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CHIRAL HETEROCYCLES FROM INTRAMOLECULAR 1,3-DIPOLAR CYCLOADDITIONS

BY

NATALKA SZCZUR BSc (Hons), MRSC-CChem

A thesis submitted to Sheffield Hallam University in partial fulfillment of the requirements for the degree of Doctor of Philosophy

September 1995

Funding Establishment: Boots Pharmaceuticals Plc

Учися, дитино!

Учися, дитино, бо вчитися треба!
учися, голубко, хай розум не спить,
хай серце і воля і дух росте в силу,
для життя, для світла треба вас учить.

Учися, дитино, бо доля не мати,
шукать її треба, сама не прийде;
а той її має, той її зазнає,
кому розум сонцем в головці зійде!

Учися, дитино, бо світ цей не батько —
широкий, розлогий, мов поле в степу!
знайти в нім дорогу той лише зуміє,
хто придбав науку, хто вчився в життю!

Учися, дитино, Бог буде з тобою,
ушанують люди, світ буде любить,
і сіяти вчися добро поміж люди,
а вічно жить будеш, не згине твій слід!

Учися, дитино, бо вчитися треба;
шукай світла правди, хай розум не спить,
чого научишся — вода не забере,
не візьме розбійник, вогонь не спалить!

Володимир Масляк.

УЧІТЕСЯ, БРАТИ МОЇ!

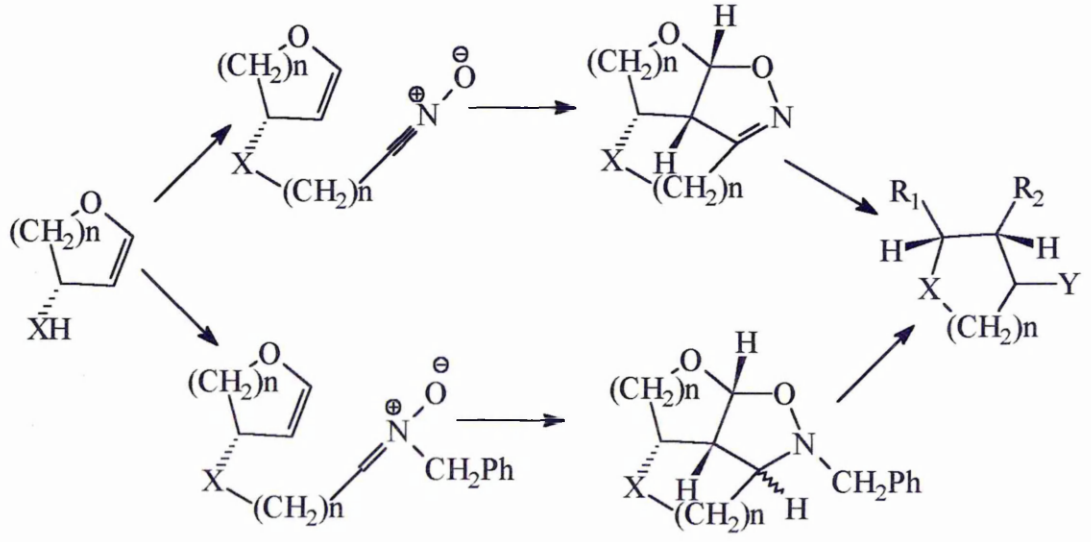
Учітеся, брати мої!
Думайте, читайте,
І чужому научайтесь, —
Свого не цурайтесь:

Тарас Шевченко, В'юнища, 1845.

Abstract

The project was concerned with investigating the synthesis of novel enantiomerically pure heterocyclic compounds of various ring size via an intramolecular 1,3-dipolar cycloaddition reaction.

The thesis begins with a general introduction to asymmetric synthesis and to 1,3-dipolar cycloadditions in chapters 1 and 2. The synthetic work described in the remaining chapters utilized the chiral template approach. Cheap readily available materials, namely aspartic acid and glucose, were used as building blocks to form suitable nitrile oxide or nitrone (1,3-dipoles) precursors for the 1,3-dipolar cycloaddition reaction. These precursors needed to contain a vinyl ether functionality (dihydrofuran or dihydropyran) for the regioselectivity of the intramolecular cycloaddition.



X = O, NH etc : Y = O or NH_2/H
R_1, R_2 = functionalised side chains

The synthetic route to pyrrolidines from aspartic acid was not successful due to the inability to alkylate the various derivatives of 3(S)-amino-γ-butyrolactone. The synthesis of nitrile oxide and nitrone precursors for the six and eight membered heterocyclic system was unsuccessful whereas the synthesis of the precursors for the five and seven membered heterocyclic systems was successful. The nitrone precursor for the seven membered ring system did not cyclise possibly due to the extra rigidity which had been introduced into the molecule, whereas the nitrile oxide and nitrone precursors to the five membered ring system cyclised to form respectively a Δ^2-isoxazoline and an isoxazolidine as single stereoisomers.

The cleavage of the Δ^2-isoxazoline and isoxazolidine produced was further investigated. It was found that the cycloadducts exhibited extra stability which was believed to be due to the oxygen in the adjoining ring. The Δ^2-isoxazoline could not be cleaved under a range of conditions but the isoxazolidine was successfully cleaved and modified to form a functionalised tetrahydrofuran.

An alternative synthesis of pyrrolidines was carried out, starting from glucose. A 3-aminoglucose derivative was prepared which underwent further reactions to give a nitrone which cyclised to an isoxazolidine as a potential precursor to functionalised pyrrolidines. A brief preliminary study of the cleavage of this system was unsuccessful.

The final chapter gives details of the experimental procedures used.

Contents

1.0 Introduction to Asymmetric Synthesis

In the synthesis of chemical compounds a mixture of stereoisomers is often observed. These isomers differ from each other only by way of the orientation of their atoms in space. Stereoisomers that are not mirror images of each other are termed diastereoisomers and have different physical properties including: melting point (mpt), boiling point (bpt), heat of combustion (Δ Hc), retention index (Rf), nuclear magnetic resonance (NMR), infra-red and mass spectra. Isomers which are non-superimposable mirror images are called enantiomers and exhibit the property of chirality or "handedness". This normally exists in a structure formed by four different groups around atoms of elements such as carbon, silicon, nitrogen, phosphorus or sulphur. (Other structural features can also lead to chirality, e.g. allenes and hindered biaryls). One chiral centre gives two distinct enantiomers and a simple example of the amino acid alanine can be seen below:

Mirror plane

Enantiomers have identical physical and chemical properties but differ in the direction which they rotate the plane of polarised light, (optical activity). An enantiomerically pure compound will be 100% of one form. Since this ideal situation is rarely obtained in synthesis, the most commonly used measure of degree of enantioselectivity achieved is the enantiomeric excess (e.e.). This is defined as the difference between the

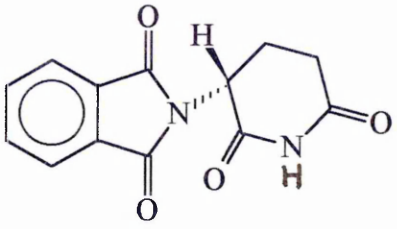
proportion of the major enantiomer and that of the minor enantiomer and is commonly expressed as a percentage. This can be seen with a mixture of isomers with a ratio of 90:10 where the resulting e.e. would be 80%. A 1:1 mixture of enantiomers is known as a racemate or racemic mixture and has an e.e. of 0%. This mixture will not rotate the plane of polarised light as the effect of one optically active species is exactly cancelled out by the other.

Over the last two decades, there has been an increase in requirements for compounds to be prepared in enantiomerically pure form. It is important to avoid a racemic mixture or a mixture of any ratio for reasons including:

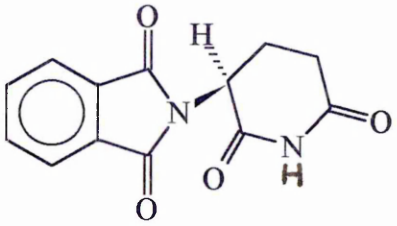
A. *Only one enantiomer is generally associated with biological activity,*

B. *Enantiomers may exhibit very different types of activity.*

This is best illustrated by the tragic case of thalidomide[1] **1**, a sedative and sleeping drug used in the early 1960's. If taken during early pregnancy it caused serious malformations in newborn children. In 1979 it was shown that it was only the (S)-(-)-enantiomer of thalidomide that possessed the damaging action. Therefore, if the (R)-(+)-enantiomer alone had been given, and no racemisation occurred in the body, no serious side effects would have appeared and the drug might still have have been in use.



1

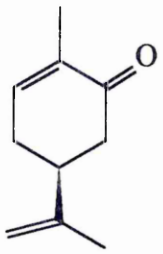


R-(+)-N-phthalylglutamic acid imide
R-(+)-Thalidomide
(sedative and sleeping aid)

S-(-)-N-phthalylglutamic acid imide
S-(-)-Thalidomide
(causes serious malformations)

Other examples[2] include: carvone **2**, where the (S) isomer has a caraway flavour and the (R) isomer a spearmint flavour; limonene **3**, where the (R) isomer has an orange flavour whereas the (S) isomer has a lemon flavour; ethambutol **4**, where a tuberculostat is obtained as well as an isomer which causes blindness and propranolol **5**, where the (S) isomer is used as a β-blocker for the treatment of heart disease but the (R) isomer acts as a contraceptive.

The structures of these compounds are illustrated below:



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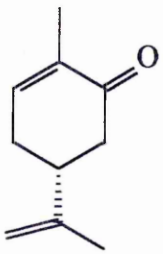
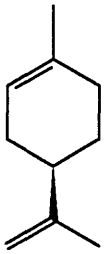


(S)-(+)-Carvone
Caraway

(R)-(-)-Carvone
Spearmint



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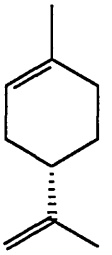
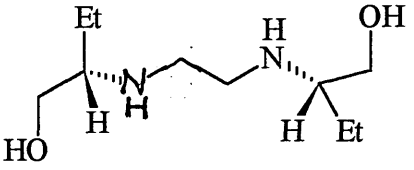


(R)-(+)-Limonene
Orange

(S)-(-)-Limonene
Lemon



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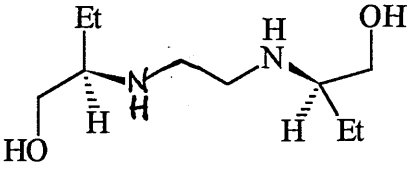
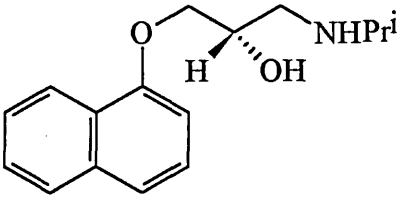


S,S-Ethambutol
Tuberculostat

R,R-Ethambutol
Causes Blindness



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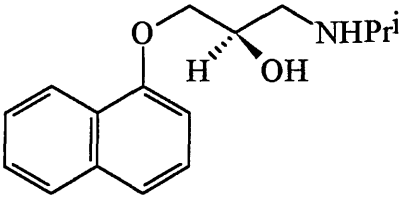
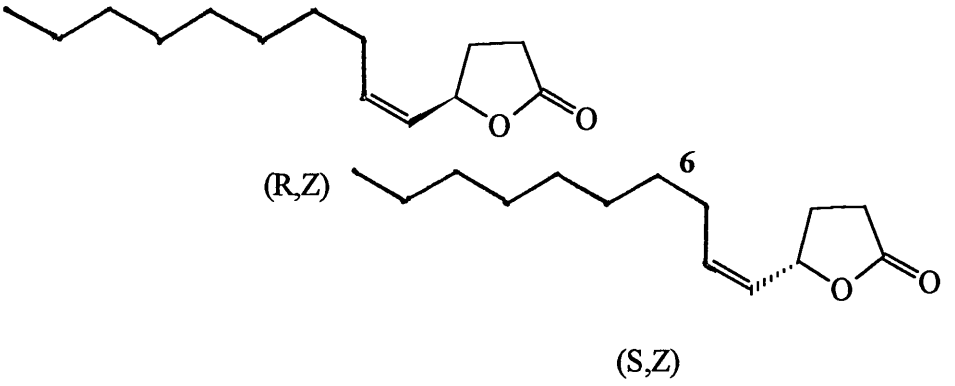


S-(-)-Propranolol
β-Blocker

R-(+)-Propranolol
Contraceptive

C. *The optically pure compound may be more than twice as active as the racemate because of antagonism.* One example is the pheromone of the Japanese beetle[2] **6** where as little as 1% of one isomer (S,Z) inhibits the other isomer (R,Z).



(S,Z)

D. *The production of materials and compounds as the required enantiomer is now a question of law in certain countries.* The pharmaceutical industry has requirements for the administration of racemic mixtures of drugs to be phased out and these to be replaced by dosages containing only the active form of the compound.

This is why enantiomeric purity is highly important in the synthesis of new drugs.

There are two general ways to obtain enantiomeric purity:

1. By making a racemate or mixture of isomers and separating it.
2. By synthesising the pure enantiomer.

1.1 Separation Methods

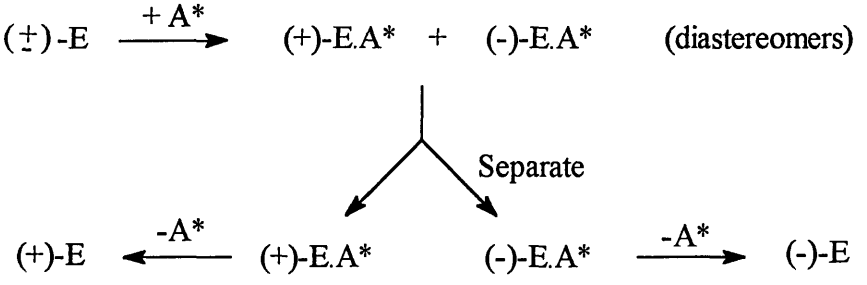
1.1.1 Resolution

Resolution is the term given to the separation of enantiomers in a racemic mixture and was first performed by Pasteur[3] in 1848.

1.1.1.1 Crystallisation

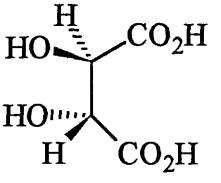
The majority of resolutions[2a] rely on the fact that diastereomers, unlike enantiomers have different physical properties. Generally a racemic compound is derivatised by reaction with a naturally occurring enantiomerically pure compound.

The overall process is illustrated below where the racemic mixture is represented by E and the resolving agent by A*.



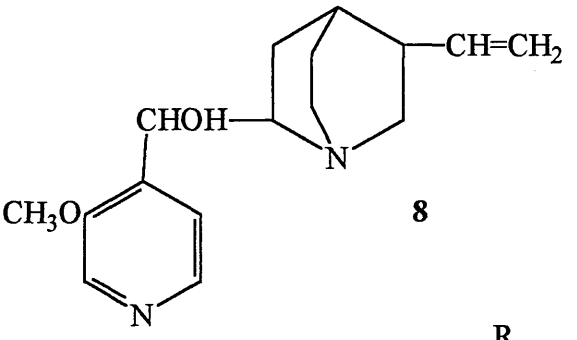
The resolving agent is recovered and can be used repeatedly.

Organic bases can be resolved by formation of salts; for example the separation of phenyl glycine derivatives[4] can be accomplished by using equimolar amounts of R,R-tartaric acid **7** in different solvents. The salt of the S-enantiomer crystallises out.



7

Organic acids can be resolved with bases such as quinine **8** and cinchonine **9**.



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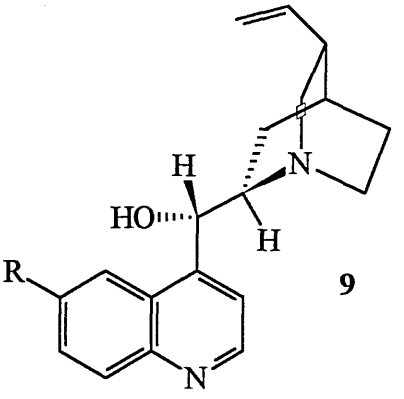


9

Resolution of alcohols[4] poses a special problem since alcohols are neither appreciably basic nor acidic. They cannot be resolved by direct formation of salts, but they can be resolved by attaching an "acidic" handle which permits the formation of salts and when it is no longer needed can be removed. Compounds other than organic bases, acids or alcohols can be resolved by the same principles just described.

1.1.1.2 Chromatography

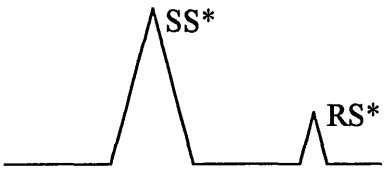
Chromatography may also be used in the separation of a racemic mixture.

A. Conventional chromatography

It is necessary to make a derivative with a chiral reagent so that diastereomers may be formed. As diastereomers have different physical properties, in this case Rf values, they can be separated using chromatography.

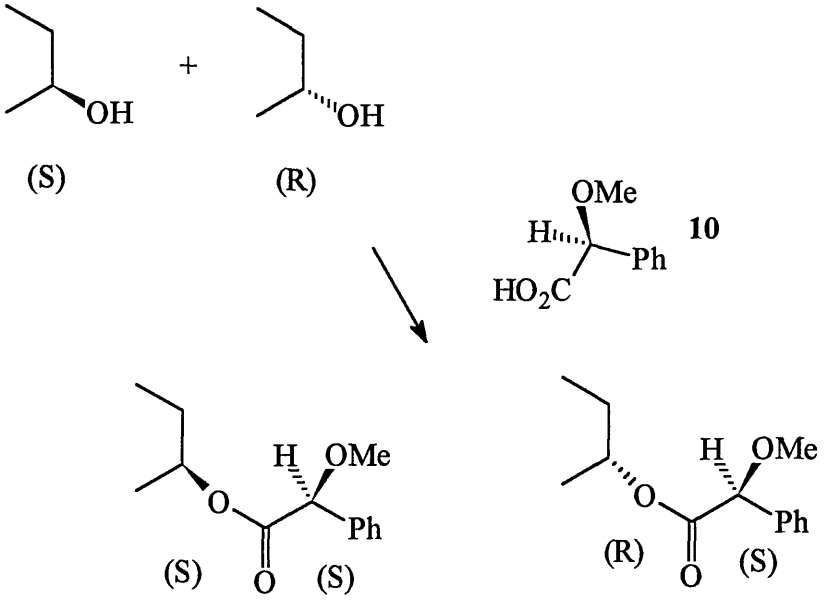
Enantiomers + Chiral Reagent ⟶ Diastereomers

(R + S) + S* ⟶ RS* + SS*



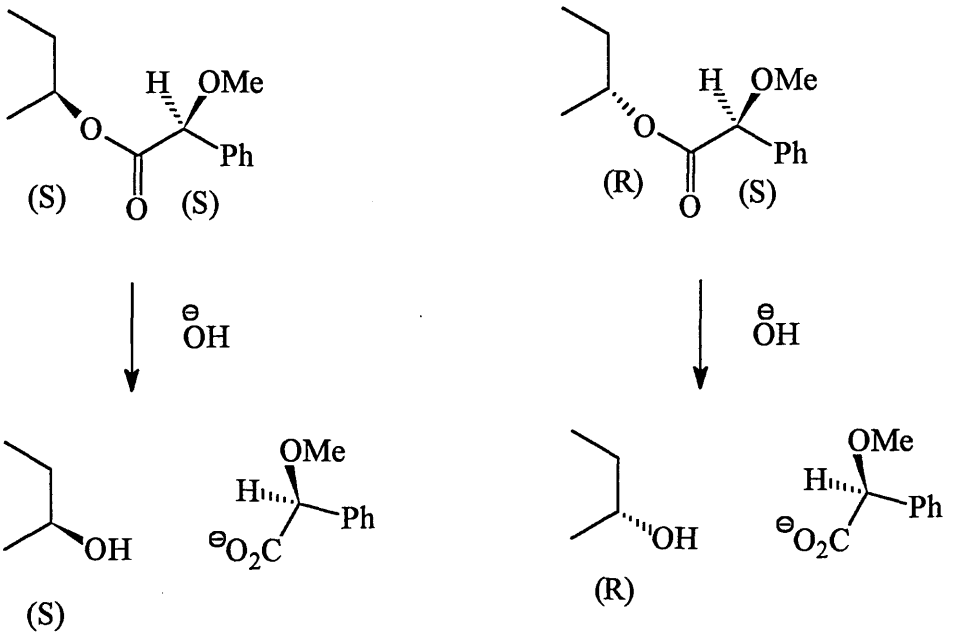
The two compounds elute at different times.

One specific example can be seen in *scheme 1* where mandelic acid[5] **10** is used as the chiral reagent.



Scheme 1

Once separated the derivatising group can then be removed by treatment with hydroxide (in this case) to regenerate the initial enantiomers, *scheme 2*.



Scheme 2

B. Chiral Chromatography

There are several different chromatographic techniques and chiral HPLC[6] is one of them. Separation can be carried out either by using a chiral stationary phase or by adding a chiral compound to the mobile phase.

In the first case a chiral agent is attached to the silica. As the racemic mixture passes down the column each enantiomer forms a different interaction with the chiral agent and complexes with different stabilities are formed. The enantiomer forming the most stable complex will be the most strongly retained and hence will elute last.

Alternatively by adding a chiral agent to the mobile phase (containing the racemic mixture) transient diastereomeric species are formed. These have different distribution properties between the mobile and stationary phases. The same interactive mechanisms are involved and different enantiomers are eluted separately.

One disadvantage is that chiral HPLC is an expensive method but it is slowly becoming more widely used on a preparative scale.

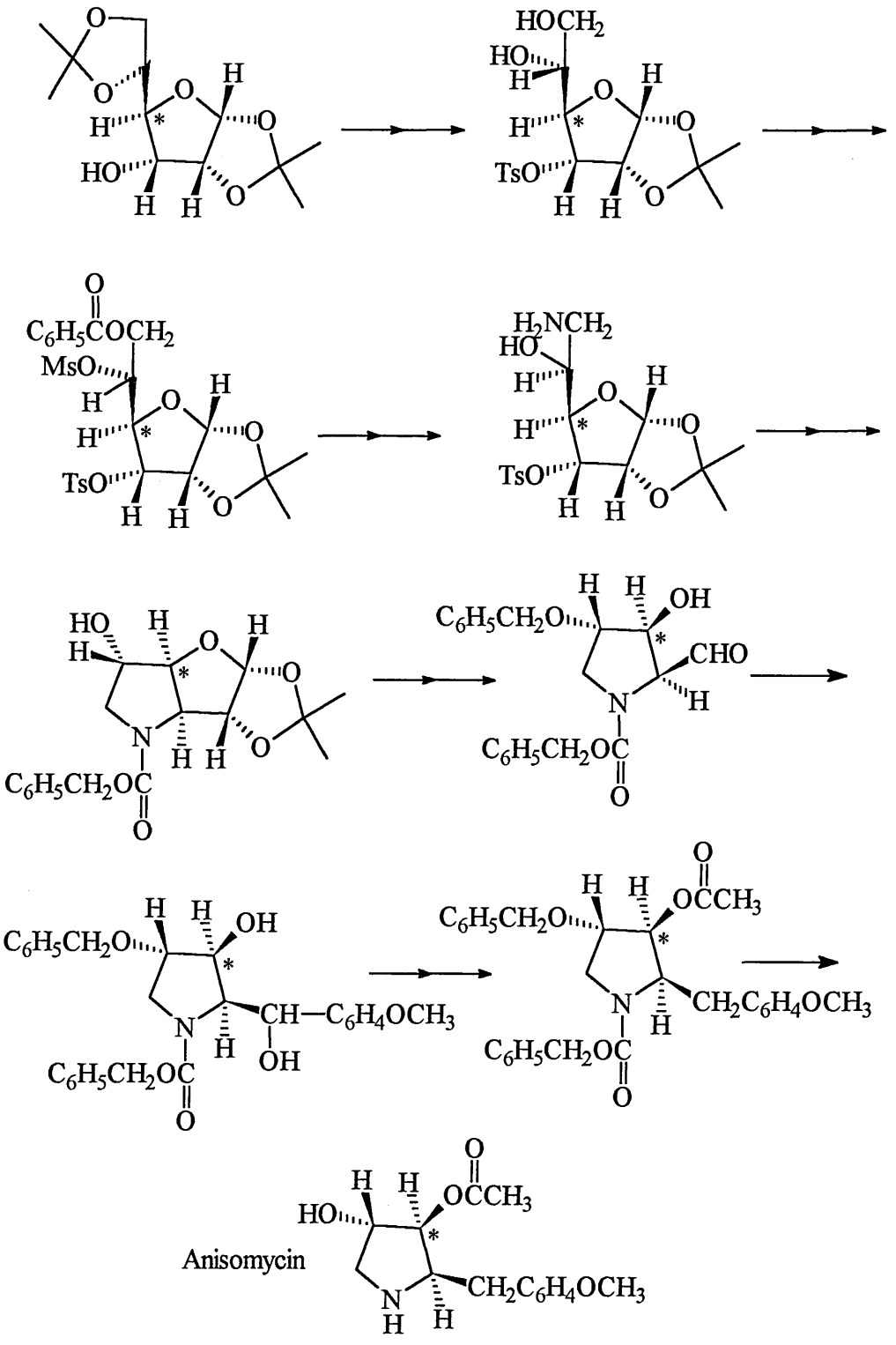
1.2 Synthetic Methods

1.2.1 The Chiral Template

The chiral pool[7] is the term given to chirally pure starting materials such as carbohydrates, amino acids, hydroxy acids and terpenes. By using these compounds in organic synthesis there is the least risk of obtaining an enantiomerically impure product. The major disadvantages of this method are that the original chiral molecule is consumed in the synthesis and the range of easily accessed compounds is relatively limited.

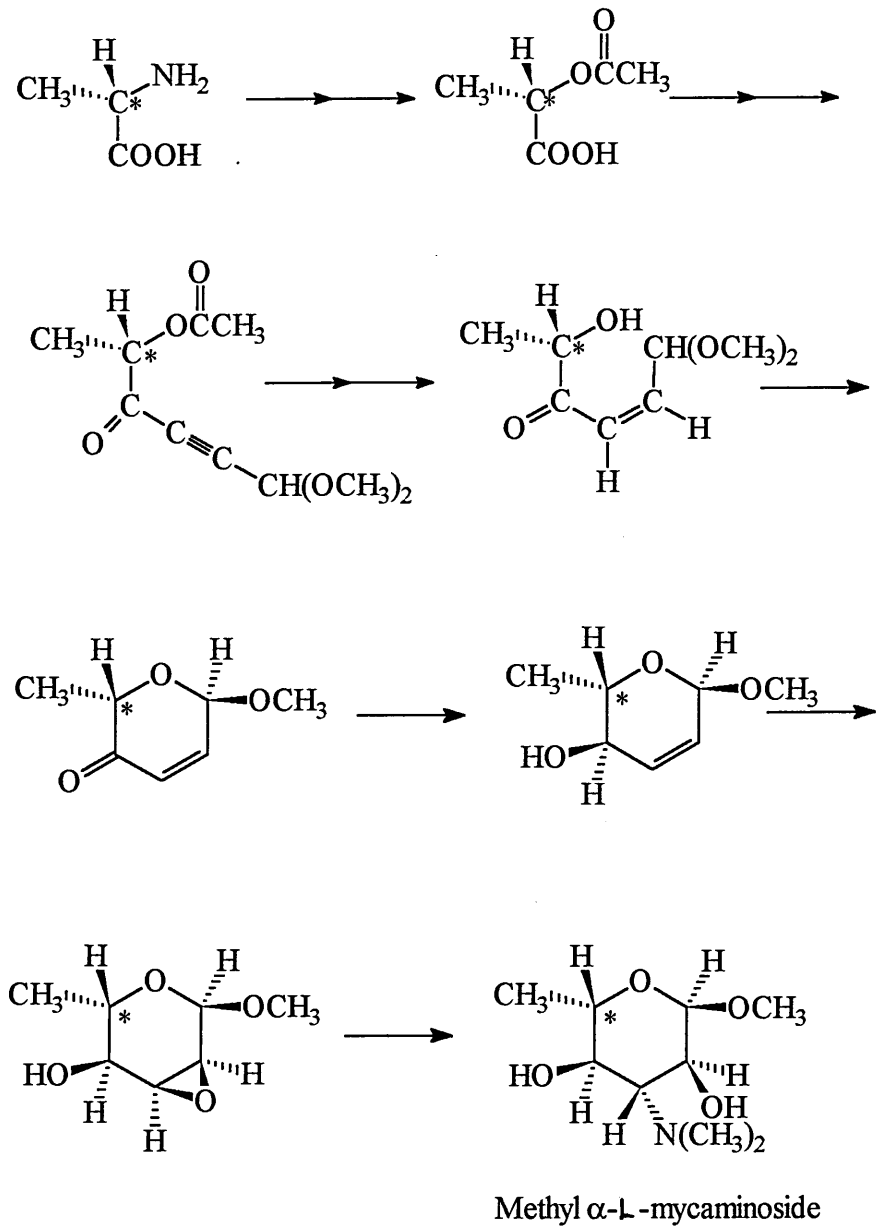
Schemes 3 and 4 show examples of how the building blocks are used in natural product synthesis.

Carbohydrates



Scheme 3

Amino Acids



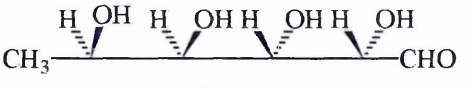
Scheme 4

In deciding to use these chiral building blocks to introduce chirality some major considerations[8] should be taken into account.

A. *Cost and bulk availability of the chiral building block.*

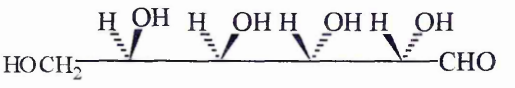
B. *Need for both enantiomers.* For a number of materials both enantiomers are available. There are, however, cases where only one enantiomer is available. For

example, D-rhamnose **11** is not commercially available but the L-enantiomer **13** is relatively inexpensive. On the other hand D-mannose **12** is substantially less expensive than the L-isomer **14**.



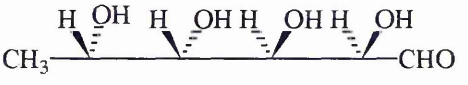
D-Rhamnose

11



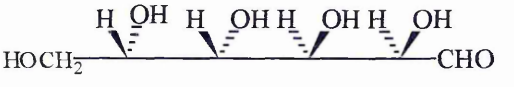
D-Mannose

12



L-Rhamnose

13



L-Mannose

14

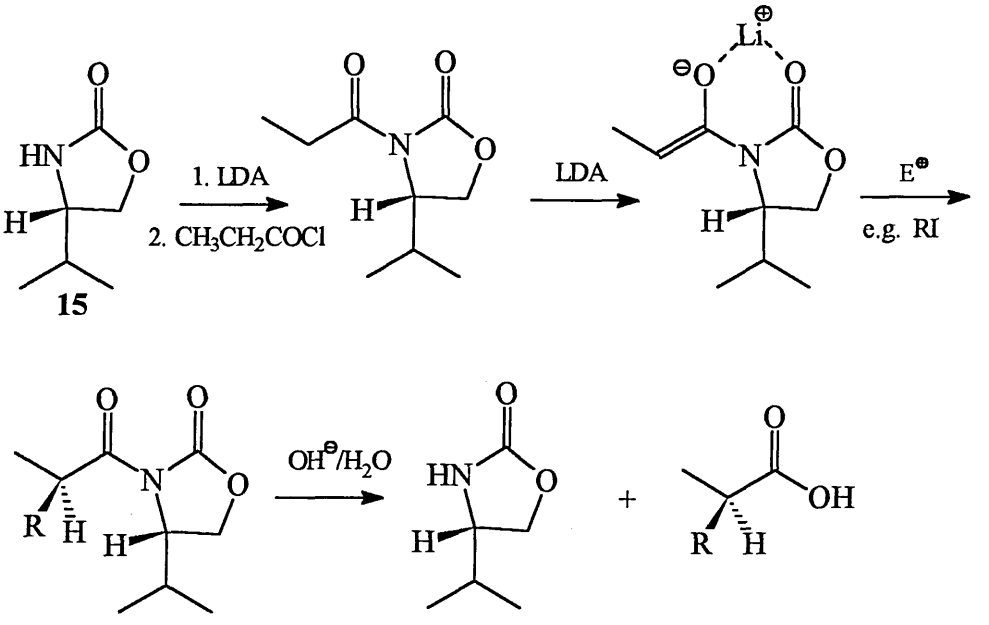
In comparing these compounds, configurational relationships are indicated. For synthetic purposes rhamnose would be an equivalent of mannose and vice versa. Enantiomeric products therefore would be most cheaply prepared from D-mannose and L-rhamnose.

C. *Enantiomeric integrity of the synthesis.* The considerations here are independent of the source of chirality. A synthetic design that allows the possibility of racemisation should be avoided. Also to be avoided are routes in which introduction of new chiral centres occurs with low stereoselectivity, resulting in major diastereomer separations and lower yields.

1.2.2 The Chiral Auxiliary

An alternative to the chiral template is to use a "chiral auxililary"[9]. This is a compound which is optically active (chiral) but does not become an integral part of the final compound compared to chiral building blocks which do. The "chiral auxiliary" induces chirality giving largely one enantiomer, and once the auxiliary has reacted it may be cleaved and then recycled. There follow two examples of this approach to asymmetric synthesis.

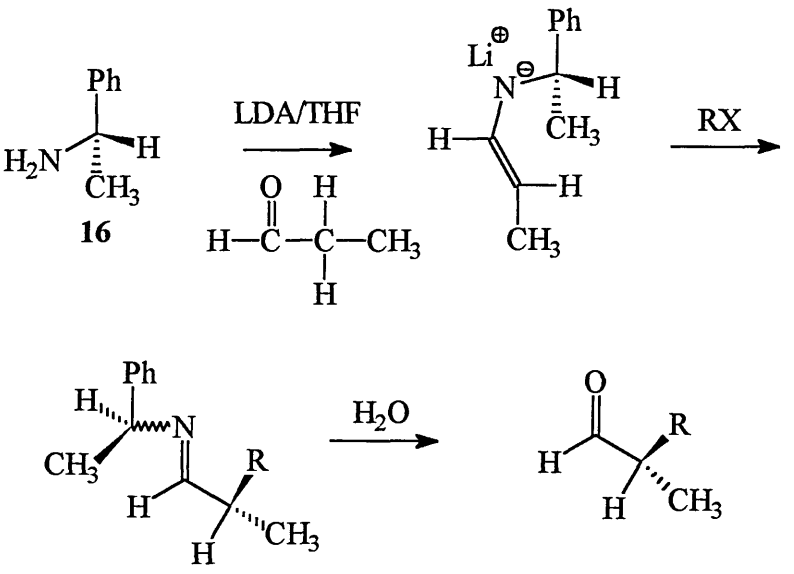
The incorporation of a chelating group into a "chiral auxiliary" has been observed to be the most useful way of obtaining stereoselection. An example of this can be seen in the use of oxazolidinone[10] **15**, *scheme 5*, where deprotonation with LDA and acylation with an acid chloride, and further LDA deprotonation forms a chelating group. The conformation is locked due to the lithium preventing rotation about the nitrogen-carbon bond and so attack by an electrophile is favoured from the front, which is the less sterically hindered side.



Scheme 5

The "chiral auxiliary" is then removed, for example by hydrolysis, and recycled.

Another example[11] can be seen in the asymmetric synthesis of aldehydes where the amine, (S) α-phenylethylamine **16** is used as the chiral auxiliary, *scheme 6*. The propanaldimine precursor is deprotonated with LDA in THF and either alkylated at -78°C or treated with an additive ($MgBr_2$) before alkylation at -78°C. After alkylation, hydrolysis predominantly yields the S-product because the chiral auxiliary forces the cation to reside primarily on the less hindered Si-face leading to electrophilic attack on the opposite Re-face.



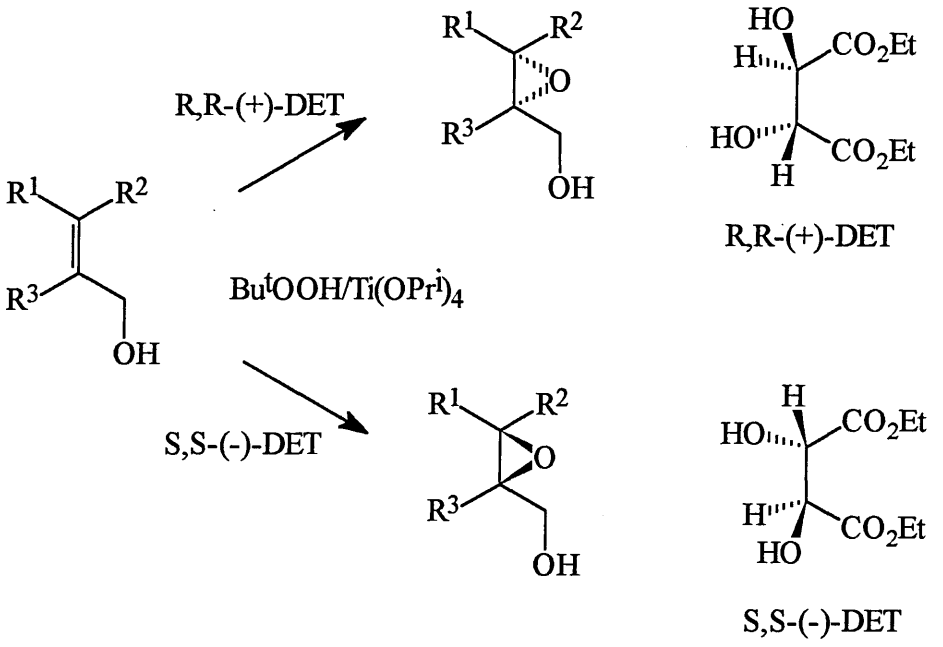
Scheme 6

1.3 Chiral Reagents

The chiral templates and chiral auxiliaries have proved to be very useful methods in the synthesis and isolation of chirally pure compounds. An alternative method uses chiral reagents to directly convert an achiral substrate to a chiral product. There are two types of chiral reagent, a synthetic one and a naturally occurring one.

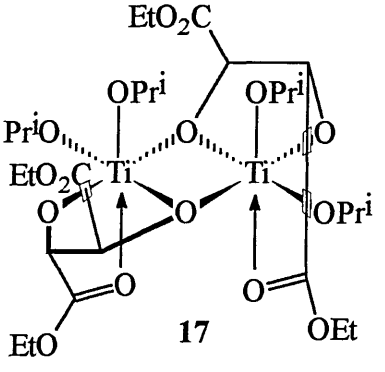
1.3.1 Synthetic Reagents

The Sharpless epoxidation uses a synthetic reagent[2a] for the synthesis of epoxy alcohols, which are obtained in very high enantiomeric excess with predictable absolute configuration, *scheme 7.*



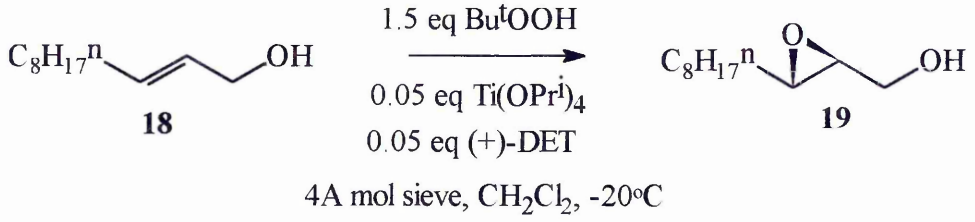
Scheme 7

The reaction is normally carried out at low temperatures (-30°C to 0°C) in dichloromethane and the chiral component, diethyl or diisopropyl tartrate (DET or DIPT) and titanium tetra-isopropoxide, are present in a catalytic amount. Both enantiomers of tartaric acid are commercially available, allowing the synthesis of either enantiomer of the epoxyalcohol. The remarkable enzyme-like selectivity is due to the complex **17** formed from the titanium salt and the tartrate.



17

An example of the conditions used is seen below in *scheme* 8 where undec-2-en-1-ol **18** is reacted to give an epoxide **19** in 96% yield with an e.e. of 95%.



Scheme 8

1.3.2 Enzymes

Enzymes[12] are naturally occurring chiral reagents and are exceptional in three main respects.

A. *They are extremely versatile and catalyse a broad spectrum of reactions.*

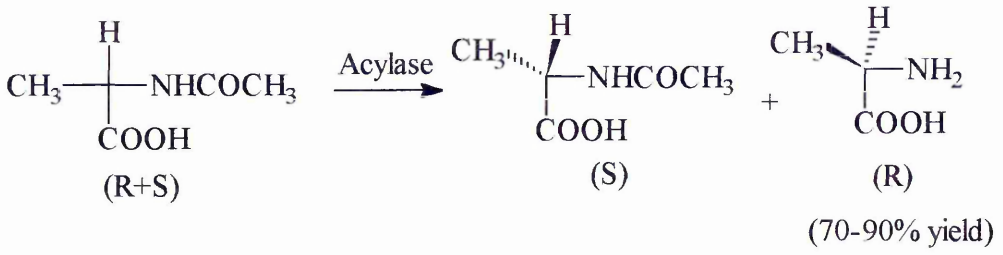
B. *They are very efficient catalysts.*

C. *They are generally very selective in terms of the type of reaction catalysed which makes them stereospecific.*

Because of this enzymes can come under both headings mentioned earlier.

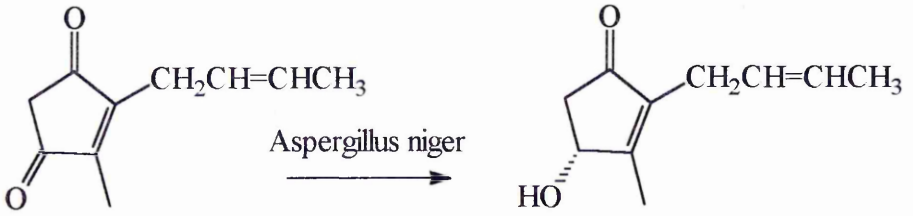
1. Separation of racemic mixtures
2. Synthesis of pure enantiomers

Enzymes have an ability to discriminate between the enantiomers of racemic mixtures. A certain enzyme will only catalyse a reaction to produce one enantiomeric form. For example, acylases[12] are specific for the hydrolysis of enantiomers in the R form and this can be classed as a separation technique.

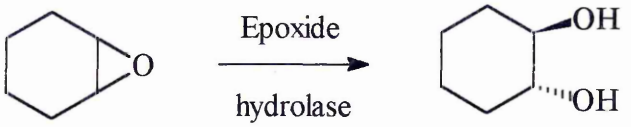


In the synthesis of pure enantiomers the enzyme catalysed reactions can be classified into groups and a few examples follow;

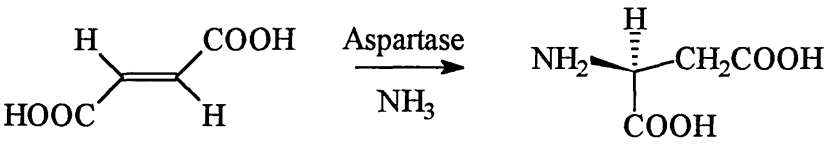
Oxidoreductases Enzymes of this group catalyse oxidation-reduction reactions.



Hydrolases There is a broad range of functional groups hydrolysed by such enzymes.



Lyases The catalysed reactions are addition reactions but can also catalyse eliminations.



(95% Yield)

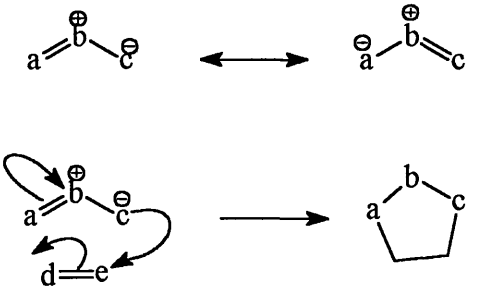
The most useful enzymes for organic chemical application are those which accept a broad structural range of substrates while retaining the ability to operate stereospecifically in every case.

Chapter 2

INTRODUCTION TO 1,3-DIPOLAR CYCLOADDITION REACTIONS

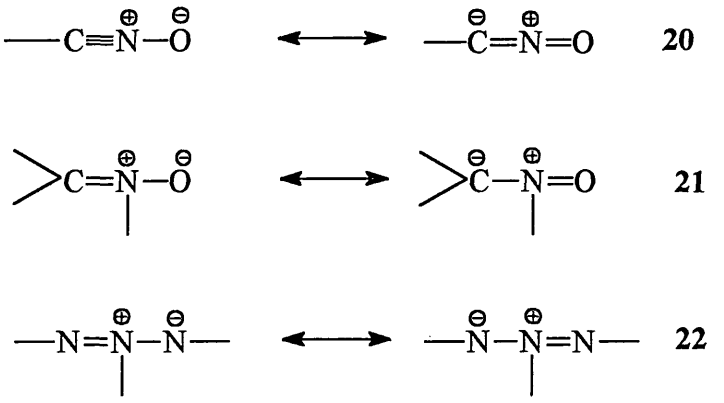
2.0 Introduction to 1,3-dipolar cycloaddition reactions

1,3-Dipolar cycloaddition reactions[13] are [π 4s + π 2s] reactions and proceed through a 6π electron "aromatic" transition state. The 4π electron component, contains only three atoms, at least one of which is a heteroatom. Cycloaddition to a double or triple bond leads to a five membered heterocyclic compound.



The 4π electron component, called the 1,3-dipole, is of such a nature that the stabilised all-octet structure can only be represented by zwitterionic forms in which the positive charge is located on the central atom and the negative charge is distributed over the two terminal atoms. The 2π electron component is called the dipolarophile.

A considerable number of 1,3-dipoles containing various combinations of carbon and hetero-atoms is theoretically possible, and many have been made, for example nitrile oxides **20**, nitrones **21** and azimes **22**.

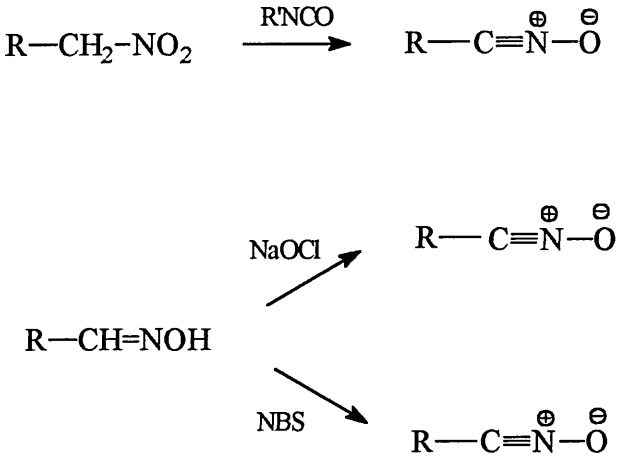


Nitrile oxides have a triple bond in one canonical form and they contain an additional π-orbital orthogonal to the allyl-anion type molecular orbital and have a linear structure whereas allyl-type 1,3-dipoles are bent.

The majority of my research has concentrated on nitrile oxides and nitrones and these will now be discussed.

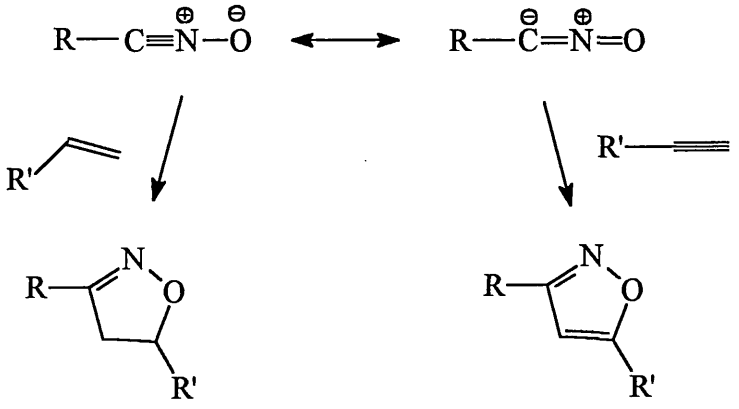
2.1 Nitrile oxides

Nitrile oxides are usually prepared "in situ" and not isolated, although some are stable, for example 2,4,6-trimethylbenzonitrile oxide[14]. Two general methods for their preparation have been used, namely the dehydration of primary nitro compounds with an isocyanate[15] and the halogenation/dehydrohalogenation of aldoximes[14], *scheme 9*. Typical reagents used for this reaction are sodium hypochlorite[16] and N-bromosuccinimide[14] (NBS).



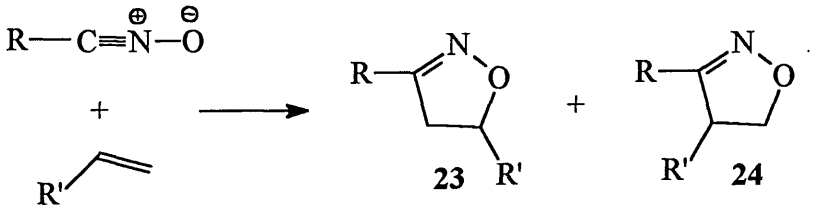
Scheme 9

The cycloaddition of nitrile oxides to acetylenic dipolarophiles leads directly to isoxazoles and a reaction with alkenes leads to Δ^2-isoxazolines, *scheme 10*.



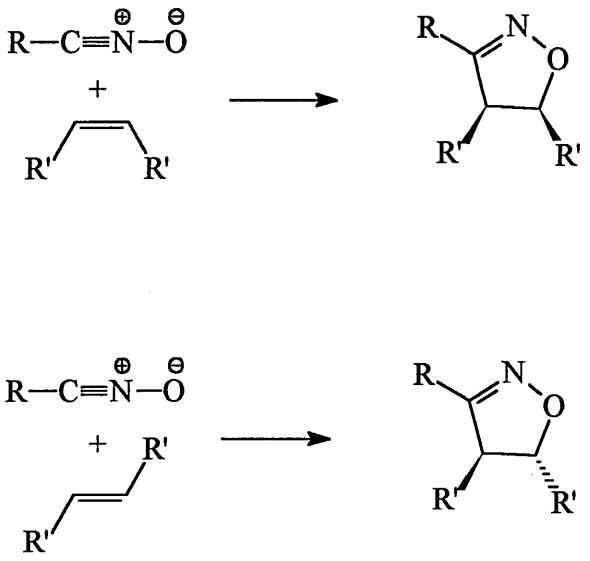
Scheme 10

The above reactions, in theory, could each give two isomers, *scheme 11*, eg. **23** and **24**,



Scheme 11

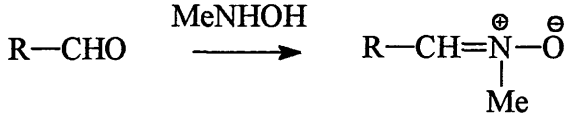
but the reaction is regioselective[13a, 17] and will preferentially give product **23** as the reaction is largely governed by atomic orbital coefficients at the ends of the conjugated system and attack will occur at the end with the larger coefficient. Caramella[18] observed the effect of heteroatoms on regioselectivity and found that, for example, the cycloaddition of vinyl ethers and nitrile oxides took place with high regioselectivity due to the presence of the oxygen. The systems that we will be looking at (see later) contain an oxygen atom (dihydrofuran or dihydropyran ring systems) so isolation of predominantly one isomer in high yield could be possible. The other contributing factor to the isolation of one isomer is that an intramolecular 1,3-dipolar cycloaddition reaction will be employed that will dictate which face of the molecule the cycloaddition might take place. In general the 1,3-dipolar cycloaddition reaction is also highly stereoselective[13a] as the substituents on the double bond retain their stereochemistry. This can be seen in *scheme 12*.



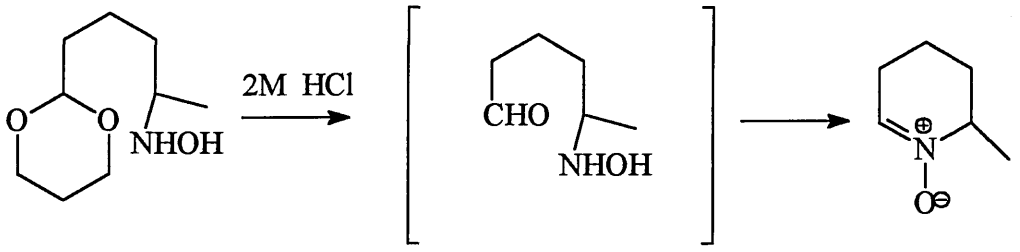
Scheme 12

2.2 Nitrones

Nitrones are also generally produced "in situ" and not isolated, although some can be. A commonly used route to nitrones is from an aldehyde or ketone and a monosubstituted hydroxylamine.

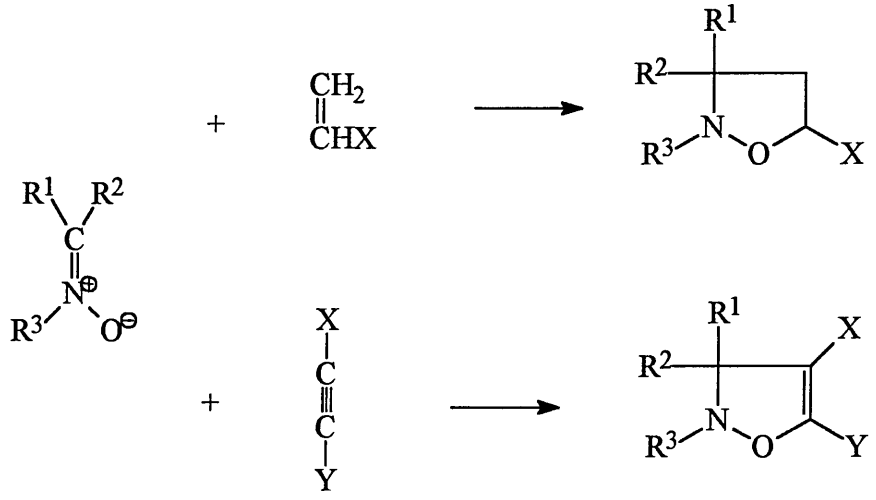


The following example, *scheme 13,* shows an intramolecular route to obtaining nitrones[13a].



Scheme 13

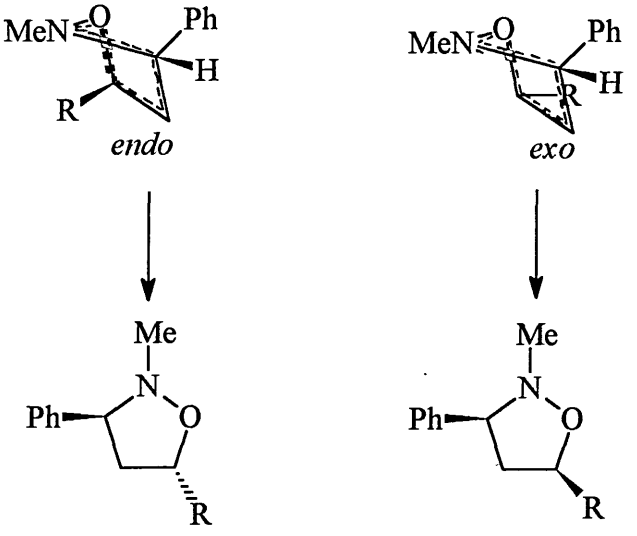
Nitrones are reactive 1,3-dipoles and with alkene and acetylenic dipolarophiles they form isoxazolidines and Δ^2-isoxazolines respectively, *scheme 14*.



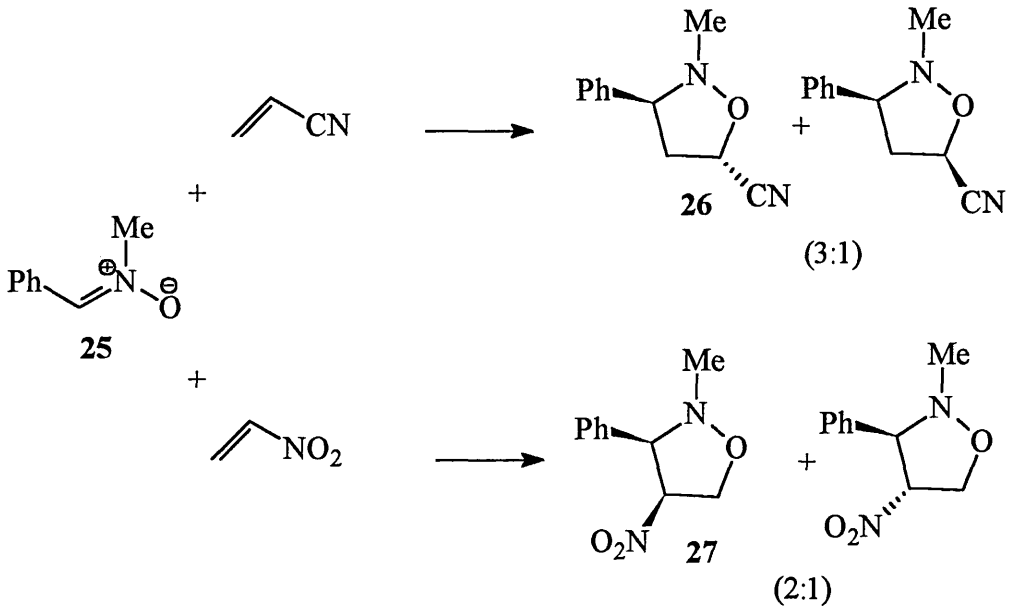
Scheme 14

The stereochemistry of nitrone cycloadditions has been the subject of several studies[13a]. Reactions with alkene dipolarophiles are stereospecific as regards the disposition of substituents on the alkene bond, but with acyclic nitrones, it is not always easy to predict the relative stereochemistry in the product and the degree of stereoselectivity may not be high. Reactions appear sometimes to favour an *endo* and sometimes an *exo*

transition state due to a complex interplay of secondary orbital interactions and steric effects.



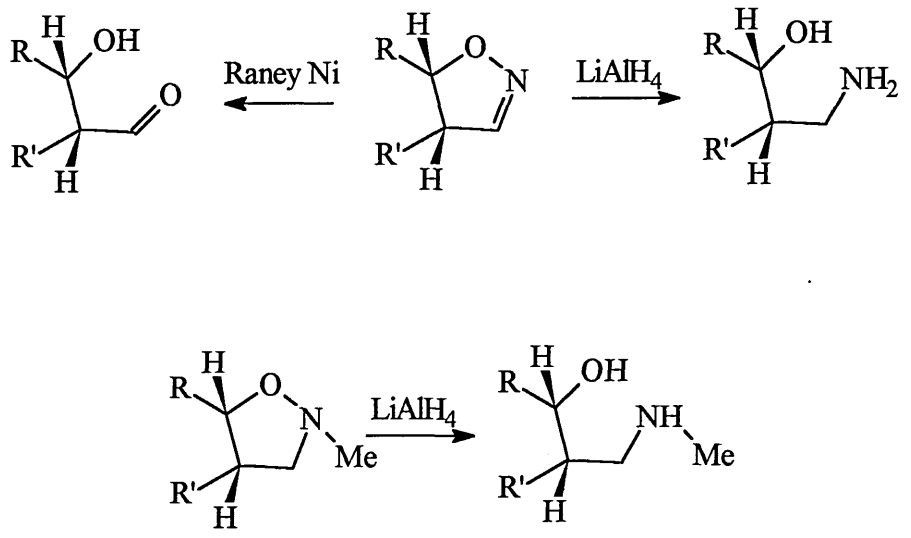
There is also the possibility of interconversion of E and Z forms of the nitrone under the conditions of the reaction before cycloaddition takes place. An example of the effect of the *endo* and *exo* transition forms combined with the E and Z forms of the nitrone can be seen in the reaction of N-methyl-C-phenylnitrone **25** with acrylonitrile which gives mainly the trans product **26**, but with nitroethylene the cis-isomer **27** predominates[13a], *scheme 15*.



Scheme 15

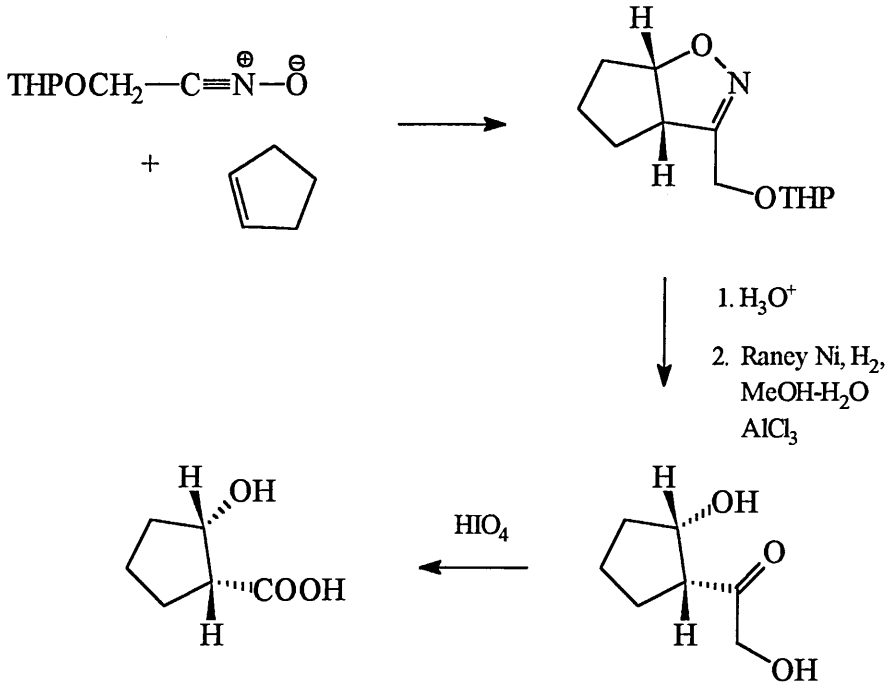
2.3 Cleavage of cycloadducts obtained from the 1,3-dipolar cycloaddition reaction.

Syntheses involving nitrile oxides and nitrones are valuable because the N-O bonds of cycloadducts are normally easily cleaved and, since the initial cycloadditions are usually stereoselective, the sequence of cycloaddition followed by ring cleavage provides a route for the stereocontrolled synthesis of a variety of acyclic and substituted cyclic compounds. There are several methods for cleavage; some reagents reduce the N-O bond first but there are some which reduce the C=N bond in isoxazolines first and lithium aluminium hydride is believed to be one of these. A few cleavage methods are illustrated in *scheme 16.*



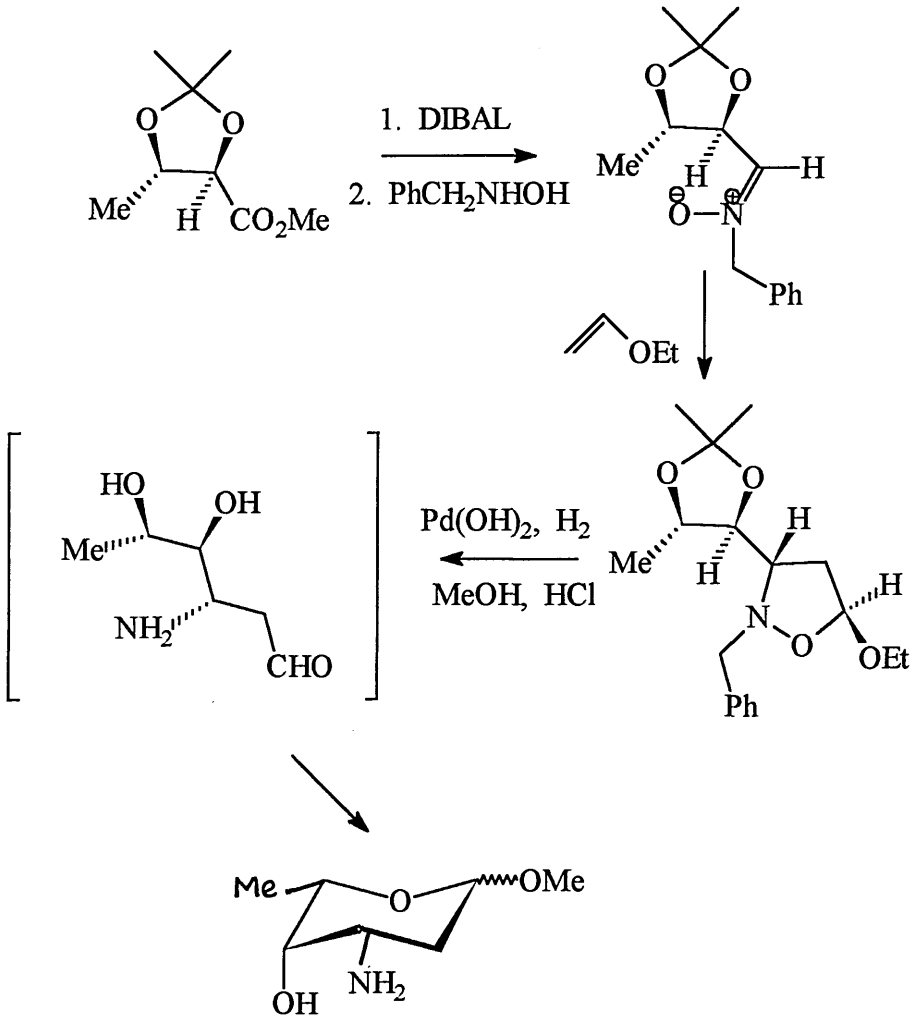
Scheme 16

A specific example[13a] for each type of system follows. The preparation of a stereochemically pure β-hydroxy-carboxylic acid from cyclopentene and a nitrile oxide is an example of how an isoxazoline can be cleaved. Deprotection followed by hydrogenolysis of the isoxazoline ring and oxidative cleavage of the ketone obtained yields the product, *scheme 17*.



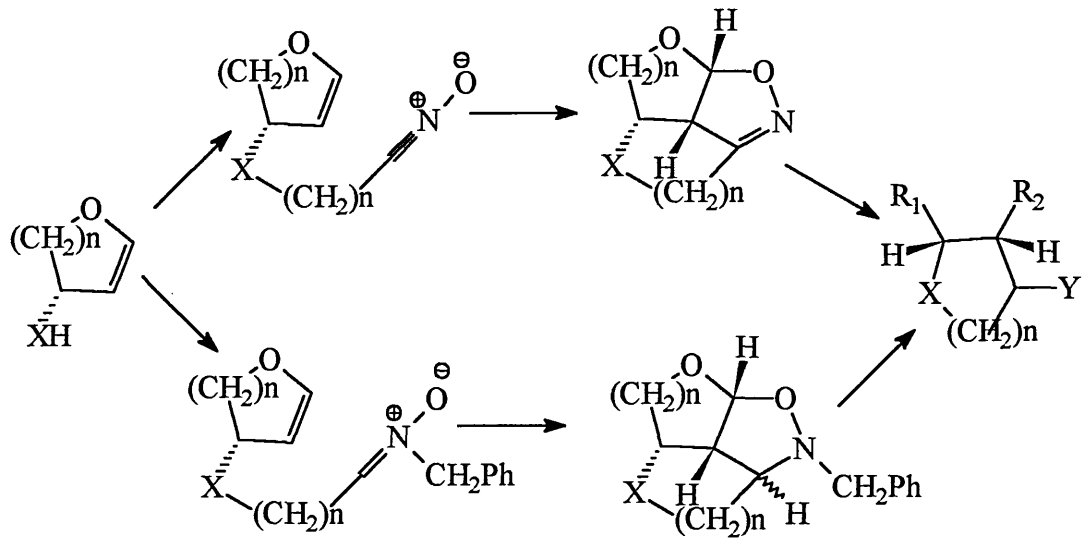
Scheme 17

The isoxazolidines obtained from the cycloaddition reaction may be cleaved to form 1,3-amino-alcohols which have been widely used in the synthesis of natural products, *scheme 18*.



Scheme 18

The objective of this research was to investigate the synthesis of novel enantiomerically pure heterocyclic ring structures obtained via an intramolecular 1,3-dipolar cycloaddition reaction.



X = O, NH etc : Y = O or NH_2/H

R_1, R_2 = functionalised side chains

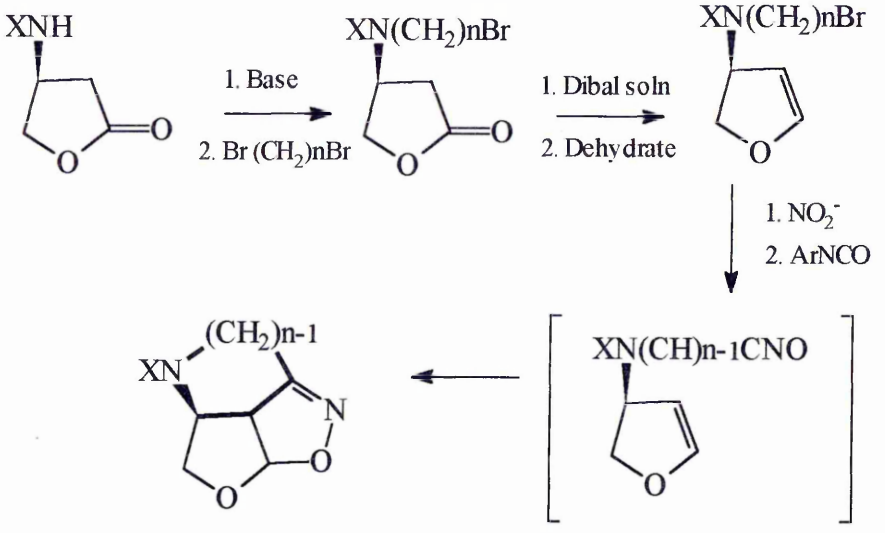
Scheme 19

The chiral template approach mentioned in chapter 1 was to be used to form suitable nitrile oxide or nitrone precursors for the intramolecular 1,3-dipolar cycloaddition reaction. Investigations into the reactions with the template aspartic acid will be discussed in chapter 3 and methyl α-D-glucopyranoside is the carbohydrate template which was used as the starting point in chapter 4. The precursors formed in both these chapters contain a vinyl ether functionality [dihydrofuran or dihydropyran] which is required for the regioselectivity of the intramolecular cycloaddition. The synthesis of the cycloadducts was to be followed by exploration into possible cleavage methods which could lead to a range of functionalised enantiomerically pure heterocyclic compounds.

3.0 Amino Acids

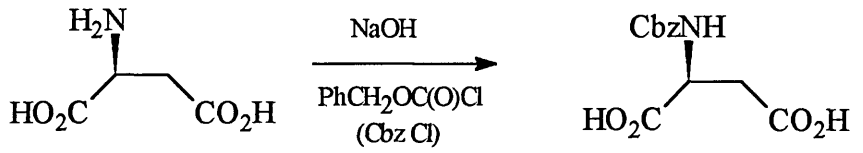
3.1 The attempted synthesis of pyrrolidines from aspartic acid

The chiral template approach, referred to in chapter one, was used in the attempted synthesis of pyrrolidines, with the amino acid aspartic acid **28** being used as the initial building block. The planned route was N-protection of a lactone, then N-alkylation, followed by reduction of the lactone carbonyl. Dehydration of this might yield a dihydrofuran ring structure which would then be converted to a nitro derivative, from which a nitrile oxide could be synthesised. As mentioned in the previous chapter nitrile oxides generally spontaneously undergo cycloaddition with alkenes and so in this case a nitrogen heterocyclic adduct would be formed, *scheme 20*.



Scheme 20

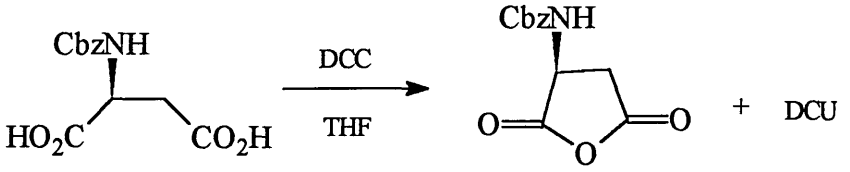
Literature methods[19] were employed in the protection of aspartic acid with an N-carbobenzyloxy (N-Cbz) group to yield 69% of N-carbobenzyloxy-aspartic acid **29** (N-Cbz-aspartic acid), *scheme 21*.



28 **29**

Scheme 21

This was used in the conversion to the anhydride **30**, where problems were encountered when N,N-dicyclohexylcarbodiimide[20] (DCC) was used as the dehydrating reagent and tetrahydrofuran (THF)was the solvent, *scheme 22*.



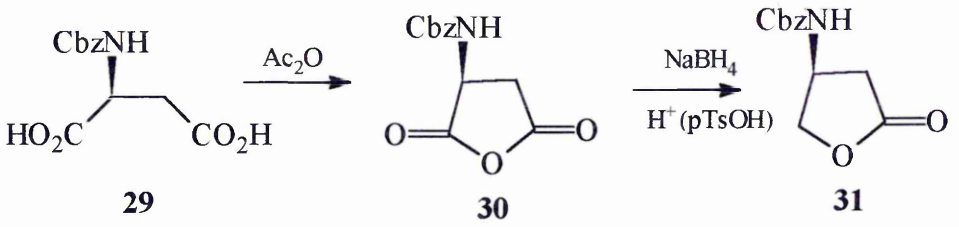
29 **30**

Scheme 22

The DCC is a coupling agent and forms N,N-dicyclohexylurea (DCU) as the by-product, and the main problem with this reaction was due to the fact that the solubility of DCU resembles that of the anhydride **30** in THF and the isolation of the pure anhydride from DCU was therefore difficult.

An alternative method[21] was tried using acetic anhydride as the dehydrating agent. This was more successful but the final step of this conversion involved freeze drying, which was not very efficient, so the remaining traces of water were azeotropically removed using toluene, and the crude anhydride **30** from this procedure was used in the next step. This involved regiospecific reduction with sodium borohydride[22], where the hydride attack takes place principally at the carbonyl group adjacent to the more

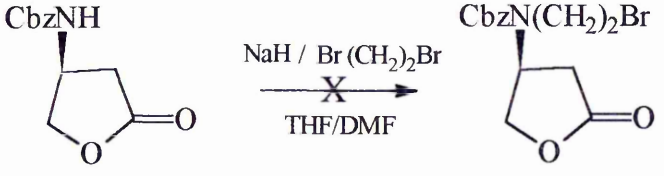
highly substituted carbon atom, followed by the removal of water using a Dean-Stark apparatus to obtain (cbz)-amino-γ-butyrolactone **31**. The yield over the two steps was 60%, *scheme 23*.



29 **30** **31**

Scheme 23

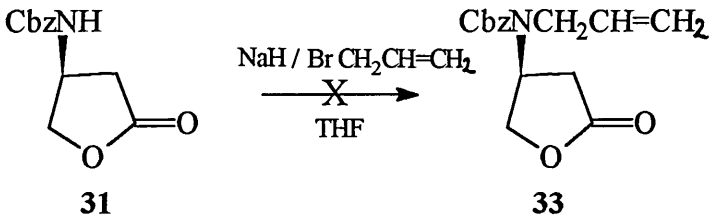
Initially the alkylation of the lactone was attempted using sodium hydride and 1,2-dibromoethane in THF. An alternative solvent, dimethylformamide (DMF), was also tried, but there was no reaction with either solvent at room temperature or on heating.



31 **32**

Scheme 24

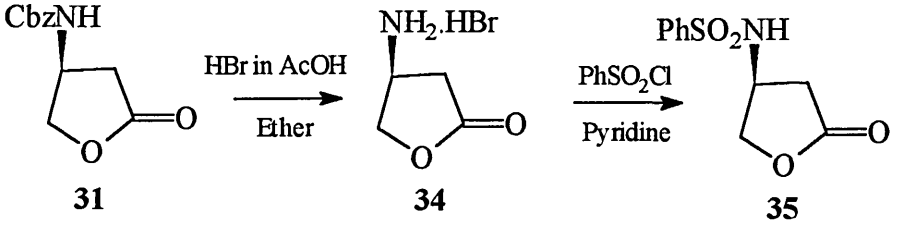
A more reactive alkylating agent (allyl bromide) was employed using the same conditions but the required compound **33** could not be obtained as no reaction occurred.



31 **33**

Scheme 25

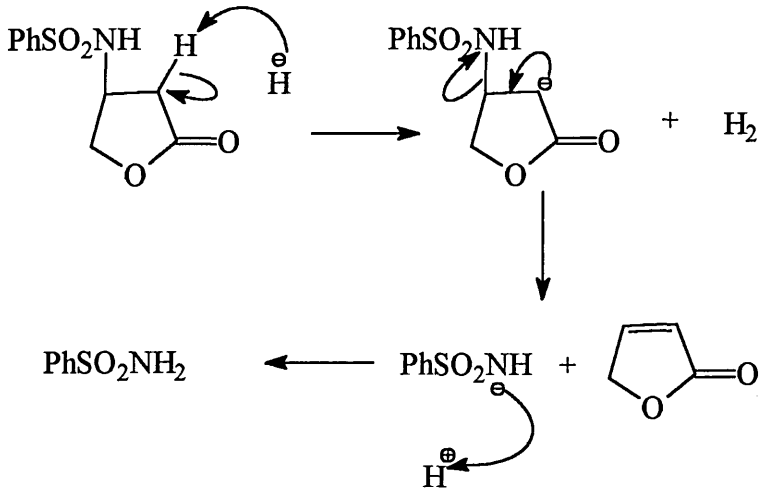
The failure of both alkylations was believed to be due to the N-hydrogen not being acidic enough. In order to make the N-hydrogen more acidic, the carbobenzyloxy protecting group was removed to give 3(S)-amino-γ-butyrolactone hydrobromide[22b] **34** which was converted to the sulphonamide[22b] **35**, *scheme 26*. It was hoped that the more electron withdrawing sulphonyl group would increase the chances of removal of the hydrogen and promote alkylation of the sulphonamide **35**.



31 **34** **35**

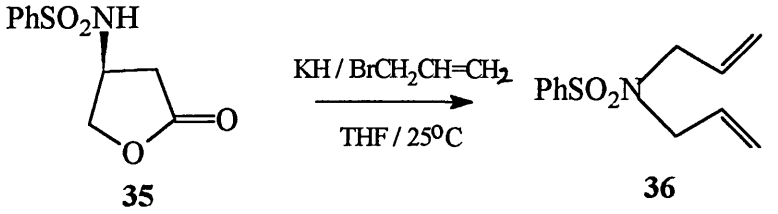
Scheme 26

The alkylations employing 1,2-dibromoethane and allyl bromide with sodium hydride, and using THF and DMF as the solvents, were repeated. There was no reaction at room temperature but on refluxing the reaction mixtures in THF, and on heating the reaction mixtures in DMF to 40°C, β-elimination occurred giving benzene sulphonamide, which was confirmed by spectral data, (NMR, IR), *scheme 27*.



Scheme 27

The alkylation of the sulphonamide was attempted using potassium hydride with 1,2-dibromoethane in THF but this also gave no reaction at room temperature since β-elimination occurred yielding benzene sulphonamide on heating. The alkylation with allyl bromide and potassium hydride gave a different elimination product from the previous alkylation attempts and spectral data confirmed this to be di-allylated benzene sulphonamide **36**, *scheme 28*.



35 **36**

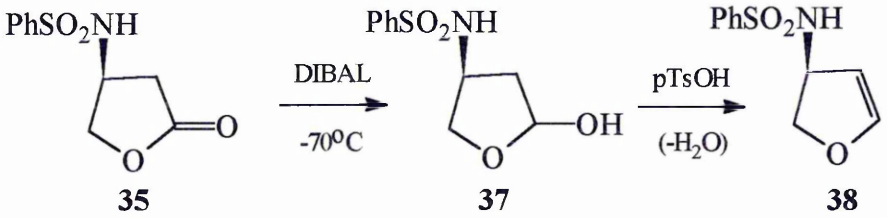
Scheme 28

Two possible explanations for this are:-

a) benzene sulphonamide was produced via β-elimination and then excess potassium hydride acted as the base in the di-alkylation of the benzene sulphonamide.

b) the sulphonamide **35** was alkylated once with allyl bromide, β-elimination followed to produce alkylated benzene sulphonamide which was then further alkylated.

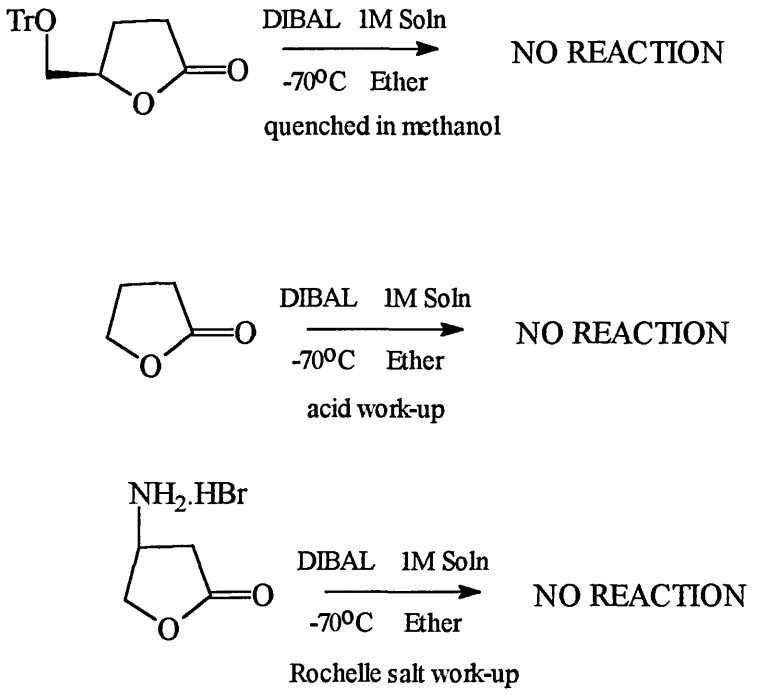
As β-elimination prevented success in the alkylations, it was decided to attempt to make the α-hydrogens less acidic by reducing the lactone **35** into a lactol **37** using diisobutylaluminiumhydride (DIBAL) solution[23], followed by dehydration[23g], leaving a dihydrofuran derivative **38**, *scheme 29*, which could hopefully be N-alkylated more easily.



35 **37** **38**

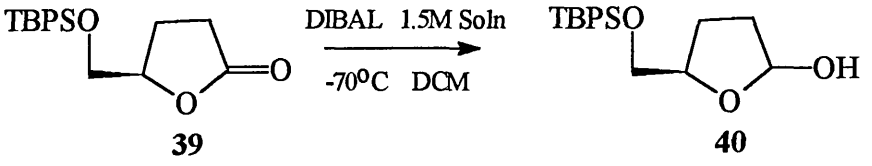
Scheme 29

The reduction was not straightforward. The reaction was carried out several times using the sulphonamide **35** as well as the carbobenzyloxy-amino-γ-butyrolactone **31** but each one resulted in the recovery of starting material. One possible reason was that the DIBAL solution was substandard so a new bottle was purchased. In order to check experimental technique some model reactions were carried out, *scheme 30*, using different methods[23] for the work-up procedure, but they also resulted in failure, with starting material being recovered in all cases.



Scheme 30

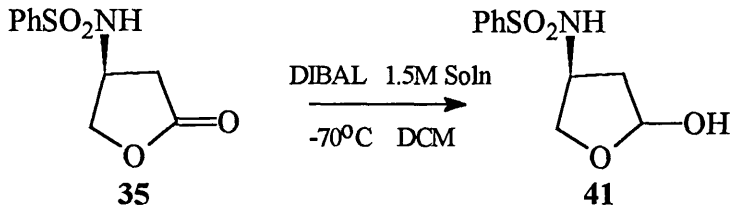
This bottle of DIBAL solution also turned out to be substandard, even though it had only recently been purchased, so a further new bottle was opened and positive results were obtained for the model reaction, *scheme 31.*



39 **40**

Scheme 31

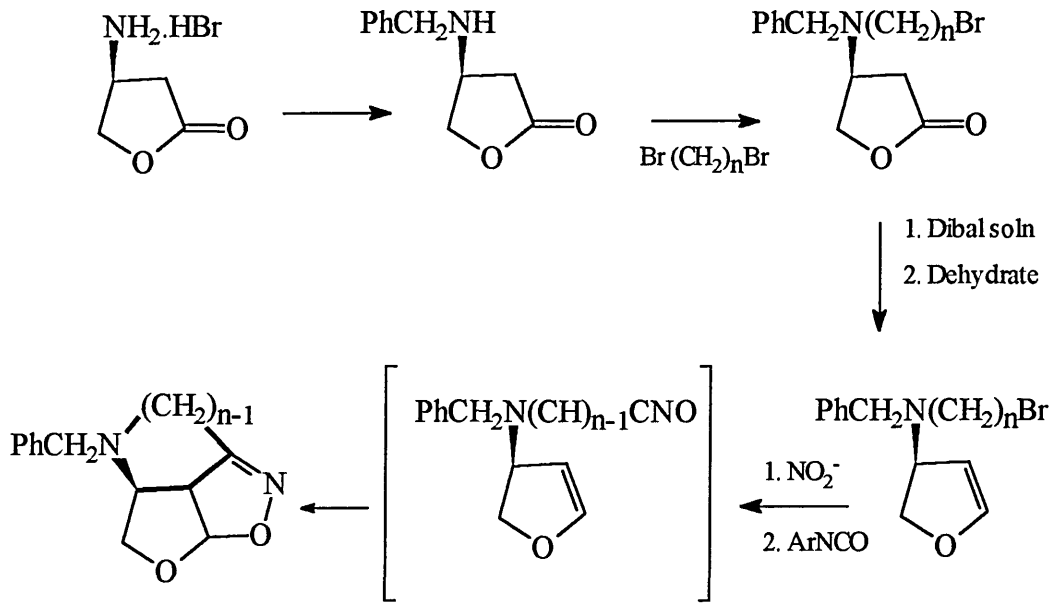
The reaction was then repeated on the sulphonamide **35** and after a few attempts the lactol **41** was produced in 18% yield by using three molar equivalents of the DIBAL solution, *scheme 32.*



Scheme 32

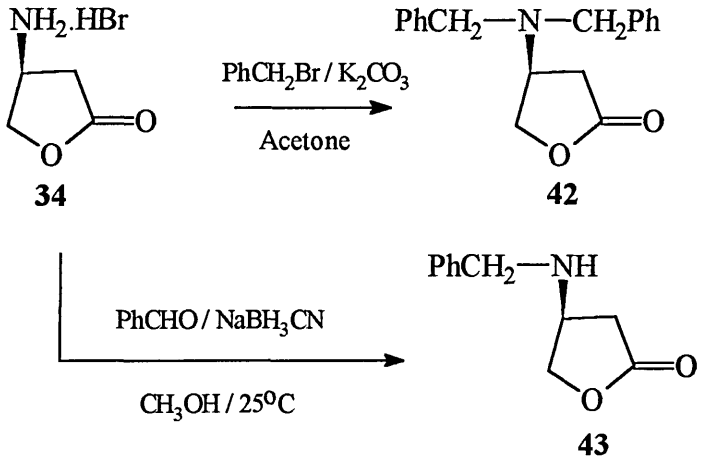
The dehydration of the lactol **41** was tried once with molecular sieves but this method was unsuccessful. This pathway was put to one side as the yield for the reduction of lactone **35** to lactol **41** was low.

It was thought that N-alkylation of a secondary amine might be more successful than that of an amide, so steps were taken to try and synthesise the N-benzylated lactone. Further alkylation of this product might then lead to a nitro derivative from which a nitrile oxide could be synthesised. It was hoped that this in turn would undergo an intramolecular 1,3-dipolar cycloaddition reaction with the dihydrofuran ring structure which would be obtained from the lactone functionality as previously discussed, *scheme 33*.



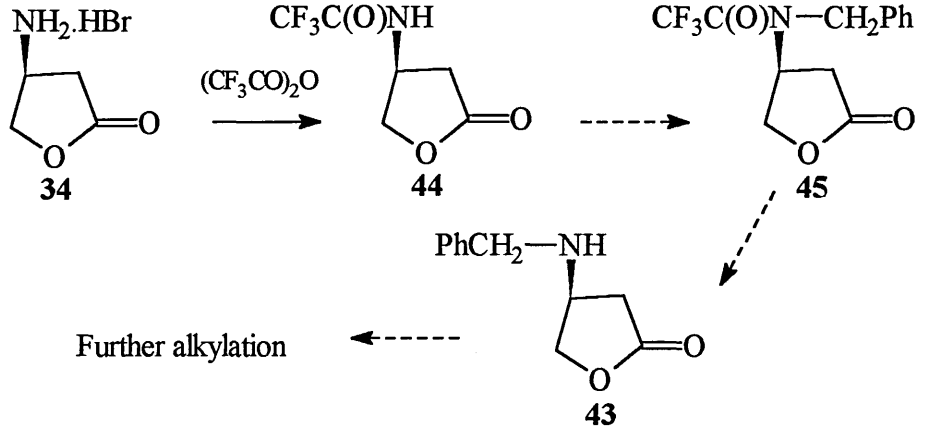
Scheme 33

A number of methods for the synthesis of the N-benzylated lactone are discussed here. Initially direct benzylation[24] of the hydrobromide salt **35** was attempted using benzyl bromide and potassium carbonate in acetone but this resulted in a dibenzylated product **42**, *scheme 34*. Then the reductive benzylation[25] using sodium cyanoborohydride and benzaldehyde in methanol was also investigated, *scheme 34*. Spectral data showed that some impurities were present as well as the required product.



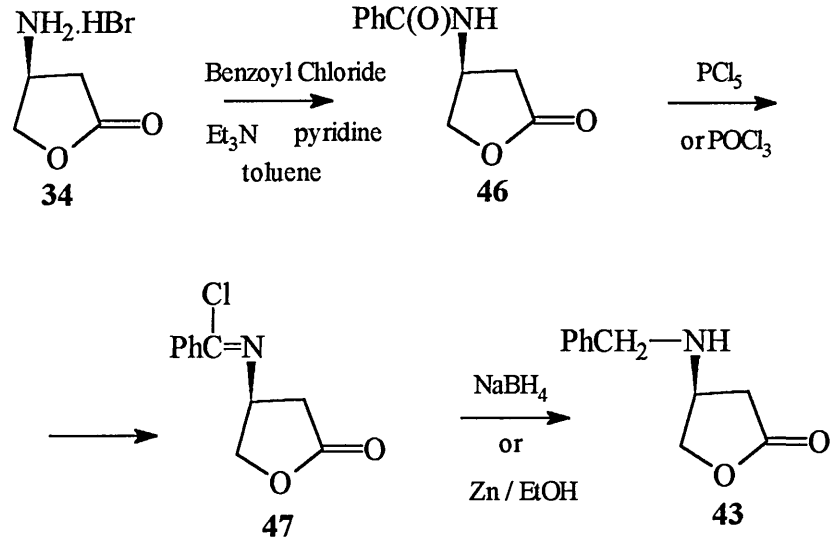
Scheme 34

Another approach towards **43** was to synthesise the trifluoroacetamide[26] **44** [which contains a group with strong electron withdrawing powers] in order to make the remaining hydrogen more acidic and therefore allow N-benzylation to take place. The trifluoroacetamide protecting group could then be removed leaving the N-benzylated secondary amine ready for further alkylation, *scheme 35*. The trifluoroacetamide was obtained in good yield (68%) but the N-alkylation was unsuccessful as starting material remained.



Scheme 35

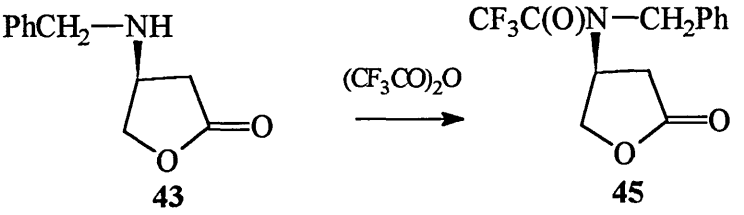
An alternative route to the N-benzyl lactone **43** would be via selective reduction of the benzamide **46**, a possible pathway involving production of the imidoyl chloride **47** followed by mild reduction with sodium borohydride[27] or zinc dust[28] in ethanol, *scheme 36.*



Scheme 36

The reduction with sodium borohydride[27] did not give the required product, but it was not clear whether failure of the reaction was due to incorrect formation of the imidoyl chloride or due to the unsuccessful reduction of this intermediate. Another method[28] was chosen with phosphorus oxy-chloride ($POCl_3$) as the reagent for the formation for imidoyl chloride and the reduction was carried out with zinc dust in ethanol. This yielded the N-benzyl lactone **43** as well as many impurities one of which was $PO(OEt)_3$. Difficulties were encountered in the separation of the required product from the impurities, especially $PO(OEt)_3$. After initial purification using column chromatography, (ethyl acetate:petrol, 8:2), the crude mixture was reacted with

trifluoroacetic anhydride[26] and the resulting N-benzyl trifluoroacetamide **45** was isolated in a yield of 20%, *scheme 37*.



43
Crude Form

45

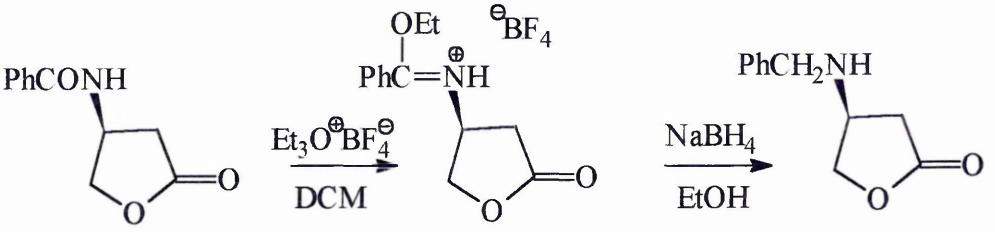
Scheme 37

This now requires hydrolysis back to the N-benzyl lactone and because this pathway is a long and time consuming method it was not pursued any further. Due to the large number of stages left to complete in this synthetic route and also the fact that an alternative synthesis of pyrrolidines discussed in chapter 4.2 was more promising, further work on this approach was not continued.

3.2 Summary and future work

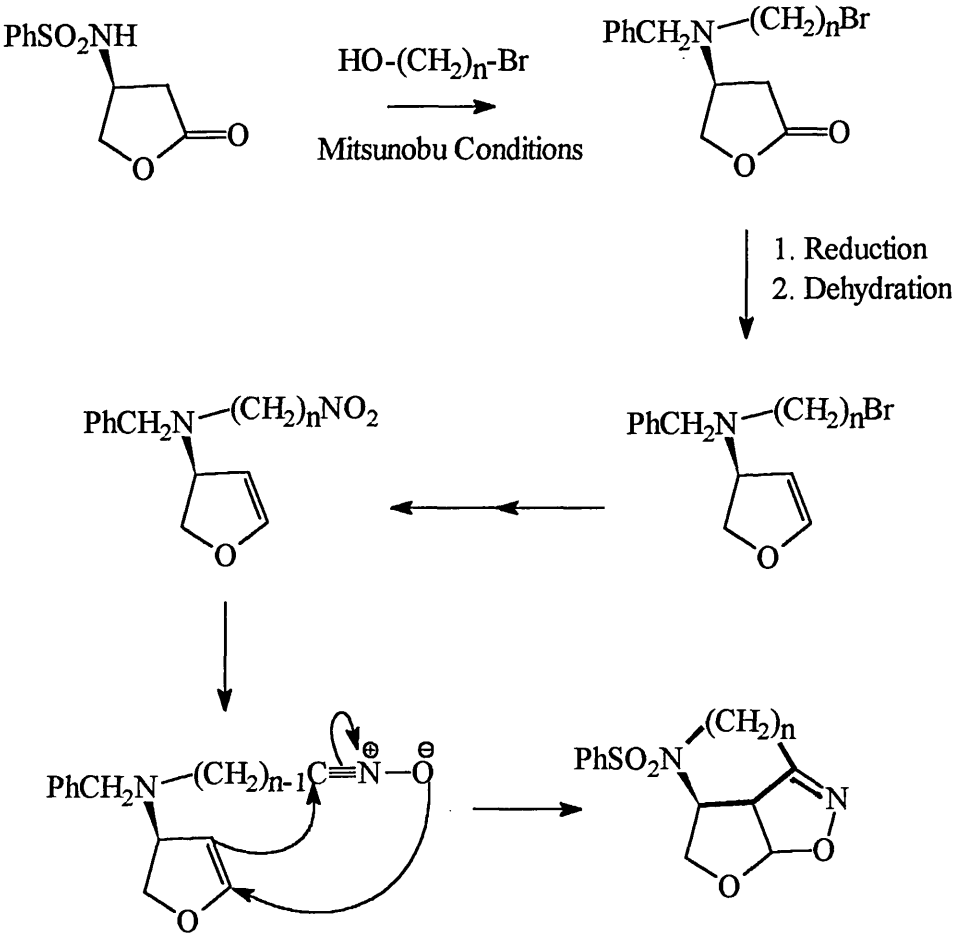
Different protecting groups were used with the lactone in the hope of one of the alkylation methods succeeding. Any future work in this area would include obtaining a greater yield from the DIBAL reduction of the lactone and pursuing different methods for the dehydration of the lactol. The other area of interest to follow up would be to optimize the yield for the reduction of the N-benzoyl lactone **46** to the N-benzylated lactone **43** and to try to further alkylate this compound in an attempt to eventually synthesise a functionalised pyrrolidine.

An alternative method[29] for the reduction of the N-benzoyl lactone **46** to N-benzyl lactone **43** which could be tried uses triethyloxoium fluoroborate in DCM to give the imino fluoroborate.The DCM is replaced by absolute ethanol and subsequent treatment with excess sodium borohydride gives the required amine, *scheme 38.*



Scheme 38

As mentioned previously there were a few problems with the alkylation methods tried. In an attempt to overcome these problems the Mitsunobu reaction[30] (discussed in more depth in section 4.2 Synthesis of pyrrolidines from glucose, p109) could be employed which involves the condensation of an alcohol and an acidic moiety such as a sulphonamide or a carboxylic acid with a triaryl or trialkylphosphine and a dialkyl azodicarboxylate. The resulting product would be equivalent to an alkylated amine with the chain length depending on the alcohol used. The reaction of the sulphonamide **35** with alcohols such as 2-bromoethanol or 3-bromo-1-propanol could give the addition of a 2 or 3 carbon chain respectively. In this example a bromide is present, so after the reduction of the lactone and dehydration of the lactol to form an alkene, the bromide could be replaced with a nitro group which in turn could be converted to a nitrile oxide precursor for the 1, 3-dipolar cycloaddition reaction, *scheme 39.*



Scheme 39

On cleaving the resulting cycloadducts, fuctionalised pyrrolidines and piperidenes would be formed depending on the length of the alcohol used initially.

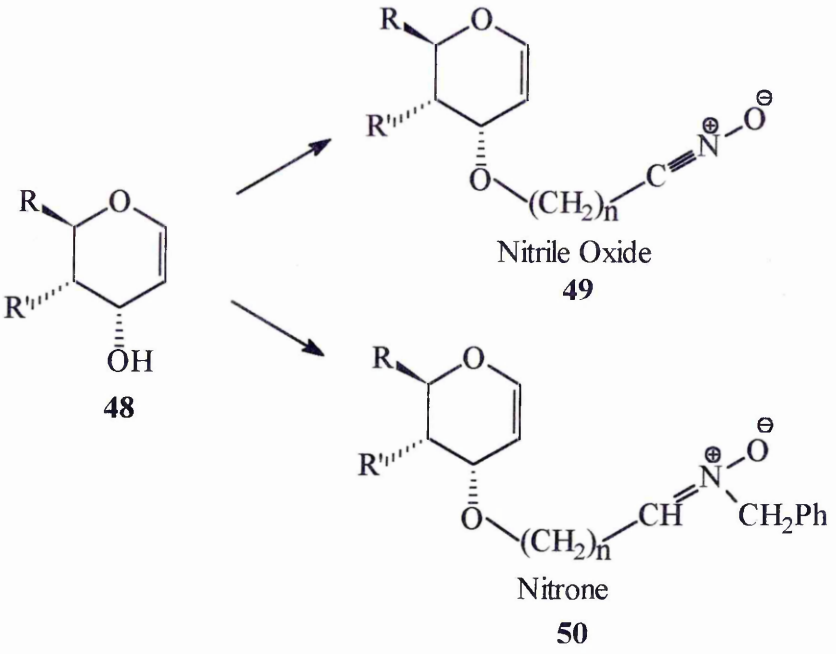
Chapter 4

CARBOHYDRATES

4.0 Carbohydrates

4.1 Synthesis of oxygen heterocycles from glucose

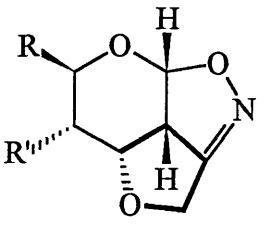
In the previous chapter the amino acid aspartic acid was used as a chiral template in an approach to the synthesis of chiral heterocyclic molecules. The same idea is being used in this chapter except a carbohydrate was used as the chiral template instead of an amino acid. By following literature methods, modifications of a simple sugar were carried out to produce a 3-hydroxy-1,2-dihydropyran **48** which on further conversion would form the precursor, nitrile oxide **49** or nitrone **50**, for the 1,3-dipolar cycloaddition reaction.

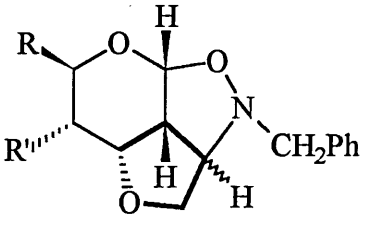


Scheme 40

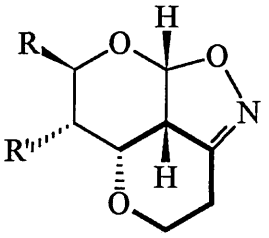
By varying the value of **n** the synthesis of several different ring sizes in the cycloadduct were attempted and these are illustrated here.

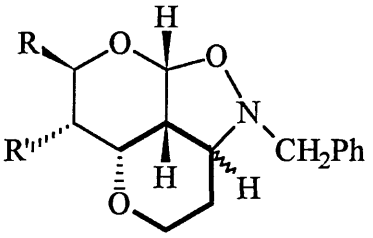
Five membered oxygen heterocyclic adducts



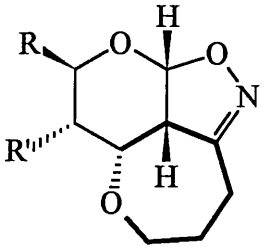


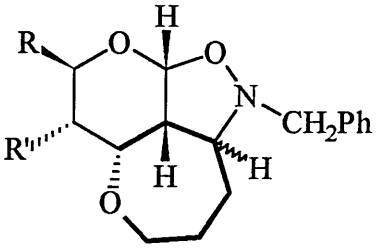
Six membered oxygen heterocyclic adducts



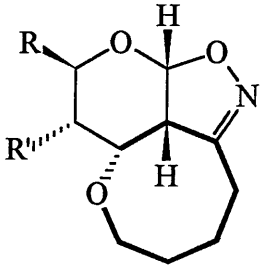


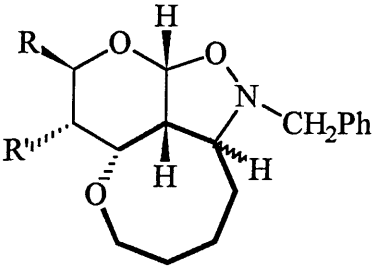
Seven membered oxygen heterocyclic adducts





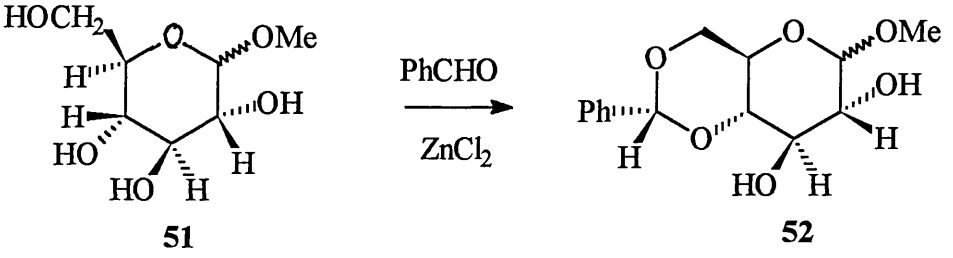
Eight membered oxygen heterocyclic adducts





4.1.1 Five membered oxygen heterocyclic adducts

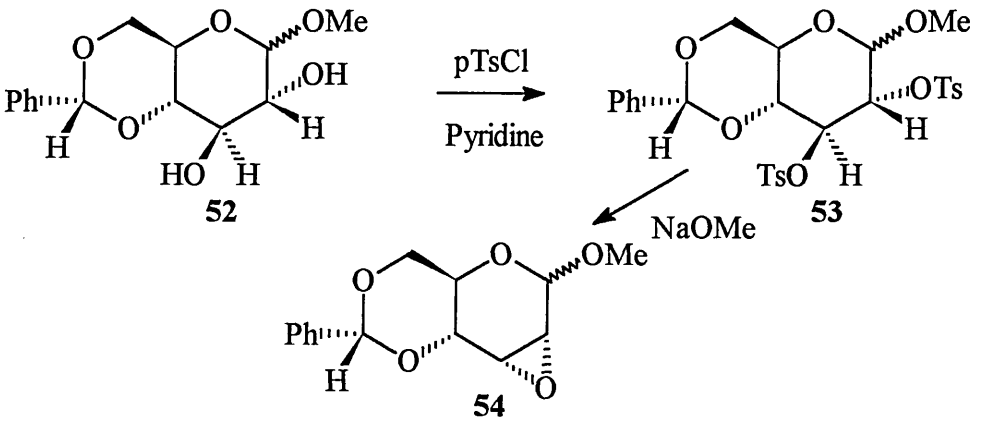
The simple sugar, methyl α-D-glucopyranoside **51** was used as the initial building block and was protected as the acetal with benzaldehyde, *scheme 41*. Initially some difficulties were encountered with this reaction resulting in low yields and quite often only starting material was recovered. The problem seemed to lie in the recrystallisation of the crude material on a large scale since this often resulted in decomposition. As a result of this the crude product, methyl 4,6-O-benzylidene-α-D-glucopyranoside[31] **52**, which was obtained in a yield of 56%, comparable to the literature value, was used for subsequent reactions.



51 **52**

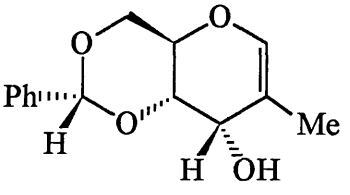
Scheme 41

The next step involved the conversion of the diol **52** into a ditosylate to give methyl 4,6-O-benzylidene-2,3-di-O-toluene-p-sulphonyl α-D-glucopyranoside[31] **53** from which the formation of the epoxide, methyl 2,3-anhydro-4,6-O-benzylidene α-D-allopyranoside[31] **54** was carried out with no problems (93% yield) *scheme 42*.



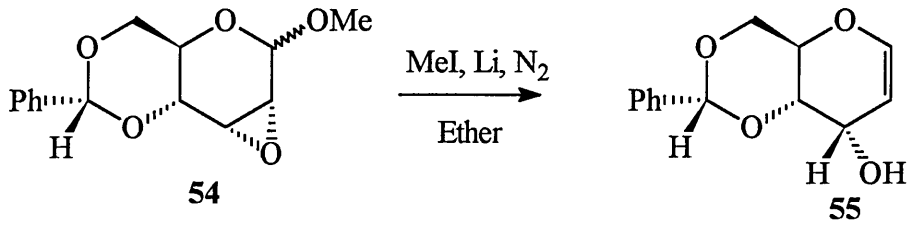
Scheme 42

Literature[32] describes the conversion of the epoxide **54** to 4,6-O-benzylidene-1,2-dideoxy-D-ribo-hexapyranose, (4,6-O-benzylidene-D-allal) **55** by using lithium iodide and butyl lithium or methyl lithium in ether. Our initial attempts to repeat this reaction resulted in a complex mixture and poor yields of the desired product. Closer inspection of the literature showed that a major product when using commercial alkyl lithiums is **56** and that more success could be achieved by preparing methyl lithium according to the directions of Feast et al[33] and using it immediately. This gave the required compound **55** in 96% yield, *scheme 43*.



56

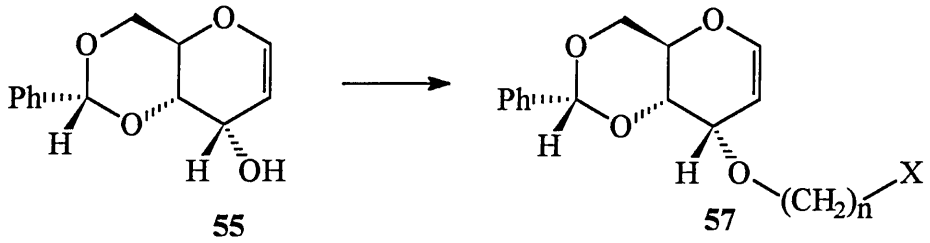
Spectral data for **55** (^{1}H NMR) showed characteristic peaks for the double bond. A doublet (6.5 δ) was observed for the C-1 proton and an apparent triplet (5.1 δ) was seen for the other alkene proton. This distinctive pattern was to be useful in further work in deciding whether or not cycloaddition had taken place.



54 55

Scheme 43

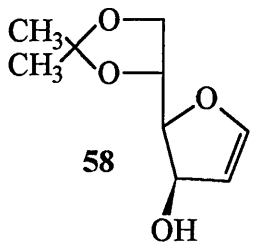
In order to obtain a precursor for the 1,3-dipolar cycloaddition reaction, a chain with a functional group was required. Alkylations carried out on the alcohol functionality of 4,6-O-benzylidene-D-allal, followed by further manipulation to form a compound **57** with a good leaving group X, would make the conversion to a nitro derivative possible and hence a nitrile oxide could be obtained. As an alternative to a good leaving group the formation of an aldehyde could lead to further conversion to a nitrile oxide or a nitrone.



55 57

Scheme 44

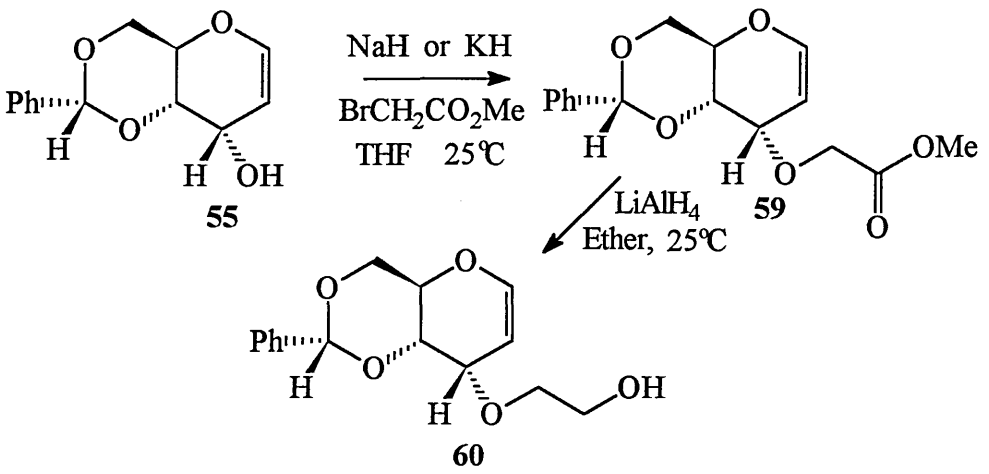
Previous experience[34] in attempting to alkylate the glycal **58** with ω-dibromoalkanes suggested that related alkylations with the alcohol **55** would also fail. The anion of the glycal **58** had preferred to behave as a base rather than a nucleophile. We hoped to get round this problem by using methyl bromoacetate for the alkylation followed by manipulation of the ester group.



58

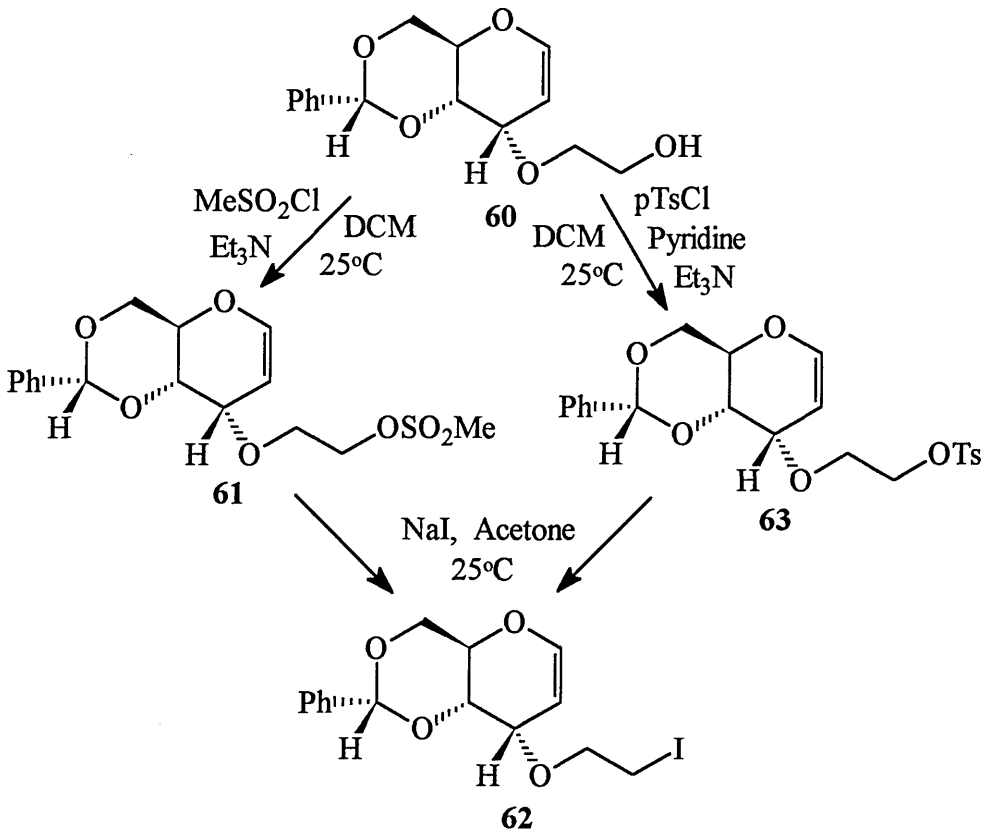
Using sodium hydride the desired ester was obtained, impure in 26% yield even after chromatography. A cleaner reaction was observed using potassium hydride instead of sodium hydride and the required product was obtained after column chromatography in 68% yield, *scheme 45*. The structure of the ester **59** was confirmed by the observation of a carbonyl peak at 1750cm^{-1} and the lack of a hydroxy group between 3600-3300cm^{-1}in its infra red spectrum, as well as by its nuclear magnetic resonance spectrum which showed the presence of the methoxy group as a singlet at 3.4 δ.

The ester **59** was reduced to the alcohol **60**, (88.5% yield), using lithium aluminium hydride in ether[35] and, in order not to lose the benzylidene protecting group, acid conditions were avoided and the reaction mixture was worked up using an aqueous solution of Rochelle salt (sodium potassium tartrate) *scheme 45*. Evidence for the successful preparation of the alcohol **60** was obtained by spectral data which showed the disappearance of the ester group and the gain of a hydroxyl group.



Scheme 45

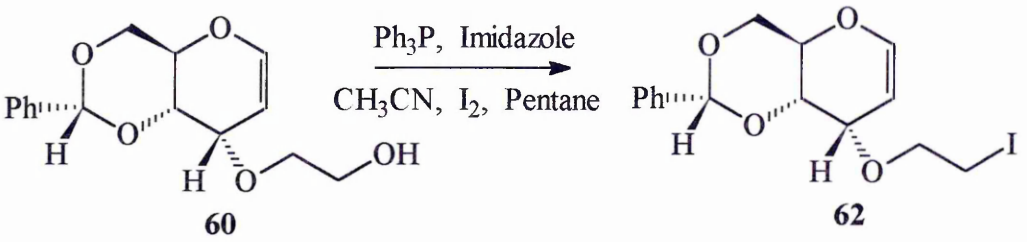
The hydroxyl group is a poor leaving group so it was converted to the mesylate **61** using methane sulphonyl chloride and triethylamine in DCM but **61** was only obtained in 8% yield, *scheme 46*. Literature methods[36] for the synthesis of mesylates and tosylates, usually use triethylamine as the base for mesylates and pyridine as the base for tosylates. The conversion to a mesylate was chosen as triethylamine is volatile and easier to remove than pyridine which is normally removed by an acid wash. As mentioned earlier acid is to be avoided as the molecule is acid labile due to the acetal protecting group. Having prepared the mesylate, the conversion to the iodide[36] **62** was attempted, *scheme 30*. Difficulties occurred here as the double bond character was lost (no instantaneous colouration with $KMnO_4$ spray on a TLC plate), and spectral data (^1H NMR) confirmed this by loss of the doublet at 6.5 δ and the triplet at 5.0 δ, but it also indicated the replacement of the mesyl group with an iodide group by observation of a peak at 3.3 δ and disappearance of the methyl peak at 3.6 δ.



Scheme 46

As an alternative the tosylate **63** was prepared, *scheme 46*, but as mentioned previously pyridine is not an ideal reagent, therefore triethylamine was used again but a small amount of pyridine was also necessary, as the reaction was unsuccessful with triethylamine alone. The work-up required plenty of water washes to remove the pyridine. The tosylate **63** (52% yield) was used in a crude form in the conversion to the iodide **62**, *scheme 46*, which was purified by column chromatography (27% yield). As the yield was quite low a direct route[37] from the alcohol **60** was attempted, *scheme 47*. Spectral data (^{1}H NMR) indicated that the iodide **62** had been prepared, as the singlet at 2.4 δ, which was due to -OH, had disappeared and a peak corresponding to

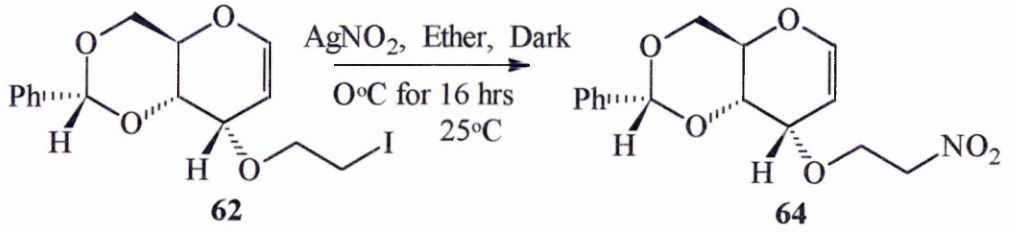
CH_2-I could be seen at 3.3 δ. However the iodide was isolated in only 20% yield after chromatography, no substantial improvement on the previous two step method.



60 **62**

Scheme 47

The next stage was to substitute the iodine atom in **62** with a nitro group[36b] to give the product **64**, *scheme 48*, which would be dehydrated with isocyanate to form the nitrile oxide precursor required for 1,3-dipolar cycloaddition reactions.

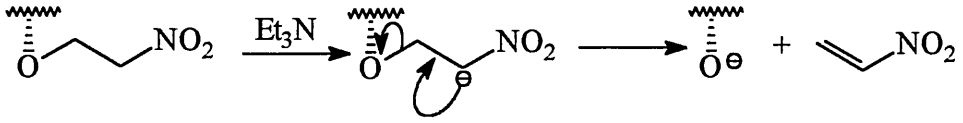


62 **64**

Scheme 48

A crude ^{1}H NMR spectrum suggested that the desired nitro derivative **64** was present as the peaks at 3.3δ, which were due to CH_2-I, had disappeared and the integration on the spectrum indicated the correct number of protons for the product but on purification by column chromatography the nitro derivative decomposed indicating its instability. Triethylamine was used in the eluent for the chromatography of this compound, as it had been for a few of the previous compounds, to prevent decomposition due to the acidic silica causing deprotection. However in this case the

triethylamine was thought to have caused the decomposition by abstracting the proton next to the nitro group, because of its acidic nature, resulting in the production of nitroethene, *scheme 49*, and observation (TLC) of 4, 6-O-benzylidene-D-allal.

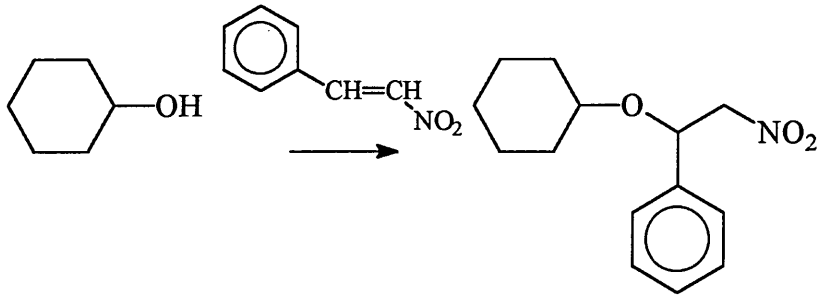


Scheme 49

Due to the sensitive nature of the nitro derivative and the inability to successfully purify it, alternative methods of production of nitro substituted derivatives of 4,6-O-benzylidene-D-allal **55** were investigated.

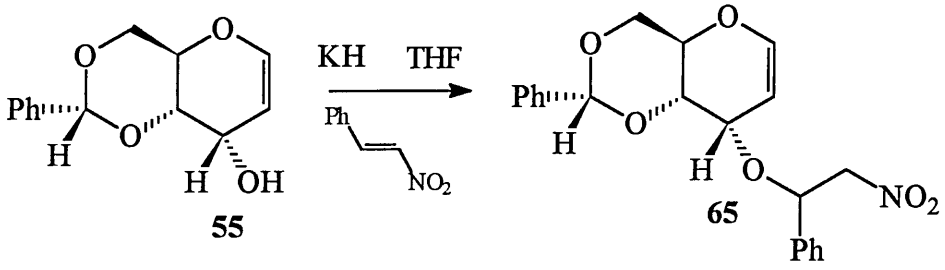
One such method involved preparing β-nitroethers from nitroalkenes and alkoxides. It was suggested from literature[38] that this Michael addition would deliver β-nitroethers in only poor to moderate yield but it has recently been reported[39] that although the reaction of lithioalkoxides with nitroalkenes, which requires six equivalents of the alkoxide, produces complex reaction mixtures, potassio- and sodioalkoxides deliver essentially pure β-nitroethers in substantial yields with only two equivalents of alkoxides. The nitroalkene which was used in our investigation was β-nitrostyrene with potassium hydride, dry THF and 4,6-O-benzylidene-D-allal. Although this would form a nitro derivative which could be further converted to a nitrile oxide for the 1,3-dipolar cycloaddition reaction it would also add another chiral centre and therefore produce another stereoisomer of the product. This would result in lower yields and also would make the interpretation of the spectra quite difficult.

In order to gain practical experience and to investigate the reaction the alkylation was carried out with cyclohexanol, *scheme 50.*



Scheme 50

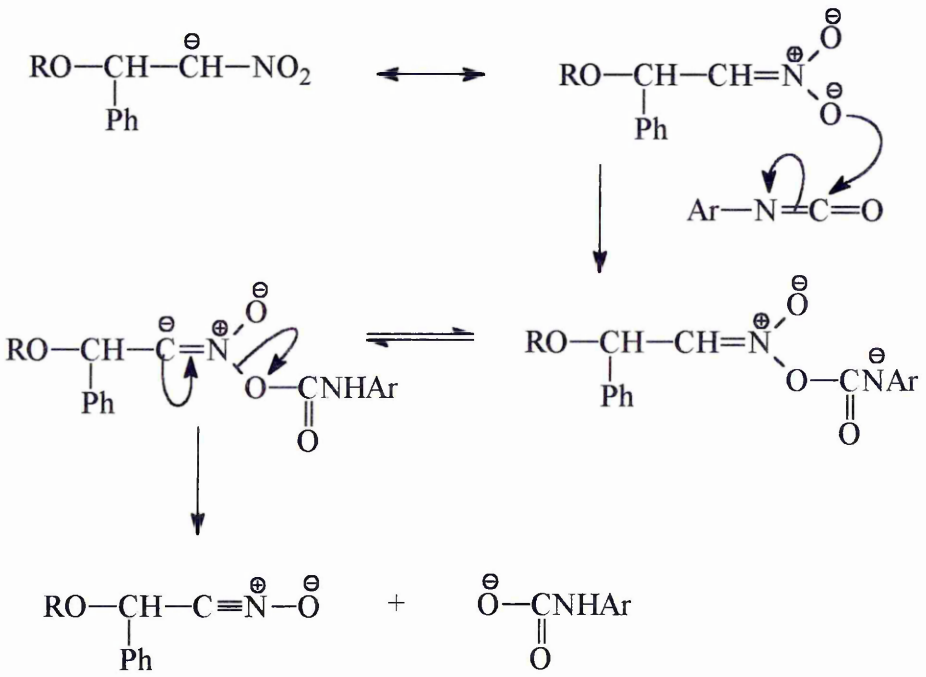
Spectral data (^{1}H NMR) showed the addition of the aromatic protons by the peaks at 7.3-8.0 δ, also the doublet at 3.9 δ showed the presence of CH_2-NO_2 and the multiplet at 5.1 δ was characteristic of protons adjacent to the oxygen (CH-O). A successful reaction was indicated by this data so the alkylation was tried on 4,6-O-benzylidene-D-allal **57**, *scheme 51.*



Scheme 51

The major disadvantage of this reaction was that 4,6-O-benzylidene-D-allal **55** was required in excess (as mentioned previously two equivalents of alkoxide were required for the reaction) and had to be recovered so as not to waste it. After purification by column chromatography the desired product **65** was obtained but in very low yield

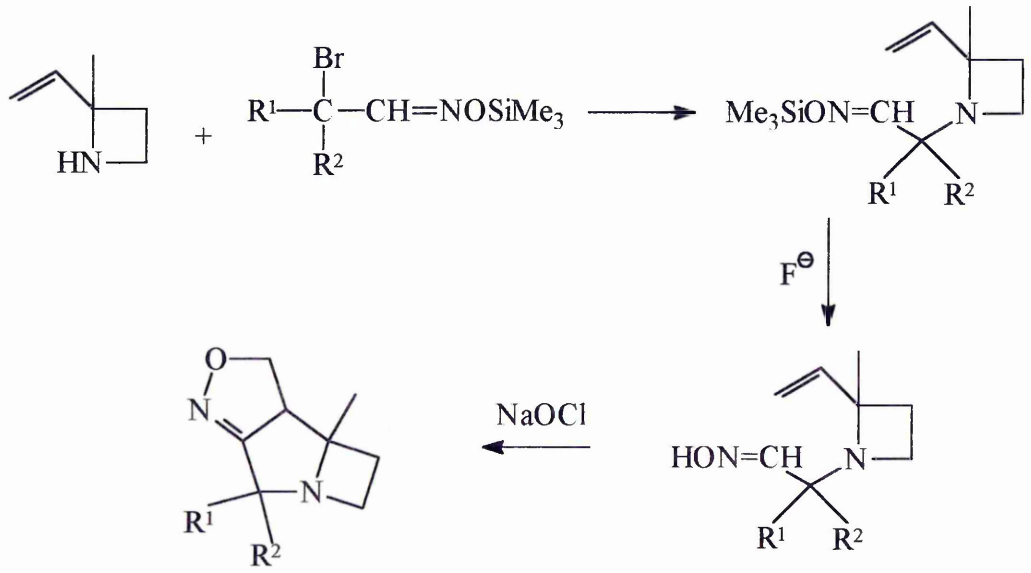
(6% yield). The acid in the work up, although required to protonate the product, may have also removed the protecting group and hence caused the low yield. In an effort to increase the yield a calculated amount of glacial acetic acid was used to protonate the product instead of hydrochloric acid, which increased the yield but only to 12%. So instead of the addition of acid in the workup, an excess of p-chlorophenyl isocyanate was added to the reaction mixture together with a catalytic amount of triethylamine. It was hoped that the nitro compound would form a nitrile oxide, *scheme 52*, which should spontaneously undergo 1,3-dipolar cycloaddition to form a cycloadduct. The excess isocyanate would react with the alcohol **55** to form a urethane by product.



Scheme 52

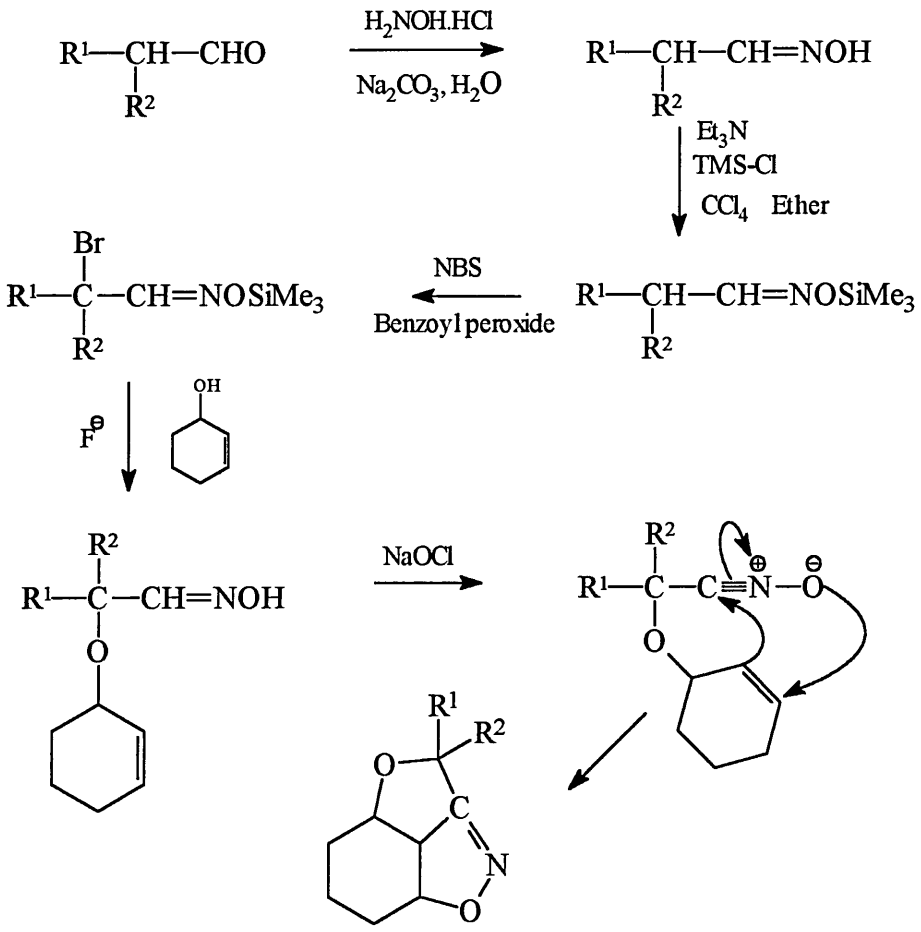
However the reaction was unsuccessful even after refluxing for quite some time. As a result this pathway was not continued.

Hassner[40] discovered a pathway to nitrile oxides based on α-brominated silyl derivatives of oximes. The nucleophilic displacement of the halogen in these O-silyl-α-bromo aldoximes, by an amine in Hassner's case, led to the silylated oxime product. This was desilylated in the presence of fluoride ions and then the unsaturated oxime was converted via a nitrile oxide to an isoxazoline by treatment with sodium hypochlorite, *scheme 53*.



Scheme 53

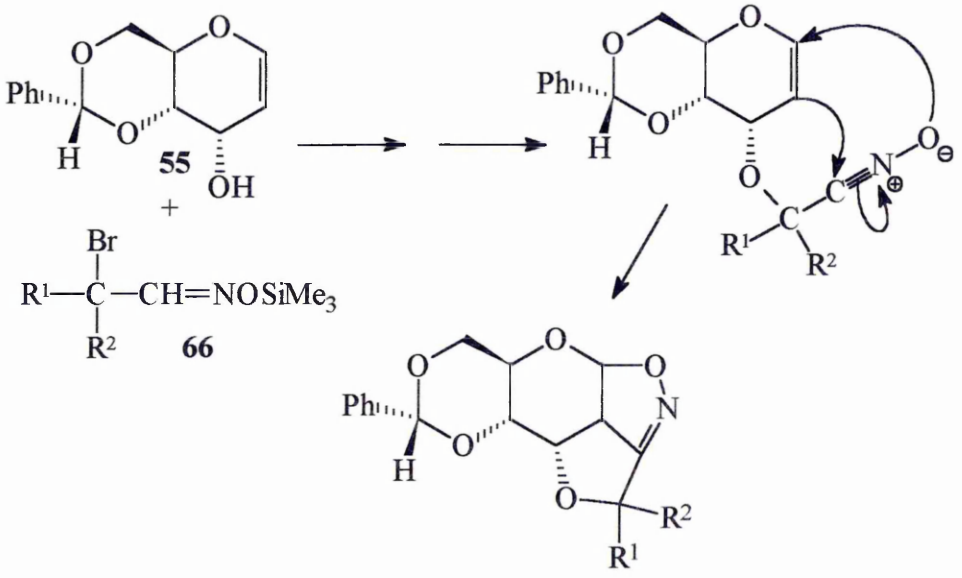
Later investigations by Padwa and Hassner[16b] found that reaction with unsaturated alcohols was also possible. One example of this reaction was with cyclohexenol, *scheme 54.*



Scheme 54

This led to our own investigations using isobutyraldehyde and propanal as the aldehydes, and 4,6-O-benzylidene-D-allal **55** as the unsaturated alcohol. The aldehydes were successfully converted to their respective oximes using hydroxylamine hydrochloride and either sodium carbonate or sodium acetate and the oximes were purified by distillation. The next step was to convert the oximes to O-trimethylsilyl 2-bromo derivatives which was a two stage reaction, carried out without isolation of the product from the first stage. This first stage involved the silylation of the oxime with trimethylsilyl chloride and triethylamine in dry freshly distilled carbon tetrachloride. The mixture was stirred at room temperature overnight and the production of the

triethylamine hydrochloride salt indicated the reaction was taking place. The solution was filtered and the salt washed with carbon tetrachloride. The filtrate was put through to the second stage which was a radical step using benzoyl peroxide, which was the radical initiator, and N-bromosuccinimide, which was the brominating agent. A few problems arose here as reproducible results were unobtainable so the product from the first stage was isolated to ensure the oxime was being silylated fully. According to Hassner and Padwa[16c] the silylation should only take 2hrs but this was found to be insufficient time so the reaction was left overnight. This did improve the reaction but some unreacted oxime still remained. The crude mixture was put through to the radical step where further problems were encountered. The stirred suspension was heated to reflux for 3.5 hrs but again reproducible results were not obtained. An alternative method of radical generation was tried which involved irradiation for 2 hrs using two 100W lamps. This provided the O-trimethylsilyl 2-bromo derivatives **66** but this step was also very erratic. Only once was sufficient bromo derivative obtained to allow an attempt at the nucleophilic displacement by the alcohol **55**, *scheme 55*.

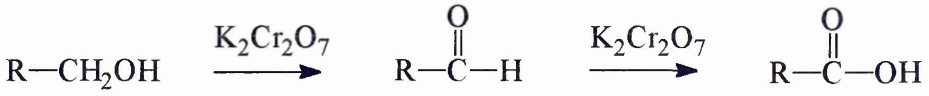


Scheme 55

A reaction was observed (TLC) between 4,6-O-benzylidene-D-allal **55** and the bromo derivative **66** by the disappearance of the spot which represented the alcohol and the appearance of a new spot suggesting that the alkylation had taken place. As such a small quantity of reagents were present, the product was not isolated but was desilylated by the addition of potassium fluoride followed by the conversion to a nitrile oxide by the treatment with sodium hypochlorite but no cycloadditon occurred. Due to the many problems and irreproducibility of the steps involved this route was abandoned.

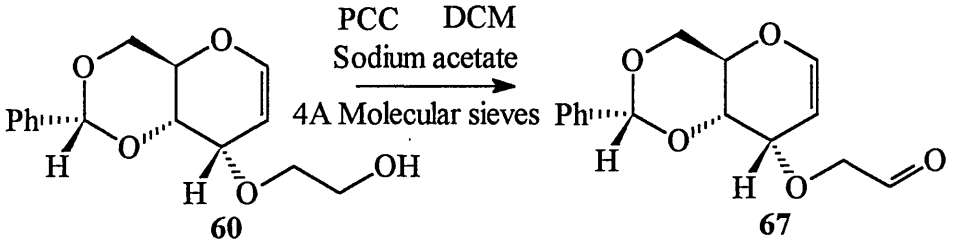
A different route for the preparation of the desired nitrile oxides and nitrones involved their synthesis from the aldehyde **67** which could be obtained from the alcohol **60** or the ester **59.**

Initially we investigated the oxidation of the alcohol **60**. Generally primary alcohols can be oxidised to aldehydes[41], most commonly by using some form of chromium VI, *scheme 56*, but the aldehyde usually needs to be removed from the reaction mixture by special techniques such as using a fractionating column before it is oxidised further to a carboxylic acid. In most cases the primary alcohol undergoes oxidation more rapidly than the corresponding aldehyde.



Scheme 56

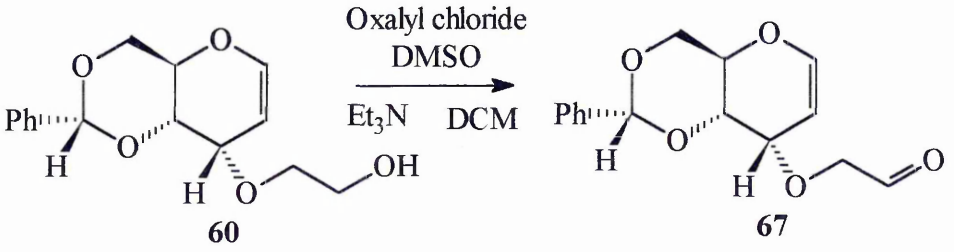
In order to stop oxidation of the aldehyde, anhydrous conditions are required to prevent the formation of hydrate thereby stopping the further oxidation to the carboxylic acid. The reagent pyridinium chlorochromate (PCC) is an oxidising agent which can be used in organic solvents and hence eliminate any hydrate problems as dry solvents can be employed. PCC[42] was used in the attempted preparation of an aldehyde, *scheme57,* and the oxidation reaction was buffered with sodium acetate. The reaction was carried out in dry DCM and after stirring for several days at room temperature starting material still remained. The reaction was repeated with the addition of 4A molecular sieves but this also resulted in recovered starting material.



Scheme 57

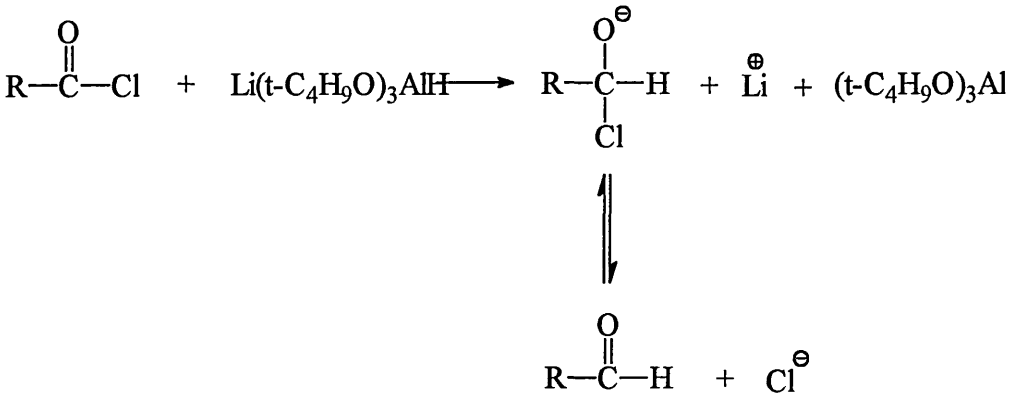
An alternative oxidation is the Swern oxidation[43] which is carried out under very mild conditions using oxalyl chloride, dimethyl sulphoxide, triethylamine and DCM. Initially a solution of oxalyl chloride in dry DCM was cooled to -50°C to -60°C and then dimethyl sulphoxide was added dropwise with stirring. After 5 minutes the alcohol was added dropwise over 10 minutes keeping the temperature constant. After a further 15 minutes stirring, triethylamine was added with the temperature still below -50°C and finally stirring was continued for 5 minutes before the reaction mixture was worked up. As this is a very quick reaction, the timing was an important factor. A

few problems were encountered so the reaction was repeated several times, altering the time between the addition of each reagent, and finally the aldehyde **67** was obtained in an increased yield of 76 %, *Scheme 58.* The aldehyde was confirmed by the observation of a singlet at 9.95 δ in the ^{1}H NMR spectra and the presence of a carbonyl peak in the infrared spectrum. The ^{1}H NMR spectrum showed a reduced integration for this aldehydic proton, so the aldehyde looked as though it was only present as two thirds of the product. Both types of spectral data indicated that many impurities were also present, but purification by column chromatography resulted in the loss of the aldehydic proton in the spectral data.



Scheme 58

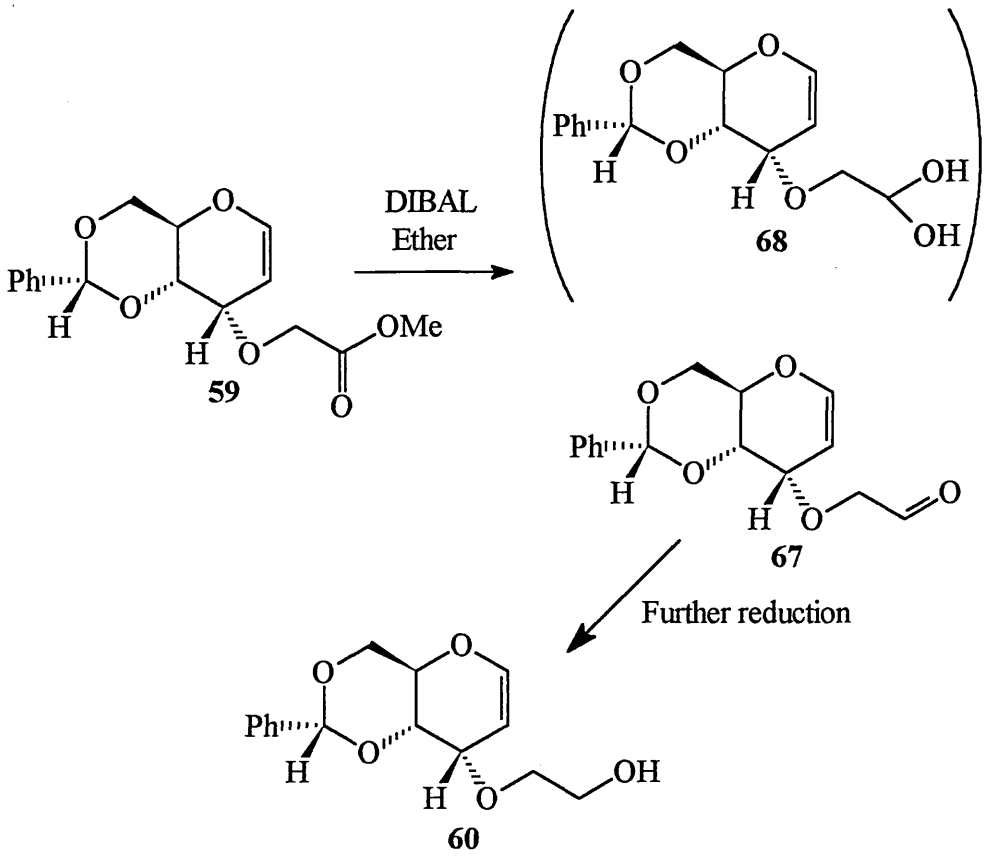
An alternative way of obtaining an aldehyde is by the reduction of acid derivatives. Selective reduction of an acyl halide is one possible route[44]. One acceptable reagent for this reaction is a tri-t-butoxy derivative of lithium aluminium hydride which is less reactive and therefore more selective, allowing the synthesis of an aldehyde, *scheme 59.*



Scheme 59

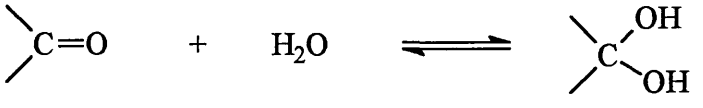
If an excess of reducing agent is used, the aldehyde is reduced further to a primary alcohol.

Since esters are generally less reactive than aldehydes, it is normally quite difficult to selectively reduce the ester to the aldehyde stage. The reducing agent, diisobutylaluminium hydride[45] is known to reduce esters to aldehydes at low temperatures, although particular care is required so the reduction doesn't continue further to the alcohol. This reagent was used in our reduction and close monitoring by TLC ensured the reaction was quenched before further reduction could occur. With perseverance the ester **59** was reduced to the aldehyde **67** in a crude yield of 97%. The aldehyde was not further purified., *scheme 60*. Spectral data confirmed the presence of the aldehyde with a singlet at 9.7 δ but the integration for this aldehydic proton was reduced again.



Scheme 60

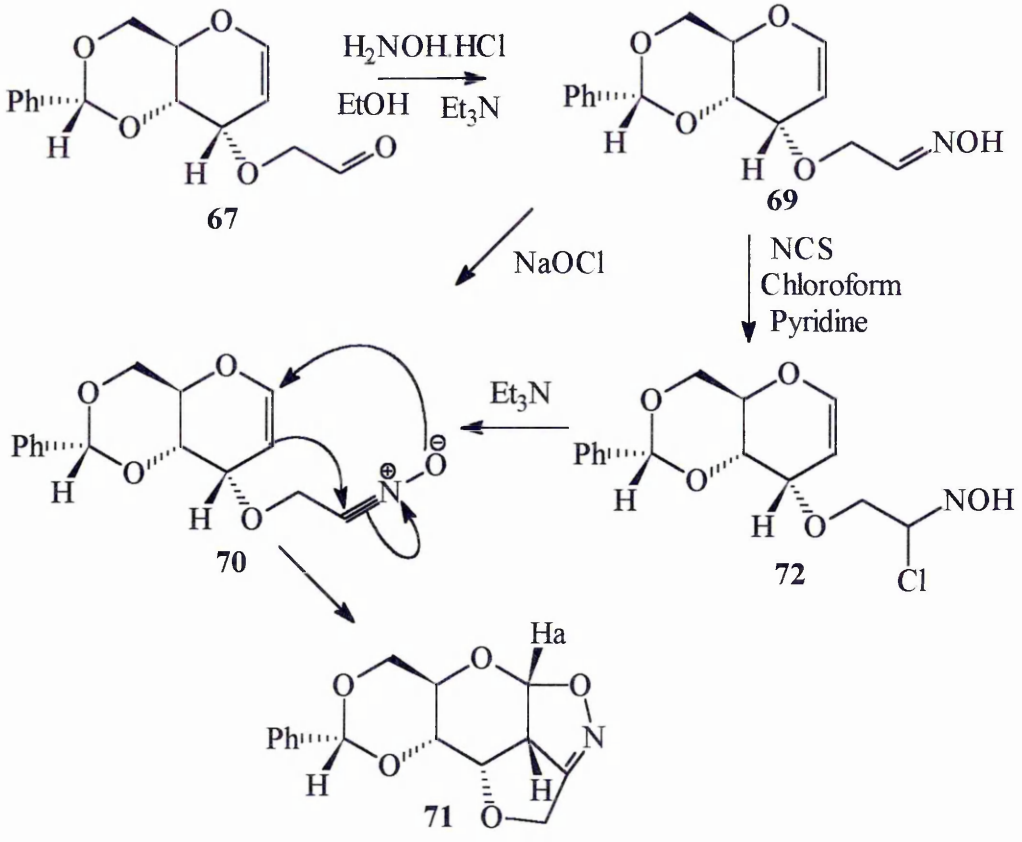
Literature[45] suggested that in similar cases of the preparation of an aldehyde, the hydrate was also present. A hydrate is normally formed when an aldehyde comes into contact with water and it is believed that the water for the hydrate **68** originated from the isolation process where the reduction was quenched to stop the reaction continuing further. The equilibrium involved may be written as :



As the hydrate **68**, *scheme 60*, was obtained as well as the aldehyde it was suspected that this was the cause of the reduced integration of the aldehydic proton in this reduction and also the previous Swern oxidation. Because the aldehyde had been

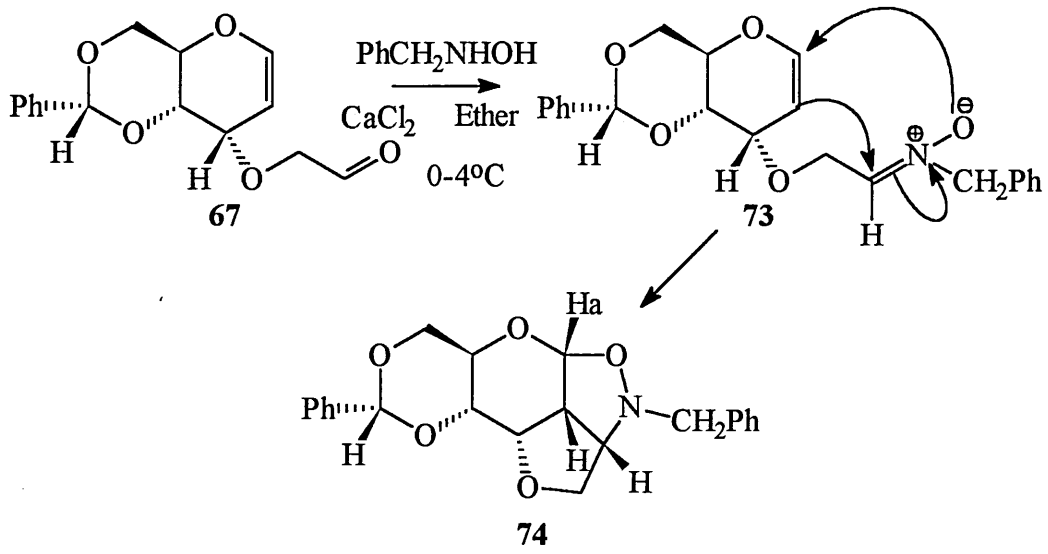
previously found to be difficult to purify it was used crude in the next step. With hindsight this is what probably caused the earlier problems in the characterisation of the aldehyde as the complex TLC caused some confusion. Overall it was established that for the preparation of the aldehyde **67**, the DIBAL reduction of the ester was a far cleaner reaction than the Swern oxidation of the alcohol **60**.

From the crude aldehyde, the oxime **69** was prepared with hydroxylamine hydrochloride and triethylamine in ethanol[46], *scheme 61*. On addition of water the compound crystallised out of solution giving pure oxime in 73% yield. Spectral data [^{13}C NMR] showed doubling of peaks indicating a mixture of isomers which is often observed in the synthesis of oximes.



Scheme 61

The oxime could be converted to a nitrile oxide in two possible ways. The first method to be tried was oxidation with sodium hypochlorite solution[40], but a crude yield of only 30% of the cyclised product **71** was obtained. As the reaction was not complete or clean the other method was considered. This involved converting the oxime to a hydroximoyl chloride **72** with N-chlorosuccinimde and a catalytic amount of pyridine in chloroform. Further dehydrochlorination with triethylamine formed the nitrile oxide[47]. This spontaneously underwent intramolecular cycloaddition as the olefinic functionality was already present in the molecule. It was later found that the initial addition of pyridine was sufficient base for the cyclisation to take place and further addition of triethylamine was not required. The five membered ring cycloadduct **71** [Δ^2-isoxazoline] was obtained in 79% yield and evidence for this synthesised product was shown by the ^{1}H NMR spectrum. It indicated the disappearance of the double bond character which was represented by the peaks at 5.0 δ and 6.5 δ and also it showed the appearance of a doublet at 5.7 δ which was due to Ha in the cyclised product, *scheme 61*. Models suggested that with such a short chain the nitrile oxide could only add to the α-face and the presence of a single stereoisomer was confirmed by spectral data. The ^{13}C and ^{1}H spectra both showed single sets of peaks as opposed to doubling of peaks observed with the oxime.



Scheme 62

A suitable nitrone precursor for the 1,3-dipolar cycloaddition reaction might be formed from the aldehyde **67** by treatment with benzyl hydroxylamine, *scheme 62.* The mixture of aldehyde, benzyl hydroxylamine and calcium chloride in ether was placed in the fridge overnight and the nitrone produced cyclised to form the crystalline product **74** (75% yield). One isomer of the isoxazolidine was obtained and this was confirmed by spectral data which didn't show any doubling of peaks but indicated cyclisation had taken place by the doublet at 5.5 δ which was due to Ha, *scheme 62.* The characteristic double bond feature had disappeared.

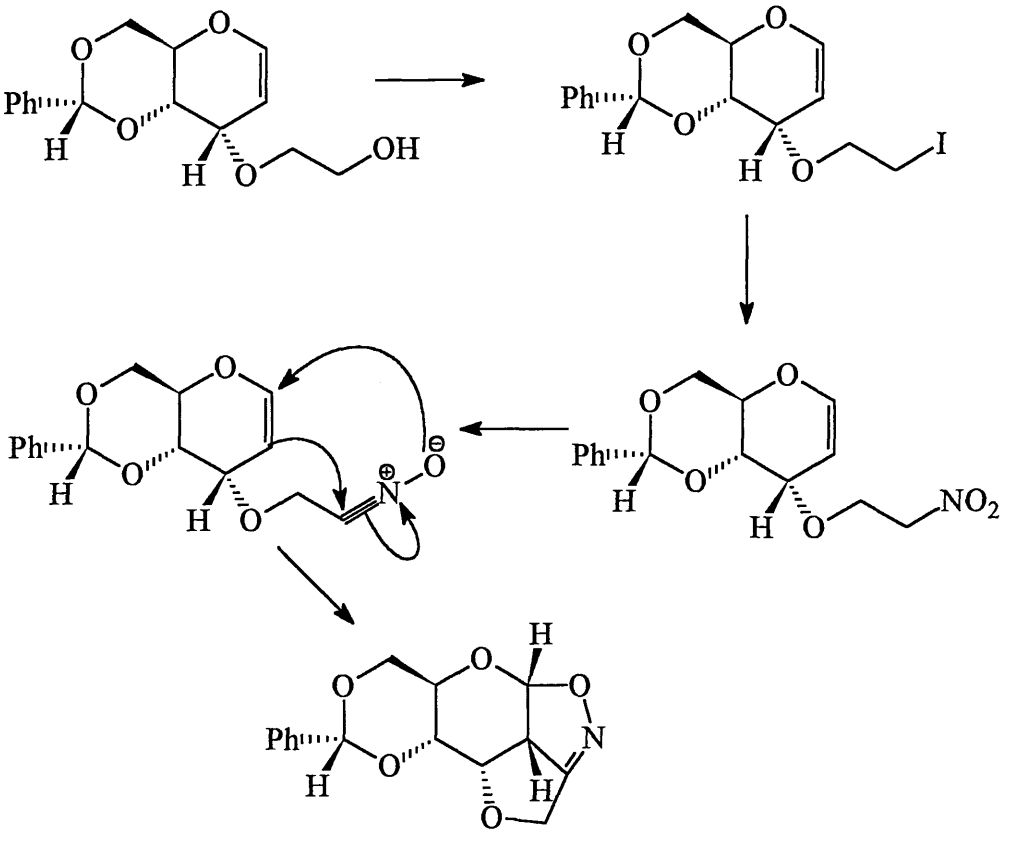
According to DeShong[45] most of the N-benzyl nitrones prepared in this manner exist exclusively in the Z-configuration, so it would be reasonable to suppose that the nitrone produced in this case was in the Z-configuration, although nitrones have been known to interconvert during a reaction. As mentioned previously in the cyclisation of the Δ^2-isoxazoline the short chain length makes the nitrone attack preferentially from

the α-face of the molecule. According to DeShong most nitrones in the Z-configuration cyclise via the endo transition state but in this case it is believed to be exo as the bulky N-benzyl group would make it difficult for the cyclisation to take place via the endo transition state. Models have been studied and they support these ideas. They have shown that the nitrone attacks preferentially from the α-face and that the cyclisation of the Z nitrone, via the exo transition state, is more favourable. However as it is possible for nitrones to interconvert between Z and E isomers[13a]; the cycloaddition of the E isomer would have to occur via the endo transition state, but models have shown that the reactive centres do not come close enough together as the N-benzyl group is causing serious steric hindrance with the rigid bicyclic part of the molecule, so it is likely that our cycloadduct was obtained exclusively via the exo transition state from the Z isomer of the nitrone.

4.1.1.1 Summary and future work

The Δ^2–isoxazoline **71** and isoxazolidine **74** were both successfully synthesised although a few problems were encountered in the several routes attempted.

One route involved the synthesis of a nitro derivative. This could then be dehydrated with an isocyanate to form a nitrile oxide, *scheme 63*. The nitro derivative had been obtained but in a very low yield and this caused problems in purification, especially with the nitro derivative being of a sensitive nature.



Scheme 63

The conversion of the alcohol to the iodide, after a few attempts, resulted in a low yield which meant that the next step could only be done on a small scale. One possibility would be to prepare a bromide from the alcohol and then substitute the bromide with an iodide in a hope that these reactions would be more efficient and give a greater yield than those already tried. The increased yield might then help to overcome some of the handling problems encountered in the next step.

Hassner[40] had discovered a pathway to nitrile oxides based on α-brominated silyl derivatives of oximes, but our attempts at applying his ideas to our systems, *scheme 54 and 55*, were not reproducible. As the O-silyl-α-bromoaldoxime had been prepared

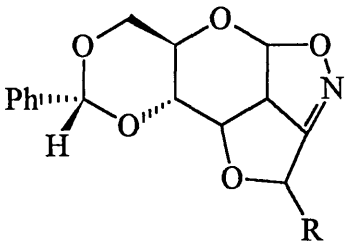
once it should be possible to obtain this compound again and further work could be done in this area to optimise the reaction conditions to suit our systems.

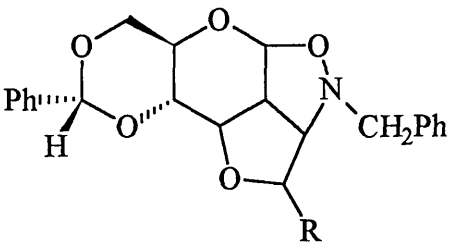
Alternative routes to the Δ^2-isoxazoline involved preparing an aldehyde from either an alcohol or an ester, *scheme 57, 58 and 60*. The synthesis of the aldehyde from the alcohol via the PCC oxidation was unsuccessful but the Swern oxidation did produce the aldehyde although impurities were present. It was the DIBAL reduction of the ester that gave the cleanest reaction and largest yield. The aldehyde was then used to synthesise the oxime which was converted to the nitrile oxide this in turn cyclised to form Δ^2-isoxazoline **71**, *scheme 61.*

The same aldehyde was reacted with benzyl hydroxylamine to form the nitrone precursor which cyclised to form the isoxazolidine **74**, *scheme 62*.

Despite the two cycloadducts **71** and **74** having been successfully synthesised further work could be undertaken to produce a range of different Δ^2-isoxazolines and isoxazolidines.

Instead of using methyl bromoacetate to form an ester, alternative α-bromoesters $RCHBrCO_2Me$ could be used, which would eventually leave an R group substituent on the five membered ring.



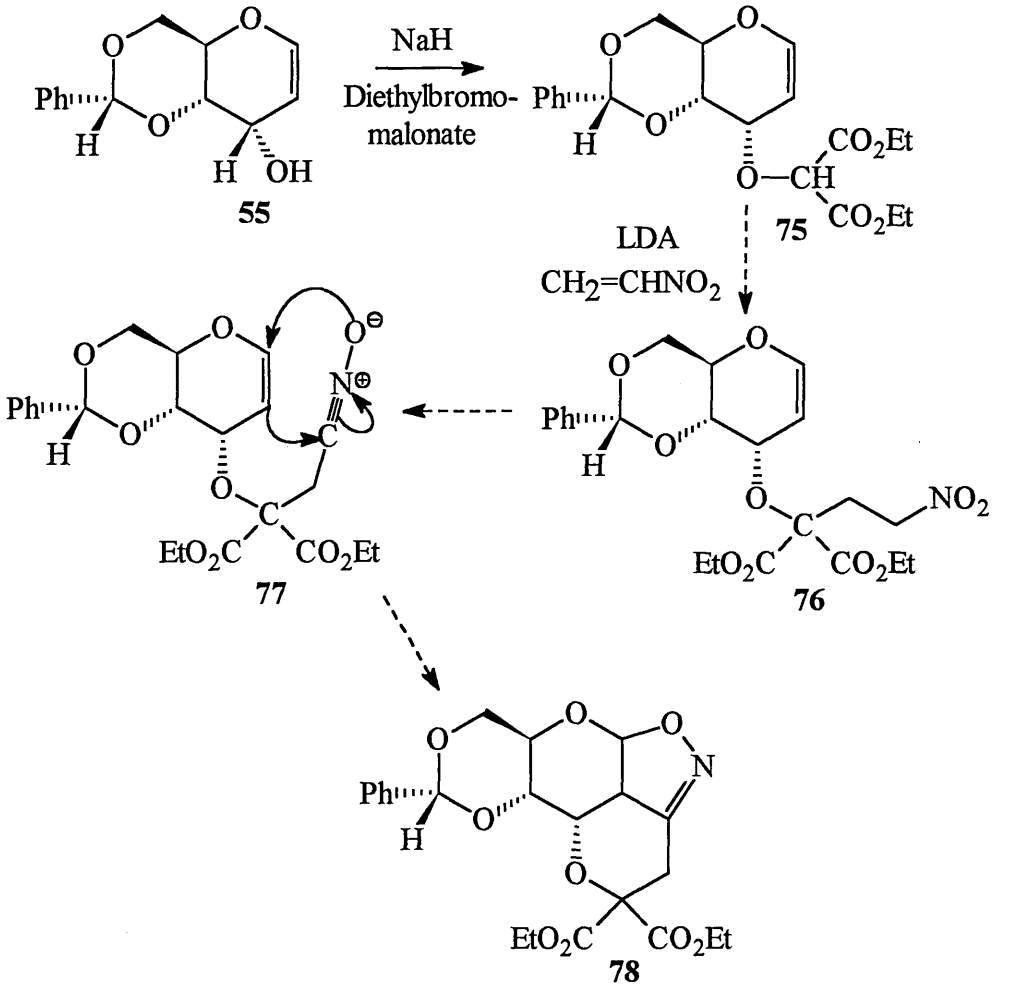


The main disadvantage of using this reagent is that another chiral centre would be formed causing diastereoisomers to be present.

4.1.2 Six membered oxygen heterocyclic adducts

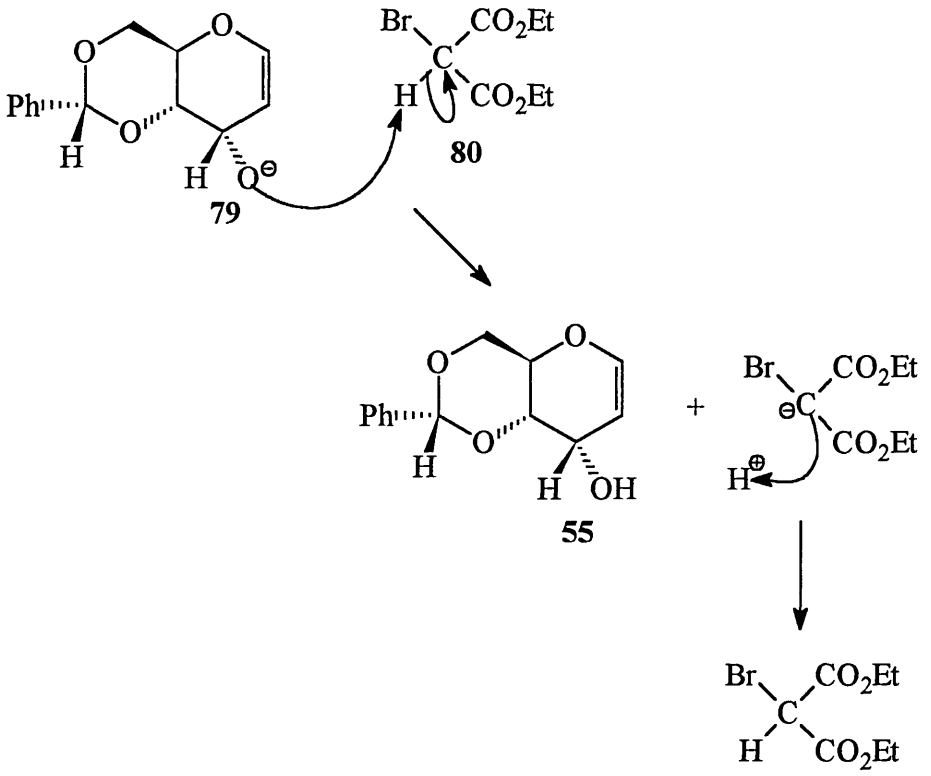
The synthetic route for the preparation of the five membered oxygen heterocyclic adducts was followed, where a simple sugar, methyl α-D-glucopyranoside **51**, was converted via several steps to 4,6-O-benzylidene-D-allal **55**.

From here it was planned to alkylate **55** with diethyl bromomalonate and sodium hydride, *scheme 64*. This would give the compound **75** with a very acidic proton which could be easily removed for further alkylation with nitroethylene to give the desired nitro derivative **76**. Conversion to the nitrile oxide **77** followed by cycloaddition could give a six membered ring adduct **78**.



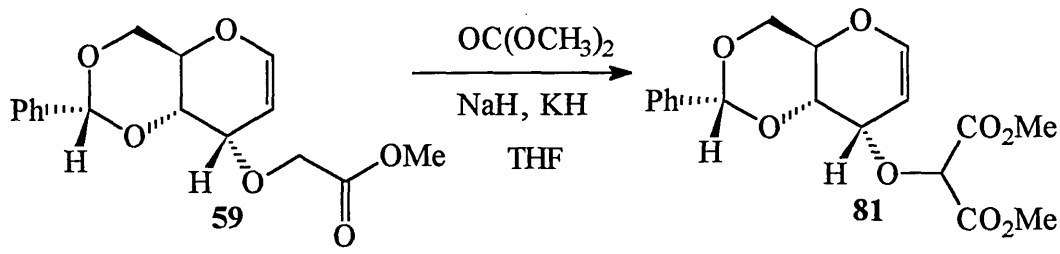
Scheme 64

However, it was not possible to alkylate the alcohol **55** with diethyl bromomalonate as the anion of the alcohol **79**, *scheme 65*, produced from treatment with sodium hydride, was behaving as a base instead of a nucleophile and so was abstracting the α-hydrogen on the diethyl bromomalonate and both reagents were recovered. This α-hydrogen was especially acidic (pKa of **80** is approximately 13) as it was between two carbonyl groups and hence was easily removed by the alkoxide (pKa of **55** is approximately 18). In the reaction work up the diethyl bromomalonate anion was protonated as a result of the isolation process so it seemed as if no reaction had taken place.



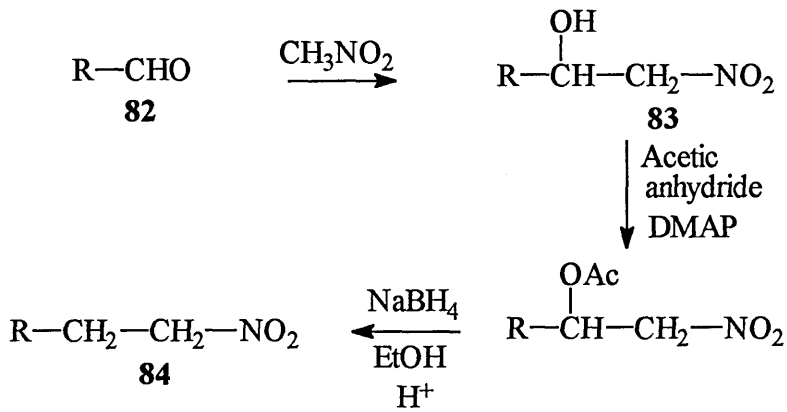
Scheme 65

The Claisen condensation is an alternative route in the formation of β-keto esters. The particular type of reaction we used was a crossed Claisen condensation[48] which is generally feasible only when one of the reactants has no α-hydrogens and thus is incapable of undergoing self-condensation. The condensation involved the ester **59** described previously, dimethyl carbonate which was the reactant with no α-hydrogens, sodium hydride and potassium hydride in dry THF, *scheme 66*. The mixture was refluxed and no solvent was collected during the reaction. Unfortunately after several attempts the acylated product **81** was not obtained and starting material was recovered each time.



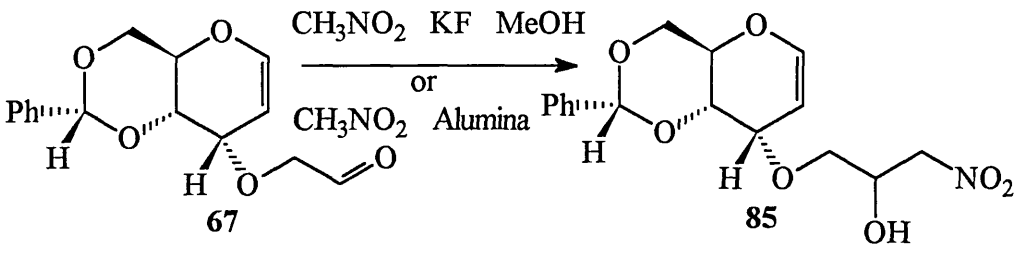
Scheme 66

One of the classical C-C bond forming processes is the Henry reaction[49] which involves the conversion of an aldehyde **82** to a nitroalkanol **83**. In order to obtain the nitrile oxide precursor, the nitroalkanol can be further acetylated, followed by reductive elimination to give a nitro derivative **84**, *scheme 67*.



Scheme 67

This could then be dehydrated with an isocyanate giving the nitrile oxide precursor required for the 1,3-dipolar cycloaddition reaction.



Scheme 68

The initial step was carried out in the protic solvent, methanol, using potassium fluoride and nitromethane[50], *scheme 68*. Unfortunately, even after 3 days stirring, there was no change to the aldehyde. Starting material was recovered each time. A method for the conversion to a nitroalcohol was reported to proceed by mixing the reagents in the absence of solvent on an alumina surface[51]. The aldehyde **67** and nitromethane were completely adsorbed by vigorous stirring with a sufficient amount of alumina and after standing for 24 hrs at room temperature the product **85** should have been isolated by washing with dichloromethane. It was believed that the alumina would be acting as a base to catalyse the reaction but starting material was recovered. It was suspected that the hydrate **68** might have been the cause of the difficulties in the conversion to the nitroalkanol.

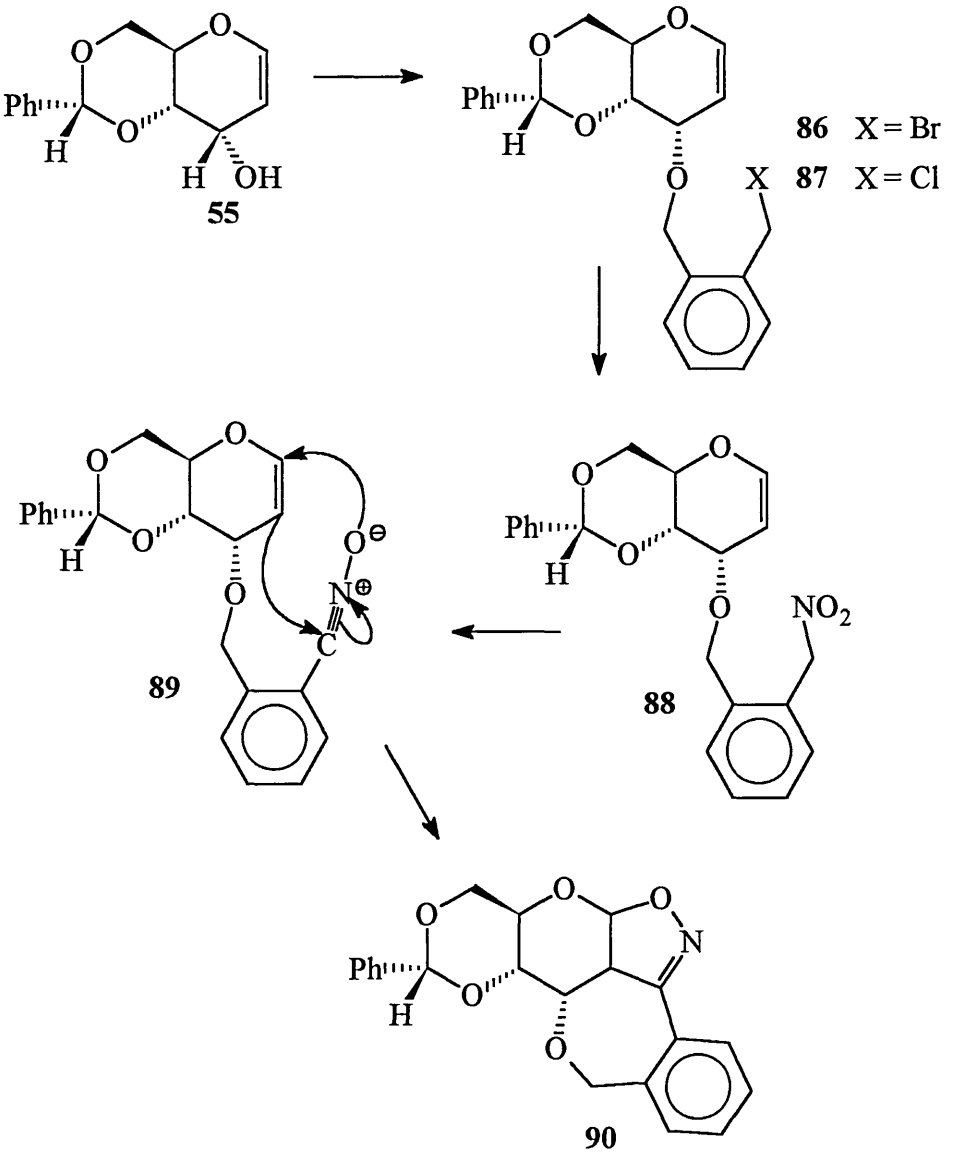
4.1.2.1 Summary and future work

The attempts for the synthesis of the six membered heterocyclic adduct had been unsuccessful where the alkylations, the Henry reaction and the Claisen condensation had failed. As mentioned previously the Claisen condensation conditions employed in our research used sodium hydride and potassium hydride in dry THF with dimethyl

carbonate and no solvent was collected during the reaction. Alternative conditions which could be tried, but were not due to limiting time factors, involve using sodium metal with the reaction reagents, diethyl or dimethyl carbonate and the ester **59** in the absence of solvent. The ethanol or methanol produced can then be removed using a Vigreux column with distillation head, leaving a residue which can be purified to give the product, which could then be further alkylated to give a nitro derivative which could be converted to the nitrile oxide precursor. On cyclising this would form a six membered heterocyclic ring adduct which after cleavage would give a functionalised tetrahydropyran.

4.1.3 Seven membered oxygen heterocyclic adducts

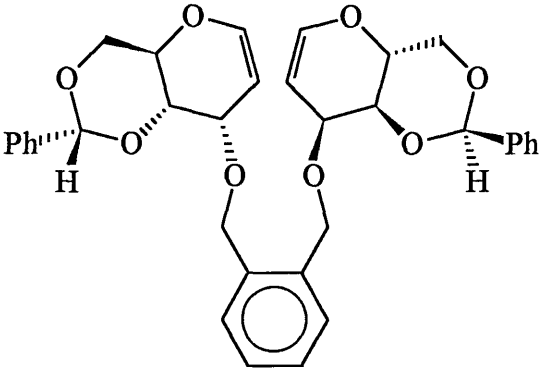
As with the five and six membered ring adducts, the starting point was the simple sugar derivative 4,6-O-benzylidene-D-allal **55**. This alcohol was alkylated with α,α'-dichloro-o-xylene and α,α'-dibromo-o-xylene in order to directly obtain a halide **86/7**, which might be converted to the nitro derivative **88** in preparation for the nitrile oxide **89**, *scheme 69.*



Scheme 69

The alkylation was initially tried with the model reagent benzyl chloride and potassium hydride in THF at room temperature, to see how easily and quickly it would take place. The reaction afforded the product as an off white solid in a yield of 80% so the alkylations using α,α'-dichloro-o-xylene and α,α'-dibromo-o-xylene were carried out. The chloride **87** was successfully prepared in a yield of 78%. The NMR (^{1}H and ^{13}C) spectra indicated the correct product and the mass spectrum showed a molecular ion of

372/4 which corresponded to the mass of the synthesised product. The isotope pattern for chlorine could be seen which helped to confirm the presence of the required compound. The bromide **84** was obtained in a lower yield of 64% and the reason for this was believed to be due to the fact that a by-product **91** was also obtained (32% yield) which was separated from **86** by flash chromatography. It was found to be a bis-ether and had been formed by the alkylation of two alcohol molecules by the same molecule of alkylating agent.



91

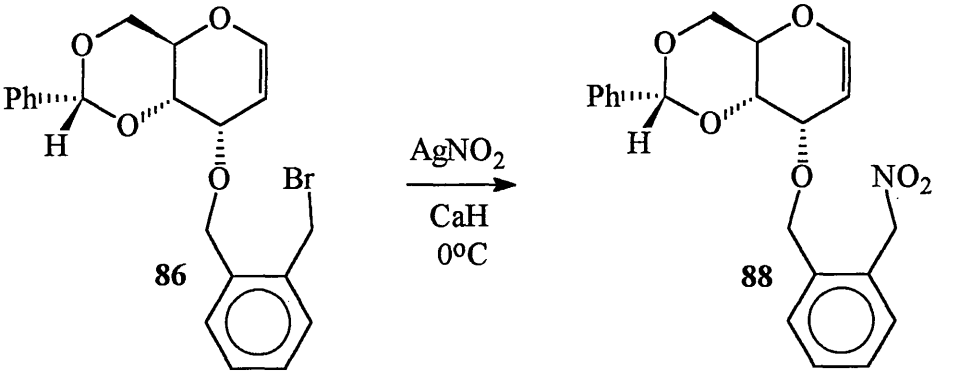
Some model reactions were carried out to investigate the conversion of benzyl halides to a nitro derivative. Kornblum[52] found the reaction from chlorides to be very reluctant so our investigations concentrated on benzyl bromide.

There are several literature methods which describe the preparation of phenylnitromethane. One of these involved reacting benzyl bromide with sodium nitrite[53] and urea in DMF at -20°C to -15°C, and an alternative method employed silver nitrite[54] and calcium hydride with benzyl bromide at 0-4°C in ether. Initially we tried the reaction using sodium nitrite and urea, but this yielded a mixture of benzoic acid and another substance which was believed to be nitrolic acid [$RC(NO_2)$=NOH].

Kornblum[53] had also observed the production of benzoic acid at room temperature, and presumed that it had been formed via the nitrolic acid. The reason for its formation at -20°C to -15°C is not clear. A slight modification was made to the method by reducing the temperature to -60°C. Phenylnitromethane was successfully synthesised but benzyl nitrite [Ph-CH_2-ONO] was also obtained together with starting material and a small amount of benzoic acid.

The alternative method using silver nitrite and calcium hydride was employed which gave phenylnitromethane and benzyl nitrite in a ratio of 3:1 (70%). The two products were not separated as these were only model reactions carried out in order to investigate the preparation of nitro derivatives from bromides.

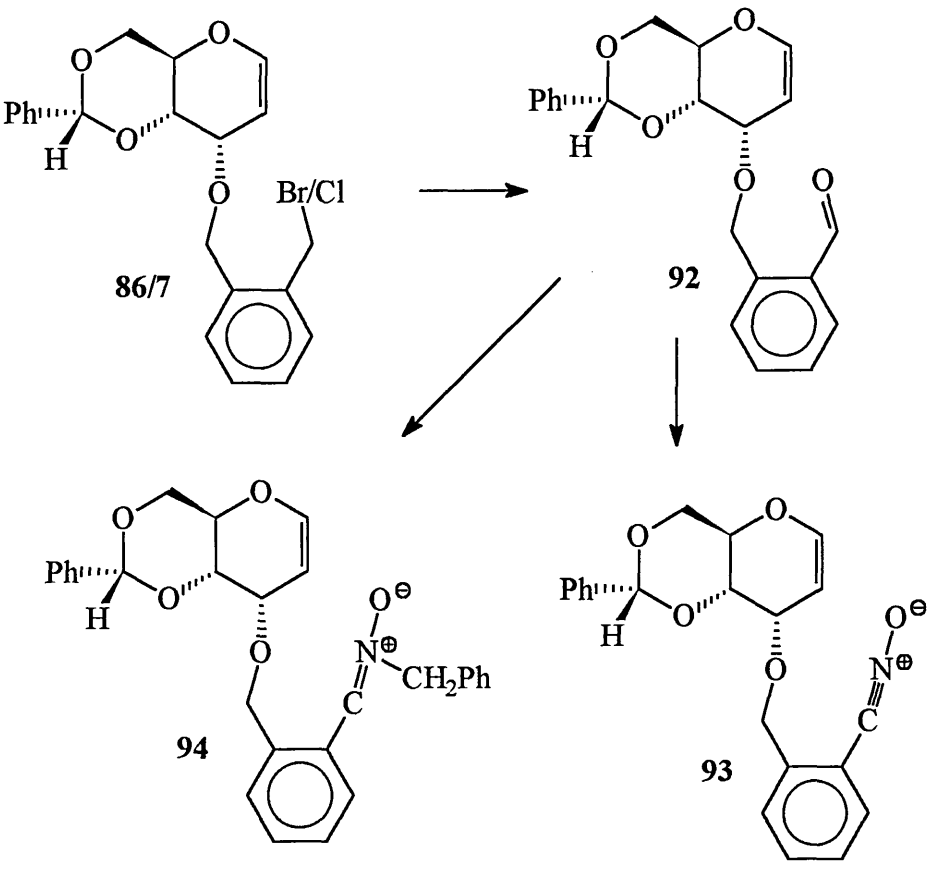
As the method which used silver nitrite had been clean and successful, it was employed in the conversion of the bromide **86** to the nitro derivative **88**, *scheme 70.*



Scheme 70

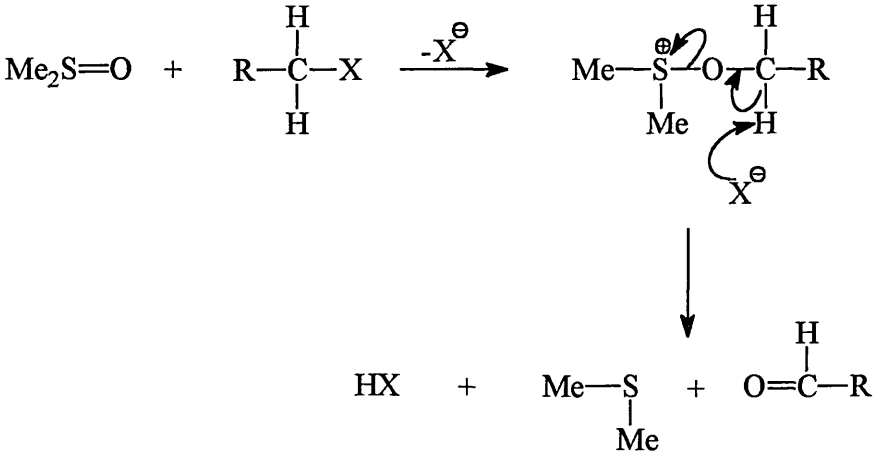
Following the model reaction conditions, the conversion had been carried out at 0-4°C but there was no reaction with **86** at this temperature, even after several days, so the mixture was left stirring at room temperature which accelerated the reaction giving the required nitro derivative **88** in a crude yield of 26%. Spectral data (infra-red, ^{1}H, ^{13}C, and GC-Mass spectra) indicated the presence of the required compound but as the reactions had been carried out on such a small scale, the quantity of product obtained after the reaction was very low and it wasn't possible to distinguish whether the nitrite ester was present as many impurities were also present. This route was not pursued any further.

In the synthesis of five membered ring adducts, the aldehyde **57** was converted to the nitrile oxide **70** and the nitrone **73** followed by cyclisation. This pathway will now be applied to the synthesis of seven membered ring adducts. If an aldehyde could be obtained directly from the halide **86/7**, then this could be further converted to the cyclised product via the nitrile oxide **93** and nitrone **94** precursors, *scheme 71*.

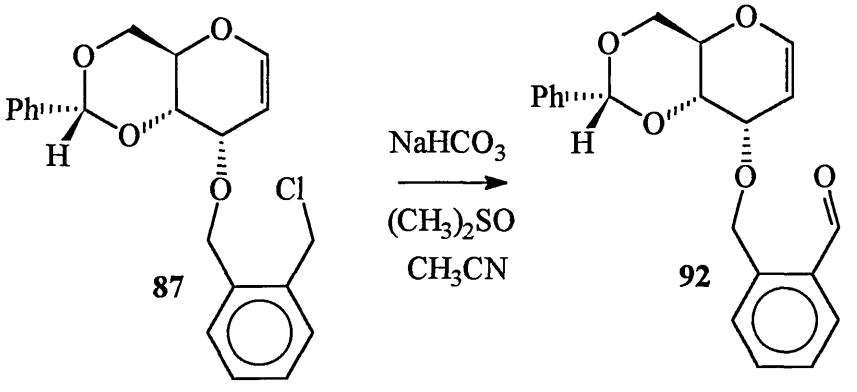


Scheme 71

Kornblum[55] found that the oxidation of halides to aldehydes could be achieved by dissolving a halide in dimethyl sulphoxide and stirring at room temperature but this was not a satisfactory procedure for benzyl halides. The temperature needed to be raised and this was done by using acetonitrile as the solvent, and an acid acceptor, sodium hydrogen carbonate, was added to the mixture. The reaction was believed to proceed via the following mechanism:



This reaction was tried on our halides and the chloride **87** was more easily converted to the aldehyde by refluxing it for 3 days with sodium hydrogen carbonate and dimethyl sulphoxide in acetonitrile. A crude yield of 83% was obtained and the ^1H NMR spectrum indicated the presence of the aldehyde with a peak at 10.6 δ. Furthermore the peak at 4.7 δ which corresponded to CH_2-Cl was no longer present showing that the chloride had been converted to the aldehyde **92**, *scheme 72*.

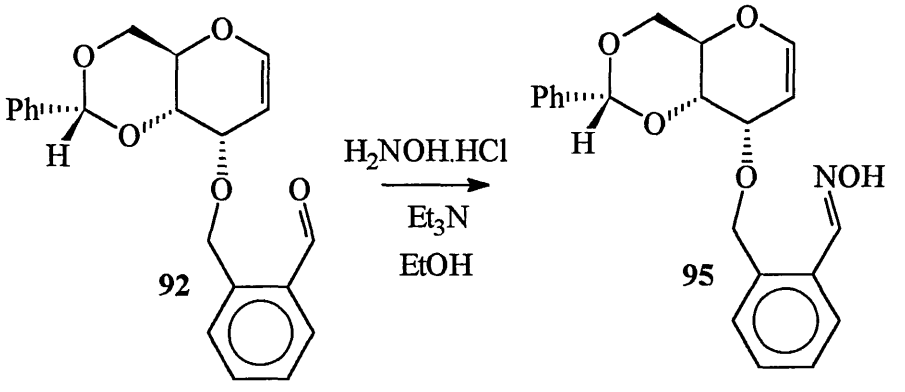


87 **92**

Scheme 72

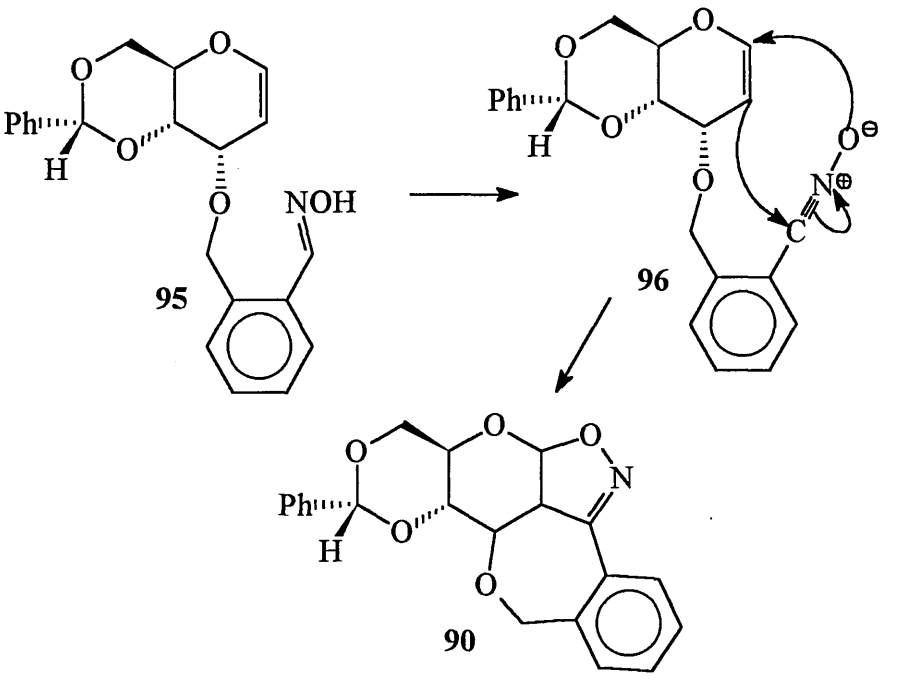
Without further purification, the aldehyde was put through to the next step which was the preparation of the oxime **95**, *scheme 73*. The oxime **95** was obtained in a yield of

82% after the aldehyde had been refluxed for 1-2 hrs with hydroxylamine hydrochloride and triethylamine in ethanol[46]. Spectral data (^{1}H NMR) showed the conversion of the aldehyde to oxime by the appearance of a peak at 8.55 δ due to (NOH) and the disappearance of the aldehydic proton at 10.6 δ.



Scheme 73

Attempts were made to convert the oxime **95** to the nitrile oxide **96** and it was hoped that it would spontaneously cyclise to form a seven membered ring adduct **90**, *scheme 74.*

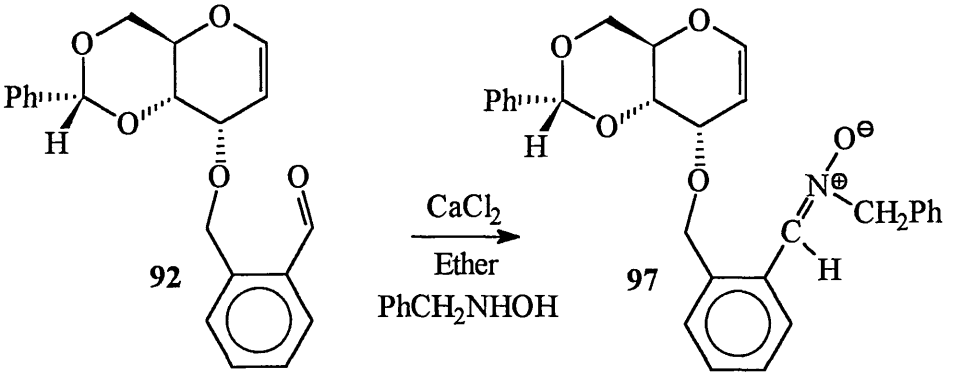


Scheme 74

The Δ^2-isoxazoline **71** had been previously prepared from the oxime **69** by reacting it with N-chlorosuccinimide and pyridine in DCM[47]. These conditions were used on the oxime **95** but no cycloaddition was observed in this case. Several spots were observed on TLC and these were isolated by chromatography. One was found to be remaining oxime (^{1}H NMR) and the ^{1}H NMR spectra of the other spots were complex although it could be seen that cyclisation had not taken place.

The nitrone precursor was made as previously described on p69. The aldehyde **92** was added to a cooled mixture of benzylhydroxylamine and calcium chloride in dry ether and was placed in the refrigerator. The cyclised product did not precipitate as before in the synthesis of the isoxazolidine **74**. A new product was formed (TLC) and this

was purified by column chromatography to give a yield of 41% of the uncyclised nitrone, *scheme 75*.



Scheme 75

As the mass spectrum would give the same mass for the cyclised product as the uncyclised product it was the NMR spectra which confirmed the uncyclised nitrone. The ^{1}H NMR spectrum showed the presence of the characteristic C_1-C_2 double bond indicating cyclisation had not taken place. Also there was a peak at 8.2 δ which was believed to be due to CH=N in the nitrone **97** and not remaining aldehyde **92** as the aldehydic peak had been found at 10.6 δ. The ^{13}C NMR spectrum backed up what had been found in the ^{1}H NMR spectrum where the C_1-C_2 double bond character was still present. Also a peak at 146.2 δ corresponding to C=N had appeared and the peak at 171.5 δ, which was due to the aldehydic proton, initially seen on the spectrum for the crude nitrone, had diminished.

It had been hoped that this nitrone **97** would also spontaneously cyclise under the conditions used but obviously more energy was required for cyclisation. Attempts

were made to cyclise the nitrone by refluxing it in several different solvents. It had been mentioned in literature[56] that cycloaddition would take place in intermolecular reactions by refluxing in benzene, but the nitrone **97** remained unchanged under these conditions. A higher boiling point solvent, toluene[57], was tried next but this also had no effect. The third and final solvent to be tried was xylene. After refluxing for quite some time instead of cyclising the nitrone began to decompose. The cyclisation was attempted on the unisolated crude nitrone. Instead of using ether as the solvent the aldehyde **92** was reacted with benzylhydroxylamine in toluene at room temperature as opposed to 0-4°C. The reaction was monitored by TLC and when the nitrone was present with no remaining aldehyde, the mixture was refluxed to try to promote cycloaddition but unfortunately the nitrone decomposed. No further attempts were made to cyclise the nitrone.

4.1.3.1 Summary and future work

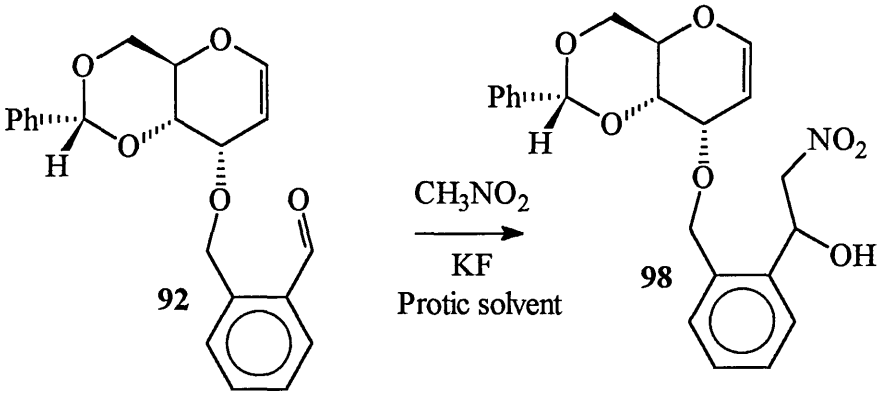
Seven membered rings have been made in the past[58] but with difficulty[59] so α,α'-dichloro-o-xylene and α,α'-dibromo-o-xylene had been chosen as alkylating agents as the benzene ring would add some rigidity to the long chain and allow the two reactive centres to come in close proximity of each other and therefore promote a reaction. As no reaction was observed it was suspected that the benzene ring may have introduced extra rigidity so the cycloaddition couldn't take place, the exact opposite of what had been hoped for.

Future attempts at synthesising seven membered ring heterocyclic ring adducts would involve alkylating 4,6-O-benzylidene-D-allal **55** with a straight chain alkylating agent so that the two reactive centres come close and allow cyclisation to take place.

4.1.4 Eight membered oxygen heterocyclic adducts

A brief attempt was made to synthesise an eight membered oxygen heterocyclic adduct. By extending the chain length it was believed that the extra flexibility might be sufficient to allow cycloaddition to take place.

The first procedure tried was an attempt to obtain a nitroalcohol, *scheme 76.*

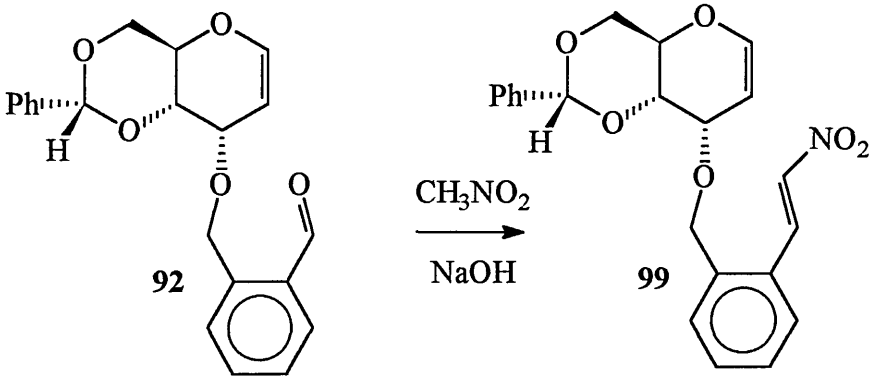


Scheme 76

The literature method[50] for the conversion of aldehydes to nitroalcohols uses nitromethane with potassium fluoride in protic solvent. The protic solvent reported was isopropanol but the aldehyde **92** wouldn't dissolve in this solvent, so other protic solvents were tried and **92** was found to dissolve in methanol. Initially the reaction

was carried out in methanol but there was no reaction (TLC). As the literature method had used isopropanol, a 1:1 mixture of methanol and isopropanol was tried. A slight reaction was observed (TLC) but even after 1 week stirring, the majority of the reaction mixture was still starting material. Finally isopropanol alone was used but as the aldehyde **92** did not dissolve in this solvent, the aldehyde and solvent were put in an ultrasonic bath to aid dissolution. The remaining reagents were then added and the reaction was stirred at room temperature. A very complex mixture (TLC) was obtained and due to the very poor separation the individual compounds could not be isolated.

It is known that nitrostyrene[60] can be obtained by reaction of benzaldehyde with nitromethane and sodium hydroxide at -10°C. The aldehyde **92** has a similar benzaldehyde functionality and so the reaction conditions utilised for the preparation of nitrostyrene were used in the attempted synthesis of the nitroderivative **99**, *scheme 77*, but spectral data didn't confirm the product **99**. The ^{1}H NMR spectrum was very messy with impurities present as well as remaining starting material.



Scheme 77

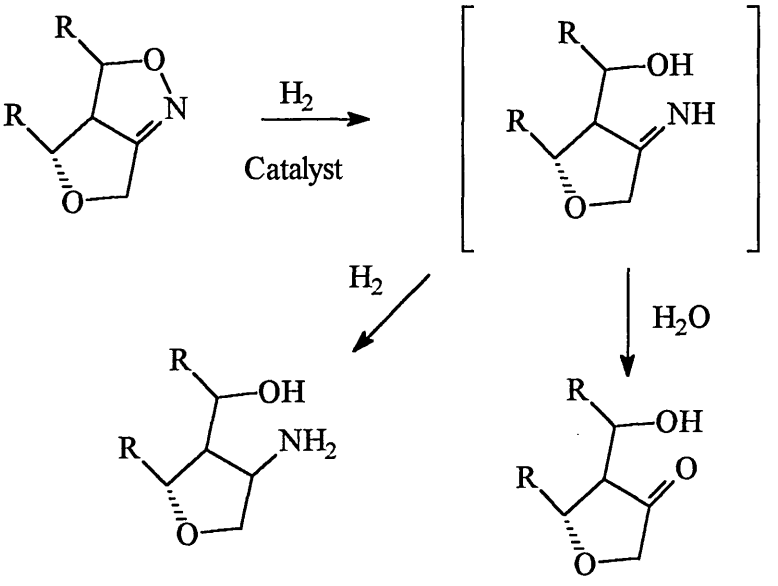
4.1.4.1 Summary and future work

There was a limited amount of aldehyde available at this stage so the conversion to the nitro derivative could only be attempted a few times, but with more aldehyde and time this could form a profitable route to an eight membered heterocyclic ring adduct.

4.1.5 Cleavage of the five membered oxygen heterocyclic adducts

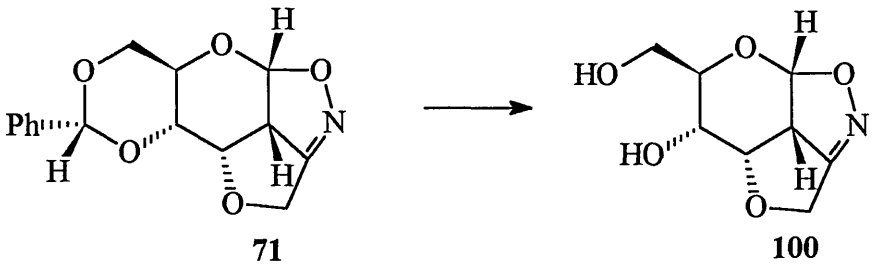
As the five membered ring adducts, Δ^2-isoxazoline **71** and isoxazolidine **74** had been successfully synthesised, several different ways of cleaving these systems were looked at. As previously mentioned in the introduction, (*scheme 16*) the cleavage of a Δ^2-isoxazoline can form a β-hydroxy ketone and 1,3-amino alcohols can also be obtained but under different reaction conditions. Isoxazolidines are generally cleaved to form 1,3-amino alcohols. Several methods were tried in the cleavage of the Δ^2-isoxazoline **71** and isoxazolidine **74** and the results from the Δ^2-isoxazoline **71** are discussed first.

According to Curran[61] it is the N-O bond which is cleaved first by supported metal type catalysts to form an imino alcohol followed by reduction or hydrolysis to the products shown in *scheme 78.* It has also been reported that some reagents such as lithium aluminium hydride reduce the C=N of an Δ^2-isoxazoline first[62], followed by the cleavage of the N-O bond.



Scheme 78

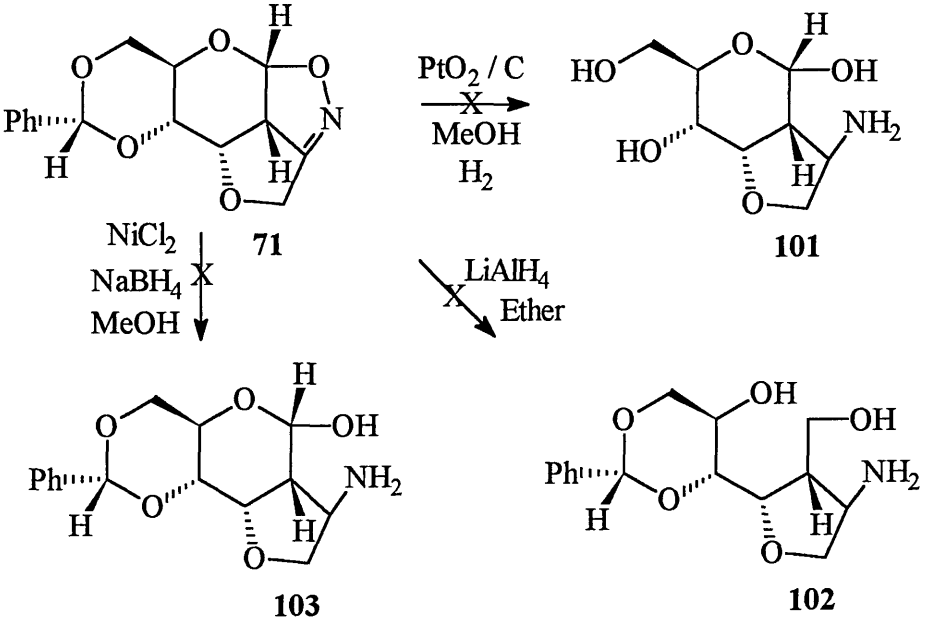
Initially we tried hydrogenolysis using platinum oxide[63] as the catalyst. The starting Δ^2-isoxazoline **71** was recovered even after stirring at room temperature in methanol for 1.5 weeks, *scheme 80.* An alternative reduction was tried which involved stirring the Δ^2-isoxazoline **71** in dry ether with lithium aluminum hydride[64] at room temperature. Even after refluxing the only reaction observed was the loss of the acetal protecting group, *scheme 79* [further reference to deprotection refers to the loss of benzaldehyde which was used to protect the diol group during future reactions]. This was confirmed by the isolation of a large amount of benzyl alcohol which resulted from the reduction of benzaldehyde released on loss of the protecting group.



71 100

Scheme 79

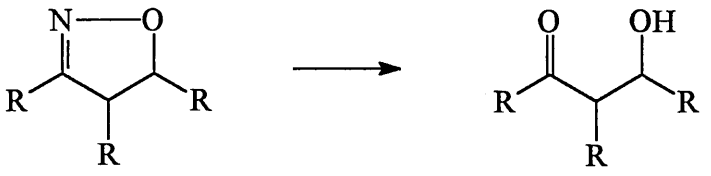
Another attempt at preparing the amino alcohol involved using nickel chloride[65] with sodium borohydride in methanol at -30°C, *scheme 80*, but unreacted starting material was recovered.



71 101 103 102

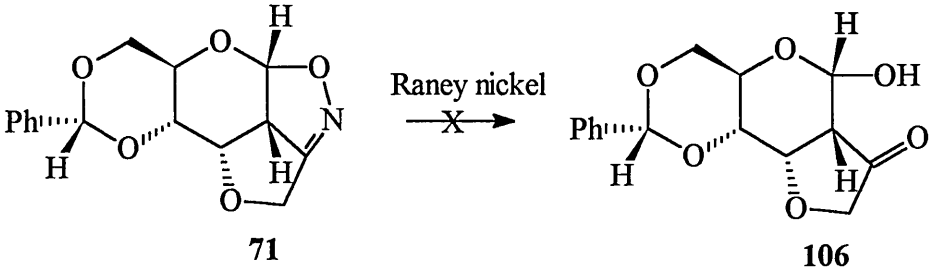
Scheme 80

Raney nickel was another catalyst used in the cleavage of Δ^2-isoxazolines **104** but this reaction forms β-hydroxy ketones **105**.



104 105

The first conditions used included boric acid[66] in the reaction mixture as well as the Δ^2-isoxazoline **71**, methanol-water mixture (5:1) and Raney nickel with hydrogen as the atmosphere, *scheme 81*. No reaction took place and starting material remained. The other reaction conditions employed Raney nickel in a deactivated form (deactivated by refluxing with acetone for 1 hour). It was stirred with the Δ^2-isoxazoline **71** and aluminium chloride[67] in a 5:1 methanol-water mixture under a hydrogen atmosphere, *scheme 81*. Once again the required product **106** was not obtained.



71 106

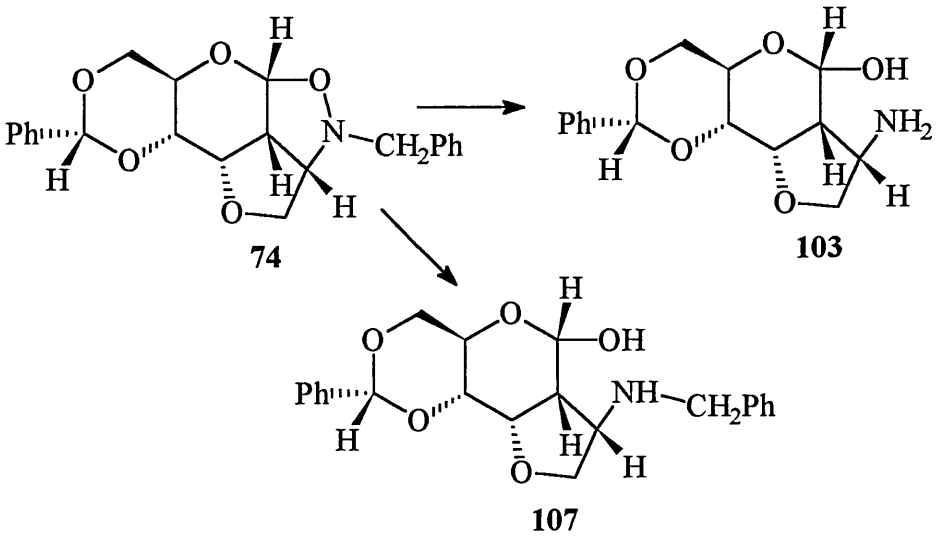
Scheme 81

4.1.5.1 Summary and future work (cleavage of Δ^2-isoxazoline)

The attempts at cleaving the Δ^2-isoxazoline have been totally unsuccessful. Each reaction resulted either in deprotection by loss of benzaldehyde or no conversion. The Δ^2-isoxazoline has exhibited extra stability which is believed to be due the oxygen in

the adjoining ring. From this it is obvious that more extreme conditions are required for the cleavage of the Δ^2-isoxazoline and if time had allowed these would have been tried.

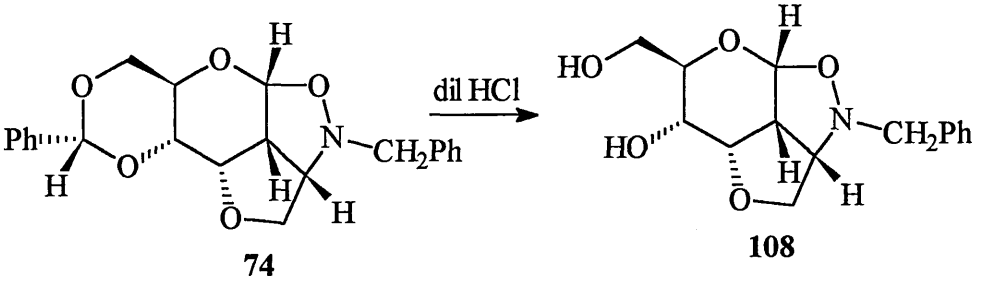
In the cleavage of the isoxazolidine **74**, the methods found would either result in the amino alcohol **103** or a secondary amino alcohol **107** as the product, *scheme 82*.



Scheme 82

In the work on the Δ^2-isoxazoline **71** it had been found that the acetal protecting group could be removed under certain reductive conditions, so in order not to be mistaken between the deprotected isoxazolidine **108** and a cleaved product, the isoxazolidine **74** was deliberately deprotected with 2M aqueous hydrochloric acid, *scheme 83*. After basification the product was purified using column chromatography. Spectral data (^{1}H NMR) showed the product to be the deprotected isoxazolidine as the singlet at 5.5 δ,

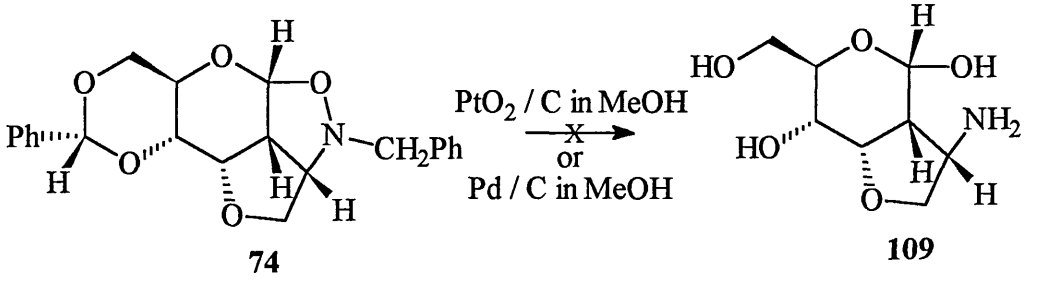
which was due to Ar-CH had disappeared and there was a reduced integration for the aromatics. The ^{13}C NMR also confirmed this to be the case. The mass spectrum gave a molecular ion of 293 which corresponded to the molecular mass of the compound.



Scheme 83

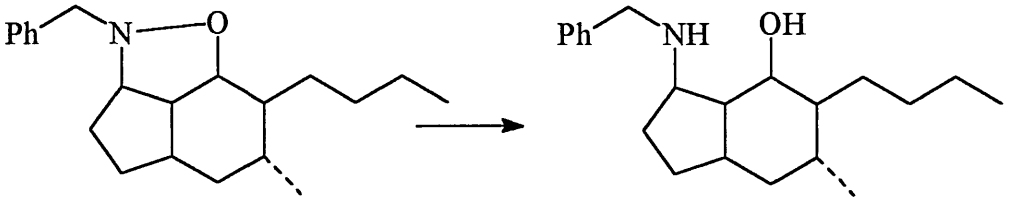
The deprotected product **108** was then used as a marker in the monitoring of cleavage reactions by thin layer chromatography.

Hydrogenolysis was also tried on the isoxazolidine **74**, *scheme 84*, even though no reaction had been seen with Δ^2-isoxazoline. Platinum oxide was used initially in methanol under an atmosphere of hydrogen but this resulted in recovered starting material whereas the reaction with palladium[68] showed slight reaction on TLC after 2 weeks stirring. It was believed that the benzyl group was being lost rather than any cleavage of the cycloadduct. These reaction conditions were not pursued further.



Scheme 84

W.R.Roush[69] had tried a variety of reagents for the cleavage of isoxazolidines and these can be seen in *scheme 85*.



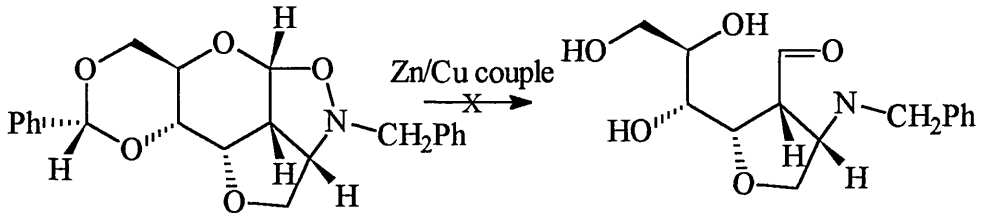
Reagent	Reaction Time	Yield
Na-Hg, EtOH	Very slow	-
Al-Hg, THF-H_2O	2-3 days	91%
$LiAlH_4$, THF	22 hrs	70%

Scheme 85

He had found the reaction with sodium amalgam to be very slow so this was not even attempted in our studies, instead the reaction with freshly prepared aluminium amalgam in aqueous THF solution was tried. Roush[69] had observed a reaction after 2-3 days but after 1.5 weeks only starting material still remained in our reaction. The alternative reagent tried on the isoxazolidine **74** was lithium aluminium hydride in refluxing THF. Roush[69] obtained a 70 % yield of amino alcohol after a reaction time of 22 hrs but after 2 weeks refluxing our major product was starting material.

A reaction involving a Zn/Cu couple has been reported[70] to reduce the N-O bond of isoxazolidines. The reaction was carried out on the isoxazolidine **74**, with freshly prepared Zn/Cu couple (copper II acetate and zinc dust in glacial acetic acid stirred

until blue colouration disappeared) in acetic acid at a temperature of 60-70°C, *scheme 86.*

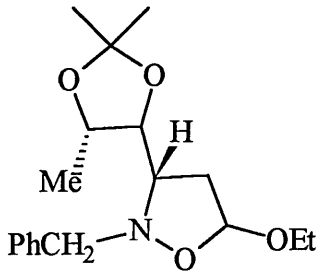


74

Scheme 86

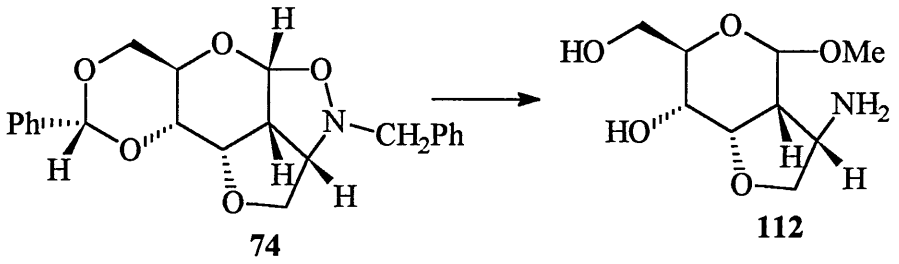
This temperature was maintained for 1.5 hours with close monitoring by TLC. The isoxazolidine reacted to form a polar product (TLC) which could not be isolated from the impurities by column chromatography. On spraying the TLC plate with 2,4-dinitrophenylhydrazine (DNP) there was no yellow/orange colouration which would be expected with an aldehyde functionality so this reaction procedure was not further pursued.

The isoxazolidine **74** seemed to be more stable than other isoxazolidines previously described in literature and the cause of this was believed to be the oxygen in the adjoining ring. A corresponding observation had been noted by P.DeShong[45] for the compound **111** where prolonged treatment with reagents such as sodium amalgam, aluminum amalgam and a variety of catalytic hydrogenation conditions had no effect.



111

He found that high pressure hydrogenation over Pearlman's catalyst under acidic conditions proved to be more fruitful. Due to the small quantities of reagents used in our synthetic methods the available high pressure equipment was inappropriate so the method was modified with an ultrasonic bath being used to mimic high pressure. This procedure seemed to be more successful than any earlier attempts, giving the deprotected and cleaved product **112** in a yield of 52%, *scheme 87*. The product **112** contained no chromophores so was not U.V. active which caused a few difficulties in monitoring the reaction. It was found that the product could be detected by spraying the TLC plate with ninhydrin which on heating would give a purple colouration to show the presence of a primary amine.



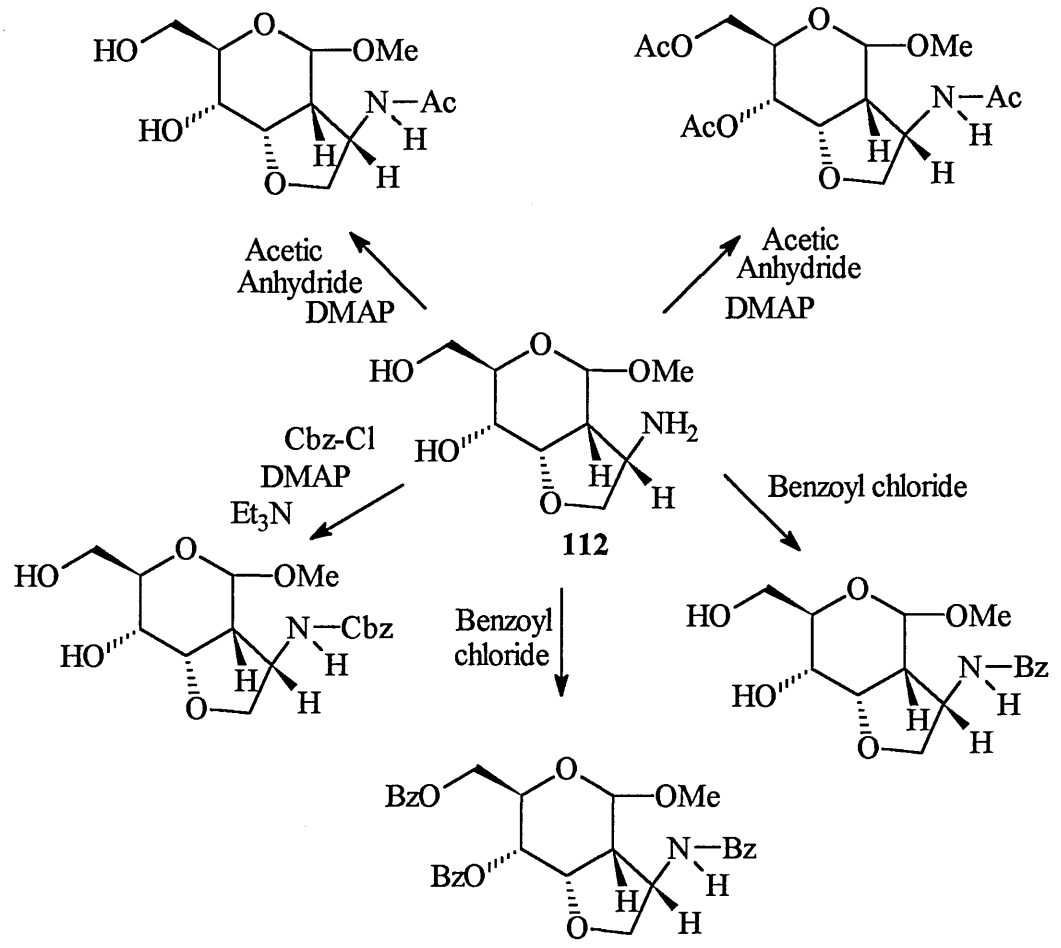
74 **112**

Scheme 87

Literature[71] indicated that amino alcohols readily absorb carbon dioxide. Spectral data showed this to be the case with the compound **112** as the mass spectrum gave a molecular ion of 263 which is exactly 44 mass units higher than that expected, which

suggested that the compound **112** had absorbed carbon dioxide. The ^{1}H NMR confirmed the product by the presence of the methoxy peaks at 3.3 δ, and two peaks were present at 5.6 δ which corresponded to the acetal grouping, O-CH-OMe. The doubling up of these peaks was believed to be due to two isomers caused by the acid catalysed interconversion at the anomeric position and this was further confirmed by the ^{13}C NMR spectrum which also showed pairing of peaks.

In attempts to further characterise this compound, direct derivatisations were tried. Several methods, *scheme 88* were attempted and these included: the acetylation of the amine functionality alone[72], and the acetylation of both the hydroxy and amine groups[73]. Other alternatives included derivatisation with a carbobenzyloxy grouping, a Schotten-Baumann[74] reaction to benzoylate the amine functionality and an attempt to benzoylate all functional groups.

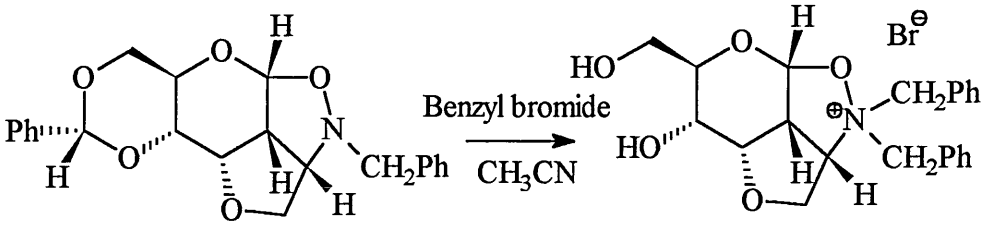


Scheme 88

These attempts at derivatising the product **112** were unsuccessful which cast a doubt on the structure of **112**.

Carruthers[75] had found an alternative way of cleaving isoxazolidines which involved preparing a quaternary salt by refluxing an isoxazolidine with benzyl bromide in DCM. He found that the salt formed in approximately 12 hrs and could be cleaved by the reduction with lithium aluminium hydride. This route was tried on the isoxazolidine **74**, but after refluxing it with benzyl bromide in DCM for 3 days there was still no reaction (TLC). The reaction was repeated with dichloroethane to achieve a higher

reflux temperature but after refluxing for 2 days, the TLC plate showed the presence of benzaldehyde which indicated that the isoxazolidine was losing its acetal protecting group. Furthermore, much starting material still remained and it looked as though the only reaction occurring here was that of acetal deprotection. Finally acetonitrile was tried in the preparation of the N-benzyl salt of the isoxazolidine. After 2 days refluxing this reaction gave a polar product (TLC) which would be expected in the synthesis of a salt. However in a more polar solvent system (ethyl acetate:methanol, 9:1), two products were being formed, these were isolated and found to be the deprotected isoxazolidine **108** (identical with the compound prepared by acid catalysed deprotection of **108**) and the quaternary salt **113** (confirmed by ^{1}H, ^{13}C NMR and FAB-MS). For some reason which is not entirely clear the acetal protecting group was being removed under the alkylation conditions but this did not matter too much as it was planned to remove it in the future steps anyway. To ensure the reaction went to completion, it was left for a week or until all the deprotected isoxazolidine had been converted to the required product **113**, *scheme 89*.



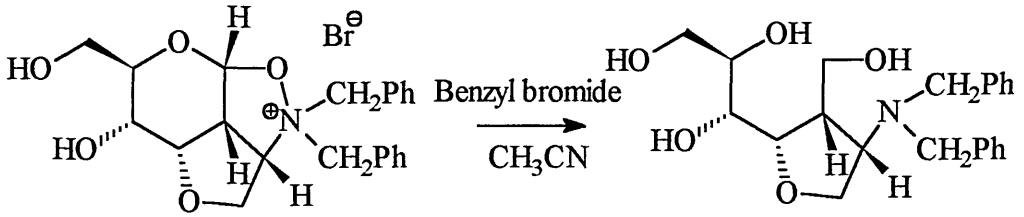
74 **113**

Scheme 89

The salt **113** was slightly soluble in acetonitrile, and therefore did not precipitate completely from the solution so the acetonitrile was removed by evaporation and a

sticky residue was then triturated with ether to form a very hygroscopic solid **113** in a yield of 77%.

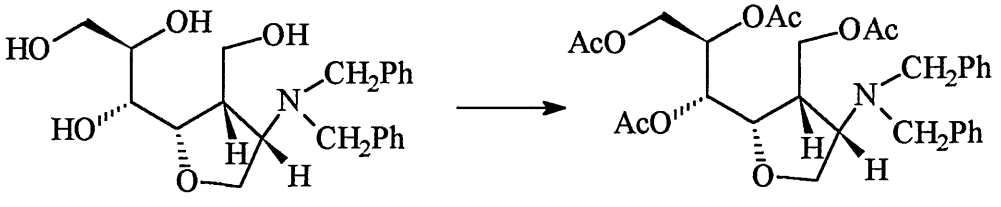
The reduction of this salt was carried out by refluxing it in dry THF with lithium aluminium hydride to form a product **114** with four hydroxy groups, (68% yield) *scheme 90.*



113 **114**

Scheme 90

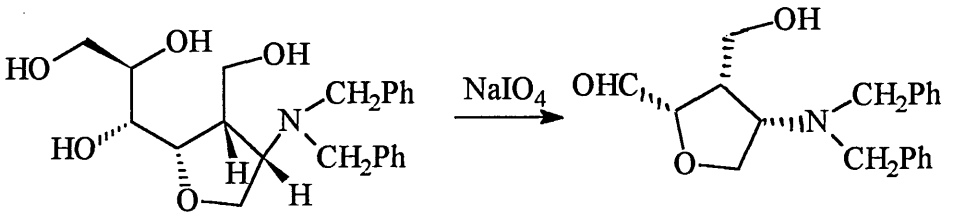
The structure of the product was confirmed by ^{1}H and ^{13}C NMR spectra. As the product was very polar attempts were made to derivatise it to make it more manageable and also to further characterise it. One method was an acetylation of all the hydroxy groups in DCM with acetic anhydride and a catalytic amount of DMAP[73], *scheme 91.* The product **115** was confirmed by the observation of a molecular ion at 555.



114 **115**

Scheme 91

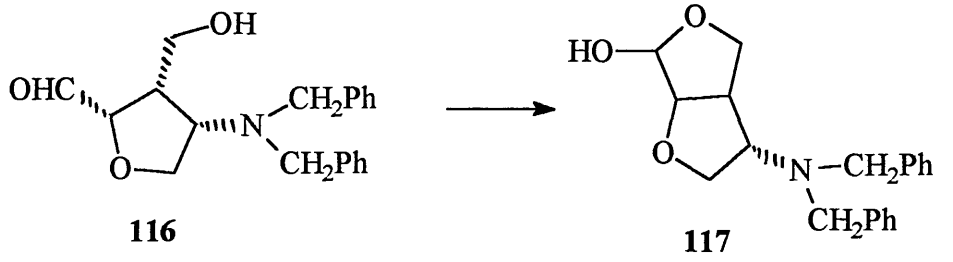
The tetraol **114** was cleaved further to form a tetrahydrofuran **116** with three different functionalities, *scheme 92*.



114 **116**

Scheme 92

The reaction was initially carried out in an ether/water mixture with sodium periodate[76], but as there was no reaction the solvent was changed to a THF/water (3:1) mixture. The reaction yielded one product (TLC) but on standing two products seemed to be present (TLC). The two compounds were separated and isolated by column chromatography. The mass spectra gave the same masses for the two components. One was believed to be the aldehyde **116** and the other was thought to be a lactol **117** which was the result of an intramolecular cyclisation reaction, *scheme 93*.

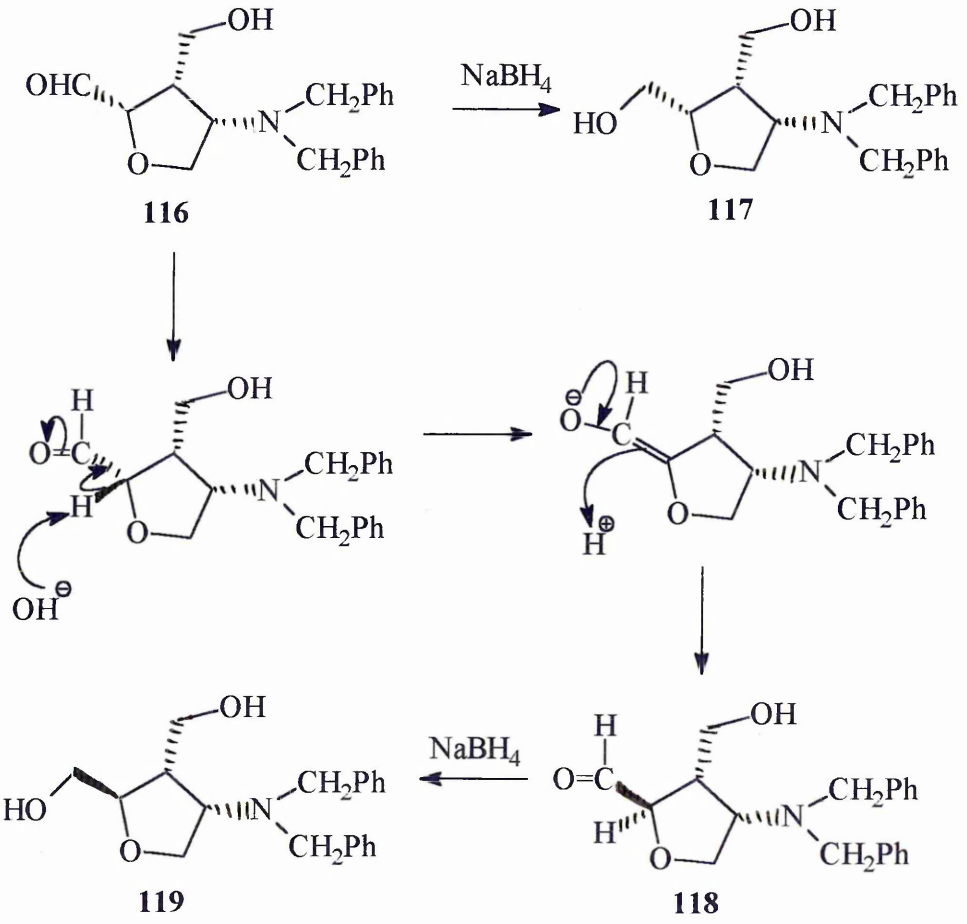


116 **117**

Scheme 93

An attempt to trap the aldehyde by carrying out a Wittig reaction[77], using the ylid $PhP{=}CHCO_2Me$ with a trace of benzoic acid in dimethoxyethane was unsuccessful but

tetraol **114** was converted to the aldehyde **116** as previously mentioned but the aldehyde was not isolated from the mixture. Once the reaction was confirmed to be complete by TLC, the reduction of the aldehyde **116** was carried out with an excess of sodium borohydride and the mixture was stirred for 7 hrs. Instead of observing one product on the ^{13}C NMR spectrum, pairing of peaks could be seen indicating that two isomers (approximately 2:1) were present. It was believed that two processes were occurring in this reaction, *scheme 94*. The first was the direct reduction of the aldehyde in the cis configuration **116** forming a diol **117** also in the cis configuration. The second reaction was thought to be caused by epimerisation, which was then followed by reduction.



Scheme 94

As the sodium borohydride was added in excess to an aqueous THF solution, reaction of sodium borohydride with water formed a base, OH^-, which initiated the epimerisation giving the aldehyde in the trans configuration **118**. This was then reduced to the alcohol **119** by the remaining sodium borohydride.

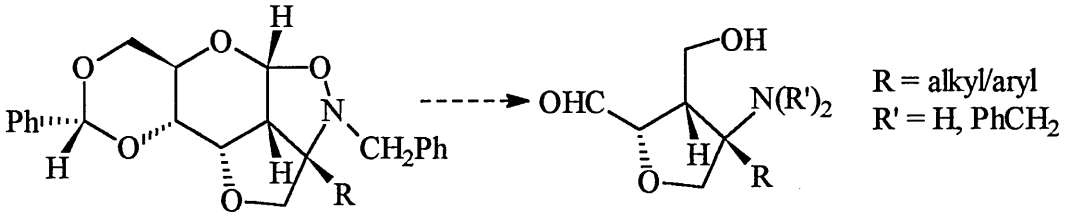
To confirm that epimerisation was indeed taking place, the aldehyde was prepared again but this time it was isolated. The quantity of aldehyde was split into two equal portions, both were dissolved in methanol and a small piece of sodium was added to each to form the methoxide ion which would initiate the epimerisation[78]. The two reactions were left stirring at room temperature and after 2 hrs sodium borohydride was added to one of the reactions whilst the other was left stirring overnight before the addition of sodium borohydride.

The sodium borohydride stopped the epimerisation by reducing the aldehyde to the alcohol. After 2 hrs, two alcohol isomers could be seen (approximately 1:1 mixture) on spectral data (^{13}C NMR), whereas the epimerisation which was left overnight showed (^{13}C NMR) that one isomer predominated. This isomer was believed to be in the trans configuration as it is less sterically hindered in this form.

4.1.5.2 Summary and future work (cleavage of isoxazolidine)

Several different methods for cleaving isoxazolidines have been attempted and the method initially used by Carruthers[75], which had been modified to suit our system, cleaved our stable isoxazolidine **74**. Following this, further modification of the tetraol **114** to the diol **119** was carried out. We have achieved the objectives discussed earlier, showing a viable route to functionalised tetrahydrofurans from simple sugars. Future work in this area would involve improving the cleavage reaction and attempting other cleavage methods.

From the experience gained during the cleavage of the cycloadducts it had been found that the cleavage of the isoxazolidine was more successful than that of the Δ^2-isoxazoline. It has been recently reported in the literature[62] that the reaction of Δ^2-isoxazolines with organolithiums in the presence of boron trifluoride forms substituted isoxazolidines. In our case this could lead to a range of isoxazolidines and hence after cleavage and modification, a range of functionalised tetrahydrofurans.

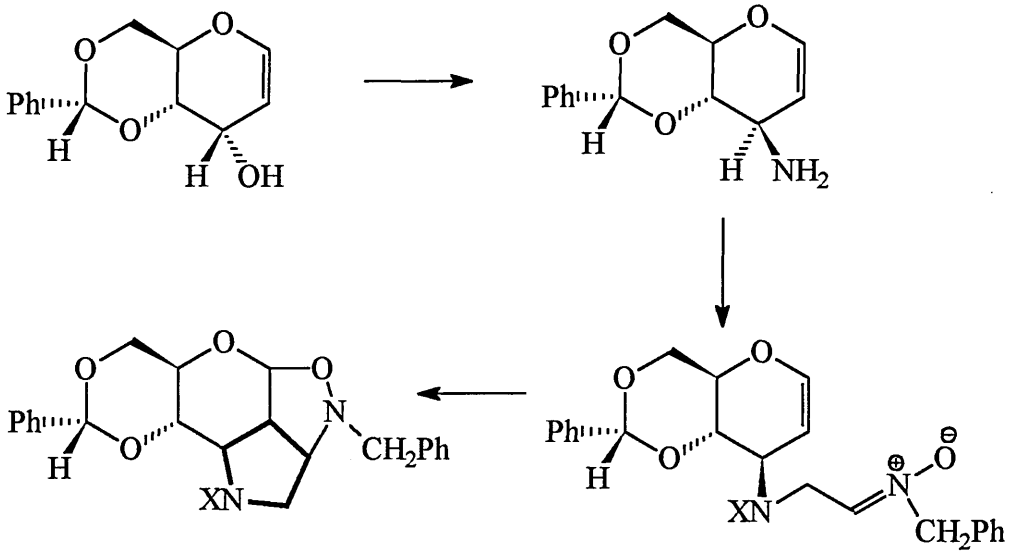


Once the larger ring heterocyclic adducts are available, cleavage of these, followed by modification, will form a wider range of enantiomerically pure functionalised heterocyclic compounds.

4.2 Synthesis of pyrrolidines from glucose

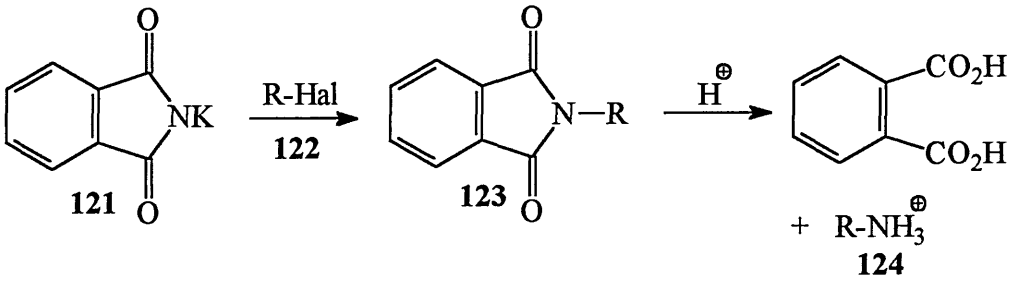
Previous attempts (chapter 3) made to synthesise pyrrolidines were unsuccessful. In this chapter we would like to discuss the preparation of pyrrolidines using the carbohydrate route. Once again methyl α-D-glucopyranoside **52** was converted to 4,6-O-benzylidene-D-allal **55**, which was used as the starting point in subsequent reactions.

In order to obtain a pyrrolidine, the replacement of the hydroxy functionality with an amine was required so further alkylation could take place to obtain a nitrone precursor for the 1,3-dipolar cycloaddition reaction, s*cheme 95*. The cycloadduct formed, when cleaved, would form a functionalised pyrrolidine.



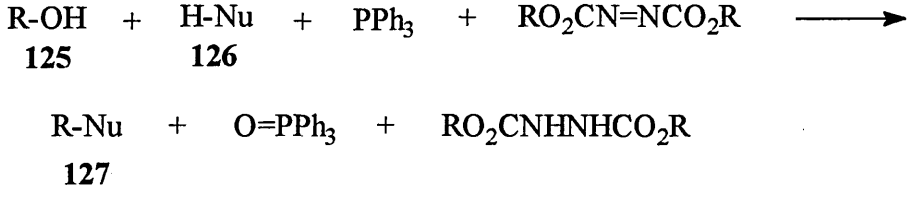
Scheme 95

The Gabriel synthesis is a well documented method[79] for the preparation of primary amines, *scheme 96*. The synthesis involves the reaction of potassium phthalimide **121** with halo-alkanes **122** which leads to N-alkylphthalimides **123**. These may then be converted to the corresponding primary amines **124** by hydrolysis or hydrazinolysis.



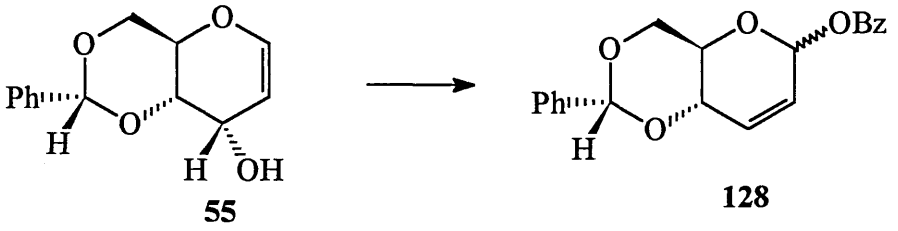
Scheme 96

The Mitsunobu[80] reaction is based on a similar idea. It involves the condensation reaction of alcohols with a triaryl or trialkylphosphine and a dialkyl azodicarboxylate. The result of having these two reagents present is that the OH is converted into a good leaving group. The alcohol **125** and an acidic compound **126** (which can be phthalimide, but also other reagents have been used) are condensed to form product **127**, while triphenyl phosphine is oxidised to triphenyl phosphine oxide and the azodicarboxylate is reduced to the hydrazine, *scheme 97*.



Scheme 97

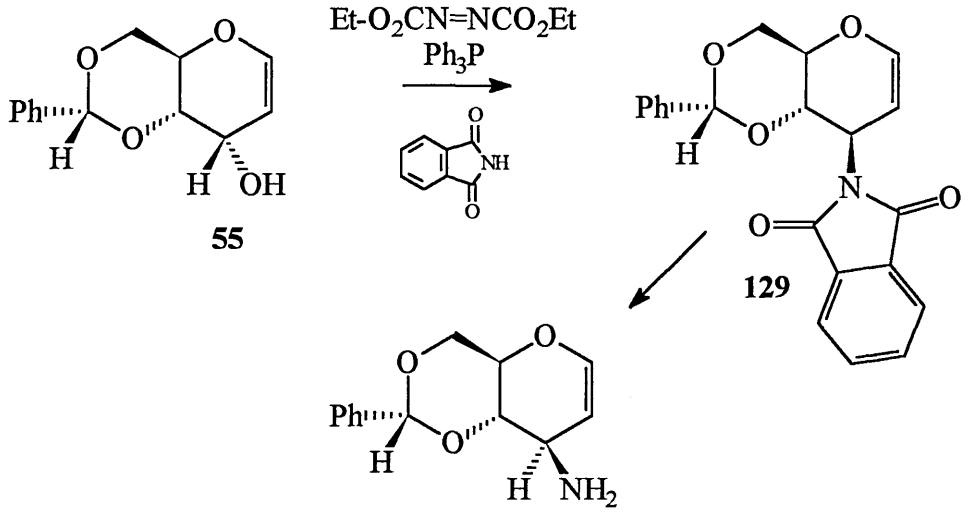
Studies of 4,6-O-benzylidene-D-allal **55** with benzoic acid[80] as the acidic compound have shown allylic rearrangement to take place during the Mitsunobu reaction giving a mixture of isomers **128**, *scheme 98*.



55 **128**

Scheme 98

Our overall objective was to substitute the hydroxy functionality by an amino group, hence phthalimide was used in our Mitsunobu reaction, *scheme 99*.

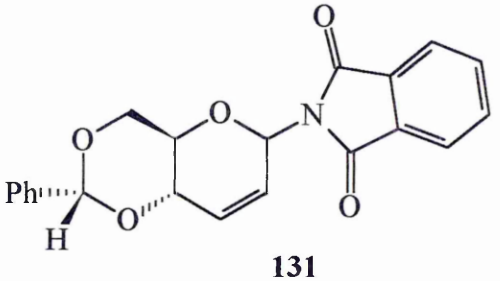


55 **129** **130**

Scheme 99

4,6-O-Benzylidene-D-allal **55** was dissolved in dry THF, and phthalimide and triphenylphosphine were added to the solution. Diethylazodicarboxylate was then added resulting in a clear orange solution which was stirred at room temperature for 40hrs. After workup and purification by column chromatography the N-alkyl phthalimide **129** was obtained in 20% yield. One spot was seen on the TLC plate and the high resolution mass spectrum gave a mass which corresponded to the required product.

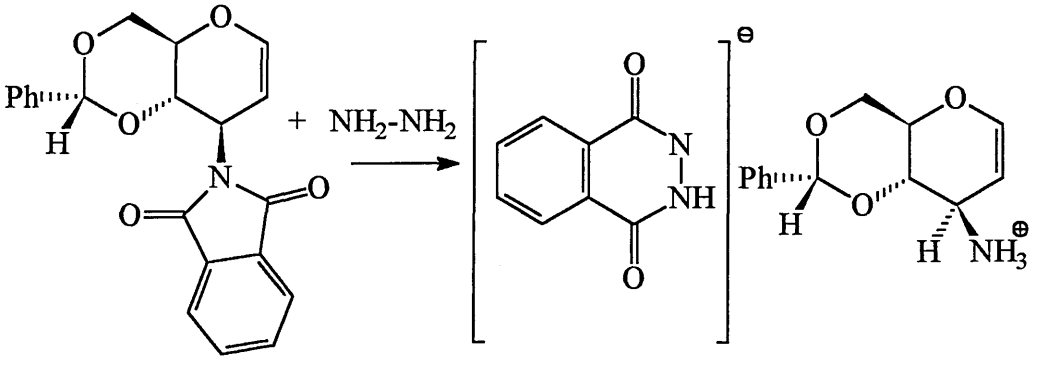
It is known[82] that complete inversion of configuration doesn't always occur in the Mitsunobu reaction and the ^{1}H NMR of the product **129** was very complex suggesting that complete inversion of configuration may have not taken place. The ^{13}C NMR spectrum showed slight pairing of peaks also suggesting a mixture of isomers. This spectrum also showed two peaks to be present (100.7 δ and 101.9 δ) as well as a peak at 102.4 δ. Peaks in this region normally correspond to a carbon in between two heteroatoms or substituted alkene carbons. The peak at 102.4 δ was due to the acetal protecting group and the peak at 100.7 δ was believed to correspond to one of the alkene protons C_2 [C_2=C_1-O]. If Ferrier rearrangement took place it would give a product **131**.



131

This product has a carbon which is adjacent to an oxygen and nitrogen atom and this carbon atom might also give a peak in the 100 δ region. The product obtained from this Mitsunobu reaction might have formed two isomers by incomplete inversion of configuration or may have Ferrier rearranged or a combination of both of these options might have taken place. It is not clear which exactly, but as mentioned previously the correct mass was obtained in the mass spectrum so the product was put forward to the next step to see the outcome.

Hydrolysis or hydrazinolysis are possible methods for converting the substituted phthalimide to an amine[80]. As hydrolysis involves using acid it would have resulted in the removal of the acetal protecting group, so this method was not attempted. Hydrazinolysis was tried on our product **129**. Hydrazine hydrate was added to **129** in ethanol and refluxed for 3hrs, *scheme 100*. The solution was basified with potassium hydroxide solution (2M) and then extracted.

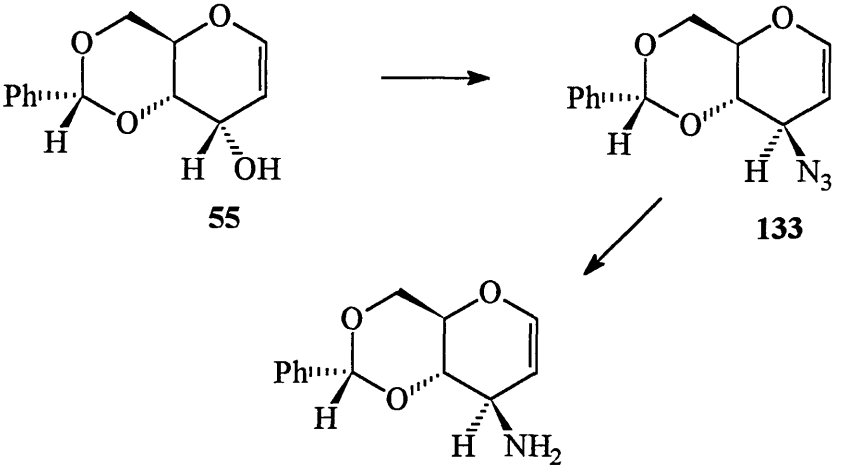


129 **132**

Scheme 100

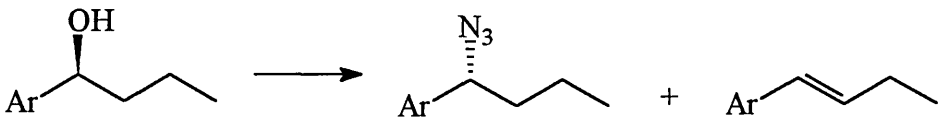
According to TLC all the starting material had gone but it was not possible to isolate the required product, phthalhydrazide being the dominant feature in the TLC. Basification of the solution would have freed the amine from the complex **132**, but as it could not be observed on TLC it was presumed that the amine had a similar R_f to the phthalhydrazide and the two were running together. However, the mass spectrum did not give a molecular ion for the amine which suggested that the amine had not been successfully synthesised.

As the amine **130** could not be successfully obtained an alternative method was investigated. This method involved the conversion of the alcohol **55** to the azide[83] **133** followed by the reduction to the amine **130**, *scheme 101*.



Scheme 101

The Mitsunobu reaction has been used to prepare azides[84] by using hydrazoic acid, zinc azide or diphenylphosphoryl azide as the nucleophile, but as well as azides elimination products were also obtained, *scheme 102*.



Scheme 102

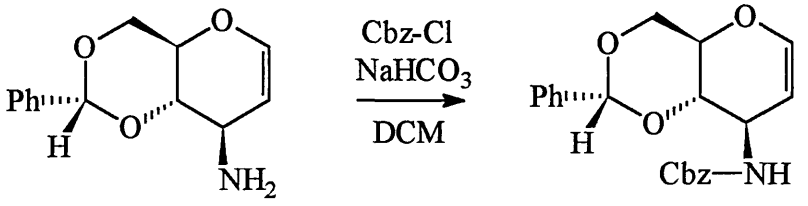
To avoid the Mitsunobu conditions the preparation of the azide **133** was carried out according to Thomson[83]. The alcohol **55** was dissolved in toluene, and diphenylphosphoric azide and a slight excess of 1,8-diazabicyclo[5.4.0]undec-7-ene were added to the mixture. After stirring for 2 days the azide was isolated and purified by column chromatography in a yield of 66%. Spectral data (^{1}H NMR) confirmed that inversion of configuration had taken place as the characteristic double bond feature (doublet at 6.5 δ and triplet at 5.1 δ) had changed to a doublet of doublets at 6.5 δ and another doublet of doublets at 4.7 δ. The mass spectrum further confirmed the azide by the presence of the molecular ion at 259.

Two methods for the conversion of the azide **133** to the amine **130** were investigated. The first involved the reaction of the azide **133** with copper II sulphate pentahydrate and sodium borohydride in methanol[85] but the TLC showed that no reaction took place over several days.

The other method involved stirring the azide **133** in DCM with triphenyphosphine[86]. After 2 days the reaction was concentrated to dryness and the residue was taken up in THF and aqueous ammonia [sp.gr. 0.88] and refluxed for 3hrs.

The product **130** obtained was contaminated with triphenylphosphine oxide which could not be separated but the mass spectrum confirmed the presence of the amine **130,** by the appearance of a peak at 233 which corresponded to the molecular mass, as well as a peak at 278 corresponding to the triphenylphosphine oxide, which was the contaminant.

The amine **130** was used in a crude form in the next step which was the protection of the amine with a carbobenzyloxy (cbz) grouping to give **134**, *scheme 103*.



130 **134**

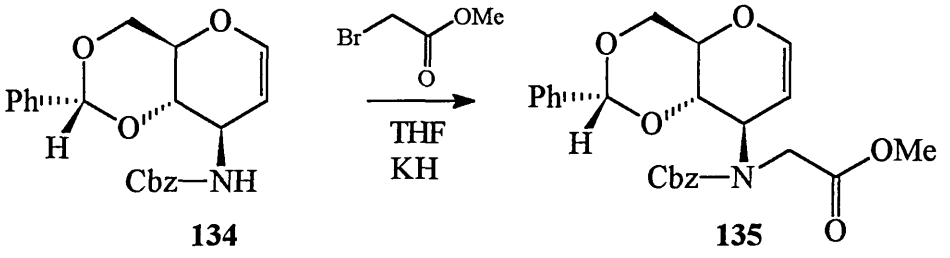
Scheme 103

The crude amine **130** containing Ph_3PO was dissolved in DCM and saturated sodium hydrogen carbonate solution was added followed by carbobenzyloxy chloride (cbz-Cl), and the two phase mixture was vigorously stirred at room temperature. The TLC showed a new product which was initially isolated by column chromatography. Spectral data (^1H NMR) indicated the product to be the cbz-protected amine **134** by the singlet at 5.2 δ which corresponded to CH_2-O, and the fact that the integration for the aromatics was increased. These findings were backed up by the ^{13}C NMR, which also showed the carbonyl carbon from the cbz group at 156.4 δ, and a mass spectrum which showed the expected molecular ion at 367. It was later found that the crude

reaction product containing triphenylphosphine oxide could be purified by recrystallisation from hot ethanol, thus avoiding the column chromatography.

As previously described in the synthesis of oxygen heterocycles from glucose (chapter 4.1), methyl bromoacetate was used in the alkylation of 4,6-O-benzylidene-D-allal **55** followed by manipulation of the ester **59** to form an aldehyde **67**. This was then used in the preparation of a nitrone precursor **73** which spontaneously cyclised to give a cycloadduct **74**.

As this route had been successful, the same idea was used in the synthesis of pyrrolidines from glucose. The protected amine **134** was alkylated with methyl bromo acetate and potassium hydride in dry THF, *scheme 104.*



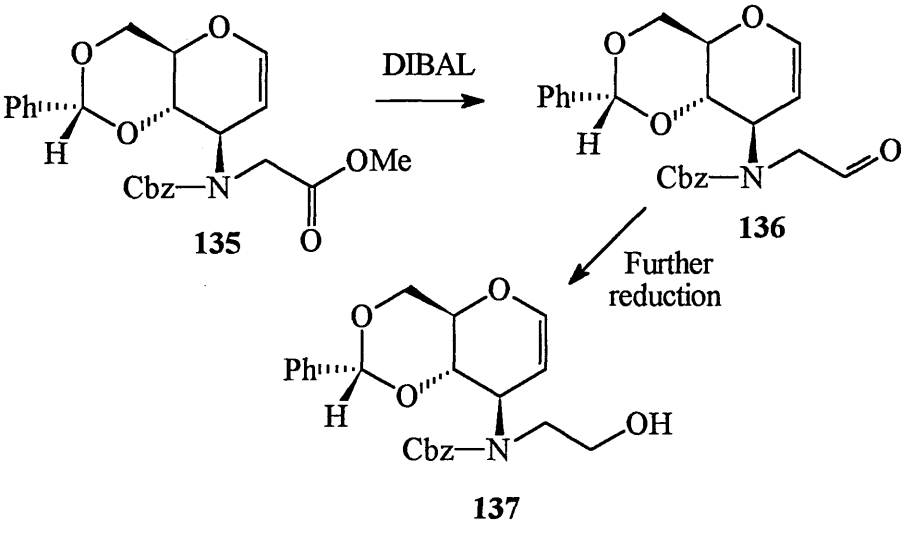
134 **135**

Scheme 104

Initially the same reaction conditions (2 molar equivalents of potassium hydride) were used here as for the alkylation of 4,6-O-benzylidene-D-allal **55** but although the starting material had all disappeared, a complex mixture resulted. However, after increasing the potassium hydride to 4 molar equivalents, the required ester **135** was obtained as an off-white solid in a yield of 83%. The IR spectrum confirmed the ester functionality to be present by the peak at 1720 cm^{-1} as well as the carbamate from the

cbz group at 1700cm^{-1}. Also the ^{1}H NMR spectrum showed the methoxy peak at 3.7 δ.

As previously mentioned (chapter 4.1) esters may be reduced to aldehydes but further reduction to alcohols is also possible[45]. To obtain a TLC marker for use in the reduction of the ester **135** to the aldehyde **136**, the ester **135** was deliberately reduced with DIBAL solution to the alcohol **137**, *scheme 105*, which was confirmed by a mass spectrum showing a molecular ion of 411.

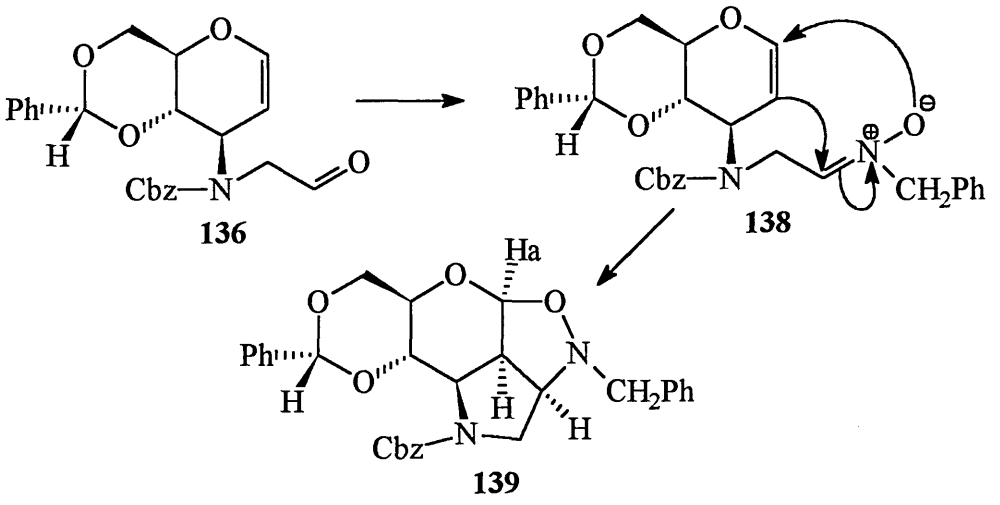


Scheme 105

The DIBAL reduction to the aldehyde was carried out on the ester at -70°C and the reaction was monitored closely by TLC. The reaction mixture was worked up using Rochelle salts to give the aldehyde **136** in a crude yield of 86%. Spectral data (^{1}H NMR) showed the disappearance of the methoxy peak at 3.7 δ and the appearance of the peak due to the aldehyde. As seen previously (chapter 4.1) there was a reduced integration for the aldehydic proton **136** indicating the presence of a hydrate. The ^{13}C

NMR spectrum further confirmed the presence of the aldehyde **136** by the peak at 198.5 δ.

The next step was to convert the aldehyde **136** to the nitrone precursor **138** for the 1,3-dipolar cycloaddition reaction which would result in the cycloadduct **139**, *scheme 106.*

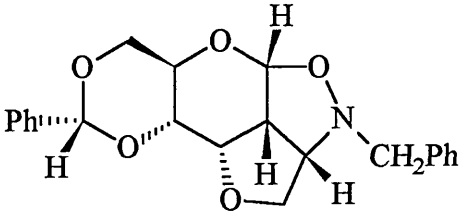


Scheme 106

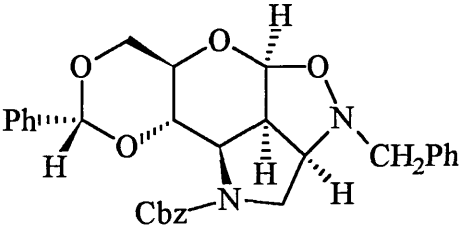
The same reaction conditions were employed as for the synthesis of the isoxazolidine **74**. As the aldehyde **136** was not soluble in ether, dry THF was used instead. A solution of aldehyde **136** in THF was added to a cooled mixture of benzyl-hydroxylamine and calcium chloride and left in the refrigerator[45]. The reaction was monitored by TLC and it was found that the new product **139** was not being formed at this temperature (0-4°C) so the mixture was removed from the refrigerator and left stirring at room temperature. Once again the reaction was monitored by TLC and after 1.5 days a new product was observed. The product did not precipitate out of solution as did the isoxazolidine **74** but was isolated by column chromatography in a

yield of 64%. The nitrone **138** which had been synthesised had spontaneously cyclised to form a cycloadduct **139**. The evidence for the synthesis of the cycloadduct **139** was shown by spectral data. The ^{1}H NMR spectrum indicated the disappearance of the double bond character (represented by the doublet of doublets at 6.4 δ and the doublet of doublets at 4.8 δ) and the appearance of a doublet at 5.5 δ which was due to the proton (Ha, *scheme 106*) in the cyclised product.

As the aldehyde was attached to the nitrogen, which was in the β-configuration, when the nitrone **138** was formed, the short chain this time will have only been able to add to the β-face giving the cycloadduct **139** with a different stereochemical arrangement to that observed in the isoxazolidine **74**.



74



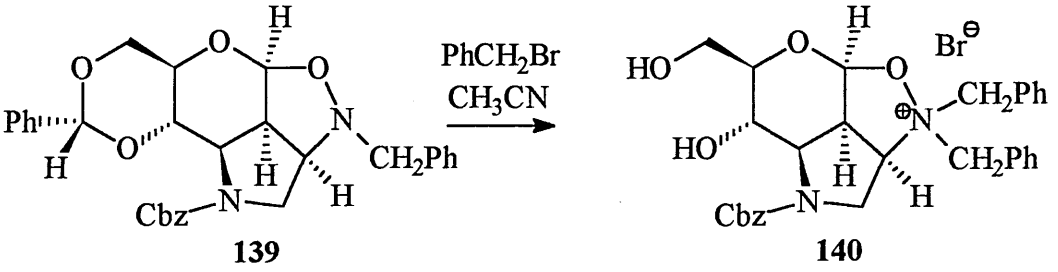
139

As mentioned previously in the synthesis of the isoxazolidine **74**, DeShong[45] had found that nitrones formed by using the conditions described earlier (p 119) exist exclusively in the Z-configuration and it had been supposed that the nitrone **73** was also in the Z-configuration. Models had been studied and supported the idea that cyclisation of the Z-nitrone **73** was more favourable via the *exo* transition state. Similar models of the two configurations of the nitrone **138** were also studied and it was found that it is

likely that the cyclisation of the Z-nitrone **138** via the exo transition state on the β-face is more favourable.

It was intended to follow the cleavage route which was analogous to that used for the cleavage of the isoxazolidine **74** but it was only pursued for a couple of steps as the time remaining did not allow further investigation.

As mentioned previously (chapter 4.1) Carruthers[75] had found a way of cleaving isoxazolidines. The first step in this method involved preparing a quaternary salt, followed by treatment with lithium aluminium hydride. The isoxazolidine **139** was refluxed with benzyl bromide in acetonitrile for 4 days, and after evaporation and trituration with ether a hygroscopic solid **140** was obtained in a yield of 91%, *scheme 107*.

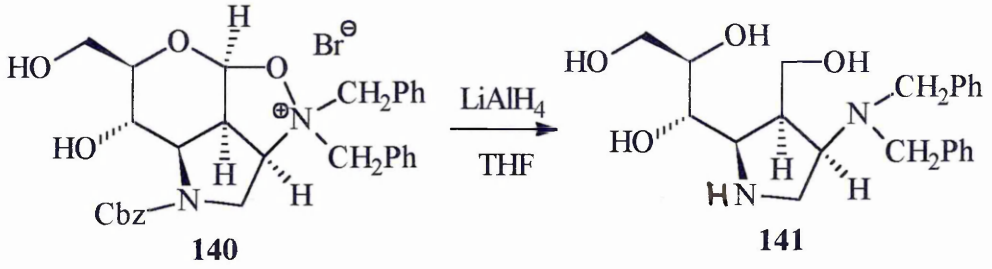


139 **140**

Scheme 107

In the quaternisation of the isoxazolidine **74** with benzyl bromide, the acetal protecting group had been removed. This was also found to occur during the preparation of the salt **140**. The mass spectrum (FAB) confirmed the salt by the peak at 517 which corresponded to the cation.

The next step in the cleavage of the isoxazolidine **139** was to reflux the salt **140** in dry THF with lithium aluminium hydride to form a product **141**, *scheme 108*.



140 **141**

Scheme 108

There was only enough time to try this reaction once. A mixture of products was obtained, predominantly benzyl alcohol, and the other compounds present were represented by minor peaks in the spectral data (^{1}H NMR). One possible explanation for the lack of the required product could be that the product was water soluble and was not extracted from the aqueous phase during the work up.

4.2.1 Summary and future work

The synthesis of the nitrogen heterocyclic ring adduct had been successful, but further investigation into the cleavage of the salt **140** is required. Reactions need to be chosen carefully to ensure the cbz group is not lost. Other ways of cleaving the isoxazolidine **139** are also necessary to obtain a functionalised pyrrolidine.

5.0 Experimental

General Information

Melting points were obtained on an Electrothermal melting point apparatus.

Infrared (IR) spectra were obtained on a Pye-Unicam SP3-100 spectrophotometer. Samples were prepared as potassium bromide (KBr) discs or liquid films.

IR data is given in cm^{-1}

^{1}H NMR spectra were obtained using a Jeol JNM PMX-60 SI 60MHz spectrometer at 60 MHz or a Bruker 250 AC spectrometer at 250 MHz.

^{13}C NMR spectra were obtained using a Bruker 250 AC spectrometer at 62.5 MHz

^{1}H NMR data is given on the δ ppm scale using tetramethylsilane as the internal reference. Abbreviations for the form of the signal are as follows: s = singlet, d = doublet, dd = double doublet, t = triplet, q = quartet, m = multiplet and b = broad. Coupling constants (J) are given in Hz. Samples for NMR spectra were prepared in deuterated chloroform unless otherwise stated.

Mass spectra and high resolution mass spectra were obtained on a VG Micromass 7070F

Optical rotation measurements and micro analyses were performed by Boots Pharmaceuticals Ltd.

Thin layer chromatography (TLC) was performed on Merck 555 Alufolien Kieselgel $60F_{254}$ plates. Flash chromatography was performed on Sorbsil C-60H (40-60mm) silica gel. and the solvents used in the chromatography were distilled.

Petrol refers to that fraction of petroleum spirit boiling between 40 and 60°C. Dry tetrahydrofuran (THF) was obtained by distillation from potassium metal. Dry diethyl ether was obtained through standing over sodium metal. Dry pyridine was obtained by distillation from potassium hydroxide and was stored over potassium hydroxide. Dry dichloromethane (DCM) was obtained by distillation from P_2O_5 and was stored over molecular sieves. Dry dimethylformamide (DMF) was obtained by heating over calcium hydride followed by distillation under reduced pressure onto 4A molecular sieves. Dry carbon tetrachloride was obtained by distillation of the solvent which had been previously stored over 4A molecular sieves. Trimethylsilylchloride was distilled at atmospheric pressure.

Pure p-toluene sulphonyl chloride was obtained by dissolution in a minimum amount of chloroform followed by dilution with 5 volumes of petrol to precipitate impurities. The filtered solution was then decolourized using Norit A, filtered and concentrated.

N-Bromosuccinimide was recystallised from hot water. N-Chlorosuccinimide was rapidly crystallised from benzene.

Methanolic hydrogen chloride was standardised using sodium hydroxide and phenolphthalein.

All reactions requiring inert atmospheres were performed under nitrogen.

All products were stored in a dessicator containing potassium hydroxide to make the atmosphere basic and thereby prevent acid catalysed decomposition.

N-Cbz-aspartic acid **29**[19]

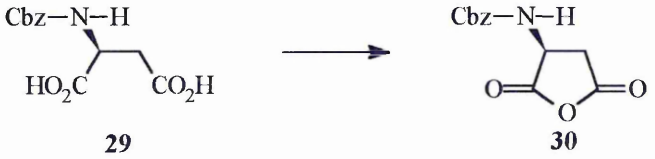
Aspartic acid **28** (10.65g, 0.08 mol) was dissolved in sodium hydroxide solution (4M, 40ml, 0.16mol). The mixture was cooled to 0°C with an ice bath. Whilst stirring vigorously, benzyl chloroformate [carbobenzyoxy chloride] (14.0g, 0.082mol) and sodium hydroxide solution (4M, 20ml, 0.08mol) were added dropwise simultaneously over a period of 30 minutes, keeping the temperature at 0°C. The mixture was allowed to warm to room temperature where stirring was continued for 1 hr. The mixture was acidified with 6M hydrochloric acid and the liberated oil was extracted with ether (4x20ml), dried ($MgSO_4$), filtered and evaporated to obtain the product, 15.5g, 73%, which crystallised very slowly.

Melting point 116-118°C (lit[19] 117-119°C)

IR (KBr) 3350 (NH), 3480-2500 (OH), 3040 (Csp^2-H), 2950 (Csp^3-H) 1720-1700 (C=O, carbamate, carboxylic acid), 1525 (NH), 1350-1010 (C-O) 680, 780 (Csp^2-H)

^1H NMR ($CD_3C(O)CD_3$, 60 MHz) 3.0 (2H, d, J = 6, CH_2), 4.6-4.9 (1H, m, CH), 5.2 (2H, s, CH_2-Ar) 6.6-6.9 (1H, bd, J = 6, NH), 7.5 (5H, s, C_6H_5), 9.9 (2H, s, CO_2H x 2)

N-Cbz aspartic anhydride **30**



Method 1[20]

To a stirred solution of N-cbz-aspartic acid **29** (6.05g, 22.6mmol) in dry THF (75ml) at 0°C was added N,N-dicyclohexylcarbodiimide (DCC) (4.31g, 21mmol) and the mixture was stirred for a further 3 hrs at 0°C. The reaction mixture was further stirred overnight at room temperature, filtered under reduced pressure and the resulting solid was washed with dry THF. The filtrate was concentrated under reduced pressure to yield a waxy solid. This was redissolved in dry THF and filtered to remove any insoluble solid. A true yield could not be obtained as the solubility of the DCU by-product resembled that of the required anhydride therefore preventing isolation of the pure anhydride.

IR (Solution in DCM) 3440 (NH, DCU), 3060 (Csp^2-H), 2995 (Csp^3-H), 1870, 1795 (C=O anhydride) 1720 (C=O, carbamate), 1510 (C=C, aromatic)

^{1}H NMR (CD_3OD, 60 MHz) [crude product] 2.8 (2H, d, J = 6, CH_2) 4.6 (1H, m, CH), 5.2 (2H, s, CH_2-Ar) 7.5 (5H, s, C_6H_5) plus many minor peaks due to impurities.

Method 2[21]

A mixture of N-cbz-aspartic acid **29** (5g, 18.7mmol) and acetic anhydride (11.9g, 116.6mmol) was stirred vigorously for 2.5 hrs at room temperature. The solution was freed in vacuo of acetic anhydride and acetic acid using a bath below 38°C. Gelation occured when most of the volatile material had been removed. Dry THF (50ml) was then added and it was evaporated until gelation occurred. The procedure was repeated using dry toluene. The product was finally freeze dried to yield 9g, 192% of product.

It was suspected that the freeze drying procedure was not very efficient so the product was dissolved in dry toluene and evaporated to form the gel. This was repeated a couple of times but toluene always remained in the final product which was used in this crude form.

Melting point 101-104°C (lit[21] 101-106°C)

IR (KBr) 3400 (NH), 3080-3020 (Csp^2-H), 2990-2940 (Csp^3-H), 1870, 1790 (C=O, anhydride), 1700 (C=O, carbamate), 1525 (C=C, aromatic)

^{1}H NMR (CD_3OD, 60 MHz) [crude product] 2.8 (2H, d, J = 6, CH_2), 4.5-4.8 (1H, m, CH), 5.2 (2H, s, CH_2-Ar), 7.5 (5H, s, C_6H_5) [peaks for toluene also seen at 2.3 and 7.3 δ].

It could be seen form the ^{1}H NMR that the product and toluene were in a 1:1 molar ratio.

3(S)-[N-(Carbobenzyloxy)-amino]-γ-butyrolactone **31**[22]

30 **31**

To a stirring slurry of sodium borohydride (2.0g, 0.052mol) in THF (50ml) at 0°C was added N-cbz-aspartic anhydride **30** (6.6g, 0.026 mol) in THF (50ml) over a period of 1hr. After stirring at room temperature for 1hr, the reaction mixture was carefully acidified to pH 2 with 6M hydrochloric acid, then concentrated to approximately one fourth the volume under reduced pressure. The result was diluted with water (20ml) and extracted with ether (4 x 20ml) and then the combined organic extracts were concentrated under reduced pressure to a heterogeneous residue. The yellow residue was taken up in benzene containing p-toluene sulphonic acid (50mg) and then water was azeotropically removed by using a Dean-Stark apparatus. After the mixture had been refluxed for 10hrs, the benzene was removed by evaporation under reduced pressure to afford a viscous orange residue which gave white crystals upon trituration with ether. The white solid was collected by filtration and the filtrate was concentrated under reduced pressure and triturated with ether to afford a second crop of white crystals, combined yield 3.5g, 56%.

Melting point 95-97°C (lit[22] 103-104°C)

$[a]_D^{22}$ -29.3° (c = 1.06, EtOH), lit $[a]_D^{20}$ -54.9° (c = 2.27, $CHCl_3$)

IR (KBr) 3340 (NH), 3080-3020 (Csp^2-H), 3000-2940 (Csp^3-H), 1780 (C=O, lactone), 1700 (C=O, carbamate), 1535 (C=C, aromatic)

^{1}H NMR (60 MHz) 2.5-2.7 (2H, m, C(O)CH-H x 2), 4.0-4.6 (3H, m, CHN, OCH_2), 5.0 (2H, s, CH_2-Ar), 5.0-5.2 (1H, bm, NH), 7.2 (5H, s, C_6H_5)

Microanalysis calculated for $C_{12}H_{13}NO_4$: C, 61.3; H, 5.5: N, 5.95. Found C, 60.8: H, 5.5; N, 5.8.

Exact mass calculated for $C_{12}H_{13}NO_4$: 235.0845. Found 235.0840.

Attempted alkylation of 3(S)-[N-(Cbz)-amino]-γ-butyrolactone

31 **32**

Method 1a The preparation of **32**

To dry THF (10ml) at room temperature, sodium hydride (60% in mineral oil) (28mg, 1.17mmol), which had been washed with petrol, and (cbz-amino)-γ-butyrolactone **31** (250mg, 1.06mmol) were added. The mixture was stirred for 1.5 hrs, then 1,2-dibromoethane (240mg, 1.27mmol) was added and stirring was continued at room temperature. The reaction was monitored by TLC (ethyl acetate:petrol, 4:7). The mixture was then poured into water and extracted with ethyl acetate (3 x 15ml), dried ($MgSO_4$), filtered and evaporated. No reaction was observed at room temperature.

Method 1b The preparation of **32**

The reaction was repeated as above except the reaction mixture was heated to reflux for several days but starting material still remained unreacted.

Method 1c The preparation of **32**

The solvent was changed from THF to DMF but at both room temperture and 40°C only starting material was recovered.

Method 2 The preparation of **33**

31 **33**

The reaction conditions used in method 1a were followed except that allyl bromide (0.19g, 2.2mmol) was used as the alkylating agent instead of dibromoethane. The reaction was tried at room temperature and at reflux but starting material remained unchanged.

3(S)-amino-γ-butyrolactone hydrobromide **34**[22b]

31 **34**

Lactone **31** (10g, 0.043mol) was added to hydrogen bromide (30% wt) solution in acetic acid (17.23g, 0.213mol) at room temperature. Then ether (15ml) was added and the mixture was stirred for 2hrs, then cooled to -5°c and filtered. The slightly off-white solids obtained were sequentially washed with ether and dry acetone to afford the product. The filtrate was concentrated under reduced pressure and similarly cooled, filtered and washed to yield a second crop of product, 6.7g, 87% (combined).

Melting point 198-200°C (lit[22b] 199-201°C)

$[a]_D^{22}$ -0.19° (c = 1.01, H_2O), lit $[a]_D^{20}$ -42.6° (c =1.08, H_2O)

IR (KBr) 3500 (NH), 3240-2500 (OH, acetic acid impurity), 1780 (C=O, lactone), 1580-1620 (NH, amine)

^1H NMR (Me_2-SO-d_6, 250 MHz) 2.5 (1H, m, C(O)CH-H), 3.0 (1H, dd, J = 10,20, C(O)CH-H), 4.15 (1H, m, CH), 4.3 (1H, d, J = 11, OCH-H), 4.5 (1H, d, J = 17, OCH-H), 8.3 (3H, bs, $^+NH_3$)

Microanalysis calculated for $C_4H_8BrNO_2$: C, 26.4; H, 4.4: N, 7.7. Found C, 26.3: H, 4.5; N, 7.5.

3(S)-[N-Benzene-sulphonamido]-γ-butyrolactone **35**[22b]

To a stirred suspension of 3(S)-amino-γ-butyrolactone hydrobromide **34** (2.0g, 0.011mol) in DCM (40ml) at 0°C was added benzene sulphonyl chloride (3.01g, 0.017mol) and pyridine (4.62g, 0.058mol). The mixture was stirred until it became homogenous and clear. The reaction was also monitored by TLC (ethyl acetate). The orangey/red solution was then carefully poured into dilute hydrochloric acid (0.5M, 100ml) and thoroughly agitated, the layers were separated and the aqueous phase was extracted twice with fresh DCM. The combined extracts were washed once with saturated aqueous sodium hydrogen carbonate, dried ($MgSO_4$), filtered and evaporated. The resulting solids were collected and washed twice with ether to afford a slightly coloured product in a yield of 2.06g, 77.7%.

Melting point 82-85°C

$[a]_D^{22}$ -18.47° (c = 0.758, EtOH).

IR (KBr) 3230 (NH), 3100-3050 (Csp^2-H), 3000-2890 (Csp^3-H), 1770 (C=O, lactone), 1340, 1170 (S=O)

^{1}H NMR (60 MHz) 2.6 (2H, m, C(O)CH-H x 2), 4.1-4.5 (3H, m, CH, OCH-H, OCH-H), 6.1 (1H, bd, NH), 7.9 (3H, m, meta and para aromatic protons), 8.1 (2H, m, ortho aromatic protons)

Microanalysis calculated for $C_{10}H_{11}NO_4S$: C, 49.8; H, 4.6: N, 5.8. Found C, 49.4: H, 4.6; N, 5.65.

Exact mass calcualted for $C_{10}H_{11}NO_4S$: 241.0409. Found 241.0411.

Attempted alkylation of 3(S)-[benzene-sulphonamido]-γ-butyrolactone **35**

35

Method 1a

To dry THF (20ml) at room temperature sodium hydride (60% in mineral oil) (32mg, 1.32mmol), previously washed in petrol, and 3(S)-[benzene-sulphonamido]-γ-butyrolactone **35** (0.29g, 1.2mmol) were added and stirred for 1hr. Effervesence was observed. 1,2-Dibromoethane (0.56g, 3.0mmol) was added to the mixture and stirring was continued at room temperature. The reaction was monitored by TLC, (ethyl acetate:petrol, 6.4). The mixture was then poured into water and extracted with ethyl acetate (3 x15ml), dried ($MgSO_4$), filtered and evaporated. Spectral data showed starting material was recovered.

Method 1b

The reaction was repeated as above except the solvent was changed from THF to DMF and the temperature was raised to 40°C. Also after the final extractions of the reaction mixture the combined organic extracts were washed with dilute hydrochloric acid (2M) to remove any excess DMF, followed by a water wash, then the extracts were dried ($MgSO_4$), filtered and evaporated.

The ^1H NMR indicated that alkylation had not taken place and that starting material remained.

Method 1c

A stronger base was investigated.

The method was carried out according to method 1a but potassium hydride (0.077g, 1.92mmol) was used instead of sodium hydride.

No reaction was observed at room temperature but on refluxing the mixture, a new product was observed on TLC (ethyl acetate:petrol, 6:4). This product was found to be benzene sulphonamide which was an elimination product.

Melting point 150-151°C (lit value for benzene sulphonamide 152-154°C)

IR (KBr) 3350, 3260 (NH_2), 1335,1160(S=O), 770,690 (Csp^2-H)

Method 2a

35

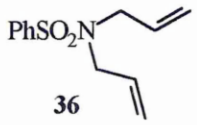
A flame dried flask fitted with an inert atmosphere and magnetic stirrer was charged with sodium hydride (60% in mineral oil) (27mg, 1.14mmol) which was washed once with petrol and the solvent removed. Dry DMF was added, followed by 3(S)-sulphonamido-γ-butyrolactone **35** (0.25g, 1.04mmol). The resultant mixture was stirred for 5 minutes and allyl bromide (0.138g, 1.14mmol) was added by syringe. The mixture was heated to 40°C for approximately 3hrs and was monitored by TLC (ethyl acetate:petrol, 1:1). It was then poured into ethyl acetate/hydrochloric acid (2M) and the aqueous layer was extracted with more ethyl acetate. The combined extracts were washed with brine, dried ($MgSO_4$), filtered and evaporated to form a white solid, 10mg, which was shown to be the elimination product, benzene sulphonamide, by spectral data.

Melting point 150-151°C (lit value for benzene sulphonamide 152-154°C)

^{1}H NMR (60 MHz) 7.5 (3H, m, meta and para aromatic protons) 8.0 (2H, m, ortho aromatic protons)

Method 2b

The reaction was carried out according to method 1a but potassium hydride (0.077g, 1.92mmol) was used instead of sodium hydride and allyl bromide (0.17g, 1.44mmol) was used instead of 1,2-dibromoethane. The reaction was monitored by TLC (ethyl acetate:petrol, 2:8). The required product was not obtained but column chromatography (ethyl acetate:petrol, 1.5:8.5) yielded, as an oil, a different by-product **36** to the one obtained previously. Its structure was found to be:

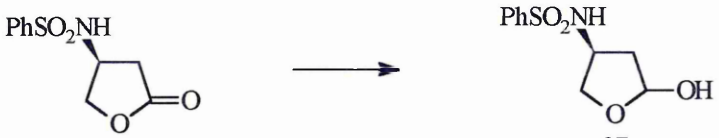


36

IR (thin film) 3090 (Csp^2-H), 3000-2860 (Csp^3-H), 1640 (C=C), 1330, 1160 (S=O)

^{1}H NMR (60 MHz) 3.9 (4H, d, J = 6, N-CH_2 x 2), 4.9-6.2 (6H, m, HC=CH_2 x 2), 7.6 (3H, m, meta and para aromatic protons), 8.0 (2H, m, ortho aromatic protons).

3(S)-[Benzene-sulphonamido]-γ-butyrolactol **37**[23]



35 **37**

A two necked flask fitted with an inert gas adapter, septum and magnetic stirrer was flame dried. Diisobutylaluminium hydride (DIBAL) in toluene (1.5M solution, 3.1mmol) was added dropwise by syringe to a stirred solution of lactone **35** (0.25g,

1.04mmol) in dry DCM (10ml) at -70°C under nitrogen. Stirring was continued for approximately 3hrs whilst monitoring by TLC (ethyl acetate). The reaction mixture was quenched with dilute hydrochloric acid (2M, 10ml) and allowed to warm to room temperature. The phases were separated and the aqueous phase was extracted with DCM (3 x 10ml). The organic extracts were combined and washed with saturated aqueous sodium hydrogen carbonate and sodium chloride solutions, dried ($MgSO_4$), filtered and evaporated to yield the product as an oil, 45.6mg, 18%.

IR (thin film) 3600-3100 (OH), 3260 (NH), 3070 (Csp^2-H), 2960-2880 (Csp^3-H), 1330, 1160 (S=O)

^1H NMR (60 MHz) 1.9 (2H, m, CH_2), 2.7 (1H, bs, OH), 3.7-4.5 (3H, m, CH, CH_2-O), 5.2-6.0 (2H, m, CH-O, NH), 7.8 (3H, m, meta and para aromatic protons) 8.1 (2H, m, ortho aromatic protons)

^1H NMR (60 MHz) [D_2O exchange]

The peak at 2.7 in the above spectrum had disappeared showing that the OH peak had been converted to OD and the integration for peaks at 5.2-6.0 had halved indicating that the NH had also been converted to ND. These observations helped to confirm that the reduction had taken place.

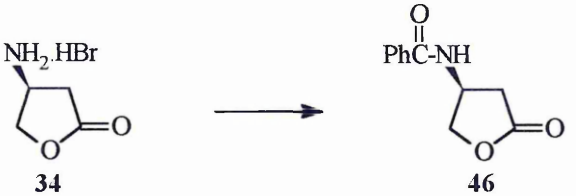
Attempted preparation of 3(S)-[N-benzene sulphonamido]-2,3-dihydrofuran **38**[23g]

37 **38**

p-Toluene sulphonic acid (0.02g, 0.1mmol) and molecular sieves (4A, 3g) were added to a solution of lactol **37** (0.05g, 0.2mmol) in anhydrous toluene (20ml) and DCM (5ml). The reaction was refluxed for 3hrs and was monitored by TLC. The mixture was filtered and the filtrate was washed with saturated sodium carbonate (10ml) and sodium chloride (10ml) solutions, dried (Na_2SO_4), filtered and evaporated.

The TLC showed that the starting material had disappeared and a number of products had been produced. The ^1H NMR spectrum indicated that the C=C bond character was not present and the method was not further pursued.

3(S)-[N-benzoyl-amino]-γ-butyrolactone **46**



34 **46**

3(S)-Amino-γ-butyrolactone hydrobromide **34** (3g, 0.016mol) was supended in pyridine (24ml) and toluene (24ml). Triethylamine (1.62g, 0.016mol) was added followed by the dropwise addition of benzoyl chloride (2.47g, 0.018mol). The mixture was refluxed for 1hr and then allowed to cool. The triethylamine salt was filtered and the

filtrate was poured into dilute hydrochloric acid (2M, 50ml) and agitated. The two phases were separated and the aqueous phase was extracted with ethyl acetate (3 x 25ml). The combined organic phases, including the toluene extract, were dried ($MgSO_4$), filtered and evaporated to yield 3.38g, 59.2% of an off-white solid.

Melting point 102-105°C

$[a]_D^{22}$ -66.53° (c = 0.496, EtOH)

^{1}H NMR (250 MHz) 2.6 (1H, dd, J = 2, 18, C(O)CH-H), 2.9 (1H, dd, J = 8, 16, C(O)CH-H), 4.4 (1H, dd, J = 2, 9, O-CH), 4.6 (1H, dd, J = 9, 7, O-CH), 4.9 (1H, m, CH), 7.4-7.8, (6H, m, NH, C_6H_5)

^{13}C NMR (62.5 MHz) 177.0, 168.2 (C=O), 132.3, 130.4, 128.9, 127.6 (aromatic), 74.8, 47.3, 34.9 (aliphatic)

Mass Spec 205 (M^+) 177, 161, 146, 131, 122, 105 (base peak), 77, 69, 51, 41.

Microanalysis calculated for $C_{11}H_{11}NO_3$: C, 64.4; H, 5.4: N, 6.8. Found C, 63.8: H, 5.2; N, 6.0.

Exact mass calculated for $C_{11}H_{11}NO_3$: 205.0739. Found: 205.0735.

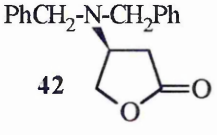
3(S)-[N-benzyl-amino]-γ-butyrolactone **43**

Method 1[24]

3(S)-Amino-γ-butyrolactone hydrobromide **34** (0.25g, 1.37mmol) was added to dry acetone (10ml) and stirred at room temperature. Anhydrous potassium carbonate (0.38g, 2.75mmol) was then added, followed by benzyl bromide (0.26g, 1.51mmol). Stirring was continued at room temperature and the reaction was monitored by TLC (ethyl acetate:petrol, 2:8).

[No reaction was observed initially so more potassium carbonate (0.38g, 2.75mmol) was added and stirring was continued for several more hours. Still no reaction was observed so more potassium carbonate (0.38g, 2.75mmol) was added and the mixture was refluxed.]

The mixture was poured into water (20ml) and aqueous mixture was extracted with DCM, dried ($MgSO_4$), filtered and evaporated. The required alkylated product **43** was not obtained but the dialkylated product **42** resulted.



IR (thin film) 3100-3040 (Csp^2-H), 2980-2820 (Csp^3-H), 1770 (C=O)

^{1}H NMR (60 MHz) 2.7 (2H, d, J = 8, CH_2-C(O)), 3.7 (4H, m, CH_2 x 2), 4.3 (1H, m), 4.5 (1H, m), 4.8 (1H, m), 7.5 (10H, s, C_6H_5 x 2)

Mass Spec 281 (M^+) 190, 132, 91 (base peak), 65.

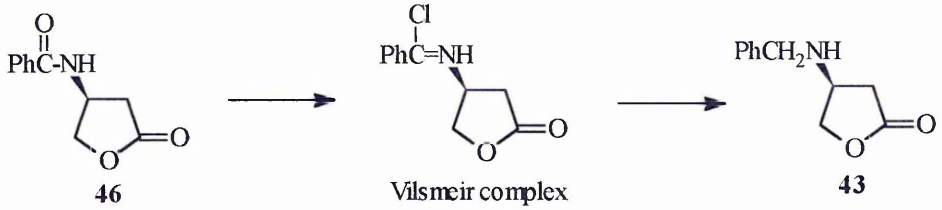
Method 2[25]

To a solution of 3(S)-amino-γ-butyrolactone hydrobromide **34** (0.2g, 1.1mmol) in absolute methanol (3ml) was added 5M HCl-methanol (few drops) followed by benzaldehyde (0.11g, 1.0mmol) and sodium cyanoborohydride (0.038g, 0.6mmol). The solution was stirred at 25°C for 72hrs. Concentrated hydrochloric acid was added until pH < 2 and then the methanol was removed by evaporation. The residue was taken up in water (10ml) and extracted with ether (3 x 5ml). The aqueous solution was brought to pH > 10 with solid potassium hydroxide, saturated with sodium choride and extracted with ether (5 x 5ml). The second organic extracts were dried ($MgSO_4$), filtered and evaporated to give 0.03g of crude product.

IR (thin film) 3300 (NH), 3090-3030 (Csp^2-H), 2980-2850 (Csp^3-H), 1770 (C=O)

^{1}H NMR (60 MHz) 2.7 (2H, m, CH_2-C(O)), 3.6-4.0 (3H, m, CH, CH_2-Ar), 4.2 (2H, m, CH_2-O), 5.0 (1H, s, NH), 7.5 (5H, s, C_6H_5)

Method 3[27]



46 Vilsmeir complex 43

3(S)-[N-Benzoyl-amino]-γ-butyrolactone **46** (0.25g, 1.22mmol) was dissolved in refluxing DCM (6ml). Phosphorus pentachloride (0.28g, 1.25mmol) was added to the mixture and left to reflux for 20hrs. Sodium borohydride (0.14g, 3.65mmol) suspended in absolute ethanol was added dropwise and the resultant mixture was left for 24hrs at room temperature. After this time the ethanol was then evaporated off and the residue partitioned between water and ethyl acetate. The organic layer was extracted with acetic acid solution and the mixture was basified with aqueous ammonia and extracted with ethyl acetate. The product was dried ($MgSO_4$), filtered and evaporated to yield 0.05g of oil.

Spectral data showed benzoyl lactone to be present with many impurities

Method 4[28]

The Vilsmeier complex **47** was prepared by warming 3(S)-[N-benzoyl]-γ-butyrolactone **46** (0.25g, 1.22mmol) at 60-90°C on a water bath with phosphorus oxychloride (0.19g, 1.22mmol) for 15-20 minutes. The resulting pale yellow complex was cooled (0 to 5°C) and zinc powder (0.4g, 6.1mmol) suspended in absolute ethanol (1ml) was added and the mixture heated on a water bath for about 15 minutes. The ethanol was

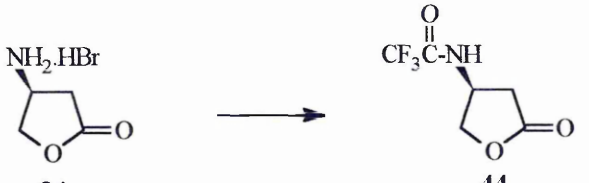
then evaporated off, water (5ml) added and filtered. The filtrate was extracted with ethyl acetate (2 x 10ml) to remove neutral impurities, basified with ammonia and re-extracted with ethyl acetate (3 x 15ml). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated to afford the product, which was purified by column chromatography (ethyl acetate:petrol, 8:2). the yield was 0.03g.

Even after column chromatography, impurities were still present; ^{1}H and ^{13}C NMR showed 3(S)-[N-benzoyl-amino]-γ-butyrolactone to be present as well as some $PO(OEt)_3$ which was difficult to remove.

Mass Spec 206 (M^++1 for 3(S)-[N-benzoyl-amino]-γ-butyrolactone **46**), 191 (M^+ for 3(S)-[N-benzyl-amino]-γ-butyrolactone **43**), 150, 133, 116, 105, 91 (base peak), 77, 65, 39.

In an attempt to separate the 3(S)-[N-benzyl-amino]-γ-butyrolactone from the impurities the mixture was put through to an acylation step.

3(S)-N-trifluoroacetamido-γ-butyrolactone **44**[26]



3(S)-Amino-γ-butyrolactone hydrobromide **34** (2g, 0.011mol) was treated with trifluoroacetic anhydride (13.85g, 0.066mol) and warmed to effect solution. The mixture was then stirred overnight and the solvent was evaporated under reduced

pressure. Several portions of DCM were added and evaporated to leave a residue which was recrystallised from DCM/ethyl acetate/petrol to yield a solid, 1.48g, 67.89%.

Melting point 117-119°C

$[a]_D^{22}$ -57.3° (c = 0.246, EtOH)

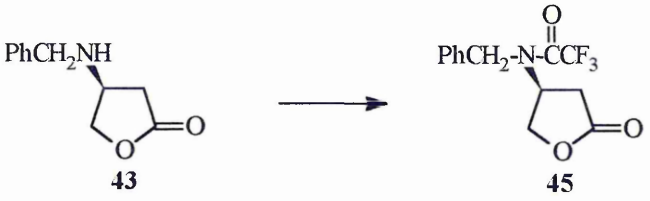
^{1}H NMR ($CD_3C(O)CD_3$ 250 MHz) 2.9 (1H, dd, J = 4, 17, C(O)CH-H), 3.2 (1H, s, NH), 3.35 (1H, dd, J = 8,16, C(O)CH-H), 4.6 (1H, dd, J = 3, 14, O-CH), 4.9 (1H, dd, J = 8.5, 8, O-CH), 5.2, (1H, m, CH)

^{13}C NMR (62.5 MHz) 183.3, 175.3 (C=O), 72.8, 47.9, 33.9 (aliphatic)

Mass Spec 198 (M^++1) 166, 139, 114, 96, 70 (base peak), 55, 43.

Microanalysis calculated for $C_6H_6F_3NO_3$: C, 36.55; H, 3.0: N, 7.1. Found C, 36.5: H, 3.1; N, 6.8.

Acylation of 3(S)-[N-benzyl-amino]-γ-butyrolactone[26]



A solution of trifluoroacetic anhydride (0.22g, 1.06mmol) in ether (2ml) was added at 0°C to a solution of crude 3(S)-[N-benzyl-amino]-γ-butyrolactone **43** (0.134g) from

the previous step, in ether (1ml). The mixture was stirred and monitored by TLC (ethyl acetate:petrol, 7:3) and then after no starting material remained (2days), the solvent was evaporated to give the product **45** which was purified by column chromatography (ethyl acetate:petrol, 7:3) in a yield of 0.067g.

Melting point 110-112°C

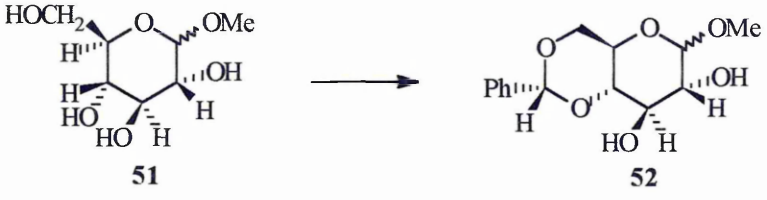
^{1}H NMR (250MHz) 2.6 (1H, dd, J = 17, 17, C(O)-CH), 2.8 (1H, dd, J = 4, 18, C(O)-CH), 4.3 (3H, m, s, CH, CH_2-Ar), 4.7 (2H, dd, J = 27, 17, CH_2-O), 7.3 (5H, m, C_6H_5)

^{13}C NMR (62.5MHz) 184.1, 174.8 (C=O), 134.5, 129.7, 129.2, 127.6 (aromatic), 70.7, 55.5, 53.1, 46.9, 32.1 (aliphatic).

Mass Spec 287 (M^+), 241, 202, 190, 134, 105, 91 (base peak), 65.

Exact mass calculated for $C_{13}H_{12}NO_3F_3$: 287.0769. Found: 287.0752.

Methyl 4,6-O-benzylidene-α-D-glucopyranoside **52**[31]



51 **52**

A mixture of purified benzaldehyde 105g (1.0 mol), methyl α-D-glucopyranoside **51** 38.8g (0.2 mol) and freshly fused and powdered anhydrous zinc chloride 29.5g (0.22 mol) was shaken vigorously in a conical flask in a mechanical shaker, for about 10 hrs, until a clear solution was obtained. The solution was allowed to stand at room temperature for a further period of 18 hrs. The clear solution was extracted by shaking

it with petrol (3x100ml), to remove the unreacted benzaldehyde. The viscous residue was then stirred with iced water (700ml) until solidification occurred. The solid was filtered and the filter cake was then washed with petrol. After removal from the Buchner funnel, the filter cake was stirred vigorously with a solution of 12g of sodium metabisulphite in 120ml of water, filtered and washed with water. The white solid was crystallised from hot water or after drying in a vacuum desiccator from a mixture of chloroform and ether. Yield was 31.00g, 56 %.

Melting point 163 °C (lit[31] 165 °C)

IR (KBr) 3600-3200 (OH), 3100-3000 (Csp^2-H), 2990-2860(Csp^3-H)

^{1}H NMR (60 MHz) 2.6 (2H, s, OH), 3.5 (3H, s, OCH_3), 3.5-4.5 (6H, m), 4.9 (1H, d, J = 6, C<u>H</u>-OCH_3), 5.8 (1H, s, C<u>H</u>-Ar) 7.7(5H, s, C_6H_5)

<u>Methyl 4,6-O-benzylidene-2,3-di-O-toluene-p-sulphonyl-α-D-glucopyranoside **53**[31]</u>

52 **53**

Pure dry redistilled pyridine (40ml) was placed in a conical flask and toluene-p-sulphonyl chloride 14.9g (0.066mol) was added with cooling. The yellow solution was allowed to stand for about 0.5 hrs at room temperature before the addition of methyl 4,6-O-benzylidene-α-D-glucopyranoside **52** 8.5g (0.03 mol) with shaking and cooling. The reaction mixture was left stirring for 5 days at room temperature, then poured on

to crushed ice (75g). The mixture of syrup and water was extracted with DCM (3x25ml), and the combined extracts were successively washed with cold dilute 2M hydrochloric acid (x2), water, saturated aqueous sodium hydrogen carbonate and water, and then dried ($MgSO_4$) and filtered. The solvent was removed by evaporation under reduced pressure and trituration of the gummy residue with ether yielded 11.91g, 67% of a cream solid.

Melting point 152-155 °C (lit[31] 152-154 °C)

IR (KBr) 3095-3000 (Csp^2-H), 2995-2830 (Csp^3-H) 1600, 1490 (C=C, Aromatic) 1350, 1170 (SO_2-O) 880, 760 (Csp^2-H)

^{1}H NMR (60 MHz) 2.3 (3H, s, CH_3), 2.5 (3H, s, CH_3), 3.5 (3H, s, OCH_3), 3.5-4.5 (5H, m), 5.2 (2H, dd, J = 3 and 6, CHx2), 5.5 (1H, s, C<u>H</u>-Ar) 7.0-8.2 (13H, m, C_6H_5, C_6H_4-SO_2)

<u>Methyl 2,3-anhydro-4,6-O-benzylidene-α-D-allopyranoside **54**[31]</u>

53 **54**

Methyl 4,6-O-benzylidene-2,3-di-O-toluene-p-sulphonyl-α-D-glucopyranoside **53** (11.7g, 0.0195mol) in DCM (150ml) was placed in a round-bottomed flask fitted with a pressure equalising funnel protected with a calcium chloride guard tube. The solution was cooled to 0°C by means of an ice-salt bath and a solution of sodium

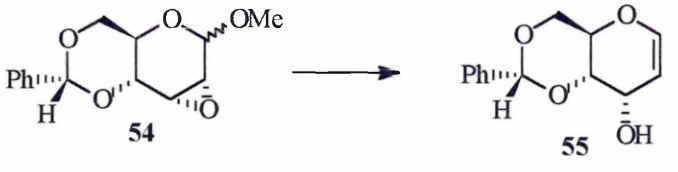
methoxide in methanol [prepared from sodium (2.3g, 0.1mol) in methanol (40ml)] was added dropwise with stirring. When addition was complete the funnel was removed and the flask was stoppered and left in a refrigerator for 48 hours and then at room temperature for a further 24 hrs. The DCM solution was extracted with water until the aqueous washings were neutral, dried ($MgSO_4$), filtered and evaporated. Yield was 4.85g, 93%.

Melting point 192-194 °C (lit[31] 195-199 °C)

IR (KBr) 3050-3010 (Csp^2-H), 2990-2820 (Csp^3-H) 1480-1360 (R-O-R) 880, 760 (Csp^2-H)

^{1}H NMR (60 MHz) 3.5 (3H, s, OCH_3), 3.5-4.5 (6H, m), 4.9 (1H, d, J = 2, C<u>H</u>-OCH_3), 5.6 (1H, s, C<u>H</u>-Ar) 7.5 (5H, m, C_6H_5)

<u>4,6-O-Benzylidene-1,2-didehydro-1,2-dideoxy-D-ribo-hexopyranose (4,6-O-benzylidene-D-allal) **55**[32,33]</u>



To a stirred suspension of small pieces of lithium metal (0.43g, 0.06mol) [previously washed twice in dry ether] in dry ether (9ml) under an inert atmosphere, a few drops of methyl iodide were added. The solution became turbid and the ether commenced to reflux gently. Methyl iodide (3.97g, 0.28mol) in dry ether (9ml) was added slowly to

the stirred solution so that gentle reflux was maintained. When addition was complete, stirring and heating were continued for a further 0.5 hrs. After cooling, methyl 2,3-anhydro-4,6-O-benzylidene-α-D-allopyranoside **54** (2.0g, 0.0076mol) was added, followed by dry ether (30-40ml). The mixture was stirred and heated under reflux for 3 hrs. Excess of lithium was removed and water was added until two clear layers were obtained. These layers were separated, and the aqueous phase was extracted with ether (6x5ml). The ether extracts were combined and washed with water (2x5ml), dried ($MgSO_4$), filtered and evaporated to yield a white solid with a yield of 1.70g, 96%.

Melting point 77-80°C (lit[33] 84-85°C)

$[a]_D^{22}$+149° (c = 1.03, EtOH) {lit[33] $[a]_D^{25}$+210° (c = 0.44, EtOH)}

IR (KBr) 3600-3100 (OH) 3100-3000 (Csp^2-H), 2995-2800 (Csp^3-H) 1630 (C=C, aliphatic) 880, 760 (Csp^2-H)

^{1}H NMR (250 MHz) 2.5 (1H, s, OH), 3.85 (2H, m), 4.2 (2H, m), 4.45 (1H, dd, J = 4, 9), 5.1 (1H, t, J = 6, C<u>H</u>=C), 5.8 (1H, s, C<u>H</u>-Ar) 6.5 (1H, d, J = 6, O-CH=C), 7.6 (5H, m, C_6H_5)

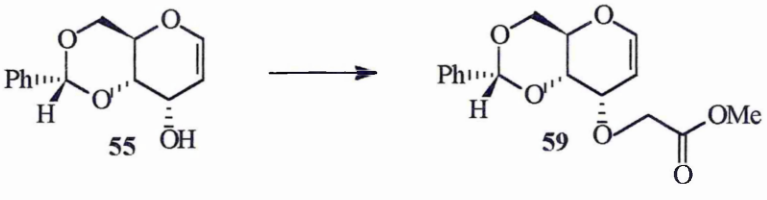
^{13}C NMR (62.5 MHz) 146.6 (O-<u>C_1</u>=), 137.4, 129.7, 128.7, 126.6 (aromatic), 102.1 (O-C-O), 101.3 (O-C_1=<u>C_2</u>), 78.4, 68.9. 64.3, 60.5

Exact mass calculated for $C_{13}H_{14}O_4$: 234.0899. Found: 234.0892.

General procedure for the alkylation of 4,6-O-benzylidene-D-allal

Potassium hydride (35% in mineral oil) was weighed into a clean dry round bottomed flask, and washed several times with petrol to remove the mineral oil. Dry THF was added followed by 4,6-O-benzylidene-D-allal **55**. Effervesence occurred and the mixture was left stirring for 0.5 hrs, then the alkylating agent was added. Stirring was continued (approx. 72 hrs) and the reaction was monitored by TLC. The reaction mixture was then poured into water and extracted with ethyl acetate (3x25ml). The combined organic phases were dried ($MgSO_4$), filtered and evaporated.

4,6-O-Benzylidene-1,2-didehydro-1,2-dideoxy-3-O-(methoxycarbonylmethyl)-D-ribo-hexopyranose **59**



The following quantities of reagents were used: potassium hydride (35% in mineral oil, 0.69g, 17.00mmol), dry THF (25ml), 4,6-O-benzylidene-D-allal **55** (1.5g, 6.41mmol), methyl bromoacetate (1.96g, 12.80mmol). The TLC solvent was ethyl

acetate: petrol 3:7 and flash chromatography (ethyl acetate: petrol 4:6) yielded the product as an off white solid 1.34g, 68%.

Melting point 82-84°C

$[a]_D^{22}$+123.71° (c = 0.98, EtOH)

IR (KBr) 3090-3000 (Csp^2-H), 2995-2880 (Csp^3-H) 1760 (C=O) 1630 (C=C, aliphatic) 780, 710 (Csp^2-H)

^{1}H NMR (250 MHz) 3.7 (3H, s, OCH_3), 3.75(1H, m), 3.8 (1H, t, J = 10), 3.9 (1H, dd, J = 10.5, 3.5), 4.0(1H, dd, J = 5.5, 3.5), 4.26 (1H, m), 4.37 (1H, d, J =7.5). 4.44 (1H, dd, J = 10.5, 5.5), 5.1 (1H, t, J = 6, CH=C), 5.6 (1H, s, C<u>H</u>-Ar), 6.5 (1H, d, J = 6, O-CH=C), 7.4-7.6 (5H, m, C_6H_5)

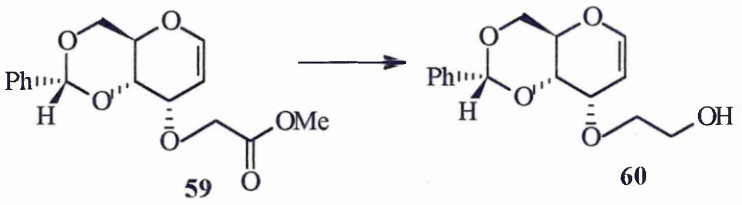
^{13}C NMR (62.5 MHz) 171.7 (C=O), 146.5 (O-<u>C_1</u>=), 137.2, 129.5, 128.7, 126.4 (aromatic), 102.2 (O-C-O), 100.0 (O-C_1=<u>C_2</u>), 79.7, 69.0, 68.8, 64.5, 52.8, 52.0

Mass Spec, 306 (M^+), 275, 215, 185, 157, 105, (base peak), 77, 39.

Exact mass calculated for $C_{16}H_{18}O_6$:306.1104 Found:306.1116

Micro analysis calculated for $C_{16}H_{18}O_6$: C, 62.75; H, 5.9. Found C, 63.2; H, 6.1.

4,6-O-Benzylidene-1,2-didehydro-1,2-dideoxy-3-O-(2-hydroxyethyll)-D-ribo-hexopyranose **60**[35]



The ester **59** (2.00g, 6.54mmol) was placed into a round bottomed flask to which dry ether (25ml) was added. Lithium aluminium hydride (0.25g, 6.54mmol) was added to this mixture, which was then stirred at room temperature and monitored by TLC (DCM). The reaction time was approximately 24 hrs. The reaction mixture was added to an aqueous solution of Rochelle salt (sodium potassium tartrate), stirred and left for 0.5 hrs and then extracted with ethyl acetate (3x25ml), dried ($MgSO_4$), filtered and evaporated. Yield was 1.61g, 88.5%.

Melting point 88-91°C

$[a]_D^{22}$+179.57° (c = 0.54, EtOH)

IR (KBr) 3600-3300 (OH) 3080-3020 (Csp^2-H), 2995-2880 (Csp^3-H) 1630 (C=C,Aliphatic) 770, 710 (Csp^2-H)

^{1}H NMR (250 MHz) 2.2-2.5 (1H, bs, OH), 3.7-4.5 (9H, m), 3.8 (3H, m), 3.6 (2H, m), 4.0 (2H, m), 4.24 (1H, dd, J = 10, 5.25), 4.46(1H, dd, J = 10.5, 5.5), 5.1 (1H, t, J = 6, CH=C), 5.6 (1H, s, CH-Ar), 6.5 (1H, d, J = 6, O-CH=C), 7.4-7.6 (5H, m, C_6H_5)

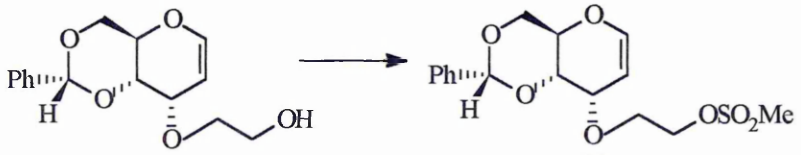
^{13}C NMR (62.5 MHz) 147.4 (O-C_1=), 137.8, 129.9, 127.8, 125.2 (aromatic), 103.6 (O-C-O), 101.6 (O-C_1=C_2), 80.4, 71.4, 69.1, 66.7, 64.5, 6.23 (aliphatic)

Mass Spec, 278 (M^+), 248, 217, 162, 157, 105, (base peak), 45, 39.

Exact mass calculated for $C_{15}H_{18}O_5$:278.1154. Found:278.1139.

Micro analysis calculated for $C_{15}H_{18}O_5$: C, 64.75; H, 6.5. Found: C, 64.8: H, 6.4.

4,6-O-Benzylidene-1,2-didehydro-1,2-dideoxy-3-O-(2-methanesulphonyloxyethyl)-D-ribo-hexopyranose **61**[36]



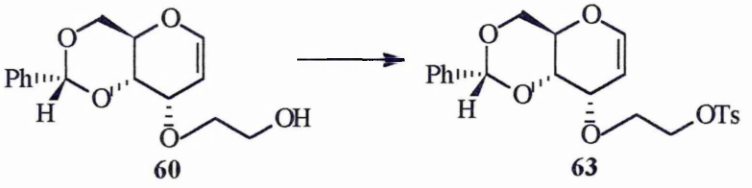
60 **61**

To a stirred mixture of the alcohol **60** (0.30g, 1.08mmol) in DCM (10ml) at 0°C were added methane sulphonyl chloride (0.15g, 1.29mmol) and triethylamine (0.20g, 1.94mmol). The mixture was stirred and monitored by TLC (ethyl acetate:petrol, 4:6). Once the reaction was complete, it was poured into water and extracted with DCM (3x15ml). The combined organic extracts were washed once with saturated aqueous sodium bicarbonate, dried ($MgSO_4$), filtered and evaporated to produce an oil. This was purified by column chromatography (ethyl acetate : petrol, 1:1) to give a yield of 0.03g, 8.0%.

IR (Thin film) 3080-3010 (Csp^2-H), 2960-2880 (Csp^3-H) 1640 (C=C, aliphatic) 770, 710 (Csp^2-H)

^{1}H NMR (60 MHz) 3.0 (3H, s, CH_3), 3.9-4.9 (9H, m), 5.1 (1H, t, J = 6, CH=C), 5.8 (1H, s, C<u>H</u>-Ar), 6.5 (1H, d, J = 6, O-CH=C), 7.3-7.9 (5H, m, C_6H_5)

<u>4,6-O-Benzylidene-1,2-didehydro-1,2-dideoxy-3-O-(2-O-toluene-p-sulphonyloxy-ethyl)-D-ribo-hexopyranose **63**[36]</u>



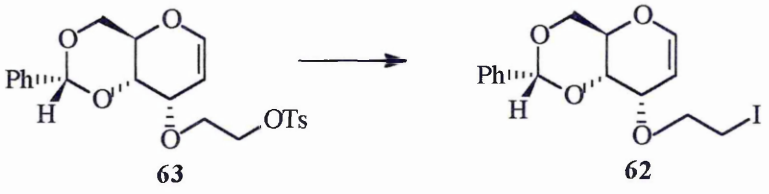
60 **63**

The alcohol **60** (0.25g, 0.89mmol) was added to a stirred solution of dry DCM (10ml), pyridine (0.28g,3.6mmol), and p-toluene sulphonyl chloride (1.17mmol). The mixture was stirred at room temperature and followed by TLC (DCM). [After 2 weeks the reaction still wasn't complete]. The reaction mixture was poured into water and extracted with ether (3x15ml). The combined organic extracts were washed with water (6x25ml), dried ($MgSO_4$), filtered and evaporated. The crude yield was 0.13g, 52%.

^{1}H NMR (60 MHz) 1.3 (3H, s, CH_3), 3.9-4.9 (9H, m), 5.1 (1H, t, J = 6, CH=C), 5.7 (1H, s, C<u>H</u>-Ar), 6.6 (1H, d, J = 6, O-CH=C), 7.5-8.0 (9H, m, C_6H_5, C_6H_4)

4,6-O-Benzylidene-1,2-didehydro-1,2-dideoxy-3-O-(2-iodoethyl)-D-ribo-hexopyranose **62**

Method 1[36]

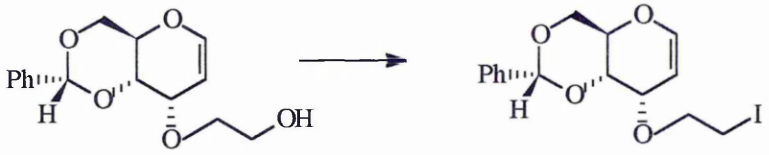


63 **62**

Sodium iodide (0.15g, 0.97mmol) was added to a solution of the tosylate **63** (0.33mmol) in dry acetone. The mixture was stirred overnight at room temperature [TLC (ethyl acetate:petrol, 3:7)]. The acetone was removed under reduced pressure and the residue partitioned between ether and water. The aqueous layer was extracted with ether and the combined organic extracts were washed with water and saturated aqueous sodium chloride, dried, ($MgSO_4$), filtered and evaporated. The product was purified by column chromatography (ethyl acetate:petrol, 2:8) which yielded 0.03g, 27%.

^{1}H NMR (60 MHz) 3.3 (2H, m, CH_2-I), 3.6-4.6 (7H, m), 5.1 (1H, t, J = 6, CH=C), 5.7 (1H, s, CH-Ar), 6.6 (1H, d, J = 6, O-CH=C), 7.5 (5H, m, C_6H_5)

Method 2[37]

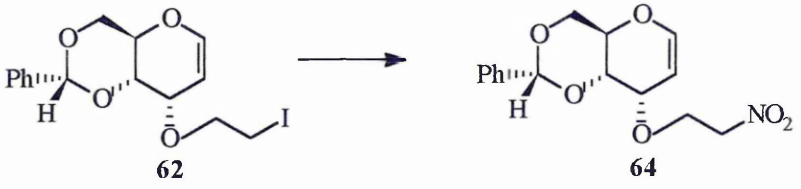


60 **62**

Triphenylphosphine (0.3g, 1.14mmol) and a solution of imidazole (0.09g, 1.28mmol) in acetonitrile (1ml) were added to a stirred solution of the alcohol **60** (0.15g, 0.54mmol) in dry ether (1.5ml). The solution was stirred under nitrogen at 0°C for 0.5hrs and then diluted with pentane (15ml). The extracts were washed successively with saturated aqueous sodium thiosulphate (5ml) and saturated aqueous cupric sulphate (5ml). Evaporation of the dried ($MgSO_4$) and filtered extracts left the crude iodo compound which was purified by column chromatography (ethyl acetate:petrol, 2:8). The yield was 0.04g, 20%.

^{1}H NMR (250 MHz) 3.2 (2H, m, CH_2-I), 3.85 (2H, m), 3.9 (1H, m), 4.05 (1H, t, J = 3), 4.1 (1H, m), 4.3 (1H, m), 4.5 (1H, dd, J = 6.3, 9.4), 5.0 (1H, t, J = 6, CH=C), 5.6 (1H, s, CH-Ar), 6.5 (1H, d, J = 6, O-CH=C), 7.5 (5H, m, C_6H_5)

4,6-O-Benzylidene-1,2-didehydro-1,2-dideoxy-3-O-(2-nitroethyl)-D-ribo-hexopyranose **64**[36b]



62 **64**

The iodide **62** (0.02g, 0.06mmol) in dry ether (1ml) was added dropwise to a stirred suspension of silver nitrite (0.02g, 0.13mmol) in dry ether (3ml) at 0°C in a flask which was protected from the light. After stirring at 0°C for 16hrs and room temperature for 48hrs, more silver nitrite (0.01g, 0.06mmol) was added. Stirring was continued for a further 72hrs at room temperature. The reaction was monitored by TLC (ethyl acetate:petrol 1:9) and, if needed, more silver nitrite (0.01g, 0.06mmol) was added every 72hrs. Filtering of the reaction mixture and evaporation of the filtrate gave the crude product 30mg, 200%.

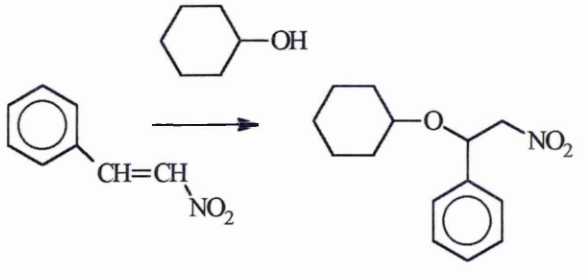
^{1}H NMR (60 MHz) [crude product] 3.7-4.9 (9H, m), 5.0 (1H, t, J = 6, CH=C), 5.7 (1H, s, C<u>H</u>-Ar), 6.5 (1H, d, J = 6, O-CH=C), 7.5 (5H, m, C_6H_5)

On attempts to purify the compound decomposition occurred.

General method of alkylation of alcohols with β-nitrostyrene[38,39]

Oil-covered potassium hydride (0.034g, 0.86mmol) was placed in a flask and washed with petroleum spirit three times. After the remaining petroleum spirit was removed by evaporation, dry THF (5ml) was added, followed by the dropwise addition of the appropriate alcohol (0.86mmol) in dry THF (3ml). The resulting mixture was stirred at room temperature for 1hr, cooled to -40°C and treated with a THF solution of β-nitrostyrene (0.064g, 0.43mmol) at the rate of 0.1ml/min. When addition was complete, the reaction was warmed to 0°C and quenched by the addition of hydrochloric acid (1M solution) until pH 6.5-7.0 was reached. The organic and aqueous layers were separated and the aqueous layer was extracted with ether (x3). The combined organic layers were then washed with 5% $NaHCO_3$, water and brine, dried (Na_2SO_4), filtered and evaporated.

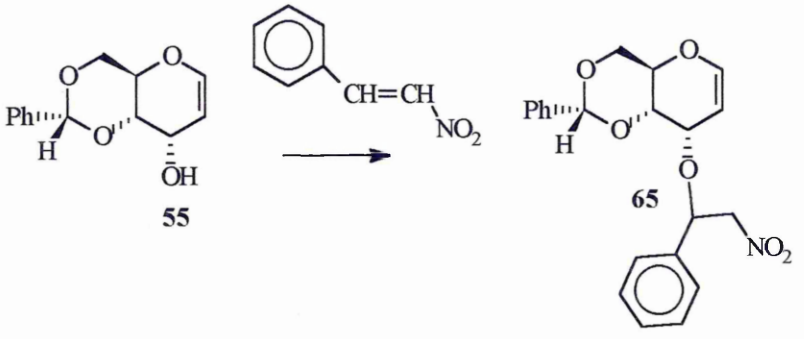
2-Nitro-1-phenylethoxy-cyclohexane



Yield was 0.1g, 15.9%

^{1}H NMR (60 MHz) 1.1-2.1 (11H, m, C_6H_{11}), 3.9 (2H, d, J = 11, CH_2-NO_2), 5.1 (1H, m, CH-O), 7.3-8.0 (5H, m, C_6H_5)

4,6-O-Benzylidene-1,2-didehydro-1,2-dideoxy-3-O-(2-nitro-1-phenylethyl)-D-ribo-hexopyranose **65**



The product was obtained by flash chromatography (ethyl acetate:petrol, 4:6).

The yield was 0.01g, 6%.

IR (Thin film) 3080-3040 (Csp^2-H), 2995-2870 (Csp^3-H), 1635 (C=C, aliphatic), 1555, 1380 (N=O)

^{1}H NMR (60 MHz) 3.8-5.5 (9H, m) 5.8 (1H, m), 6.7 (1H, m), 7.1-7.9 (10H, m, C_6H_5x2)

Mass Spec, 384 (M^+), 337, 319, 256, 233, 217, 149, 127, 105, (base peak)

2-Methylpropanal oxime[46]

A three necked round bottomed flask, which was fitted with a reflux condenser, a thermometer and a separatory funnel, was charged with hydroxylamine hydrochloride (87.00g, 1.25mol), cold water (150mls) and isobutyraldehyde (72.11g 1.00mol). Stirring was started and a solution of anhydrous sodium carbonate (66.25g, 0.63mol) in water (125mls) was addded at such a rate that the temperature of the reaction mixture did not rise above 45°C. Stirring was continued at room temperature for an hour after the addition of the sodium carbonate solution was complete. The oily layer on top of the reaction mixture was separated and washed with two portions of water. The washed product was transferred to a Claisen flask and distilled to yield 51.64g, 59% of oxime with a boiling point of 140°C/760mm.

IR (Thin film) 3500-3200 (OH, alcohol) 2980-2880 (Csp^3-H) 1650 (C=N)

^1H NMR (60 MHz) [two isomers present in ratio of 3:1] 1.1 (3Hx4, d, J = 6.5, CH_3x4, both isomers), 2.5 (1H, m, CH, isomer 1), 3.2 (1H, m, CH, isomers 2), 6.6 (1H, d, J = 6.5, CH=N, isomer 1), 7.5 (1H, d, J = 6.5, CH=N, isomer 2), 9.4 (1Hx2, s, NOHx2, both isomers)

Propanal oxime[46]

A round bottomed flask, [which was fitted with a reflux condenser] was charged with hydroxylamine hydrochloride (40g, 0.58mol), cold water (100mls) and propanal (72.11g 1.00mol) and sodium acetate (80g, 1.00mol) The flask was heated and stirred in a water bath and the reaction was monitored by NMR. Once reaction was complete, the mixture was extracted with dichloromethane as the oxime was soluble in aqueous solution. The combined organic extracts were then washed with a saturated solution of sodium bicarbonate to remove any contaminating acetic acid. This sodium bicarbonate wash was then re-extracted with dichloromethane to retrieve any dissolved oxime. The product was transferred to a Claisen flask and distilled to yield 13.74g, 54% of oxime with a boiling point of 134°C/760mm.

IR (Thin film) 3500-3200 (OH, alcohol) 2980-2880 (Csp^3-H) 1650 (C=N)

^1H NMR (60 MHz) [two isomers present in ratio of 1.5:1] 1.1 (3Hx2, t, J = 7, CH_3x2, both isomers), 2.0-2.8 (2Hx2, m, CH_2x2, both isomers), 7.0 (1H, t, J = 6, CH=N, isomer 1), 7.8 (1H, t, J = 6, CH=N, isomer 2) 9.6 (1Hx2, s, NOHx2, both isomers)

O-Trimethylsilyl 2-bromo aldoxime **66**[16c]

66

To a solution of the aldoxime (0.05mol) and triethylamine (5.06g, 0.05mol) in dry carbon tetrachloride (100ml) at 0-5°C under nitrogen was added dropwise trimethyl silyl chloride (5.43g, 0.05mol) in dry carbon tetrachloride (20ml). The mixture was slowly brought to room temperature and was stirred overnight at room temperature. The solution was filtered and the triethylamine hydochloride salt was washed with carbon tetrachloride. To the combined filtrate was added freshly crystallised and dried N-bromosuccinimide (8.9g, 0.05mol) and benzoyl peroxide (0.61g, 2.5mmol). The stirred suspension was heated at reflux for 3.5hrs or irradiated for 2hrs using two 100W lamps under an inert (nitrogen) atmosphere. The solution was filtered and the filtrate was washed with a 10% sodium thiosulphate solution and twice with water and dried over sodium sulphate. Removal of the solvent under reduced pressure gave the product as an oil.

O-Trimethylsilyl-2-bromo-2-methyl propanal oxime yielded 4.21g, 53%.

IR(Thin film) 3500-3200 (OH due to some unreacted oxime) 2990-2880 (Csp^3-H) 1255, 850, 750 ($SiCH_3$)

^1H NMR (60 MHz) 0.1 (9H, s, $SiCH_3x3$), 2.0 (6H, s, CH_3x2), 8.0 (1H, s, CH=N)

O-Trimethylsilyl-2-bromo-propanal oxime yielded 3.89g, 40%.

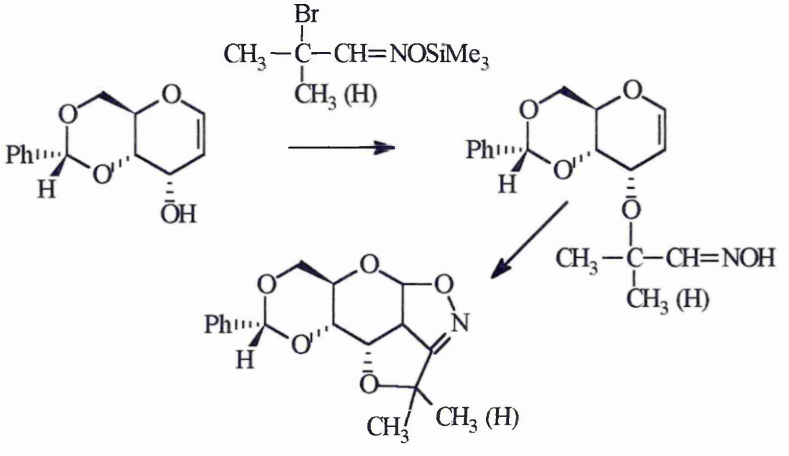
IR(Thin film) 3500-3200 (OH due to some unreacted oxime) 2990-2890 (Csp^3-H) 1250, 840, 750 ($SiCH_3$)

^1H NMR (60 MHz) [two isomers present in ratio of 3:1] 0.1 (9H, s, $SiCH_3x3$), 1.8 (6H, s, CH_3x2), 1.9 (6H, s, CH_3x2), 4.7 (1H, m, CH-Br), 5.1(1H, m, CH-Br), 7.8 (1H, m, CH=N), 8.1 (1H, m, CH=N),

The reaction was also stopped before the addition of NBS to characterise the silylated oxime.

^1H NMR (60 MHz) 0.1 (9H, s, $SiCH_3x3$), 1.1 (6H, m, CH_3x2), 3.6 (1H, m, CH), 7.8 (1H, d, J = 6, CH=N)

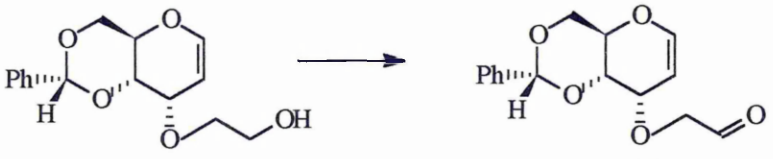
Attempted cyclisation of 4,6-O-benzylidene-D-allal alkylated with O-trimethylsilyl-2-bromo aldoxime[16b]



4,6-O-Benzylidene-D-allal **55** (0.49g, 2.1mmol) was dissolved in dry THF (10ml). To this mixture was added O-trimethylsilyl 2-bromo aldoxime **66** (2.1mmol) followed by a

1M solution of tetrabutylammonium fluoride in THF (2.1ml, 2.1mmol). The reaction mixture was stirred at room temperature and monitored by TLC (ethyl acetate:petrol, 2:8). This mixture was then cooled to 0°C where aqueous sodium hypochlorite solution (2.31mmol) was added dropwise with vigorous stirring. The mixture was stirred at room temperature and monitored by TLC (ethyl acetate:petrol 1:9). After 36 hrs the reaction was worked up by concentration of the organic layer under reduced pressure, and the aqueous residue was extracted with DCM. The combined organic extracts were washed with water (twice) and a saturated sodium chloride solution, dried ($MgSO_4$), filtered and evaporated. NMR analysis of the crude product did not indicate the presence of any of the cyclised product, so the reaction was abandoned.

4,6-O-Benzylidene-1,2-didehydro-1,2-dideoxy-3-O-(formylmethyl)-D-ribo-hexopyranose **67**



60 **67**

Method 1 PCC Oxidation[42]

To a stirred slurry of pyridinium chlorochromate (1.74g, 8.1mmol) sodium acetate (0.066g, 0.8mmol) and powdered 4A molecular sieves (0.75g) in dry DCM (40ml) under nitrogen, at room temperature, was added slowly a solution of the alcohol **60** (0.90g, 3.23mmol) in dry DCM (8ml). After being stirred for 2.5hrs at room

temperature the reaction mixture was filtered on silica gel with elution by ether. Evaporation yielded a residue, 0.36g, 40.44%.

The aldehyde **67** was not confirmed by spectral data.

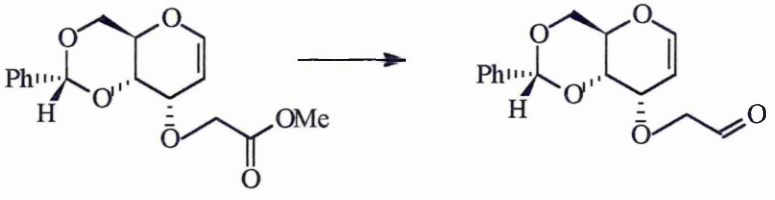
Method 2 Swern oxidation[43]

A solution of oxalyl chloride (0.132g, 1.04mmol) in dry DCM (6ml) was cooled to approximately -60°C. Dimethyl sulphoxide (0.169g, 2.16mmol) was added dropwise at a rapid rate with stirring. After 5 minutes, the alcohol **60** (0.25g, 0.8mmol) was added dropwise over 10 minutes, keeping the temperature at -60°C. After stirring for 15 minutes, triethylamine (0.63ml) was added dropwise, keeping the temperature below -50°C. Stirring was continued for 5 minutes. The mixture was allowed to warm to room temperature and water (3.5ml) was added. The aqueous layer was separated and extracted twice with DCM (5ml). The organic phases were washed twice with saturated sodium chloride solution (5ml), dried ($MgSO_4$), filtered and evaporated to give the crude product containing aldehyde/hydrate. Crude yield was 0.19g.

IR (Thin film) 3700-3300 (OH, due to hydrate), 3090-3040 (Csp^2-H), 2990-2880 (Csp^3-H), 2720 (CH, aldehyde), 1740, 1700 (C=O, due to the product and oxalyl chloride), 1630 (C=C, aliphatic).

^{1}H NMR (60 MHz) 3.5-4.9 (5H, m) 4.5 (2H, s, CH_2-C=O) 5.1 (1H, t, J = 6, CH=) 5.7 (1H, s, CH-Ar) 6.6 (1H, d, J = 6, O-CH=), 7.5 (5H, s, C_6H_5), 9.95 (0.75H, s, HC=O), [there was a reduced integration for the aldehydic proton due to the hydrate].

Method 3 Dibal reduction[45]

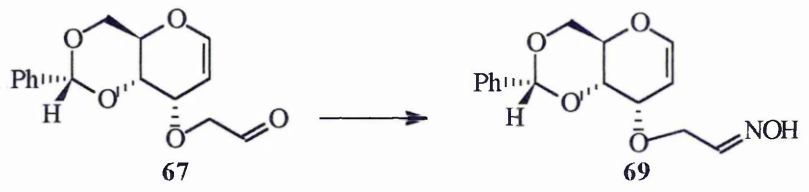


Diisobutylaluminium hydride (1.5M solution in toluene, 7.63ml, 0.011mol) was added over 0.5hrs to a solution of ester **59** (1g, 3,27mmol) in dry ether (25ml) at -78°C. The mixture was stirred for 1hr at -78°C and then quenched with water (10ml). The reaction mixture was allowed to warm to room temperature, and was then poured into an aqueous potassium sodium tartrate solution. This was stirred vigorously and left to stand for approximately 0.5hrs. The mixture was extracted with ethyl acetate (3x25ml), dried ($MgSO_4$), filtered and evaporated to yield a viscous residue of aldehyde and hydrate, 0.87g, 97%.

IR (Thin film) 3600-3300 (OH, due to hydrate), 3080-3040 (Csp^2-H), 2980-2880 (Csp^3-H), 1710 (C=O), 1630 (C=C, aliphatic).

^{1}H NMR (250 MHz) 3.5-4.5 (5H, m) 4.1 (2H, s, CH_2-C=O) 5.0 (1H, t, J = 6, CH=) 5.6 (1H, s, CH-Ar) 6.5 (1H, d, J = 6, O-CH=), 7.4 (5H, m, C_6H_5), 9.7 (0.5H, s, HC=O), [there was a reduced integration for the aldehydic proton due to the hydrate].

4,6-O-Benzylidene-1,2-didehydro-1,2-dideoxy-3-O-(formylmethyl)-D-ribo-hexopyranose oxime **69**[46]



67 **69**

A mixture of aldehyde **67** (0.87g, 3.15mmol), hydroxylamine hydochloride (0.87g, 13mmol), ethanol (8.7ml) and triethylamine (0.87ml, 0.63g, 6.2mmol) was refluxed for 1hr. The reaction was monitored by TLC (ethyl acetate:petrol, 4:6) to ensure completion. The mixture was left to cool and on the addition of water (10ml) the oxime crystallised out of solution. The solid was filtered, washed with water and dried to give a yield of 0.67g, 73%.

Melting point 173°C

IR (KBr) 3600-3200 (OH), 3080-3020 (Csp^2-H), 2990-2880 (Csp^3-H), 1630 (C=C, aliphatic).

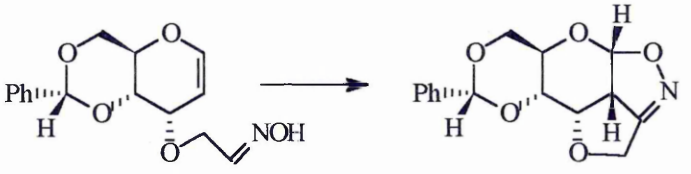
^{1}H NMR (250 MHz) 3.8 (1H, t, J =9), 4.0 (2H, m), 4.3 (2H, m), 4.4 (2H, m) 5.0 (1H, dd, J = 7, 11, C-CH=) 5.6 (1H, s, CH-Ar) 6.5 (1H, m, O-CH=), 7.2-7.5 (6H, m, C_6H_5, C=NOH).

^{13}C NMR (62.5 MHz) 149.7 (C=NOH), 146.1 (O-$\underline{C}_1$=), 137.5, 129.5, 128.7, 126.6 (Aromatic), 102.3 (O-C-O), 99.9/99.8 (O-C_1=$\underline{C}_2$), 79.4/79.2, 69.7, 69.0/68.9, 68.0/67.9, 64.7, (Aliphatic)

Mass Spec, 291 (M^+), 233, 171, 143, 105, (base peak) 81, 55

Exact mass calculated for $C_{15}H_{17}O_5N$: 291.1107. Found 291.1102

Δ^2-Isoxazoline **71**[47]



69 **71**

N-Chlorosuccinimide (0.28g, 2.13mmol) was stirred in a flask containing dry DCM (5ml) and pyridine (0.25ml). The oxime **69** (0.62g, 2.13mmol) was added at room temperature in one portion and the solution was stirred overnight [TLC (ethyl acetate:petrol, 1:1)]. For larger batches it was advisable to cool the solution with water and add the oxime in portions. The mixture was washed with water (3x10ml), dried ($MgSO_4$), filtered and evaporated. The yield was 0.5g, 81%.

Melting point 149°C

$[a]_D^{22}$ +81.4° (c = 0.2174, EtOH)

IR (KBr) 3080-3020 (Csp^2-H), 2990-2880 (Csp^3-H),1670 (C=N)

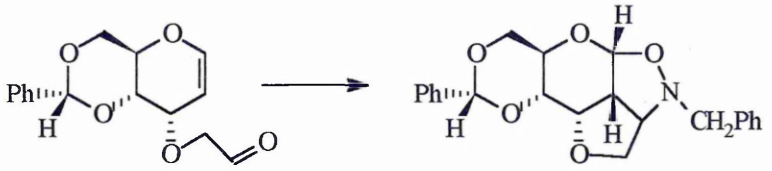
^{1}H NMR (250 MHz) 3.55 (1H, t, J = 10), 5.65 (1H, dd, J =4.4, 9.5,), 3.95 (1H, m), 4.3 (1H, t, J = 8) 4.4 (2H, m), 4.65 (2H, m), 5.6 (1H, s, CH-Ar) 5.7 (1H, d, J = 7.5, O-CH-O), 7.2-7.5 (5H, m, C_6H_5).

^{13}C NMR (62.5 MHz) 163.7 (C=N-O), 137.1, 129.5, 128.6, 126.5 (Aromatic), 102.4, 99.7 (O-C-O), 77.8, 69.2, 67.4, 61.8, 60.9, 53.2 (Aliphatic)

Mass Spec, 289 (M^+), 268, 233, 183, 140, 105, 79, (base peak) 53, 36.

Exact mass calculated for $C_{15}H_{15}O_5N$: 289.0950. Found: 289.0942.

Isoxazolidine **74**[45]



Aldehyde **67** (1.8g, 6.52mmol) in dry ether (15ml) was added dropwise to a cooled mixture of benzylhydroxylamine (0.96g, 7.83mmol) and calcium chloride (0.36g, 3.26mmol) in dry ether (30ml). The reaction was stirred at 0°C for 1-2hrs and then placed in the refrigerator for 48hrs. The crystals formed were filtered and recrystallised from DCM/ether. The yield was 1.87g, 75.4%.

Melting point 147°C

IR (KBr) 3070-3030 (Csp^2-H), 2990-2860 (Csp^3-H),1200-1010 (C-O)

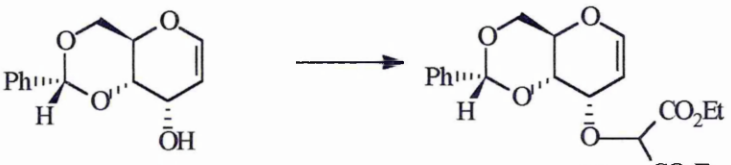
^{1}H NMR (250 MHz) 3.4 (1H, dd, J = 14.6, 7.3), 3.6-3.7 (3H, m), 3.8 (1H, dd, J = 9.5, 3.3), 3.95 (1H, d, J = 13.2), 4.1 (1H, d, J = 13.2), 4.2 (1H, dd, J = 7.5, 3.3), 4.4 (1H, dd, J = 10.4, 5.6), 4.6 (1H, dt, J = 9.8, 5.5), 5.5 (1H, d, J = 6.9, O-CH-O) 5.6 (1H, s, CH-Ar), 7.3-7.6 (10H, m, C_6H_5x2).

^{13}C NMR (62.5 MHz) 137.6, 136.5, 129.3, 129.1, 128.8, 128.7, 128.0, 126.7 (aromatic), 102.7 (O-C-O), 97.5 (O-C(Ar)-O), 77.9, 74.1, 72.8, 72.6, 69.8, 62.3, 59.8, 50.7 (aliphatic)

Mass Spec, 381 (M^+), 354, 275, 232, 216, 160, 91 (base peak), 69, 45.

Exact mass calculated for $C_{22}H_{23}O_5N$: 381.1576. Found 381.1594.

4,6-O-Benzylidene-1,2-didehydro-1,2-dideoxy-3-O-(diethoxycarbonylmethyl)-D-ribo-hexopyranose oxime **75**

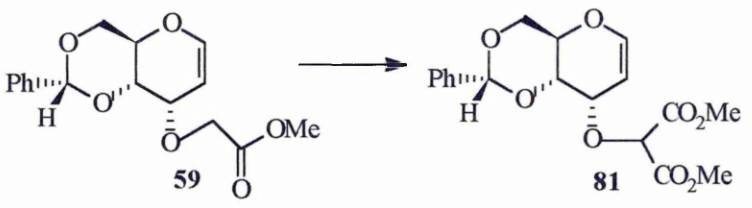


55 **75**

Sodium hydride (60% in mineral oil, 0.034g, 1.39mmol) was weighed into a clean dry round bottomed flask, and washed several times with petrol to remove the mineral oil. Dry THF (5-10ml) was added followed by 4,6-O-benzylidene-D-allal **55** (0.25g, 1.07mmol). Effervesence occurred and the mixture was left stirring for 0.5 hrs, then diethyl bromomalonate (0.56g, 2.35mmol) was added. Stirring was continued (approx. 4 hrs) and the reaction was monitored by TLC (ethyl acetate:petrol, 2:8). The reaction mixture was then poured into water and extracted with ethyl acetate (3x25ml). The combined organic phases were dried ($MgSO_4$), filtered and evaporated.

The reaction was unsuccessful and resulted in recovered starting material.

4,6-O-Benzylidene-1,2-didehydro-1,2-dideoxy-3-O-(dimethoxycarbonylmethyl)-D-ribo-hexopyranose oxime **81**[48]



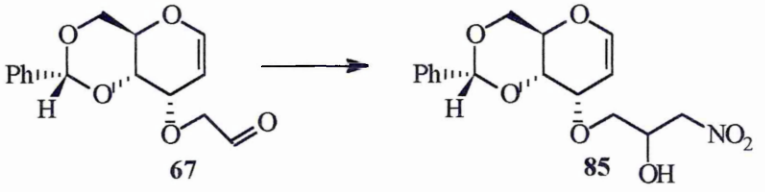
A round bottomed flask was equipped with a stirrer bar, a reflux condenser, and a pressure equalising dropping funnel bearing a nitrogen inlet. The flask was flushed with nitrogen and charged with dimethyl carbonate (0.074g, 0.82mmol), dry THF (5ml) and sodium hydride (0.025g, 1.02mmol). The suspension was stirred and heated to reflux temperature, at which time the slow, dropwise addition of the ester **59** (0.1g, 0.33mmol) in dry THF (2ml) was begun. After 2 minutes powdered potassium hydride (approx 2mg) was added to initiate the reaction. The addition of the ester was continued over 1hr. The mixture was stirred and heated at reflux for another 0.5hrs, monitored by TLC (ethyl acetate:petrol, 4:6), cooled in an ice bath for 20 minutes and hydrolysed by slowly adding acetic acid. The contents of the flask were then poured into aqueous sodium chloride and this mixture was then extracted with chloroform (4x10ml). The combined organic extracts were dried ($NaSO_4$), filtered and evaporated.

Starting material was recovered.

Conversion of aldehyde to nitroalcohol

4,6-O-Benzylidene-1,2-didehydro-1,2-dideoxy-3-O-(2-hydroxy-3-nitropropyl)-D-ribo-hexopyranose oxime **85**

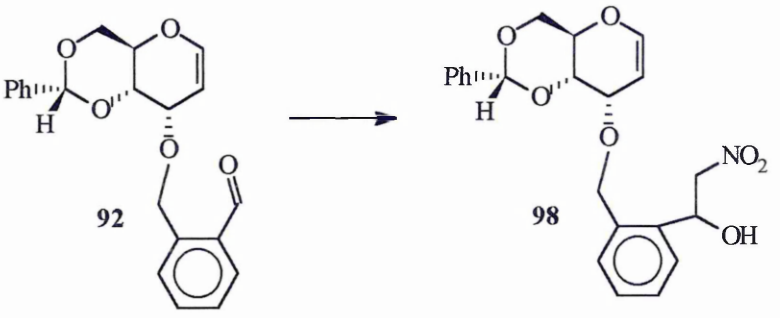
Method 1a[50]



To a solution of aldehyde **67** (0.2g, 0.73mmol) in methanol (5ml) was added anhydrous potassium fluoride (0.0023g, 0.04mmol) and nitromethane (0.097g, 1.6mmol). This mixture was stirred overnight and then monitored by TLC (ethyl acetate:petrol, 2:8). After several days stirring starting material still remained, (TLC). [Molecular sieve powder was added to a repeat reaction in case any water was present and this was impairing the reaction. This repeat reaction also resulted in unreacted starting material.]

4,6-O-Benzylidene-1,2-didehydro-1,2-dideoxy-3-O-(2-(1-hydroxy-2-nitroethylphenylmethyl)-D-ribo-hexopyranose **98**

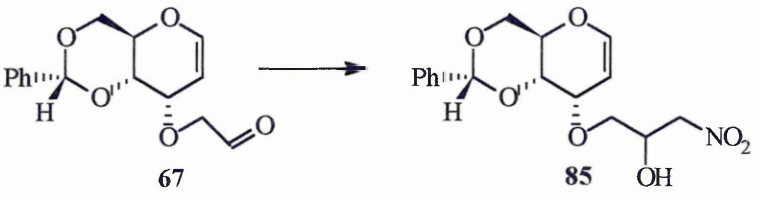
Method 1b



The procedure was as in method 1a above but the solvent was changed. Initially the reaction was carried out in methanol as before, then a mixture of methanol and isopropanol was tried followed finally by isopropanol alone. Each reaction mixture was monitored by TLC (ethyl acetate:petrol, 2:8). There was no reaction with methanol as the solvent; under the other conditions the mixture yielded several new compounds which could not be isolated, as well as a large amount of remaining starting material. By using isopropanol alone a very complex mixture containing remaining starting material was obtained and due to the very bad separation each compound could not be isolated.

4,6-O-Benzylidene-1,2-didehydro-1,2-dideoxy-3-O-(2-hydroxy-3-nitropropyl)-D-ribo-hexopyranose oxime **85**

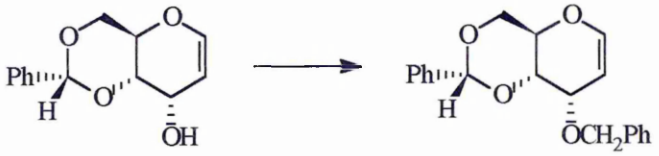
Method 2[51]



A small round bottomed flask equipped with a stirrer bar was charged with nitromethane (0.17g, 0.62mmol) and cooled with an ice-water bath. The aldehyde **67** (0.038g, 0.62mmol) was added and the mixture stirred for 2-3 minutes. Chromatographic alumina (activity I according to Brockmann, 0.15g) was added and stirring was continued for 1hr at room temperature. After standing for 24hrs, the alumina was filtered off and washed with DCM (3x5ml). The filtrate was evaporated at reduced pressure to give a crude yield of 0.18g.

The TLC and ^{1}H NMR showed a complex mixture and it was not pursued any further.

4,6-O-Benzylidene-1,2-didehydro-1,2-dideoxy-3-O-(benzyl)-D-ribo-hexopyranose



Method followed was the general procedure for alkylation of 4,6-O-benzylidene-D-allal.(p150)

The following quantities of reagents were used: potassium hydride (35% in mineral oil, 0.05g, 1.28mmol), dry THF (5ml), 4,6-O-benzylidene-D-allal **55** (0.25g, 1.07mmol), benzyl chloride (0.20g, 1.60mmol). The TLC solvent was DCM and flash chromatography (ethyl acetate: petrol 1:9) afforded the product as an off-white solid 0.28g, 80%.

Melting point 97-98°C

$[a]_D^{22}$+171.43° (c = 0.26, EtOH)

IR (KBr) 3090-3010 (Csp^2-H), 2995-2810 (Csp^3-H) 1630 (C=C,Aliphatic)

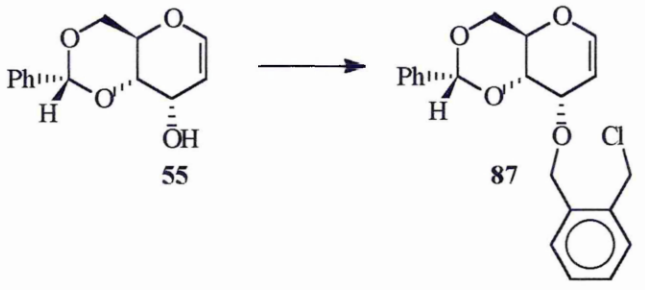
^{1}H NMR (250 MHz) 3.9 (1H, t, J = 10), 4.0 (1H, dd, J = 10, 3.5), 4.1 (1H, dd, J = 6, 3.5), 4.4 (1H, dd, J = 10, 5.5), 4.5 (1H, dd, 10, 5.5), 4.75 (1H, d, J = 12), 5.0 (2H, dd, J = 12, 6), 5.65 (1H, s, C<u>H</u>-Ar) 6.47 (1H, d, J = 6, O-CH=C), 7.3-7.6 (10H, m, C_6H_5x2)

^{13}C NMR (62.5MHz) 146.0 (O-C_1=), 139.3, 137.9, 129.5, 128.7, 128.1, 127.8, 126.6 (aromatic), 102.3 (O-C-O), 100.6 (O-C_1=C_2), 79.8, 73.3, 69.2, 67.4, 64.8

Mass Spec, 324, 323(M^+-1), 281, 274, 218, 187, 127, 91 (base peak), 77, 39.

Micro analysis calculated for $C_{20}H_{20}O_4$:C, 74.1; H, 6.2. Found: C, 73.7; H, 6.5.

4,6-O-Benzylidene-1,2-didehydro-1,2-dideoxy-3-O-(2-chloromethylphenylmethyl)-D-ribo-hexopyranose **87**



The following quantities of reagents were used: potassium hydride (35% in mineral oil, 0.18g, 1.60mmol), dry THF (5ml), 4,6-O-benzylidene-D-allal **55** (0.25g, 1.07mmol), : α,α'-dichloro-o-xylene (0.37g, 2.35mmol). The TLC solvent was ethyl acetate: petrol, 1:9 and flash chromatography (ethyl acetate: petrol, 1:9, 1% triethylamine) afforded the product as a yellow solid 0.31g, 78%.

Melting point 94-95°C

$[a]_D^{22}$+0.55° (c = 0.18, EtOH)

IR (KBr) 3100-3000 (Csp^2-H), 2995-2800 (Csp^3-H) 1630 (C=C, aliphatic) 880, 760 (Csp^2-H)

^{1}H NMR (250 MHz) 3.8 (1H, t, 10), 4.0 (1H, dd, 10, 3.5), 4.1 (1H, dd, 6, 3.5), 4.35 (1H, dd, J = 10, 5.5), 4.6 (1H, dd, J = 10, 5.5), 4.7 (2H, s,CH_2-Cl), 4.8 (1H, d, J =

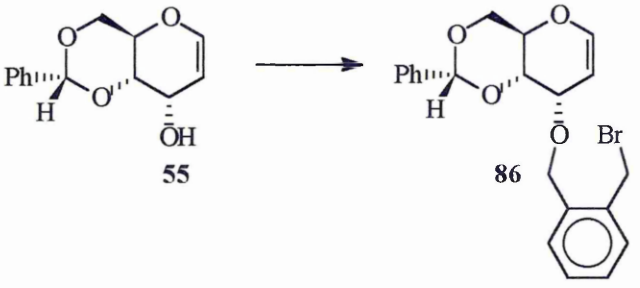
12), 5.0 (2H, dd, J = 12, 6), 5.6 (1H, s, CH-Ar)) 6.5 (1H, d, J = 6, O-CH=C), 7.3-7.6 (9H, m, C_6H_5, C_6H_4)

^{13}C NMR (62.5 MHz) 145.8 (O-C_1=), 137.7, 137.4, 136.5, 130.5, 130.0, 129.4, 129.0, 128.6, 126.6 (Aromatic), 101.9 (O-C-O), 99.8 (O-C_1=C_2), 79.2, 70.6, 68.7, 67.5, 64.5, 43.8

Mass Spec, 372/4 (M^+), 371, 337, 336, 218, 187, 139, 127, 91 (base peak), 77, 55, 39.

Exact mass calculated for $C_{21}H_{21}O_4Cl$: 372.1128. Found: 372.1126

4,6-O-Benzylidene-1,2-didehydro-1,2-dideoxy-3-O-(2-bromomethylphenylmethyl)-D-ribo-hexopyranose **86**



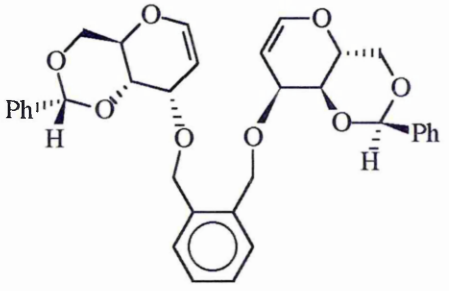
The following quantities of reagents were used: potassium hydride (35% in mineral oil, 0.18g, 1.60mmol), dry THF (5ml), 4,6-O-benzylidene-D-allal **55** (0.25g, 1.07mmol), : α,α'-dibromo-o-xylene (0.62g, 2.35mmol). The TLC solvent was ethyl acetate: petrol 2:8 and flash chromatography (ethyl acetate: petrol 1:9, 1% triethylamine) afforded the product as a light brown solid 0.29g, 64%.

Melting point 91-94°C

IR (KBr) 3100-3000 (Csp^2-H), 2995-2800 (Csp^3-H) 1630 (C=C, aliphatic) 880, 760 (Csp^2-H)

^{1}H NMR (250 MHz) 3.8 (1H, t, 10), 4.0 (1H, dd, 10, 3.5), 4.1 (1H, dd, 6, 3.5), 4.35 (1H, dd, J = 10, 5.5), 4.6 (1H, dd, J = 10, 5.5), 4.75 (2H, s, CH_2-Br), 4.85 (1H, d, J = 12), 5.0 (2H, dd, J = 12, 6), 5.8 (1H, s, C<u>H</u>-Ar)) 6.6 (1H, d, J = 6, O-CH=C), 7.4-7.6 (9H, m, C_6H_5, C_6H_4)

^{13}C NMR (62.5 MHz) 146.1 (O-<u>C_1</u>=), 137.5, 137.0, 136.5, 130.9, 130.3, 129.5, 129.3, 128.7, 126.6 (aromatic), 102.2 (O-C-O), 100.3 (O-C_1=<u>C_2</u>), 79.5, 70.0, 69.7, 67.9, 64.8, 31.7, (aliphatic)



91

Further elution in the flash chromatography gave a by-product **91** where two molecules of 4,6-O-benzylidene-D-allal **55** had attached to one molecule of α,α'-dibromo-o-xylene. Yield was 0.20g, 32%.

Melting point 140°C

$[a]_D^{22}$+237.03° (c = 0.10, EtOH)

IR (KBr) 3064-3034 (Csp^2-H), 2969-2858 (Csp^3-H) 1639 (C=C, aliphatic)

^{1}H NMR (250 MHz) 3.8 (6H, m), 4.3 (2H, m), 4.45 (2H, dd, J = 10.3, 5.3), 4.85 (6H, q, J = 12.4, t, J = 5.5), 5.7 (2H, s, CH-Arx2) 6.4 (2H, d, J = 6, O-CH=Cx2), 7.2-7.55 (14H, m, C_6H_5x2, C_6H_4)

^{13}C NMR (62.5 MHz) 147.3, 144.6 (O-C_1=), 137.9, 137.2, 129.8, 129.1, 127.8, 127.5, 126.1, 125.4 (aromatic), 103.6, 101.1 (O-C-O), 102.2, 98.8 (O-C_1=C_2), 80.6, 70.6, 68.3, 65.9, 63.5 (aliphatic)

Micro analysis calculated for $C_{34}H_{34}O_8$: C, 71.6; H, 6.0; Found: C, 72.3; H, 6.1.

Phenylnitromethane

Method 1[53]

Benzyl bromide (0.25g,1.46mmol) was poured into a stirred mixture of DMF (5ml), sodium nitrite (0.18g, 2.53mmol), and urea (0.20g, 3.25mmol) which was maintained at -20 to -15°C. After 5 hrs the reaction mixture was poured into a large quantity of iced water layered with ether. The aqueous phase was extracted with ether (4x25ml) and the combined organic extracts were washed with water (4x25ml), dried ($MgSO_4$), filtered and evaporated to yield 40% of crude product which was believed to be a mixture of nitrolic acid [$RC(NO_2)$=NOH] and benzoic acid.

Method 2

As for method 1 but reaction was carried out at -60°C throughout. After 7hrs the reaction yielded two isomers; Ph-CH_2-NO_2 and Ph-CH_2-ONO with benzoic acid present as an impurity as well remaining starting material.

IR (Thin film) 3700-2700 (b, OH, carboxylic acid), 3060-3010 (Csp^2-H), 2960-2860 (Csp^3-H) 1710 (C=O, carboxylic acid), 1550, 1380 (N=O, nitro) 700, 660 (Csp^2-H)

^{1}H NMR (60 MHz) [crude product, two isomers present] 5.6 (2H, s, CH_2), 5.9 (2H, s, CH_2), 7.5, 7.6 (5Hx2, sx2,C_6H_5x2)

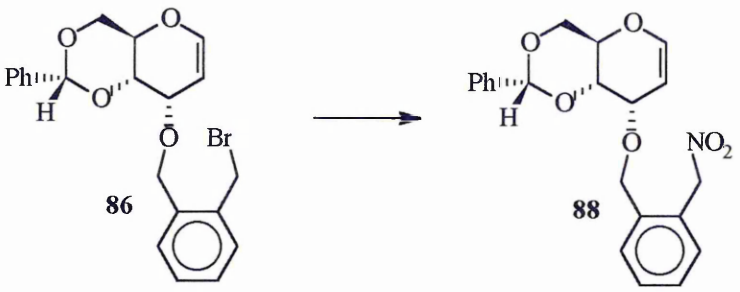
Method 3[54]

A slurry of silver nitrite (0.29g, 1.88mmol) and calcium hydride (0.0029g, 0.07mmol) in dry ether (10ml) was cooled to 0°C in a three necked flask. Benzyl bromide (0.25g, 1.46mmol) was added dropwise to the stirred mixture over a period of 1hr [TLC (ethyl acetate:petrol, 1:9)]. After stirring at 0°C in the dark for a total of 26hrs the reaction mixture was filtered, the silver salts were washed with ether and the washings were added to the original filtrate which was dried ($MgSO_4$), filtered and evaporated. The yield was 0.14g, 70%.

IR (Thin film) 3060-3010 (Csp^2-H), 2960-2860 (Csp^3-H) 1550, 1380 (N=O,nitro) 700, 660 (Csp^2-H)

^{1}H NMR (60 MHz) [two isomers present in ratio of 3:1] 5.6 (2H, s, CH_2), 5.8 (2H, s, CH_2), 7.5 (5H, s, C_6H_5), 7.6 (5H, s, C_6H_5)

4,6-O-Benzylidene-1,2-didehydro-1,2-dideoxy-3-O-(2-nitromethylphenylmethyl)-D-ribo-hexopyranose **88**



A slurry of silver nitrite (0.024g, 0.16mmol) and calcium hydride (0.0003g, 0.006mmol) in dry THF (5ml) was cooled to 0°C in a three necked flask. The bromo compound **86** (0.05g, 0.12mmol) in dry THF (1ml) was added dropwise to the stirred mixture over a period of 1hr. After stirring at room temperature in the dark for a total of 26hrs [TLC (ethyl acetate:petrol, 2:8)] and, if needed, more silver nitrite (0.01g, 0.06mmol) was added every 72hrs. The reaction mixture was filtered, the silver salts were washed with THF and the washings were added to the original filtrate which was dried ($MgSO_4$), filtered and evaporated. The yield was 0.012g, 26%.

IR (Thin film) 3080-3020 (Csp^2-H), 2990-2880 (Csp^3-H) 1640 (C=C Aliphatic) 1550, 1370 (N=O,nitro).

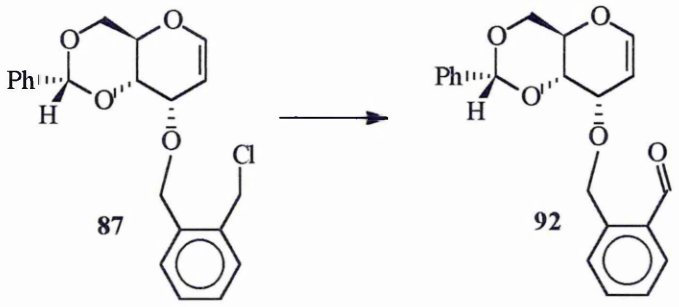
^{1}H NMR (60 MHz) 3.9-5.5 (10H, m), 5.8 (1H, s, C<u>H</u>-Ar), 6.7 (1H, d, J = 6, O-CH=C), 7.5-7.9 (9H, m, C_6H_5, C_6H_4)

^{13}C NMR (62.5 MHz) 146.1 (O-<u>C_1</u>=), 137.5, 137.0, 136.5, 130.9, 130.3, 129.5, 129.3, 128.7, 126.6 (Aromatic), 102.2 (O-C-O), 100.5 (O-C_1=<u>C_2</u>), 79.5, 70.0, 69.7, 67.9, 64.8, 53.7, (Aliphatic)

GC-MS 384 (M^++1), 337, 217, 171

Although the data indicated the presence of the required compound, the yield was low and impurities were present, so this route was not pursued any further.

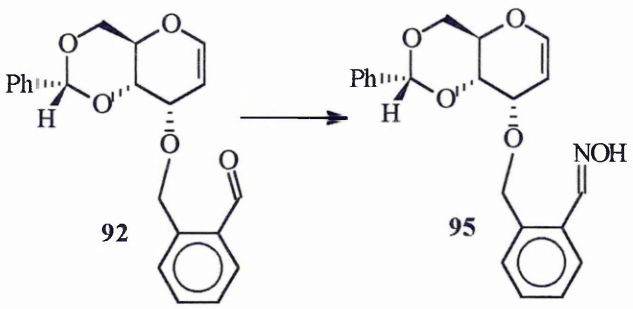
4,6-O-Benzylidene-1,2-didehydro-1,2-dideoxy-3-O-(2-formylphenylmethyl)-D-ribo-hexopyranose **92**[55]



A round bottomed flask was charged with the chloride **87** (0.60g, 1.61mmol), sodium hydrogen carbonate (0.22g, 2.59mmol), dimethyl sulphoxide (5.5g, 0.07mol) and acetonitrile (10ml) which was refluxed for 72hrs, [TLC (ethyl acetate:petrol, 2:8)]. The mixture was poured onto iced water (50ml) and extracted with ethyl acetate (3x15ml). The combined organic extracts were washed with water, dried ($MgSO_4$), filtered and evaporated to give an oil 0.47g, 83%.

^{1}H NMR (60 MHz) 3.5-5.3 (8H, m) 5.8 (1H, s, CH-Ar), 6.5 (1H, d, J = 6, O-CH=C) 7.3-8.0 (9H, m, C_6H_5, C_6H_4) 10.6 (1H, s, CHO).

4,6-O-Benzylidene-1,2-didehydro-1,2-dideoxy-3-O-(2-formylphenylmethyl)-D-ribo-hexopyranose oxime **95**[46]



A mixture of aldehyde **92** (0.32g, 1.50mmol), hydroxylamine hydrochloride (0.46g, 6.60mmol), ethanol (5ml) and triethylamine (0.5ml) was refluxed for 1-2 hrs. The reaction was monitored by TLC (ethyl acetate:petrol, 2:8). Water (10ml) was added to the mixture, which was extracted with ethyl acetate, dried ($MgSO_4$), filtered and evaporated. The product was purified using column chromatography (ethyl acetate:petrol, 2:8). to yield an oil 0.27g, 82%. [A mixture of isomers is present, the major isomer is reported].

IR (thin film) 3600-3100 (OH) 3070-3040 (Csp^2-H), 2990-2870 (Csp^3-H),1630 (C=C, aliphatic)

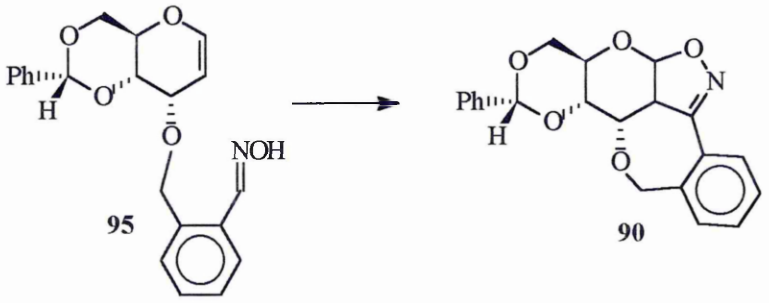
^{1}H NMR (250 MHz) 3.85 (1H, t, J = 10), 4.0 (1H, dd, J = 10.5, 3.5), 4.1 (1H, dd, J = 6, 3.5), 4.36 (1H, dd, 10.5, 5.5), 4.5 (1H, dd, J = 10.5, 5.5), 4.8 (1H, d, J = 12), 5.0 (1H, t, J = 12), 5.1 (1H, d, J = 12), 5 6 (1H, s, CH-Ar), 6.4 (1H, d, J = 6, O-CH=C), 7.3-7.8 (10H, m, C_6H_5, C_6H_4 and CH=N) 8.5 (1H, s, NOH).

^{13}C NMR (62.5 MHz) 149.2 (C=N), 146.1/146.1 (O-C_1=) 137.7/137.5, 131.1, 130.4/130.3, 129.8, 129.7, 129.5/129.2, 128.7, 128.3, 127.5/127.4, 126.7 (aromatic),

102.4, (O-C-O), 100.4/100.2 (O-C=C_2) 79.7/79.1, 71.6/71.3, 69.2, 67.9/67.2, 64.8/64.3 (aliphatic)

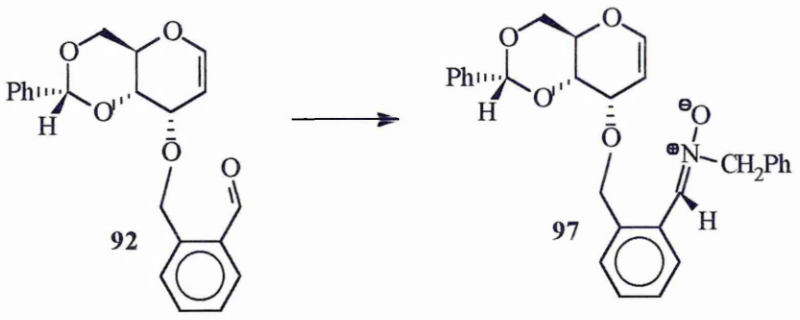
Mass Spec, 367 (M^+), 350, 302, 261, 218, 171, 150 (base peak) 135, 105, 91, 77, 53, 39.

Attempted preparation of the isoxazoline **90**[47]



The same method as for the Δ^2-isoxazoline **71** was followed but spectral data showed the double bond character to be present which suggested that no cycloaddition had taken place.

4,6-O-Benzylidene-1,2-didehydro-1,2-dideoxy-3-O-(2-formylphenylmethyl)-D-ribo-hexopyranose-N-benzylnitrone **97**[45]



Aldehyde **92** (0.26g, 0.74mmol) in dry ether (5ml) was added dropwise to a cooled mixture of benzylhydroxylamine (0.1g, 0.81mmol) and calcium chloride (0.082g, 0.74mmol) in dry ether (15ml). The reaction was stirred at 0°C for 1-2hrs and then placed in the refrigerator for 48hrs. The product was purified by column chromatography (ethyl acetate:petrol, 1:1). The yield was 0.14g, 41.2%.

Melting point 128°C

IR (KBr) 3060-3030 (Csp^2-H), 2995-2890 (Csp^3-H),1630 (C=C, aliphatic)

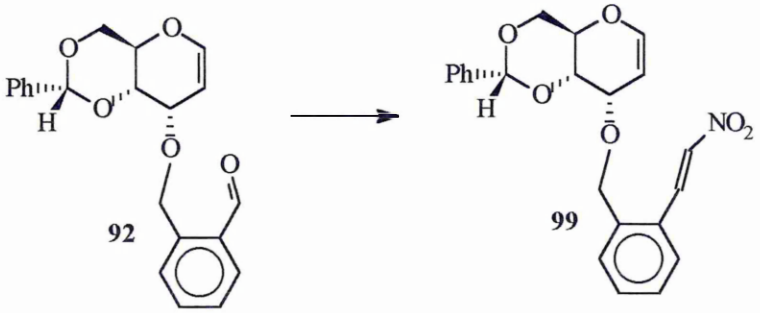
^{1}H NMR (250 MHz) 3.8 (1H, t, J = 10.5), 4.0 (2H, m) 4.2 (1H, m) 4.4 (1H, dd, J = 10.5, 5.5), 4.6 (1H, d, J = 11), 4.6 (1H, d, J = 13.5), 4.78 (1H, d, 13.5), 4.9 (1H, t, J = 5.5), 5.1 (1H, d, J = 11), 5.7 (1H, s, CH-Ar), 6.4 (1H, d, J = 6, O-CH=C) 7.3-7.6 (10H, m, C_6H_5x2) 8.2 (1H, s, CH=N).

^{13}C NMR (62.5 MHz) 146.2 (C=N), 137.5 (O-C_1=C), 136.2, 134.2, 132.2, 130.4, 130.3, 130.2, 129.6, 129.3, 129.0, 128.9, 128.8, 128.7, 126.5, 126.2 (Aromatic), 102.7 (O-C-O), 100.2 (O-C=C_2), 79.8, 76.8, 71.3, 69., 67.5, 64.9 (Aliphatic)

Mass Spec,458 (M^++1), 440, 411, 335, 322, 253, 240, 171, 132, 119, 91 (base peak) 83, 39.

Exact mass calculated for $C_{15}H_{18}O_5$:457.1889. Found:457.1905

4,6-O-Benzylidene-1,2-didehydro-1,2-dideoxy-3-O-(2-nitroethenylphenylmethyl)-D-ribo-hexopyranose **99**[60]



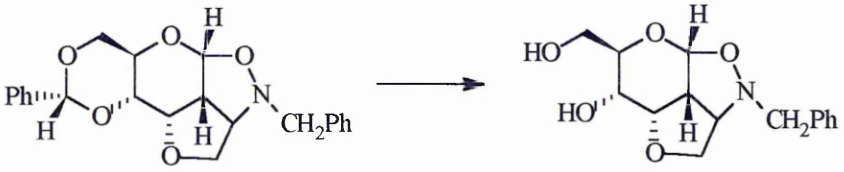
Nitromethane (0.017g, 0.28mmol) was placed in a three necked round bottomed flask with the aldehyde **92** (0.1g, 0.28mmol) and methanol (1.5ml).The reaction mixture was then cooled to about -10°C with an ice-salt bath. Sodium hydroxide (0.012g, 0.5mmol) was dissolved in iced water (1ml) and then added dropwise to the nitromethane mixture with vigorous stirring. After standing for about 15mins, ice-water (5-10ml) was added. The resulting cold solution was just acidified with an aqueous solution of hydrochloric acid. The aqueous solution was extracted with dichoromethane (3x10ml), dried ($MgSO_4$), filtered and evaporated to give a crude yield of 0.036g, 32%.

IR (Thin film) 3600-3400 (OH), 3060-3010 (Csp^2-H), 2990-2820 (Csp^3-H), 1680 (C=O, aldehyde), 1630 (C=C, aliphatic), 1380 (N=O) [the other N=O peak was absent therefore the required product was not confirmed]

^{1}H NMR (60 MHz) 3.7-5.7 (9H, m) 5.8 (1H, s, CH-Ar), 6.7 (1H, d, J = 7, O-CH=C) 7.7 (9H, m), 10.5 (1H, s, CHO) [the spectrum had many impurities as well as remaining starting material]

As the required product could not be confirmed this method was abandoned.

Deprotected isoxazolidine **108**



74 **108**

To a solution of isoxazolidine **74** (0.1g, 0.26mmol) in dry THF (5ml) was added 2M aqueous hydrochloric acid (0.5ml). The reaction mixture was stirred at room temperature and monitored by TLC (ethylacetate:petrol, 4:6). Once the reaction had gone to completion, the mixture was basified until blue with litmus with 2M aqueous sodium hydroxide. This was then extracted with ethyl acetate (3x5ml), the combined organic extracts were dried ($MgSO_4$), filtered and evaporated. The product was purified using column chromatography (ethyl acetate:methanol, 9.5:0.5). The yield was 0.066g, 86%.

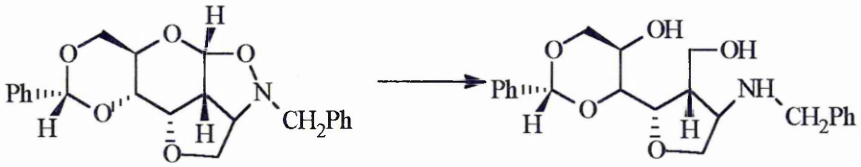
IR (Thin film) 3600-3200 (OH), 3060-3015 (Csp^2-H), 2995-2860 (Csp^3-H).

^{1}H NMR (CD_3OD, 250 MHz) 2.1-2.5 (2H, bs, OH), 3.4 (1H, dd, J = 14.8, 7.8), 3.75 (4H, m), 3.95 (4H, m), 4.2 (2H, m), 5.6 (1H, d, J = 8, O-CH-O), 7.3, (5H, m, Ph).

^{13}C NMR (62.5 MHz) 138.2, 130.4, 129.7, 129.2 (aromatic), 99.7 (O-C-O), 85.9, 80.3, 78.7, 71.7, 69.7, 66.7, 63.4, 58.4 (aliphatic)

Mass Spec 293 (M^+), 258, 223, 196, 149, 91 (base peak), 42, 39.

Attempted cleavage of isoxazolidine **74**



74

Method 1[69]

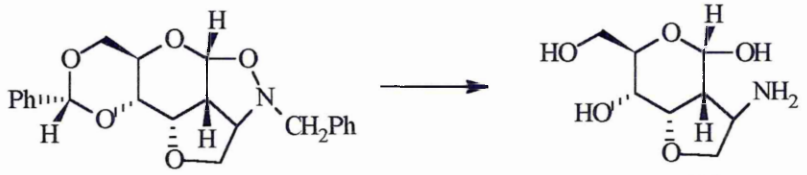
Lithium aluminium hydride (0.015g, 0.4mmol) was added to a solution of isoxazolidine **74**, (0.1g,0.26mmol) in dry THF (10ml). The mixture was refluxed for 8 days and monitored by TLC (ethyl acetate:petrol, 1:1). The reaction mixture was poured into an aqueous solution of Rochelle salt and stirred vigorously. This was left to stand for 0.5-1hr or until the gel had disappeared. The solution was then extracted with dichloromethane (3x15ml). The combined organic phases were dried ($MgSO_4$), filtered and evaporated to give a crude yield of 73mg, 74%. Starting material still remained.

Method 2[69]

The above method was followed but an excess of aluminium amalgam was used instead of lithium aluminium hydride. There was no reaction.

Cleavage product **109**

Method 1[68]



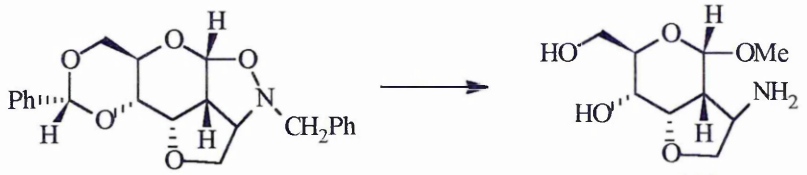
74 **109**

A small round bottomed flask was charged with isoxazolidine **74** (0.1g,0.26mmol) and dry methanol (10ml) was added to this, followed by a catalyst (30mg), (a) PtO_2/C (b) Pd/C [both catalysts were tried]. The flask containing this mixture was attached to a hydrogenator and left to stir under hydrogen. The reaction mixture was monitored by TLC (ethyl acetate:petrol, 7:3). After stirring for 24hrs the reaction mixture was filtered through celite and the solvent removed by evaporation.

Reaction (a) there was no reaction, starting material remained.

Reaction (b) it was believed that the benzyl group was being lost and no cleavage was occurring.

Method 2[45]



74 112

A small round bottomed flask was charged with isoxazolidine **74** (0.1g, 0.26mmol), methanolic hydrochloric acid (10%, 0.5ml, 1.37mmol), methanol (10ml) and Pearlman's catalyst (10-20mg). The flask was blown with hydrogen gas and then fitted with a hydrogen balloon and placed in an ultrasonic bath for 8-12hrs. In this time the water reached a temperature of 50°C. The reaction mixture was monitored by TLC(ethyl acetate:petrol, 1:1). The reaction mixture was filtered through celite and the filtrate was basified with ammonium hydroxide solution, then evaporated to give an oil, 35mg, 51%. The product was purified using column chromatography (dichloromethane: methanol:2M ammonium hydroxide, 6:6:1)

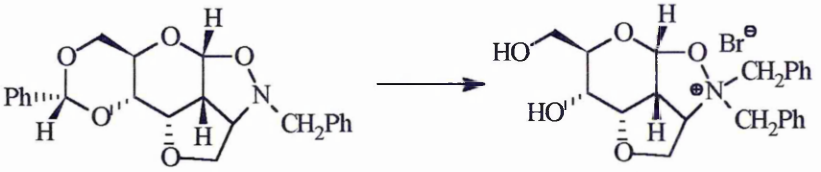
IR (Thin film) 3600-3200 (OH), 2995-2860 (Csp^3-H).

^1H NMR (D_2O, 250 MHz) 2.8 (1H, m), 3.3-4.1 (12H, m), 4.5-4.8 (4H, m), 5.6 (1H, s, O-CH-OCH_3), 5.7 (0.5H, d, J = 4).

^{13}C NMR (62.5 MHz) 101.8/101.7, 87.9/87.8, 87.4, 86.3/85.7, 81.3, 74.5/74.3, 65.1/64.2, 56.4/55.9, 54.1/53.4 (aliphatic)

Mass Spec 263 (M+44, believed to be due to absorbed CO_2), 239, 230, 197, 183, 163, 149, 121, 105, 69, 57, 43 (base peak)

Quaternary salt **113**[75]



74 **113**

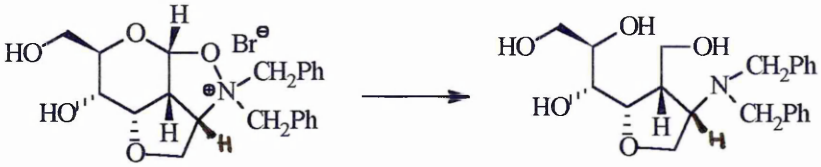
Benzyl bromide (0.13g, 1.18mmol) was added to isoxazoline **74** (0.3g, 0.79mmol) in acetonitrile (20ml) was refluxed for 4 days. The acetonitrile was removed by evaporation and the residue was triturated with ether. The resulting solid was washed several times with ether to remove any excess benzyl bromide. As the salt was very hygroscopic, it was stored under ether until required. The yield was 0.284g, 77%.

^{1}H NMR (250 MHz, CF_3COOD) 4.1 (4H, m), 4.45 (5H, m), 4.78 (3H, dd, J = 12, 7.5), 5.0 (2H, m), 5.3 (1H, m), 6.1 (1H, d, J = 5.5, O-CH-O), 7.5, (10H, m, Phx2).

^{13}C NMR (62.5 MHz, CF_3COOD) 134.1, 133.8, 132.6, 132.4, 132.2, 131.9, 127.1 (aromatic), 106.9 (O-C-O), 79.7, 78.0, 72.3, 70.1, 68.6, 67.8, 66.2, 65.8, 62.6, (aliphatic)

Mass Spec 385 (M+1-Br), 324, 295, 197, 182, 91 (base peak), 61

4-(R)-Dibenzylamino-3-(R)-hydroxymethyl-2-(S)-(1-(R),2-(R),3-trihydroxypropyl)-tetrahydrofuran **114**[75]



113 **114**

To a suspension of the salt **113** (0.12g, 0.26mmol) in dry THF (10ml) was added lithium aluminium hydride (0.099g, 2.6mmol). This reaction mixture was refluxed for 24-48hrs, and was monitored by TLC (ethyl acetate:methanol, 9.5:0.5). The reaction mixture was poured into an aqueous solution of Rochelle salt and stirred vigorously. The solution was left for 0.5hrs until the gel which had formed had disappeared. This was then extracted with dichloromethane (3x25ml). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated to yield an oil 0.068g, 68%.

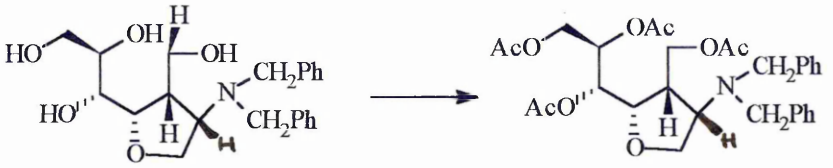
IR (Thin film) 3600-3100 (OH), 3070-3020 (Csp^2-H), 2990-2840 (Csp^3-H).

^{1}H NMR (250 MHz) 2.5-2.8 (4H, bs, OH), 3.4-4.2 (14H, m), 4.7 (1H, s), 7.3, (10H, m, C_6H_5x2).

^{13}C NMR (62.5 MHz) 136.6, 129.3, 129.0, 128.9, 128.7, 128.0, 127.6, (aromatic), 76.6, 73.3, 72.3, 69.6, 66.3, 62.6, 62.5, 56.7, 49.2, 30.0, (aliphatic)

Mass Spec 387 (M+), 369, 326, 296, 238, 196, 106, 91 (base peak), 43

4-(R)-Dibenzylamino-3-(R)-acetoxymethyl-2-(S)-(1-(S),2-(R),3-triacetoxypropyl)-tetrahydrofuran **115**[73]



114 **115**

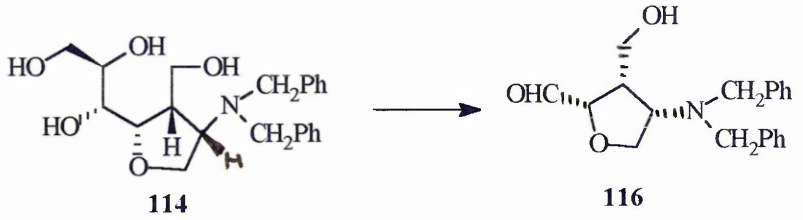
The hydroxy compound **114** (0.1g, 0.26mmol) was dissolved in dichloromethane (2ml), to which acetic anhydride (0.12g, 1.17mmol) and a catalytic amount of 4(N,N-dimethylamino)pyridine were then added at 0°C. The reaction mixture was allowed to stand at the same temperature for 1hr before stirring at room temperature whilst being monitored by TLC (ethyl acetate:petrol, 9.5:0.5). The dichloromethane solution was washed with water and brine , dried ($MgSO_4$), filtered and evaporated. The product was purified by column chromatography (ethyl acetate:petrol, 9.05:0.5). The yield was 0.073g, 51%.

^{1}H NMR (250 MHz) 2.0 (3H, s, CH_3), 2.1 (3H, s, CH_3), 2.15 (3H, s, CH_3), 2.2 (3H, s, CH_3), 3.1-4.2 (11H, m), 4.4 (2H, s, CH_2), 4.6 (2H, s, CH_2), 7.3, (10H, m, C_6H_5x2).

^{13}C NMR (62.5 MHz) 132.0, 130.5, 129.2, 128.8, 128.7, 128.0, 127.6, 126.7 (aromatic), 77.2, 71.6, 70.7, 69.4, 62.7, 62.3, 57.4, 49.3, 42.5, 30.0, 25.6, 21.0 (aliphatic)

Mass Spec 555 (M+), 496, 464, 406, 317, 308, 378, 178, 148, 91 (base peak), 43

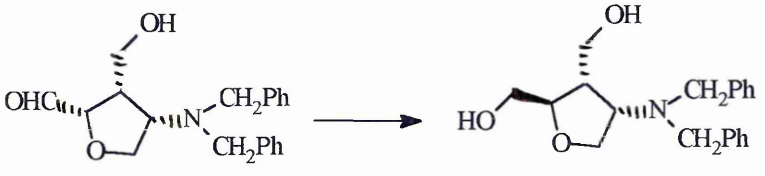
4-(R)-dibenzylamino-2-(R)-formyl-3(R)-hydroxymethyl-tetrahydrofuran **116**[76]



114 **116**

The hydroxy compound **114** (0.2g, 0.52mmol) was dissolved in a THF-water mixture (3:1, 30ml) which was cooled to 0°C. Sodium periodate (0.14g, 0.65mmol) was added and the mixture was stirred at 0°C for 10mins and then at room temperaure for 1hr. The reaction was monitored by TLC (ethyl acetate:methanol, 9.5:0.5). The mixture was concentrated by evaporation and following addition of water (10-15ml) it was extracted with dichloromethane (3x15ml). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated and put straight through to the sodium borohydride reduction without purification.

2-(S),3-(R)-bis(hydroxymethyl)-4-(R)-dibenzylamino-terahydrofuran **118**



116 **118**

The aldehyde **116** (0.1g, 0.3mmol) was dissolved in dry methanol, to which sodium metal (0.02, 0.87mmol) was added. The reaction mixture was stirred at room temperature for 72hrs to effect epimerisation[78], then sodium borohydride (0.04g,

1.06mmol) was added and the mixture was stirred for a further 7hrs. The mixture was concentrated and water (20ml) was added. The resulting solution was extracted with ethyl acetate (3x25ml), dried ($MgSO_4$), filtered and evaporated. The yield was 0.096g, 96%.

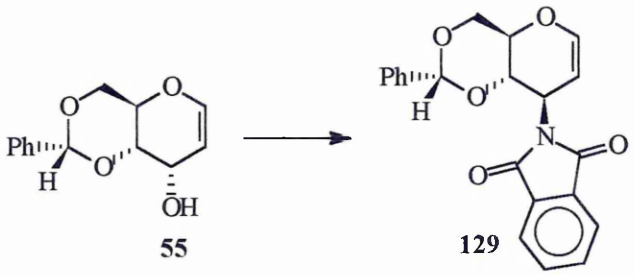
IR (Thin film) 3500-3200 (OH), 3080-3010 (Csp^2-H), 2990-2860 (Csp^3-H).

^1H NMR (250 MHz) 2.7 (2H, bs, OH), 3.5 (4H, d, J = 14.5, CH_2), 3.6-3.85 (7H, m with d, J = 14.5, 3.7), 3.9 (1H, m), 4.2 (1H, m, CH-N), 7.5, (10H, m, C_6H_5x2).

^{13}C NMR (62.5 MHz) 139.8/138.6, 129.6/129.1, 128.7, 127.6/127.5 (aromatic), 81.3, 65.3, 61.8, 57.1, 55.2, 45.2, 42.3 (aliphatic).

Mass Spec 327 (M+), 296, 277, 236, 148, 91 (base peak),77, 39.

3-β-Amino-4,6-O-benzylidene-1,2-didehydro-1,2,3-trideoxy-N-phthalimido-D-ribo-hexopyranose **129**[80]



The alcohol **55** (0.25g, 1.07mmol) was dissolved in dry THF (10ml) under nitrogen and phthalimide (0.24g, 1.61mmol) and triphenylphosphine (0.42g, 1.6mmol) were added to the solution. Diethyl azodicarboxylate (0.27g, 1.6mmol) was then slowly

added to the white slurry, which resulted in a clear orange solution. The mixture was stirred at room temperature for 40hrs [TLC (ethyl acetate:petrol, 1:1]. The mixture was quenched by the addition of brine (10ml). The layers were separated and the aqueous layer was washed with ether (5ml). The combined organic fractions were dried ($NaSO_4$), filtered and evaporated and the product was purified using column chromatography (ethyl acetate:petrol, 1:1). The yield was 0.077g, 20%.

Melting point 142-144°C

IR (KBr) 3091-3013 (Csp^2-H), 2976-2868 (Csp^3-H), 1725 (C=O), 1643 (C=C, aliphatic).

^1H NMR (250 MHz) (complex spectrum suggesting a mixture of isomers) 3.8-4.0 (2H, m), 4.05-4.8 (3H, m), 5.8 (2H, s, m, O-CH-O, CH=C-O), 6.3 (1H, C=CH-O), 7.3-7.5, (5H, m, C_6H_5), 7.6-7.8 (4H, m, C_6H_4).

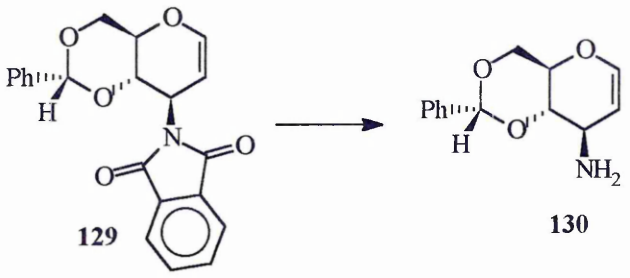
^{13}C NMR (62.5 MHz) 167.9/167.0 (C=O), 146.3/145.6 ($C=C_1$-O), 137.6/137.3, 134.8/134.5, 132.0/131.7, 129.5/129.2, 128.5/128.0, 126.6/126.4, 124.4/124.0 (aromatic), 102.4/102.2 (O-C-O), 100.7/100.5 (C_2=C-O), 75.3/75.2, 70.9/70.6, 69.1/69.0 (aliphatic), 49.9/48.3 (C-N).

Mass Spec 363 (M^+), 272, 242, 214, 186, 149, 105 (base peak), 77, 43.

Exact mass calculated for $C_{21}H_{17}O_5$:363.1107. Found:363.1120.

3-β-Amino-4,6-O-benzylidene-1,2-didehydro-1,2,3-trideoxy-D-ribo-hexopyranose

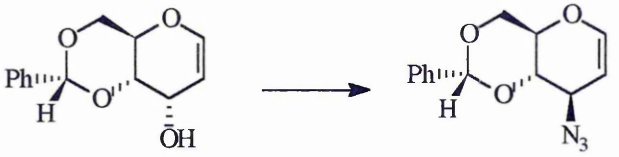
130[80]



To a solution of phthalimide **129** (5mg, 0.014mmol) in ethanol (95%, 1.0ml) was added hydrazine hydrate (85%, 2mg, 0.055mmol), and the mixture was refluxed under nitrogen for 3hrs. The ethanol was evaporated and the residue taken up in 2M potassium hydroxide solution (1ml). The basic solution was extracted with ether (4x2ml) and the combined ether extracts were washed with brine and dried (K_2CO_3), filtered and evaporated. No starting material remained but T.L.C. showed a complex mixture which was heavily contaminated with phthalahydrazide and wasn't investigated further as an alternative route was followed.

3-β-Azido-4,6-O-benzylidene-1,2-didehydro-1,2,3-trideoxy-D-ribo-hexopyranose

133[83]



55 **133**

The reaction was carried out by dissolving the alcohol **55** (2g, 8.55mmol) and diphenylphosphoric azide (2.82g, 10mmol) in toluene (16ml). To the mixture was added a slight excess of 1,8-diazabicyclo[5.4.0]undec-7ene, (9.4mmol). After stirring for 2 days at room temperature and monitoring by TLC (ethyl acetate:petrol, 4:6), the azide was isolated by addition of water (20ml) and extraction with ethyl acetate (3x20ml). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated. The azide was purified by column chromatography (ethyl acetate:petrol, 2:8) to give 1.46g, 66% of white solid.

Melting point 76-77°C

IR (KBr) 3090-3010 (Csp^2-H), 2195, 2102 (N_3) 2995-2865 (Csp^3-H), 1630 (C=C, aliphatic).

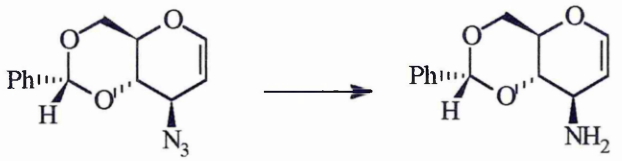
^{1}H NMR (250 MHz) 3.8-4.0 (3H, m), 4.3 (1H,m), 4.4 (1H, m), 4.7 (1H, dd, J = 6, 1.5, CH=C-O), 5.7(1H, s, O-CH-O), 6.5 (1H, dd, J = 6, 1.5, C=CH-O), 7.4-7.6, (5H, m, C_6H_5).

^{13}C NMR (62.5 MHz) 145.5 ($C=C_1$-O), 136.7, 129.2, 128.3, 126.0 (aromatic), 101.5 (O-C-O), 99.5 (C_2=C-O), 78.4, 68.8, 68.3, 57.3 (aliphatic).

Mass Spec 259 (M+), 217, 171, 149, 105 (base peak), 96, 41.

Exact mass calculated for $C_{13}H_{13}O_3N_3$:259.0957. Found:259.0968.

3-β-Amino-4,6-O-benzylidene-1,2-didehydro-1,2,3-trideoxy-D-ribo-hexopyranose **130**



133 **130**

Method 1[85]

To a cooled (0°C-5°C), stirred solution of copper (II) sulphate pentahydrate (1mg, 0.04mmol) in methanol (5ml) was added sodium borohydride (5mg, 0.13mmol). To the resulting black suspension was added the azide **133** (100mg, 0.4mmol) in methanol (2ml). Reaction was continued by the addition of sodium borohydride (10mg, 0.26mmol) in four portions during 1hr. TLC showed that no reaction took place over several days.

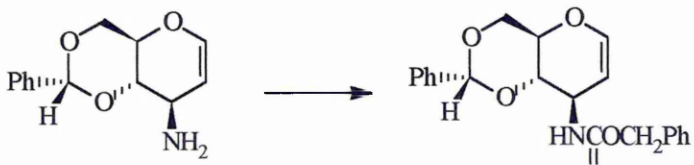
Method 2[86]

To a stirred solution of azide **133** (1g, 3.86mmol) in dichloromethane (30ml) was added triphenylphosphine (1.52g, 5.79mmol). The reaction was left stirring for 2 days and then concentrated to dryness. The residue was taken up in THF (30ml) and aqueous ammonia (sp.gr.0.88, 5ml) was added, following which the solution was

stirred vigorously at reflux (65°C) for 3hrs. The reaction mixture was concentrated, diluted with water and extracted into ether (3x25ml). The organic extracts were combined, dried ($MgSO_4$), filtered and evaporated to give a crude yield of 2.39g, containing triphenylphosphine oxide as a contaminant which could not be separated.

Mass spec 278 ($Ph_3P=O$), 233 (M+), 205, 196, 162, 105, 72, 43.

4,6-O-Benzylidene-3-β-N-benzyloxycarbonylamino-1,2-didehydro-1,2,3-trideoxy-D-ribo-hexopyranose **134**



130 **134**

The crude amine **130** (1g) containing triphenylphosphine oxide was dissolved in DCM (20ml). To this mixture saturated sodium hydrogen carbonate solution (20ml) was added followed by benzyl chloroformate (0.72g, 4.25mmol). The two phase mixture was vigorously stirred at room temperature for 20-24hrs, [monitored by TLC (ethyl acetate:petrol, 6:4)]. The layers were separated and the aqueous layer was extracted twice with DCM (2x10ml). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated. The pure product was obtained by recrystallisation from hot ethanol yielding 0.38g, 27% over two steps.

Melting point 208-210°C

IR (KBr) 3400 (NH), 3090-3010 (Csp^2-H), 2995-2865 (Csp^3-H), 1700, (C=O), 1630 (C=C, aliphatic).

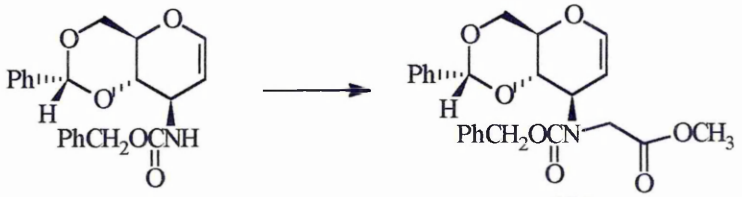
^1H NMR (250 MHz) 3.8 (2H, t, J = 10.5), 3.99 (1H, dt, J = 10, 5), 4.4 (1H, dd, J = 10.5, 5), 4.55 (1H, tt, J = 8.5, 1.9, CH=C-O), 4.8 (2H, bs and d, J = 6), 5.1 (2H, s, CH_2-O), 5.55 (1H, s, O-CH-O), 6.35 (1H, dd, J = 6, 2, C=CH-O), 7.5 (10H, m, C_6H_5x2).

^{13}C NMR (62.5 MHz) 156.4 (C=O), 144.5 ($C=C_1$-O), 137.3, 136.7, 129.5, 128.8, 128.6, 128.4, 128.2, 126.5 (aromatic), 102.8 (O-C-O), 102.0 (C_2=C-O), 78.4, 69.7, 68.6, 67.2, 49.2 (aliphatic).

Mass Spec 367 (M^+), 323, 276, 246, 230, 170, 162, 105, 91 (base peak), 51.

Exact mass calculated for $C_{21}H_{21}O_5N$:367.1420. Found:367.1442.

4,6-O-Benzylidene-3-β-N-[(N-benzyloxycarbonyl)-(N-methyoxycarbonylmethyl)]-amino-1,2-didehydro-1,2,3-trideoxy-D-ribo-hexopyranose **135**



134 **135**

Potassium hydride (35% mineral oil, 0.5g, 4.30mmol) was weighed out into a dry round bottomed flask. This was then washed several timed with petrol to remove the oil. Any remaining petrol was blown off with nitrogen gas. Dry THF (30ml) was then

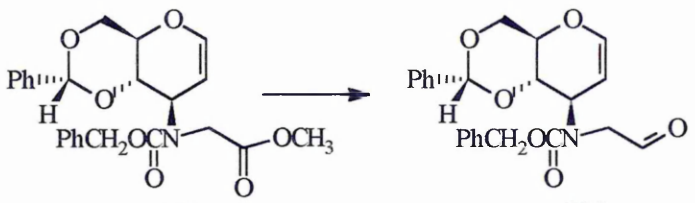
added to the potassium hydride followed by N-carbobenzyloxy amine **134** (0.4g, 1.09mmol). The mixture was stirred at room temperature for 0.5hrs before the addition of methyl bromoacetate (0.42g, 2.73mmol). Stirring was continued at room temperature for 16 hrs and monitored by TLC (ethyl acetate:petrol, 4:6). The reaction was poured into water (50ml) and the mixture was extracted with ethyl acetate (3x25ml), dried ($MgSO_4$), filtered and evaporated to yield an off-white sticky solid 0.4g, 83%.

IR (Thin film) 3080-3010 (Csp^2-H), 2995-2880 (Csp^3-H), 1720 (C=O, ester), 1700 (C=O, amide), 1630 (C=C, aliphatic).

^1H NMR (250 MHz) 3.7 (3H, s, OCH_3), 3.8 (4H, t, J = 11), 4.0 (1H, dd, J = 5, 9), 4.2 (0.5H, q, J = 7), 4.4 (1.5H, dd, J = 5.7, 11.5), 4.5 (1H, t, J = 7), 4.8 (2H, t, J = 6, CH_2), 5.5 (1H, s, O-CH-O), 6.4 (1H, d, J = 6, C=CH-O), 7.5, (10H, m, C_6H_5x2).

Mass Spec 439 (M+), 367, 304, 274, 246, 185, 105, 91 (base peak), 39.

4,6-O-Benzylidene-3-β-N-[(N-benzyloxycarbonyl)-(N-formylmethyl)]amino-1,2-didehydro-1,2,3-trideoxy-D-ribo-hexopyranose **136**[45]



135 **136**

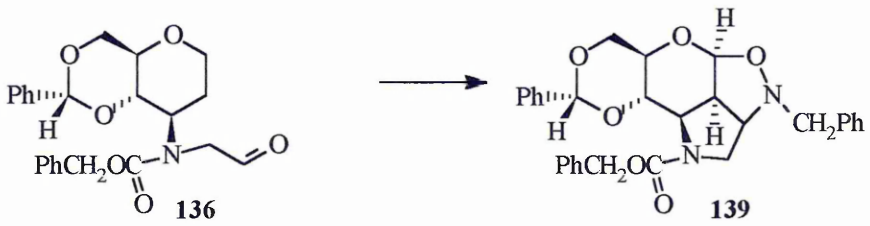
To a mixture of N-carbobenzyloxy-ester **135** (0.63g, 1.44mmol) in dry dichloromethane (20ml) at -78°C was added DIBAL solution (1.5M in toluene, 3.35ml, 5.03mmol) dropwise over a 0.5hr period. After addition the reaction mixture was stirred for a further hour at -78°C. The reaction mixture was quenched with water (7ml) and allowed to reach room temperature, then it was poured into an aqueous solution of Rochelle salts. Ethyl acetate (20ml) was added and this was stirred vigorously and left to stand for approximately 1hr or until the gel had dissappeared. The mixture was then extracted using ethyl acetate (3x25ml), dried ($MgSO_4$), filtered and evaporated to yield 0.5g, 86%. The product was used crude in the next step.

^{1}H NMR (CD_3COCD_3, 250 MHz) 4.2 (5H, m), 4.6 (1H, m), 5.0 (1H, m), 5.4 (3H, s and d, J = 11, CH_2, CH=C-O), 6.0 (1H, s, O-CH-O), 6.8 (1H, dd, J = 4.6, 32, C=CH-O), 7.7, (10H, m, C_6H_5x2), 9.9 (0.6H, d, J = 3, CHO) [there was a reduced integration for the aldehydic proton due to the hydrate].

^{13}C NMR (62.5 MHz) 198.5 (C=O, aldehyde), 155.9 (C=O), 146.6 ($C=C_1$-O), 137.4, 136.8, 129.4, 128.7, 128.6, 128.4, 128.2, 126.5 (aromatic), 101.9 (O-C-O), 101.1 (C_2=C-O), 78.2, 75.4, 69.6, 68.6, 67.2, 49.2 (aliphatic).

Mass Spec 410 (M^++1), 354, 318, 288, 246, 162, 105, 91 (base peak),39.

Isoxazolidine **139**[45]



Aldehyde **136** (0.35g, 0.86mmol) in dry THF (5ml) was added dropwise to a cooled mixture of benzylhydroxylamine (0.13g, 1.03mmol) and calcium chloride (0.048g, 0.43mmol) in dry THF (10ml). The reaction was stirred at room temperature and monitored by TLC (ethyl acetate:petrol, 4:6). The reaction mixture was filtered and the solvent removed under reduced pressure to give a residue which was purified by column chromatography (ethyl acetate:petrol, 4:6). The yield was 0.28g, 64%.

Melting point 128-130°C

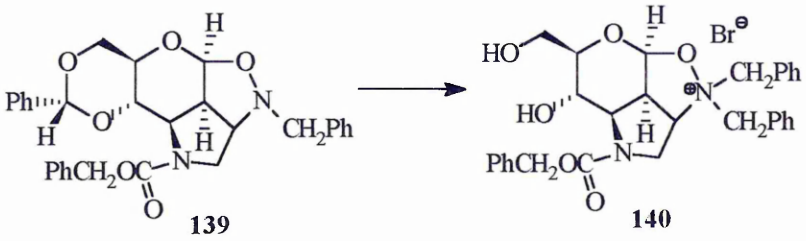
^{1}H NMR (250 MHz) 3.0 (1H, d, J = 10), 3.5 (4H, m), 3.9 (3H, m), 4.4 (3H, m), 5.0 (2H, m), 5.5 (1H, d, J = 4.5), 5.55 (1H, s), 7.4, (15H, m, C_6H_5x3)

^{13}C NMR (62.5 MHz) 154.6 (C=O), 137.6, 129.8, 129.5, 129.2, 128.9, 128.6, 128.4, 126.5 (aromatic), 101.0, 97.8 (O-C-O), 78.2, 70.6, 69.4, 67.6, 64.7, 62.2, 57.2, 53.5, 47.6 (aliphatic).

Mass Spec 514 (M^+), 496, 408, 335, 307, 217, 173, 91 (base peak),41.

Exact mass calculated for $C_{30}H_{30}O_6N_2$:514.2104. Found:514.2107.

Quaternary salt **140**[73]



Benzyl bromide (1.2g, 0.7mmol) was added to isoxazolidine **139** (0.2g, 0.39mmol) in acetonitrile (10ml) was refluxed for 4 days. The acetonitrile was removed by evaporation and the residue was triturated with ether. The resulting solid was washed several timed with ether to remove any excess benzyl bromide. As the salt was very hygroscopic, it was stored under ether until required. The yield was 0.21g, 91%.

^{1}H NMR (250 MHz, CF_3COOD) 3.95 (1H, m), 4.0 (4H, s), 4.15 (1H, m), 4.25 (1H, m), 4.35 (1H, m), 4.45 (2H, m), 4.55 (1H, m), 4.5 (1H, m), 4.84 (1H, m), 5.1 (1H, d, J = 2.3) 5.2 (2H, m), 7.2 (15H, m, Ph x 3)

^{13}C NMR (62.5 MHz, CF_3COOD) 133.3, 133.1, 132.7, 132.4, 131.9, 131.8, 131.6, 131.0, 130.8. 130.6, 130.4, 129.9 (aromatic), 97.2, (O-C-O), 79.2, 73.1, 67.9, 66.0, 65.1, 59.9, 57.5, 56.5, 55.5, 54.2, 54.1 (aliphatic)

Mass Spec (FAB) 517 (597-Br), 427, 378, 288, 210, 196, 91 (base peak), 68.

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