The Synthesis of homochiral ligandsand their application to asymmetric fluorinating reagents

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The Synthesis of Homochiral Ligands and their Application to Asymmetric Fluorinating Reagents

by

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Department of Chemistry

University of Durham

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" With men this is impossible; but with god all things are possible"

New Testament 26

" Blessed are they that have not seen and yet have believed "

New Testament 29

Abstract

This thesis is concerned with the synthesis of homochiral ligands and their application to asymmetric fluorinations. Initial work focused on the synthesis of homochiral pyridine based ligands and the determination of their optical purity. 2-Acetylpyridine was reduced using bakers' yeast in the presence of an enzyme inhibitor to give a homochiral pyridyl alcohol. A double asymmetric reduction of 2,6-diacetylpyridine was also achieved using bakers' yeast and the resulting diol was also found to be homochiral.

Derivatives of the above pyridyl alcohols were then reacted with 10% F_2/N_2 in the presence of a suitable counterion to form N-fluoropyridinium salts. These reagents were then used to fluorinate a range of silyl ketene acetals and metal enolates to assess their ability as asymmetric electrophilic fluorinating reagents. Although the reagents achieved fluorination, they were found to be poor asymmetric fluorinating reagents.

A new synthetic route into the pyrrolidine based amine (2S)-(diphenyl)methylpyrrolidine was developed and its use in a number of asymmetric transformations was investigated. Both DAST and Ishikawa's reagent have proved successful in achieving the replacement of alcohol hydroxyl groups by fluorine. Development of a nucleophilic asymmetric fluorinating reagent based on DAST and Ishikawa's reagent was attempted using (2S)-(diphenyl)methylpyrrolidine as the precursor amine. The homochiral derivatives of DAST and Ishikawa's reagent which were developed, only achieved limited success as fluorinating reagents and the fluorinated products were found to be racemic.

(2S)-(Diphenyl)methylpyrrolidine was also found to act as a chiral solvating reagent with certain carboxylic acids and alcohols, these showing chemical non-equivalence by ^1H NMR. Two (2S)-(diphenyl)methylpyrrolidine units were also coupled together by a two and three carbon bridge forming two novel diamines. Initial studies on the ability of these amines to act as asymmetric catalysts in dihydroxylation reactions using osmium tetroxide and asymmetric addition reactions of Grignard reagents to aldehydes are also described.

Memorandum

The research described in this thesis has been carried out at the Department of Chemistry, University of Durham between October 1991 and 1994. It is the original work of the author unless otherwised stated.

A three month period of research was spent at Glaxo Group Research, the industrial case sponsors of this project. Chiral HPLC and X-ray crystal data shown is this thesis were supplied by Glaxo Group Research on my behalf.

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My parents for their belief in me over the last six years and also their financial support.

Maggie and Billy my two dogs who have supplied a good excuse to escape from the rigours of Organic Chemistry

Last but not least Organic Chemistry for proving to be an extremely hard mistress to please.

Publications

D. Bailey, D. O' Hagan, U. Dyer and R. B. Lamont,
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Conferences Attended

a) " Stereochemistry at Sheffield "
University of Sheffield
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b) " Stereochemistry at Sheffield "
University of Sheffield
Sheffield
December 1992.

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d) " 19th International Conference on Fluorine Chemistry " (Poster)
Yokohama
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Presentations

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b) " Towards an Asymmetric Fluorinating Reagent" (Lecture)
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Abbreviations

AD-mix.	Asymmetric dihydroxylation mixture.
BINAL-H.	Binapthol aluminium hydride.
BPPM.	(2S,4S)-N-*tert*-butoxycarbonyl-1,4-diphenylphosphino-2-diphenyl phosphinomethylpyrrolidine.
CBS.	Corey, Bakshia, Shilata reduction procedure.
Cp_2TiCl_2.	Dicyclopentadienyltitanium dichloride.
DAST.	Diethylaminosulphur trifluoride.
DCC.	1,3-Dicyclohexylcarbodiimide.
$(DHQD)_2$-Phal	(Dihydroquinidine)$_2$-Phthalazine.
DMAP	4-Dimethylaminopyridine.
$[Eu(tfc)_3]$.	Tris[3-(trifluoromethylhydroxymethylene)-(+)-camphorato].
GC.	Gas chromatography.
GC-MS.	Gas chromatography coupled with mass spectroscopy.
HCLA.	Homochiral lithium amide.
HFP.	Hexafluoropropene.
HMPA.	Hexamethylphosphoramide.
HPLC	High pressure liquid chromatography.
IpC.	Isopinocamphenylborane.
LDA.	Lithium Diisopropylamine.
LHMDS.	Lithium hexamethyldisilazane.
MTPA.	α-Methoxy-α-trifluoromethylphenylacetic acid.
NAD(P) H.	Nicotinamide adenine dinucleotide phosphate.
NFQNF.	N-Fluoroquinuclidinium fluoride.
NMR.	Nuclear magnetic resonance.
PET.	Positron emission tomography.
PPM.	(2S,4S)-4-diphenylphosphino-2-diphenylphosphinomethylpyrrolidine.
RAMP.	(R)-1-Amino-2-methoxymethylpyrrolidine.
SAMP.	(S)-1-Amino-2-methoxymethylpyrrolidine.
TAE.	(R)-(-)-2,2,2-Trifluoro-1-(9 anthryl)ethanol.
TBAF.	Tetrabutylammonium fluoride.
TBDMSCl.	*tert*-Butyldimethylsilyl chloride.
TMSCl.	Chlorotrimethylsilane.
p-TsOH.	*p*-Toluenesulfonyl chloride.

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CHAPTER 1

An Introduction to Organofluorine Chemistry and Fluorinating Reagents

1. Introduction

The introduction of fluorine is known to alter the chemical and physical properties of organic compounds, thus leading to useful modifications in their biological selectivity and activity.[1-21] A surge in the number of publications and presentations relating to organofluorine compounds is a vindication of its contemporary usefulness and a number of informative monographs and reviews have been written on the subject of organofluorine compounds.[22-28]

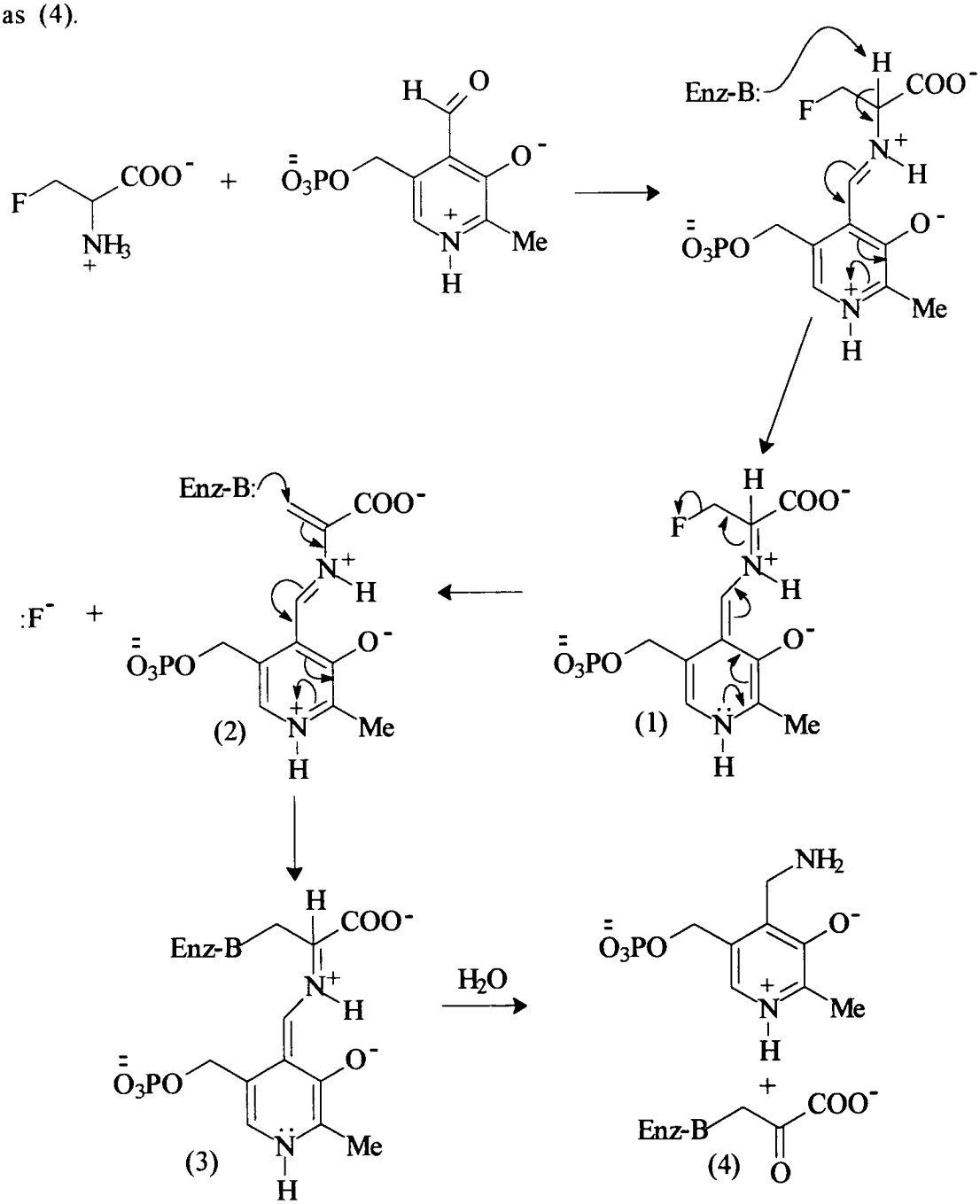
1.1. Historical viewpoint

In 1896 Swarts synthesised methyl fluoroacetate and so heralded the beginning of organofluorine chemistry.[29] During the 1930s Midgley and Herne prepared a range of fluorocarbons,[30] and pioneered their use as thermally and chemically stable refrigerants and lubricants. The biological effects of fluorine on organic molecules has long been known and some noxious fluorinated compounds were developed during World War II by Saunders and co-workers.[31] In 1944 Marais [32] isolated the toxin monofluoroacetate from the South African plant *Dichapetalum cymosum*. The evolution of this compound as an inhibitor of the Kreb's cycle, a key part of respiration has been documented.[33] Selective monofluorination of 9α-hydrocortisone acetate, the first biologically significant molecule, was achieved in 1954 by Fried.[34] Since then selective fluorination, for the purpose of modifying biological activity, has been carried out routinely by medicinal and bio-organic chemists.

1.2. Effects of fluorine substitution on organic molecules

The electronegativity of fluorine is much higher than hydrogen (4.0 vs 2.1) [35] and it is strongly electron-withdrawing along σ bonds and through electrostatic field effects.[36,37] Thus fluorine can change the electron distribution of a molecule, which in turn can alter reactions at neighbouring carbon centres. The size of a fluorine atom is very similar to that of hydrogen respectively (Van der Waal's radi 1.35 Å vs 1.10 Å) [38] and hence the replacement of hydrogen for fluorine in an organic compound does not dramatically alter the steric profile of that organic compound. Fluorine may also be employed as a leaving group in addition-elimination processes where its superior leaving

group ability relative to hydrogen is important. Such applications have led to very effective enzyme inhibitors, an example being fluoroalanine.[39] Fluoroalanine is very similar from a steric point of view to alanine, the natural enzyme substrate. This enables it to be accepted by the enzyme alanine racemase. The proposed mechanism (Scheme 1) involves abstraction of the α-proton from the fluorinated aminoacid to give the intermediate (1) in which, formally, a negative charge is located β to the fluorine atom. Fluorine thus becomes a good leaving group at the active site of the enzyme. The loss of fluorine as fluoride generates the alkylating agent (2), which is then attacked by the enzyme to generate (3). Hydrolysis then leads to irreversible inactivation of the enzyme as (4).



Scheme 1

Fluorinated analogues of the naturally occurring catecholamines have been used to study the interaction between drugs and receptor sites in the body. Norepinephrine (5) is known to control such physiological processes as blood pressure and heart rate.[40] The presence of fluorine in norepinephrine (5) alters the electronic distribution of the catechol ring and hence its interaction with positively charged receptor sites in the body. Such studies have led to a greater understanding of how norepinephrine interacts with α and β adrenergic receptors.[41] Representations of how norepinephrine and its fluorinated analogues bind with adrenergic receptors can be considered as follows (Figure 1).

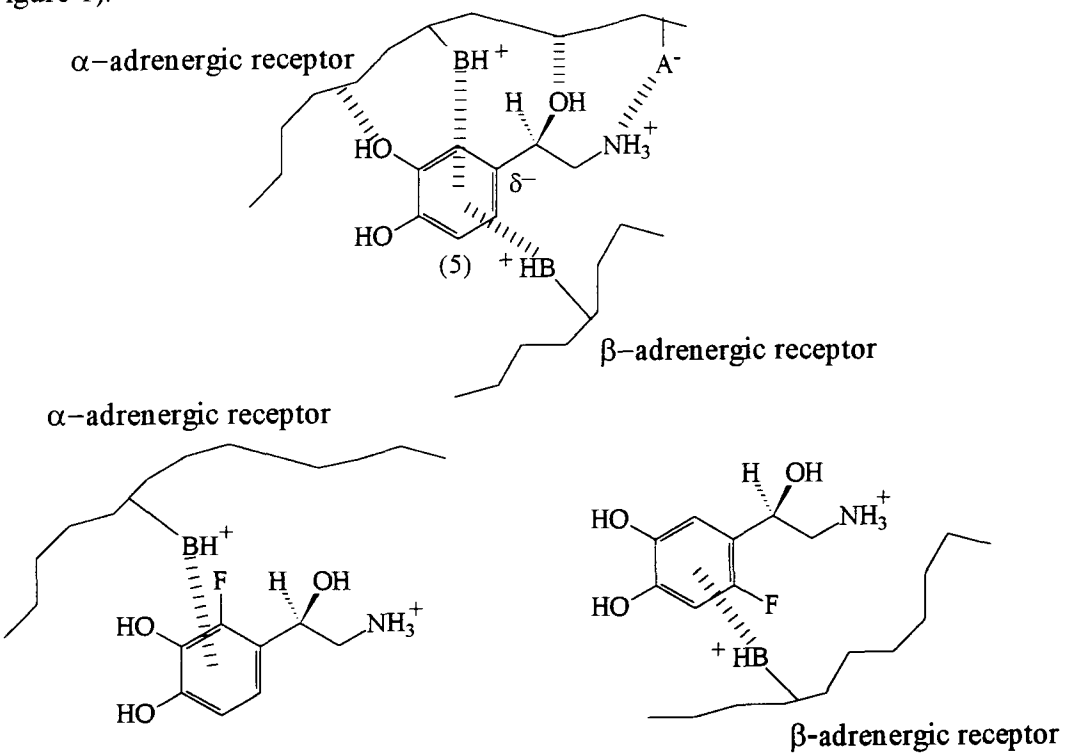
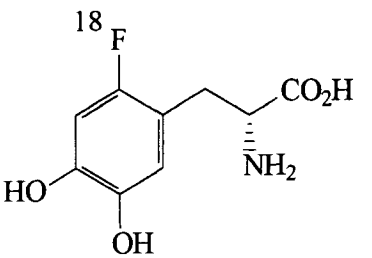


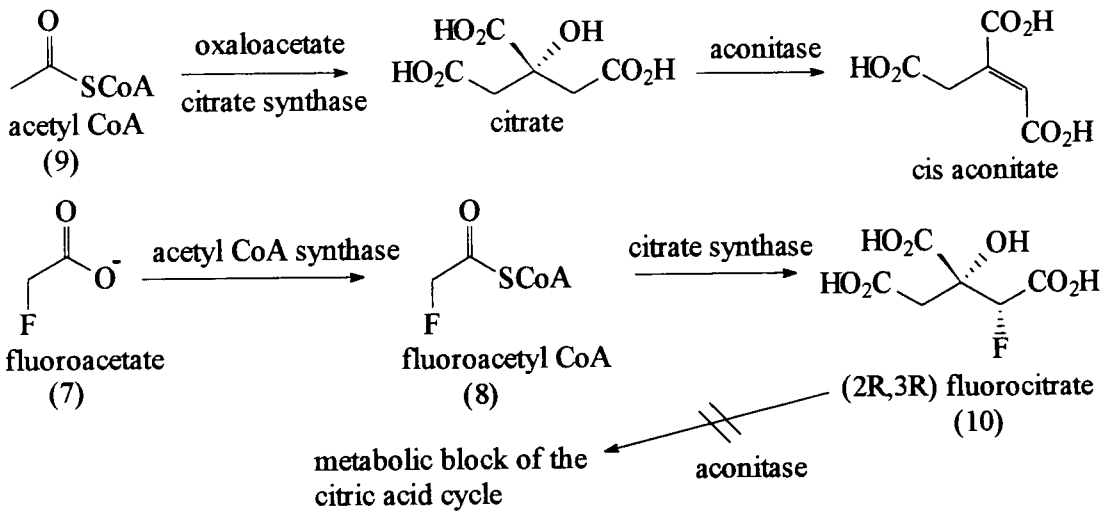
Figure 1

Fluorine substitution in amines has been used to study the fate of bioactive molecules in the body. For example the fluorinated amine 6α-[^{18}F]-fluoro-L-dopa (6) has been used for brain imaging in Parkinson's disease patients. ^{18}F Positron emission tomography (PET) uses the shortlived isotope (half life 110 mins) fluorine ^{18}F, which decays by positron emission. This technique is especially useful for the study of living tissue and complements more traditional techniques such as X-ray.[42]



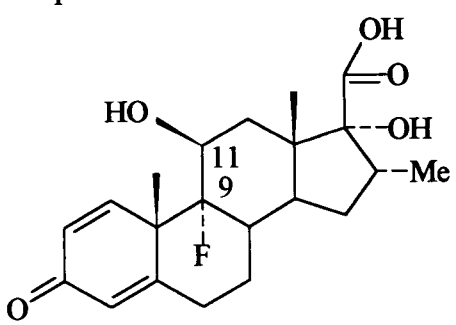
(6)

Some fluorinated carboxylic acids and esters also display biological activity. Naturally occurring fluoroacetate (7) is toxic to all cells when activated to fluoroacetyl coenzyme A (fluoroacetyl CoA, 11) (8), because it leads to the inhibition of the citric acid (Krebs') cycle, a central pathway responsible for generating metabolic energy. Fluoroacetyl CoA competes with acetyl CoA (9) for the enzyme citrate synthase, where it reacts with oxaloacetate to generate (2R,3R)-fluorocitrate (10). Fluorocitrate is a powerful inhibitor of the next enzyme on the pathway, aconitase and this leads to a disruption of respiration as shown below (Scheme 2).[33]



Scheme 2

The strong electron withdrawing effect of fluorine can have a pronounced influence on the acidity of adjacent functional groups. For example the introduction of fluorine at the 9 position in cortisol (9α-fluorocorticosteroid) (11) has been found to increase the acidity of the 11-ß hydroxyl group, resulting in enhanced hydrogen bonding through the hydroxyl group to steroid receptors in the liver.[34]

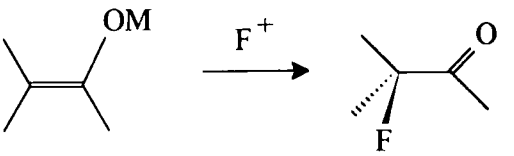


(11)

The use of fluorine to modify and probe the reactivity of organic compounds has been illustrated by the above examples. Fluorination has also been used to modify the properties of carbohydrates,[43,44,45] prostaglandins,[46] steroids,[5,34] acids and esters [47] and amino acids.[48]

1.3. Prerequisite for practical fluorinating reagents

Fluorine can be introduced into organic molecules by two main strategies. Either (a) the use of fluorinated synthetic building blocks or (b) direct fluorination technology. Direct fluorination methodology requires the insertion of preferably one fluorine substituent at a specific site of a biologically active compound. There are numerous fluorination techniques but most, if not all, have limitations. They are typically highly reactive, explosive or toxic. Although a variety of tamed fluorinating reagents have been developed in the past there is still an ongoing need for improved methods of fluorination. One of the most challenging problems, and a focus of this project is the transformation of metal enolates or silyl enol ethers into α-fluorocarbonyl compounds in a regioselective and stereoselective manner, using electrophilic fluorinating reagents. Such a transformation can be represented as below (Scheme 3)



Scheme 3

The ideal fluorinating reagent can be envisaged as having the following specifications:-

1) safe to handle
2) isolatable
3) efficient
4) regioselective
5) stereoselective
6) recyclable

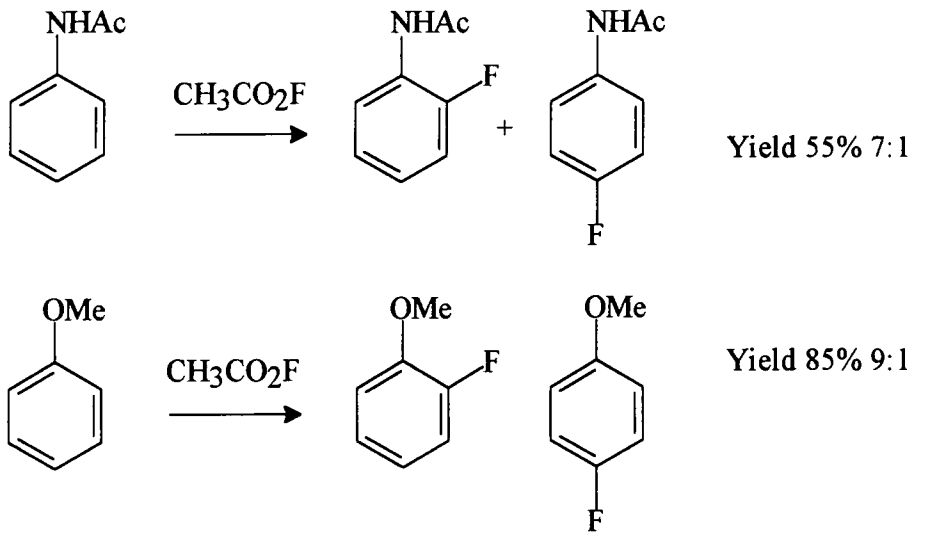
All of the fluorination techniques reviewed in the next section fail to meet one, or more of the listed requirements.

1.4. Electophilic Fluorinating Reagents

1.4.1. Acetyl hypofluorite

If elemental fluorine is bubbled through a suspension of sodium acetate or sodium fluoride in $CFCl_3$ and acetic acid, acetyl hypofluorite CH_3COOF is generated. This reagent possesses an electrophilic fluorine which is less polarizable, and hence less reactive than fluorine in related reagents eg. CF_3COOF, CF_3CF_2OF and CF_3OF.[49] In

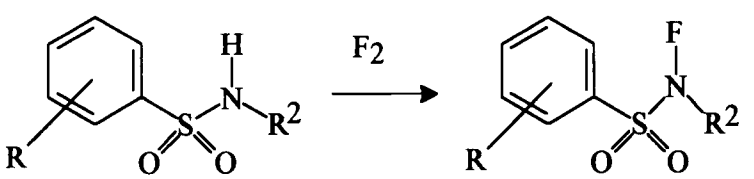
contrast to direct fluorination with elemental fluorine, CH_3COOF is highly regioselective in its reactions with strongly activated aromatic systems. Some typical reactions of CH_3COOF with activated aromatics are shown below (Scheme 4).



Scheme 4

1.4.2. **N-Fluorosulphonamides**

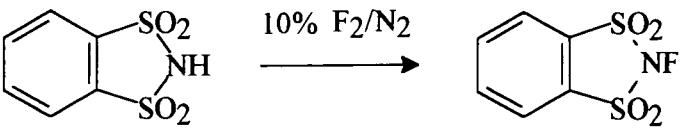
N-Fluorosulphonamides (12) (Scheme 5) introduced by ***Barnette*** in 1984 are stable electrophilic fluorinating reagents.[50]



(12)

Scheme 5

The presence of α-hydrogen atoms on the N-alkyl residue (R^2) is however a limitation of this reagent, as an undesired elimination of HF can occur during the fluorination of carbanions. Furthermore an N-t-butyl group suffers from adverse steric effects giving very low yields in the preparation of the corresponding N-fluorosulphonamide. N-Fluoro-o-benzenedisulphonamide (13), a more recent electrophilic fluorinating reagent based on the sulphonamide system, is easily prepared and is shelf stable. This reagent fluorinates enolates, azaenolates and carbanions in good to excellent yields. N-Fluoro-o-benzenedisulphonamide (13) is readily prepared (Scheme 6) in greater than 90% yield by treatment of o-benzenedisulphonamide with a 10% mixture of molecular fluorine in nitrogen.[51] A number of transformations have been reported with this reagent and these are summarised below (Table 1).



(13)

Scheme 6

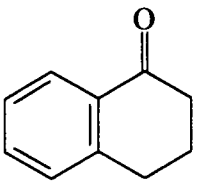
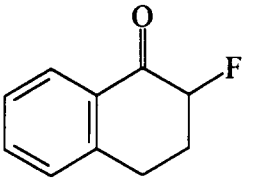
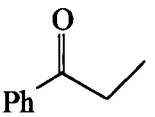
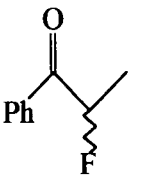
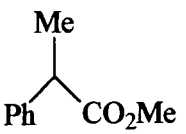
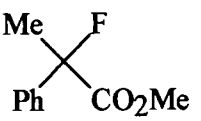
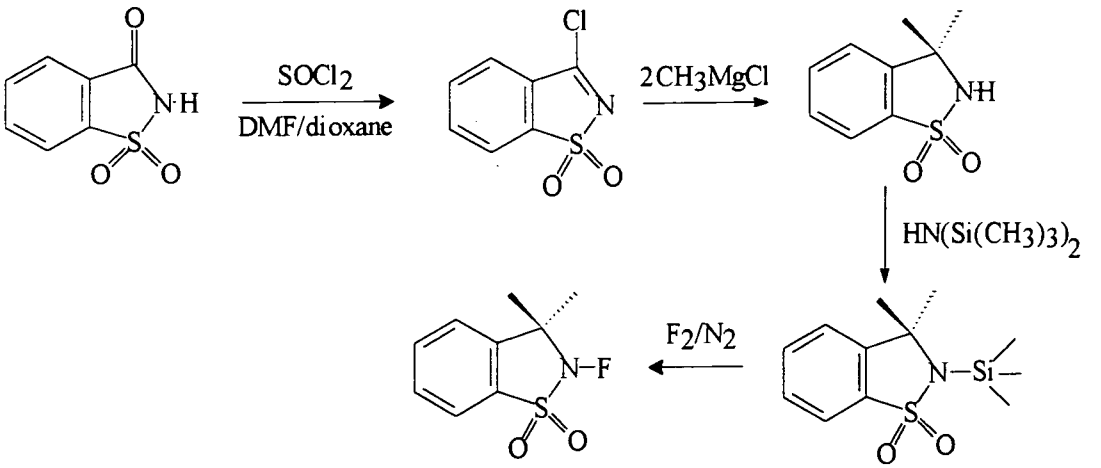
Substrate	Product	% yield
		55
		87
		55
PhMgBr	PhF	80

Table 1. Fluorination of enolates and carbanions in ether using N-fluorosulphonamide

1.4.3. **N-Fluorosultams**

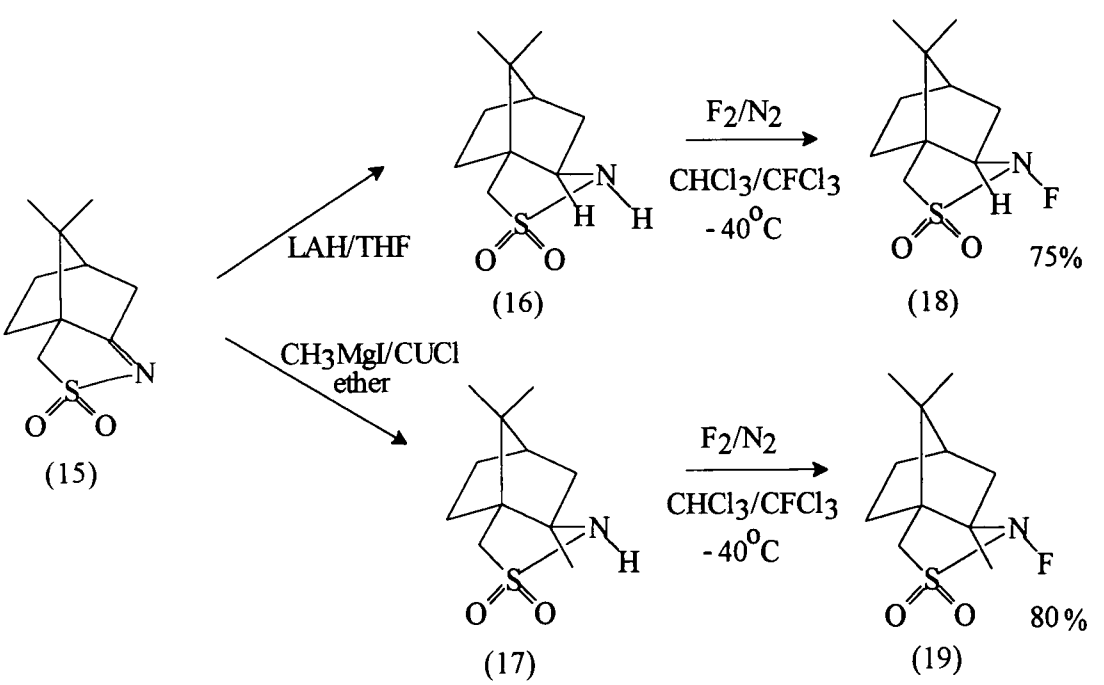
N-Fluorosaccharin (14) is easily prepared in 100g quantities from saccharin by treatment with 10% F_2/N_2 at low temperature. The synthetic route from saccharin is as follows (Scheme 7).



(14)

Scheme 7

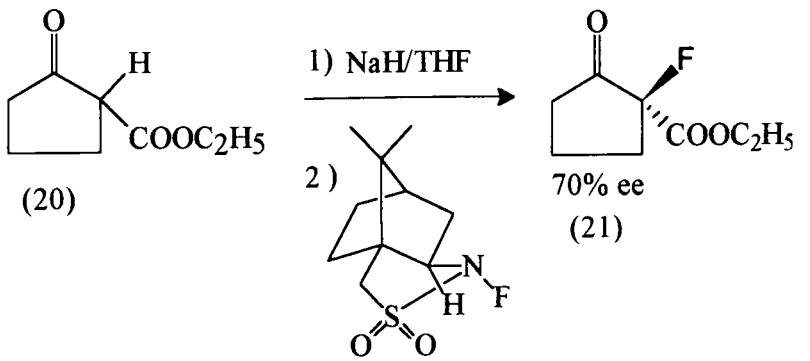
N-Fluorosaccharin (14) has been used to generate a range of α-fluorocarbonyl compounds from metal enolates.[52] This N-fluorosultam proved to be a versatile and easily accessible fluorinating reagent having considerable advantages over the commercially available N-alkyl-N-fluorosulphonamides. In particular the absence of α hydrogen atoms prevented base induced HF elimination. Attempts have been made to design a stereoselective reagent (Scheme 8) by reducing the sulphonyl imine of optically pure camphor-10-sulphonyl chloride (15). The resulting homochiral ligands (16) and (17) were then fluorinated to generate the crystalline N-fluorocamphor reagents (18) and (19), available in both enantiomeric forms.[53]



(15) (16) (17) (18) (19)

Scheme 8

All of these N-fluorosultams are claimed to be air stable and show no exothermic decomposition below 100°C. Fluorination of the prochiral enolate of ethyl cyclopentanone-2-carboxylate (20) (Scheme 9) with the N-fluorocamphor reagent (18), gave ethyl 1-fluoro-2-oxocyclopentane-1-carboxylate (21) with an enantiomeric excess of 70%.[53] This is the highest reported % ee for any asymmetric fluorination to date.

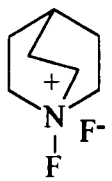


Scheme 9

The enantiomeric excess obtained above, was not reproduced in other ß-keto esters. Replacement of the α-H adjacent to the N-atom in (18) by a methyl group, giving (19) substantially reduced the enantioselectivity of the above reaction.[53]

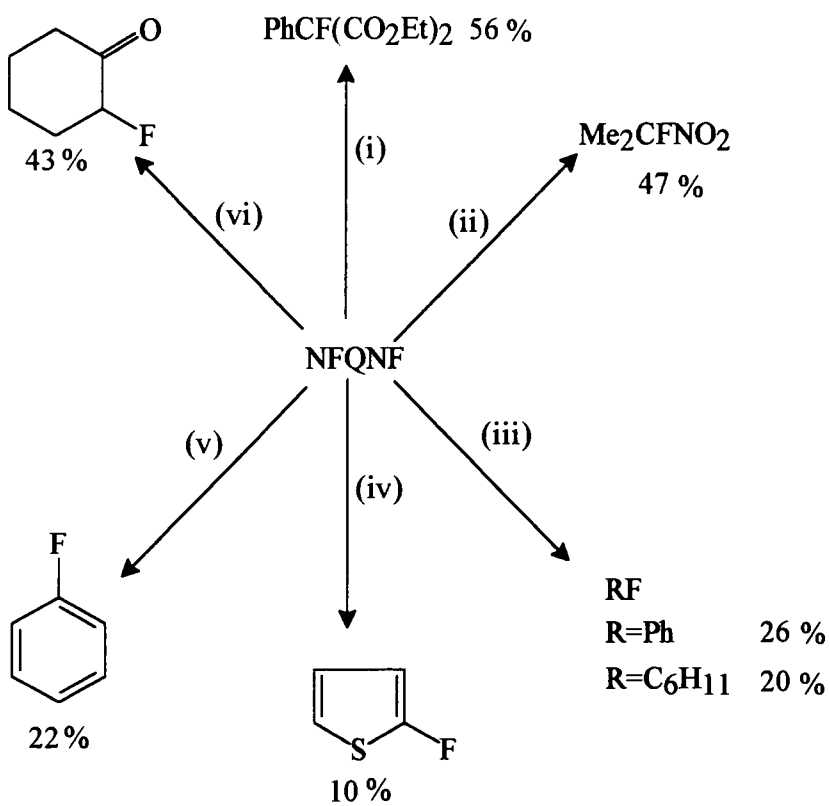
1.4.4. N-Fluoroquinuclidinium fluoride

N-Fluoroquinuclidinium fluoride (NFQNF) (22) can be obtained in good yield by the direct fluorination of quinuclidine. Undiluted fluorine is passed into a cold solution (-78°C) of quinuclidine in trichloromethane and quinuclidinium fluoride is generated as a white hygroscopic solid.[54,55]



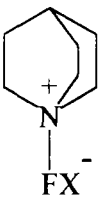
(22)

Some products of N-fluoroquinuclidinium fluoride reactions are shown below (Scheme 10).



Scheme 10. i) $PHC(CO_2Et)_2\ Na^+$ in THF, -10°C to -20°C. ii) $Me_2CNO_2^-\ Li^+$ in MeOH, 0°C. iii) RMgX in Et_2O. iv) 2-thienyl-lithium in Et_2O, 0°C to 20°C. v) $PhSiCl_3$ in THF, -50°C to -20°C. vi) $CH_2CH_2OCH_2CH_2N\text{-}CH{=}CH(CH_2)_3CH_2$ in CH_2Cl_2, -196°C to 20°C.

Bank's found that the hygroscopic nature of reagent (22) is reduced by replacing the fluoride counterion by triflate (trifluoromethanesulphonate).[56] The resulting crystalline N-fluoroquinuclidinium salts (23) are now commercially available and site selective fluorinations using it are summarised below (Table 2).



$X^- = CF_3SO_3^-(TfO^-)$

$X^- = BF_4^-$

(23)

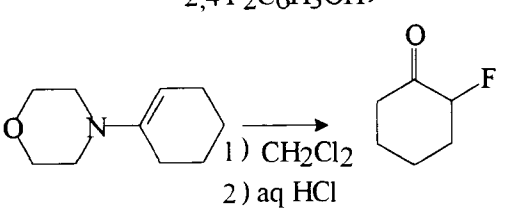
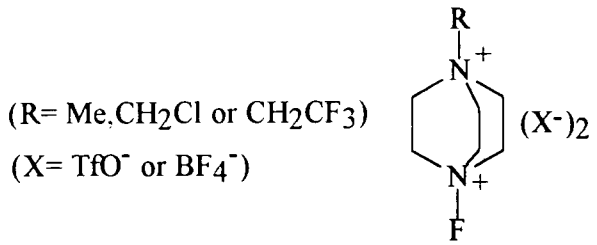
Reaction	Salts used and yield% of product			
	F^-	$CF_3SO_3^-$	$CF_3CO_2^-$	$C_3F_7CO_2^-$
$PhMgBr \xrightarrow[20^oC]{Et_2O} PhF$	26	26	—	—
$PhC^-(CO_2Et)_2\ Na^+ \xrightarrow[-10-\ 20^oC]{THF} PhCF(CO_2Et)_2$	56	52	—	—
$Me_2C^-NO_2\ Li^+ \xrightarrow[20^oC]{MeOH} Me_2CFNO_2$	47	72	56	61
$PhSO_2Na \xrightarrow[20^oC]{MeOH} PhSO_2F$	—	94	—	—
$PhOH \xrightarrow{NaOH}$ 2 FC_6H_4OH, 4 FC_6H_4OH, 2,4 $F_2C_6H_3OH$	—	100	—	—
 1) CH_2Cl_2 2) aq HCl	43	58	67	88

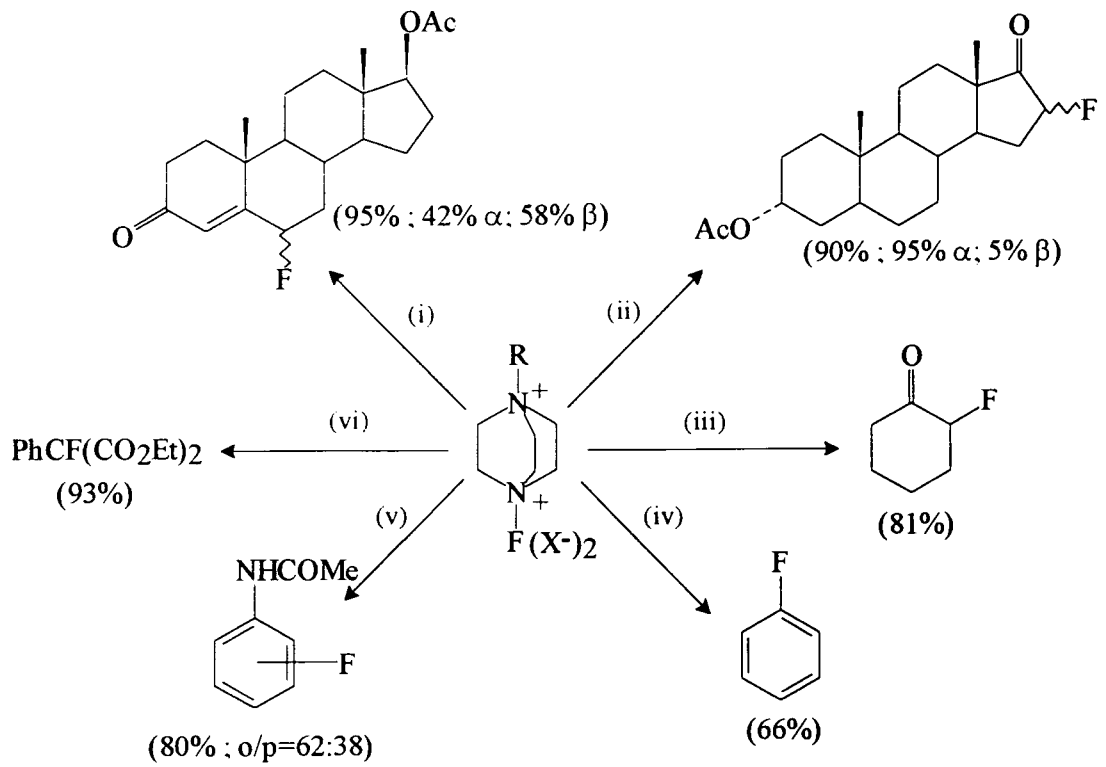
Table 2. Site-specific electrophilic fluorination with N-fluoroquinuclidinium salts

N-Fluoroquinuclidinium salts containing a second quaternary bridgehead nitrogen are more powerful fluorinating reagents.[57] Furthermore the fluorination power of this class of reagents can be tuned through variation in the electronegativity of the R group on the second quaternary nitrogen. The salt of 1-alkyl-4-fluoro-1-4-diazoniabicyclo [2.2.2] octane (24) has smoothly and selectively fluorinated a variety of substrates (Scheme 11).

(R= Me,CH_2Cl or CH_2CF_3)
(X= TfO^- or BF_4^-)



(24)

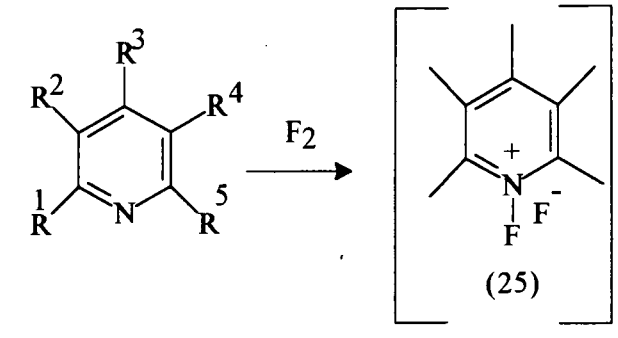


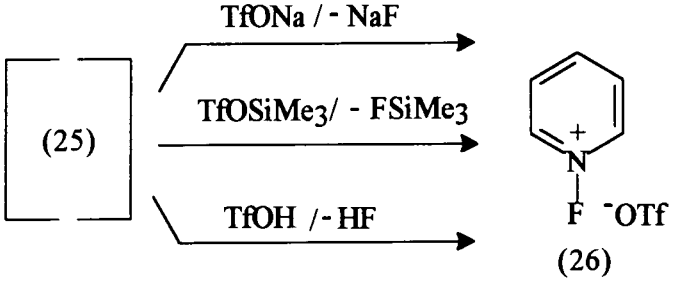
Scheme 11. i) Testosterone enol diacetate, MeCN, 15min at 25°C (R=CH_2Cl, X^- =BF_4^-). ii) androsterone enol diacetate, MeCN, 2hr, 25°C (R = CH_2Cl, X^- = BF_4^-); iii) 1-morpholinocyclohex-1-ene, CH_2Cl_2, 20°C (R = CH_2CF_3, X^- = TfO^-). iv) PhMgBr, 25°C, 2h, Et_2O (R=CH_2Cl, X^- =TfO^-). v) PhNHCOMe, refluxing MeCN, 15min (R=CH_2Cl, X^- = BF_4^-); vi) Sodio derivative of diethylphenylmalonate, tetrahydrofuran-dimethylformamide (2 : 1), 25°C, 30min (R = Me, X^- = TfO^-), reactant ratios = 1 : 1 molar. Yields refer to isolated products.

Steroids in the form of the appropriate enol acetates are rapidly and selectively fluorinated at room temperature giving the 6 or 16-fluoro compounds in high yields. Highly stabilised carbanions such as the sodium salt of diethyl phenylmalonate give fluoro derivatives in high yields, but the reagents were found to be less effective with more reactive carbanion systems such as ketone-derived metal enolates. Grignard reagents are smoothly converted to the corresponding mono-fluoro compounds.

1.4.5. N-Fluoropyridinium triflates

H.Meinert *et al.*[58] reported that when fluorine (F_2) diluted with nitrogen was bubbled through a solution of pyridine in $CFCl_3$ at -80°C a pyridine-F_2 adduct (25) was formed as a hygroscopic white precipitate and that it decomposed violently above -2°C. It was suggested that the instability of the pyridine-F_2 adduct was due to the nucleophilicity of F^- and might be improved by exchanging F^- for a non-nucleophilic anion such as triflate. as shown below (Scheme 12).[59] The N-fluoropyridinium triflate salt (26) produced was found to be thermally stable and non-hygroscopic crystalline solids.





Scheme 12

The fluorinating ability of these salts can be tuned by the introduction of electron withdrawing or donating substituents onto the pyridine nucleus and their fluorinating ability increased in the order of 27 < 26 < 28 < 29 (Figure 2).[60]

26) $R^{1\sim5}$=H	
27) $R^{1,3,5}$=Me	$R^{2,4}$=H
28) $R^{1,3,5}$=H	$R^{2,4}$=Cl
29) $R^{1,5}$=COOMe,	$R^{2,3,4}$=H
30) $R^{1,5}$=CH_2OCOMe,	$R^{2,3,4}$=H
31) $R^{1,5}$=CH_2OMe	$R^{2,3,4}$=H

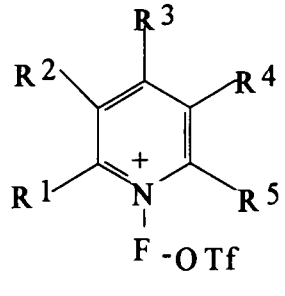
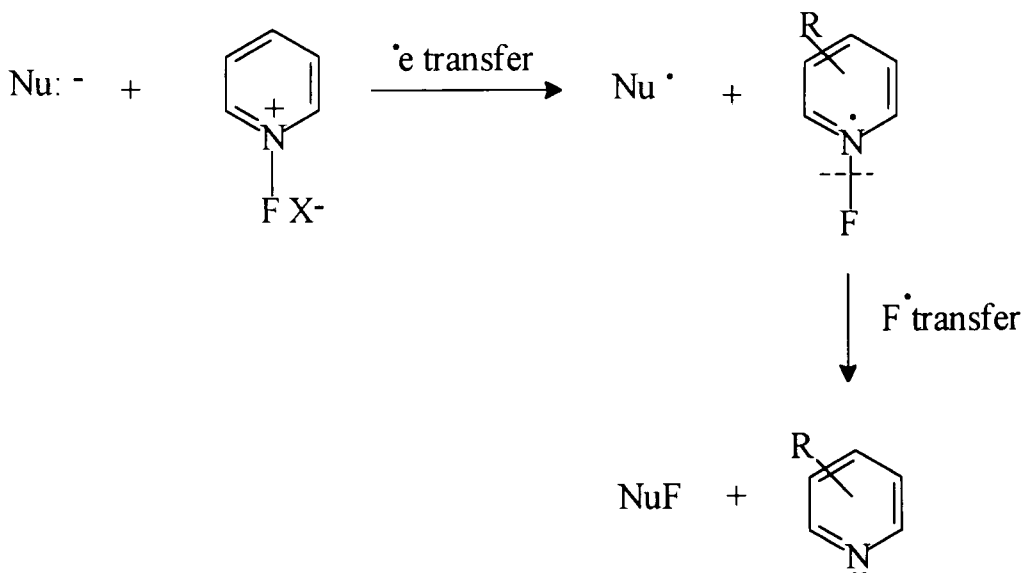


Figure 2

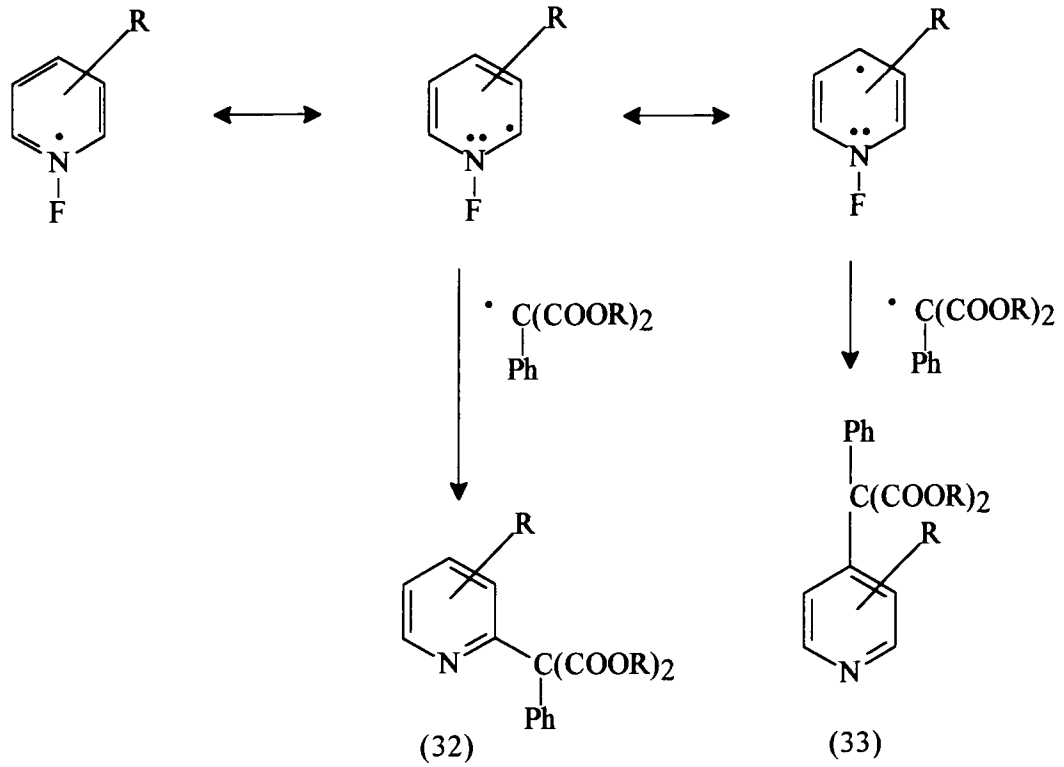
The reactivity of (29) was found to be so high as to smoothly fluorinate phenol at room temperature. Fluorinating ability was also found to change according to substituents on α methyl groups. For example salt (30) having an acetoxy group on the α-methyl group was a stronger fluorinating reagent than salt (31) having a methoxy substituent at the α-methyl group. It is clear that the fluorinating ability is closely related to the electron density of the nitrogen-fluorine bond and by changing the side groups on pyridine one can match reagent and substate. The effect of different counterions was also investigated with BF_4^-, SbF_6^- and ClO_4^-, resulting in a decrease in reactivity.[61] A variety of substrates, including aromatics, enol ethers, carbanions, alkyl and aryl organometallics were fluorinated in good yields, under mild conditions using the triflates 26-31.[61]

N-Fluoropyridinium salts appear to provide positive fluorine (F^+) during fluorination reactions. However this should not be the case in view of the high ionisation potential of the fluorine atom and the high-electron affinity of the electron-deficient pyridinium ring system. All fluorinations by N-fluoropyridinium salts can be rationalised by a one electron-transfer process as shown below (Scheme 13).[61]



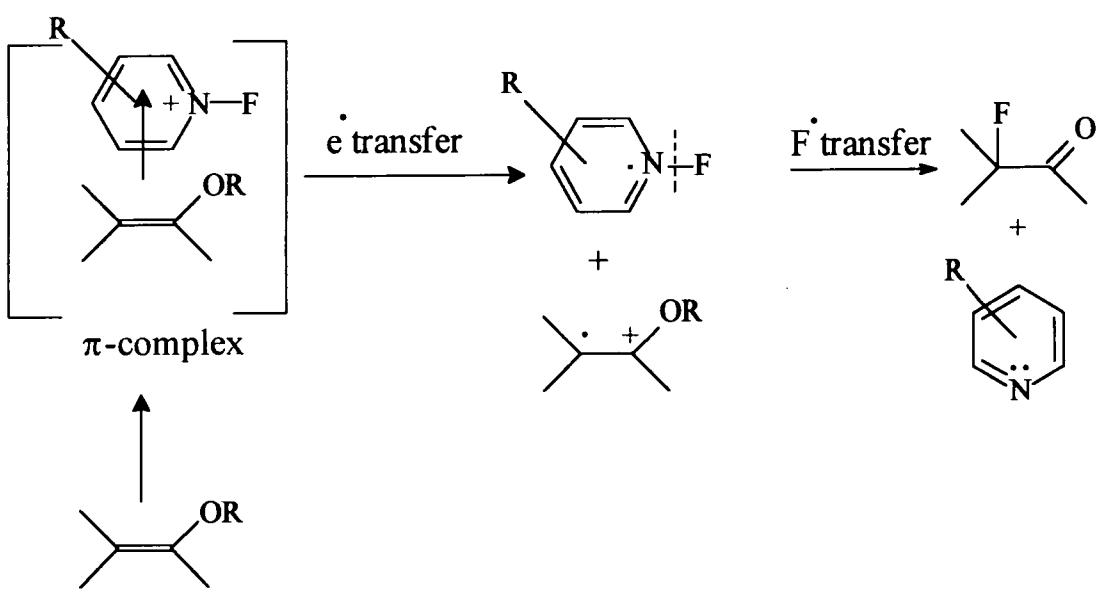
Scheme 13

This mechanism is supported by the observed difference between reactions with organolithiums and Grignard reagents. The latter Grignard reagents react with the N-fluoropyridinium triflates to give the corresponding fluoro compounds while the former do not. This is most probably because Grignard reagents react by a one-electron transfer process.[62] Additionally reaction of diethyl phenylmalonate with N-fluoropyridinium triflate gave by-products (32) and (33) (Scheme 14) and these may also be explained by the one electron transfer mechanism.



Scheme 14

The fluorination of enol ethers by N-fluoropyridinium salts may also involve a one-electron transfer process. A reaction mechanism can be considered as follows (scheme 15).[61]



Scheme 15

1.5. Nucleophilic Fluorinating Reagents

1.5.1. F-Propene-dialkylamine fluorinating reagents

Yarovenko *et al.*[63] found that the reaction of chlorotrifluoroethene with diethylamine generated the adduct 2-chloro-1,1,1-2-trifluorotriethylamine (34) (Scheme16). This adduct proved a useful mono-fluorinating reagent for the conversion of hydroxyl groups into fluorine.

$$Et_2NH + CF_2{=}CFCl \longrightarrow \underset{(34)}{Et_2NCF_2CHFCl}$$

$$ROH + Et_2NCF_2CHFCl \longrightarrow RF + Et_2NC(=O)CHFCl + HF$$

Scheme 16

Ishikawa *et al.*[64] developed a related reagent from diethylamine and hexafluoropropene. This reagent exists as a mixture of α,α-difluoroalkamine (35) and α-fluoroenamine (36) (Scheme 17), and is useful for the conversion of primary, secondary and tertiary hydroxyl groups into fluorine (Table 3).[64]

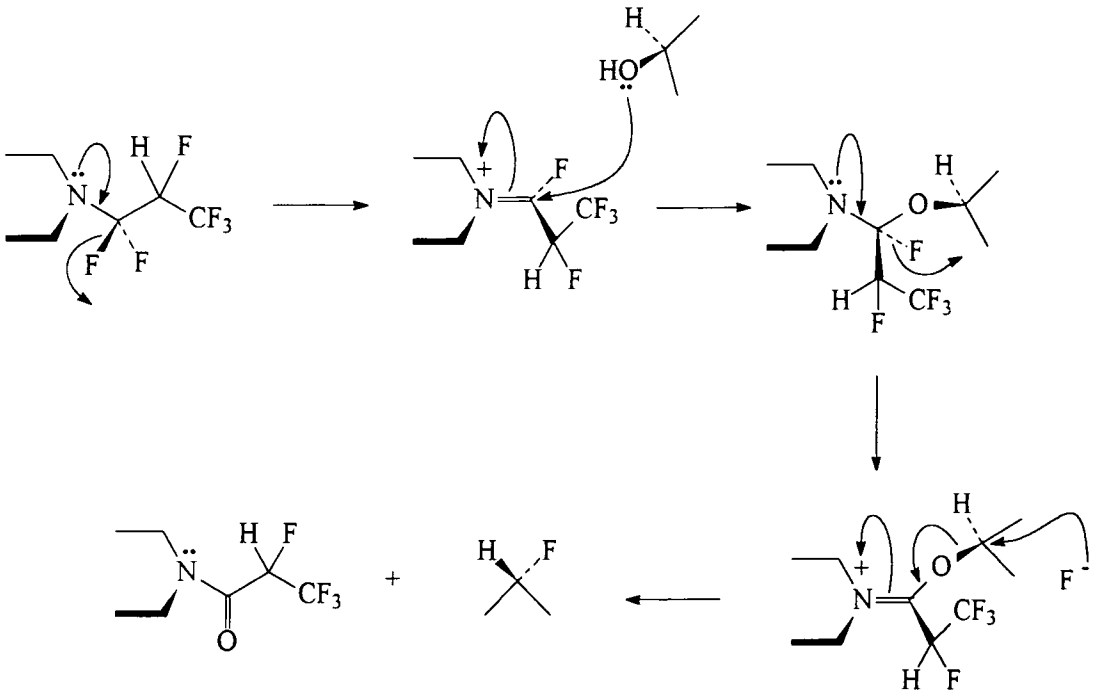
$$Et_2NH + CF_2{=}CFCF_3 \longrightarrow \underset{(35)}{Et_2NCF_2CHFCF_3} + \underset{(36)}{Et_2N(F)C{=}C(F)CF_3}$$

Scheme 17

		Product Yield %		
Substrate	**Solvent**	**R-F**	**Alkene**	**R_2O**
cyclohexanol	Et_2O	4	cyclohexene 78%	-
$PhCH(OH)Me_3$	Et_2O	56	-	29
PhCH(OH)Et	Et_2O	65	-	20
$PHCH(OH)CO_2Et$	Et_2O	66	-	-
cholesterol	CH_2Cl_2	83	-	-
t-butanol	CCl_4	73	Isobutylene 9%	-
$C_6H_{13}CH(OH)CH_3$	Et_2O	62	octene 25%	-

Table 3. Fluorination of secondary and tertiary-alcohols

This reagent has since been used for the preparation of chiral fluorinated products starting from chiral hydroxy esters [65] and chiral secondary alcohols.[66] These reactions are thought to proceed by inversion of configuration at carbon as shown below (Scheme 18).



Scheme 18

1.5.2. **Diethylaminosulphur trifluoride (DAST) and related reagents**

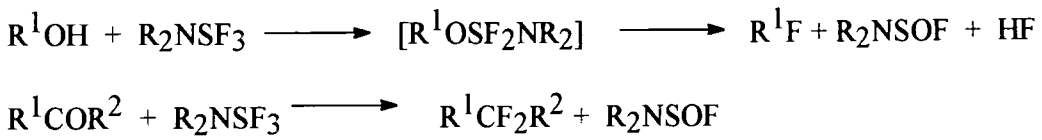
Among the fluorinating reagents containing nitrogen and sulphur two reagents have proved the most versatile. Dimethylaminosulphur trifluoride (37) [67,68] and diethylaminosulphur trifluoride (DAST) (38) [69,70] have been available for over 20 years and their use as fluorinating reagents is well documented.[71] Both of these reagents are prepared by treatment of the appropriate dialkylaminotrimethylsilane with sulphur tetrafluoride (Scheme 19).

$$R_2NSi(CH_3)_3 + SF_4 \longrightarrow R_2NSF_3 + SiF(CH_3)_3$$

37, R=CH_3
38, R=C_2H_5

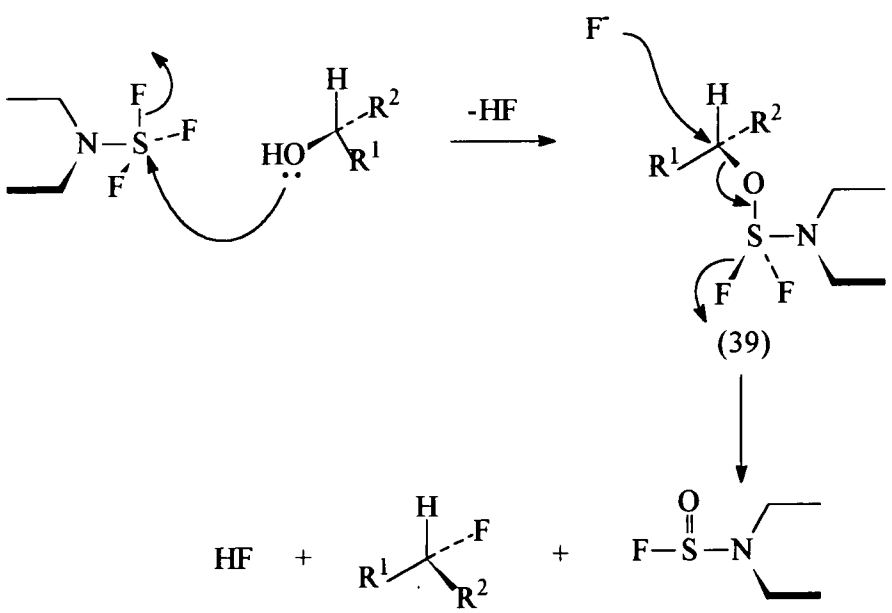
Scheme 19

DAST which is commercially available, is the most widely used fluorinating reagent as a consequence of its versatility in the fluorination of a range of functional groups. Among the most popular transformations using DAST are the conversion of primary, secondary, tertiary, allylic and benzylic alcohols[72,73] into monofluorinated species, and the conversion of aldehydes[72,74,75,76,77] and ketones[78] into geminal difluorides (Scheme 20).



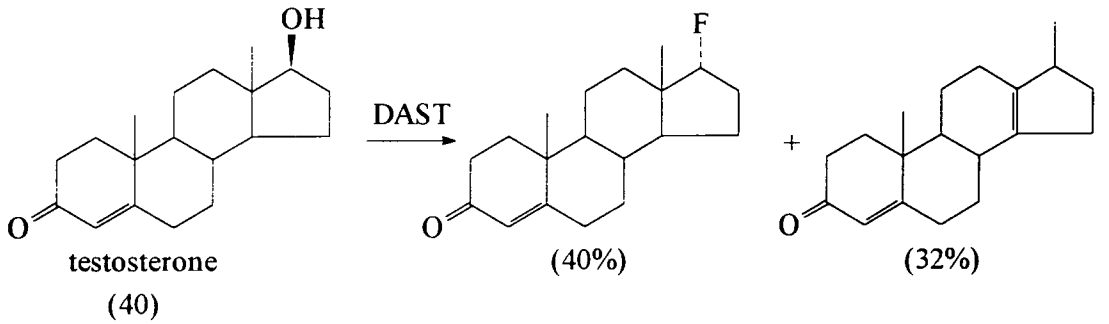
Scheme 20

Mechanistically the reaction of DAST with hydroxyl groups is considered to proceed in a similar way to that of sulphur tetrafluoride.[79] The first step involves nucleophilic attack by the hydroxyl group on to sulphur, generating hydrogen fluoride and a intermediate such as (39). This is then accompanied by S_N2 attack on (39) by fluoride.[80] This mechanism is shown below (Scheme 21).



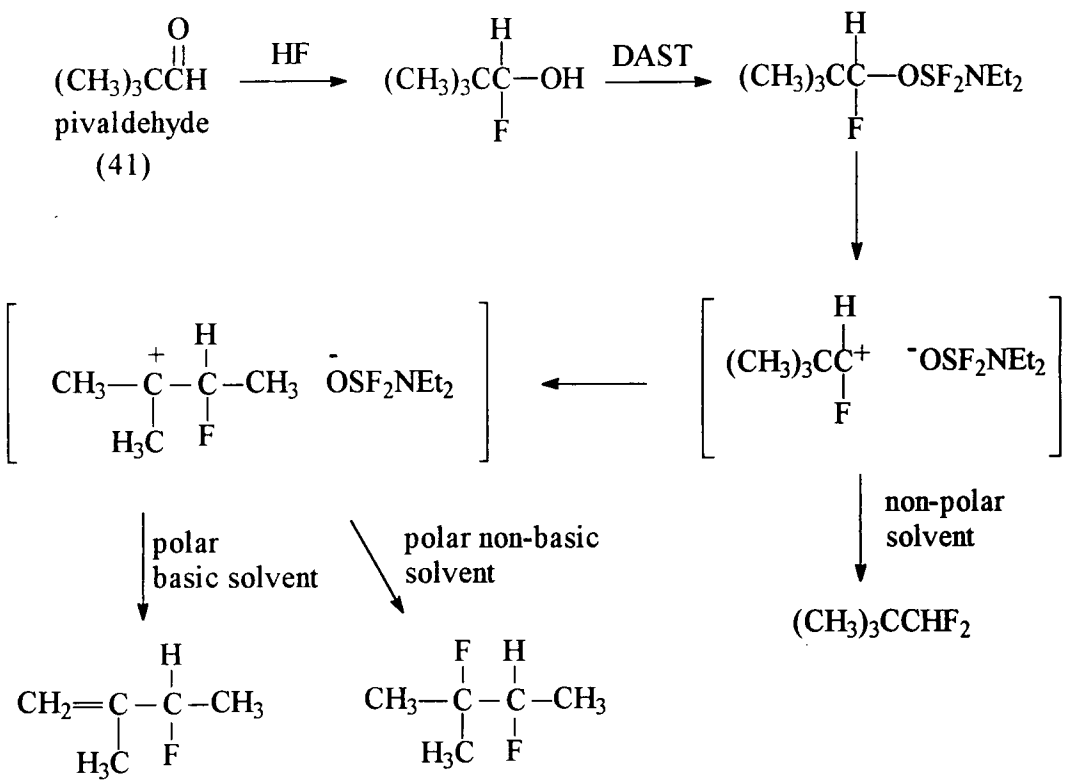
Scheme 21

The replacement of hydroxyl groups by fluorine using DAST is not always straightforward. Dehydration is often significant with these reagents and this is consistent with the formation of intermediate carbocations.[72,81,82] For example testosterone (40) undergoes dehydration followed by a Wagner-Meerwein rearrangement to give a mixture of products as shown below (Scheme 22).[83]



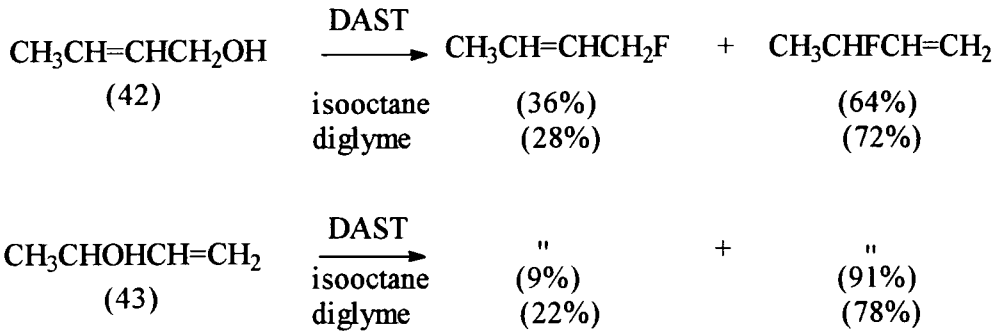
Scheme 22

Rearrangements often occur when DAST reacts with alcohols, indicative of carbocation intermediates.[72] For example a rearrangement takes place when DAST reacts with pivaldehyde (41) (Scheme 23).[72]



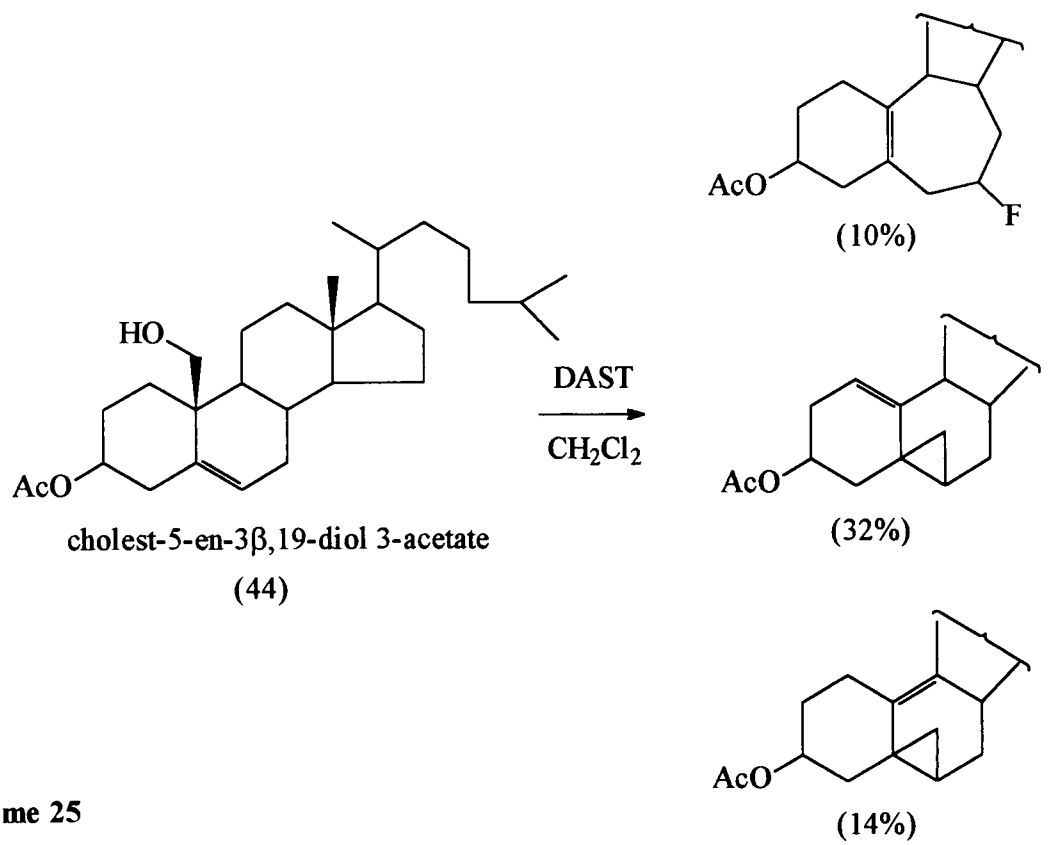
Scheme 23

Allylic rearrangements have been observed when DAST reacts with allylic alcohols.[72,73,84] For example crotyl alcohol (42) and isocrotyl alcohol (43)[72] undergo the rearrangements shown below (Scheme 24).



Scheme 24

Skeletal rearrangements can also occur and an example of this is the reaction between DAST and cholest-5-en-3β,19-diol 3-acetate (44) below (Scheme 25).[85]

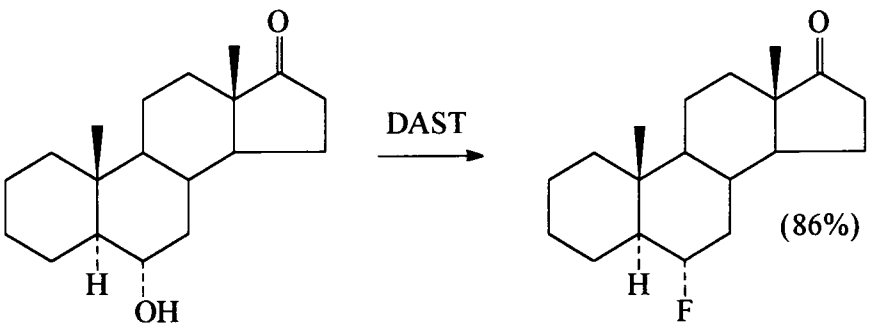


cholest-5-en-3β,19-diol 3-acetate
(44)

Scheme 25

The fluorination of aliphatic secondary hydroxyl compounds with DAST is generally considered to proceed by an S_N2 mechanism, with inversion of configuration being seen. For example treatment of (2S)-octanol with DAST generates (2R)-fluorooctane in 97.6% enantiomeric excess.[86] Inversion of configuration has also been reported for the preparation of dimethyl fluoromalonate,[87] and in the synthesis of fluorinated analogues of carbohydrates,[88,89] and steroids.[81,90]

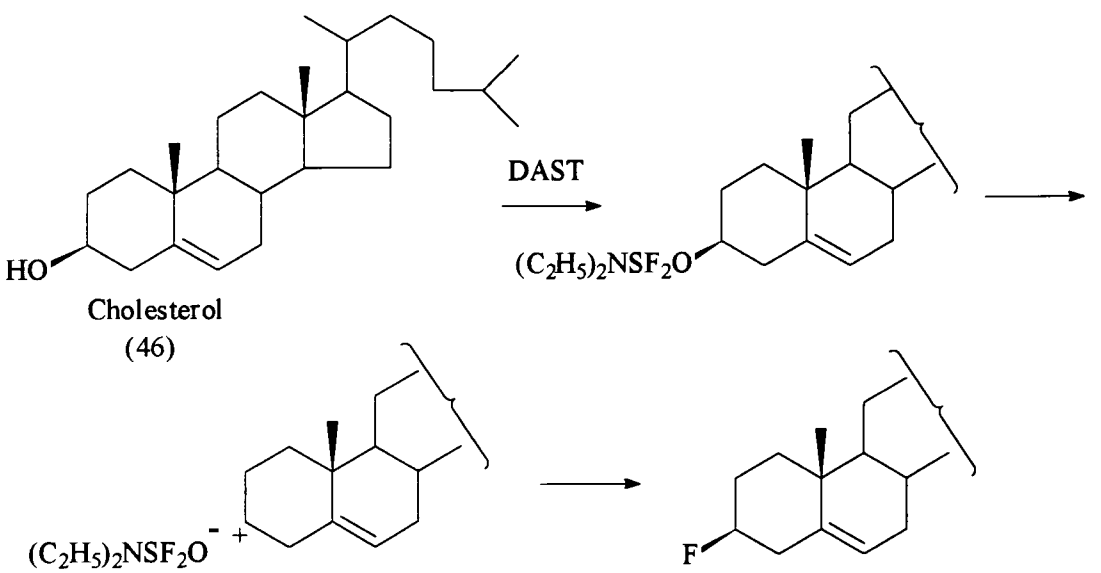
However, retention of configuration has been observed in certain cases where DAST reacts with hydroxy compounds. For example treatment of 6α-hydroxy-5α-androstan-17-one (45) with DAST affords the fluorinated product with retention of configuration (Scheme 26).[90] In this case inversion of configuration would lead to excessive steric hindrance in the transition state of the S_N2 substitution process.



6α-hydroxy-5α-androstan-17-one
(45)

Scheme 26

In most examples, retention of configuration can be attributed to neighbouring group participation. An example is the conversion of cholesterol (46) to its fluorinated analogue with retention of configuration (Scheme 27).[81]

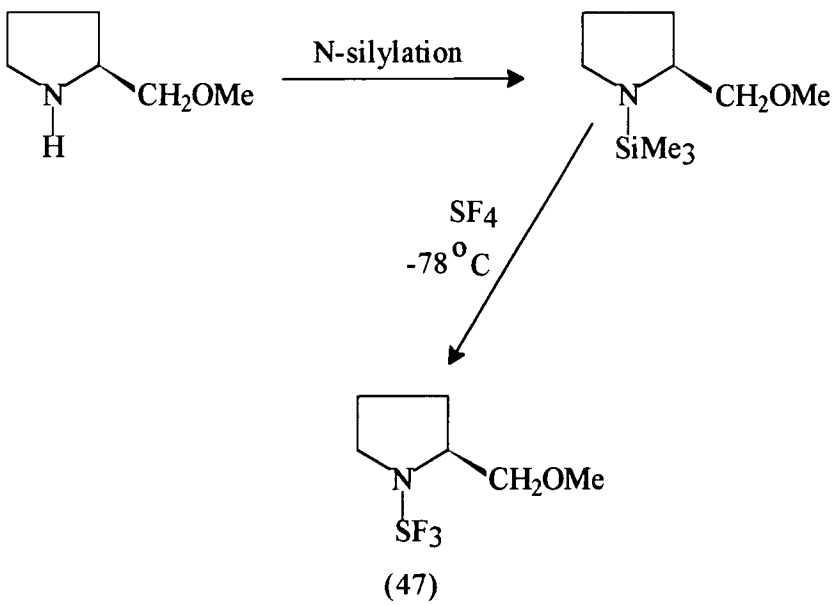


Cholesterol
(46)

Scheme 27

1.5.2.1. (2S)-(Methoxymethyl)pyrrolidin-1-ylsulphur trifluoride

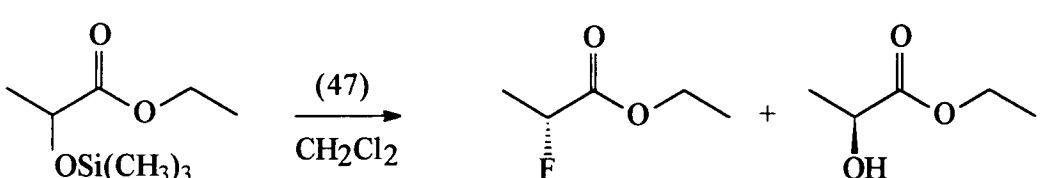
(2S)-(Methoxymethyl)pyrrolidin-1-ylsulphur trifluoride (47) was reported as the first homochiral aminofluorosulphurane and was found to be one of the most stable aminofluorosulphuranes to date. This reagent has shown a degree of enantioselectivity in the fluorination of 2-(trimethylsilyloxy)octane and ethyl-2-(trimethylsilyloxy) propionate (48), and is prepared as follows (Scheme 28).[80]



(47)

Scheme 28

Fluorination of 2-(trimethylsilyloxy)octane using 1:1 equivalents of (47) gave 2-fluorooctane and octenes in a ratio of 74/26. DAST gave a 71/29 ratio of the same products. The addition of 0.5 equivalents of (47) to racemic 2-(trimethylsiloxy)octane resulted in a moderate kinetic resolution, an 8% e.e. being recorded for the residual alcohol. Fluorination of ethyl 2-(trimethylsilyloxy)propionate (48) with 0.5 equivalents of (47) gave ethyl 2-fluorpropionate (49) in 16% e.e., with the residual alcohol (50) isolated in 50% e.e (Scheme 29).[80]



(48) 16% e.e. (49) 56% e.e. (50)

Scheme 29

1.6. **Towards new asymmetric fluorinating reagents**

All of the fluorinating reagents that are available to the organic chemist have limitations. If fluorine chemistry is to play an even greater role in the arena of asymmetric synthesis, reagents need to be developed that can deliver fluorine in a regioselective and stereoselective manner. New working practices and safety guidelines controlling the storage and use of chemicals mean that the reagents must be shelf stable and require the use of non-specialised equipment.

The concern of this research project has been to develop new asymmetric fluorinating reagents. A reagent capable of achieving regioselective and stereoselective control must impose some degree of steric constraint on fluorine. Such constraints could be supplied by one or more adjacent chiral centres carrying large pendant groups. Ideally these groups could be easily modified, such that the steric requirements of the reagent can be matched to the substrate.

1.6.1. **Electrophilic fluorinating reagents**

Since the N-fluorosultams (N-fluorocamphor reagent) have already been surveyed as possible asymmetric electrophilic fluorinating reagents, the focus of this research has been the synthesis of asymmetric N-fluoropyridinium triflates. A number of homochiral N-fluoropyridinium triflates that could meet the requirements of an ideal asymmetric electrophilic fluorinating reagent are shown below (Figure 3).

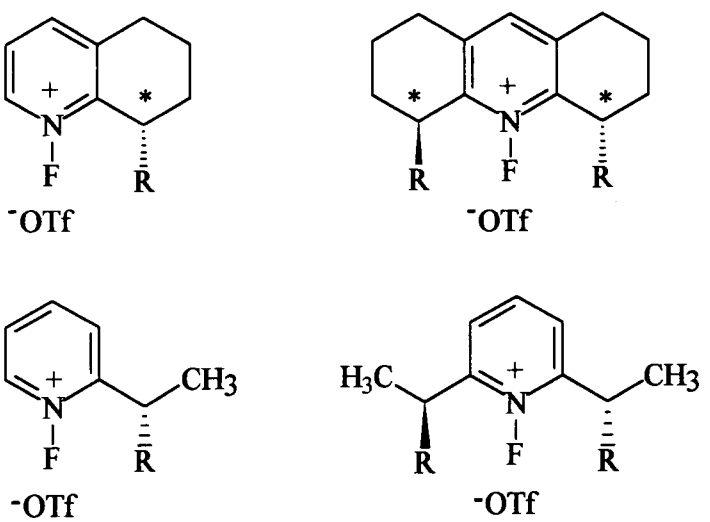
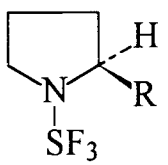


Figure 3

1.6.2. Nucleophilic fluorinating reagents

1.6.2.1. Homochiral DAST reagents

As already discussed *Sampson's* reagent (S)-(methoxymethyl)pyrrolidine-1-ylsulphur trifluoride (47) achieved only limited success as an asymmetric fluorinating reagent. A possible improvement that could be made to this reagent is to increase the steric bulk at the stereogenic centre by incorporation of side groups. It was an aim of this project to synthesise the pyrrolidine analogues below (Figure 4) and assess their ability as asymmetric fluorinating reagents.

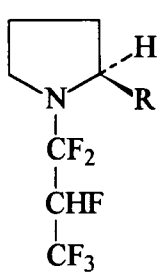


R=$CH(CH_3)_2$
$C(CH_3)_2OMe$
$C(Ph)_2OH$
$C(Ph)_2OMe$
$CH(Ph)_2$

Figure 4. Homologues of DAST

1.6.2.2. Homochiral *Ishikawa's* reagents

Homochiral derivatives of *Ishikawa's* reagent have not been reported in the literature. It was hoped that treatment of homochiral pyrrolidines with hexafluoropropene would allow us access to the reagents below (Figure 5). Theoretically these homochiral reagents should work in a similar way to Sampson's reagent considering that they fluorinate via an S_N2 mechanism. Obviously to achieve a kinetic resolution 0.5 equivalents of reagent must be added to one equivalent of an alcohol.



R=$CH(CH_3)_2$
$C(CH_3)_2OMe$
$C(Ph)_2OH$
$C(Ph)_2OMe$
$CH(Ph)_2$
CH_2OMe

Figure 5. Homologues of Ishikawa's reagent

CHAPTER 2

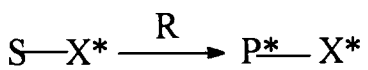
Asymmetric Synthesis of Homochiral Pyridine Systems

2.1 Introduction

Asymmetric synthesis is undoubtedly the single area of organic synthesis that has exploded during the 1980s and 1990s. This exciting area of chemistry is concerned with the conversion of achiral starting materials into homochiral systems. In most biologically active compounds, the desired activity is possessed by a single enantiomer, the other isomers may be inactive, or in extreme cases, cause undesirable side effects.

Nature itself is the biggest pool of chirality, and many compounds are tapped from it in enantiomerically pure form. Asymmetric synthesis is concerned with mimicking nature to produce new enantiomerically pure starting materials, for applications in agriculture and medicine. The main strategies used in asymmetric synthesis are as follows:-

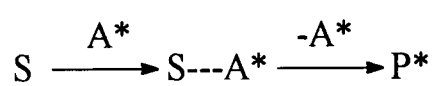
(a) In the *substrate controlled method* a new stereogenic centre is formed in a substrate **S** under the influence of a group X* on the adjacent stereogenic centre. If the reagent is denoted by **R** and the product by **P**, then the reaction may be represented as follows (Scheme 30).



* homochiral centre

Scheme 30

(b) In *auxiliary controlled methods* an achiral substrate is made homochiral by the influence of a chiral auxiliary A*. This auxiliary can then be used to direct subsequent reactions or to create diastereomers, which are then separable by physical techniques. Removal of A* then leads to homochiral products (Scheme 31).



Scheme 31

(c) Thirdly chiral reagents R*, can be used which convert achiral substrates directly into homochiral products (Scheme 32).

$$S \xrightarrow{R^*} P^*$$

Scheme 32

(d) This category involves the conversion of an achiral substrate to a homochiral product using an asymmetric catalyst (Scheme 33).

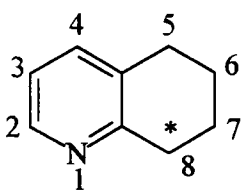
$$S \xrightarrow[cat^*]{R} P^*$$

Scheme 33

This method has the distinct advantage over (c) since it is uses enantiomerically pure starting materials in the most economical way. Included in this class are biotransformations using enzymes.

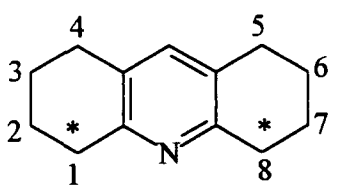
2.2 Objectives

The focus of this research was to develop asymmetric fluorinating reagents and as an initial objective the synthesis of ligands for homochiral N-fluoropyridinium triflates was addessed. Homologues of pyridine 5,6,7,8-tetrahydroquinoline (51) and 1,2,3,4,5,6,7,8-octahydroacridine (52), both commercially available,[91] were chosen as initial candidates for the development of such ligands. These systems are ideal candidates, since chiral centres (*) can potentially be introduced at positions 1 and 8, adjacent to the pyridine nitrogen.



(51)

5,6,7,8-tetrahydroquinoline

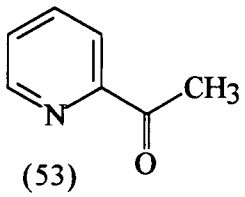


(52)

1,2,3,4,5,6,7,8-octahydroacridine

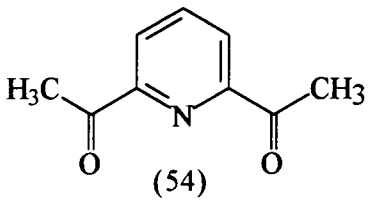
Additionally rigidity in these systems is high due to the fused ring, thus minimising conformational flexibility.

Other targets were acyclic pyridiniun triflates accessible from 2-acetylpyridine (53) and 2,6-diacetylpyridine (54), both commercially available starting materials.[91]



(53)

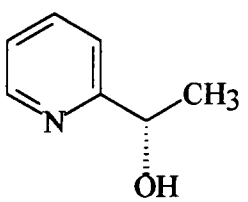
2-acetylpyridine



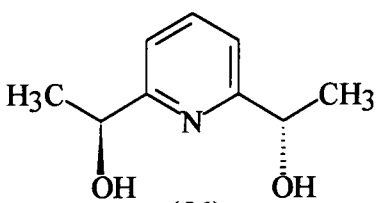
(54)

2,6-diacetylpyridine

Asymmetric reduction of the keto groups in these compounds was judged as an appropriate means of obtaining the required homochiral alcohols 2-(1-hydroxyethyl)pyridine (55) and 2,6-diethyl(α-hydroxy)pyridine (56). Additionally a range of functional groups can be added to the hydroxy groups in order to place steric constraints on the pyridyl fluorine.



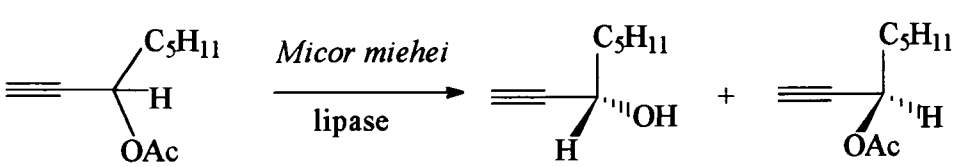
(55)



(56)

2.3 **Resolution of homochiral pyridines using lipase enzymes**

Enzymes have become very useful tools for asymmetric transformations. A class of enzymes that find frequent use in organic synthesis are lipase enzymes. These enzymes belong to a general group called hydrolases, which catalyse the formation and cleavage of ester groups. Their use in asymmetric synthesis results from their ability to hydrolyse one enantiomer of a racemic ester faster than the other, effectively achieving a kinetic resolution. An example of this is shown below (Scheme 34).[92]



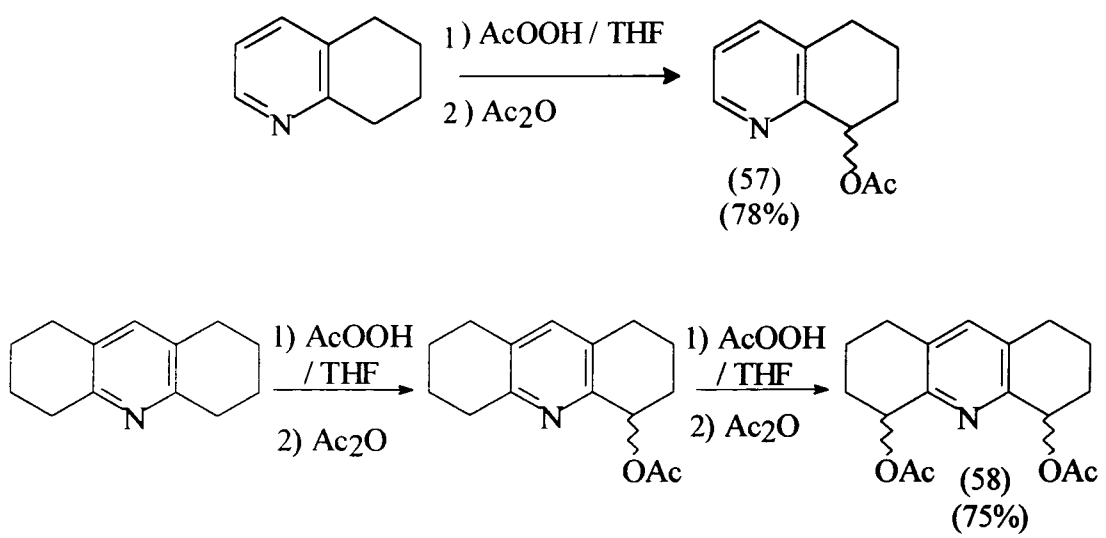
(87-97% ee)
(40% conversion)

Scheme 34

Two strategies can be used for such resolutions. The first is to stop the enzyme hydrolysis at 40% conversion, giving optically enriched alcohol, or alternatively the reaction can be stopped at 60% conversion, giving optically enriched ester. The beauty of such a reaction in an optimised system is that both enantiomers can be obtained in optically pure form.

It was envisaged that chirality could be introduced at position 8 in 5,6,7,8-tetrahydroquinoline (51) and positions 1 and 8 in 1,2,3,4,5,6,7,8-octahydroacridine (52) by enzyme hydrolysis of acetoxy groups. Thus 8-acetoxy-5,6,7,8-tetrahydroquinoline (57) and 1,8-diacetoxy-1,2,3,4,5,6,7,8-octahydroacridine (58) became our synthetic targets. The synthesis of both of these compounds has been reported using hydrogen peroxide and acetic anhydride.[93,94] Under these conditions however, the reactions were found to be problematic, forming black tars.

A two stage synthesis was found to be the best way of generating the required acetates. In the first stage peracetic acid was used as an oxidising agent generating the corresponding N-oxides as white crystalline solids. Formation of the required acetates was then achieved by refluxing the N-oxides with acetic anhydride. Synthetic routes to these compounds are shown below (Scheme 35).



Scheme 35

1,8-Diacetoxy-1,2,3,4,5,6,7,8-octahydroacridine (58) was found to be a 1:1 mixture of the *meso* (R,S) and R,R, S,S diastereomers. Separation of the *meso* component from the R,R and S,S forms was achieved by column chromatography. X-ray crystal structure analysis of the R,R and S,S mixture (Figure 6) (X-ray data see Appendix I) provided an unambiguous assignment and indicated that the acetate groups are in a rigid conformation, one acetate group above the plane of the pyridyl ring and the other below it. Fluorination of the pyridine nitrogen in either the R,R or S,S forms would appear to lead to an ideal fluorinating reagent, in which the fluorine is situated in a chiral pocket, flanked by two chiral centres.

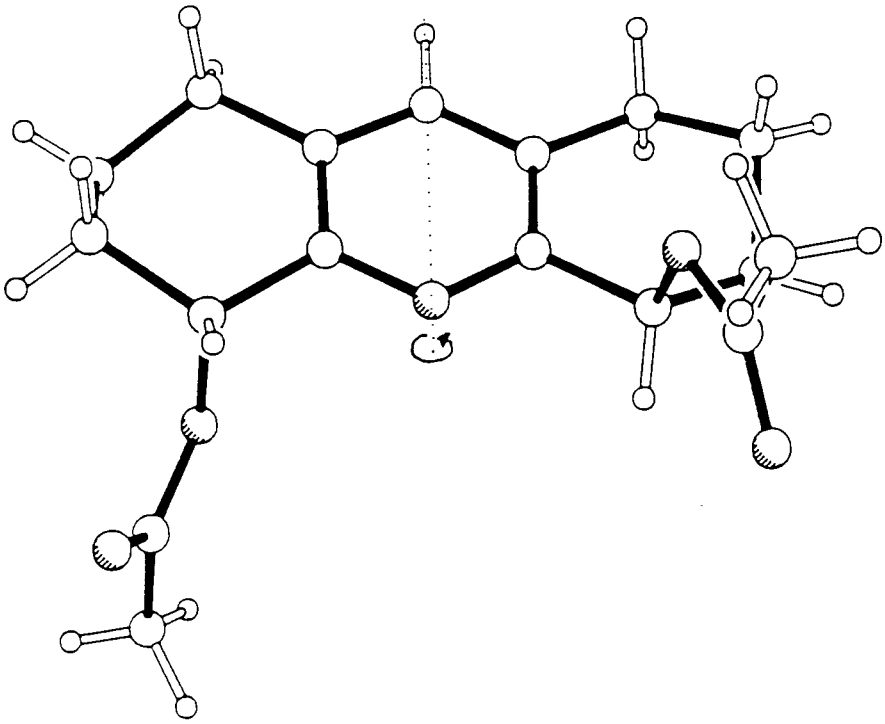


Figure 6. X-ray crystal structure of (R,R),(S,S)-1,8-diacetoxy-1,2,3,4,5,6,7,8-octahydroacridine (58)

2.3.1 Attempted resolution of 8-acetoxy-tetrahydroquinoline and (R,R),(S,S)-1,8-Diacetoxy-1,2,3,4,5,6,7,8-octahydroacridine

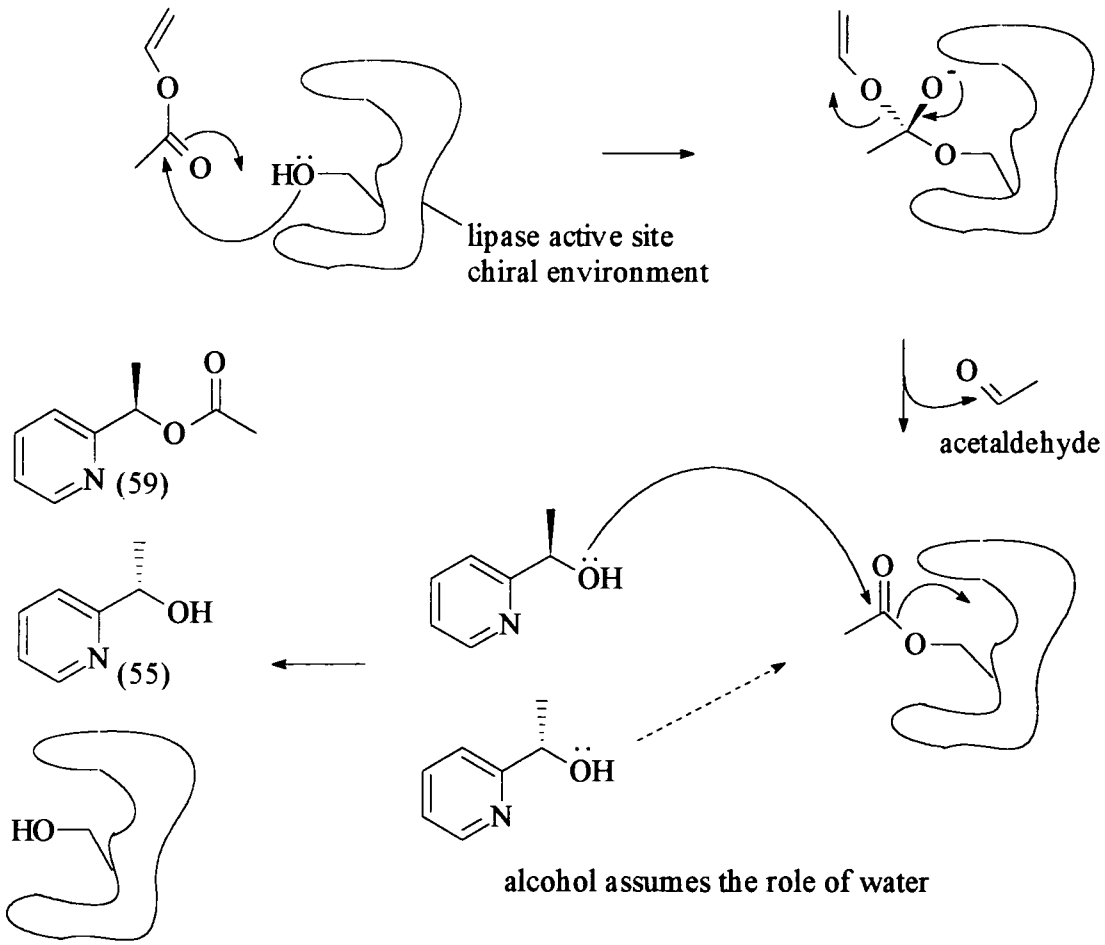
Enzyme resolutions are generally carried out in aqueous buffer solutions, simply by mixing the substrate and enzyme together and keeping the reaction temperature at 35°C.[95] Under these conditions a range of commercially available lipases (Table 4) were screened, but were unable to hydrolyse the acetates.

Enzyme	Activity u/g
a) *Rhizopus*	150000
b) *Rhizopus*	80000
c) *Azpergillus*	60000
d) *Pseudomonas*	30000
e) *Mucor*	10000
f) *Candida cylindracea*	10000

Table 4

Insolubility of the substrates in aqueous buffer is a clear reason for the resistance to enzyme hydrolysis. This solubility problem was overcome however, by forming water soluble N-oxide derivatives of the two acetate systems. Although these showed good solubility in aqueous buffer they were not hydrolysed by the above enzyme systems. On analysis this is not surprising as sterically bulky esters generally prove to be resistant to lipase hydrolysis. A enzyme mediated transesterification reaction was also attempted in organic solvents using *Candida cylindracea.*[96] Under these conditions this enzyme has been shown to resolve bulky esters including tertiary systems. Unfortunately transesterification of (57) and (58) was unsuccessful, only leading to the recovery of unreacted starting materials. It was concluded that the two acetate systems were unsuitable substrates for enzyme hydrolysis and alternative methodology would be needed.

Lipase resolutions can be carried out in aqueous or organic solvents as already discussed. A third form of lipase resolution is an irreversible transesterfication reaction.[97] This technique involves loading the serine residue of the lipase with vinyl acetate. The racemic alcohol to be resolved is then introduced to the enzyme and a transesterification reaction takes place. One enantiomer of the racemic alcohol is transesterified faster than the other resulting in a kinetic resolution. This mechanism is shown below (Scheme 36) for 2-(1-hydroxyethyl)pyridine (55).

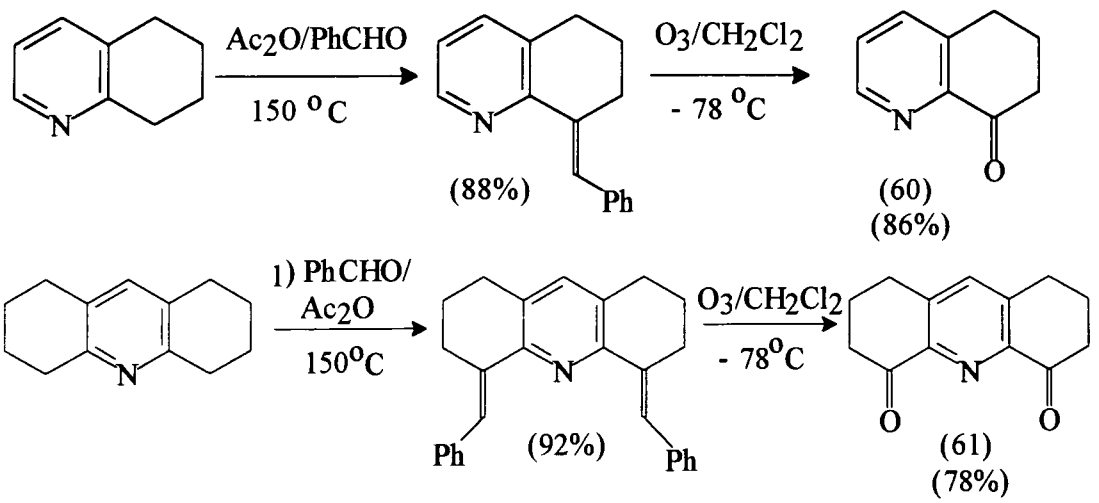


Scheme 36. Transesterification of 2-(1-hydroxyethyl)pyridine using lipase enzymes

After 24 hours the transesterification of 2-(1-hydroxyethyl)pyridine (55) using the lipase enzyme *Candida cylindracea* gave (2S)-(1-acetoxyethyl)pyridine (59) in 30% yield, $[\alpha]_D^{25} = +53.7^o$, ($[\alpha]D = +100.3^o$, 96% e.e)[98] has been reported. The enantiomeric excess was determined to be 50% by ^1H NMR using the chiral shifts reagent [Eu(tfc)$_3$] and this was consistent with the value estimated from the optical rotation.

2.4. Synthesis of homochiral pyridines using asymmetric reductions

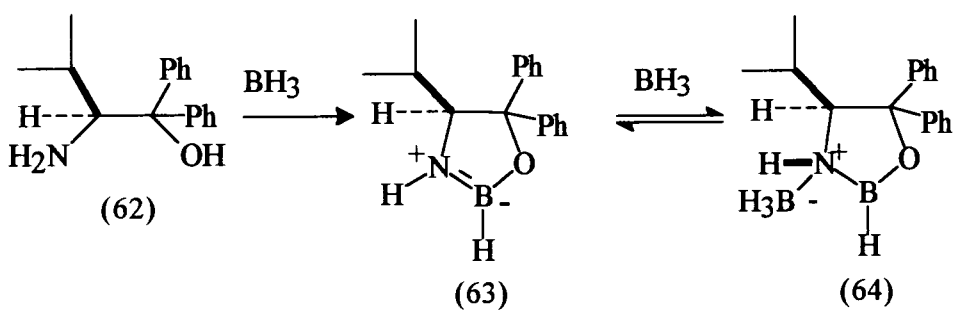
Optically active alcohols are important starting materials for chiral synthesis.[99] Their synthesis by the reduction of prochiral ketones with chiral reducing agents has been actively pursued in recent years and many new reagents have been developed for this purpose.[100] The outstanding successes in this area of chemistry led us to prepare the ketones 8-oxo-5,6,7,8-tetrahydroquinoline (60)[101] and 1,8-dioxo-1,2,3,4,5,6,7,8-octa hydroacridine (61)[102] as follows (Scheme 37), and to attempt reductions using a range of asymmetric reducing agents.



Scheme 37

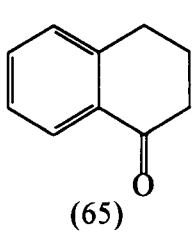
2.4.1 Corey Bakshia and Shilata, CBS reduction

The above ketone systems were reduced using Corey, Bakshia and Shilata **CBS** reduction procedure which involves the use of a catalytic amount of a oxazaborolidine. This is formed by the reaction of the chiral amino-alcohol R-(-)-1,1-diphenylprolinol (62) with borane-THF (Scheme 38). Neither the borane-THF or the oxazaborolidine (63) reduce ketones rapidly, but in combination the reagents form complex (64) which has been found to reduce ketones in high yield and in a highly stereoselective manner.[103,104]



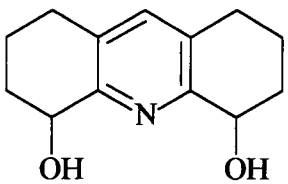
Scheme 38

This procedure for example has been used to reduce α-tetralone (65), an analogous system in steric terms to 8-oxo-5,6,7,8-tetrahydroquinoline (60), giving the R-enantiomer in 89% e.e.[103]

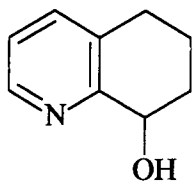


(65)

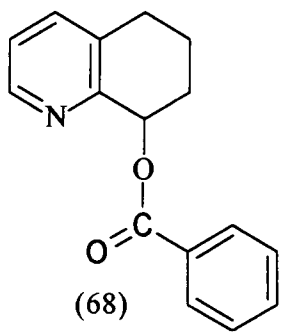
1,8-Dioxo-1,2,3,4,5,6,7,8-octahydroacridine (61) was accordingly subjected to the **CBS** reduction, giving the diol 1,8-dihydroxy-1,2,3,4,5,6,7,8-octahydroacridine (66) in 51% yield. Determination of the diol's optical purity was achieved by ^1H NMR analysis of its diacetate derivative (58) using chiral shifts reagent [Eu(tfc)$_3$]. This method demonstrated that no stereoselectivity was imparted with the **CBS** reduction. Similarly reduction of 8-oxo-5,6,7,8-tetrahydroquinoline (60) gave the racemic alcohol 8-hydroxy-5,6,7,8-tetrahydroquinoline (67), as determined by chiral HPLC of its 8-benzoyloxy-5,6,7,8-tetrahydroquinoline derivative (68).[105]



(66)



(67)

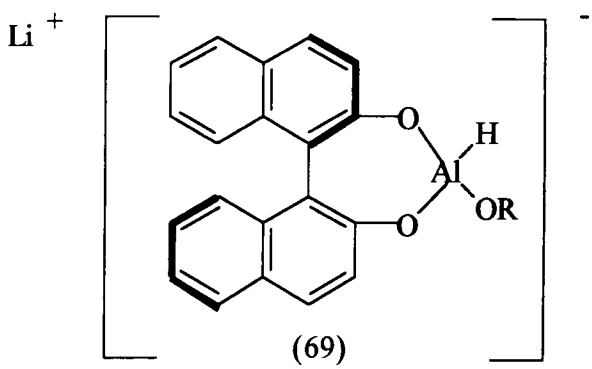


(68)

2-Acetylpyridine (53) and 2,6-diacetylpyridine (54) also gave racemic alcohols when reduced by this method. The lack of stereoselectivity obtained with pyridine based ketones suggests that co-ordination of the carbonyl oxygen to the cyclic oxazoborolidine is disrupted. Alternative complexation involving the nitrogen lone pair is probably the cause of this.

2.4.2 **Binapthol aluminium hydride BINAL-H**

The chiral reducing reagent BINAL-H (69) has been found to reduce a wide variety of carbonyl substrates in high optical yields and in a predictable manner.



(69)
(R)-BINAL-H

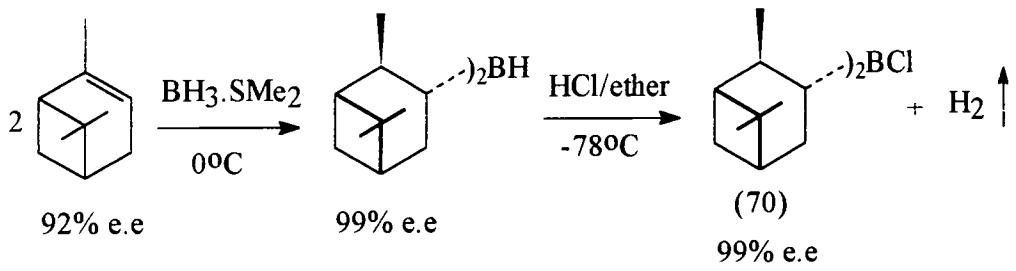
α-Tetralone (65) for example was reduced with a 62 % e.e.[106] One disadvantage with this system is that the chiral auxiliary is not used in catalytic amounts and requires a 3:1

ratio of reagent to ketone, which is expensive. The BINAL-H reduction is proposed to proceed via a six membered transition state, in which hydride delivery to the carbonyl is controlled by both the size and electronic properties of the groups attached to it.[106]

Reductions of 8-oxo-5,6,7,8-tetrahydroquinoline (60) and 1,8-Dioxo-1,2,3,4,5,6,7,8-octahydroacridine (61) were attempted using the BINAL-H reduction, but this only resulted in the recovery of unreacted ketones.

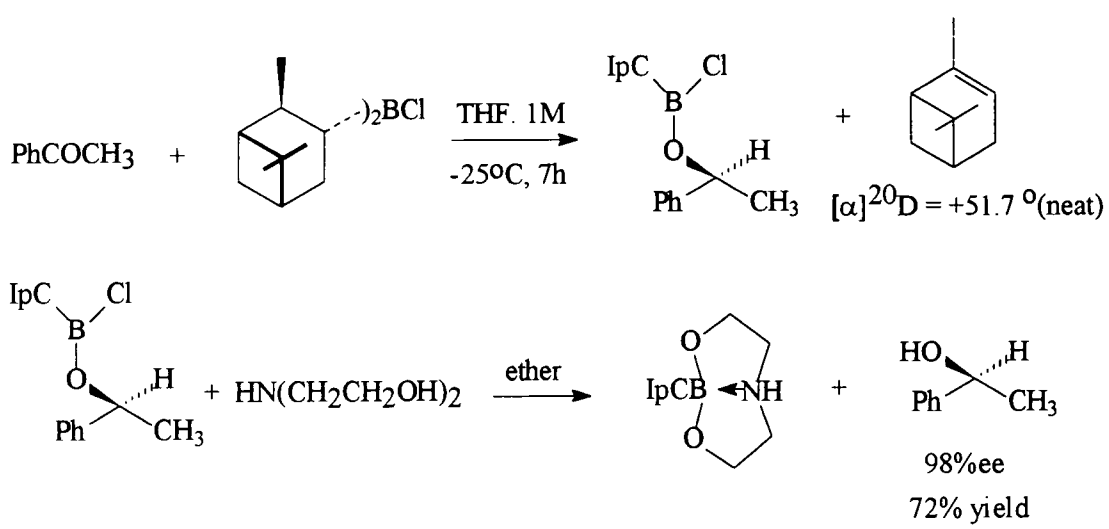
2.4.3 **Diisopinocamphenylchloroborane reductions**

Diisopinocamphenylchloroborane (70) is readily prepared in high chemical yield and optical purity (99% e.e) from (+)-α-pinene (92% e.e) via hydroboration, followed by treatment with a dry hydrogen chloride in ether (Scheme 39).[107]



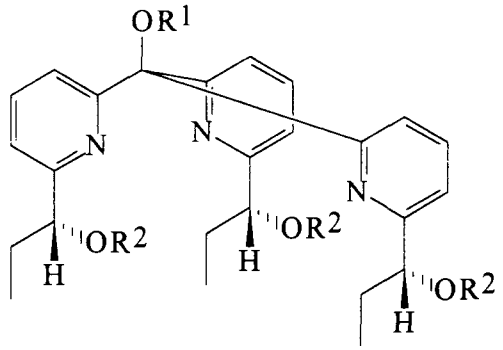
Scheme 39

This reagent readily reduces ketones and has proved effective for the asymmetric reduction of aromatic prochiral ketones.[107] For example the reagent achieved a 98% e.e in the reduction of acetophenone (Scheme 40).

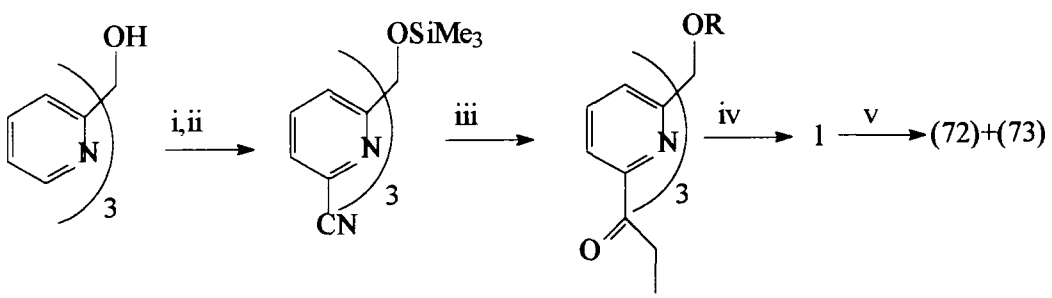


Scheme 40

Enantiomerically pure C_3-symmetric tripodal pyridine ligands (71), (72) and (73) have also been synthesised using the above diisopinocamphenylchloroborane reagent (Scheme 41),[108] and this was clearly an attractive precedent for the intended reductions of 2-acetylpyridine (53) and 2,6-diacetylpyridine (54).



(71) R^1=R^2=H
(72) R^1=H, R^2=Me
(73) R^1=R^2=Me



Scheme 41. i) m-chloroperbenzoic acid; (ii) N,N-dimethylcarbamoyl chloride, trimethylsilyl cyanide; (iii) EtMgBr; (iv) (-)-IpC_2BCl, 2,2'-iminodiethanol; (v) NaH, MeI.

Reduction of 2-acetylpyridine (53) using (+)-diisopinocamphenylchloroborane gave only the corresponding racemic alcohol (55) in 58% yield. 2,6-Diacetylpyridine (54), however, proved more interesting. 2 Mol equivalents of the asymmetric reducing reagent gave, consistently the racemic diol (56). However repetition of the reaction using 1 Mol equivalent of diisocamphenylchloroborane gave the mono-reduced product 2-acetyl-6(α-hyroxy)ethylpyridine (74) with $[\alpha]_D$ = -7.06. Conversion of the mono-reduced alcohol (74) to its 2-acetyl-6-(α-(2'S)-methylbutyryloxy)ethylpyridine derivative (75) and subsequent chiral HPLC using a Chiracel OD-H column gave an enantiomeric excess of 47% (Figure 7 and 8).[105] Although interesting, the % e.e was still only moderate to poor and alternative methods were sought.

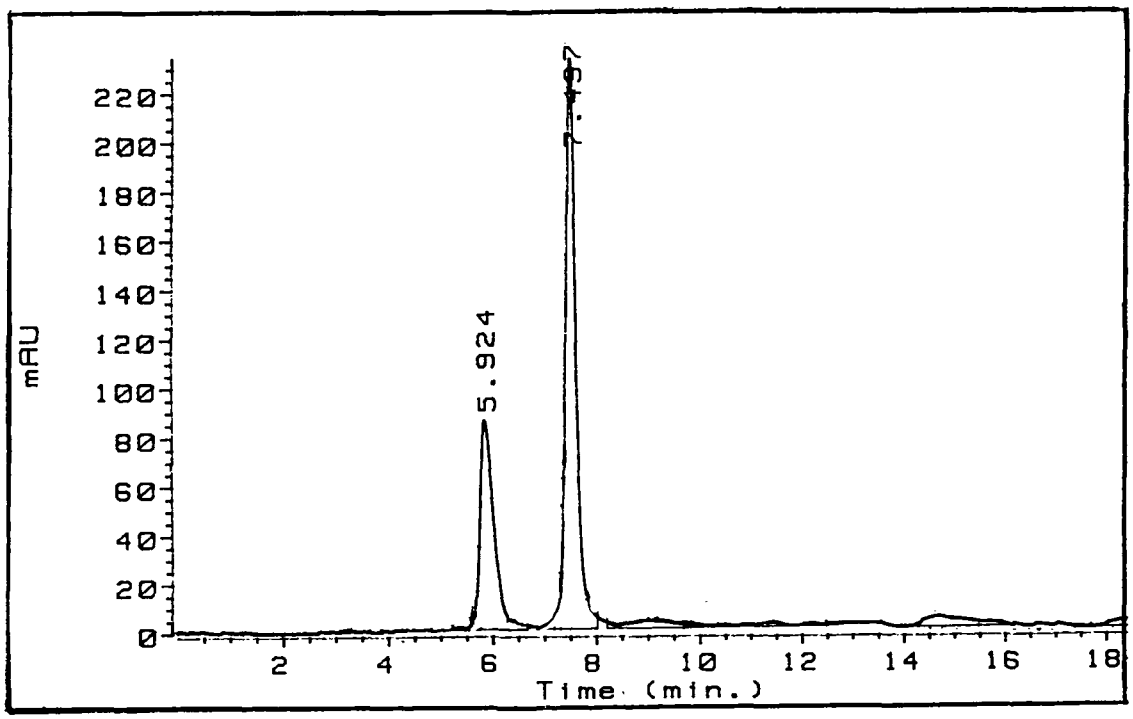


Figure 7. Chiral HPLC of optically enriched 2-acetyl-6-(α-(2'S)-methylbutyryloxy)ethylpyridine (75)

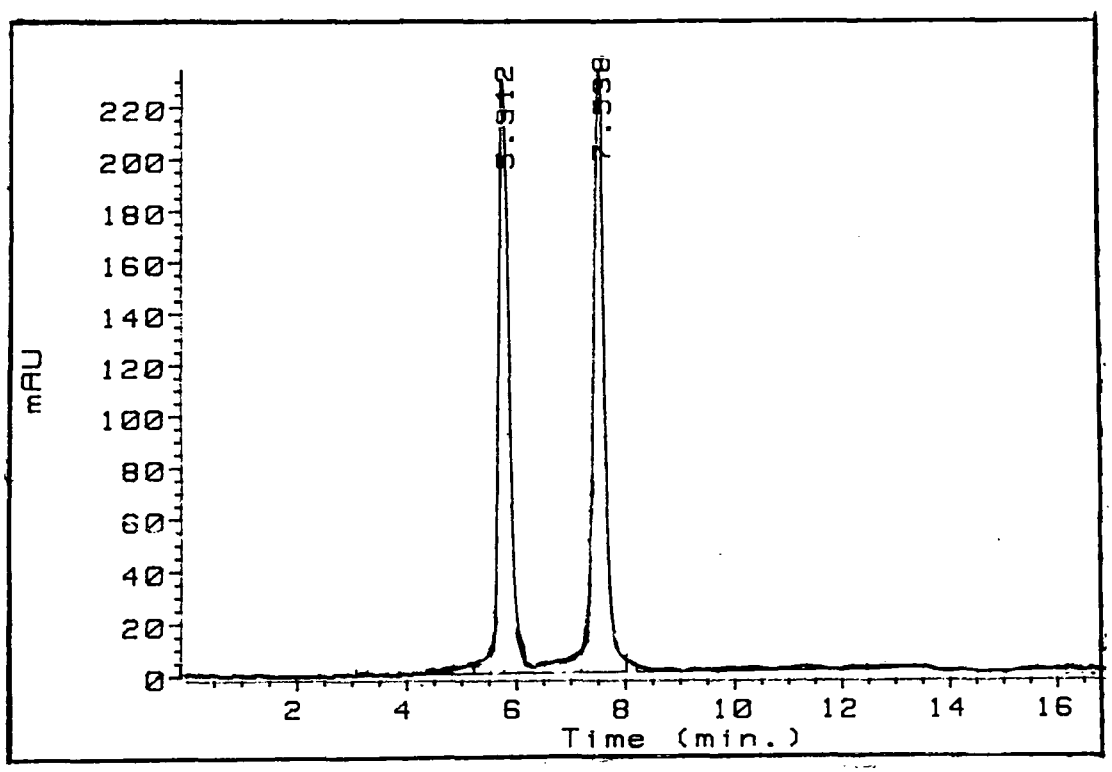


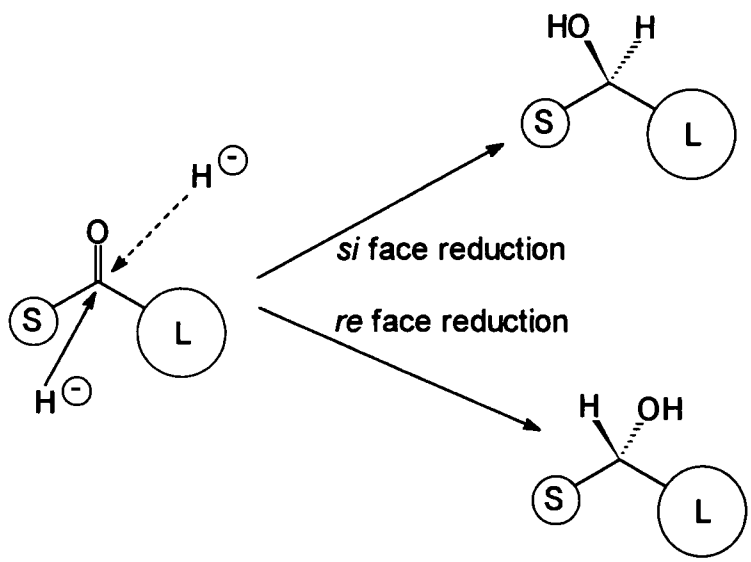
Figure 8. Chiral HPLC of (±) 2-acetyl-6-(α-(2'S)-methylbutyryloxy)ethylpyridine (75)

2.4.4 Bakers' yeast reductions

2.4.4.1 Introduction

The word yeast is derived from an Anglo-Saxon verb to foam or froth. Yeasts are a heterogeneous group of fungi which live either as saprophytes (live on rotting wood) or as parasites and are mostly unicellular.[109] The genus *Saccharomyces* is composed of species which ferment a variety of sugars to ethanol and carbon dioxide. Commercially available *Saccharomyces cerevisiae*, strains of which are used as bakers', brewers' or wine yeast has been used in organic synthesis to provide efficient access to many homochiral compounds. Bakers' yeast is known to contain a selection of different enzymes which have been used for a number of functional group transformations. Examples of these are reduction of carbon-carbon double bonds,[110-113] ester hydrolysis,[114,115] dehydrogenation,[116-118] cyclisation reactions,[119-121] acyloin condensations,[122,123] and the reduction of ß-keto esters, keto acids and α,ß-unsaturated carbonyl compounds.[124]

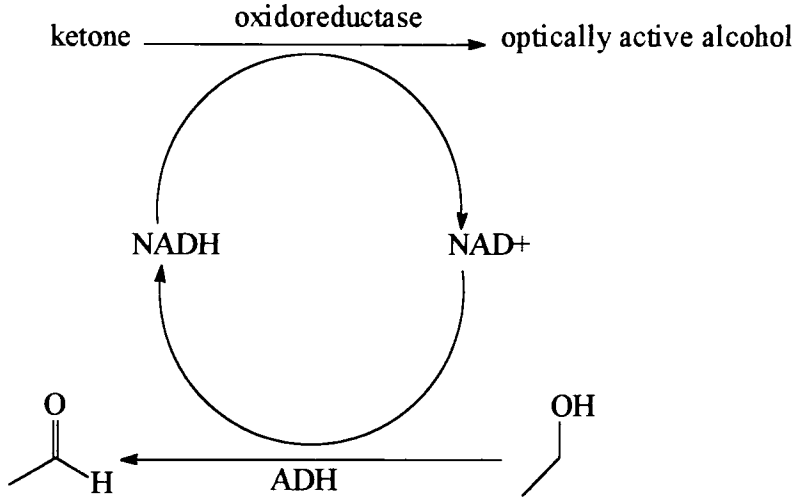
The enantioselective reduction of carbonyl compounds using bakers' yeast is usually attributed to the steric influence of the two substituents on the carbonyl group, the enzyme being able to distinguish between the *re* and *si*-faces of the substrate (Scheme 42).[125]



Scheme 42

Sih has shown that bakers' yeast produces several dehydrogenase enzymes with opposite facial selectivity and that these deliver hydrogen at different rates for different substrates.[125] Glucose plays an important role in yeast reductions and is known to stimulate the process of glycolysis by NAD(P)H. It has also been found that the

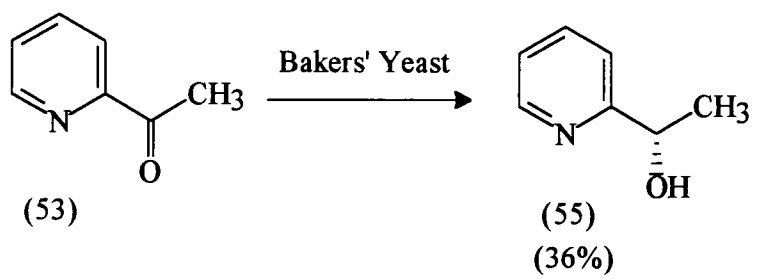
addition of glucose resets dehydrogenase-levels in the yeast so improving both the chemical yield and stereoselectivity towards D-alcohols.[126] The interplay between ethanol and the co-factor NADH can be envisaged as follows (Scheme 43).[127]



Scheme 43

2.4.4.2 Bakers' yeast reductions of mono-ketones

Bakers' yeast has been found to reduce 2-acetylpyridine (53) to (2S)-(1-hydroxyethyl) pyridine (55) in 36% yield and 96% e.e (Scheme 44).[128]



(53) (55) (36%)

Scheme 44

This reaction in our hands generated (55) in 35% yield, $[\alpha]_D$=21.8°, 85% e.e. It was reasoned that two or more dehydrogenase enzymes may be operating simultaneously, with opposite stereoselectivities. Therefore in order to improve the selectivity, one of the dehydrogenase enzymes could be inhibited or activated in preference to the other.[126,129] Allyl alcohol has been used as a selective inhibitor in the bakers' yeast reduction of keto esters resulting in higher % e.e values due to selective inhibition of one of the alcohol dehydrogenase enzymes.[126,129] Accordingly 2-acetylpyridine (53) was reduced using bakers' yeast in the presence of allyl alcohol and (55) was recovered in 34% yield, $[\alpha]_D$= -29.14°. The optical purity was ascertained by chiral HPLC using a chiracel OD column, and was found to be 98% e.e (Figures 9, 10 and 11).[105]

Derivatisation of (55) to its 2-(α-4'-bromobenzoyloxy)ethylpyridine derivative (76) and recrystallisation gave optically pure material. X-ray crystallography showed that homochiral 2-(α-4'-bromobenzoyloxy)ethylpyridine (76) had the absolute configuration (S) (Figure 12) (X-ray data see Appendix II) as anticipated.

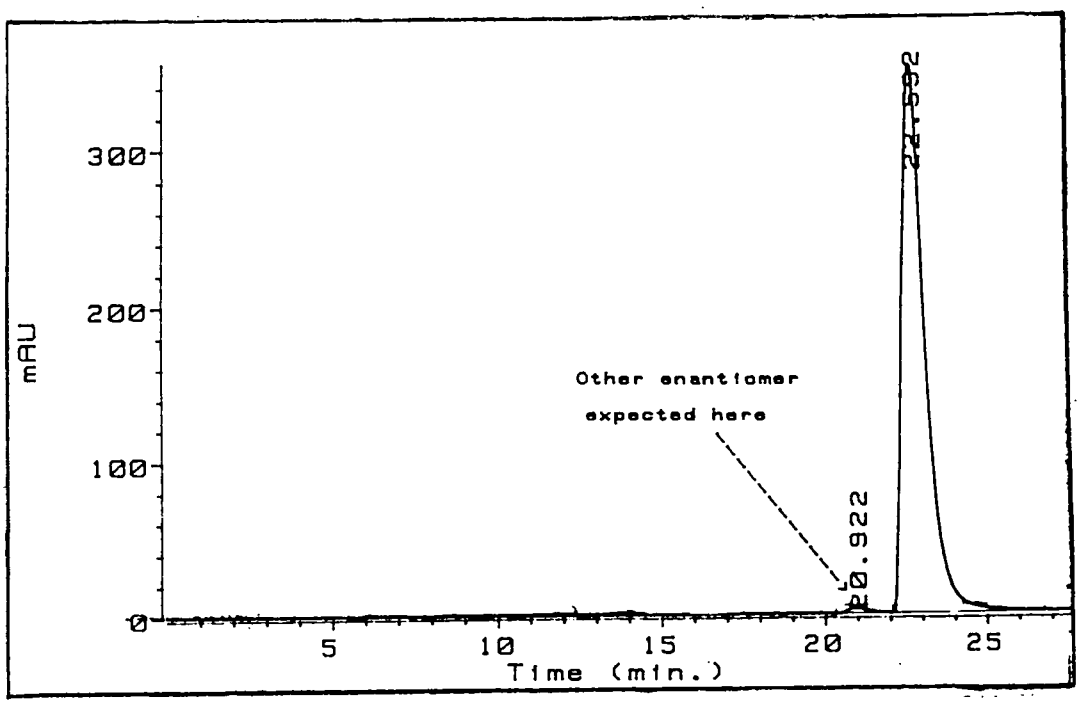


Figure 9. Chiral HPLC of (2S)-(1-hydroxyethyl)pyridine (55)

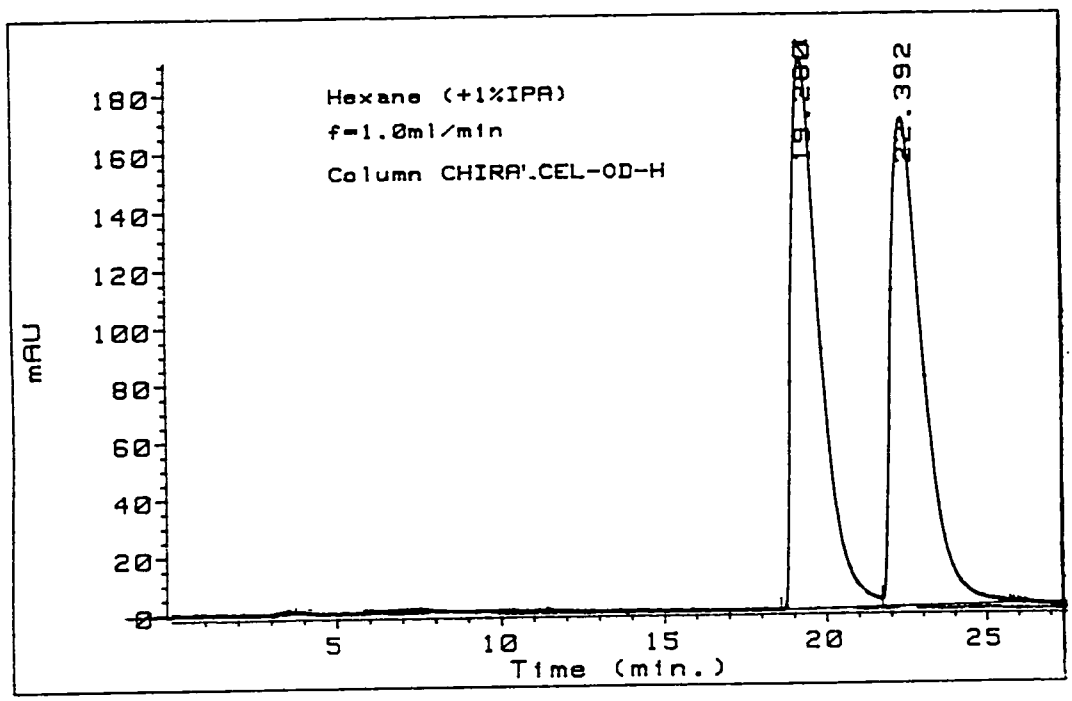


Figure 10. Chiral HPLC of racemic 2-(1-hydroxyethyl)pyridine (55)

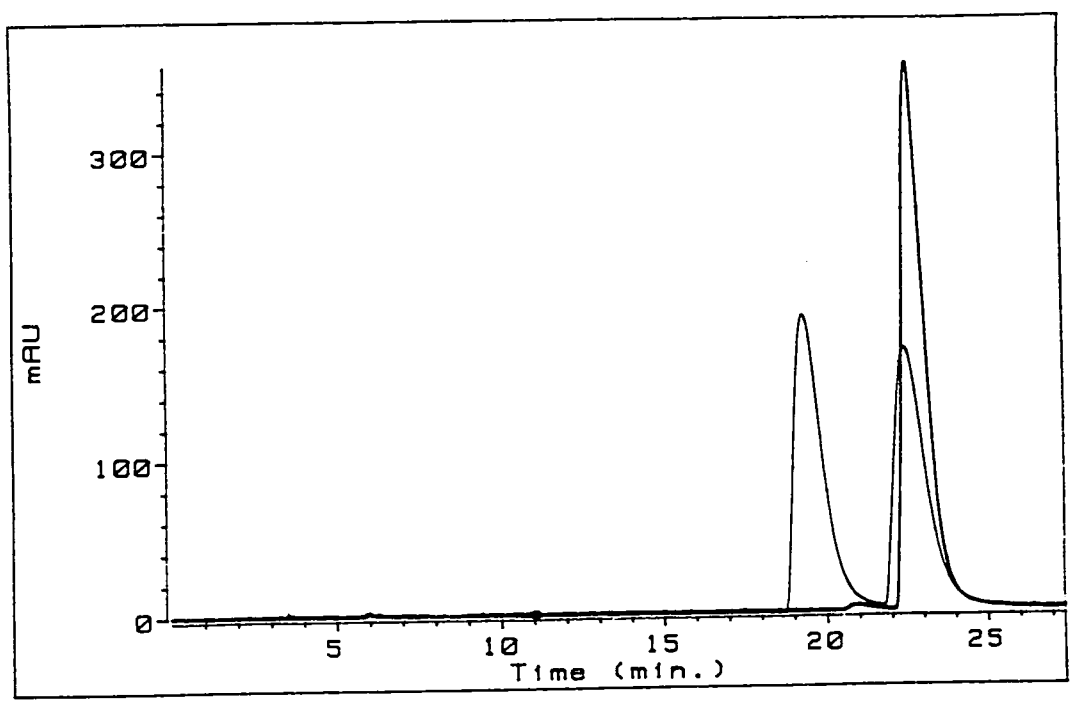
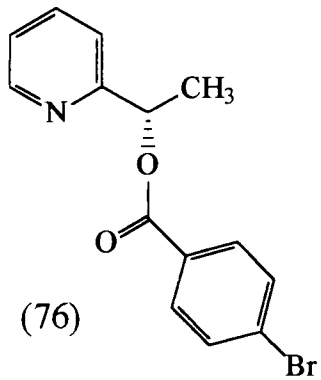


Figure 11. Overlay of racemic 2-(1-hydroxyethyl)pyridine (55) on (2S)-(1-hydroxyethyl)pyridine (55)



(76)

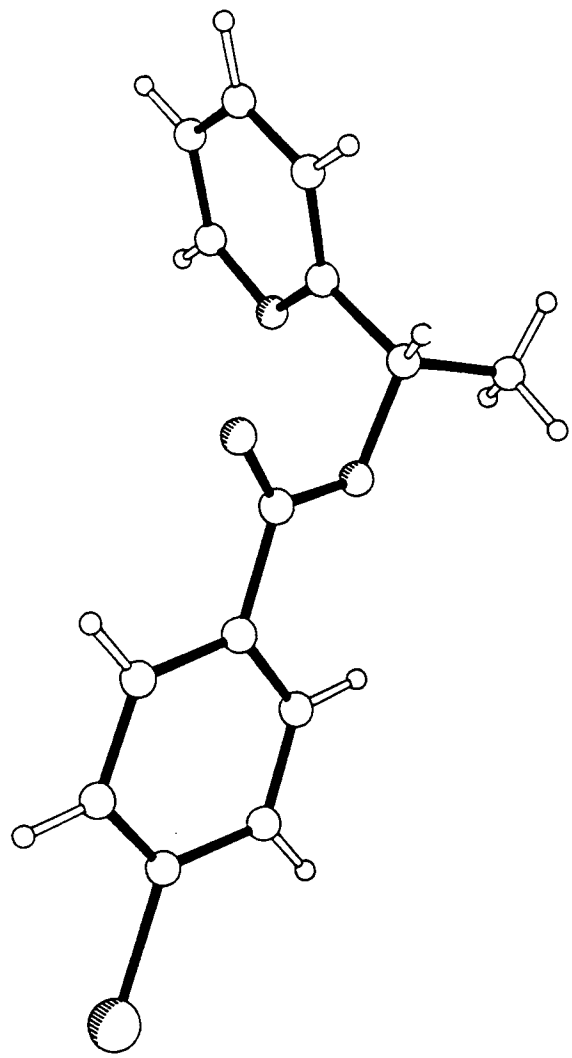
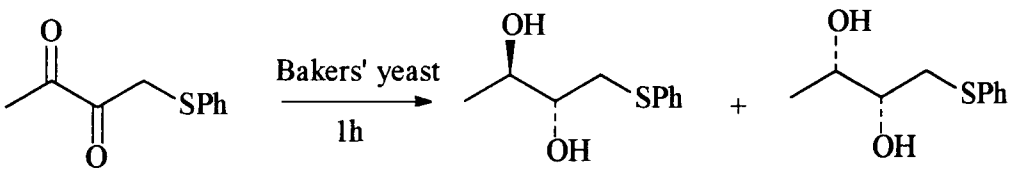


Figure 12. X-ray crystal structure of (2S)-(α-4'-bromobenzoyloxy)ethylpyridine (76)

Bakers' yeast reduction of 8-oxo-5,6,7,8-tetrahydroquinoline (60) was attempted, but this only resulted in the recovery of unreacted ketone.

2.4.4.3 Bakers' yeast reductions of diketones

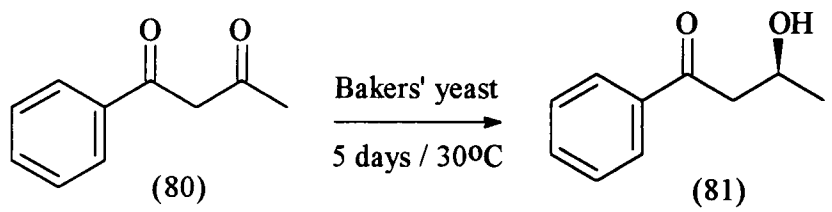
The synthesis of optically active diols has been achieved by catalytic hydrogenation of C_2 symmetrical ketones.[130] However, this process requires the use of high pressure and complex organometallic reagents. Bakers' yeast is known to reduce 1,2 diketones to 1,2 diols.[124] For example the reduction of the diketone (77) below (Scheme 45) gives *anti* (78) and *syn* (79)-isomeric diols in a 86:14 ratio. Optically pure diol was obtained after recrystallisation, and has been used for the synthesis of γ-lactones of natural origin.[131]



(77) (86%) (78) (14%) (79)

Scheme 45

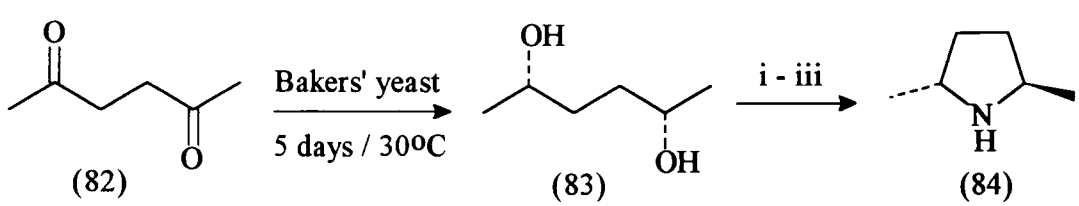
β-Diketones are often reduced to give products in which only one carbonyl is reduced. For example the β-diketone (80) below (Scheme 46) yields the mono-reduced product (81) as a single enantiomer.[132]



(80) (81)

Scheme 46

Unlike β-diketones, 1,4-diketones are reduced by bakers yeast to their corresponding diols. The 1,4-diketone (82) below (Scheme 47) was reduced to its (S,S) *syn* diol (83), and was then converted to (-)-(2R,5R)-2,5-dimethylpyrrolidine (84) using chemical methods.[133]

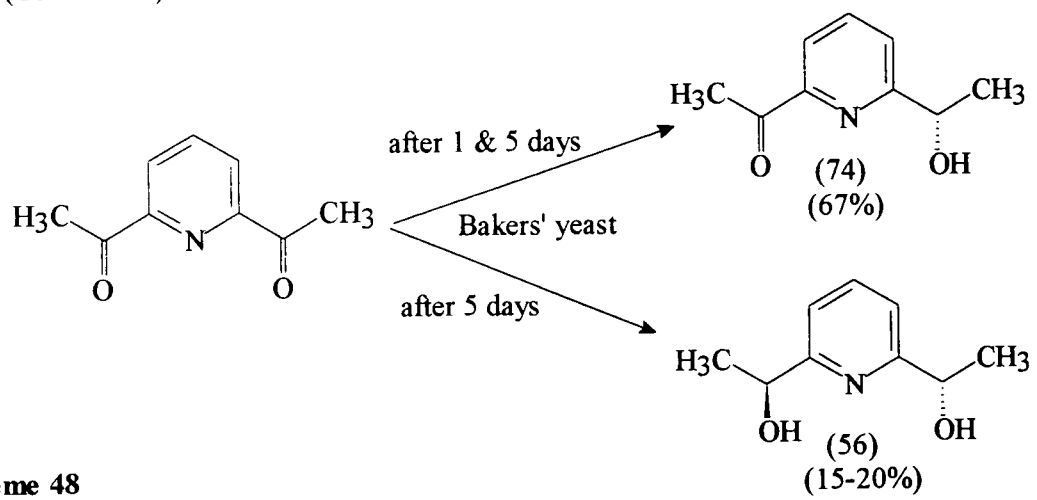


(82) (83) (84)

Scheme 47. i) Et_3N, methanesulfonyl chloride. ii) benzylamine, 25°C, 96h, NaOH. iii) glacial acetic acid, 10% $Pd(OH)_2/C$, H_2, 30-40 Psi, NaOH.

2.4.4.4 Bakers' yeast reduction of pyridyl diketones

For our purposes we subjected 2,6-diacetylpyridine (54) to the bakers' yeast reduction which after one day gave the mono reduced product, 2-acetyl-6(α-hyroxy)ethylpyridine (74) which was generated in 67% yield, $[\alpha]_D$= -7.18° and 85% e.e, with none of the required diol (56). When the yeast reduction was left for a full 5 days 2,6-diethyl(α-hydroxy)pyridine (56), $[\alpha]_D$= -19.18 was produced and could be isolated in 15-20 % yield (Scheme 48).

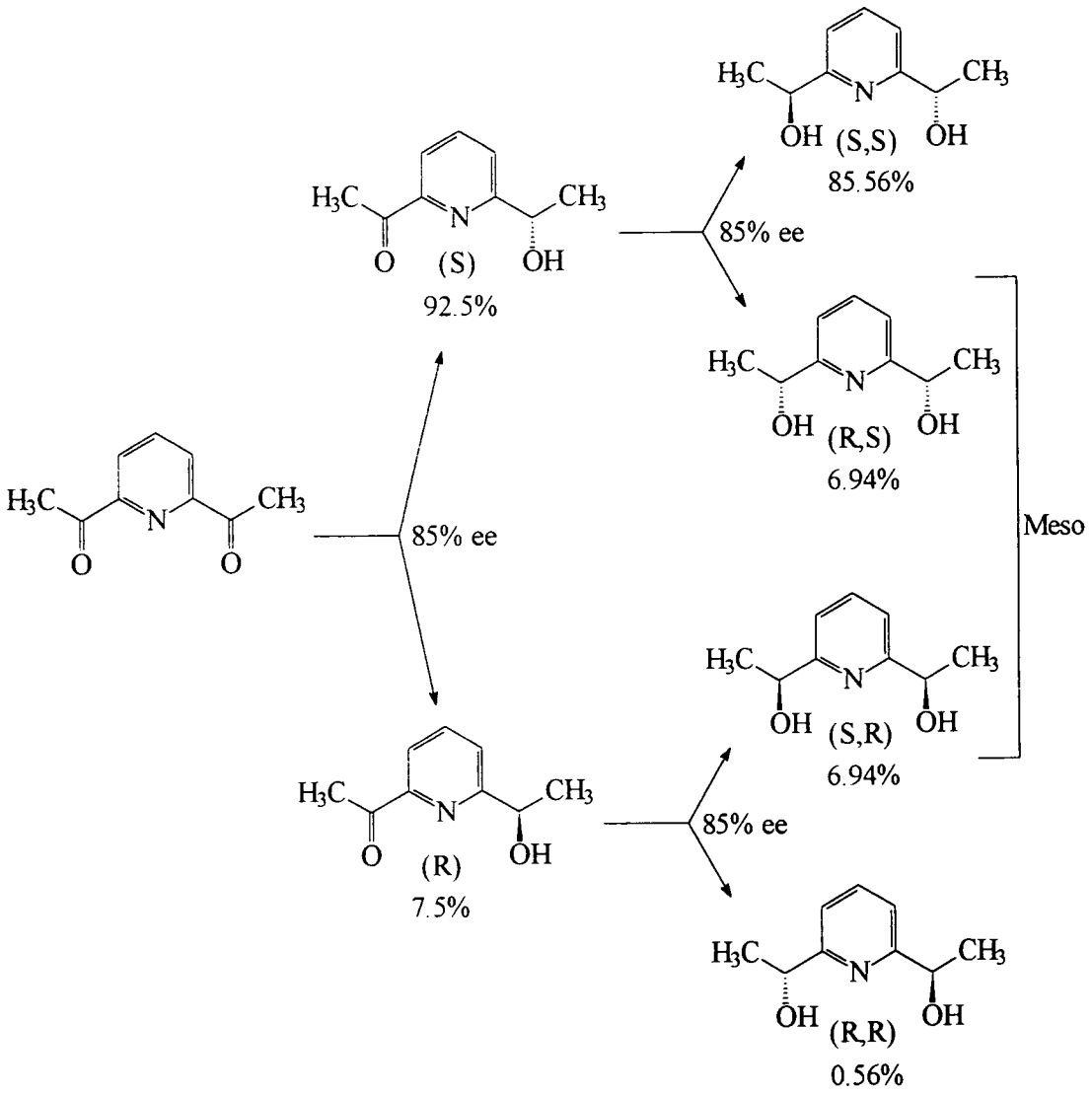


Scheme 48

This diol was converted to its 2,6-diethyl(α-4'-bromobenzoyloxy)pyridine derivative (85). ^{1}H NMR of (85) showed it to be a mixture of predominantly two diastereomers in a ratio of 87:13. The minor *meso* (R,S) diastereomer could be completely removed after one recrysallisation.

Soai [134] has described a relationship between the amount of *meso* component formed in a double asymmetric reduction and the overall enantiomeric excess of the reaction. This relationship also assumes that the degree of enantioselectivity achieved in the first reduction is the same as that in the second reduction.

For example (Scheme 49) if an 85% enantiomeric excess is achieved in favour of the (S) enantiomer, then only 7.5% of the (R) enantiomer will be formed. If the same selectivity is seen for the second reduction, then each mono-reduced enantiomer will produce 6.94% *meso* giving a total of 13.88%. The enantiomers (S,S) and (R,R) will then be formed in a ratio of 85.56 : 6.94 giving an overall enantiomeric excess of 98.69% for the di-reduction. A chiral amplification is seen over the two steps, with the enantiomeric excess increasing from 85% to 98.69% provided that the *meso* component can be removed. This chiral amplification process is demonstrated below for 2,6-diacetylpyridine (54) (Scheme 49).



Scheme 49. The relationship between mono and di reductions for bakers' yeast reduction of 2-acetylpyridine

2,6-Diacetylpyridine (54) was then reduced by bakers' yeast in the presence of allyl alcohol to try to improve the selectivity and this gave 2,6-diethyl(α-hydroxy)pyridine (56), with an $[\alpha]_D^{=}$ -26.84. This optical rotation was substantially higher than that obtained from the uninhibited bakers' yeast reduction. The presence of the minor *meso* diastereomer in the dibromobenzoate derivative (85) could not be detected at all by ^1H NMR. Clearly the allyl alcohol had worked as a selective alcohol dehydrogenase inhibitor. Following Soai's relationship [134] the diol should be essentially optically pure.

An accurate determination of the optical purity was achieved by chiral HPLC analysis of the dibromobenzoate derivative (85) using a chiralcel OD column (Figure 13, 14 and 15).[105] Analysis of the racemic material gave 3 peaks in a ratio of 1:2:1 as expected for a mixture of (R,R) : *meso* (R,S) : (S,S) stereoisomers. Using the same procedure, the homochiral derivative gave a single peak. Assurance of the high degree of

of optical purity was obtained by spiking the homochiral derivative (85) with 0.5% of the racemic material. This racemic material consists of (R,R) : *meso* (R,S and S,R) : (S,S) stereoisomers in a percentage ratio of 0.125 : 0.25 : 0.125. Since the homochiral derivative (85) was seen to contain 0.125% *meso*, only 0.0625% of the second enantiomer can be present. Using the above information the optical purity of the homochiral dibromobenzoate derivative (85) can be stated, with confidence, as being greater than 99.875%. X-ray crystallography of a suitable crystal confirmed the absolute configuration as (S,S) (Figure 16) (X-ray data see Appendix III).

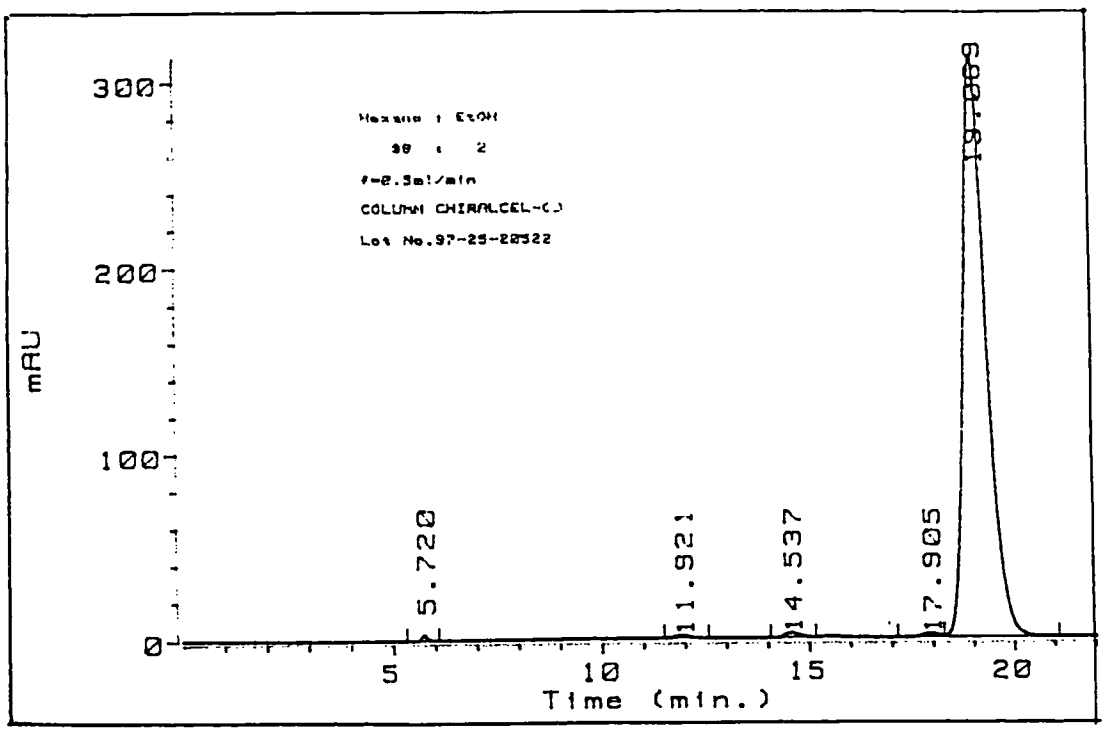


Figure 13. Chiral HPLC of (2S),(6S)-diethyl(α-4'-bromobenzoyloxy)pyridine (85)

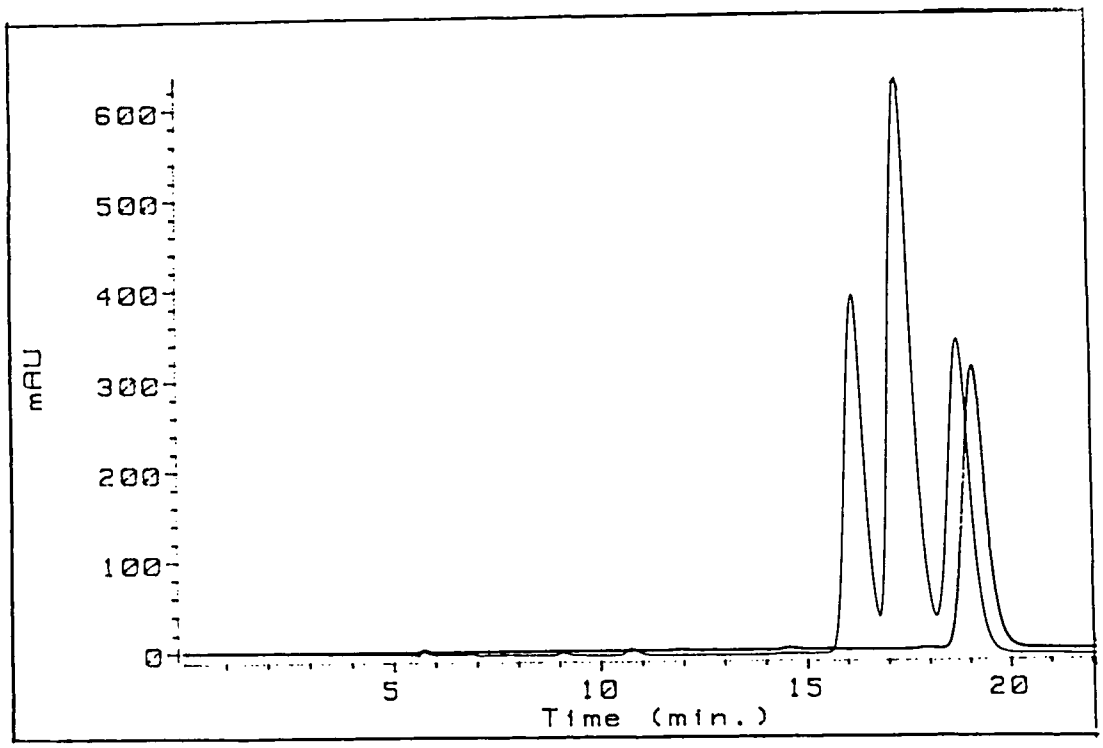


Figure 14. Overlay of racemic 2,6-diethyl(α-4'-bromobenzoyloxy)pyridine (85) on (2S),(6S)-diethyl(α-4'-bromobenzoyloxy)pyridine (85)

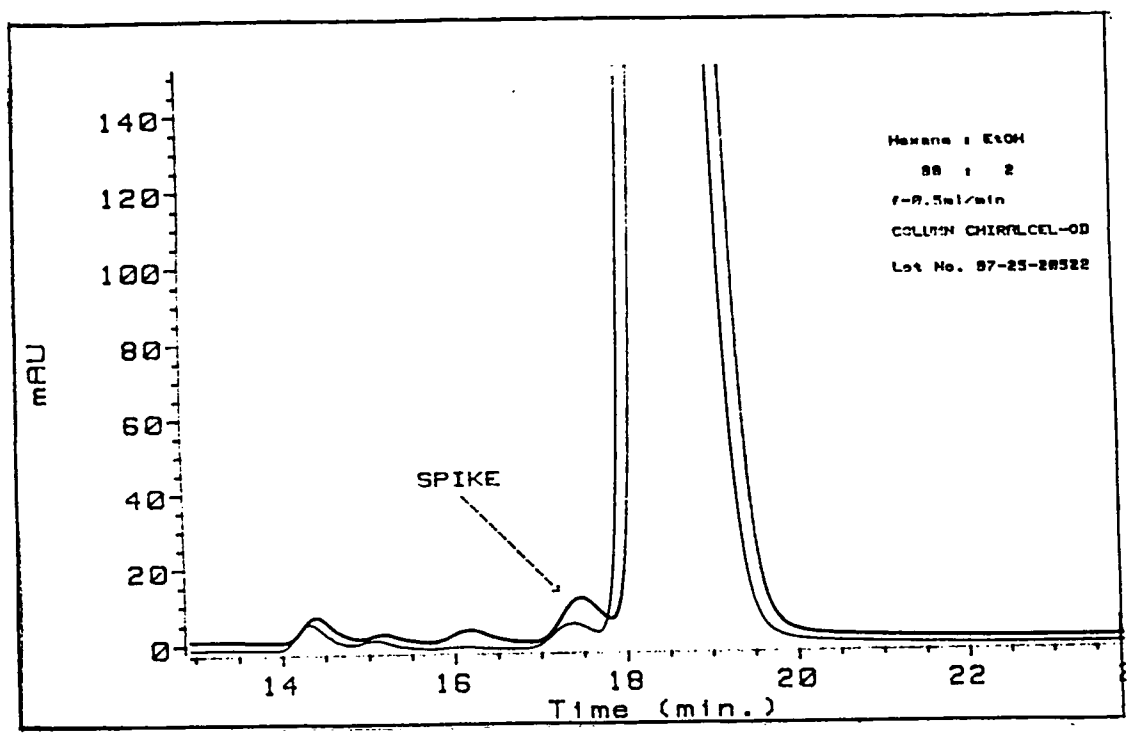
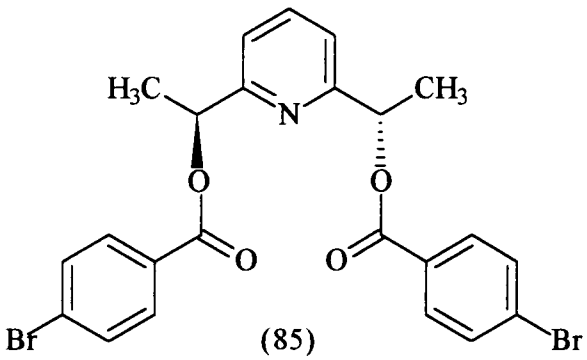


Figure 15. (2S),(6S)-diethyl(α-4'-bromobenzoyloxy)pyridine (85) spiked with 0.5 % racemic 2,6-diethyl(α-4'-bromobenzoyloxy)pyridine (85)



(85)

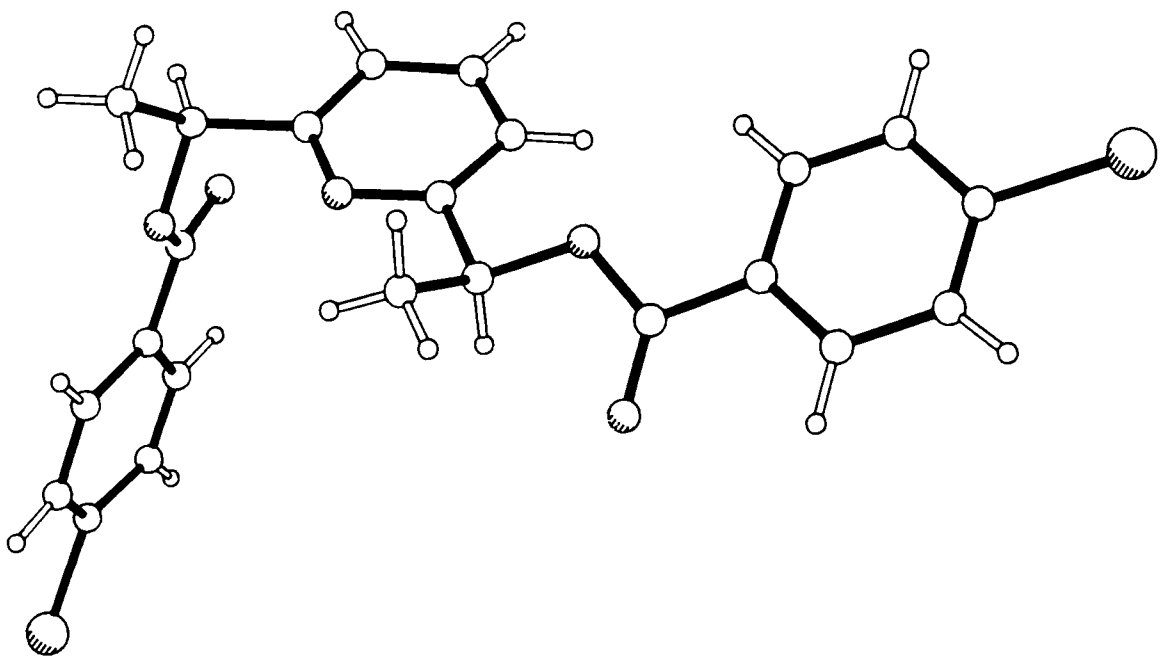
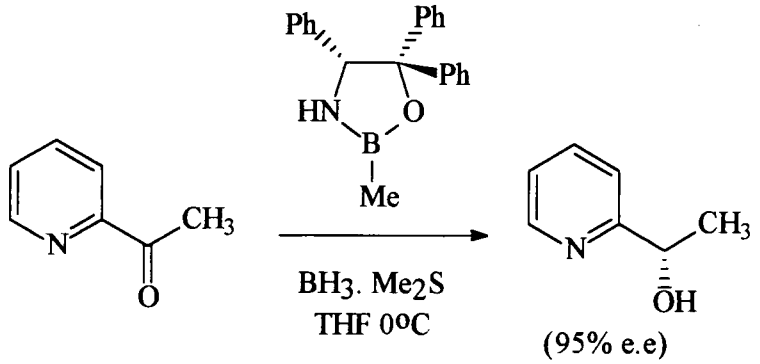


Figure 16. X-ray crystal structure of
(2S),(6S)-diethyl(α-4'-bromobenzoyloxy)pyridine (85)

Bakers' yeast reduction of 1,8-dioxo-1,2,3,4,5,6,7,8-octahydroacridine (61) was attempted but this only resulted in the recovery of unreacted ketone.

2.5 **Conclusions**

The reaction of pyridyl ketones with asymmetric reducing agents, in our hands, gave pyridyl alcohols that were either racemic or had low enantiomeric excesses. Since the completion of this work the asymmetric reduction of 2-acetylpyridine has been achieved as follows (Scheme 50).[135]

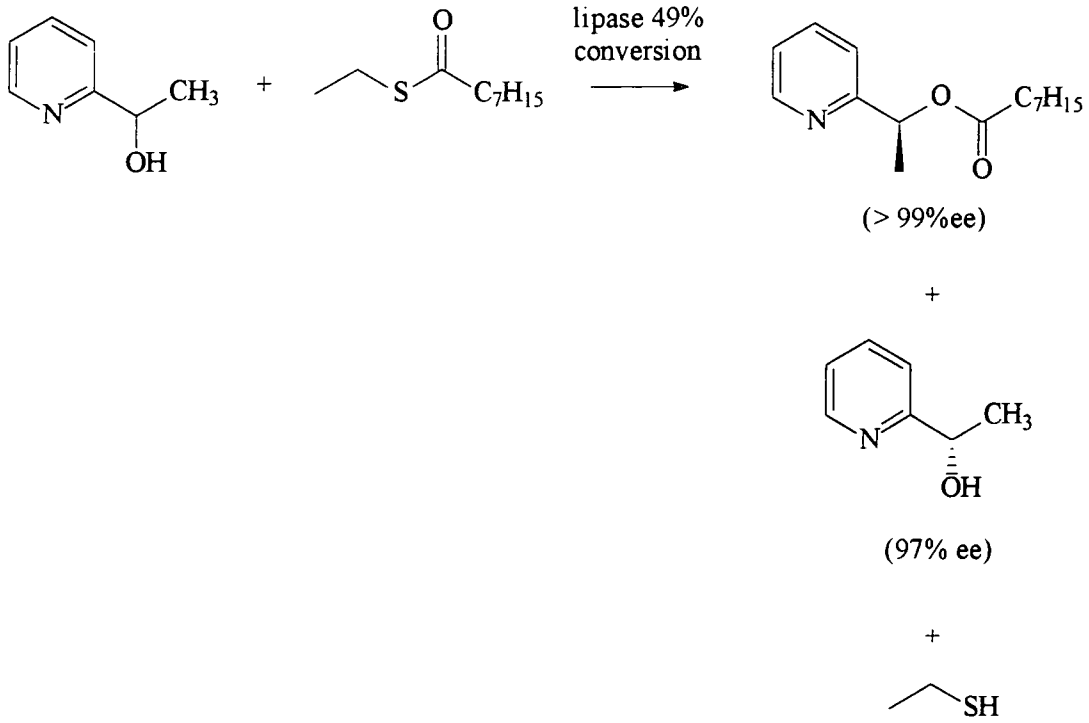


Scheme 50

Reduction of 2-acetylpyridine (53) using the above asymmetric reducing agent gave the pyridyl alcohol in lower e.e values than obtained by biotransformation techniques. These reagents also appear unable to achieve a double asymmetric reduction and this has been a drawback to their use in the work undertaken.

Bakers' yeast reduction of 2-acetylpyridine and 2,6-diacetylpyridine gave the corresponding mono and di-pyridyl alcohols in high enantiomeric excesses where all chemical methods failed in our hands. Double asymmetric reduction of 2,6-diacetyl pyridine (54) using allyl inhibited bakers' yeast was a new biotransformation and has now been published by us.[136]

Resolution of (±)-2-(1-hydroxyethyl)pyridine (55) was achieved in moderate enantiomeric excess using the lipase enzyme *Candida cylindracea.* The enantiomeric excess obtained was however, too low for the purpose of asymmetric fluorinations. Recently the resolution of (±)-2-(1-hydroxyethyl)pyridine (55) was achieved in a transesterification reaction using the lipase enzyme *Candida antartica* and this is shown below (Scheme 51).[137]



Scheme 51

CHAPTER 3

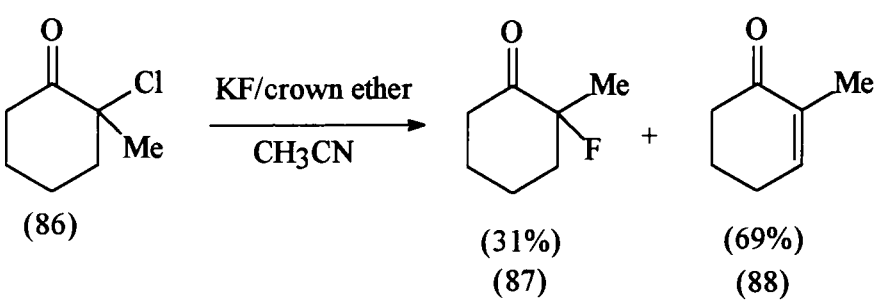
Asymmetric fluorination of esters and ketones using N-fluoropyridinium triflates

3.1 Introduction

Esters and ketones with one or two fluorine atoms at the α-carbon are an important class of fluorinated compounds which have found use as biological probes.[138] A variety of methods have been utilised to incorporate a fluorine atom adjacent to an ester, acid or keto group and some of these are summarised below.

3.1.1 Halogen exchange

Halogen exchange has been used in many reactions in which a good leaving group is present.[29,138-143] For example the reaction of 2-chloro-2-methylcyclohexanone (86) with potassium fluoride gave 2-fluoro-2-methylcyclohexanone (87) and its elimination product (88) as below (Scheme 52).

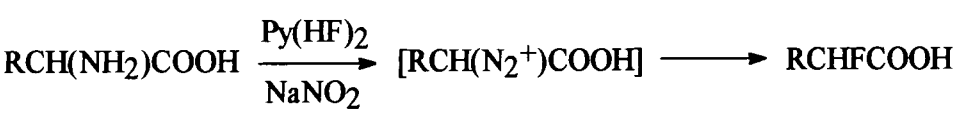


(86) (31%) (87) (69%) (88)

Scheme 52

3.1.2 HF-pyridine

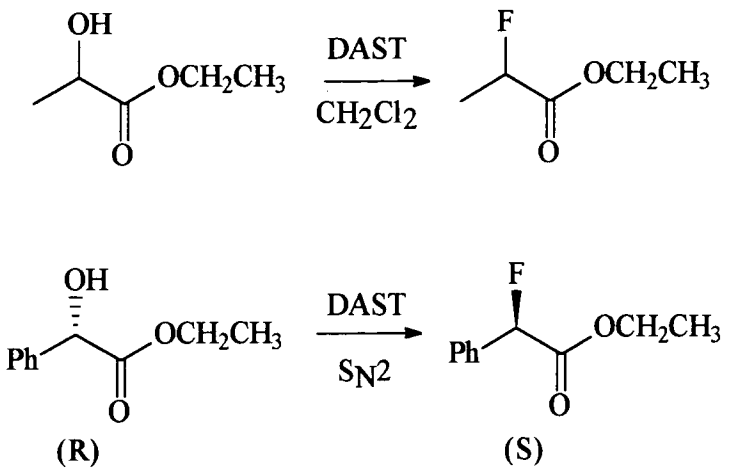
Anhydrous hydrogen fluoride is one of the most inexpensive fluorinating reagents, but is difficult to handle. Olah *et al.*[144] developed the pyridinium fluoride reagent HF-pyridine, which is a stable source of hydrogen fluoride that has been used to deaminate amino acids through diazonium intermediates (Scheme 53).



Scheme 53

3.1.3 Reactions of hydroxy esters with DAST and fluoroalkamine reagents

The nucleophilic fluorinating reagents, DAST (38) and Ishikawa's reagent, (34) react with α-hydroxy esters |giving α-fluorinated esters (Scheme 54).[63,71,86]



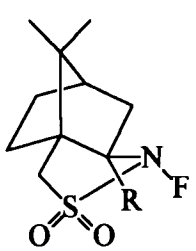
Scheme 54

3.1.4 Electrophilic Fluorinating reagents

Electrophilic fluorinating reagents have already been discussed in Chapter 1. Among these are those containing an N-F bond and CH_3COOF.

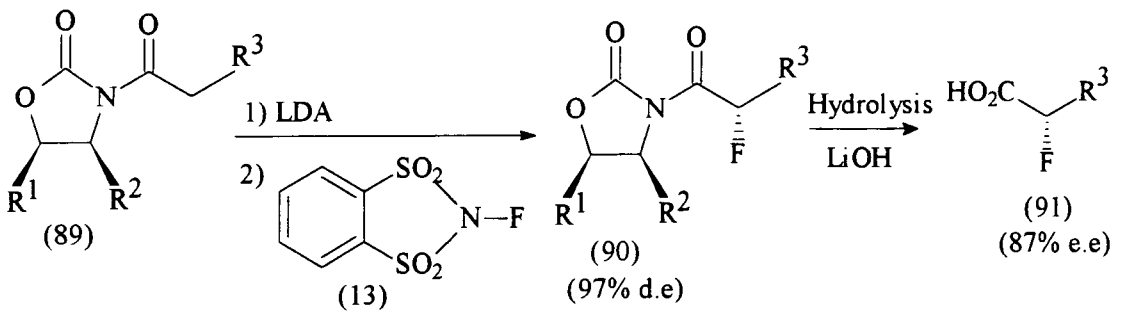
3.2 Methods of preparing homochiral α-fluorinated esters

The two camphor derived N-fluorocamphor reagents (18) and (19) have been used for the enantioselective fluorination of lithium and sodium enolates of esters and ketones [52] and have already been discussed in Chapter 1.



(18) R=H
(19) R=CH_3

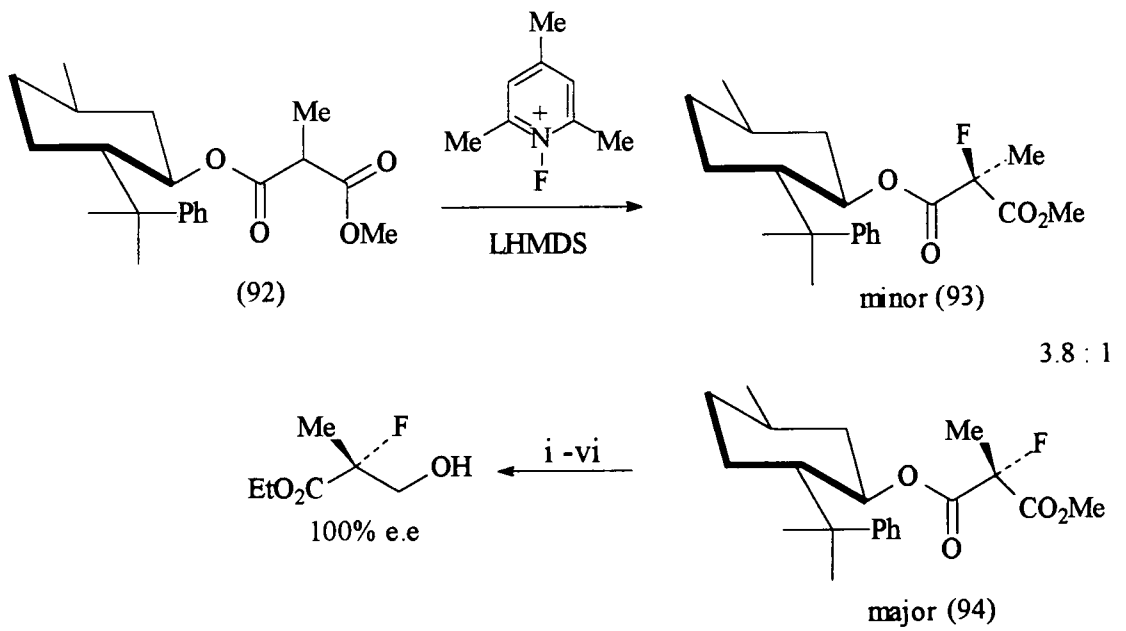
An alternative approach to acquiring chiral fluorinated products is to use the Evan's chiral auxiliary oxazolidone, as shown below (Scheme 55). By this method the substrate (89) was fluorinated with good diastereoselectivity using N-fluoro-o-benzenedi sulphonamide (13). Hydrolysis of (90) gave the fluorinated acid (91) in 86% e.e.[145]



$R^1 = H$, $R^2 = i$-Pr, $R^3 = n$-Bu

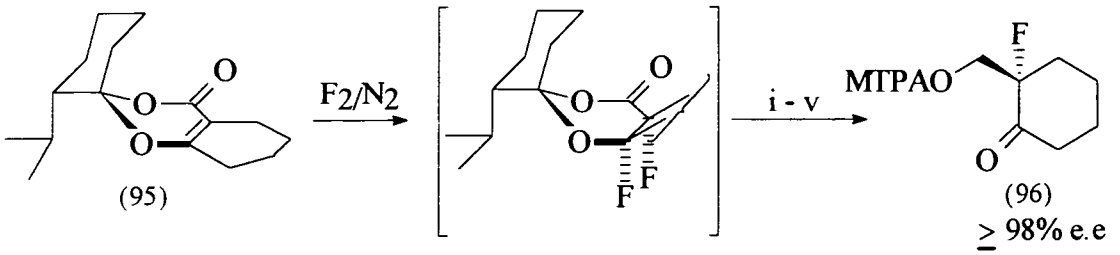
Scheme 55

Another application where a chiral auxiliary has been used is in the fluorination of half ester of α-alkylmalonate (92). α-Fluoro-α-alkylmalonates (93) and (94) were produced with moderate diastereoselectivity (Scheme 56).[146]



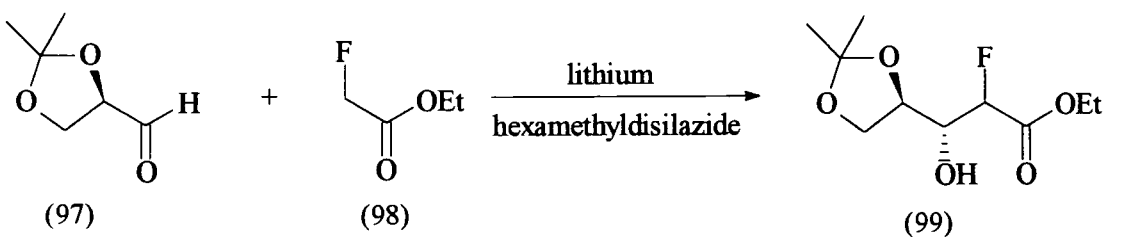
Scheme 56. i) LiOH, r.t. ii) $(COCl)_2$. iii) Bu_4NBH_4. iv) TBDMSCl, Et_3N, DMAP. v) KO_2, 18-crown-6, r.t. vi) HCl, EtOH.

Cis addition of fluorine across the double bond of dioxane (95) has led to the enantioselective preparation of α-fluorinated β-keto-acid (96) below (Scheme 57).[147]



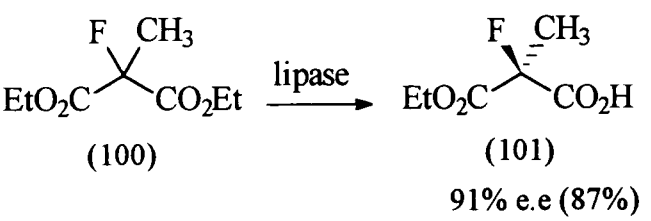
Scheme 57. i) K_2CO_3, MeOH, 5°C, 30 min. ii) $CH(OMe)_3$, catalytic *p*-TsOH, MeOH, reflux, 5h. iii) $NaBH_4$, MeOH, 50°C, 3-5h. iv) 10% HCl, acetone, r.t, 10 min. v) MTPA, DCC, DMAP, CH_2Cl_2, r.t, 12h.

Carbon-carbon bond forming reactions have been utilised to form chiral mono-fluorinated esters. For example the aldol condensation of (R)-2,3-isopropylidene glyceraldehyde (97) with ethyl fluoroacetate (lithium enolate) (98) afforded a equimolar mixture of the two condensation diastereomers (99) having the same configuration at the hydroxyl stereocentre, but scrambling at the fluorinated carbon (Scheme 58).[148]



Scheme 58

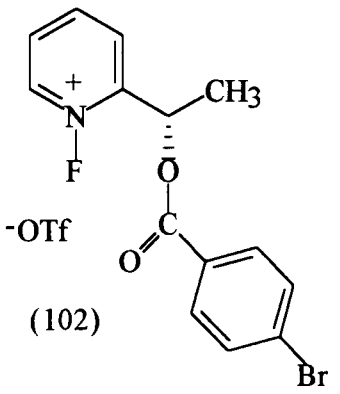
Enzymatic methods have proved effective for the preparation of α-fluorinated carboxylic acids and esters. For example asymmetric hydrolysis of 2-fluoro-2-methylmalonate (100) with the enzyme *Candida cylindracea* gave 2-fluoro-2-alkylmalonic acid mono-ester (101) in optically active form (Scheme 59).[149-151]



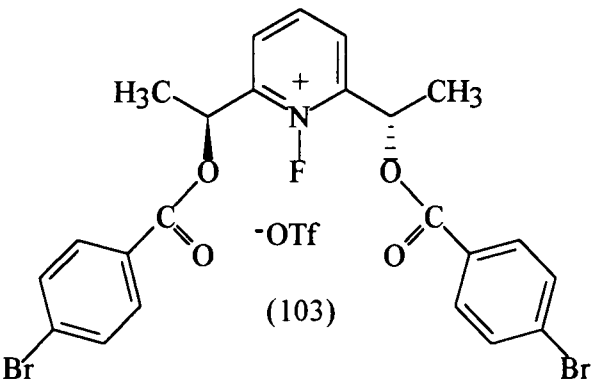
Scheme 59

3.3 Objectives

Preparation of homochiral pyridines (76) and (85) was described in Chapter 2. Direct fluorination of these compounds in the presence of a suitable counterion, such as triflate should give the respective homochiral N-fluoropyridinium species (102) and (103) shown below.



(102)



(103)

Using these target fluorinating reagents it was hoped that fluorine could be asymmetrically induced into a number of metal enolates and silyl ketene acetals of simple keto esters.

3.4 Preparation of N-fluoropyridinium triflate and its homochiral analogues

3.4.1 N-Fluoropyridinium triflate

N-Fluoropyridinium triflate (26) was prepared in comparable yields to that stated in the literature.[59] It was found to act as a fluorinating reagent if used immediately after it had been prepared. However, if kept overnight under anhydrous conditions the reagent lost its fluorinating ability. Commercially available material [91] failed to act as a fluorinating reagent in our hands and was viewed as non-shelf stable. Incorporation of fluorine onto the pyridine nitrogen in this reagent was evident by ^{1}H NMR. Coupling between fluorine and the pyridine ring protons gave the following coupling constants, $^3J_{H\text{-}F}$ 22.5 Hz, $^5J_{H\text{-}F}$ 4.8 Hz, and $^4J_{H\text{-}F}$ 2.0 Hz. Differences in the ^{1}H NMR spectra between pyridine and N-fluoropyridinium triflate can be seen below (Figure 17 and 18).

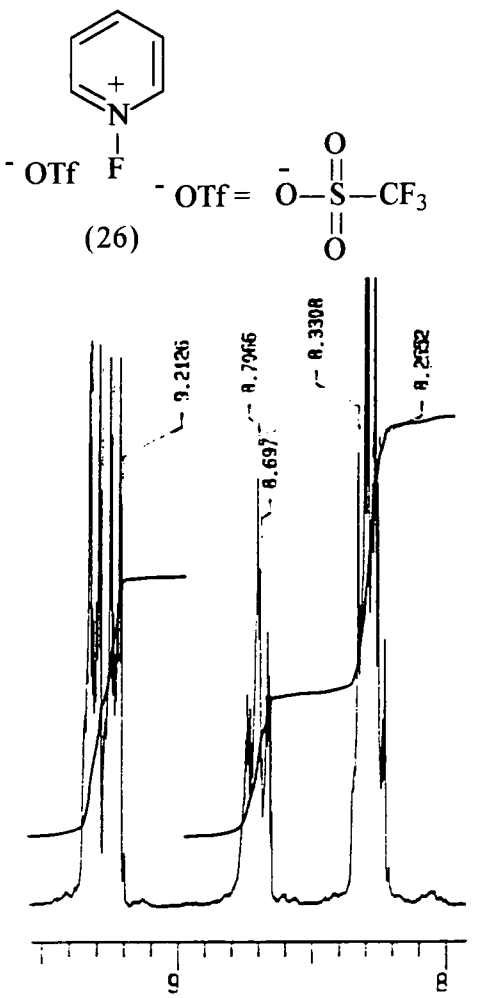


Figure 17. ^{1}H NMR of N-fluoropyridinium triflate

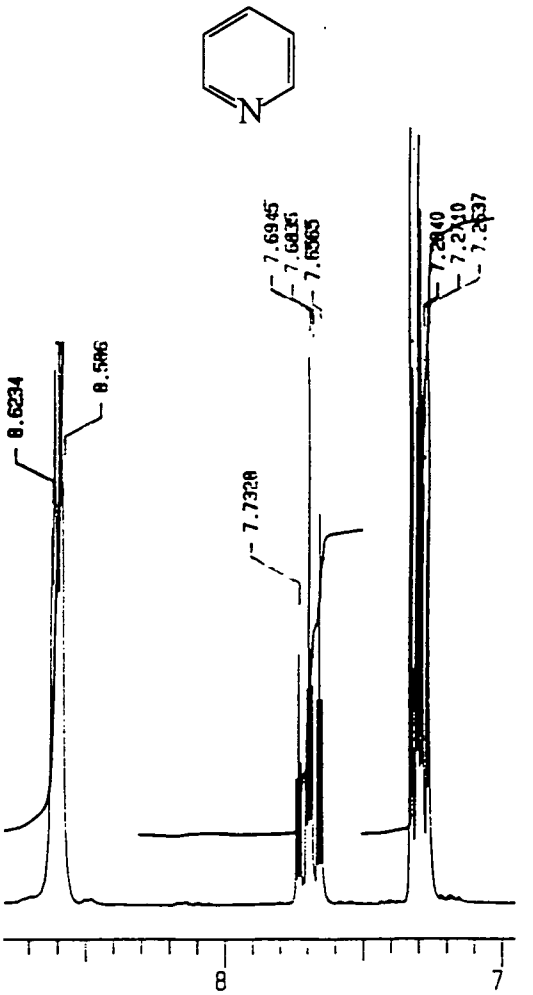
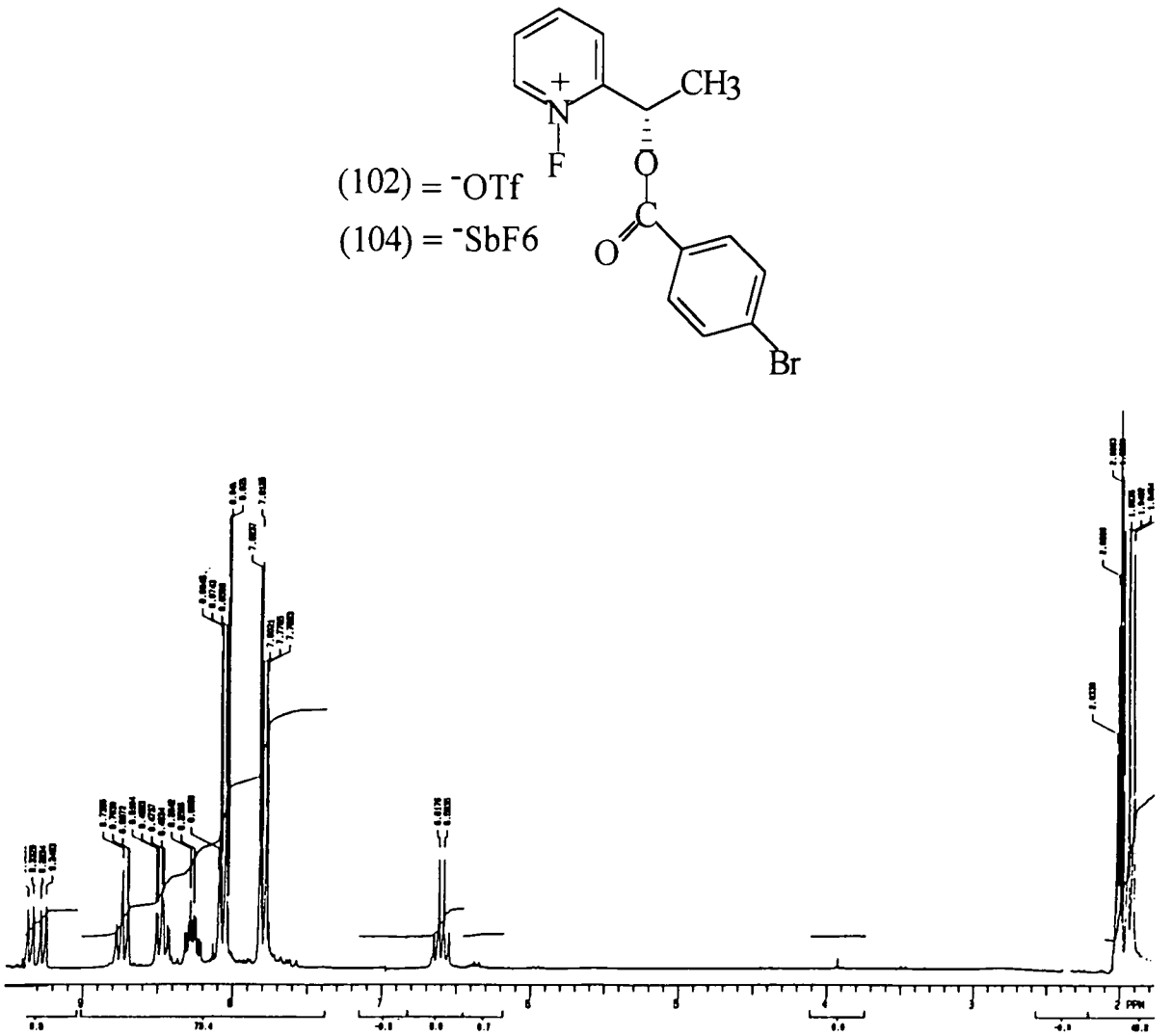


Figure 18. ^{1}H NMR of pyridine

3.4.2 N-Fluoro 2-(α-4'-bromobenzoyloxy)ethylpyridinium triflate

N-Fluoro 2-(α-4'-bromobenzoyloxy)ethylpyridinium triflate (102) was prepared in both racemic and homochiral forms by the same method used to prepare N-fluoropyridinium triflate (26).[59] This compound is a stable cream coloured solid which was found to act as a fluorinating reagent, but also lost its fluorinating ability with time. Incorporation of fluorine onto the pyridine nitrogen was again evident from ^{1}H NMR (Figure 19). Coupling between fluorine and the proton next to the pyridine nitrogen gave a coupling constant of, $^{3}J_{H\text{-}F}$ 16.9 Hz and this is comparable with $^{3}J_{H\text{-}F}$ 22.5 Hz obtained for N-fluoropyridinium triflate (Figure 17). Replacement of the triflate counterion by hexafluoroantimonate gave N-Fluoro 2-(α-4'-bromobenzoyloxy)ethylpyridinium hexafluoroantimonate (104) as a free flowing solid. This compound showed similar fluorinating ability to (102). Mass spectroscopy of (102) and (104) using (FAB) gave masses of 324 and 326 corresponding to the calculated molecular ion (M^{+}) and (M+2) respectively, which are consistent with the expected isotope ratio for one bromine atom.



^{1}H NMR Spectra of N-Fluoro 2-(α-4'-bromobenzoyloxy)ethylpyridinium triflate (102)
Figure 19.

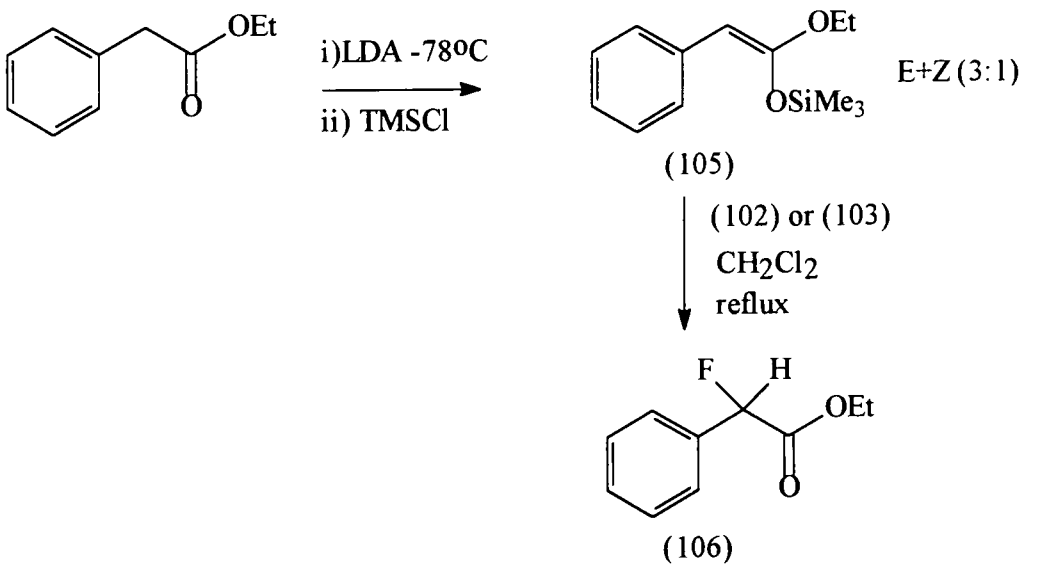
3.4.3 N-Fluoro 2,6-diethyl(α-4'-bromobenzoyloxy)pyridinium triflate (103)

N-Fluoro 2,6-diethyl(α-4'-bromobenzoyloxy)pyridinium triflate (103) was prepared in both racemic and homochiral forms by direct fluorination of 2,6-diethyl(α-4'-bromobenzoyloxy)pyridine (85) using a 10% mixture of fluorine in nitrogen. This compound, unlike the previous N-fluoropyridinium triflates, existed as a white hygroscopic semi-solid. The presence of the N-F bond in this reagent is not so apparent by ^{1}H NMR, due to the absence of protons ortho to the pyridine nitrogen. Mass spectroscopy (FAB), however gave masses of 550, 552 and 554 in a ratio of 1:2:1 corresponding to molecular ions M^+, M+2 and M+4 respectively, which are consistent with the expected isotope ratio from the bromine atoms. The fluorinating ability of this compound was also lost with time and it was also used directly after preparation.

3.5 Fluorinations using homochiral N-fluoropyridinium triflates

3.5.1 Fluorination of ethyl phenylacetate silyl ketene acetals

Fluorination of a mixture of E and Z isomers (3:1) of ethyl phenylacetate trimethylsilyl ketene acetal (105) using chiral fluorinating reagents (102) and (103), gave ethyl 2-fluorophenylacetate (106) below (Scheme 60). This is illustrated below.



Scheme 60

Reagent (102) was found to give the fluorinated product (106) with an enantiomeric excess of less than 10% as determined by ^1H NMR using chiral shifts reagent [Eu(tfc)$_3$]. Regions of splitting in the ^1H NMR can be seen below (Figures 20 and 21)

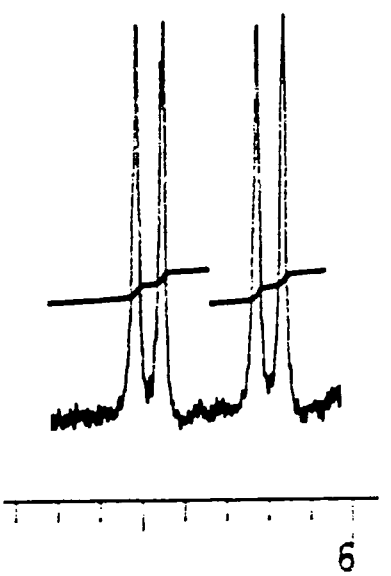


Figure 20. ^1H NMR of racemic (44) in the presence of [Eu(tfc)$_3$]

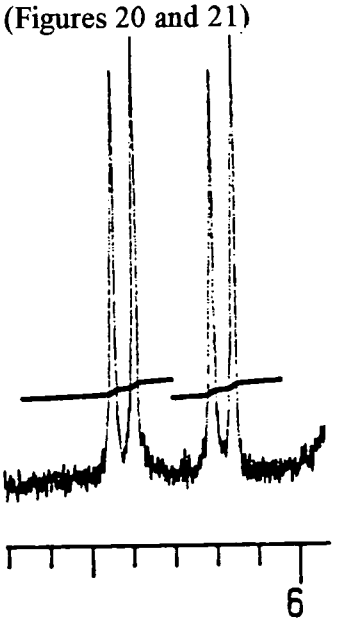
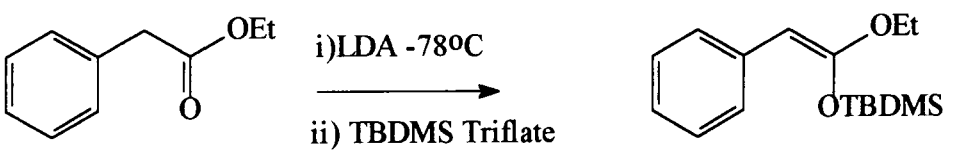


Figure 21. ^1H NMR of optically enriched (44) in the presence of [Eu(tfc)$_3$]

Fluorination of (105) using the C_2 symmetric fluorinating reagent (103) gave racemic fluorinated product (106) as determined by ^1H NMR using [Eu(tfc)$_3$]. The fluorination of a mixture of E and Z isomers could however, lead to opposite enantiomers, even if the reaction is stereospecific. Thus it was judged important to try to evaluate this by fluorination of a single geometric isomer. Synthesis of ethyl phenylacetate trimethylsilyl ketene acetal (105) using LDA as a base in the presence of hexamethylphosphoramide (HMPA), is known to favour formation of the Z geometric isomer.[152] In the event we were able to prepare the single Z geometric isomer in 59% using this methodology. Fluorination of the Z isomer using the fluorinating reagents (102) and (103) failed to give any fluorinated product after repeated attempts. This suggests that out of a mixture of E and Z isomers the E isomer is fluorinated predominantly.

The steric influence of the trimethylsilyl protecting group and the ethoxy group can be considered as similar. Use of a *tert*-butyldimethylsilyl protecting group (TBDMS) should result in a considerable difference in the steric influence of the two groups, which potentially will be recognised by the asymmetric fluorinating reagent, resulting in higher enantiomeric excesses of the fluorinated products. Synthesis of ethyl phenylacetate *tert*-butyldimethylsilyl ketene acetal (107) using LDA as a base was achieved in 37 % as below (Scheme 61).



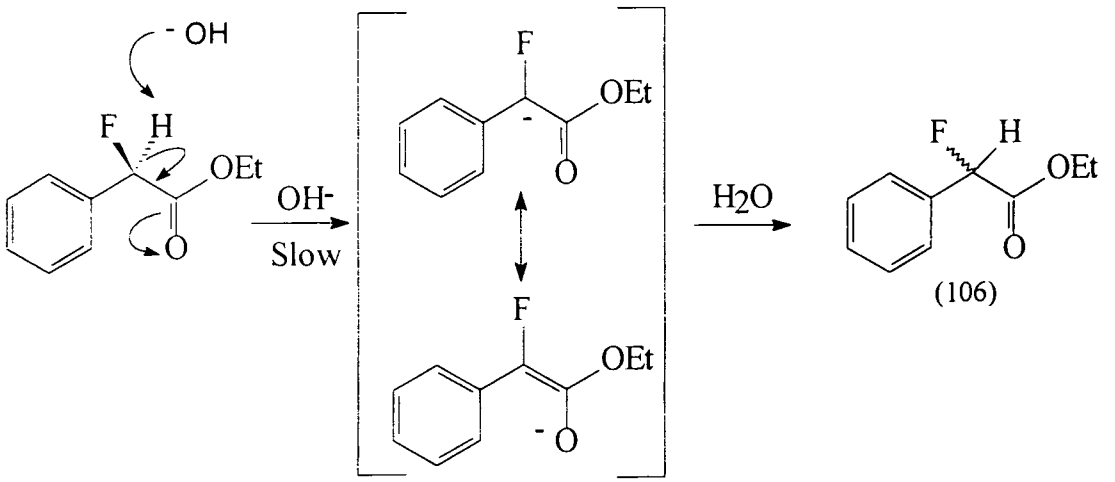
E+Z isomers (3:1)
(107)

Scheme 61

Fluorination of ethyl phenylacetate *tert*-butyldimethylsilyl ketene acetal (107), also a mixture of E and Z isomers in a ratio of 3:1 was achieved using homochiral fluorinating reagents (102) and (103). Determination of the optical purity of (106) by ^1H NMR using [Eu(tfc)$_3$] showed it to have an enantiomeric excess of less than 10%. Fluorination of (107) using the C_2 symmetric fluorinating reagent (103) gave racemic fluorinated product. Fluorination of ethyl phenylacetate *tert*-butyldimethylsilyl ketene acetal Z isomer (107) also gave no fluorinated product. It is apparent that the steric influence of the silyl protecting group does not influence the level of asymmetric induction achieved with the homochiral fluorinating reagents (102) and (103)

3.5.2 Fluorination of ethyl 2-phenylpropionate silyl ketene acetals

A possible origin of the low enantiomeric excesses in the fluorination of ethyl phenylacetate trimethylsilyl ketene acetal (105) could be racemisation of the chiral centre in ethyl 2-fluorophenylacetate (106) by a process envisaged as follows (Scheme 62).[153]



Scheme 62

Loss of optical activity would occur with C-H bond breakage, because bonds to the carbanion carbon need to assume a planar configuration if delocalisation and stabilisation are to occur on the adjacent C=O bond (Figure 22).

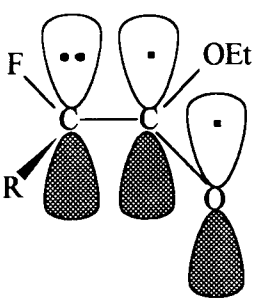
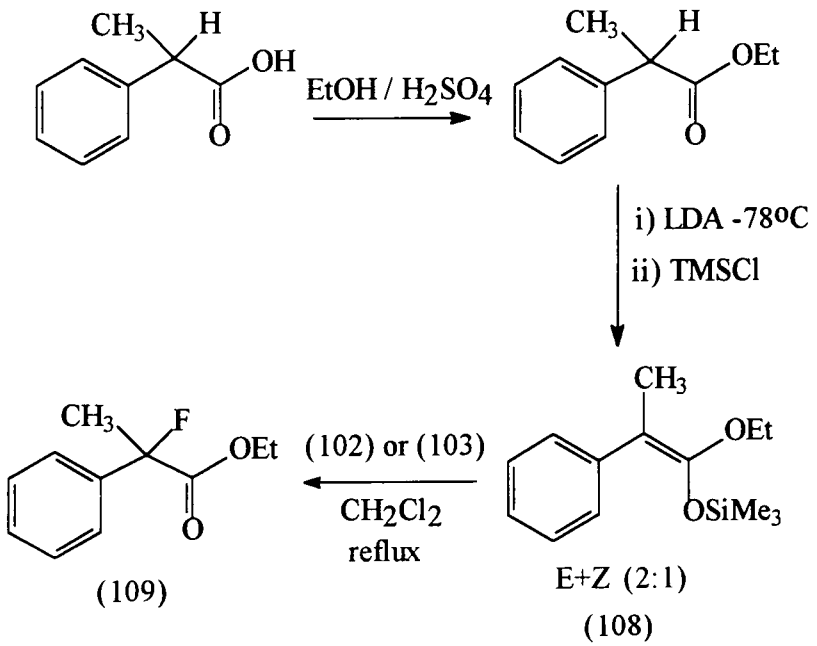


Figure 22.

Subsequent protonation is then equally likely to occur from either side leading to a racemic mixture. This potential for racemisation can however be removed by replacing the proton α to the fluorine with a methyl group. Exchange of the hydrogen atom for a methyl group α to the carbonyl group also leads to an increase in steric effects and hence may improve the asymmetric induction from the homochiral fluorinating reagents.

Fluorination of the trimethylsilyl ketene acetal of ethyl 2-phenylpropionate E and Z isomers (108) in a ratio of (2:1) with chiral fluorinating reagents (102) and (103) gave ethyl 2-fluoro-2-phenylpropionate (109), as shown below (Scheme 63).



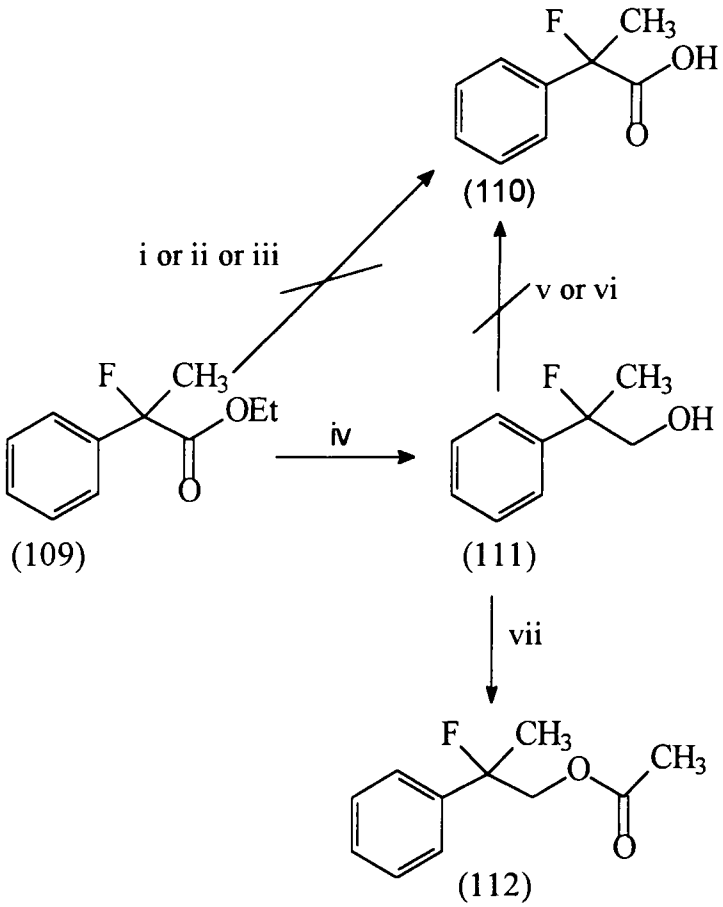
Scheme 63

Determination of the optical purity by ^{1}H NMR using [Eu(tfc)$_3$] was unsuccessful and no signals in the ^{1}H NMR were resolved. Other methods were thus sought, and in paticular derivatisation to generate diastereomers was pursued. Hydrolysis of the ester (109) to the free acid (110) was attempted by various ester cleavage methods (Scheme 64), but this caused elimination of fluoride, as determined by ^{19}F NMR.

Reduction of the ester group to the corresponding primary alcohol (111) and derivatisation to its corresponding acetate (112) was achieved as shown below (Scheme 64). Subsequent analysis by ^{1}H NMR and ^{19}F NMR in the presence of chiral shifts reagent [Eu(tfc)$_3$] showed no chemical shift non-equivalence.

Oxidation of alcohol (111) to the corresponding carboxylic acid (Scheme 64) was attempted using a number of oxidising agents. However, this only led to the conversion of the alcohol to its corresponding aldehyde, or the elimination of the fluorine group as fluoride.

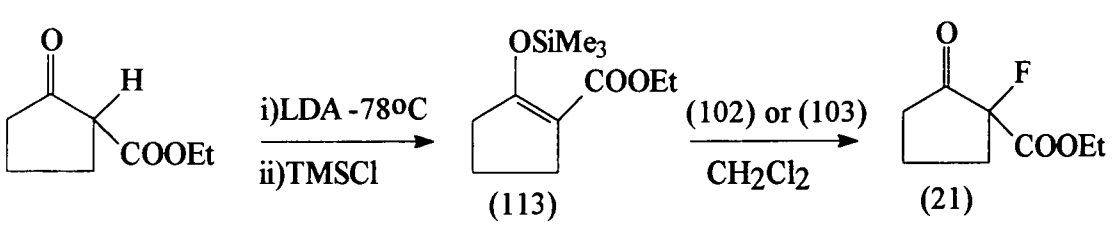
Resolution of the fluorinated ester was finally accomplished by chiral HPLC using a Chiracel OJ column,[105] and in the event both of the homochiral fluorinating reagents produced racemic products.



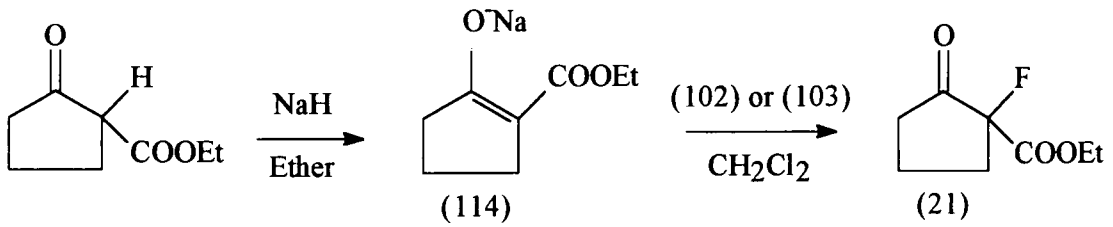
Scheme 64. i) LiOH, MeOH, H_2O.[154] ii) NaOH, MeOH, H_2O.[155] iii) TMSI, reflux.[156] iv) $LiAlH_4$, Et_2O.[157] v) RuO_4, $NaIO_4$, CCl_4:CH_3CN:H_2O (2:2:1).[158] vi) $Na_2Cr_2O_7$, H_2SO_4.[159] vii) DMAP, CH_3COCl, CH_2Cl_2.

3.5.3 Fluorination of trimethylsily ketene acetal and metal enolates of ethyl 2-oxocyclopentanecarboxylate

Both the trimethylsilyl ketene acetal (113) and the sodium enolate (114) of the ethyl 2-oxocyclopentane-1-carboxylate were fluorinated using homochiral fluorinating reagents (102) and (103) to give ethyl 1-fluoro-2oxocyclopentane-1-carboxylate (21) as shown below (Scheme 65 and 66).

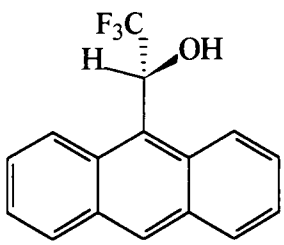


Scheme 65



Scheme 66

Enantiomeric resolution of (21) has been reported using ^1H NMR in the presence of the chiral solvating agent (R)-(-)2,2,2-trifluoro-1-(9 anthryl)ethanol (TAE) (115).[52] Repetition of this method in our hands however, showed no resolution by ^1H NMR or ^{19}F NMR.

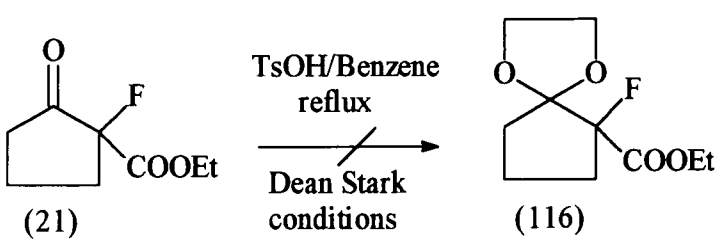


(115)

(R)-(-)2,2,2-trifluoro-1-(9 anthryl)ethanol (TAE)

Chiral shift reagent, [Eu(tfc)$_3$] also proved unsuccessful in resolving the enantiomers of (21). A possible approach for determining the optical purity of (21) was to convert it to a carboxylic acid and then derivatise it using a chiral auxiliary. Hydrolysis of the ester was attempted by a number of methods,[154,155,156] but these resulted in elimination of fluoride from the molecule, as seen by ^{19}F NMR.

An attempt was made to convert the keto group in (21) into the cyclic acetal (116) as below (Scheme 67).[160] It was hoped that the introduction of more oxygen atoms into the molecule would allow the enantiomers to be resolved more readily using chiral shift reagents. Formation of the cyclic acetal shown below under Dean Stark conditions was however unsuccessful.



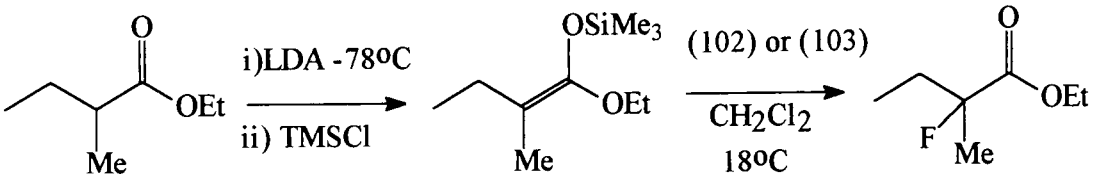
Scheme 67

Chiral HPLC and chiral GC also failed to separate these enantiomers and the situation at present is unresolved. This is disappointing since asymmetric fluorination of this system

would allow a direct comparison with the enantiomeric excess obtained with the N-fluorocamphor reagent,[52] the only other system where a high % e.e (70%) has been reported.

3.5.4 Fluorination of trimethylsily ketene acetal of ethyl 2-methylbutyrate

Ethyl 2-methylbutyrate trimethylsilyl ketene acetal (117) was fluorinated using the homochiral fluorinating reagents (102) and (103) to give ethyl 2-fluoromethylbutyrate (118), as shown below (Scheme 68).

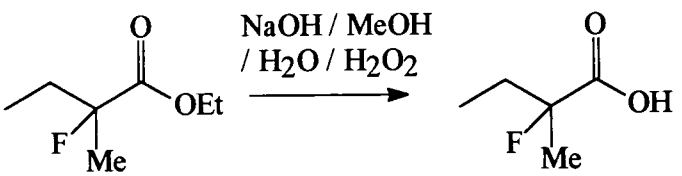


(117)
E+Z (1:1)

(118)

Scheme 68

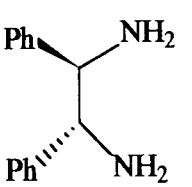
Hydrolysis of the fluorinated ester (118) was achieved as shown below (Scheme 69) to give 2-fluoro-2-methylbutyric acid (119) in 52% yield.



(118) (119)

Scheme 69

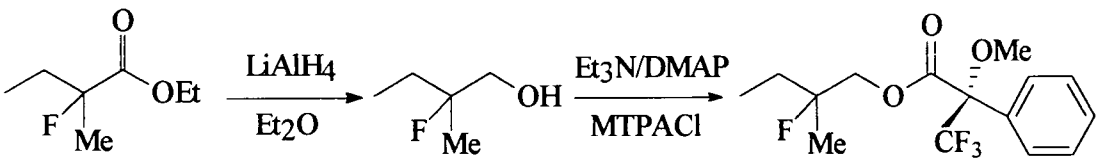
Resolution of the enantiomers of 2-methylbutyric acid have previously been achieved by ^1H NMR, using the chiral solvating agent 1,2-diphenyl-1,2-diaminoethane (120).[161] However, in our hands this method failed to separate the enantiomers of the α-fluorinated acid (50).



(120)

1,2-diphenyl-1,2-diaminoethane

An alternative approach was to reduce the ester group in (118) to a primary alcohol (121) using lithium aluminium hydride (Scheme 70). Derivatisation of the alcohol using excess α-methoxy-α-trifluoromethyl phenylacetic acid (MTPA)[162] will generate diastereomeric esters (122) which are potentially distinguishable by ^{1}H NMR and ^{19}F NMR. Using this approach racemic alcohol (121) gave diastereomeric MTPA esters (122) in a ratio of 3:1, as determined by ^{19}F NMR. Clearly there is a kinetic preference for the formation of one diastereomer over the other. The same ratio of diastereomers was seen for the potentially optically enriched alcohol (121). By comparison of the diastereomeric ratios it can be concluded that the homochiral fluorinating reagents (102) and (103) showed no stereoselectivity in the fluorination of (117). Chiral HPLC and chiral GC were used in an attempt to confirm the racemic nature of fluorinated ester (118). However, these techniques were unable to resolve the fluorinated ester (118).



(118) (121) (122)

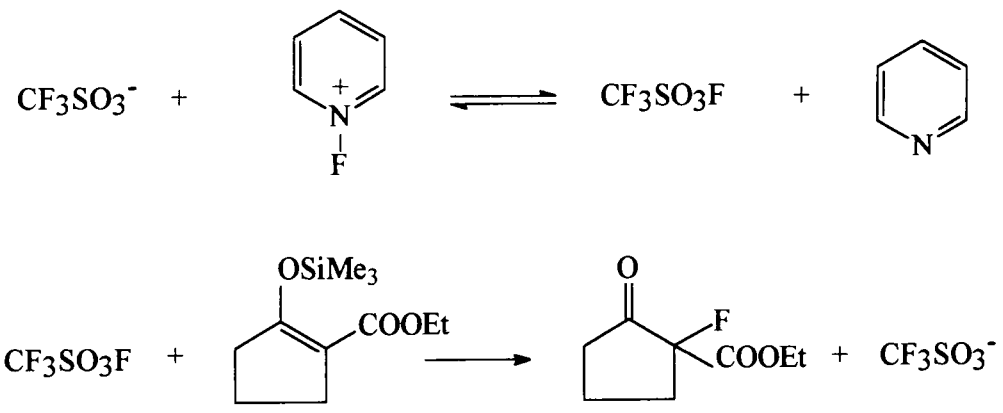
Scheme 70

3.6 Comments on stereoselectivity

Homochiral fluorinating reagent (102) achieved some stereoselectivity during the fluorination of ethyl phenylacetate trimethylsilyl ketene acetal (105). A 10% enantiomeric excess for the fluorinated product could not be improved by increasing the size of the silyl protecting group or by increasing the size of the groups α to the carbonyl group.

Determination of the enantiomeric excesses of the fluorinated products has proved problematic. Fluorine at the α position to the carbonyl group was eliminated during acid or base hydrolysis, thus ruling out the formation of diastereomers. Chiral HPLC and chiral GC methods were unable to separate the enantiomers of ethyl 1-fluoro-2-oxocyclopentane-1-carboxylate (21), and hence no comparison between reagents (102), (103) and the N-fluoro-camphor reagent (18) could be made.

Mechanistically the N-fluoropyridinium reagents are postulated to fluorinate by a one electron transfer process. However, to our knowledge this mechanism has not been studied in any detail. It is possible that in solution the triflate counterion may be involved in the fluorination process as shown below (Scheme 71).



Scheme 71

The above CF_3SO_3F moiety can be postulated to exist due to the number of fluorinating reagents that contain oxygen-bound fluorine. Examples of these reagents are $CsSO_4F$,[163,164] CF_3OF[165] and CF_3COOF, CF_3CF_2OF.[166,167] Fluorinating reagent (104) was synthesised with a SbF_6^- counterion instead of triflate and was used to fluorinate the sodium enolate of ethyl 2-oxocyclopentanecarboxylate (114) giving the fluorinated product ethyl 1-fluoro-2-oxocyclopentane-1-carboxylate (21) in a 54% conversion as judged by ^1H NMR. The effect of changing the counterion has not been assessed because of the inability to resolve the fluorinated product.

3.7 Conclusions

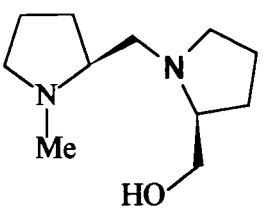
Two new homochiral fluorinating reagents were prepared during this work and at best they were found to be poor asymmetric fluorinating reagents. A possible reason for the poor enantiomeric excesses obtained with these reagents is the absence of a co-ordinated transition state between the enolate and the fluorinating reagent. In reactions, such as aldol condensations, this co-ordinated transition state has proved important in the stereochemical outcome of the reaction.

CHAPTER 4

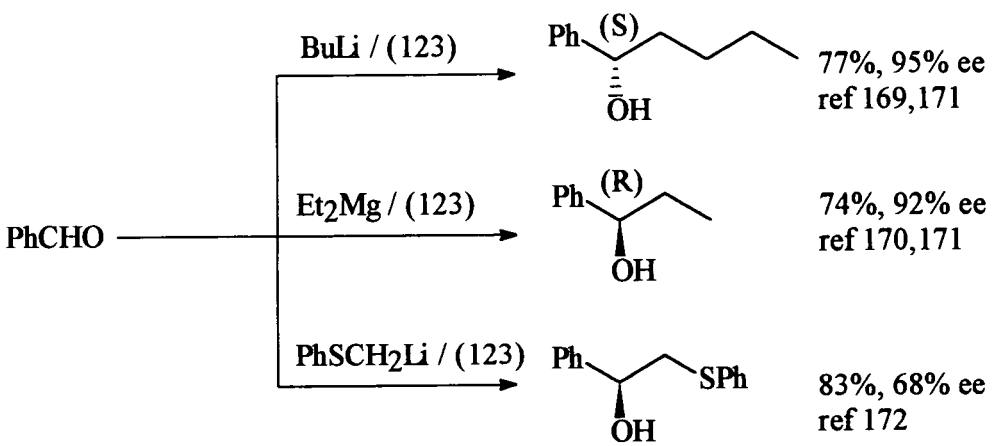
Diethylzinc reactions using chiral catalysts (2S)-(1-hydroxyethyl)pyridine and (2S),(6S)-diethyl(α-hydroxy)pyridine

4.1.1 Introduction

Enantioselective addition of organozinc reagents to aldehydes affords optically active secondary alcohols. This transformation has attracted a significant level of interest over the last few years and has developed from the 1970s when Mikayama *et al.*[168-171] used the β-amino alcohol (123) in the enantioselective addition of alkyllithium and dialkylmagnesium reagents to benzaldehyde (Scheme 72).



(123)

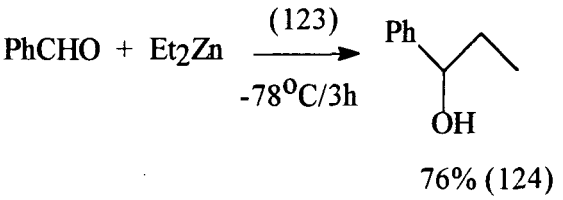


Scheme 72

Although these reagents often give high enantioselectivies, they need to be used in stoichiometric amounts.

Organozinc reagents have been utilised in many organic reactions such as the Simmons Smith [172] and Reformatsky reactions.[173] It is only recently however that diethylzinc has been used for the addition to aldehydes. Its reaction with aldehydes is much slower

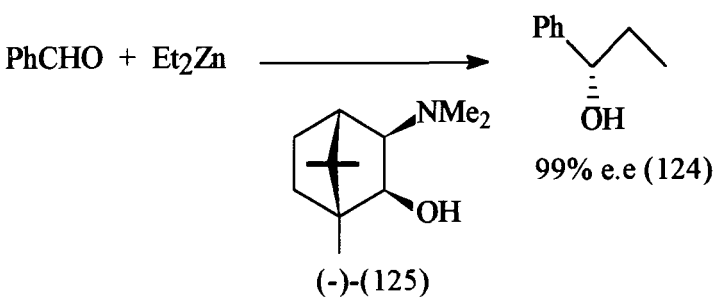
than the corresponding reactions of alkyllithium and Grignard reagents,[174] however, donor atoms such as the nitrogen and oxygen of chiral ligands co-ordinate with the zinc to generate chiral complexes which influence reactivity and can differentiate the *re* or *si* faces of aldehydes. The clean nucleophilic addition of diethylzinc to benzaldehyde was reported by Mukaiyama *et al.*[170, 171] in the presence of ß-amino alcohol (123) derived from (S)-proline. This ß-amino alcohol was found to accelerate (catalyse) the carbon-carbon bond forming reaction of diethylzinc with benzaldehyde, to afford 1-phenylpropan-1-ol (124) in 76% yield (Scheme 73).[170,171] No asymmetric induction was observed in this reaction, but this led to a surge in the development of chiral ß-amino alcohols that could induce stereoselectivity.



Scheme 73

4.1.2 Enantioselective diethylzinc reactions

The first highly enantioselective catalytic addition of diethylzinc to benzaldehyde was reported by Noyori *et al.*[175] in 1986. The amino alcohol (-)-3-*exo*(dimethylamino) isoborneol (125)[176,177] catalysed the addition to afford (S)-1-phenylpropan-1-ol (124) with 99% e.e and in 98% yield (Scheme 74).

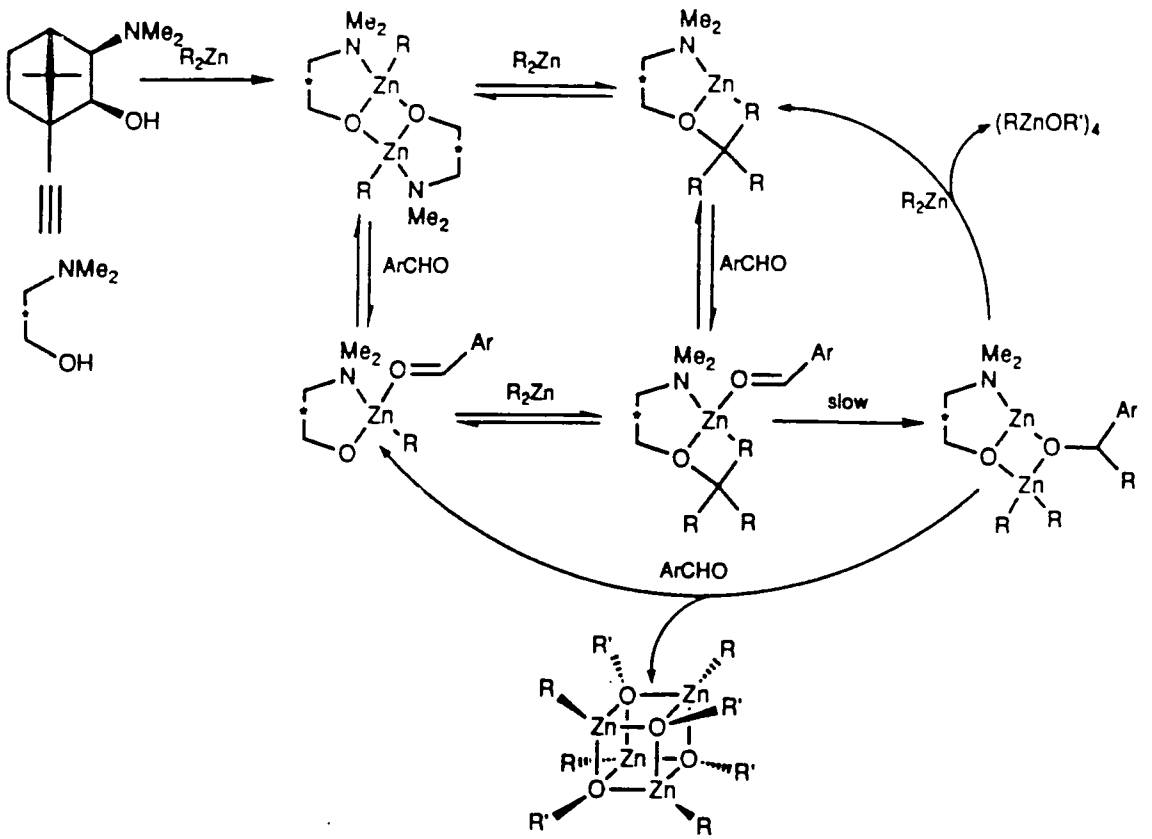


Scheme 74

Since these early days a large number of amino alcohols have been developed and used to catalyse the enantioselective addition of diethylzinc to aldehydes. These have recently been reviewed.[178]

4.1.3 Mechanistic aspects of diethylzinc reactions

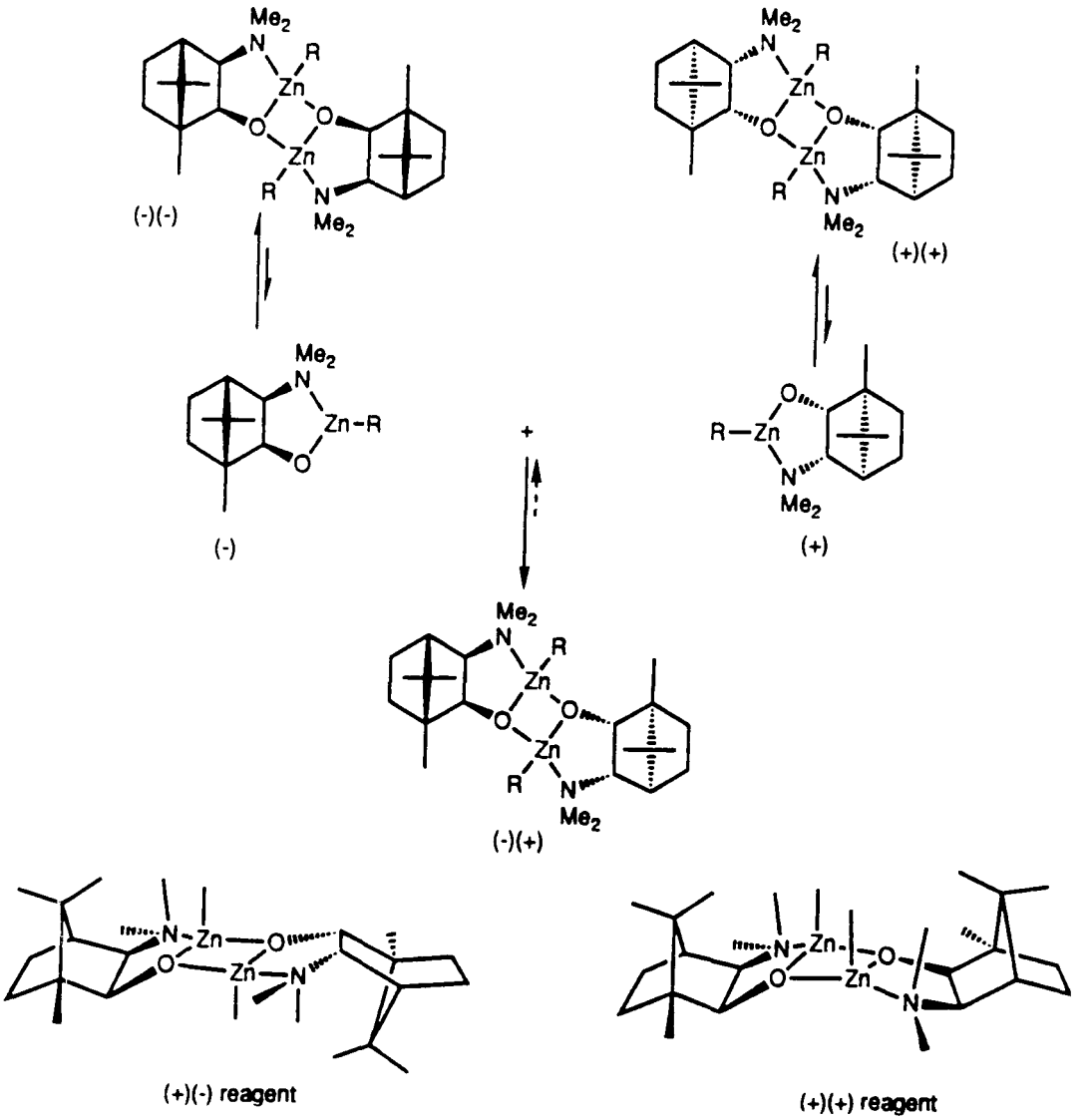
Diethylzinc reacts with aldehydes in the presence of an amino alcohol by a catalytic cycle in which the product is released rapidly, in order that a new substrate (aldehyde) can be acted upon. This is achieved by the formation of a stable $(RZnOR')_4$ species and release of the amino alcohol for further reactions. On hydrolysis the $(RZnOR')_4$ breaks down to give optically enriched secondary alcohols. The catalytic cycle can be seen below (Scheme 75).



Scheme 75 (Taken from M. Kitamura, S. Okada, S. Suga, R. Noyori., *J. Am. Chem. Soc.*, 1989, 111, 4028).

An interesting association exists between the enantiomeric purity of the catalyst and that of the product. The optical purity of the product obtained is often higher than that of the chiral catalyst used.[179] During the reaction of benzaldehyde with diethylzinc using chiral catalyst (125) (8 mol %) with a low e.e of 15%, the (S)-1-phenylpropan-1-ol (124) is formed in 95% e.e. This chiral amplification can be explained by interactions between diethyl zinc and the chiral amino alcohol which combine to form a reactive RZnX species. In the absence of the aldehyde these monomers dimerise to produce

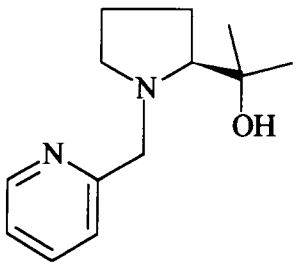
diastereomeric complexes which react with the aldehyde at different rates to produce active species involved in the catalytic cycle. The *meso*, (+)(-) form is more stable and less reactive and effectively pulls the minor enantiomer out of the reaction mixture, leaving only enantiomerically pure reactive monomer. These enantiomeric recognition processes were proposed by Horeau *et al* [180] and Wynberg *et al* [181] and are shown below (Scheme 76).



Scheme 76 (Taken from H. Wynberg, B. Feringa., *Tetrahedron*, 1976, **32**, 2831).

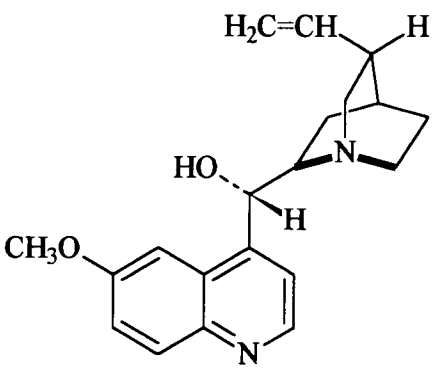
4.1.4 Pyridine containing ligands for diethylzinc reactions

Chiral catalysts that are used in diethylzinc reactions and which contain analogues of pyridine are known. For example the chiral prolinol derivative (126) with a pyridylmethyl substituent on the nitrogen atom has been reported by Chelucci *et al.* [182]



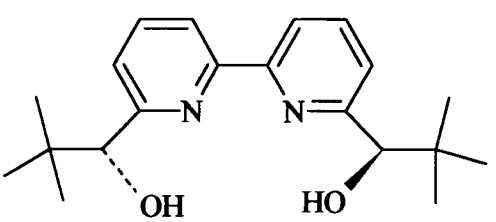
(126)

The lithium alkoxide of ligand (126) catalyses the addition of diethylzinc with benzaldehyde to afford (R)-1-phenylpropan-1-ol (124) in 60% e.e. Another example of a pyridine containing ligands which catalyses diethylzinc reactions are the Cinchona alkaloids.[183,184] Quinine (127) (2.0 mol%) catalyses the reaction of diethylzinc with benzaldehyde to afford (R)-1-phenylpropan-1-ol (124) in 68% e.e.



(127)

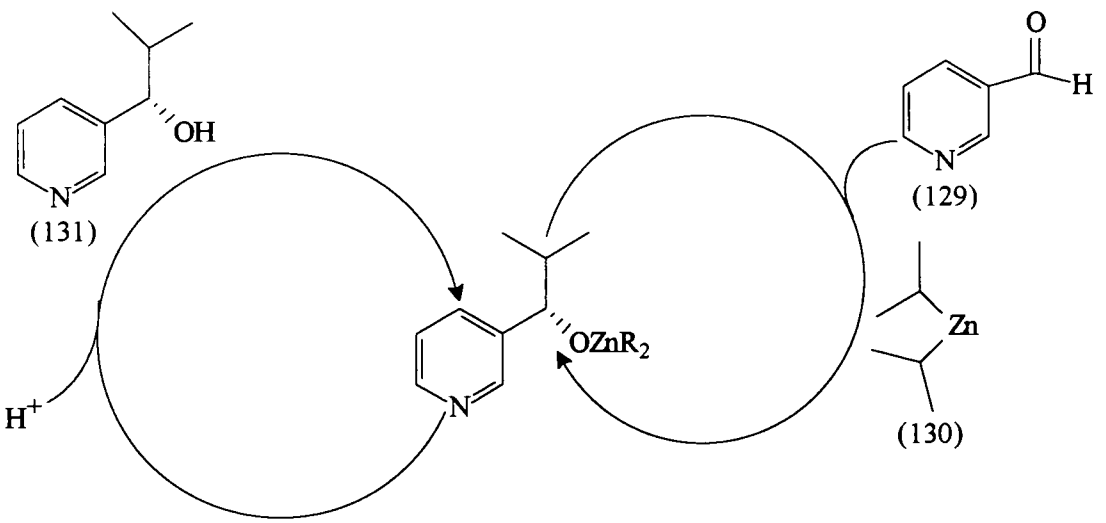
The above pyridine systems have chiral centres associated with an attached amino alcohol. An example of a pyridine system that contains a chiral centre α to the pyridine ring is the (R,R) bipyridyl diol (128) below. This diol has been reported by Bolm *et al.* to afford aromatic alcohols with 80-92% e.e.[185, 186]



(128)

4.1.5 Pyridyl alcohols in self-catalytic reactions

One of the key defining characteristics of organisms is their ability to self-replicate. In a reaction involving diethylzinc where the product and the chiral catalyst are the same (chiral-self recatalysis) the reaction system becomes a real self-reproduction system for chiral molecules. Optically active 3-pyridylalkyl alcohols have been found to reproduce themselves with the same configuration during the enantioselective addition of diethylzinc reagents to 3-pyridinecarboxaldehyde (129).[187] For example when 3-pyridinecarboxaldehyde (129) was treated with diisopropylzinc (130) (2.0mmol) in the presence of the chiral catalyst (-)-2-methyl-1-(3-pyridyl)propan-1-ol (131) (86% e.e) (20 mol %), an increased amount of (131) with 47% e.e was obtained. This self replication cycle can be represented as follows (Scheme 77).



Scheme 77

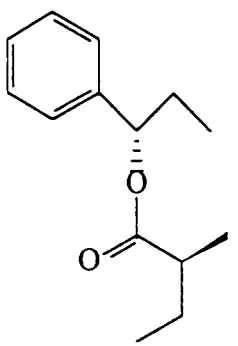
4.2 Objectives

Homochiral pyridylalcohols (2S)-(1-hydroxyethyl)pyridine (55) and (2S),(6S)-diethyl (α-hydroxy)pyridine (56) prepared in Chapter 2 are analogous systems to the bipyridyl diol (128) reported by Bolm *et.al.*[185,186] These pyridyl systems were judged potential chiral catalysts for diethylzinc reactions and it was hoped that they would lead to products with high enantiomeric excesses.

4.3 Diethylzinc reactions using (2S) (1-hydroxyethyl)pyridine (55)

Nucleophilic addition of diethylzinc to benzaldehyde has been carried out in the presence of the homochiral pyridyl alcohol (2S)-(1-hydroxyethyl)pyridine (55). This ligand was found to catalyse the diethylzinc reaction at an initial concentration of

2mol% of the benzaldehyde used. The 1-phenylpropan-1-ol (124) produced from the reaction was found to have a specific rotation of $[\alpha]_D$ = -11.26 where as optically pure 1-phenylpropan-1-ol (124) has specific rotation of $[\alpha]_D$ = - 47.17°.[188] Using the optical rotation a 24% e.e was estimated. Conversion of 1-phenylpropan-1-ol (124) to its (R,S)-α-(2'S)-methylbutyroyloxy)propylbenzene derivative (132) and subsequent ^1H NMR analysis showed no chemical shift non-equivalence for the two possible diastereomers. The optical purity of 1-phenylpropan-1-ol (124) was finally determined by ^1H NMR analysis of (R,S)-α-(2'S)-methylbutyroyloxy)propylbenzene (132) in the presence of chiral shifts reagent [Eu(tfc)$_3$]. Under these conditions the diastereomers of (R,S)-α-(2'S)-methylbutyroyloxy)propylbenzene (132) were distinguishable, splitting patterns being seen between δ 2.0 and 3.0 ppm. These patterns suggested a 39% e.e (Figure 23 and 24).



(132)

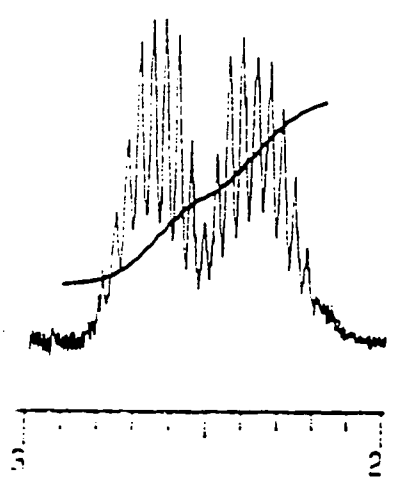


Figure 23. ^1H NMR of racemic (132) using [Eu(tfc)$_3$]

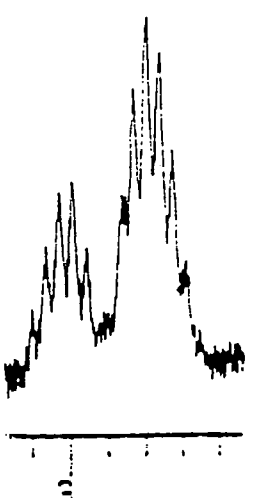
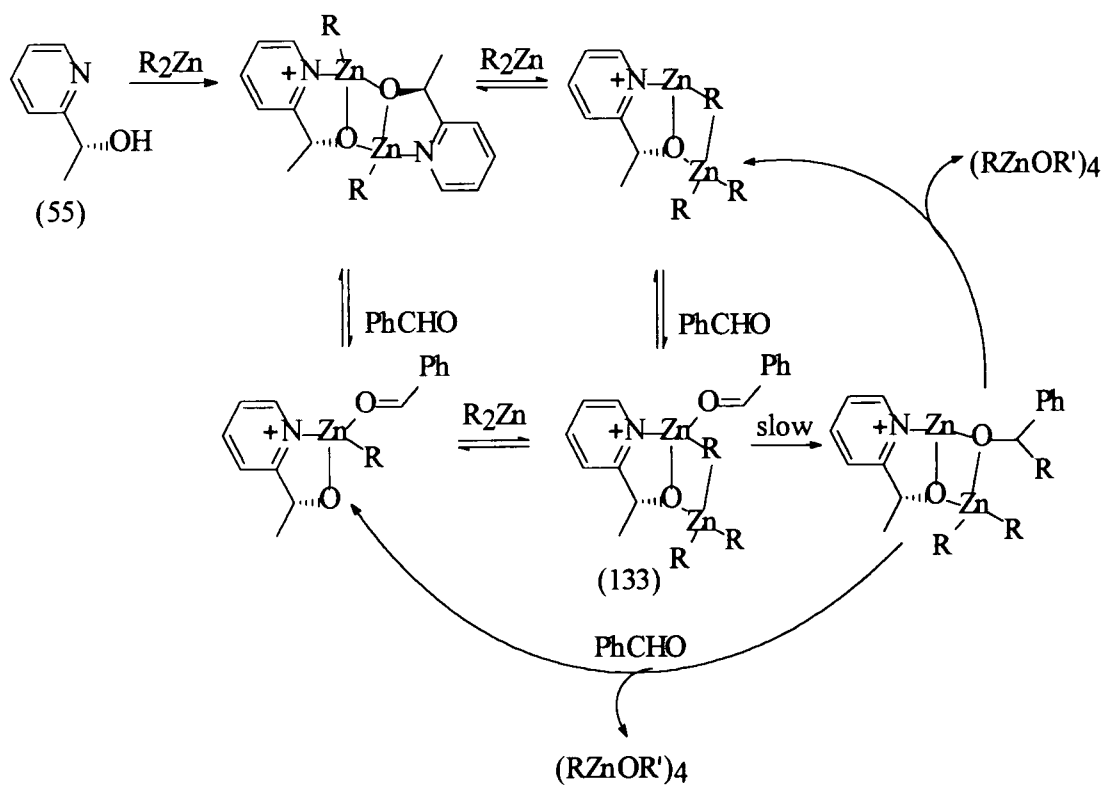


Figure 24. ^1H NMR of optically enriched (132) using [Eu(tfc)$_3$]

mol% catalyst	% e.e
2	39
10	35
20	36

Table 5. Enantiomeric excesses obtained using (2S) (1-hydroxyethyl)pyridine (55) as a chiral catalyst

This 39% enantiomeric excess obtained using (2S) (1-hydroxyethyl)pyridine (55) as a chiral catalyst, is consistent with those obtained for secondary alcohols such as β-amino alcohols.[188] Increasing the level of homochiral pyridyl catalyst (55) from 2mol% to 10% and 20% relative to benzaldehyde, did not improve the optical purity of the product 1-phenylpropan-1-ol (124). These low enantiomeric excesses may be a result of weak co-ordination between the pyridine nitrogen and zinc. In complex (133) below (Scheme 78) the zinc-nitrogen bond may break allowing rotation of the bonded aldehyde group. Addition of an alkyl group at the *re* or *si* faces of the carbonyl group will ultimately result in a loss of optical activity.



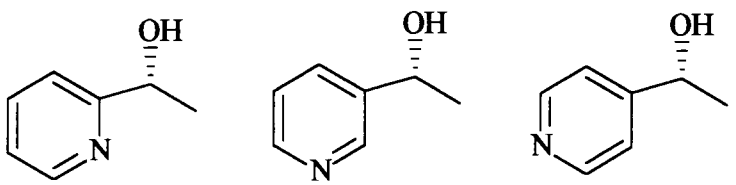
Scheme 78

4.4 Diethylzinc reactions using (2S),(6S)-diethyl(α-hydroxy) pyridine (56) as a chiral catalyst

(2S),(6S)-Diethyl(α-hydroxy)pyridine (56) failed to catalyse the diethylzinc reaction with benzaldehyde and no 1-phenylpropan-1-ol (124) was generated. A possible reason for this is that the second hydroxyl group breaks up the co-ordination between the pyridine nitrogen and zinc, and hence (56) cannot participate in the required catalytic cycle.

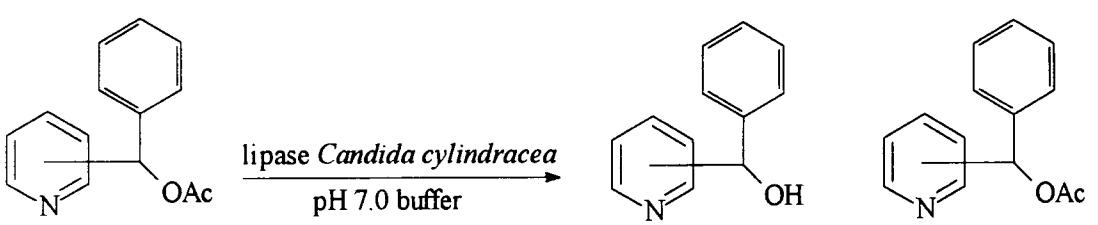
4.5 Enzymatic synthesis of optically active α-hydroxybenzyl pyridines

An improvement in the enantioselectivity of the above diethylzinc reactions could possibly be achieved by using pyridyl alcohols with larger pendant groups. Further, optically enriched chiral pyridyls could also be potential catalysts for asymmetric synthesis. Structural isomers (134) and (135), of 2-(1-hydroxyethyl)pyridine (55), have been prepared in optically pure form using the lipase enzyme from *Pseudomonas*, sp (SAM II).[189]



(55) (134) (135)

We aimed to test if the lipase from *Candida cylindracea* could resolve a range of structural isomers of α-hydroxybenzylpyridines (Scheme 79). This lipase is particularly adept at resolving bulky esters and was judged a good candidate catalyst for these resolutions. It was also of interest to measure the positional effect of nitrogen (ortho, meta or para) on the resolution.



2-pyridyl ± (136)
3-pyridyl ± (138)
4-pyridyl ± (140)

R or S
2-pyridyl ± (137)
3-pyridyl ± (139)
4-pyridyl ± (141)

S or R

Scheme 79

The lipase mediated hydrolysis of 2-(α-acetoxy)benzylpyridine (136), using *Candida cylindracea* proceeded to a 30% conversion of 2-(α-hydroxy)benzylpyridine (137) after two full days. Analysis by ^{1}H NMR in the pesence of chiral shifts reagent [Eu(tfc)$_3$] showed that the acetate derivative of alcohol (137) was racemic. This was later confirmed by chiral HPLC analysis of the pyridyl alcohol (137) using a chiracel ODH column,

Lipase resolution of 3-(α-acetoxy)benzylpyridine (138) using *Candida cylindracea* proceeded to a 32 % conversion of 3-(α-hydroxy)benzylpyridine (139) after two full days. The isolated alcohol was found to have $[\alpha]_D$ = +9.64. Chiral HPLC using a Chiracel ODH column showed the alcohol to have an 89.8% e.e. Chiral HPLC traces for optically enriched and racemic 3-(α-hydroxy)benzylpyridine (139) can be seen below (Figure 25, 26 and 27).

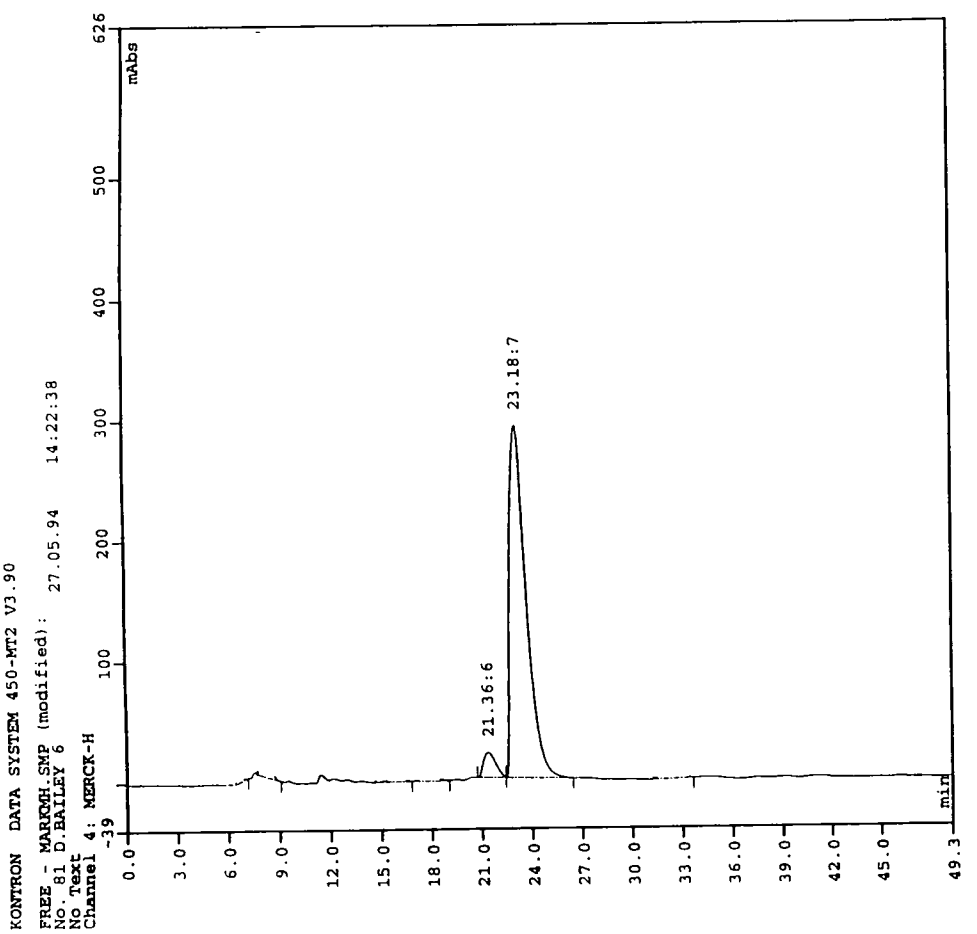


Figure 25. Chiral HPLC trace for optically enriched 3-(α-hydroxy)benzylpyridine

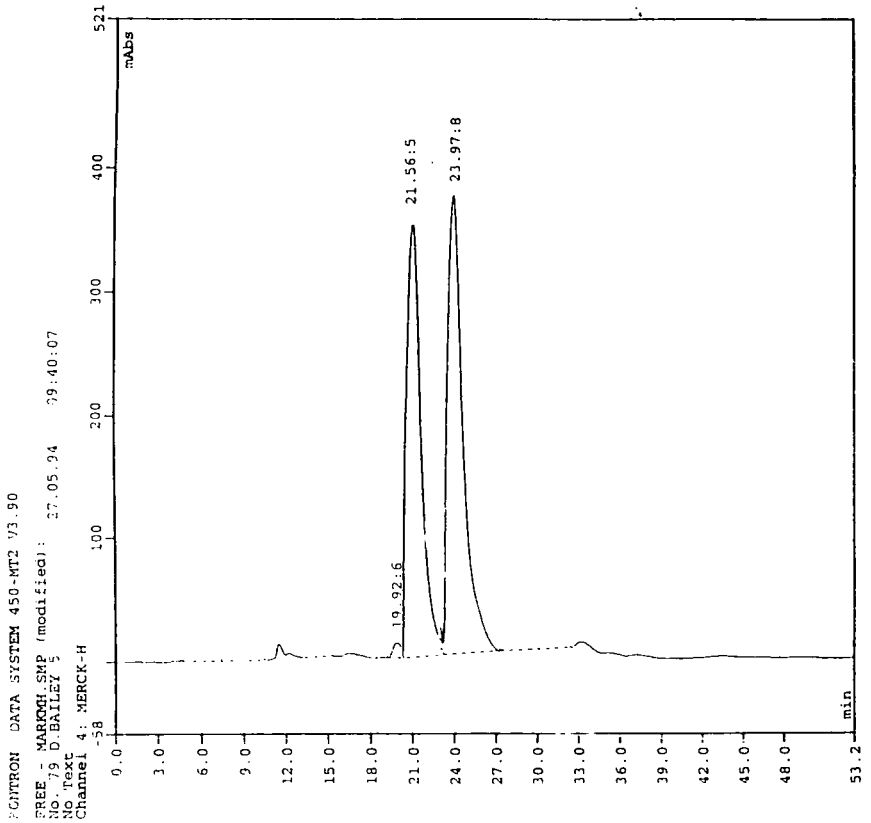


Figure 26. Chiral HPLC trace for racemic 3-(α-hydroxy)benzylpyridine

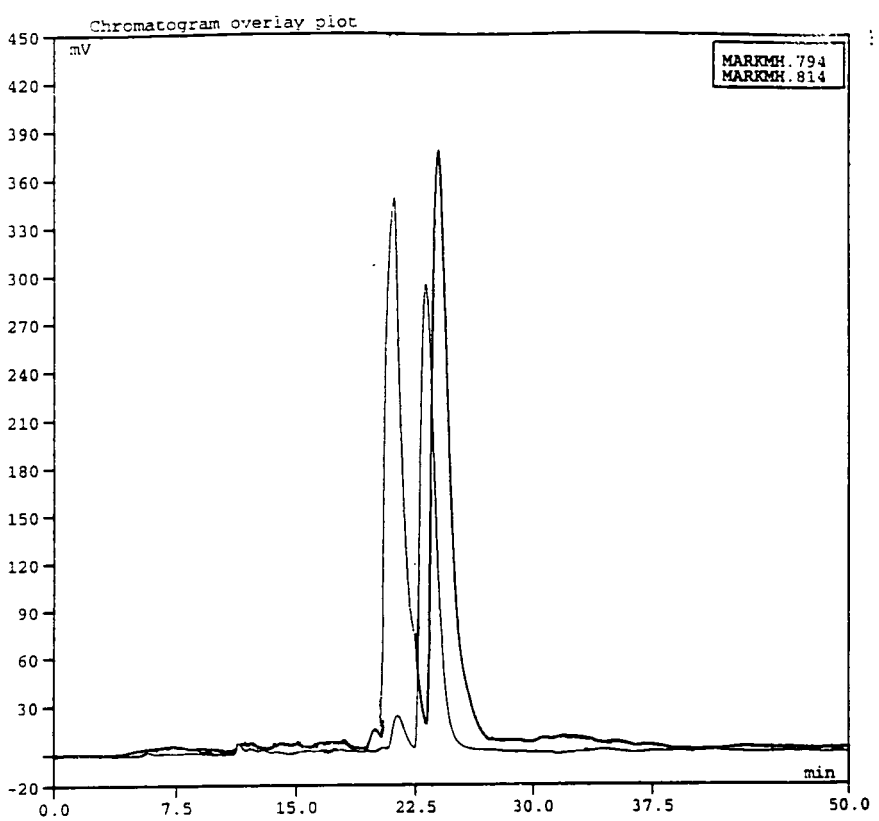


Figure 27. Chiral HPLC trace for 3-(α-hydroxy)benzylpyridine optically enriched overlayed on racemic

After 3 days the lipase resolution of 4-(α-acetoxy)benzylpyridine (140) had proceeded to 23% conversion. Isolated 4-(α-hydroxy)benzylpyridine (141) from the enzyme reaction was found to have $[\alpha]_D$ = +44.4. Chiral HPLC using a Chiracel ODH column demonstrated that the alcohol had a 76.5% e.e. The chiral HPLC traces for optically enriched and racemic 4-(α-hydroxy)benzylpyridine (141) are shown below (Figure 28, 29 and 30).

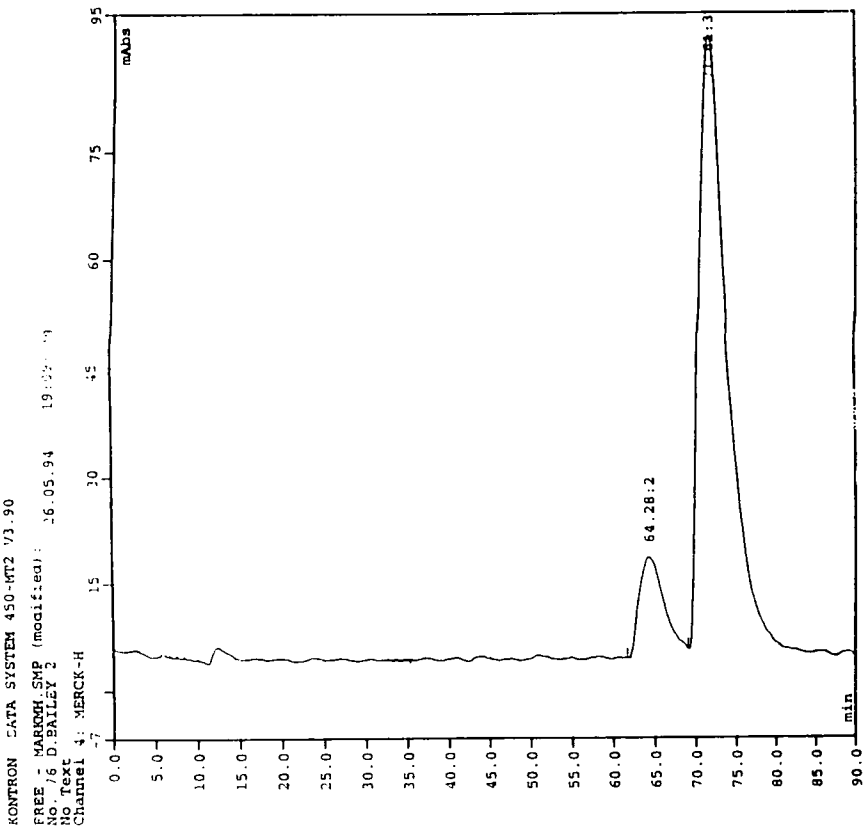


Figure 28. Chiral HPLC trace for optically enriched 4-(α-hydroxy)benzylpyridine

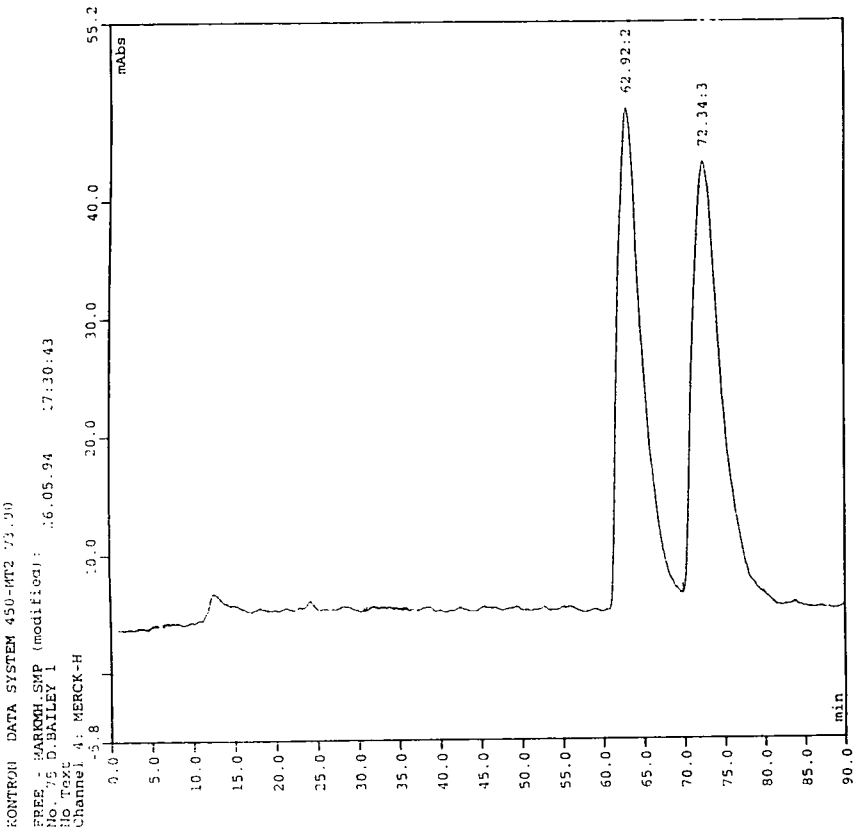


Figure 29. Chiral HPLC trace for racemic 4-(α-hydroxy)benzylpyridine

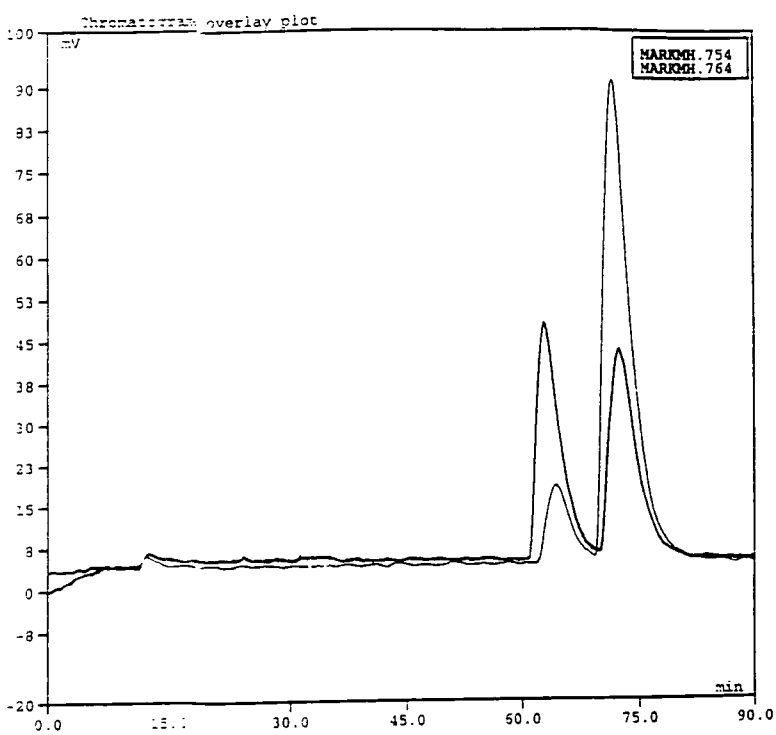
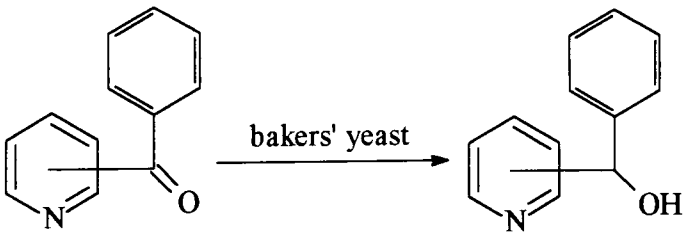


Figure 30. Chiral HPLC trace for 4(α-hydroxy)benzylpyridine optically enriched overlayed on racemic

Enzymatic synthesis of optically active α-hydroxybenzylpyridines has recently been achieved using bakers' yeast (Table 6) and the lipase enzyme *PS* (Table 7).[190]

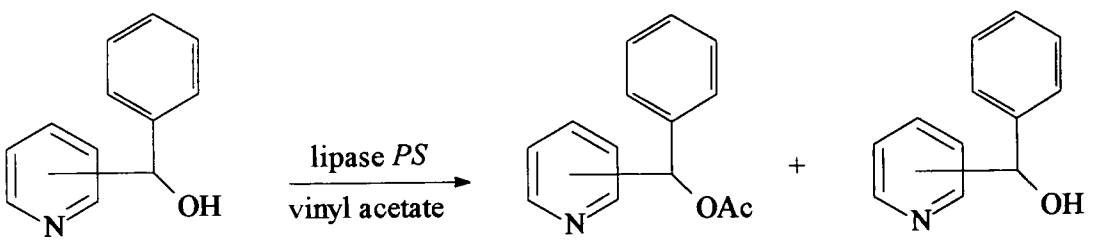


2-pyridyl
3-pyridyl
4-pyridyl

2-pyridyl ± (137)
3-pyridyl ± (139)
4-pyridyl ± (141)

Substrate	Time h	Yield %	$[\alpha]_D$ in $CHCl_3$	% e.e	config
2-pyridyl (137)	106	86	+26.5	26	-
3-pyridyl (139)	96	89	-4.3	36	-
4-pyridyl (141)	106	86	-63.6	86	(S)

Table 6. Synthesis of optically active α-hydroxybenzylpyridines using bakers' yeast



2-pyridyl ± (136)
3-pyridyl ± (138)
4-pyridyl ± (140)

2-pyridyl ± (137)
3-pyridyl ± (139)
4-pyridyl ± (141)

Substrate	Time	yield %	$[\alpha]_D$ in $CHCl_3$	% e.e
2-pyridyl (136)	9 days	31	-24.0	57
3-pyridyl (138)	6 days	39	+1.2	24
4-pyridyl (140)	90h	38	+21.8	12

Table 7. Synthesis of optically active α-hydroxybenzylpyridines using lipase enzyme *PS*.

The absolute configuration of 4-(α-hydroxy)benzylpyridine (141) produced by the lipase *Candida cylindracea* has been assigned as (S) according to Horeau's method.[190,191]

4.6 **Conclusions**

(2)-(1-Hydroxyethyl)pyridine (55) proved to be a poor homochiral catalyst for the reaction between diethylzinc and benzaldehyde. However, the enantiomeric excesses obtained are comparable with the use of other secondary amino-alcohols as chiral catalysts.[178] The *Candida cylindracea* lipase has proved a useful enzyme for the production of homochiral 3 and 4 substituted α-hydroxybenzylpyridines, and offers an alternative to the use of bakers' yeast and lipase PS. The stereoselectivity obtained during the enzyme hydrolysis of 3-(α-acetoxy)benzylpyridine (138) might be explained by hydrogen bonding between the pyridine nitrogen and a functional group at the active site of the enzyme. For example a carboxylate residue could be a possible binding site for the nitrogen of pyridine. Binding to this residue may prevent the substrate from turning in the enzyme pocket, and hence, hydrolysis involving the serine residue takes place stereoselectively. This is represented below (Figure 31)

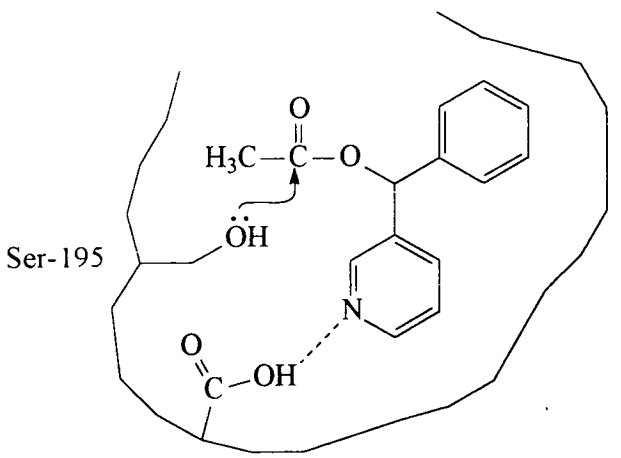


Figure 31. Lipase resolution of 3-(α-acetoxy)benzylpyridine (138)

A similar situation can be considered for the enzyme hydrolysis of 4-(α-acetoxy)benzylpyridine (140). However, since the pyridine nitrogen is further away from the carboxylate residue hydrogen bonding is weaker and some rotation of the molecule in the enzyme pocket takes place. This ultimately leads to a drop in stereoselectivity (Figure 32).

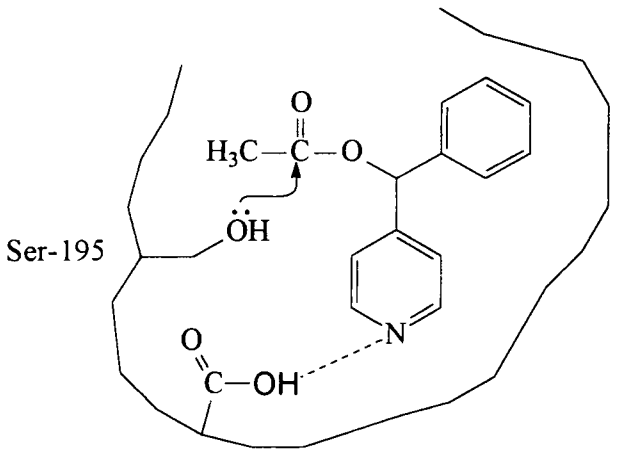


Figure 32. Lipase resolution of 4-(α-acetoxy)benzylpyridine (140)

Consistent with this enzyme hydrolysis, 2-(α-acetoxy)benzylpyridine (136) would take place with no stereoselectivity due to the absence of this secondary hydrogen bonding. The molecule is free to turn in the enzyme pocket and hydrolysis by the serine residue 195 takes place indiscriminately (Figure 33).

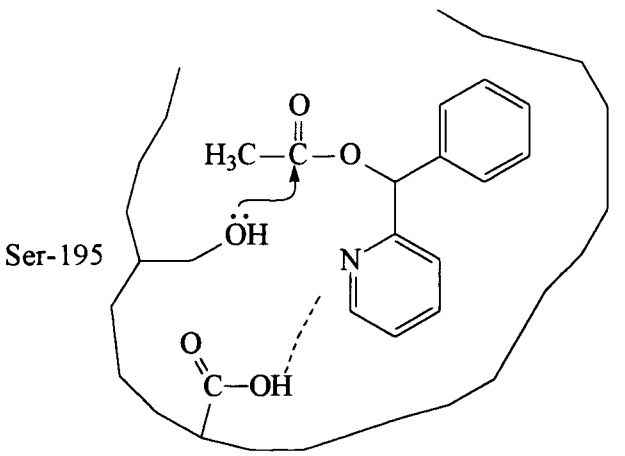


Figure 33. Lipase resolution of 2-(α-acetoxy)benzylpyridine (136)

Absolute configurations of the α-hydroxybenzylpyridines have not been determined by X-ray crystallography since suitable crystals could not be obtained. The absolute configuration of 4-(α-hydroxy)benzylpyridine (141) obtained using the lipase *Candida cylindracea* can be assigned as configuration (R) according to Horeau's method.[191]

CHAPTER 5

Section A

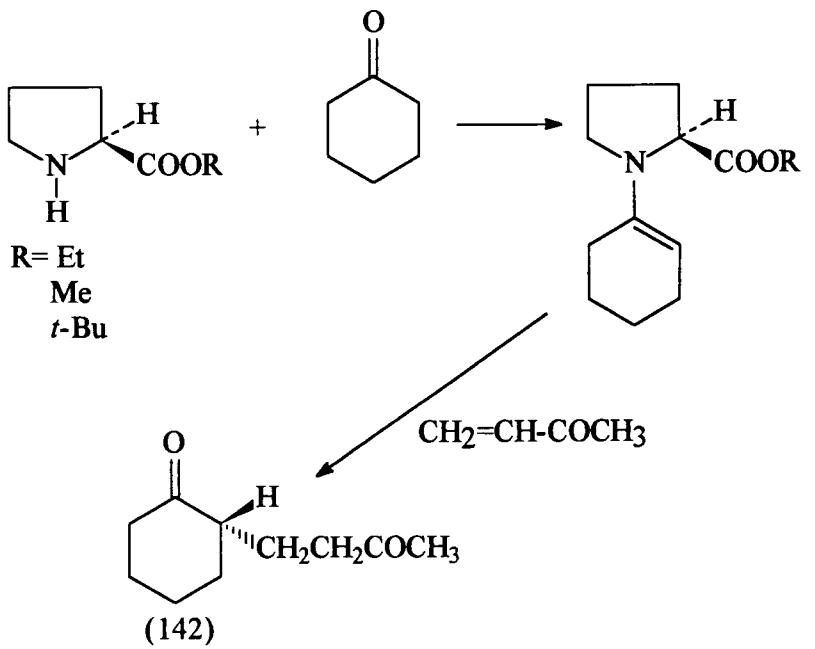
Homochiral bases derived from (S)-(-)-proline

5.1 Introduction

Amino acids, the building blocks for proteins, have become important in the arena of asymmetric synthesis due to their availability in homochiral form. In particular the amino acid (S)-proline, in which the amino group forms part of a pyrrolidine ring, has found extensive use as a starting material for the production of chiral auxiliaries. Examples of the use of proline for this purpose are discussed below.

5.1.1 Stork Enamine Chemistry

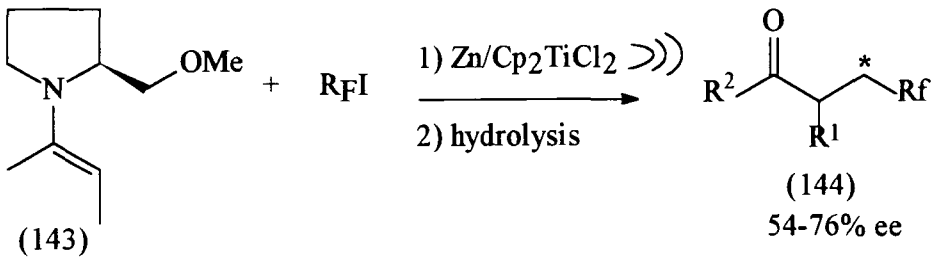
Esters of proline have been used in the asymmetric synthesis of optically active α-alkyl-cyclohexanone (142) by the way of enamine alkylation (Scheme 80).[192]



(142)

Scheme 80

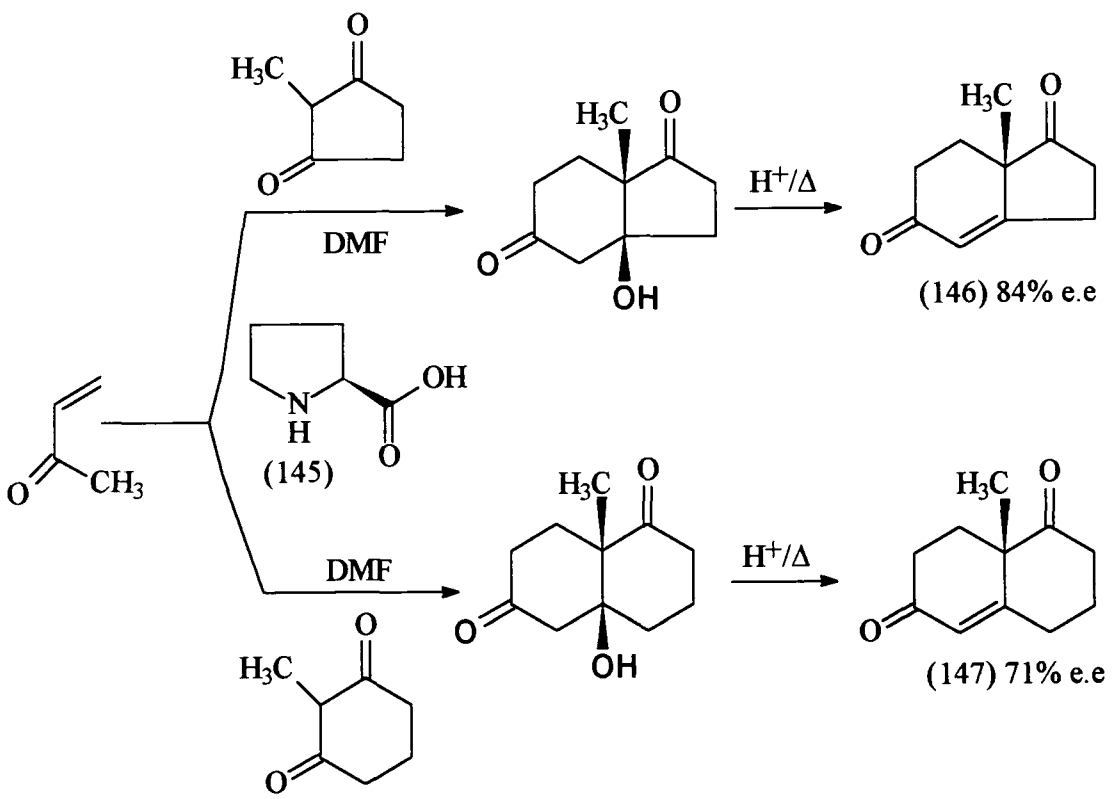
Similarly a perfluoroalkyl chain was introduced α to a carbonyl group using chiral enamines derived from prolinol.[193] Treatment of (143) below with a peralkyliodide in the presence of dicyclopentadienyltitanium dichloride / Zinc (Cp_2TiCl_2, Zn) powder and ultra sound afforded the corresponding α-perfluoroalkyl ketones (144) (Scheme 81).



Scheme 81

5.1.2 Asymmetric cyclisations using (S)-proline

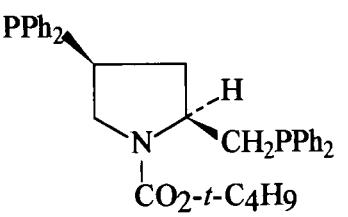
In the so called *Eder-Sauer-Wiechert-Hajos* reaction [194,195] (S)-proline (145) has been used in asymmetric Michael additions of vinyl ketones to cyclic diketones. For example 7-α-alkyl-5,6,7,7-α-tetrahydro-1,5-indanones (146) and 8-α-alkyl-α-2,3,4,5,6,7,8,8-octahydro-1,6-napthalenediones (147) have been synthesised in high percentage e.e using this technique (Scheme 82), and these are useful starting materials in the synthesis of steroids.[194,195]



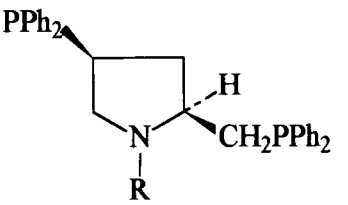
Scheme 82

5.1.3 (S)-Proline in asymmetric hydrogenation reactions

The first preparative transfer of hydrogen to π-systems by rhodium (1) phosphorane complexes was achieved by Wilkinson *et al.*,[196] using $(C_6H_5)_3PPh_2Cl$. The year 1961 saw the development of optically active tertiary phosphoranes by Horner *et.al.*,[197] and this led to the production of chiral Wilkison complexes with a high level of asymmetric induction.[198] In the 1970's (2S,4S)-N-*tert*-butoxycarbony-l,4-diphenylphosphino-2-diphenylphosphinomethylpyrrolidine (BPPM) (148) and (2S,4S)-4-diphenylphosphino-2-diphenylphosphinomethylpyrrolidine (PPM) (149) were developed as catalysts for homogeneous asymmetric hydrogenation.[199-204]

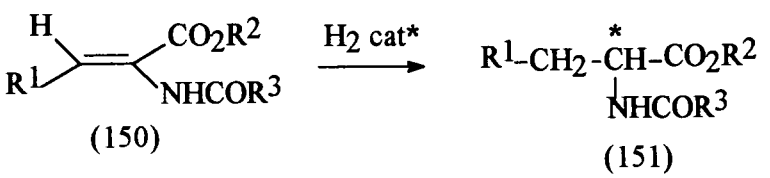


(BPPM)
(148)



(PPM)
(149)

Homogeneous catalytic hydrogenation of dehydroamino acids (150) with Wilkinson's catalysts containing (BPPM) and (PPM) led to amino acid derivatives (151) with very good optical yields (Scheme 83) and these are summarised below (Table 8).



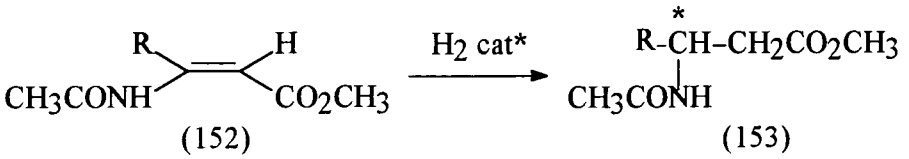
(150) (151)

Scheme 83

R^1	R^3	Phosphine	% ee config	ref
C_6H_5	CH_3	148	91 (R)	198
p-H_3CO-C_6H_4	CH_3	148	87 (R)	198
H	$OCH_2C_6H_5$	148	50 (R)	200
H	$OCH_2C_6H_5$	149 R= $COCH_3$	57 (R)	200
C_6H_5	CH_3	149 R= CO-t-C_4H_9	59 (R)	200
C_6H_5	CH_3	149 R= CONH-cyclo-C_6H_{11}	91 (S)	203

Table 8. Homogeneous catalytic hydrogenation of dehydroamino acids (150) R^2=H

Achiwa *et al.*[203] have also reported the catalytic asymmetric hydrogenation of methyl β-acetylaminoacrylate (152) with Wilkinson's catalyst, containing (BPPM) and (PPM). The resulting β-alanines (153) were obtained with optical purities up to 55% e.e (Scheme 84).



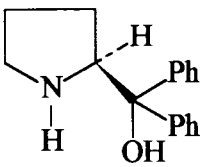
(152) (153)

Scheme 84

The use of (S)-proline derivatives and other naturally occurring amino acids in asymmetric hydrogentions has been reviewed.[205]

5.1.4 (S)-Proline in asymmetric reductions

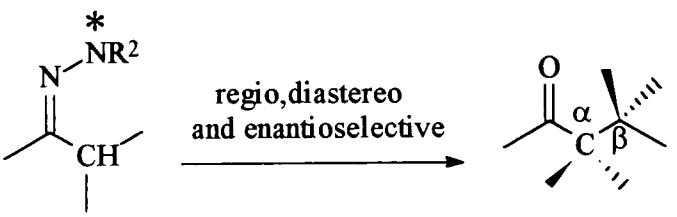
(2S)-(α-Hydroxy-α,α-diphenyl)methylpyrrolidine (154) is of considerable significance as a precursor to the **CBS** chiral reducing agents.[103,104] This reducing agent has already been discussed in Chapter 2



(154)

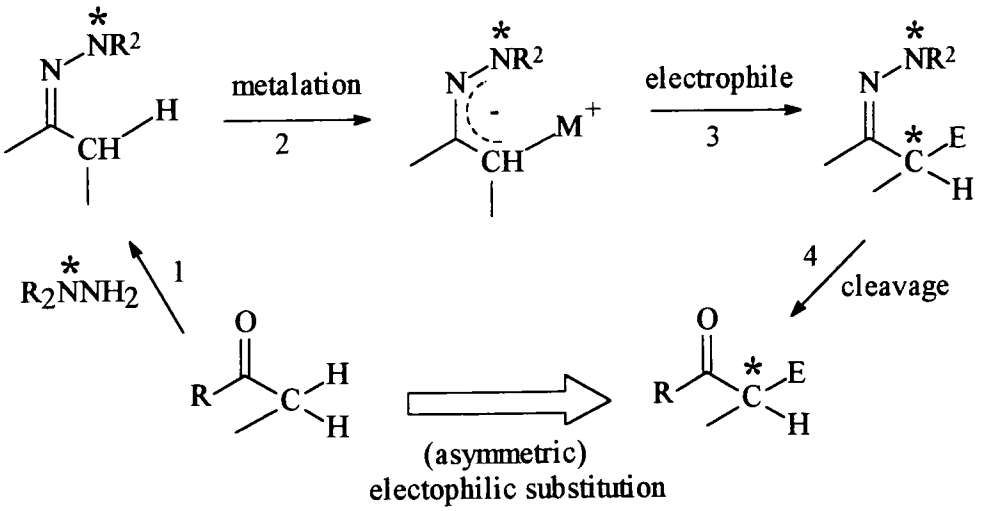
5.1.5 Alkylation of chiral hydrazones containing (S)-proline derivatives

Alkylation of chiral hydrazones (Scheme 85) allows the construction of C-C bonds α to the carbonyl group and this can generate one or two chiral centres at the α and β positions.



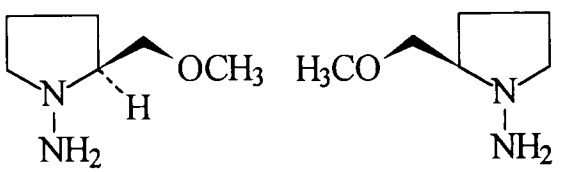
Scheme 85

The general procedure for carrying out electrophilic substitution at the α carbonyl group of aldehydes and ketones is shown below (Scheme 86).



Scheme 86

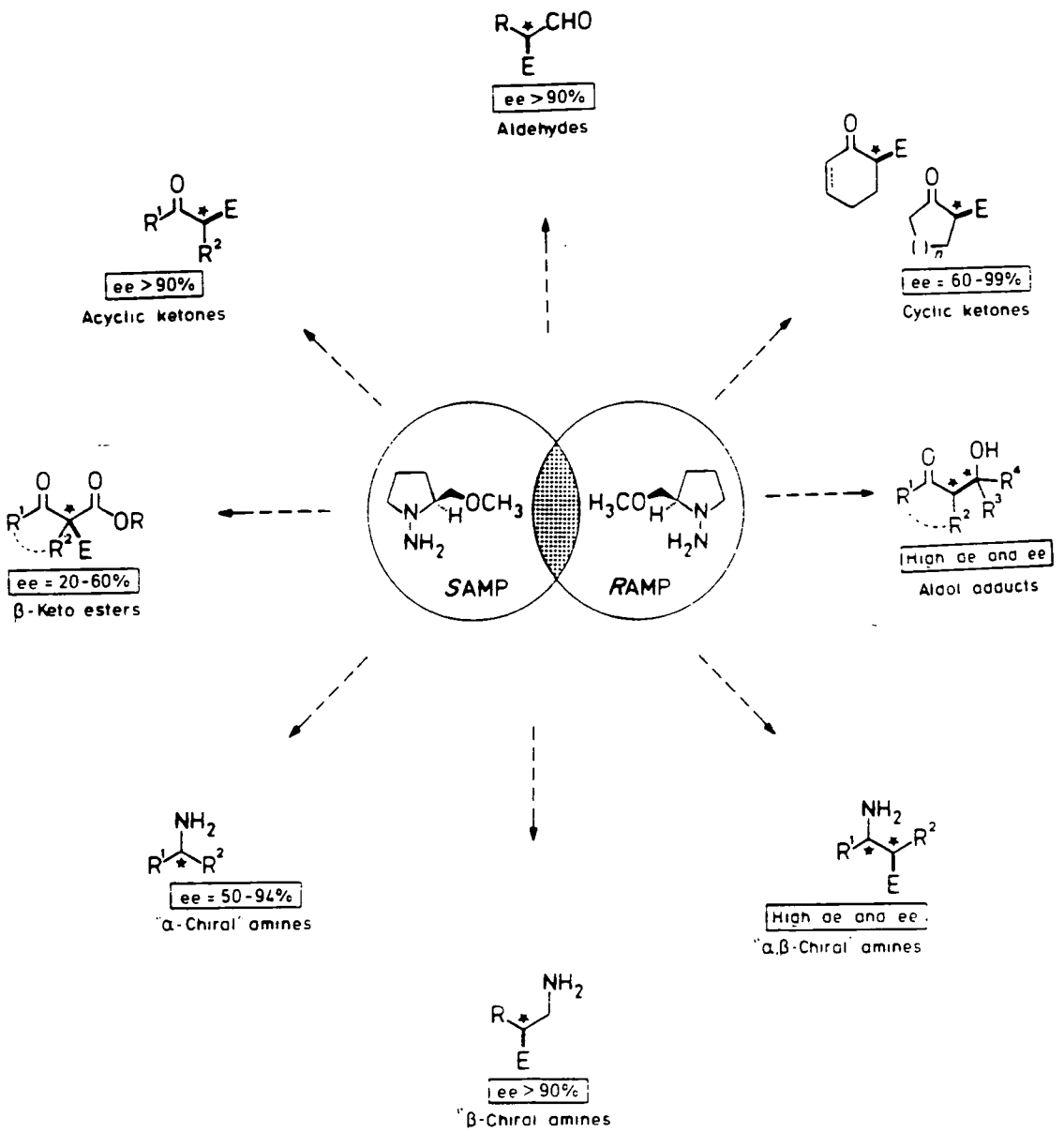
In order to achieve the asymmetric induction during the carbon-carbon forming reaction the chiral amine (S)-1-amino-2-methoxymethylpyrrolidine (155) (SAMP) [206] and (R)-1-amino-2-methoxymethylpyrrolidine (156) (RAMP) [207] were used.



(155) SAMP

(156) RAMP

The synthetic scope of SAMP and RAMP hydrazone methodology has been reviewed [208] and a summary of its versatility is outlined below (Scheme 87).



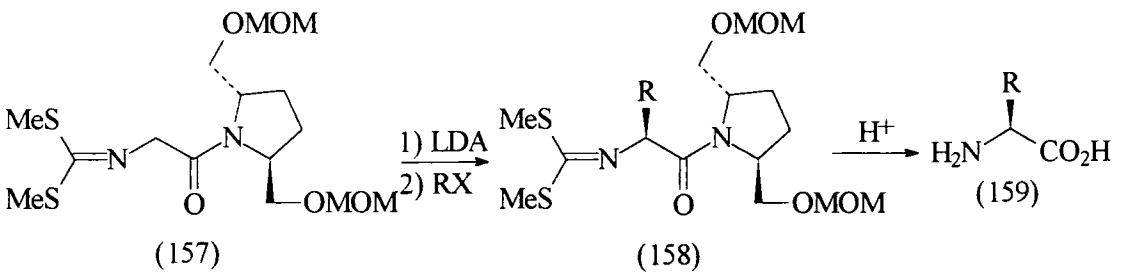
Primary amines

Scheme 87. Synthetic scope of SAMP-/RAMP-hydrozone method

5.2 The use of C_2 symmetric pyrrolidines in asymmetric synthesis

5.2.1 Asymmetric synthesis of α-amino acids

Amide enolates that bare trans-2,5-disubstituted pyrrolidines as chiral auxiliaries have been found to react diastereoselectively with various electrophiles to give α-substituted amides. These can then be hydrolysed to give the corresponding α-substituted amino acids in high enantiomeric purity. For example the alkylation of chiral enolate N-[N-bis(methylthio)methyleneglycol-trans-2,5-bis-(methoxymethoxy)pyrrolidine (157), gave the alkylated amides (158) in high diastereomeric excess. Hydrolysis of these gave the corresponding α-amino acids (159) in high e.e (Scheme 88) (Table 9).[209]



(157) (158) (159)

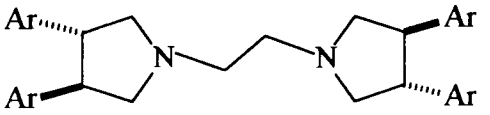
Scheme 88

Alkylated amide			α-amino acid		
RX	**Yield**	**% d.e**	**Yield**	**% e.e**	**config**
MeI	85	98	97	95	(S)
$PhCH_2Br$	92	98	92	97	(S)
$pMeOC_6H_4CH_2Br$	91	96	88	95	(S)
Me_2CHCH_2OTf	68	97	96	97	(S)

Table 9. Alkylation of 2S, 5S amide (157)

5.2.2 C_2 symmetric amines in asymmetric addition reactions

Design of chiral ligands, and their application to the asymmetric addition of organometallics to carbonyl compounds, is a current challenge of substantial international interest.[170,210] Diamines (160) and (161) consisting of two *trans*-3,4-diarylpyrrolidine units bridged by an ethylene chain, have proved effective in forming a well organised chelate complex with organometallics. The chiral ligand-mediated asymmetric reactions of arylmagnesium bromides with aldehydes has produced the corresponding carbinols in 40-75% e.e (Table 10).[211]



(160) : Ar = Ph

(161) : Ar = *m*-xylene

The origins of enantiofacial selectivity, is probably related to the formulated structure shown below (Figure 34)

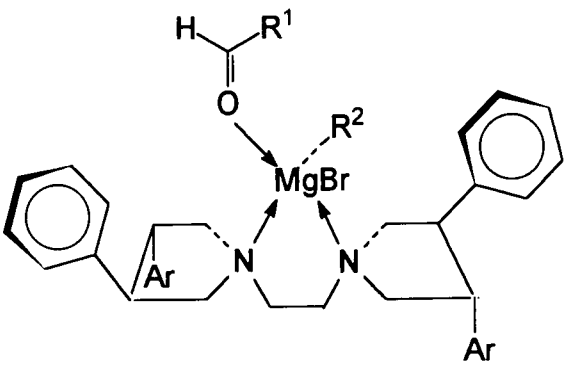


Figure 34.

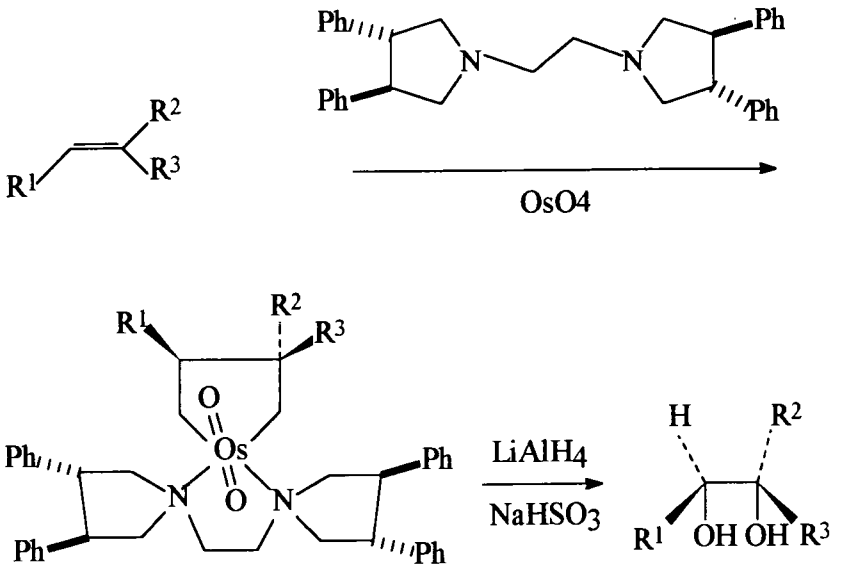
$$R^1CHO + R^2MgBr \xrightarrow{(160) \text{ or } (161)} R^1R^2CHOH$$

R^1	R^2	Ligand	Temp °C	$[\alpha]_D$	e.e (%) config	% Yield
Ph	α-nap	160	-45	-65.3	55 (S)	94
Ph	α-nap	161	-100	-88.0	75 (S)	94
c-hex	Ph	160	-100	-15.6	55 (S)	68
i-pr	Ph	160	-100	-22.6	47 (S)	68

Table 10. Asymmetric reactions of arylmagnesium bromides with aldehydes mediated by chiral diamine ligand 1&2

5.2.3 C_2 symmetric amines in asymmetric dihydroxylation reactions

Homochiral C_2 symmetric pyrrolidine amines have also been found to be efficient ligands for the enantiofacial dihydroxylation of carbon-carbon double bonds using osmium tetroxide (Scheme 89) (Table 11).[212]



Scheme 89

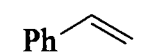
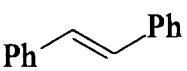
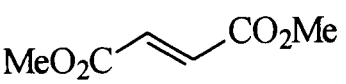
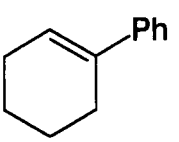
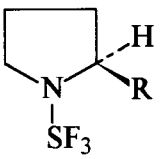
Ligand (160)	Olefin	diol product		
		Yield	e.e	cofig
(-)		71	90	(S)
(+)		71	96	(RR)
(-)		67	93	(RR)
(-)		83	83	(SS)

Table 11. Enantioselective Cis dihydroxylation of olefins with OsO_4 using (-)-(160) and (+)-(160)

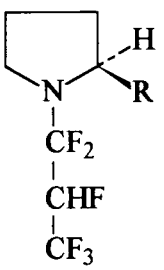
5.3 **Objectives**

The aim of this work was to synthesise the homochiral pyrrolidine analogues of DAST (Figure 35) and Ishikawa's reagent (Figure 36) and assess their ability as asymmetric fluorinating reagents. Syntheses of such reagents have not been reported, apart from Sampson' reagent (47), which has already been discussed (Chapter 1).



R =$CH(CH_3)_2$
$C(CH_3)_2OMe$
$C(Ph)_2OH$
$C(Ph)_2OMe$
$CH(Ph)_2$
CH_2OMe Sampson's reagent (47)

Figure 35. DAST homologues



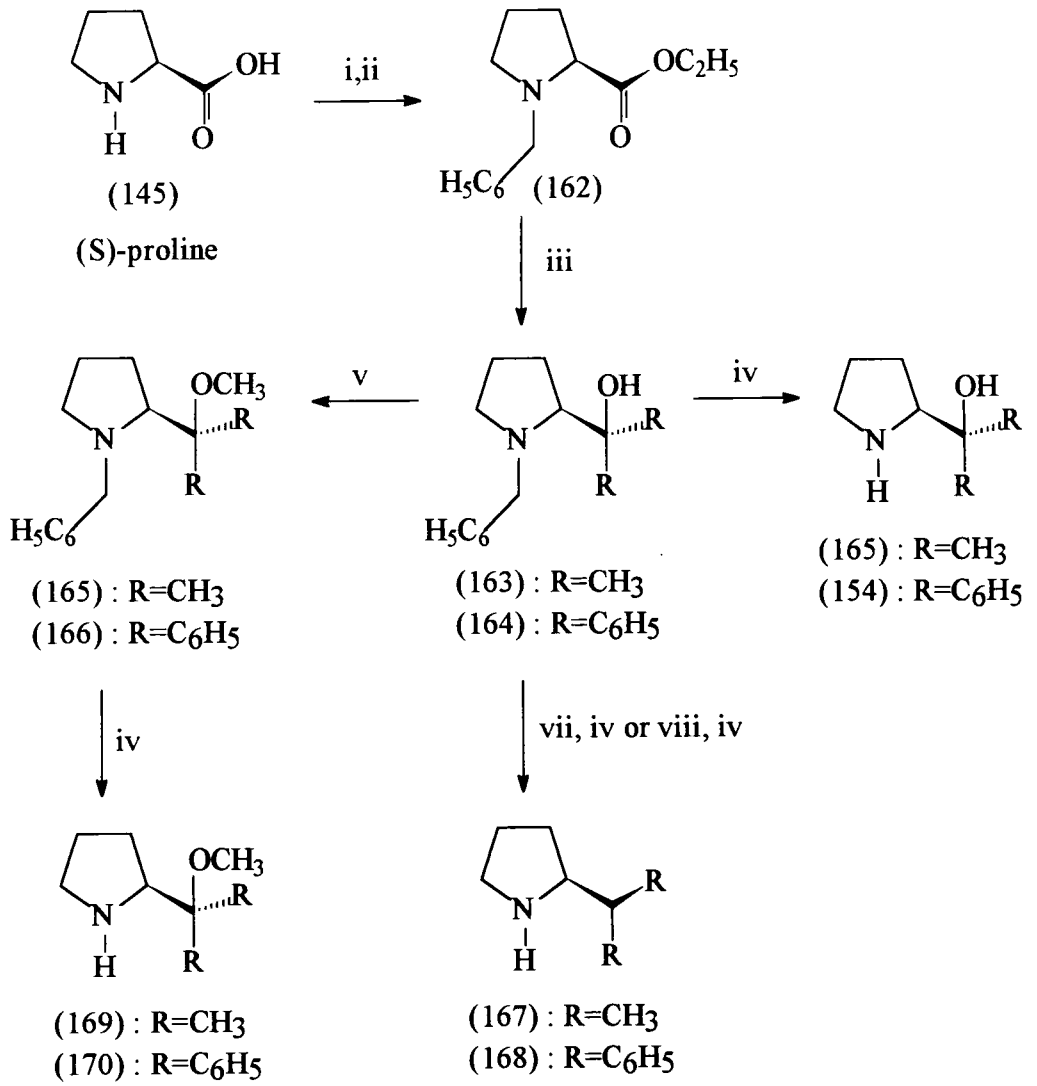
R =$CH(CH_3)_2$
$C(CH_3)_2OMe$
CH_2OMe
$C(Ph)_2OH$
$C(Ph)_2OMe$
$CH(Ph)_2$

Figure 36. Homologues of Ishikawa's reagent

5.4 Synthesis of homochiral pyrrolidines

5.4.1 Preparation of (2S)-(α-methoxy α,α-diphenyl)methyl pyrrolidine

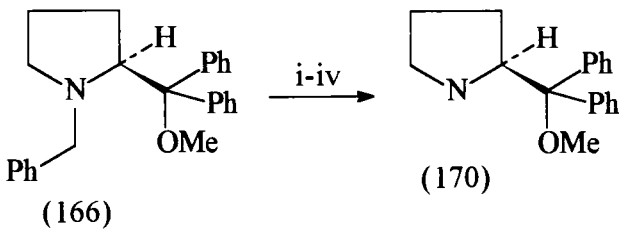
A variety of enantiomerically pure chiral auxiliaries based on (S)-proline (145) have been synthesised bearing sterically demanding side chains attached to the pyrrolidine ring, as shown below (Scheme 90).[213]



Scheme 90. i) $SOCl_2$, EtOH. ii) DCC, $C_6H_5CH_2OH$. iii) RMgX or RLi, Et_2O. iv) H_2/ Pd/C 10% EtOH v) NaH, MeI, THF. vi) $LiAlH_4$, THF. vii) $SOCl_2$, Et_3N, THF. viii) Li, $NH_{3(l)}$ ($R=C_6H_5$).

Repetition of the above synthetic scheme would lead to candidates needed for the synthesis of the required asymmetric fluorinating reagents, and our approach started here. In the event a number of the above synthetic steps proved difficult to repeat.

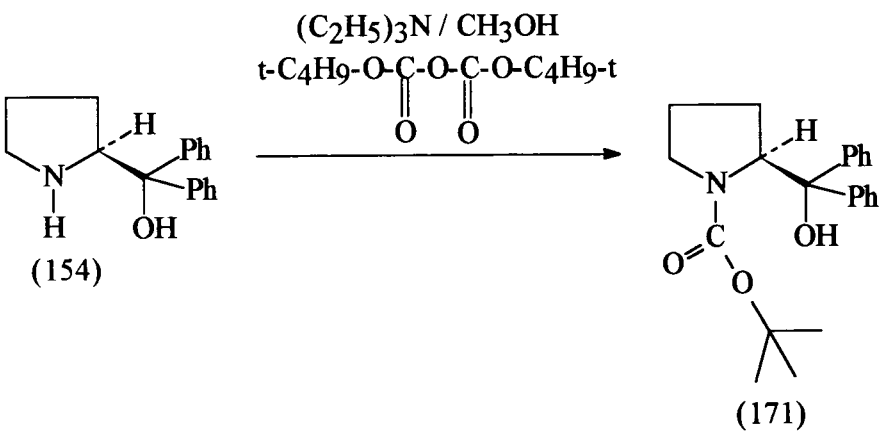
Methylation of the hydroxyl group in (164) was only possible in (15%) yield. It was found that changing the solvent system to a mixture of DMF/THF increased the rate of methylation but not the yield. When the reaction was carried out in pure DMF no methylation of the hydroxyl group was seen. Methylation of the hydroxyl group in (164) was also attempted using Meerwein's reagent (trimethyloxonium tetrafluoroborate) in the presence of the proton sponge 1,8-bis(dimethylamino)naphthalene,[214] but no methylation was observed. Removal the N-benzyl protecting group from (166) to yield the free amine (170) was attempted using a range of hydrogenation procedures but all of these were unsuccessful in our hands, despite considerable efforts (Scheme91).



(166) (170)

Scheme 91. i) H_2, Pd / C.[213] ii) Pd / NaOH.[215] iii) PtO_2 / H_2.[216] iv) HCOOH, Pd / C.[217]

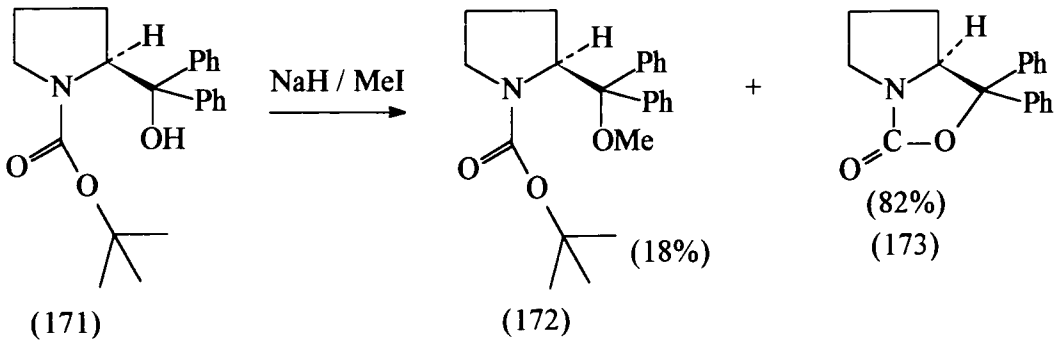
It was envisaged that the problem of hydrogenation could be avoided by protecting the amine of (2S)-(α-hydroxy-α,α-diphenyl)methylpyrrolidine (154) as a N-*tert*-butoxy carbamate ester (171).[218] This was achieved in a straight forward manner with di-*tert*-butyl dicarbonate in (94%) yield (Scheme 92).



(154) (171)

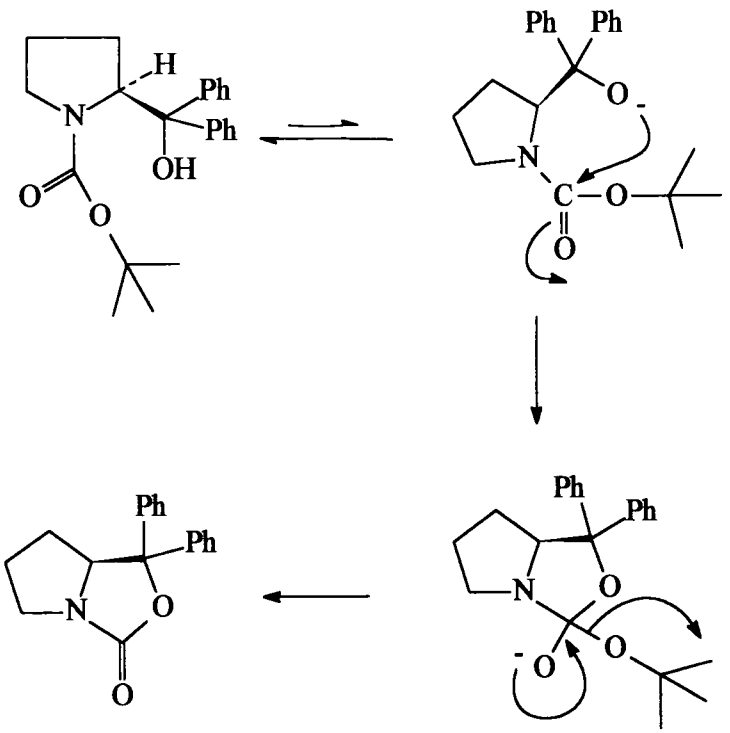
Scheme 92

Methylation of N-*tert*-butoxycarbamate-(2S)-(α-hydroxy-α,α-diphenyl)methyl pyrrolidine (171) using NaH and MeI gave the methyl ether (172) in only (18%) yield. The major product of this reaction was the cyclic carbamate (5S)-[3.3.0]-1-aza-2-oxo-3-oxa-4,4-diphenyl-bicyclooctane (173), which was produced in (82%) yield (Scheme 93).



Scheme 93

Under the above conditions the hydroxyl group in the 2-position behaves as a nucleophile attacking the carbamate carbonyl, with cyclisation and displacement of the *tert*-butoxyl group (Scheme 94).

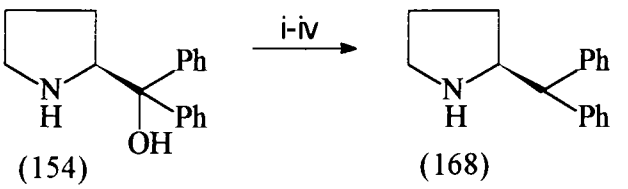


Scheme 94

Separation of the methyl ether (172) from the cyclic product (173) was achieved by column chromatography. Cleavage of the N-*tert*-butoxycarbamate ester (172) was attempted using trifluoroacetic acid in the presence of an antioxidant, 1,2-ethanedithiol.[219] This cleavage step proved problematic too, due the preferential cleavage of the carbon-methoxy bond, which could be seen during the reaction by the disappearance of the methoxy signal in the ^{1}H NMR spectrum.

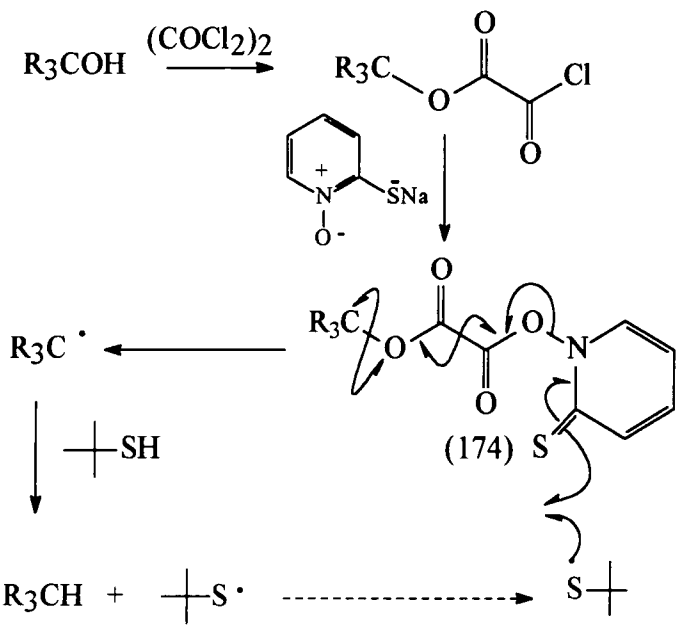
5.4.2 Synthesis of (2S)-(diphenyl)methylpyrrolidine (168)

Synthesis of (2S)-(diphenyl)methylpyrrolidine (168) was attempted by removal the hydroxyl group from (2S)-(α-hydroxy-α,α-diphenyl)methylpyrrolidine (154). A number of methods were tried, but in our hands none of these methods proved successful (Scheme 95).



Scheme 95. i) Li, NH_3.[215] ii) $AlCl_3$, $LiAlH_4$.[220] iii) PtO_2/H_2, CF_3COOH or $NaBH_4$, CF_3COOH.[221] iv) 1) PBr_3, HBr, 2) $LiAlH_4$.[222]

Hydroxyl groups of a large number of tertiary alcohols have been removed by radical deoxygenation.[223] This method involves deoxygenation of oxalyl thiohydroxamine (174). The advantage of this procedure is that it avoids the need for dehydration followed by catalytic hydrogenation and hence racemisation of the chiral centre. Preparation of the oxalyl thiohydroxamine (174) was achieved by reaction of the sodium salt of 2-mercaptopyridine-N-oxide with the half oxalic acid chloride of the tertiary alcohol. On reaction with a non-nucleophilic mercaptan derivative, (174) undergoes smooth fragmentation with the loss of two molecules of CO_2. Capture of the resultant tertiary radical by hydrogen atom abstraction from the thiol then generates the required product. The overall procedure for deoxygenation of tertiary alcohols can be envisaged as follows (Scheme 96).



Scheme 96

Although the preparation of compound (168) has already been reported, [213,226] these methods are not straight forward. This is the first preparation of compound (168) using the above procedure, and this procedure has been carried out on a 100g scale, with no purification of the intermediate compounds required.

^{1}H-^{1}H COSY, HETCOR and DEPT NMR analysis of (2S)-(diphenyl)methylpyrrolidine (168) can be seen in (Figures 37, 38, 39). X-ray crystal analysis of the hydrogen chloride salt of amine (168) (Figure 40) confirmed the successful synthesis of compound (168) and also confirmed the absolute configuration as (S), as expected. Since the amine (161) was synthesised from optically pure (S)-proline (145), it should of course be optically pure. Chiral HPLC analysis of the free amine using an Chiracel ODH column [105] was unsuccessful. Derivatisation of the free amine using N-trifluoroacetylimadazole (TFAI) [227] gave derivatives in which the enantiomers were separable and chiral HPLC analysis of these derivatives, using a Chiracel OD-H column, showed the free amine to be optically pure. (Figure 41, 42, 43).

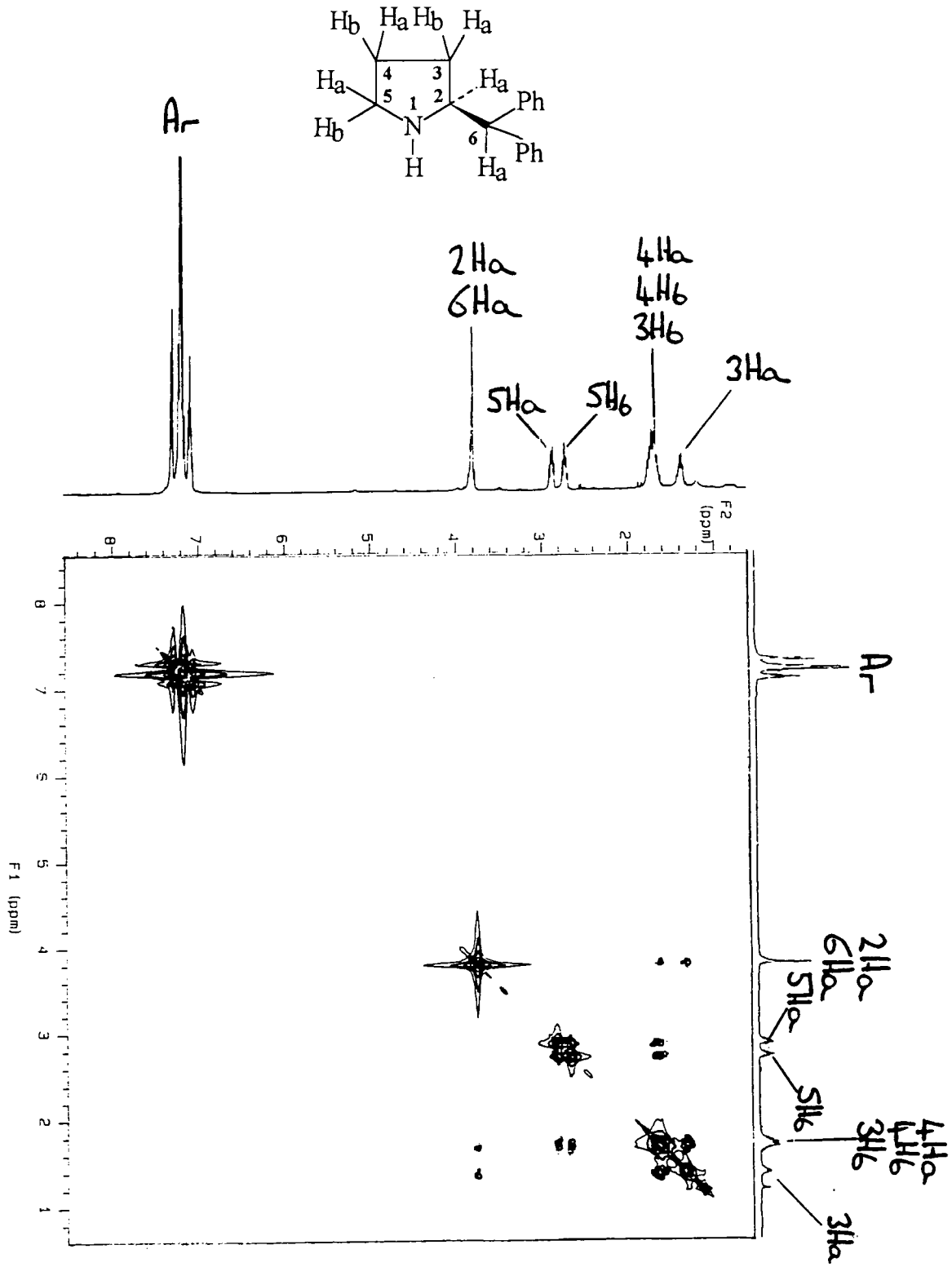


Figure 37. ^{1}H-^{1}H COSY of (2S)-(diphenyl)methylpyrrolidine (168)

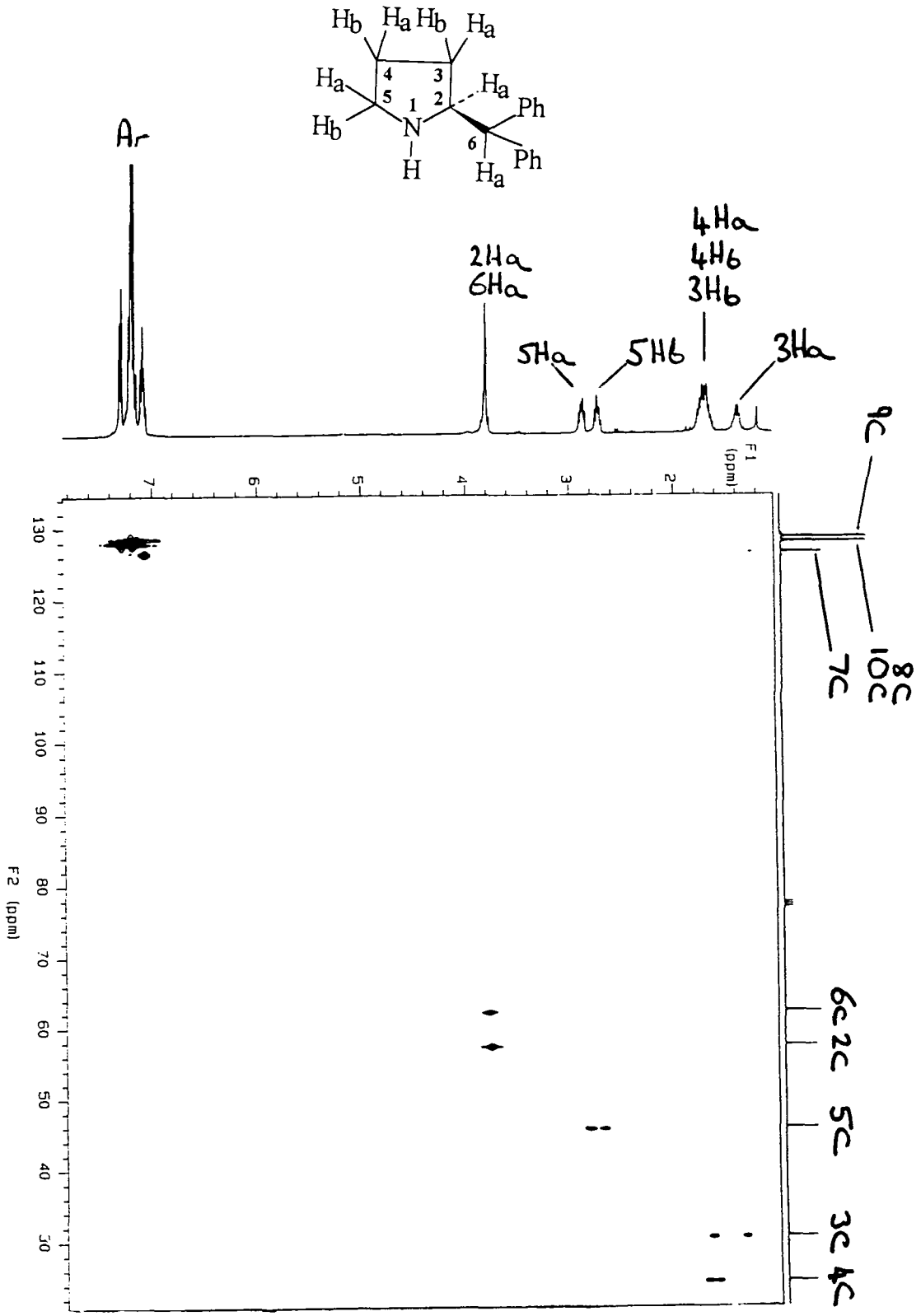


Figure 38. ^{1}H-^{13}C HETCOR of (2S)-(diphenyl)methylpyrrolidine (168)

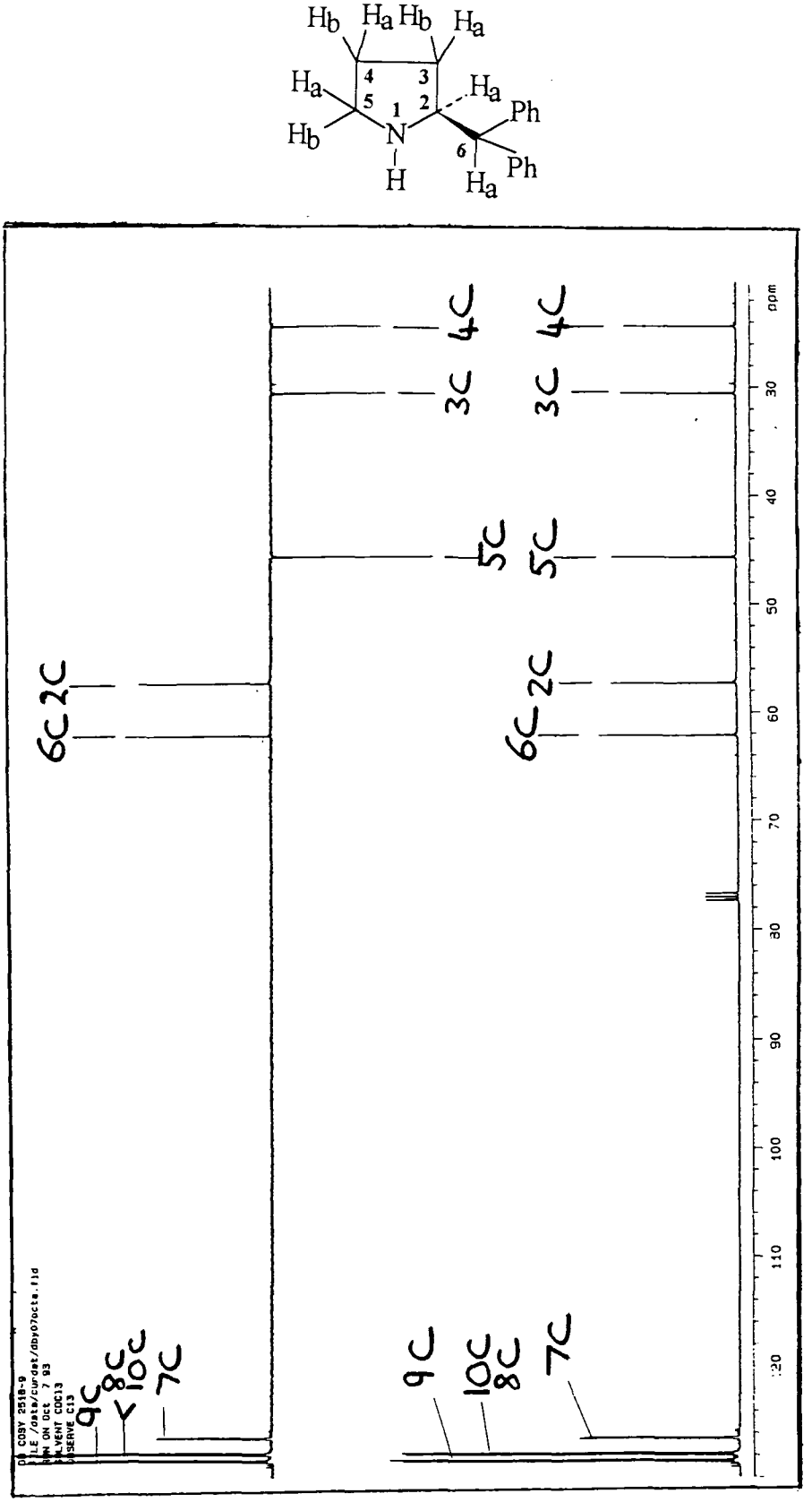


Figure 39. DEPT of (2S)-(diphenyl)methylpyrrolidine (168)

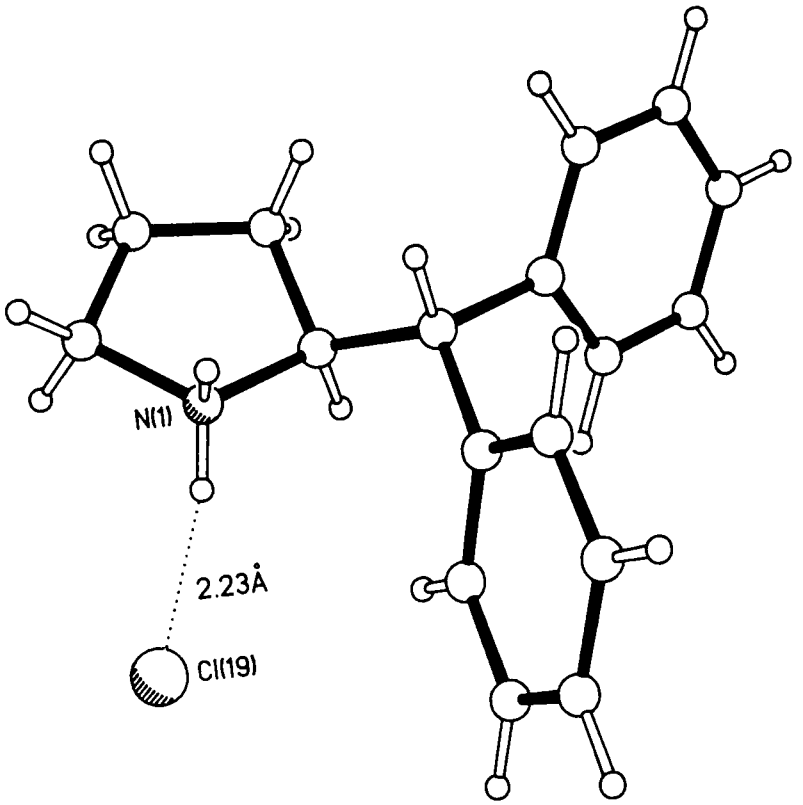


Figure 40. X-Ray crystal structure of (2S)-(diphenyl)methylpyrrolidine (168) HCl salt

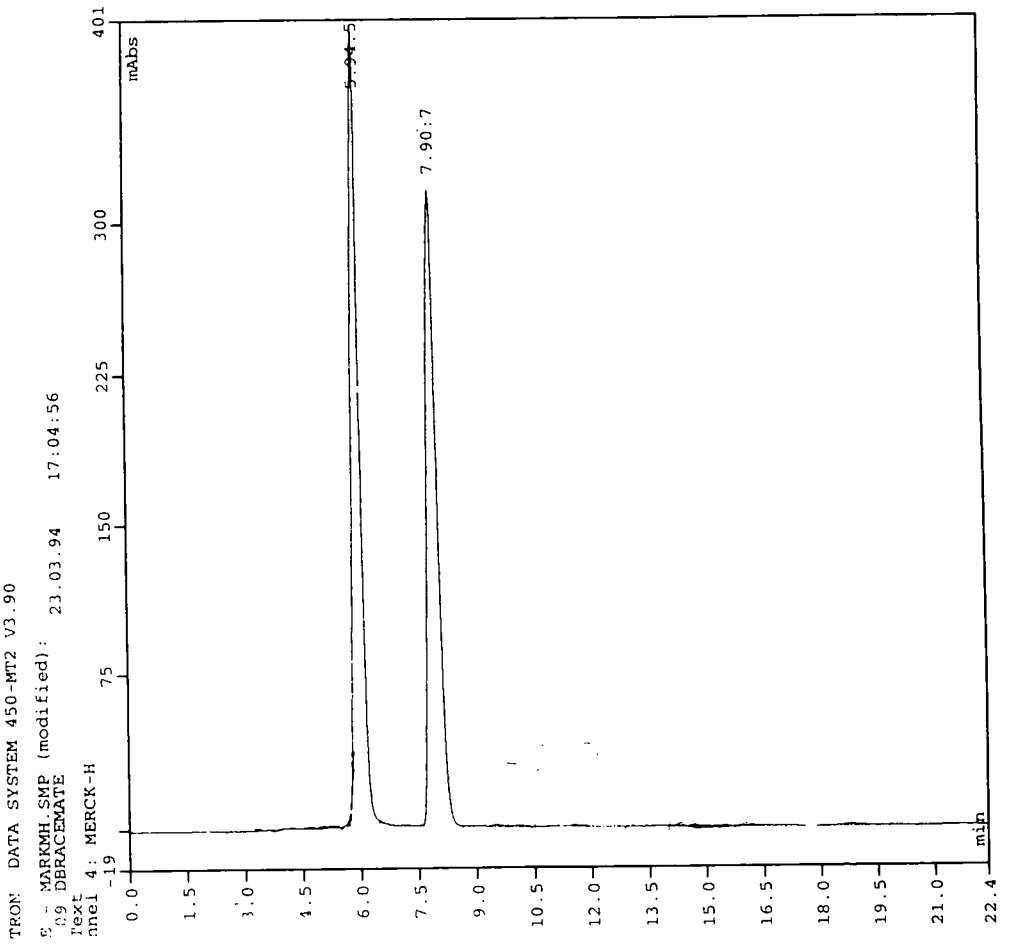


Figure 41. Chiral HPLC of (±)-2-(diphenyl)methylpyrrolidine (168)

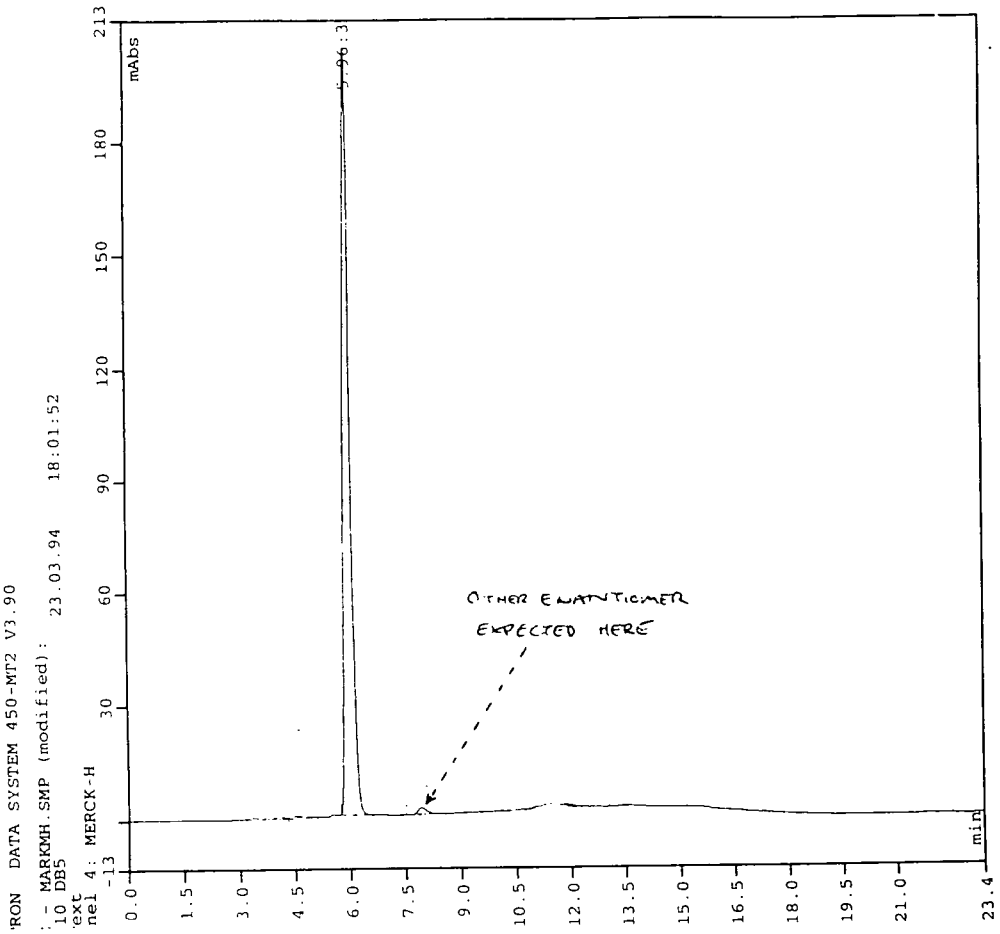


Figure 42. Chiral HPLC of (2S)-(diphenyl)methylpyrrolidine (168)

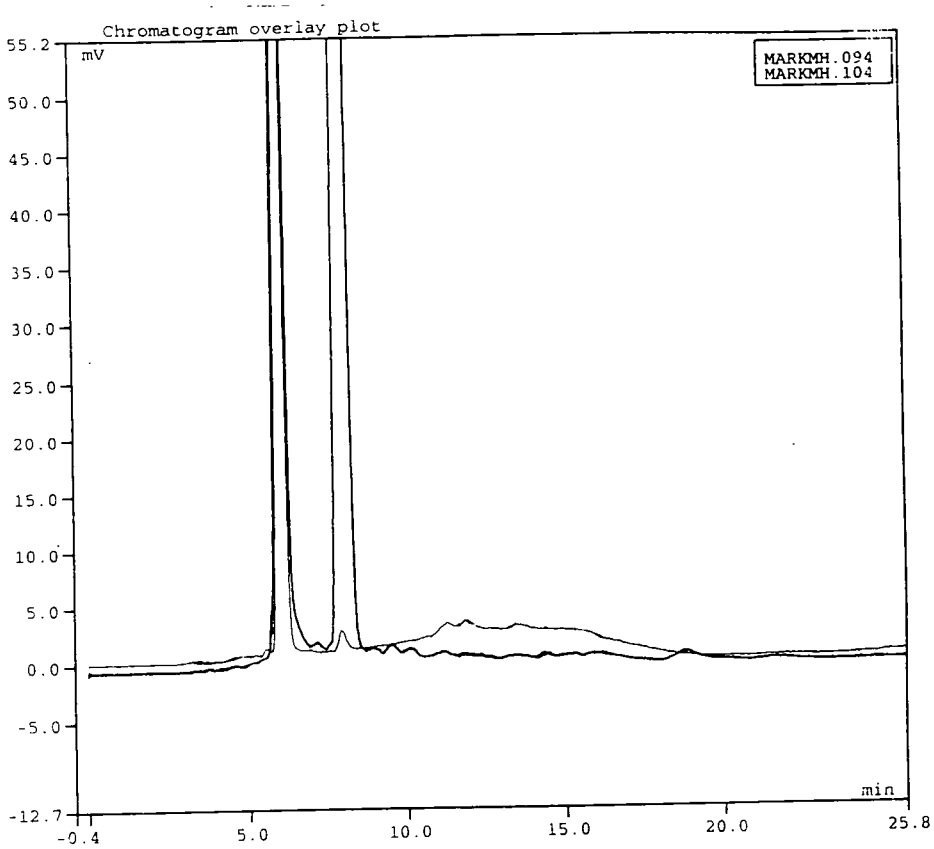
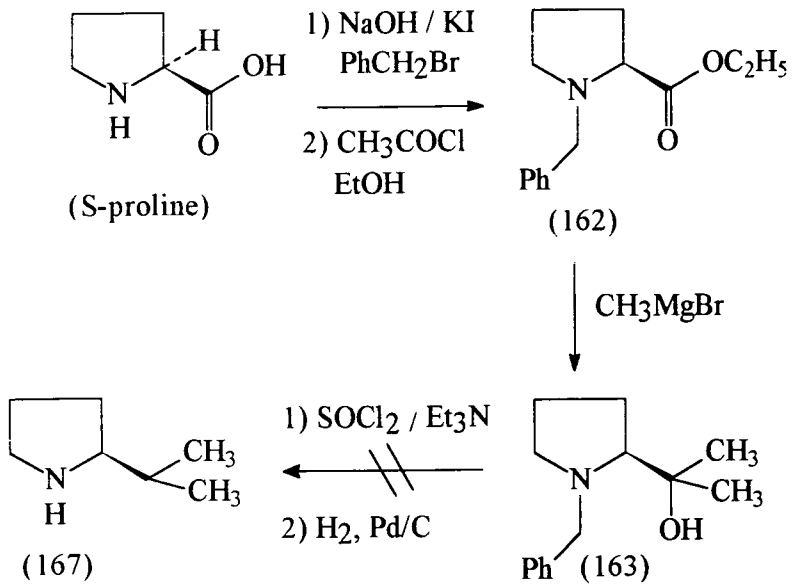


Figure 43. Overlay of (±)-2-(diphenyl)methylpyrrolidine on (2S)-(diphenyl)methylpyrrolidine (168)

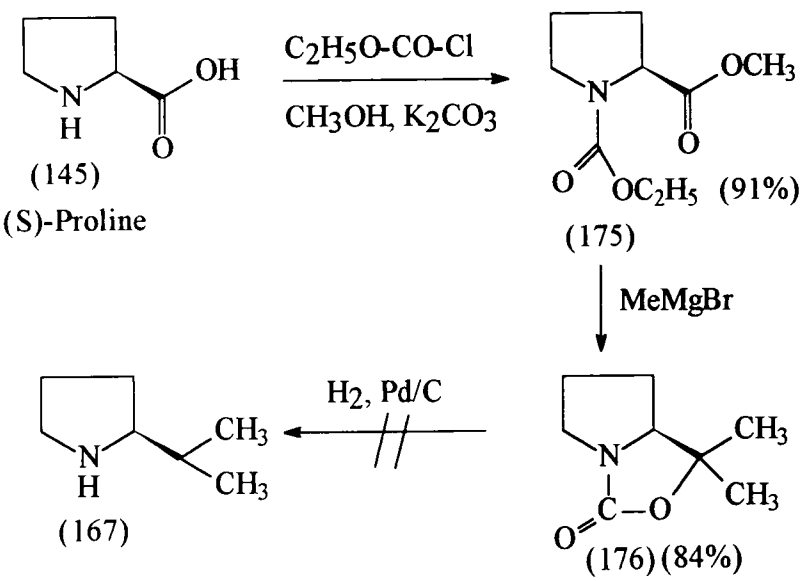
5.4.3 Synthesis of (S)-2-(1-methyl)ethylpyrrolidine

Preparation (2S)-(1-methyl)ethylpyrrolidine (167) has been reported by the synthetic scheme shown below (Scheme 98).[213] Repetition of this route gave products in low yields and the final stage of the synthesis did not work in our hands under the conditions stated.



Scheme 98

Attempts to prepare (2S)-(1-methyl)ethylpyrrolidine (167) in a similar way to (2S)-(diphenyl)methylpyrrolidine (168) (Scheme 99) proved unsuccessful. Hydrogenenolytic removal of CO_2 from the cyclic intermediate (5S)-[3.3.0]-1-aza-2-oxo-3-oxa-4,4-dimethyl-bicyclooctane (176) did not work and a range of other hydrogenation procedures were attempted, [a) Pd /C, H_2.[213] b) Pd / NaOH, H_2.[215] c) PtO_2, H_2.[216] d) Pd / C HCOOH,[217]] but these failed to give the required free amine.



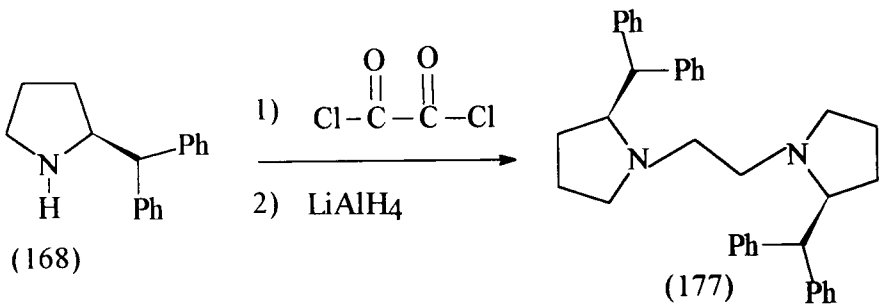
Scheme 99

This is presumably due to the methyl groups being unable to stabilise an intermediate radical and promote homolytic cleavage, unlike the previous case with two phenyl groups.

5.4.4 C_2 symmetric analogues of (2S)-(diphenyl)methyl pyrrolidine

In order to obtain new C_2 symmetric ligands which could potentially be used as catalysts in asymmetric reactions, two novel diamines were synthesised based on (2S)-(diphenyl)methylpyrrolidine (168). These amines consist of two (2S)-(diphenyl) methylpyrrolidine units bridged by a C_2-ethylene or a C_3-propyl chain.

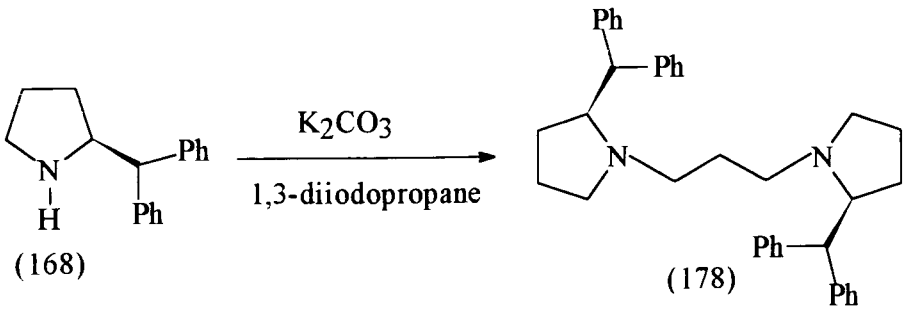
The preparation of diamine N,N'-1,2-ethane-bis((2S)-(diphenyl)methylpyrrolidine) (177) was achieved by a two stage synthesis.[212,228] In the first instance the free amine (168) was treated with 0.5 equivalents of oxalyl chloride to afford a 1,2-dicarbonyl bridged intermediate. Without purification this intermediate was reduced with an excess of lithium aluminium hydride [228] to liberate the diamine N,N'-1,2-ethane-bis((2S)-(diphenyl)methylpyrrolidine) (177) in (54 %) yield (Scheme 100).



Scheme 100

The integrity of this new diamine (177), has been confirmed by high resolution mass spectroscopy, ^{1}H-^{1}H COSY and HETCOR NMR analysis (Figure 44 and 45), as well as other routine analytical techniques.

The preparation of diamine N,N'-1,3-propane-bis((2S)-(diphenyl)methylpyrrolidine) (178) was achieved in a one pot reaction by reacting (2S)-(diphenyl)methylpyrrolidine (168) with potassium carbonate and 1,3-diiodopropane (Scheme 101).[228] The overall yield of this reaction was (92%). ^{1}H-^{1}H COSY NMR (Figure 46) and high resolution mass spectroscopy have confirmed the integrity of this new compound.



Scheme 101

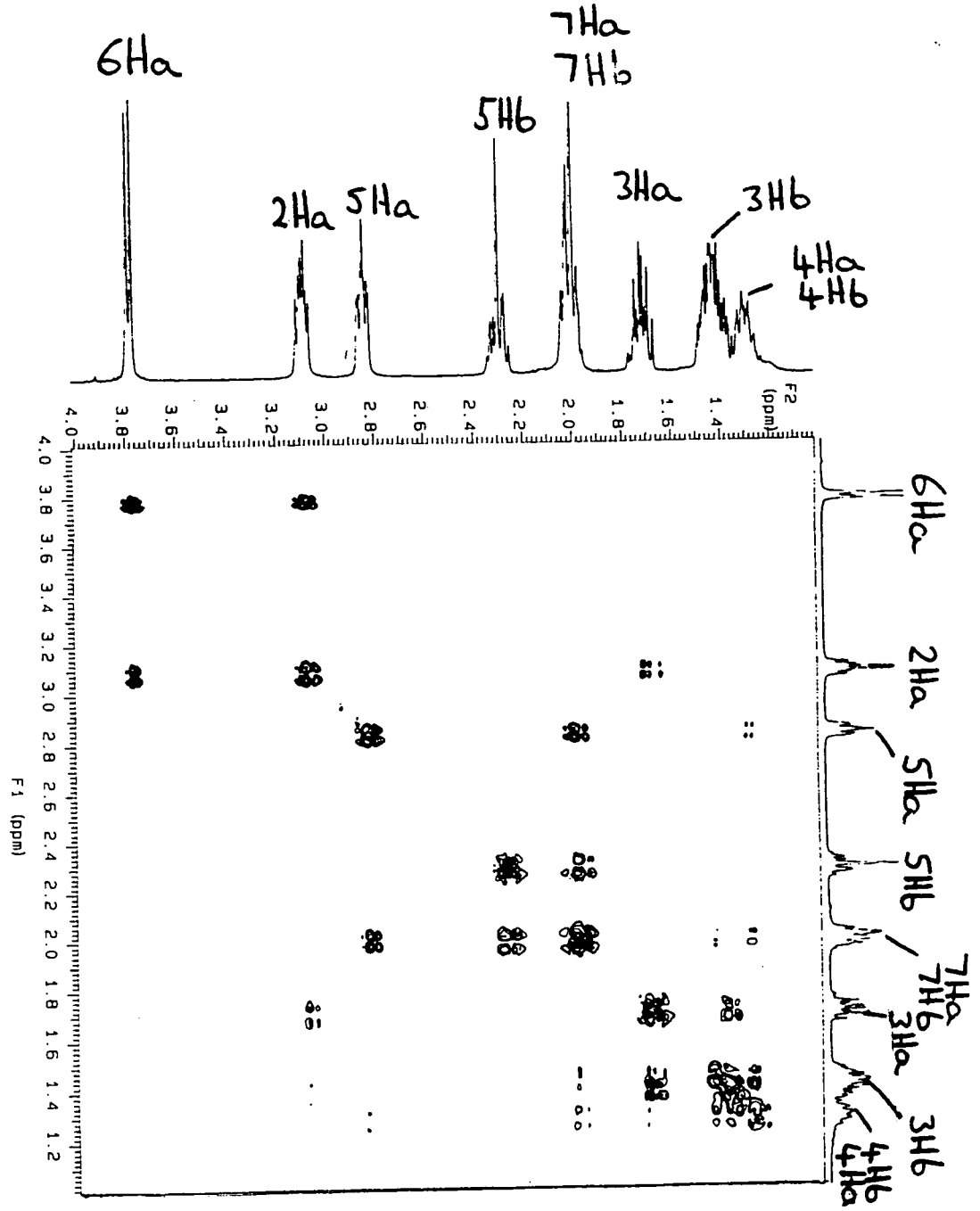


Figure 44. ^1H-^1H COSY of N,N'-1,2-ethane-bis((2S)-(diphenyl)methyl pyrrolidine) (177)

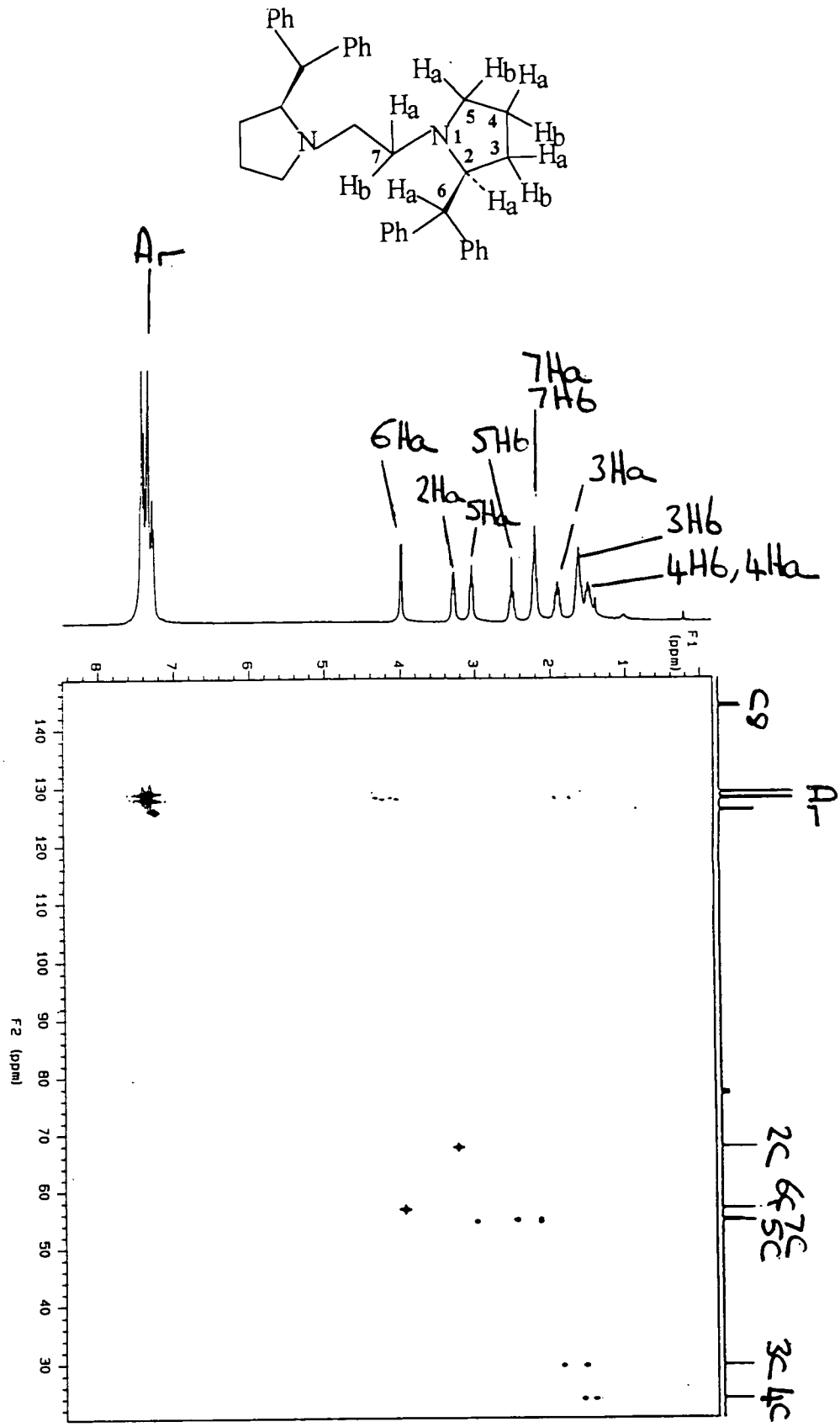


Figure 45. ^{1}H-^{13}C HETCOR of N,N'-1,2-ethane-bis((2S)-(diphenyl)methyl pyrrolidine) (177)

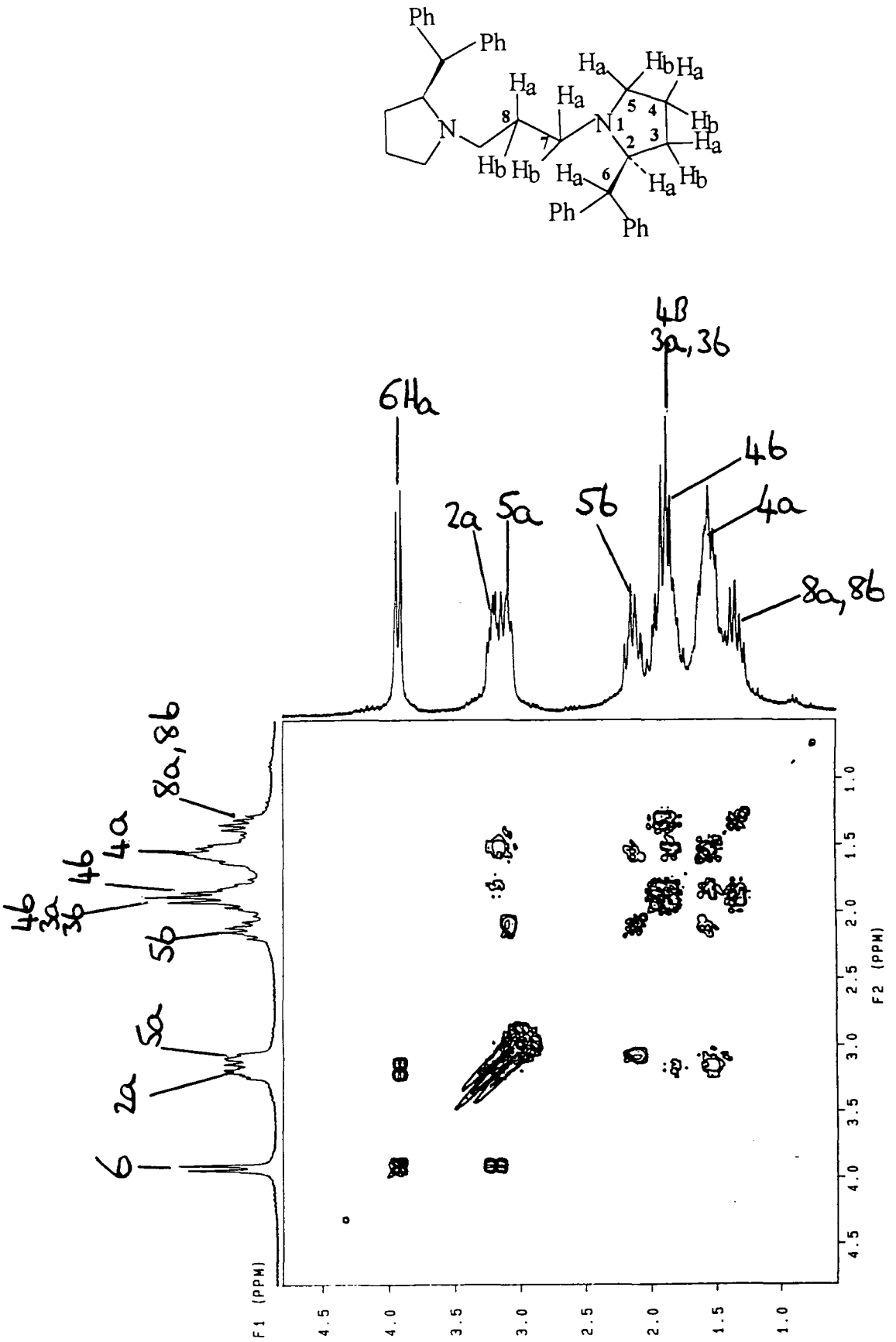


Figure 46. ^{1}H-^{1}H COSY of N,N'-1,3-propane-bis((2S)-(diphenyl)methylpyrrolidine) (178)

5.4.5 **Conclusions**

The free amine (2S)-(diphenyl)methylpyrrolidine (168) was finally synthesised by hydrogenation of (5S)-[3.3.0]-1-aza-2-oxo-3-oxa-4,4-diphenyl-bicyclooctane (173). Synthesis of amine (168) by this route is novel and this procedure has been successfully carried out on a 100g scale. Two novel C_2 symmetric diamines N,N'-1,2-ethane-bis((2S)-(diphenyl)methyl pyrrolidine) (177) and N,N'-1,3-propane-bis((2S)-(diphenyl) methylpyrrolidine) (178) have also been prepared by coupling two (2S)-(diphenyl)methylpyrrolidine units together. The prospect of finding a use for these amines as ligands for asymmetric synthesis is exciting. Initial studies on the effectiveness of the amines as ligands in osmium catalysed asymmetric dehydroxylation reactions, and also asymmetric reactions of arylmagnesium bromides with aldehydes have been carried out and are discussed later in this chapter.

The syntheses of homochiral pyrrolidine ligands using the conditions stated by Enders *et al*, [213] proved more difficult than expected. Methylation of the hydroxyl group in N-benzyl-(2S)-(α-hydroxy-α,α-diphenyl)methylpyrrolidine (164) proved particularly difficult, and could not be repeated in the yields stated by Enders *et al.*[213] Removal of the N-benzyl protecting group in N-benzyl-(2S)-(α-methoxy-α,α-diphenyl)methylpyrrolidine (166) could not be accomplished in our hands. A range of hydrogenation catalysts were tried, including Pealman's catalyst (Pd /NaOH H_2),[215] which is the catalyst of choice for the cleavage of N-benzyl groups, but all of these failed to achieve this transformation.

Attempts to prepare (2S)-(diphenyl)methylpyrrolidine (168) were also unsuccessful using the synthetic route reported by Enders *et al.*[213] Removal of the hydroxyl group in (2S)-(α-hydroxy-α,α-diphenyl)methylpyrrolidine (154) was attempted using a number of deoxygenation procedures but these also failed in our hands.

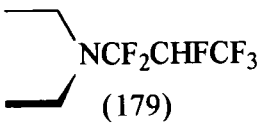
CHAPTER 5

Section B

5.5 Development of nucleophilic fluorinating reagents based on (2S)-(diphenyl)methylpyrrolidine

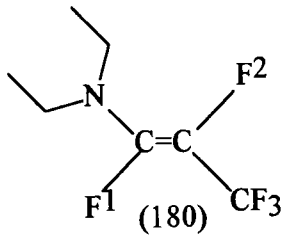
5.5.1 Ishikawa's reagent and its reactions with secondary alcohols

The preparation of Ishikawa's reagent (179) and (180) was repeated to gain experience in the handling and use of hexafluoropropene. This reagent is a colourless liquid and was found to be shelf stable for months when stored in polyethylene containers at 0°C. Ishikawa's reagents exists as a mixture of difluoroalkamine (179) and α-fluoroenamine (180) in a ratio of (1.6 : 1.0) respectively, as shown below (Figure 47). ^{19}F NMR (Figure 48) clearly shows these two components and they can be assigned in the following manner.



(179)

δ -75.26 = CF_3
δ - 83.45, - 88.95 = AB system CF_2
δ - 207.43 = CHF



(180)

δ - 63.73 = CF_3
δ - 119.10 = F^1
δ - 198.74 = F^2

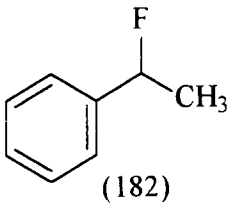
Figure 47

Ishikawa's reagent was found by us to react readily with a range of secondary alcohols replacing the hydroxyl group with fluorine (Table 12).

Substrate R	Reaction conditions, Product % conversion Solv	Temp/°C	Time/h	R-F
$PhCH(OH)CO_2Me$	Et_2O	r.t	24	55
$PhCH(OH)CH_3$	Et_2O	r.t	24	25
$PhCH_2CH(OH)(CH2)_2CH_3$	Et_2O	r.t	24	73

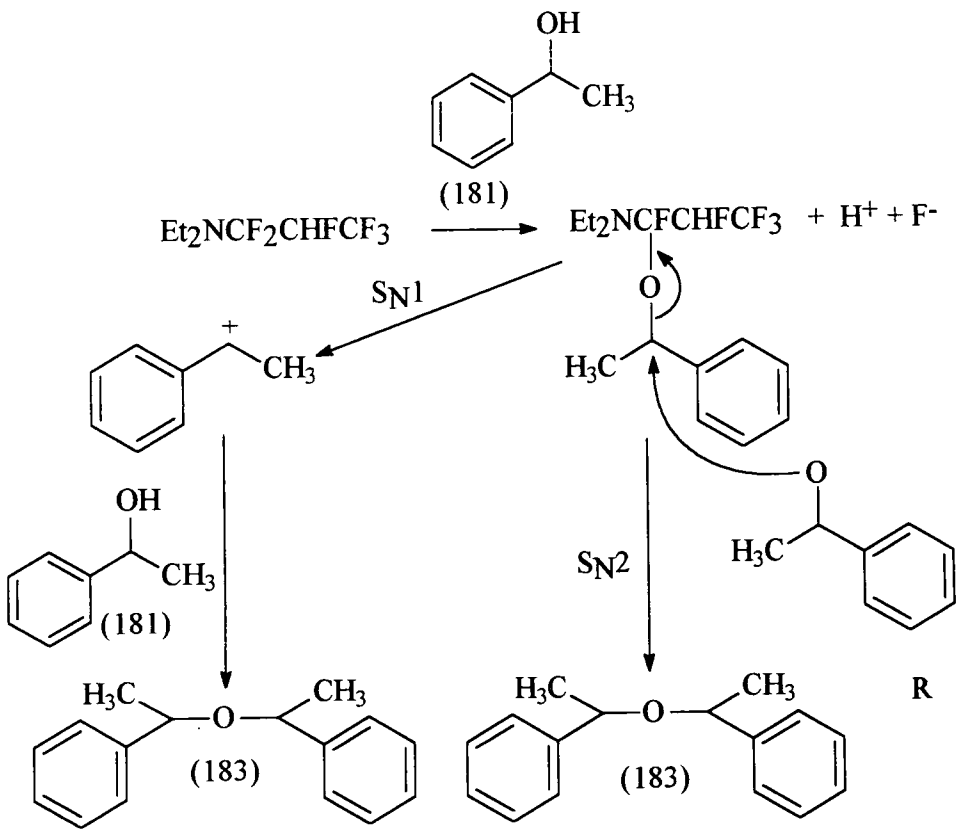
Table 12. Fluorination of secondary alcohols with Ishikawa's reagent (179) & (180)

Reaction of 1-phenylethanol (181) with Ishikawa's reagent gave a 25% conversion to the fluorinated product, 1-fluoro-1-phenylethane (182).



(182)

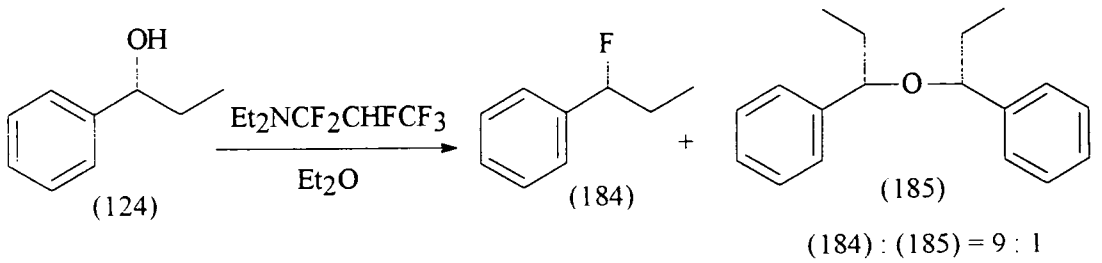
However the major product generated was the bis-(-1-phenylethyl)ether (183), as a mixture of three stereoisomers. ^1H NMR of bis-(1-phenylethyl)ether (183) showed a diastereomeric ratio of (1:1) (Figure 49). Formation of this bis-(1-diphenylethyl)ether can be envisaged by the following rationale (Scheme 102).



Scheme 102.

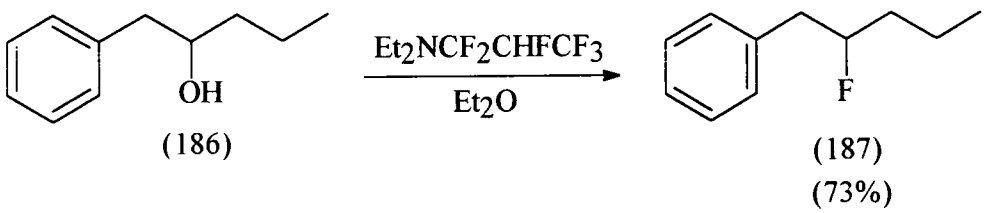
This mechanism was probed for its relative S_N1 and S_N2 character using optically pure (R)-(+)-1-phenylethanol (181) as a starting material. ^1H NMR of the resultant ether (183) showed the presence of two diastereomers, but now in a ratio of (2:1) (Figure 50). If an S_N2 process is followed then only one diastereomer is expected, with an absolute configuration of (S,R) (*meso*). Since 33% of the diastereomer, presumably with the (R,R) configuration, is observed, it is clear that a significant amount of S_N1 substitution is occuring.

Increasing the length of the alkyl chain length by using 1-phenylpropan-1-ol (124) led to a change in the ratios of fluorinated and bis ether products. It was found that 1-fluoro-1-phenylpropane (184) was formed in preference to the bis (1-phenyl propyl)ether (185) in a 9:1 ratio, as determined by GC/MS (Scheme 103).



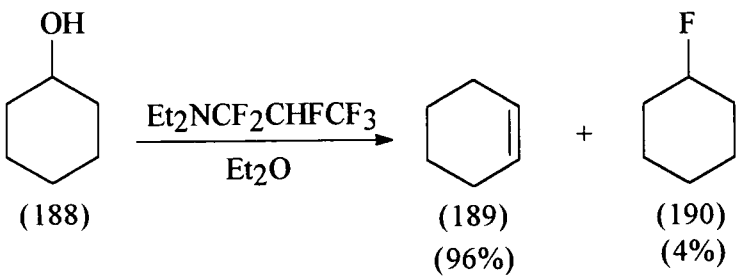
Scheme 103. (ratios of products determined by GC/MS)

1-Phenylpentan-2-ol (186), however, reacted with Ishikawa's reagent to give 2-fluoro-1-phenylpentane (187) in 73% isolated yield (Scheme 104), with none of the bis ether being seen by GC/MS analysis.



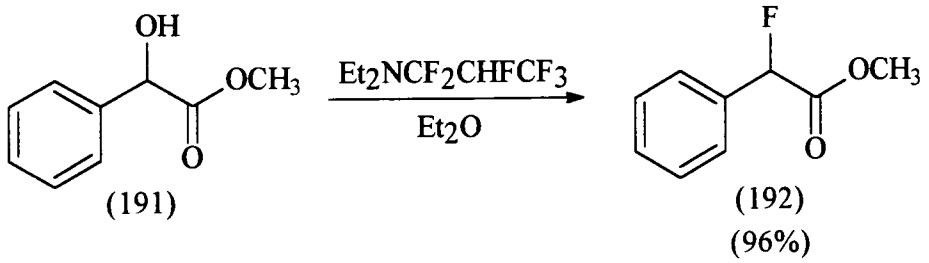
Scheme 104.

The reaction of cyclohexanol (188) with Ishikawa's reagent gave predominantly the elimination product, cyclohexene (189) (Scheme 105). Fluorocyclohexane (190) was only produced in 4% yield as determined by GC/MS.



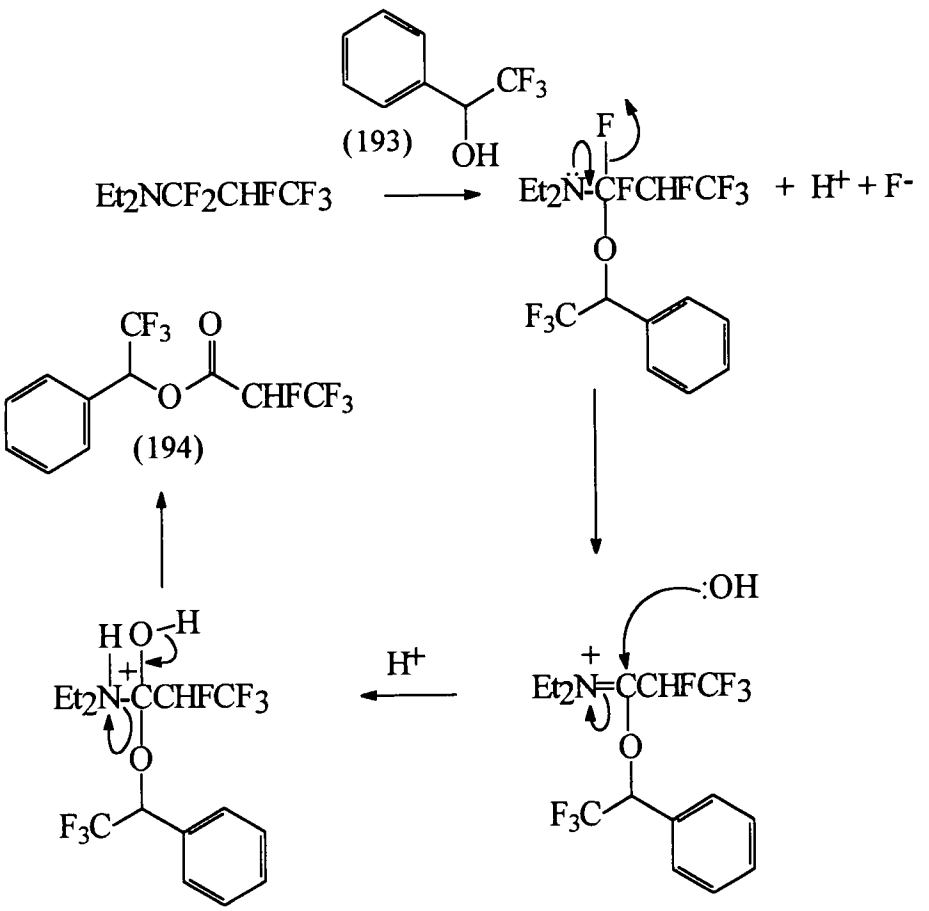
Scheme 105. (ratios of products determined by GC/MS)

Methyl mandelate (191) reacted with Ishikawa's reagent to give 55% of the isolated fluorinated product methyl 2-fluorophenylacetate (192) (Scheme 106).



Scheme 107.

It was envisaged that if 2,2,2-trifluoro-1-phenylethanol (193) was used instead of 1-phenylethanol (181) then substitution of the hydroxyl group by fluorine would be preferred over the formation of ethers, due to the inductive effect of the CF_3 reducing the nucleophilicity of the hydroxyl group. In the event the reaction of 2,2,2-trifluoro-1-phenylethanol (193) with Ishikawa's reagent gave none of the expected fluorinated product. The only product was the ester 2,2,2-trifluoro-1-phenylethyl 2',3',3',3'-tetrafluoropropionate (194). The anticipated S_N2 process may have been prevented in this case due to the steric and possibly electrostatic influences of the CF_3 group. Formation of ester (194) can however be rationalised by the process shown below (Scheme 108).



Scheme 108.

^1H NMR (Figure 51) clearly indicates that ester (194) is a mixture of diastereomers, as expected. Two non-superimposable doublet of quartets are evident at δ 5.41 and 5.15 ppm in a ratio of 1:1, due to coupling between the CHF and CF_3 groups. The proton next to the oxygen linker is seen at δ 6.28 ppm as two overlapping non-superimposable quartets, also in a ratio of 1: 1.

The rection of Ishikawa's reagent with the above secondary alcohols is summarised below (Table 13).

		Product Yield %		
Substrate	**Solvent**	**R-F**	**Other Products**	**R_2O**
PhCH(OH)Me	Et_2O	25% (b) (182)	-	75 (183)
PhCH(OH)Et	Et_2O	25% (a) (184)	-	10 (185)
cyclohexanol	Et_2O	4% (a) (190)	94% (189) (a)	-
$PHCH_2CH(OH)Et$	Et_2O	73% (c) (187)	-	-
$PHCH(OH)CO_2CH_3$	Et_2O	55% (c) (192)	-	-
$PhCH(OH)CF_3$	Et_2O	-	100% (194) (c)	-

Table 13. Fluorination of secondary and tertiary-alcohols. a) GC/MS yields, b) ^1H NMR yields. c) Isolated yields

Table 13 clearly shows that the R group attached to the hydroxyl functional group determines which products are formed during the reaction. Electronic effects also have a bearing on the reaction mechanism and strongly electron withdrawing R groups favour the formation of products such as (194). A methyl R group favours the formation of bis ethers such as (183) and larger R groups lead predominantly to the required fluorinated products R-F.

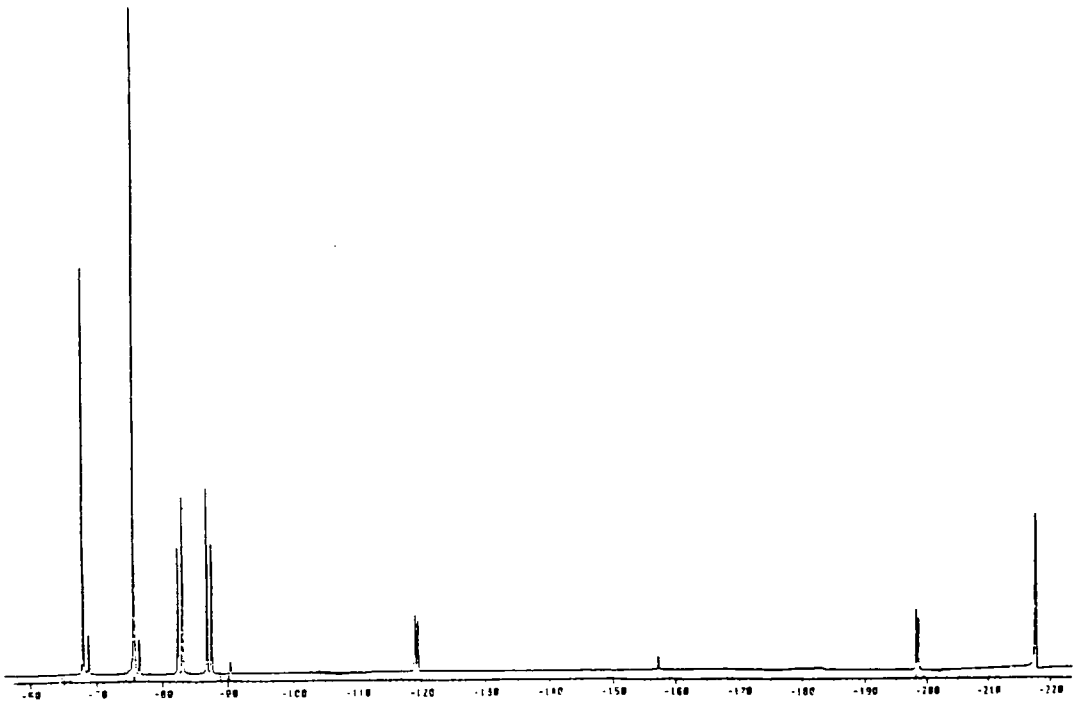


Figure 48. ^{19}F NMR of Ishikawa's reagent (179) & (180)

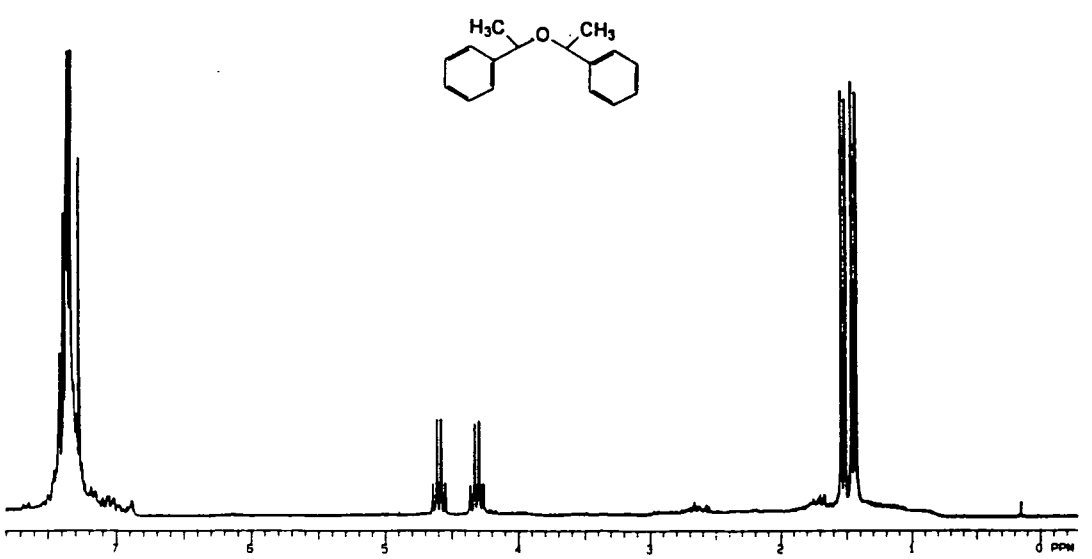


Figure 49. ^{1}H NMR of bis-(1-phenylethyl)ether (183)

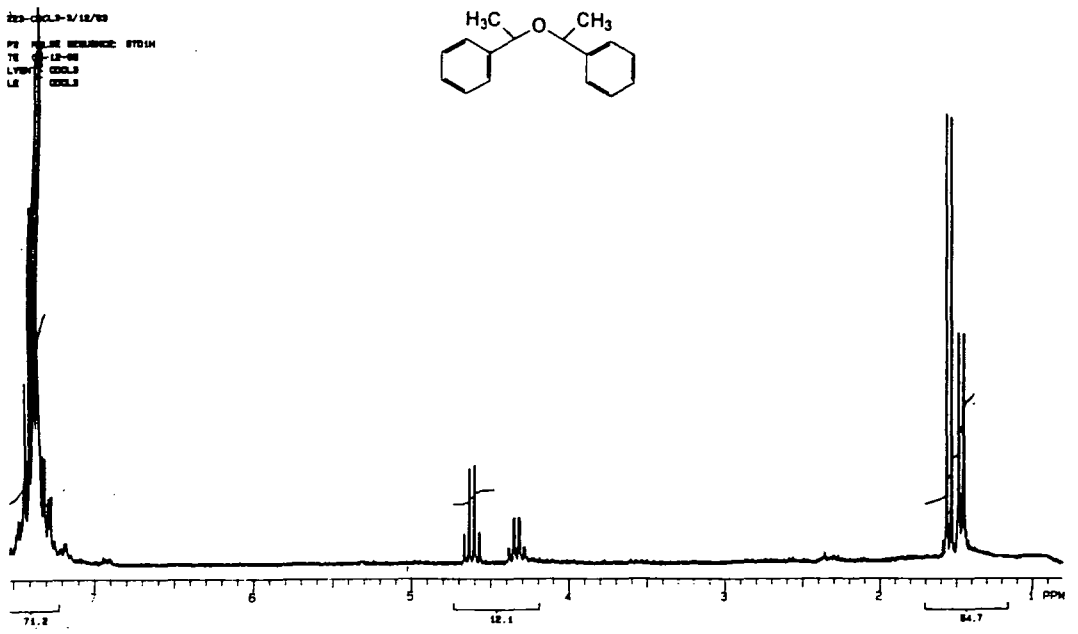


Figure 50. ^{1}H NMR of bis-(1-phenylethyl)ether (183) from (R)-1-phenylethanol

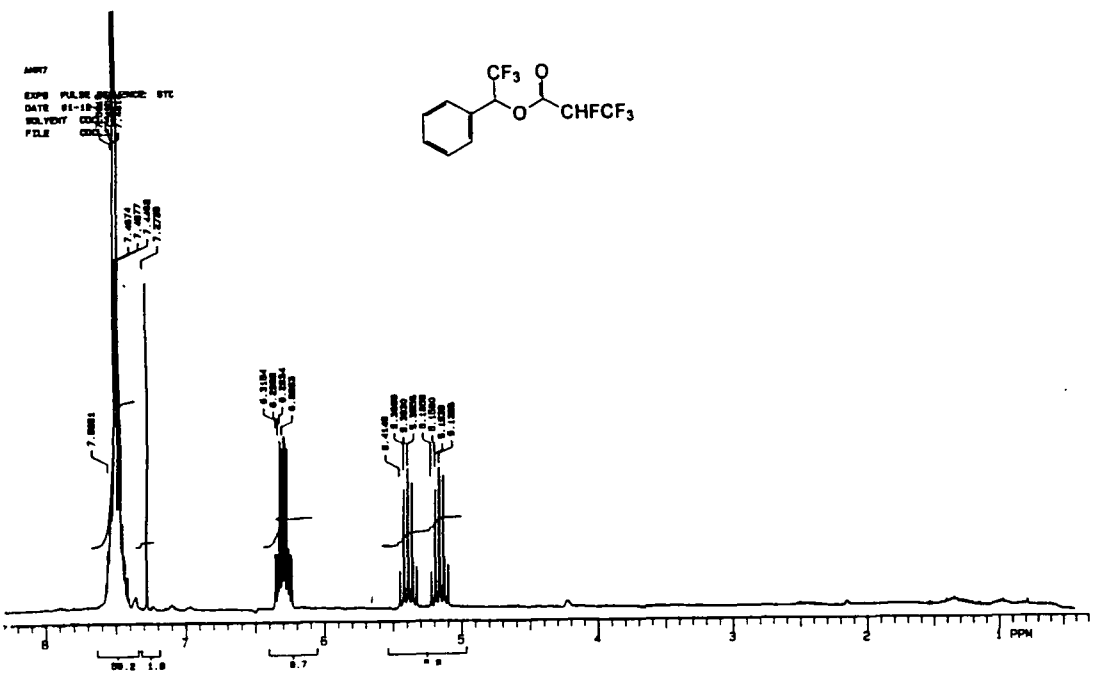
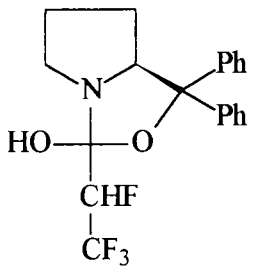


Figure 51. ^{1}H NMR of 2,2,2-trifluoro-1-phenylethyl 2',3',3',3'-tetrafluoropropionate (194)

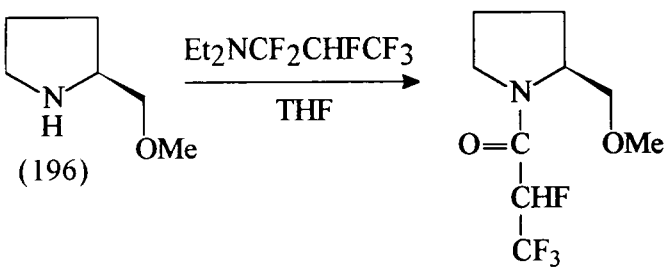
5.5.2 Homochiral pyrrolidine analogues of Ishikawa's reagent

(2S)-(α-Hydroxy-α,α-diphenyl)methylpyrrolidine (154) prepared in section (A) was treated with hexafluoropropene under anhydrous conditions. ^{19}F NMR of the resultant product showed the presence of only a CF_3 and a CHF group. The absence of the anticipated CF_2 group can be rationalised by cyclisation of the free hydroxyl group onto the CF_2 group, resulting in loss of fluoride. Rapid hydrolysis then results in structure (195) below. This structure was confirmed by mass spectroscopy and infrared analysis, which clearly show the OH stretching frequency. All other analytical data are consistent with this conclusion.



(195)

Clearly protection of the hydroxyl group as a methyl ether should prevent cyclisation on to the CF_2 group. Accordingly (2S)-(methoxymethyl)pyrrolidine (196) [91] was treated with hexafluoropropene under anhydrous conditions (Scheme 109). ^{19}F NMR showed the presence of only CHF and CF_3 groups. Since the methoxyl group cannot cyclise, rapid hydrolysis of the CF_2 group must have taken place. ^{1}H NMR, infrared spectroscopy and mass spectroscopy analysis are all consistent with the amine (197) shown below.



(196) (197)

Scheme 109.

(2S)-(Methoxymethyl)pyrrolidine (196) [91] was also treated with hexafluoropropene under anhydrous conditions and then immediately reacted with a range of secondary alcohols, but this led to the recovery of the unreacted alcohols in all cases. Pyrrolidine and piperidine which do not contain oxygen atoms have been reacted with hexafluoropropene to generate stable analogues of Ishikawa's reagent.[229] It is evident therefore that the inclusion of oxygen destabilises the CF_2 group, making it very

susceptible to hydrolysis. (2S)-(diphenyl)methylpyrrolidine (168) prepared in section (A), and containing no oxygen was reacted with hexafluoropropene (HFP) under anhydrous conditions. The difluoroalkamine, (2S)-(diphenyl)methylpyrrolidine-N-1,1,2,3,3,3-hexa fluoropropane (198) and α-fluoroenamine (199) showed peaks in the ^{19}F NMR (Figure 52) which are consistent with those obtained for Ishikawa's reagent (Figure 48). In this case generation of the required adduct was not problematic.

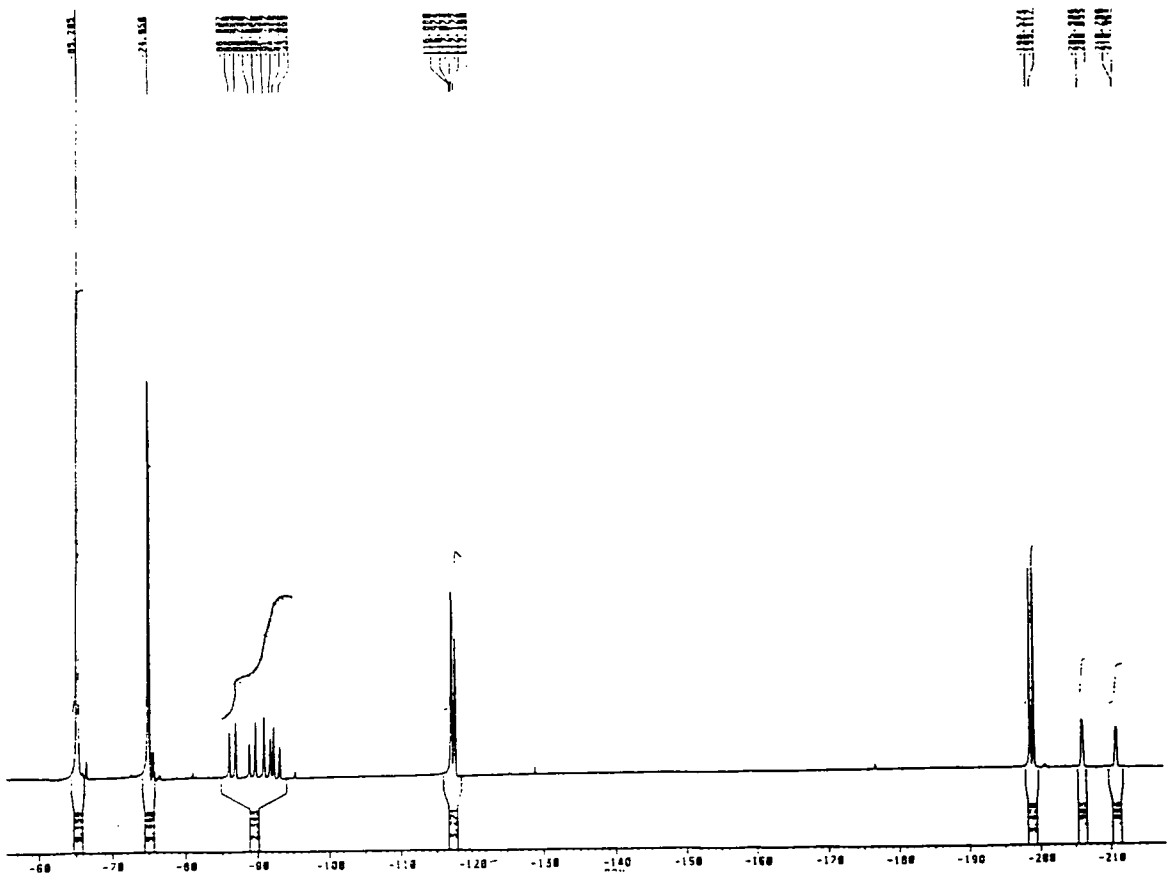
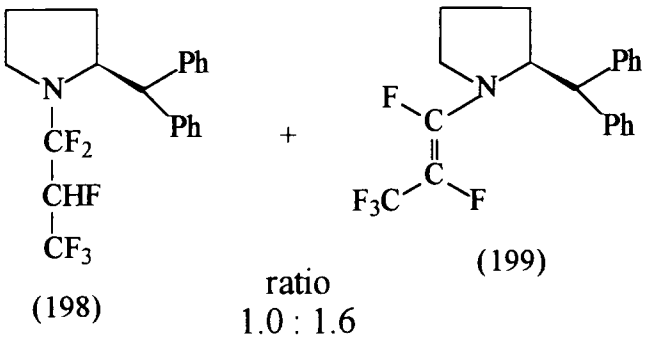


Figure 52. ^{19}F NMR of (2S)-(diphenyl)methylpyrrolidine-N-1,1,2,3,3,3-hexafluoro propane (198) & α-fluoroenamine (199)

The ratio of difluoroalkamine (198) to α-fluoroenamine (199) found in this reaction was found to be (1.0 : 1.6) in favour of the α-fluoroenamine (199), the reverse of that found when hexafluoropropene is reacted with diethylamine, generating Ishikawa's reagent.



(198) ratio 1.0 : 1.6 (199)

With this homochiral analogue of Ishikawa's reagent in hand attempts were made to assess its capacity to effect a kinetic resolution in the fluorodehydroxylation of secondary alcohols. For example reaction of 1-phenylethanol (181) with 0.5 equivalents of (198 & 199) gave 1-fluoro-1-phenylethane (182) in 15% yield. The predominant product was the bis(-1-phenylethyl)ether (183) as expected. Determination of the enantiomeric excess of the fluorinated product was attempted by chiral GC, but the enantiomers were inseparable. Conversion of the residual alcohol (181) to its acetate derivative and analysis by chiral G.C using a BTA column [230] established the residual alcohol as racemic.

Fluorination of (±) methyl mandelate (191) using (198 & 199) gave methyl 2-fluorophenylacetate (192) in (6%) yield. Analysis of the fluorinated product by G.C using a BTA column showed it to be racemic. Conversion of the residual alcohol to its acetate derivative and analysis by chiral G.C using a BTA column also established the residual alcohol as racemic.

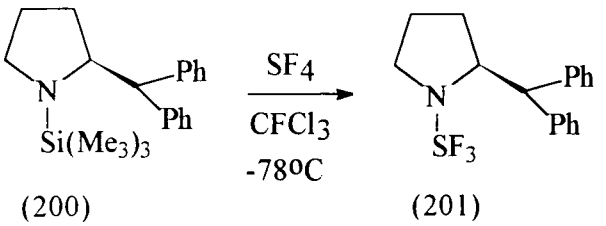
The fluorination of (±)-1-phenyl-2-pentanol (186) by (197 & 198) was unsuccessful and only starting material was recovered from the reaction. This may be attributed to steric factors caused by the longer alkyl chain attached to the hydroxyl moiety.

It was anticipated that the fluorination yields might increase by adding an external F^- source such as tetrabutylammonium fluoride (TBAF), since the rate of an S_N2 reaction is dependant on both the concentration of the substrate and the nucleophile (F^-). However, adding TBAF had a detrimental effect on the reactions and only unreacted starting materials were recovered.

5.5.3 **Homochiral pyrrolidine analogues of DAST**

Extending the strategy above, the homochiral pyrrolidine (2S)-(diphenyl)methyl pyrrolidine (168) was used to prepare a novel DAST analogue. Preparation of the homochiral DAST reagent (2S)-(diphenyl)methylpyrrolidine-N-sulphur trifluoride (201)

was achieved by treatment of (2S)-(diphenyl)methylpyrrolidine-N-trimethylsilane (200) with sulphur tetrafluoride (Scheme 110).



(200) (201)

Scheme 110

^{19}F NMR of the reaction product confirmed that the SF_3 group had been incorporated onto the pyrrolidine nitrogen. DAST (38) gives a broad and featureless peak at +35ppm in the ^{19}F NMR spectrum. A similar broad and featureless peak was also seen for the prepared (2S)-(diphenyl)methylpyrrolidine-N-sulphur trifluoride (201). The hygroscopic nature of compound has made critical analysis difficult. Mass spectroscopy did not give the required molecular ion, but did show a mass fragment of 306 (M+H) corresponding to the amine plus a SF_2 group. This reagent, unlike DAST could not be purified by distillation because of its highly viscous nature and high boiling point.

Reaction of 0.5 equivalents of (2S)-(diphenyl)methylpyrrolidine-N-sulphur trifluoride (201) with (±) methyl mandelate (191) gave methyl 2-fluorophenylacetate (192) in (22%) yield. It was clearly of interest to establish if reagent (201) had selectively fluorinated one of the two enantiomers of (±) methyl mandelate (191), effectively achieving a kinetic resolution. The ability of (201) to act as an asymmetric fluorinating reagent was assessed by ^1H NMR of methyl 2-fluorophenylacetate (192) in the presence of [Eu(tfc)$_3$]. Resultant splitting patterns in the ^1H NMR spectrum showed the fluorinated product (192) to be racemic. Conversion of the residual alcohol to its acetate derivative and subsequent chiral HPLC using a Chiracel-ODH column[103] showed the alcohol also to be racemic. In methyl mandelate the benzyl group may accommodate a stable carbocation and fluorination may proceed to a large extent by an S_N1 mechanism. The possibility of this was investigated using optically pure (R)-methyl mandelate. If fluorination proceeded solely by an S_N2 process then (S)-methyl 2-fluorophenylacetate (192) should be produced in an optically pure state. ^1H NMR of (S)-methyl 2-fluorophenylacetate (192) in the presence of chiral shifts reagent [Eu(tfc)$_3$] should give a doublet at δ 5.5-5.0 ppm corresponding to the methine proton, $^2J_{HF}$ = 47 Hz. In the event two doublets in a ratio of 2:1 were observed, showing that fluorination of methyl mandelate proceeded by both S_N1 and S_N2 type processes (Figure 53, 54 & 55).

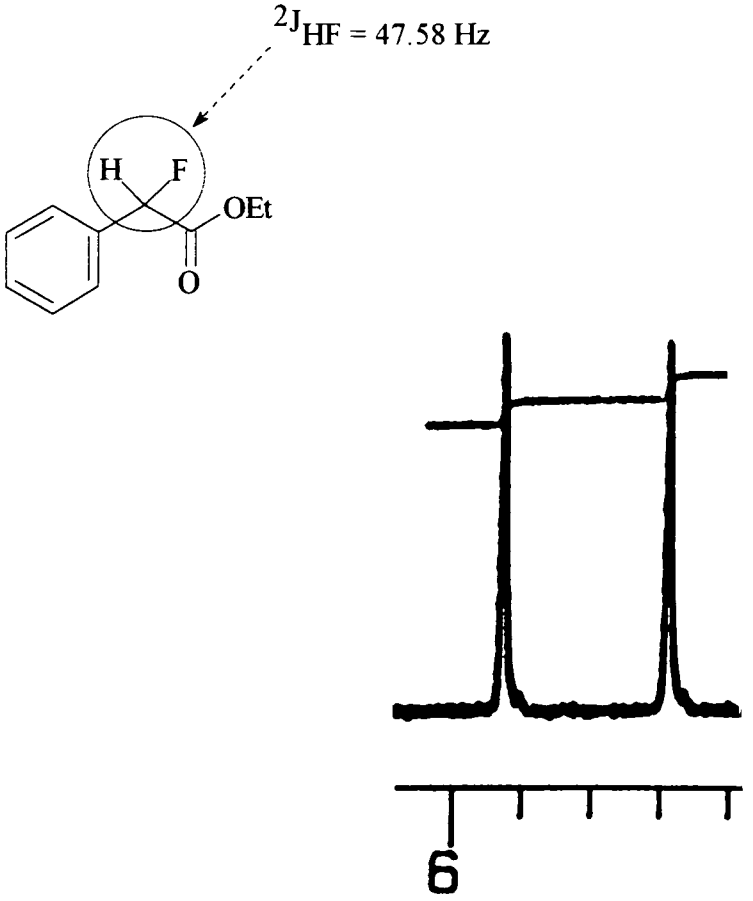


Figure 53. ^1H NMR of (S)-methyl 2-fluorophenylacetate (192) no [Eu(tfc)$_3$] added

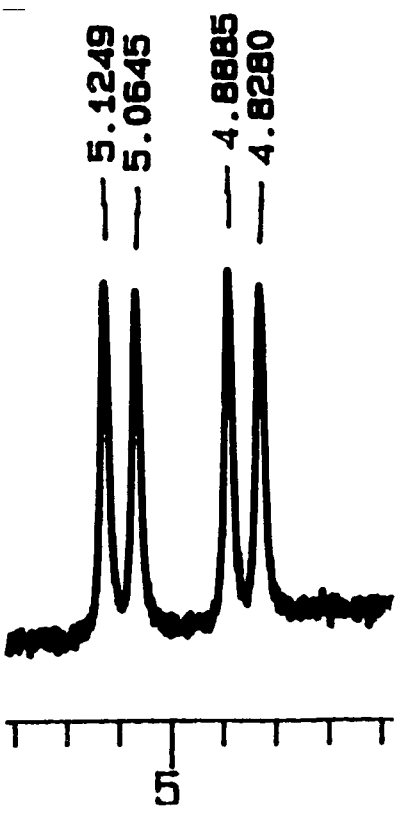


Figure 54. ^1H NMR of (±)-methyl 2-fluorophenylacetate (192) in the presence of [Eu(tfc)$_3$]

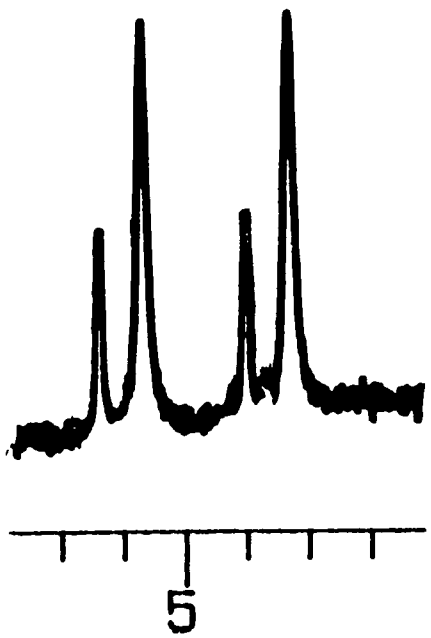
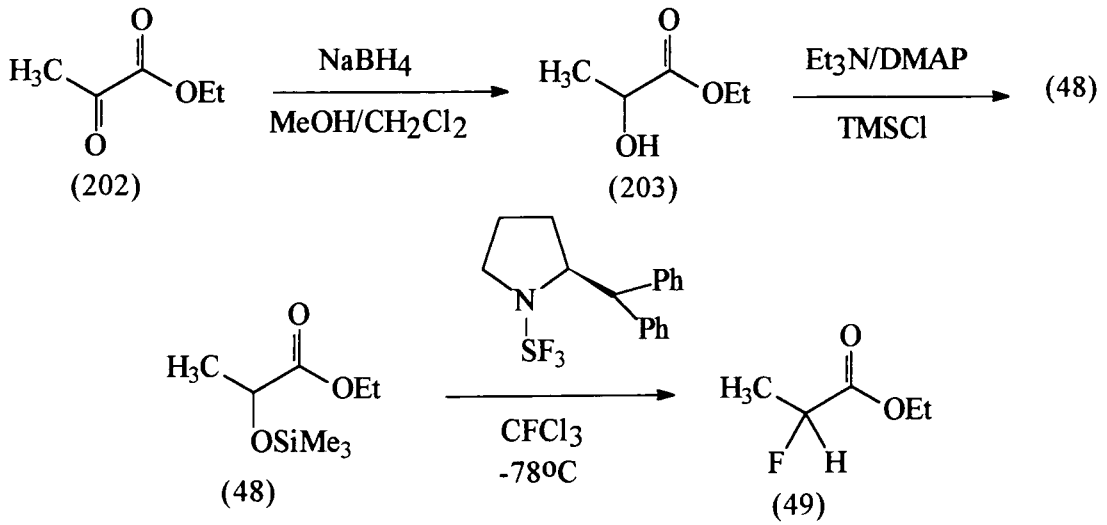


Figure 55. ^{1}H NMR of methyl 2-fluorophenylacetate (192) in the presence of [Eu(tfc)$_3$] produced by reaction of (R)-(-)-methyl mandelate with reagent (201)

In aliphatic systems such as ethyl lactate (203) a stable carbocation is unlikely to occur and hence the fluorination should proceed predominantly by a S_N2 mechanism. This should allow us to assess the true potential of our homochiral fluorinating reagent (201), without the possibility of a competing S_N1 reaction. Ethyl lactate (203) was prepared in racemic form by reduction of ethyl pyruvate (202) with $NaBH_4$. The free hydroxyl group was then converted to its trimethylsilyl ether, ethyl 2-(trimethylsilyloxy) propanoate (48), before reaction with 0.5 equivalents of the homochiral fluorinating reagent, (2S)-diphenylmethylpyrrolidine-N-sulphur trifluoride (201). After 4h at -78°C ethyl 2-fluoropropanoate (49) was recovered in (22%) yield with no evidence of elimination (Scheme 111). ^{19}F NMR of the resultant ethyl 2-fluoropropanoate (49) in the presence of [Eu(tfc)$_3$] established yet again that the fluorinated product was racemic.



(49)

Scheme 111

5.5.4 **Conclusions part B**

Ishikawa's reagent reacts with a wide range of secondary alcohols giving the corresponding fluorinated products in moderate to good yields. In the majority of cases these reactions are accompanied by undesirable side reactions, such as dimerisation or elimination. Mechanistically fluorination occurs by a mixture of S_N1 and S_N2 processes which are dependant on the structure of the substrate alcohol.

Development of an asymmetric fluorinating reagent based on homochiral pyrrolidine analogues of Ishikawa's reagent has proved unsuccessful. Pyrrolidine structures containing pendant oxygen atoms were found to form highly unstable analogues of Ishikawa's reagent, which hydrolysed instantaneously to give amides or cyclised products. Homochiral pyrrolidine ligands devoid of oxygen react with hexafluoro-propene in the same manner as diethylamine, giving mixtures of α-fluoroenamines and difluoroalkyl amines. Reaction of (198 & 199) with secondary alcohols gave racemic fluorinated products. A possible reason for this is the absence of an ordered transition state between the fluorinating reagent and the alcohol, the reagents relying solely on steric constraints to impart chirality.

Development of an asymmetric DAST reagent based on homochiral (2S)-(diphenyl)methylpyrrolidine (168) has also proved unsuccessful. It seems likely that the stereoselectivity achieved using Sampson's (2S)-(methoxymetyl)pyrrolidin-N-sulphur trifluoride (47), (Chapter 1 section 1.6.2.1) is dependant on co-ordination of the methyl ether on to the SF_3 group. Absence of oxygen in reagent (201) may be the reason why asymmetric fluorination was not achieved, even though it has much larger pendant groups.

CHAPTER 5

Section C

5.6 Use of (2S)-(diphenyl)methylpyrrolidine and its C_2 analogues in asymmetric reactions

5.6.1 Homochiral Lithium Amide Base (HCLA)

Under kinetically controlled conditions homochiral lithium amide bases (204), (205), (206) and (207) (Figure 56) have been used in reactions where a symmetrically substituted cyclic, prochiral ketone is converted directly into optically active products via selective removal of one of a pair of enantiotopic protons.[231] For example treatment of *cis* 2,6-dimethylcyclohexanone (208) with a range of HCLA bases, followed by an electrophilic quench with acetic anhydride gave 1-acetoxy-2,6-dimethylcyclohex-1-ene (209) (Scheme 112) in moderate enantiomeric excesses.[231,232,233] as shown below (Table 14).

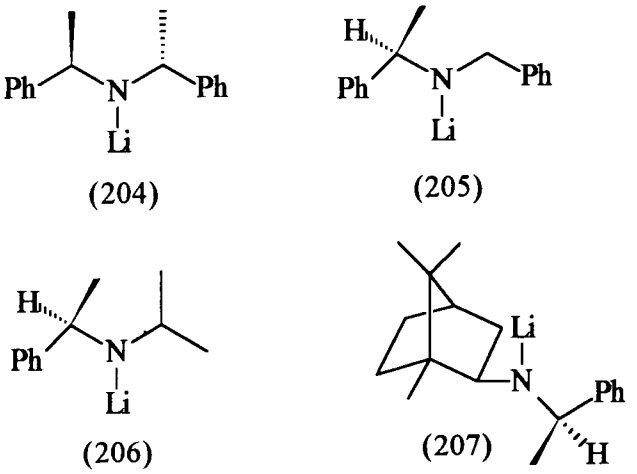
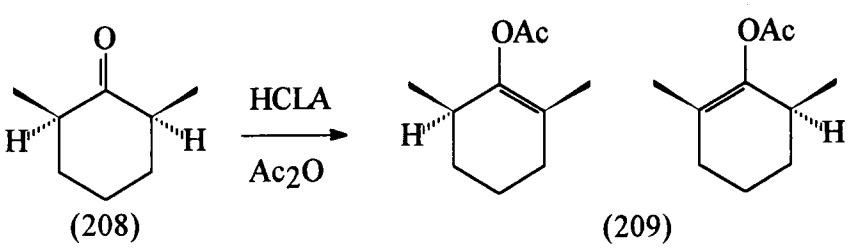


Figure 56. Homochiral lithium amide bases (HCLA)



Scheme 112. Reaction of HCLA with cis 2,6-dimethylcyclohexanone

Base	Yield	%ee	R or S
204	71	43	R
205	75	29	R
206	71	32	S
207	65	65	S

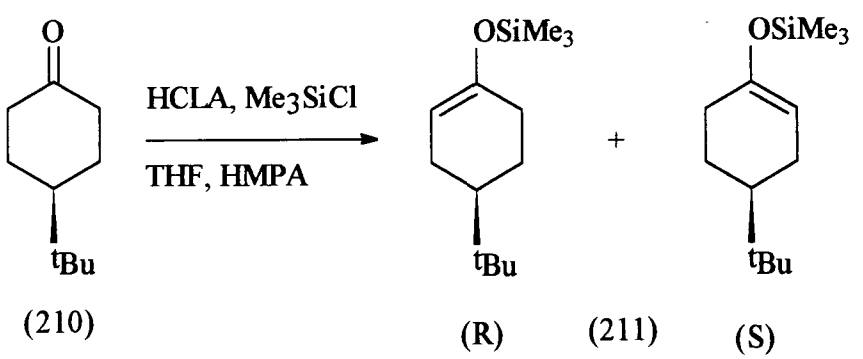
Table 14. % E.e values obtained by reacting HCLA with cis 2,6-dimethylcyclohexanone

5.6.2 (2S)-(Diphenyl)methylpyrrolidine as an HCLA base

It has already been stated that the syntheses of the target homochiral pyrrolidine amines is difficult by literature methods, and hence they have not been tested as HCLA bases.[231] Work already detailed in this Chapter has demonstrated that (2S)-(diphenyl)methylpyrrolidine (168) can be prepared on a large scale with relative ease. The ability of (2S)-(diphenyl)methylpyrrolidine to act as a HCLA base has thus been investigated.

Following a previous protocol [231] *cis*-2,6-dimethylcyclohexanone (207) was treated with LDA and then quenched with acetyl chloride to give 1-acetoxy-2,6-dimethyl cyclohex-1-ene (209). ^{1}H NMR of (209) in the presence of a chiral shift reagent [Eu(tfc)$_3$] induced splitting of the $OCOCH_3$ signal, into two singlets of equal intensity, thus showing the material to be racemic. This initial experiment was repeated using lithiated (2S)-(diphenyl)methylpyrrolidine (168) as the HCLA base and the 1-acetoxy-2,6-dimethylcyclohex-1-ene (209) produced was also shown to be racemic.

Trimethylchlorosilane has been used as an internal quenching agent in the enantioselective deprotonation of other symmetrically substituted cyclohexanones including 4-*tert*-butylcyclohexanone (210) (Scheme 113) below.[231]

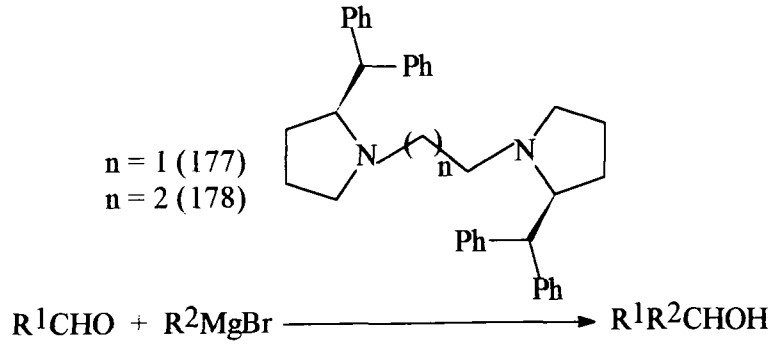


(210) (R) (211) (S)

Scheme 113

Enantiomeric deprotonation of 4-*tert*-butylcyclohexanone (210) was attempted using lithiated (2S)-(diphenyl)methylpyrrolidine (168) as the HCLA base but *in situ* quenching with TMSCl gave none of the anticipated product (211).

5.7 Asymmetric reactions of arylmagnesium bromides with aldehydes mediated by chiral diamine ligand (177) & (178)

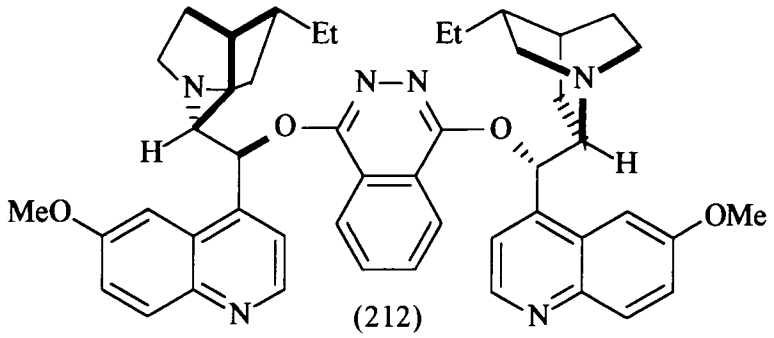


Scheme 114

The reaction of isopropylaldehyde and cyclohexaldehyde (Scheme 114) with phenyl magnesium bromide in the presence of the C_2 symmetric diamines (177) and (178) gave the expected carbinols. These carbinols proved to be racemic, as determined by optical rotation. The possible reason for the lack of asymmetric induction here, may be that, positionally the phenyl groups are so close to the amine groups, that they prevent co-ordination of the pyrrolidine nitrogens with the magnesium atom of the Grignard reagent.

5.8 Asymmetric dihydroxylation reactions mediated by chiral diamine ligand (177) & (178)

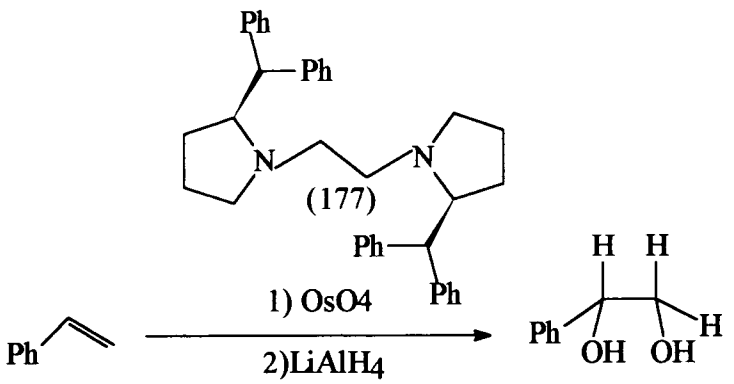
Sharpless *et al.* have developed osmium catalysed asymmetric dihydroxylation reactions in which phthalazine ligands are used in catalytic amounts (1mol% of the amount of olefin).[234] This ligand is commercially available as a ready to use asymmetric dihydroxylation mixture (AD-mix). The ligand $(DHQD)_2$-PHAL (212), used in AD-mix-β is shown below.



(212)

$(DHQD)_2$-PHAL,
Used in AD-Mix-β

As discussed in section 5.2.3 C_2 symmetric diamines consisting of two pyrrolidine rings joined together have been used in stoichiometric amounts to achieve enantiofacial dihydroxylation of olefins. Our newly developed C_2 symmetric diamine (177) and osmium tetroxide have been used stoichiometrically in the dihydroxylation of styrene as shown below (Scheme 115). This reaction was however, unsuccessful with no diol recovered from reaction.



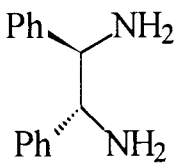
Scheme 115

A reaction was attempted in which osmium tetroxide and diamine (177) were used catalytically, the osmium tetroxide being regenerated by N-methylmorpholine-N-oxide oxidatively. *Cis* hydroxylation of styrene was achieved in 84% yield. The diol obtained however, was determined to be racemic by optical rotation. It again seems likely that the bulky phenyl groups are preventing co-ordination to the osmium and hence dihydroxylation is occuring directly with osmium tetroxide.

5.9 Homochiral pyrrolidine amines as chiral solvating agents

5.9.1 Introduction

The surge in enantioselective synthesis has led to an increased demand for accurate and reliable methods for the determining enantiomeric purity. The majority of non-chirotopical methods used for the determination of enantiomeric purity of carboxylic acids are indirect and involve the formation of diastereomeric esters or amides prior to NMR or HPLC analysis.[235] NMR methods that rely upon the formation of short lived diastereoselective complexes include analysis with chiral lanthanide shifts reagents and chiral solvating reagents.[236] The C_2 symmetric amine 1,2-diphenyl-diaminoethane (120),[237] a chiral solvating reagent, is effective in resolving a range of pharmacologically important anti-inflammatory agents and also halo acids which are susceptible to racemisation by other methods of analysis.[237a]



(120)

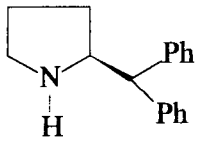
1,2-diphenyl-diaminoethane

In seeking a suitable chiral solvating reagent there are several obvious criteria which should be met. The compound should be readily soluble in common non-polar solvents (*e.g.*, $CDCl_3$, C_6D_6). It should possess a relatively simple ^1H NMR spectrum such that it does not obscure the observation of anisochronous resonances. Both enantiomers should be readily available so that if problems of solubility are encountered with one set of diastereomeric salts, the other can be screened in parallel. Finally the amine should possess anisotropic groups (*e.g.*, phenyl rings, carbonyl groups or localised lone pairs) that will give rise to chemical shift non-equivalence. The chiral amine (168) and C_2 symmetric diamines (177) and (178) developed by us meet these requirements and their ability to resolve a variety of chiral carboxylic acids and secondary alcohols has been assessed.

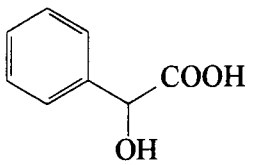
5.9.2 (2S)-(Diphenylmethyl)pyrrolidine as a chiral solvating reagent

The preparation of the samples for ^1H NMR experiments was straightforward. Typically 10mmol of the racemic alcohol or acid was added to the amine or diamine for a 1:1 stiochiometry. A series of mono-carboxylic acids containing aromatic rings or α-halogen

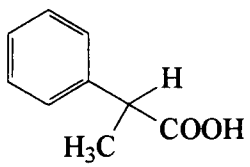
atoms showed chemical-shift non-equivalence with the homochiral amine (168). Values of $\Delta\delta_H$ using the amine and carboxylic acids in a ratio of 1:1 are shown in the Table below.



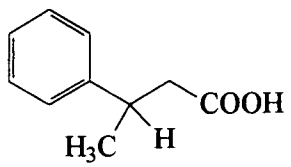
(168)



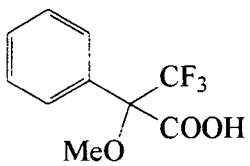
(213)



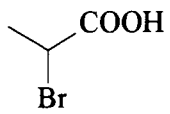
(214)



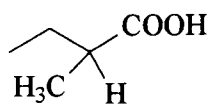
(215)



(216)



(217)



(218)

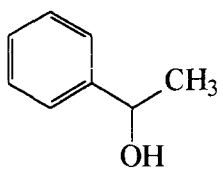
substrate	observed resonance	solvent	$\Delta\delta_H$
213	CH(OH)	$CDCl_3$	0.028
214	CH	$CDCl_3$	0.009
215	CH_3		0.011
	CH_2	$CDCl_3$	0.054
	CH		0
	CH_3		0
216	OMe	$CDCl_3$	0.006
217	CH_3	$CDCl_3$	0.017
	CHBr		0
218	CH_3	$CDCl_3$	0
	CH		0

Table 15. ^1H NMR shift non-equivalence observed (293K) for mono carboxylic acids with amine (168)

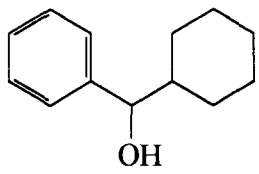
Splitting patterns obtained for mandelic acid (213) and 2-phenylpropionic acid (214) can be seen in (Figure 57 and 58)

Using amine (168) as a chiral solvating reagent with di-carboxylic acids proved problematic as the complexed acids were seen to drop out of solution during the NMR experiments. A range of other deuterated solvents failed to keep the complexes in solution.

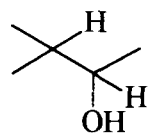
Certain secondary alcohols containing an aromatic ring have shown chemical shift non-equivalence with amine (168). Values of $\Delta\delta_H$ obtained using the amine with secondary alcohols in a ratio of 1:1 are shown below (Table 16). Splitting patterns obtained for 2-phenylethanol (181) can be seen below (Figure 59)



(181)



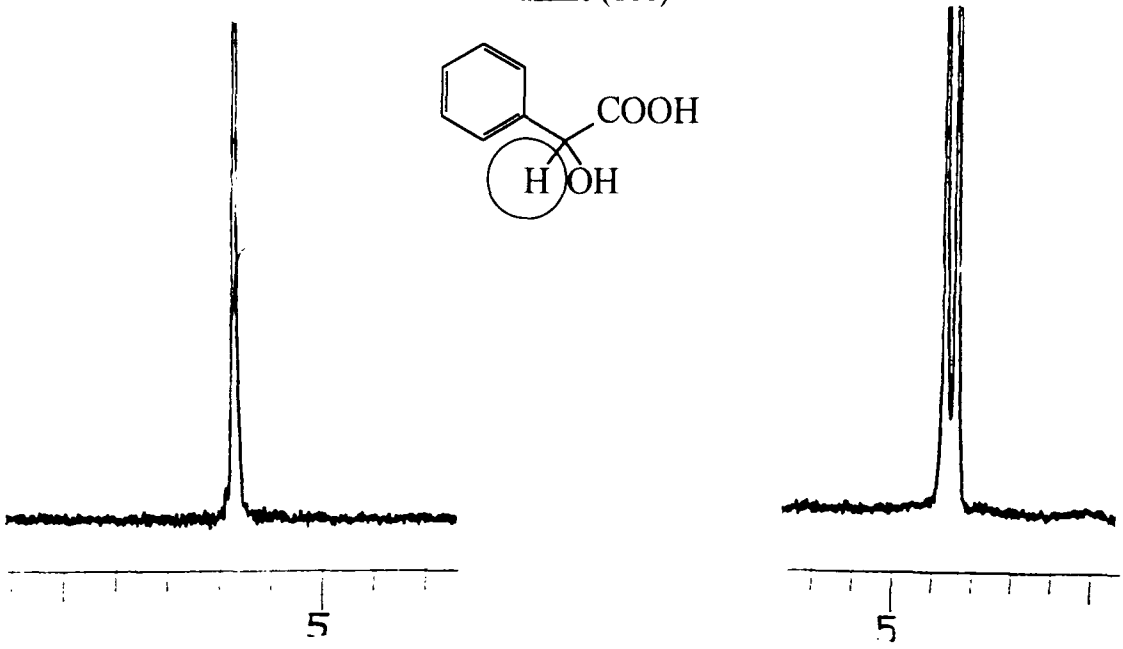
(219)



(220)

Substate	observed resonance	solvent	$\Delta\delta_H$
181	CH	$CDCl_3$	0.012
	CH_3		0
219	CH	$CDCl_3$	0.007
220	CH	$CDCl_3$	0

Table 16. ^1H NMR shift non-equivalence observed (293K) for secondary alcohols with amine (168)



mandelic acid (213)

mandelic acid & amine (168)

Figure 57. ^1H NMR Splitting patterns for (±) mandelic acid in the presence of amine (168)

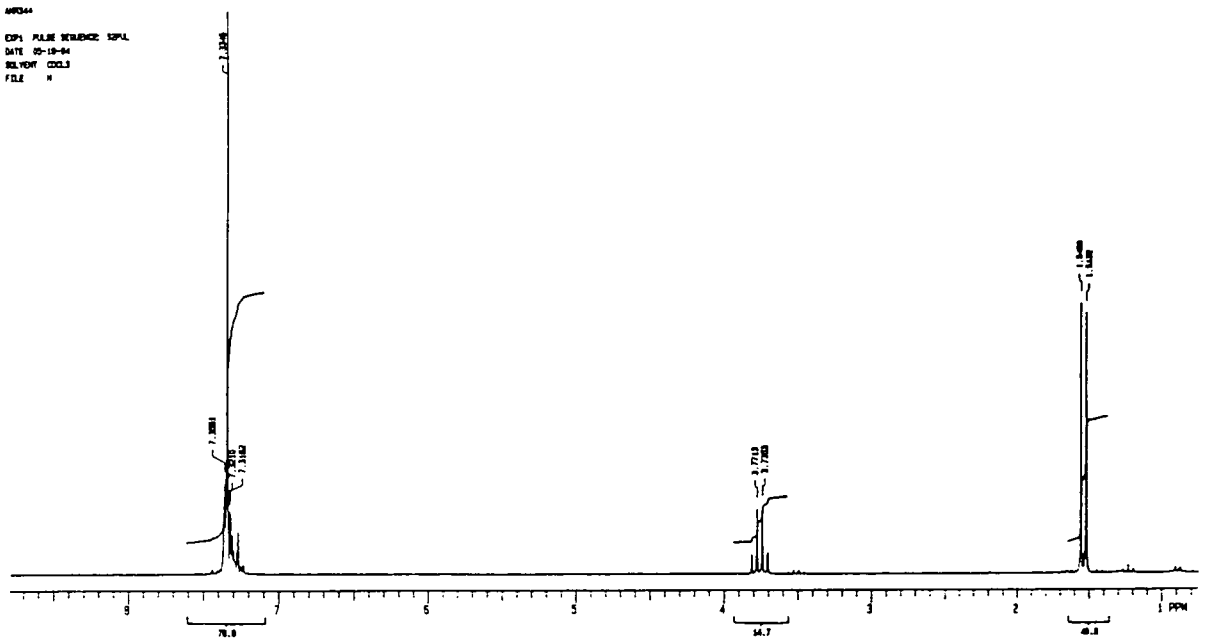


Figure 58. ^{1}H NMR of 2-phenylpropionic acid (214)

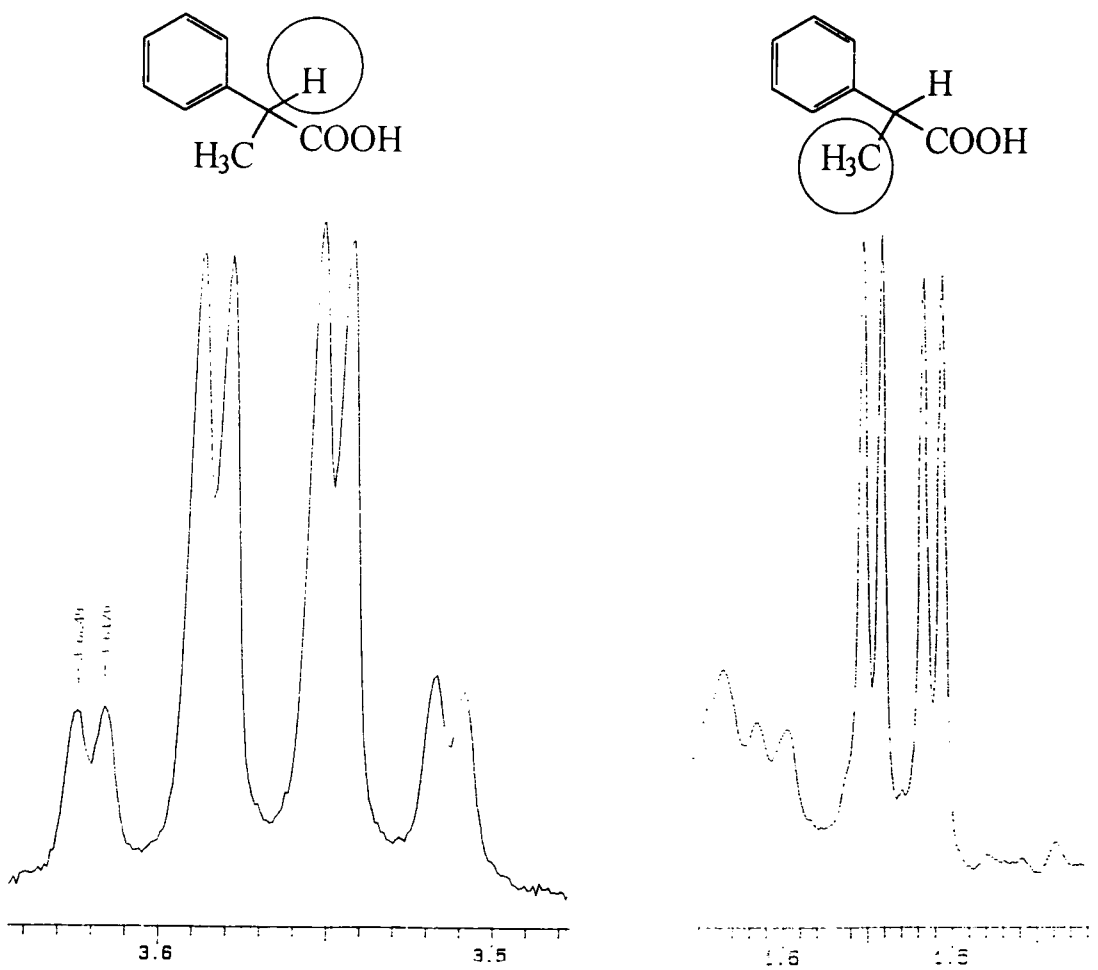
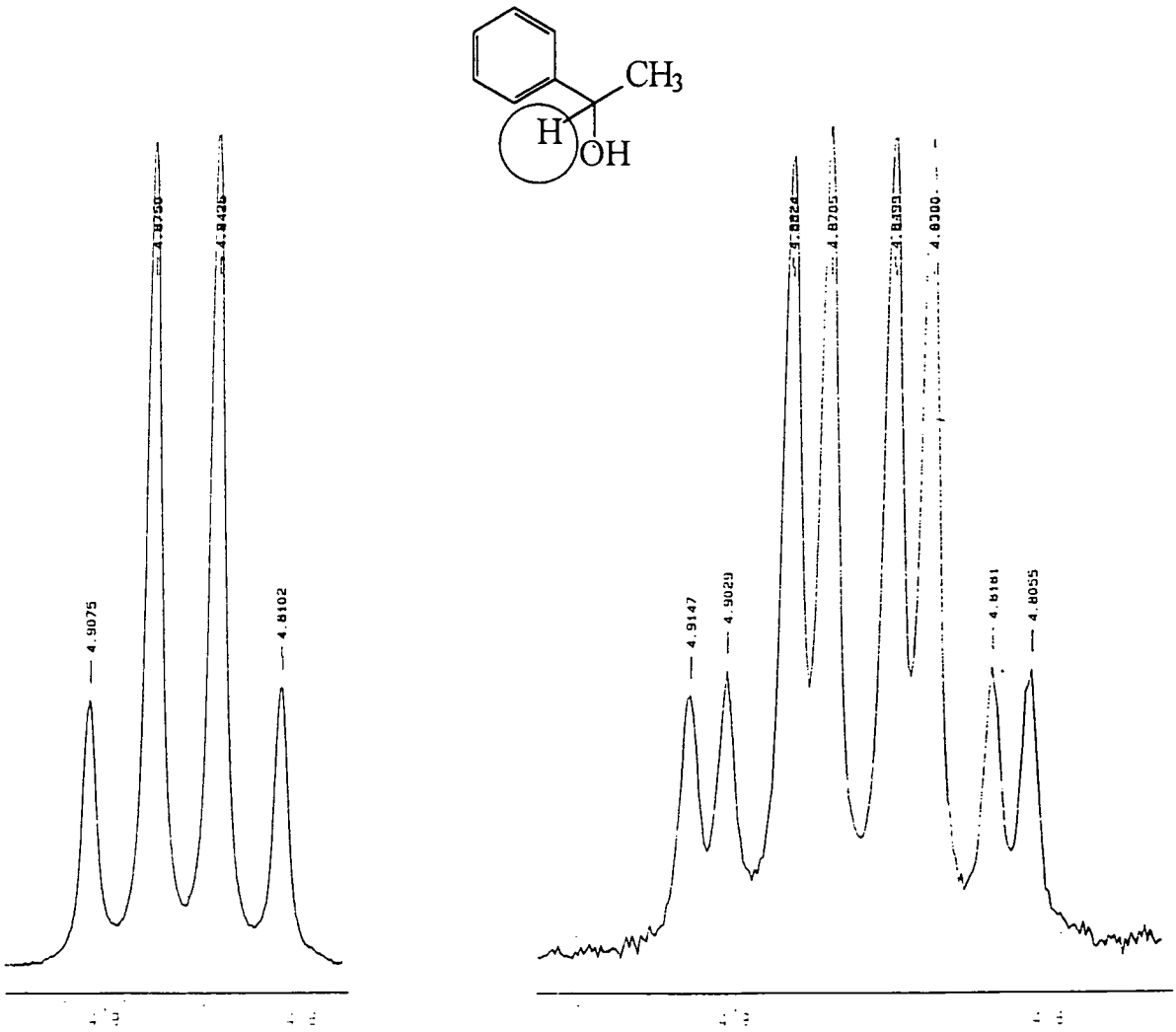


Figure 59. ^{1}H NMR Splitting patterns for (±) 2-phenylpropionic acid (214) in the presence of amine (168)



2-phenylethanol (181)

2-phenylethanol & amine (168)

Figure 60. ^{1}H NMR Splitting patterns for (±) 2-phenylethanol (181) in the presence of amine (168)

5.9.3 **Conclusions part C**

(2S)-(Diphenyl)methylpyrrolidine (168) and its C_2 analogues (177) and (178) have been used in a number of asymmetric reactions. These initial studies suggest that they are poor chiral catalysts in a range of asymmetric transformations. However, synthesis of these compounds came close to the completion of this PhD and these compounds could still prove to be effective chiral catalysts or auxiliaries in other asymmetric reactions.

(2S)-(Diphenyl)methylpyrrolidine (168) is a good chiral solvating agent in ^{1}H NMR experiments and a number of mono-carboxylic acids have shown chemical-shift non-equivalence in its presence. Mono-carboxylic acids containing an aromatic ring showed good chemical shift non-equivalence with amine (168), while aliphatic mono-carboxylic

were not resolved by the amine. This phenomenon can be attributed to π-π interactions between the aromatic rings of both the acid and the amine after the securing of electrostatic interactions between the ammonium and carboxylate groups. Chemical-shift non-equivalence was also seen with aromatic secondary alcohols in the presence of amine (168), although the $\Delta\delta_H$ values obtained were relatively small.

The C_2 diamines (177) and (178) proved to be poor chiral solvating reagents and only very small chemical shifts were seen with 2-phenylpropionic acid (214). None of the other monocarboxylic acids or secondary alcohols showed chemical-shift non-equivalence with these diamines.

CHAPTER 6

Experimental

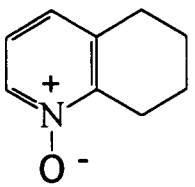
Introduction

IR spectra were recorded on a Perkin-Elmer F.T. 1720X or 1600 spectrometer. Low resolution mass spectra were recorded on a VG Analytical 7070E organic mass spectrometer, while gas chromatograph-mass spectra (GC-MS) were recorded using a Hewlett Packard 5890 Series II gas chromatograph connected to a VG Mass Lab Trio 1000. Solution state NMR spectra were recorded on Varian Gemini 200MHz (^{1}H at 200.057MHz, ^{13}C at 50.289MHz), Varian XL-200 (^{1}H at 200.057MHz), Varian VXR 400(S) (^{1}H at 399.952MHz, ^{13}C at 100.577MHz, ^{19}F at 376.25MHz) and Bruker AC 250 (^{1}H at 250.133, ^{19}F at 235.342MHz). Chemical shifts are quoted relative to Me_4Si ($\delta = 0$) for ^{1}H and ^{13}C, in chloroform-*d* ($CDCl_3$). Flash Chromatography was carried out using Fluka silica gel-60 (35-70μm) or Sorbsil-C60-H (40-60μm). X-ray crystal data was collected on a Siemens R3m/v diffractometer. All computations were carried out using the SHELXTL PLUS (μ-VAX II) system of programs. Chiral high pressure liquid chromatography (HPLC) was carried out on a Perkin Elmer series 410 chromatograph using a Hewlett Packard 1040A detection system. All chiral gas chromatography was carried out on a Perkin Elmer 80500 chromatograph.

Section A

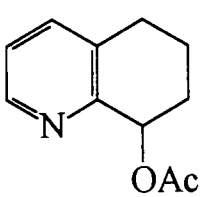
Asymmetric Reductions of Pyridyl Systems

1) 5,6,7,8-Tetrahydroquinoline-N-oxide



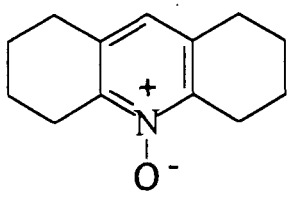
Peracetic acid (32%)(13ml, 60.0mmol) was added to a solution of 5,6,7,8-tetra hydroquinoline (4.0g, 30.3mmol) in THF (100ml). The solution was heated at 95°C for 12h, cooled and then diluted with chloroform (30ml). The chloroform layer was washed with 4M KOH (20ml), dried over $MgSO_4$ and concentrated to give a colourless oil. Cooling in ice gave 5,6,7,8,-tetrahydroquinoline-N-oxide as a white solid (4.17g, 93%). m.p. 63-64°C; δ_H (200 MHz; $CDCl_3$; Me_4Si) 8.14 (1 H, d, PyrH), 7.02 (2 H, m, PyrH), 2.94 (2H, t, CH_2), 2.77 (2 H, t, CH_2), 1.90 (2 H, m, CH_2), 1.79 (2 H, m, CH_2); δ_C ($CDCl_3$) 149.18, 137.27, 136.82, 126.74, 122.43, 29.03, 25.13, 22.29, 22.09; ν_{max} (KBr)/ cm^{-1} 2934, 2866, 1684, 1595, 1482, 1440, 1255(N-O), 1194, 1073, 971; (Found M^+, 149.0835. $C_9H_{11}NO$ requires M, 149.0841).

2) 8-Acetoxy-5,6,7,8-tetrahydroquinoline (57)



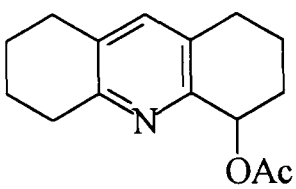
A solution of 5,6,7,8-tetrahydroquinoline-N-oxide (4.0g, 26.8mmol) in acetic anhydride (60ml) was heated at 95°C for 12h. The acetic anhydride was then removed under reduced pressure to give a black viscous liquid which on distillation (110°C/0.1mmHg) gave 8-acetoxy-5,6,7,8-tetrahydroquinoline as a clear oil (4.01g, 78%). δ_H (200 MHz; $CDCl_3$; Me_4Si) 8.39 (1 H, d, PyrH), 7.37 (1 H, d, PyrH), 7.08 (1 H, dd, PyrH), 5.94 (1 H, t, CH), 2.75 (2 H, m, CH_2), 2.08 (3 H, s, CH_3), 2.04 (4 H, m, CH_2); δ_C ($CDCl_3$) 170.72, 153.63, 148.12, 137.57, 133.98, 123.48, 71.23, 29.39, 28.75, 21.78, 18.76; ν_{max} (neat)/ cm^{-1} 2965, 2895, 1730 (C=O), 1550, 1450, 1370 1245 (C-O), 1165, 960; (Found: $[M + H]^+$ 192.0946. $C_{11}H_{13}NO_2$ + H requires M, 192.1024).

3) 1,2,3,4,5,6,7,8-Octahydroacridine-N-oxide



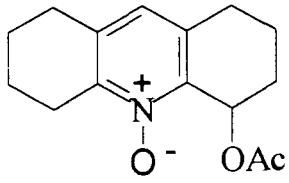
Peracetic acid (32%) (14ml, 64.0mmol) was added to a solution of 1,2,3,4,5,6,7,8-octahydroacridine (6.0g, 32.1mmol) in THF (100ml). The solution was heated at 95°C for 12h, cooled and then diluted with chloroform (30ml). The chloroform layer was washed with 4N KOH (20ml) and dried over $MgSO_4$. Concentration followed by recrystallisation gave colourless crystals of 1,2,3,4,5,6,7,8-octahydroacridine-N-oxide (5.8g, 89%). m.p. 140-141°C (lit, [94] 142-143°C); δ_H (200 MHz; $CDCl_3$; Me_4Si) 11.05 (1 H, s, NOH, D_2O, Ex.), 6.94 (1 H, s, PyrH), 2.99 (4 H, t, CH_2), 2.76 (4 H, t, CH_2), 1.8 (8 H, m, CH_2); δ_C ($CDCl_3$) 147.39, 132.77, 130.42, 28.73, 25.35, 22.44, 22.14; ν_{max} (KBr)/ cm^{-1} 2924, 2849, 1591, 1491, 1340, 1281(N-O), 1225, 1165, 1093, 971; *m/z* 203 (M^+)

4) 1-Acetoxy-1,2,3,4,5,6,7,8-octahydroacridine



A solution of 1,2,3,4,5,6,7,8-octahydroacridine-N-oxide (5.5g,27mmol) in acetic anhydride (80ml) was heated at 95°C for 12h. The acetic anhydride was removed under reduced pressure to leave an amber oil. The residual oil was purified over silica gel eluting with ethyl acetate/petrol (9:1) to give 1-acetoxy-1,2,3,4,5,6,7,8-octahydro-acridine as a white solid (5.1g, 77%). m.p. 51-52°C; δ_H (200 MHz; $CDCl_3$; Me_4Si) 7.16 (1 H, s, PyrH), 5.87 (1 H, t, CH), 2.95 (2 H, t, CH_2), 2.16 (4 H, m, CH_2), 1.96 (3 H, s, CH_3), 1.73 (8 H, m, CH_2); δ_C ($CDCl_3$) 170.83, 155.86, 150.29, 138.11, 132.57, 131.06, 71.99, 32.60, 29.44, 29.01, 28.40, 23.60, 23.11, 22.00, 18.70; ν_{max} (KBr)/ cm^{-1} 2934, 2859, 1735(C=O), 1565, 1454, 1370, 1236(C-O), 1122; m/z 246 $(M + H)^+$.

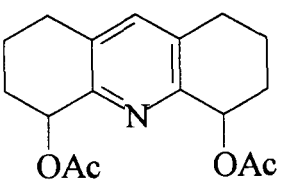
5) 1-Acetoxy-1,2,3,4,5,6,7,8-octahydroacridine-N-oxide



Peracetic acid (5.0ml, 22.85mmol) was added to a solution of 1-acetoxy-1,2,3,4,5, 6,7,8-octahydroacridine (3.6g, 14.7mmol) in THF (100ml). The solution was stirred at 95°C for 5h, cooled and then diluted with chloroform (30ml). The chloroform layer was washed with 4M KOH (20ml), dried over $MgSO_4$ and then concentrated to give 1-acetoxy-1,2,3,4,5,6,7,8-octahydroacridine-N-oxide a white solid (3.3g, 86%). m.p. 96-97°C; δ_H (200 MHz; $CDCl_3$; Me_4Si) 6.82 (1 H, s, PyrH), 6.42 (1 H, t, CH), 2.90 (2 H, t, CH_2), 2.73 (4 H, m, CH_2), 2.08 (3 H, s, CH_3), 1.79 (8 H, m, CH_2); δ_C ($CDCl_3$) 170.72, 151.67, 137.34, 135.61, 134.08, 126.50, 64.10, 29.43, 29.08, 28.32, 25.20, 22.47, 22.19, 21.54, 17.65; ν_{max} (KBr)/ cm^{-1} 2924, 2847, 1729(C=O), 1584, 1495, 1429, 1368, 1306(N-O), 1234(C-O), 1151, 1095, 973; *m/z* 261 (M^+).

$C_{15}H_{19}NO_3$ calc;	C, 68.99: H, 7.33: N, 5.33
Found;	C, 68.91: H, 7.26: N, 5.29

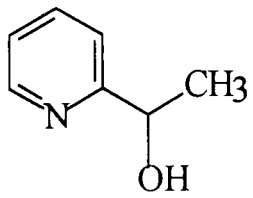
6) 1,8-Diacetoxy-1,2,3,4,5,6,7,8-octahydroacridine (58)



A mixture of 1-acetoxy-1,2,3,4,5,6,7,8-octahydroacridine-N-oxide (3.0g, 11.5mmol) and acetic anhydride (60ml, 426mmol) was heated at 110°C for 12h. The acetic anhydride was removed under reduced pressure and the residue purified over silica gel eluting with ethyl acetate/petrol (1:1) to give 1,8-diacetoxy-1,2,3,4,5,6,7,8-octahydro acridine (2.6g, 75%) as a white crystalline solid (diastereomeric mixture). m.p. 180-181°C (lit [94] 179-179.5°C); δ_H (200 MHz; $CDCl_3$; Me_4Si) 7.18 (1 H, s, PyrH), 5.93 (2 H, m, CH), 2.78 (4 H, m, CH_2), 2.11 (3 H, s, CH_3), 2.08 (3 H, s, CH_3), 2.02 (8 H, m, CH_2); δ_C ($CDCl_3$) 171.18, 170.80, 151.95, 138.05, 137.96, 133.21, 133.01, 71.31, 71.20, 29.48, 28.56, 21.91, 21.78, 19.45, 19.11; ν_{max} (KBr)/ cm^{-1} 2951, 2875, 1750 (C=O), 1450, 1370, 1250(C-O), 1065, 1026, 985; *m/z* 304 $(M + H)^+$.

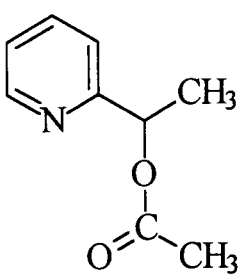
$C_{17}H_{21}NO_4$;	C, 67.31: H, 6.97: N, 4.61: O, 21.11.
found;	C, 67.27: H, 7.01: N, 4.48: O, 21.24.

7) 2-(1-Hydroxyethyl)pyridine (55)



A solution of 2-acetylpyridine (10.0g, 82.6mmol) in MeOH, CH_2Cl_2 (1:1) (40ml) was added to a slurry of $NaBH_4$ (0.78g,20.6mmol) in MeOH (10ml) and the solution stirred for 1h. The reaction was quenched with acetone (0.5ml) and allowed to warm to 18°C. The solution was diluted with CH_2Cl_2 (30ml), washed with 1M KOH (2 x 20ml), dried over $MgSO_4$ and concentrated to give 2-(1-hydroxyethyl)pyridine as a colourless oil (9.1g, 89%) yield. δ_H (200 MHz; $CDCl_3$; Me_4Si) 8.44 (1 H, d, PyrH), 7.65 (1 H, dd, PyrH), 7.37 (1 H, d, PyrH), 7.15 (1 H, dd, PyrH), 5.20 (1 H, s, OH, D_2O Ex), 4.88 (1 H, q, CH), 1.48 (3 H, d, CH_3); δ_C ($CDCl_3$) 164.29, 148.45, 137.36, 122.58, 120.21, 69.79, 24.56; ν_{max} (neat)/ cm^{-1} 3400(OH), 2970, 1590, 1565, 1475, 1430, 1125, 1075, 1010, 900; *m/z* 124 $(M + H)^+$.

8) 2-(1-Acetoxyethyl)pyridine (59)

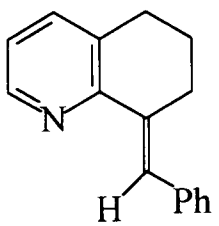


A solution of 2-(1-hydroxyethyl)pyridine (2.0, 16.3mmol) in CH_2Cl_2 (20ml) was added to a solution of dimethylaminopyridine (0.2g, 1.6mmol) and triethylamine (1.97g, 19.6mmol) in CH_2Cl_2 (50ml). The solution was stirred for 15min then acetyl chloride (1.54g, 19.6mmol) was added dropwise and the solution was stirred for 12h. The solvent was removed under reduced pressure and the crude product purified over silica gel, eluting with ethyl acetate/ petrol (2:8), gave 2-(1-acetoxyethyl)pyridine a clear oil (2.18g, 81%). δ_H (200 MHz; $CDCl_3$; Me_4Si) 8.58 (1 H, d, PyrH), 7.67 (1 H, dd, PyrH), 7.32 (1 H, dd, PyrH), 7.19 (1H, t, PyrH), 5.92 (1 H, q, CH), 2.11 (3 H, s, CH_3), 1.59 (3 H, d, CH_3); δ_C ($CDCl_3$) 165.61, 160.73, 149.78, 137.27, 123.18, 120.93, 73.51, 21.78, 21.20; ν_{max} (neat)/ cm^{-1} 2956 (CH_3), 1750 (C=O), 1597, 1460, 1370, 1230(C-O); *m/z* 166($[M + H)^+$. (Found: $[M + H]^+$ 166.0842. $C_9H_{11}NO_2$ + H requires M, 166.0868).

9) 2-(1-Acetoxyethyl)pyridine (59) (*Candida cylindracea* in organic solvent)

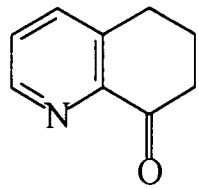
2-(1-Hydroxyethyl)pyridine (5.0g, 40.0mmol) and vinyl acetate (3.46g, 40.0mmol) were added to a suspension of *Candida cylindracea* (20.0g) in n-hexane (60ml). The suspension was stirred for 24h and then filtered. The solvent was removed under reduced pressure and the crude product purified over silica gel, eluting with ethyl acetate/ petrol (2:8) gave 2-(1-acetoxyethyl)pyridine a clear oil (1.98g, 30%). $[\alpha]_D$ = +53.7° (c1.08, $CHCl_3$) [lit [97] $[\alpha]_D$ = +100.3° (c 1.67, $CHCl_3$); δ_H (200 MHz; $CDCl_3$; Me_4Si) 8.58 (1 H, d, PyrH), 7.67 (1 H, dd, PyrH), 7.32 (1 H, dd, PyrH), 7.19 (1H, t, PyrH), 5.92 (1 H, q, CH), 2.11 (3 H, s, CH_3), 1.59 (3 H, d, CH_3); δ_C ($CDCl_3$) 165.61, 160.73, 149.78, 137.27, 123.18, 120.93, 73.51, 21.78, 21.20; ν_{max} (neat)/ cm^{-1} 2956 (CH_3), 1750 (C=O), 1597, 1460, 1370, 1230(C-O); *m/z* 166$(M + H)^+$.

10) (E)-8-Benzylidene-5,6,7,8-tetrahydroquinoline



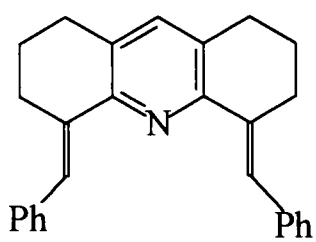
A mixture of 5,6,7,8-tetrahydroquinoline (3.0g, 22.5mmol), benzaldehyde (4.77g, 45.0mmol) and acetic anhydride (4.59g, 45mmol) were heated at 150°C for 48h. The excess reagents were removed by distillation under reduced pressure and the residue further distilled (85-90°C, 0.015mmHg) to give 8-benzylidene-5,6,7,8,-tetrahydro quinoline (4.37g, 88%). δ_H (200 MHz; $CDCl_3$; Me_4Si) 8.46 (1 H, d, PyrH), 7.99 (1 H, s, CH), 7.38 (6 H, m, CH), 7.03 (1 H, m, CH), 2.80 (4 H, m, CH_2), 1.78 (2 H, t, CH_2); δ_C ($CDCl_3$) 153.37, 147.75, 138.41, 137.49, 135.94, 133.18, 130.18, 128.61, 127.41, 127.25, 122.47, 30.29, 28.53, 23.24; ν_{max} (neat)/ cm^{-1} 3024(C_2=CRH), 2926, 2853, 1582, 1460, 1438, 805(C_2=CRH), 758, 698; *m/z* 221 (M^+).

11) 8-Oxo-5,6,7,8-tetrahydroquinoline (60)



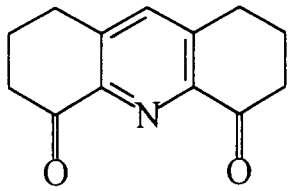
Ozone was bubbled through a solution of 8-benzylidene-5,6,7,8-tetrahydroquinoline (4.0g, 18.1mmol) in CH_2Cl_2 (150ml) at -70°C until a blue colour persisted. The dissolved ozone was purged by bubbling N_2 (blue colour dissapears) and then Me_2S (5ml) was added and the mixture stirred at 18°C for 12h. The solution was concentrated under reduced pressure to give a brown oil. Residual benzaldehyde was removed by distillation under reduced pressure (40-60°C, 0.015mmHg) and the crude product purified over silica gel eluting with ethyl acetate/petrol (2:8) to give 8-oxo-5,6,7,8-tetrahydroquinoline (60) (2.38g, 89.4%) as a pale yellow solid. m.p 100-102 °C (lit [93] m.p 101- 102 °C) (2.38g, 89.4%). δ_H (200 MHz; $CDCl_3$; Me_4Si) 8.75 (1 H, d, PyrH), 8.15 (1 H, d, PyrH), 7.69 (1 H, dd, PyrH), 3.02 (2 H, t, CH_2), 2.81 (2 H, t, CH_2), 2.16 (2 H, m, CH_2); δ_C ($CDCl_3$) 197.0 (C=O), 149.28, 138.4, 130.4, 128.7, 127.6, 40.02, 29.47, 23.05; ν_{max} (neat)/ cm^{-1} 2882, 1740(C=O), 1552, 1422, 1272, 1174, 1033, 966, 890; *m/z* 248 $(M + H)^+$.

12) (E,E)-1,8-Dibenzylidene-1,2,3,4,5,6,7,8-octahydroacidine



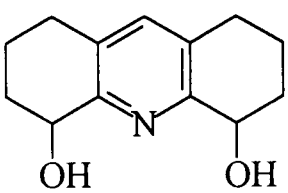
A mixture of 1,2,3,4,5,6,7,8-octahydroacridine (6.0g, 32mmol), benzaldehyde (30g, 283mmol) and acetic anhydride (30g, 293mmol) were heated at 150°C for 8h. The reaction mixture was cooled in ice, the precipitate collected and washed with cold ethanol 95% (30ml) to give 1,8-dibenzylidene-1,2,3,4,5,6,7,8-octahydroacridine a pale yellow solid (10.9g, 94%). m.p. 185-186°C (lit [102] 184-185°C); δ_H (200 MHz; $CDCl_3$; Me_4Si) 8.22 (1 H, s, PyrH), 7.45 (12 H, m, CH), 2.98 (8 H, m, CH_2) ,1.93 (4 H, m, CH_2); δ_C ($CDCl_3$) 150.56, 138.78, 138.13, 136.36, 131.97, 130.25, 128.64, 127.13, 126.76, 30.04, 28.73, 23.58; ν_{max} (KBr)/ cm^{-1} 2946, 1504, 1458, 1402, 1262, 1108, 912, 772, 694; *m/z* 363 (M^+)

13) 1,8-Dioxo-1,2,3,4,5,6,7,8-octahydroacridine (61)



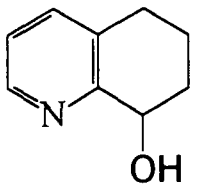
Ozone was bubbled through a solution of 1,8-dibenzylidene-1,2,3,4,5,6,7,8-octahydro acridine (5.46g,15.0mmol) in CH_2Cl_2 (150ml) at -70°C until a blue colour persisted. The dissolved ozone was purged by bubbling N_2 (blue colour disappears) and then Me_2S (5ml) was added and the mixture stirred at 18°C for 12h. The solution was concentrated to give a brown oil which was diluted with CH_2Cl_2 (50ml) and washed with water (4x50ml). The combined CH_2Cl_2 extracts were dried over $MgSO_4$. Removal of the solvent under reduced pressure gave a dark oil which was purified over silica gel eluting first with CH_2Cl_2 then MeOH to give 1,8-dioxo-1,2,3,4,5,6,7,8-octahydroacridine a dark solid (2.54g, 78%). m.p. 150-151°C (lit [102] 150-151°C); δ_H (200 MHz; $CDCl_3$; Me_4Si) 7.65 (1 H, s, PyrH), 3.06 (4 H, t, CH_2), 2.80 (4 H, t, CH_2), 2.19 (4 H, m, CH_2); δ_C ($CDCl_3$) 195.87, 147.98, 144.13, 139.44, 40.19, 29.72, 22.75; ν_{max} (KBr)/ cm^{-1} 2940, 1700(C=O), 1588, 1450, 1318, 1255, 1210, 1165, 740; mass spectrum *m/z* 216 $(M + H)^+$.

14) 1,8-Dihydroxy-1,2,3,4,5,6,7,8-octahydroacridine (66)



A solution of 1,8-diacetoxy-1,2,3,4,5,6,7,8-octahydroacridine (2.0g, 6.6mmol) in THF (20ml) was added to a solution of NaOMe (0.71g,13.2mmol) in THF (20ml) and the reaction heated under reflux for 12h. Half the solvent volume was removed and water (50ml) added. The solution was extracted into chloroform/ethanol (9:1),(3x50ml) and the combined extracts dried over $MgSO_4$. Purification over silica gel eluting with ethyl acetate gave 1,8-Dihydroxy-1,2,3,4,5,6,7,8-octahydroacridine (66) as a white solid (diastereomeric mixture) (1.27g, 88%). m.p. 155-156°C (lit [94] 156.5-158°C); δ_H (200 MHz; $CDCl_3$; Me_4Si) 7.16 (1 H, s, PyrH), 5.12 (2 H, s, OH, D_2O, Ex), 4.72 (2 H, m, CH), 2.74 (4 H, t, CH_2), 1.97 (8 H, m, CH_2); δ_C ($CDCl_3$) 155.78, 155.73, 138.55, 131.43, 131.37, 68.77, 68.61, 31.55, 28.75, 19.74, 19.52; ν_{max} (KBr)/ cm^{-1} 3389(OH), 2930, 2860, 1569, 1455, 1306(C-O), 1079, 1065, 965; *m/z* 220 $(M + H)^+$. (Found: $[M + H]^+$ 220.1324. $C_{13}H_{17}NO_2$ + H requires M, 220.1338).14)

15) 8-Hydroxy-5,6,7,8-tetrahydroquinoline (67)



A solution of 8-acetoxy-5,6,7,8-tetrahydroquinoline (2.0g,10.5mmol) in methanol (10ml) was added to a mixture of solid KOH (1.0g) in methanol (20ml) and the mixture refluxed for 4h. The reaction was cooled and then extracted into ether (4x20ml). The combined ether extracts were dried over $MgSO_4$ and concentrated to give 8-Hydroxy-5,6,7,8-tetrahydroquinoline (67) as a white solid (0.97g, 62%). m.p. 64-65°C (lit, [93] 64-65°C); δ_H (200 MHz; $CDCl_3$; Me_4Si) 8.25 (1 H, d, PyrH), 7.26 (1 H, d, PyrH), 6.98 (1 H, dd, PyrH), 4.67 (1 H, t, CH), 4.3 (1 H, s, OH, D_2O Ex.), 2.64 (2 H, m, CH_2), 2.0 (4 H, m, CH_2); δ_C ($CDCl_3$) 157.49, 146.40, 136.83, 133.62, 122.15, 69.23, 30.64, 28.19, 22.76; ν_{max} (KBr)/ cm^{-1} 3201(OH), 2924, 2875, 1578, 1449, 1331, 1289(C-O), 1159, 1082, 969; *m/z* 150 $(M + H)^+$.

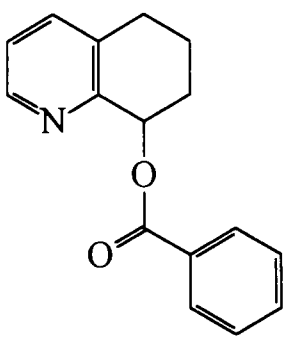
16) 1,8-Dihydroxy-1,2,3,4,5,6,7,8-octahydroacridine (66) by CBS Reduction of (61)

A solution of borane in THF (2.73mmol, 2.73ml, 1.0M solution) was added dropwise to a stirred solution of (R)-diphenylprolinol (0.035g, 0.137mmol, 5mol%) in THF at 20°C. After stirring for 2.5h at 20°C a solution of the 1,8-dioxo-1,2,3,4,5,6,7,8-octahydroacridine (0.6g, 2.78mmol) in THF (4 volumes, 10ml) was added dropwise (ensuring the temperature < 30°C) over 15 min. MeOH was cautiously added and the solution stirred for 30 min. The solution was then concentrated under reduced pressure to give a black solid which was purified over silica gel, eluting with ethyl acetate to give 1,8-Dihydroxy-1,2,3,4,5,6,7,8-octahydroacridine (66) as a white solid (diastereomeric mixture) (0.3g, 49%). δ_H (200 MHz; $CDCl_3$; Me_4Si) 7.16 (1 H, s, PyrH), 5.12 (2 H, s, OH, D_2O, Ex), 4.72 (2 H, m, CH), 2.74 (4 H, t, CH_2), 1.97 (8 H, m, CH_2); δ_C ($CDCl_3$) 155.78, 155.73, 138.55, 131.43, 131.37, 68.77, 68.61, 31.55, 28.75, 19.74, 19.52; ν_{max} (KBr)/ cm^{-1} 3389(OH), 2930, 2860, 1569, 1455, 1306(C-O), 1079, 1065, 965; *m/z* 220 $(M + H)^+$

17) 8-Hydroxy-5,6,7,8-tetrahydroquinoline (67) by CBS Reduction of (60)

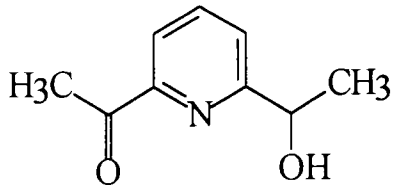
A solution of borane in THF (16.2ml, 16.2mmol, 1.0M solution) was added dropwise to a stirred solution of (R)-diphenylprolinol (0.20g, 0.80mmol, 5mol%) in dry THF (10ml) at 20°C. After stirring for 2.5h at 20°C a solution of 8-oxo-5,6,7,8-tetrahydroquinoline (60) (2.38g, 16.2mmol) in THF (20ml) was added dropwise over 15min. The solution was stirred for a further 30 min and then MeOH (20ml) was added. The solution was concentrated under reduced pressure and purified over silica gel, eluting with ethyl acetate to give 8-Hydroxy-5,6,7,8-tetrahydroquinoline (67) as a white solid (0.71g, 29%); δ_H (200 MHz; $CDCl_3$; Me_4Si) 8.25 (1 H, d, PyrH), 7.26 (1 H, d, PyrH), 6.98 (1 H, dd, PyrH), 4.67 (1 H, t, CH), 4.3 (1 H, s, OH, D_2O Ex.), 2.64 (2 H, m, CH_2), 2.0 (4 H, m, CH_2); δ_C ($CDCl_3$) 157.49, 146.40, 136.83, 133.62, 122.15, 69.23, 30.64, 28.19, 22.76; ν_{max} (KBr)/ cm^{-1} 3201(OH), 2924, 2875, 1578, 1449, 1331, 1289(C-O), 1159, 1082, 969; *m/z* 150 $(M + H)^+$.

18) 8-Benzoyloxy-5,6,7,8-Tetrahydroquinoline (68)



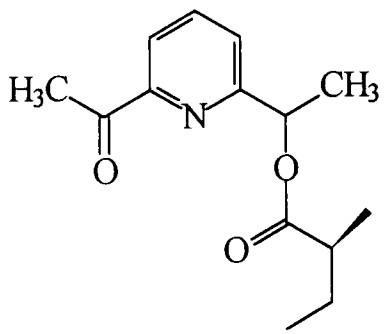
A mixture of 8-Hydroxy-5,6,7,8-tetrahydroquinoline (67) (0.4g, 2.68 mmol), pyridine (2ml) and benzoyl chloride (1.50g, 10mmol) was heated under reflux for 1h. A solution of $NaHCO_3$ (5.0%, 25ml) was then added and the reaction mixture extracted into ether (2x20ml). The combined ether extracts were combined dried over $MgSO_4$, and concentrated to give the crude benzoate purification over silica eluting with ethyl acetae/petrol (3:7) gave 8-Benzoyloxy-5,6,7,8-Tetrahydroquinoline (68) as a colourless oil (0.45g, 66%). δ_H (200 MHz; $CDCl_3$; Me_4Si) 8.53 (1 H, d, PyrH), 8.03 (1 H, d, PyrH), 7.36 (5 H, m, ArH), 7.18 (1 H, m, PyrH), 6.26 (1 H, t, CH), 2.87 (2 H, m, CH_2), 2.14 (4 H, m, CH_2); δ_C ($CDCl_3$) 166.41, 153.66, 148.14, 137.86, 134.26, 133.22, 131.15, 130.25, 128.66, 123.68, 71.65, 29.65, 28.92, 18.97; ν_{max} (KBr)/ cm^{-1} 2941, 2867, 1714(C=O), 1600, 1574, 1449, 1350, 1314, 1269(C-O), 1110, 1067, 1025, 952; *m/z* 254 $(M + H)^+$. (Found: $[M + H]^+$ 254.1164. $C_{16}H_{15}NO_2$ + H requires M, 254.1181).

19) 2-acetyl-6(α-hyroxy)ethylpyridine (74)



A solution of 2,6-diacetyl pyridine (1.0g, 6.12mmol) in CH_2Cl_2/MeOH (1:1) (30ml) was added to a slurry of $NaBH_4$ (0.03g, 0.8mmol) in MeOH (10ml) and stirred for 1h. The reaction was quenched with (0.5ml) acetone, washed with 1M KOH (2x 20ml) and dried over $MgSO_4$. Concentration and purification over silica gel eluting with ethyl acetate gave 2-acetyl-6(α-hyroxy)ethylpyridine as a semi solid (0.72g, 71%). δ_H (200 MHz; $CDCl_3$; Me_4Si) 7.89 (2 H, m, PyrH), 7.53 (1 H, d, PyrH), 7.50 (1 H, d, PyrH), 4.98 (1 H, q, CH), 2.73 (3 H, s, CH_3), 1.57 (3 H, d, CH_3); δ_C ($CDCl_3$) 199.66, 162.78, 151.93, 137.0, 123.48, 120.21, 68.84, 25.81, 24.19; ν_{max} (neat)/ cm^{-1} 3400(OH), 2996, 2932, 1700(C=O), 1595, 1450, 1375, 1260(C-O), 1120, 1080; *m/z* 166 $(M + H)^+$.

20) 2-acetyl-6-(α-(2'S)-methylbutyryloxy)ethylpyridine (75)



(S)-2-Methylbutyric anhydride (0.12g, 0.60mmol) was added to a solution of 2-acetyl-6(α-hyroxy)ethylpyridine (74) (0.1g, 0.60mmol) in pyridine (4.0ml). The reaction was heated under reflux for 12h and the excess pyridine removed under reduced pressure. The crude product was purified over silica gel eluting with ethyl acetate/petrol (1:9) to give 2-acetyl-6-(α-(2'S)-methylbutyryloxy)ethylpyridine (75) a clear oil (0.115g, 77%); δ_H (200 MHz; $CDCl_3$; Me_4Si) 7.95 (1 H, d, PyrH), 7.81 (1 H, dd, PyrH) 7.53 (1 H, d, PyrH), 5.97 (1 H, q, CH), 2.71 (3 H, s, CH_3), 2.48 (1 H, m, CH), 1.64 (3 H, d, CH_3), 1.62 (2 H, m, CH_2), 1.20 (3 H, m, CH_3), 0.94 (3 H, dt, CH_3); δ_C ($CDCl_3$) 200.71 (C=O), 176.35, 162.04 160.28, 137.96, 124.03, 120.73, 72.87, 41.63, 27.23, 26.14, 21.05, 17.07, 12.08; ν_{max} (neat)/ cm^{-1} 2980, 2960, 2850, 1750(C=O), 1700(C=O), 1580, 1460, 1360, 1290(C-O), 1181, 1150(C-O), 1080; mass spectrum *m/z* 250 $(M + H)^+$. (Found 250.1437 $[M + H]^+$. $C_{14}H_{19}NO_3$ + H requires M 250.1443).

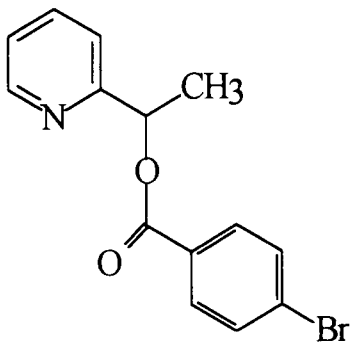
21) 2-(1-Hydroxyethyl)pyridine (55) bakers' yeast

A mixture of 2-acetylpyridine (5.0g, 41.3mmol), bakers' yeast (*Sacchromyces cerevisiea*) (50g) and glucose (100g) in tap water (150ml) were stirred for 10min at 35°C. A further addition of bakers' yeast (50g) and glucose (100g) was added and the solution diluted with tap water (600ml). A further addition of bakers' yeast and glucose was added after 2h and the fermentation continued for 48h. The cultured broth was extracted in batches (100ml), into ethyl acetate (50ml). The combined ether extracts were dried over $MgSO_4$ and concentrated to give a crude lime green oil. The crude product was purified over silica gel eluting with ethyl acetate/petrol (1:1) to give 2-(1-hydroxyethyl)pyridine as a colourless oil (1.8g, 35%). $[\alpha]_D$ = - 21.8 ° (c 6.4, $CHCl_3$) [lit [127] $[\alpha]_D$ = - 25.1° (c 1.5, $CHCl_3$) ; δ_H (200 MHz; $CDCl_3$; Me_4Si) 8.44 (1 H, d, PyrH), 7.65 (1 H, dd, PyrH), 7.37 (1 H, d, PyrH), 7.15 (1 H, dd, PyrH), 5.20 (1 H, s, OH, D_2O Ex), 4.88 (1 H, q, CH), 1.48 (3 H, d, CH_3); δ_C ($CDCl_3$) 164.29, 148.45, 137.36, 122.58, 120.21, 69.79, 24.56; ν_{max} (neat)/ cm^{-1} 3400(OH), 2970, 1590, 1565, 1475, 1430, 1125, 1075, 1010, 900; *m/z* 124 $(M + H)^+$.

22) 2-(1-Hydroxyethyl)pyridine (55) (allyl alcohol inhibited bakers' yeast)

Bakers' yeast (*Sacchromyces cerevisiea*) (50g) was added to a vigorously stirred solution of glucose (100g) in water (150ml) and the suspension was kept at 35°C for 30min. 2-Acetylpyridine (6.0g, 49.6mmol) and allyl alcohol (1.43g, 24.6mmol) were then added. Three solutions of glucose (100g) in tap water (150ml) and bakers' yeast (50g) were added at 2h intervals and the solution fermented for 48hrs. The suspension was extracted in aliquots (100ml) into ethyl acetate (50ml) and the combined organic extracts were dried over $MgSO_4$. Concentration gave a crude lime green oil which was purified over silica gel eluting with ethyl acetate/petrol(1:1) to give 2-(1-hydroxyethyl)pyridine a clear oil (2.1g, 34%). $[\alpha]_D$= -29.14° (c 4.94, $CHCl_3$); δ_H (200 MHz; $CDCl_3$; Me_4Si) 8.44 (1 H, d, PyrH), 7.65 (1 H, dd, PyrH), 7.37 (1 H, d, PyrH), 7.15 (1 H, dd, PyrH), 5.20 (1 H, s, OH, D_2O Ex), 4.88 (1 H, q, CH), 1.48 (3 H, d, CH_3); δ_C ($CDCl_3$) 164.29, 148.45, 137.36, 122.58, 120.21, 69.79, 24.56; ν_{max} (neat)/ cm^{-1} 3400(OH), 2970, 1590, 1565, 1475, 1430, 1125, 1075, 1010, 900; *m/z* 124 $(M + H)^+$.

23) 2-(α-4'-Bromobenzoyloxy)ethylpyridine (76)



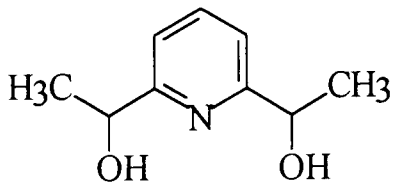
A solution of 4-bromobenzoyl chloride (1.96g, 8.9mmol) in CH_2Cl_2 (10ml) and pyridine (5ml) was added to a solution of 2-(1-hydroxyethyl)pyridine (1.0g, 8.1mmol) in CH_2Cl_2 (30ml). The reaction was refluxed for 1h, cooled to 18°C and then purified over silica gel eluting with ethyl acetate/petrol (20:80) to give 2-(α-4'-bromobenzoyloxy)ethylpyridine as a white crystalline solid (1.18g, 43%). m.p. 38-39°C; δ_H (200 MHz; $CDCl_3$; Me_4Si) 8.59 (1 H, d, PyrH), 7.96 (2 H, d, ArH), 7.66 (1 H, dd, PyrH), 7.56 (2 H, d, ArH), 7.43 (1 H, d, PyrH), 7.20 (1 H, dd, PyrH), 6.17 (1 H, q, CH), 1.75 (3 H, d, CH_3); δ_C ($CDCl_3$) 165.32, 160.5, 149.68, 137.23, 132.09, 131.64, 129.53, 128.55, 123.18, 120.71, 74.34, 21.17; ν_{max} (neat)/ cm^{-1} 2970, 1725(C=O), 1600, 1580, 1470, 1415, 1400, 1260(C-O), 1170, 1100, 1060, 1010, 770; *m/z* 305 & 307 (M^+).

$C_{14}H_{12}NO_2Br$ calc; C, 55.08: H, 3.97: N, 4.59: Br, 25.87.
Found; C, 55.06: H, 3.93: N, 4.54: Br, 25.83.

24) (2S)-(α-4'-Bromobenzoyloxy)ethylpyridine (76)

A solution of 4-bromobenzoyl chloride (3.93g, 17.9mmol) in CH_2Cl_2 (10ml) pyridine (5ml) were added to a solution of 2-(1-hydroxyethyl)pyridine (2.0g, 16.3mmol) in CH_2Cl_2 (30ml). The reaction was refluxed for 1h, cooled to 18°C and then purified over silica gel eluting with ethyl acetate/petrol (2:8) to give (2S)-ethyl-(1-4-bromobenzoyloxy)pyridine a white crystalline solid (2.16g, 43%). $[\alpha]_D$= +44.17° (c 1.13, $CHCl_3$); δ_H (200 MHz; $CDCl_3$; Me_4Si) 8.59 (1 H, d, PyrH), 7.96 (2 H, d, ArH), 7.66 (1 H, dd, PyrH), 7.56 (2 H, d, ArH), 7.43 (1 H, d, PyrH), 7.20 (1 H, dd, PyrH), 6.17 (1 H, q, CH), 1.75 (3 H, d, CH_3); δ_C ($CDCl_3$) 165.32, 160.5, 149.68, 137.23, 132.09, 131.64, 129.53, 128.55, 123.18, 120.71, 74.34, 21.17; ν_{max} (neat)/ cm^{-1} 2970, 1725(C=O), 1600, 1580, 1470, 1415, 1400, 1260(C-O), 1170, 1100, 1060, 1010, 770; *m/z* 305 & 307 (M^+).

25) 2,6-Diethyl(α-hydroxy)pyridine (56)



A solution of 2,6-diacetylpyridine (3.0g, 18.38mmol) in MeOH/Ch_2Cl_2 (50:50) (40ml) was added to a slurry of $NaBH_4$ (0.69g, 18.38mmol) in MeOH (10ml) and stirred for 1h. The reaction was quenched with acetone (0.5ml) and diluted with CH_2Cl_2 (20ml). The solution was washed with 1M KOH (2x20ml), dried over $MgSO_4$ and concentrated to give a 2,6-diethyl(α-hydroxy)pyridine (56) as a clear viscous oil (2.79g, 91%). δ_H (200 MHz; $CDCl_3$; Me_4Si) 7.66 (1 H, t, PyrH), 7.23 (2 H, d, PyrH), 4.85 (2 H, q, CH), 4.04 (2 H, s, OH, D_2O Ex), 1.48 (6 H, d, CH_3); δ_C ($CDCl_3$) 162.74, 138.10, 118.62, 69.73, 24.43; ν_{max} (neat)/ cm^{-1} 3400(OH), 1600, 1580, 1450, 1400, 1370, 1170, 1125, 1070, 925, 900; *m/z* 168 $(M + H)^+$. [Found 168.1023 $[M + H]^+$, $C_9H_{13}NO_2$ + H requires 168.1025].

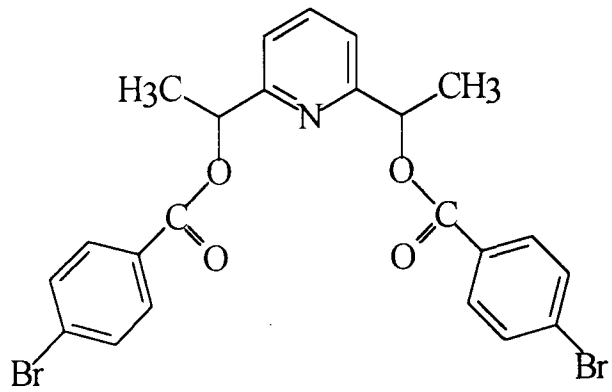
26) 2-acetyl-6(α-hyroxy)ethylpyridine (74) & 2,6-diethyl(α-hydroxy)pyridine (56) using (bakers' yeast)

2,6-Diacetylpyridine (3.0g, 18.4mmol) was added to a vigorously stirred solution of glucose (100g) in water (150ml) and bakers' yeast (*Sacchromyces cerevisiea*) (50g). Three additions of glucose (100g) in tap water (150ml) and bakers' yeast (50g) were added at 2h intervals and the suspension fermented for 24hrs. The suspension was extracted in aliquots (100ml) into ethyl acetate (50ml) and the combined organic extracts were dried over $MgSO_4$. Concentration and purification over silica gel, eluting with ethyl acetate/petrol (1:1), gave 2-acetyl-6(α-hyroxy)ethylpyridine (74) as a semi solid (2.0g, 66%). $[\alpha]_D$= -7.18° (c 2.21, $CHCl_3$); δ_H (200 MHz; $CDCl_3$; Me_4Si) 7.89 (2 H, m, PyrH), 7.53 (1 H, d, PyrH), 7.50 (1 H, d, PyrH), 4.98 (1 H, q, CH), 2.73 (3 H, s, CH_3), 1.57 (3 H, d, CH_3); δ_C ($CDCl_3$) 199.66, 162.78, 151.93, 137.0, 123.48, 120.21, 68.84, 25.81, 24.19; ν_{max} (neat)/ cm^{-1} 3400(OH), 2996, 2932, 1700(C=O), 1595, 1450, 1375, 1260(C-O), 1120, 1080; *m/z* 166 $(M + H)^+$, and 2,6-diethyl(α-hydroxy)pyridine (56) as a clear viscous oil (0.48g, 15%) yield. $[\alpha]_D$= -19.18° (c 4.06, $CHCl_3$); δ_H (200 MHz; $CDCl_3$; Me_4Si) 7.66 (1 H, t, PyrH), 7.23 (2 H, d, PyrH), 4.85 (2 H, q, CH), 4.04 (2 H, s, OH, D_2O Ex), 1.48 (6 H, d, CH_3); δ_C ($CDCl_3$) 162.74, 138.10, 118.62, 69.73, 24.43; ν_{max} (neat)/ cm^{-1} 3400(OH), 1600, 1580, 1450, 1400, 1370, 1170, 1125, 1070, 925, 900; *m/z* 168 $(M + H)^+$.

27) 2-acetyl-6(α-hyroxy)ethylpyridine (74) & 2,6-diethyl(α-hydroxy)pyridine (56) using (allyl alcohol supplememted bakers' yeast)

2,6-Diacetylpyridine (5.0g, 30.6mmol) was added with allyl alcohol (0.88g, 15.3mmol) to a vigorously stirred solution of glucose (100g) in water (150ml) and bakers' yeast (*Sacchromyces cerevisiea*) (50g). Three additions of glucose (100g) in tap water (150ml) and bakers' yeast (50g) were added at 2h intervals and the suspension fermented for 5days. The suspension was extracted in aliquots (100ml) into ethyl acetate (50ml). The combined extracts were dried over $MgSO_4$ and concentrated to give a lime green oil. The crude product was purified over silica gel eluting with ethyl acetate/petrol (1:1) to give 2-acetyl-6(α-hyroxy)ethylpyridine (74) as a semi solid in (3.48g, 69%). $[\alpha]_D$= -7.50° (c 1.50, $CHCl_3$); δ_H (200 MHz; $CDCl_3$; Me_4Si) 7.89 (2 H, m, PyrH), 7.53 (1 H, d, PyrH), 7.50 (1 H, d, PyrH), 4.98 (1 H, q, CH), 2.73 (3 H, s, CH_3), 1.57 (3 H, d, CH_3); δ_C ($CDCl_3$) 199.66, 162.78, 151.93, 137.0, 123.48, 120.21, 68.84, 25.81, 24.19; ν_{max} (neat)/ cm^{-1} 3400(OH), 2996, 2932, 1700(C=O), 1595, 1450, 1375, 1260(C-O), 1120, 1080; *m/z* 166 $(M + H)^+$, and 2,6-diethyl(α-hydroxy)pyridine (56) as a clear viscous oil (0.49g, 9.6%) yield $[\alpha]_D$= -26.84° (c 2.98, $CHCl_3$); δ_H (200 MHz; $CDCl_3$; Me_4Si) 7.66 (1 H, t, PyrH), 7.23 (2 H, d, PyrH), 4.85 (2 H, q, CH), 4.04 (2 H, s, OH, D_2O Ex), 1.48 (6 H, d, CH_3); δ_C ($CDCl_3$) 162.74, 138.10, 118.62, 69.73, 24.43; ν_{max} (neat)/ cm^{-1} 3400(OH), 1600, 1580, 1450, 1400, 1370, 1170, 1125, 1070, 925, 900; *m/z* 168 $(M + H)^+$.

28) 2,6-Diethyl(α-4'-bromobenzoyloxy)pyridine (85)



A solution of 4-bromobenzoyl chloride (5.18g, 23.6mmol) in (CH_2Cl_2) was added to a solution of 2,6-diethyl(α-hydroxy)pyridine (56) (2.0g, 11.96mmol) in pyridine (10ml). The solution was heated under refluxed for 24h and then cooled to 18°C. Purification over silica gel eluting with ethyl acetate/petrol (4:6) gave 2,6-diethyl(α-4'-bromo benzoyloxy)pyridine (85) as a crystalline white solid (mixture of diastereomers) (4.2g, 66%). m.p. 118-119°C; δ_H (200 MHz; $CDCl_3$; Me_4Si) 7.93 (1 H, d, PyrH), 7.66 (2 H, t, PyrH), 7.59 (4 H, d, ArH), 7.33 (4 H, d, ArH), 6.18 (2 H, q, CH), 1.73 (6 H, d, CH_3); δ_C ($CDCl_3$) 165.56, 160.27, 138.02, 137.98, 132.23, 131.71, 129.68, 128.68, 119.42, 119.37, 74.49, 74.35, 21.27; ν_{max} (neat)/ cm^{-1} 2974, 1725(C=O), 1590, 1460, 1400, 1370, 1270(C-O), 1225, 1175, 1200, 1070, 1010, 840, 750(C-Br); m/z 531, 533, 535 (1:2:1) (M^+, $[M + 2]^+$, $[M + 4]^+$)

$C_{23}H_{19}Br_2NO_4$ calc; C, 51.98: H, 3.61: Br, 29.73: N, 2.64.
Found; C, 51.90: H, 3.59: Br, 29.68: N, 2.62.

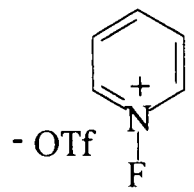
29) (2S),(6S)-Diethyl(α-4'-bromobenzoyloxy)pyridine (85)

A solution of 4-bromobenzoyl chloride (0.19g, 0.87mmol) in (CH_2Cl_2) was added to a solution of 2,6-diethyl(α-hydroxy)pyridine (56) $[\alpha]_D$= -26.84° (c 2.98, $CHCl_3$) (0.1g, 0.59mmol) in pyridine (4ml). The solution was heated under refluxed for 24h then cooled to 18°C. Purification over silica gel eluting with ethyl acetate/petrol (4:6) gave (2S),(6S)-diethyl(α-4'-bromobenzoyloxy)pyridine (85) as a crystalline white solid (0.06g, 19%) $[\alpha]_D$= -100 (c1.10, $CHCl_3$). δ_H (200 MHz; $CDCl_3$; Me_4Si) 7.93 (1 H, d, PyrH), 7.66 (2 H, t, PyrH), 7.59 (4 H, d, ArH), 7.33 (4 H, d, ArH), 6.18 (2 H, q, CH), 1.73 (6 H, d, CH_3); δ_C ($CDCl_3$) 165.56, 160.27, 138.02, 137.98, 132.23, 131.71, 129.68, 128.68, 119.42, 119.37, 74.49, 74.35, 21.27; ν_{max} (neat)/ cm^{-1} 2974, 1725(C=O), 1590, 1460, 1400, 1370, 1270(C-O), 1225, 1175, 1200, 1070, 1010, 840, 750(C-Br); m/z 531, 533, 535 (1:2:1) (M^+, $[M + 2]^+$, $[M + 4]^+$)

Section B

Preparation of N-Fluoropyridinium triflates

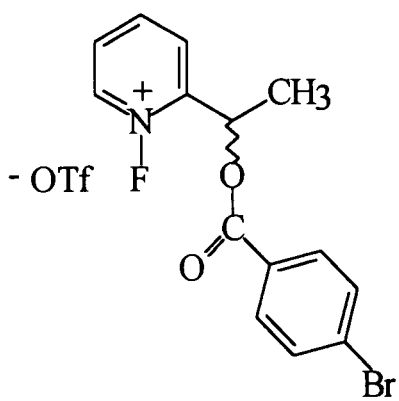
30) N-Fluoropyridinium triflate (26)



Fluorine diluted with N_2 (10%, F_2 by volume) was bubbled through a cold (-40°C) vigorously stirred solution of pyridine (1.0g, 12.6mmmol) and lithium triflate (1.96g, 12.6mmol) in dry acetonitrile (15ml) for 2h. The contents of the reaction were filtered to remove finely divided lithium triflate which precipitated during the reaction. Concentration gave a white sticky solid which was dissolved in a minimum quantity of acetone and reprecipitated by slow addition of ether, to give N-fluoropyridinium triflate as colourless crystals (2.41g, 77.4%). m.p. 185-186°C (lit [58] 185-187 °C); δ_H (200 MHz; CD_3CN; Me_4Si) 9.91 (2 H, dd, PyrH) $^3J_{H-F}$ 22.5 Hz, 8.75 (1 H, m, PyrH) $^5J_{H-F}$ 4.8 Hz, 8.41 (2 H, m, PyrH) $^4J_{H-F}$ 2.0 Hz; δ_C (CD_3CN) 146.74-146.69 $^5J_{C-F}$ 10.0Hz, 136.91-136.81 $^3J_{C-F}$ 20.0 Hz, 129.97; *m/z* (FAB 98 [M^+] 149 [M^-]).

$C_6H_5NF_4O_3S$ calc; C, 29.15: H, 2.04: N, 5.66: S, 12.94.
Found; C, 29.06: H, 2.05: N, 5.69: S, 13.10.

31) N-Fluoro 2-(α-4'-bromobenzoyloxy)ethylpyridinium triflate (102)



Fluorine diluted with N_2 (10%, F_2 by volume) was bubbled through a vigorously stirred solution of 2-(α-4'-bromobenzoyloxy)ethylpyridine (1.0g, 3.27mmol) and lithium triflate

(0.56g, 3.59mmol) in dry acetonitrile (15ml) for 2h. The contents of the reaction were filtered to remove the finely divided lithium triflate which precipitated. Concentration gave a sticky yellow solid which was recrystallised from ethyl acetate by the slow addition of ether to give N-Fluoro 2-(α-4'-bromobenzoyloxy)ethylpyridinium triflate (102) as a white solid (1.43g, 92%). δ_H (200 MHz; CD_3CN; Me_4Si) 9.29 (1 H, dd, PyrH) $^3J_{H-F}$ 16.9 Hz, 8.70 (1 H, m, PyrH), 8.46 (1 H, m, PyrH), 8.28 (1 H, m, PyrH), 8.06 (2 H, d, ArH), 7.80 (2H, d, ArH), 6.61 (1 H, q, CH), 1.94 (3 H, d, CH_3); δ_C (CD_3CN) 173.92, 153.44, 142.82, 140.08, 137.84, 137.35, 135.27, 134.30, 133.50, 123.17, 71.80, 24.46; ν_{max} (KBr)/ cm^{-1} 2970, 1725(C=O), 1600, 1580, 1470, 1415, 1400, 1260(C-O), 1170, 1100, 1060, 1010, 850; *m/z* (FAB 324 [M^+] & 326 [M+2] , 149 [M^-]).

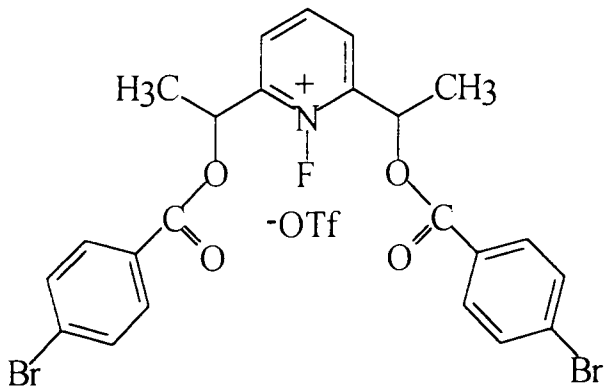
$C_{15}H_{12}NO_5SF_4Br$ calc; C, 37.99: H, 2.55: N, 2.95: S, 6.76: Br, 18.85.
Found; C, 37.88: H, 2.47: N, 3.05: S, 6.41: Br, 18.81.

32) N-Fluoro 2-(α-4'-bromobenzoyloxy)ethylpyridinium hexafluoroantimonate (104)

Fluorine diluted with N_2 (10%, F_2 by volume) was bubbled through a vigorously stirred solution of 2-(α-4'-bromobenzoyloxy)ethylpyridine (1.0g, 3.27mmol) and hexafluoro antimonate (0.88g, 3.59mmol) in dry acetonitrile (15ml) for 2h. Concentration gave a sticky yellow solid which was recrystallised from ethyl acetate by the slow addition of ether to give N-Fluoro 2-(α-4'-bromobenzoyloxy)ethylpyridinium hexafluoroantimonate (104) as a white solid (1.54g, 84%). δ_H (200 MHz; CD_3CN; Me_4Si) 9.28 (1 H, dd, PyrH) $^3J_{H-F}$ 22.5Hz, 8.73 (1 H, m, PyrH), 8.45 (1 H, m, PyrH), 8.27 (1 H, m, PyrH), 8.08 (2 H, d, ArH), 7.80 (2 H, d, ArH), 6.61 (1 H, q, CH), 1.99 (3 H, d, CH_3); δ_C (CD_3CN) 170.34, 153.43, 142.64, 140.04, 137.91, 137.35, 135.24, 134.56, 134.19, 123.19, 71.80, 24.46; ν_{max} (KBr)/ cm^{-1} 3108, 2980, 1724(C=O), 1590, 1494, 1444, 1400, 1306, 1262(C-O), 1092, 1011, 849, 824; *m/z* (FAB 324 [M^+] & 326 [M+2], 216 [M^-]).

$C_{15}H_{12}NO_5SF_4Br$ calc; C, 31.12: H, 2.44: N, 2.59: Br, 14.62.
Found; C, 31.05: H, 2.17: N, 2.68: Br, 14.59.

33) N-Fluoro 2,6-diethyl(α-4'-bromobenzoyloxy)pyridinium triflate (103)

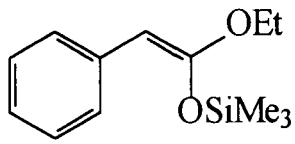


Fluorine diluted with nitrogen (10%. F_2 by volume) was bubbled through a vigorously stirred solution of 2,6-diethyl(α-4'-bromo benzoyloxy)pyridine (85) (1.0g, 1.88mmol) and lithium triflate (0.32g, 2.06mmol) in dry acetonitrile (15ml) for 2h. The contents of the reaction were filtered to remove the finely divided lithium triflate which precipitated. Concentration gave a sticky yellow solid which was recrystallised from ethyl acetate by the slow addition of ether to give N-Fluoro 2,6-diethyl(α-4'-bromobenzoyloxy)pyridinium triflate (103) as a white hydroscopic solid (0.94g, 72%) yield. δ_H (200 MHz; CD_3CN; Me_4Si) 8.77 (1 H, m, PyrH), 8.48 (2 H, d, PyrH), 8.05 (4 H, d, ArH), 7.83 (4 H, d, ArH), 6.66 (2 H, q, CH), 1.98 (6 H, m, CH_3); δ_C (CD_3CN) 169.94, 155.36, 153.65, 140.10, 137.87, 137.36, 134.56, 133.75, 71.94, 24.53; ν_{max} (KBr)/ cm^{-1} 3096, 2989, 1729(C=O), 1633, 1590, 1485, 1447, 1399, 1264(C-O), 1173, 1093, 1029, 949, 813; *m/z* (FAB 550 [M^+], 552 [M+2], 554 [M+4], ratio 1:2:1, 149 [M^-]).

Section C

Fluorinations using N-fluoro 2-(α-4'-bromo benzoyloxy) ethylpyridinium triflate (102)

34) Ethyl phenylacetate trimethylsilyl ketene acetal E and Z isomers (105)



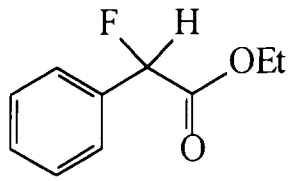
A solution of n-butyllithium in hexane (2.5M, 4.4ml, 11.0mmol) was added dropwise to a solution of diisopropylamine (1.54ml, 11.0mmol) under N_2 in dry THF (20ml) at -78°C. A solution of ethyl phenylacetate (1.64g, 10.0mmol) in THF (10ml) was added dropwise and the solution was stirred for 15min at -78°C. Chlorotrimethylsilane (1.4ml, 11.0mmol) was added dropwise and the solution stirred for a further 15min and then allowed to warm to 18°C. The solution was diluted with n-hexane (50ml), washed with $NaHCO_3$ (2x20ml) and then dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude product distilled (41°C, 0.015mmHg) to give ethyl phenyl acetate trimethylsilyl ketene acetal as a mixture of E and Z isomers (3:1) (1.47g, 66%). δ_H (200 MHz; $CDCl_3$; Me_4Si) 7.20 (5 H, m, ArH), 4.62 (1 H, s, CH) (E), 4.43 (1 H, s, CH) (Z), 4.02 (2 H, m, CH_2), 1.25 (3 H, m, CH_3), 0.24 (9 H, s, CH_3); ν_{max} (neat)/ cm^{-1} 2985, 2960, 2855, 1694 (C=C), 1600, 1550, 1450, 1265 ($SiMe_3$), 1190, 1100 (Si-O), 910; *m/z* 224 [M+ H].

35) Ethyl phenylacetate trimethylsilyl ketene acetal Z isomer (105)

A solution of n-butyllithium in hexane (2.5M, 4.4ml, 11.0mmol) was added dropwise to a solution of diisopropylamine (1.54ml, 11.0mmol) under N_2 in a mixture of 23% HMPA in THF (25ml) at -78°C. A solution of ethyl phenylacetate (1.64g, 10.0mmol) in THF (10ml) was added dropwise and the solution was stirred for 15min at -78°C. Chlorotrimethylsilane (1.4ml, 11.0mmol) was then added dropwise and the solution stirred for a further 15min and then allowed to warm to 18°C. The solution was diluted with n-hexane (50ml), washed with $NaHCO_3$ (2x20ml) and then dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude product distilled (41°C,0.015mmHg) to give the Z isomer of ethyl phenylacetate trimethylsilyl ketene acetal (1.32g, 59%); δ_H (200 MHz; $CDCl_3$; Me_4Si) 7.20 (5 H, m, ArH), 4.41 (1 H, s,

CH) (Z), 4.06 (2 H, m, CH_2), 1.27 (3 H, m, CH_3), 0.26 (9 H, s, CH_3); ν_{max} (neat)/ cm^{-1} 2983, 2964, 2852, 1691 (C=C), 1600, 1552, 1450, 1263 ($SiMe_3$), 1191, 1105 (Si-O), 912; *m/z* 224 [M+ H].

36) Ethyl 2-fluorophenylacetate (106)

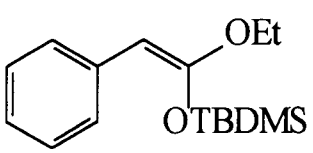


A solution of ethyl phenylacetate trimethylsilyl ketene acetal (0.47g, 2.10 mmol) in CH_2Cl_2 (5ml) was added to an immediately prepared solution of N-Fluoro 2-(α-4'-bromobenzoyloxy)ethylpyridinium triflate (1.0g, 2.10mmol) in CH_2Cl_2 (5ml). The reaction mixture was heated under reflux for 12h and then the solvent was removed under reduced pressure to afford a mixture of fluorinated and unfluorinated products. These were separated over silica gel eluting with ethyl acetate/petrol (1:10) to give ethyl 2-fluorophenylacetate as a colourless oil in 52% conversion as judged by ^1H NMR; δ_H (200 MHz; $CDCl_3$; Me_4Si) 7.30 (5 H, m, ArH), 5.69 (1 H, d, CH) $^2J_{H-F}$ 47.8Hz, 4.16 (2 H, q, CH_2), 1.19 (3 H, t, CH_3); δ_F (250MHz) -181.55 (1 F, d, CF) $^2J_{H-F}$ 47.4Hz; *m/z* 182 (M^+).

37) *tert*-Butyldimethylsilyl triflate

Triflic acid (14ml, 0.16mol) was added dropwise to *tert*-butyldimethylsilyl chloride (24g, 0.16mol) at 23°C and the resulting mixture heated at 60°C for 10hr. The crude mixture was directly distilled (0.015mmHg, 20°C) to give *tert*-butyldimethylsilyl triflate as a colourless liquid (39.3g, 93%) (60°C, 7mmHg). δ_H (200 MHz; $CDCl_3$; Me_4Si) δ 0.45 and δ 1.00.

38) Ethyl phenylacetate *tert*-butyldimethyllsilyl ketene acetal E and Z isomers (107)



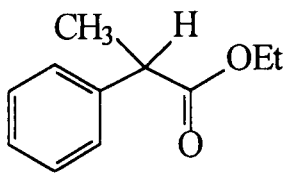
A solution of n-butyllithium in hexane (2.5M, 8.1ml, 20.1mmol) was added dropwise to a solution of diisopropylamine (2.8ml, 20.1mmol) under N_2 in dry THF (20ml) at -78°C. A solution of ethyl phenylacetate (3.0g, 18.3mmol) in THF (10ml) was added dropwise and the solution stirred for 15min at -78°C. *tert*-Butyldimethylsilyl triflate

(5.79g, 21.9mmol) was added dropwise and the solution stirred for a further 15min and then allowed to warm to 18°C. The solution was diluted with n-hexane (50ml), washed with $NaHCO_3$ (2x20ml) and then dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude product distilled (61°C 0.015mmHg) to give ethyl phenylacetate *tert*-butyldimethyllsilyl ketene acetal as a mixture of E and Z isomers (2:1) (3.71g, 73%). δ_H (200 MHz; $CDCl_3$; Me_4Si) 7.40 (5 H, m, ArH) (Z), 7.22 (5 H, m, ArH) (E), 4.64 (1 H, s, CH) (E), 4.50 (1 H, s, CH) (Z), 4.03 (2 H, q, CH_2) (E), 3.80 (2 H, q, CH_2) (Z), 1.31 (3 H, m, CH_3), 0.92 (9 H, s, CH_3), 0.22 (6 H, s, CH_3); ν_{max} (neat)/ cm^{-1} 2980, 2960, 2850, 1690(C=C), 1650, 1600, 1550, 1450, 1250($SiMe_2$), 1190, 1100(Si-O), 900; m/z 279 [M+ H].

39) Ethyl phenylacetate *tert*-butyldimethyllsilyl ketene acetal Z isomer (107)

A solution of n-butyllithium in hexane (2.5M, 4.4ml, 11.0mmol) was added dropwise to a solution of diisopropylamine (1.54ml, 11.0mmol) under N_2 in a mixture of 23% HMPA in THF (25ml) at -78°C. A solution of ethyl phenylacetate (1.64g, 10.0mmol) in THF (5.0ml) was added dropwise and the solution stirred for 15min at -78°C. *tert*-Butyldimethylsilyl triflate (2.98g, 11.3mmol) was added dropwise and the solution stirred for a further 15min and then allowed to warm to 18°C. The solution was diluted with (50ml) of n-hexane, washed with $NaHCO_3$ (2x20ml) and then dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude product distilled (61°C, 0.015mmHg) to give ethyl phenylacetate *tert*-butyldimethyllsilyl ketene acetal Z isomer (1.04g, 37%). δ_H (200 MHz; $CDCl_3$; Me_4Si) 7.40 (5 H, m, ArH) (Z), 4.50 (1 H, s, CH) (Z), 3.80 (2 H, q, CH_2) (Z), 1.28 (3 H, t, CH_3), 0.94 (9 H, s, CH_3), 0.20 (6 H, s, CH_3); ν_{max} (neat)/ cm^{-1} 2982, 2964, 2855, 1693 (C=C), 1601, 1554, 1450, 1251 ($SiMe_2$), 1190, 1106 (Si-O), 903; *m/z* 279 [M+ H].

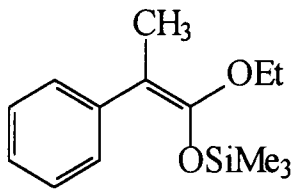
40) Ethyl 2-phenylpropionate



Dry ethanol (50ml) was added to a mixture of 2-phenylpropionic acid (2.0g, 13.3mmol) and concentrated sulphuric acid (0.5ml) and the solution was refluxed for 12h. Removal of the excess ethanol and distillation (45°C,0.015mmHg) gave ethyl-2-phenyl propionate as a colourless oil (2.1g, 88.6%). δ_H (200 MHz; $CDCl_3$; Me_4Si) 7.31 (5 H, m, ArH), 4.13 (2 H, m, CH_2), 3.73 (1 H, q, CH), 1.53 (3 H, d, CH_3), 1.20 (3 H, t,

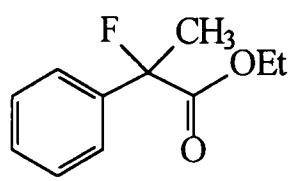
CH_3); δ_C ($CDCl_3$) 174.97, 141.24, 129.08, 127.96, 127.55, 61.16, 46.06, 19.12, 14.60; ν_{max} (neat)/ cm^{-1} 2990, 2930, 1750(C=O), 1600, 1500, 1450, 1370(C-CH_3), 1340, 1250(C-O), 1200, 1170, 1100, 1070, 860; m/z 178 (M^+).

41) Ethyl 2-phenylpropionate trimethylsilyl ketene acetal (E+Z) (108)



A solution of n-butyllithium in hexane (2.5M, 4.4ml, 11.0mmol) was added dropwise to a solution of diisopropylamine (1.54ml, 11.0mmol) under argon in dry THF (20ml) at -78°C. A solution of ethyl 2-phenylpropionate (1.80g, 10.1mmol) in THF (10ml) was added dropwise and the solution stirred for 15min at -78°C. Chlorotrimethylsilane (1.4ml, 11.0mmol) was added dropwise and the solution stirred for a further 15min then allowed to warm to 18°C. The solution was diluted with n-hexane (50ml), washed with $NaHCO_3$ (2x20ml) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude product distilled (61°C, 0.015mmHg) to give ethyl 2-phenyl propionate trimethylsilyl ketene acetal (1.60g, 67%) as a mixture of E and Z isomers (2:1). δ_H (200 MHz; $CDCl_3$; Me_4Si) 7.26 (5 H, m, ArH), 3.93 (2 H, q, CH) (E), 3.70 (2 H, q, CH) (Z), 1.95 (3 H, s, CH_3) (E), 1.91 (3 H, s, CH_3) (Z), 1.30 (3 H, t, CH_3) (E), 1.33 (3 H, t, CH_3) (Z), 0.27 (9 H, s, CH_3); ν_{max} (neat)/ cm^{-1} 2992, 2963, 2856, 1697(C=C), 1598, 1556, 1450, 1360(C-CH_3), 1260 ($SiMe_3$), 1193, 1103(Si-O), 920; *m/z* 238 (M^+).

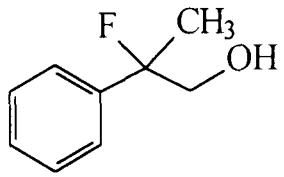
42) Ethyl 2-fluoro-2-phenylpropionate (109)



A solution of ethyl 2-phenylpropionate trimethylsilyl ketene acetal (0.49g, 2.06mmol) in CH_2Cl_2 (5ml) was added to an immediately prepared solution of N-Fluoro 2-(α-4'-bromobenzoyloxy)ethylpyridinium triflate (1.0g, 2.10mmol) in CH_2Cl_2 (5ml). The reaction mixture was heated under reflux for 12h and then the solvent was removed under reduced pressure to afford a mixture of fluorinated and unfluorinated products.

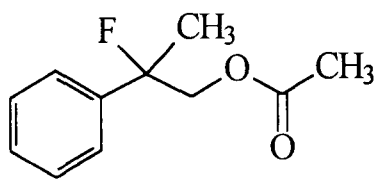
These were separated over silica gel eluting with ethyl acetate/petrol (1:10) to give ethyl 2-fluoro-2-phenylpropionate in 23% conversion as judged by ^1H NMR; δ_H (200 MHz; $CDCl_3$; Me_4Si) 7.16 (5 H, m, ArH), 4.05 (2 H, q, CH_2), 1.74 (3 H, d, CH_3) $^3J_{H-F}$ 22.3Hz, 1.17 (3 H, t, CH_3); δ_F (250MHz) -151.40 (1 F, q, CF) $^3J_{H-F}$ 23.8Hz; *m/z* 196 (M^+). (Found: M^+ 196.0899. $C_{11}H_{13}O_2F$ requires M, 196.0899).

43) 2-Fluoro-2-phenylpropanol (111)



A solution of ethyl 2-fluoro-2-phenylpropionate (0.28g, 1.40mmol) in dry ether (5ml) was added to a suspension of $LiAlH_4$ (53mg, 1.40mmol) in dry ether (5ml) at -10°C. and the mixture was stirred for 1h, quenched by the addition of water and then extracted into ether (3x 10ml). The combined extracts were dried over $MgSO_4$ and the solvent removed under reduced pressure to afford a colourless oil (0.2g), which was a mixture of fluorinated and unfluorinated products. The mixture was judged by ^1H NMR to contain 21% of the product 2-fluoro-2-phenylpropanol. δ_H (200 MHz; $CDCl_3$; Me_4Si) 7.35 (5 H, m, ArH), 3.72 (2 H, m, CH_2), 2.72 (1 H, s, OH, D_2O Ex), 1.73 (3 H, d, CH_3) $^3J_{H-F}$ 22.65 Hz; δ_F (250MHz) -156.86 (1 F, m, CF); *m/z* 154 (M^+).

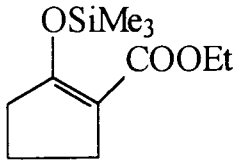
44) 2-Fluoro-2-phenylpropyl acetate (112)



A solution of fluorinated and unfluorinated products (0.2g), containing 2-fluoro-2-phenylpropanol (21%) as judged by ^1H NMR in CH_2Cl_2 (5ml) was added to a solution of dimethylamino pyridine (15mg, 0.12mmol) and triethylamine (0.13g, 1.29mmol) in CH_2Cl_2 (50ml). The solution was stirred for 15min and then acetyl chloride (0.11g, 1.41mmol) was added dropwise and the solution was stirred for 1h. The solvent was removed under reduced pressure and the crude product was purified over silica gel, eluting with ethyl acetate/ petrol (1:9), to afford a colourless oil (0.1g), a mixture of fluorinated and unfluorinated products. The mixture was judged by ^1H NMR to contain 21% of the product 2-fluoro-2-phenylpropyl acetate. δ_H (200 MHz; $CDCl_3$;

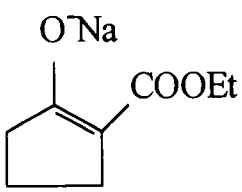
Me_4Si) 7.29 (5 H, m, ArH), 4.1 (2 H, m, CH_2), 2.09 (3 H, s, CH_3), 1.74 (3 H, d, CH_3) $^3J_{H-F}$ 22.65 Hz; δ_F (250MHz) -153.95 (1 F, m, CF); *m/z* 196 (M^+).

45) Ethyl 2-oxocyclopentanecarboxylate trimethylsilyl ketene acetal (113)



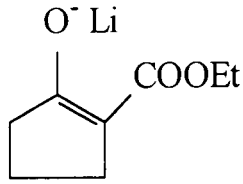
A solution of n-butyllithium in hexane (2.5M, 14.1ml, 35.2mmol) was added dropwise to a solution of diisopropylamine (4.93ml, 35.2mmol) under N_2 in THF (20ml) at -78°C. A solution of ethyl 2-oxocyclopentanecarboxylate (5.0g, 32.0mmol) in THF (5.0ml) was added dropwise and the solution stirred for 15min at -78°C. Chlorotrimethylsilane (4.34ml, 35.2mmol) was added dropwise and the solution stirred for a further 15min and then allowed to warm to 18°C. The solution was diluted with n-hexane (50ml), washed with $NaHCO_3$ (2x20ml) and then dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude product distilled (75°C, 0.015mmHg) to give ethyl 2-oxocyclopentanecarboxylate trimethylsilyl ketene acetal (3.6g, 49%). δ_H (200 MHz; $CDCl_3$; Me_4Si) 3.96 (2 H, q, CH_2), 2.33 (2 H, m, CH_2), 2.21 (2 H, m, CH_2), 1.61 (2 H, m, CH_2), 1.06 (3 H, t, CH_3), 0.048 (9 H, s, CH_3); δ_C ($CDCl_3$) 165.27, 109.23, 107.30, 59.61, 36.35, 29.50, 19.64, 14.87, 0.96; ν_{max} (neat)/ cm^{-1} 2980, 2900, 2870, 1690 (C=O), 1640 (C=C), 1550, 1405, 1380, 1300 ($SiMe_3$), 1225 (C-O), 1130(Si-O), 1025 (cm^{-1}); *m/z* 228 (M^+).

46) Ethyl 2-oxocyclopentanecarboxylate sodium enolate (114)



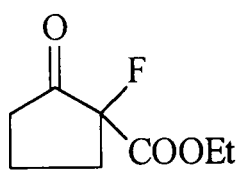
A solution of ethyl 2-oxocyclopentanecarboxylate (4.0g, 25.6mmol) in ether (10ml) was added to a dispersion of NaH (1.02g, 26.96mmol) in ether (20ml). The solution was stirred for 1h and a yellow solid formed which was filtered, washed with ether (4x40ml) and air dried to give ethyl 2-oxocyclopentanecarboxylate sodium enolate (3.52g, 77%). m.p. 183-184°C; δ_H (200 MHz; $CDCl_3$; Me_4Si) 3.91 (2 H, q, CH_2), 2.39 (2 H, t, CH_2), 1.94 (2 H, t, CH_2), 1.57 (2 H, m, CH_2), 1.11 (3 H, t, CH_3); δ_C ($CDCl_3$) 166.93, 99.23, 86.57, 56.13, 38.35, 29.01, 20.13, 15.50; ν_{max} (KBr)/ cm^{-1} 2959, 2862, 1690(C=O), 1650(C=C) 1250(C-O), 1160, 1050, 990 ; *m/z* FAB 155 (M^-).

47) Ethyl 2-oxocyclopentanecarboxylate lithium enolate



A solution of n-butyllithium in hexane (1.6M, 17.6, 28.2mmol) was added to a solution of ethyl 2-oxocyclopentanecarboxylate (4.0g, 25.6mmol) in ether (10ml) at -78°C. The solution was stirred for 1h and then the solvent was removed under reduced pressure to leave a white solid which was filtered, washed with ether (4x40ml) and air dried to give ethyl 2-oxocyclopentane carboxylate lithium enolate (3.27g, 79%). m.p. 183-184°C; δ_H (200 MHz; $CDCl_3$; Me_4Si) 3.98 (2 H, q, CH_2), 2.49 (2 H, t, CH_2), 1.74 (2 H, t, CH_2), 1.49 (2 H, m, CH_2), 1.07 (3 H, t, CH_3); δ_C ($CDCl_3$) 165.63, 98.23, 85.65, 54.19, 38.49, 27.63, 20.06, 14.75; ν_{max} (KBr)/ cm^{-1} 2959, 2864, 1694 (C=O) 1635 (C=C), 1498, 1269 (C-O), 1180, 1055, 998; *m/z* FAB 155 (M^-).

48) Ethyl 1-fluoro-2-oxocyclopentane-1-carboxylate (21)



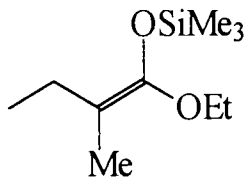
A solution of ethyl 2-oxocyclopentanecarboxylate trimethylsilyl ketene acetal (1.35g, 6.0mmol) in CH_2Cl_2 (10ml) was added to an immediately prepared solution of N-Fluoro 2-(α-4'-bromobenzoyloxy)ethylpyridinium triflate (2.85g, 6.0mmol) in CH_2Cl_2 (5ml) at -40°C. The reaction mixture was stirred for a further 12h and then the solvent was removed under reduced pressure to afford a mixture of fluorinated and unfluorinated products. These were separated over silica gel eluting with ethyl acetate/petrol (2:10) to give ethyl 1-fluoro-2-oxocyclopentane-1-carboxylate in 56% conversion as judged by ^1H NMR. δ_H (200 MHz; $CDCl_3$; Me_4Si) 4.28 (2 H, q, CH_2), 2.49 (2 H, t, CH_2), 2.06 (2 H, m, CH_2), 1.81 (2 H, m, CH_2), 1.81 (3 H, t, CH_3); δ_F (250MHz) -164.08 (1 F, t, CF) $^3J_{H-F}$ 23.2Hz; *m/z* 174 (M^+).

49) Ethyl 1-fluoro-2-oxocyclopentane-1-carboxylate (21)

A solution of ethyl 2-oxocyclopentanecarboxylate sodium enolate (0.86g, 4.82mmol) in CH_2Cl_2 (10ml) was added to an immediately prepared solution of N-Fluoro 2-(α-4'-bromobenzoyloxy)ethylpyridinium triflate (2.28g, 4.82mmol) in CH_2Cl_2 (5ml) at -

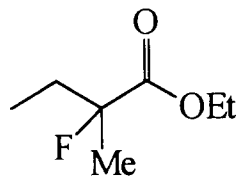
40°C. The reaction mixture was stirred for 12h and then the solvent was removed under reduced pressure to leave a mixture of fluorinated and unfluorinated products. These were separated over silica gel eluting with ethyl acetate/petrol (2:10) to give ethyl 1-fluoro-2-oxocyclopentanecarboxylate in 10% conversion as judged by ^1H NMR. δ_H (200 MHz; $CDCl_3$; Me_4Si) 4.28 (2 H, q, CH_2), 2.49 (2 H, t, CH_2), 2.06 (2 H, m, CH_2), 1.81 (2 H, m, CH_2), 1.81 (3 H, t, CH_3); δ_F (250MHz) -164.08 (1 F, t, CF) $^3J_{H-F}$ 23.2Hz; *m/z* 174 (M^+).

50) Ethyl 2-methylbutyrate trimethylsilyl ketene acetal (117)



A solution of n-butylithium in hexane (2.5M, 8.8ml, 22.0mmol) was added dropwise to a solution of diisopropylamine (3.1ml, 22.0mmol) under argon in dry THF (20ml) at -78°C. A solution of ethyl 2-methylbutyrate (2.60g, 20.0mmol) in THF (5ml) was added dropwise and the solution stirred for 15min at -78°C. Chlorotrimethylsilane (2.7ml, 22.0mmol) was added dropwise and the solution allowed to warm to 18°C. The solvent was removed under reduced pressure and the crude product distilled (55°C, 0.01mmHg) to give ethyl 2-methylbutyrate trimethylsilyl ketene acetal as a mixture of E and Z isomers in a ratio of (2:1) (2.96g, 73%). δ_H (200 MHz; $CDCl_3$; Me_4Si) 3.76 (2 H, q, CH_2), 1.96 (2 H, m, CH_2), 1.54 (3 H, s, CH_3) (E), 1.50 (3 H, s, CH_3) (Z), 1.21 (3 H, t, CH_3) (E), 1.20 (3 H, t, CH_3) (Z), 0.92 (3 H, t, CH_3), 0.18 (9 H, s, CH_3); *m/z* 202 (M^+)

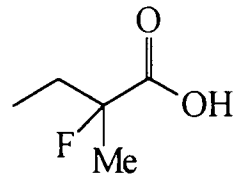
51) Ethyl 2-fluoro-2-methylbutyrate (118)



A solution of ethyl 2-methylbutyrate trimethylsilyl ketene acetal (0.85g, 4.20mmol) in CH_2Cl_2 (5ml) was added to an immediately prepared solution of N-Fluoro 2-(α-4'-bromobenzoyloxy)ethylpyridinium triflate (2.0g, 4.20mmol) in CH_2Cl_2 (5ml). The reaction mixture was stirred at 20°C for 12h and then the solvent was removed by distillation at 40°C to afford a mixture of fluorinated and unfluorinated products. Further distillation gave ethyl 2-fluoro-2-methylbutyrate in 33% conversion as judged by ^1H NMR. δ_H (200 MHz; $CDCl_3$; Me_4Si) 4.10 (2 H, q, CH_2), 1.50 (2 H, m, CH_2)

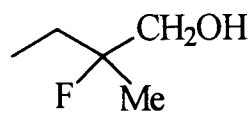
1.37 (3 H, d, CH_3) $^3J_{H-F}$ 21.44 Hz, 1.14 (3 H, t, CH_3), 0.77 (3 H, t, CH_3); δ_F (250MHz) -159.02 (1 F, m, CF); *m/z* 148 (M^+).

52) 2-Fluoro-2-methylbutyric acid (119)



A solution of ethyl 2-fluoro-2-methylbutyrate (0.15g, 1.0mmol) in MeOH (2ml) was added to a solution of NaOH (0.12g, 3.0mmol) in MeOH/ H_2O (1:1) (3ml). An aliquot of H_2O_2 (0.2ml) (30%) was added and the solution was stirred for 2h. The reaction was quenched with $NaBH_4$ (76mg, 2.0mmol) and the solvent removed under reduced pressure to leave a white solid. The resulting solid was acidified with HCl in ether (5ml) and the ether extract was then dried over $MgSO_4$. Removal of the ether afforded 2-fluoro-2-methylbutyric acid in 32% conversion as judged by ^1H NMR δ_H (200 MHz; $CDCl_3$; Me_4Si) 1.9 (2 H, m, CH_2), 1.60 (3 H, d, CH_3) $^3J_{H-F}$ 21.2Hz, 1.00 (3 H, t, CH_3); δ_F (250MHz) -158.62 (1 F, m, CF); m/z 120 (M^+)

53) 2-Fluoro-2-methylbutanol (119)



A solution of ethyl 2-fluoro-2-methylbutyrate (0.20g, 1.35mmol) in dry ether (5ml) was added to a suspension of $LiAlH_4$ (51mg, 1.35mmol) in dry ether (5ml) at -10°C, and the mixture was stirred for 1h, quenched by the addition of water and then extracted into ether (3x 10ml). The combined extracts were dried over $MgSO_4$ and the solvent removed under reduced pressure to afford a colourless oil (0.15g), which was a mixture of fluorinated and unfluorinated products. The mixture was judged by ^1H NMR to contain 32% of the product 2-fluoro-2-methylbutanol. δ_H (200 MHz; $CDCl_3$; Me_4Si) 3.45 (2 H, m, CH_2), 2.73 (1 H, s, OH, D_2O Ex), 1.73 (2 H, m, CH_2), 1.51 (3 H, t, CH_3) $^3J_{H-F}$ 21.2 Hz, 0.97 (3 H, m, CH_3); δ_F (250MHz) -156.67 (1 F, m, CF); *m/z* 106 (M^+)

Section D

Fluorinations using N-Fluoro 2,6-diethyl(α-4'-bromobenzoyloxy)pyridinium triflate (103)

54) Ethyl 2-fluorophenylacetate (106)

A solution of ethyl phenylacetate trimethylsilyl ketene acetal (0.27g, 1.21mmol) in CH_2Cl_2 (5ml) was added to an immediately prepared solution of N-Fluoro 2,6-diethyl(α-4'-bromobenzoyloxy)pyridinium triflate (103) (0.84g, 1.21mmol) in CH_2Cl_2 (5ml). The reaction mixture was heated under reflux for 12h and then the solvent was removed under reduced pressure to leave a mixture of fluorinated and unfluorinated products. These were separated over silica gel eluting with ethyl acetate/petrol (1:10) to give ethyl 1-fluorophenylacetate in 40% conversion as judged by ^1H NMR; δ_H (200 MHz; $CDCl_3$; Me_4Si) 7.30 (5 H, m, ArH), 5.69 (1 H, d, CH) $^2J_{H-F}$ 47.8Hz, 4.16 (2 H, q, CH_2), 1.19 (3 H, t, CH_3); δ_F (250MHz) -181.55 (1 F, d, CF) $^2J_{H-F}$ 47.4Hz; *m/z* 182 (M^+).

55) Ethyl 2-fluoro-2-phenylpropionate (109)

A solution of ethyl 2-phenylpropionate trimethylsilyl ketene acetal (0.44g, 1.85mmol) in CH_2Cl_2 (5ml) was added to an immediately prepared solution of N-Fluoro 2,6-diethyl(α-4'-bromobenzoyloxy)pyridinium triflate (103) (1.29g, 1.87mmol) in CH_2Cl_2 (5ml). The reaction mixture was heated under reflux for 12h and then the solvent was removed under reduced pressure to leave a mixture of fluorinated and unfluorinated products. These were separated over silica gel eluting with ethyl acetate/petrol (1:10) to give ethyl 2-fluoro-2-phenylpropionate in 25% conversion as judged by ^1H NMR; δ_H (200 MHz; $CDCl_3$; Me_4Si) 7.16 (5 H, m, ArH), 4.05 (2 H, q, CH_2), 1.74 (3 H, d, CH_3) $^3J_{H-F}$ 22.3Hz, 1.17 (3 H, t, CH_3); δ_F (250MHz) -151.40 (1 F, q, CF) $^3J_{H-F}$ 23.8Hz; *m/z* 196 (M^+). (Found: M^+ 196.0899. $C_{11}H_{13}O_2F$ requires M, 196.0899).

56) Ethyl 1-fluoro-2-oxocyclopentane-1-carboxylate (21)

A solution of ethyl 2-oxocyclopentanecarboxylate trimethylsilyl ketene acetal (0.42g, 1.84mmol) in CH_2Cl_2 (10ml) was added to an immediately prepared solution of N-Fluoro 2,6-diethyl(α-4'-bromobenzoyloxy)pyridinium triflate (103) (1.28g, 1.84mmol) in CH_2Cl_2 (5ml) at -40°C. The reaction mixture was stirred for a further 12h and then the solvent was removed under reduced pressure to give a mixture of fluorinated and unfluorinated products. These were separated over silica gel eluting with ethyl

acetate/petrol (2:10) to give ethyl 1-fluoro-2-oxocyclopentane-1-carboxylate in 55% conversion as judged by ^{1}H NMR. δ_H (200 MHz; $CDCl_3$; Me_4Si) 4.28 (2 H, q, CH_2), 2.49 (2 H, t, CH_2), 2.06 (2 H, m, CH_2), 1.81 (2 H, m, CH_2), 1.81 (3 H, t, CH_3); δ_F (250MHz) -164.08 (1 F, t, CF) $^{3}J_{H-F}$ 23.2Hz; *m/z* 174 (M^+).

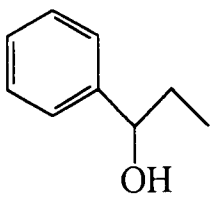
57) **Ethyl 2-fluoro-2-methylbutyrate (118)**

A solution of ethyl 2-fluoro-2-methylbutyrate trimethylsilyl ketene acetal (0.38g, 1.84mmol) in CH_2Cl_2 (5ml) was added to an immediately prepared solution of N-fluoropyridinium-2,6-diethyl-(di-α-4-bromobenzoyloxy) triflate (1.28g, 1.84mmol) in CH_2Cl_2 (5ml). The reactionreaction mixture was stirred at 20°C for 12h and then the solvent was removed by distillation at 40°C to leave a mixture of fluorinated and unfluorinated products. Further distillation gave ethyl 2-fluoro-2-methylbutyrate in 33% conversion as judged by ^{1}H NMR. δ_H (200 MHz; $CDCl_3$; Me_4Si) 4.10 (2 H, q, CH_2), 1.50 (2 H, m, CH_2) 1.37 (3 H, d, CH_3) $^{3}J_{H-F}$ 21.44 Hz, 1.14 (3 H, t, CH_3), 0.77 (3 H, t, CH_3); δ_F (250MHz) -159.02 (1 F, m, CF); *m/z* 148 (M^+).

Section E

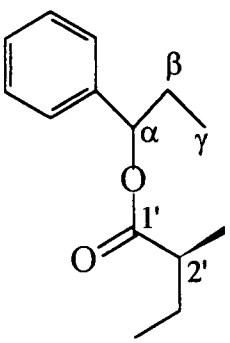
Diethylzinc reactions using (2S)-(1-hydroxyethyl) pyridine as chiral catalysts

58) (±) 1-Phenylpropan-1-ol (124)



A solution of propiophenone (0.50g, 3.72mmol) in MeOH/CH_2Cl_2 (1:1) (10ml) was added to a slurry of $NaBH_4$ (0.70g, 18.50mmol) in MeOH (10ml) and the reaction was stirred for 1h. The reaction was quenched with acetone (0.5ml), diluted with CH_2Cl_2 (20ml) and then washed with 1M KOH (2x5ml). The CH_2Cl_2 extract was then dried over $MgSO_4$ and concentrated to give 1-phenylpropan-1-ol as a clear oil (0.47g, 93%). δ_H (200 MHz; $CDCl_3$; Me_4Si) 7.33 (5 H, m, ArH), 4.58 (1 H, t, CH), 1.76 (2 H, dq, CH_2), 0.91 (3 H, t, CH_3); δ_C ($CDCl_3$) 145.11, 128.86, 127.94, 126.49, 76.46, 32.35, 10.64; ν_{max} (neat)/ cm^{-1} 3390 (OH), 2985, 2930, 2870, 1490, 1450, 1200, 1085(C-O), 1045, 1025, 975; *m/z* 136 (M^+).

59) (R,S)-α-(2'S)-Methylbutyroyloxy)propylbenzene (132)



(S)-2-Methylbutyric anhydride (0.22g, 1.16mmol) was added to a solution of 1-phenylpropan-1-ol (0.158g, 1.16mmol) in pyridine (3ml). The solution was heated under reflux for 12h and the excess pyridine removed under reduced pressure. The crude product was purified over silica gel eluting with ethyl acetate / petrol (1:9) to give (±) propyl-(α-(2S)-methylbutyroxy)benzene as a clear oil (0.24g, 94%). δ_H (200 MHz; $CDCl_3$; Me_4Si) 7.26 (5 H, m, ArH), 5.59 (1 H, t, CH), 2.34 (2 H, dq, CH_2), 1.81 (1 H,

m, CH), 1.42 (2 H, m, CH_2), 1.06 (3 H, t, CH_3), 0.81 (6 H, m, CH_3); δ_C ($CDCl_3$) 176.47, 141.35, 128.82, 127.83, 126.94, 77.42, 41.82, 29.99, 27.28, 17.11, 12.11, 10.65; ν_{max} (neat)/ cm^{-1} 2985, 2880, 1735(C=O), 1500, 1450, 1370, 1260(C-O), 1185, 1150, 1075, 1030; *m/z* (220) (M^+).

60) Diethylzinc reduction of benzaldehyde using (2S)-(1-hydroxyethyl)pyridine (2mol%) as an asymmetric catalyst.

A mixture containing (2S)-(1-hydroxyethyl)pyridine (7.4mg, 0.06mmol) (2mol%) $[\alpha]_D$= -24.22 (c 2.8, $CHCl_3$), benzaldehyde (0.318g, 3.0mmol) and cyclohexane (7.5ml) was heated under reflux for 20min and then cooled to 0°C. Diethylzinc in hexane (1M, 6.6ml) was added to the ice cooled mixture over a period of 5min and the mixture stirred for 24h. The reaction was quenched with HCl (1M, 10ml), extracted into CH_2Cl_2 (2x20ml), and the combined CH_2Cl_2 extracts dried over $MgSO_4$. Removal of the solvent under reduced pressure, followed by purification of the crude products over silica gel, eluting with ethyl acetate/petrol (2:8), gave 1-phenylpropan-1-ol (0.087g, 21%). $[\alpha]_D$= -11.26 (c12.43, $CHCl_3$); δ_H (200 MHz; $CDCl_3$; Me_4Si) 7.33 (5 H, m, ArH), 4.58 (1 H, t, CH), 1.76 (2 H, dq, CH_2), 0.91 (3 H, t, CH_3); δ_C ($CDCl_3$) 145.11, 128.86, 127.94, 126.49, 76.46, 32.35, 10.64; ν_{max} (neat)/ cm^{-1} 3390 (OH), 2985, 2930, 2870, 1490, 1450, 1200, 1085(C-O), 1045, 1025, 975; *m/z* 136 (M^+).

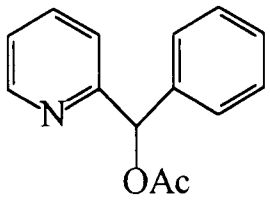
61) Diethylzinc reduction of benzaldehyde using (2S)-(1-hydroxyethyl) pyridine (10mol%) as an asymmetric catalyst.

A mixture containing (2S)-(1-hydroxyethyl)pyridine (0.037g, 0.3mmol) (10mol%) $[\alpha]_D$= -24.22 (c2.8, $CHCl_3$), benzaldehyde (0.318g, 3.0mmol) and cyclohexane (7.5ml) were heated under reflux for 20min and then cooled to 0°C. Diethylzinc in hexane (1M solution 6.6ml) was added to the ice cooled mixture over a period of 5min and the mixture stirred for 24h. The reaction was quenched with HCl (1M, 10ml) extracted into CH_2Cl_2 (2x20ml) and the combined CH_2Cl_2 extracts dried over $MgSO_4$. Removal of the solvent under reduced pressure, followed by purification of the crude products over silica gel, eluting with ethyl acetate/petrol (2:8) gave 1-phenylpropan-1-ol (0.098g, 24%). $[\alpha]_D$= -18.08 (c 8.85, $CHCl_3$); δ_H (200 MHz; $CDCl_3$; Me_4Si) 7.33 (5 H, m, ArH), 4.58 (1 H, t, CH), 1.76 (2 H, dq, CH_2), 0.91 (3 H, t, CH_3); δ_C ($CDCl_3$) 145.11, 128.86, 127.94, 126.49, 76.46, 32.35, 10.64; ν_{max} (neat)/ cm^{-1} 3390 (OH), 2985, 2930, 2870, 1490, 1450, 1200, 1085(C-O), 1045, 1025, 975; *m/z* 136 (M^+).

Section F

Synthesis of α-hydroxybenzylpyridines

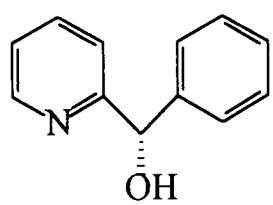
62) 2-(α-Acetoxy)benzylpyridine (136)



A solution of 2-(α-hydroxybenzyl)pyridine (3.99g, 21.6mmol) in CH_2Cl_2 (20ml) was added to a solution of triethylamine (2.18g, 21.6mmol) and dimethylaminopyridine (0.27g, 2.16mmol) in CH_2Cl_2 (50ml). The solution was stirred for 15min and then acetyl chloride (1.92g, 23.8mmol) was added dropwise and the solution stirred for a further 12h. The solvent was removed under reduced pressure and the crude product purified over silica gel, eluting with ethyl acetate/ petrol (3:7) to give 2-(α-acetoxy)benzyl pyridine (3.82g, 77.8%) as a white crystalline solid. m.p. 76-77°C; δ_H (200 MHz; $CDCl_3$; Me_4Si) 8.55 (1 H, m, PyrH), 7.58 (1 H, m, PyrH), 7.41 (1 H, m, PyrH), 7.25 (5H, m, CH), 7.12 (1 H, m, PyrH), 6.88 (1 H, s, CH), 2.15 (3 H, s, CH_3); δ_C ($CDCl_3$) 170.33, 159.64, 149.94, 139.54, 137.28, 129.05, 128.66, 127.84, 123.16, 121.36, 78.41, 21.66; ν_{max} (KBr)/ cm^{-1} 2943, 1737(C=O), 1592, 1575, 1498, 1452, 1432, 1371, 1225(C-O), 1150, 1100, 1025, 998; *m/z* 228 [M +H]

$C_{14}H_{13}NO_2$ calc; C, 73.98: H, 5.77: N, 6.17.
Found; C, 74.01: H, 5.75: N, 6.18.

63) 2-(α-Hydroxy)benzylpyridine (137)

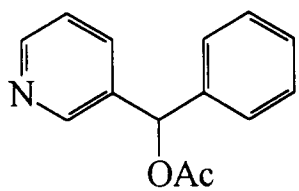


A solution of bromobenzene (7.85g, 50.0mmol) in dry ether (10ml) was added to magnesium turnings (1.2g, 50.0mmol) and a crystal of iodine in dry ether (10ml). After the addition was complete the mixture was heated under reflux for 10min. The flask was cooled in ice and then a solution of 2-pyridinecarboxaldehyde (5.36g, 50.0mmol) in ether

(10ml) was added. After the addition was complete the mixture was stirred at 18°C for 30min and then poured into ice water (20ml). The aqueous layer was separated and washed with ether (3x10ml) and the combined ether layers were washed with water (10ml) and then dried over $MgSO_4$. Removal of the solvent left a pale yellow solid which was purified over silica gel, eluting with ethyl acetate/petrol (1:1), to give 2-(α-hydroxy)benzylpyridine as a white solid (4.83g, 52%). m.p. 69-70°C; δ_H (200 MHz; $CDCl_3$; Me_4Si) 8.44 (1 H, d, PyrH), 7.53 (1 H, m, PyrH), 7.39 (1 H, m, PyrH), , 7.26 (5 H, m, ArH), 7.08 (1 H, m, PyrH), 5.79 (1 H, s, CH), 5.60 (1 H, s, OH, D_2O Ex); δ_C ($CDCl_3$) 161.11, 148.37, 143.80, 137.49, 129.02, 128.20, 127.49, 122.91, 121.77, 75.82; ν_{max} (KBr)/ cm^{-1} 3390(OH), 1595, 1570, 1497, 1470, 1450, 1400, 1310, 1195, 1150, 1100(C-O), 1070, 1025; *m/z* 185 (M^+)

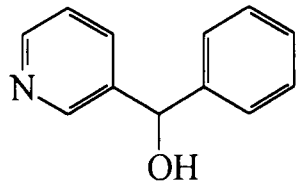
$C_{12}H_{11}NO$ calc; C, 77.80: H, 5.99: N, 7.57.
Found; C, 77.73: H, 5.95: N, 7.62.

64) 3-(α-Acetoxy)benzylpyridine (138)



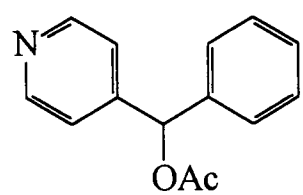
A solution of 3-(α-hydroxybenzyl)pyridine (9.47g, 51.2mmol) in CH_2Cl_2 (20ml) was added to a solution of triethylamine (5.17g, 51.2mmol) and dimethylaminopyridine (0.62g, 5.1mmol) in CH_2Cl_2 (50ml). The solution was stirred for 15min then acetyl chloride (4.53g, 56.3mmol) was added dropwise and the solution was stirred for a further 12h. The solvent was removed under reduced pressure and the crude product purified over silica gel, eluting with ethyl acetate/petrol (2:8), to give 3-(α-acetoxy)benzylpyridine (3.73g, 29%) as a clear oil; δ_H (200 MHz; $CDCl_3$; Me_4Si) 8.86 (1 H, s, PyrH), 8.49 (1 H, d, PyrH), 7.59 (1 H, d, PyrH) 7.30 (6 H, m, CH) 6.87 (1 H, s, CH), 2.12 (3 H, s, CH_3); δ_C ($CDCl_3$) 170.25, 149.28, 148.66, 139.53, 136.59, 135.54, 129.24, 128.80, 127.49, 124.03, 75.23, 21.58; ν_{max} (neat)/ cm^{-1} 3060, 2932, 1741(C=O), 1592, 1576, 1495, 1426, 1370, 1231(C-O), 1022, 979; *m/z* 228 [M+H].

65) 3-(α-Hydroxy)benzylpyridine (139)



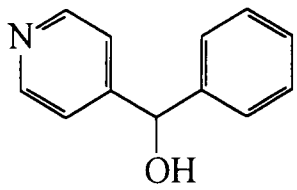
A solution of phenylmagnesium bromide (1M in THF) (102mls, 102mmol) was added to a solution of 3-pyridinecarboxaldehyde (10.0g, 93.3mmol) in THF (50ml) at 0°C. The reaction was stirred for 15min then heated under reflux for 12h. The reaction was cooled to 18°C then quenched by pouring into a cold saturated NH_4Cl solution. The product was extracted into ethyl acetate and the organic extracts dried over $MgSO_4$. Concentration under reduced pressure gave a pale yellow oil, which was purified over silica gel, eluting with ethyl acetate/petrol 2:8 to give 3-(α-hydroxy)benzylpyridine (9.87g, 57%) as a clear oil. δ_H (200 MHz; $CDCl_3$; Me_4Si) 8.31 (1 H, d, PyrH), 8.11 (1 H, d, PyrH), 7.67 (1 H, m, PyrH), 7.26 (5 H, m, ArH), 7.12 (1 H, m, PyrH), 5.70 (1 H, s, CH); δ_C ($CDCl_3$) 148.10, 144.19, 141.00, 135.19, 129.04, 128.48, 128.10, 127.09, 124.03, 73.87; ν_{max} (neat)/ cm^{-1} 3175 (OH), 1593, 1579, 1477, 1451, 1425, 1373, 1244, 1186, 1080 (C-O), 1049, 1026, 857; *m/z* 185 (M^+).

66) 4-(α-Acetoxy)benzylpyridine (140)



A solution of 4-(α-hydroxybenzyl)pyridine (2.96g, 16.1mmol) in CH_2Cl_2 (20ml) was added to a solution of triethylamine (1.63g, 16.1mmol) and dimethylaminopyridine (0.2g, 1.60mmol) in CH_2Cl_2 (50ml). The solution was stirred for 15min then acetyl chloride (1.4g, 17.7mmol) was added dropwise and the solution was stirred for a further 12h. The solvent was removed under reduced pressure and the crude product purified over silica gel, eluting with ethyl acetate to give 4-(α-acetoxy)benzylpyridine as a clear oil (2.44g, 67%). δ_H (200 MHz; $CDCl_3$; Me_4Si) 8.38 (2 H, d, PyrH), 7.11 (7 H, m, CH) 6.65 (1 H, s, CH), 1.91 (3 H, s, CH_3); δ_C ($CDCl_3$) 169.98, 150.36, 149.27, 139.27, 129.12, 128.87, 127.80, 121.75, 75.84, 21.25; ν_{max} (neat)/ cm^{-1} 2939 1742(C=O), 1596, 1572, 1495, 1448, 1424, 1365, 1222(C-O), 1148, 1098, 1020, 996 (cm^{-1}); m/z 228 [M+H].

67) 4-(α-Hydroxybenzyl)pyridine (141)



A solution of phenylmagnesium bromide (1M in THF) (102mls, 102mmol) was added to a solution of 4-pyridinecarboxaldehyde (10.0g, 93.3mmol) in THF (50ml) at 0°C. The reaction was stirred for 15min then heated under reflux for 12h. The reaction was cooled to 18°C then quenched by pouring into a cold saturated NH_4Cl solution. The product was extracted into ethyl acetate and the organic extracts dried over $MgSO_4$. Concentration under reduced pressure gave a pale yellow oil, which was purified over silica gel, eluting with ethyl acetate/petrol 2:8 to give 4-(α-hydroxy)benzylpyridine (4.66g, 27%) as a white solid. m.p. 68-69°C; δ_H (200 MHz; $CDCl_3$; Me_4Si) 8.32 (2 H, m, PyrH), 7.31 (7 H, m, CH) 5.74 (1 H, m, CH), δ_C ($CDCl_3$) 154.18, 149.58, 143.60, 129.20, 128.51, 127.32, 121.95, 75.10; ν_{max} (KBr)/ cm^{-1} 3362(OH), 1593, 1576, 1492, 1472, 1450, 1403, 1315, 1173, 1145, 1096(C-O), 1065, 1022; *m/z* 185 (M^+).

$C_{12}H_{11}NO$ calc; C,77.80: H,5.99: N,7.57.
Found; C,77.81: H,6.02: N,7.53.

General procedure for kinetic resolutions using *Candida cylindracea* lipase

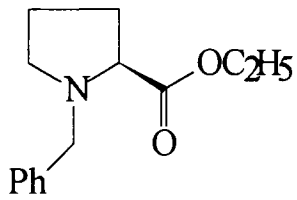
68) Kinetic resolution of 4-(α-acetoxy)benzylpyridine

A mixture of 4-(α-acetoxy)benzylpyridine (1.0g, 5.4mmol), *Candida cylindracea* lipase (2.0g) and phosphate buffer pH 7 (30ml) were stirred at room temperature. The progress of the reaction was monitored by ^1H NMR and after 3 days the reaction had reached 27% conversion. The reaction mixture was extracted into ethyl acetate (3x30ml) and the combined organic extracts were dried over $MgSO_4$. Concentration under reduced pressure and purification over silica gel, eluting with ethyl acetate/petrol (1:1) gave 4-(α-hydroxy)benzylpyridine (0.14g, 14%) in 76.5 % ee as evaluated by chiral HPLC using a Chiracel ODH analytical column, eluting with n-hexane (+1% IPA).

Section G

Homochiral bases derived from (S)-proline

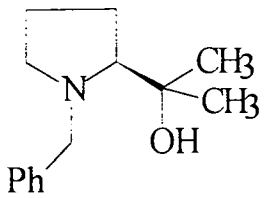
69) (2S)-N-benzyl-2-carboxyethylpyrrolidine (162)



Benzyl chloride (40ml, 275mmol) was added dropwise to a stirred solution of (S)-(-)-proline (25g, 217mmol), water (162ml), NaOH (110ml), KI (550mg, 3.25mmol), and tetrabutylammonium hydroxide (1M, 100mg) under N_2. The mixture was heated at 65°C for 2h and then NaOH (2M, 28ml) and benzyl bromide (10.7ml, 95mmol) were added. After 1h the reaction was neutralised with HCl (1M) to pH7 and then partial concentred under reduced pressure. The addition of ethanol (100ml) precipitated N-benzyl-(S)-proline containing salts (57g). Without further purification a solution of the crude N-benzyl (S)-proline salts (57g) in ethanol (100ml) were added to a solution of acetyl chloride (37.5g, 475mmol) and anhydrous ethanol (125ml) under N_2 at -10°C. The solution was heated at 50°C for 3h then concentrated under reduced pressure. The crude product was diluted with ethyl acetate (200ml), washed firstly with 2M NaOH (3x30ml) until pH12 and then brine (50ml). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. Distillation (98°C, 0.05mmHg) gave (2S)-N-benzyl-2-carboxyethylpyrrolidine (13.4g, 28%), as a colourless liquid. $[\alpha]_D^{25}$ = - 64.86° (neat); δ_H (200 MHz; $CDCl_3$; Me_4Si) 7.33 (5 H, m, ArH), 4.14 (2 H, q, CH_2), 3.93, 3.56 (2 H, AB-system, CH), 3.25 (2 H, m, CH_2N), 2.36 (1 H, m, CHN), 1.95 (4 H, m, CH_2), 1.27 (3 H, t, CH_3); δ_C ($CDCl_3$) 174.26, 141.70, 129.38, 128.28, 127.29, 65.18, 60.64, 58.43, 53.18, 29.29, 22.92, 14.28, ν_{max} (neat)/ cm^{-1} 2980, 2890, 2800 (N-CH_2), 1730 (C=O), 1600, 1450, 1370, 1270 (C-O), 1180, 1040; *m\z* 233 (M^+).

$C_{14}H_{19}NO$ calcd; C, 72.07: H, 8.20: N, 6.00
found; C, 72.31: H, 8.26: N, 6.14.

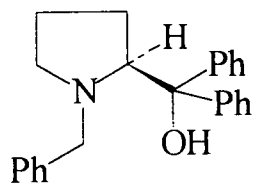
70) (2S)-N-Benzyl-2-(α-hydroxy-α-methyl)ethylpyrrolidine (163)



A solution of methylmagnesium bromide in ether/toluene (1.4M, 108.75mls, 152mmol) was added to a solution of (2S)-N-benzyl-2-carboxyethylpyrrolidine (13.4g, 60.9 mmol) in ether (20ml) at 0°C. The reaction mixture was heated under reflux for 2h, cooled to room temperature and then quenched with aqueous NH_4Cl solution. The aqueous layer was extracted into ethyl acetate (4x50ml) and the combined extracts dried over $MgSO_4$. Concentration under reduced pressure, followed by distillation (96°C, 0.25mmHg), gave (2S)-N-benzyl-2-(α-hydroxy-α-methyl)ethylpyrrolidine as a colourless liquid (10.4g, 78%). $[\alpha]_D^{25}$ = - 49° (neat); δ_H (200 MHz; $CDCl_3$; Me_4Si) 7.33(5 H, m, ArH), 4.23, 3.62 (2 H, AB-system, NCH_2), 2.96 (2 H, m, CH_2N), 2.86 (1H, s, OH), 2.51 (1 H, m, CHN), 1.84 (4 H, m, CH_2), 1,23 (6 H, d, CH_3); δ_C ($CDCl_3$) 128.30, 128.11, 126.82, 72.89, 72.73, 63.11, 55.38, 28.55, 25.28, 27.77, 25.11; ν_{max} (neat)/ cm^{-1} 3430 (OH), 2968, 2871, 2790 (N-CH_2), 1494, 1452, 1373 (C-CH_3), 1298 (O-H), 1155, 1122 (C-O), 1070, 941; *m/z* 219 (M^+).

$C_{14}H_{21}NO$ calcd; C, 76.67: H, 9.65: N, 6.38.
found; C, 76.82: H, 9.81: N, 6.29.

71) (2S)-N-Benzyl-2-(α-hydroxy-α,α-diphenyl)methyl pyrrolidine (164)

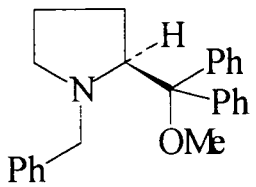


(S)-1,1-Diphenylprolinol (4.0g, 15.78mmol) and benzyl chloride (2.19g, 17.36mmol) were added to a solution of potassium carbonate (20%, 50ml) and the solution heated under reflux for 1h. The reaction was extracted into ethyl acetate (3x30ml) and the combined organic extracts dried over $MgSO_4$. Removal of the solvent under reduced pressure gave a white solid which was recrystallised from (petrol/ethyl acetate) to give (2S)-N-benzyl-2-(α-hydroxy-α,α-diphenyl)methylpyrrolidine (2.83g, 52%) as colourless

crystals. m.p. 113-114°C, (lit [213] 113-115°C); δ_H (200 MHz; $CDCl_3$; Me_4Si) 7.72-6.93 (15H, m, ArH), 4.65 (1 H, s, OH), 3.94 (1 H, m, CHN), 3.22, 3.11 (2 H, AB-system, NCH_2), 2.86 (2 H, m, CH_2N), 1.71 (4 H, m, CH_2); δ_C ($CDCl_3$) 147.81, 146.52, 139.28, 128.46, 127.98, 126.74, 126.24, 125.47, 77.77, 70.56, 60.41, 55.35, 29.61, 23.96; ν_{max} (KBr)/ cm^{-1} 3400 (OH), 3050, 2800 (N-CH_2), 1600, 1500, 1450, 1280 (O-H), 1040 (C-O)900; *m\z* 343 [M+H]

$C_{24}H_{25}NO$ calcd; C, 83.92: H, 7.33: N, 4.08.
found; C, 83.89: H, 7.31: N, 4.10.

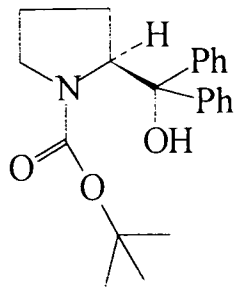
72) (2S)-N-Benzyl-2-(α-methoxy-α,α-diphenyl)methyl pyrrolidine (166)



A solution of (2S)-N-benzyl-2-(α-hydroxy-α,α-diphenyl)methylpyrrolidine (2.50g, 7.28 mmol) was added to a suspension of NaH (0.27g, 7.28mmol) in THF (20ml) at 0°C under N_2. The reaction was stirred for 5min then a solution of MeI (0.44ml, 1.02g, 7.28mmol) in THF (1ml) was added. The reaction was allowed to warm to 18°C, was heated under reflux for 24h, and then quenched with NH_4Cl solution. The aqueous layer was extracted into ethyl acetate (3x20ml) and the combined organic extracts dried over $MgSO_4$. Concentration under reduced pressure and purification over silica gel, eluting with ethyl acetate/petrol (4:6) gave (2S)-N-Benzyl-2-(α-methoxy-α,α-diphenyl)methyl-pyrrolidine (0.39g, 15%) as a yellow solid. m.p. 73-74°C, (lit [213] 72-74°C); δ_H (200 MHz; $CDCl_3$; Me_4Si) 7.73-7.15 (15 H, m, ArH), 3.92 (1 H, m, CHN), 4.34, 3.07 (2 H, AB-system, NCH_2), 2.93 (3H, s, OCH_3), 2.53 (2 H, m, CH_2N), 1.94 (2 H, m, CH_2), 1.31 (2 H, m, CH_2); δ_C ($CDCl_3$) 141.05, 140.67, 130.26, 128.52, 127.96, 127.18, 127.06, 126.31, 87.60, 70.28, 61.86, 54.71, 51.79, 28.81, 23.48; ν_{max} (KBr)/ cm^{-1} 3090, 2980, 2890, 2800 (C-O-CH_3), 1600, 1500, 1450, 1380 (C-CH_3) 1260, 1130 (C-O), 1080, 920; *m\z* 357 (M^+).

$C_{25}H_{27}NO$ calcd; C, 83.99: H, 7.61: N, 3.91.
found; C, 83.86: H, 7.69: N, 3.94.

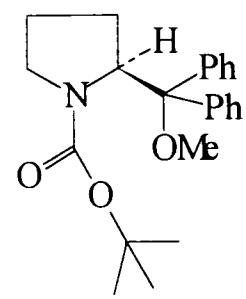
73) (2S)-N-*tert*-Butoxycarbamate-2-(α-hydroxy-α,α-diphenyl) methylpyrrolidine (171)



Di-*tert*-butyl dicarbonate (35.2g, 78.94mmol) was added to a solution of (S)-(-)-1,1-diphenylprolinol (10.0g, 39.47mmol) in methanol (50ml) and triethylamine (5.62g, 59.2mmol). The solution was heated at 40°C for 10min and then stirred at 18°C for a further 1h. The reaction was quenched with 1M hydrochloric acid and then extracted into ethyl acetate (3x50ml). The combined organic extracts were dried over $MgSO_4$ and removal of the solvent under reduced pressure gave (2S)-N-*tert*-butoxycarbamate-2-(α-hydroxy-α,α-diphenyl)methylpyrrolidine (13.17g, 94%) as a white crystalline solid. m,p. 121-122°C. δ_H (200 MHz; $CDCl_3$; Me_4Si) 7.37 (10 H, m, CH), 4.95 (1 H, m, CHN), 2.95, 3.46 (2 H, AB-system, CH_2N), 2.07 (4 H, m, CH_2), 1.24 (9H, s, CH_3); δ_C ($CDCl_3$) 146.32, 143.65, 128.03, 127.65, 126.88, 81.52, 80.37, 65.67, 47.68, 29.57, 28.18, 22.75; ν_{max} (KBr)/ cm^{-1} 3369 (OH), 3049, 2854, 1656 (C=O), 1457, 1390, 1243 (O-H), 1161, 1093 (C-O), 1035, 989; *m/z* 354 [M+H].

$C_{22}H_{27}NO_3$calcd; C, 74.76: H, 7.70: N, 3.96.
found; C, 74.75: H, 7.72: N, 4.04.

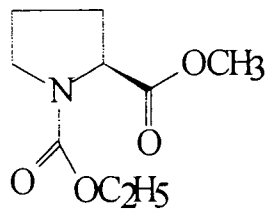
74) (2S)-N-*tert*-Butoxycarbamate-2-(α-methoxy-α,α-diphenyl) methylpyrrolidine (172)



A solution of (2S)-N-*tert*-butoxycarbamate-2-(α-hydroxy-α,α-diphenyl)methyl pyrrolidine (13.0g, 36.67mmol) was added to a suspension of NaH (2.03g, 55.0mmol) in THF (30ml) at 0°C under N_2 and the reaction stirred for 5min. A solution of MeI (3.88ml,

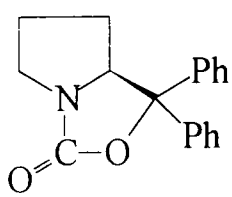
7.77g, 55.0mmol) in THF (5ml) was added and the reaction heated under reflux for 24h. The reaction was quenched with NH_4Cl solution and the aqueous layer extracted into ethyl acetate (3x20ml). The combined organic extracts were dried over $MgSO_4$ and concentration under reduced pressure gave a yellow oil. Purification over silica gel eluting with ethyl acetate/petrol (4:6) gave (2S)-N-*tert*-butoxycarbamate-2-(α-methoxy-α,α-diphenyl)methylpyrrolidine as a clear oil (2.44g, 18%). δ_H (200 MHz; $CDCl_3$; Me_4Si) 7.38 (10 H, m, ArH), 4.93 (1 H, m, CHN), 3.36, 2.52 (2H, AB-system, CH_2N), 2.98 (3 H, s, OCH_3), 1.98 (4 H, m, CH_2), 1.22 (9 H, s, CH_3); δ_C ($CDCl_3$) 156.07, 130.34, 129.96, 128.07, 127.57, 79.44, 53.10, 48.17, 30.20, 28.84, 28.22, 23.66; ν_{max} (neat)/ cm^{-1} 3056, 2925, 1693 (C=O), 1600, 1493, 1446, 1386, 1285 (C-O), 1253, 1170, 1074 (C-O), 875; *m/z* 368 (M+H).

75) (2S)-N-Ethylcarbamate-2-carboxymethylpyrrolidine (175)



A solution of (S)-(-)-proline (25.0g,217.0mmol) in dry methanol (150ml) was added to anhydrous K_2CO_3 (28.6g,217mmol) followed by the addition of ethyl chloroformate (49.0g,434mmol) over 5min at 25°C. The reaction mixture was stirred for 12h at 0°C and then the excess MeOH was removed under reduced pressure and water (100ml) was added. The reaction was extracted into chloroform (3x50ml) and the combined organic extracts were washed with brine (2x30ml) and then dried over $MgSO_4$. Removal of the solvent under reduced pressure gave (2S)-N-ethylcarbamate-2-carboxymethylpyrrolidine (two conformers 1:1) (39.5g, 91%) as a colourless oil (lit [225]) . δ_H (200 MHz; $CDCl_3$; Me_4Si) 4.12 (2H, m, CH_2), 3.92 (2 H, m, CH_2), 3.49 (3 H, s, OMe), 3.33 (1 H, m, CH), 1.9 (4 H, m, CH_2), 1.03 (3 H, m, CH_3); δ_C ($CDCl_3$) (two conformers 1:1) 172.72, 172.58, 154.52, 153.98, 60.68, 58.45, 58.19, 51.46, 46.14, 45.74, 30.27, 29.31, 23.74, 22.92, 14.077, 14.02; ν_{max} (neat)/ cm^{-1} 2980, 2881, 1748 (C=O), 1704 (C=O), 1414, 1381, 1348, 1277 (C-O), 1173, 1090, 920; *m/z* 202 (M +H)

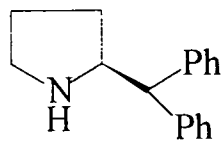
76) (5S)-[3.3.0]-1-Aza-2-oxo-3-oxa-4,4-diphenyl-bicyclooctane (173)



A solution of phenylmagnesium bromide in THF (1.0M, 386ml, 386mmol) was added to a solution of (S)-2-carboxymethyl-N-ethylformylpyrrolidine (39.0g, 193mmol) in THF (100ml) under an inert atmosphere of N_2 at 0°C. The solution was warmed to 18°C and then heated under reflux for 3h. The reaction was then added to an ice cold solution of NH_4Cl and the aqueous layer extracted into ethyl acetate (4x100ml). The combined organic extracts were dried over $MgSO_4$ and the solvent removed under reduced pressure to give (5S)-[3.3.0]-1-aza-2-oxo-3-oxa-4,4-diphenyl-bicyclooctane (44.0g, 82%) as a white crystalline solid. m.p. 148-149°C, δ_H (200 MHz; $CDCl_3$; Me_4Si) 7.53-7.21 (10 H, m, ArH), 4.53 (1 H, m, CH), 3.64, 3.31 (2 H, AB-system, CH_2N), 1.83 (4 H, m, CH_2); δ_C ($CDCl_3$) 160.02, 139.86, 128.19, 126.60, 124.99, 85.44, 68.72, 45.58, 28.51, 24.39; ν_{max} (neat)/ cm^{-1} 2969, 2863, 1976, 1757 (C=O), 1583, 1492, 1447, 1374, 1255 (C-O), 1177, 1095, 964; *m/z* (EI) 279.1 (M^+, 27%), 105.0 (100%).

$C_{18}H_{17}NO_2$calcd; C,77.38: H,6.14: N,5.02.
found; C,77.40: H,6.14: N,5.01.

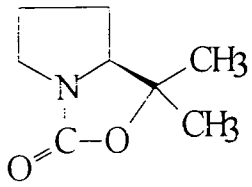
77) (2S)-(Diphenyl)methylpyrrolidine (168)



A mixture of (5S)-[3.3.0]-1-aza-2-oxo-3-oxa-4,4-diphenyl-bicyclooctane (5.0g, 17.9mmol) and Pd/C (1.0g) (10%) in methanol (100ml) was hydrogenated at room temperature for 48h. The catalyst was filtered off and the methanol removed under reduced pressure. Purification, firstly over silica gel eluting firstly with ethyl acetate then methanol followed by distillation gave (2S)-(diphenyl)methylpyrrolidine (two absolute ring conformers 1:1) (2.8g, 67%) as a colouless oil. b.p. (135°C, 0.01 mmHg) $[\alpha]_{D=}$−7.84 (c2.05, $CHCl_3$) [lit [213], $[\alpha]_{D=}$−7.8 (c2.11, $CHCl_3$)]. δ_H (200 MHz; $CDCl_3$; Me_4Si) 7.28 (10 H, m, Arh), 3.89 (2 H, m, CH), 2.93, 2.85 (2H, AB-system, CH_2N), 1.69 (3 H, m, CH_2) 1.37 (1 H, m,CH_2) ; δ_C ($CDCl_3$) 142.86, 142.78, 128.58, 128.43, 127.95, 126.39, 62.08, 57.23, 45.60, 30.47, 24.29; ν_{max} (neat)/ cm^{-1} 3405 (NH), 2962, 1596, 1494, 1450, 1399, 1348, 1112, 1076, 1031, 910; *m/z* (CI) 238.4 (M^+, 39%, 84.1, 19%); (Found: $[M + H]^+$ 238.1790. $C_{17}H_{19}N$ + H requires M, 238.1596).

$C_{17}H_{20}Cl$ (salt) calcd; C, 74.69: H, 7.38: N, 5.13: Cl, 12.80.
Found.; C, 74.65: H, 7.62: N, 4.98: Cl, 12.71.

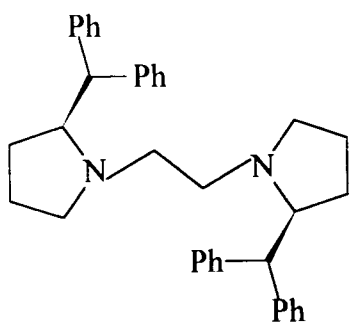
78) (5S)-[3.3.0]-1-Aza-2-oxo-3-oxa-4,4-dimethyl-bicyclooctane (176)



A solution of methyl magnesium bromide in THF (1.44M, 68.75ml, 99mmol) was added to a solution of (S)-2-carboxymethyl-N-ethylformylpyrrolidine (10.0g, 49.5mmol) in THF (30ml) under N_2 at 0°C. The solution was warmed to 18°C and then heated under reflux for 3h. The reaction was then added to an ice cold solution of NH_4Cl and the aqueous layer extracted into ethyl acetate (4x50ml). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure to give (5S)-[3.3.0]-1-aza-2-oxo-3-oxa-4,4-dimethyl-bicyclooctane (6.45g, 84%) as a white crystalline solid. m.p. 58-59°C; δ_H (200 MHz; $CDCl_3$; Me_4Si) 3.54 (2 H, m, CH_2), 3.10 (1 H, m, CH), 1.98 (4 H, m, CH_2), 1.45 (3 H, s, CH_3), 1.31 (3 H, s, CH_3); δ_C ($CDCl_3$) 160.78, 79.50, 68.98, 45.36, 28.66, 26.38, 25.40, 22.82; ν_{max} (neat)/ cm^{-1} 2972, 2878, 1734 (C=O), 1467, 1396, 1289 (C-O), 1234, 1168, 1104, 1065, 987; *m/z* 155 (M^+)

$C_8H_{13}NO_2$calcd: C, 61.90: H, 8.45: N, 9.03.
found.: C, 61.86: H, 8.53: N, 8.97.

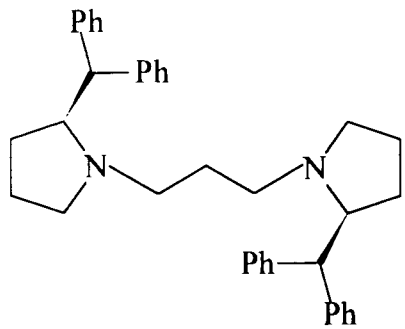
79) N,N'-1,2-ethane-bis((2S)-(diphenyl)methylpyrrolidine) (177)



Oxalyl chloride was added to a solution of (2S)-(diphenyl)methylpyrrolidine (3.0g, 12.6mmol) triethylamine (2.11ml, 1.53g, 15.0mmol) and DMAP (0.15g, 1.26mmol) at -78°C. After 10min the solution was warmed to 0°C and stirred for 8h. The solution was filtered and the solvent removed under reduced pressure to leave a brown solid. Without purification this solid was dissolved in dry THF (30ml) and the resulting solution added to a slurry of $LiAlH_4$ (0.71g,18.9mmol) in THF (10ml) at 0°C. After 8h the reaction was quenched with NaOH (0.2M, 5ml), filtered and the reaction mixture extracted into ethyl acetate (2x20ml). The combined organic extracts were dried over

$MgSO_4$ and concentrated to give a yellow oil. Purification over neutral alumina eluting with n-hexane/ethyl acetate (9:1) gave N,N'-1,2-ethane-bis((2S)-(diphenyl)methyl pyrrolidine) (1.70g, 54%) as a white solid. m.p. 103-104°C; $[\alpha]_D$= -49.54 (c 1.09, $CHCl_3$); δ_H (200 MHz; $CDCl_3$; Me_4Si) 7.31 (20 H, m, ArH), 3.96 (2 H, d, CH), 3.25 (2 H, m, CHN), 3.00, 2.17 (4 H, ABsystem, CH_2), 2.47, 2.19 (4 H, ABsystem, CH_2), 1.56-1.92 (8 H, m, CH_2); δ_C ($CDCl_3$) 144.73, 144.29, 129.81, 129.62, 128.80, 128.51, 126.74, 126.51, 68.30, 57.44, 55.63, 55.30, 30.27, 24.51; ν_{max} (KBr)/ cm^{-1} 2962, 2791 (N-CH_2), 1599, 1493, 1449, 908, 735, 699; *m/z* (CI) 501.3 [M+H, 25.3%], 236.2 (100%); (Found: $[M + H]^+$ 501.3266. $C_{36}H_{40}N_2$ + H requires M, 501.3269).

80) N,N'-1,3-propane-bis((2S)-(diphenyl)methylpyrrolidine) (178)

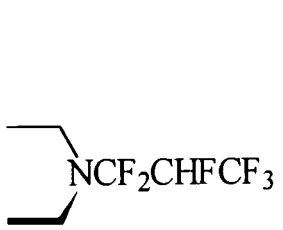


A solution of (2S)-(diphenyl)methylpyrrolidine (2.0g, 8.4mmol) was added to slurry of K_2CO_3 in EtOH (30ml). After 15min 1,3-diodopropane (0.42ml, 4.2mmol) was added and the solution refluxed for 8h. The reaction was filtered and then concentrated under reduced pressure. Purification over neutral alumina eluting with n-hexane/ethyl acetate (9:1) gave a colourless oil which crystallised on standing to give N,N'-1,3-propane-bis((2S)-(diphenyl)methylpyrrolidine) (2.0g, 92%) as a white solid. m.p. 73-74°C; $[\alpha]_D$= -25.5 (c 1.73, $CHCl_3$); δ_H (200 MHz; $CDCl_3$; Me_4Si) 7.28 (20 H, m, ArH) 3.98 (2 H, d, CH), 3.20 (2 H, m, CHN), 2.0 (10 H, m, CH_2), 1.73-1.45 (8 H, m, CH_2); δ_C ($CDCl_3$) 144.62, 144.32, 129.62, 129.46, 128.66, 128.47, 126.54, 126.43, 68.39, 57.62, 55.05, 54.94, 30.56, 24.21; ν_{max} (KBr)/ cm^{-1} 2959, 2788 (N-CH_2), 1493, 1449, 753, 699 (cm^{-1}); *m/z* (CI) 515.4 [M+H, 22.8%], 84 (100%); (Found: $[M + H]^+$ 515.3426. $C_{37}H_{42}N_2$ + H requires M, 515.3426).

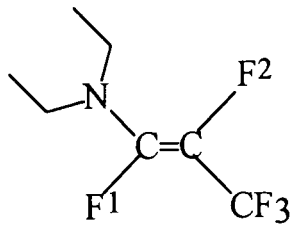
Section H

Preparation and reactions of Ishikawa's reagent

81) Ishikawa's reagent (diethylamine N-1,1,2,3,3,3-hexafluoro propane) (179 & 180)



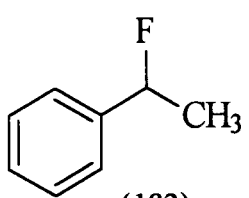
(179)



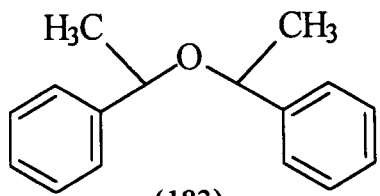
(180)

Hexafluoropropene (41.0g, 270mmol) was bubbled through a solution of diethylamine (10.0g, 130mmol) in dry diethyl ether (20ml) under N_2 at 0°C. All of the diethylamine had reacted after 2h and the reaction mixture was allowed to warm to 18°C. The crude product was purified by distillation (51-53°C, 40mmHg) (lit [63], 56-57°C, 58mmHg) to 7give diethylamine N-1,1,2,3,3,3-hexafluoropropane (26.0g, 89%). δ_H (200 MHz; $CDCl_3$; Me_4Si) 5.05, 4.83 (1 H, m, CHF) $^2J_{H-F}$ 52.3Hz, 3.18 (2 H, m, CH_2), 2.95 (2 H, m, CH_2), 1.16 (3 H, m, CH_3); δ_F (250MHz) -218.42 (1 H, m, CHF), -198.98 (1 H, m, CF), -119.28 (1 H, d, CF), -89.81,-83.46 (2 F, ABsystem, CF_2), -75.26 (3 F, s, CF_3), -65.73 (3 F, s, CF_3).

82) Preparation of 1-fluoro-1-phenylethane (182) & bis(-1-phenylethyl)ether (183) using Ishikawa's reagent



(182)

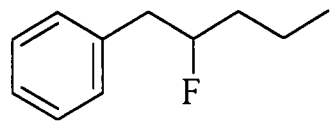


(183)

1-Phenylethanol (1.0g,8.18mmol) was added to a solution of diethylamine N-1,1,2,3,3,3-hexafluoropropane (1.84g, 8.18mmol) in dry ether (30ml) and the reaction was heated under reflux for 3h. The reaction was quenched with water (10ml), the organic layer was extracted into ether (2x20ml) and the combined organic extracts dried over $MgSO_4$. Removal of the solvent under reduced pressure and purification over silica gel eluting with neat petrol (40/60) gave a mixture of 1-fluoro-1-phenylethane (182) 25% and bis(-1-phenylethyl)ether (183) (a mixture of diastereomers) 75% as judged by ^1H NMR.

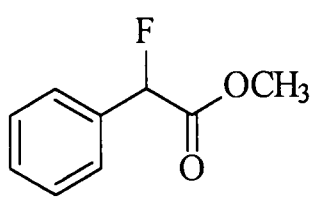
1-fluoro-1-phenylethane δ_H (200 MHz; $CDCl_3$; Me_4Si) 7.39 (5 H, m, ArH), 5.80, 5.60 (1 H, dq, CH) $^2J_{HF}$ 47.5Hz, 1.74,1.64 (3 H, dd, CH_3) $^3J_{H-F}$ 25Hz; δ_F (250MHz) -167.7 (1 F, dq, CHF); *m/z* 124 (M^+). Bis(-1-phenylethyl) ether. δ_H (200 MHz; $CDCl_3$; Me_4Si) 7.39 (10 H, m, ArH), 4.60 (1 H, q, CH), 4.35 (1 H, q, CH), 1.55 (3 H, d, CH_3), 1.47 (3 H, d, CH_3); mass spectrum m/z 244 $(M^+ + NH4)^+$ (Found: $[M + NH_4]^+$ 244.1704. $C_{16}H_{18}O + NH_4^+$ requires M, 244.1701).

83) Preparation of 2-fluoro-1-phenylpentane (187) using Ishikawa's reagent



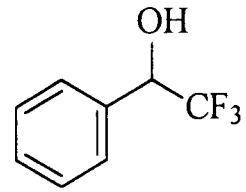
A solution of 1-phenylpentan-2-ol (1.0g, 6.08mmol) in ether (10ml) was added to a solution of diethylamine N-1,1,2,3,3,3-hexafluoropropane (1.97g, 9.12mmol) in dry ether and the solution heated under reflux for 3h. The reaction was quenched with water (10ml), the organic layer was extracted into ether (2x20ml) and the combined organic extracts dried over $MgSO_4$. Removal of the solvent under reduced pressure followed by purification over silica gel, eluting with neat petrol (40/60) gave 2-fluoro-1-phenylpentane (102) (0.72g, 73%) as a clear liquid; δ_H (200 MHz; $CDCl_3$; Me_4Si) 7.25 (5 H, m, ArH), 4.79, 4.55 (1 H, m, CHF) $^2J_{H-F}$ 48Hz, 2.87 (2 H, m, CH_2), 1.50 (4 H, m, CH_2), 0.93 (3 H, t, CH_3); δ_F (250MHz) -179.30 (1 F, m, CHF); m/z 166 (M^+) (Found M^+ 166.1157. $C_{11}H_{15}F$ requires M, 166.1147)

84) Preparation of methyl 2-fluorophenylacetate (192) using Ishikawa's reagent



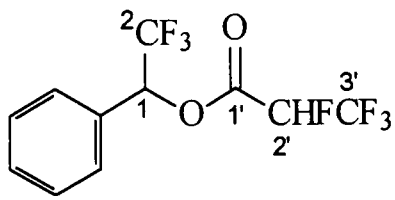
A solution of (±) methyl mandelate (1.0g, 6.0mmol) in ether was added to a solution of diethylamine N-1,1,2,3,3,3-hexafluoropropane (1.3g, 6.0mmol) in ether (30ml) and the reaction heated under reflux for 3h. The reaction was quenched with water (10ml), the organic layer extracted into ether (2x20ml) and the combined organic extracts were dried over $MgSO_4$. Removal of the solvent under reduced pressure followed by purification over silica gel, eluting with ether/petrol (8:92), gave methyl 2-fluorophenylacetate as a clear oil (0.72g, 55%). δ_H (200 MHz; $CDCl_3$; Me_4Si) 7.46 (5 H, m, ArH), 5.91, 5.72 (1 H, d, CHF) $^2J_{H-F}$ 47.58Hz, 3.79 (3 H, s, CH_3); δ_F (250MHz) -180.33 (1 F, d, CHF) $^2J_{H-F}$ 47.53Hz; m/z 168 (M^+). (Found M^+ 168.0586. $C_9H_9O_2F$ requires M, 168.0586)

85) Preparation of 2,2,2-Trifluoro-1-phenylethanol (193)



A solution of 2,2,2-trifluoroacetophenone (5.0g,28.7mmol) in MeOH (5ml) was added to a slurry of $NaBH_4$ (1.09g,28.7mmol) in CH_2Cl_2/MeOH (1:1) (30ml). The reaction was stirred at 25°C for 4h then quenched with water (10ml) and extracted into CH_2Cl_2 (2x20ml). The combined organic extracts were dried over $MgSO_4$ and the crude oil distilled under reduced pressure to give 2,2,2-trifluoro-1-phenylethanol as a colourless oil (4.6g, 91%). δ_H (200 MHz; $CDCl_3$; Me_4Si) 7.45 (5 H, m, ArH), 4.97 (1 H, q, CH), 3.64 (1 H, s, OH, D_2O, ex); δ_F (250MHz) -78.18 (3 F, d, CF_3); ν_{max} (neat)/ cm^{-1} 3404 (OH), 3069, 2919, 1495, 1457, 1358, 1266, 1206, 1171, 1063 (C-O), 866; *m/z* 176 (M+). (Found M+ 176.0449. $C_8H_7OF_3$ requires M, 176.0448).

86) Preparation of 2,2,2-trifluoro-1-phenylethyl 2',3',3',3'-tetrafluoropropionate (194) using Ishikawa's reagent

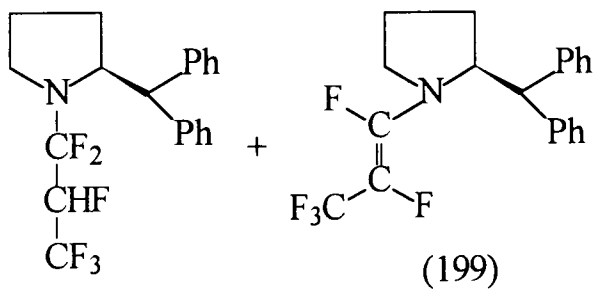


A solution of 2,2,2-trifluoro-1-phenylethanol (3.25g, 18.46mmol) in ether was added to a solution of diethylamine N-1,1,2,3,3,3-hexafluoropropane (6.0g, 27.7mmol) in dry ether (30ml). The mixture was heated under reflux for 3h and then quenched with water (10ml) The organic layer was extracted into ether (2x20ml) and the combined organic extracts dried over $MgSO_4$. Removal of the solvent under reduced pressure followed by purification over silica gel, eluting with ether petrol (1:9) gave 2,2,2-trifluoro-1-phenylethyl 2',3',3',3'-tetrafluoropropionate (194) (3.41g, 61%) as a clear oil . δ_H (200 MHz; $CDCl_3$; Me_4Si) 7.48 (5 H, m, ArH), 6.31 (1 H, m, CH), 5.41, 5.15 (1 H, m, CHF), δ_F (250MHz) -76.09 (3 F, d, CF_3), -76.81 (3 F, d, CF_3) -205.26 (1 F, m, CHF); ν_{max} (neat)/ cm^{-1} 3041, 2972, 1791 (C=O), 1498, 1458, 1356, 1272 (C-O), 1137, 1010, 871; *m/z* 304 (M+). (Found M^+ 304.0334. $C_{11}H_7F_7O_2$ requires M, 304.0334).

Section I

Preparation and reactions of chiral analogues of Ishikawa's reagent and DAST

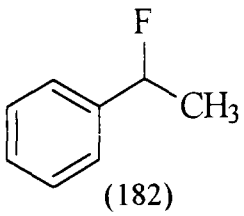
87) (2S)-(Diphenyl)methylpyrrolidine-N-1,1,2,3,3,3-hexa-fluoropropane



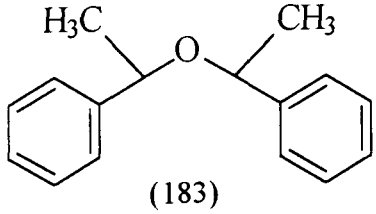
(198) (199)

Hexafluoropropene (1.40g,9.26mmol) was bubbled through a solution of (2S)-(diphenyl) methylpyrrolidine (1.0g, 4.21mmol) in dry THF (20ml) under N_2 at 0°C. All of the (2S)-(diphenyl)methylpyrrolidine had reacted after 2h and the reaction mixture allowed to warm to 18°C. Filtration under N_2 and concentration under reduced pressure gave (2S)-(diphenyl)methylpyrrolidine-N-1,1,2,3,3,3-hexafluoropropane (1.50g, 92.3%) as a clear oil. δ_H (200 MHz; $CDCl_3$; Me_4Si) 7.34 (10 H, m, ArH), 5.19, 4.92 (1 H, m, CHF) $^2J_{H-F}$ 54Hz, 4.3 (1 H, m, CH), 4.1 (1 H, d, CH), 3.65 (1 H, m, CH_2) 3.32 (1 H, m, CH_2) 3.13 (2 H, m, CH_2), 2.02 (4 H, m, CH_2); δ_F (250MHz) -210 (1 F, m, CHF), -205.90 (1 F, m, CHF), -199.18,-198.57 (1 F, d, CF), -117.49,-116.97 (1 F, d, CF), -88.79 (1 F, m, CF_2), -74.96 (1 F, s, CF_3), -65.20 (3 F, s, CF_3).

88) Preparation of 1-fluoro-1-phenylethane (182) & bis(-1-phenylethyl)ether (183) using (2S)-(diphenyl)methyl pyrrolidine-N-1,1,2,3,hexafluoropropane



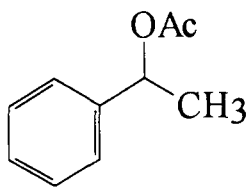
(182)



(183)

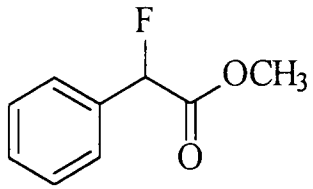
1-Phenylethanol (1.0g, 8.18mmol) was added to a solution of (2S)-(diphenyl)methyl-pyrrolidine-N-1,1,2,3,3,3-hexafluoropropane (1.58g, 4.09mmol) in dry ether (30ml) and the solution kept at 0°C for 3h. The reaction was quenched with water (10ml), the organic layer was extracted into ether (2x20ml) and the combined organic extracts dried over $MgSO_4$. Removal of the solvent under reduced pressure and purification over silica gel eluting with neat petrol (40/60) gave a mixture of 1-fluoro-1-phenylethane 10% and bis(-1-phenylethyl)ether 90% as judged by ^1H NMR. 1-fluoro-1phenylethanol. δ_H (200 MHz; $CDCl_3$; Me_4Si) 7.39 (5 H, m, ArH), 5.80, 5.60 (1 H, dq, CH) $^2J_{HF}$ 47.5Hz, 1.74,1.64 (3 H, dd, CH_3) $^3J_{H-F}$ 25Hz; δ_F (250MHz) -167.7 (1 F, dq, CHF); *m/z* 124 (M^+). Bis(-1-phenylethyl)ether. δ_H (200 MHz; $CDCl_3$; Me_4Si) 7.39 (10 H, m, ArH), 4.60 (1 H, q, CH), 4.35 (1 H, q, CH), 1.55 (3 H, d, CH_3), 1.47 (3 H, d, CH_3); mass spectrum m/z 244 $(M^+ + NH4)^+$

89) Ethyl(α-acetoxy)benzene



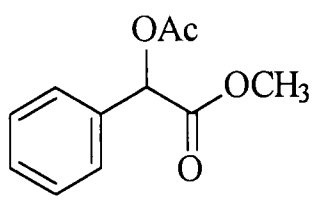
A solution of 1-phenyl ethanol (1.0g, 8.18mmol) in CH_2Cl_2 was added to a solution of DMAP (0.09, 0.8mmol) and Et_3N (1.1ml, 8.18mmol) the solution was stirred for 15min then acetyl chloride (0.7ml, 9.81mmol) was added and the solution stirred for 1h. The solvent was removed under reduced pressure and purification over silica gel eluting with ether/petrol (1:9) gave ethyl(α-acetoxy)benzene as a clear oil (1.19g, 89%). δ_H (200 MHz; $CDCl_3$; Me_4Si) 7.39 (5 H, m, Ar), 5.96 (1 H, q, CH), 2.11 (3 H, s, CH_3), 1.60 (3 H, d, CH_3); δ_C ($CDCl_3$) 170.82, 142.19, 129.09, 128.38, 126.60, 72.83, 22.72, 21.84; ν_{max} (neat)/ cm^{-1} 3032, 2981, 2854, 1743(C=O), 1495, 1453, 1371, 1240(C-O), 1209, 1065, 944; *m/z* 164 (M^+)

90) Preparation of methyl 2-fluorophenylacetate (192) by a kinetic resolution of racemic (±) methyl mandelate using (2S)-(diphenyl)methylpyrrolidine-N-1,1,2,3,3,3-hexafluoro propane



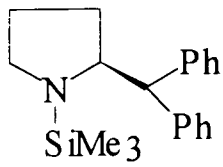
A solution of (±) methyl mandelate (1.0g, 6.0mmol) in THF (10ml) was added to a solution of (2S)-(diphenyl)methylpyrrolidine-N-1,1,2,3,3,3-hexafluoropropane (0.7g, 3.0 mmol) in THF (30ml) and the solution stirred for 3h at 0°C. The reaction was quenched with water (10ml), the organic layer extracted into ether (2x20ml) and the combined organic extracts dried over $MgSO_4$. Removal of the solvent followed by purification over silica gel eluting with ether/petrol (8:92) gave methyl 2-fluorophenylacetate as a clear oil (0.05g, 6%). δ_H (200 MHz; $CDCl_3$; Me_4Si) 7.46 (5 H, m, ArH), 5.91, 5.72 (1 H, d, CHF) $^2J_{H-F}$ 47.58Hz, 3.79 (3 H, s, CH_3); δ_F (250MHz) -180.33 (1 F, d, CHF) $^2J_{H-F}$ 47.53Hz; m/z 168 (M^+).

91) Methyl 2-acetoxyphenylacetate



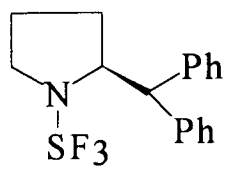
A solution of methyl mandelate (0.24g,1.46mmol), DMAP (0.02g, 0.15mmol) and Et_3N (0.2ml,1.46mmol) in CH_2Cl_2 (20ml) were stirred for 15min then acetyl chloride (0.12ml,1.72mmol) was added and the solution stirred for a further 1h. The solvent was removed under reduced pressure and purification over silica gel eluting with ether/petrol (3:7) gave methyl 2-acetoxyphenylacetate (0.29g, 96%) as a clear oil . δ_H (200 MHz; $CDCl_3$; Me_4Si) 7.31 (5 H, m, ArH), 5.93 (1 H, s, CH), 3.70 (3 H, s, OCH_3), 2.18 (3H, s, CH_3); δ_C ($CDCl_3$) 170.80, 169.81, 134.23, 129.77, 129.30, 128.15, 74.94, 53.09, 21.17; ν_{max} (neat)/ cm^{-1} 2995, 2933, 1748(C=O), 1726(C=O) 1595, 1498, 1450, 1372 (C-CH_3), 1343, 1251 (C-O), 1206, 1174, 1095, 1072, 866; *m/z* 208 (M^+) (Found M^+ 208.0732. $C_{11}H_{12}O_4$ requires M, 208.0736)

92) (2S)-(Diphenyl)methylpyrrolidine-N-trimethylsilane (200)



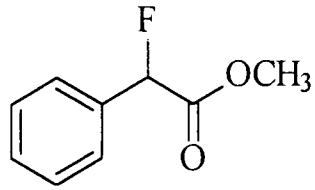
A solution of (2S)-(diphenyl)methylpyrrolidine (2.0g, 8.43mmol), Et_3N (1.40ml, 10.16 mmol) and DMAP (0.1g, 0.84mmol) in THF (30ml) was stirred at 25°C for 1h. Chlorotrimethylsilane (1.28ml, 10.1mmol) was added and after 1h the solution was filtered under N_2 and the solvent removed under reduced pressure. Distillation (110°C,0.01mmHg) gave (2S)-(diphenyl)methylpyrrolidine-N-trimethylsilane as a clear oil (2.08g, 79%). δ_H (200 MHz; $CDCl_3$; Me_4Si) 7.74 (10 H, m, ArH), 4.27 (1 H, m, CH), 4.05 (1 H, d, CH), 3.30 (2 H, m, CH_2), 1.90 (4 H, m, CH_2), 0.01(9 H, s, $SiMe_3$); δ_C ($CDCl_3$) 145.07, 130.03, 128.90, 126.70, 64.01, 56.49, 46.20, 32.28, 26.16, 0.06; *m/z* 308 (M^+)

93) (2S)-(Diphenyl)methylpyrrolidine-N-sulphur trifluoride (201)



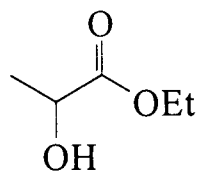
Sulphur tetrafluoride (0.41g, 3.79mmol) was bubbled into a solution of (2S)-(diphenyl) methylpyrrolidine-N-trimethylsilane (1.0g, 3.23mmol) in $CFCl_3$ (10ml) at -78°C. The solution was allowed to warm 25°C and then the reaction flushed with N_2 for 1h. The solvent was removed under reduced pressure to give (2S)-(diphenyl)methylpyrrolidine-N-sulphur trifluoride (1.02g, 98%) as a viscous oil (1.02g, 98%). δ_H (200 MHz; $CDCl_3$; Me_4Si) 7.23 (10 H, m, ArH), 4.85 (2 H, m, CH), 3.1 (2 H, m, CH_2), 2.1-1.8 (4 H, m, CH_2); δ_C ($CDCl_3$) 140.18, 140.15, 128.10, (m,Ar), 61.66, 56.69, 42.30, 30.87, 30.79, 23.98; δ_F (250MHz) +35.62 (3 F, br, SF_3); *m/z* $C_{17}H_{18}NSF_2$ 306 (M +H)

94) Preparation of methyl 2-fluorophenylacetate (192) by a kinetic resolution of racemic (±) methyl mandelate using (2S)-(diphenyl)methylpyrrolidine-N-sulphur trifluoride



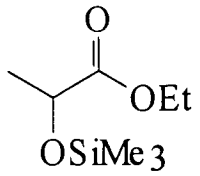
A solution of (±) methyl mandelate (0.69g, 4.2mmol) was added to a solution of (2S)-(diphenyl)methylpyrrolidine-N-sulphur trifluoride (0.68g, 2.10mmol) in $CFCl_3$ (5ml) at -78°C. After 3h the reaction was quenched with water (5ml), extracted into CH_2Cl_2 (2x20ml) and dried over $MgSO_4$. Removal of the solvent under reduced pressure followed by purification over silica gel eluting with ether/petrol (8:92) gave methyl-2-fluorophenylacetate (0.14g, 39%) as a colourless oil. δ_H (200 MHz; $CDCl_3$; Me_4Si) 7.46 (5 H, m, ArH), 5.91, 5.72 (1 H, d, CHF) $^2J_{H-F}$ 47.58Hz, 3.79 (3 H, s, CH_3); δ_F (250MHz) -180.33 (1 F, d, CHF) $^2J_{H-F}$ 47.53Hz; m/z 168 (M^+).

95) (±) Ethyl lactate (203)



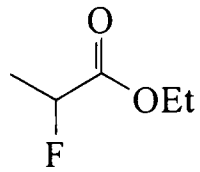
A solution of ethyl pyruvate (20.0g, 172mmol) in CH_2Cl_2 was added to a slurry of $NaBH_4$ (3.25g, 86.1mmol) in EtOH/CH_2Cl_2 (1:1) (100ml) at 0°C. The reaction was stirred at 25°C for 4h then quenched with water (10ml) and extracted into CH_2Cl_2 (2x20ml). The combined organic extracts were dried over $MgSO_4$ and the crude liquid distilled under reduced pressure to give ethyl lactate (18.5g, 90%) as a colourless liquid . δ_H (200 MHz; $CDCl_3$; Me_4Si) 4.14 (2 H, q, CH_2), 3.59 (1 H, q, CH), 1.33 (3 H, d, CH_3), 1.16 (3 H, t, CH_3); δ_C ($CDCl_3$) 176.05, 67.15, 61.83, 20.64, 14.46; ν_{max} (neat)/ cm^{-1} 3403 (OH), 2981, 2937, 1735 (C=O), 1450, 1373, 1213 (C-O), 1133 (C-O), 1048, 932; *m/z* 119 [M + H]

96) (±) Ethyl 2-(trimethylsilyloxy)propanoate (48)



A solution of ethyl lactate (3.0g, 25.4mmol), Et_3N (8.85ml, 63.55mmol) and dimethylaminopyridine (0.77g, 6.35mmol) was stirred at 18°C for 1h and then chlorotrimethylsilane (4.8ml, 38.1mmol) was added. After 1h the solution was filtered and the solvent removed under reduced pressure. Distillation (22°C,0.1mmHg) gave ethyl 2-(trimethylsilyloxy)propanoate as a colouless liquid (3.89g, 80%). δ_H (200 MHz; $CDCl_3$; Me_4Si) 4.22 (1 H, q, CH), 4.08 (2 H, q, CH_2), 1.30 (3 H, d, CH_3), 1.16 (3 H, t, CH_3) 0.03 (9 H, s, CH_3); δ_C ($CDCl_3$) 174.01, 68.12, 60.87, 21.46, 14.31, 0.00; ν_{max} (neat)/ cm^{-1} 2958, 1684(C=O), 1601, 1549, 1440, 1365, 1251($SiMe_3$), 1226(C-O), 1149(C-O), 1010, 846; *m/z* 191 [M + H].

97) Preparation of ethyl 2-fluoropropanoate (49) by a kinetic resolution of (±) ethyl 2-(trimethylsilyloxy)propanoate (48) using (2S)-(diphenyl)methylpyrrolidine-N-sulphur trifluoride

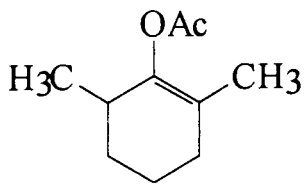


A solution of ethyl 2-(trimethylsilyloxy)propanoate (1.33g,7.0mmol) in $CFCl_3$ (30ml) was added to a solution of freshly prepared (2S)-(diphenyl)methylpyrrolidine-N-sulphur trifluoride (1.0g,3.50mmol) at -78°C and the solution stirred under N_2 for 3h. The reaction was quenched with water (10ml) and the solvent layer separated. Distillation of the organic layer at atmospheric pressure gave ethyl 2-fluoropropanoate as a colourless liquid (0.128g, 27%); δ_H (200 MHz; $CDCl_3$; Me_4Si) 5.21, 4.97 (1 H, dq, CHF) $^2J_{H-F}$ 47.5Hz, 4.32 (2 H, m, CH_2), 1.70, 1.58 (3 H, dd, CH_3) $^3J_{H-F}$ 23.64Hz, 1.47 (3 H, t, CH_3); δ_F (250MHz) -184.51(1 F, dq, CHF); *m/z* 121 [M + H].

Section J

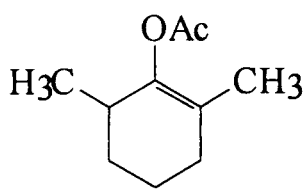
(2S)-(Diphenyl)methylpyrrolidine homochiral lithium amide base (HCLA)

98) (±) 1-Acetoxy-2,6-dimethylcyclohex-1-ene (209)



A solution of n-butyllithium in hexanes (2.5M, 7.10ml, 17.4mmol) was added to a solution of diisopropylamine (2.43ml, 17.4ml) under N_2 at -78°C. After 30min the cooling bath was removed and the reaction stirred at room temperature for 2h before cooling to -78°C. A solution of 2,6-dimethylcyclohexanone (2.0g,15.84mmol) in THF (2ml) was added dropwise and the reaction allowed to warm very slowly to -40°C over 12h. The reaction was then quenched with acetyl chloride (1.49g, 18.97mmol) and stirred for 40min before dilution with ether and pouring into 2N HCl (aq) (50ml). The organic layer was washed with 2N HCl aq (2x50ml), brine (50ml) and was then dried over $MgSO_4$. Removal of the solvent under reduced pressure followed by purification over silica gel, eluting with ether/n-hexane (5:95), gave 1-acetoxy-2,6-dimethylcyclohex-1-ene (1.67g, 63%) as a clear oil (lit [231]). δ_H (200 MHz; $CDCl_3$; Me_4Si) 2.41 (1 H, m, CH), 2.15 (3 H, s, CH_3), 2.04 (2 H, m, CH_2), 1.87 (2 H, m, CH_2), 1.65 (2 H, m, CH_2), 1.51 (3 H, br, s, CH_3), 0.97 (3 H, d, CH_3); δ_C ($CDCl_3$) 169.1, 145.6, 120.5, 31.8, 31.6, 30.7, 20.7, 20.2, 18.3, 16.4; ν_{max} (neat)/ cm^{-1} 2930, 2870, 1760(C=O), 1715(C=C); (m/z) 168 (M^+).

99) Preparation of 1-acetyloxy-2,6-dimethylcyclohex-1-ene (209) using HCLA (2S)-(diphenyl)methylpyrrolidine



A solution of n-butyllithium in hexane (2.5M, 1.49ml, 3.40mmol) was added to a solution of (2S)-(diphenyl)methylpyrrolidine (0.81g, 3.40mmol) in THF under N_2. After 30min the cooling bath was removed and the reaction stirred at room temperature for 2h before cooling to -78°C. A solution of 2,6-dimethylcyclohexanone (0.42g, 3.40mmol) in

THF (2ml) was added dropwise and the reaction allowed to warm very slowly to -40°C over 12h. The reaction was then quenched with acetyl chloride (0.4ml, 5.60mmol) and stirred for a further 40min before dilution with ether and pouring into 2N HCl (aq) (50ml). The organic layer was washed with 2N HCl (2x10ml), brine (20ml) and was then dried over $MgSO_4$. Removal of the solvent under reduced pressure followed by purification over silica gel, eluting with ether/n-hexane (5:95) gave 1-acetoxy-2,6-dimethylcyclohex-1-ene (0.33g, 58%) as a clear oil. δ_H (200 MHz; $CDCl_3$; Me_4Si) 2.41 (1 H, m, CH), 2.15 (3 H, s, CH_3), 2.04 (2 H, m, CH_2), 1.87 (2 H, m, CH_2), 1.65 (2 H, m, CH_2), 1.51 (3 H, br, s, CH_3), 0.97 (3 H, d, CH_3); δ_C ($CDCl_3$) 169.1, 145.6, 120.5, 31.8, 31.6, 30.7, 20.7, 20.2, 18.3, 16.4; ν_{max} (neat)/ cm^{-1} 2930, 2870, 1760(C=O), 1715(C=C); (m/z) 168 (M^+).

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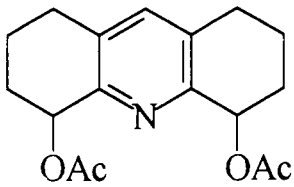
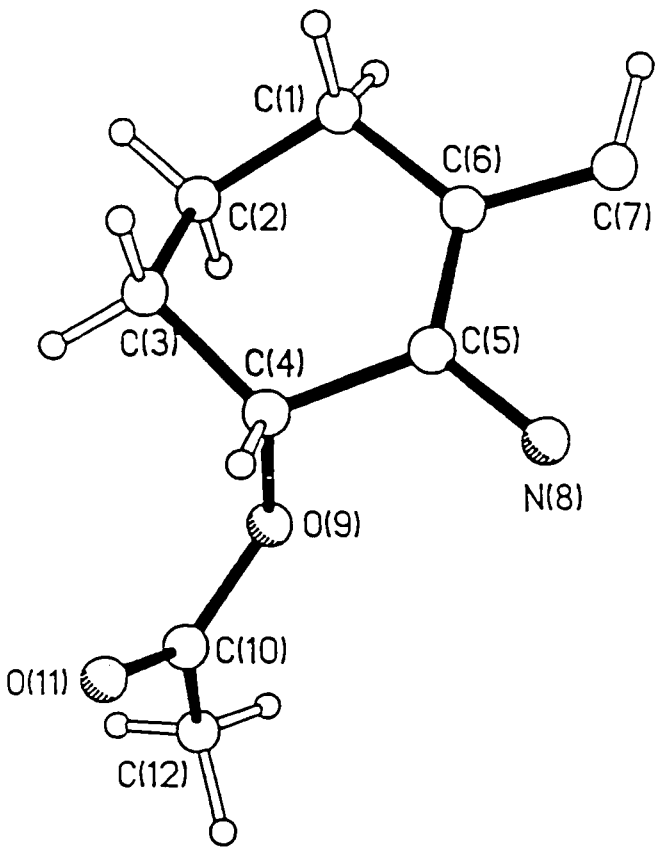
Appendix I

X-ray crystal data for (R,R),(S,S)-1,8-diacetoxy-1,2,3,4,5,6,7,8-octahydroacridine (58)



Asymmetric unit



Crystal Data:

$C_{17}H_{21}NO_4$ M = 303.36, Monoclinic, a = 10.417 (9), b = 17.28(1), c = 8.973 (5)Å, β = 101.85(6) ^{o}, V = 1581 (4) Å^3 (by least-squares refinement on diffraction angles for 12 automatically centred reflections, λ = 1.54178Å). Space group *C2/c* (No. 15), Z = 4 (½ of the molecule in the asymmetric unit), D_C = 1.27g cm^{-3}, F(000) = 648, U(Cu-Kα) = 7.0 cm^{-1}. The data crystal was mounted in a capillary tube and had approximate dimensions 0.74 x 0.58 x 0.30 mm.

Data collection and Processing:

Three-dimensional, room temperature (295K) X-ray data was collected on Siemens R3m/V diffractometer with monochromatised Cu-Kα X-radiation. 2θ/ω mode with scan range (ω) 1.14^{o} plus Kα separation and variable scan speed (1.95 - 14.65^{o} min $^{-1}$). 1198 reflections were measured (3 < 2θ < 115^{o}, min. *hkl* -12 0 0, max. *hkl* 12 19 10) of which 1075 were unique [R(σ) = 0.028, Friedel opposites merged] and 930 had $I > 3\sigma(I)$. Two control data monitored every 98 reflections showed no appreciable decay during 17.45 hrs of exposure of the crystal to X-rays.

Structure Analysis and Refinement:

Direct methods resulted in the location of all the non-hydrogen atoms in the asymmetric unit. N (8) and C (7) lay on the the 2-fold ratation axis and had site occupation factors of 0.5. Full matrix least squares refinement was employed with anisotopic thermal parameters for all the non-hydrogen atoms. Hydrogen atoms were refined in riding mode. Individual weights were applied according to the scheme $w = [\sigma^2(F_o) + 0.0004[F_o|^2]^{-1}$, refinement converged at R =0.054, Rw = 0.062, goodness-of- fit = 3.09. Maximum and mean shift / error in the final cycle of refinement was 0.005 and 0.001 repectively. The final electron density difference synthesis showed no peaks > 0.25 or holes < - 0.26 eÅ^{-3}. All computations were carried out using the SHELXTL PLUS (μ-VAX II) system of programs. *

* G. M Sheldrick, SHELXTL PLUS - Release 4.11/V (Copyright 1990 Siemens Analytical X-ray Instr., Inc)

Supplementary Material

Table 17. Atomic coordinates
Table 18. Bond lengths
Table 19. Bond angles
Table 20. Anisotopic displacement coefficients
Table 21. Hydrogen coordinates

Atom	x	y	z	U(eq)
N (8)	5000	3866 (1)	2500	39 (1)
O (9)	7865 (2)	3551 (1)	3164 (2)	50 (1)
C (7)	5000	5465 (1)	2500	39 (1)
C (5)	5967 (2)	4260 (1)	2072 (2)	37 (1)
C (6)	5992 (2)	5069 (1)	2000 (2)	37 (1)
C (4)	7066 (2)	3780 (1)	1697 (3)	47 (1)
C (1)	7037 (2)	5494 (2)	1402 (3)	48 (1)
O (11)	8244 (3)	2398 (1)	2216 (3)	98 (1)
C (3)	7922 (3)	4222 (2)	821 (3)	60 (1)
C (10)	8397 (3)	2842 (2)	3261 (4)	59 (1)
C (2)	8273 (2)	5014 (2)	1482 (3)	59 (1)
C (12)	9205 (4)	2694 (3)	4788 (5)	79 (2)

Table 17. Atomic coordinates (x 10^4) and equivalent isotopic displacement coefficients ($Å^2$ x 10^3) [Equivalent isotpic u defined as one third of the trace of the orthogonalized Uij tensor]

N (8) - C (5)	1.336 (3)
N (8) - C (5A)	1.336 (3)
O (9) - C (4)	1.460 (3)
C (9) - C (10)	1.341 (3)
C (7) - C (6)	1.389 (3)
C (7) - C (6A)	1.389 (3)
C (5) - C (6)	1.400 (3)
C (5) - C (4)	1.506 (4)
C (6) - C (1)	1.501 (4)
C (4) - C (3)	1.512 (4)
C (1) - C (2)	1.522 (4)
O (11) - C (10)	1.196 (4)
C (3) - C (2)	1.507 (4)
C (10) - C (12)	1.475 (5)

Table 18. Bond lengths (Å) with estimated standard deviations in parentheses

C (5) - N (8) - C (5A)	118.7 (3)
C (4) - O (9) - C (10)	117.2 (2)
C (6) - C (7) - C (6A)	120.9 (3)
N (8) - C (5) - C (6)	123.0 (2)
N (8) - C (5) - C (4)	115.8 (2)
C (6) - C (5) - C (4)	121.2 (2)
C (7) - C (6) - C (5)	117.1 (2)
C (7) - C (6) - C (1)	121.1 (2)
C (5) - C (6) - C (1)	121.8 (2)
O (9) - C (4) - C (5)	105.4 (2)
O (9) - C (4) - C (3)	108.5 (2)
C (5) - C (4) - C (3)	113.3 (2)
C (6) - C (1) - C (2)	112.6 (2)
C (4) - C (3) - C (2)	112.0 (2)
O (9) - C (10) - O (11)	123.2 (3)
O (9) - C (10) - C (12)	111.6 (3)
O (11) - C (10) - C (12)	125.2 (3)
C (1) - C (2) - C (3)	110.1 (2)

Table 19. Bond angles (^{o}) with estimated standard deviations in parentheses

Atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
N (8)	38 (1)	34 (1)	42 (1)	0	5 (1)	0
O (9)	47 (1)	42 (1)	59 (1)	13 (1)	8 (1)	8 (1)
C (7)	40 (2)	31 (2)	43 (2)	0	4 (1)	0
C (5)	34 (1)	37 (1)	37 (1)	3 (1)	2 (1)	-1 (1)
C (6)	32 (1)	38 (1)	38 (1)	-1 (1)	2 (1)	2 (1)
C (4)	44 (1)	47 (1)	47 (1)	10 (1)	5 (1)	-3 (1)
C (1)	42 (1)	50 (1)	51 (1)	-5 (1)	11 (1)	8 (1)
O (11)	140 (2)	49 (1)	109 (2)	34 (1)	35 (2)	7 (1)
C (3)	51 (2)	78 (2)	54 (2)	23 (1)	19 (1)	11 (1)
C (10)	59 (2)	44 (2)	79 (2)	11 (1)	29 (1)	21 (1)
C (2)	39 (1)	76 (2)	63 (2)	1 (1)	14 (1)	21 (1)
C (12)	68 (2)	77 (2)	96 (3)	24 (2)	24 (2)	49 (2)

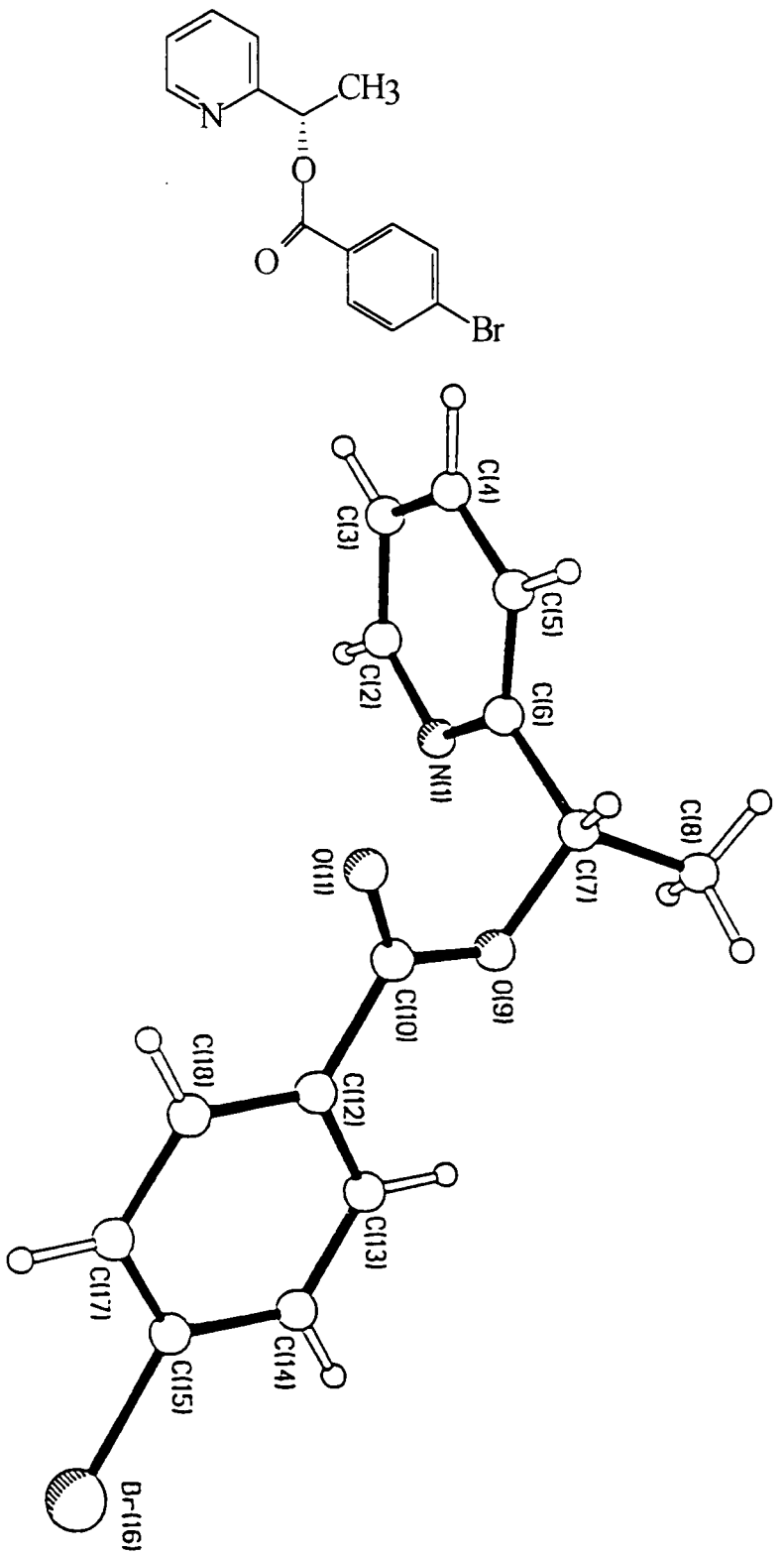
Table 20. Anisotopic displacement coefficients (Å2 x 103) of the form exp ($-2\pi^2$ (h^2 a$\star^2 U_{11}$+... + 2hka$\star$b$\star U_{12}$)

Atom	x	y	z	U
H (7)	5000	6094	2500	53 (10)
H (4A)	6710	3326	1145	45 (6)
H (1A)	7253	5962	1978	54 (7)
H (1B)	6694	5637	362	53 (7)
H (3A)	7472	4279	-219	87 (10)
H (3B)	8707	3928	832	69 (8)
H (2A)	8721	4960	2524	70 (8)
H (2B)	8851	5269	934	59 (7)
H (12C)	10059 (46)	2688 (23)	4738 (40)	109 (13)
H (12B)	9148 (33)	3041 (21)	5548 (41)	86 (13)
H (12A)	8951 (46)	2210 (32)	5218 (50)	143 (16)

Table 21. H-Atom coordinates (x 10^4) and isotropic displacement coefficient ($Å^2$ x 10^3)

Appendix II

X-ray crystal data for (2S)-(α-4'-bromobenzoyloxy)ethylpyridine (76)



Crystal Data:

$C_{14}H_{12}BrNO_2$ M = 306.16, Orthorombic, a = 5.604(1), b = 7.973(3), c = 29.121(8) Å, V = 1301(1) Å^3 (by least-squares refinement on diffraction angles for 16 automatic centred reflections, λ = 1.54178Å). Space group $P2_12_12_1$ (No 19), Z = 4, D_c = 1.56g cm^{-3}, $F(000)$ = 616, U(Cu-Kα) = 4.28 mm^{-1}. The data crystal was crystallised from ethyl acetate / petrol 1:9.

Data collection and Processing:

Three-dimensional, room temperature (295K) X-ray data was collected on a Siemens R3m/V diffractometer with monochromatised Cu-Kα X-radiation. 2θ/ω mode with scan range (ω) 1.14^o plus Kα separation and variable scan speed (4.88 - 14.65^o min $^{-1}$). 1964 reflections were measured (3 < 2θ < 115^o, min. *hkl* -7 0 0, max. *hkl* 7 9 32) of which 1764 were unique [R(σ) = 0.058, Friedel opposites merged] and 1698 had $I > 3\sigma(I)$. Two control data monitored every 98 reflections showed no appreciable decay during 17.68 hrs of exposure of the crystal to X-rays.

Structure Analysis and Refinement:

Initially direct methods only resulted in the location of the bromine atom. Allowing the Br atom to refine anisotopically, all further non-hydrogen atoms were located in a difference fourier map. Full matrix least squares refinement was employed with anisotopic thermal parameters for all the non-hydrogen atoms. Hydrogen atoms were refined in riding mode. Individual weights were applied according to the scheme $w = [\sigma^2(F_o) \div 0.0008[F_o|^2]^{-1}$, refinement converged at R = 0.045, Rw = 0.062, goodness-of-fit = 1.94. The absolute configuration was unambiguously determined by refining the η parameter of Rogers, [+] [η = 0.98 (7)]. maximum and mean shift/error in the final cycle of refinement was 0.071 and 0.014 respectively. All computations were carried out using the SHELXTL PLUS (μ-VAX II) system of programs.[*]

+ D. Rogers, *Acta Cryst.*, (1981), **A37**, 734.

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Supplementary Material

Table 22. Atomic coordinates
Table 23. Bond lengths
Table 24. Bond angles
Table 25. Anisotopic displacement coefficients
Table 26. Hydrogen coordinates

Atom	x	y	z	U (eq)
Br (16)	179 (1)	3897 (1)	-1266 (1)	67 (1)
O (11)	5362 (7)	5231 (5)	838 (1)	65 (1)
N (1)	285 (10)	4004 (6)	1711 (2)	69 (2)
O (9)	1642 (6)	6206 (5)	950 (1)	53 (1)
C (14)	-274 (9)	5400 (6)	-385 (2)	49 (1)
C (17)	3320 (9)	3776 (6)	-502 (2)	52 (2)
C (7)	2210 (9)	6691 (6)	1420 (2)	50 (2)
C (8)	356 (12)	7967 (7)	1544 (2)	71 (2)
C (2)	318 (14)	2723 (6)	2006 (2)	67 (2)
C (18)	3991 (9)	4169 (6)	-54 (2)	50 (2)
C (13)	391 (9)	5697 (6)	58 (2)	51 (2)
C (4)	3897 (13)	3735 (9)	2320 (2)	75 (2)
C (10)	3381 (9)	5494 (6)	699 (2)	47 (2)
C (12)	2588 (8)	5134 (5)	224 (1)	44 (1)
C (15)	1209 (10)	4388 (6)	-661 (2)	51 (2)
C (6)	2135 (9)	5176 (6)	1732 (1)	47 (1)
C (3)	2144 (12)	2540 (7)	2317 (2)	67 (2)
C (5)	3926 (9)	5061 (6)	2031 (1)	48 (2)

Table 22. Atomic coordinates (x 10^4) and equivalent isotopic displacement coefficients ($Å^2$ x 10^3) [Equivalent isotpic u defined as one third of the trace of the orthogonalized Uij tensor]

Br (16) -C (15)	1.896 (5)
O (11) -C (10)	1.200 (7)
N (1) -C (2)	1.336 (7)
N (1) - C (6)	1.397 (7)
O (9) -C (7)	1.455 (6)
O (9) -C (10)	1.344 (6)
C (14) -C (13)	1.364 (7)
C (14) -C (15)	1.408 (7)
C (17) -C (18)	1.393 (7)
C (17) -C (15)	1.361 (7)
C (7) -C (8)	1.498 (8)
C (7) -C (6)	1.512 (7)
C (2) -C (3)	1.374 (9)
C (18) -C (12)	1.366 (6)
C (13) -C (12)	1.397 (7)
C (4) -C (3)	1.369 (10)
C (4) -C (5)	1.351 (8)
C (10) -C (12)	1.481 (6)
C (6) -C (12)	1.332 (7)

Table 23. Bond lengths (Å) with estimated standard deviations in parentheses

C (2) - N (1) - C (6)	118.2 (5)
C (7) - O (9) - C (10)	117.4 (4)
C (13) - C (14) - C (15)	118.5 (5)
C (18) - C (17) - C (15)	118.1 (5)
O (9) - C (7) - C (8)	104.8 (4)
O (9) - C (7) - C (6)	110.2 (4)
C (8) - C (7) - C (6)	112.4 (4)
N (1) - C (2) - C (3)	121.1 (6)
C (17) - C (18) - C (12)	121.8 (5)
C (14) - C (13) - C (12)	120.9 (4)
C (3) - C (4) - C (5)	123.4 (6)
O (11) - C (10) - O (9)	124.1 (4)
O (11) - C (10) - C (12)	124.0 (4)
O (9) - C (10) - C (12)	111.9 (4)
C (18) - C (12) - C (13)	118.8 (4)
C (18) - C (12) - C (10)	119.4 (4)
C (13) - C (12) - C (10)	121.7 (4)
Br (16) - C (15) - C (14)	117.9 (4)
Br (16) - C (15) - C (17)	120.4 (4)
C (14) - C (15) - C (17)	121.7 (4)
N (1) - C (6) - C (7)	121.9 (4)
N (1) - C (6) - C (5)	122.8 (4)
C (7) - C (6) - C (5)	115.3 (4)
C (2) - C (3) - C (4)	117.6 (5)
C (4) - C (5) - C (6)	116.9 (5)

Table 24. Bond angles (°) with estimated standard deviations in parentheses

Atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
Br (16)	82 (1)	66 (1)	54 (1)	3 (1)	-12 (1)	-7 (1)
O (11)	53 (2)	81 (2)	60 (2)	19 (2)	-8 (2)	-3 (2)
N (1)	77 (3)	68 (3)	63 (3)	-3 (3)	0 (2)	-2 (2)
O (9)	49 (2)	69 (2)	40 (2)	6 (2)	3 (1)	4 (2)
C (14)	43 (3)	51 (2)	53 (3)	9 (2)	-4 (2)	7 (2)
C (17)	58 (3)	45 (3)	53 (3)	11 (2)	7 (2)	5 (2)
C (7)	59 (3)	43 (2)	46 (3)	-4 (2)	0 (2)	2 (2)
C (8)	74 (4)	63 (3)	76 (4)	3 (3)	14 (3)	6 (3)
C (2)	91 (4)	47 (3)	62 (3)	-4 (3)	10 (3)	2 (2)
C (18)	46 (3)	52 (3)	53 (3)	6 (2)	2 (2)	18 (2)
C (13)	51 (3)	49 (2)	52 (3)	10 (2)	6 (2)	7 (2)
C (4)	80 (4)	93 (4)	54 (3)	11 (4)	-6 (3)	2 (3)
C (10)	46 (3)	47 (3)	47 (3)	-9 (2)	-2 (2)	11 (2)
C (12)	45 (3)	42 (2)	44 (2)	0 (2)	4 (2)	12 (2)
C (15)	59 (3)	44 (3)	50 (3)	-5 (2)	2 (2)	11 (2)
C (6)	51 (3)	55 (3)	37 (2)	-5 (2)	3 (2)	-3 (2)
C (3)	93 (4)	62 (3)	48 (3)	18 (3)	3 (3)	1 (3)
C (5)	53 (3)	61 (3)	31 (2)	-3 (2)	-14 (2)	0 (2)

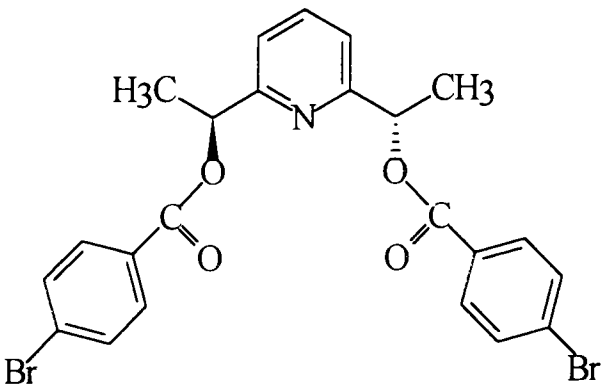
Table 25. Anisotopic displacement coefficients (Å2 x 103) of the form exp ($-2\pi^2$ (h^2 a★$^2U_{11}$+... + 2hka★b★U_{12})

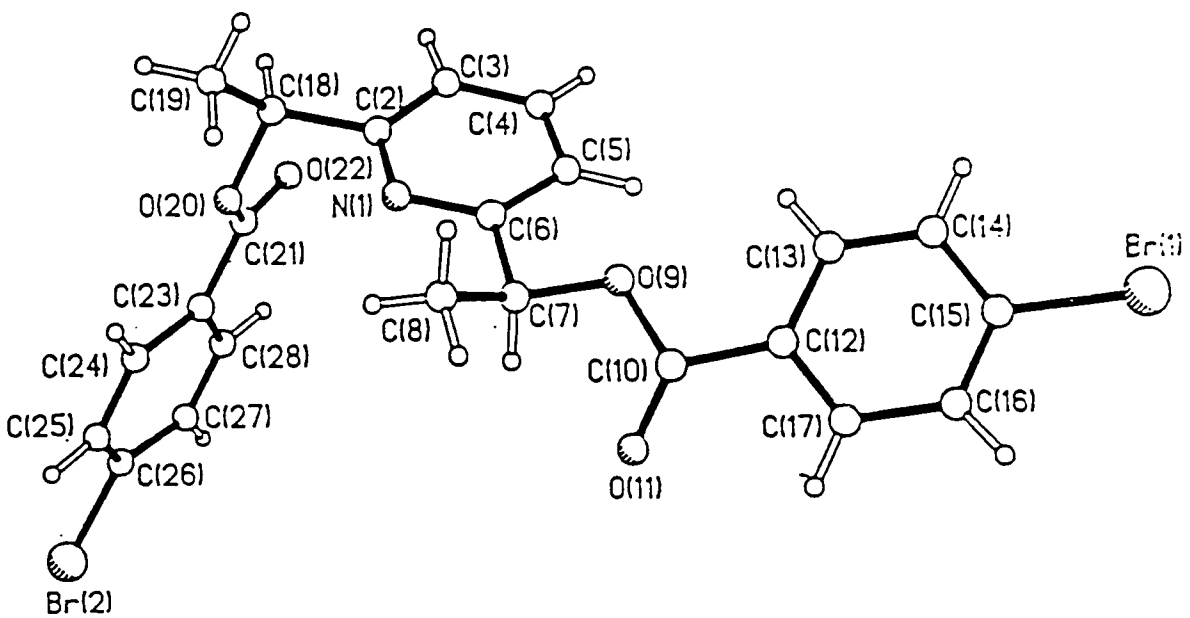
Atom	x	y	z	U
H (14)	-1727	5861	-506	37 (11)
H (17A)	4320	3124	-701	63 (16)
H (7A)	3753	7213	1426	27 (10)
H (8A)	-1181	7437	1536	65 (17)
H (8B)	389	8871	1326	172 (50)
H (8C)	654	8397	1846	62 (16)
H (2A)	-975	1933	2009	91 (22)
H (18A)	5459	3730	66	63 (15)
H (13A)	-654	6316	257	60 (15)
H (4A)	5195	3607	2532	508 (60)
H (3A)	2219	1598	2522	87 (22)
H (5A)	5151	5901	2047	121 (28)

Table 26. H-Atom coordinates (x 10^4) and isotropic displacement coefficient (Å^2 x 10^3)

Appendix III

X-ray crystal data for (2S),(6S)-diethyl(α-4'-bromobenzoyloxy)pyridine (85)





Crystal data:

$C_{23}H_{19}NO_4Br_2$, M = 533.22, orthorombic, $P2_12_12_1$, a = 6.945(1), b = 15,923(3), c = 19.898(6) Å, V=2200(2) $Å^3$, λ = 1.54178Å, z = 4, D_c = 1.61gcm^{-3}, F(000) = 1064, u(Cu-Kα) = 4.95mm^{-1}. Siemens R3m/V diffractometer, 2989 independent reflections measured ($3 < 2\theta < 115^o$) of which 1964 reflections had $I > 3.0\sigma(I)$. The structure was solved using direct methods. Full matrix least squares refinement with anisotopic thermal parameters was used for all non-hydrogen atoms. All hydrogen atoms were refined in riding mode but with individual isotropic temperature factors. Individual weights were applied according to the scheme $w = [\sigma^2(F_o) + 0.0050 \mid F_o \mid^2]^{-1}$, refinement converged at R 0.078, R_w 0.083, goodness-of-fit = 1.24. The eta test of Rogers[+] [η = 1.0 (1)] was used to determine the absolute configuration of the molecule. All computations were carried out using the SHELXTL PLUS (μ-VAX II) system of programs.[*]

+ D. Rogers, *Acta Cryst.*, (1981), A37, 734.

* G. M, Sheldrich, SHELXTL Plus - release 4.11 / V. (Copywright 1990 Siemens Analytical X-ray Instr.)

Supplementary Material

Table 27. Atomic coordinates
Table 28. Bond lengths
Table 29. Bond angles
Table 30. Anisotopic displacement coefficients
Table 31. Hydrogen coordinates

Atom	x	y	z	U(eq)
Br (1)	719 (3)	8093 (1)	7594 (1)	78 (1)
Br (2)	13850 (4)	6774 (1)	252 (1)	101 (1)
O (20)	9143 (12)	4369 (5)	2555 (4)	48 (2)
C (2)	6623 (19)	4445 (8)	3402 (6)	45 (2)
N (1)	7592 (16)	4946 (7)	3825 (6)	44 (2)
C (6)	6523 (17)	5458 (8)	4213 (6)	37 (2)
O (9)	6391 (11)	6266 (5)	5227 (4)	41 (2)
O (22)	6686 (13)	4563 (7)	1821 (5)	65 (2)
C (19)	9272 (23)	3326 (8)	3396 (7)	63 (2)
O (11)	8224 (14)	7400 (6)	5443 (5)	58 (2)
C (18)	7869 (19)	3849 (9)	2982 (6)	49 (2)
C (10)	6823 (18)	6985 (8)	5556 (6)	41 (2)
C (3)	4632 (21)	4413 (9)	3365 (8)	63 (3)
C (17)	5808 (19)	7850 (8)	6507 (6)	45 (2)
C (13)	3539 (19)	6791 (8)	6092 (6)	47 (2)
C (24)	11691 (18)	5223 (9)	1728 (7)	45 (2)
C (7)	7649 (16)	6035 (8)	4669 (6)	38 (2)
C (16)	4393 (19)	8099 (8)	6970 (5)	48 (2)
C (28)	9023 (22)	5676 (11)	1062 (7)	73 (3)
C (15)	2612 (18)	7721 (9)	6973 (7)	49 (2)
C (25)	12885 (20)	5705 (9)	1322 (8)	66 (3)
C (26)	12173 (21)	6132 (10)	795 (8)	59 (3)
C (21)	8338 (18)	4682 (8)	1993 (6)	43 (2)
C (8)	9446 (19)	5626 (10)	4960 (7)	60 (3)
C (23)	9693 (18)	5188 (8)	1599 (6)	42 (2)
C (12)	5399 (17)	7196 (7)	6082 (6)	37 (2)
C (14)	2202 (18)	7041 (8)	6548 (6)	46 (2)
C (5)	4492 (19)	5490 (10)	4181 (7)	57 (2)
C (4)	3560 (21)	4963 (10)	3740 (8)	67 (3)
C (27)	10202 (21)	6143 (9)	662 (7)	59 (3)

Table 27. Atomic coordinates (x 10^4) and equivalent isotopic displacement coefficients ($Å^2$ x 10^3) [Equivalent isotpic u defined as one third of the trace of the orthogonalized Uij tensor]

Br (1) -C (15)	1.899 (13)
Br (2) -C (26)	1.881 (15)
O (20) -C (18)	1.480 (15)
O (20) -C (21)	1.346 (15)
C (2) - N (1)	1.341 (17)
C (2) - C (18)	1.533 (19)
C (2) -C (3)	1.386 (20)
N (1) -C (6)	1.345 (16)
C (6) -C (7)	1.509 (17)
C (6) -C (5)	1.413 (17)
O (9) -C (10)	1.351 (15)
O (9) -C (7)	1.461 (14)
O (22) -C (21)	1.212 (16)
C (19) -C (18)	1.524 (20)
C (10) -C (12)	1.198 (16)
C (3) -C (4)	1.478 (17)
C (17) -C (16)	1.371 (22)
C (17) -C (12)	1.405 (17)
C (13) -C (12)	1.372 (17)
C (13) -C (14)	1.444 (18)
C (24) -C (25)	1.357 (18)
C (24) -C (23)	1.389 (20)
C (7) -C (8)	1.413 (17)
C (16) -C (15)	1.523 (18)
C (28) -C (23)	1.375 (18)
C (28) -C (27)	1.400 (20)
C (15) -C (14)	1.363 (21)
C (25) -C (26)	1.405 (19)
C (26) -C (27)	1.345 (22)
C (21) -C (23)	1.394 (21)
C (5) -C (4)	1.466 (18)
C (17) -C (12)	1.376 (21)

Table 28. Bond lengths (Å) with estimated standard deviations in parentheses

C (18) - N (20) - C (21)	115.8 (9)
N (1) - C (2) - C (18)	115.4 (11)
N (1) - C (2) - C (3)	123.8 (12)
C (18) - C (2) - C (3)	120.7 (12)
C (2) - N (1) - C (6)	116.3 (11)
N (1) - C (6) - C (7)	115.3 (10)
N (1) - C (6) - C (5)	123.2 (12)
C (7) - C (6) - C (5)	121.5 (11)
C (10) - O (9) - C (7)	116.7 (9)
O (20) - C (18) - C (2)	107.7 (11)
O (20) - C (18) - C (19)	103.5 (10)
C (2) - C (18) - C (19)	113.8 (11)
O (9) - C (10) - O (11)	123.8 (11)
O (9) - C (10) - C (12)	112.7 (10)
O (11) - C (10) - C (12)	123.4 (11)
C (2) - C (3) - C (4)	119.2 (14)
C (16) - C (17) - C (12)	118.3 (12)
C (12) - C (13) - C (14)	119.4 (11)
C (25) - C (24) - C (23)	120.1 (12)
C (6) - C (7) - O (9)	107.5 (9)
C(6) - C (7) - C (8)	113.1 (11)
O (9) - C (7) - C (8)	108.0 (9)
C (17) - C (16) - C (15)	120.6 (12)
C (23) - C (28) - C (27)	123.2 (14)
Br (1) - C (15) - C (16)	119.3 (10)
Br (1) - C (15) - C (14)	119.5 (9)
C (16) - C (15) - C (14)	121.1 (12)
C (24) - C (25) - C (26)	120.9 (13)
Br (2) - C (26) - C (25)	119.4 (11)
Br (2) - C (26) - C (27)	119.5 (11)
C (25) - C (26) - C (27)	121.0 (14)
O (20) - C (21) - O (22)	124.8 (12)
O (20) - C (21) - C (23)	112.4 (10)
O (22) - C (21) - C (23)	122.9 (12)
C (24) - C (23) - C (28)	116.4 (12)
C (24) - C (23) - C (21)	123.7 (12)
C (28) - C (23) - C (21)	120.0 (12)
C (10) - C (12) - C (17)	118.1 (11)
C (10) - C (12) - C (13)	120.5 (11)
C (17) - C (12) - C (13)	121.0 (11)
C (13) - C (14) - C (15)	119.3 (12)
C (6) - C (5) - C (4)	118.5 (13)
C (3) - C (4) - C (5)	118.8 (13)
C (28) - C (27) - C (26)	118.2 (13)

Table 29. Bond angles (^{o}) with estimated standard deviations in parentheses

Atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
Br (1)	78 (1)	85 (1)	70 (1)	4 (1)	26 (1)	-28 (1)
Br (2)	116 (2)	73 (1)	114 (2)	-7 (1)	54 (1)	19 (1)
O (20)	50 (3)	56 (4)	37 (3)	2 (3)	7 (3)	-4 (3)
C (2)	52 (4)	40 (4)	44 (4)	-4 (4)	8 (4)	-1 (4)
N (1)	44 (4)	44 (4)	43 (4)	-4 (4)	4 (4)	0 (4)
C (6)	40 (4)	37 (4)	35 (4)	1 (4)	-3 (4)	3 (4)
O (9)	37 (3)	43 (4)	44 (3)	2 (3)	7 (3)	-15 (3)
O (22)	41 (4)	86 (4)	68 (4)	-10 (4)	-2 (4)	-3 (4)
C (19)	87 (5)	34 (4)	68 (4)	11 (4)	21 (4)	-1 (4)
O (11)	60 (4)	57 (4)	58 (4)	-28 (4)	11 (3)	-15 (3)
C (18)	55 (4)	59 (4)	32 (4)	0 (4)	8 (4)	-2 (4)
C (10)	52 (4)	33 (4)	38 (4)	4 (4)	6 (4)	3 (4)
C (3)	66 (4)	60 (4)	62 (4)	-24 (4)	2 (4)	-21 (4)
C (17)	52 (4)	40 (4)	44 (4)	-1 (4)	-6 (4)	-3 (4)
C (13)	60 (4)	43 (4)	36 (4)	-7 (4)	-4 (4)	9 (4)
C (24)	43 (4)	55 (4)	37 (4)	-4 (4)	-1 (4)	-10 (4)
C (7)	37 (4)	34 (4)	42 (4)	-3 (4)	12 (4)	-16 (4)
C (16)	70 (4)	49 (4)	26 (4)	-10 (4)	-5 (4)	-18 (4)
C (28)	50 (4)	101 (5)	68 (4)	15 (4)	14 (4)	30 (4)
C (15)	41 (4)	64 (4)	43 (4)	2 (4)	10 (4)	4 (4)
C (25)	37 (4)	61 (4)	99 (5)	-14 (4)	18 (4)	-34 (4)
C (26)	74 (4)	53 (4)	52 (4)	3 (4)	-2 (4)	12 (4)
C (21)	46 (4)	51 (4)	31 (4)	-1 (4)	6 (4)	-18 (4)
C (8)	41 (4)	70 (4)	69 (4)	-1 (4)	4 (4)	-20 (4)
C (23)	46 (4)	40 (4)	41 (4)	1 (4)	5 (4)	-24 (4)
C (12)	44 (4)	31 (4)	37 (4)	-2 (4)	2 (4)	5 (4)
C (14)	52 (4)	45 (4)	41 (4)	-2 (4)	18 (4)	14 (4)
C (5)	35 (4)	75 (4)	61 (4)	-14 (4)	12 (4)	-11 (4)
C (4)	56 (4)	75 (4)	69 (4)	1 (4)	-6 (4)	-47 (4)
C (27)	86 (5)	51 (4)	41 (4)	14 (4)	-4 (4)	18 (4)

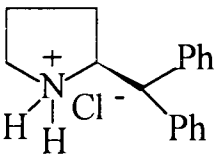
Table 30. Anisotopic displacement coefficients (Å2 x 103) of the form exp ($-2\pi^2$ (h^2 a★$^2U_{11}$+... + 2hka★b★U_{12})

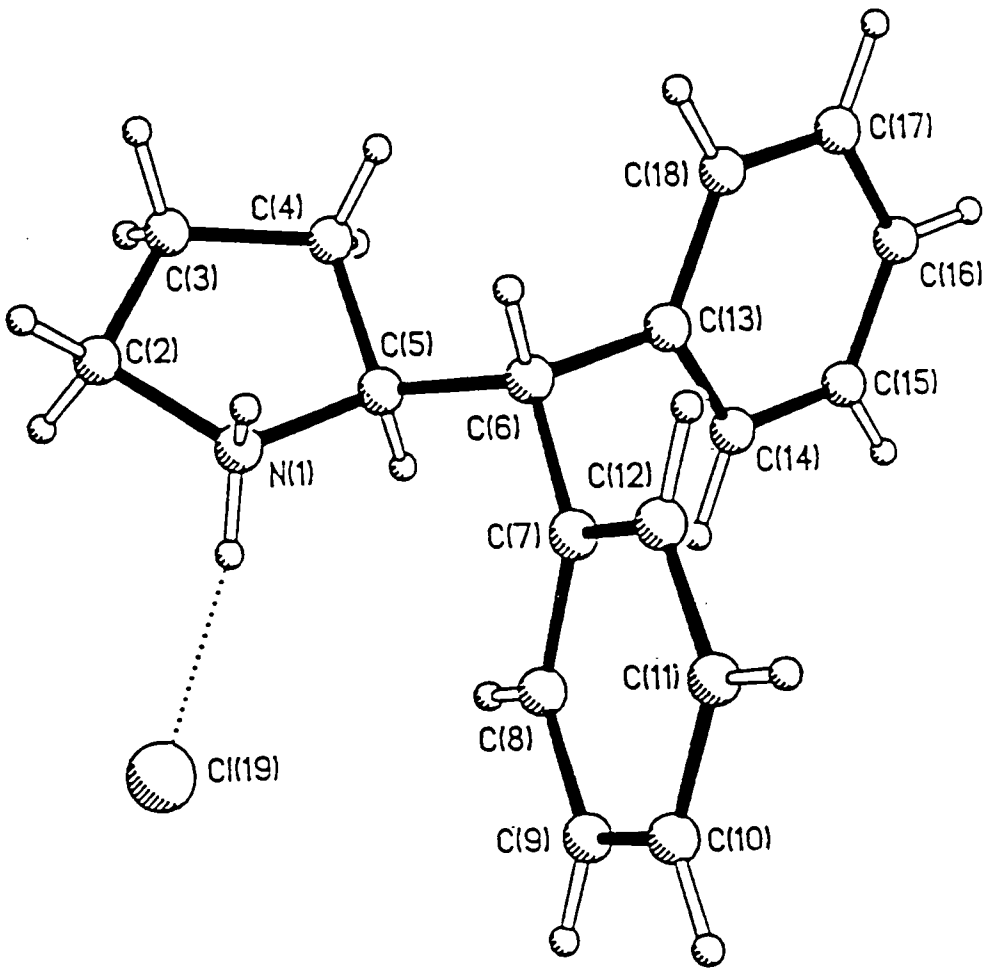
Atom	x	y	z	U
H (19A)	10031	2946	3131	81 (5)
H (19B)	10105	3715	3622	81 (5)
H (19C)	8545	3015	3722	81 (5)
H (18A)	7090	3483	2711	62 (5)
H (3A)	4041	4019	3063	16 (5)
H (17A)	7015	8143	6480	66 (5)
H (13A)	3240	6355	5776	46 (5)
H (24A)	12183	4878	2085	94 (5)
H (7A)	7990	6525	4414	92 (5)
H (16A)	4664	8526	7299	68 (5)
H (28A)	7670	5650	964	28 (5)
H (25A)	14235	5754	1418	45 (5)
H (8A)	10116	6030	5231	32 (5)
H (8B)	9083	5154	5233	52 (5)
H (8C)	10272	5440	4603	59 (5)
H (14A)	1007	6744	6595	48 (5)
H (5A)	3798	5869	4467	66 (5)
H (4A)	2182	4972	3704	130 (5)
H (27A)	9696	6485	307	58 (5)

Table 31. H-Atom coordinates (x 10^4) and isotropic displacement coefficient ($Å^2$ x 10^3)

Appendix IV

X-Ray crystal data for (2S)-(diphenyl)methylpyrrolidine HCl salt (168)





Crystal data:

$C_{17}H_{19}N.$ HCl, M = 273.81, orthorombic, a = 8.177(2), b = 11.766(4), c = 16.091(5) Å, V=1548(1)Å^3, λ = 1.54178 Å, space group $P2_12_12_1$ (No. 19), z = 4, D_c = 1.17gcm^{-3}, F(000) = 584, u(Cu-Kα) = 2.08mm^{-1}. Siemens R3m/V diffractometer, 2322 independent reflections measured ($3 < 2\theta < 115^o$) of which 2108 were unique and 1509 had $I > 2.0\ \sigma(I)$. Full matrix least squares refinement was employed with anisotopic thermal parameters for all non-hydrogen atoms. Hydrogen atoms were refined in riding mode with individual isotropic temperature factors. Individual weights were applied according to the scheme $w = [\sigma^2(F_o) + 0.0050 \mid F_o \mid^2]^{-1}$ and refinement converged at R 0.052, R_w 0.051, goodness-of-fit = 1.09. The absolute configuration was unambiguously determined by refining the Rogers eta parameter[+] [η = 0.92(7)]. All computations were carried out using the SHELXTL PLUS (μ-VAX II) system of programs.[*]

+ D. Rogers, *Acta Cryst.*, (1981), A37, 734.

* G. M, Sheldrich, SHELXTL Plus - release 4.11 / V. (Copywright 1990 Siemens Analytical X-ray Instr.)

Supplementary Material

Table 32. Atomic coordinates
Table 33. Bond lengths
Table 34. Bond angles
Table 35. Anisotopic displacement coefficients
Table 36. Hydrogen coordinates

Atom	x	y	z	U(eq)
CL (19)	-1265 (2)	-18686 (1)	-4223 (1)	62 (1)
C (8)	-3292 (6)	-16245 (4)	-3223 (1)	39 (2)
N (1)	-2691 (6)	-16635 (4)	-5176 (3)	41 (2)
C (7)	-3900 (6)	-15359 (4)	-3705 (3)	34 (2)
C (12)	-5453 (7)	-14945 (5)	-3506 (4)	50 (2)
C (13)	-1970 (6)	-13773 (4)	-4087 (3)	40 (2)
C (6)	-2928 (6)	-14809 (4)	-4395 (3)	35 (2)
C (14)	-908 (7)	-13858 (5)	-3417 (3)	53 (2)
C (5)	-1781 (6)	-15602 (4)	-4876 (3)	39 (2)
C (18)	-2138 (7)	-12724 (4)	-4475 (3)	47 (2)
C (4)	-1017 (9)	-15095 (5)	-5654 (3)	61 (2)
C (2)	-2063 (9)	-16941 (6)	-6021 (4)	63 (2)
C (17)	-1280 (8)	-11791 (5)	-4194 (4)	61 (2)
C (10)	-5708 (9)	-16307 (6)	-2406 (4)	63 (3)
C (11)	-6330 (8)	-15419 (6)	-2855 (4)	65 (2)
C (16)	-230 (8)	-11889 (6)	-3523 (5)	67 (3)
C (15)	-41 (8)	-12921 (6)	-3140 (4)	69 (3)
C (9)	-4192 (8)	-16714 (5)	-2587 (3)	52 (2)
C (3)	-1173 (20)	-15941 (7)	-6286 (6)	151 (6)

Table 32. Atomic coordinates (x 10^4) and equivalent isotopic displacement coefficients ($Å^2$ x 10^3) [Equivalent isotpic u defined as one third of the trace of the orthogonalized Uij tensor]

C (8) -C (7)	1.391 (7)
C (8) -C (9)	1.375 (8)
N (1) -C (5)	1.505 (7)
N (1) -C (2)	1.498 (8)
C (7) - C (12)	1.397 (7)
C (7) - C (6)	1.512 (7)
C (12) -C (11)	1.387 (9)
C (13) -C (6)	1.532 (7)
C (13) -C (14)	1.388 (7)
C (13) -C (18)	1.389 (7)
C (6) -C (5)	1.533 (7)
C (14) -C (15)	1.384 (9)
C (5) -C (4)	1.520 (7)
C (18) -C (17)	1.380 (8)
C (4) -C (3)	1.429 (10)
C (2) -C (3)	1.448 (13)
C (17) -C (16)	1.384 (10)
C (10) -C (11)	1.369 (10)
C (10) -C (9)	1.360 (9)
C (16) -C (15)	1.370 (10)

Table 33. Bond lengths (Å) with estimated standard deviations in parentheses

C (7) - C (8) - C (9)	121.6 (5)
C (5) - N (1) - C (2)	108.4 (4)
C (8) - C (7) - C (12)	117.3 (4)
C (8) - C (7) - C (6)	122.9 (4)
C (12) - C (7) - C (6)	119.8 (4)
C (7) - C (12) - C (11)	120.2 (5)
C (6) - C (13) - C (14)	120.9 (4)
C (6) - C (13) - C (18)	120.7 (4)
C (14) - C (13) - C (18)	118.4 (5)
C (7) - C (6) - C (13)	111.8 (4)
C (7) - C (6) - C (5)	115.6 (4)
C (13) - C (6) - C (5)	109.6 (4)
C (13) - C (14) - C (15)	120.8 (5)
N (1) - C (5) - C (6)	110.5 (4)
N (1) - C (5) - C (4)	104.9 (4)
C (6) - C (5) - C (4)	115.4 (4)
C (13) - C (18) - C (17)	120.6 (5)
C (5) - C (4) - C (3)	106.0 (6)
N (1) - C (2) - C (3)	104.2 (6)
C (18) - C (17) - C (16)	120.3 (5)
C (11) - C (10) - C (9)	119.6 (6)
C (12) - C (11) - C (10)	120.9 (6)
C (17) - C (16) - C (15)	119.6 (6)
C (14) - C (15) - C (16)	120.2 (6)
C (8) - C (9) - C (10)	120.4 (5)
C (4) - C (3) - C (2)	113.7 (8)

Table 34. Bond angles (^{o}) with estimated standard deviations in parentheses

Atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C (19)	67 (1)	41 (1)	80 (1)	8 (1)	16 (1)	6 (1)
C (8)	47 (4)	35 (3)	36 (3)	-1 (3)	1 (3)	0 (3)
N (1)	58 (3)	29 (3)	36 (3)	3 (2)	9 (2)	-4 (2)
C (7)	34 (3)	37 (3)	32 (3)	-1 (3)	-2 (2)	-11 (2)
C (12)	40 (3)	53 (4)	55 (3)	-2 (3)	3 (3)	-12 (3)
C (13)	45 (3)	35 (3)	41 (3)	-2 (3)	11 (3)	0 (3)
C (6)	38 (3)	33 (3)	35 (3)	4 (2)	-4 (2)	9 (2)
C (14)	52 (4)	55 (4)	53 (4)	-18 (3)	-4 (3)	3 (3)
C (5)	46 (4)	35 (3)	35 (3)	-6 (2)	8 (3)	-3 (3)
C (18)	59 (4)	42 (4)	39 (4)	0 (3)	11 (3)	3 (3)
C (4)	80 (5)	54 (4)	50 (4)	-13 (4)	25 (4)	2 (3)
C (2)	84 (5)	69 (4)	36 (4)	1 (4)	18 (4)	-7 (3)
C (17)	78 (4)	38 (3)	67 (4)	-12 (3)	33 (4)	0 (4)
C (10)	65 (5)	83 (5)	41 (4)	-32 (5)	11 (3)	-16 (4)
C (11)	46 (4)	86 (5)	62 (4)	-11 (4)	12 (4)	-27 (4)
C (16)	64 (5)	61 (5)	75 (5)	-23 (4)	19 (4)	-22 (4)
C (15)	61 (5)	80 (5)	67 (5)	-23 (4)	-5 (4)	-11 (4)
C (9)	67 (5)	52 (4)	35 (3)	-13 (3)	7 (3)	-4 (3)
C (3)	309 (15)	73 (5)	70 (6)	-83 (7)	88 (8)	-25 (5)

Table 35. Anisotopic displacement coefficients (Å2 x 103) of the form

$\exp(-2\pi^2 (h^2 a\star^2 U_{11} + \ldots + 2hka\star b\star U_{12})$

Atom	x	y	z	u
H (8A)	-2223	-16536	-3348	62 (18)
H (1A)	-3955 (70)	-164415 (45)	-5277 (30)	65 (17)
H (1B)	-2453 (58)	-17191 (40)	-4822 (30)	35 (15)
H (12A)	-5899	-14335	-3830	69 (20)
H (6A)	-3704	-14536	-4796	16 (10)
H (14A)	-777	-14574	-3140	51 (16)
H (5A)	-933	-15837	-4502	52 (17)
H (18A)	-2865	-12652	-4941	24 (12)
H (4A)	-1583	-14412	-5807	144 (33)
H (4B)	116	-14918	-5565	162 (38)
H (2A)	-1340	-17582	-5986	158 (38)
H (2B)	-2938	-17119	-6398	110 (29)
H (17A)	-1408	-11067	-4462	72 (19)
H (10A)	-6349	-16647	-1972	95 (24)
H (11A)	-7383	-15111	-2717	101 (25)
H (16A)	367	-11236	-3333	118 (26)
H (15A)	693	-12983	-2677	54 (17)
H (9A)	-3738	-17325	-2267	57 (17)
H (3A)	-1742	-15614	-6750	279 (81)
H (3B)	-105	-16161	-6474	269 (73)

Table 36. H-Atom coordinates (x 10^4) and isotropic displacement coefficient ($Å^2$ x 10^3)

Appendix V

List of Lectures and Seminars
Colloquia, Lectures and Seminars given by invited Speakers
from Aug 1991 to April 1994

1991

Oct 17	Dr. J. A. Salthouse, University of Manchester Son et Lumiere - a demonstration lecture
Oct 31	Dr. R. Keeley, Metropolitan Police Forensic Science Modern Forensic Science
Nov 6	Prof. B. F. G. Johnson, Edinburgh University Cluster - surface analogies
Nov 7	Dr. A. R. Butler, St. Andrews University Traditional Chinese herbal drugs : a different way of treating disease
Nov 13	*Prof. D. Gani, St. Andrews University The chemistry of PLP-dependent enzymes
Nov 20	*Dr. R. More O'Ferrall, University College, Dublin Some acid-catalysed rearrangements in organic chemistry
Nov 28	Prof. I. M. Ward, IRC in Polymer Science, University of Leeds The SCI lecture : the science and technology of oriented polymers
Dec 4	Prof. R. Grigg, Leeds University Palladium-catalysed cyclisation and ion-capture processes
Dec 5	Prof. A. L. Smith, ex Unilever Soap, detergents and black puddings
Dec 11	Dr. W. D. Cooper, Shell Research Colloid Science : theory and practice

1992

Jan 22	Dr. K. D. M. Harris, St. Andrews University Understanding the properties of solid inclusion compounds
Jan 29	*Dr. A. Holmes, Cambridge University Cycloaddition reactions in the science of the synthesis of piperidine and indolizidine natural products
Jan 30	*Dr. M. Anderson, Sittingbourne Research Centre, Shell Research Recent advances in the safe and selective chemical control of insect pests
Feb 12	Prof. D. E. Fenton, Sheffield University Polynuclear complexes of molecular clefts as models for copper biosites

Feb 13	*Dr. J. Saunders, Glaxo Group Research Limited Molecular modelling in drug discovery
Feb 19	*Prof. E. J. Thomas, Manchester University Applications of organostannanes to organic synthesis
Feb 20	Prof. E. Vogel, University of Cologne Porphyrins : molecules of interdisciplinary interest
Feb 25	*Prof. J. F. Nixon, University of Sussex Phoosphalkynes : new building blocks in inorganic and organometallic chemistry
Feb 26	Prof. M. L. Hitchman, Strathclyde University Chemical vapour deposition
Mar 5	Dr. N. C. Billingham, University of Sussex Degradable Plastics - Myth or magic?
Mar 11	*Dr. S. E. Thomas, Imperial College Recent advances in organoiron chemistry
Mar 12	Dr. R. A. Hahn, ICI Imagedata Electronic Photography - an image of the future
Mar 18	Dr. H. Maskill, Newcastle University Concerted or stepwise fragmentation in a deamination-type reaction
Apr 7	Prof. D. M. Knight, Philosophy Department, University of Durham Interpreting experiments : the beginning of electrochemistry
May 13	*Dr. J.-C. Gehret, Ciba Geigy, Basel Some aspects of industrial agrochemical research
Oct 15	Dr. M. Glazer, Dr. S. Tarling, Oxford University & Birbeck College, London It pays to be British - the chemists role as an expert witness in patent litigation
Oct 20	Dr. H. E. Bryndza, Du Pont Centra Research Synthesis, reactions and thermochemistry of metal (alkyl) cyanide complexes and their impact on olefin hydrocyanation catalysis
Oct 22	*Prof. A. Davies, University College, London The behaviour of hydrogen as a pseudometal
Oct 28	Dr. J. K. Cockcroft, University of Durham Recent developments in powder diffraction
Oct 29	Dr. J. Emsley, Imperial College, London The shocking history of phosphorus
Nov 4	Dr. T. P. Kee, University of Leeds Synthesis and co-ordination chemistry of silylated phosphites
Nov 5	*Dr. C. J. Ludman, University of Durham Explosions, a demonstration lecture
Nov 11	*Prof. D. Robins, Glasgow University Pyrrolizine alkaloids : biological activity, biosynthesis and benefits
Nov 12	Prof. M. R. Truter, University College, London Luck and logic in host-guest chemistry
Nov 18	Dr. R. Nix, Queen Mary College, London Characterisation of heterogeneous catalysts

Nov 25	Prof. L. D. Quint, University of Massachusette, Amherst Fragmentation of phosphorus heterocycles as a route to phosphoryl species with uncommon bonding
Nov 26	*Dr. D. Humber, Glaxo, Greenford AIDS - the development of a novel series of inhibitors of HIV
Dec 2	*Prof. A. Hegarty, University College, Dublin Highly reactive enols stabilised by steric protection
Dec 2	Dr. R. A. Aitken, University of St. Andrews The versatile cycloaddition chemistry of $Bu_3P.CS_2$
Dec3	Prof. P. Edwards, Birmingham University What is metal?
Dec 9	Dr. A. N. Burgess, ICI Runcorn The structure of perfluorinated ionomer membranes

1993

Jan 20	Dr. D. C. Clary, University of Cambridge Energy flow in chemical reactions
Jan 21	Prof. L. Hall, Cambridge NMR - Window to the human body
Jan 27	*Dr. W. Kerr, University of Strathclyde Development of the Paulsen-Khand Annulation Reaction : organocobalt mediated synthesis of natural and unnatural products
Jan 28	Prof. J. Mann, University of Reading Murder, Magic and Medicine
Feb 3	*Prof. S. M. Roberts, University of Exeter Enzymes in organic synthesis
Feb 10	Dr. D. Gillies, University of Surrey NMR and molecular motion in solution
Feb 11	Prof. S. Knox, Bristol University Organic Chemistry at polynuclear metal centres
Feb 17	Dr. R. W. Kemmitt, University of Leicester Oxatrimethylenemethane metal complexes
Feb 18	Dr. I. Fraser, ICI Wilton Reactive processing of composite materials
Feb 22	Prof. D. M. Grant, University of Utah Single crystals, molecular structure and chemical shift anisotropy
Feb 24	Prof. C. J. M. Stirling, University of Sheffield Chemistry on the flat-reactivity of ordered systems
Mar 10	Dr. P. K. Baker, University College of North Wales, Bangor Chemistry of highly versatile 7-coordinate complexes
Mar 11	Dr. R. A. Y. Jones, University of East Anglia The chemistry of wine making
Mar 17	*Dr. R. J. K. Taylor, University of East Anglia Adventures in natural product synthesis
Mar 24	Prof. I. O. Sutherland, University of Liverpool Chromogenic reagents for cations

	Structural patterns in alkali metal chemistry
Feb 23	Prof. P. M. Maitlis FRS, University of Sheffield Why rhodium in homogeneous catalysis
Mar 2	Dr. C. Hunter, University of Sheffield Non-covalent interactions between aromatic molecules
Mar 9	Prof. F. Wilkinson, Loughborough University of Technology Nanosecond and Picosecond Laser Flash Photolysis
Mar 10	*Prof. S. V. Ley, University of cambridge New Methods for Organic Synthesis
Mar 25	Dr. J. Dilworth, University of Essex Technetium and Rhenium Compounds with applications as imaging agents
Apr 20	Prof. P. Parsons, University of Reading New methods and strategies in natural product synthesis
May 12	*Prof D.A Humphreys, McMaster University, Canada Bringing Knowledge to Life