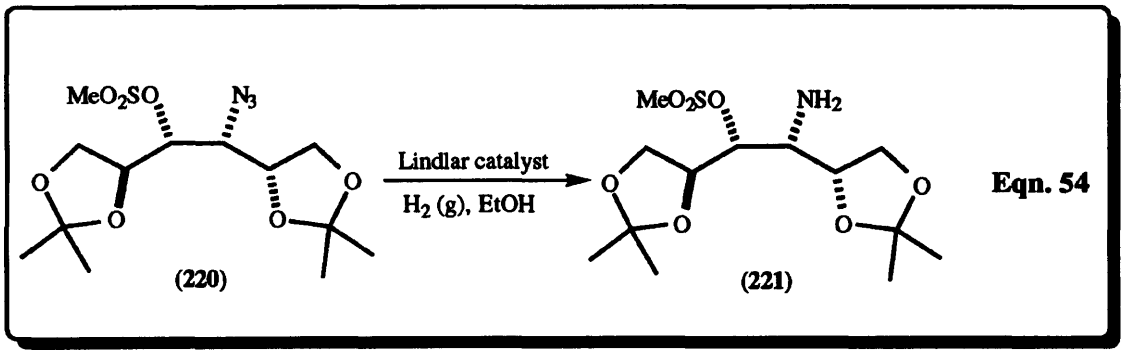
The reduction of the dithioacetate **(252)** was attempted using both lithium aluminium hydride[198] and lithium borohydride in diethyl ether at 0 ^{0}C[199], unfortunately these reactions were unsuccessful and there was insufficient time to explore other reducing agents.

II.5.9 Future Work

A) Based on D-mannitol

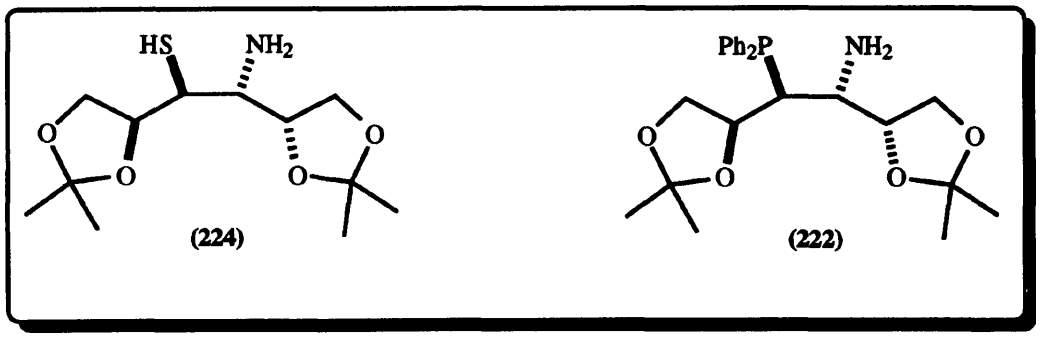
There are several possibilities which could to be explored leading on from the work already carried out on the D-mannitol-based compounds.

(i) In order to obtain the amino mesylate **(221)** on a large scale using Lindlar catalyst (5% $Pd/CaCO_3$) it should be possible to carry out this hydrogenation using a scale of 0.5 g of **(220)** and carrying out 5-10 reactions simultaneously **(Eqn. 54)**.

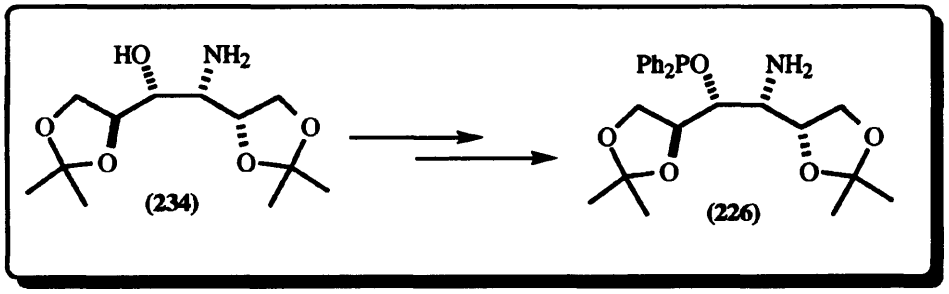


Eqn. 54

Therefore, amino phosphine **(222)** and amino thiol **(224)** ligands can be obtained as outlined at the beginning of the chapter 4, **(scheme 31)**.

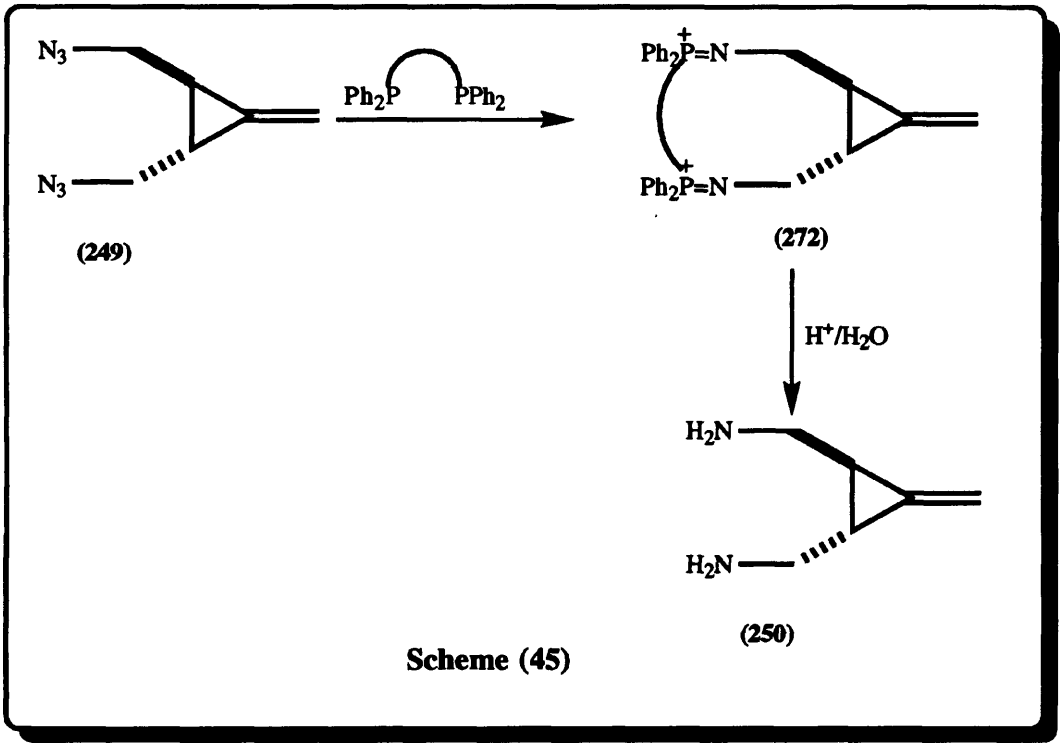


(ii) By suitable protection and deprotection of the amino group of the compound **(234)**, the amino alcohol **(234)** could be converted into a useful aminophosphinite ligand **(226)**.



B) **Feist's acid-based ligands**:

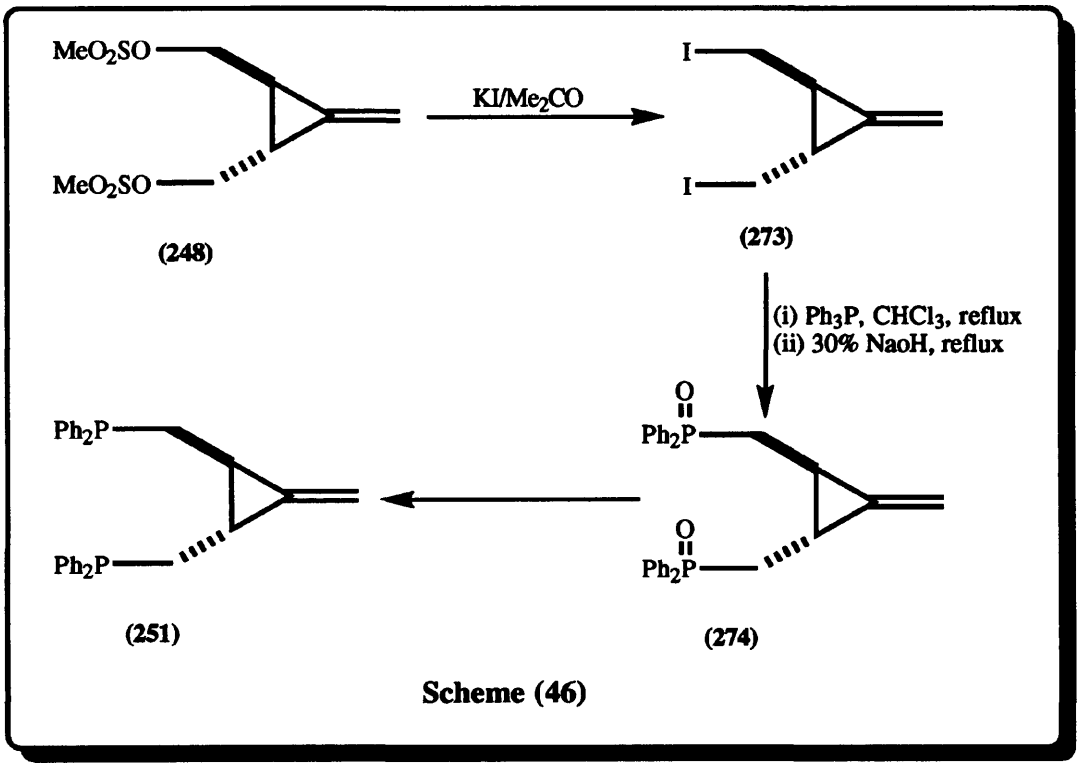
If time had permitted it was intended to explore the possibility of preparing the diamine ligand using an aza-Wittig intermediate[161] as shown in the following **scheme (45)**.



(249) (272) (250)

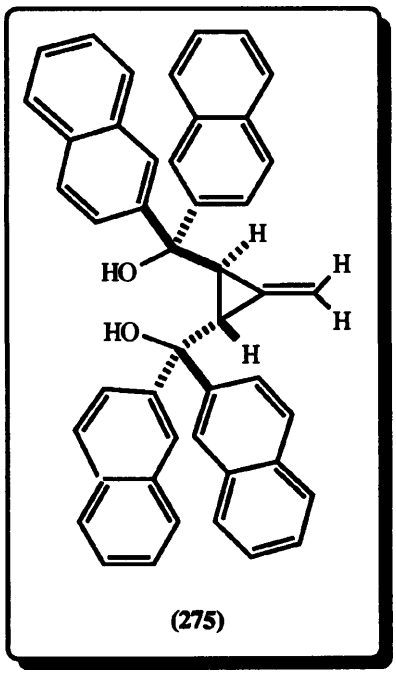
Scheme (45)

It is possible that the diphosphine **(251)** can be obtained by converting the dimesylate **(248)** to the diiodo compound **(273)**[200] followed by reaction with triphenyl-phosphine and reduction to the desired diphosphine ligand **(251), scheme (46).** This procedure has been used with some success for the preparation of β-aminophosphine.



Scheme (46)

(iii) The α-phenyl substituents of the diol **(246)** derived from Feist's acid **(244)** could be replaced with more bulky β-naphthyl substituents **(275)** which could be more effective ligand in various asymmetric induction reactions in the presence of $TiCl_4$ or $Ti(^{i}OPr)_4$.



(275)

III. EXPERIMENTAL

Chapter 6

III.6.A General Techniques

Reactions involving moisture sensitive compounds were carried out under anhydrous conditions and routinely performed under an argon atmosphere.

^{1}H NMR spectra were recorded on an XL300 spectrometer, field frequency 300 MHz. Tetramethylsilane was used as an external or internal standard for all samples. ^{13}C NMR (75.5 MHz) and ^{31}P NMR (32.4 MHz) spectra were recorded on a Brüker WP80 instrument. The deuterated forms of chloroform, dimethyl sulfoxide and water were used as solvents .

Infrared (IR) spectra were recorded on a Perkin-Elmer spectrometer PE298 in the range 4000-600 cm^{-1}. Elemental analyses were carried out by the UMIST microanalytical service. Low resolution mass spectroscopy spectra were recorded on a Kratos MS45 instrument with a digital data output from a P.D.P. 8/1 computer. Fast atom bombardment (FAB) spectroscopy (MS) was done in a solution of *p* -nitrobenzyl alcohol on a VG update AEI-M5902 instrument with an 8 KeV Xenon beam and an accelerating potential of 8 KeV. Melting points were determined on a Gallenkamp apparatus and are uncorrected.

Thin layer chromatography (TLC) was carried out on Merck Kiesegel 60 F_{254} pre-coated, aluminium-backed, TLC plates. The plates were visualized by ultra-violet light and then stained by the use of either iodine, 5% sulphuric acid solution, or an acidic ethanolic solution containing 1% *p*- anisaldehyde, followed by heating.

Silica gel, Kieselgel 60H (Merck) (particle sizes 0.04-0.063mm), was used for flash chromatography. Dry column flash chromatography (DCFC) was performed using TLC grade Merck Kieselgel 60H.

III.6.B Purification of chemicals and solvents[201-203]

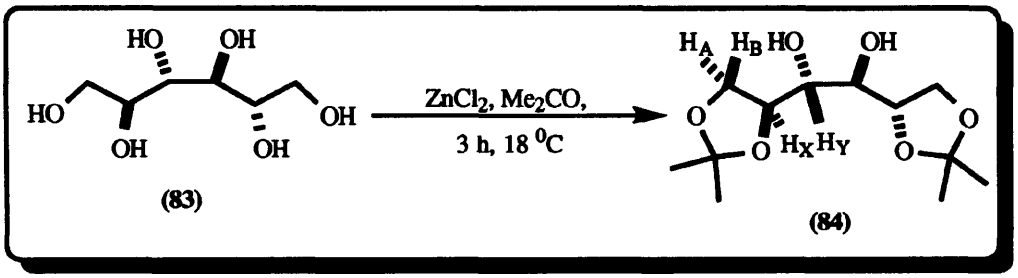
Diethyl ether and tetrahydrofuran were distilled from sodium and benzophenone then stored over sodium wire under argon. Ethanol and methanol were distilled from magnesium ethoxide and stored over molecular sieve 4 Å. Acetone was distilled from anhydrous potassium carbonate and stored over molecular sieve 4 Å. Acetonitrile, chloroform, and dichloromethane were distilled from phosphorus pentaoxide and stored over molecular sieve 4 Å.

Ethyl acetate and hexane were distilled from anhydrous magnesium sulphate then stored over molecular sieve 4 Å. Triethylamine was distilled from potassium hydroxide and stored under argon over molecular sieve 4 Å. N, N-dimethylformamide was distilled under reduced pressure and stored under argon over molecular sieve 4 Å. Thionyl chloride was first distilled from quinoline and then from linseed oil. Methanesulfonyl chloride and 1-iodobutane were distilled under reduced pressure.

Anhydrous pyridine, D-mannitol, zinc chloride, triphenylphosphine, sodium azide, ruthenium(III) chloride hydrate, Lindlar catalyst (5% $Pd/CaCO_3$), 5% Pd/C, trifluoroacetic acid, diethylzinc (1.1M in toluene), trimethylsilyl chloride, methanesulfonyl chloride, diphenylphosphoryl azide (DPPA), diethylazadicarboxylate (DEAD) were supplied by Aldrich chemical company and used as obtained unless otherwise stated.

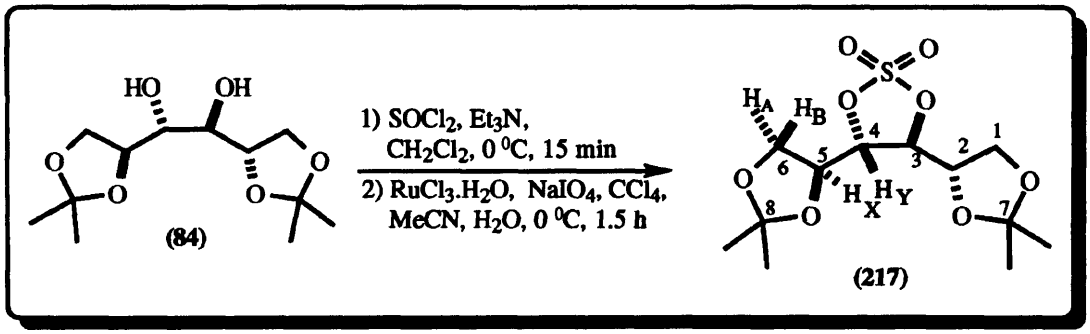
Chlorodiphenylphosphine, L-(-)-menthol, potassium thioacetate, L-(-)-quinine, (R)-(+)-α-methylbenzylamine, titanium tetraisopropoxide, and titanium tetrachloride were obtained from Acros Chimica and used without further purification. Silica gel F_{254} was supplied by Fluka.

III.6.1 Preparation of 1,2:5,6-*O*-isopropylidene-D-mannitol (84)



Zinc chloride (124.0 g, 0.91 mole) and dry acetone (620 cm^3) were charged to a round-bottomed flask (1*l*). The stoppered flask was gently swirled until the zinc chloride dissolved. D-Mannitol (79.0 g, 0.434 mole) was then added and the mixture was stirred at 18 °C for 3 h. Unreacted D-mannitol (17.5 g) was removed by filtration, and the filtrate was quickly added to a solution of potassium carbonate (155.0 g) in water (155 cm^3) containing diethyl ether (620 cm^3). The mixture was stirred vigorously via a mechanical stirrer for 1.5 h at 23-25 °C. The mixture was then filtered and the filtrate was concentrated under reduced pressure to give a precipitate as a slurry. This was washed with acetone and dried under vacuum at 50 °C for 4 h to give **(84)** as a white crystalline solid [50.73 g, 0.213 mole, 57%, based on the amount of D-mannitol that dissolved in the reaction mixture (lit.,[155] 55% yield)]; m.p 120 °C (lit.,[68] 118-120 °C); δ_H (300 MHz, D_2O): 1.30 (6H, s, 2 x CH_3); 1.40 (6H, s, 2 x CH_3); 2.68 (2H, d, $^3J_{X,Y}$ 7.5 Hz, 2 x H_X); 4.0 (2H, dd, $^2J_{AB}$ 8.5 Hz, $^3J_{AX}$ 5 Hz, 2x H_A), 4.10 (2H, dd, $^2J_{BA}$ 8.5 Hz, $^3J_{B,X}$ 5.5 Hz, 2 x H_B), 4.20 (m, 2H, 2 x H_Y) ppm .

III.6.2 Preparation of the 3,4-sulfonyldioxy-1,2:5,6-di-*O*-isopropylidene-D-mannitol (217)

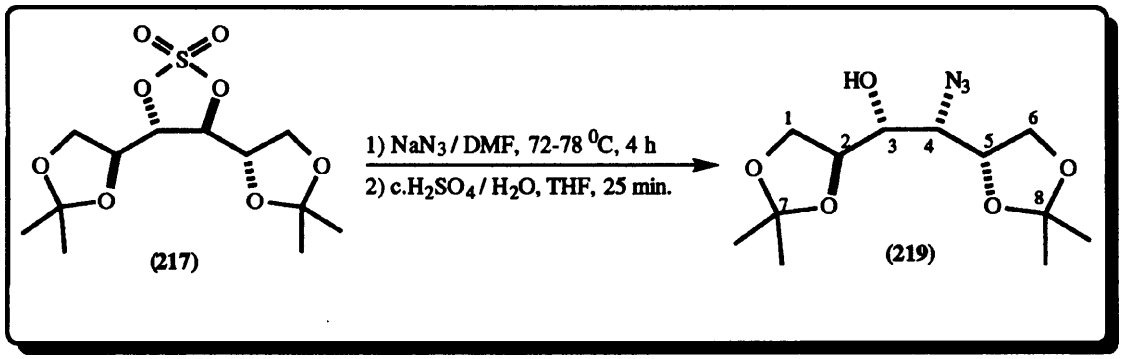


To a cooled (ice-water), stirred solution of 1,2:5,6-di-*O* -isopropylidene-D-mannitol (**84**) (20.0 g, 76.30 mmol) and triethylamine (43 cm^3, 31.22 g, 308.5 mol) in dichloromethane (190 cm^3) was added dropwise thionyl chloride (8.2 cm^3, 13.13 g, 111.90 mmol) in dichloromethane (19 cm^3) via a pressure equalizing funnel over a period of 15 min. Stirring was continued for a further 15 min at 0 °C. The reaction was monitored by TLC (EtOAc-hexane, 1: 2). The reaction mixture was diluted with cold diethyl ether (400 cm^3) and washed with cold water (2 x 400 cm^3) and brine (400 cm^3). The organic layer was dried ($MgSO_4$), filtered and evaporated. The concentrate was dried under vacuum for 2 h to afford the cyclic sulfite intermediate (**216**) as a light brown solid (21.0 g, 68.20 mmol, 89%).

To the solid was added a cold solution of tetrachloromethane and acetonitrile (412 cm^3, 1:1). After cooling in an ice bath, cold water (330 cm^3) was added. Ruthenium trichloride monohydrate (80.24 mg, 0.387 mmol) and sodium periodate (33.0 g, 154.0 mmol) were added simultaneously, and the reaction mixture was stirred vigorously using a mechanical stirrer at 0 °C. The reaction was monitored by TLC (EtOAc-hexane, 1 : 2).

After 90 min stirring, diethyl ether (400 cm^3) was added and the two layers were separated. The aqueous layer was extracted with diethyl ether (2 x 200 cm^3) and the combined organic extracts were washed with brine (2 x 250 cm^3), dried ($MgSO_4$) and filtered. Concentration of the filtrate under reduced pressure gave the crude product (24.0g) as a pale pink solid. Recrystallization from dry acetone gave the pure product as a colourless crystalline solid (16.0g, 49.35 mmol, 65%); (lit.[156], 94%), m.p., 117-119 ^0C [lit,[156] 124.0-126.0 ^0C (118.5 ^0C decomp.)]; $[\alpha]_D^{23}$ +26.9^0 (c 2.9, $CHCl_3$), [lit.,[156] $[\alpha]_D^{24}$ +28.7^0; c 2.9, $CHCl_3$); [Found: C, 44.2; H, 6.4; S, 10.1. Calc. for $C_{12}H_{20}O_8S$: C, 44.46; H, 6.2; S, 9.9%]; ν_{max} ($CHBr_3$ film): 2990 m, 2940 w, 2900 w (C-H, alkane, str.), 1445 w (C-H, alkane, def.), 1380 [$S(=O)_2$ asym. str.], 1205 [$S(=O)_2$ symm. str.], 1050, 945, 910, 825, 780, 680, various strong (S-O-C str.) cm^{-1}; δ_H (300 MHz, $CDCl_3$): 1.28 (6H, s, 2 x CH_3), 1.40 (6H, s, 2 x CH_3), 4.05 (2H, 2d, $^2J_{AB}$ 9.6 Hz, $^3J_{AX}$ 3.5 Hz, 2 x H_A), 4.15 (dd, 2H, $^2J_{BA}$ 9.6 Hz, $^3J_{BX}$ 6.1 Hz, $2H_B$), 4.40 (2H, m, 2 x H_X) and 4.65 (2H, m, 2 x H_Y) ppm; δ_C (75.5 MHz, $CDCl_3$): 24.7 (2 x CH_3), 26.6 (2 x CH_3), 66.0 (C-1 and C-6), 73.2 (C-2 and C-5), 82.3 (C-3 and C-4) and 110.9 (C-7 and C-8) ppm.

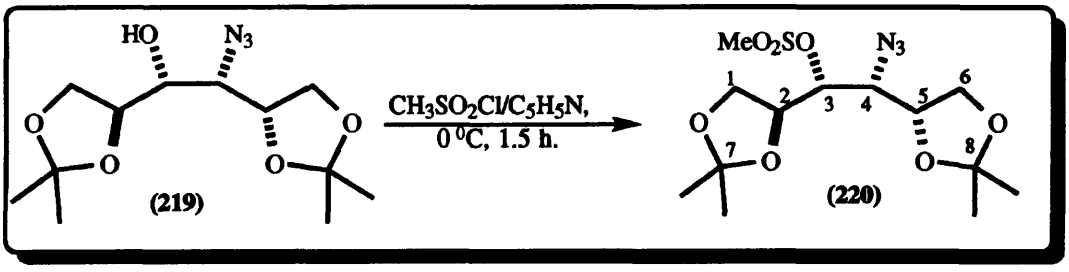
III.6.3 Preparation of 1,2:5,6-di-*O* -isopropylidene-4-azido-3-hydroxyl-D-mannitol (219)



A mixture of 3,4- sulfonyldioxy-1,2:5,6-di-*O* -isopropylidene-D-mannitol (12.0 g, 37.03 mmol), and NaN_3 (3.63 g, 74.07 mmol) in dry DMF (185 cm^3) was stirred under argon for 4 h at 72-78 °C. The solvent was then removed under reduced pressure at 50 °C. The residue was suspended in dry THF (370 cm^3) and c.H_2SO_4 (1.85 cm^3) and water (0.67 cm^3) were added to the stirred suspension. The hydrolysis was followed by TLC (hexane-EtOAc, 2:1). After 25 min. an excess of sodium bicarbonate (30.0 g) was added and the reaction mixture was stirred for 30 min. after which it was filtered through a Celite and silica gel bed. The filtrate was concentrated to half volume then dissolved in diethyl ether (300 cm^3). The organic phase was washed with water (2 x 150 cm^3), dried ($MgSO_4$) and filtered. The filtrate was concentrated to give a pale yellow oil (8.70 g, 30.31 mmol, 82%) (lit.,[156] 91%). A small amount was purified by flash chromatography (EtOAc-hexane, 1:2) to give a colourless oil [Found: C, 51.5; H, 7.4; N, 13.9. Calc. for $C_{12}H_{21}N_3O_5$: C, 50.2; H, 7.4; N, 14.6%]; ν_{max} (neat film): 3450 br.(OH str.), 2980 w, 2930 w (C-H, alkane, str.), 2110 vs (N_3 str.), 1160 s, 1065 s, (C-O-C, str.) cm^{-1}; δ_H (300 MHz, $CDCl_3$): 1.35 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 1.50 (s, 3H, CH_3), 2.75 (d, 1H, ^3J 6.1 Hz, OH), 3.33 (1H, t, ^3J 5.5 Hz, H_3), 3.80-4.21 (m,

6H); 4.48 (1H, dt, ^3J 5.1, 6.5 Hz, H_4) ppm; (FAB) m/z: 288 $(M+H)^+$, 100%; (EI) m/z: 43 $(N_3+H)^+$, 100%; (CI) m/z: 305 $[M+18]^+$, 7.5%.

III.6.4 Preparation of 1,2:5,6-di-*O* -isopropylidene-4-azido-3-*O* -mesyl-D-mannitol (220)



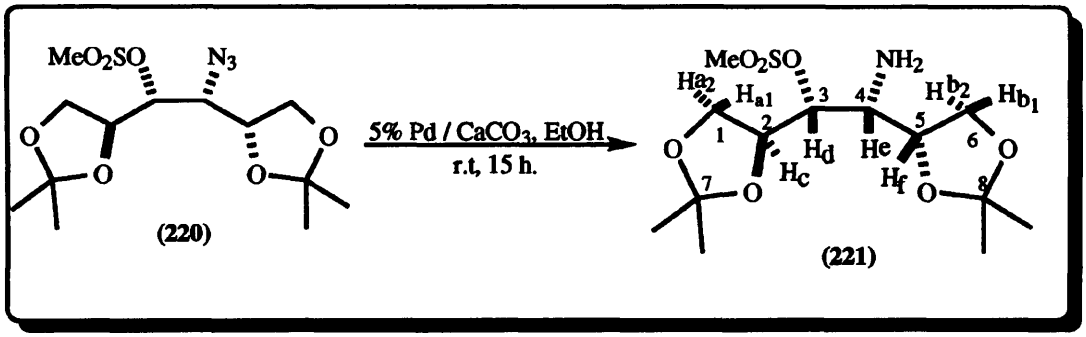
To a 100 ml round-bottomed, 3-necked flask was added 4-azido-3-hydroxy-1,2:5,6-di-*O*- isopropylidene-D-mannitol **(219)** (3.50 g, 12.20 mmol) and dry pyridine (30.0 cm^3, 29.34 g, 370.9 mmol) and the mixture was stirred at 0 °C. Methanesulfonyl chloride (1.12 cm^3, 1.66 g, 14.47 mmol) in dry pyridine (20.0 cm^3) was added dropwise over 15 min. The solution was left to stir for 1.5h and was stored in the refrigerator for 5 days. Water (2.30 cm^3) was then added with stirring over 15 min. The mixture was poured into cold water (90 cm^3) and was extracted with $CHCl_3$ (3 x 110 cm^3). The organic extract was washed with 10% HCl (2 x 110 cm^3), water (225 cm^3), 5% aqueous Na_2CO_3 solution (225 cm^3) and finally water (225 cm^3). The organic layer was dried ($MgSO_4$), filtered and the solvent removed under reduced pressure to give the required product

(220) as a pale yellow oil (4.37 g, 12.0 mmol, 98%) (lit.,[153] 86% crude yield). [Found: C, 43.6; H, 6.0; N, 11.7; S, 8.8. Calc. for $C_{13}H_{23}O_7N_3S$: C, 42.75; H, 6.3.; N, 11.50 and S, 8.78%]; ν_{max}(neat film): 2930, 2870 (C-H, alkane, str.), 2110 (N_3, str.), 1455 (C-H, alkane, def.), 1370 [$S(=O)_2$, asym. str.], 1220 [$S(=O)_2$, sym. str.], 940, 910, 850, 800 (various S-O-C str.) cm^{-1}; δ_H (300 MHz, $CDCl_3$): 1.28 (3H, s, CH_3), 1.35 (3H, s, CH_3), 1.39 (3H, s, CH_3), 1.41 (3H, s, CH_3), 3.07 (3H, s, SCH_3), 3.72 (m, 7H) and 4.60 (dd, 1H, ^3J 5Hz, ^2J 3 Hz, H_3) ppm; δ_C (75.5 MHz, $CDCl_3$): 25.0 (CH_3), 25.1 (CH_3), 26.1 (CH_3), 26.30 (CH_3), 38.6 (SCH_3), 65.0 (C-6), 66.3 (C-1), 73.2 (C-5), 75.1 (C-2), 77.3 (C-4), 79.3 (C-3), 109.5 (C-7 and C-8) and 110.0 (C-7 and C-8) ppm; (EI) m/z: 366 $(M+H)^+$, 9.2%, 43 $(N_3+H)^+$, 100%.

III.6.5 Preparation of palladium hydroxide [$Pd(OH)_2$], 20% on carbon

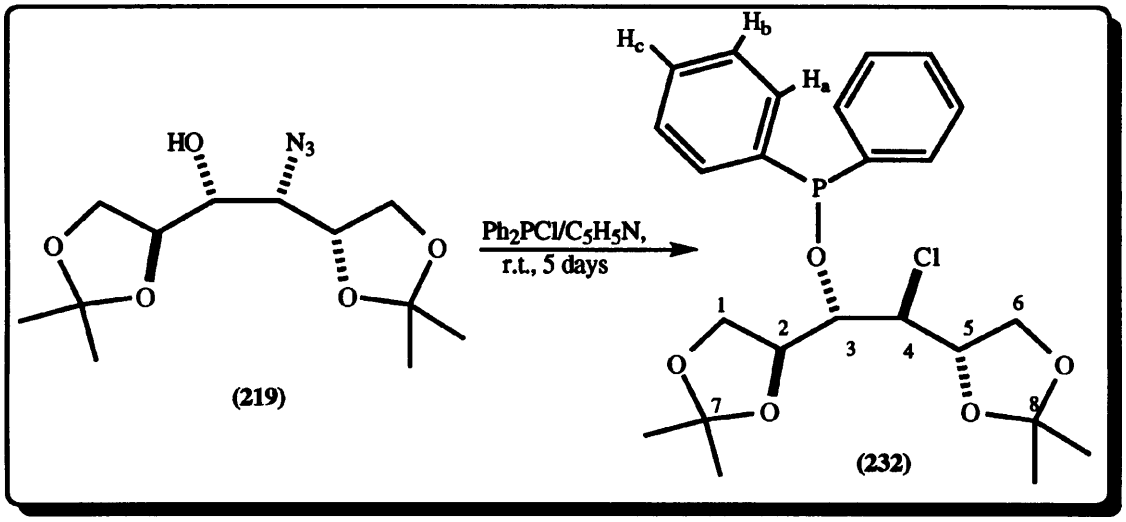
Palladium chloride (1.00 g, 5.64 mmol), carbon (DarcO G-60, 2.40 g) and deionised water (25.0 cm^3) were mixed rapidly whilst heating to 80 °C. Lithium hydroxide monohydrate (0.50 g, 12.2 mmol) dissolved in water (2.0 cm^3) was added in one portion and the heating was stopped. The mixture was stirred overnight, filtered and washed with 0.5% v/v aqueous acetic acid (20.0 cm^3). The cake was dried under suction then *in vacuo* (60 °C) to yield the product (3.00 g).

III.6.6 Preparation of 4-amino-3-*O*-mesyl-1,2:5,6-di-*O*- isopropylidene-D-mannitol (221)



To a round-bottomed flask (100 cm^3), was added 4-azido-3-*O* -mesylate-1,2:5,6-di-*O* -isopropylidene-D-mannitol (0.50 g, 1.37 mmol) in dry ethanol (25 cm^3) and Lindlar catalyst (5% $Pd/CaCO_3$, 0.20 g). The mixture was then stirred under hydrogen gas (1 atm) at room temperature. The reaction was followed by TLC (hexane-EtOAc, 3:1) until there was no starting material present (15 h). The catalyst was removed by filtration and the filtrate concentrated, washed with diethyl ether and evacuated to give the desired amine product as a white solid (0.413 g, 1.22 mmol, 89%). Recrystallization from ethanol gave the pure white crystalline product; amino mesylate (221), m.p. 167-169 °C; [Found: C, 46.0; H, 7.5; N, 4.13; S, 9.45; $C_{13}H_{25}O_7NS$ requires C, 46.03; H, 7.4; N, 4.13 and S, 9.45%]; ν_{max}(Nujol mull): 3400 w, 3300 w (NH_2 str.), 1620 (NH_2 deform), 1375 [$S(=O)_2$ asym. str.], 1180 [$S(=O)_2$ sym. str.], 935, 905, 860, 780 various (S-O-C) cm^{-1}; δ_H (300 MHz, $CDCl_3$): 1.29 (3H, s, CH_3), 1.34 (3H, s, CH_3), 1.39 (3H, s, CH_3), 1.42 (3H, s, CH_3), 3.09 (3H, s, SCH_3), 3.83 (1H, dd, *J* 3.5, 7Hz, Ha_1), 3.89 (1H, dd, *J* 6.5, 9 Hz, Ha_2), 3.98 (1H, dd, *J* 7, 9 Hz, Hb_1), 4.09 (1H, dd, *J* 1, 6.5 Hz, Hb_2), 4.14 (1H, dd, *J* 1, 6.5 Hz, H_d), 4.31 (1H, dd, *J* 1, 6.5 Hz, H_c), 4.34 (1H, dd, *J* 1.5, 6.5 Hz, H_f), 4.67 (1H, dd, *J* 3.5, 5.5 Hz, H_e) and 5.22 (2H, s, NH_2) ppm; (FAB) m/z: 228 $\{M-[(CH_3SO_3) + (NH_2)]\}^+$ 15%; 244 ($M-CH_3SO_3$), 100%; 583 $(2M-CH_3SO_3)^+$, 80%.

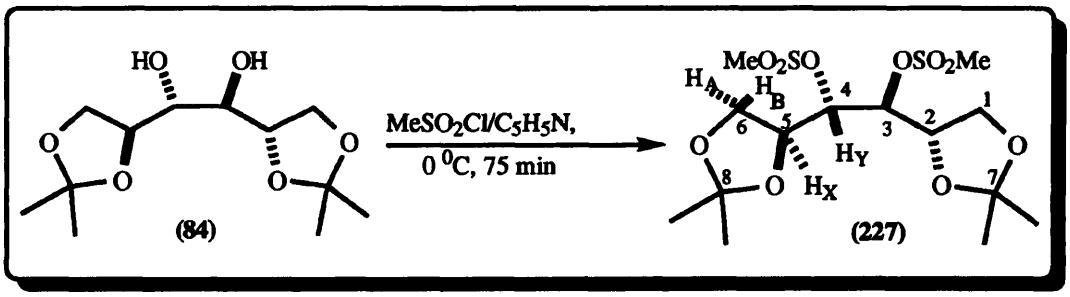
III.6.7 Preparation of 4-chloro-3-*O* -diphenylphosphinito-1,2:5,6-di-*O* -isopropylidene-D-mannitol (232)



4-Azido-3-hydroxy-1,2:5,6-di-*O* -isopropylidene-D-mannitol **(219)** (0.30 g, 1.05 mmol) in dry pyridine (7cm^3) were stirred under argon at room temperature for 5 min. Chlorodiphenylphosphine (0.28 cm^3, 0.35 g, 1.57 mmol) was added dropwise over a period of a 5 min. and a white precipitate of pyridinium hydrochloride formed immediately. The reaction mixture was stirred at room temperature until no starting material was present [5 days, TLC (EtOAc-hexane, 2:1)]. The white precipitate was removed by filtration. The filtrate was poured into water (10 cm^3), extracted with chloroform (3 x 12 cm^3). The organic extracts were combined and washed with 10% HCl (2 x 11 cm^3), water (1 x 22 cm^3), 5% aqueous Na_2CO_3 (1 x 22 cm^3) and water (1 x 22 cm^3) and dried ($MgSO_4$). After filtration, the organic layer was concentrated to afford an impure oily solid (0.68 g). Recrystallization from ethanol and further purification using DCFC (hexane-EtOAc, 1:2 as eluant) gave the product 1,2:5,6-di-*O* -isopropylidene-4-chloro-3-*O* -diphenylphosphinito-D-mannitol **(232)** as a white solid slightly contaminated with nitrogen residues; m.p. 164-

165 °C; [Found: C, 62.1; H, 6.6; N, 2.9; P, 6.5; Cl, 7.4; $C_{24}H_{30}ClO_5P$ requires C, 60.1; H, 6.5; P, 6.7; Cl, 7.5%]; ν_{max} ($CHBr_3$ mull): 3010 (C=C-H str., aromatic), 2980 m, 2920 w (C-H, alkane, str.), 1440 (C-H, alkane, def.), 1140 m, 725 w (P-Ph str.), 850 (asym. P-O-CH str.) cm^{-1}; δ_H (300 MHz, $CDCl_3$), 1.13 (3H, s, CH_3), 1.19 (3H, s, CH_3), 1.24 (3H, s, CH_3), 1.28 (3H, s, CH_3), 4.0 (6H, m, aliphatic protons), 4.20 (1H, m, H_4), 4.40 (1H, m, H_3), 7.43 [6H, m, aromatic (H_b and H_c)] and 7.83 (4H, m, H_a) ppm; δ_C (75.5 MHz, $CDCl_3$): 25.2 (CH_3), 25.4 (CH_3), 26.4 (CH_3), 26.5 (CH_3), 67.1 (C-6), 68.1 (C-1), 73.5 (C-5), 73.5 (C-2), 76.1 (C-4), 76.7 (C-3), 109.8 (C-8), 110 (C-7), 127.7-133.2 (4C, aromatic carbons) ppm; δ_P (32.4 MHz, $CDCl_3$): +23.10 ppm; m/z (FAB): 465 (M+H), 12.6%, 422 $(M\text{-}Me_2C)^+$ 42%, 201$(OPPh_2)^+$ 100%.

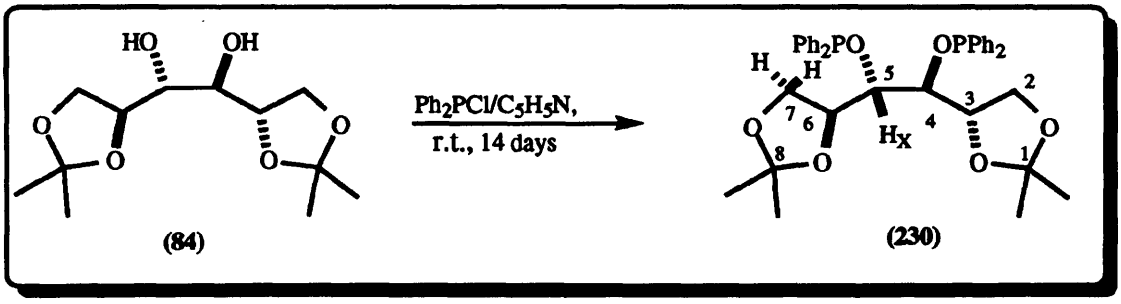
III.6.8 Preparation of 3,4-bis(*O* -mesyl)-1,2:5,6-di-*O* -isopropylidene-D-mannitol (227)



To a solution of 1,2:5,6-di-*O* -isopropylidene-D-mannitol **(84)** (1.0 g, 3.82 mmol) in dry pyridine (9.50 cm^3) at 0 °C was added dropwise methanesulphonyl chloride (0.70 cm^3, 1.034 g, 9.03 mmol) in dry pyridine (6.50 cm^3). The solution was stirred for 75 min and was stored in the refrigerator for 6 days. Water (0.75 cm^3) was then added with stirring over 10 min. The mixture was poured into cold water (28 cm^3) and was extracted with $CHCl_3$ (3 x 35 cm^3).The combined $CHCl_3$ extract was washed with 10% HCl (2 x 35 cm^3), water (1 x 70 cm^3), 5% Na_2CO_3 (1 x 70 cm^3) and finally water (1 x 70 cm^3). The organic layer was dried ($MgSO_4$), filtered, and concentrated to leave a pale yellow oil which was washed several times with diethyl ether to afford the crude bismesylate product (227) (1.40 g, 3.35 mmol, 88%) as a white solid. A small sample was recrystallised from ($CHCl_3$-hexane, 1:10) to give colourless crystals, m.p. 129-130 °C; [Found: C, 40.0; H, 6.30; S, 15.7. $C_{14}H_{26}O_{10}S_2$ requires C, 40.2; H, 6.22; S, 15.33%]; ν_{max} ($CHBr_3$ mull): 3010, 2990, 2925 (C-H, alkane, str.), 1410 m, 1450 w (C-H, alkane, def.), 1370 [$S(=O)_2$ asym. str.], 1220 [$S(=O)_2$, sym str.], 940, 910, 865, 760 various (S-O-C) cm^{-1}; δ_H (300MHz, $CDCl_3$): 1.35 (6H, s, 2 x CH_3), 1.48 (6H, s, 2 x CH_3), 3.16 (6H, s, 2 x SCH_3), 4.17 [4H, m, 2(H_A+H_B)], 4.25 (2H, m, 2 x H_X), 4.95 (2H, dd, ^3J 5.5 Hz, ^2J

3 Hz, 2 x H_y) ppm; δ_C (75.5MHz, $CDCl_3$): 25.0 (2 x CH_3); 26.4 (2 x CH_3); 38.8 (2 x SCH_3); 66.3 (C-1 and C-6), 73.3 (C-2 and C-5), 78.8 (C-3 and C-4), 110.1 (C-7 and C-8) ppm; m/z (FAB): 419 $(M+H)^+$, 100%; 403 $(M-CH_3)^+$, 24% and 837 $(2M+H)^+$, 5%.

II.6.9 Preparation of 3,4-bis(*O* -diphenylphosphinito)-1,2:5,6-di-*O*- isopropylidene-D-mannitol (230)



1,2:5,6-Di-*O* -isopropylidene-D-mannitol **(84)** (2.0 g, 7.63 mmol) was dissolved in dry pyridine (15 cm^3). Chlorodiphenylphosphine (4.11 cm^3, 5.1 g, 22.9mmol) was added dropwise over a period of 10 min under an argon atmosphere. The reaction mixture was stirred at room temperature for two weeks and was monitored by TLC (hexane-EtOAc, 2:1), after which a fine white precipitate of pyridinium hydrochloride was removed by filtration. The filtrate was poured into water (60 cm^3) and extracted with chloroform (3 x 60 cm^3). The combined $CHCl_3$ extracts were washed with 10% HCl (2 x 50 cm^3), water

(1 x 100 cm^3), 5% Na_2CO_3 (1 x 100 cm^3), water (1 x 100 cm^3), and dried ($MgSO_4$). The filtrate was concentrated to give the crude product as an oil (3.50 g); TLC (EtOAc-hexane, 2:1) showed 3 main spots. The crude product was purified by DCFC to afford unreacted diol (1.0 g, 3.82 mmol, 50%, Rf, 0.0) and two other compounds. Attempts were made to further purify these by recrystallization from ethanol, but both were contaminated with some unchanged chlorodiphenylphosphine. The data for these compounds are given below:

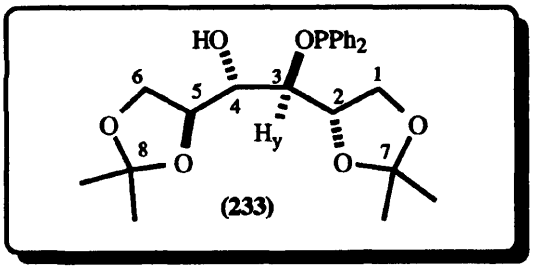
(i) 3,4-bis(*O* -diphenylphosphinito)-1,2:5,6-di-*O* -isopropylidene-D-mannitol (230):

(0.80 g, 1.27 mmol, 16.6%, Rf, 0.20), m.p. 150-155 °C; [Found: C, 63.0; H, 5.5; P, 11.3 ; $C_{36}H_{40}P_2O_6$ requires: C, 68.6; H, 6.35; P, 9.83%]; ν_{max} ($CHBr_3$ mull) 3010 m (C-H str., aromatic), 1600 s (C=C str. aromatic), 1140 m (P-Ph str.), 860 (P-OC str.), 740 m, 700 m (P-Ph) cm^{-1}; δ_H (300MHz, $CDCl_3$): 1.10-1.30 (m, ~ 12H, 4 x CH_3), 3.80-4.10 (m, ~ 6H); 4.30 (m, 2H, H_y), 7.3-7.80 (m, ~ 20H, aromatic protons), δ_C (75.5 MHz, $CDCl_3$): 24.5 (2 x CH_3), 25.9 (2 x CH_3), 69.8 (C-1 and C-6), 74.5 (C-2 and C-5), 78.41 (C-3 and C-4), 103.4 (C-7 and C-8), 128-133.60 (m, ~ 24C, aromatic carbons) ppm;

(ii) 4-*O* -diphenylphosphinito-3-hydroxy-1,2:5,6-di-*O* -isopropylidene-D-mannitol (233)

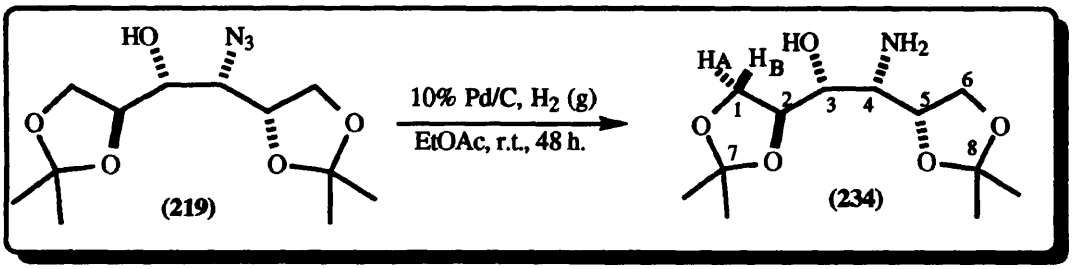
(0.1 g, 2.24 mmol, 29.4% yield, Rf, 0.60), m.p. 145 °C; [Found: C, 63.1; H, 6.6; P, 6.6. $C_{24}H_{31}PO_6$ requires C, 64.6; H, 6.95; P, 6.95%]; ν_{max} ($CHBr_3$ mull): 3500-3100 s,

br (OH str.), 3010 m (C-Hstr., aromatic), 1600 s (C=C str., aromatic), 1140 m (P-Ph str.), 860 m (P-O-C str.), 740 m, 700 m (P-Ph) cm^{-1}; δ_H (300 MHz, $CDCl_3$): 1.18 (s, CH_3), 1.20 (s, CH_3), 1.30 (s, CH_3), 1.40 (s, CH_3), 3.40 (s, 1H, OH), 3.60-4.20 (m, 7H, aliphatic protons), 4.70 (1H, m, H_y) ppm; m/z (FAB): 201 $(OPPh_2)^+$, 42%, 447 $(M+H)^+$, 13%; (EI) m/z: 201 ($OPPh_2$), 25%; (CI) 219 ($OPPh_2+NH_4$), 80%.



(233)

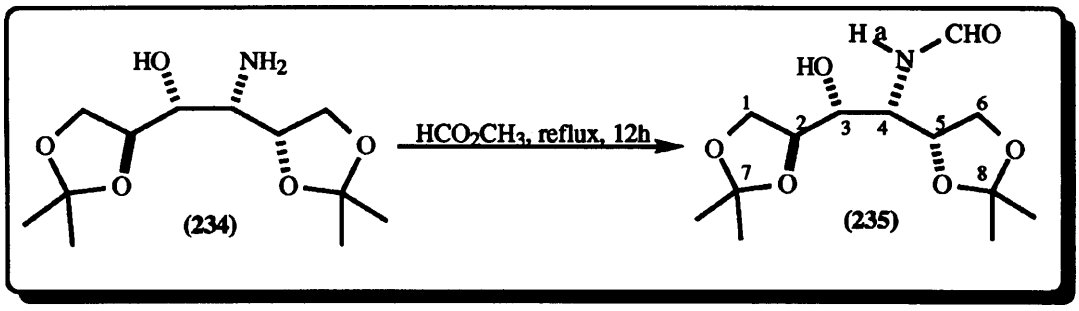
III.6.10 Preparation of 4-amino-3-hydroxy-1,2:5,6-di-*O* -isopropylidene-D-mannitol (234)



3-Azido-4-hydroxy-1,2:5,6-di-*O* -isopropylidene-D-mannitol **(219)** (2.0 g, 6.97 mmol) was dissolved in dry ethyl acetate (15 cm^3) and the mixture stirred under an atmosphere of argon at room temperature for 10 min. Palladium on carbon (10% Pd/C, 0.20 g) was added quickly and the mixture was stirred for a further 10 min. The reaction mixture was put under a hydrogen atmosphere (*via* a balloon) and stirred at room temperature for 48 h, after which time TLC (EtOAc-hexane, 1:2) showed that there was no azide present. The mixture was filtered through Celite (which was washed thoroughly with ethyl acetate). The filtrates and washings were concentrated to afford a white solid; 4-amino-3-hydroxy-1,2:5,6-di-*O* -isopropylidene-D-mannitol **(234)** (1.60 g, 6.13 mmol, 88%). A small amount was recrystallized from dry ethanol to afford white crystals, m.p. 83 °C ; $[\alpha]_D^{25}$ -9.7° (c 2.0, $CHCl_3$); [Found: C, 54.9; H, 9.1; N, 5.5. $C_{12}H_{23}O_5N$ requires C, 55.2; H, 8.8; N, 5.4%]; ν_{max} (Nujol mull): 3280 m 3060 s, (NH_2 str.), 3290-3020 s, br (OH str.), 1600 s (N-H bend.), 1160 m, 1050 m (C-O-C str.) cm^{-1}; δ_H (300 MHz, $CDCl_3$); 1.25 (s, CH_3), 1.26 (s, CH_3), 1.29 (s, CH_3), 1.30 (s, CH_3), 2.25 (2H, s, NH_2), 2.84 (1H, t, ^3J 5 Hz, OH), 3.65 (1H, t, ^3J 5.6 Hz, H_4), 3.69 (m, 2H, H_2 & H_5),

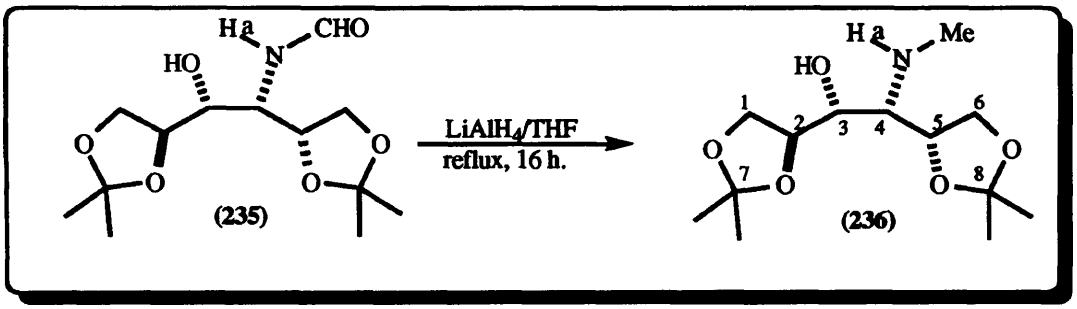
4.13 (m, 4H, H_A& H_B), 4.30 (1H, q, ^3J 6Hz, H_3) ppm; δ_C (75.5 MHz, $CDCl_3$): 25.3 (CH_3), 25.4 (CH_3), 26.1 (CH_3), 26.6 (CH_3), 66.7 (C-6), 67.1 (C-1), 74.2 (C-4), 76.2 (C-5), 76.7 (C-2), 77.4 (C-3), 108.1 (C-8), 109.4 (C-7) ppm; m/z (FAB): 262 $(M+H)^+$, 100%.

III.6.11 Preparation of 4-N-(formamido)-3-hydroxy-1,2:5,6-di-*O* -isopropylidene-D-mannitol (235)



In a 3-necked, round-bottomed flask, fitted with a condenser, 4-amino-3-hydroxy-1,2:5,6-di-*O* -isopropylidene-D-mannitol (**234**) (1.0 g, 3.83 mmol) was suspended in an excess of methyl formate (9.0 cm^3, 8.72 g, 145.50 mmol). The mixture was stirred at reflux for 12 h and then at room temperature for 6 h when TLC (hexane-EtOAc, 1:1) showed no starting material was present. The reaction mixture was concentrated under vacuum to afford a white precipitate of the 4-N-amino alcohol (**235**) (1.0g, 3.46 mmol, 90%). A small amount was recrystallized from $CHCl_3$-hexane (1:20), m.p. 135 °C; $[\alpha]_D^{25}$ +44.8° (c 2.0, $CHCl_3$); [Found: C, 53.4; H, 8.6; N, 4.6. $C_{13}H_{23}NO_6$ requires C, 54.0; H, 8.0; N, 4.8%]; ν_{max} (Nujol mull): 3400 m (N-H str.), 3370-3120 w, br (OH str.), 1650 s (O=C-NH str.), 1160 w, 1060 m (C-O-C str.); δ_H (300 MHz, $CDCl_3$): 1.34 (s, CH_3), 1.36 (s, CH_3), 1.42 (s, CH_3), 1.44 (s, CH_3), 3.0 (1H, dd, ^3J 6, 8.5 Hz, OH), 3.72 (m, 2H), 4.00-4.28 (5H, m), 4.65 (1H, dt, ^3J 6.5, 2 Hz, H_3), 6.16 (d, ^3J 8 Hz, NH), 8.30 (1H, s, CHO) ppm; δ_C (75.5 MHz, $CDCl_3$): 24.7 (CH_3), 25.1 (CH_3), 26.0 (CH_3), 26.3 (CH_3), 66.0 (C-6), 66.6 (C-1), 73.5 (C-4), 74.0 (C-3), 79.2 (C-5), 82.1 (C-2), 109.3 (C-8), 109.5 (C-7), 161.2 (C=O) ppm; m/z (FAB): 290 $(M+H)^+$, 78%.

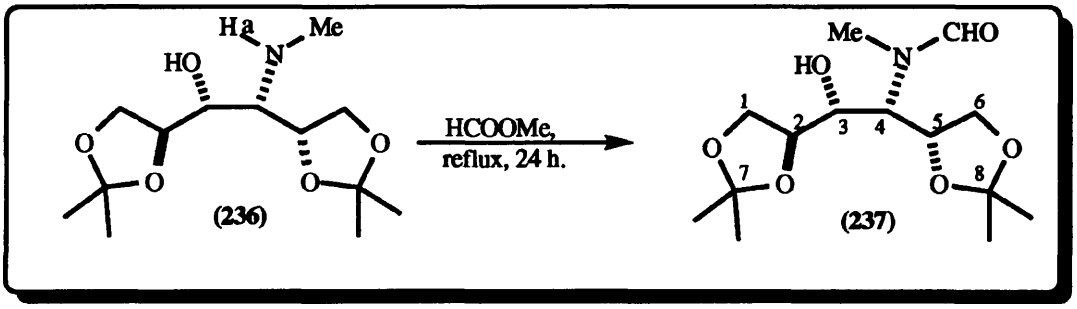
III.6.12 Preparation of 4-N-(methylamino)-3-hydroxy-1,2:5,6-di-*O* -isopropylidene-D-mannitol (236)



In a 3-necked, round-bottomed flask, 4-N-(formamido)-3-hydroxy-1,2:5,6-di-*O* -isopropylidene-D-mannitol (**235**) (0.80 g, 2.77 mmol) and lithium aluminium hydride (0.21 g, 5.34 mmol) were suspended in dry THF (24 cm^3) under an argon atmosphere. The mixture was refluxed for 12 h when TLC (hexane-EtOAc, 1:1) indicated only a slight amount of starting material still present plus a new spot. The reaction mixture was then refluxed for a further 4 h and stirred overnight at room temperature. The reaction was quenched with 5% w/w of potassium hydroxide (0.7 cm^3), filtered, and washed with boiling THF (24 x 10 cm^3). The filtrate was dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a pale brown oil, which was purified by DCFC (EtOAc-hexane, 1:1) followed by Kügelröhr bulb-to-bulb distillation (120 °C / 5mmHg) to afford 4-N-(methylamino)-3-hydroxy-1,2:5,6-di-*O* -isopropylidene-D-mannitol (**236**) (0.305 g, 1.11 mmol, 40%) as a pale yellow oil; $[\alpha]_D^{25}$ +8.60 ° (c 2.0, $CHCl_3$); Found: C, 56.4; H, 8.8; N, 4.8. $C_{13}H_{25}NO_5$ requires C, 56.7; H, 9.1; N, 5.1%]; ν_{max} (neat film): 3560 w (NH str.), 3540-3200 m, br (OH str.), 2980 m, 2930 w, 2880 w (C-H, alkane str.), 1660 (C-NH str.), 1150 m, 1060 s, (C-O-C str.) cm^{-1}; δ_H (300 MHz, $CDCl_3$): 1.25 (s, CH_3), 1.35 (s, CH_3), 1.42 (s, CH_3), 1.46 (s, CH_3), 2.40 (3H, s, NCH_3), 2.63 (1H, dd, *J* 5.5,

3.5 Hz, OH), 3.66 (m, 1H), 3.85-4.15 (m, 6H), 4.37 (1H, q, ^3J 6.5 Hz, H_a) ppm; δ_C (75.5 MHz, $CDCl_3$): 25.0 (CH_3), 25.0 (CH_3), 26.3 (CH_3), 26.6 (CH_3), 34.4 (N-CH_3), 66.6 (C-6), 67.5 (C-1), 70.0 (C-4), 71.0 (C-5), 74.9 (C-2), 75.1 (C-3), 108.7 (C-8) and 109.2 (C-7) ppm; m/z (FAB): 276 $(M+H)^+$, 100%.

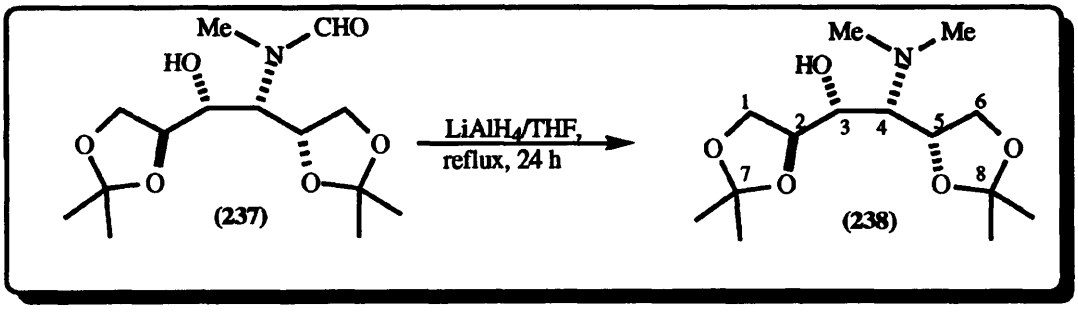
III.6.13 Preparation Of 4-N-methyl-N-(formamido)-3-hydroxy-1,2:5,6-di-*O*- isopropylidene-D-mannitol (237)



A mixture of 4-N-(methylamino)-3-hydroxy-1,2:5,6-di-*O*-isopropylidene-D-mannitol **(236)** (0.26 g, 0.45 mmol) and an excess of methyl formate (2.93 cm^3, 2.32 g, 38.71 mmol) was refluxed for 12 h. TLC (EtOAc-hexane, 2:1) showed some starting material was still present and the mixture was refluxed for a further 12 h until TLC showed only a trace of starting material. The reaction mixture was stirred at room temperature for 5 h. The mixture was concentrated by removal of the volatiles and the residue was purified by column chromatography (EtOAc-hexane, 2:1) to afford the methyl formamido alcohol **(237)** (0.253 g, 8.35 mmol, 88%) as a yellow oil; $[\alpha]_D^{25}$ -26.3° (c 0.44, $CHCl_3$); ν_{max} (neat film): 3700-3100 s, br, (OH str.), 2990 m, 2930 w (C-H, alkane str.), 1659 s

(O=C-N str.), 1380 m (C-N str.), 1150 m, 1055 s, (C-O-C str.) cm^{-1}; δ_H (300 MHz, $CDCl_3$): 1.23 (s, CH_3), 1.28 (s, CH_3), 1.35 (s, CH_3), 1.40 (s, CH_3), 2.94 (1H, s OH), 3.10 (3H, s, NCH_3), 3.74 (m, 2H), 4.13 (m, 5H), 4.60 (1H, q, ^3J 7.5 Hz, H_3), 8.10 (1H, s, CHO) ppm; δ_C (75.5 MHz, $CDCl_3$): 25.0 (CH_3), 25.3 (CH_3), 26.4 (CH_3), 26.5 (CH_3), 26.6 (NCH_3), 66.2 (C-6), 67.4 (C-1), 73.5 (C-4), 75.8 (C-5), 76.2 (C-2), 77.2 (C-3), 108.7 (C-8), 109.4 (C-7), 164.0 (C=O) ppm; m/z (FAB): 304 $(M+H)^+$, 64%; 607 $(2M+H)^+$, 24%.

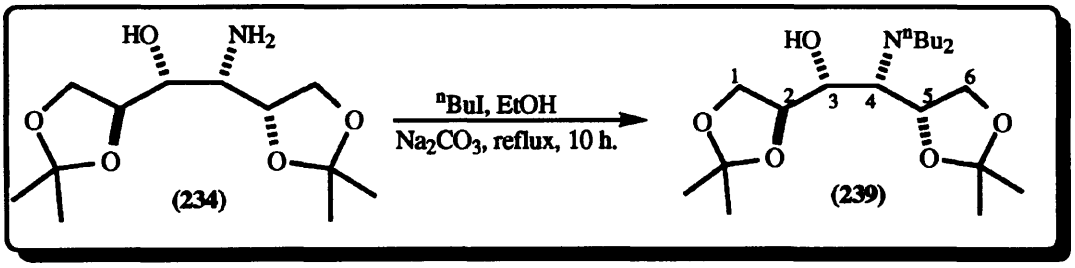
III.6.14 Preparation of 4-N,N-(dimethylamino)-3-hydroxy-1,2:5,6-di-*O* -isopropylidene-D-mannitol (238)



In a 3-necked, round-bottomed flask, 4-N-methyl-N-(formamido)-3-hydroxy-1,2: 5,6-di-*O* -isopropylidene-D-mannitol (**237**) (0.13 g, 2.1 mmol) and lithium aluminium hydride (0.22 g, 5.70 mmol) were suspended in dry THF (25 cm^3) under an argon atmosphere. The mixture was heated at reflux for 24 h, when TLC (hexane-EtOAc, 2:1)

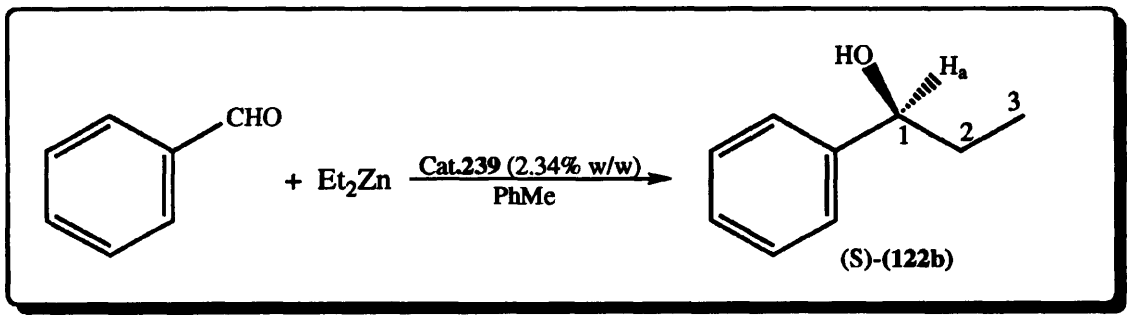
showed no starting material was present. The mixture was cooled to room temperature and 5% w/w potassium hydroxide (0.50 cm^3) was added to quench the reaction. The solid precipitate was filtered off and washed several times with boiling THF (4 x 10 cm^3). The filtrate was dried ($MgSO_4$) and then concentrated to give a pale brown oil which was purified by DCFC (hexane-EtOAc, 5:1) to afford 4-N,N-(dimethylamino)-3-hydroxy-1,2:5,6-di-*O*- isopropylidene-D-mannitol (**238**) as a yellow oil (0.36 g, 1.25 mmol, 60%). A small amount was purified further by Kügelröhr bulb-to-bulb distillation under reduced pressure to obtain a colourless oil $[\alpha]_D^{26}$ +25.10° (c 0.44, $CHCl_3$); [Found: C, 57.7; H, 9.5; N, 4.2. $C_{14}H_{27}NO_5$ requires C, 58.1; H, 9.3; N, 4.8%]; ν_{max} (neat film): 3400-3150 m br. (OH str.), 2960 m, 2870 w (C-H, alkane str.), 1345 m (C-N str.) cm^{-1}; δ_H (300 MHz, $CDCl_3$): 1.35 (s, CH_3), 1.37 (s, CH_3), 1.40 (s, CH_3), 1.42 (s, CH_3), 2.51 (6H, s, $2NCH_3$), 3.50 (1H , t, ^3J 6.5 Hz, OH), 3.70-3.73 (m, 4H), 3.09-4.11 (m, 2H), 4.50 (1H, q, ^3J 7 Hz, H_3) ppm; m/z (FAB): 290 (M+H), 100%.

III.6.15 Preparation of 4-N,N-(dibutylamino)-3-hydroxy-1,2:5,6-di-*O* -isopropylidene-D-mannitol (239)



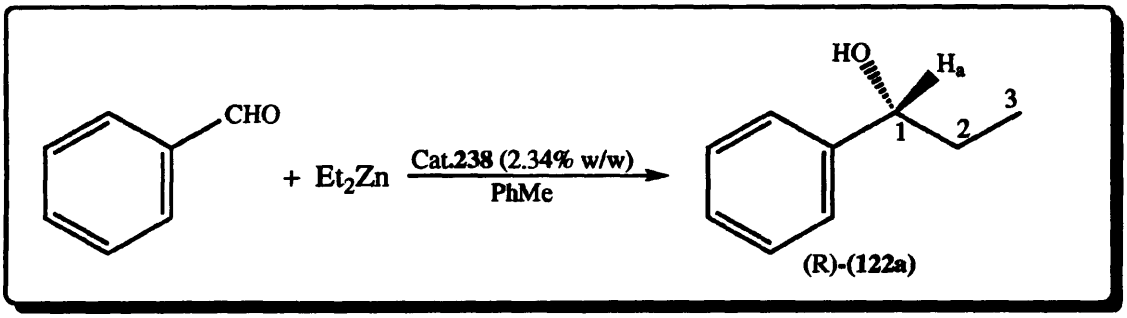
In a 3-necked, round-bottomed flask, fitted with a reflux condenser, 4-amino-3-hydroxy-1,2:5,6-di-*O* -isopropylidene-D-mannitol **(234)** (1.50 g, 5.75 mmol), freshly distilled 1-iodobutane (1.65 cm^3, 2.12 g, 11.50 mmol), and sodium carbonate (1.23 g, 11.50 mmol) were suspended in dry ethanol (11.0 cm^3). The mixture was stirred at reflux for 10h, then at room temperature for 10 h. The precipitate (sodium iodide) was removed by filtration and washed thoroughly using dry ethanol. The solvent was removed to obtain the crude product (1.90 g) which was purified twice by DCFC (EtOAc-hexane, 1: 5) followed by Kügelröhr bulb-to-bulb distillation (150 °C/7 mmHg) to give the dibutylamino alcohol (**239**) as a pure colourless oil (0.55 g, 1.47 mmol, 26%); $[\alpha]_D^{25.5}$ +12.50° (c 0.45 , $CHCl_3$); [Found: C, 64.1; H, 10.2; N, 4.1. $C_{20}H_{39}NO_5$ requires C, 64.3; H, 10.46; N, 3.75%]; ν_{max} (neat film): 3500-3200 m br. (OH str.), 2985 m, 2930 w, 2875 w, (C-H, alkane str.), 1350 m (C-N str.), 1140 m, 1050 m (C-O-C str.) cm^{-1}; δ_H (300 MHz, $CDCl_3$): 0.85 (m, 5H), 1.12 (s, CH_3), 1.24 (s, CH_3), 1.28 (s, CH_3), 1.32 (s, CH_3), 1.37 (m, 7H), 1.52 (m, 3H), 2.60 (t, *J* 7 Hz, 2H), 2.67 (1H, dd, ^3J 2, 4 Hz, OH), 3.42 (q, *J* 7 Hz, 1 H), 3.58 (1H, dd, ^3J 3.5, 8 Hz, H_4), 3.86-4.10 (m, 5H), 4.30 (1H, q, ^3J 6 Hz, H_3) ppm; m/z (FAB): $(M+H)^+$, 100%.

III.6.16 Enantioselective addition of diethylzinc to benzaldehyde catalyzed by (+)-4-N,N-(dibutylamino)-3-hydroxy-1,2:5,6 -di-*O*-isopropylidene-D-mannitol (239)



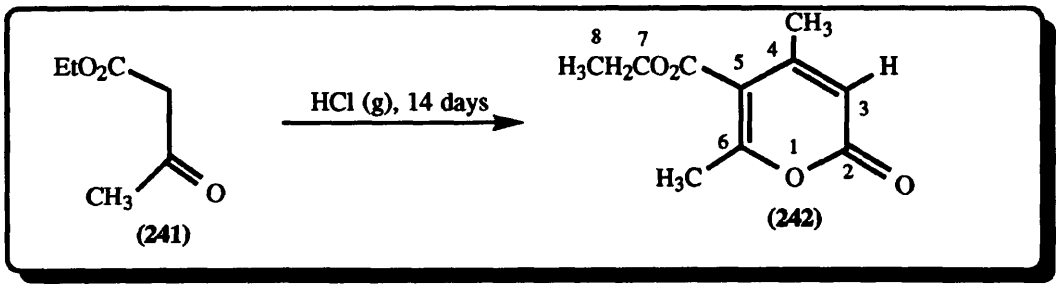
In a 3-necked, round-bottomed flask, equipped with reflux condenser, 4-N,N-(dibutylamino)-3-hydroxy-1,2:5,6-di-*O* -isopropylidene-D-mannitol (0.034 g, 0.09 mmol) in dry toluene (8 cm^3) was stirred at room temperature for five min under argon. Benzaldehyde (0.40 cm^3, 0.425 g, 3.94 mmol) was added and the mixture was heated at 55 °C for 20 min. The pale yellow solution was allowed to cool to 0 °C. Diethylzinc (1.1M, 8.0 cm^3, 8.8 mmol) was then added dropwise over a period of 10 min, under argon, resulting in a dark yellow solution. The reaction mixture was stirred at room temperature for 48 h. 1M HCl (20 cm^3) was then added dropwise and the mixture was extracted with dichloromethane (4 x 30 cm^3). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated to afford crude (S)-1-phenylpropanol **(122b)** (0.31g). This was purified by column chromatography (hexane-EtOAc, 5:1) followed by Kügelröhr bulb-to-bulb distillation (100 °C/5 mmHg) to give the product **(122b)** as a colourless oil (0.21g, 1.54 mmol, 39% yield), $[\alpha]_D^{24}$ -30.0° (c 0.20, $CHCl_3$), 66% **e.e.** [lit.,[163] $[\alpha]_D$ -45.45^0 (c 5.15, $CHCl_3$)]; [Found: C, 79.1; H, 8.5. Calc. for $C_9H_{12}O$ C, 79.4; H, 8.8%]; δ_H (300 MHz, $CDCl_3$): 0.93 (3H, t, $^3J_{2,3}$ 7 Hz, CH_3), 1.70 (1H, br s, OH), 1.81-1.84 (2H, m, CH_2), 4.60 (1H, t, $^3J_{a,2}$ 6.5 Hz, H_a), 7.34-7.36 (5H, m, aromatics) ppm.

III.6.17 Enantioselective addition of diethylzinc to benzaldehyde catalyzed by (+)-4-N,N-(dimethylamino)-3-hydroxy-1,2:5,6 -di-*O* -isopropylidene-D-mannitol (238)



The experimental procedure was used as described earlier (**III.6.16**) and on same scale. (R)-(+)-1-Phenylpropanol (**122a**), was prepared by the reaction of benzaldehyde with diethylzinc in toluene catalyzed by 4-N,N-(dimethylamino)-3-hydroxy-1,2:5,6-di-*O*-isopropylidene-D-mannitol (**238**) in 80% yield; $[\alpha]_D^{23}$ +10.0° (c 0.2, $CHCl_3$), 22% **e.e.**; [lit.,[163] $[\alpha]_D$ -45.45^0 (c 5.15, $CHCl_3$)].

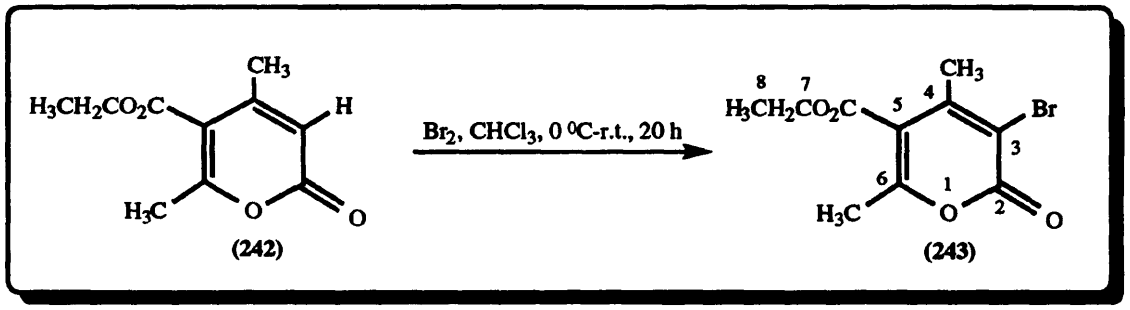
III.6.18 Preparation of 5-carboethoxy-4,6-dimethyl-2-pyrone (242)



Ethyl acetoacetate **(241)** (1000 g, 7.70 mole) was cooled with an ice-salt bath and treated with a rapid stream of dry hydrogen chloride gas over an eight hour period. The resultant liquid was protected from moisture and stored in the dark for one week. The mixture was cooled again and saturated with hydrogen chloride gas as before. After a further week the liquid was shaken with water (2000 cm^3) and with 1M sodium carbonate solution (500 cm^3). The aqueous washings were concentrated to small bulk *in vacuo* and the residue was dried in an evacuated desiccator over sodium hydroxide. The sodium carbonate washings were acidified with hydrochloric acid and extracted with diethyl ether (2 x 300 cm^3). The extracts, together with the residue from the aqueous washings and diethyl ether (500 cm^3) were added to the main bulk of the oil (in the desicator), which was then dried ($MgSO_4$) and filtered. The diethyl ether was removed and the residue was distilled under reduced pressure to give the pyrone **(242)** (435.0 g, 2.22 mol, 58%) as a pale yellow liquid; (lit.[166], 46%), b.p. 150-170 °C at 21-20 mmHg (lit.,[166] 160-190 °C at 20 mmHg); [Found: C, 60.9; H, 6.3. Calc. for $C_{10}H_{12}O_4$ C, 61.2; 6.2%]; ν_{max} (neat film): 3070 w, 2980 s, 2930 w (C-H, alkane str.), 1720 vs (C=O str.), 1630 s (C=O str.), 1550, 1400 vs, 1300 vs, 1150 s, 1080 vs (C-O-C str.), 1020 s, 960 s, 860 s, 780 s and 640 w cm^{-1}; δ_H (300 MHz, $CDCl_3$): 1.35 (3H, t, $^3J_{7,8}$ 7.5 Hz, CH_3), 2.2 (3H, s, CH_3), 2.35 (3H, s, CH_3), 4.3 (2H, q, $^3J_{7,8}$ 7.5 Hz, CH_2), 6.00 (1H, s, C-H) ppm; δ_C (75.5

MHz, $CDCl_3$): 13.7 (CH_3), 19.4 (CH_3), 21.0 (CH_3), 61.3 (CH_2), 111.6 (C-3), 112.1 (C-4), 154.3 (C-5), 160.5 (C-6), 164.5 (C=O), 165.3 (C=O) ppm; m/z (FAB): 197 $(M+H)^+$, 100%; 393 $(2M+H)^+$, 41%.

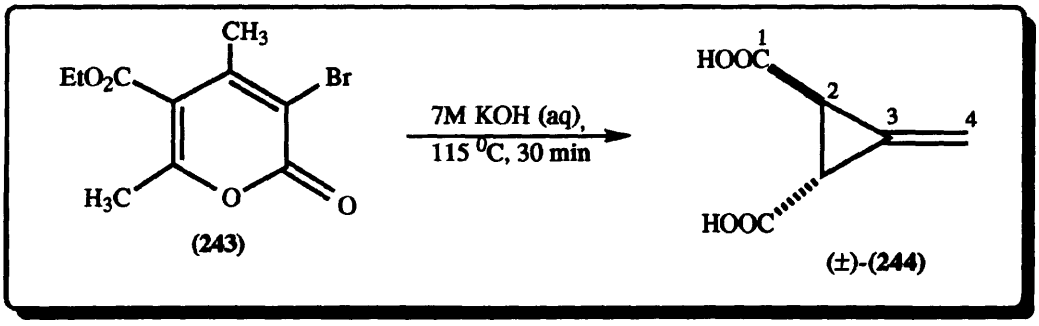
III.6.19 Preparation of 3-bromo-5-carboethoxy-4,6-dimethyl-2-pyrone (243)



To an ice-cold solution of 5-carboethoxy-4,6-dimethyl-2-pyrone **(242)** (430.0 g, 2.19 mol) in chloroform (870 cm^3) was added bromine (130 cm^3, 403.26 g, 2.52 mol) dropwise with occasional shaking over a period of 30 min. After the addition was complete the mixture was stirred overnight. The hydrogen bromide was then removed on a steam bath. The cooled solution was diluted with diethyl ether (930 cm^3), washed with water (100 cm^3), dilute sodium carbonate solution (2 x 515 cm^3), dried ($MgSO_4$) and filtered. The solvent was removed *in vacuo* and the residue recrystallized from methanol to give the desired product **(243)** as large, pale yellow plates (480 g, 1.75 mole, 80%), (lit.,[166] 90%); m.p. 87-89 °C (lit.,[166] 87 °C); [Found: C, 43.9; H, 4.2; Br, 29.2. Calc. for $C_{10}H_{11}O_4Br$ C, 43.7; H, 4.0; Br, 29.2%]; ν_{max} (Nujol mull): 1720 vs (C=O str.), 1630 s (C=O str.), 1540 w, 1460 vs, 1380 s, 1350 w, 1290 m, 1260 m, 1150 m, 1100 m, 1050

w, 1010 w, 985 m, 925, 850 m, 750 m, 680 w and 660 w cm^{-1}; δ_H (300 MHz, $CDCl_3$): 1.30 (3H, t, $^3J_{7,8}$ 7.5 Hz, CH_3), 2.30 (s, 6H, 2 x CH_3); 4.30 (2H, q, $^3J_{7,8}$ 7.5 Hz, CH_2) ppm; δ_C (75.5 MHz, $CDCl_3$): 14.1 (CH_3), 18.9 (CH_3), 21.8 (CH_3), 62.1 (CH_2), 110.1 (C-3), 114.1 (C-4), 151.9 (C-5); 157.4 (C-6), 161.0 (C=O), 164.9 (C=O) ppm; m/z (FAB): 275, 276 $(M+H)^+$, 100%.

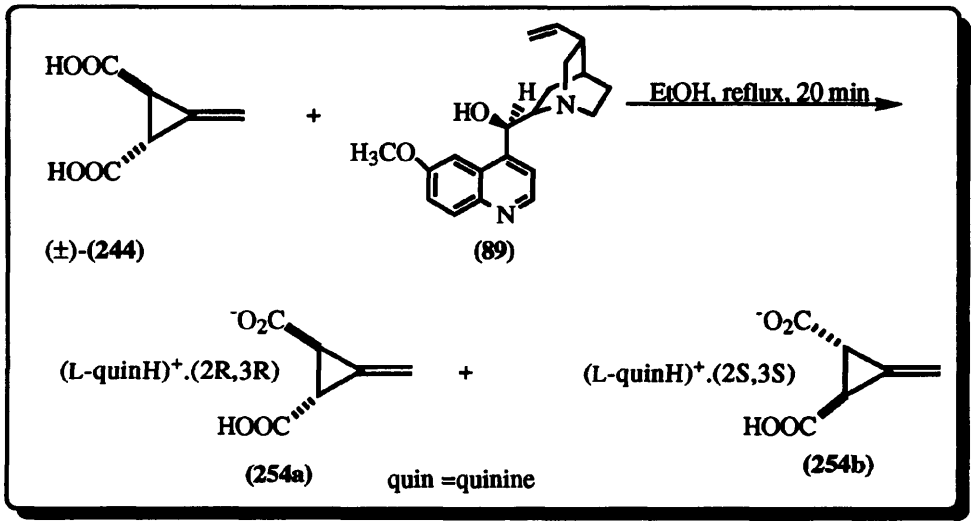
III.6.20 Preparation of (±)-*trans* -1-methylenecyclopropane-2,3-dicarboxylic acid (Feist's acid) (244)



To a stirred, boiling solution of potassium hydroxide (7M, 615 cm^3) at *ca*. 115 °C (oil bath at 150-160 °C) was added molten 3-bromo-5-carboethoxy-4,6-dimethyl-2-pyrone **(243)** (120.0 g, 0.44 mol) in portions over 20 min and the mixture was boiled for an additional 30 min. To the cooled (ice bath), stirred mixture was added 50% w/w sulphuric acid (225.60 cm^3) in small portions over a 20 min period. The mixture was then filtered under suction and the precipitated salts were washed thoroughly with diethyl ether. The aqueous layer was extracted with diethyl ether (5 x 300 cm^3) and the combined ether

extracts were dried ($MgSO_4$), filtered and concentrated and stored in the freezer overnight. Filtration, followed by washing with cold diethyl ether, afforded **(244)** as a pale yellow solid (30.0 g). The filtrate was refluxed gently with activated carbon (Norite A), filtered and again concentrated, to give a second crop of yellow crystals (4.0 g). Total yield of **(244)** (34.0 g, 0.24 mol, 55%) (lit.,[166] 80%). An analytical sample was obtained by recrystallization from diethyl ether to give colourless needles, m.p. 200-202 °C (lit.,[166] 200 °C); [Found: C, 50.4; H, 4.0. Calc. for $C_6H_6O_4$ C, 50.7; H, 4.2%]; ν_{max} (Nujol mull): 3500-2500 br.s (OH str.), 1700 br.s (C=O str.), 1470 s, 1320 s, 1300 s, 1210 m, 1100 s, 980 m, 920 m, 790 m, 680 m, 660 s cm^{-1}; δ_H (300 MHz, DMSO-d_6): 2.85 (2H, t , ^3J 2 Hz, 2 x CH), 5.9 (2H, t , ^2J 2 Hz, CH_2), 12.9-13.2 (br.s, < 2H, COOH) ppm; δ_C (DMSO-d_6): 29.5 (C-2), 110.0 (C-4), 133.5 (C-3), 174.0 (C-1) ppm; m/z (FAB): 143 $(M+H)^+$, 100%.

III.6.21 Method (a): Resolution of Feist's acid via L-(-)-quinine



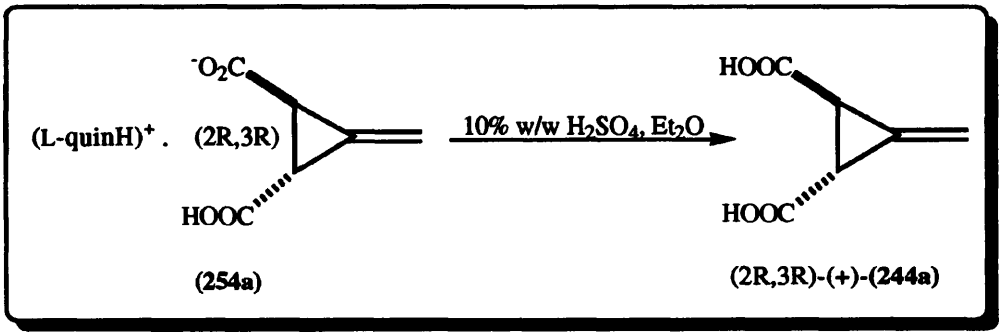
Into a round-bottomed flask (1*l*) equipped with a reflux condenser L-(-)-quinine **(89)** (34.27 g, 105.63 mmol) and dry ethanol (121 cm^3) were added and stirred for 5 min. A solution of (±)-**(244)** (15.0 g, 105.63 mmol) in dry ethanol (67 cm^3) was added in one batch to the flask to give a white precipitate, which completely dissolved on heating under reflux for 20 min. The solution was allowed to cool to room temperature slowly and left to stand undisturbed for five days. Filtration gave a white solid, this was the quinine salt of Feist's acid **(254a)** (28.0 g); m.p. 180-182 °C, $[\alpha]_{546}^{23}$ -165 ° (c 0.4, EtOH) [lit.,[72] 30.21 g, m.p.184-186 °C; $[\alpha]_{546}$ -154 ° (0.4, EtOH)]. The crude salt **(254a)** was recrystallized several times, from dry ethanol. The results from these recrystallizations are summarized in **Table (3)**. Further recrystallisation did not change the optical rotation and melting point.

Table (3)

No. of recrestallizations	Weight of the diastereomer salt (g) ( )[a]	m.p ^{0}C ( )[a]	$[\alpha]_{546}^{23}$ ^{0} (c 0.4, EtOH) ( )[a]
(i)	23.0 (21.33)	182-184 (191-193)	-161- (-154.0)
(ii)	16.0 (14.0)	178-179 (194-195)	-165.1 (-146.0)
(iii)	12.5 (13.2)	181-182 (196-197)	-156.0 (-140.0)
(iv)	10.0 (11.4)	183-185 (196-197)	-145.0 (-139.7)
(v)	9.1 (9.6)	No change	No change

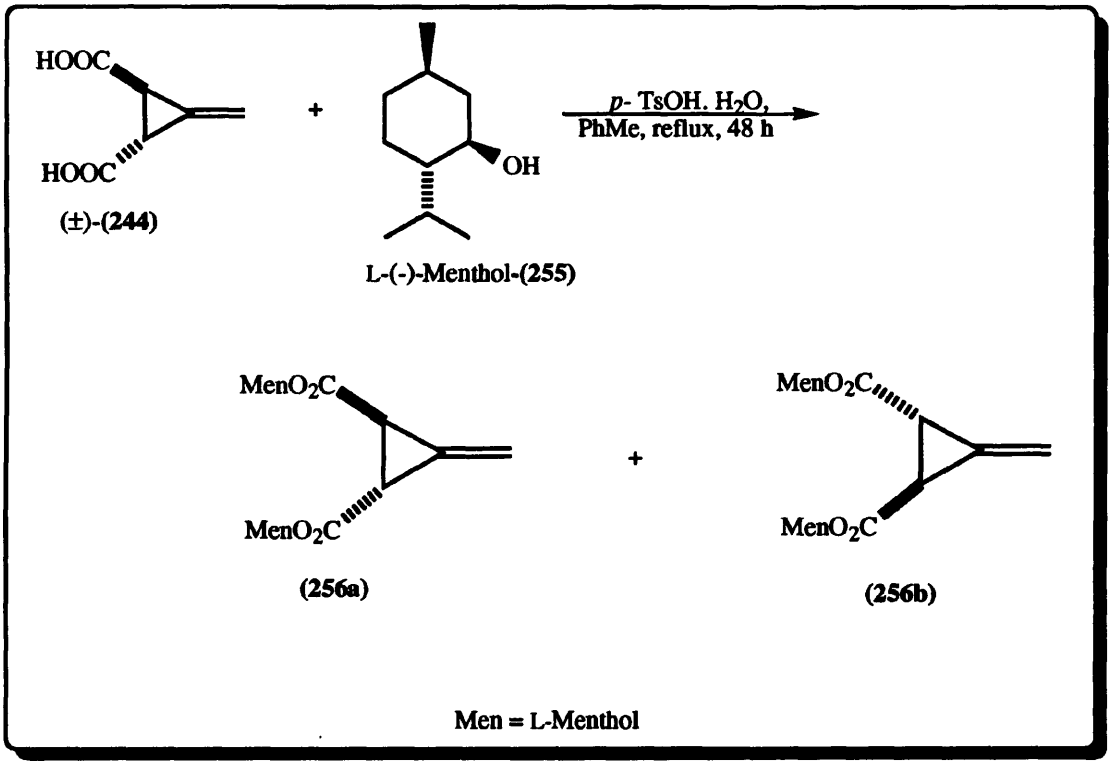
[a] The values in parenthesis are those given in ref. **(72)**.

III.6.22 Regeneration of (2R,3R)-(+)-1-methylenecyclopropane-2,3-dicarboxylic (244a)



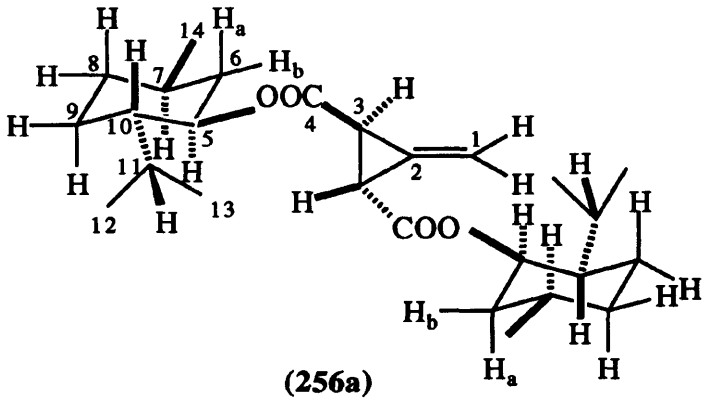
The quinine salt of (2R,3R)-(-)-1-methylcyclopropane-2,3-dicarboxylic acid **(254a)** (9.0 g, 19.30 mmol) was dissolved in 10% w/w H_2SO_4 (320 cm^3). The resultant solution was extracted with diethyl ether (6x 275 cm^3). The combined diethyl ether extracts were washed with acidified brine (pH 2) (2 x 275 cm^3), dried ($MgSO_4$) then filtered. The solvent was evaporated to give pure Feist's acid **(244a)** as a white solid (2.30 g, 16.20 mmol, 84%), m.p 202 °C; $[\alpha]_{546}^{23}$ +116.1°, $[\alpha]_D^{25}$ +86.2° (c 0.76, EtOH) [lit.,[72] m.p 203-205 °C, $[\alpha]_{546}$ +179.3°, $[\alpha]_D^{25}$ +151.6° (c 0.76, EtOH)].

III.6.23 Method (b): Preparation of dimenthyl (2R,3R)-1-methylene-cyclopropane-2,3-dicarboxylate (256a)



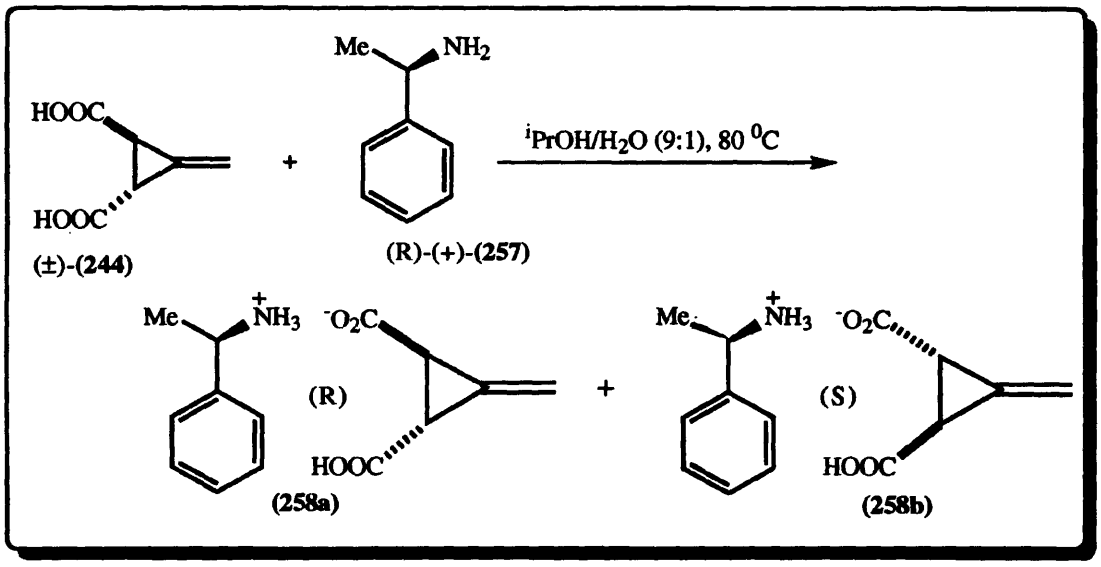
In a round-bottomed flask equipped with a Dean-Stark apparatus and a reflux condenser, (±)-Feist's acid **(244)** (18.0 g, 126.76 mmol), L-(-)-menthol (39.72 g, 254.2 mmol) and *p* -toluenesulphonic acid monohydrate (0.17 g, 0.90 mmol) were suspended in dry toluene (240 cm^3). The reaction mixture was refluxed for 48 h and monitored by TLC (hexane-EtOAc, 40:1). The amount of water collected was *ca.* 4.50 cm^3 (4.6 cm^3 calculated for 100% conversion). The reaction mixture was allowed to cool to room temperature and then diluted with diethyl ether (400 cm^3), washed with a saturated solution of sodium carbonate (1 x 300 cm^3), followed by a mixture of methanol and water (150:250 cm^3 respectively), and finally brine (1 x 250 cm^3). The organic layer was then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a pale-yellow oil (51.75 g). TLC (hexane-EtOAc, 40:1) showed one major spot plus two spots for the

unreacted starting materials. The oily mixture was cooled to -75 °C (Cardice/methanol) and diethyl ether (*ca.* 5.0 cm^3) was added with stirring until the temperature reached 0 °C. The mixture was then stirred for a further 30 min and placed under vacuum to obtain white crystals of L-(-)-menthol (1.20 g) on the walls of the flask. The remaining liquid was decanted off and was further purified by column chromatography using a mixture of hexane and ethyl acetate (40:1) as eluant, to yield hygroscopic white crystals of the menthyl ester **(256)** (38.60 g, 92.34 mmol, 73% based on racemic Feist's acid), m.p 76 °C; $[\alpha]_D$ -62.36° (c 0.47, $CHCl_3$). Recrystallizations were carried out from methanol until the pure menthyl ester **(256a)** was obtained and the specific rotation was constant; (i) 24.30 g, 17.20 mmol, m.p 79 °C, $[\alpha]_D^{25}$ -113.76° (c 0.47, $CHCl_3$); (ii) 19.2 g, 45.93 mmol, m.p 84 °C, $[\alpha]_D^{25}$ -117.5° (c 0.47, $CHCl_3$); (iii) 15.6 g, 37.52 mmol, m.p 84.5 °C, $[\alpha]_D^{25}$ -122° (c, 0.42, $CHCl_3$), *ca* . 59% based on one enantiomer of Feist's acid. [Found: C, 74.3; H, 10.3. $C_{26}H_{42}O_4$ requires C, 74.6; H, 10.1%]; ν_{max} (Nujol mull): 1730 s (C=O str.), 1170 s (C-O-C str.) cm^{-1}; δ_H (300 MHz, $CDCl_3$): 0.80 (12 H, d, $^3J_{11,13} = {}^3J_{11,12}$ 6.75 Hz, 4 x CH_3), 0.90 (6H, s, 2 x CH_3), 0.93-1.95 [18H, complex m, 2(H_6-H_{11})], 2.85 (2H, t, $^4J_{3,1}$ 2.5 Hz, 2 x H_3), 4.69 (2H, dt, $^3J_{5,6a}$ 11 Hz, $^3J_{5,6b}$ 4.5 Hz, 2 x H_5), 5.62 (2H, complex m, 2 x H_1) ppm; δ_C (75.5 MHz, $CDCl_3$): 16.3 (CH_3), 20.7 (CH_3), 21.9 (CH_3), 23.4 (C-8), 25.7 (C-9), 26.3 (C-6), 31.3 (C-7), 34.1 (C-11); 40.6 (C-10), 46.8 (C-3), 75.2 (C-5), 105.6 (C-1); 129.5 (C-2), and 163.7 (C=O) ppm; m/z (FAB): 417 $(M-H)^+$, 70%.



(256a)

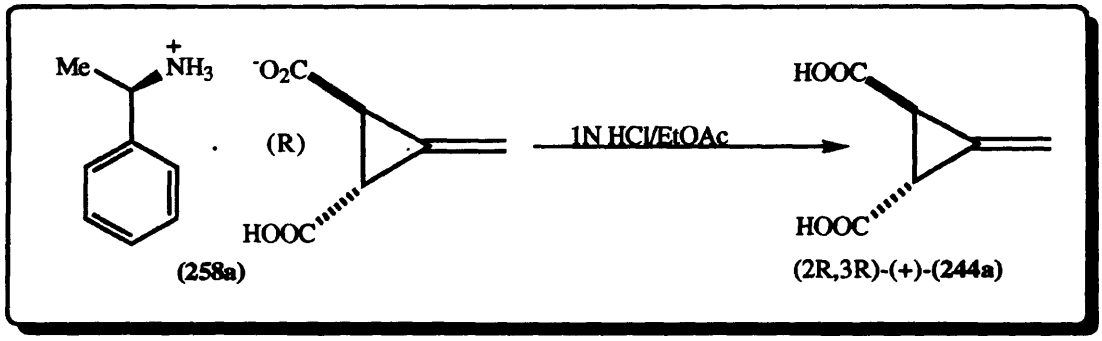
III.6.24 Method (c): Preparation of the (R)-(α)-methylbenzylammonium salt of (2R,3R)-(+)-methylenecyclopropane-2,3-dicarboxylic acid (1:1) (258a).



A mixture of (±)-*trans*-1-methylcyclopropane-2,3-dicarboxylic acid **(244)** (8.0 g, 56.34 mmol), isopropanol (72 cm^3) and distilled water (8.0 cm^3) was heated on a steam bath (*ca.* 80 °C) until it had completely dissolved. The resulting solution was removed from the steam bath and with stirring, (R)-(+)-α-methyl-benzylamine **(257)** (6.82 g, 56.4 mmol) was added slowly over a period of 15 min followed by the addition of an excess of isopropanol (12 cm^3). After 5 min the solution was gradually allowed to cool to room temperature and left to stand overnight. The crystalline material which precipitated was collected by filtration and washed with ice-cold isopropanol (1:10) in three portions (24, 20 and 17 cm^3). The slurry was dried under vacuum at 50 °C for 6 h to obtain the ammonium salt **(258a)** as a white solid (6.57 g, 25 mmol, 89%; based on one diastereomer salt of Feist's acid), m.p 221-224 °C [lit[169], m.p ^{0}C (unreported), 89%]; $[\alpha]_D^{25}$ +90.34 °, $[\alpha]_{546}^{23}$ +92.32. (c 0.352, H_2O) (lit[169], $[\alpha]_D^{23.5}$ +86.1°, $[\alpha]_{546}$ +103.1°, c 0.57, H_2O). The

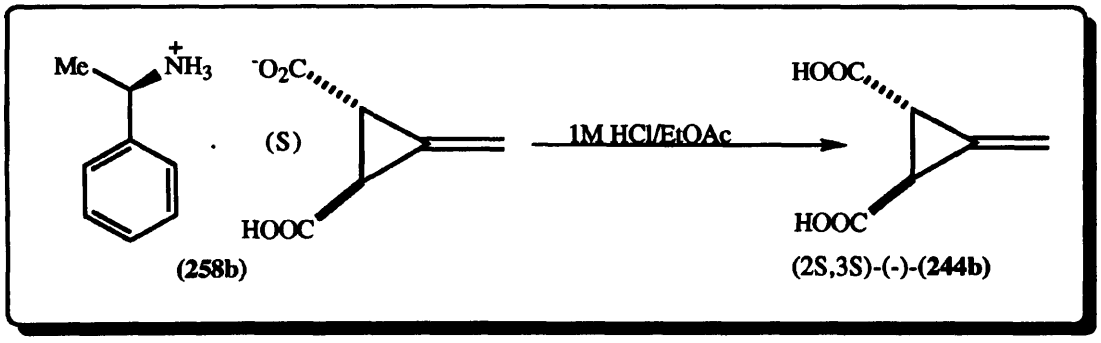
crude material was recrystallized twice from a mixture of isopropanol and water (3.2:1.0 cm^3) to afford good crystals of (R)-(α)-methylbenzylammonium salt of (+)-1-methylene-cyclopropane-(2R,3R)-dicarboxylic acid (1:1) **(258a)** (5.4 g, 20.53 mmol, 73%) (lit[169], 71%); m.p 222-225 °C (lit[169], 218-223 ° C); $[\alpha]_D^{25}$ +102.46° (c 0.61, H_2O) (lit.,[169] $[\alpha]_D$ +94.7° ; c 0.61, H_2O). A small sample was recrystallized further but no change in the specific rotation or melting point was observed; [Found: C, 63.6; H, 6.8; N, 5.4. Calc. for $C_{14}H_{17}NO_4$ C, 63.9; H, 6.5; N, 5.3%].

III.6.25 Regeneration of (2R,3R)-(+)-1-methylenecyclopropane-2,3-dicarboxylic acid (244a)



The (R)-(α)-methylbenzylammonium salt of (2R,3R)-(+)-1-methylenecyclopropane -2,3-dicarboxylic (1:1) (**258a**) (2.50 g, 9.51 mmol) was dissolved in a mixture of ethyl acetate and 1N HCl (35.5 cm^3) and stirred for 2 min. The aqueous layer was separated and extracted with ethyl acetate (3 x 25 cm^3) and the combined organic layers were washed with 1N HCl (1 x 17.0 cm^3), brine (1 x 17 cm^3) and dried ($MgSO_4$). After filtration, the solution was concentrated under reduced pressure to afford (2R,3R)-(+)-methylenecyclo-propane-2,3-dicarboxylic acid (**244a**) as a white solid (1.24 g, 8.75 mmol, 92%); m.p. 204-206°C; $[\alpha]_{546}^{23}$ + 155.5° (c 0.70, EtOH), [lit.,[72] m.p 203-205 °C; $[\alpha]_{546}$ +176° (c 0.70, EtOH)].

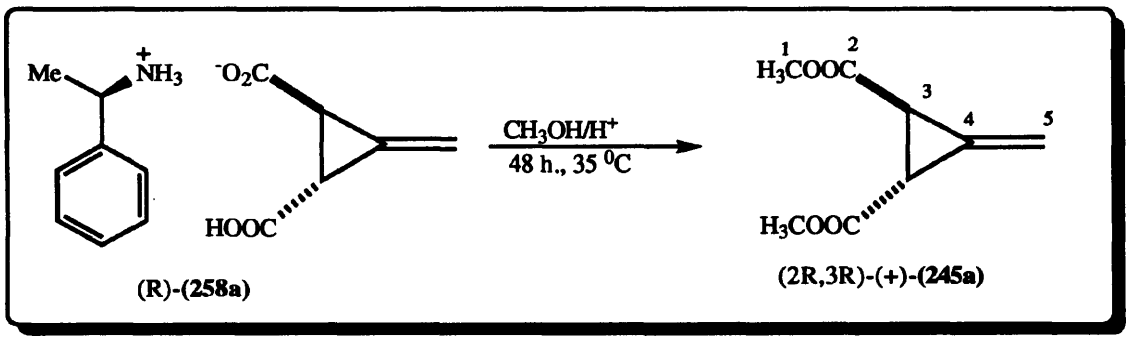
III.6.26 Regeneration of (2S,3S)-(-)-1-methylcyclopropane-2,3-dicarboxylic acid (244b)



The mother liquor obtained from the resolution of (R)-(α)-methylbenzylammonium salt of (2R,3R)-(+)-1-methylenecyclopropane-2,3-dicarboxylic (1:1) **(258a)** acid (18.10, 38.4 mmol) was concentrated under reduced pressure to give a pale brown semi-solid. This was dissolved in water (36 cm^3) and 1N HCl (108 cm^3) and stirred for 5 min before extracting with ethyl acetate (4 x 100 cm^3). The combined organic layers were washed with 1N HCl (1 x 44 cm^3), brine (1 x 44 cm^3) and dried ($MgSO_4$). After filtration the solution was concentrated under reduced pressure to afford (2S,3S)-(-)-1-methylenecyclopropane-2,3-dicarboxylic acid **(244b)** as a white solid (5.23 g, 36.83 mmol, 96%); m.p 202 °C, (lit.[169], m.p. 199.21 -199.7 °C); $[\alpha]_{546}^{23}$ -95.3° (c 0.81, EtOH) [lit.,[169] $[\alpha]_{546}$ -131.3°, (c 0.81, EtOH)].

III.6.27 Preparation of dimethyl (2R,3R)-(+)-1-methylenecyclopropane-2,3-dicarboxylate (245a)

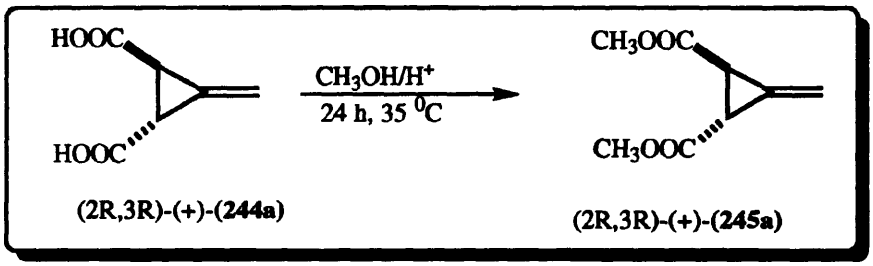
Method (a):



A mixture of (R)-(α)-methylbenzylammonium salt of (2R,3R)-(+)-1-methylene-cyclopropane-2,3-dicarboxylic acid (1:1) **(258a)** (0.50 g, 6.61 mmol), methanol (6 cm^3) and conc. sulfuric acid (0.012 cm^3, via microsyringe) was stirred at 35 °C for 48 h. The reaction mixture was then quenched with saturated sodium carbonate solution (0.20 cm^3) and the solvent was removed *in vacuo*. The residue was extracted with diethyl ether (10 cm^3) and the extract washed with water (2 x 2.50 cm^3), saturated sodium carbonate (2 x 2.5 cm^3) and dried ($MgSO_4$). After filtration the diethyl ether was removed *in vacuo* and the product was washed again with diethyl ether (3 cm^3) and evacuated (twice) to give the dimethyl ester **(245a)** as an oil (0.23 g, 1.39 mmol, 71%) (lit[169], 100%). Further purification was carried out by DCFC (hexane-EtOAc, 3:1) to afford white crystals of the dimethyl (2R,3R)-(+)-1-methylenecyclopropane-2,3-dicarboxylate **(245a)** (165 mg, 0.97 mmol, 51%) m.p 34-35 °C (lit[169], 34.1-34.9 °C); $[\alpha]_D^{25}$ +123.3°, (c 0.76, CCl_4) (lit.[169], $[\alpha]_D$ +124.8°, c 0.76, CCl_4); [Found: C, 56.5; H, 5.8. Calc. for $C_8H_{10}O_4$ C, 56.5; H, 5.9%]; ν_{max} (Nujol mull): 1740 s (C=O str.), 1450 s, 1380 s, 1300 m, 1160 m, 1110 m,

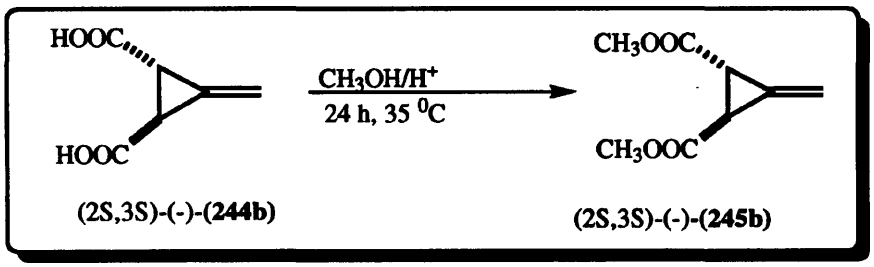
1050 w, 1000 m, 920 m, 900 m, 820 w, 790 m, 720 w, 660 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 2.82 (2H, t, , ^3J 2.5 Hz, 2 x CH), 3.72 (6H, 5, 2 x CH_3), 5.60 (2H, t , ^2J 2.5 Hz, CH_2) ppm; δ_C (75.5 MHz, $CDCl_3$): 26.3 (C-3), 53.1 (C-1); 107.4 (C-5), 129.5 (C-4), 170.4 (C-2) ppm; m/z (FAB): 171 $(M+H)^+$, 100%.

III.6.28 Method (b):



A mixture of (2R,3R)-(+)-1-methylenecyclopropane-2,3-dicarboxylic acid **(244a)** (0.80 g, 5.63 mmol), methanol (18 cm^3) and conc. sulfuric acid (0.04 cm^3) was stirred at 35 °C for 24 h. The reaction was quenched with saturated sodium carbonate solution (0.40 cm^3) and the solvent was removed *in vacuo*. Diethyl ether (15 cm^3) was added and the ether extract was washed with water (2 x 3 cm^3), saturated sodium carbonate solution (2 x 3 cm^3) and dried ($MgSO_4$) then filtered. The diethyl ether was removed *in vacuo* to give pure, colourless crystals of (2R,3R)-(+)-dimethyl ester **(245a)** (0.74 g, 4.34 mmol, 89%) (lit[169], 99%), m.p 33-34 °C (lit[169], 32-33 °C); $[\alpha]_D^{25}$ +133.3° (c 0.76, CCl_4) (lit.,[169] $[\alpha]_D$ +124.8°, c 0.76, CCl_4).

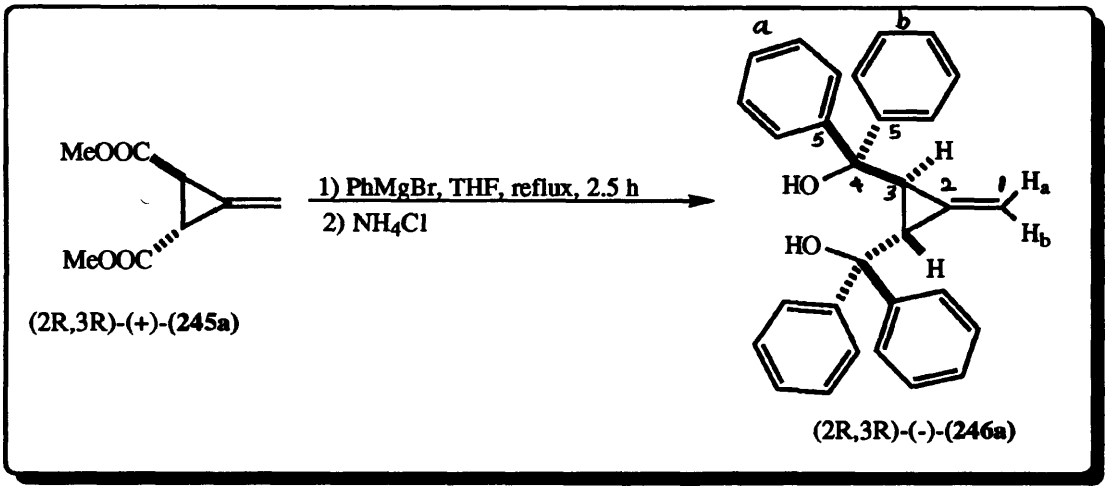
III.6.29 Preparation of dimethyl (2S,3S)-(-)-1-methylenecyclopropane-2,3-dicarboxylate (245b)



The dimethyl (2S,3S)-(-)-1-methylenecyclopropane-2,3-dicarboxylate **(245b)** was prepared using the procedure described in **III.6.28 Method (b)** employing (2.51 g, 17.7 mmol) of (-)-(2S,3S)-Feist's acid (**244b**), in 85% yield.$[\alpha]_D^{25}$ -70.8^0 (c o.83, CCl_4).

All data for this product were in full agreement with those for the (2R,3R)-(+)-dimethyl ester **(245a)** described earlier.

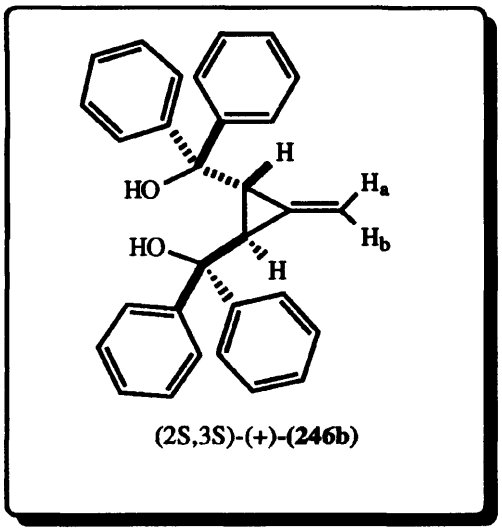
III.6.30 Synthesis of (2R,3R)-(-)-bis(diphenylmethanol)-1-methylene cyclopropane (246a)



To a 3-necked, round-bottomed flask (500 cm^3) equipped with an addition funnel and condenser was added magnesium turnings (1.0 g, 41.14 mmol), dry THF (4 cm^3) and a few crystals of iodine. A few drops of bromobenzene, as a solution in dry THF (13 cm^3, 3.14 M, 40.82 mmol), were added under argon to the stirred mixture to initiate the reaction. The remaining bromobenzene solution was added slowly over 15 min so as to maintain gentle reflux. When the addition was complete the mixture was refluxed for 45 min and then cooled gradually to 0 °C. A solution of dimethyl (2R,3R)-(+)-1-methylenecyclopropane-2,3-dicarboxylate **(245a)** (0.50 g, 2.94 mmol) in dry THF (16 cm^3) was added dropwise under argon and the mixture was stirred at room temperature overnight. The mixture was then refluxed for 2.5 h and saturated aqueous ammonium chloride solution (35 cm^3) was added slowly at 0 °C. The mixture was extracted with ethyl acetate (3 x 30 cm^3) and the extract was washed with brine (2 x 30 cm^3), dried ($MgSO_4$), filtered and concentrated to give an impure yellow oil (1.30 g). This was purified by column chromatography using a mixture of (hexane-EtOAc, 4:1) as eluant to afford a white solid (Rf, 0.44) of (2R,3R)-(-)-bis(diphenylmethanol)-1-methylenecyclopropane **(246a)** (0.70

g, 1.68 mmol, 58%). Further purification was carried out by recrystallization from a mixture of (hexane-EtOAc, 3:1) to afford the product as white crystals (0.50 g, 1.2 mmol, 42%), m.p, 130-131 °C, $[\alpha]_D^{25}$ -276.0° (c 0.25, CCl_4); [Found: C, 86.0; H, 6.0. $C_{30}H_{26}O_2$ requires C, 86.1; H, 6.2%]; ν_{max} (Nnujol mull): 3600-3100 br (OH str.); 3020 (C-H str., aromatic), 3000 (C=C-H str., methylene), 1160 m, 1090 w, 1050 w, 1020 w, 990 w, 890 m, 740 m, 690 s cm^{-1}; δ_H (300 MHz, $CDCl_3$): 1.78 (2H, s, 2 OH, identified by shaking with D_2O), 2.38 (2H, m, 2 x CH), 5.43 (2H, m, H_a + H_b), 7.08-7.22 (20H, m, aromatic) ppm; δ_C (75.5 MHz, $CDCl_3$): 29.0 (C-3), 73.6 (C-4), 107.6 (C-1), 134.6 (C-2), 127.1, 127.4, 127.5, 128.2 (6C-H, aromatics), 146.2, 146.8 (C-5a and C-5b) ppm; m/z (FAB): 417 $(M-H)^+$, 18%; 401 $(M-OH)^+$, 80%; and 205 $[M-(Ph_2C.H_2O)]^+$, 100%.

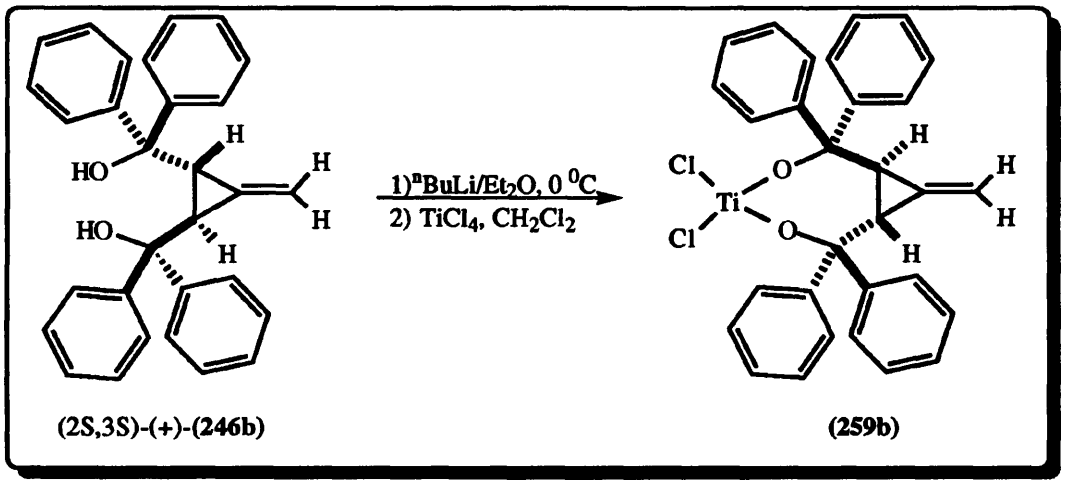
III.6.31 Synthesis of (2S, 3S)-(+)-bis(diphenylmethanol)-1-methylene-cyclopropane (246b)



(2S,3S)-(+)-(**246b**)

The (2S,3S)-(+)-enantiomer (**246b**) was prepared as a white solid in 81% by the same procedure as described in the synthesis of (2R,3R)-(-)-diol (**246a**) **(Method III.6.30)** using the same quantities. This solid was further purified by recrystallization from a mixture of (hexane-EtOAc, 3:1) to afford crystals of (2S,3S)-(+)-bis(diphenyl-methanol)-1-methylenecyclopropane (**246b**) in 51% yield; m.p 130-131 °C, $[\alpha]_D^{25}$ + 50° (c 0.25, CCl_4). All other data were in full agreement with those reported for (2R,3R)-(-)-enantiomer (**246a**).

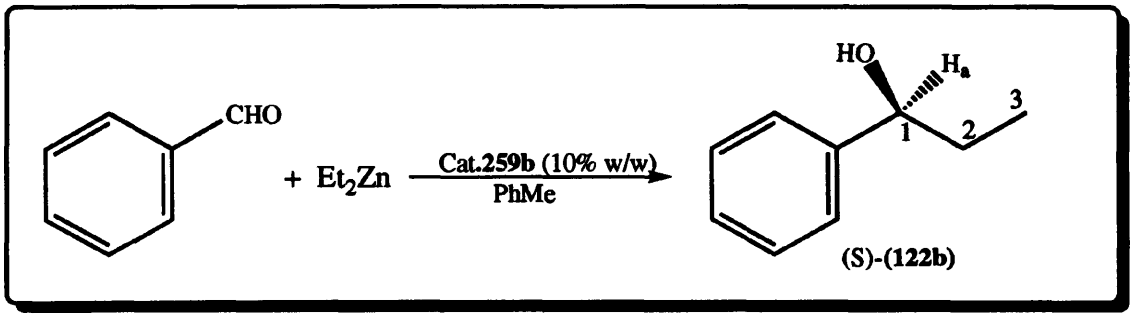
III.6.32 Synthesis of (2S,3S)-1-methylenecyclopropane-tetraphenyldimethanolatotitanium dichloride (259b)



(2S,3S)-(+)-(246b) (259b)

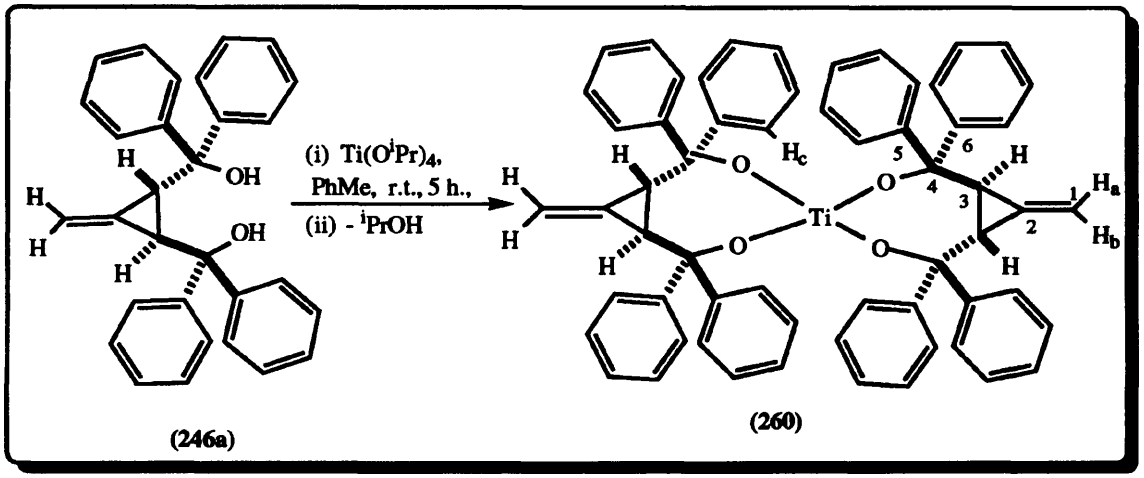
(2S,3S)-(+)-Bis(diphenylmethanol)-1-methylenecyclopropane (**246b**) (0.20 g, 0.48 mmol) was suspended in dry diethyl ether (1.50 cm^3). The solution was deoxygenated for 15 min. n-Butyllithium (0.6 cm^3, 0.96 mmol, 1.6M) was then added dropwise to the stirred solution at 0 °C under an argon atmosphere. The resulting slurry was dissolved in dry dichloromethane (4 cm^3) and titanium tetrachloride (0.4 cm^3) was added slowly under an inert atmosphere of argon. The mixture turned red and was left to stir for 15 min, when TLC (hexane-EtOAc, 4:1) showed no starting material remained. This solution was used immediately in the next stage (**III.6.33**).

III.6.33 Enantioselective addition of diethylzinc to benzaldehyde catalyzed *in situ* by 1-methylenecyclopropane-(2S,3S) (α,α,α',α')-tetraphenyldimethanolatotitanium dichloride (259b).



To a solution of the chiral titanium complex **(259b)** was added freshly-distilled benzaldehyde (0.50 cm^3, 0.51 g, 4.8 mmol), the mixture was stirred at room temperature for 15 min. Diethylzinc (8.70 cm^3, 1.1M, 9.6 mmol, toluene) was added slowly and the mixture was stirred at room temperature for 24 h. Hydrochloric acid (1M, 15 cm^3) was added slowly to the reaction mixture at 0 °C. The mixture was then extracted with dichloromethane (4 x 25 cm^3) and the extract dried ($MgSO_4$), filtered and concentrated to afford a light brown oil (0.55 g). This was purified by column chromatography (hexane-EtOAc 3:1) to afford 1-phenylpropanol (0.30 g, 2.21 mmol, 46%) as a pale yellow oil. Further purification was carried out using bulb-to-bulb Kügelröhr distillation under reduced pressure (100 °C/5 mmHg) to afford (S)-(-)-1-phenylpropanol **(122b)** (0.20 g, 1.471 mmol, 31%), $[\alpha]_D^{25}$ -15.3° (c 1.8, $CHCl_3$), 34% **e.e.** [lit.[163], $[\alpha]_D$ -45.45^0, (c 5.15, $CHCl_3$)].

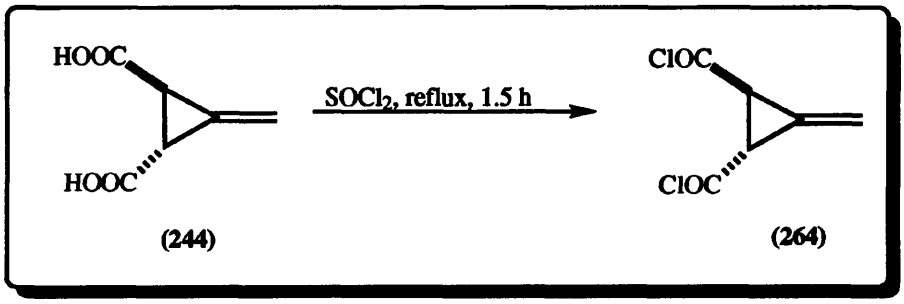
II.6.34 Preparation of bis[1-methylenecyclopropane-(2R,3R)-(α,α,α',α')-tetraphenyldimethoxy] titanate (260)



In a round-bottomed flask equipped with reflux condenser, (2R,3R)-(-)-bis(diphenylmethanol)-1-methylenecyclopropane (246a) (0.12g, 0.29 mmol), was dissolved in deoxygenated, freshly-distilled toluene (15 cm^3). The solution was stirred under an atmosphere of argon for 10 min. Titanium tetraisopropoxide (0.1 cm^3, 0.1g, 0.35 mmol) was added and the mixture was stirred at room temperature for 3 h. TLC (hexane-EtOAc, 2:1) indicated the presence of some unreacted diol. After a further 2 h no further reaction was observed by TLC. The reaction solvent was distilled off under reduced pressure (40 °C/15 mm Hg) to remove the isopropanol liberated during the reaction. After concentration under high vacuum (40 °C, 4 h) a white precipitate of the titanate complex was obtained. Thi was contaminated with a slight amount of the reagent and the starting material. The mixture was recrystallized repeatedly from a mixture of (EtOAc-hexane, 1:2) to afford the pure titanate complex (260) (0.15 g, 0.17 mmol, 60% yield), m.p. 194-196 °C, [Found: C, 81.5; H, 5.9. $(C_{30}H_{24}O_2)_2Ti$ requires C, 81.8, H, 5.5%]; δ_H (300 MHz, $CDCl_3$): 1.84 (2H, m, CH); 5.53 (2H, m, H_a+H_b), 7.20 (16H, m,

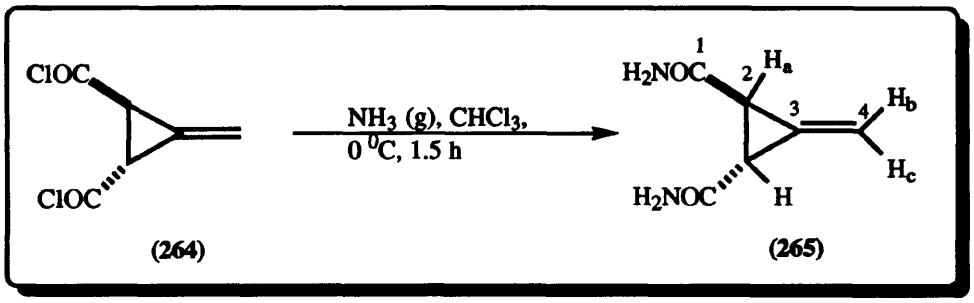
aromatics), 7.26 (4H, m, $4H_C$) ppm; δ_C (75 MHz, $CDCl_3$): 28.8 (C-3), 76.6 (C-4), 107.3 (C-1), 126.1, 126.7, 126.9, 127.2, 128.0, 129.0 [6 x (C-H), aromatics], 134.4 (C-2), 146.0, 146.5 (C-5 and C-6) ppm; m/z (FAB): 881 $(M+H)^+$, 100%.

III.6.35 Preparation of (±)-*trans* -2,3-bis(chlorocarbonyl)-1-methylene-cyclopropane (264)



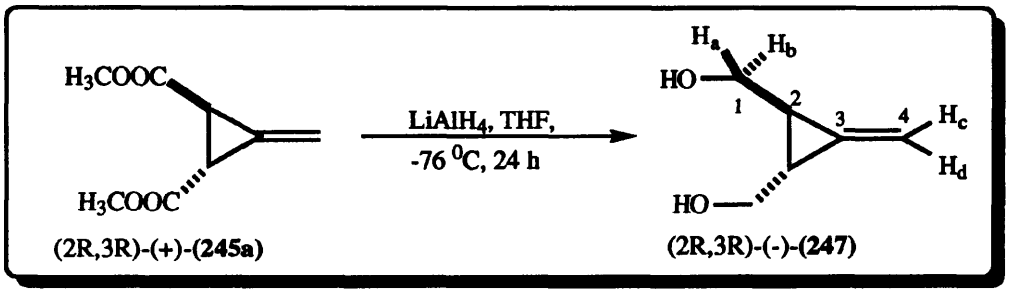
In a 3-necked, round-bottomed flask, fitted with a reflux condenser and a gas bubbler, an excess of freshly distilled thionyl chloride (15.0 cm^3, 24.54 g, 215 mmol) was added slowly over a period of 15 min to (±)-Feist's acid **(244)** (2.0 g, 40 mmol.) under an atmosphere of argon. The mixture was refluxed gently (*ca*. 70 °C) for 1.5 h when a deep greenish colour was observed. The reaction was monitored by IR spectroscopy and refluxing was continued for 1.5 h. The IR spectrum showed the starting material had reacted totally. The excess of thionyl chloride was then removed under high vacuum at room temperature to yield a deep green liquid **(264)** (1.97 g, 11.0 mmol, 79%), (lit.[166], 93%); ν_{max} (neat film): 1800 s (COCl str.). The crude acid chloride **(264)** was used without further purification.

III.6.36 Preparation of (±)-*trans* -1-methylenecyclopropane-2,3-dicarboxamide (265)



A solution of (±)-*trans* -2,3-bis(chlorocarbonyl)-1-methylenecyclopropane **(264)** (1.80 g, 10.06 mmol) in dry chloroform (30 cm^3) was saturated with NH_3 gas at 0 °C with stirring for 1.5 h. The reaction mixture was dissolved in methanol and filtered to remove ammonium chloride. The filtrate was then evaporated under reduced pressure to give the diamide **(265)** as an off-white solid (1.40 g, 10 mmole, 100%). A small amount was recrystallized from methanol for analysis; m.p. 230 °C; [Found: C, 51.5; H, 6.0; N, 19.7. $C_6H_8O_2N_2$ requires C, 51.4; H, 5.7; N, 20.0%]; ν_{max} (Nujol mull): 3370 w, 3310 w (NH_2 str.), 1700 s (C=O str.), δ_H (300MHz, DMSO-d_6): 2.40 (2H, m, 2 x H_a), 5.35 (2H, m, H_b+H_c), 7.70 (2H, s, NH_2) ppm; δ_C (75.5MHz, DMSO-d_6): 29.5 (C-2), 107.7 (C-4), 136.0 (C-3), 174.2 (C-1) ppm; m/z (FAB): 136 $(M-4H)^+$, 72%.

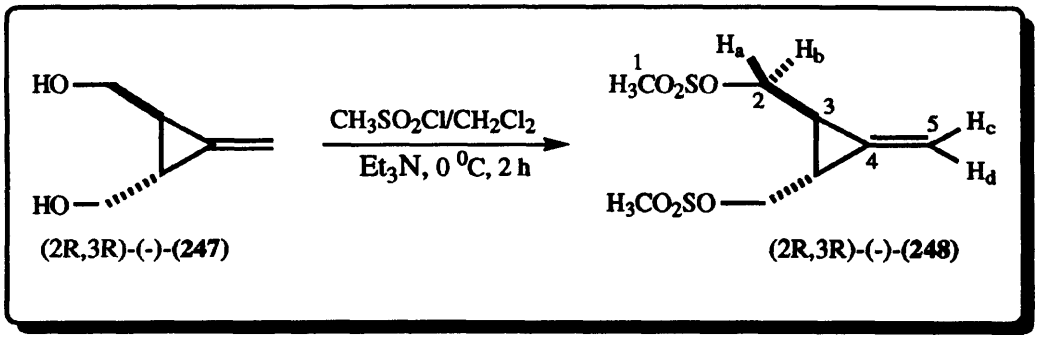
III.6.37 Preparation of (2R,3R)-(-)-bis-(hydroxymethyl)-1-methylenecyclopropane (247)



To a stirred suspension of lithium aluminium hydride (3.0 g, 79.05 mmol) in dry THF (80 cm^3) at -76 °C under argon was added dimethyl (2R,3R)-(+)-1-methylenecyclopropane-2,3-dicarboxylate **(245a)** (6.0 g, 35.3 mmol) in dry THF (24 cm^3) dropwise over a 30 min period. The mixture was allowed to warm to room temperature over 6 hours and stirred overnight at 20 °C. The mixture was then cooled (ice bath) and 10% hydrochloric acid (12 cm^3) was added slowly. The solid was filtered under suction, washed thoroughly with diethyl ether and the combined filtrate and washings were dried ($MgSO_4$). After filtration the solvent was removed *in vacuo* to afford **(247)** as a hygroscopic white solid (4.02 g, 35.3 mmol, 82%) (lit.,[167] 85%); m.p. 39-40 °C (lit.,[167] 38-39 °C); $[\alpha]_D^{23}$ -108.5° (c 0.24, CCl_4) (lit.,[167] $[\alpha]_D$ -116.3° c 1.75, $CHCl_3$); [Found: C, 62.9; H, 8.9. Calc. for $C_6H_{10}O_2$: C, 63.2; H, 8.8%]; ν_{max} (neat film): 3300-3000 br. s (OH str.), 2920 s, 2870 s (C-H, alkane str.), 1720 m (C=C str.), 1400 br. m, 1280 w, 1130 s, 1090 m, (C-O-C str.), 1030 s and 895 s cm^{-1}; δ_H (300 MHz, $CDCl_3$): 1.68 (2H, m, 2 x H_2), 2.85 (>2H, s, 2 x OH), 3.20 (2H, dd, $^2J_{a,b}$ 11.5 Hz, $^3J_{a,2}$ 9.5 Hz, H_a); 3.9 (2H, dd, $^2J_{b,a}$ 11.5 Hz, $^3J_{b,2}$ 4.5 Hz, H_b), 5.45 (2H, t, $^2J_{4c,4d}$ 1.5 Hz, H_{4c} and H_{4d}) ppm; δ_C (75.5 MHz, $CDCl_3$): 24.8 (C-2), 64.0 (C-1), 105.5 (C-4), 134.1 (C-3) ppm; m/z (CI), 132

$(M+NH_4)^+$, 100%.

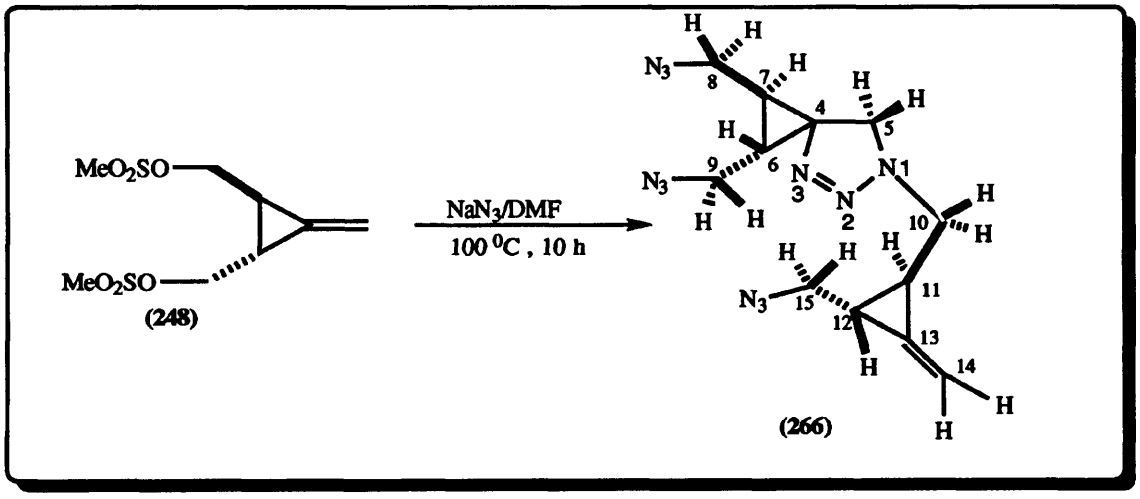
III.6.38 Preparation of (2R,3R)-(-)-bis-*O*- (mesylmethyl)-1-methylenecyclopropane (248)



Methanesulfonyl chloride (8.42 cm^3, 12.45 g, 108.72 mmol) was added dropwise to an ice-cold solution of (2R,3R)-(-)-bis-(hydroxymethyl)-1-methylenecyclopropane (**247**) (4.13 g, 36.23 mmol) in dichloromethane (135 cm^3) and dry triethylamine (20 cm^3) under argon. The reaction mixture was stirred at 0 °C for 2 h when TLC (hexane-EtOAc, 3:1) showed no starting material was present. The reaction mixture was poured into 10% w/w Na_2CO_3 (60 cm^3) and extracted with chloroform (3 x 70 cm^3). The two layers were separated and the organic layer was washed further with 10% w/w Na_2CO_3 (2 x 140 cm^3), water (1 x 140 cm^3) and brine (1 x 140 cm^3). The organic layer was dried ($MgSO_4$), filtered and evaporated under reduced pressure to give an oil which when triturated with cold diethyl ether under vacuum afforded the bismesylate (**248**) as a white solid (7.73 g, 28.63 mmol, 96%). An analytical sample was obtained by recrystallization from $CHCl_3$-hexane (1:15) to give colourless crystals, m.p. 70-71 °C; $[\alpha]_D^{23}$ -21.63 (c 1.55, CCl_4); [Found: C, 35.4; H, 5.4; S, 23.2. $C_8H_{14}S_2O_6$ requires C, 35.3; H, 5.1; S, 23.6%]; ν_{max} (Nujol mull): 1380 s [$S(=O)_2$ asym. str.], 1230 s [$S(=O)_2$ symm. str.], 960, 910,

820, 740, 730 (various S-O-C str.) cm^{-1}; δ_H (300 MHz, $CDCl_3$): 1.90 (2H, m, 2 x CH), 3.0 (6H, s, 2 x CH_3), 4.0 (2H, dd, $^2J_{a,b}$ 11 Hz, $^3J_{a,3}$ 5.5 Hz, 2 x H_a), 4.30 (2H, dd, $^2J_{b,a}$ 11 Hz, $^3J_{b,3}$ 8.5 Hz, 2 x H_b), 5.60 (2H, m, H_c and H_d) ppm; δ_C (75.5 MHz, $CDCl_3$): 21.0 (C-3), 37.9 (C-2), 70.6 (C-1), 108.6 (C-5), 130.8 (C-4) ppm; m/z (FAB): 271 $(M+H)^+$, 70%; 256 ($M-CH_3$), 50%.

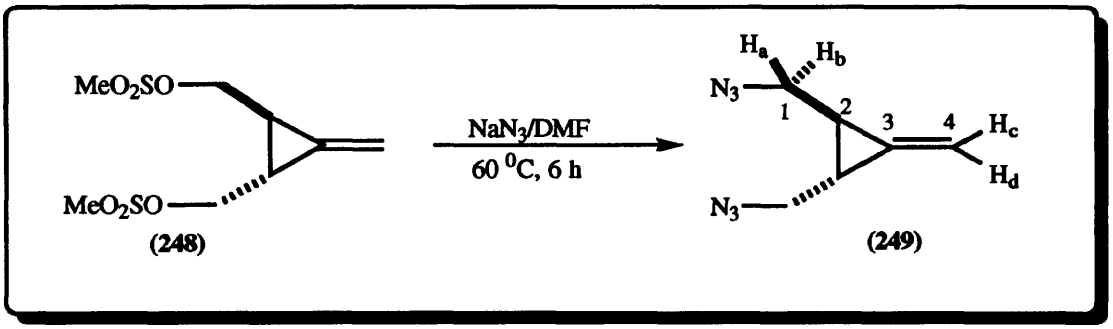
III.6.39 Preparation of (±)-N[1][*trans* -2-methyl-3-(azidomethyl)-1-methylenecyclopropane]-4-spiro[2,4]-1,2,3-triazol-6,7-*trans*-bis(azidomethyl)heptane (266)



In a 3-necked, round-bottomed flask, (±)-*trans*-2,3-bis-*O*-(mesylmethyl)-1-methylenecyclopropane (1.0 g, 3.70 mmol) and sodium azide (1.20 g, 18.45 mmol) were dissolved in dry DMF (20 cm^3) and the mixture was heated at 100 °C. The reaction was

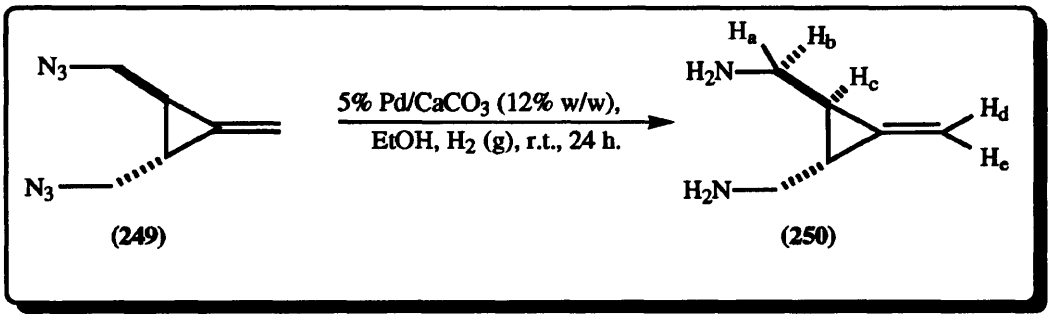
followed by TLC (hexane -EtOAc, 4:1) and after a period of 10 h TLC showed no starting material was present. The reaction mixture was allowed to cool to room temperature and was poured into water (100 cm^3) and extracted with diethyl ether (3 x 60 cm^3). The combined organic layers were washed with H_2O (1 x 100 cm^3), brine (1 x 100 cm^3), dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford the crude product as brown oil (1.20 g). The crude product was purified by DCFC (hexane-EtOAc, 8:1) to give pale yellow triazoline derivative (**266**) (0.75 g, 2.3 mmol, 62% yield); ν_{max} (neat film): 3000 m (HC=C str.), 2920w, 2860 w (C-H, alkane str.), 2110 vs (N_3 str.), 1670 vs (C=C str.), 1450 (C-H, alkane def.) cm^{-1}; δ_H (300 MHz, $CDCl_3$): 1.46 (1H, q, ^3J 14 Hz, CH), 1.68 (2H, m, 2 x CH), 1.96 (1H, m, CH), 3.18 - 3.37 and 3.18-3.68 (10H, m, 5 x CH_2), 5.61 (2H, m, H_a and H_b) ppm; δ_C (75.5 MHz, $CDCl_3$): 20.7 (C-8), 21.0 (C-9), 27.2 (C-15), 29.8 (C-10); 30.4 (C-5), 47.8 (C-7), 48.0 (C-6); 50.0 (C-11), 52.7 (C-12), 65.6 (C-4), 107.5 (C-14) and 133.9 (C-13) ppm; m /z (FAB): 329 $(M+H)^+$, 100%.

III.6.40 Preparation of (±)-*trans* -2,3-bis(azidomethyl)-1-methylene-cyclopropane (249)



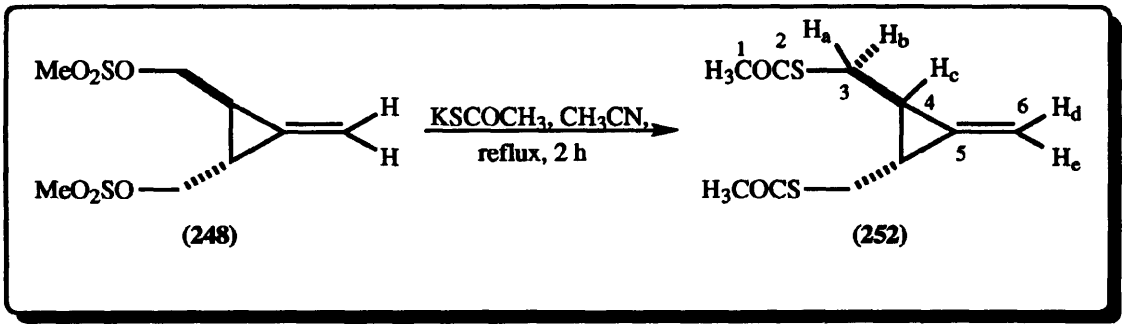
In a 3-necked, round-bottomed flask, (±)-*trans* -2,3-bis-*O* -(mesylmethyl)-1-methylenecyclopropane **(248)** (3.0 g, 11.07 mmol) and sodium azide (8.64 g, 132.90 mmol) were dissolved in dry DMF (50 cm^3) and the mixture was heated at 60 °C. After 6 h TLC (hexane -EtOAc, 5:1) showed no starting material was present. The reaction mixture was allowed to cool to room temperature and was poured into water (250 cm^3) and extracted with diethyl ether (3 x150 cm^3). The combined organic extracts were washed with H_2O (1 x 250 cm^3), brine (1 x 250 cm^3), dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford the crude diazide **(249)** as a light brown oil (1.63 g, 9.94 mmol, 90% yield). The crude product was purified by DCFC (hexane-EtOAc, 5:1) to give **(249)** as a pale yellow oil (1.52 g, 9. 27 mmol, 84% yield); [Found: C, 45.7; H, 5.1; N, 49.2. $C_6H_8N_6$ requires C, 43.9; H, 4.9; N, 51.2%]; ν_{max} (neat film): 3060 m (HC=C str.), 2980 w 2920 w, 2860 w (C-H, alkane str.), 2110 vs (N_3 str.), 1670 vs (C=C str.), 1445 (C-H, alkane def.) cm^{-1}; δ_H (300 MHz, $CDCl_3$): 1.75 (2H, m, 2 x CH), 3.25 (4H, d, $^3J_{1,2}$ 6.5 Hz, H_a and H_b), 5.61 (2H, m, H_c and H_d) ppm; δ_C (75.5 MHz, $CDCl_3$): 21.1 (C-1), 52.7 (C-2), 107.9 (C-4), 133.0 (C-3) ppm; m /z (FAB): 165 $(M+H)^+$, 100%.

III.6.41 Preparation of (±)-*trans* -2,3-bis(aminomethyl)-1-methylene-cyclopropane (250)



In a round-bottomed flask, (±)-*trans* -2,3-bis-(azidomethyl)-1-methylcyclopropane **(249)** (0.25 g, 15.24 mmol) was dissolved in dry ethanol (7 cm^3), and the solution was stirred for 5 min under an atmosphere of argon. 5% $Pd/CaCO_3$ (Lindlar catalyst, 0.03g, 12% equiv.) was added and the mixture was stirred for 10 min. at room temperature under argon. The reaction mixture was placed under hydrogen (via balloon) for 24 h. TLC (hexane-EtOAc, 2:1) showed that all starting material had reacted. The reaction mixture was filtered through Celite, dried ($MgSO_4$), filtered, concentrated and dried under high vacuum for 6 h to yield the unstable diamine **(250)** (0.10 g, 0.893 mmol, 60%); ν_{max} (neat film): 3320 w, 3260 m (NH_2 str.); 2900 br s, 2850 w (C-H, alkane str.), 1650 (C=C str.), 1580 (C-NH_2 def.), 1450 (C-H, alkane def.) cm^{-1}; δ_H (300 MHz, DMSO-d_6): 1.02 (2H, dd, $^3J_{c,a} = {}^3J_{c,b}$ 6.0 Hz, H_c); 3.30 (4H, m, H_a and H_b); 5.80 (2H, apparent t, $^2J_{e,d}$ 1.5 Hz, H_d and H_e); 8.33 (<4H, br s, NH_2) ppm.

III.6.42 Preparation of *trans* -2,3-bis(methylthioacetato)-1-methylenecyclopropane (252)



In a 3-necked, round-bottomed flask fitted with a reflux condenser, (±)-trans-2,3-bis-*O* -(mesylemethyl)-1-methylenecyclopropane (**248**) (0.50 g, 1.85 mmol) and potassium thioacetate (0.53 g, 4.63 mmol) were dissolved in acetonitrile (10 cm^3). The reaction mixture was stirred at room temperature for 5 h when TLC (hexane-EtOAc, 5:1) showed that the reaction was incomplete. The mixture was refluxed for a further 2 h and left to stir at room temperature overnight, when TLC showed no mesylate was present. The reaction mixture was quenched with H_2O (100 cm^3) and extracted with chloroform (3 x 40 cm^3). The organic layers were washed with H_2O (1 x 100 cm^3), brine (1 x 100 cm^3), dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a crude brown oil (0.416 g, 1.81 mmole, 98%). Further purification was carried out by dissolving the crude product in chloroform and passing it through silica gel to obtain the pure dithioacetate (**253**) as a pale brown oil (0.385 g, 1.67 mmol, 90%); [Found: C, 52.3; H, 6.5; S, 27.8. $C_{10}H_{14}S_2O_2$ requires C, 52.2; H, 6.1; S, 27.7%]; δ_H (300 MHz, $CDCl_3$): 1.45 (2H, m, 2 x H_c), 2.27 (6H, s, 2 x CH_3), 2.90 (4H, m, H_a and H_b), 5.40 (apparent t, $^2J_{d,e}$ 2 Hz, H_d and H_e) ppm; δ_C (75.5 MHz, $CDCl_3$): 20.7 (C-4), 30.5 (C-3), 31.7 (C-1), 105.0 (C-6), 138.1 (C-5), 195.1 (C=O) ppm; m/z (FAB): 231 $(M+H)^+$, 25%.

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