# The Nitrile Oxide/Isoxazoline Route to Carbon-linked Disaccharides

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*Because the universe was full of ignorance all around and the scientist panned through it like a prospector crouched over a mountain stream, looking for the gold of knowledge among the gravel of unreason, the sand of uncertainty and the whiskery eight-legged swimming things of superstition.*

Terry Pratchett, "Witches Abroad", 1991

## Acknowledgements

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## Post Graduate Lectures (1989-1992)

Departmental Seminars, three years attendance

Organic Photochemistry (Dr. G. Tennant), 1989, 5 lectures

Recent Advances in Organic Chemistry (various lecturers) 1990, 1991, 2 x 5 lectures

Medicinal Chemistry (Prof. R. Baker) 1990, 1991, 2 x 5 lectures.

The Technology of Detergent Products (Dr. C. Adams, Unilever) 1991, 5 lectures.

Discovery, Development and Pharmacology of Zoladex (various lectures, ICI Pharmaceuticals) 1992, 5 lectures.

Aspects and Applications of NMR Spectroscopy (various lecturers) 1992, 5 lectures.

Departmental German course passed (1989).

## Glossary of Terms, Symbols and Abbreviations

| | |
|---|---|
| b.p. | boiling point |
| COSY | Correlation Spectroscopy |
| DMF | *N*,*N*-dimethylformamide |
| DMSO | dimethylsulphoxide |
| ether | diethyl ether |
| FAB | Fast Atom Bombardment |
| FMO | Frontier Molecular Orbital |
| g | gram |
| hr | hour |
| HOMO | Highest Occupied Molecular Orbital |
| Hz | Hertz |
| i.r. | infra-red |
| *J* | coupling constant |
| lit. | literature value |
| LUMO | Lowest Unoccupied Molecular Orbital |
| M | Moles per litre |
| $M^+$ | Molecular ion |
| M equiv. | Molecular equivalents |
| min | minute |
| ml | millilitres |
| mmHg | pressure in millimetres of mercury |
| mmol | millimole |
| MO | Molecular Orbital |
| mol | mole |
| m.p. | melting point |
| ms | mass spectrometry |

| | |
|---|---|
| *m/z* | mass to charge ratio |
| n.m.r. | nuclear magnetic resonance |
| p.s.i. | pounds per square inch |
| TFA | trifluoroacetic acid |
| THF | tetrahydrofuran |
| t.l.c. | thin layer chromatography |
| TMS | tetramethylsilane |
| TOCSY | TOtal Correlation SpectroscopY |
| $[\alpha]$ | optical rotation |
| $\delta$ | chemical shift |
| $\nu_{max}$ | wave number of absorbance maximum |

# Abstract

A route to carbon-linked disaccharides (two monosaccharide units linked by a carbon bridge rather than a glycosidic oxygen) employing nitrile oxide/isoxazoline chemistry has been investigated. This convergent approach is based on cycloaddition of sugar-derived alkene and nitrile oxide fragments, followed by ring cleavage and functional group manipulation of the resulting 2-isoxazoline. Careful selection of the nitrile oxide and alkene fragments defines much of the stereochemistry of the products.

Two ω-unsaturated hexofuranoses were chosen for study: 3-*O*-benzyl-5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hex-5-enofuranose (**37**) derived from D-glucose and methyl 5,6-dideoxy-2,3-*O*-isopropylidene-α-D-*lyxo*-hex-5-enofuranoside (**137**), which has the opposite configuration to (**37**) at $C_2$, derived from D-mannose. Four nitrile oxides were employed in cycloadditions to these alkenes: ethoxycarbonylformonitrile oxide (**36**) was used as a model 1,3-dipole to probe the π-facial selectivity of cycloadditions to alkene (**137**), and three pyranose 1-nitrile oxides (**122**), (**146**) and (**150**), derived from D-xylose, D-arabinose and D-galactose respectively.

Additions to alkene (**37**) proceeded with a high degree of π-facial selectivity (56-82% d.e.) in favour of the 2-isoxazoline with *erythro* configuration. Similar selectivity was noted in additions to alkene (**137**). This selectivity can be explained in terms of the "inside alkoxy effect" proposed by Houk and modified to include the "homoallylic effect" put forward by De Micheli.

Reductive hydrolytic cleavage of the 2-isoxazolines to release the latent β-hydroxy ketone functionality was carried out by both Pd/C and Ra-Ni catalysed hydrogenolysis. In the Pd/C case significant loss of the 3-*O*-benzyl protecting group was noted, however, Ra-Ni hydrogenolysis afforded the required β-hydroxy ketones ((1→6)-carbonyl-linked *C*-disaccharides) in moderate yield (43→56%) along with a

minor product identified as an epimeric mixture of the corresponding γ-amino alcohols ((1→6)-aminomethylene-linked *C*-disaccharides).

Finally, reduction of the β-hydroxy ketone functionality and subsequent removal of the isopropylidene protecting groups afforded the dipyranose (1→6)-hydroxymethylene-linked *C*-disaccharides.

## Contents

# 1 Introduction

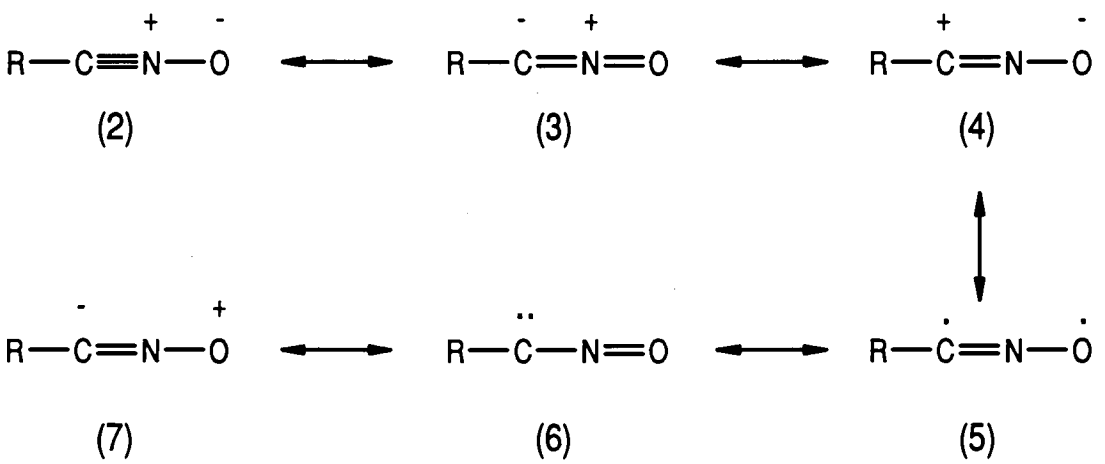
The research described in this thesis is concerned with the application of nitrile oxide/isoxazoline chemistry to the synthesis of carbon-linked disaccharides. These compounds are of interest due to their similarity to natural sugars and their potential use as inhibitors of glycosidases. In this introduction three topics are discussed : firstly, after a brief overview of 1,3-dipoles, the chemistry of nitrile oxides and isoxazolines is described. Secondly, glycosidases and uses of inhibitors of these enzymes are discussed and finally other approaches to carbon-linked disaccharides are reviewed.

Much work has been carried out in the field of 1,3-dipolar chemistry since 1,3-dipoles were first classified by Huisgen[1]. Due to the size of this field 1,3-dipoles will not be extensively reviewed in this introduction. Further information on 1,3-dipolar chemistry can be found in Padwa's comprehensive "1,3-Dipolar Cycloaddition Chemistry"[2]. More details on nitrile oxides can be obtained from "The Nitrile Oxides"[3] by Grundmann and Grünager, Torssell's text entitled "Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis"[4] and from a recent review "Recent Advances in Synthetic Applications of Nitrile Oxide Cycloaddition"[5] by Kanemasa and Tsuge.

## 1.1 1,3-Dipoles

1,3-Dipoles are defined as systems which can be represented by zwitterionic octet structures of type (**1**) and which undergo 1,3-cycloadditions to dipolarophiles[6]. They possess an allyl anion type π-system and can be considered as heteroallyl anions but with no net charge. Although the zwitterionic octet structure (**1**) is the most common representation of a 1,3-dipole, the structure is best presented as a hybrid of all possible resonance forms as shown in Scheme 1 for a nitrile oxide.

(1)

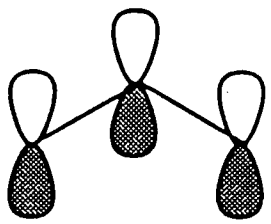


**Scheme 1**

The main resonance forms are the octet structures (**2**) and (**3**) which probably contribute most to the hybrid in the ground state, the sextet structures (**4**) and (**7**), the diradical (**5**) and the carbene form (**6**). The importance of the diradical species has been much debated and is discussed in Section 1.2.1.

There are two classes of 1,3-dipoles; the allyl type (**8**) which have a bent structure and the propargyl-allenyl type (**9**) which are linear due to the presence of an

additional orthogonal π-bond. The most common 1,3-dipoles are shown in Table 1[7] in their full octet forms.



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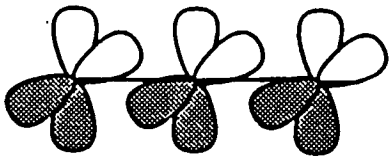


(9)

**Table 1** - Common 1,3-Dipoles

## Propargyl-Allenyl Type

### Nitrilium Betaines

| | |
|---|---|
| $RC{\equiv}\overset{+}{N}{-}\overset{-}{C}R_2$ | Nitrile Ylides |
| $RC{\equiv}\overset{+}{N}{-}\overset{-}{N}R$ | Nitrile Imines |
| $RC{\equiv}\overset{+}{N}{-}\overset{-}{O}$ | Nitrile Oxides |
| $RC{\equiv}\overset{+}{N}{-}\overset{-}{S}$ | Nitrile Sulphides |

### Diazonium Betaines

| | |
|---|---|
| $N{\equiv}\overset{+}{N}{-}\overset{-}{C}R_2$ | Diazoalkanes |
| $N{\equiv}\overset{+}{N}{-}\overset{-}{N}$ | Azides |
| $N{\equiv}\overset{+}{N}{-}\overset{-}{O}$ | Nitrous Oxide |

## Allyl Type

### Central N

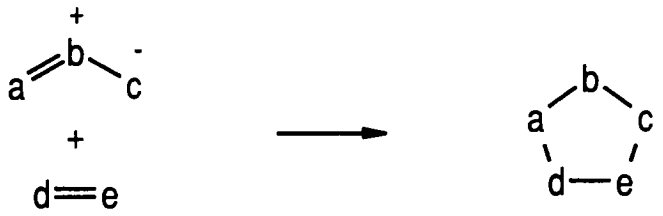
| | |
|---|---|
| $R_2C{=}\overset{+}{N}R{-}\overset{-}{C}R_2$ | Azomethine Ylides |
| $R_2C{=}\overset{+}{N}R{-}\overset{-}{N}R$ | Azomethine Imines |
| $R_2C{=}\overset{+}{N}R{-}\overset{-}{O}$ | Nitrones |
| $RN{=}\overset{+}{N}R{-}\overset{-}{N}R$ | Azimines |
| $RN{=}\overset{+}{N}R{-}\overset{-}{O}$ | Azoxy Compounds |
| $O{=}\overset{+}{N}R{-}\overset{-}{O}$ | Nitro Compounds |

### Central O

| | |
|---|---|
| $R_2C{=}\overset{+}{O}{-}\overset{-}{C}R_2$ | Carbonyl Ylides |
| $R_2C{=}\overset{+}{O}{-}\overset{-}{N}R$ | Carbonyl Imines |
| $R_2C{=}\overset{+}{O}{-}\overset{-}{O}$ | Carbonyl Oxides |
| $RN{=}\overset{+}{O}{-}\overset{-}{N}R$ | Nitrosimines |
| $RN{=}\overset{+}{O}{-}\overset{-}{O}$ | Nitrosoxides |
| $O{=}\overset{+}{O}{-}\overset{-}{O}$ | Ozone |

## 1.2 1,3-Dipolar Cycloaddition

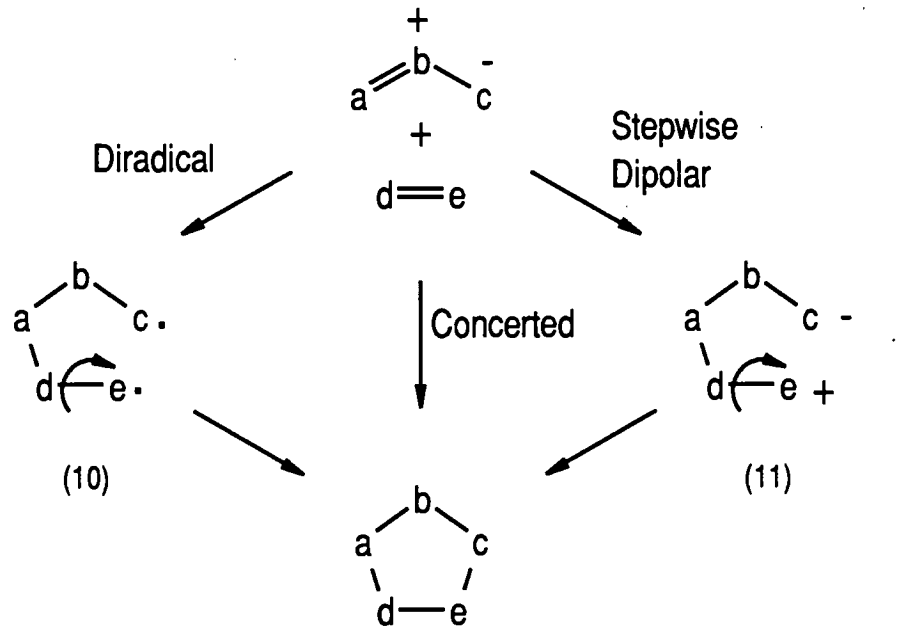
The most widely used reaction of 1,3-dipoles is their [3+2 → 5] addition to multiple bonds (dipolarophiles) to form 5-membered heterocyclic rings. This is one of the most general methods of synthesis of 5-membered heterocycles and is illustrated in Scheme 2.



**Scheme 2**

### 1.2.1 Reaction Mechanism

Three possible mechanisms have been put forward to explain the 1,3-dipolar cycloaddition reaction[8]. Firstly a concerted process with simultaneous, but not necessarily synchronous, formation of two new σ-bonds has been proposed by

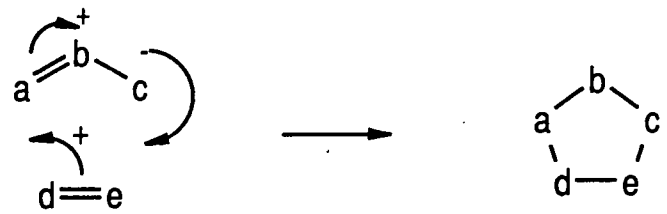



**Scheme 3**

Huisgen[9-12] (Section 1.2.1.1). Firestone[13-16] has argued for a stepwise diradical mechanism (Section 1.2.1.2), and the third mechanism is a stepwise dipolar addition *via* a zwitterionic intermediate (Section 1.2.1.3). These three mechanisms are illustrated in Scheme 3.

### 1.2.1.1 The Concerted Mechanism

The most widely accepted mechanism is that put forth by Huisgen[9] which involves a concerted process with simultaneous formation of two σ-bonds (Scheme 4).




**Scheme 4**

It has been proposed[9] that the addition proceeds *via* a two plane orientation complex (Figure 1) formed by the reactants approaching each other in parallel planes. Propargyl-allenyl type dipoles must bend in order to form this arrangement.

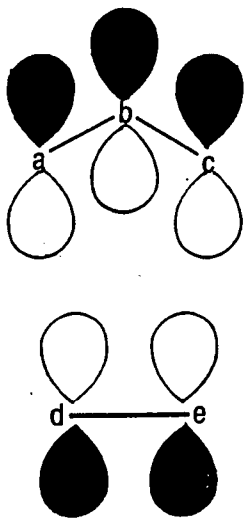



**Figure 1**

The most significant evidence in favour of this mechanism is that the addition proceeds with retention of the configuration of the reactants. Both new σ-bonds must therefore be formed simultaneously although not necessarily synchronously. The large negative entropy of activation ($\Delta S^{\#}$) obtained experimentally for 1,3-dipolar cycloadditions indicates that a highly ordered transition state is involved, as would be expected with the orientation complex associated with a concerted reaction. The fact that solvent polarity has little effect on the rate of addition is inconsistent with a zwitterionic intermediate and suggests a concerted process with no charged intermediate.

Another point in favour of this mechanism is that 1,3-dipolar cycloadditions obey the Woodward-Hoffmann[17] selection rules for conservation of orbital symmetry as would be expected for a concerted process.

### 1.2.1.2 The Stepwise Diradical Mechanism

The mechanism proposed by Firestone[13] is based on a two step process with a spin-paired diradical intermediate (Scheme 3). Diradical intermediates of type (**10**) have previously been rejected on the grounds that they should be capable of free rotation around the d-e bond hence leading to loss of stereochemistry. Firestone[13] counters this argument by proposing that the activation energy for single bond rotation in the intermediate is much greater than that for ring closure or decomposition to reactants, and hence no loss of stereochemistry would be observed.

He has also argued[13] that for addition to an acetylenic dipolarophile some enhancement of rate should be seen over addition to ethylenic dipolarophiles if a concerted mechanism is in operation. This would be due to extra stability in the transition state from the formation of an aromatic ring. No enhancement is observed experimentally and Firestone claims that this points to a two step process with the first step being rate determining. Huisgen[11] has countered this by proposing a non-

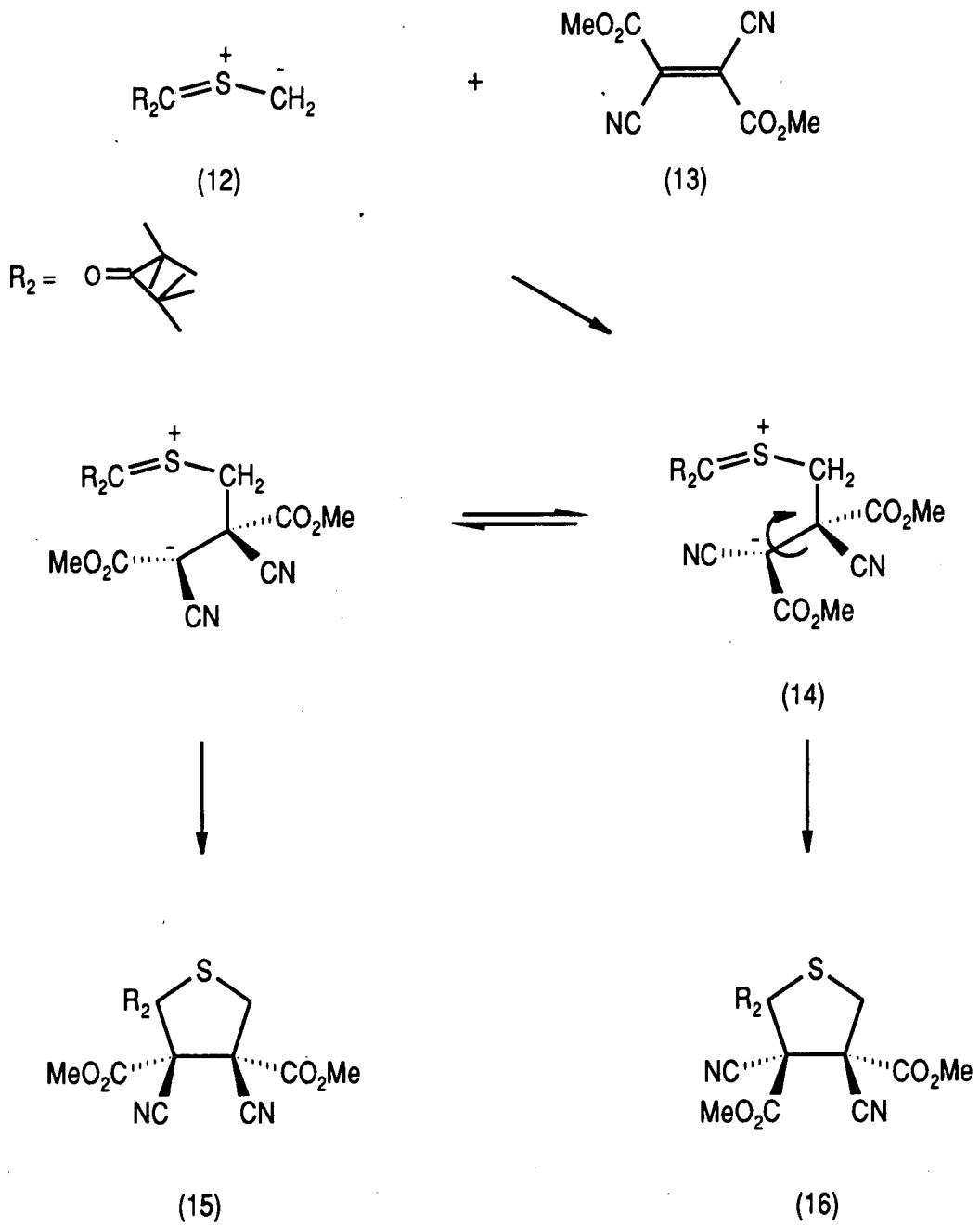
planar transition state for the concerted process which resembles the orientation complex and hence no aromatic stabilisation is possible in the transition state.

Firestone has also claimed[15] that the regioselectivity of 1,3-dipolar cycloadditions is consistent with a diradical mechanism, the reaction proceeding *via* the most stabilised radical. Frontier molecular orbital theory, however, provides a satisfactory explanation of regioselectivity based on a concerted mechanism (Section 1.2.2.2).

### 1.2.1.3 The Stepwise Dipolar Mechanism

The stepwise dipolar mechanism involving a zwitterionic intermediate (**11**) (see Scheme 3) was rejected at an early stage as an explanation for general 1,3-dipolar cycloadditions on two main grounds[9]. Firstly, 1,3-dipolar cycloadditions proceed with retention of stereochemistry whereas there would be loss of configuration due to bond rotation in any zwitterionic intermediate (**11**). Secondly, solvent polarity has very little effect on the rate of 1,3-dipolar cycloadditions. This, therefore, strongly suggests that no charged intermediate such as (**11**) is formed in the reaction.

Huisgen, however, has found that it is possible to force the reaction to proceed *via* a stepwise dipolar mechanism under extreme conditions[18]. In a cycloaddition between a dipole with very high π-molecular orbitals (MOs) and a dipolarophile with very low π-MOs the reaction is very strongly dipole HOMO controlled. This renders the energy contribution by the alternative frontier orbital interaction (dipole-LUMO / dipolarophile-HOMO) negligible and hence it can no longer counteract the large negative entropy of activation. In this case the reaction takes place *via* a stepwise dipolar mechanism with loss of stereochemistry. To prove this Huisgen used a thiocarbonyl ylide (**12**) as the dipole and dimethyl dicyanofumarate (**13**) as the dipolarophile. The formation of two cycloadducts (**15**) and (**16**) was attributed to loss of stereochemistry by rotation in the zwitterionic intermediate (**14**) (Scheme 5).




**Scheme 5**

### 1.2.2 Frontier Molecular Orbital Theory of 1,3-Dipolar Cycloadditions

Although the mechanism of 1,3-dipolar cycloadditions can be understood in terms of the Woodward-Hoffmann rules[17], this approach does not explain the reactivity and regioselectivity of these reactions. In fact the regioselectivity of 1,3-dipolar cycloadditions was considered at one time to be strong evidence for a

diradical mechanism. Fukui's[19] approach based on consideration of the interaction of frontier molecular orbitals (FMOs), however, provides a good explanation of both reactivity and regioselectivity.

During formation of the transition state the major interactions come from the overlap of the FMOs of the reactants, *i.e.* the highest occupied molecular orbital (HOMO) of each reactant overlaps with the lowest unoccupied molecular orbital (LUMO) of the other reactant. A simple example of this is shown in Figure 2 for cycloaddition of the allyl anion to ethene.

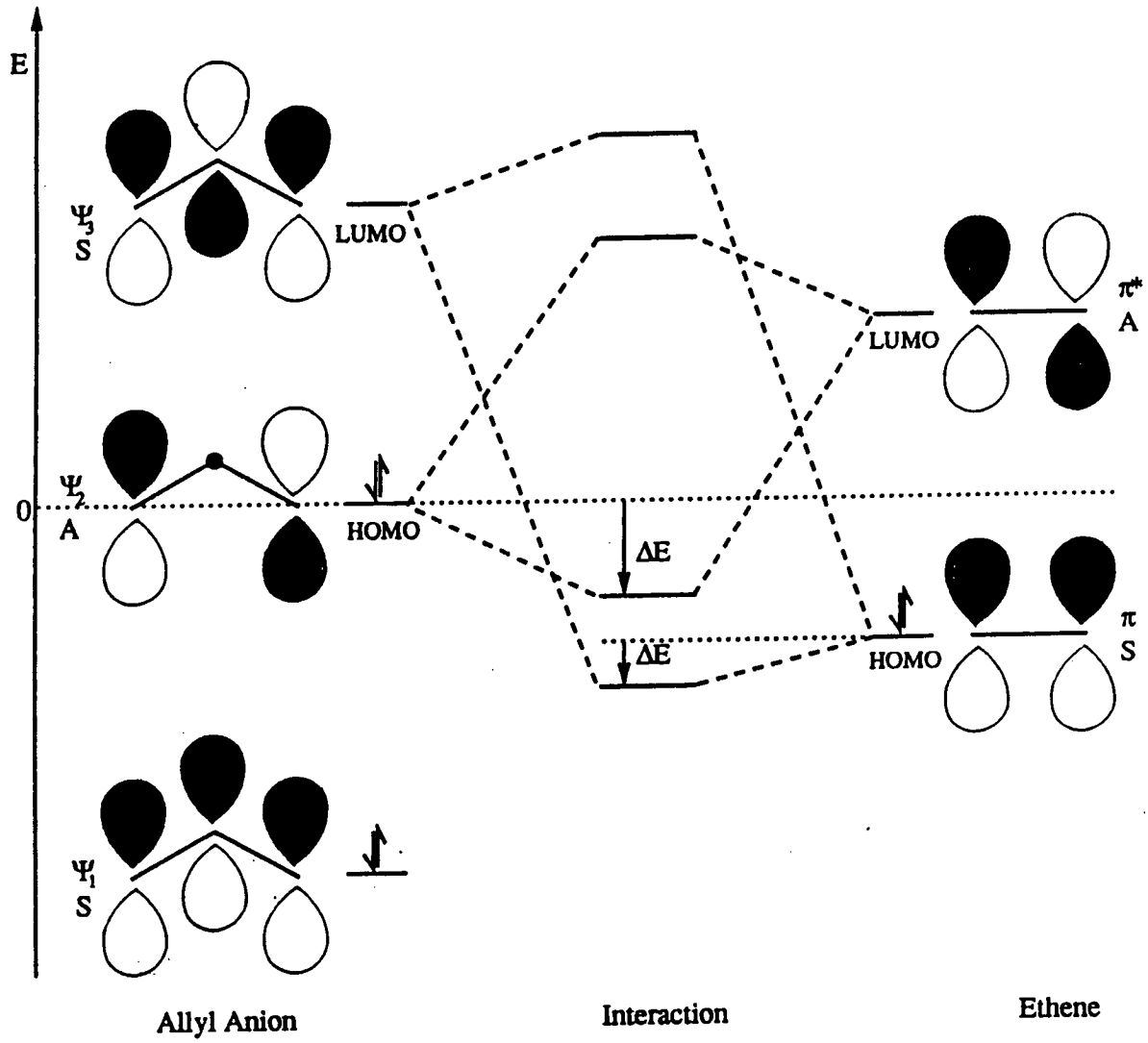
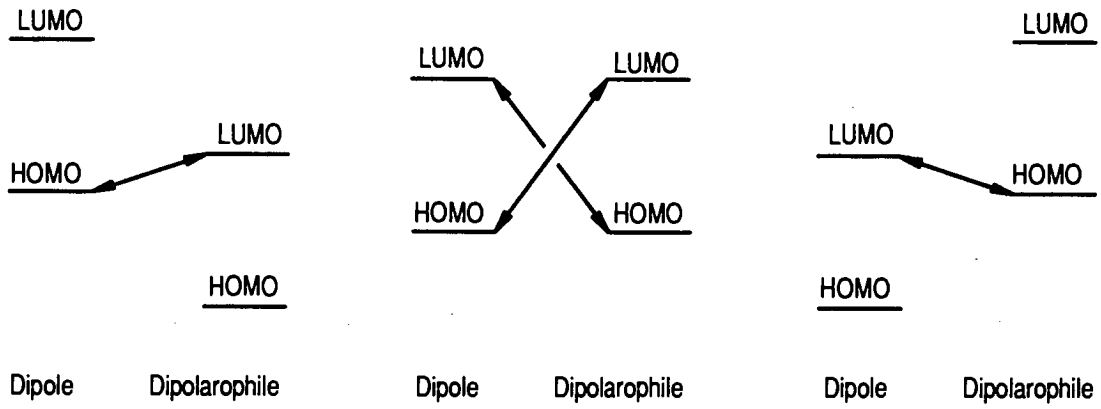



**Figure 2**

### 1.2.2.1 Reactivity

The rate of a 1,3-dipolar cycloaddition is dependent on the stabilisation energy ($\Delta E$) (Figure 2) gained upon overlap of the FMOs. The larger the energy gap between the FMOs, the smaller is the FMO overlap and hence $\Delta E$ and the rate will be lower.

Sustmann[20] has classified 1,3-dipolar cycloadditions into three types (Figure 3) based on their FMO interactions. Using this classification it is possible to qualitatively predict the effect of substituents upon reaction rates. Electron donating and conjugating groups on the dipole and conjugating and withdrawing groups on the dipolarophile will increase the rate of a Sustmann type I cycloaddition. These groups will have an opposite effect on a Sustmann type III system, and donating, withdrawing and conjugating groups will augment the rate in a type II system.




**Type I**

**Dipole HOMO Controlled**

**Type II**

**Dipole HOMO + LUMO Controlled**

**Type III**

**Dipole LUMO Controlled**

**Figure 3**

### 1.2.2.2 Regioselectivity

The ability to explain the regioselectivity of 1,3-dipolar cycloadditions is one of the greatest triumphs of FMO theory.

Unlike the simple case of the addition of the allyl anion to ethene (Figure 2) the presence of heteroatoms in the dipole and substituents on both reactants in a cycloaddition lead to varying sizes of orbitals. Regioselectivities can be predicted from a knowledge of the coefficients of these orbitals by applying the rule[21] that the dominant interaction is that in which the maximum orbital overlap is obtained. This is achieved by combining orbitals of similar sizes (see Figure 4).

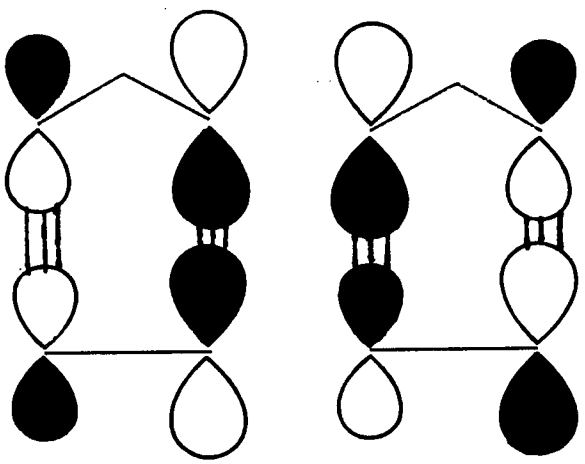
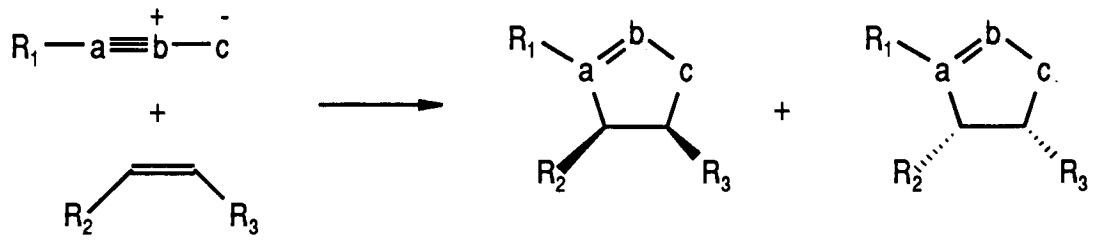



**Figure 4**

### 1.2.3 Stereoselectivity

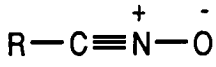
As has been mentioned earlier (Section 1.2.1) 1,3-dipolar cycloadditions proceed with retention of the stereochemistry of the dipolarophile except under extreme conditions (Section 1.2.1.3). Two possible stereoisomers, however, may be formed for each regioisomer as the dipole may attack the dipolarophile from two distinct faces (Scheme 6). Stereochemical control of the cycloaddition is normally exercised by steric factors, the dipole approaching from the least hindered side.



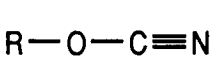

**Scheme 6**

## 1.3 Nitrile Oxides

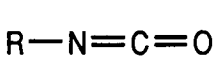
Nitrile oxides (**17**) are members of the nitrilium betaine family of propargyl-allenyl 1,3-dipoles and are isomeric with cyanates (**18**) and isocyanates (**19**). Most members of the series have the fulmido group (-CNO) bonded to carbon, although the parent of the family, formonitrile oxide (fulminic acid, H-CNO) is an exception and its chemistry differs from other members of the series.



(17)



(18)



(19)

Nitrile oxide chemistry has a long history[3,22] extending back almost two hundred years. Formonitrile oxide was the first of the series to be prepared in 1800 and the most commonly used member of the family, benzonitrile oxide, was generated in 1886. Cycloaddition reactions of nitrile oxides to alkenes were first discovered in 1950 and Huisgen's work on 1,3-dipolar cycloadditions led to an upsurge of interest in the area in the 1960's. Over the last decade Jäger[23], Kozikowski[24], Curran[25], Torssell[26] and others have turned nitrile oxide chemistry into an important tool for the synthesis of natural products.

### 1.3.1 Generation of Nitrile Oxides

Due to the tendency of nitrile oxides to dimerise they are rarely isolated but instead are generated *in situ* at low concentration. Although nitrile oxides have been detected as intermediates in a variety of reactions only three methods are normally employed for preparative purposes. These routes to nitrile oxides are summarised in Scheme 7.

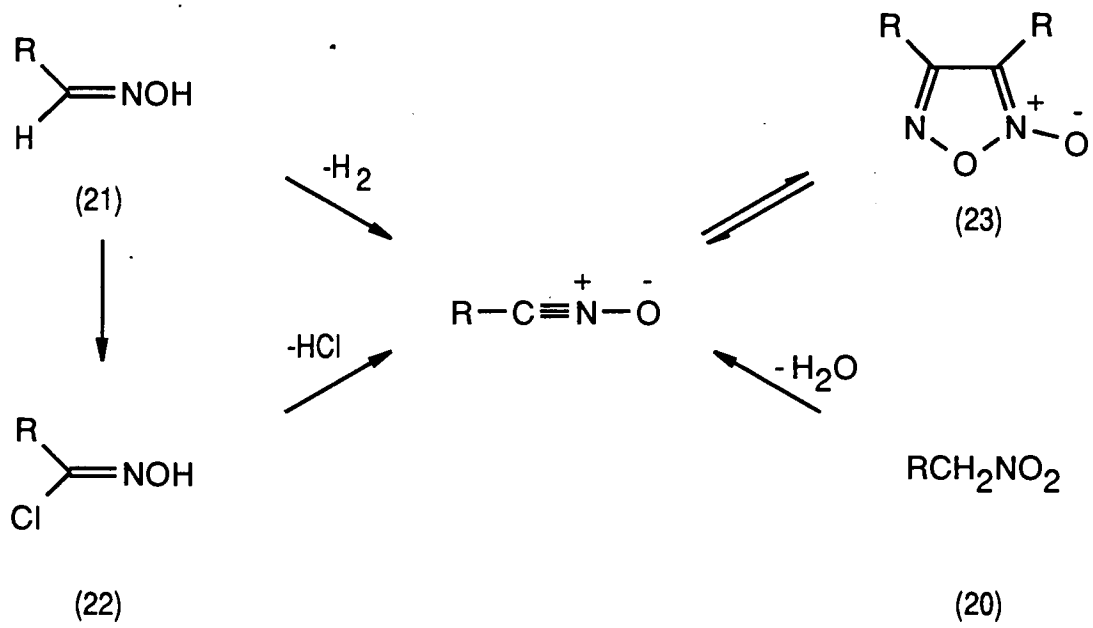
One of the most commonly used methods of generation is the Mukaiyama[27] dehydration of a primary nitro compound (**20**) using a catalytic amount of base and an isocyanate as a dehydrating agent. The proposed mechanism for this reaction is

shown in Scheme 8. Other dehydrating agents have also been used with varying degrees of success, among them acid chlorides[28] and anhydrides[29], phosphorus oxychloride[30] and *p*-toluenesulphonic acid[31].

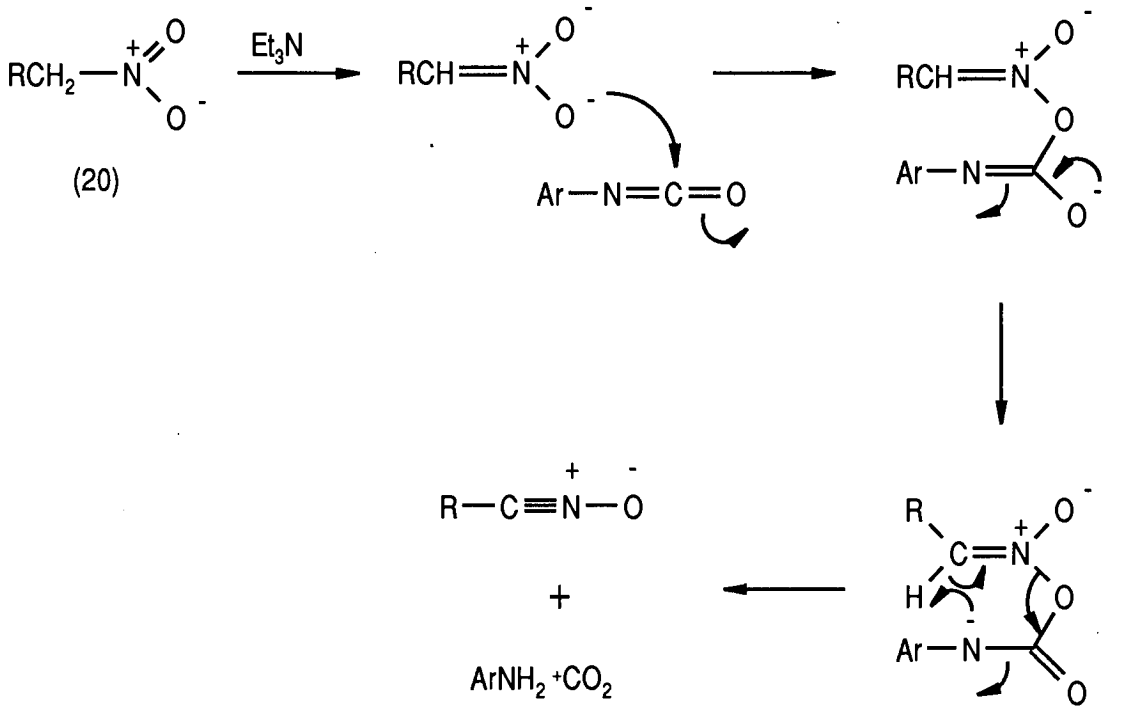
An equally important method is the oxidation of aldoximes (**21**). This may be carried out directly by $Pb(OAc)_4$[32] or more usually by conversion to a hydroximoyl chloride (**22**) (or bromide), followed by dehydrohalogenation by base ($NEt_3$[33,34] or recently KF[35]), heat[36-38] or *via* an organotin intermediate[39,40].

Although some hydroximoyl chlorides may be prepared by direct chlorination[41], milder methods which avoid over-chlorination can be used to generate the hydroximoyl chloride (or bromide) *in situ*. For example N-chlorosuccinimide (NCS)[42-44], N-bromosuccinimide (NBS)[45], nitrosyl chloride[46,47], sodium hypochlorite[48] and hypobromite[49] and chloramine-T[50] have all been used successfully to generate nitrile oxides *via* their hydroximoyl halides.

Thermal cleavage of furoxan dimers (**23**)[51-53] has also been employed to generate nitrile oxides.




**Scheme 7**

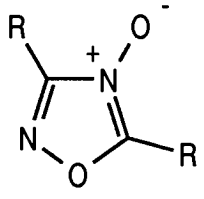


**Scheme 8**

### 1.3.2 Reactions of Nitrile Oxides

Owing to their high reactivity nitrile oxides participate in a number of reactions[54,55] which are summarised in Scheme 9.

In the absence of a dipolarophile two possible modes of decay are available to nitrile oxides. Firstly they can dimerise to yield furoxans (1,2,5-oxadiazole-2-oxides) (**23**). Other dimers, the 1,2,4-oxadiazole-4-oxide (**24**) and 1,4,2,5-dioxadiazine (**25**), are sometimes also formed. These dimers, especially the furoxan (**23**), are often afforded as by-products in cycloaddition reactions. Above 110°C nitrile oxides can undergo thermal rearrangement to give isomeric isocyanates (**19**).



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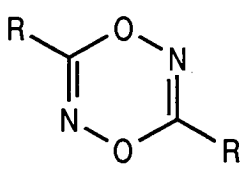
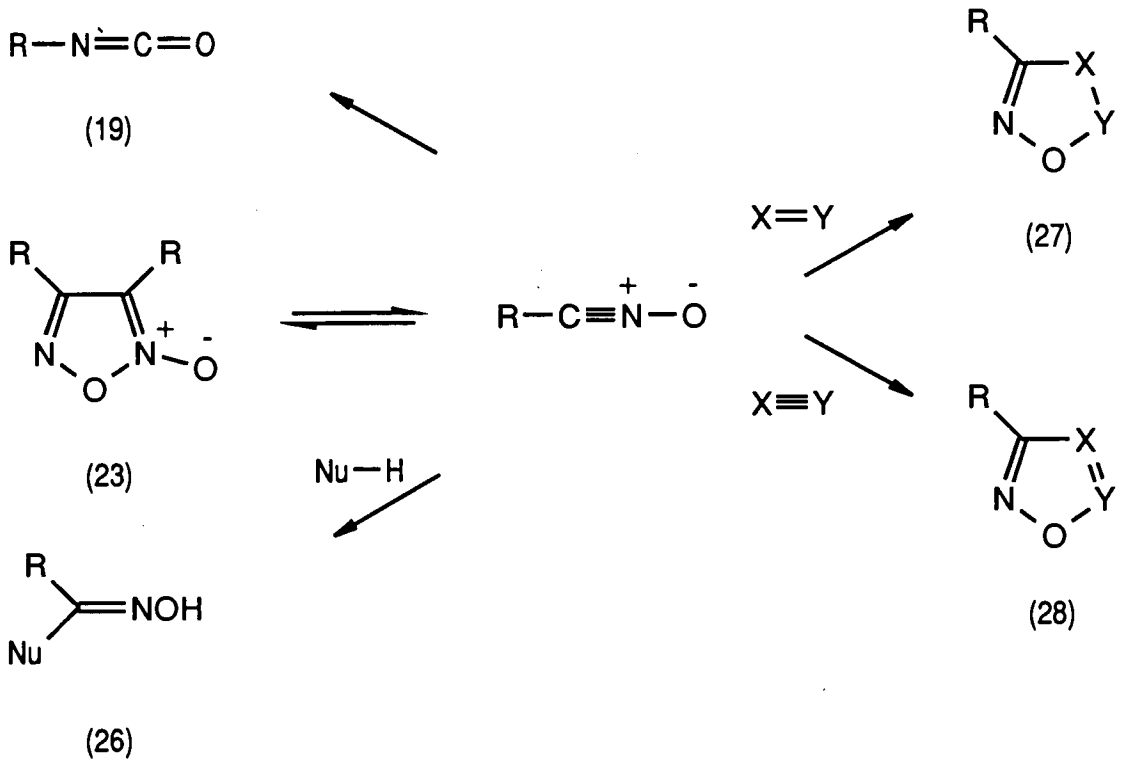


(25)

Nitrile oxides can undergo nucleophilic attack at the carbon atom by compounds containing an acidic hydrogen to produce substituted oximes (**26**).

The most synthetically useful reaction of nitrile oxides is their 1,3-dipolar cycloaddition to double (*e.g.* C=C, C=S, C=O, C=N) or triple bonds (*e.g.* C≡C, C≡N) to give five membered heterocycles (**27**) and (**28**).

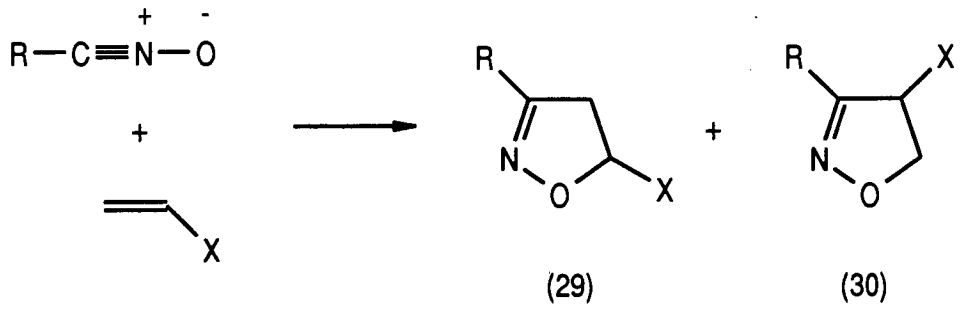



**Scheme 9**

### 1.3.3 Nitrile Oxide Cycloaddition to Alkenes

One of the most widely used reactions of nitrile oxides is their 1,3-dipolar cycloaddition to alkenes to yield 2-isoxazolines. Cycloaddition to mono- and 1,1-disubstituted alkenes are normally regiospecific yielding the 5-substituted-2-isoxazoline. When, however, a dipolarophile with a strong electron withdrawing group is used a mixture of the 5-substituted (**29**) and 4-substituted-2-isoxazolines (**30**) is obtained (Scheme 10). 1,2-Disubstituted alkenes react with retention of

stereochemistry to produce a mixture of regioisomers. More highly substituted alkenes are much less reactive.



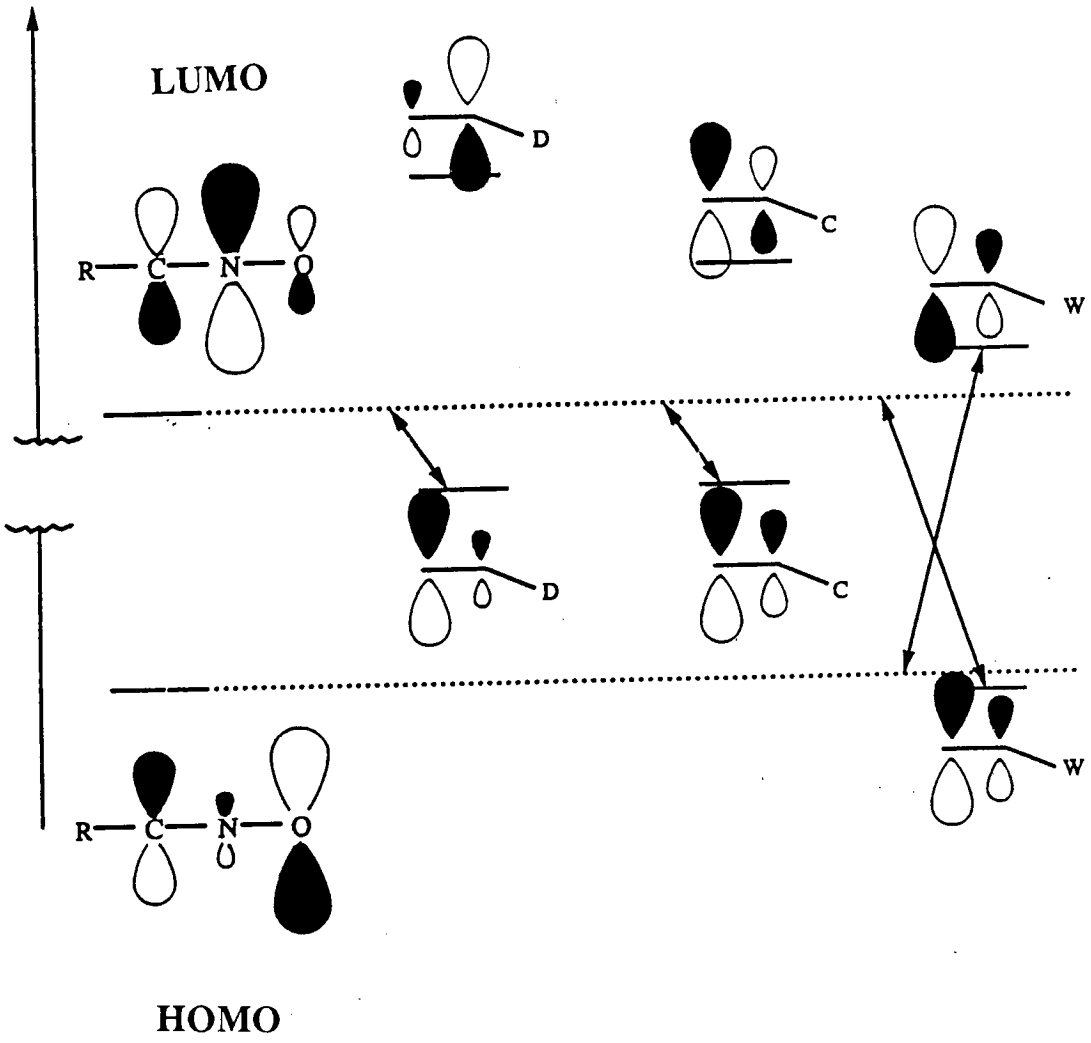

(29) (30)

| R | X | Ratio [56] | | |
|---|---|---|---|---|
| Ph | $CH_3$ | 100 | : | 0 |
| Ph | $CO_2CH_3$ | 95 | : | 5 |

**Scheme 10**

The reactivity of the dipolarophile is increased by electron withdrawing, donating and conjugating groups and by the presence of strain in the molecule.

The regioselectivity of these reactions can be explained by applying FMO theory (see Section 1.2.2.2). For dipolarophiles with conjugating or electron donating substituents (Figure 5) the dominant interaction is LUMO-dipole/HOMO-dipolarophile (Sustmann type III). Electron withdrawing substituents lower the HOMO and LUMO such that the HOMO-dipole/LUMO-dipolarophile interaction becomes much more significant (Sustmann type II) and hence more 4-substituted product is formed.




D = Electron Donating Group

C = Conjugating Group

W = Electron Withdrawing Group

**Figure 5**

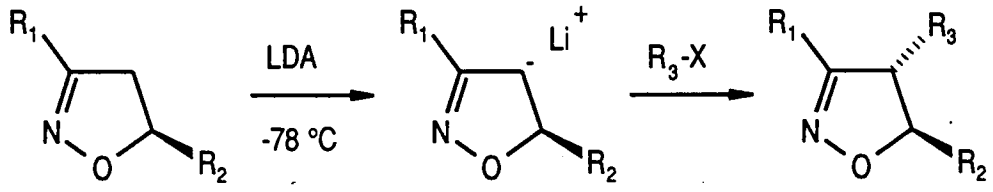
## 1.4 The Synthetic Utility of Nitrile Oxide/Isoxazoline Chemistry

Although the importance of nitrile oxide cycloadditions in the synthesis of 5-membered heterocycles has been realised for many years it is only recently that the wider synthetic applications of this chemistry have been recognised[57].

The upsurge in interest in this area is due to the realisation that 2-isoxazolines are masked intermediates for a variety of functionalities[24], and to the discovery of methods for unmasking these functionalities.

This has led to the development of the nitrile oxide/isoxazoline route to natural products and analogues, involving three basic steps: firstly the 1,3-dipolar cycloaddition of a nitrile oxide to an alkene provides a method of carbon-carbon bond formation with predictable regio- and stereochemistry, from readily available precursors. The second step, if required, is modification of the isoxazoline. 2-Isoxazolines are stable to many reagents thereby allowing substituents to be manipulated without destroying the isoxazoline ring.

It is also possible to modify the isoxazoline ring itself. Jäger[58] has developed a method of substituting at the 4-position of the isoxazoline ring by deprotonation and reaction of the resulting anion with an electrophile. This yields the 4-substituted isoxazoline in a highly stereoselective manner with the electrophile approaching from the less hindered face (see Scheme 11).




**Scheme 11**

The final step is ring cleavage to release the masked functionality. Scheme 12 summarises the latent functionalities present in the isoxazoline ring.

One of the most important functionalities latent in 2-isoxazolines is the β-hydroxy ketone. This offers an alternative[25] to the aldol condensation which does not have the problems normally associated with aldol reactions: cross and self-aldol side reactions, reversibility, selective enolate formation and lack of stereocontrol. It is noteworthy that a different carbon-carbon bond is formed in each approach (Figure 6).

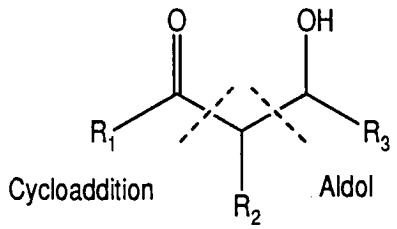



**Figure 6**

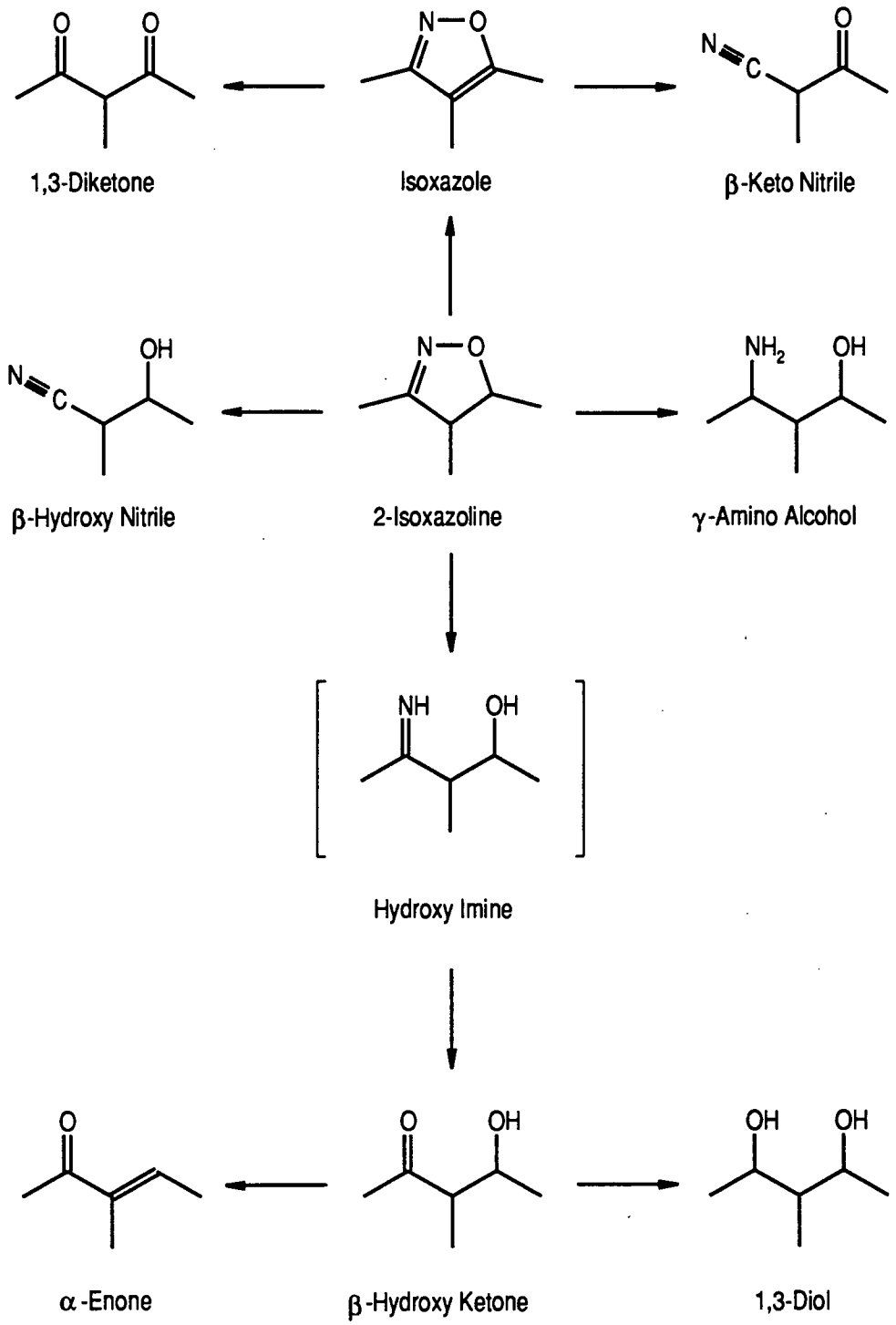
A variety of techniques have been used to ring-open 2-isoxazolines to β-hydroxy ketones. All these methods proceed *via* hydrolysis of an imine intermediate (see Scheme 12). The most widely used of these is catalytic hydrogenolysis[25] with palladium on charcoal or Raney-nickel under acidic conditions. Other reagents used include titanium trichloride[26], molybdenum hexacarbonyl[59] and ozone[60]. The β-hydroxy ketones then provide access to 1,3-diols by reduction and to α-enones by dehydration.

Another important functionality latent in the isoxazoline ring is the γ-amino alcohol. Jäger[23] has developed a stereoselective route to γ-amino alcohols based on lithium aluminium hydride reduction of the isoxazoline. The diastereoselectivity of this process is heavily dependent on the substituents of the isoxazoline ring.

Oxidation of 2-isoxazolines yields isoxazoles, which provides a route[61] to 1,3-diketones and β-keto nitriles.

β-Hydroxy nitriles may be obtained from 2-isoxazolines by two methods: firstly by base deprotonation[26] and rearrangement of 3-unsubstituted isoxazolines.

Alternatively thermal decarboxylation[62] of isoxazoline-3-carboxylic acids yields the β-hydroxy nitriles.




**Scheme 12**

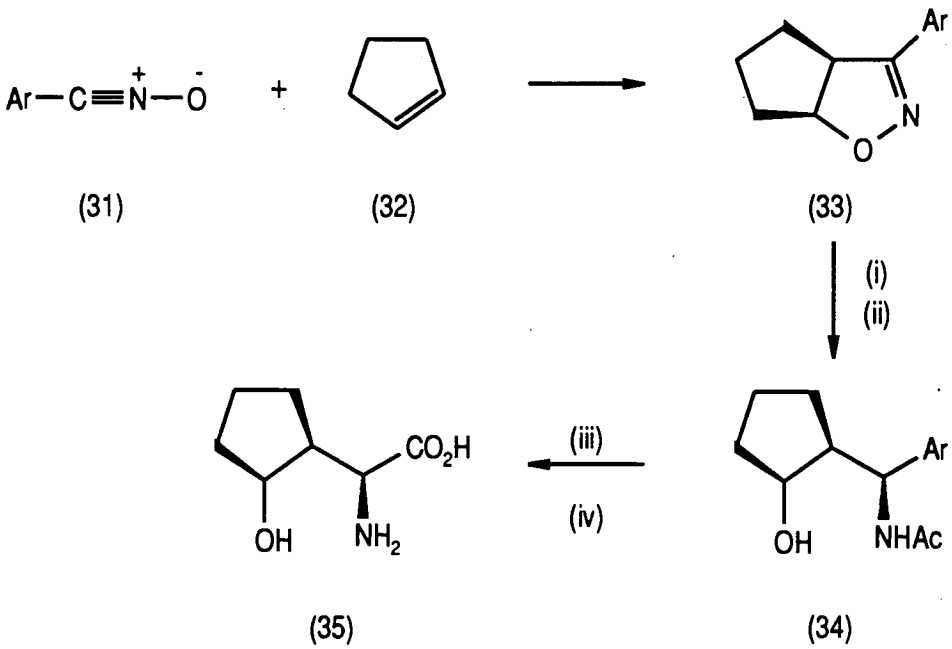
### 1.4.1 Examples of the Nitrile Oxide/Isoxazoline Approach to the Synthesis of Natural Products

This section gives three examples to illustrate the use of the nitrile oxide/isoxazoline approach in the preparation of natural products and analogues. For further examples see references 24 and 63.

#### 1.4.1.1 γ-Hydroxy-α-Amino Acids

Several syntheses of natural and unnatural γ-hydroxy-α-amino acids have been carried out using the nitrile oxide/isoxazoline approach[63].

Jäger and co-workers[64] have utilised the stereoselective $LiAlH_4$ reduction of isoxazolines in the synthesis of β-hydroxycyclopentyl glycine (**35**) (Scheme 13). Cycloaddition of an aromatic nitrile oxide (**31**) to cyclopentene (**32**) yielded isoxazoline (**33**), which upon $LiAlH_4$ reduction followed by acetylation produced a single γ-amino-alcohol (**34**). Oxidative aryl cracking followed by deprotection gave the γ-hydroxy-α-amino acid (**35**) in 40% overall yield.



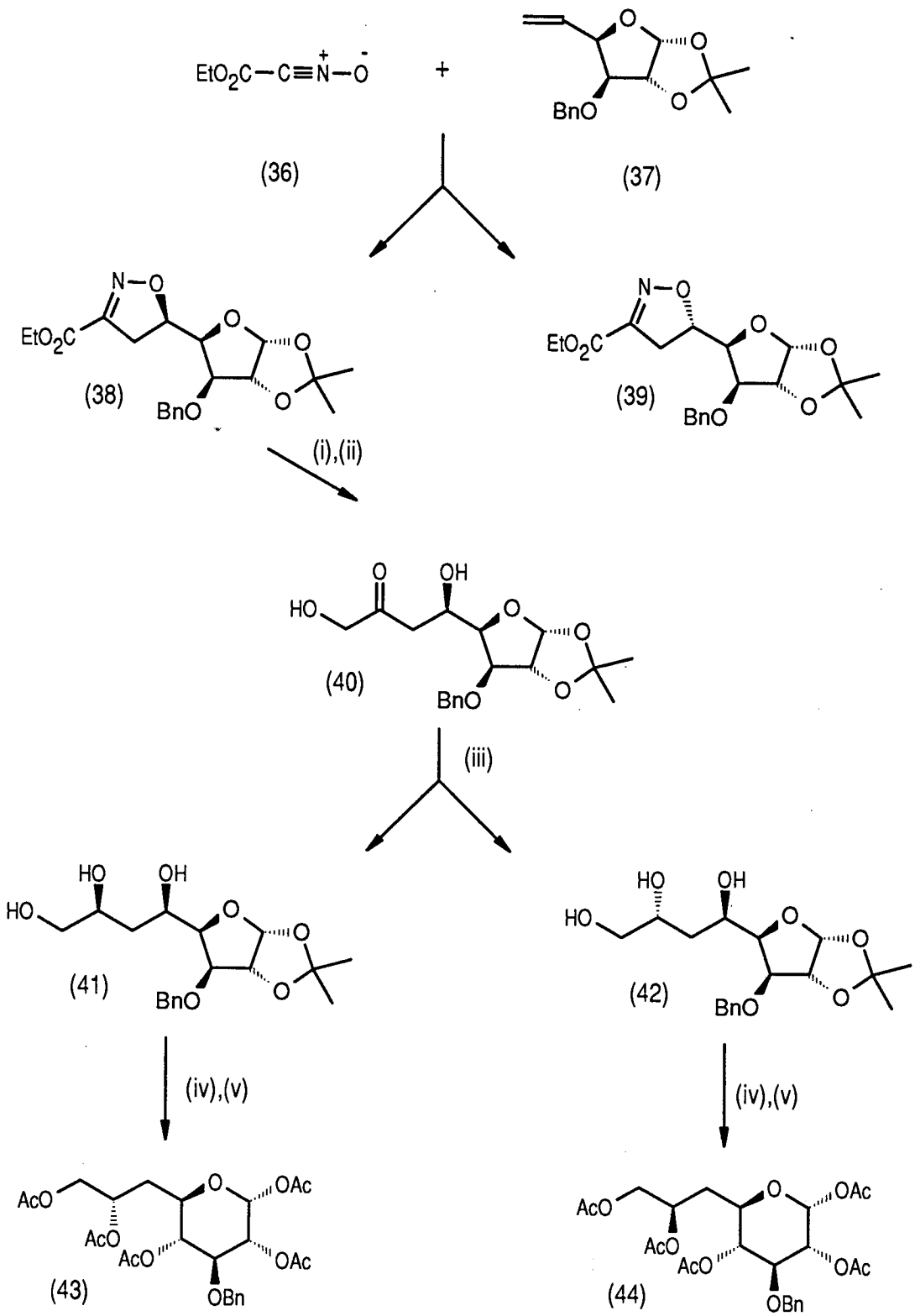

(i) $LiAlH_4$ ; (ii) Acetylation ; (iii) $RuCl_3$, $NaIO_4$ ; (iv) 6N HCl

**Scheme 13**

### 1.4.1.2 Higher Sugars

Higher sugars are monosaccharides with more than six contiguous carbons. They are found as fragments of some natural antibiotics such as the tunicamycins[65].

Paton and Young[66] have applied the nitrile oxide/isoxazoline approach to the synthesis of higher sugars including 6-deoxyoctoses (**43**) and (**44**) (Scheme 14). Cycloaddition of a two-carbon nitrile oxide, ethoxycarbonylformonitrile oxide (**36**), generated from the corresponding hydroximoyl chloride, to a six-carbon sugar alkene (**37**), derived from D-glucose, yielded an 86:14 mixture of diastereomeric isoxazolines (**38**) and (**39**). The major isomer (**38**) was converted to β-hydroxy ketone (**40**) by reduction of the ester function to hydroxymethyl followed by palladium/charcoal hydrogenolysis. β-Hydroxy ketone (**40**) was reduced to a mixture of 1,3-diols (**41**) and (**42**) which were separated by chromatography and then deprotected and acetylated to yield the 6-deoxy-D-*gluco*-octopyranoses (**43**) and (**44**). 6-Deoxy-nonose and -decose derivatives have been prepared by a similar route[66].




(i) $NaBH_4$ ; (ii) Pd/C, $H_2$, $B(OH)_3$, $MeOH/H_2O$ ; (iii) $NaBH_4$ ; (iv) TFA, $H_2O$ ; (v) $Ac_2O$, $ZnCl_2$

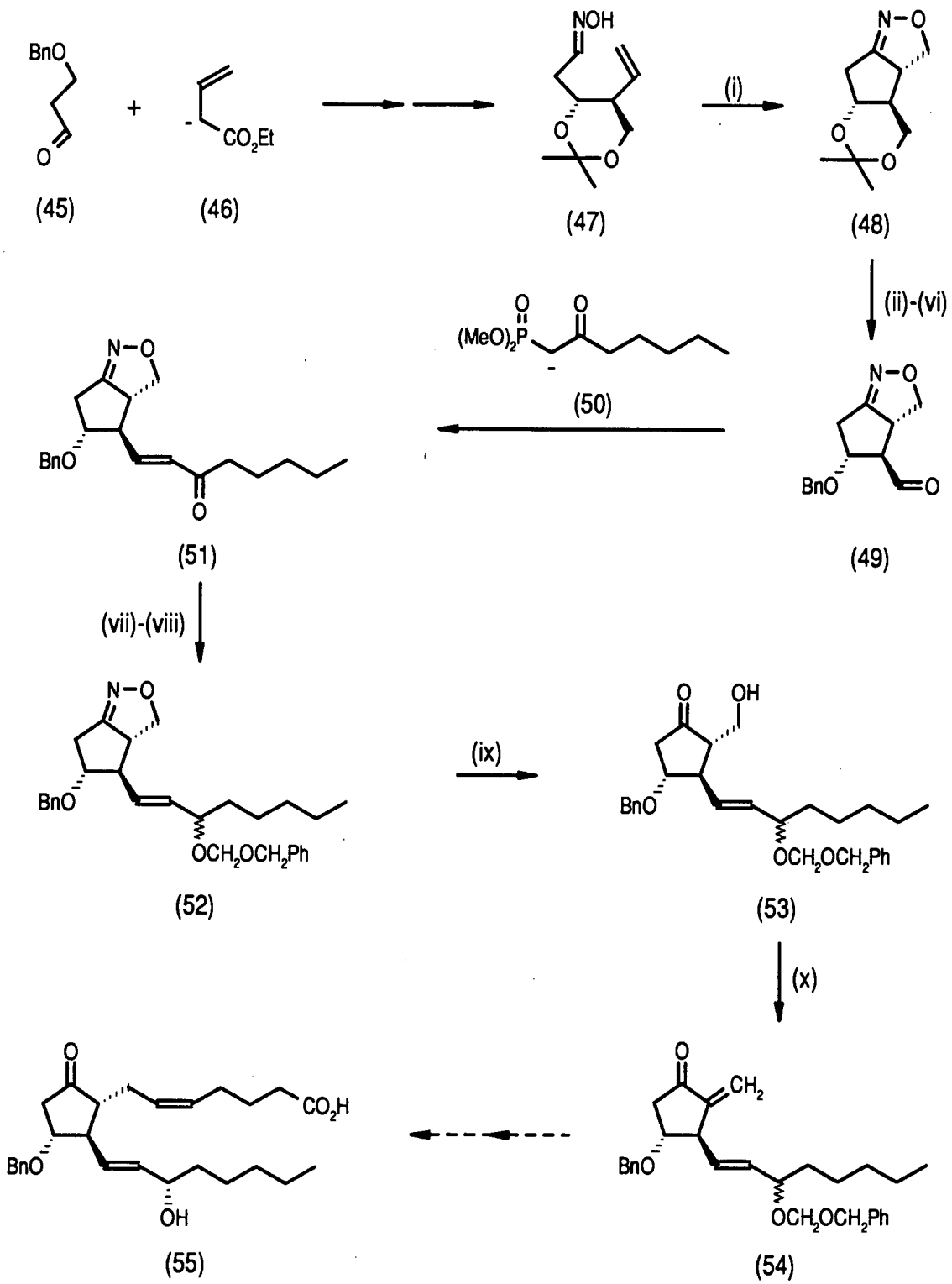
**Scheme 14**

### 1.4.1.3 Prostaglandins

The two previous examples of the nitrile oxide/isoxazoline approach have involved the linking together of two fragments by intermolecular cycloadditions. Intramolecular cycloadditions, however, have also proved to be very useful in natural product synthesis[24,63], especially as they tend to be more stereoselective due to steric considerations.

Kozikowski and Stein[67] have used the intramolecular nitrile oxide cycloaddition reaction in the synthesis of prostaglandin intermediate (**54**) (Scheme 15). Such prostaglandins have attracted much interest due to their role as biological regulators. Intermediate (**54**) has previously been used in the synthesis of prostaglandin $F_{2\alpha}$[68] ($PGF_{2\alpha}$) (**55**) and hence synthesis of (**54**) may be considered a formal synthesis of $PGF_{2\alpha}$.

Oxime (**47**) was prepared from the anion of ethyl crotonate (**46**) and 3-(phenylmethoxy)propanal (**45**). An intramolecular cycloaddition was carried out by oxidation of oxime (**47**) to the nitrile oxide by sodium hypochlorite, to yield isoxazoline (**48**); no other isomer was detected. A number of protection/deprotection steps were carried out, followed by Swern oxidation to produce aldehyde (**49**). This was coupled to phosphonate anion (**50**) *via* a Wittig reaction to produce enone (**51**). (**51**) was reduced and the allylic alcohol formed protected to yield (**52**). The isoxazoline ring was then cleaved to the β-hydroxy ketone (**53**) by catalytic hydrogenolysis (Raney-Ni) and then dehydrated to the α-enone (**54**).




(i) NaOCl ; (ii) Amberlyst-15, MeOH ; (iii) $^{t}Bu(Me)_2SiCl$, Imidiazole, DMF ; (iv) NaH, BnBr, $^{n}Bu_4NI$ ; (v) $^{n}Bu_4NF$ ; (vi) DMSO, $(COCl)_2$, $NEt_3$ ; (vii) $NaBH_4$, $CeCl_3$, MeOH ; (viii) $PhCH_2OCH_2Cl$, $^{i}Pr_2NEt$ ; (ix) Ra-Ni, $H_2$, $BCl_3$, MeOH/$H_2O$ ; (x) MsCl, Pyridine

**Scheme 15**

## 1.5 Glycosidases

Glycoside hydrolases (glycosidases) are enzymes which catalyse the hydrolysis of glycosidic linkages in oligo- and polysaccharides, and in complex carbohydrates such as glycolipids and glycoproteins.

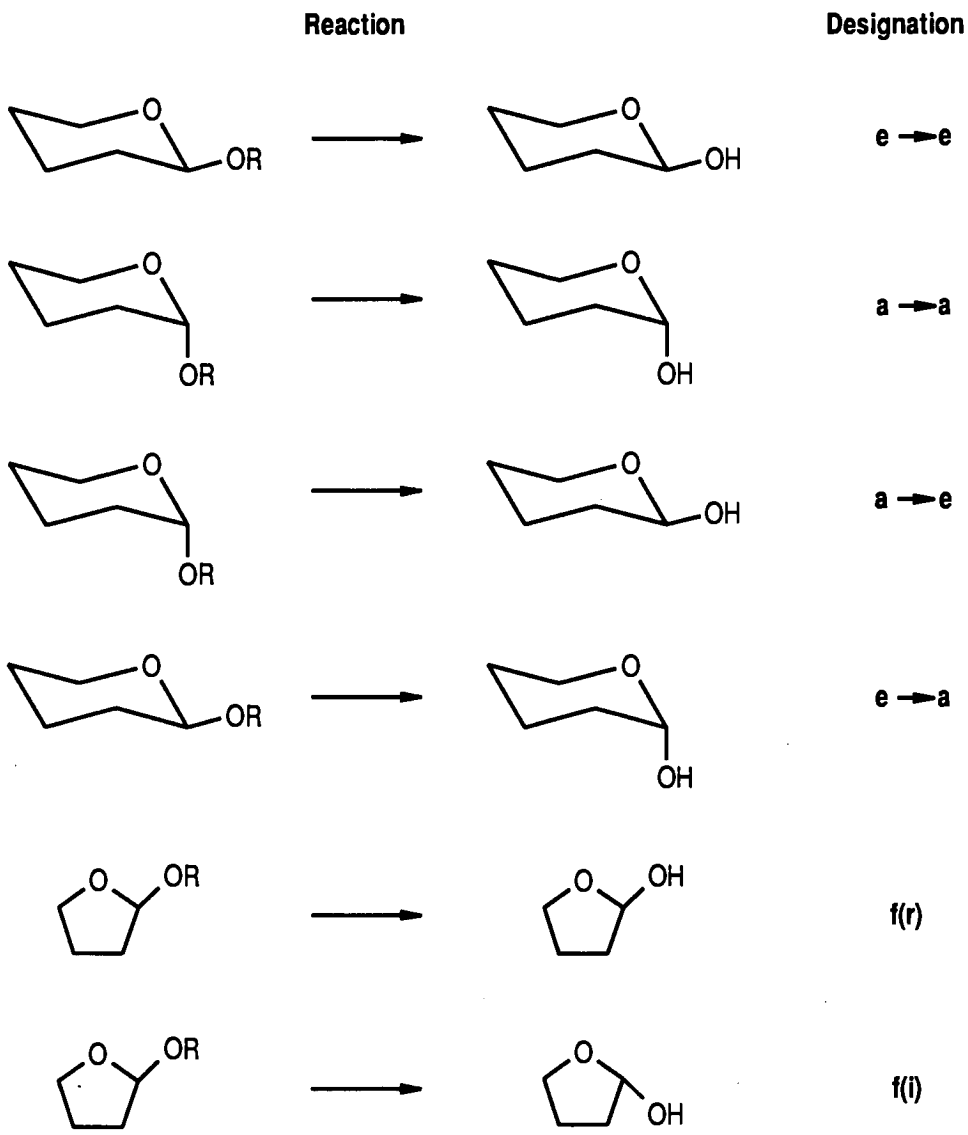
They are utilised by almost all organisms in a variety of roles. Extracellular glycosidases are used to degrade large molecules to prepare them for uptake by the organisms, for example the breakdown of large carbohydrates in the gut of animals. Intracellular lysomal glycosidases are involved with the degradation and turnover of cellular glycoproteins and glycolipids. Glycosidases also play a significant role in the biosynthesis of the carbohydrate chains of *N*-linked glycoproteins (see Section 1.5.2).

### 1.5.1 Mechanism of Hydrolysis[69,70]

Glycoside hydrolases can be divided into a number of classes[69] based on several criteria: the anomeric configuration of substrate, whether the substrate is a pyranose or furanose ring, and whether the configuration of the anomeric position is retained or inverted upon hydrolysis (Table 2). Despite this all glycosidase reactions can be considered formally as nucleophilic substitutions at the saturated carbon of the anomeric centre.

Two mechanisms have been put forward for retaining glycosidases (glycosidases which catalyse the hydrolysis of glycosidic linkages with retention of anomeric configuration). Koshland proposed a double displacement mechanism involving three basic steps (Scheme 16). The first step involves protonation of the glycosidic oxygen by an enzymic acid catalyst group followed by displacement of the glycone by an enzyme-bound carboxylate anion to form a covalently bonded intermediate (**57**). This is formed *via* a glycosyl cation-like transition state (**56**). Water then attacks the anomeric centre and displaces the carboxylate group *via* another glycosyl cation-like transition state (**58**).

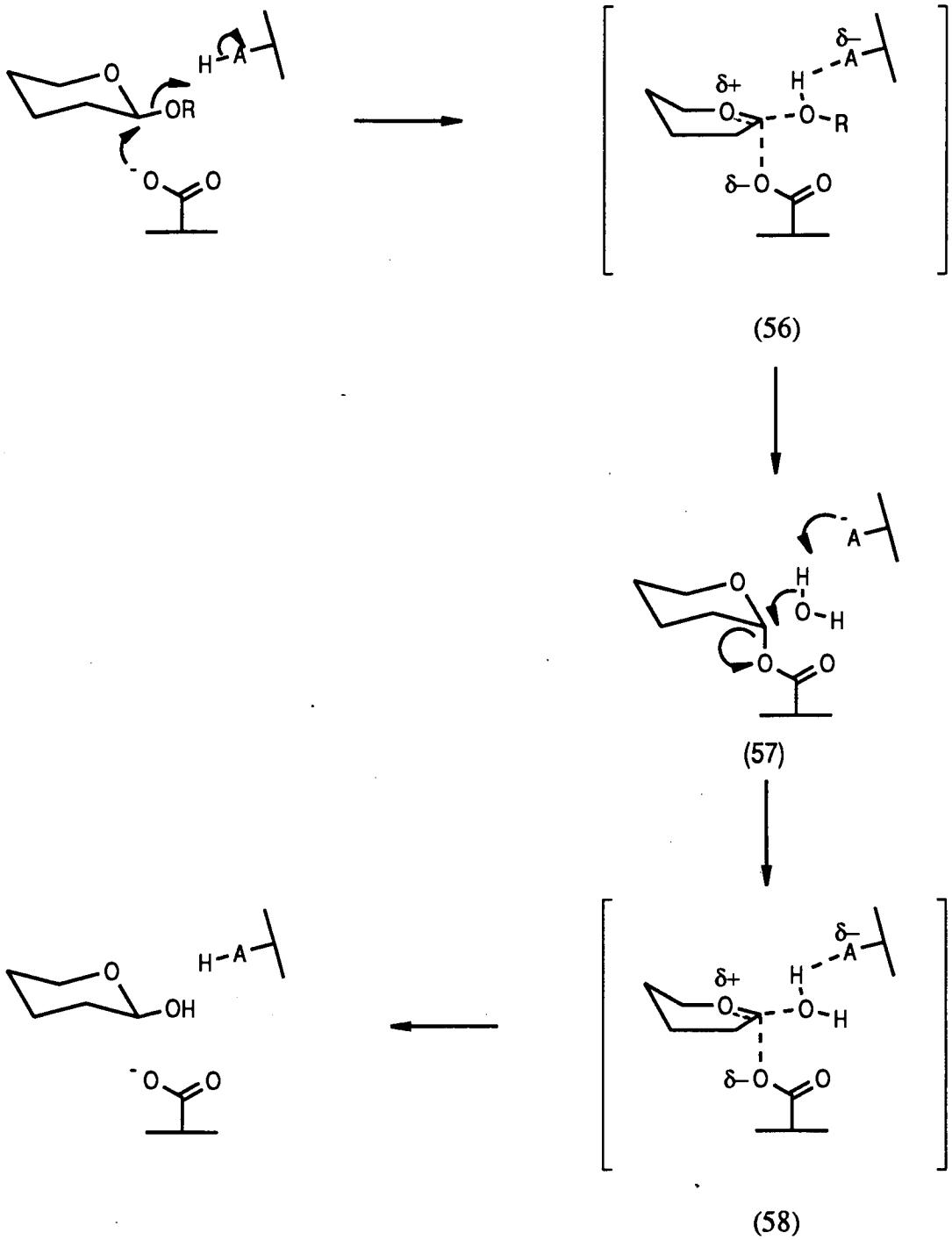
**Table 2** - Classification of Glycosidases




An alternative mechanism has been put forward involving formation of an ion-pair between the glycosyl cation and an enzyme-bound carboxylate anion (Figure 7).

Inverting glycosidases are thought to use a Koshland single displacement mechanism which involves protonation of the glycosidic oxygen followed by displacement of the glycone by attack of water *via* a glycosyl cation-like transition

state. Unlike Koshland's double displacement mechanism no covalently bound intermediate is involved.




**Scheme 16**

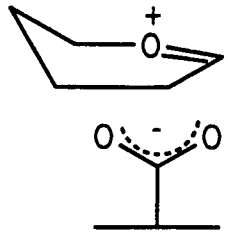
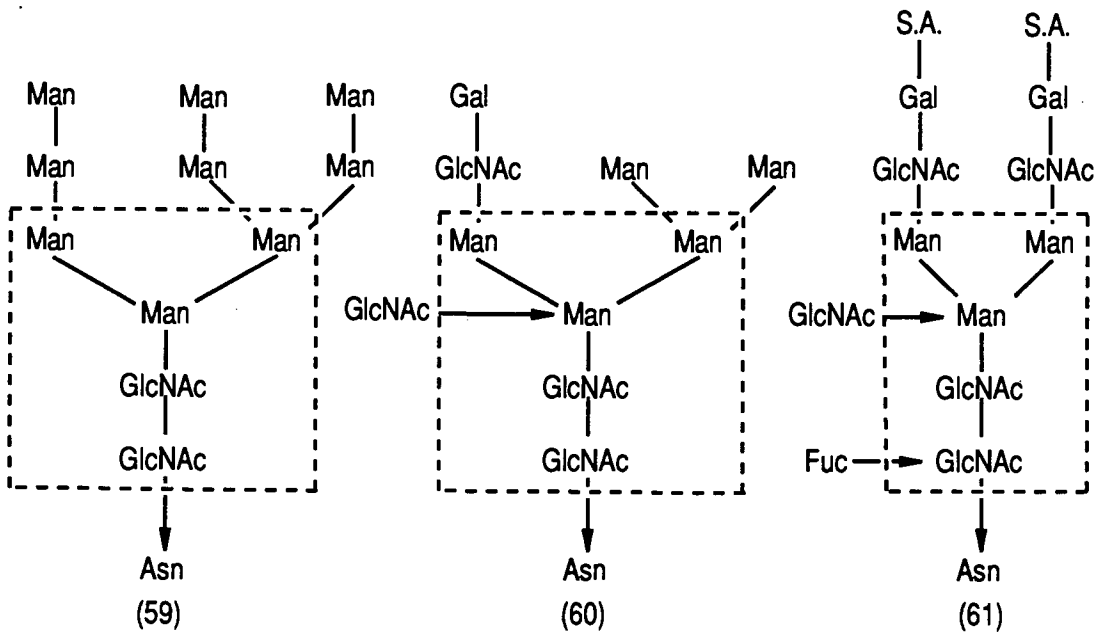


**Figure 7**

### 1.5.2 Glycosidases in Glycoprotein Processing[71]

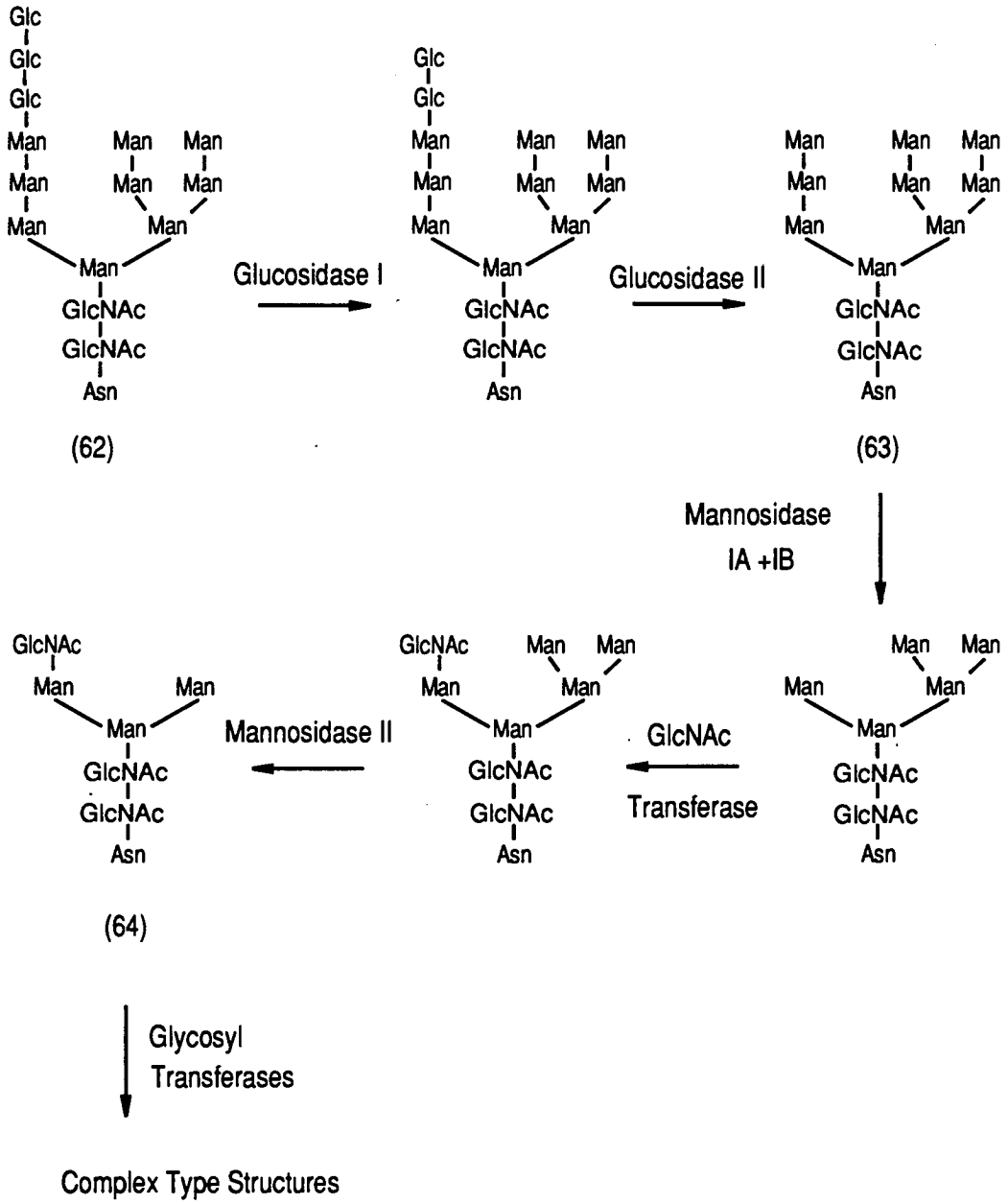
Asparagine-linked (*N*-linked) glycoproteins are commonly found in eukaryotic cells especially as cell surface proteins. The oligosaccharide chains of these glycoproteins are thought to be involved in cell to cell recognition, adhesion and differentiation processes due to their ability to confer specificity at the cell surface owing to the large number of possible oligosaccharide structures. These chains are divided into three classes: high mannose (**59**), hybrid (**60**) and complex (**61**) all of which have the same pentasaccharide core.




Man - Mannose ; GlcNAc - N-Acetylglucosamine ; S.A. - Sialic Acid ; Gal - Galactose ;

Fuc - Fucose ; Asn - Asparagine

All *N*-linked oligosaccharides are derived from a common precursor $Glc_3Man_9(GlcNAc)_2$ (**62**), which is synthesised in the endoplasmic reticulum and is then transferred to the appropriate asparagine residue of the forming protein. The oligosaccharide chains then undergo a series of processing steps, which are catalysed by glycosidases (called "trimming" or "processing" glycosidases), as the glycoprotein passes through the endoplasmic reticulum and the Golgi apparatus (Scheme 17).




**Scheme 17**

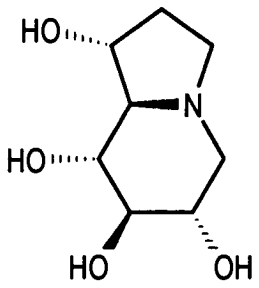
Firstly, the three glucose residues are removed by the action of glucosidases I and II to leave the $Man_9(GlcNAc)_2$-protein system (**63**), which may give rise to high mannose type structures or undergo further processing to give hybrid and complex type oligosaccharides. This further processing involves removal of four mannose residues by mannosidases 1A and 1B, transfer of GlcNAc onto the structure by GlcNAc transferase I, and then removal of two more mannose residues by mannosidase II. The $GlcNAcMan_3$ $(GlcNAc)_2$-protein system (**64**) is then ready for glycosyl transferase-catalysed addition of a variety of sugars. Additional GlcNAc residues can be added as well as galactose, fucose, sialic acid *etc.* to give a wide range of complex type structures.

### 1.5.3 Glycosidase Inhibitors

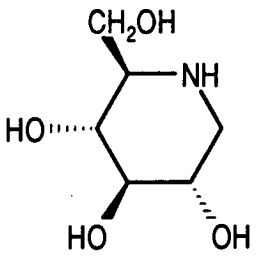
Over the last few years a number of inhibitors of glycosidases have been isolated from natural sources and others synthesised. These compounds have been reviewed recently by Elbein[72] and by Winchester[73] and so only a few examples will be discussed here.

Various naturally occurring polyhydroxylated alkaloids have been found to inhibit glycosidases. Castanospermine (**65**) and deoxynojirimycin (**66**), for example, are both strong inhibitors of glucosidases, whereas swainsonine (**68**) and deoxymannojirimycin (**69**) are potent inhibitors of mannosidases. Pyrrolizidine alkaloids are also known to be powerful inhibitors, examples include 2R,5R-dihydroxymethyl-3R,4R-dihydroxpyrrolidine (DMDP; a glucosidase inhibitor) (**67**) and 1,4-dideoxy-1,4-imino-D-mannitol (DIM; a mannosidase inhibitor) (**70**).

All of these compounds are reversible inhibitors which are thought to mimic the glycosyl cation-like transition state (see Section 1.5.1). The inhibition is pH dependent and it is considered likely that the protonated inhibitor forms an ion-pair with a carboxylate anion in the active site of the enzyme.



(65)



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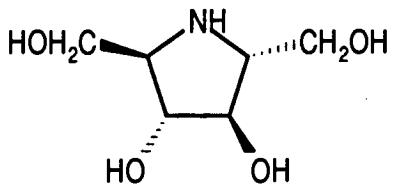
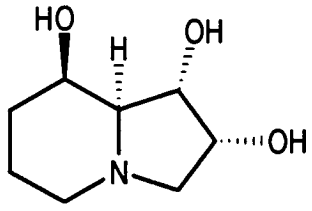
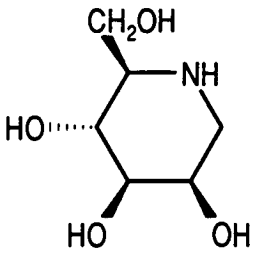


(67)

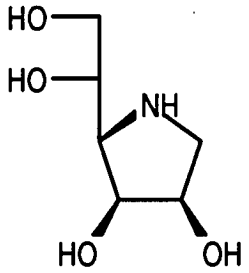
**Glucosidase Inhibitors**



(68)



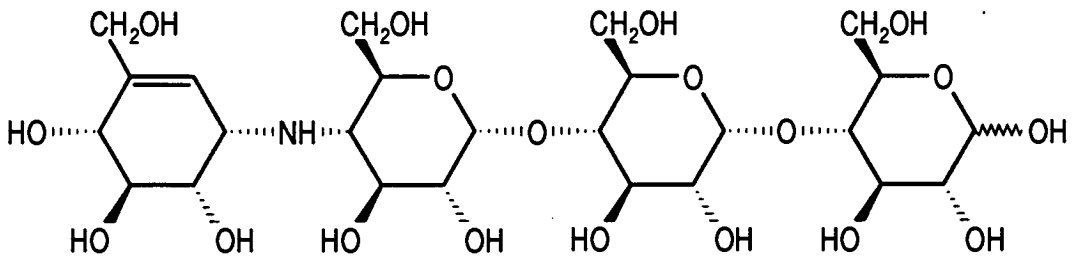
(69)



(70)

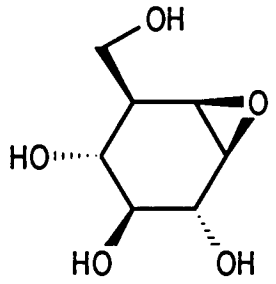
**Mannosidase Inhibitors**

A number of pseudo-oligosaccharidic glycosidase inhibitors have been isolated from microbial broths; these include acarbose (**71**) which is an inhibitor of intestinal α-glucosidases[74]. Its mode of action is though to be similar to that of the polyhydroxylated alkaloids with the cyclohexene ring at the non-reducing end mimicking the glycosyl cation-like transition state and the protonated nitrogen linker forming an ion-pair with an active site carboxylate.



(71)

Irreversible inhibitors have also been reported, for example cyclophellitol (**72**), which is a glucosidase inhibitor. This compound has a structure similar to that of the enzyme's natural substrate and hence is taken up by the enzyme. Its mode of action is believed to involve protonation of the epoxide oxygen followed by nucleophilic attack by an active site carboxylate anion to leave the inhibitor covalently bound to the enzyme.




(72)

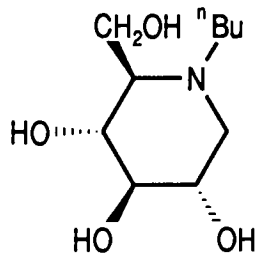
### 1.5.4 Uses of Glycosidase Inhibitors

#### 1.5.4.1 Antiviral

Many viruses have heavily glycosylated envelope proteins which play an important role in viral infectivity processes. For example, the HIV virus has an envelope glycoprotein gp120 which binds to the CD4 lymphocytes of the virus' target cell (human T-cells). The formation of this CD4/gp120 complex allows the virus to enter the cell.

Several glucosidase inhibitors, especially *N*-butyl deoxynojirimycin (**73**)[75-77], have been found to decrease the infectivity of the HIV virus. This is thought to be due to inhibition of glycoprotein processing glucosidases which results in incomplete processing of the oligosaccharide chains on gp120. Proper binding of gp120 with the CD4 lymphocyte is therefore prevented and the virus cannot enter the cell. This may be as a result of the CD4/gp120 complex not achieving the correct conformation.

Inhibitors of trimming mannosidases, such as *N*-methyl deoxymannojirimycin (**74**), have also been reported[78] to cause some reduction in HIV infectivity.

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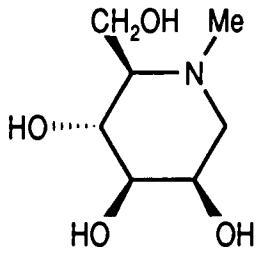



(74)

### 1.5.4.2 Anti-Cancer

Most deaths in cancer patients are caused, not by primary cancer, but by metastases[79]. This is the process where cancer cells invade the blood vessels or lymphatic system and are transported round the body to set up secondary tumours. Any treatment, therefore, which can prevent this process could be of great therapeutic value when coupled with treatment for the primary cancer (*e.g.* surgery or radiotherapy).

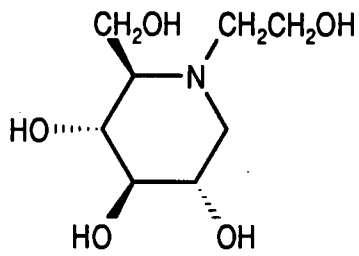
It has been noted[80] that there is a direct link between the increase in size of Asn-linked oligosaccharides on tumour cell surface glycoproteins and their metastic capability. Therefore inhibitors of trimming glycosidases may be able to prevent the metastic process by blocking the synthesis of large complex-type Asn-linked oligosaccharides. These defects in the Asn-linked oligosaccharides are thought to increase the susceptibility of the cell to lysis by natural killer cells[81,82] and to block the colonisation phase of metastasis by interfering with the binding of the cancer cells to their target organs[83,84].

Preliminary work has already been carried out in this field and the mannosidase inhibitor swainsonine (**68**)[81-84] has been successfully used to block metastasis of B16FlO melanoma and MDAY-D2 lymphoid tumour cells in mice.

### 1.5.4.3 Diabetes and Anti-obesity

In recent years a number of compounds that inhibit intestinal disaccharidases[73,74,85] have been isolated from natural sources or synthesised. The ability of these compounds to slow absorption of carbohydrates from the small intestine has stimulated a great deal of interest. Acarbose[86] (**71**) and miglitol[87,88] (**75**) have been shown to aid control of blood glucose levels in patients suffering from diabetes mellitus by slowing carbohydrate absorption. They are particularly effective in treatment of insulin-dependent (type 1) diabetes[86,87] where their use can allow insulin injections to be given just before a meal without danger of hyperglycaemia.

Another possible use of inhibitors of intestinal disaccharidases is for treatment of obesity. Recent studies using the sucrase/maltase inhibitor AO-128[89] (**76**) indicate that treatment with disaccharidase inhibitors may be effective against visceral fat obesity (fat accumulation in the abdominal cavity). This type of obesity is frequently associated with cardiac dysfunction, hypertension and other complications.

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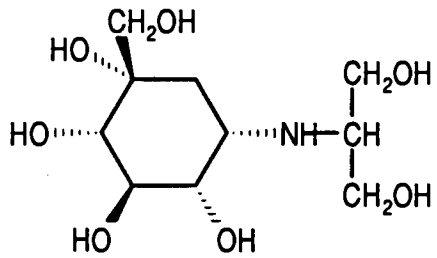



(76)

### 1.5.4.4 Insect Antifeedants

Inhibitors of intestinal disaccharidases are known to have toxic effects on specific insect species[90]. For example, DMDP (**67**) is toxic to the larvae of the bruchid *C. maculatas* and *Spodoptera littoralis* Boisd. caterpillars, but nymphs of *L. migratoria* were unharmed even when force fed large doses of DMDP. This selective effect may be useful in developing insecticides which target specific insect species.

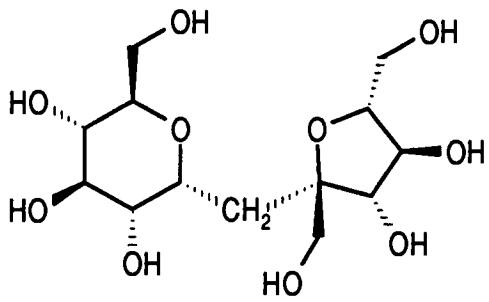
Some amino-sugar derivatives deter insects from feeding (possibly by binding to taste receptors) and hence may be useful in crop protection. Castanospermine[90] (**65**) and DMDP[91] (**67**), for example, are both locust antifeedants.

### 1.5.4.5 Enzymology

Glycosidase inhibitors have several applications in the field of enzymology[73]. Selective glycosidase inhibitors have been used to probe the mechanism of action of glycosidases and as assays for specific glycosidases in tissue extracts. Amino-sugars are used to selectively or completely block glycosidases during the isolation of glycoconjugates to prevent their hydrolysis. Reversible inhibitors also find applications as affinity chromatography ligands for the separation of glycosidases.

## 1.6 Carbon-Linked Disaccharides

Compounds consisting of two monosaccharide units linked by a carbon bridge rather than a glycosidic oxygen are termed carbon-linked disaccharides (*C*-disaccharides). For example, *C*-sucrose[92] (**77**) is the *C*-disaccharide analogue of sucrose (**78**).



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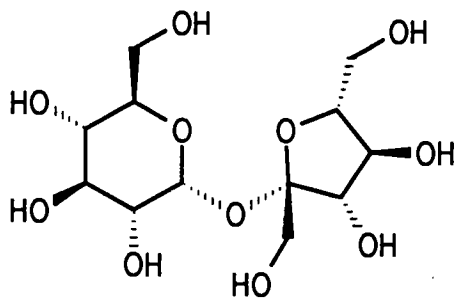
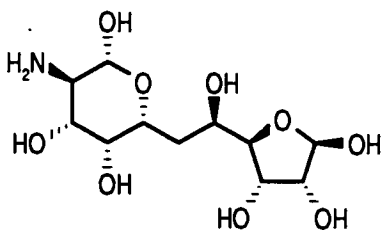


(78)

Several *C*-disaccharide fragments have been found in nature. For example, the dialdose tunicamine (**79**), which is a component of several naturally occurring antibiotics of the tunicamycin[65], streptovirudin[93] and corynetoxin[94] families, can be considered as 2-amino-2,6-deoxy-D-galactose linked at $C_6$ to $C_5$ of D-*allo*-pentofuranose. Palytoxin[95], the principle toxin isolated from marine soft corals of the genus *Palythoa*, also contains a *C*-disaccharide fragment (**80**).



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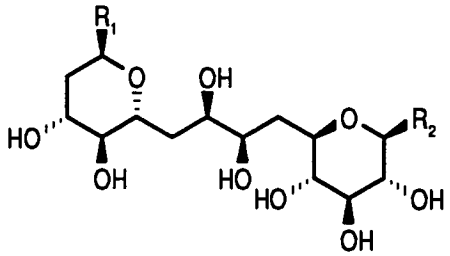


(80)

The considerable interest in the synthesis of *C*-disaccharides over the past decade can be attributed not only to their presence in natural antibiotics, but also to

their close structural and conformational relationship[96] to normal *O*-linked disaccharides. Owing to this they may be useful as inhibitors of glycosidases (Section 1.5). Inhibitors of these enzymes have attracted particular interest as they have many potential uses, for example as anti-viral, anti-cancer and anti-diabetes agents. *C*-disaccharides are very good candidates as glycosidase inhibitors as they are very similar to the enzymes' natural substrates, thereby giving good enzyme specificity and binding, and due to the carbon bridge the enzymes would not be able to catalyse the hydrolysis of the glycosidic bond.

### 1.6.1 Synthesis of *C*-Disaccharides

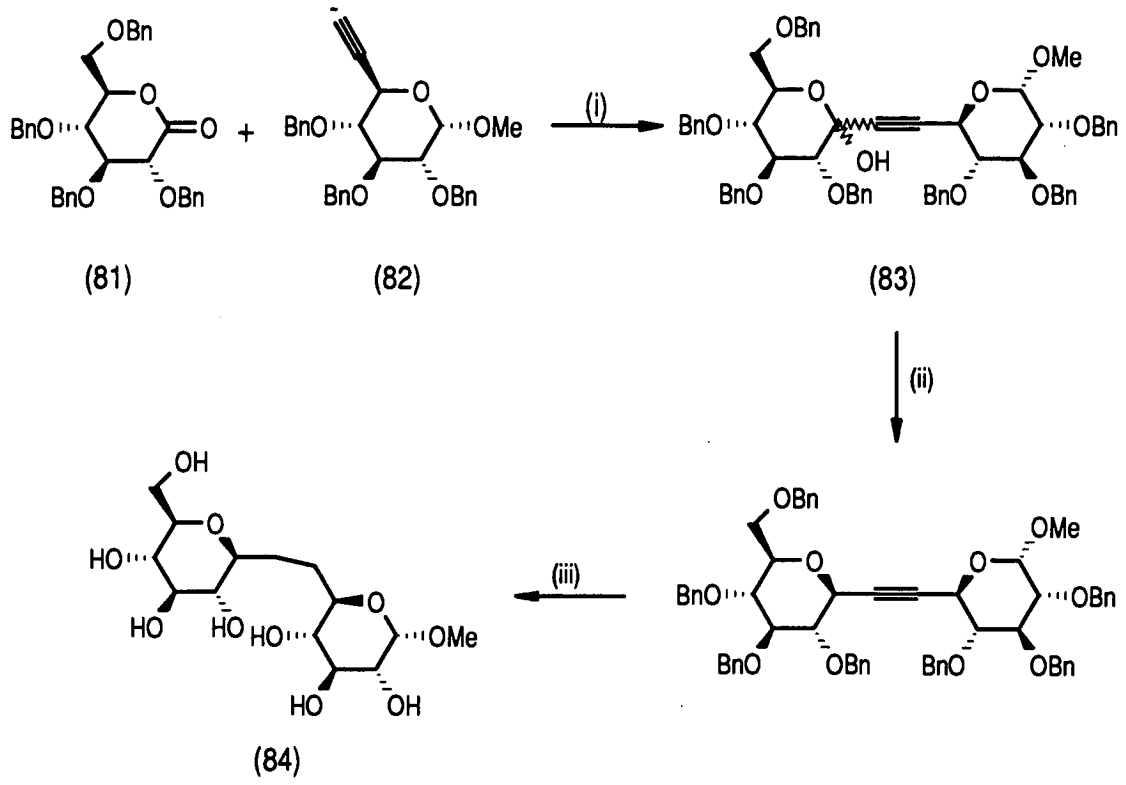
To date there has been no systematic review of the synthesis of *C*-disaccharides and the subject is therefore discussed in detail below.

#### 1.6.1.1 Carbonyl Addition Reactions

One of the most frequently used methods of synthesis of *C*-disaccharides involves the addition of a sugar anion to a carbonyl group (aldehyde, ketone, ester or lactone).

This was the approach utilised by Rouzand and Sinay[97] who carried out the first stereoselective synthesis of a *C*-disaccharide. They reacted glucopyranolactone derivative (**81**) with a pyranose acetylenic anion (**82**), derived from D-glucose, to yield a hemiacetal (**83**). Subsequent stereoselective reduction of the hemiacetal function followed by hydrogenation yielded D-Glc-*C*-β-(1→6)-D-GlcOMe (**84**) (Scheme 18).

This method was also used by Daly and Armstrong[98] to afford a β-(1→4)-linked *C*-disaccharide with an acetylenic bridge.

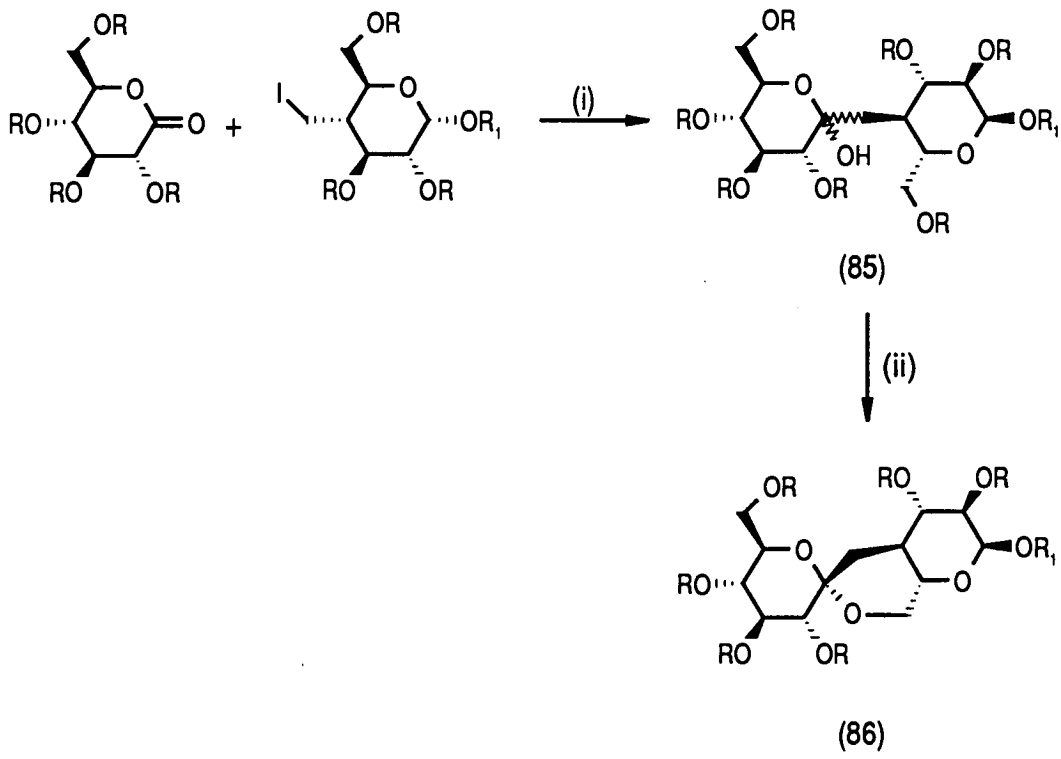



(i) BuLi ; (ii) $Et_3SiH$ , $BF_3$-$Et_2O$ ; (iii) $H_2$ , Pd/C

**Scheme 18**

Sinay has extended this method to include addition of sulphone-stabilised, lithiated anions to aldehydes[99] and esters[100] to produce β-(1→5)-*C*-disaccharides with hydroxymethylene[99] and carbonyl bridges. The diastereofacial selectivity in both cases was moderate (3:1).

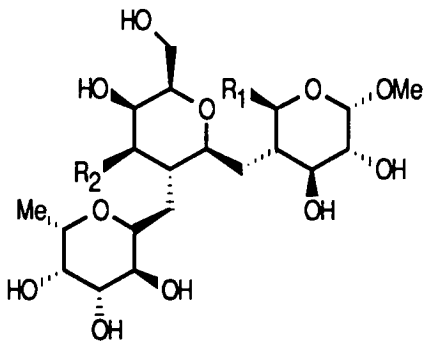
Schmidt and co-workers have adopted a very similar approach using additions of $C_1$, sulphoxide-stabilised, lithiated anions to aldehydes for the synthesis of β–(1→4)- and β–(1→3)-linked *C*-disaccharides with a hydroxymethylene linker[101]. They have also employed metal/halide exchange reactions to generate seven carbon nucleophiles which they added to pyanolactones to produce methylene-bridged β-(1→4)-linkages[102]. A spiroketal *C*-disaccharide analogue[103] (**86**) was also formed by this route when attempted reduction of hemiacetal (**85**) resulted in intramolecular glycoside bond formation (Scheme 19).




(i) n-BuLi ; (ii) $BF_3$-$OEt_2$

**Scheme 19**

During the course of his work in the field of higher sugars Fraser-Reid has synthesised a number of (2→5)[104] and (5→6)[105]-linked *C*-disaccharides by aldol condensation reactions. As part of his work[96] on the preferred conformation of *C*-glycosides Kishi has prepared and carried out conformational analysis on several carbon-linked trisaccharides[106]. He utilised aldol condensation reactions as the key stage in the stepwise linkage of the three monosaccharide units. He has synthesised four *C*-trisaccharides of basic structure (**87**) with varying substituents at the C(5) and C(3') positions.



(87)

### 1.6.1.2 The Nitro-Aldol Approach

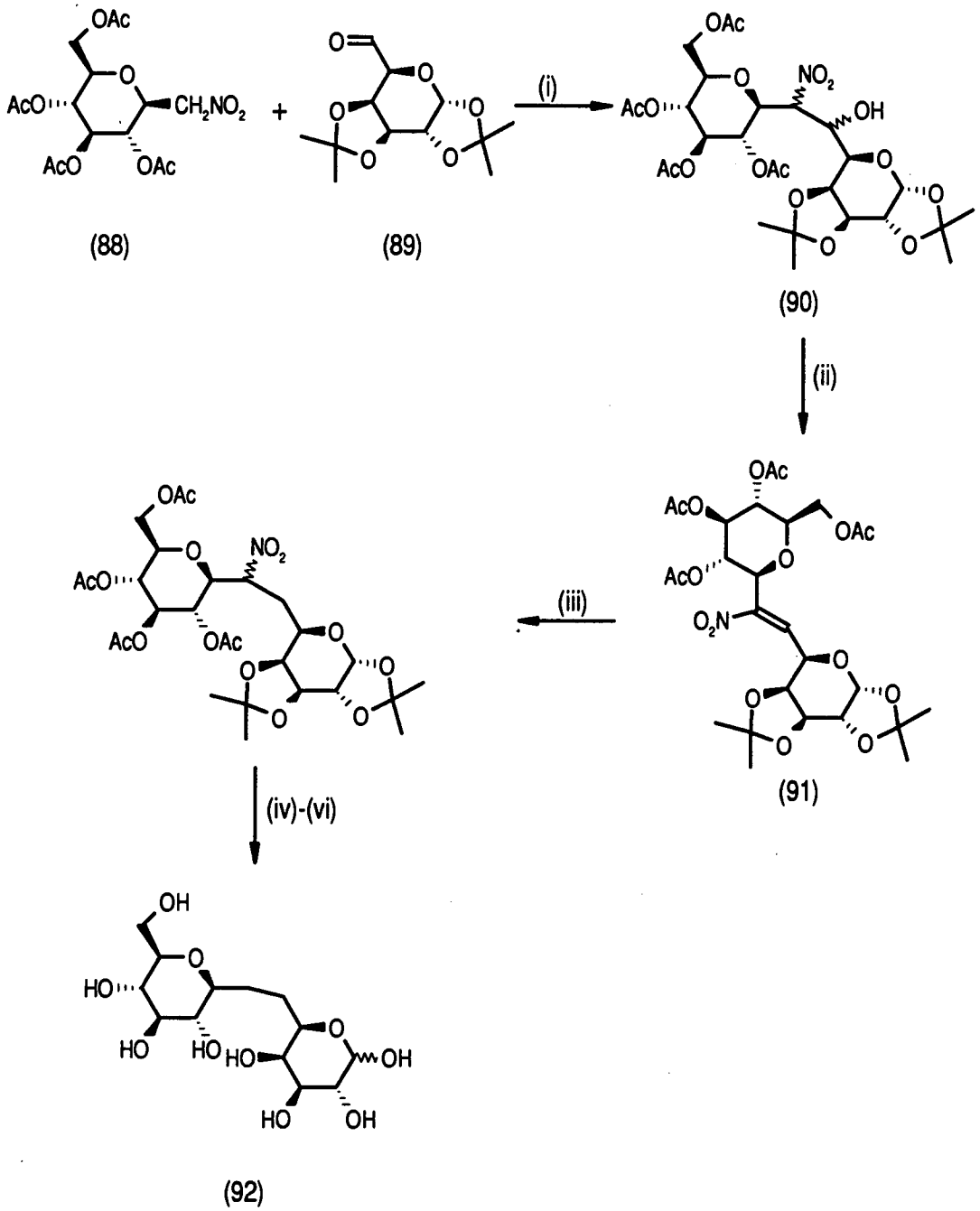
A number of research groups have investigated the base or fluoride ion catalysed addition of nitrosugars to aldehydes as a method of linking together two monosaccharide units.

As part of his work[107] on the synthesis of the tunicamycin family of antibiotics Suami has prepared the *C*-disaccharide tunicamine (**79**) which is a key fragment of the tunicamycins. He used both base-catalysed addition of a six carbon nitrosugar to a five carbon aldehyde[108] and the fluoride ion catalysed addition of a five carbon nitrosugar to a six carbon aldehyde[109]. In the former case low stereoselectivity resulted in four products and, although the latter reaction was stereospecific, attempts to remove the nitro group were not stereoselective.

Vasella and co-workers have synthesised a β-(1→5)-*C*-disaccharide[110,111] with a hydroxymethylene bridge *via* a $Bu^t_4NF$ catalysed addition of a furanose nitrosugar to a galactose-derived alkene, followed by radical denitration[111]. They have also prepared a *C*-disaccharide analogue[112] with a direct carbon-carbon link between the two rings *via* a similar route.

Recently Martin and Lai[113] have applied similar methodology to the synthesis of β-(1→6) and β,β-(1→1)-linked *C*-disaccharides. In the synthesis of D-Glc-*C*-β-(1→6)-D-Gal derivative (**92**) (Scheme 20) they carried out a KF-catalysed addition of an α-glucopyranosylnitromethane derivative (**88**) to an aldehyde (**89**), derived from D-galactose, to produce a 7-deoxy-7-nitrotridecitol compound as a mixture of

diastereomers (**90**). Elimination of acetic acid led to nitroalkene (**91**) which, after reduction and radical denitration, yielded the (1→6)-*C*-disaccharide (**92**) upon deprotection (β/α ratio 2.4/1).




(i) KF , 18-crown-6 ; (ii) $Ac_2O$ , Pyridine ; (iii) $NaBH_4$ ; (iv) $Bu_3SnH$ , AIBN, Δ ;

(v) MeONa , MeOH ; (vi) Amberlite IR-120 ($H^+$) , $H_2O$ , Δ

**Scheme 20**

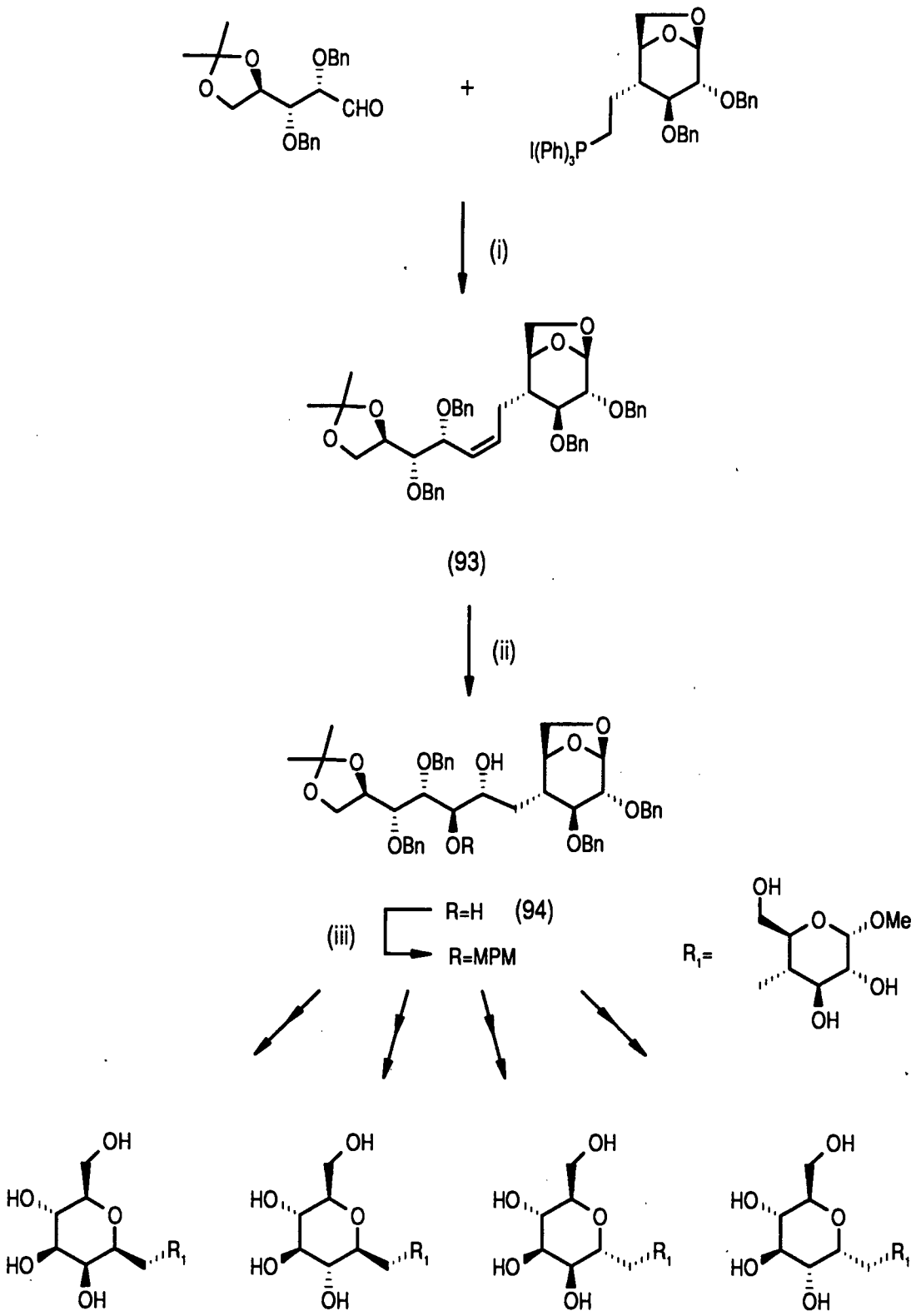
### 1.6.1.3 The Wittig Approach

The Wittig reaction, when combined with stereoselective methods of olefinic bond manipulation provides a powerful approach to the synthesis of *C*-disaccharides.

Kishi[114,115] has applied the Wittig reaction to preparation of (1→4)-linked *C*-disaccharides to great effect. He has based his approach around the synthesis of olefin (**93**) (Scheme 21), which was prepared by a Wittig condensation, followed by catalytic osymylation to produce diol (**94**). The preferred formation of diol (**94**) is in accord with Kishi's empirical rule[116] for osymylations which predicts that the major product will have an *erythro* relationship between a pre-existing hydroxyl and the new hydroxyl introduced at an adjacent carbon. By using a chiral diamine[117] in the osmylation step selectivity as high as 58:1 in favour of (**94**) was obtained in this case. Selective protection of the 2'-hydroxyl then allows cyclisation to form the second pyranose ring. He has developed cyclisation routes[115] which allow him to obtain either anomer and also to control the stereochemistry at $C_{2'}$, thereby producing a range of *C*-disaccharides (Scheme 21).

Several other groups have utilised this Wittig/osmylation approach. Nicotra *et al.*[118] have synthesised a*C*-sucrose analogue by this method and Jarosz *et al*[119-121] have prepared several (6→6)-linked *C*-disaccharides using this route. Ramaz and Zamojski[122,123] have also used it to make tunicamine and Secrist and Wu[124] have utilised Wittig methodology to synthesise an unsaturated *C*-disaccharide related to tunicamine.

Armstrong and Teegarden[125] have applied Wittig technology to the preparation of α-methyl-1',2'-dideoxycellobioside (**95**), a (1→4)-*C*-disaccharide analogue with a direct carbon-carbon bond between the two rings. This was synthesised by condensation of a pyranose Wittig reagent with an acyclic aldehyde, followed by bromonium ion induced cyclisation of the resulting olefin (Figure 8).

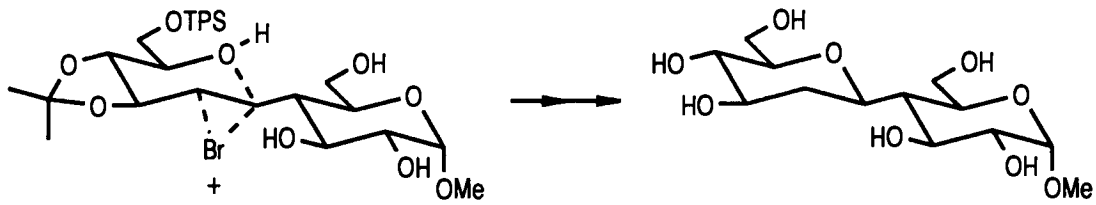



(i) n-BuLi , THF ; (ii) $OsO_4$ , *N,N'*-bis(mesitylmethyl)-(R,R')-1,2-diphenyl-1,2-diaminoethane ;

(iii) MPM-Br , NaH

**Scheme 21**

Attempts to use the *cis*-olefin to produce the α-anomer failed and using the *trans*-olefin produced only 38% of the required product along with a number of by-products.

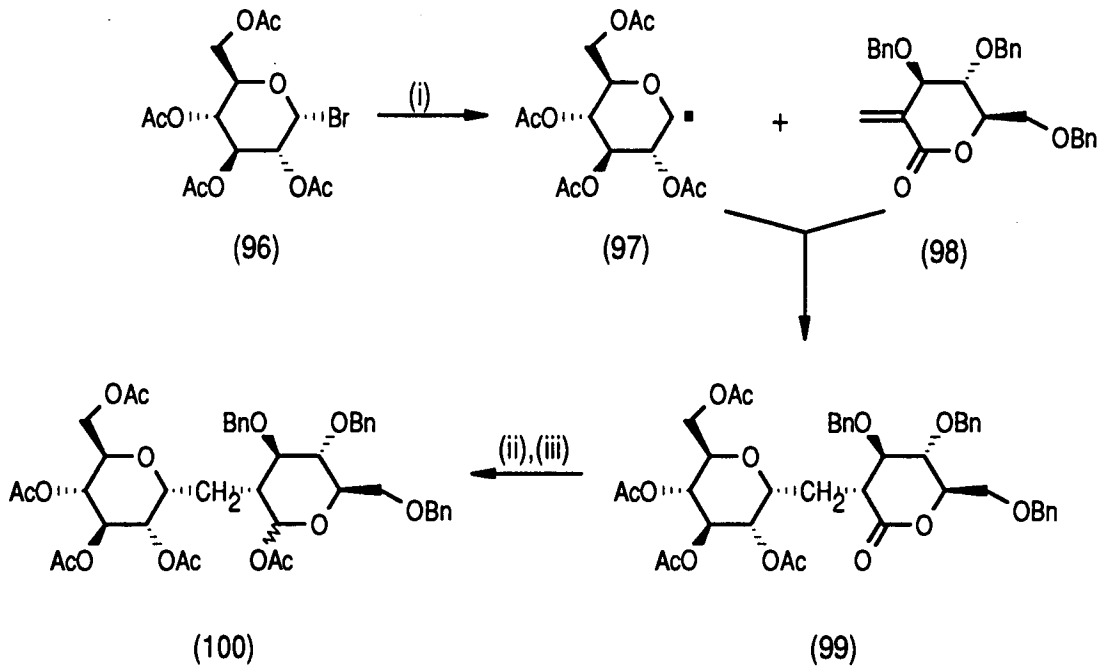



(95)

**Figure 8**

### 1.6.1.4 The Radical Addition Method

Giese and co-workers have developed a route to *C*-disaccharides in which the key step is addition of glycosyl radicals to α-methylene lactones. By this approach they have prepared a number of (1→2)-methylene-linked disaccharides[126,127] including carbon analogues of kojibiose, ristobiose and α-L-fucopyranosyl (1→2)-D-galactose.This method is illustrated in Scheme 22 for methylene-linked kojibiose[127]. The glycosyl radical (**97**) was generated from bromo-D-glucose derivative (**96**) and the α-methylene lactone (**98**) was obtained from the corresponding glycal *via* a glycopyranosyl-phenylsulphoxide[128]. Addition of radical (**97**) to α-methylene lactone (**98**) afforded lactone (**99**) which was subsequently reduced to give the protected methylene-linked kojibiose (**100**). Although the diastereoselectivity was high in this case, in general the selectivity for the hydrogen transfer from $Bu_3SnH$ to the adduct radical was low (60:40). Using this approach (2→4) and (2→6)-methylene-linked lactones have also been prepared[126].



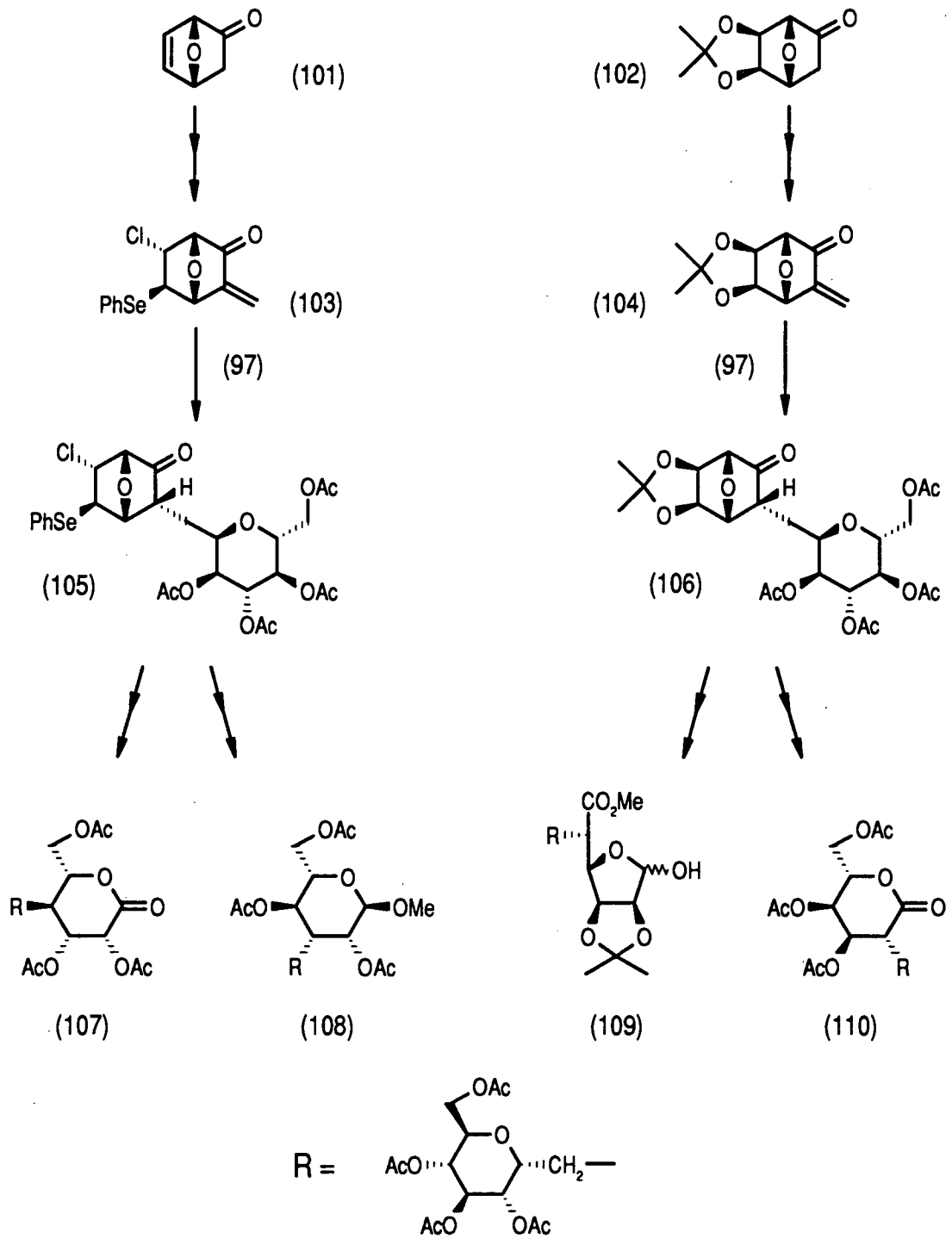

(i) $Bu_3SnH$ , AIBN ; (ii) $Na[Al(OC_2H_4OMe)_2(OEt)H]$ ; (iii) $Ac_2O$ , Pyridine

**Scheme 22**

Vogel and Bimwala[129,130] have also used Giese's approach to make a number of α–(1→2), α–(1→3), α–(1→4) and α–(1→5)-*C*-disaccharides. They employed 7-oxobicyclo[2.2.1]heptan-2-one derivatives (**101**) and (**102**), which they refer to as "Naked Sugars", as the source of α-methylene lactones (**103**) and (**104**) (Scheme 23). Addition of radical (**97**) to α-methylene lactone (**103**) produced an 8:1 mixture of *endo* anomers; no *exo* product was detected. This indicates very high selectivity for the hydrogen transfer from the $Bu_3SnH$ to the adduct radical. High levels of stereoselectivity were also found in addition to α-methylene lactone (**104**). Further manipulation of the resulting 7-oxobicyclo[2.2.1]heptan-2 one derivatives yielded *C*-disaccharides (**107**) and (**108**) from adduct (**105**), and (**109**) and (**110**) from adduct (**106**).

Other groups have also utilised radical reactions in the synthesis of *C*-disaccharides. Motherwell *et al*[131] have prepared a (1→6)-linked *C*-disaccharide with a difluoromethylene ($CF_2$) linker *via* addition of a glucopyranosyl radical to a

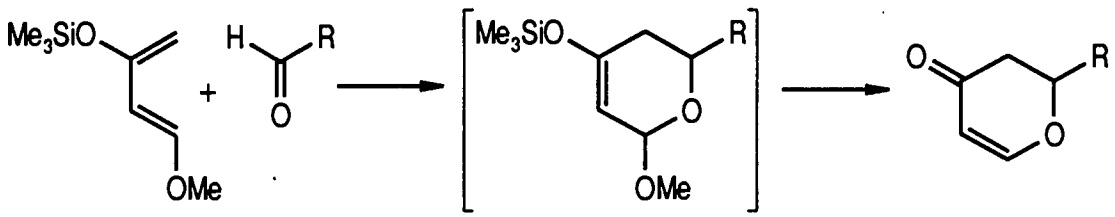
difluoroenol ether. Myers and co-workers[132] have synthesised tunicamine by a radical cyclisation of an allylic alcohol and an aldehyde *via* a silicon linked cyclic intermediate.




**Scheme 23**

### 1.6.1.5 The Cycloaddition Approach

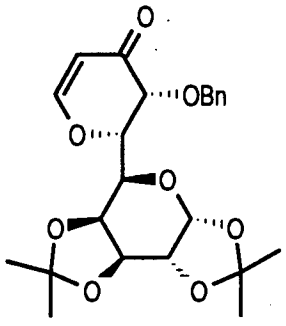
Danishefsky *et al* have applied a Diels-Alder cycloaddition approach to the synthesis of *C*-disaccharides and *C*-disaccharide analogues. This route is based on the regiospecific, Lewis-acid catalysed cycloaddition of siloxydienes (**111**) to sugar aldehydes (**112**) to construct the second pyran ring. Facile elimination of the trimethylsilyl and methoxy groups from the initial cycloadduct (**113**) affords dihydropyrone (**114**) (Scheme 24).




(111) (112) (113) (114)

**Scheme 24**

A similar approach has been used to prepare *C*-disaccharide analogues[133] such as (**115**) in which the two rings are directly linked and also hydroxymethylene-bridge derivatives[134], *e.g.* (**116**). The high diastereoselectivity of these cycloadditions is noteworthy as both (**115**) and (**116**) were isolated as single isomers.

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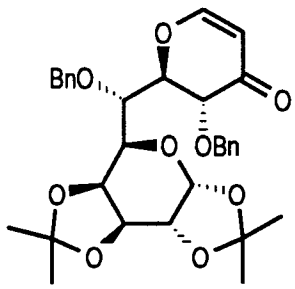
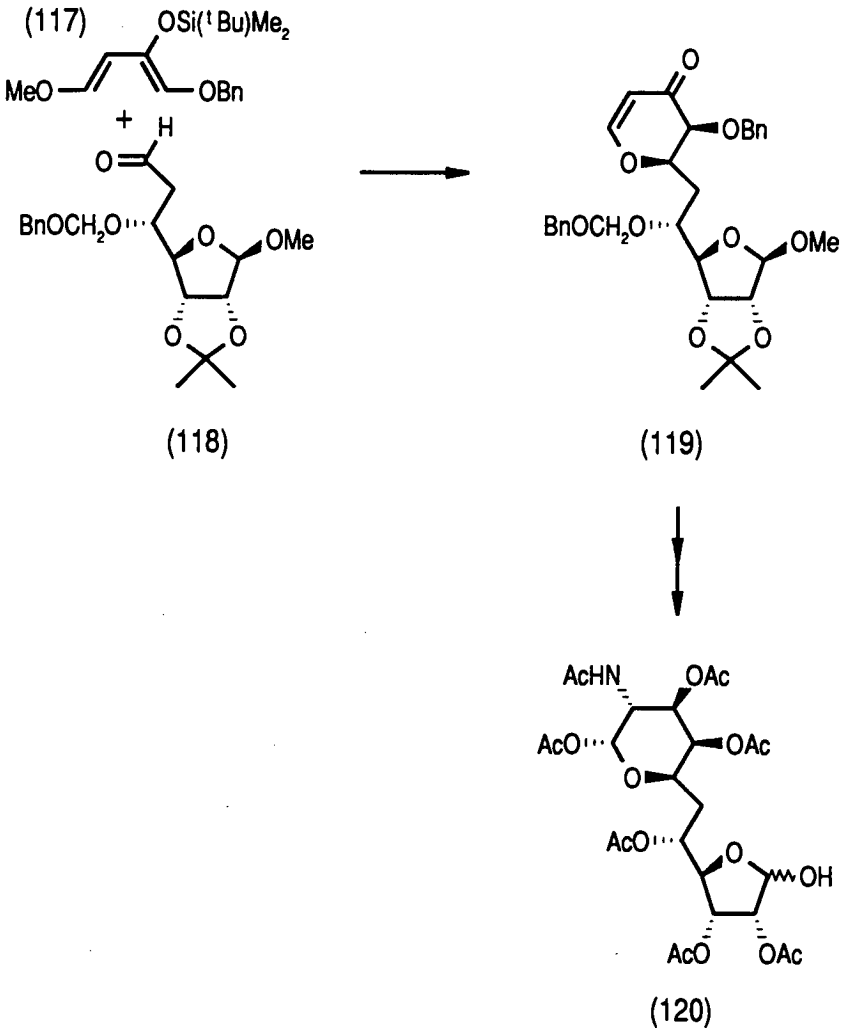



(116)

A Diels-Alder cycloaddition was also the principal step in Danishefsky's route[135,136] to tunicamine derivative (**120**). Diene (**117**) added regio- and stereospecifically to aldehyde (**118**) to give cycloadduct (**119**) which afforded (**120**) upon funtionalisation of the new pyran ring (Scheme 25).




**Scheme 25**

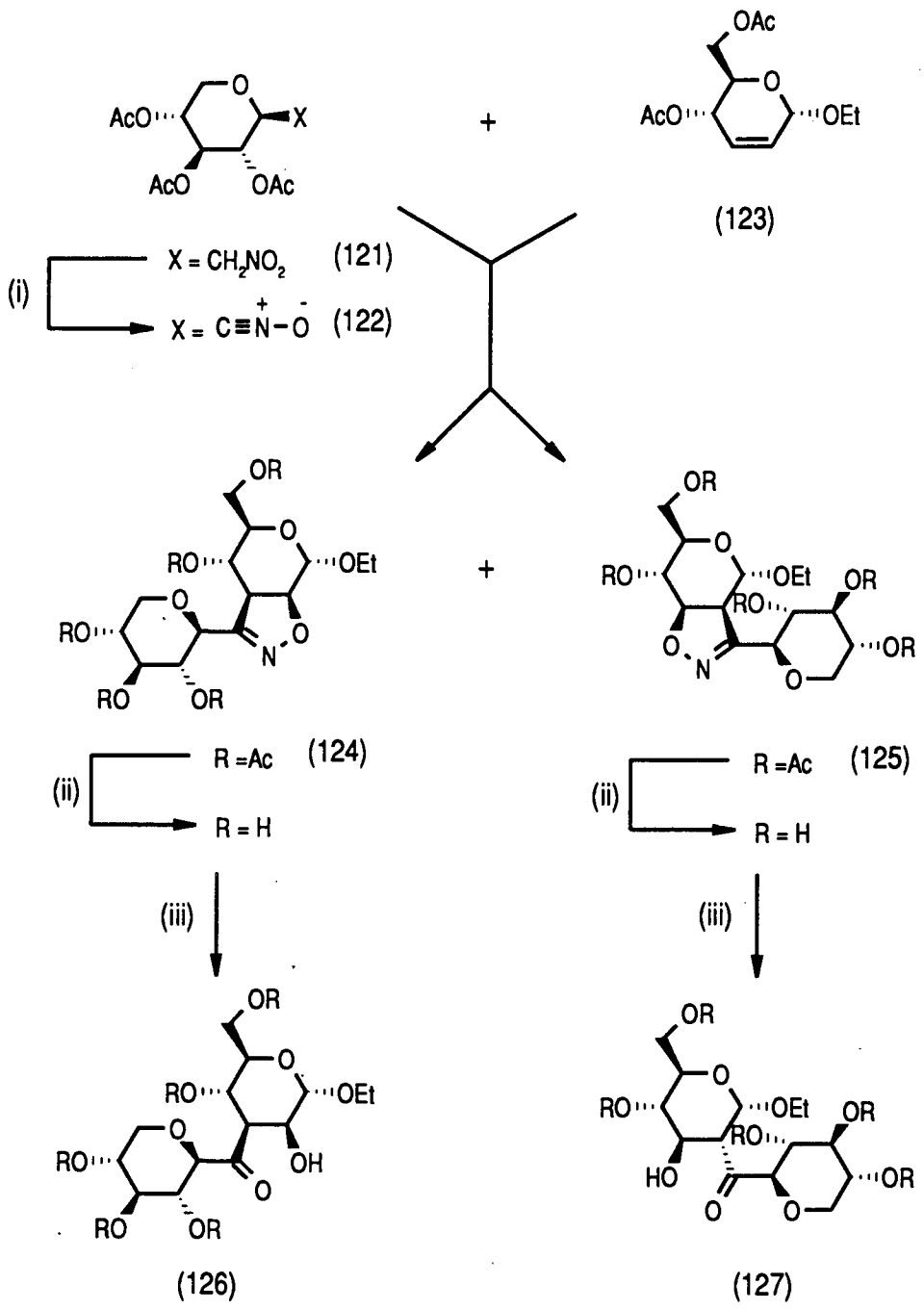
Diels-Alder cycloaddition chemistry has also been used by Jurczak[137-138] for the synthesis of *C*-disaccharide analogues similar to (**115**) and by Danishefsky to prepare *C*-disaccharides as intermediates to higher sugars[139,140].

An alternative cycloaddition route to *C*-disaccharides has been taken by Paton and co-workers[141]. They have utilised nitrile oxide cycloaddition chemistry to

prepare (1→2) and (1→3)-linked *C*-disaccharides. Cycloaddition of sugar nitrile oxide (**122**), generated from D-xylose *via* the nitromethyl derivative (**121**), to sugar alkene (**123**) yielded a 1:1 mixture of the regiomeric isoxazolines (**124**) and (**125**). It is noteworthy that the addition was completely facespecific; the nitrile oxide adding to the top face of the alkene. Deacetylation, followed by catalytic hydrogenolysis afforded two *C*-disaccharides (**126**) and (**127**) (Scheme 26). Formation of ethyl 2-*C*-β-D-xylopyranosyl-α-glucopyranoside (**127**) rather than the expected mannose analogue was attributed to facile epimerisation at C-2.

### 1.6.1.6 Other Approaches

Several other approaches have been designed for the synthesis of *C*-disaccharides. Kishi has used Ni(II)/Cr(II) mediated coupling reactions of vinyl iodides with aldehydes to synthesise *C*-sucrose[92] and methylene-linked isomaltose and gentibiose[142]. Jarosz and Fraser-Reid[143-145] have utilised organotin reactions to produce unsaturated *C*-disaccharides and Hanessian[146] has also adopted this approach. Nicotra and co-workers[147,148] have carried out "easy" syntheses of *C*-disaccharides by condensing glycosidic enolic systems with glycosyl cations where both reactants come from the same precursor. De Raadt and Stutz[149] synthesised unsaturated α–(1→6)-*C*-disaccharides by coupling tri-O-acetyl-D-glucal with pyranose and furanose allylsilanes *via* a $BF_3$ catalysed "carbon-Ferrier rearrangement". Casiraghi *et al*[150] have synthesised a difuranose *C*-disaccharide *via* condensation between a sugar aldehyde and 2-(trimethylsiloxy) furan, as an intermediate in the synthesis of higher sugars.




(i) Tolylene di-isocyanate , $NEt_3$ , $CH_2Cl_2$ , $\Delta$ ; (ii) KCN , MeOH ;

(iii) Raney-Ni , $H_2$ , $B(OH)_3$ , $H_2O$ , MeOH

**Scheme 26**

# 2. RESULTS AND DISCUSSION

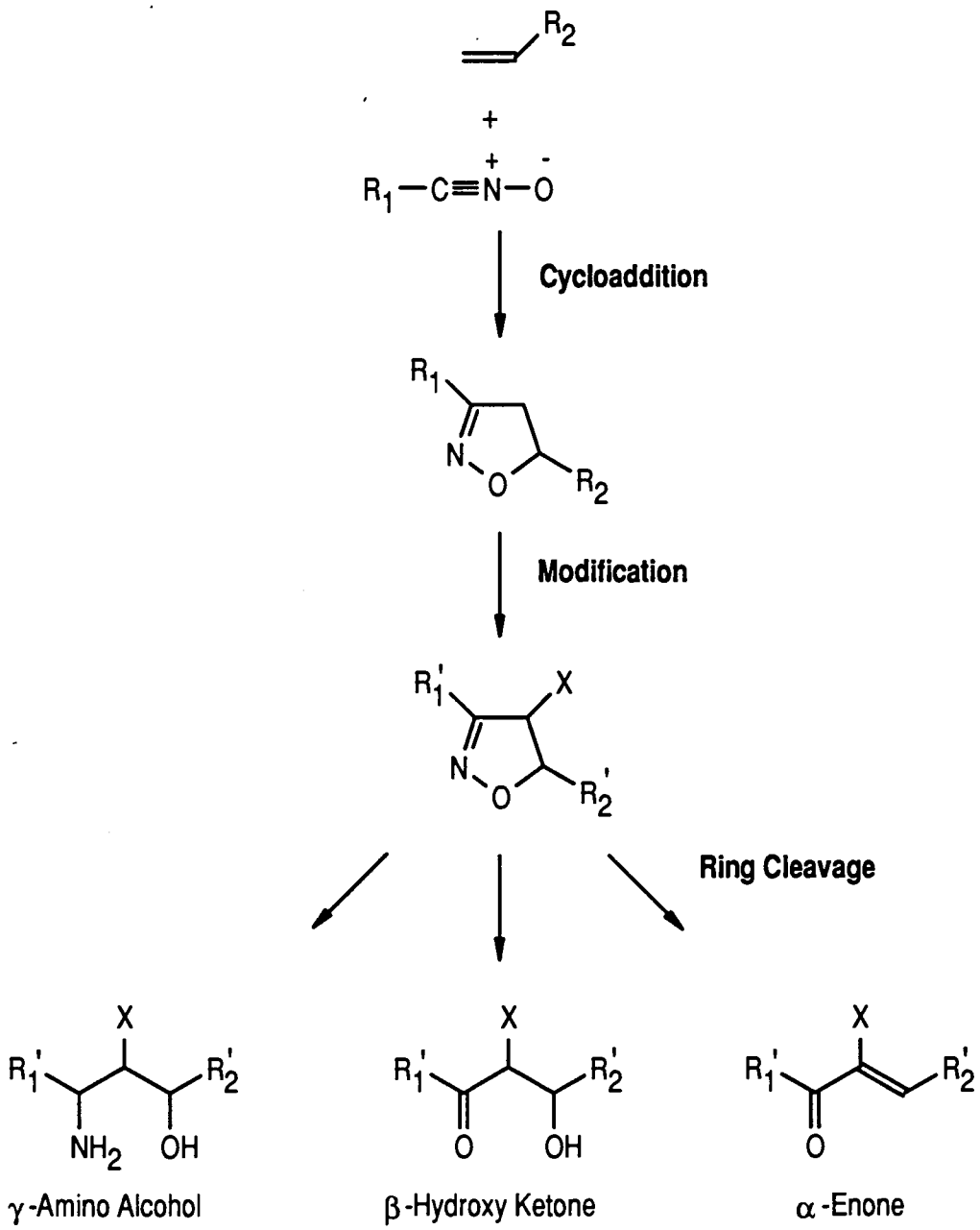
## 2.1 Programme of Research

Carbon-linked disaccharides (*C*-disaccharides) are compounds consisting of two monosaccharide units linked by a carbon bridge rather than a glycosidic oxygen. They provide a tempting target to the synthetic chemist due to the challenge of linking together two highly chiral rings in a stereospecific manner. It is due, however, to their potential use as inhibitors of glycosidases and their close structural and conformational relationship[96] to *O*-linked disaccharides that so much interest in their synthesis has been generated. Possible applications of glycosidase inhibitors (Section 1.5) include use as anti-viral, anti-cancer and anti-diabetes agents.

Since the first stereoselective synthesis of a *C*-disaccharide by Rouzand and Sinay in 1983[97] a variety of approaches have been employed (Section 1.6) including carbonyl and radical addition reactions, Wittig methodology and cycloaddition chemistry. The objective of the work presented in this thesis was to develop a general, convergent approach to *C*-disaccharide synthesis. In carrying out this objective it was desirable to employ reactions with a high degree of stereochemical control, using readily available starting materials, which would allow the synthesis of *C*-disaccharides with a variety of functionality on the carbon bridge linking the two monosaccharide units.

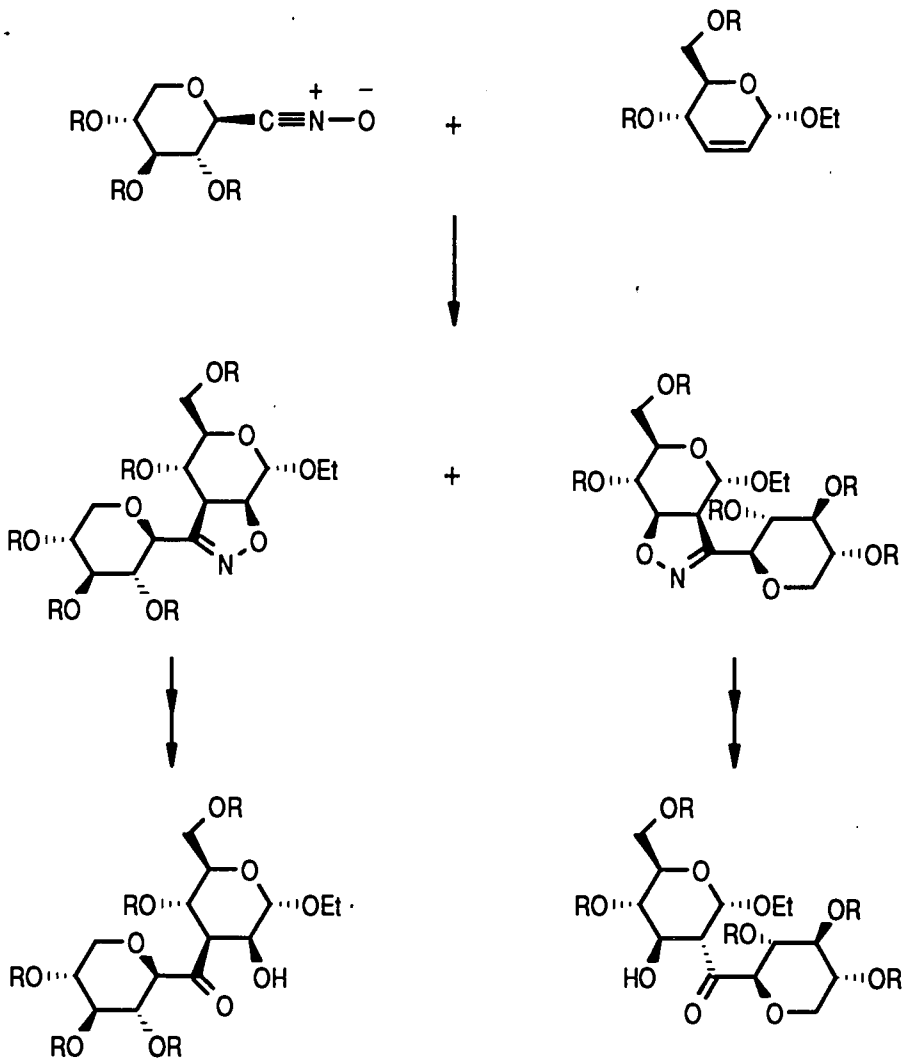
A route based on nitrile oxide/isoxazoline chemistry was selected as it seemed well suited to the objectives outlined above. Nitrile oxide/isoxazoline chemistry (Section 1.4) has been widely used in the synthesis of natural products and analogues[24,63]. This approach involves three basic steps (Scheme 27): firstly nitrile oxide cycloaddition to alkenes to yield 2-isoxazolines provides a method of linking together two units with predictable regio- and stereochemistry. Both nitrile oxides and alkenes are readily obtained by well established methods from inexpensive starting materials. The 2-isoxazolines formed are relatively stable and hence modification of side chains and/or introduction of substituents at the 4-position of the

isoxazoline ring (Section 1.4) may be carried out. The final step involves ring cleavage of the heterocycle to afford a variety of functionality (Section 1.4), for example β-hydroxy ketones, γ-amino alcohols and α-enones. This final step when coupled with further functional group manipulation allows introduction of a variety of functionality into the *C*-disaccharide bridge.




**Scheme 27**

This method has already been applied by Paton *et al.*[141] to the synthesis of (1→2)- and (1→3)-linked *C*-disaccharides (Section 1.6.1.5) in which the monosaccharide units are linked by a carbonyl bridge (Scheme 28).

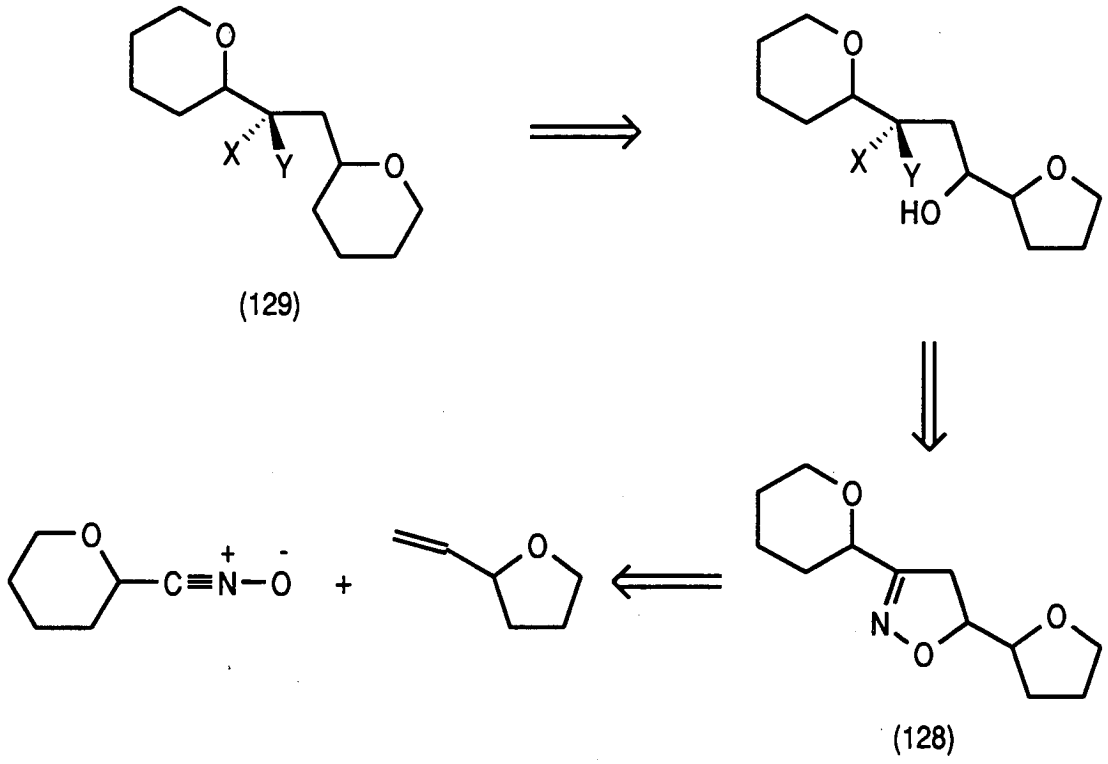


**Scheme 28**

The purpose of the research described in this thesis is to extend this approach to the synthesis of (1→6)-linked *C*-disaccharides. The route selected is summarised in the retrosynthetic analysis shown in Scheme 29.

The first step involves the cycloaddition of a pyranose 1-nitrile oxide to an ω-unsaturated hexofuranose to afford a 3,5-disubstituted-2-isoxazoline (**128**). This is

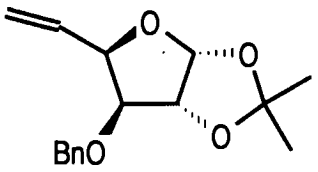
the crucial carbon-carbon bond forming process which establishes the link between the two monosaccharide units. On the basis of previous cycloadditions to sugar-based alkenes it is expected to occur with some degree of stereoselectivity[66,151]. Subsequent steps involved the ring-cleavage of the isoxazoline to release the required functionality, followed by functional group manipulation and deprotection to afford the dipyranose *C*-disaccharide (**129**).



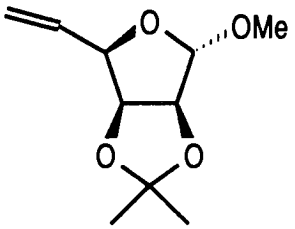

**Scheme 29**

The compounds selected for investigation were two furanose alkenes (**37**) and (**137**), derived from D-glucose and D-mannose respectively, and four nitrile oxides: ethoxycarbonylformonitrile oxide (**36**), which was used as a model dipole, and three pyranose 1-nitrile oxides (**122**), (**146**) and (**150**) generated from the corresponding 2,6-anhydro-1-deoxy-1-nitroalditols.

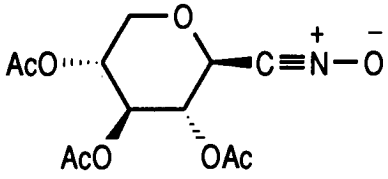
Both alkenes and the precursors to all four nitrile oxides were known compounds which could be readily prepared by literature methods or modifications thereof.




(37)




(137)

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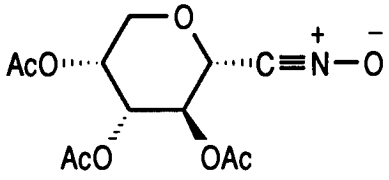


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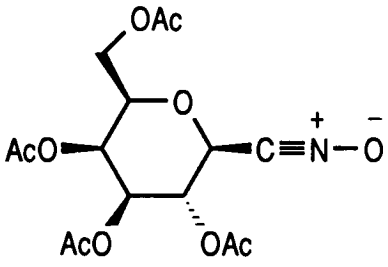


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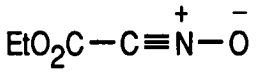
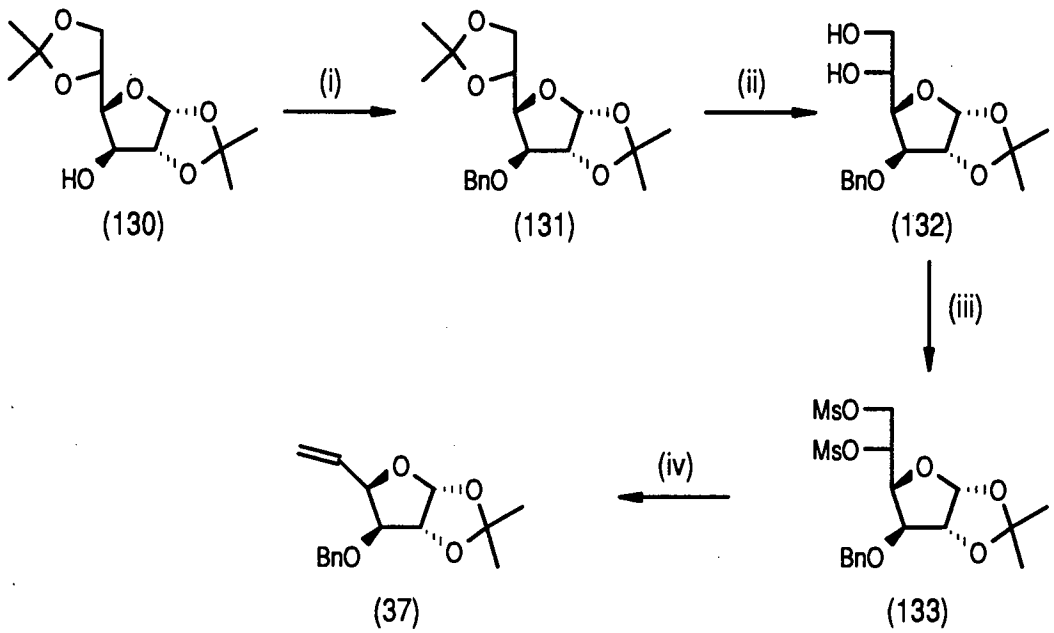



(36)

## 2.2 Synthesis of Alkenes

### 2.2.1 3-*O*-Benzyl-5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hex-5-enofuranose (37)

Alkene[152] (**37**) was prepared from commercially available diacetone-D-glucose (**130**) in four steps (Scheme 30) in an overall yield of 58%. Firstly the free 3-hydroxyl group was protected by benzylation[153] followed by selective hydrolysis[154] of the 5,6-isopropylidene group to yield diol (**132**). This diol was then treated with mesyl chloride and pyridine[155] to give the crystalline dimesylate (**133**) in 64% overall yield from diacetone-D-glucose (**130**) after recrystallisation. No purification of (**131**) or (**132**) was necessary and the crude products were carried through to be purified at the dimesylate stage. Dimesylate (**133**) was converted to alkene (**37**) in 90% yield by means of a modified[156] Tipson-Cohen reaction[157] utilising a zinc/copper couple. As the product decomposed on prolonged storage it was prepared from the stable dimesylate (**133**) just before use.

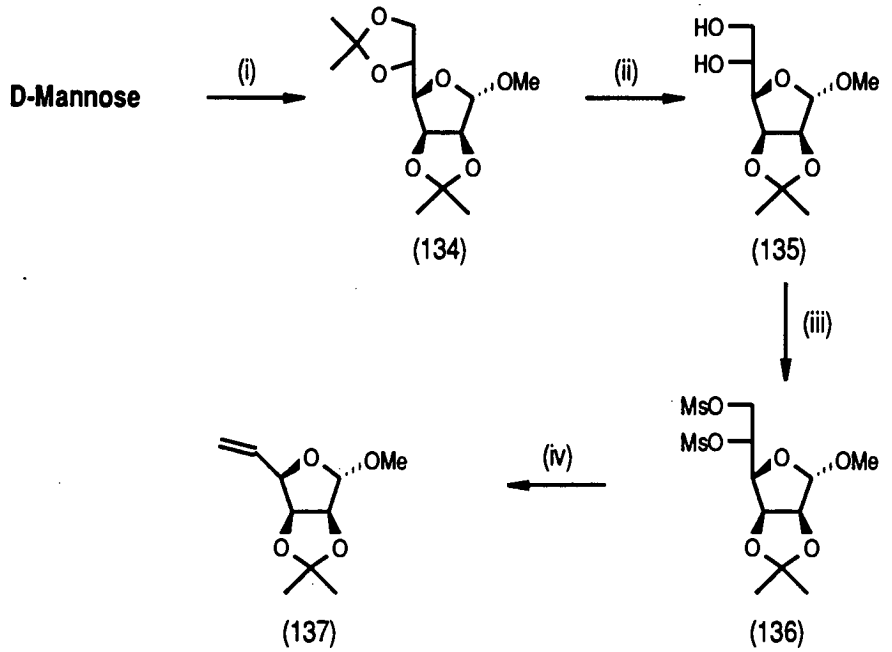



(i) NaH, BnCl; (ii) AcOH, $H_2O$, 40°C; (iii) MsCl, pyridine; (iv) Zn/Cu couple, NaI, 133°C

**Scheme 30**

### 2.2.2 Methyl 5,6-Dideoxy-2,3-*O*-isopropylidene-α-D-*lyxo*-hex-5-enofuranoside (137)

Alkene[158] (**137**), which possesses the opposite configuration to *xylo*-alkene (**37**) at $C_2$, was prepared in 43% overall yield from D-mannose (Scheme 31) by a similar route to that used for the synthesis of *xylo*-alkene (**37**). Acid catalysed reaction of D-mannose with acetone and methanol afforded the α-methyl furanoside[159] (**134**) protected by isopropylidene groups at the 2,3- and 5,6-positions. Selective hydrolysis of the 5,6-isopropylidene group, followed by mesylation of the resulting diol (**135**), afforded the dimesylate[159] (**136**) as a crystalline solid in 48% overall yield from D-mannose after recrystallisation. As in the synthesis of *xylo*-alkene (**37**) purification at an earlier stage was not necessary and the crude products were carried through to dimesylate (**136**). Zinc/copper couple mediated reduction[156] of dimesylate (**136**) afforded *lyxo*-alkene (**137**) in 89% yield. Similarly to *xylo*-alkene (**37**) this alkene was found to decompose on prolonged storage and hence it was prepared from the dimesylate just before use.




(i) Acetone, Methanol, conc. HCl, reflux; (ii) conc. HCl, $H_2O$, 23°C; (iii) MsCl, pyridine; (iv) Zn/Cu couple, NaI, 133°C

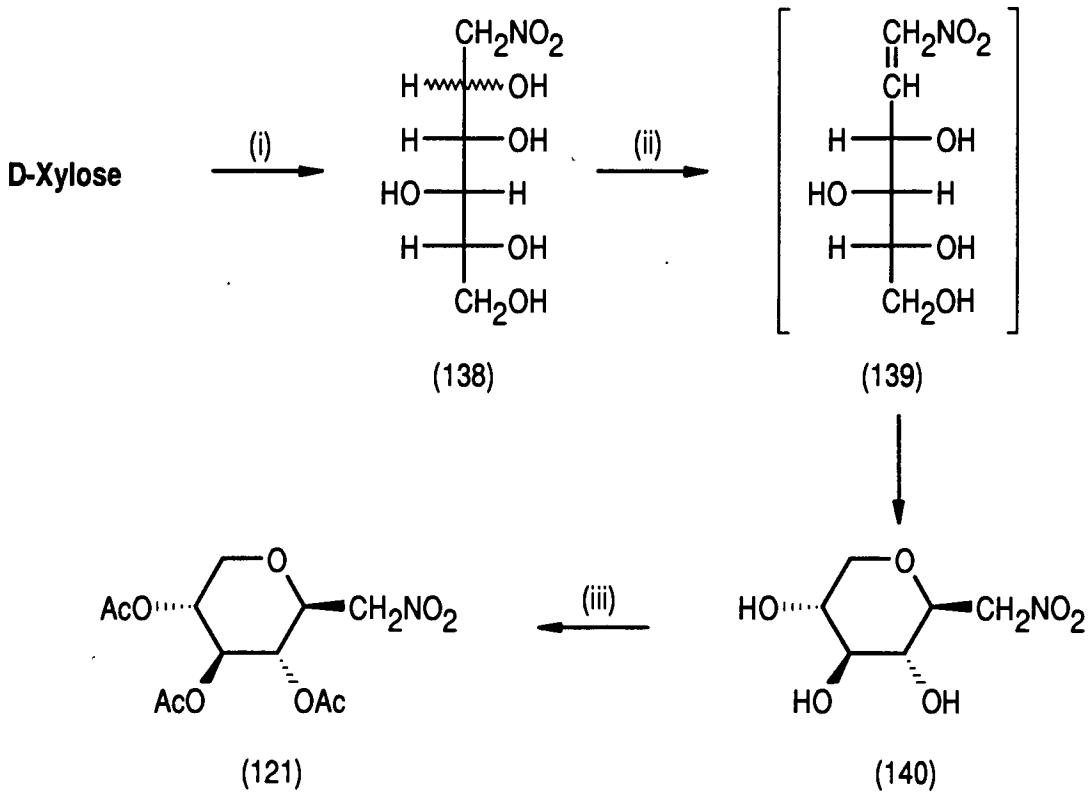
**Scheme 31**

## 2.3 Synthesis of Nitrile Oxide Precursors

Three pyranose 1-nitrile oxides were selected for use in cycloaddition reactions: (**122**) derived from D-xylose, (**146**) from D-arabinose and (**150**) from D-galactose. All three were generated *in situ* by dehydration of the corresponding 2,6-anhydro-1-deoxy-1-nitroalditols under modified Mukaiyama[27] conditions. Although the precursors to these nitrile oxides are literature compounds, only the generation and cycloaddition of nitrile oxide (**122**) has been described previously[141]. Ethoxycarbonylformonitrile oxide (**36**), which is a widely used nitrile oxide, was generated *in situ* from ethyl chloro-oximinoacetate (**152**) by dehydrochlorination with base.

### 2.3.1 3,4,5-Tri-*O*-acetyl-2,6-anhydro-1-deoxy-1-nitro-D-gulitol (121)

β-Xylopyranosylnitromethane derivative (**121**) was synthesised in three steps from D-xylose (Scheme 32) in 46% overall yield using a modified[160] version of the procedure of Köll *et al.*[161]. D-Xylose was converted into nitroalditol (**138**) by a Fischer-Sowden reaction[162]. The product was not isolated but carried straight through to β-xylopyranosylnitromethane (**140**) by refluxing (**138**) in water and (**140**) was isolated in 49% overall yield from D-xylose. None of the α-isomer (**141**) was isolated. This cyclisation is thought to proceed via dehydration to α-nitroolefin (**139**) followed by nucleophilic attack at $C_2$ by the $C_6$ hydroxyl group[163]. Cyclisations of this type afford preferentially the product which can adopt the least hindered chair conformation[163]. β-Isomer (**140**) which adopts the $^4C_1$ conformation (shown by $^1H$ n.m.r. coupling constants of acetylated derivative (**121**)[161]) has all substituents equatorial whereas α-isomer (**141**) is less favoured due to the presence of the axial nitromethyl group (Figure 9). Sowden[163] has shown that the β:α ratio in this cyclisation is in the order of 50:1. (**140**) Was then acetylated to afford 3,4,5-tri-*O*-acetyl-2,6-anhydro-1-deoxy-1-nitro-D-gulitol (**121**) in 94% yield.




(i) $CH_3NO_2$, NaOMe; (ii) $H_2O$, reflux; (iii) Acetic anhydride, triflic acid

**Scheme 32**

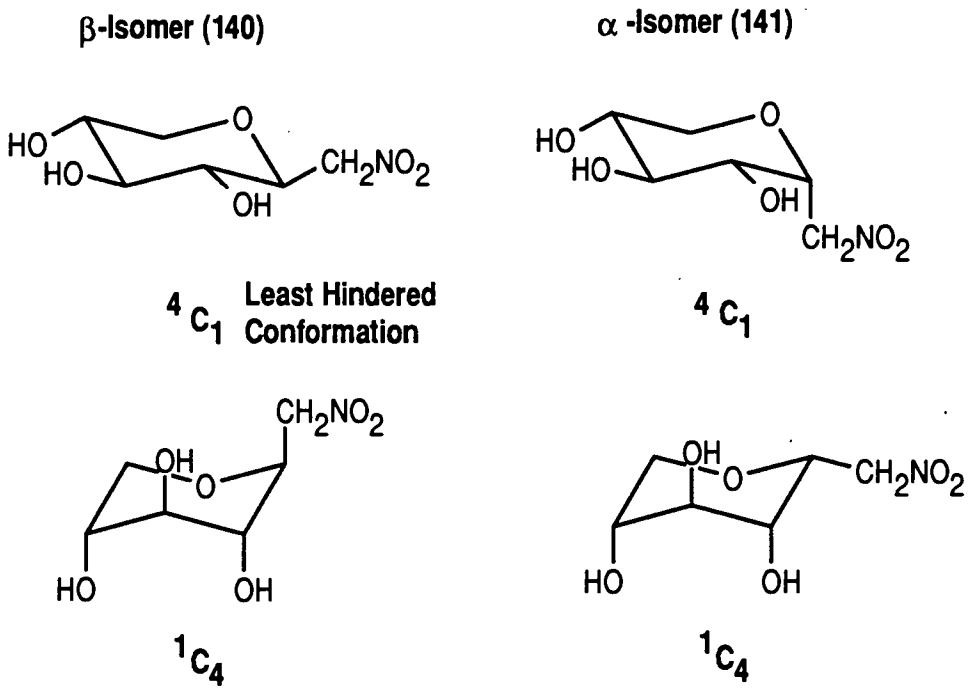
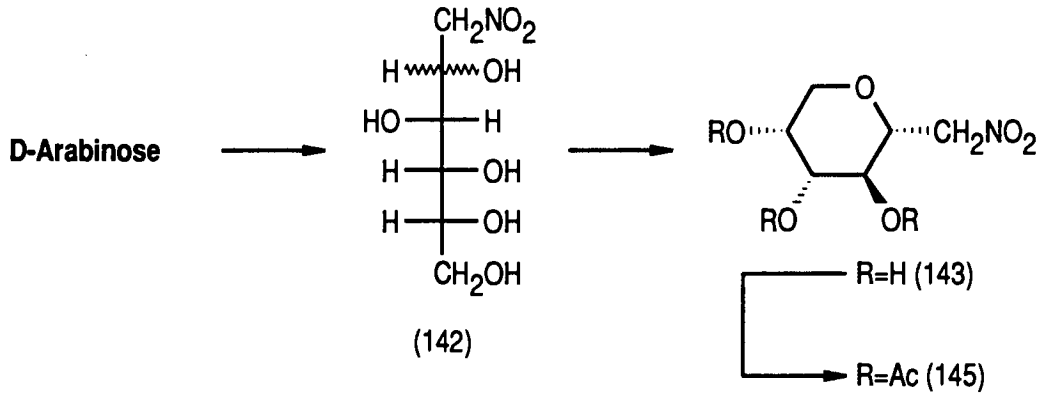



**Figure 9**

### 2.3.2 3,4,5-Tri-*O*-acetyl-2,6-anhydro-1-deoxy-1-nitro-D-mannitol (145)

α-Arabinopyranosylnitromethane derivative (**145**) was prepared from D-arabinose in 38% overall yield (Scheme 33) by the route outlined above for β-xylopyranosylnitromethane derivative (**121**). α-Arabinopyranosylnitromethane (**143**), was isolated in 38% overall yield from D-arabinose; none of the β-isomer (**144**) was isolated. The α-isomer was formed preferentially as it adopts a less hindered $^1C_4$ conformation (shown by $^1H$ n.m.r. coupling constants) than the β-isomer (Figure 10). Acetylation of (**143**) afforded the target compound, 3,4,5-tri-*O*-acetyl-2,6-anhydro-1-deoxy-1-nitro-D-mannitol (**145**), in 99% yield.




**Scheme 33**

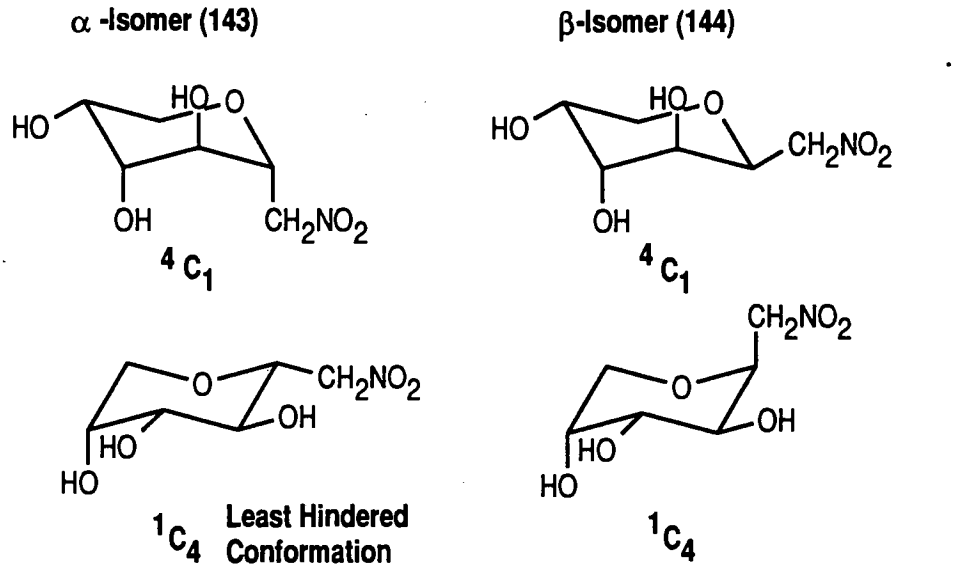
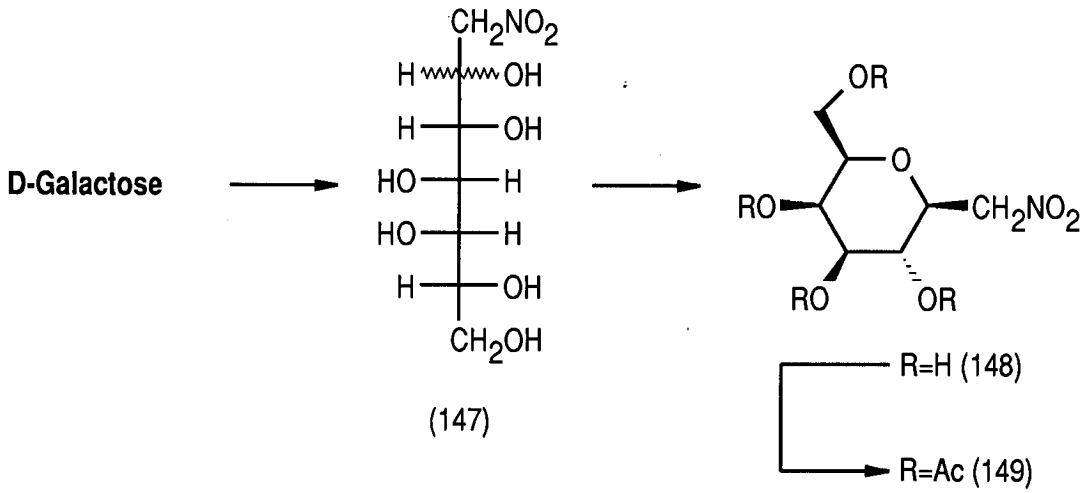



**Figure 10**

### 2.3.3 3,4,5,7-Tetra-*O*-acetyl-2,6-anhydro-1-deoxy-1-nitro-D-*glycero*-L-*manno*-heptitol (149)

β-Galactopyranosylnitromethane derivative (**149**) was prepared from D-galactose in 43% overall yield (Scheme 34) utilising the route outlined above for β-xylopyranosylnitromethane derivative (**121**). No α-isomer was obtained from the cyclisation process. As in the xylose case this is due to the fact that the β-galactopyranosylnitromethane can adopt a less hindered $^4C_1$ conformation than the α-isomer.




**Scheme 34**

### 2.3.4 Ethyl Chloro-oximinoacetate (152)

The title compound was prepared[164] in 36% yield by nitrosation of glycine ethyl ester hydrochloride (**151**) by hydrochloric acid and sodium nitrite (Scheme 35).

$$EtO_2CCH_2\overset{+}{N}H_3\bar{C}l \xrightarrow{NaNO_2/HCl} EtO_2CCCl{=}NOH$$

(151) (152)

**Scheme 35**

## 2.4 Nitrile Oxide Cycloaddition Reactions

### 2.4.1 Cycloadditions to 3-*O*-Benzyl-5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hex-5-enofuranose (37)

A number of nitrile oxide cycloadditions to *xylo*-alkene[66,165,166] (**37**) and its derivatives[166,167] have been reported in the literature. In all cases the reaction occurred with good stereoselectivity and it was therefore hoped that cycloaddition of pyranose 1-nitrile oxides (**122**), (**146**) and (**150**) to *xylo*-alkene (**37**) would also proceed in a highly stereoselective manner. Pyranose 1-nitrile oxides (**122**), (**146**) and (**150**) were generated *in situ* by Mukaiyama dehydration[27] (Scheme 36, see Section 1.3.1 for mechanism) of 2,6-anhydro-1-deoxy-1-nitroalditols (**121**), (**145**) and (**149**) respectively.

$$R\text{-}CH_2\text{-}NO_2 \xrightarrow[NEt_3]{TDI} R\text{-}C{\equiv}\overset{+}{N}\text{-}\overset{-}{O}$$

**Scheme 36**

Tolylene di-isocyanate (TDI) was selected as the dehydrating agent and triethylamine was used as the base. Phenyl isocyanate is more widely used, but it suffers from the disadvantage that removal of excess isocyanate at the end of the cycloaddition is often difficult and requires rigourous chromatography. This problem is avoided by the use of a di-isocyanate, such as TDI, and quenching the completed reaction with diaminoethane. The by-product is thus an insoluble polymeric urea which can readily be removed by filtration.

All cycloaddition products were characterised by $^1H$ and $^{13}C$ n.m.r. spectroscopy, optical rotation and FAB mass spectrometry, and in the case of (**153**), X-ray crystallography data was also obtained. Chemical formulae were verified by high resolution FAB mass spectrometry or elemental analysis.

Diastereomeric cycloadduct ratios were determined by comparison of the integrals of the anomeric proton signals in the $^1H$ n.m.r. spectrum of the crude mixture. Due to the concurrence of the anomeric proton signals of alkene (**37**) and the cycloadducts in the same region it was necessary to remove excess alkene before measuring the product ratio. The excess alkene could then be used in subsequent cycloadditions.

### 2.4.1.1 2,3,4-Tri-*O*-acetyl-β-xylopyranosyl-1-nitrile Oxide (122)

The cycloaddition of D-xylose-derived nitrile oxide (**122**) to a 1,2-disubstituted alkene to give a mixture of regiomeric isoxazolines has previously been reported[141]. This was carried out by slow addition of the nitrile oxide precursor dissolved in dichloromethane to a solution of excess alkene and TDI with a catalytic amount of triethylamine in refluxing dichloromethane. These conditions were designed to maintain a low concentration of nitrile oxide in the presence of a large excess of dipolarophile and hence minimise the competing dimerisation to furoxan. As this cycloaddition[141] proceeded in good yield (66%) it was decided to use the same conditions for the cycloaddition of nitrile oxide (**122**) to ω-unsaturated hexofuranose (**37**). However, as monosubstituted alkenes are more reactive towards nitrile oxides than 1,2-disubstituted alkenes the cycloaddition was initially carried out at room temperature. No cycloadducts were isolated under these conditions and most of the nitrile oxide precursor (**121**) was recovered. As a repeat reaction in refluxing dichloromethane resulted in isolation of a very small quantity (2%) of the desired cycloadducts a series of experiments was carried out to determine the optimum conditions. The same general procedure outlined above was used for all these experiments in which the yield of cycloadducts, as a function of varying temperature and addition time of nitrile oxide precursor. was studied (Table 3).

**Table 3** - Optimisation of Conditions for Cycloadditions of Nitrile Oxide (**122**) to Alkene (**37**)

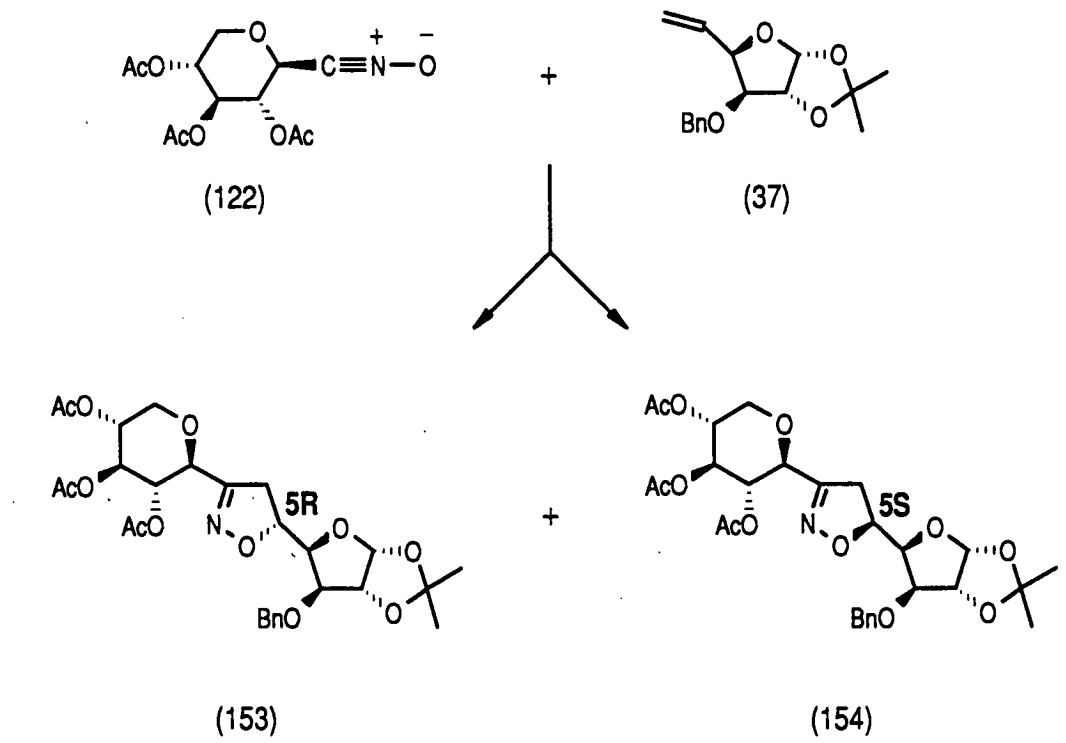
| Temp (°C) | Solvent | Addition Time (hrs) | Combined Yield of Cycloadducts (%) |
|---|---|---|---|
| 20 | $CH_2Cl_2$ | 14 | 0 |
| 40 | $CH_2Cl_2$ | 14 | 2 |
| 83 | $ClCH_2CH_2Cl$ | 14 | 8 |
| 83 | $ClCH_2CH_2Cl$ | 48 | 39 |
| 111 | Toluene | 14 | 66 |
| 111 | Toluene | 48 | 93 |

The optimised conditions for addition of nitrile oxide (**122**) to alkene (**37**) consisted of slow addition of a solution of the nitrile oxide precursor (1 equivalent) in toluene, *via* a motorised syringe pump, to a refluxing solution of alkene (**37**) (4 equivalents), TDI (3 equivalents) and triethylamine (0.5 equivalents) in toluene over a period of 48 hrs. Excess TDI was consumed by addition of diaminoethane thus forming an isoluble urea which was removed by filtration. The cycloadducts were then purified by chromatography. All cycloadditions of pyranose 1-nitrile oxides (**122**), (**146**) and (**150**) were carried out using this procedure.

Using the procedure outlined above the addition of (**122**) to (**37**) gave a pair of diastereomeric 2-isoxazolines (**153**) and (**154**), which were isolated in the ratio of 78:22 and a combined yield of 93% (Scheme 37).

The stereochemistry of the major isoxazoline (**153**) was determined by X-ray crystal structure analysis which verified that the new chiral centre at $C_5$ had R configuration and therefore the $C_4$-$C_5$ bond had the *erythro* relationship (Figure 11). This is consistent with previously reported[66,166] cycloadditions to *xylo*-alkene (**37**) in which the major cycloadduct always possessed the 5R configuration. X-ray analysis revealed that the isoxazoline ring exists in an envelope-type arrangement

where $C_6$-$C_7$-$N_7$-$O_5$ form the best plane with a torsion angle of 1.4° and $C_5$ is situated ~ 0.3 Å below the plane (full X-ray data is presented the Appendix ).




**Scheme 37**

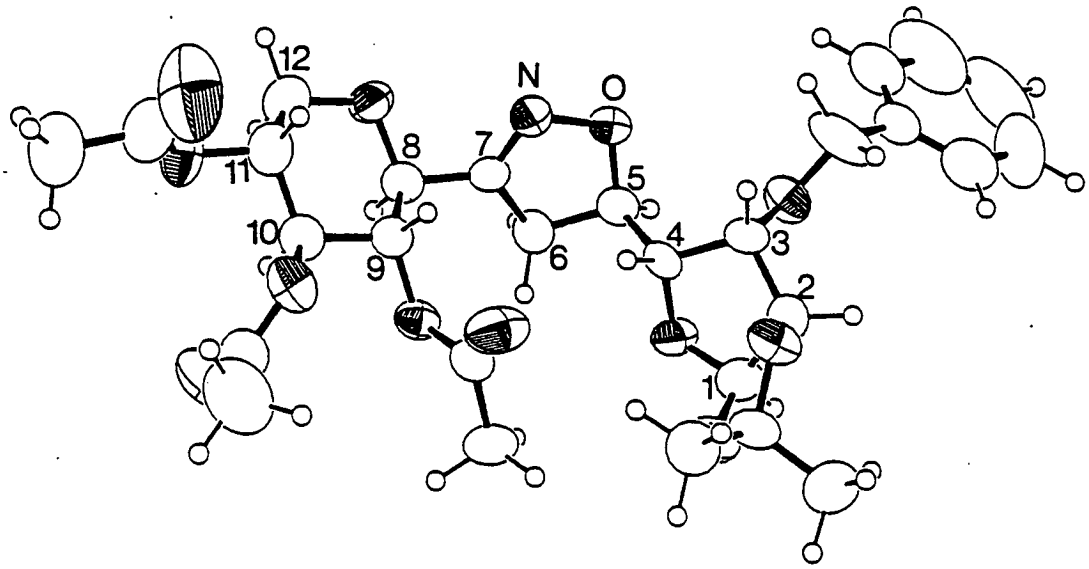
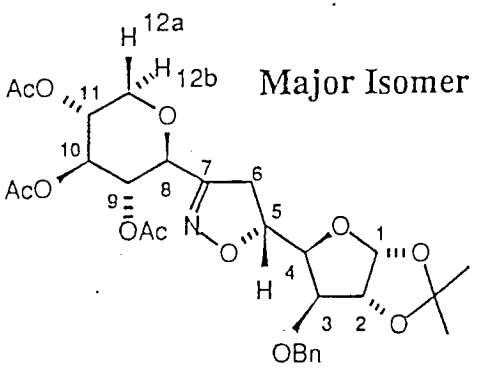
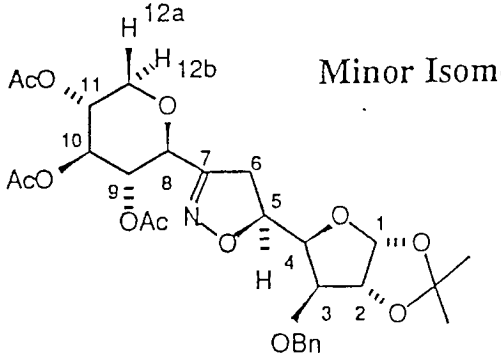



**Figure 11**

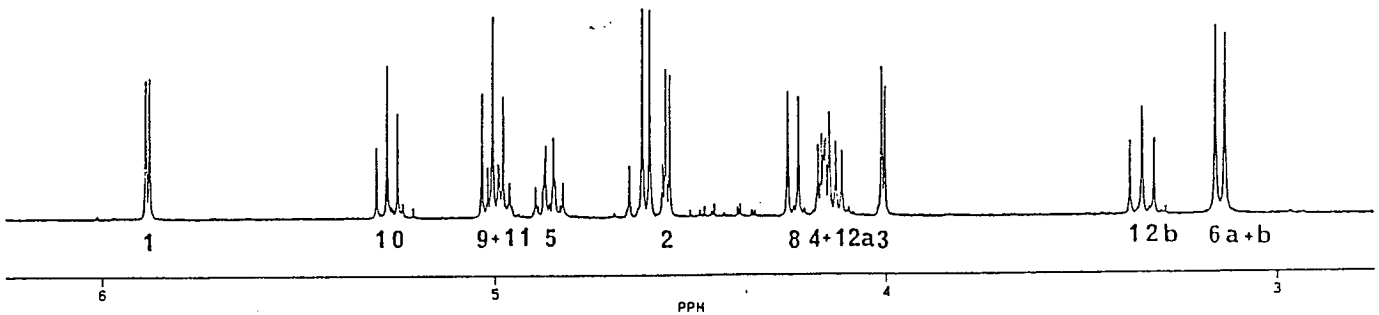



Major Isomer




Minor Isomer

Major Isomer




Minor Isomer

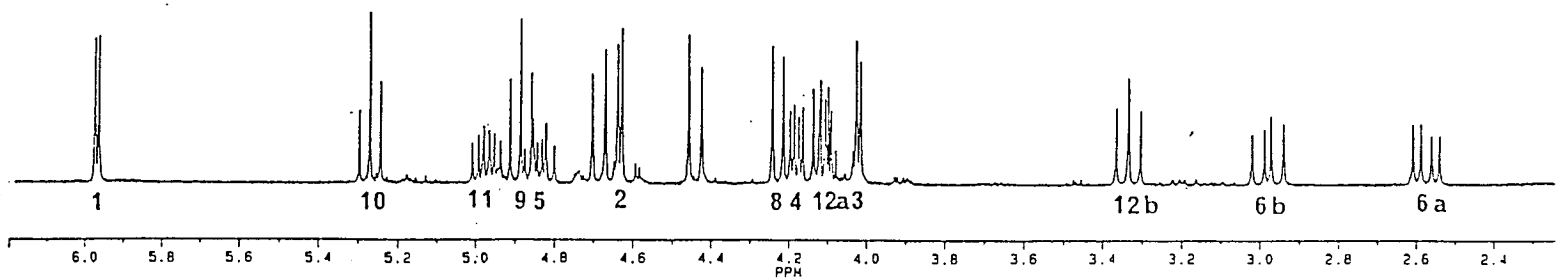



Figure 12

Proton n.m.r. of (**153**) in $CDCl_3$ indicates that the conformation of the isoxazoline ring in solution differs from that in the crystal. The signals for $H_{6a}$ and $H_{6b}$ are coincident and appear as a doublet; the couplings for $H_5$-$H_{6a}$ and $H_5$-$H_{6b}$ are both 9.0 Hz (compare this with the pair of doublets observed for $H_{6a}$ and $H_{6b}$ of minor isomer (**154**); see Figure 12). This is inconsistent with the dihedral angles of $H_5$-$C_5$-$C_6$-$H_{6a}$ = 98.6° and $H_5$-$C_5$-$C_6$-$H_{6b}$ = 24.6° obtained by X-ray crystallography and it is therefore concluded that the ring adopts a different conformation in solution. Further evidence for a conformational difference in the molecule between the solution and crystalline phases is provided by $J_{4,5}$ which at 7.2 Hz is smaller than that expected for the *anti* arrangement (dihedral angle = 176.9°) observed by X-ray analysis. This indicates that the dihedral angle between $H_4$ and $H_5$ is smaller in the solution phase.

Both $^1H$ n.m.r. coupling constants and X-ray data confirm that the pyranose ring of cycloadduct (**153**) adopts a $^4C_1$ chair conformation (Figure 13). This is the same conformation as that taken up by nitrile oxide precursor (**121**) (Section 2.3.1.) from which (**153**) and (**154**) were synthesised. Relevant coupling constants and the corresponding torsion angles for (**153**) are shown in Table 4.

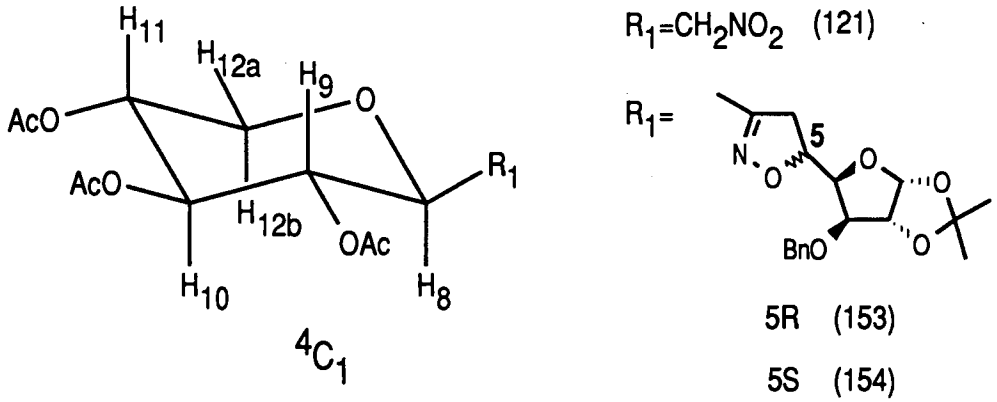
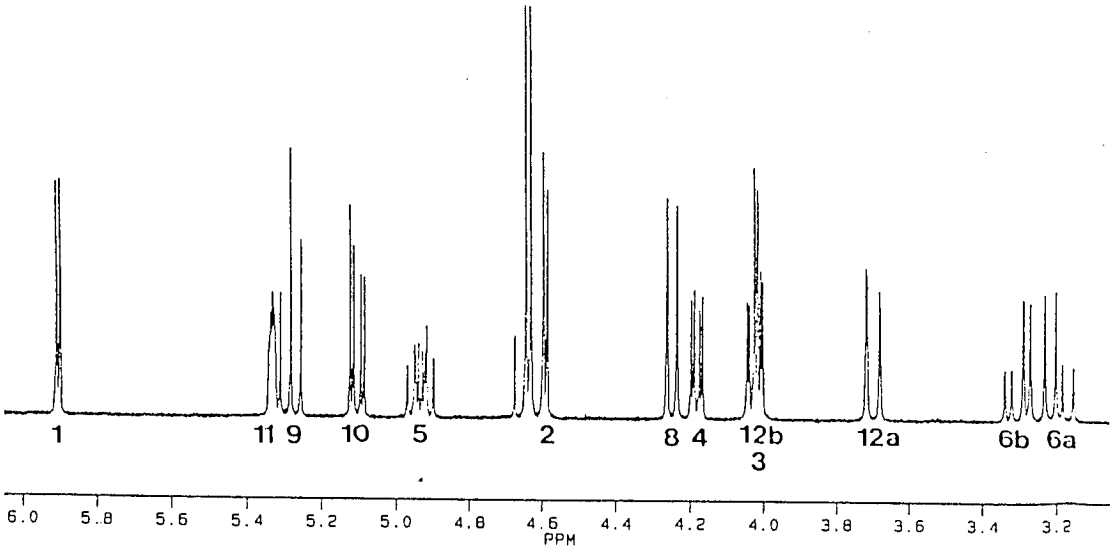



**Figure 13**


1
11 9
10
5
2
8 4
12b
3
12a
6b 6a
6.0
5.8
5.6
5.4
5.2
5.0
4.8
4.6
4.4
4.2
4.0
3.8
3.6
3.4
3.2
PPM

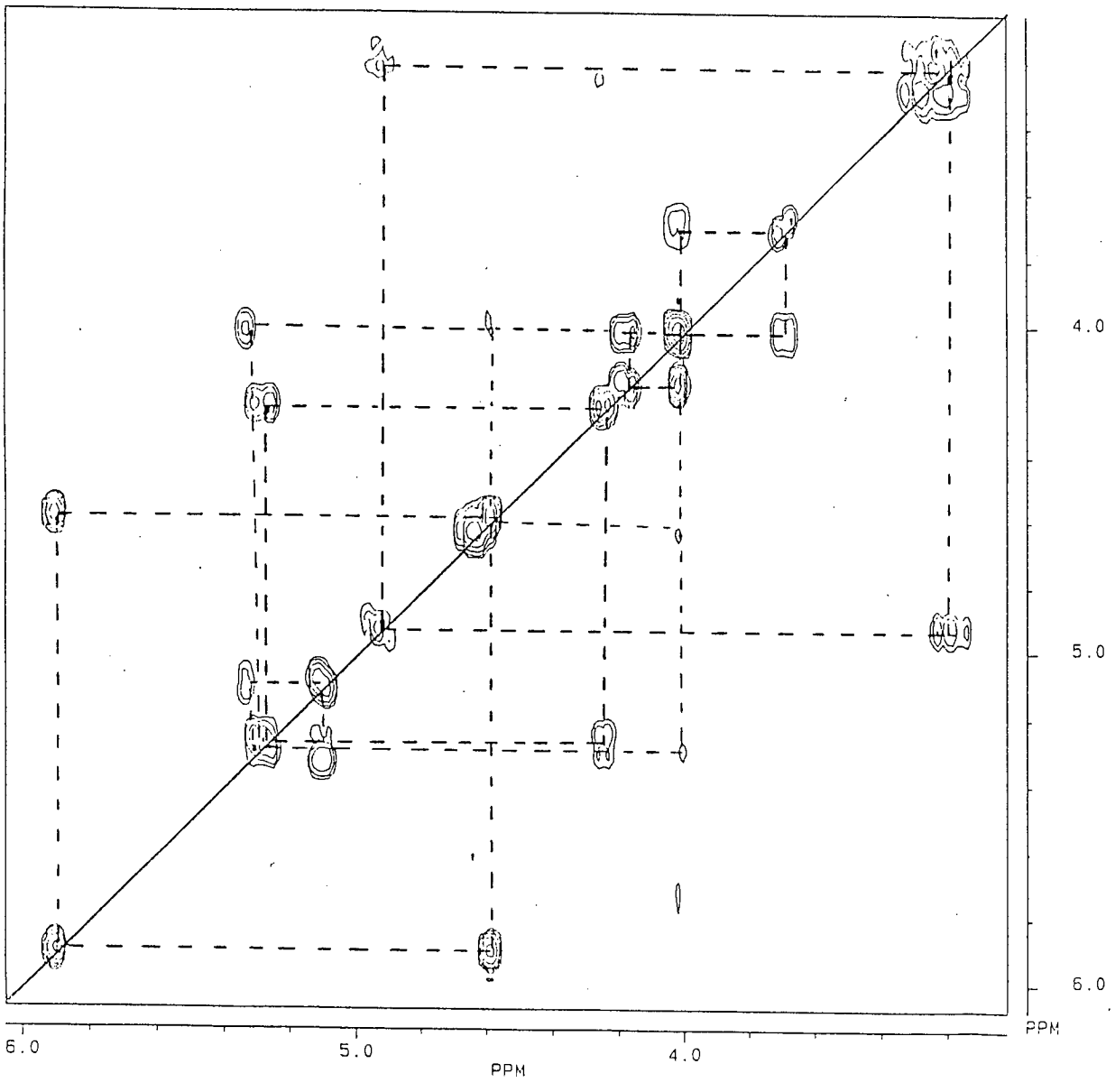

4.0
5.0
6.0
PPM
6.0
5.0
4.0
PPM

**Figure 14**

Proton n.m.r. coupling constants for the pyranose ring of minor isomer (**154**) are very similar to those of (**153**) and hence the pyranose ring of (**154**) must also adopt a $^4C_1$ conformation (Figure 13).

**Table 4** - $^1H$ n.m.r. Coupling Consts. *vs.* H-C-C-H Torsion Angles for Cycloadduct (**153**)

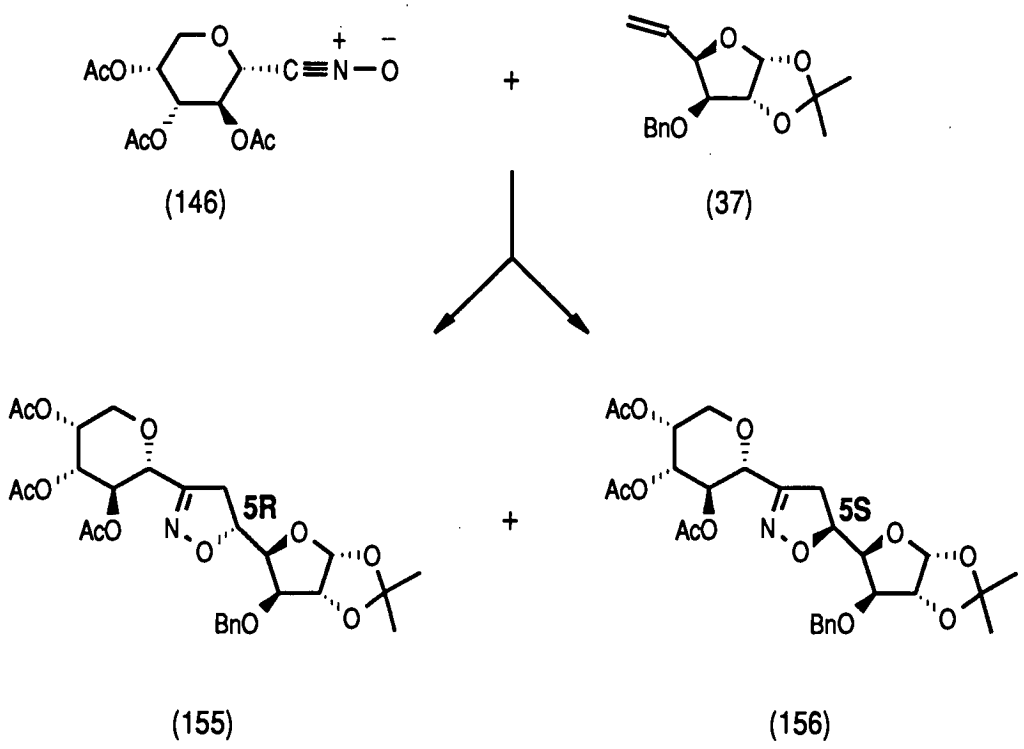
| Coupling | *J* (Hz) | Torsion Angle |
|---|---|---|
| 8,9 | 9.9 | 174.5° |
| 9,10 | 9.5 | 174.8° |
| 10,11 | 9.5 | 176.4° |
| 11,12a | 5.7 | 57.7° |
| 11,12b | 10.7 | 178.1° |

### 2.4.1.2 2,3,4-Tri-*O*-acetyl-α-arabinopyranosyl-1-nitrile Oxide (146)

Cycloaddition of D-arabinose-derived nitrile oxide (**146**) to *xylo*-alkene (**37**) was carried out using the optimised conditions determined for addition of nitrile oxide (**122**) to the same alkene (Section 2.4.1.1). A mixture of diastereomeric 2-isoxazolines (**155**) and (**156**) was obtained in a ratio of 80:20 and in a combined yield of 89% (Scheme 38).

The major isomer (**155**) was assigned as having R configuration at $C_5$ by comparison of its properties (Section 2.4.1.4) with those of cycloadduct (**153**) for which the stereochemistry was established unambiguously by X-ray analysis.

The $^1H$ n.m.r. spectrum of major isoxazoline (**155**) was assigned with the aid of the COSY spectrum shown in Figure 14. The presence of large diaxial couplings between $H_8$ and $H_9$ in cycloadducts (**155**) and (**156**) (9.8 and 9.7 Hz respectively) indicates that the pyranose ring in both cycloadducts adopts the same chair conformation as that found in the nitrile oxide precursor (**145**) (Figure 15).




**Scheme 38**

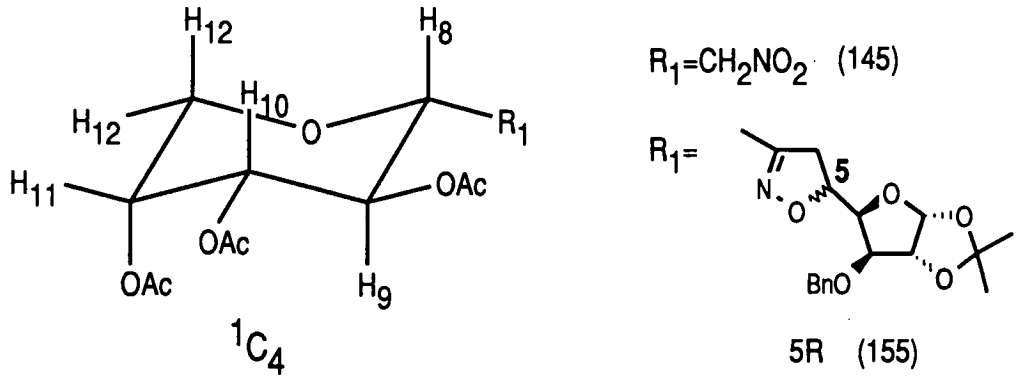
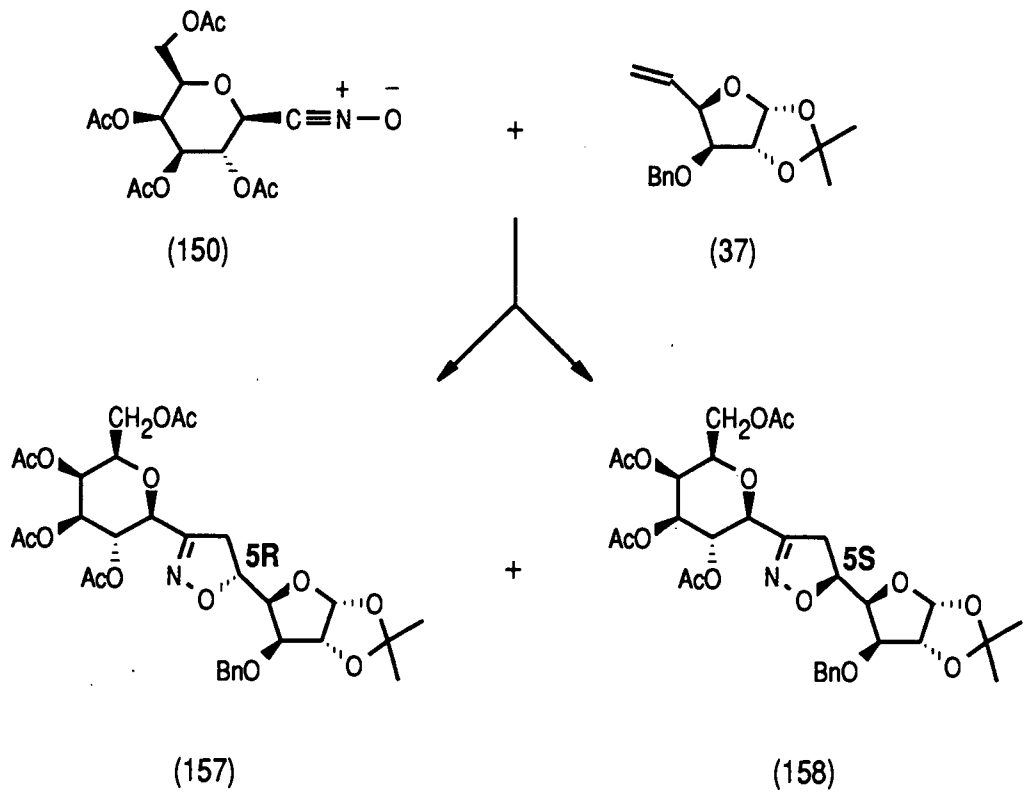



**Figure 15**

### 2.4.1.3 2,3,4,6-Tetra-*O*-acetyl-β-galactopyranosyl-1-nitrile Oxide (150)

Cycloaddition of pyranose 1-nitrile oxide (**150**) to *xylo*-alkene (**37**) was carried out using the same optimised conditions (Section 2.4.1.1) utilised for additions of nitrile oxides (**122**) and (**146**) to the same alkene. A pair of $C_5$ epimeric

2-isoxazolines (**157**) and (**158**) were isolated in a ratio of 91:9 and an overall yield of 61% (Scheme 39).




**Scheme 39**

The major cycloadduct (**157**) was assigned 5R configuration on the basis of t.l.c. and spectral similarities with (**153**) whose structure was determined by X-ray crystallography.

Proton n.m.r. coupling constants for the pyranose ring of (**157**) and (**158**) are consistent with a chair conformation. Coupled with the presence of large diaxial couplings between $H_8$ and $H_9$ (9.8 and 9.7 Hz respectively), this indicates that the pyranose rings in both cycloadducts adopt the $^4C_1$ conformation (Figure 16). This shows that no significant conformational change is undergone by the pyranose ring of the nitrile oxide precursor (**149**), which also possessed the $^4C_1$ conformation, upon cycloaddition.

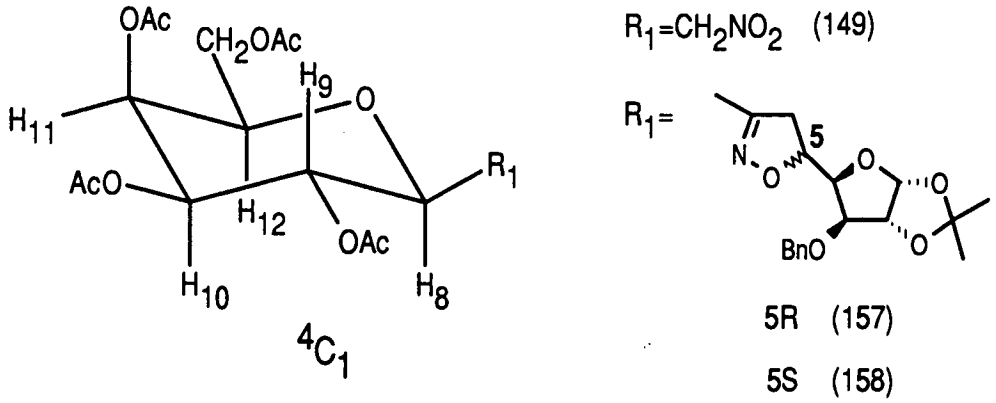



**Figure 16**

### 2.4.1.4 General Comparisons

The assignment of 5R stereochemistry to the major isomers and 5S to the minor products obtained from cycloaddition of nitrile oxides (**146**) and (**150**) to *xylo*-alkene (**37**) was based upon comparison of their properties with those of major cycloadducts (**153**) the structure of which was verified by X-ray analysis.

**T.l.c.** - In all solvent systems used the minor isomer always had the smaller $R_f$ value on silica.

**$^1$H n.m.r.** - The chemical shift for the anomeric proton of the minor isomers is *ca.* 0.1 ppm higher than that of the major. This facilitated the ratio determination of the mixtures by allowing comparison of the integrals of the anomeric proton peaks.

The signals for the protons of the methylene of the 3-*O*-benzyl protecting group are well separated in the minor isomers ($\Delta\delta \sim 0.25$ ppm), whereas they are near coincident in the major isomers ($\Delta\delta \sim 0.05$ ppm).

The signals for the methylene group of the isoxazoline ring ($H_{6a}$ and $H_{6b}$) show a marked difference between the major and minor adducts. In the major isomers they occur at higher chemical shift values and are closer together than in the minor isomers, coinciding in the case of (**153**) (Figure 12).

It is also noteworthy that the $\delta_H$ values for $H_9$ of the major isomers obtained from nitrile oxides (**122**) and (**150**) are over 0.1 ppm higher than that of the corresponding minor isomers yet no significant difference between the major and minor isomer $\delta_H$ values for $H_8$ was observed. In contrast the differences in the δ-values for $H_8$ and $H_9$ between major isomer (**155**) and minor isomer (**156**), in which the pyranose ring adopts a different chair conformation to the cases above, are very similar.

These trends are shown in Table 5 (full $^1H$ n.m.r. data can be found in Tables 21 and 22).

**Table 5** - $^1H$ n.m.r. Chemical Shift Trends in Cycloadducts to *Xylo*-alkene (**37**)

| Compound | $H_1$ | $H_{6a}$ | $H_{6b}$ | $H_8$ | $H_9$ | Ph $CH_2$ |
|---|---|---|---|---|---|---|
| (**153**) | 5.88 | 3.15 | 3.15 | 4.24 | 5.00 | 4.58, 4.64 |
| (**154**) | 5.97 | 2.57 | 2.98 | 4.23 | 4.88 | 4.44, 4.68 |
| (**155**) | 5.90 | 3.19 | 3.30 | 4.25 | 5.28 | 4.61, 4.66 |
| (**156**) | 5.97 | 2.67 | 3.11 | 4.18 | 5.19 | 4.45, 4.68 |
| (**157**) | 5.89 | 3.25 | 3.19 | 4.32 | 5.23 | 4.62, 4.66 |
| (**158**) | 5.98 | 2.61 | 3.01 | 4.30 | 5.10 | 4.44, 4.71 |

The $^1H$ n.m.r. coupling constants indicate that in all three cycloadditions the conformation of the pyranose ring of the nitrile oxide fragment is not significantly altered upon cycloaddition, *i.e.* the pyranose ring of both the minor and major isomers adopts the same chair conformation as the nitrile oxide precursor from which it was synthesised.

**$^{13}C$ n.m.r.** - The only significant variation in the $\delta_C$ values of the major and minor isomers is that of the epimeric centre $C_5$. The $C_5$ resonance for the minor

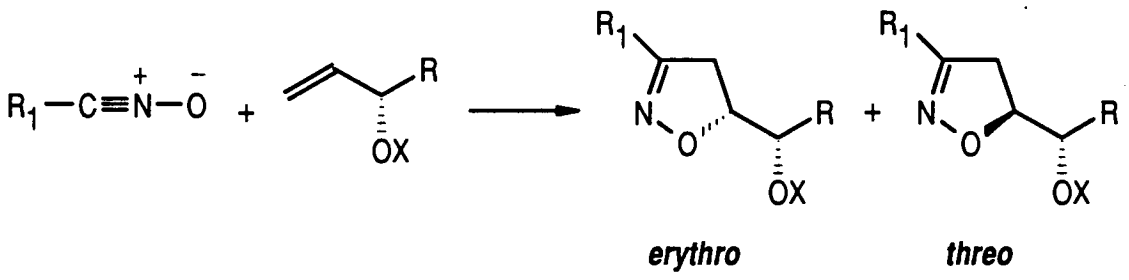
isomer always occurs at a higher chemical shift value; for example (**155**) and (**156**) give $C_5$ signals at 76.7 and 79.4 ppm respectively.

**Optical Rotation** - In all cases the major isomer has a more negative optical rotation value than the minor isomer. It is noteworthy that the difference between the [α] values of the major and minor isomers was very similar (~ 80°) for the cycloadducts obtained from the two six-carbon nitrile oxides (**122**) and (**146**). The [α] difference between the cycloadducts obtained from the seven-carbon nitrile oxide (**150**) was 56°.

### 2.4.1.5 Stereoselectivity

In recent years there has been growing interest in the π-facial selectivity of nitrile oxide cycloaddition reactions[168] owing to their use in the stereoselective synthesis of natural products[24,63]. Cycloadditions employing chiral nitrile oxides and achiral alkenes have generally been found to give poor diastereoselectivity[169-171], an effect attributed to the distance between the existing asymmetric centre and the forming stereocentre at $C_5$ of the isoxazoline.

Cycloaddition to chiral alkenes, on the other hand, have afforded more promising results[168]. A great deal of interest has been focused on cycloadditions to monosubstituted alkenes possessing an allylic stereocentre bearing an oxygen substituent (Scheme 40). This area is of particular relevance to the work presented in this thesis and the results are therefore examined in detail.




**Scheme 40**

The presence of an allylic ether function leads to fair to excellent π-facial stereoselectivity in favour of the *erythro* product[172]. This selectivity has been shown to increase as the size of the alkyl group R increases. In contrast allylic alcohols show little π-facial selectivity, but slightly favour the opposite (*threo*) isomer.

Two theories have been proposed to explain these observations. The most widely accepted is the "inside alkoxy effect" put forward by Houk[172]. This is based on a Felkin[173]-Anh[174] type transition state in which the allylic substituents are staggered with respect to the incoming nitrile oxide oxygen (Figure 17).

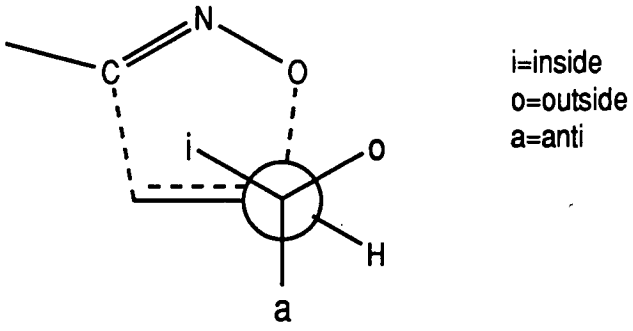



**Figure 17**

Six possible transition states of this type can be drawn for cycloaddition to a chiral allyl ether ($CH_2$ = CH.CHOR'R) (Figure 18). Three of these (**A, B** and **C**) lead to the major *erythro* product and the remaining three (**A', B'** and **C'**) afford the minor *threo* isomer.

Theoretical calculations on the relative energies of these transition states carried out by Houk[172] place them in ascending order: **A<A'<B<B'<C'<C**. In the lowest energy transition state (**A**) the alkoxy group (OR') is in the *inside* position with the hydrogen in the most sterically demanding *outside* position and the alkyl group (R) in the least sterically hindered *anti* position. It was concluded that this transition state is responsible for the formation of the favoured *erythro* isomer with the second lowest energy transition state **A'** leading to formation of the minor *threo* isomer.

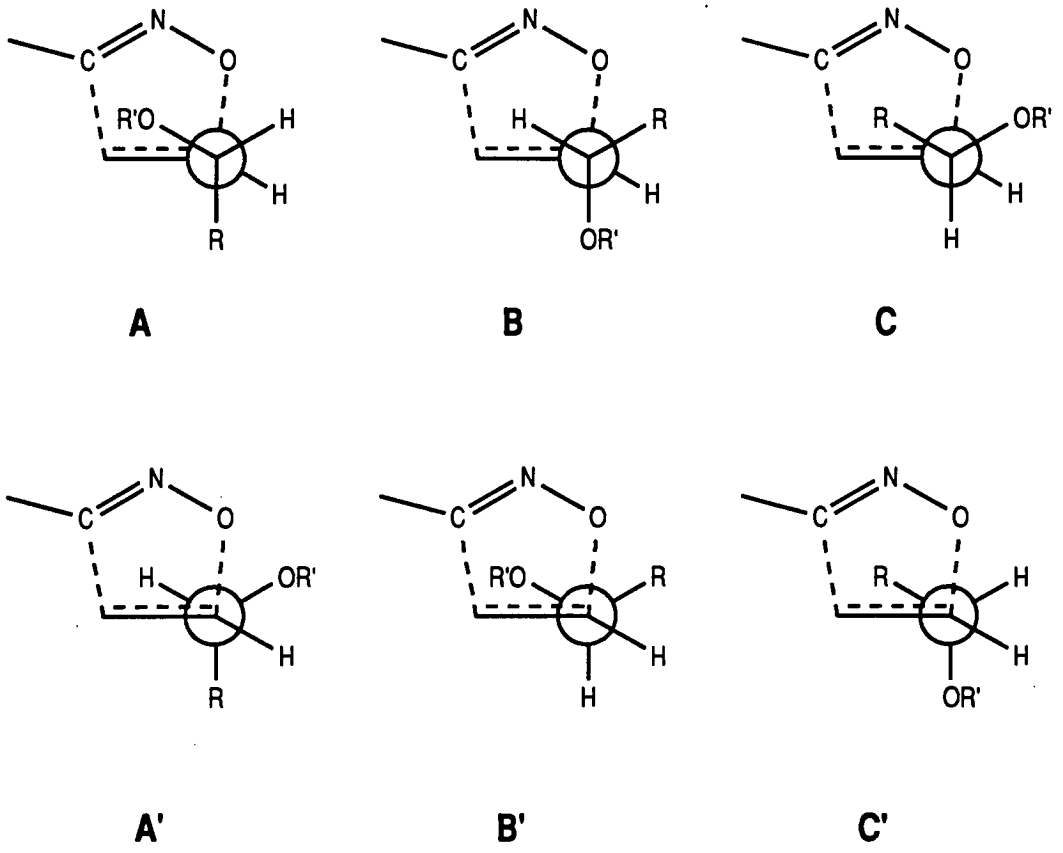
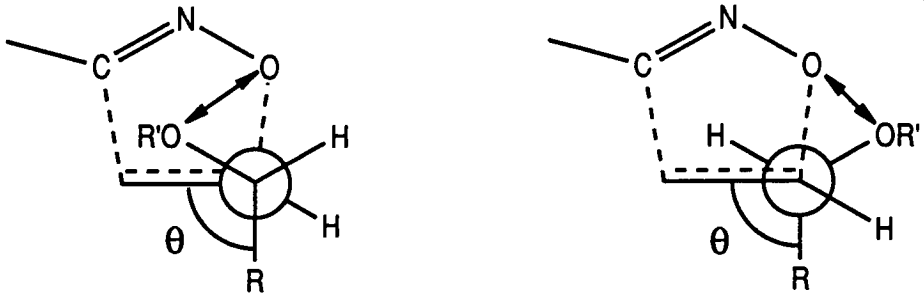



**Figure 18**

The increase in π-facial selectivity noted as the size of alkyl group R increases is explained by examining the effect of varying C = CCR dihedral angle θ on transition states **A** and **A'**. As R increases in size θ increases (Figure 19). This has a stabilising effect on **A** as it reduces unfavourable lone pair interactions between the alkoxy and nitrile oxide oxygens. In transition state **A'**, however, increasing θ brings the alkoxy and nitrile oxide oxygens closer together and hence destabilises this transition state with respect to **A**.




A A'

**Figure 19**

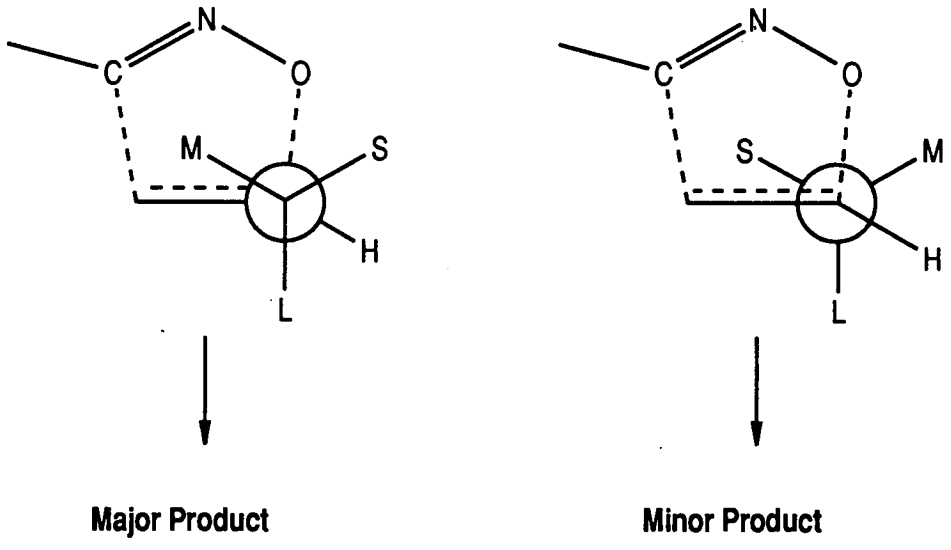
The preference of the alkoxy group for the *inside* position over the *anti* position is explained by Houk[172] in terms of secondary orbital interactions. The nitrile oxide cycloaddition process is mildly electrophilic and thus the π-bond of the allylic ether becomes electron deficient in the transition state. Hence electron-donating substituents stabilise the transition state but electron-withdrawing substituents destabilise it. When the alkoxy group is *anti* it becomes electron withdrawing due to overlap between $\sigma^*_{CO}$ and the π-bond orbital. However, in the *inside* position the alkoxy group is near the plane of the π-bond and this unfavourable overlap is minimised. In this position the transition state is further stabilised by maximal overlap of the π-orbital with the electron-donating $\sigma_{CH}$ and $\sigma_{CR}$ orbitals.

The low stereoselectivity observed for allylic alcohols may be explained by competing hydrogen-bonded versions of transition states **A** and **A'** (OH hydrogen-bonded to the nitrile oxide oxygen), where **A'** is slightly preferred. This hypothesis is supported by the observation that diastereoselectivities of nitrile oxide cycloadditions to allylic alcohols are solvent dependent with a reversal of stereoselectivity to slightly favour the *erythro* isomer occurring when the cycloaddition is carried out in a good hydrogen-bonding acceptor such as DMF.

Kozikowski[175,176] has proposed an alternative explanation in which the alkoxy group is antiperiplanar to the incoming nitrile oxide oxygen in the transition

state (transition state **B** in Figure 18). He argues that this minimises secondary antibonding interactions - a direct contradiction of Houk's arguments for the "inside alkoxy effect". This proposal, however, fails to explain the experimentally observed increase in diastereoselectivity as the size of R increases. On the contrary for transition state **B** increasing the size of the R group in the sterically hindered *outside* position should depress the *erythro* diastereoselection[168].

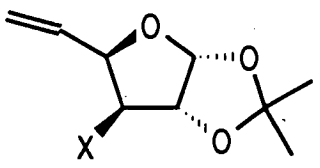
Houk has extended[177] his model to include cycloadditions to chiral vinyl alkenes with substituents that vary only in size. The lowest energy transition state has the large group (L) *anti*, the smallest group (S) in the sterically crowded *outside* position and the medium group (M) *inside* (Figure 20). The minor product is obtained from the transition state in which the M and S groups are reversed. In the absence of an alkoxy group, however, the diastereoselectivities are lower.




**Major Product** **Minor Product**

**Figure 20**

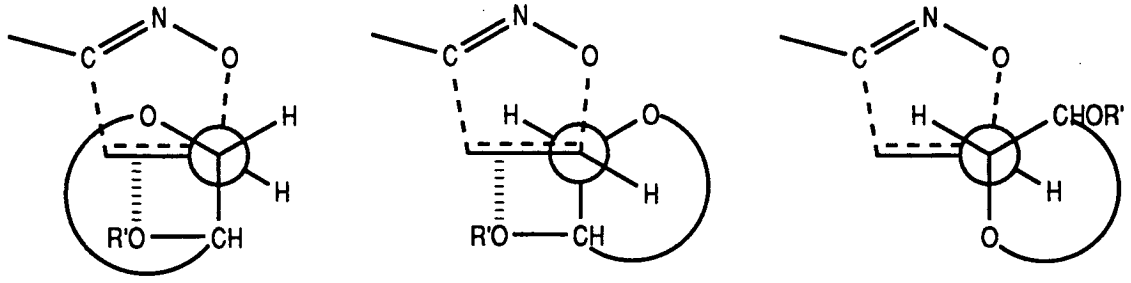
De Micheli and co-workers[166] have investigated the diastereoselectivity of nitrile oxide cycloadditions to alkene (**159**) with a variety of substituents at the 3-position.



(159)

X = H ; OH ; OMe ; OBn ; $OCH_2$-2,6-$Cl_2C_6H_3$ ; $OCOCH_3$ ; $OSO_2CH_3$ ; $OCONH_2$

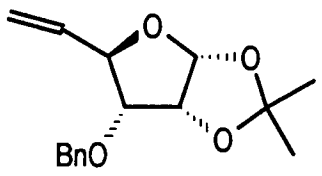
This work revealed that cycloaddition to alkenes of type (**159**) bearing an oxygen substituent in the 3-position (a homoallylic oxygen) resulted in significantly higher *erythro* selectivity than theoretical calculations based on Houk's "inside alkoxy effect" model predicted. For example, for addition of formonitrile oxide to alkene (**159**) where X = OMe the experimentally observed selectivity was 96.5:3.5 compared with a calculated value of 67:33. As these calculations only consider steric effects De Micheli *et al.* concluded that the homoallylic oxygen must exert a stereoelectronic effect on the selectivity. They proposed that for transition states **A** and **A'**, where R is *anti,* the homoallylic oxygen lone pairs may have an unfavourable through space interaction with the π-bond, thereby having a destabilising effect. In the third most populated transition state **B**, however, this interaction cannot take place and therefore the importance of **B** relative to **A** and **A'** is increased leading to increased *erythro* selectivity (Figure 21).




**A** **A'** **B**

**Figure 21**

The importance of the effect of the homoallylic oxygen on diastereoselectivity has been reinforced by work carried out by Paton *et al.*[178] in which they investigated cycloadditions to *ribo*-alkene (**160**) which is epimeric to *xylo*-alkene (**37**) at the 3-position. Addition of ethoxycarbonylformonitrile oxide (**36**) to (**160**) showed no selectivity whereas addition of benzonitrile oxide resulted in a 60:40 mixture in favour of the *threo* isomer. This exception to the "inside alkoxy effect" model has not as yet been explained.

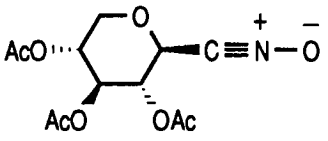



(160)

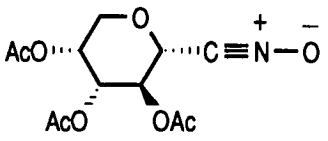
Table 6 compares the diastereoselectivities of cycloaddition of pyranose 1-nitrile oxides (**122**), (**146**) and (**150**) to *xylo*-alkene (**37**) with additions of other nitrile oxides to (**37**) reported by De Micheli[166], and Paton and Young[66].

**Table 6** - Diastereoselectivities of Cycloadditions to Alkene (**37**)

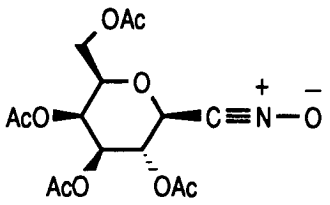
| Nitrile Oxide | Diastereoselectivity *erythro : threo* |
|---|---|
| (**122**) | 78:22 |
| (**146**) | 80:20 |
| (**150**) | 91:9 |
| (**36**) | 86:14[66] |
| (**36**) | 85.5:14.5[166] |
| (**161**) | 94.2:5.8[166] |
| (**162**) | 96.8:3.2[166] |



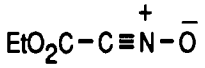
(122)



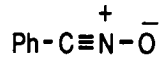
(146)



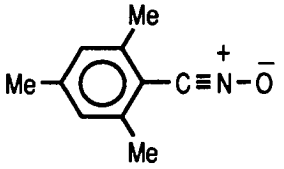
(150)



(36)



(161)



(162)

As can be seen from Table 6 the π-facial selectivity of the addition of D-galactose-derived nitrile oxide (**150**) is comparable with additions of other nitrile oxides reported in the literature. The diastereoselectivity obtained with nitrile oxides (**122**) and (**146**) is only slightly lower than that observed for ethoxycarbonylformonitrile oxide. This slight drop may be due to the additions of (**122**), (**146**) and (**150**) being carried out at higher temperatures (111°C) than those reported in the literature (room temperature additions ~ 25°C).

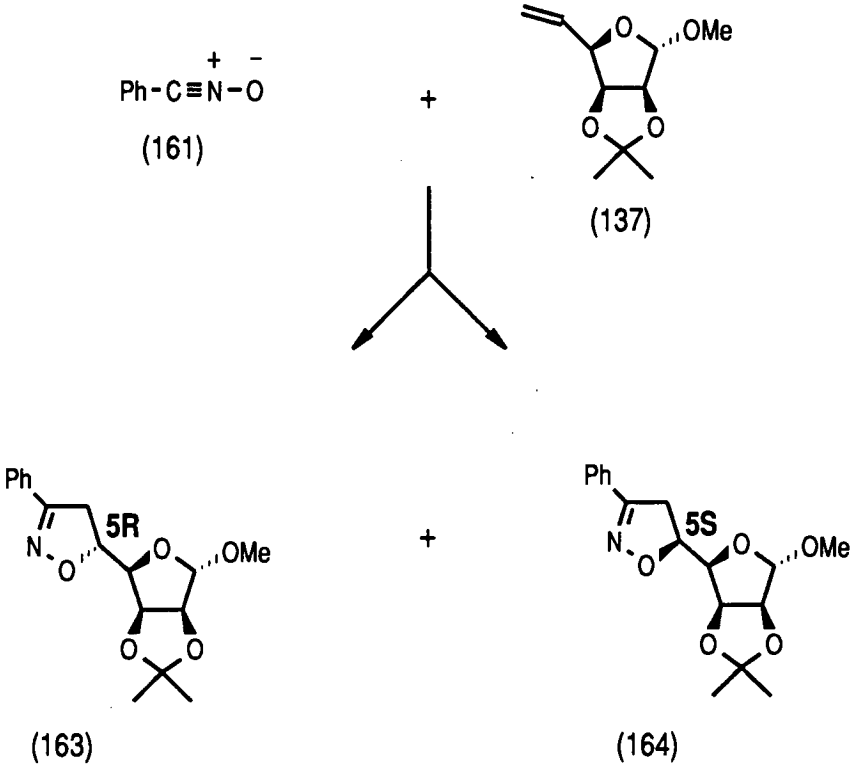
It was therefore concluded that the π-facial selectivity observed for the additions of pyranose 1-nitrile oxides (**122**), (**146**) and (**150**) to *xylo*-alkene (**37**) is consistent with a modified Houk[172] view in which the "inside alkoxy effect" is reinforced by the effect of the homoallylic oxygen[166] to give greater *erythro* selectivity.

### 2.4.2 Cycloadditions to Methyl 5,6-Dideoxy-2,3-*O*-isopropylidene-α-D-*manno*-hex-5-enofuranoside (137)

Cycloadditions to *xylo*-alkene (**37**) proceed with moderate to high diastereoselectivity (56%-94% d.e.) in favour of the *erythro* isomer (Section 2.4.1). In contrast additions to *ribo*-alkene (**160**), which is epimeric with (**37**) at $C_3$, show little stereoselection and in one case favour the *threo* isomer (20% d.e.)[178].

To date there have been no reports of nitrile oxide cycloadditions to *lyxo*-alkene (**137**) which has the opposite stereochemistry to (**37**) at $C_2$. It was therefore decided to carry out additions of model dipoles, benzonitrile oxide (**161**) and ethoxycarbonylformonitrile oxide (**36**), to this alkene before cycloadding pyranose 1-nitrile oxides in order to determine what, if any, effect the reversal of configuration at this site, remote from the addition, would have on the diastereoselectivity.

The addition of benzonitrile oxide (**161**) to *lyxo*-alkene (**137**) was carried out by K.E. McGhie and G. Kirkpatrick[179]. They obtained a diastereomeric mixture of isoxazolines (**163**) and (**164**) in a ratio of 82:18 and a combined yield of 82% (Scheme 41). The structure of the major isomer (**163**) was confirmed by X-ray crystallography.

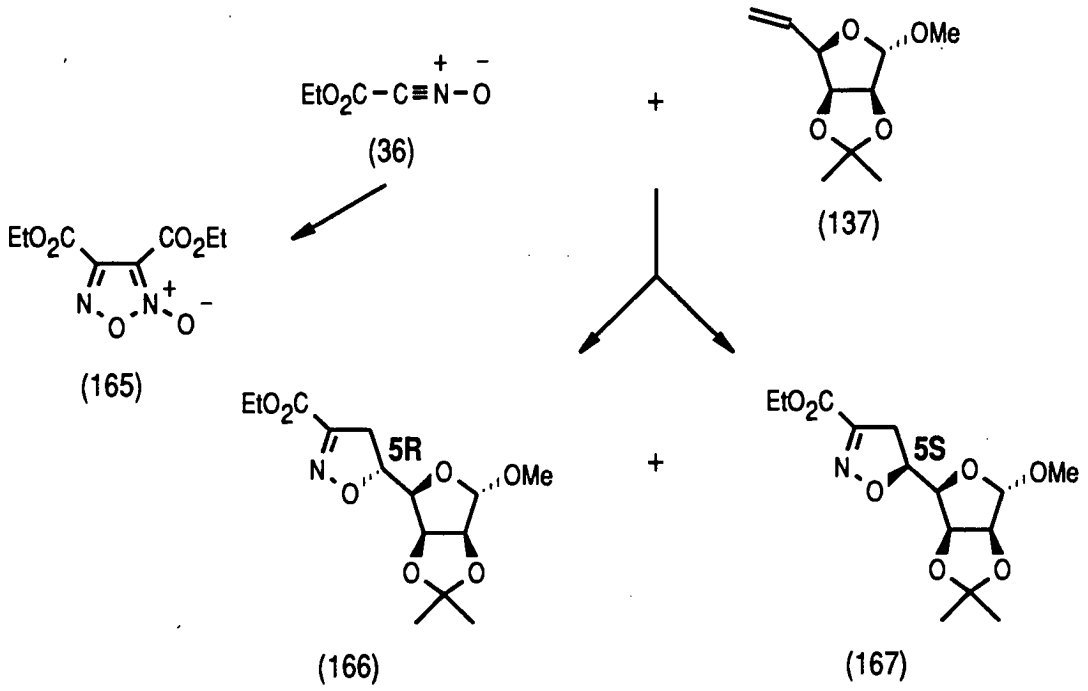



**Scheme 41**

Determination of the diastereomeric ratio was carried out by comparison of the integrals of the $OCH_3$ signals in the $^1H$ n.m.r. spectrum of the mixture in the case of addition of benzonitrile oxide (**161**).

### 2.4.2.1 Ethoxycarbonylformonitrile Oxide (36)

Ethoxycarbonylformonitrile oxide (**36**) was generated from ethyl chloro-oximinoacetate (**152**) by dehydrohalogenation with base. The cycloaddition was performed by the slow addition of triethylamine (1.2 equivalents) in dry ether, *via* a motorised syringe pump, to an ice-cooled solution of the alkene (**37**) (1.5 equivalents) and ethyl chloro-oximinoacetate (**152**) (1 equivalent) in ether, over a period of 40 hrs. These conditions were employed to minimise the formation of the furoxan dimer (**165**) by maintaining a low concentration of the dipole in the presence of excess dipolarophile. After chromatography furoxan (**165**) (24%) and a pair of diastereomeric isoxazolines (**166**) and (**167**) in a ratio of 82:18 (76% combined yield) were isolated (Scheme 42).

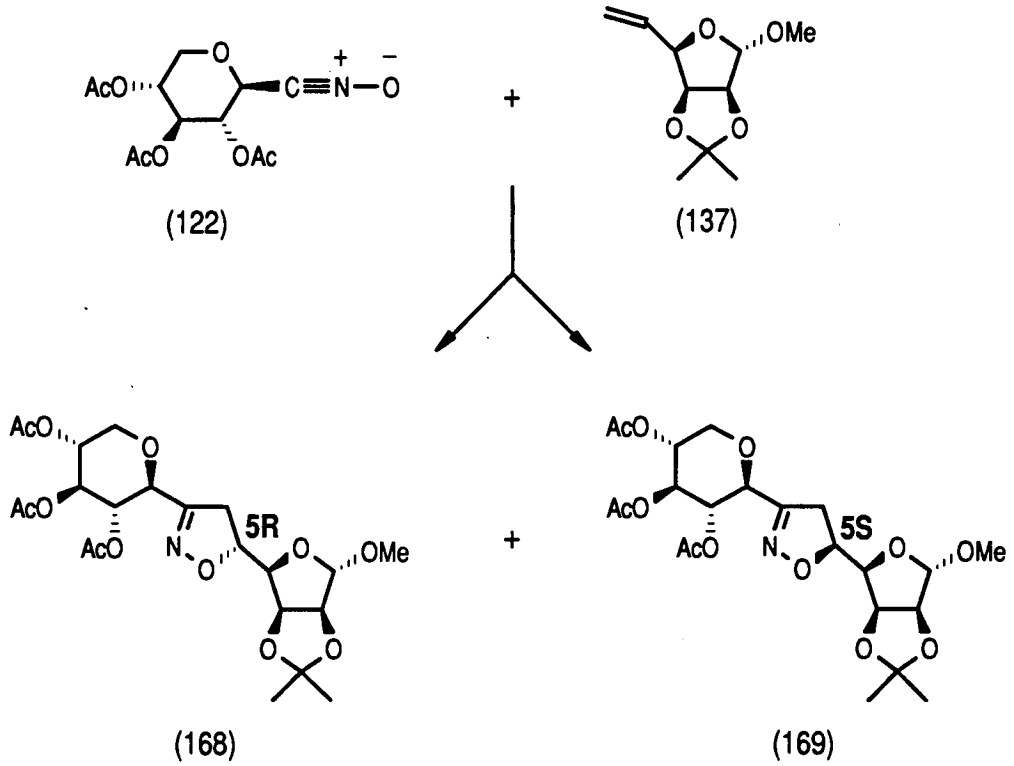



**Scheme 42**

The major isomer (**166**) was assigned the R configuration at $C_5$ by comparison of its spectral properties with those of (**163**), the stereochemistry of which was unambigously assigned by X-ray analysis[179].

### 2.4.2.2 2,3,4-Tri-*O*-acetyl-β–xylopyranosyl-1-nitrile Oxide (122)

The cycloaddition of pyranose 1-nitrile oxide (**122**) to *lyxo*-alkene (**137**) was carried out utilising the conditions developed for addition of this nitrile oxide to *xylo*-alkene (**37**) (Section 2.4.1.1). A large amount of unreacted nitrile oxide precursor (**121**) was isolated along with a mixture of diastereomeric isoxazolines (**168**) and (**169**) in a ratio of 79:21 and a combined yield of 36% (80% based on a consumed starting material - Scheme 43). This mixture of isoxazolines was inseparable by chromatography but a small sample of the pure major isomer (**168**) was obtained by repeated recrystallisation. This compound was assigned 5R stereochemistry also on the basis of spectral similarities with (**163**).




(122) (137) (168) (169)

**Scheme 43**

Due to the inseparability of the isoxazoline mixture no attempt was made to optimise this reaction or to carry either isomer on to a later stage.

As in the addition of (**122**) to *xylo*-alkene (**37**) $^1$H n.m.r. indicated that the pyranose ring of the major isomer (**168**) adopted the same $^4C_1$ conformation as the nitrile oxide precursor (**121**) (Section 2.4.1.1).

### 2.4.2.3 General Comparisons

**T.l.c.** - As in the case of the *xylo*-alkene cycloadducts the major isomer has the larger $R_f$ value on silica in all solvent systems used. However, the $R_f$ value difference between the isomers was smaller in the *lyxo*-alkene cycloadducts, being coincidental for isomers (**168**) and (**169**).

**Optical Rotation** - The cycloadducts of the *lyxo*-alkene follow the trend established by the *xylo*-alkene cycloadducts in that the major isomer has the more negative optical rotation value.

**$^1$H n.m.r.** - In a similar fashion to the *xylo*-alkene-derived isoxazolines the anomeric proton peak of the minor isomer occurs *ca.* 0.1 ppm higher than that of the major. In these cases, however, the peaks overlap with the $H_5$ signal and could not be used for ratio determination. Instead the $H_4$ signals were compared to determine the diastereomeric ratios for the additions of ethoxycarbonylformonitrile oxide (**36**) and pyranose 1-nitrile oxide (**122**). The $OCH_3$ signals were compared for the addition of benzonitrile oxide (**161**) to alkene (**137**). In each case furoxan and excess alkene were removed before carrying out the ratio determination.

The signals for the methylene group of the isoxazoline ring ($H_{6a}$ and $H_{6b}$) show a similar pattern to that shown by the *xylo*-alkene-derived products (Section 2.4.1.5). Again the signals for the major isomer occur close together and are coincident in the case of (**163**) and (**164**), whereas the minor isomer peaks are more widely spaced.

These trends are summarised in Table 6.

**Table 6** - Trends in the $^1H$ n.m.r. of *Lyxo*-alkene Cycloadducts

| Compound | $H_1$ (ppm) | $H_{6a}$ (ppm) | $H_{6b}$ (ppm) |
|---|---|---|---|
| **(163)**[179] | 4.91 | 3.45 | 3.45 |
| **(164)**[179] | 4.99 | 3.12 | 3.57 |
| **(166)** | 4.86 | 3.20 | 3.32 |
| **(167)** | 4.96 | 2.99 | 3.40 |
| **(168)*** | 4.89 | 3.16 | 3.08 |

* - No n.m.r. data was obtained for minor isomer (**169**).

**Stereoselectivity** - Table 7 summarises the π-facial selectivity of the additions to *lyxo*-alkene (**137**) and the corresponding additions to *xylo*-alkene (**37**).

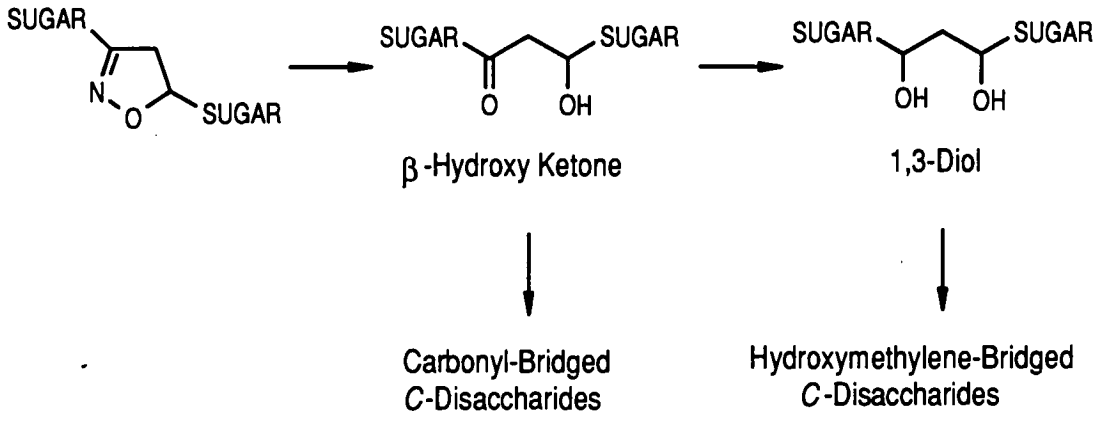
**Table 7** - Selectivity of Additions to *Lyxo*-alkene (**137**) and *Xylo*-alkene (**37**)

| Nitrile Oxide | π-Facial Selectivity | |
|---|---|---|
| | To *Lyxo*-alkene (137) *erythro:threo* | To *Xylo*-alkene (37) *erythro:threo* |
| **(36)** | 82:18 | 85.5:14.5[166] |
| **(122)** | 79:21 | 78:22 |
| **(161)** | 82:18[179] | 94.2:5.8[166] |

As can be seen from Table 7 the selectivity of additions to *lyxo*-alkene (**137**) is comparable with that of additions to *xylo*-alkene (**37**) which has the opposite configuration at $C_2$. It is therefore concluded that the configuration at $C_2$, which is remote from the site of the cycloaddition, has little or no effect on the π-facial selectivity of these additions. The selectivity observed may be explained in terms of the "inside alkoxy effect"[172] and the "homoallylic effect"[166] (Section 2.4.1.5).

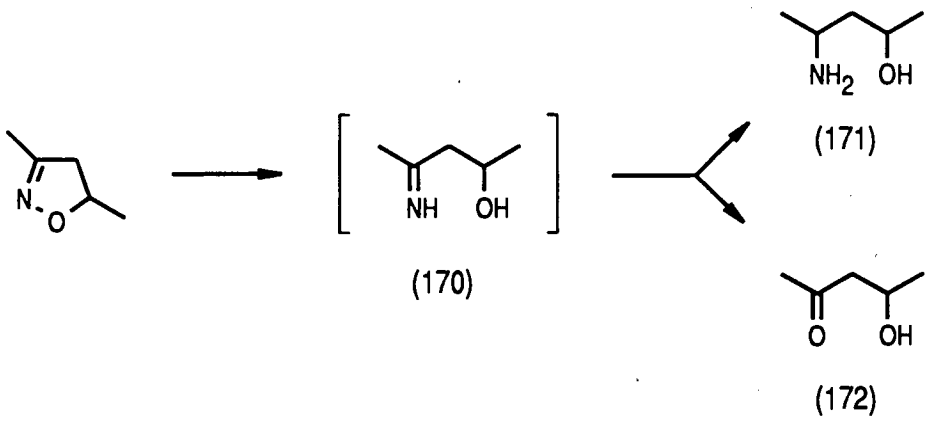
## 2.5 2-Isoxazoline Ring Cleavage to β-Hydroxy Ketones

It has been shown (Section 2.4) that nitrile oxide cycloaddition chemistry can be successfully used to link together two monosaccharide units. The next step in this route to *C*-disaccharides is to release the masked functionality latent in the isoxazoline ring. Hydrolytic ring cleavage to the β-hydroxy ketone was selected for investigation as this would allow access not only to carbonyl bridged *C*-disaccharides, but through simple carbonyl reduction, give hydroxymethylene-bridged *C*-disaccharides (Scheme 44).



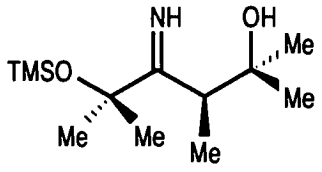

**Scheme 44**

Since the first ring cleavage of a 2-isoxazoline to a β-hydroxy ketone was reported by Torssell[180] in 1978 a number of methods of releasing this functionality have been developed (Section 1.4). The most commonly used technique is catalytic hydrogenolysis[25] employing palladium on charcoal (Pd/C) or Raney nickel (Ra-Ni). Supported metal catalysts such as these tend to cleave weak interheteroatom bonds faster than carbon-heteroatom multiple bonds. Hence the N-O bond of the 2-isoxazoline ring is cleaved first to give a β-hydroxy imine intermediate (**170**) (Scheme 45). This intermediate can then be further reduced to the γ-amino alcohol (**171**) or undergo hydrolysis to the β-hydroxy ketone (**172**).

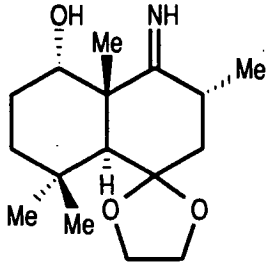



**Scheme 45**

Under mildly acidic conditions (pH 5.5-6.0) the intermediate β-hydroxy imine usually undergoes rapid hydrolysis[25] and is not detected. Some stable β-hydroxy imines such as (**173**)[181] and (**174**)[182] have, however, been isolated from hydrogenolysis reactions. These compounds were subsequently converted to β-hydroxy ketones when resubjected to hydrolysis conditions, thereby providing strong evidence for the proposed mechanism[25]. The slow rate of hydrolysis of these compounds was attributed to steric hindrance by bulky neighbouring groups.

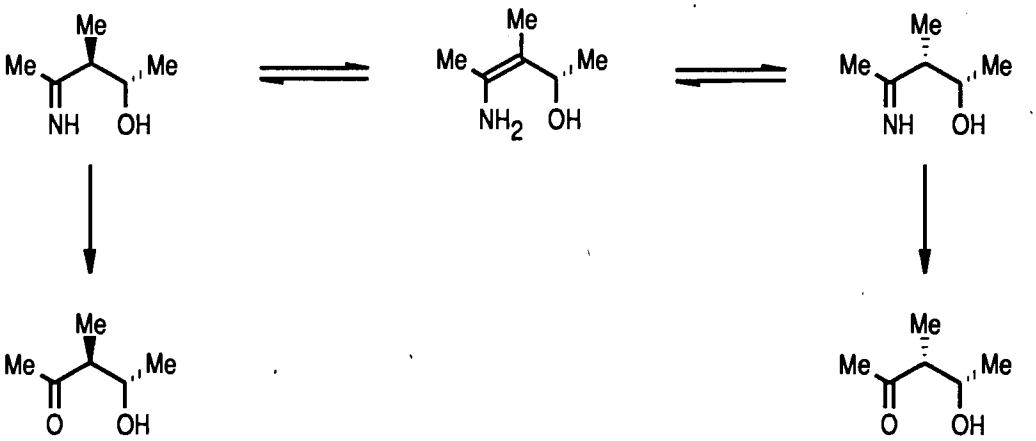



(173)




(174)

It has been reported that in some cases epimerisation occurs leading to a mixture of diastereomers. Curran[25] has proposed that this is due to tautomerisation of the intermediate β-hydroxy imine (Scheme 46). This can be prevented by rapid hydrolysis of the imine intermediate.



**Scheme 46**

These hydrogenolysis reactions are usually carried out in an aqueous methanol solution in the presence of acid. The purpose of this acid additive is threefold[25]: firstly to facilitate imine hydrolysis by protonation of the imine nitrogen, secondly to neutralise the ammonia formed during the hydrolysis and finally, in the case of Ra-Ni, to neutralise any remaining hydroxide on the catalyst. Several acidic additives have been used including acetic acid[183], concentrated HCl[60], aluminium[60] and boron[67] trichlorides, acetate and phosphate buffers[184] and trimethyl borate[184]. In recent years boric acid[184] has become widely accepted as the best available. This is attributed to its particular effectiveness in minimising epimerisation. It has been suggested[25] that this is due to hydrolysis of the β-hydroxy imine *via* a cyclic borate ester (Figure 22). There is, however, no proof for the existence of this intermediate.

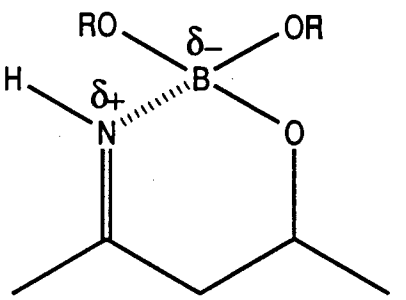


**Figure 22**

Investigations were undertaken into both Pd/C and Ra-Ni catalysed hydrogenolysis of the major isomers obtained from cycloaddition to *xylo*-alkene (**37**). In all cases boric acid was used as the acidic additive. No attempt was made to unmask the corresponding minor isomers due to lack of material. These investigations are summarised in Sections 2.5.1→2.5.3.

### 2.5.1 Deacetylation of 2-Isoxazolines

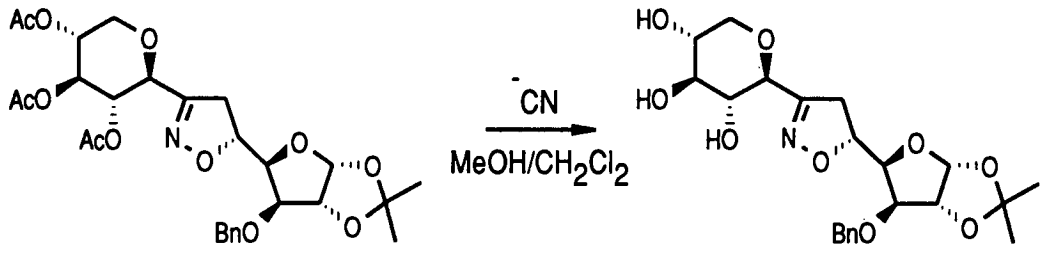
Paton *et al.*[141] have investigated the Pd/C and Ra-Ni catalysed ring opening to β-hydroxy ketones of isoxazolines obtained from addition of nitrile oxide (**122**) to a cyclic alkene (Section 1.6.1.5). They found that ring cleavage of the acetyl protected isoxazolines afforded several products. They attributed[185] this to partial deacetylation during ring cleavage leading to a number of semi-acetylated β-hydroxy ketones. This was supported by the observation that ring opening of the deacetylated isoxazoline proceeding to a single β-hydroxy ketone in good yield.

A pilot experiment on the Ra-Ni catalysed ring cleavage of the acetylated isoxazoline (**153**), the major isomer obtained from addition of (**122**) to *xylo*-alkene (**37**) (Section 2.4.1.1), also led to a mixture of a large number of products and therefore all isoxazolines were deacetylated before hydrogenolysis.

The deprotection of (**153**), (**155**) and (**157**) was carried out using a modification of the cyanide-catalysed deacetylation procedure of Herzig and co-workers[186]. This method was selected as it is a simple, mild method of deacetylation which has proven to be very efficient in the deprotection of polyacetylated sugars[141,186].

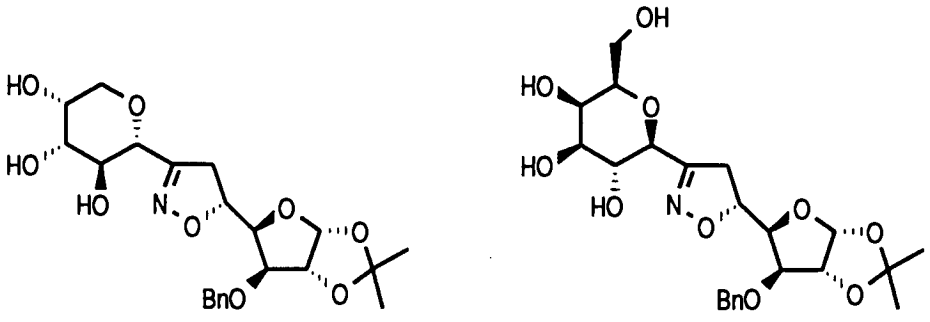
All three isoxazolines were deacetylated by stirring with a catalytic amount of KCN in a methanol/dichloromethane (7:3) solvent system (dichloromethane was added to improve the solubility of the acetylated isoxazolines). Deprotection of (**153**) and (**155**) proceeded in excellent yield (94% and 96%) to afford the deacetylated isoxazolines (**175**) and (**176**) respectively; neither required purification. This is

illustrated in Scheme 47 for the deacetylation of (**153**). In the case of (**157**) the deacetylated isoxazoline (**177**) was isolated in only 55% yield after purification by preparative t.l.c. The difficulty in removing the polar product from the silica may contribute to the low yield in this example.



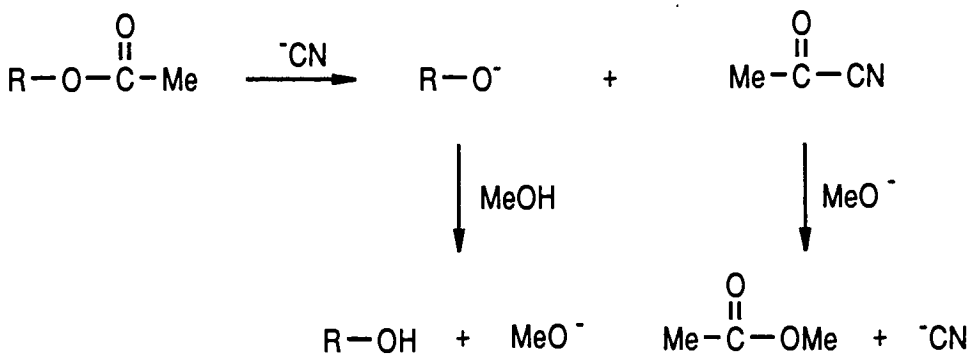

(153) (175)

**Scheme 47**




(176) (177)

These deprotections are believed[186] to involve nucleophilic acyl substitution by the cyanide ion, followed by rapid methanolysis of the resulting acyl cyanide to regenerate $^-$CN (Scheme 48). Displacement of the first acyl group is rate limiting as the free hydroxyl formed activates the neighbouring acyl group to attack by cyanide (Figure 23).



Scheme 48

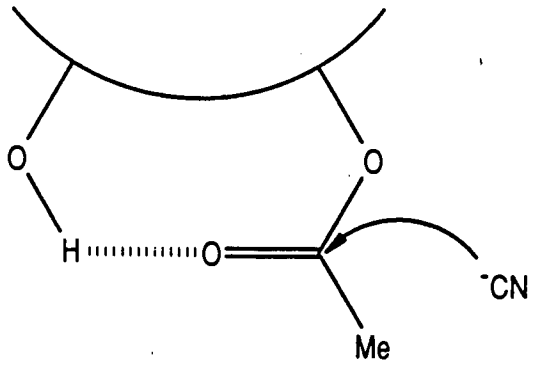
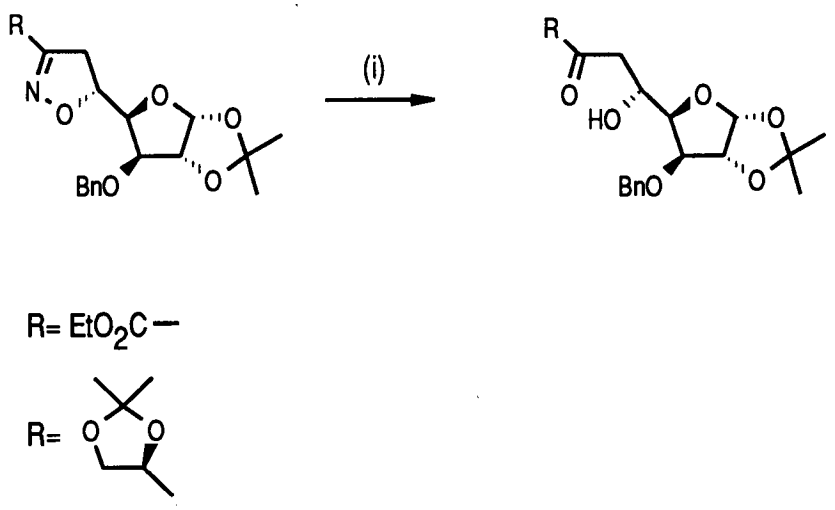


Figure 23

### 2.5.2 Pd/C Catalysed Hydrogenolysis of 2-Isoxazoline (175)

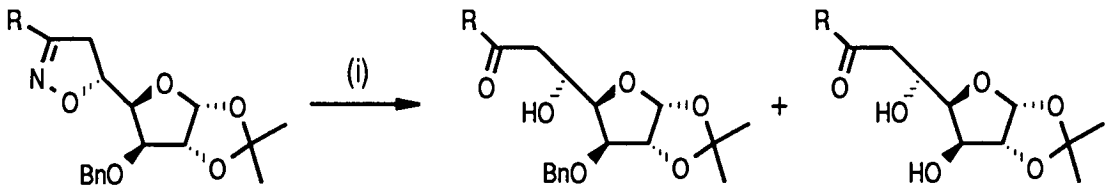
The Pd/C catalysed ring opening of 2-isoxazolines obtained from *xylo*-alkene (**37**) has previously been reported by Paton and Young[66] (Section 1.4.1.2). They obtained the corresponding β-hydroxy ketones (6-deoxy-7-ulose derivatives) in good yield without loss of the benzyl protecting group at the 3-position (Scheme 49). The retention of the benzyl group under similar conditions to those normally used for its removal[187] was attributed[156] to partial catalyst poisoning by the boric acid which was used as the acidic additive.



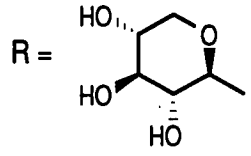

(i) Pd/C , $H_2$ , $B(OH)_3$ , MeOH , $H_2O$

**Scheme 49**

It was decided to investigate the ring cleavage of deacetylated isoxazoline (**175**) utilising these conditions[156]. (**175**) (1 equivalent), 10% Pd/C (100 mg per mmol of isoxazoline) and boric acid (6 equivalents) were dissolved in a 5:1 methanol/water solution. It was necessary to add a small amount of THF to aid dissolution of the isoxazoline. The solution was then stirred vigorously under a $H_2$ atmosphere and the reaction monitored by t.l.c. Even after 5 days unreacted isoxazoline was still present and only 25% (based on consumed starting material) of the required 6-deoxy-7-ulose derivative (**178**) was isolated (Scheme 50). The major fraction obtained consisted of an inseparable mixture of debenzylated materials including debenzylated 6-deoxy-7-ulose derivative (**179**). The low reactivity of this system to Pd/C hydrogenolysis may be due to greater steric hindrance at the 3-position of the isoxazoline ring compared with the examples investigated by Paton and Young.



(175) (178) (179)



(i) Pd/C , $H_2$ , $B(OH)_3$ , MeOH , $H_2O$ , THF

**Scheme 50**

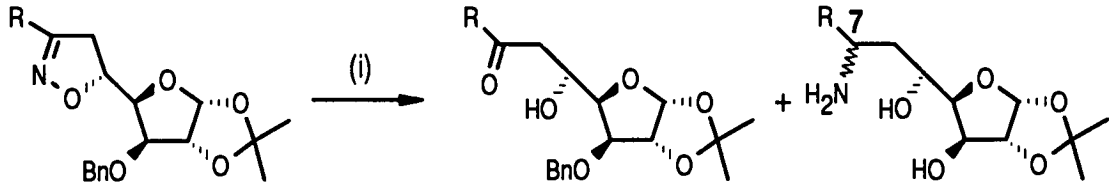
### 2.5.3 Raney-Ni Catalysed Hydrogenolysis of 2-Isoxazolines

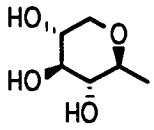
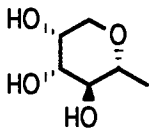
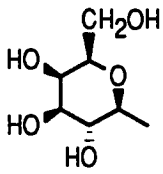
Due to the low yield, the difficulty of separation of the product from the starting material and the extended reaction times for Pd/C catalysed hydrogenolysis of 2-isoxazoline (**175**), it was decided to carry out studies on the alternative Ra-Ni catalysed reaction.

For the ring opening of (**175**) the procedure of Curran[184] using W-2 Raney nickel and boric acid in a 5:1 methanol/water solution was adopted. As in the Pd/C hydrogenolysis reactions THF was added to aid dissolution of the isoxazoline. This reaction proceeded at a much greater rate than the Pd/C catalysed reaction, with all the isoxazoline being consumed in *ca.* 6 hrs. After preparative t.l.c. the desired 6-deoxy-7-ulose derivative (**178**) was isolated in 55% yield with no indication of debenzylation (Scheme 51). A second baseline fraction was obtained which was identified as a diastereomeric mixture of γ-amino alcohols (**180**) and (**181**) (18% combined yield). This mixture was not separable by chromatography but strong evidence for this assignment was provided by $^{13}C$ n.m.r. of the crude mixture which showed two characteristic $CHNH_2$ resonances at 48.2 and 53.7 ppm. These peaks

were attributed to the 7R (**180**) and 7S (**181**) isomers respectively by comparison with a series of γ-amino alcohols prepared by Jäger and Schohe[188], of basic structure (**188**) in which the *erythro* isomer always possessed the higher $\delta_C$ value for the *C*$HNH_2$ resonance.

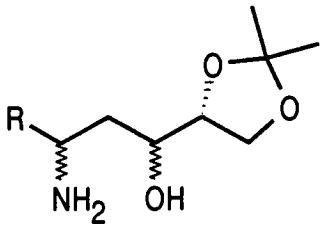
This identification was supported by FAB mass spectrometry and t.l.c. staining with ninhydrin, which is specific for amines. Further supporting evidence was provided by acetylation of the (**180**)/(**181**) fraction (acetic anhydride, pyridine) which afforded a mixture of acetylated compounds which showed infra red absorptions in the 1630-1675 $cm^{-1}$ region, consistent with amide functionality. These acetylated compounds decomposed rapidly and therefore could not be analysed further.




| | | | |
|---|---|---|---|
| R =  | (175) | (178) | 7R (180)<br>7S (181) |
| R =  | (176) | (182) | 7R (183)<br>7S (184) |
| R =  | (177) | (185) | 7R (186)<br>7S (187) |

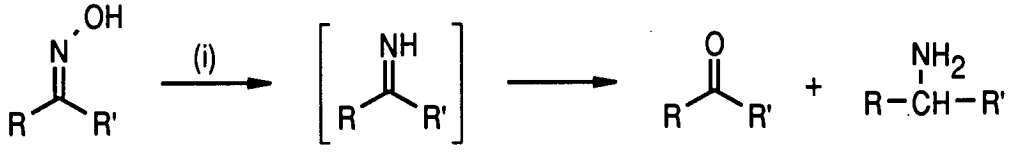
(i) Ra-Ni , $H_2$ , $B(OH)_3$ , MeOH , $H_2O$ , THF

**Scheme 51**



(188)

As hydrolysis of β-hydroxy imines is usually rapid under these conditions[25] the formation of γ-amino alcohols (**180**) and (**181**) was unexpected. Curran *et al.*[189] have, however, reported that reduction of oximes using these conditions produces mixtures of the corresponding ketones (**190**) and amines (**191**) (Scheme 52). They discovered that the over-reduction of the imine intermediate (**189**) to amines could be suppressed by partial deactivation of the Ra-Ni catalyst by addition of 2-5 equivalents of acetone.



(189) (190) (191)

(i) Pd/C , $H_2$ , $B(OH)_3$ , MeOH , $H_2O$ , Acetone

**Scheme 52**

Hydrogenolysis of (**175**) in the presence of five equivalents of acetone, however, resulted not only in longer reaction times as expected (~ 12 hrs.) but a slightly lower yield of the desired 6-deoxy-7-ulose derivative (**178**). Attempts to speed up the hydrolysis of the β-hydroxy imine intermediate by using twice the amount of boric acid did not have any significant effect. These results of these experiments are summarised in Table 8.

**Table 8** - Reductive Hydrolytic Ring Cleavage of (**175**)

| Conditions | Reaction Time (hrs.) | Yield of β-Hydroxy Ketone (178) | Combined Yield of γ-Amino Alcohols (180) & (181) |
|---|---|---|---|
| $B(OH)_3$ (6 equiv.) | 6 | 55% | 18% |
| $B(OH)_3$ (6 equiv.) Acetone (5 equiv.) | 12 | 51% | 16% |
| $B(OH)_3$ (12 equiv.) | 6 | 54% | 16% |

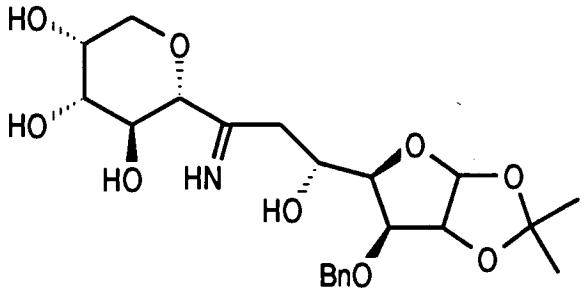
Hydrogenolysis of (**176**) and (**177**) was carried out utilising the initial conditions used for ring cleavage of (**175**). In each case a 6-deoxy-7-ulose derivative, (**182**) and (**185**) respectively, was obtained in moderate yield along with a mixture of diastereomeric γ-amino alcohols. These mixtures could not be separated and were identified by t.l.c. and $^1H$ n.m.r. comparison with the mixture of (**180**) and (**181**) which had been identified by $^{13}C$ n.m.r. This assignment was supported by FAB mass spectrometry. The results of these ring openings are shown in Table 9.

**Table 9** - Raney Nickel Hydrogenolysis of 2-Isoxazolines

| 2-Isoxazoline | Yield of β-Hydroxy Ketone | Combined Yield of γ-Amino Alcohols |
|---|---|---|
| (**175**) | 55% | 18% |
| (**176**) | 56% | 14% |
| (**177**) | 43% | 18% |

During the ring opening of isoxazoline (**176**) an extra t.l.c. spot was observed at a slightly lower $R_f$ value than that for β-hydroxy ketone (**182**). Upon work-up of

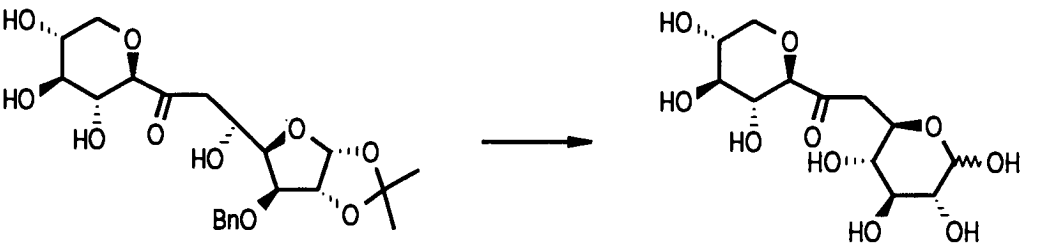
the reaction mixture this spot was no longer observed and only β-hydroxy ketone (6-deoxy-7-ulose) (**182**) and γ-amino alcohols (**183**) and (**184**) were isolated. This extra spot is tentatively assigned to the β-hydroxy imine intermediate (**192**). Based on this assignment it is hypothesised that the relatively high stability of (**192**) to hydrolysis results in the formation of γ-amino alcohols (**183**) and (**184**) by the competing hydrogenation reaction. This explanation could be extended to the formation of γ-amino alcohols in the ring cleavage of isoxazolines (**175**) and (**177**) if the β-hydroxy imine intermediates in these reactions were also resistant to hydrolysis. No extra spots were, however, observed for these reactions and it must be stressed that the spot attributed to β-hydroxy imine (**192**) was never isolated and so there is no concrete evidence for its structure.




(192)

It is noteworthy that there was no indication of debenzylation during these Ra-Ni catalysed ring cleavage reactions. Similar preference for isoxazoline ring cleavage over *O*-debenzylation has previously been reported[190-192], though in some cases[67,176] partial deactivation of the Ra-Ni catalyst by acetone was carried out to minimise the loss of the benzyl group.

6-Deoxy-7-ulose derivatives (**178**), (**182**) and (**185**) may be considered as protected carbonyl-linked *C*-disaccharides. Removal of the isopropylidene protecting group would lead to the formation of a dipyranose system linked (1→6) by a carbonyl bridge. This is illustrated for 6-deoxy-7-ulose (**178**) in Scheme 53).



(178)

**Scheme 53**

These 6-deoxy-7-ulose compounds are, however, relatively sensitive and decompose readily. Partial decomposition is noted within a few days even at -40°C under argon. Consequently these compounds were not deprotected as it was thought that they might not survive the deacetylation conditions.

The γ-amino alcohols which were also formed in the ring cleavage of isoxazolines (**175**), (**176**) and (**178**) can also be considered as protected (1→6)-*C*-disaccharides, this time with an aminomethylene bridge.

### 2.5.4 General Comparisons of β-Hydroxy Ketones

It has been shown in the preceding section that β-hydroxy ketones (6-deoxy-7-ulose derivatives) may be prepared in moderate yield (43-56%) by hydrogenolysis of deacetylated 2-isoxazolines. These compounds possess some notable characteristics which are discussed below.

**I.R.** - Each shows a strong carbonyl absorption in the region 1710-1720 $cm^{-1}$ which is consistent with values reported[180] for other β-hydroxy ketones. A broad OH absorption is also observed with $\nu_{max}$ at 3350-3420 $cm^{-1}$.

**T.L.C.** - All three β-hydroxy ketones have a smaller $R_f$ value on silica than the corresponding 2-isoxazolines. They are readily visualised by staining with Brady's reagent, although it is noteworthy that the deacetylated isoxazolines are also stained by this reagent upon heating the plate.

**FAB Mass Spectrometry** - In all three cases in addition to a parent ion peak a significant amount of the corresponding α-enone $M^+$+1 fragment ion was detected. This is consistent with dehydration of the β-hydroxy ketone within the spectrometer. In the case of the debenzylated fraction obtained from the Pd/C hydrogenolysis of (**175**) only the debenzylated α-enone $M^+$+1 peak was observed, no parent β-hydroxy ketone peak was noted.

**$^{13}$C n.m.r.** - The $^{13}$C n.m.r. spectrum of each β-hydroxy ketone is very similar to that of the 2-isoxazoline from which it was obtained. The main exceptions occur for carbons 5-8 (Figure 24). The characteristic carbon chemical shift changes between the 2-isoxazolines and the corresponding β-hydroxy ketones are illustrated in Table 10 for isoxazoline (**177**) and its ring cleaved product (**185**).

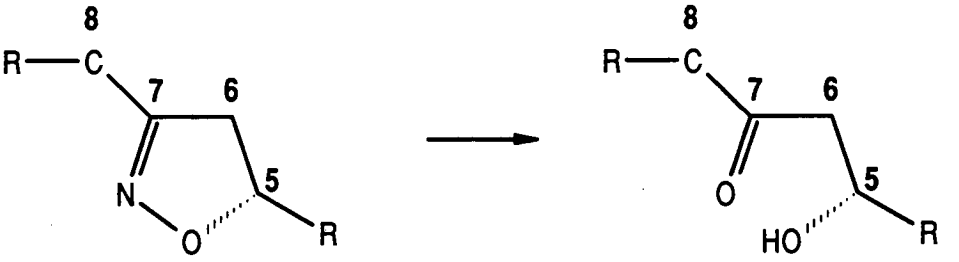



**Figure 24**

**Table 10** - $\delta_C$ Values for $C_5$-$C_8$ for (**177**) and (**185**)

| Carbon | $\delta_C$ (ppm) | | | |
|---|---|---|---|---|
| | $C_5$ | $C_6$ | $C_7$ | $C_8$ |
| Isoxazoline (**177**) | 75.9 | 35.5 | 156.8 | 74.6 |
| β-Hydroxy ketone (**185**) | 63.2 | 43.4 | 206.8 | 83.3 |

**$^1$H n.m.r.** - As in the $^{13}$C n.m.r., the main difference between the 2-isoxazolines and the corresponding β-hydroxy ketones in the proton n.m.r. occur in the region of the reaction site ($H_4$-$H_8$) (Figure 25). Tables 11 and 12 illustrate the

difference in $\delta_H$ values and coupling constants for isoxazoline (**177**) and β-hydroxy ketone (**185**).

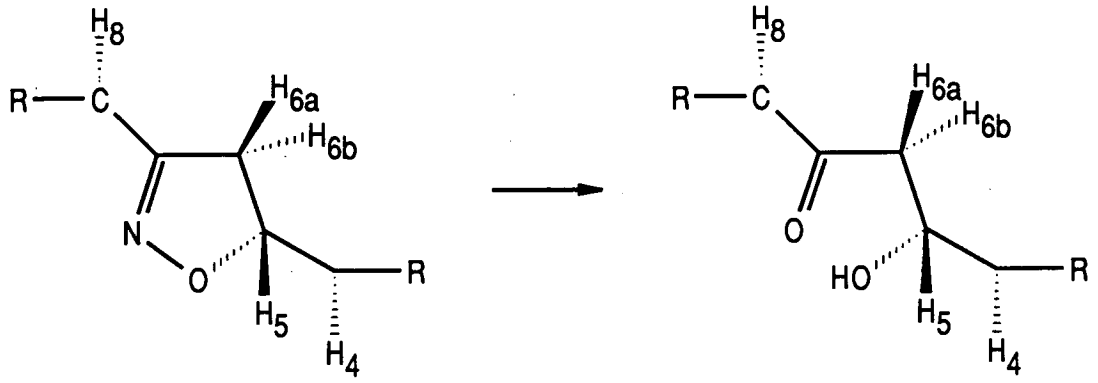



**Figure 25**

**Table 11** - $\delta_H$ Values for $H_4$-$H_8$ for (**177**) and (**185**)

| | $\delta_H$ (ppm) | | | | |
|---|---|---|---|---|---|
| | **$H_4$** | **$H_5$** | **$H_{6a}$** | **$H_{6b}$** | **$H_8$** |
| Isoxazoline (**177**) | 4.16 | 4.84 | 3.18 | 3.12 | 4.03 |
| β-Hydroxy ketone (**185**) | 4.00 | 4.50 | 3.02 | 2.91 | 3.66 |

**Table 12** - $^1$H n.m.r. Coupling Constants for (**177**) and (**185**)

| | *J*(Hz) | | |
|---|---|---|---|
| **Coupling** | **4,5** | **5,6a** | **5,6b** |
| Isoxazoline (**177**) | 7.3 | 10.1 | 8.0 |
| β-Hydroxy Ketone (**185**) | 8.9 | 3.2 | 9.0 |

As can be seen from Table 12 the $J_{5,6a}$ and $J_{5,6b}$ values are consistent with a large diaxial coupling and a smaller axial-equatorial coupling. This is consistent with the β-hydroxy ketone functionality adopting a hydrogen-bonded cyclohexene-like, half-chair conformation (Figure 26) in which the bulky furanose substituent occupies

the less sterically demanding quasi-equatorial position. An alternative half-boat conformation may be adopted, but in this arrangement the furanose substituent would be in a more sterically hindered position. Very similar $H_5$-$H_{6a}$ and $H_5$-$H_{6b}$ couplings are shown for β-hydroxy ketones (**178**) and (**182**) indicating that the same hydrogen-bonded arrangement is adopted for all three β-hydroxy ketones.

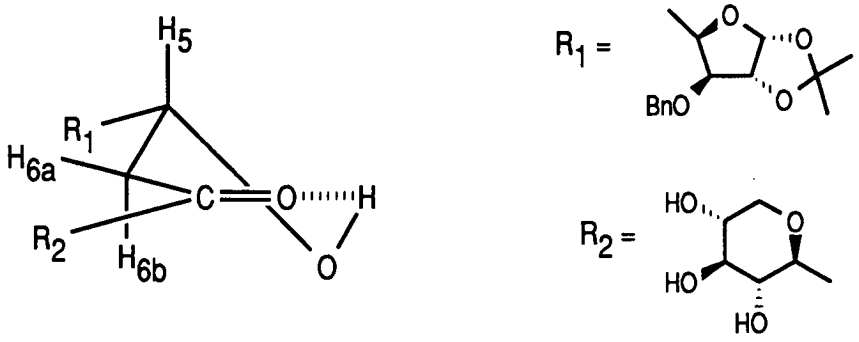
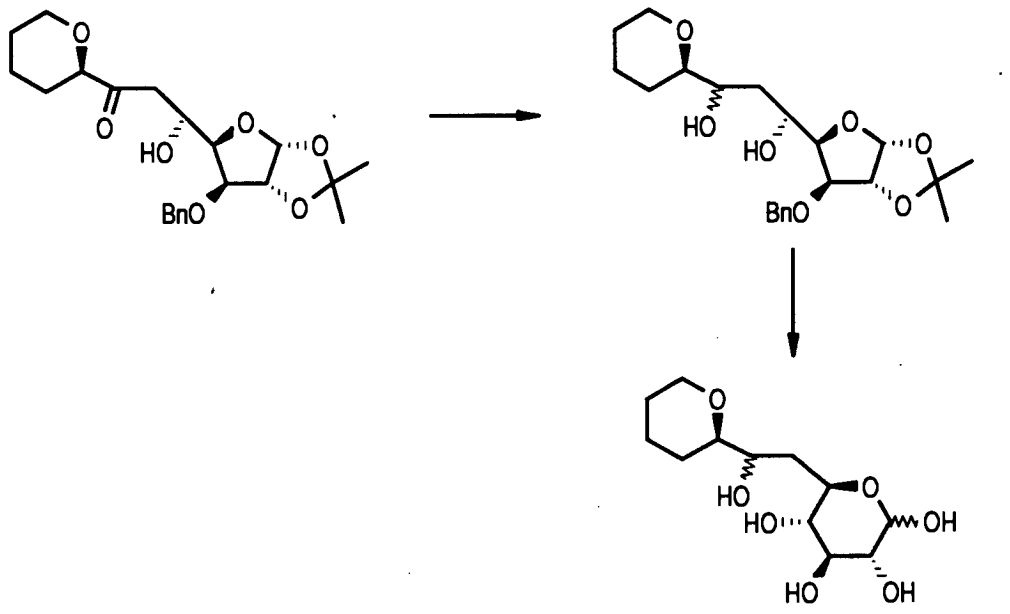



**Figure 26**

## 2.6 Reduction of β-Hydroxy Ketones to 1,3-Diols

In the previous section it has been demonstrated that Raney nickel catalysed hydrogenolysis of 2-isoxazolines affords β-hydroxy ketones (6-deoxy-7-uloses) as the major products. The relative instability of these compounds has already been discussed and this renders them unsuitable for deprotection to the dipyranose (1→6)-carbonyl-linked *C*-disaccharides.

Reduction of the carbonyl of these 6-deoxy-7-uloses to a secondary alcohol would give access to a series of protected (1→6)-hydroxymethylene-linked *C*-disaccharides. These compounds are likely to be much more stable and therefore suitable for deprotection to yield the dipyranose *C*-disaccharide (Scheme 54).




**Scheme 54**

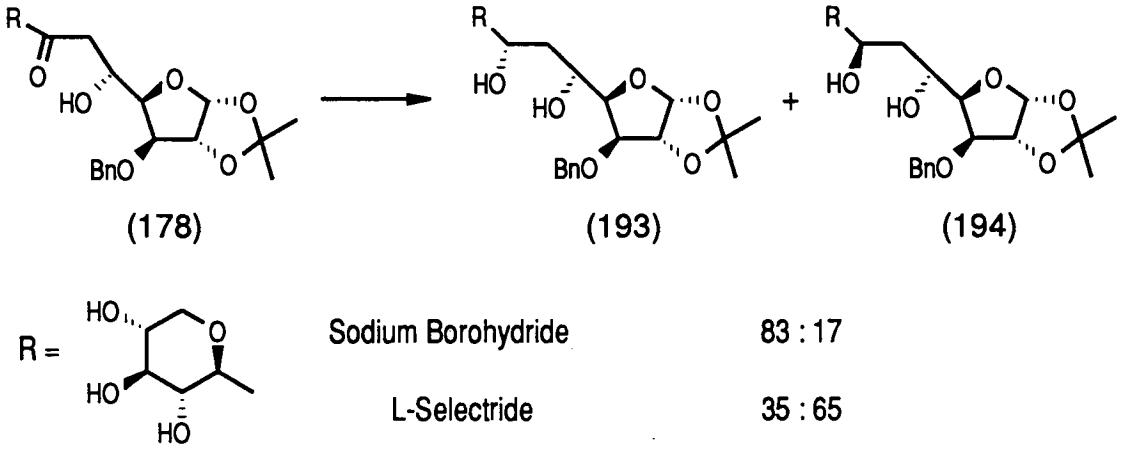
The reduction of the carbonyl functionality creates a new chiral centre ($C_7$). In order to establish the configuration of this new centre and investigate the stereoselectivity of these reactions the decision was taken to carry out reductions of 6-deoxy-7-uloses (**178**) and (**182**). These deoxyuloses have opposite configuration at

$C_8$, the position next to the carbonyl, and it was thought that this may have a significant effect on the selectivity of these reductions.

Two reducing agents were chosen to carry out these reductions: sodium borohydride and L-selectride (lithium tri-*sec*-butylborohydride). Sodium borohydride was selected as it is an easily handled reducing agent which was likely to provide access to both isomers. In contrast reductions of similar β-hydroxy ketones by L-selectride have been reported[66] to give a high degree of stereoselectivity (95:5) and it was hoped that similarly high selectivity might be obtained from reduction of (**178**) and (**182**).

### 2.6.1 Reduction of 6-Deoxy-7-ulose (178)

Deoxyulose (**178**) was reduced by sodium borohydride in ethanol/water to afford a mixture of two hydroxymethylene-linked *C*-disaccharides (**193**) and (**194**) in a ratio of 83:17 and a combined yield of 76% (Scheme 55). These were separated by preparative t.l.c. and characterised by $^1H$ and $^{13}C$ n.m.r. spectroscopy, optical rotation and FAB mass spectrometry. The ratio was determined by comparison of the integrals of the anomeric proton signals in the $^1H$ n.m.r. of the crude mixture. The assignment of stereochemistry at $C_7$ is discussed in Section 2.6.3.



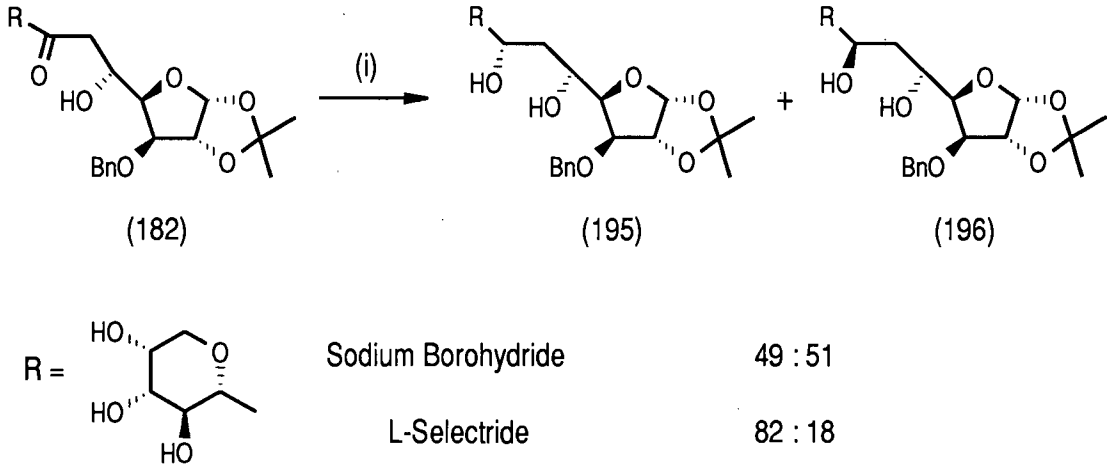

**Scheme 55**

Reduction of (**178**) by L-selectride at -78°C in THF gave a 79% yield of (**193**) and (**194**) in the ratio 35:65 (Scheme 55).

### 2.6.2 Reduction of 6-Deoxy-7-ulose (182)

Sodium borohydride reduction of (**182**) in ethanol/water afforded an inseparable mixture of hydroxymethylene-linked *C*-disaccharides (**195**) and (**196**) in an overall yield of 48% and a ratio of 59:51 (Scheme 56).

Reduction of the carbonyl group in (**182**) by L-selectride (-78°C, THF) gave (**195**) and (**196**) in a ratio of 82:18 and a yield of 93% (Scheme 56). As in the reductions of (**178**) the ratios of these mixtures were determined by comparison of the anomeric proton signals in the $^1$H n.m.r. spectra of the crude mixtures. As (**195**) and (**196**) could not be separated by chromatography, neither was fully characterised. However $^1$H n.m.r. analysis of the mixture obtained from L-selectride reduction ((**195**):(**196**) 82:18), involving a series of decoupling experiments, led to the assignment of the signals due to the major component (**195**) and from this the configuration of this component at the new chiral centre was determined (see Section 2.6.3).




**Scheme 56**

### 2.6.3 Determination of Stereochemistry at the New Chiral Centre

As mentioned earlier one of the problems raised by reduction of the carbonyl functionality of deoxyuloses (**178**) and (**182**) is the assignment of configuration at the new chiral centre formed during the reaction. This was carried out by comparison of the $^1H$ n.m.r. spectra of the two products formed in each case.

The main differences between the $^1H$ n.m.r. spectra of (**193**) and (**194**), the products isolated from reduction of (**178**), occur in the $H_4$-$H_9$ region (Figure 27). The relevant data for these compounds is displayed in Tables 13 and 14.

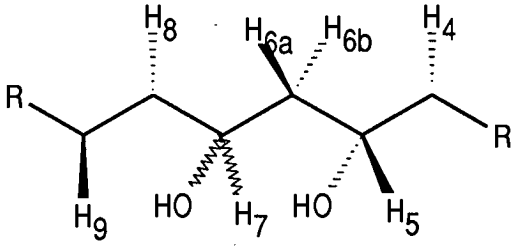



**Figure 27**

**Table 13** - $\delta_H$ Values of $H_4$-$H_9$ for (**193**) and (**194**) in $C_5D_5N$

| | $\delta_H$ (ppm) | | | | | | |
|---|---|---|---|---|---|---|---|
| | **$H_4$** | **$H_5$** | **$H_{6a}$** | **$H_{6b}$** | **$H_7$** | **$H_8$** | **$H_9$** |
| (**193**) | 4.53 | 4.82 | 2.80 | 2.41 | 4.93 | 3.83 | 4.07 |
| (**194**) | 4.63 | 5.12 | 2.97 | 2.17 | 5.28 | 3.66 | 4.51 |

**Table 14** - $^1H$ n.m.r. Coupling Constants for (**193**) and (**194**)

| | *J* ($H_2$) | | | | | |
|---|---|---|---|---|---|---|
| | **5-6a** | **5-6b** | **6a-6b** | **6a-7** | **6b-7** | **7-8** |
| (**193**) | 2.4 | 10.0 | 14.4 | 2.4 | 10.0 | 3.3 |
| (**194**) | 2.1 | 10.1 | 13.8 | 11.3 | 2.1 | 1.7 |

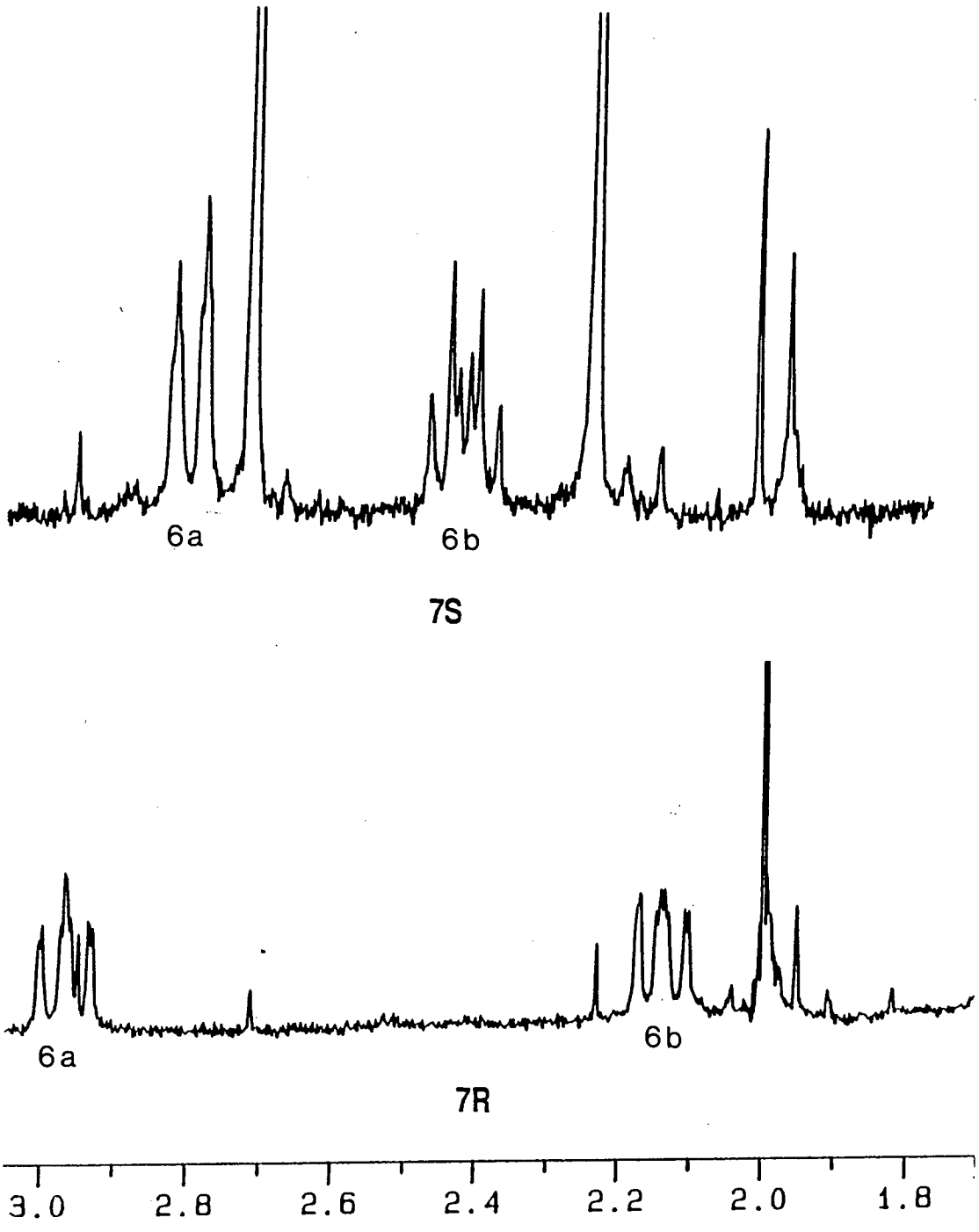



**Figure 28**

The most characteristic differences are observed in the resonances due to $H_{6a}$ and $H_{6b}$. For (**193**) these appear as a pair of doublets of triplets with a small triplet coupling for $H_{6a}$ and a large triplet coupling for $H_{6b}$. In contrast the $H_{6a}$ and $H_{6b}$ signals for (**194**) consist of two sets of eight lines, each with one small coupling and two large couplings (see Figure 28 and Table 14).

The $H_{6a}$ and $H_{6b}$ couplings for (**193**) are consistent with the adoption of a hydrogen-bonded chair conformation by the 1,3-diol functionality (Figure 29); *i.e.* two axial-equatorial couplings (2.4 Hz) for $H_{6a}$ and two axial-axial couplings (10.0 Hz) for $H_{6b}$. This chair conformation allows both bulky substituents (R and R') to occupy the sterically favourable equatorial position. In order for (**194**) to adopt a similar hydrogen-bonded chair conformation one of the substituents must take up the sterically more demanding axial position (Figure 29). Due to this (**194**) is distorted from this arrangement as is shown by the coupling constants in Table 14.

On the basis of this $^1H$ n.m.r. data the new chiral centre at $C_7$ was assigned S for (**193**) and R for (**194**). A similar pattern to that of (**193**) is seen for the $H_{6a}$ and $H_{6b}$ signals of (**195**), the major isomer obtained from L-selectride reduction of deoxyulose (**182**). This was therefore assigned as 7S configuration.

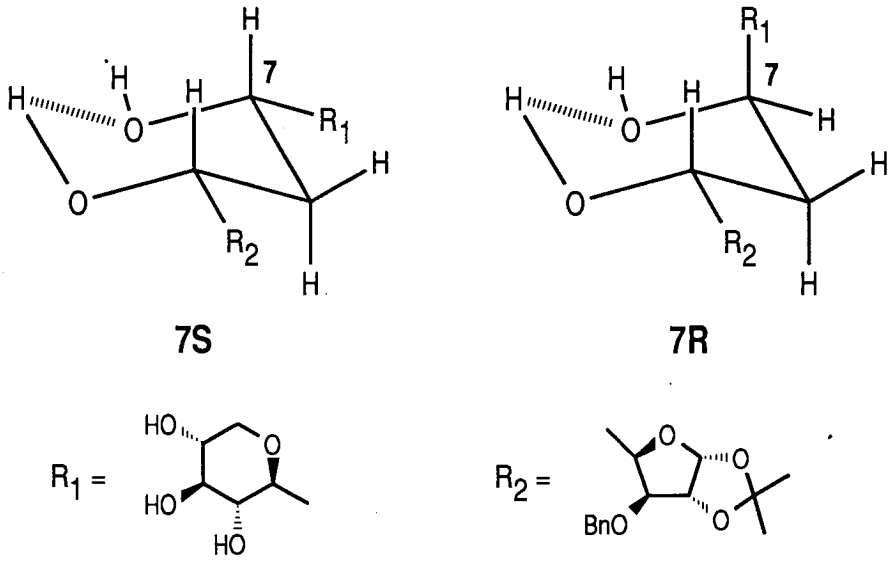
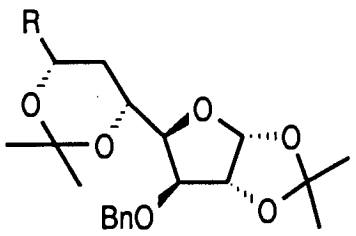
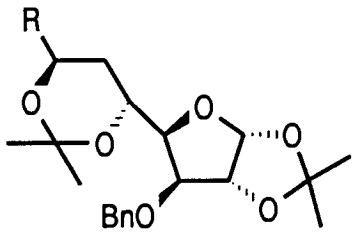



**Figure 29**

Similar characteristic patterns in the $^1H$ n.m.r. spectra of epimeric 1,3-diols have previously been noted in the synthesis of higher sugars[156]. The same assignment of stereochemistry was given to the new chiral centre using similar arguments to those above. These assignments were later proven by $^1H$ n.m.r. analysis of the corresponding 5,7-*O*-isopropylidene derivatives, (**197**) and (**198**). This technique could not be applied to the 1,3-diols obtained from reduction of (**178**) and (**182**) as the presence of several free hydroxyl groups would result in the formation of a number of isopropylidene derivatives.




(197)




(198)

Another noteworthy feature of the $^1H$ n.m.r. spectra of (**193**) and (**194**) is the large chemical shift difference between the $H_9$ signals of these two epimers ($\Delta\delta_H$ = 0.44). This may be due to hydrogen bonding between the $C_9$ hydroxyl and the $C_7$ hydroxyl group in (**194**), the isomer in which the 1,3-diol hydrogen-bonded chair conformation cannot be taken up.

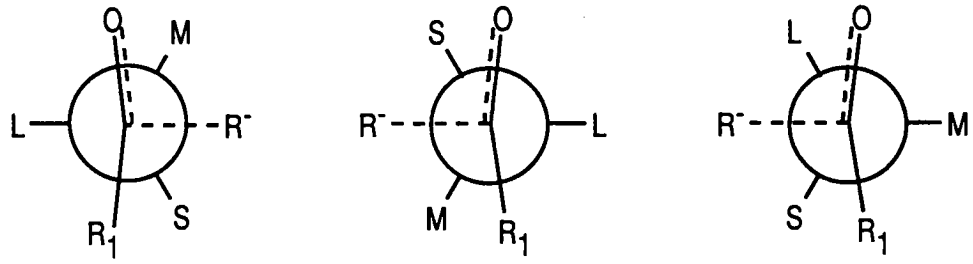
### 2.6.4 Rationalisation of Stereoselectivity

The selectivities observed in reductions of deoxyuloses (**178**) and (**182**) are listed in Table 15.

**Table 15** - Selectivity of Carbonyl Reductions

| Deoxyulose | Reagent | Selectivity 7S:7R |
|---|---|---|
| (**178**) | $NaBH_4$ | 83:17 |
| (**178**) | L-Selectride | 35:65 |
| (**182**) | $NaBH_4$ | 49:51 |
| (**182**) | L-Selectride | 82:18 |

It is noteworthy that in both the L-selectride reductions the major product possesses the $C_7$-$C_8$ *threo* configuration. This may be rationalised in terms of the Felkin[173]-Anh[174] model which is based on hydride attack on a staggered, reactant-like transition state. The three most stable transition states for reduction of a carbonyl adjacent to a chiral centre are shown in Figure 30.




**A1** **B1** **B2**

$R^-$ = Incoming Hydride

**Figure 30**

Felkin[173] proposes that the most important interactions involve $R_1$ and $R^-$ and hence, in a system in which the substituents differ only in size, transition state **A1** would be favoured as this minimises steric interactions with these groups.

This picture is changed upon the introduction of polar groups which have an unfavourable interaction with the incoming hydride. Hence transition states in which polar groups are close to $R^-$ are destabilised.

The equivalent transition states for the reduction of (**178**), which possesses S configuration at the carbon next to the carbonyl ($C_8$), are shown in Figure 31.

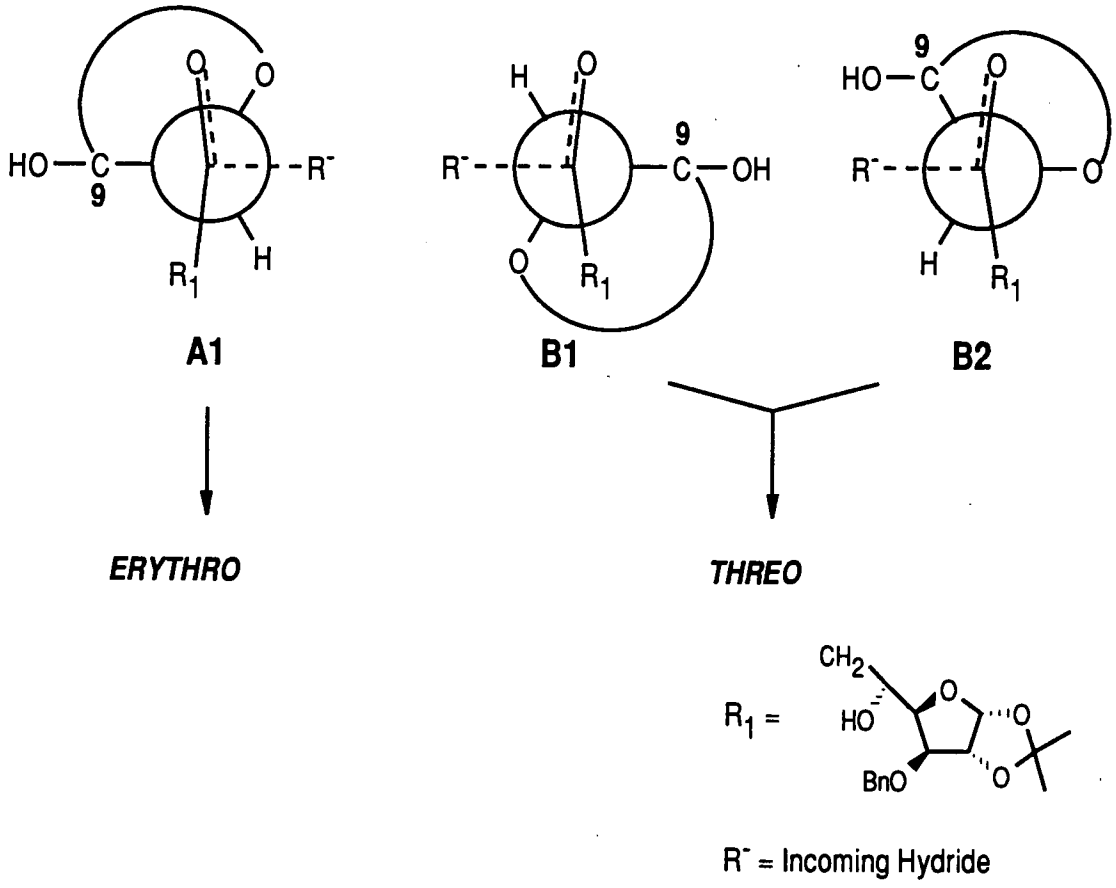



**Figure 31**

The oxygen of the pyranose ring is closer to the point of hydride attack than the $C_9$ hydroxyl group, and hence will have a greater destabilising effect on transition states in which $R^-$ is close to this group (**A1** and **B1**). It is therefore proposed that the

most stable transition state is **B2** and this state is therefore responsible for formation of the major *threo* isomer (**193**). The minor *erythro* isomer is presumably formed from the next lowest energy transition state **A1**.

The same arguments can also be applied to the L-selectride reduction of (**182**), the three lowest transition states of which are shown in Figure 32. Again formation of the major *threo* isomer is attributed to transition state **B2** with the minor *erythro* isomer being formed from **A1**.

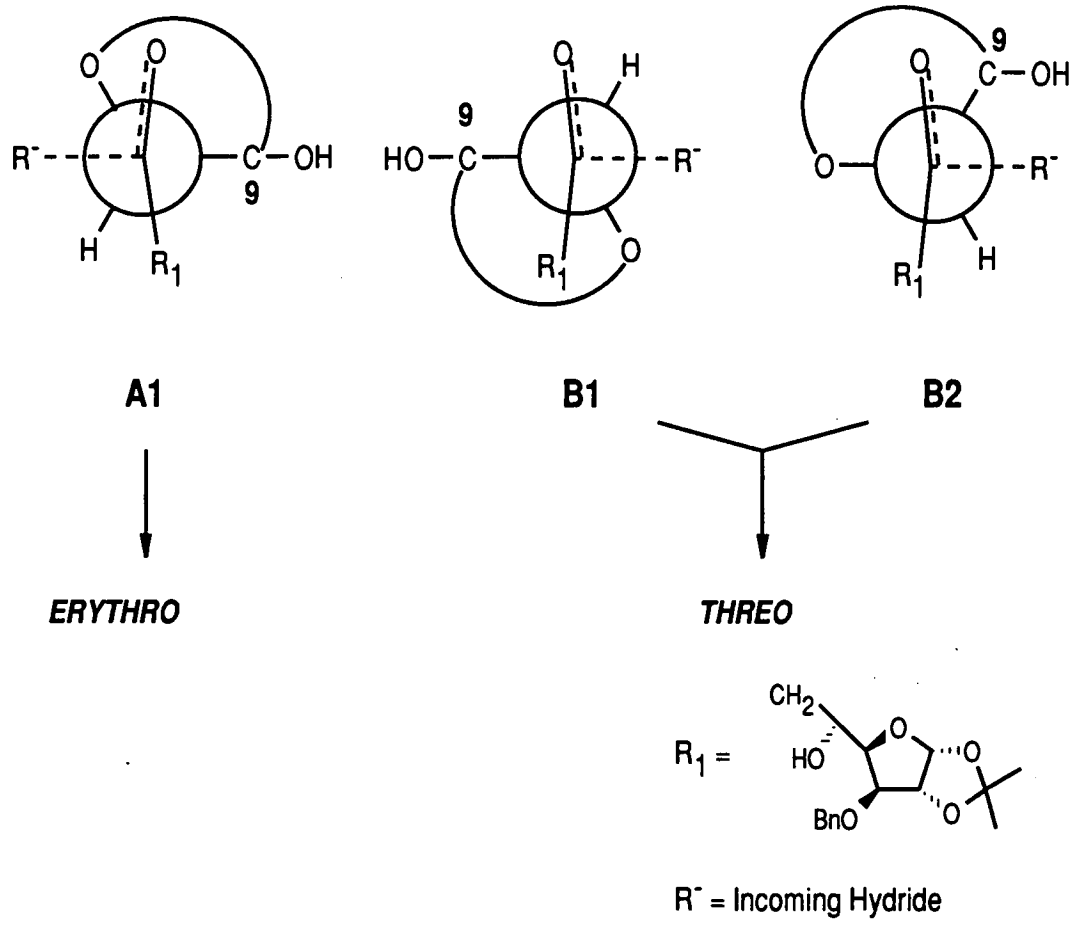



**Figure 32**

An interesting feature in the reductions of (**178**) is the reversal of selectivity observed between L-selectride and sodium borohydride. The rationalisation for the selectivity of the L-selectride reaction has already been discussed above. Much

controversy has surrounded the mechanism of sodium borohydride reductions and many theories have been put forward to explain the observed stereoselectivity[193]. Wigfield[193] has rationalised this selectivity in terms of steric interactions within a product-like transition state. The sodium borohydride reduction of (**178**) is consistent with this model as the *erythro* product (**193**), in which the 1,3-diol functionality can adopt a sterically favoured hydrogen-bonded chair conformation (Figure 29), is formed preferentially to the *threo* isomer (**194**) in which a sterically hindered distorted conformation is adopted.

The reversal in selectivity seen in reduction of (**178**) can therefore be explained *via* a reactant-like transition state for L-selectride reduction which leads to predominantly the *threo* isomer and a product-like transition state for $NaBH_4$ reduction leading to the sterically less hindered *erythro* isomer.

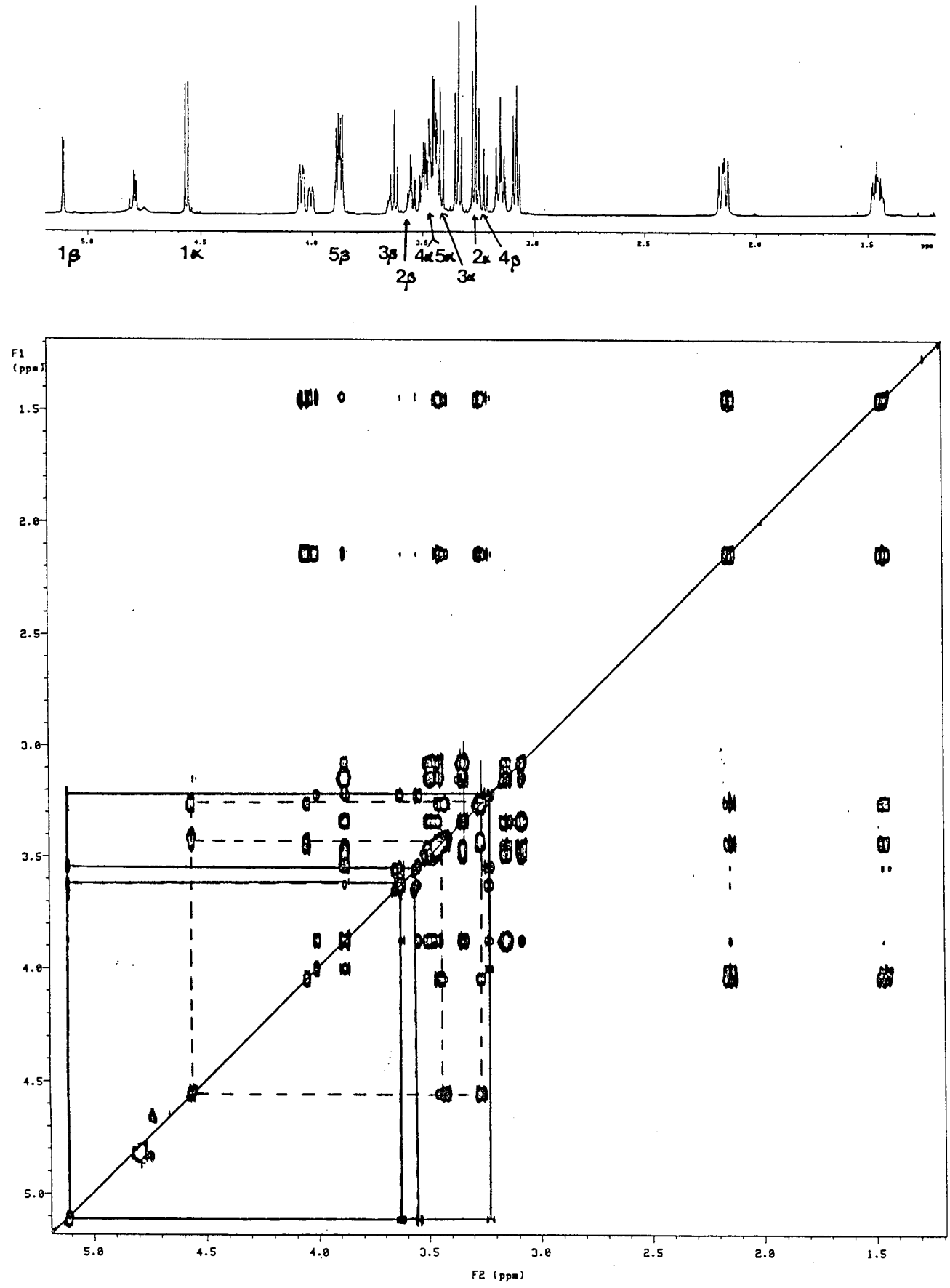


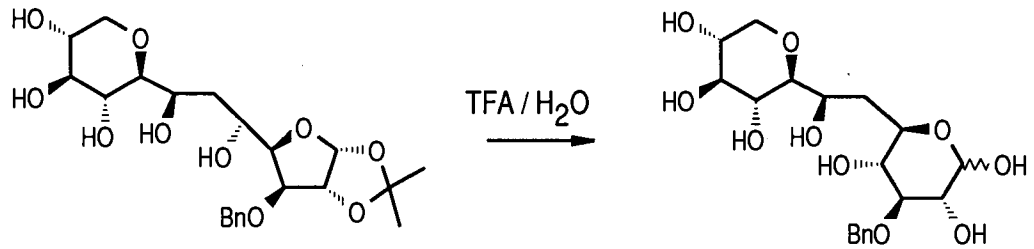

Figure 33

## 2.7 Deprotection to Dipyranose *C*-disaccharides

In the previous section it has been shown that protected hydroxymethylene-linked *C*-disaccharides can be synthesised in good yield by the reduction of 6-deoxy-7-uloses. To prove that these compounds would form dipyranose *C*-disaccharides (**194**) was selected as an example to undergo deacetalation.

The 1,2-*O*-isopropylidene protecting group was removed by hydrolysis with trifluoroacetic acid and water to afford a mixture of deacetalised compounds in 92% yield.

This mixture was identified as a pair of hydroxymethylene-linked dipyranose *C*-disaccharides (**199**) and (**200**) in an α:β ratio of 38:62 (Scheme 57), by $^1$H n.m.r. with the aid of COSY and TOSCY (Figure 33) 2-D n.m.r. spectra.




(194)

α (199)

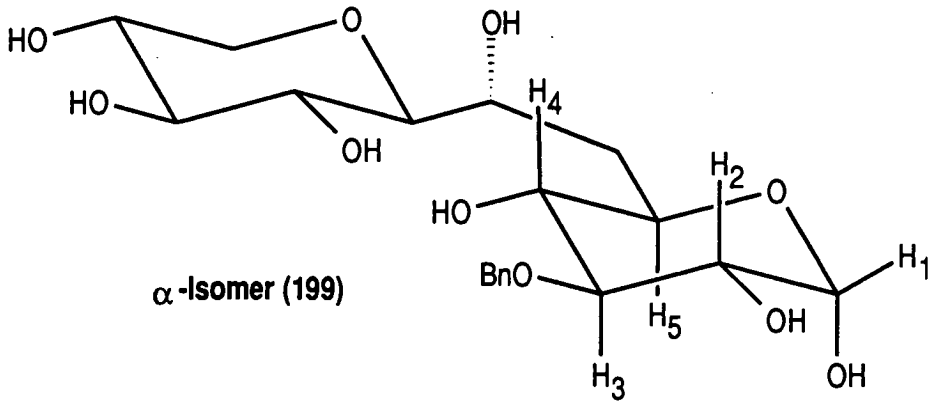
β (200)

**Scheme 57**

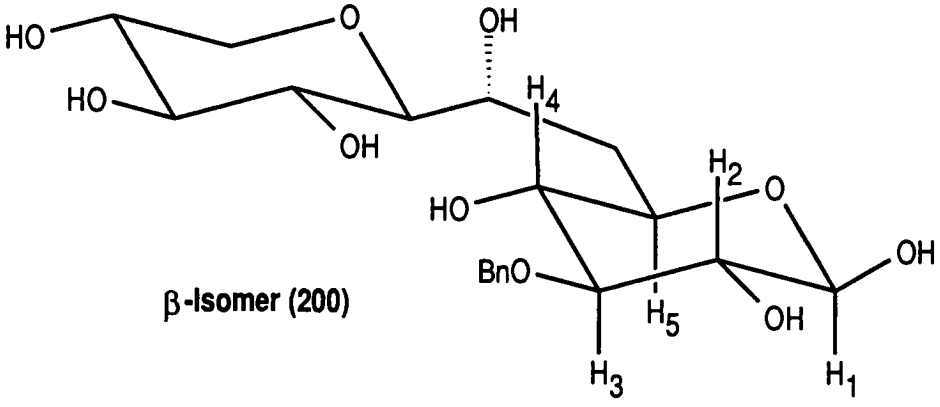
The large $J_{2,3}$, $J_{3,4}$ and $J_{4,5}$ values (9.3-9.8 Hz) observed for both anomers are consistent with D-*gluco* stereochemistry in which $H_2$, $H_3$, $H_4$ and $H_5$ are all axial (Figure 34). The $J_{4,5}$ value for the β-isomer (**200**) was not determined as the signals for both $H_4$ and $H_5$ were concealed within the complex multiplet at 3.42-3.52.

The anomeric proton signals for the two anomers are well separated ($\Delta\delta_H$ = 0.55 ppm) as can be seen from Figure 33. The $J_{12}$ value of 3.9 Hz observed for the signal at higher chemical shift is consistent with the α-isomer and the signal with a $J_{12}$ value of 8.7 Hz corresponds to the β-isomer.

These couplings confirm that deacetalation of (**194**) affords an anomeric mixture of hydroxymethylene-linked dipyranose *C*-disaccharides in which the pyranose ring at the reducing end possesses D-*gluco* stereochemistry.




α-Isomer (199)




β-Isomer (200)

**Figure 34**

## 2.8 Conclusions

The work presented in this thesis demonstrates that nitrile oxide/isoxazoline chemistry may be successfully used in the synthesis of (1→6)-linked *C*-disaccharides. Selection of the appropriate nitrile oxide precursors and alkenes, when coupled with the variety of methods available for 2-isoxazoline ring cleavage, allows a wide range of *C*-disaccharides to be prepared with a variety of functionality on the bridge.

It has been shown that pyranose 1-nitrile oxides will undergo cycloaddition to ω-unsaturated monosaccharides to afford 2-isoxazolines in moderate to excellent yield (42-93%) and with high diastereoselectivity (56-82% d.e.). Changes in stereochemistry at a position remote from the site of cycloaddition do not have a significant effect on the π-facial selectivity.

Unmasking of the isoxazoline ring by Raney nickel hydrogenolysis gives protected (1→6)-carbonyl-linked *C*-disaccharides with the corresponding aminomethylene-linked derivatives as minor by-products. Carbonyl reduction gives access to a series of (1→6)-hydroxymethylene-linked *C*-disaccharides which may be deprotected to afford the corresponding dipyranose derivatives.

In summary a number of (1→6)-*C*-disaccharides with carbonyl, hydroxymethylene and aminomethylene linkers have been prepared utilising nitrile oxide/isoxazoline chemistry. To date none of these compounds have been tested as glycosidase inhibitors.

# 3. Experimental

## 3.1 General Techniques

### 3.1.1 Instrumentation

Elemental analyses were performed by Miss E. Stevenson using a Carlo Erba elemental analyser model 1106.

Infra-red spectra were recorded as films on a Bio-Rad FTS-7 spectrometer.

FAB mass spectra and exact mass measurements were recorded by Mr. A. Taylor on a Kratos MS50TC instrument using thioglycerol matrix.

Melting points were measured on a Gallenkamp capillary tube apparatus and are uncorrected.

$^1$H n.m.r. spectra were recorded on Bruker WP200SY and WH360 or Varian VSX600 instruments by Miss H. Grant, Mr. J.R.A. Millar and Dr. D. Reed. Two-dimensional spectra were recorded on the WH360 and VSX600 instruments. Chemical shifts ($\delta$) in all spectra are measured in parts per million using tetramethylsilane ($\delta = 0.0$) as the reference signal.

Optical rotations were measured on a Perkin Elmer 141 polarimeter using 2 ml of filtered solution.

X-ray diffraction analyses were performed on a Stoë STADI-4 four circle diffractometer by Dr. A. Blake and Dr. R.O. Gould.

### 3.1.2 Chromatography

Preparative thin layer chromatography was carried out on glass plates (20 x 20 cm) coated with a layer of Kieselgel $GF_{254}$ (0.5 mm) containing 13% calcium sulphate and a fluorescent indicator.

Analytical t.l.c. was carried out on Merck aluminium-backed plates coated with Kieselgel $GF_{254}$ (0.2 mm).

Dry flash chromatography was carried out with a variety of sintered funnels filled with Kieselgel $GF_{254}$ and eluted under water pump vacuum.

Wet flash chromatography was carried out with Kieselgel 60 (230-400 mesh) and eluted under nitrogen at 2-5 psi.

### 3.1.3 Solvents and Reagents

All reagents and solvents were standard laboratory grade and were used as supplied unless otherwise stated.

Dry ether and toluene was Analar grade dried over sodium wire.

Dry acetone was Analar grade stored over 4A molecular sieve.

Pyridine was dried by distillation from and stored over potassium hydroxide.

Dry THF was freshly distilled from sodium and benzophenone.

Acetic anhydride was purified by fractional distillation and stored over 4A molecular sieve.

## 3.2 Synthesis of Sugar Alkenes

### 3.2.1 3-*O*-Benzyl-5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hex-5-enofuranose (37)

The title alkene was synthesised in four steps from commercially available diacetone-D-glucose (Scheme 30).

#### 3.2.1.1 3-*O*-Benzyl-1,2:5,6-di-*O*-isopropylidene-α-D-*gluco*-furanose (131)

The title compound was prepared by the procedure of Iwashige and Saeki[153]. A suspension of sodium hydride (80% dispersion in mineral oil, 5.16 g) in DMSO (60 ml) was stirred at room temperature under nitrogen. A solution of diacetone-D-glucose (22.5 g, 86 mmol) in DMSO (60 ml) was added dropwise and the resulting mixture stirred for 45 mins. Benzyl chloride (25 ml) was added dropwise and the mixture stirred for 1 hr after which it was poured onto an ice-water slurry (300 ml). The product was extracted into ether (3 x 250 ml) and washed with water (4 x 100 ml) to remove unreacted starting material. The organic layer was dried ($MgSO_4$) and evaporated to dryness to yield an oil which was not purified but taken directly on to the next stage.

#### 3.2.1.2 3-*O*-Benzyl-1,2-*O*-isopropylidene-α-D-*gluco*-furanose (132)

This compound was prepared according to the literature[154]. Crude oil (**131**) was dissolved in a solution of glacial acetic acid (60 ml) and water (40 ml) and stirred at 40°C for 16 hrs. The solution was neutralised by dropwise addition of a saturated solution of potassium carbonate. The product was extracted into chloroform (3 x 100 ml), dried ($MgSO_4$) and the solvent removed *in vacuo* to yield an oil which was carried straight onto the next stage.

### 3.2.1.3 3-*O*-Benzyl-1,2-*O*-isopropylidene-5,6-bis-*O*-methanesulphonyl-α-D-*gluco*-furanose (133)

The title compound was prepared by the method of Paulsen and Stoye[155]. Crude oil (**132**) was dissolved in pyridine (35 ml) and mesityl chloride (11 ml) was added to the ice-cooled solution. The mixture was stirred overnight while being cooled with an ice/water/salt bath. The sandy-coloured solid formed was dissolved in chloroform/water mixture (1:1, 100 ml) and the aqueous layer extracted with chloroform (3 x 25 ml). The combined organics were washed with 1M sulphuric acid (50 ml), then saturated sodium hydrogen carbonate solution (50 ml) and then dried ($MgSO_4$). The volume was reduced by half *in vacuo* and activated charcoal was added. The solution was refluxed for 30 mins, filtered and the solvent evaporated to yield a yellow solid. The crude product was recrystallised from ethanol to yield fine white needles (25.9 g, 64% from diacetone-D-glucose), m.p. 124-125°C (lit[155] - 124-125°C); *m/z* (FAB) - 467 ($M^+$+1)

### 3.2.1.4 3-*O*-Benzyl-5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hex-5-enofuranose (37)

This was prepared by reduction[156] of dimesylate (**133**). (**133**) (12.8 g, 27.5 mmol), sodium iodide (20.6 g, 137.5 mmol, dried over $P_2O_5$), Zn/Cu couple (prepared[194] from 9 g of zinc powder), DMF (130 ml) and dimethoxyethane (22 ml) were stirred together at reflux for 70 mins. After cooling the mixture was poured into water (500 ml) with rapid stirring. Toluene (200 ml) was added and the mixture was filtered through celite. The filter pad was washed with toluene (2 x 200 ml) and the washes used to extract the aqueous layer. The combined organics were washed with water (2 x 100 ml), dried ($MgSO_4$) and the solvent removed *in vacuo* to produce a syrup which was purified by dry flash chromatography (silica gel, hexane/ether 70:30) to yield a colourless oil (6.81 g, 90%); $\delta_H$ (200 MHz, $CDCl_3$) see Table 16; $\delta_C$ (50 MHz, $CDCl_3$) - 137.2 (Ph quat.), 132.1 ($C_5$), 128.0, 127.4, 127.2 (5 x Ph CH),

118.5 ($C_6$), 111.1 (isopropyl. quat.), 104.5 ($C_1$), 83.1, 82.5, 81.2 ($C_2$, $C_3$, $C_4$), 71.6 ($PhCH_2$), 26.4, 25.9 (2 x isopropyl $CH_3$); *m/z* (FAB) - 277 ($M^+$+1).

**Table 16** - $^1H$ n.m.r. Data for *Xylo*-alkene (**37**)

| Resonance | $\delta_H$ (ppm) | Coupling | *J* (Hz) |
|---|---|---|---|
| H(1) | 5.97 | 1,2 | 3.8 |
| H(2) | 4.63 | 2,3 | 0 |
| H(3) | 3.89 | 3,4 | 3.1 |
| H(4) | 4.64 | 4,5 | 7.1 |
| H(5) | 6.03 | 5,6a | 10.4 |
| H(6a) | 5.32 | 5,6b | 17.3 |
| H(6b) | 5.44 | 6a,6b | 1.6 |
| $PhCH_2$ | 4.54, 4.65 | $PhCH_2$ | 12.2 |
| Ph | 7.31-7.35 | | |
| Isopropyl $CH_3$ | 1.32, 1.51 | | |

### 3.2.2 Methyl 5,6-dideoxy-2,3-*O*-isopropyl-α-D-*lyxo*-hex-5-enofuranoside (137)

This alkene was prepared in four steps from D-mannose (Scheme 31).

#### 3.2.2.1 Methyl 2,3:5,6-Di-*O*-isopropylidene-α-D-*manno*-furanoside (134)

The title compound was prepared by a literature[159] method. A solution of D-mannose (10 g, 56 mmol), 2,2-dimethoxypropane (34 ml), acetone (33 ml), methanol (33 ml) and concentrated hydrochloric acid (1 ml) was refluxed for 2 hrs. The solution was cooled, water added (100 ml) and concentrated to ~ 100 ml at < 30°C. The product was not isolated but instead carried directly onto the next stage.

### 3.2.2.2 Methyl 2,3-*O*-Isopropylidene-α-D-*manno*-furanoside (135)

This compound was prepared according to a literature[159] method. To the stirred solution of (**134**) prepared in Section 3.2.2.1, methanol (100 ml) and concentrated hydrochloric acid (2.5 ml) were added and the resulting solution was stirred at 23°C for 200 mins. The solution was then neutralised by addition of sodium hydrogen carbonate solution (1M, 75 ml) and then concentrated to remove the methanol. The resulting aqueous solution was continuously extracted with chloroform for 3 hrs in a liquid-liquid extractor, the extract dried ($MgSO_4$) and then concentrated to a syrup. This syrup was not purified but taken directly onto the next stage.

### 3.2.2.3 Methyl 2,3-*O*-Isopropylidene-5,6-di-*O*-methylsulphonyl-α-D-*manno*-furanoside (136)

This compound was prepared according to a literature[159] method. Syrup (**135**) was dissolved in pyridine (50 ml) and mesityl chloride (15 m) added while keeping the stirred solution below 35°C. The solution was stirred at 20°C for 2 hrs and then excess mesityl chloride was decomposed by slow addition of water keeping the temperature below 50°C. More water (1500 ml) was added and the product filtered off, washed with water and dried. The crude product was recrystalised from ethanol to yield white needles (10.4 g, 48% from D-mannose); m.pt. 145-146°C (lit[159] m.pt. 144.5-146.0°C); *m/z* (FAB) - 392 ($M^+$+2), 391 ($M^+$+1).

### 3.2.2.4 Methyl 5,6-Dideoxy-2,3-*O*-isopropylidene-α-D-*lyxo*-hex-5-enofuranoside (137)

This alkene was prepared by reduction of dimesylate (**136**) using the same procedure as that for preparation of alkene (**37**) (see Section 3.2.1.4). The crude alkene was purified by dry flash column chromatography (silica gel, hexane/ether 80:20) to yield a colourless oil (3.4 g dimesylate (**136**) produced 1.6 g of alkene

(**137**), 89% yield); $\delta_H$ (200 MHz, $CDCl_3$) see Table 17; $\delta_C$ (50MHz, $CDCl_3$) - 132.2 ($C_5$), 119.0 ($C_6$), 112.4 (isopropyl. quat.), 107.0 ($C_1$), 85.2 ($C_4$), 81.3, 81.0 ($C_2$+$C_3$), 54.5 ($OCH_3$), 25.9, 24.8 (isopropyl. $CH_3$); *m/z* (FAB) - 201 ($M^+$+1).

**Table17** - $^1H$ n.m.r. Data for *Lyxo*-alkene (**137**)

| Resonance | $\delta_H$ (ppm) | Coupling | *J* (Hz) |
|---|---|---|---|
| $H_1$ | 4.89 | 1,2 | 0 |
| $H_2$ | 4.55 | 2,3 | 5.9 |
| $H_3$ | 4.66 | 3,4 | 3.6 |
| $H_4$ | 4.37 | 4,5 | 7.4 |
| $H_5$ | 5.97 | 4,6a | 0.9 |
| $H_{6a}$ | 5.32 | 4,6b | 1.1 |
| $H_{6b}$ | 5.38 | 5,6a | 10.1 |
| $OCH_3$ | 3.32 | 5,6b | 18.1 |
| Isopropyl $CH_3$ | 1.29, 1.45 | 6a, 6b | 1.6 |

## 3.3 Synthesis of Nitrile Oxide Precursors

### 3.3.1 Acetylated 2,6-Anhydro-1-deoxy-1-nitroalditols

These compounds were prepared in three steps from D-xylose, D-arabinose and D-galactose using a modified[160] version of the procedure of Köll *et al.*[161]

#### 3.3.1.1 1-Deoxy-1-nitroalditols

The title compounds were prepared from the corresponding aldoses by a modified Fischer-Sowden[162] reaction using the general procedure described below.

**General Procedure.** The aldose (0.17 mol) suspended in a methanol (50 ml), nitromethane (90 ml) mixture was mechanically stirred while protected from moisture (oven-dried glassware, Ca $Cl_2$ guard tube). A sodium methoxide solution (5.25 g Na in 175 ml MeOH, 0.23 mol) was added over 10 mins and the mixture was stirred for 24 hrs. The light brown solid formed was filtered off, washed with ice-cold methanol (100 ml) and pulled as dry as possible. The solid was then dissolved in ice-cold water (250 ml) and rapidly deionised by forcing through a column of amberlite IR-120 ($H^+$) ion-exchange resin (500 g) under nitrogen pressure, ensuring that the eluant is acidic at all times. The column was quickly washed with water (125 ml) and the combined eluant and washings concentrated to remove methanol and nitromethane. The product was not isolated but taken straight on to the next step.

#### 3.3.1.2 2,6-Anhydro-1-deoxy-1-nitroalidtols

These compounds were prepared by acid-catalysed cyclisation of the products from Section 3.3.1.1 using the procedure of Köll *et al.*[161]

**General Procedure.** The solution of 1-deoxy-1-nitroalidtol in water (~ 300 ml) from Section 3.3.1.1 was refluxed for 24 hrs, activated charcoal (5 g) added and the mixture refluxed for a further two hrs. The mixture was filtered hot, concentrated *in vacuo* and then co-evaporated with methylated spirits (3 x 250 ml). The semi-

crystalline mass was taken up in warm ethanol and cooled until the product crystallised out.

#### 3.3.1.2.1 2,6-Anhydro-1-deoxy-1-nitro-D-gulitol (140)

The crude product was recrystallised from ethanol to afford large white needles (15.8 g; 49% from D-xylose); m.p. 134-136°C (lit[163] - 135-136°C); $\delta_C$ (90 MHz, $CD_3OD$) - 76.2 ($C_1$), 77.6, 76.7, 70.4, 69.1 ($C_2$, $C_3$, $C_4$, $C_5$), 68.9 ($C_6$); *m/z* (FAB) - 194 ($M^+$+1).

#### 3.3.1.2.2 2,6-Anhydro-1-deoxy-1-nitro-D-mannitol (143)

The crude product was recrystallised from ethanol to afford fine white needles (12.2 g; 38% from D-arabinose); m.p. 169-170°C (lit[163] - 170-171°C); $\delta_C$ (50 MHz, $D_2O$) - 76.6 ($C_1$), 76.9, 73.1, 68.7, 67.6 ($C_2$, $C_3$, $C_4$, $C_5$), 70.0 ($C_6$); *m/z* (FAB) - 194 ($M^+$+1).

#### 3.3.1.2.3 2,6-Anhydro-1-deoxy-1-nitro-D-*glycero*-L-*manno*-heptitol (148)

The crude product was recrystallised from a methanol/water mixture (4:1) to yield fine white needles (13.4 g, 52% from D-galactose) m.p. 197-199°C (lit[161] - 199-200°C) ; $\delta_C$ (50 MHz, $D_2O$) - 76.5 ($C_1$), 78.7, 76.4, 73.7, 68.9, 67.7 ($C_2$, $C_3$, $C_4$, $C_5$, $C_6$), 61.1 ($C_7$); *m/z* (FAB) - 224 ($M^+$+1).

### 3.3.1.3 Acetylated 2,6-Anhydro-1-deoxy-1-nitroalditols

The acetylation of 2,6-anhydro-1-deoxy-1-nitroalditols (**140**), (**143**) and (**148**) was carried out by the method of Köll *et al.*[161]

**General Procedure.** Trifluoromethanesulphonic acid (0.15 ml) was added to a stirred, ice-cooled solution of the 2,6-anhydro-1-deoxy-1-nitroalditol in acetic anhydride (15 ml) and the solution left to warm up to room temperature and stirred overnight. The solution was added to an ice/water mixture (45 ml) and stirred for 1

hour. The product was extracted into chloroform (3 x 50 ml), dried ($MgSO_4$) and the solvent removed *in vacuo*. The crude syrup formed was co-evaporated with toluene (5 x 50 ml) to remove acetic acid, dissolved in chloroform and stirred for 30 mins with activated charcoal. The solution was then filtered and the solvent evaporated off to leave the crude product.

#### 3.3.1.3.1 3,4,5-Tri-*O*-acetyl-2,6-anhydro-1-deoxy-1-nitro-D-gulitol (121)

Obtained from (**140**) using the general procedure above and recrystallised from ethyl acetate to afford fine white needles (yield 94%); m.p. 164-165°C (lit.[161] - 164-165°C); $\delta_H$ (200 MHz, $CDCl_3$) see Tables 18 and 19; $\delta_C$ (50 MHz, $CDCl_3$) - 169.8, 169.5 (3 x acetate carbonyls), 75.8 ($C_1$), 74.8, 73.0, 69.4, 68.5 ($C_2$, $C_3$, $C_4$, $C_5$), 66.5 ($C_6$), 20.3 (3 x Acetate $CH_3$); *m/z* (FAB) - 320 ($M^+$+1).

#### 3.3.1.3.2 3,4,5-Tri-*O*-acetyl-2,6-anhydro-1-deoxy-1-nitro-D-mannitol (145)

Obtained from (**143**), using general procedure above, as a white foam (yield 89%); $\delta_H$ (360 MHz, $CDCl_3$) see Table 18 and 19; $\delta_C$ (50 MHz, $CDCl_3$) - 170.0, 169.8 (3 x acetate carbonyls), 76.1 ($C_1$), 75.1, 70.9, 68.1, 66.7 ($C_2$, $C_3$, $C_4$, $C_5$), 67.8 ($C_6$), 20.7, 20.4 (3 x acetate $CH_3$); *m/z* (FAB) - 320 ($M^+$+1).

#### 3.3.1.3.3 3,4,5,7-Tetra-*O*-acetyl-2,6-anhydro-1-deoxy-1-nitro-D-*glycero*-L-*manno*-heptitol (149)

Obtained from (**148**), using general procedure above, as a white foam (yield 82%) $\delta_H$ (200 MHz, $CDCl_3$) see Table 18 and 19; $\delta_C$ (50 MHz, $CDCl_3$) - 170.1, 169.9, 169.8, 169.7 (4 x acetate carbonyls), 75.8 ($C_1$), 74.5, 74.2, 71.2, 67.0, 66.4 ($C_2$, $C_3$, $C_4$, $C_5$, $C_6$), 60.9 ($C_7$), 20.4 (4 x acetate $CH_3$); *m/z* (FAB) - 392 ($M^+$+1).

**Table 18** - $^1H$ n.m.r. Chemical Shift Values for Nitroalditols (**121**), (**145**) and (**149**)

| Resonance | $\delta_H$ (ppm) | | |
|---|---|---|---|
| | (121) | (145) | (149) |
| $H_{1a}$ | 4.35 | 4.37 | 4.37 |
| $H_{1b}$ | 4.46 | 4.53 | 4.56 |
| $H_2$ | 4.13 | 4.13 | 4.23 |
| $H_3$ | 4.84 | 5.10 | 5.11* |
| $H_4$ | 5.21 | 5.06 | 5.09* |
| $H_5$ | 4.94 | 5.29 | 5.43 |
| $H_{6a}$ | 4.08 | 3.67 | 3.95 |
| $H_{6b}$ | 3.29 | 3.98 | - |
| $H_{7a}$ | - | - | 4.07* |
| $H_{7b}$ | - | - | 4.07* |
| Acetate $CH_3$ | 1.97 (x2), 2.11 | 1.97, 2.04, 2.11 | 1.94, 1.97, 2.03, 2.11 |

* -2nd Order

**Table 19** - $^1H$ n.m.r. Coupling Constants for Nitroalditols (**121**), (**145**) and (**149**)

| Coupling | $J_{(Hz)}$ | | |
|---|---|---|---|
| | (121) | (145) | (149) |
| 1a, 1b | 13.4 | 13.3 | 13.5 |
| 1a, 2 | 3.1 | 2.7 | 2.8 |
| 1b, 2 | 8.6 | 9.2 | 9.1 |
| 2,3 | 10.0 | 9.7 | 9.7 |
| 3,4 | 9.4 | 9.7 | nd |
| 4,5 | 9.4 | 3.2 | 2.8 |
| 5,6a | 5.6 | 1.2 | 1.2 |
| 5,6b | 10.6 | 2.1 | - |
| 6a,6b | 11.2 | 13.3 | - |
| 6,7a | - | - | nd |
| 6,7b | - | - | nd |
| 7a,7b | - | - | nd |

nd - not determined

### 3.3.2 Ethyl Chloro-oximinoacetate (152)

The title compound was prepared from glycine ethyl ester hydrochloride utilising the procedure of Skinner[164]. To a well stirred solution of glycine ethyl ester hydrochloride (30 g, 0.21 mmol) in water (90 ml) at -35°C (cardice/acetone bath) was added concentrated hydrochloric acid (36%, 18 ml, 0.21 mmol) followed by dropwise addition of sodium nitrite (14.5 g, 0.21 mmol) in water (25 ml). The same quantities of hydrochloric acid and sodium nitrite were again added and the solution was left to stir for 1 hr. The precipitate formed was filtered off, washed with petroleum ether (b.p. 40-60°C, 5 ml) and then dried to afford a white crystalline solid (11.5 g, 36%) m.p. 75-78°C (lit.[164] - 79-80°C); *m/z* (FAB) - 152 ($M^+$+1).

## 3.4 Nitrile Oxide Cycloadditions

### 3.4.1 Cycloadditions of Nitrile Oxides to 3-*O*-Benzyl-5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hex-5-enofuranose (37)

Three nitrile oxides (**122**), (**146**) and (**150**) were added to *xylo*-alkene (**37**). All three were generated from the corresponding nitroalditols (**121**), (**145**) and (**149**) using a modified Mukaiyama[27] procedure utilising tolylene di-isocyanate (TDI) as the dehydrating agent. A series of reactions was carried out (see Table 20) to establish the optimum conditions for these cycloadditions using 2,3,4-tri-*O*-acetyl-β-xylopyranosyl-1-nitrile oxide (**122**)

These conditions were set out in the general procedure below and were also used for cycloadditions of nitrile oxides (**146**) and (**150**) to alkene (**37**).

**Table 20** - Optimisation of Cycloaddition of Nitrile Oxide (**122**) to *xylo*-alkene (**37**)

| Temp | Solvent | Addition Time (hrs) | Combined Yield of Cycloadducts (%) |
|---|---|---|---|
| R.T. | $CH_2Cl_2$ | 14 | 0 |
| Reflux (40 °C) | $CH_2Cl_2$ | 14 | 2 |
| Reflux (83 °C) | $ClC_2H_4Cl$ | 14 | 8 |
| Reflux (83 °C) | $ClC_2H_4Cl$ | 48 | 39 |
| Reflux (111 °C) | Toluene | 14 | 66 |
| Reflux (111 °C) | Toluene | 48 | 93 |

General Procedure. A solution of the acetylated nitro alditol (3.1 mmol) in toluene (50 ml) was added to a stirred, refluxing solution of alkene (**37**) (12.4 mmol), TDI (9.3 mmol) and triethylamine (1.6 mmol) in toluene (50 ml) *via* a syringe pump over a period of 48 hrs. The solution was refluxed for a further 10 hrs, then cooled to 0°C and ether (20 ml) added. Diaminoethane (12.6 mmol) in ether (5 ml) was added over

30 mins to the ice-cooled solution which was then stirred for a further 30 mins. The precipitated polymeric urea was filtered off through celite and the filter pad washed with ether (50 ml) and $CHCl_3$ (50 ml). The filtrate and washings were combined and reduced *in vacuo*. The residue was dissolved in ethyl acetate (10 ml) and filtered through a silica pad which was then washed with ethyl acetate (2 x 10 ml). The combined filtrate and washings were reduced *in vacuo* to afford an oil. Excess alkene was removed by dry flash chromatography (silica; hexane/ether, 7:3) and 10% of the mixture of products was set aside for ratio determination by $^1H$ n.m.r. The mixture of isoxazolines was then separated by wet flash column chromatography (silica; hexane/ether).

### 3.4.1.1 2,3,4-Tri-*O*-acetyl-β-xylopyranosyl-1-nitrile Oxide (122)

Cycloaddition of nitrile oxide (**122**) to *xylo*-alkene (**37**) was carried out utilising the general procedure outlined above. A mixture of diastereomeric isoxazolines (**153**) and (**154**) in a ratio of 78:22 (determined by $^1H$ n.m.r) was obtained, which was separated by wet flash column chromatography (silica; hexane/ether gradient elution 9:1→6:4). The major adduct, which was obtained as large white needles (73%), was identified as *5R-5-(3-*O*-benzyl-1,2,-*O*-isopropylidene-α-D-*xylo*-tetrofuranos-4-yl)-3-(2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl)-2-isoxazoline* (**153**); m.p. 144-145°C (from methanol); $[\alpha]_D^{21}$ :- 132.6° ( c = 0.98, $CHCl_3$); [Found C, 58.04; H, 5.91; ;N, 2.39: $C_{28}H_{35}O_{12}N$ requires C, 58.22; H, 6.11; N, 2.43]; $\delta_H$ (360 MHz, $CDCl_3$) see Tables 21 and 22; $\delta_C$ (50MHz, $CDCl_3$) - 169.9, 169.7 (3 x acetate carbonyls), 156.0 ($C_7$), 137.3 (Ph quat.), 128.4, 127.8, 127.5 (5 x Ph CH), 111.8 (isopropyl. quat.), 105.1 ($C_1$), 82.5, 81.3, 80.0 ($C_2$, $C_3$, $C_4$), 77.5 ($C_5$), 74.3, 72.7, 69.0, 68.8 ($C_8$, $C_9$, $C_{10}$, $C_{11}$), 72.3 (Ph$CH_2$), 66.6 ($C_{12}$), 35.8 ($C_6$), 26.7, 26.1 (2 x isopropyl. $CH_3$), 20.5 (3 x acetate $CH_3$); *m/z* (FAB) 578.22370 ($M^+$+1, $C_{28}H_{36}O_{12}N$ requires 578.22373). The identity of this compound was confirmed by x-ray crystallography (Appendix). The minor adduct, which was isolated as an oil

20%), was identified as *5S-5-(3-O-benzyl-1,2,-O-isopropylidene-α–D-xylo-tetrofuranos-4-yl)-3-(2,3,4-tri-O-acetyl-β-D-xylopyranosyl)-2-isoxazoline* (**154**); $[\alpha]_D^{24}$ : -53.5° (c = 1.89, $CHCl_3$); $\delta_H$ (360 MHz, $CDCl_3$) see Tables 21 and 22; $\delta_C$ (50 MHz, $CDCl_3$) - 169.9, 169.8 (3 x acetate carbonyls), 154.7 ($C_7$), 136.8 (Ph. quat.), 128.5 128.0, 127.7 (5 x Ph CH), 111.9 (isopropyl. quat.), 105.6 ($C_1$), 82.1, 81.9, 81.8 ($C_2$, $C_3$, $C_4$), 79.7 ($C_5$), 74.2, 72.4, 68.9, 68.8 ($C_8$, $C_9$, $C_{10}$, $C_{11}$), 71.7 (Ph*C*$H_2$), 66.6 ($C_{12}$), 35.0 ($C_6$), 26.7, 26.4 (2 x isopropyl $CH_3$), 20.5 (3 x acetate $CH_3$); *m/z* (FAB) 578.22370 ($M^+$+1, $C_{28}H_{36}O_{12}N$ requires 578.22373).

### 3.4.1.2 *2,3,4-Tri-O-acetyl-α-arabinopyranosyl-1-nitrile Oxide* (146)

Cycloaddition of nitrile oxide (**146**) to *xylo*-alkene (**37**) was carried out using the general procedure above. A mixture of diastereomeric isoxazolines (**155**) and (**156**) (ratio 80:20, determined by $^1H$ n.m.r.) was obtained which was separated by wet flash chromatography (silica, hexane/ether, gradient elution 9:1→6:4). The major adduct, which was obtained as a white foam (71%) was identified as *5R-5-(3-O-benzyl-1,2,-O-isopropylidene-α–D-*xylo*-tetrofuranos-4-yl)-3-(2,3,4-tri-O-acetyl-α-D-arabinopyranosyl)-2-isoxazoline* (**155**); $[\alpha]_D^{24}$ - 48.0 (c = 1.71, $CHCl_3$); $\delta_H$ (360 MHz, $CDCl_3$) see Tables 21 and 22; $\delta_C$ (50 MHz, $CDCl_3$) - 170.1, 169.8 (3 x acetate carbonyls), 155.6 ($C_7$), 137.3 (Ph quat.), 128.3, 127.7, 127.6 (5 x Ph CH), 111.9 (isopropyl. quat.), 105.0 ($C_1$), 82.6, 81.3, 80.3 ($C_2$, $C_3$, $C_4$), 76.7 ($C_5$), 74.6, 70.8, 68.2, 66.3 ($C_8$, $C_9$, $C_{10}$, $C_{11}$), 72.3 (Ph*C*$H_2$), 67.8 ($C_{12}$), 36.2 ($C_6$), 26.4, 26.3 (2 x isopropyl. $CH_3$), 20.8, 20.5 (3 x acetate $CH_3$); *m/z* (FAB) - 578.22370 ($M^+$+1, $C_{28}H_{36}O_{12}N$ requires 578.22373). The minor adduct, which was isolated as a colourless oil (18%), was identified as *5S-5-(3-O-benzyl-1,2,-O-isopropylidene-α–D-*xylo*-tetrofuranos-4-yl)-3-(2,3,4-tri-O-acetyl-α-D-arabinopyranosyl)-2-isoxazoline* (**156**); $[\alpha]_D^{24}$: + 32.4° (c = 0.84, $CHCl_3$); $\delta_H$ (360 MHz, $CDCl_3$) see Tables 21 and 22; $\delta_C$ (50 MHz, $CDCl_3$)- 170.0,169.8(3x acetate carbonyls), 155.2 ($C_7$),136.9 (Ph quat.),

128.4, 127.9, 127.7 (5 x Ph CH), 112.0 (isopropyl. quat.), 105.5 ($C_1$), 81.9, 81.5 ($C_2$, $C_3$, $C_4$), 79.4 ($C_5$), 74.6, 70.7, 68.2, 66.1 ($C_8$, $C_9$ $C_{10}$, $C_{11}$), 71.6 (Ph$CH_2$), 68.0 ($C_{12}$), 35.1 ($C_6$), 26.8, 26.3 (2 x isopropyl $CH_3$), 20.8, 20.5 (3 x acetate $CH_3$), *m/z* (FAB) - 578.22370 ($M^+$+1, $C_{28}H_{36}O_{12}N$ requires 578.22373).

### 3.4.1.3 *2,3,4,6-Tetra*-O-*acetyl*-β-*galactopyranosyl-1-nitrile Oxide* (150)

Cycloaddition of nitrile oxide (**150**) to *xylo*-alkene (**37**) was carried out using the general procedure above. A mixture of diastereomeric isoxazolines (**157**) and (**158**) in a ratio of 91:9 (determined by $^1H$ n.m.r.) was obtained which was separated by wet flash column chromatography (silica, hexane/ether, gradient elution 9:1→1:1). The major adduct, which was obtained as a white foam (56%), was identified as *5R-5-(3*-O-*benzyl-1,2,*-O-*isopropylidene*-α–*D*-xylo-*tetrofuranos-4-yl)-3-(2,3,4,6-tetra*-O-*acetyl*-β-*D-galactopyranosyl)-2-isoxazoline* (**157**); $[\alpha]_D^{24}$: - 73.0° (c = 1.5, $CHCl_3$); $\delta_H$ (360 MHz, $CDCl_3$) see Tables 21 and 22; $\delta_C$ (50 MHz, $CDCl_3$) - 170.1, 169.9, 169.7 (4 x acetate carbonyls), 156.0 ($C_7$), 137.2 (Ph quat.), 128.2, 127.7, 127.5 (5 x Ph CH), 111.8 (isopropyl. quat.), 105.0 ($C_1$), 82.4, 81.2, 80.1 ($C_2$, $C_3$, $C_4$), 77.4 ($C_5$), 74.2, 73.9, 71.0, 67.1, 66.0 ($C_8$, $C_9$, $C_{10}$, $C_{11}$, $C_{12}$), 72.2 (Ph$CH_2$), 61.3 ($C_{13}$), 35.9 ($C_6$), 26.6, 26.0 (2 x isopropyl $CH_3$), 20.4 (4 x acetate $CH_3$); *m/z* (FAB) 650.24488 ($M^+$+1, $C_{31}H_{40}O_{14}N$ requires 650.24486). The minor adduct, which was isolated as a colourless oil (5%), was identified as *5S-5-(3*-O-*benzyl-1,2,*-O-*isopropylidene*-α–*D*-xylo-*tetrofuranos-4-yl)-3-(2,3,4,6-tetra*-O-*acetyl*-β-*D-galactopyranosyl)-2-isoxazoline* (**158**); $[\alpha]_D^{24}$: -16.8° (c = 0.74, $CHCl_3$); $\delta_H$ (360 MHz, $CDCl_3$) see Tables 21 and 22; $\delta_C$ (50 MHz, $CDCl_3$) - 170.2, 169.9, 169.7 (4 x acetate carbonyls), 154.5 ($C_7$), 137.0 (Ph quat.), 128.4, 127.9, 127.6 (5 x Ph CH), 111.9 (isopropyl. quat.), 105.6 ($C_1$), 81.9, 81.7 ($C_2$, $C_3$, $C_4$), 79.4 ($C_5$), 74.4, 74.1, 70.9, 67.2, 66.0 ($C_8$, $C_9$, $C_{10}$, $C_{11}$, $C_{12}$), 71.4 (Ph$CH_2$), 61.4 ($C_{13}$), 35.0 ($C_6$), 26.6, 26.4 (2 x isopropyl. $CH_3$),

20.5, 20.4 (4 x acetate $CH_3$); *m/z* (FAB) 650.24488 ($M^+$+1, $C_{31}H_{40}O_{14}N$ requires 650.24486).

**Table 21** - $^1H$ n.m.r. Chemical Shift Values for *Xylo*-alkene (**37**) Cycloadducts

A - Major (5R) Isomer

B - Minor (5S) Isomer

| | $\delta_H$ (ppm) | | | | | |
|---|---|---|---|---|---|---|
| **Resonance** | **A (153)** | **B (154)** | **A (155)** | **B (156)** | **A (157)** | **B (158)** |
| $H_1$ | 5.88 | 5.97 | 5.90 | 5.97 | 5.89 | 5.98 |
| $H_2$ | 4.56 | 4.63 | 4.59 | 4.63 | 4.58 | 4.64 |
| $H_3$ | 4.00 | 4.02 | 4.02 | 3.96 | 4.03 | 4.01 |
| $H_4$ | 4.16 | 4.18 | 4.18 | 4.22 | 4.18 | 4.20 |
| $H_5$ | 4.86 | 4.83 | 4.93 | 4.86 | 4.89 | 4.88 |
| $H_{6a}$ | } 3.15 | 2.57 | 3.19 | 2.67 | 3.25 | 2.61 |
| $H_{6b}$ | | 2.98 | 3.30 | 3.11 | 3.19 | 3.01 |
| $H_8$ | 4.24 | 4.23 | 4.25 | 4.18 | 4.32 | 4.30 |
| $H_9$ | 5.00 | 4.88 | 5.28 | 5.19 | 5.23 | } 5.10* |
| $H_{10}$ | 5.27 | 5.27 | 5.10 | 5.08 | 5.11 | |
| $H_{11}$ | 5.00 | 4.97 | 5.33 | 5.33 | 3.45 | 5.45 |
| $H_{12a}$ | 4.13 | 4.11 | 3.70 | 3.65 | 3.95 | 3.94 |
| $H_{12b}$ | 3.35 | 3.33 | 4.02 | 3.95 | - | - |
| $H_{13a}$ | - | - | - | - | } 4.08* | } 4.10* |
| $H_{13b}$ | - | - | - | - | | |
| $PhCH_2$ | 4.58,4.64 | 4.44,4.68 | 4.61,4.66 | 4.45,4.68 | 4.62,4.66 | 4.44,4.71 |
| Ph | 7.26-7.37 | 7.28-7.40 | 7.26-7.34 | 7.27-7.39 | 7.27-7.35 | 7.28-7.38 |
| Acetate $CH_3$ | 2.00,2.02 | 1.98,2.02,2.03 | 1.99,2.00,2.15 | 2.00,2.01,2.16 | 1.98,2.02,2.14 | 1.99,2.02,2.03, 2.16 |
| Isopropyl $CH_3$ | 1.28,1.45 | 1.31,1.49 | 1.30,1.55 | 1.30,1.45 | 1.29,1.46 | 1.31,1.50 |

* - Second Order Multiplet

**Table 22** - $^1$H Coupling Consts. for *Xylo*-alkene (**37**) Cycloadducts

A - Major (5R) Isomer

B - Minor (5S) Isomer

| | *J* (Hz) | | | | | |
|---|---|---|---|---|---|---|
| **Coupling** | **A (153)** | **B (154)** | **A (155)** | **B (156)** | **A (157)** | **B (158)** |
| 1,2 | 3.7 | 3.9 | 3.7 | 3.9 | 3.7 | 3.9 |
| 2,3 | 0 | 0 | 0 | 0 | 0 | 0 |
| 3,4 | 3.3 | 3.8 | 3.2 | 3.9 | 3.2 | 3.7 |
| 4,5 | 7.2 | 8.2 | 8.1 | 7.7 | 7.6 | 8.4 |
| 5,6a | 9.0 | 7.6 | 11.2 | 8.8 | 10.1 | 7.5 |
| 5,6b | 9.0 | 11.4 | 6.6 | 11.0 | 8.0 | 11.3 |
| 6a,6b | 0 | 17.4 | 17.9 | 17.1 | 17.6 | 17.4 |
| 8,9 | 9.9 | 9.9 | 9.8 | 9.7 | 9.8 | 9.7 |
| 9,10 | 9.5 | 9.7 | 10.1 | 9.7 | 10.0 | nd |
| 10,11 | 9.5 | 9.5 | 3.5 | 3.5 | 3.3 | 2.8 |
| 11,12a | 5.7 | 5.6 | 1.2 | 1.1 | 1.1 | 1.2 |
| 11,12b | 10.7 | 10.5 | 2.1 | 2.0 | - | - |
| 12a,12b | 11.2 | 11.4 | 13.0 | 13.3 | - | - |
| 12,13a | - | - | - | - | 6.5 | 6.4 |
| 12,13b | - | - | - | - | 6.5 | 6.4 |
| 13a,13b | - | - | - | - | nd | nd |
| PhC$H_2$ | 11.8 | 11.8 | 11.7 | 11.9 | 11.7 | 12.0 |

* - Second Order Multiplet

nd - Not Determined

### 3.4.2 Cycloadditions of Nitrile Oxides to Methyl 5,6-dideoxy-2,3-*O*-isopropylidene-α-D-*manno*-hex-5-enofuranoside (137)

#### 3.4.2.1 Ethoxycarbonylformonitrile Oxide (36)

A solution of triethylamine (3.96 mmol) in Na dried ether (40 ml) was added *via* a syringe pump to an ice-cooled, stirred solution of *lyxo*-alkene (**137**) (4.95 mmol) and ethyl chloro-oximinoacetate (**152**) (3.3 mmol) in Na dried ether (20 ml), over a

period of 40 hrs. The solution was stirred for a further 10 hrs. and then added to water (100 ml). The ether layer was separated off and the aqueous layer extracted three times with ether (3 x 30 ml). The combined organics were dried ($MgSO_4$) and concentrated *in vacuo*. The crude syrup was purified by dry flash column chromatography (silica; hexane/ether, gradient elution 9:1→6:4) to afford unreacted alkene (**137**) (0.45 g), 3,4-diethoxycarbonylfuroxan (**165**) (90 mg, 24% identified by t.l.c. comparison with authentic sample) and a mixture of diastereomeric isoxazolines (**166**) and (**167**) in a ratio of 82:18 (ratio determination by $^1H$ n.m.r.). This mixture was separated by wet flash column chromatography (silica; hexane/ether gradient elution 9:1→6:4). The major cycloadduct, which was obtained as white needles (0.64 g, 62%), m.p. 72-73°C (from ethanol), was identified as *5R-5 (1-methyl-2,3-*O*-isopropylidene-*α*-D-*lyxo*-tetrofuranos-4-yl)-3-carbethoxy-2-isoxazoline* (**166**); $[\alpha]_D^{24}$: -43.8° (c = 1.02, $CHCl_3$); $\delta_H$ (360 MHz, $CDCl_3$) see Tables 23 and 24; $\delta_C$ (90 MHz, $CDCl_3$) - 159.4 ($C_8$), 150.9 ($C_7$), 112.1 (isopropyl. quat.), 106.6 ($C_1$), 84.5, 80.7, 78.9, 78.8 ($C_2$, $C_3$, $C_4$, $C_5$), 62.0 ($C_9$), 54.8 ($OCH_3$), 36.0 ($C_6$), 26.1, 24.7 (2 x isopropyl. $CH_3$), 14.7 ($C_{10}$); *m/z* (FAB) - 316.13963 ($M^+$+1, $C_{14}H_{22}O_7N$ requires 316.13961). The minor cycloadduct, which was obtained as a colourless oil (0.14 g, 14%), was identified as *5S-5(1-methyl-2,3-*O*-isopropylidene-*α*-*lyxo*-tetrofuranos-4-yl)-3-carbethoxy-2-isoxazoline* (**167**); $[\alpha]_D^{24}$: +90.1° (c = 1.64, $CHCl_3$); $\delta_H$ (360 MHz, $CDCl_3$) see Tables 23 and 24; $\delta_C$ (90 MHz, $CDCl_3$) - 159.3 ($C_8$), 150.4 ($C_7$), 112.4 (isopropyl. quat.), 107.0 ($C_1$), 84.5, 82.6, 80.8 ($C_2$,$C_3$,$C_4$), 79.4 ($C_5$), 62.1 ($C_9$), 55.0, ($OCH_3$), 36.7 ($C_6$), 26.4, 25.2 (2 x isopropyl. $CH_3$), 14.8 ($C_{10}$); *m/z* (FAB) - 316.13963 ($M^+$+1, $C_{14}H_{22}O_2N$ requires 316.13961).

### 3.4.2.2 2,3,4-Tri-*O*-acetyl-β-xylopyranosyl-1-nitrile Oxide (122)

Cycloaddition of nitrile oxide (**122**) to *lyxo*-alkene (**137**) was carried out on a 1.6 mmol scale utilising the general procedure outlined in Section 3.4.1. The crude syrup obtained was separated by wet flash chromatography (silica; hexane/ether,

gradient elution 9:1→6:4) to afford unreacted alkene (**137**) (1.1 g), unreacted nitroalditol (**121**) (275 mg) and a mixture of diastereomeric isoxazolines (**168**) and (**169**) (combined yield 275 mg, 36% or 80% based on consumed starting material), in a ratio of 79:21 (determined by $^1$H n.m.r.). This mixture of isoxazolines was inseparable by chromatography but repeated recrystallisation from methanol afforded a small amount (45 mg) of the pure major cycloadduct as fine white needles, m.p. 121-122°C (from methanol). This was identified as *5R-5(1-methyl-2,3-O-isopropylidene-α-D-*lyxo*-tetrofuranos-4-yl)-3-(2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl)-2-isoxazoline.* $[\alpha]_D^{24}$: -84.5° (c = 0.3, $CDCl_3$); $\delta_H$ (360 MHz, $CDCl_3$) see Tables 23 and 24; $\delta_C$ (50 MHz, $CDCl_3$) - 169.8 (3 x acetate carbonyls), 155.8 ($C_7$), 112.6 (isopropyl. quat.), 107.1 ($C_1$), 84.7, 79.2, 79.1 ($C_2$, $C_3$, $C_4$), 78.0 ($C_5$), 74.3, 72.5, 68.9 ($C_8$, $C_9$, $C_{10}$, $C_{11}$), 66.6 ($C_{12}$), 54.5 ($OCH_3$), 35.4 ($C_6$), 25.7, 24.2 (2 x isopropyl. $CH_3$), 20.5 (3 x acetate $CH_3$); *m/z* (FAB) - 502.19245 ($M^+$+1, $C_{22}H_{32}O_{12}N$ requires 502.19243).

**Table 23** - $^1H$ n.m.r. Chemical Shift Values for *Lyxo*-alkene (**137**) Cycloadducts

A - Major (5R) Isomer

B - Minor (5S) Isomer

| Resonance | $\delta_H$ (ppm) | | |
|---|---|---|---|
| | **A (166)** | **B (167)** | **A (168)** |
| $H_1$ | 4.86 | 4.96 | 4.89 |
| $H_2$ | 4.52 | 4.54 | 4.55 |
| $H_3$ | 4.71 | 4.69 | 4.74 |
| $H_4$ | 4.06 | 4.01 | 3.97 |
| $H_5$ | 5.03 | 4.97 | 4.88 |
| $H_{6a}$ | 3.20 | 2.99 | 3.16 |
| $H_{6b}$ | 3.32 | 3.40 | 3.08 |
| $H_8$ | - | - | 4.26 |
| $H_9$ | - | - | 5.00 |
| $H_{10}$ | - | - | 5.29 |
| $H_{11}$ | - | - | 5.01 |
| $H_{12a}$ | - | - | 4.15 |
| $H_{12b}$ | - | - | 3.36 |
| $CH_3CH_2$ | 4.29 | 4.32 | - |
| $CH_3CH_2$ | 1.32 | 1.34 | - |
| $OCH_3$ | 3.26 | 3.32 | 3.30 |
| Isopropyl $CH_3$ | 1,26,1.42 | 1.26,1.41 | 1.30,1.46 |
| Acetate $CH_3$ | - | - | 2.00,2.03 |

**Table 24** - $^1$H n.m.r. Coupling Consts. for *Lyxo*-alkene (**137**) Cycloadducts

A - Major (5R) Isomer

B - Minor (5S) Isomer

| Coupling | *J*(Hz) | | |
|---|---|---|---|
| | **A (166)** | **B (167)** | **A (168)** |
| 1,2 | 0 | 0 | 0 |
| 2,3 | 6.0 | 6.0 | 5.9 |
| 3,4 | 3.7 | 3.8 | 3.7 |
| 4,5 | 5.3 | 8.5 | 6.4 |
| 5,6a | 11.2 | 9.1 | 10.5 |
| 5,6b | 8.3 | 11.2 | 8.5 |
| 6a,6b | 18.1 | 18.0 | 18.7 |
| 8,9 | - | - | 9.6 |
| 9,10 | - | - | 9.6 |
| 10,11 | - | - | 9.6 |
| 11,12a | - | - | 5.7 |
| 11,12b | - | - | 11.1 |
| 12a,12b | - | - | 11.1 |
| $CH_3CH_2$ | 7.1 | 7.1 | - |

## 3.5 Synthesis of β-Hydroxy Ketones

### 3.5.1 Deacetylation of 2-Isoxazolines

The major isoxazoline cycloadducts (**153**), (**155**) and (**157**) from cycloaddition reactions to *xylo*-alkene (**37**) were deacetylated, before ring-opening to β-hydroxy ketones, using the general procedure outlined below.

**General Procedure**[186]. The polyacetylated isoxazoline (1 M equiv.) and potassium cyanide (0.5 M equiv.) were stirred together in a mixed methanol / methylene chloride solvent system (7:3, 6 ml per mmol polyacetylated isoxazoline) at room temperature until all the starting material had been consumed, reaction monitored by t.l.c. (silica; methylene chloride/methanol 95:5). The solvent was removed *in vacuo*, the residue dissolved in ethyl acetate and filtered through a pad of silica to remove KCN. The silica pad was washed with ethyl acetate and the combined filtrate and washings were concentrated *in vacuo*. The crude deacetylated isoxazoline was then purified by recrystallisation or preparation t.l.c., but in many cases purification was not necessary.

#### 3.5.1.1 Synthesis of *5R-5-(3-O-benzyl-1,2,-O-isopropylidene-α-D-xylo-tetrofuranos-4-yl)-3-(β-D-xylopyranosyl)-2-isoxazoline* (175)

Obtained from (**153**) using the general procedure outlined above as small white needles (94%) m.p. 108-109°C; $[\alpha]_D^{20}$: -110.4° (c = 1.0, THF); $\delta_H$ (360 MHz, $CD_3COCD_3$) see Tables 25 and 26; $\delta_C$ (50MHz, $CD_3COCD_3$) - 156.4 ($C_7$), 137.2 (Ph quat.), 127.4, 126.8 (5 x Ph CH), 110.4 (isopropyl. quat.), 104.3 ($C_1$), 81.3, 80.8, 79.4 ($C_2$, $C_3$, $C_4$), 77.6 ($C_5$), 75.9, 75.0, 70.7, 69.1 ($C_8$, $C_9$, $C_{10}$, $C_{11}$), 70.8 ($PhCH_2$), 69.1 ($C_{12}$), 35.0 ($C_6$), 25.3, 24.6 (2 x isopropyl. $CH_3$); *m/z* (FAB) - 452.19207 ($M^+$+1, $C_{22}H_{30}NO_9$ requires 452.19204).

### 3.5.1.2 Synthesis of *5R-5-(3-O-benzyl-1,2,-O-isopropylidene-α-D-xylo-tetrofuranos-4-yl)-3-(α-D-arabinopyranosyl)-2-isoxazoline* (176)

Obtained from (**155**) using the general procedure outlined above as a white foam (99%): no further purification was necessary; $[\alpha]_D^{24}$: -94.7° (c = 1.35, THF); $\delta_H$ (360 MHz, $CD_3COCD_3$) see Tables 25 and 26; $\delta_C$ (50 MHz, $CD_3COCD_3$) - 156.7 ($C_7$), 137.2 (Ph quat.), 127.4, 126.8 (5 x Ph CH), 110.5 (isopropyl. quat.), 104.3 ($C_1$), 81.4, 80.7, 79.7, ($C_2$, $C_3$, $C_4$), 76.0 ($C_5$), 75.0, 73.2, 68.3, 68.0 ($C_8$, $C_9$, $C_{10}$, $C_{11}$), 70.8 (Ph*C*$H_2$), 69.4 ($C_{12}$), 35.3 ($C_6$), 25.4, 24.7 (2 x isopropyl. $CH_3$); *m/z* (FAB) - 452.19207 ($M^+$+1, $C_{22}H_{30}NO_9$ requires 452.19204).

### 3.5.1.3 Synthesis of *5R-5-(3-O-benzyl-1,2,-O-isopropylidene-α-D-xylo-tetrofuranose-4-yl)-3-(β-D-galactopyranosyl)-2-isoxazoline* (175)

Obtained from (**157**) using the general procedure outlined above as a colourless gum (55%) after purification by preparative t.l.c. (silica; methylene chloride methanol, 9:1); $[\alpha]_D^{22}$: - 65.5° (c = 1.86, THF); $\delta_H$ (360 MHz, $CD_3COCD_3$) see Tables 25 and 25; $\delta_C$ (50 MHz, $CD_3COCD_3$) - 156.8 ($C_7$), 137.2 (Ph quat.), 127.4, 126.8 (5 x Ph CH), 110.4 (isopropyl. quat.), 104.3 ($C_1$), 81.4, 80.7, 79.5 ($C_2$, $C_3$, $C_4$). 78.4, 75.9 ($C_5$), 73.8, 68.4, 67.9 ($C_9$, $C_{10}$, $C_{11}$, $C_{12}$), 74.6 ($C_8$), 70.8 (Ph*C*$H_2$), 60.6 ($C_{13}$), 35.5 ($C_6$), 25.3, 24.7 (2 x isopropyl. $CH_3$); *m/z* (FAB) - 482.20259 ($M^+$+1, $C_{23}H_{32}NO_{10}$ requires 482.20260).

**Table 25** - $^1H$ n.m.r. Chemical Shift Values for Deacetylated Isoxazolines

| Resonance | $\delta_H$ (ppm) | | |
|---|---|---|---|
| | (175) | (176) | (177) |
| $H_1$ | 5.90 | 5.90 | 5.90 |
| $H_2$ | 4.76 | 4.76 | 4.77 |
| $H_3$ | 4.03 | 4.03 | 4.03 |
| $H_4$ | 4.15 | 4.19 | 4.16 |
| $H_5$ | 4.87 | 4.87 | 4.84 |
| $H_{6a}$ | 3.17 | } 3.15 | 3.18 |
| $H_{6b}$ | 3.09 | | 3.12 |
| $H_8$ | 4.01 | 3.96 | 4.03 |
| $H_9$ | 3.47 | 3.81 | 3.82 |
| $H_{10}$ | 3.41 | 3.59 | 3.56 |
| $H_{11}$ | 3.55 | 3.89 | 3.98 |
| $H_{12a}$ | 3.89 | 3.65 | 3.62 |
| $H_{12b}$ | 3.26 | 3.93 | - |
| $H_{13a}$ | - | - | } 3.72* |
| $H_{13b}$ | - | - | |
| $PhCH_2$ | 4.63,4.76 | 4.64,4.76 | 4.64,4.76 |
| Ph | 7.30-7.42 | 7.30-7.42 | 7.30-7.42 |
| Isopropyl. $CH_3$ | 1.29,1.42 | 1.28,1.41 | 1.28,1.42 |
| OH | 4.29,4.35,4.44 | | 3.82,4.09,4.19 |

* - Second Order Multiplet

**Table 26** - $^1$H n.m.r. Coupling Constants for Deacetylated Isoxazolines

| Coupling | *J*(Hz) | | |
|---|---|---|---|
| | (175) | (176) | (177) |
| 1,2 | 3.7 | 3.7 | 3.7 |
| 2,3 | 0 | 0 | 0 |
| 3,4 | 3.2 | 3.2 | 3.2 |
| 4,5 | 7.2 | 7.1 | 7.3 |
| 5,6a | 10.3 | 8.8 | 10.1 |
| 5,6b | 7.4 | 8.8 | 8.0 |
| 6a,6b | 17.4 | 0 | 17.6 |
| 8,9 | 9.8 | 9.6 | 9.6 |
| 9,10 | 9.5 | 9.4 | 9.2 |
| 10,11 | 9.4 | 3.5 | 3.5 |
| 11,12a | 5.3 | 1.0 | 1.0 |
| 11,12b | 10.4 | 1.8 | - |
| 12a,12b | 11.1 | 12.4 | - |
| 12,13a | - | - | 5.9 |
| 12,13b | - | - | 5.9 |
| 13a,13b | - | - | nd |
| PhC$H_2$ | 11.8 | 11.7 | 11.7 |

nd - Not Determined

### 3.5.2 Reductive Hydrolytic Cleavage of 2-Isoxazolines to β-Hydroxy Ketones

β-Hydroxy ketones were prepared from deacetylated isoxazolines (**175**), (**176**) and (**177**) *via* Raney-Nickel catalysed hydrogenolysis (Section 3.5.2.2). Initial work was carried out on the palladium on charcoal hydrogenolysis of (**175**) (Section 3.5.2.1).

### 3.5.2.1 Palladium on Charcoal Hydrogenolysis[156] of (175)

Deacetylated isoxazoline (**175**) (200 mg, 0.44 mmoles), Pd/C (44 mg) and boric acid (164 mg) were stirred together at room temperature in a methanol/$H_2O$ mixture (5:1, 16 ml). THF (1 ml) was added to aid dissolution and the solution was degassed using a water pump and flushed with hydrogen several times. The solution was then left to stir vigorously under a hydrogen atmosphere ($H_2$ filled balloon) and the reaction was monitored by t.l.c. (silica; methylene chloride/methanol 9:1). After 5 days starting material was still present and two other spots were visible. The Pd/C was filtered off through celite and the solution was concentrated *in vacuo*. Methanol was added and evaporated several times to remove any remaining boric acid as the volatile trimethyl borate to afford a glass. This mixture of starting material and two other spots was separated by careful preparative t.l.c. (silica; methylene chloride/methanol 95:5) to yield in order of elution: unreacted isoxazoline (**175**) (20 mg); *8,12-anhydro-3-*O*-benzyl-6-deoxy-1,2-*O*-isopropylidene-*α*-D-*gulo*-D-*gluco*-7-dodeco-1,4-furanosulose* (**178**) as a colourless glass (45 mg, 25% based on reacted isoxazoline); $\nu_{max}$ (film) 3417 $cm^{-1}$ (OH), 1718 $cm^{-1}$ (C=O); $\delta_H$ (360 MHz, $CD_3OD$) see Tables 27 and 28 (Section 3.5.2.2); $\delta_C$ (50 MHz, $CD_3OD$) - 206.8 ($C_7$), 137.4 (Ph quat.), 127.5, 127.1, 126.9 (5 x Ph CH), 110.9 (isopropyl. quat.), 104.5 ($C_1$), 83.6 ($C_8$), 82.0, 81.6, 80.7 ($C_2$, $C_3$, $C_4$), 77.5, 71.1, 68.9 ($C_9$, $C_{10}$, $C_{11}$), 71.3 (Ph$CH_2$), 68.9 ($C_{12}$), 63.3 ($C_5$), 45.8 ($C_6$), 25.2, 24.5 (2 x isopropyl $CH_3$); *m/z* (FAB) 455.19172 ($M^+$+1, $C_{22}H_{31}O_{10}$ requires 455.19170), 437.18116 (α-enone $M^+$+1, $C_{22}H_{29}O_9$ requires 437.18114) and an inseparable mixture of debenzylated compounds (70 mg) containing *.8,12-anhydro-6-deoxy-1,2-*O*-isopropylidene-α-D-*gulo*-D-*gluco*-7-dodeco-1,4-furanosulose* (**179**); $\delta_C$ (50 MHz, D6 DMSO) - 205.7 ($C_7$), 110.3 (isopropyl. quat.), 104.2 ($C_1$), 84.8, 84.1, 82.8, 77.7, 72.6, 71.3, 69.3 ($C_{12}$), 62.5 ($C_5$), 44.4 ($C_6$), 26.6, 26.2 (2 x isopropyl. $CH_3$); *m/z*(FAB) - 365.14479 (α-enone $M^+$+1, .$C_{15}H_{25}O_{10}N$ requires 365.14476).

### 3.5.2.2 Raney-Nickel Hydrogenolysis of 2-Isoxazolines

β-Hydroxyketones were prepared from deacetylated isoxazolines (**175**), (**176**) and (**177**) using the general procedure outlined below.

**General Procedure.** Ra-Ni (50 mg per mmol of isoxazoline; under MeOH) was added to a stirred solution of the isoxazoline (1 M equiv.) and boric acid (6 M equiv.) in methanol/THF/$H_2O$ (5:5:1, 35 ml per mmol of isoxazoline). The solution was then degassed with a water pump and flushed several times with hydrogen before leaving to stir vigorously under a hydrogen atmosphere ($H_2$ filled balloon). The reaction was monitored by t.l.c. (silica; methylene chloride/methanol 9:1) and after all the starting material had been consumed (4-12 hrs.) the Ra-Ni was filtered off and the solvent removed *in vacuo*. Methanol was added and evaporated off several times to remove any remaining boric acid as the volatile trimethyl borate ester. The crude material was then purified by preparative t.l.c..

### 3.5.3.1 Raney Nickel Hydrogenolysis of 2-Isoxazoline (175)

This was carried out using the general procedure outlined above. After preparative t.l.c. 6-deoxy-7-alose (**178**) was isolated in 55% yield as a colourless glass (for characterisation see Section 3.5.2 and Tables 28 and 29). A colourless oil (visualised on t.l.c. by ninhydrin staining) was also isolated which was identified as an inseparable mixture of γ-amino alcohols *7-amino-8,12-anhydro-3-*O*-benzyl-6,7-dideoxy-1,2-*O*-isopropylidene-*α*-D-*glycero*-L-*galacto*-D-*gluco*-dodecofuranose* (**180**) and *.7-amino-8,12-anhydro-3-*O*-benzyl-6,7-dideoxy-1,2-*O*-isopropylidene-*α*-D-*glycero*-L-*talo*-D-*gluco*-dodecofuranose* (**181**); (18% combined yield); $\delta_C$ (50 MHz, $CD_3COCD_3$) - 48.2 ($C_7$ of (**180**)), 53.7 ($C_7$ of (**181**)); *m/z* (FAB) - 456.22336 ($M^+$+1, $C_{22}H_{34}O_9N$ requires 456.22334).

The yields of (**178**) and γ-amino alcohols (**180**) and (**181**) obtained from hydrogenolysis of (**175**) utilising the general procedure above and modifications thereof are shown in Table 27.

**Table 27** - Raney Nickel Hydrogenolysis of (**175**)

| Conditions | Reaction Time (hrs.) | Yield of β-Hydroxy Ketone (178) | Combined Yield of γ-Amino Alcohols (180) + (181) |
|---|---|---|---|
| General Procedure | 6 | 55% | 18% |
| $B(OH)_3$ (6 equiv.) Acetone (5 equiv.) | 12 | 51% | 16% |
| $B(OH)_3$ (12 equiv.) | 6 | 54% | 16% |

### 3.5.3.2 Raney Nickel Hydrogenolysis of 2-Isoxazoline (176)

This was carried out using the general procedure above. At the end of the reaction three product spots were observed on t.l.c., however, after work-up only two product spots were visible. After preparative t.l.c. a colourless glass was isolated which was identified as *8,12-anhydro-3-O-benzyl-6-deoxy-1,2-O-isopropylidene-α-D-manno-D-gluco-7-dodeco-1,4-furanosulose* (**182**); (56% yield); $\nu_{max}$ (film) 3355 $cm^{-1}$ (OH), 1717 $cm^{-1}$ (C=O); $\delta_H$ (360 MHz, $CD_3COCD_3$) see Tables 28 and 29; $\delta_C$ (50 MHz, $CD_3COCD_3$) - 206.9 ($C_7$), 137.5 (Ph quat.), 127.3, 126.8, 126.6 (5 x Ph CH), 110.2 (isopropyl. quat.), 104.2 ($C_1$), 83.4 ($C_8$), 81.6, 81.3, 80.5 ($C_2$, $C_3$, $C_4$), 72.9, 67.7 (x 2) ($C_9$, $C_{10}$, $C_{11}$), 70.8 (Ph$CH_2$), 68.7 ($C_{12}$), 63.0 ($C_5$), 43.1 ($C_6$), 25.3, 24.7 (2 x isopropyl. $CH_3$); *m/z* (FAB) - 457.2073 ($M^+$+3, $C_{22}H_{33}O_{10}$) requires 457.20735), 437.18116 (α-enone $M^+$+1, $C_{22}H_{29}O_9$ requires 437.18114).

A colourless oil (visualised on t.l.c. by ninhydrin staining) was also isolated which was identified as an inseparable mixture of γ-amino alcohols *7-amino-8,12-anhydro-3-O-benzyl-6,7-dideoxy-1,2-O-isopropylidene-α-D-glycero-D-talo-D-gluco-dodecofuranose* (**183**) and *.7-amino-8,12-anhydro-3-O-benzyl-6,7-dideoxy-1,2-O-isopropylidene-α-D-glycero-D-galacto-D-gluco-dodecofuranose* (**184**);(14% yield); *m/z* (FAB) - 456.22336 ($M^+$+1, $C_{22}H_{34}O_9N_1$ requires 456.22334).

### 3.5.3.3 Raney Nickel Hydrogenolysis of 2-Isoxazoline (177)

This was carried out using the general procedure outlined above. After preparative t.l.c. a colourless glass was isolated which was identified as *8,12-anhydro-3-O-benzyl-6-deoxy-1,2-O-isopropylidene-α-D-glycero-L-manno-D-gluco-7-trideco-1,4-furanosulose* (**185**); (43% yield); $\nu_{max}$ (film) - 3385 $cm^{-1}$ (OH), 1710 $cm^{-1}$ (C=O); $\delta_H$ (360 MHz, $CD_3COCD_3$) - see Tables 28 and 29; $\delta_C$ (50 MHz, $CD_3COCD_3$) - 206.8 ($C_7$), 137.6 (Ph quat.), 127.4, 126.8, 126.6 (5 x Ph CH), 110.2 (isopropyl. quat.), 104.2 ($C_1$), 83.3 ($C_8$), 81.7, 81.4, 80.5 ($C_2$, $C_3$, $C_4$), 78.4, 73.9, 68.4, 68.0 ($C_9$, $C_{10}$, $C_{11}$, $C_{12}$), 70.8 (Ph$CH_2$), 63.2 ($C_5$), 60.9 ($C_{13}$), 43.4 ($C_6$), 25.4, 24.7 (2 x isopropyl. $CH_3$); *m/z* (FAB) - 485.202274 ($M^+$+1, $C_{23}H_{33}O_{11}$ requires 485.20227), 467.19173 (α-enone $M^+$+1, $C_{23}H_{31}O_{10}$ requires 467.19170).

A colourless oil (visualised on t.l.c. by ninhydrin staining) was also isolated which was identified as an inseparable mixture of γ-amino alcohols *7-amino-8,12-anhydro-3-O-benzyl-6,7-dideoxy-1,2-O-isopropylidene-α-D-threo-L-talo-D-gluco-dodecofuranose* (**186**) and *.7-amino-8,12-anhydro-3-O-benzyl-6,7-dideoxy-1,2-O-isopropylidene-α-D-threo-L-galacto-D-gluco-dodecofuranose* (**187**); (18% yield); *m/z* (FAB) - 486.23393 ($M^+$+1, $C_{23}H_{36}O_{10}N_1$ requires 486.23390).

**Table 28** - $^1H$ n.m.r. Chemical Shift Values for β-Hydroxy Ketones

| Resonance | $\delta_H$ (ppm) | | |
|---|---|---|---|
| | **(178)** | **(182)** | **(185)** |
| $H_1$ | 5.93 | 5.85 | 5.85 |
| $H_2$ | 4.76 | 4.74 | 4.74 |
| $H_3$ | 4.12 | 4.06 | 4.06 |
| $H_4$ | 4.11 | 4.01 | 4.00 |
| $H_5$ | 4.58 | 4.50 | 4.50 |
| $H_{6a}$ | 3.08 | 2.97 | 3.02 |
| $H_{6b}$ | 2.97 | 2.87 | 2.91 |
| $H_8$ | 3.81 | 3.60 | 3.66 |
| $H_9$ | 3.50 | 3.89 | 3.85 |
| $H_{10}$ | 3.43 | 3.58 | 3.54 |
| $H_{11}$ | 3.59 | 3.87 | 3.95 |
| $H_{12a}$ | 4.03 | 3.61 | 3.60 |
| $H_{12b}$ | 3.30 | 3.97 | - |
| $H_{13a}$ | - | - | 3.74 |
| $H_{13b}$ | - | - | 3.80 |
| Ph$CH_2$ | 4.73, 4.78 | 4.67, 4.76 | 4.67, 4.75 |
| Ph | 7.35-7.49 | 7.27-7.43 | 7.27-7.43 |
| Isoprop. $CH_3$ | 1.39, 1.54 | 1.28, 1.43 | 1.28, 1.43 |

**Table 29** - $^1$H n.m.r. Coupling Constants for β-Hydroxy Ketones

| Coupling | *J* (Hz) | | |
|---|---|---|---|
| | (178) | (182) | 185) |
| 1,2 | 3.8 | 3.8 | 3.8 |
| 2,3 | 0 | 0 | 0 |
| 3,4 | 3.3 | 3.0 | 3.0 |
| 4,5 | 7.8 | 8.7 | 8.9 |
| 5,6a | 3.4 | 3.0 | 3.2 |
| 5,6b | 8.8 | 9.0 | 9.0 |
| 6a,6b | 17.3 | 17.3 | 17.4 |
| 8,9 | 9.3 | 8.9 | 9.6 |
| 9,10 | 9.3 | 8.9 | 9.2 |
| 10,11 | 9.3 | 3.6 | 3.4 |
| 11,12a | 5.4 | 1.6 | 0.7 |
| 11,12b | 10.5 | 2.6 | - |
| 12a,12b | 11.0 | 12.1 | - |
| 12,13a | - | - | 5.1 |
| 12,13b | - | - | 6.7 |
| 13a,13b | - | - | 11.4 |
| Ph$CH_2$ | 11.8 | 11.7 | 11.7 |

### 3.5.4 Acetylation of γ-Amino Alcohols (180) and (181)

The inseparable mixture of γ-amino alcohols (**180**) and (**181**) (36 mg, 8 x $10^{-5}$ moles) was dissolved in dry pyridine (4 ml), and acetic anhydride (0.2 ml) and a catalytic amount of dimethylaminopyridine (DMAP) were added. The mixture was then stirred at room temperature for 16 hrs. The solution was concentrated *in vacuo* and the two major t.l.c. spots separated by preparative t.l.c. The fraction with higher $R_f$ value gave $\nu_{max}$ (film) - 3369 $cm^{-1}$ (OH), 1751 $cm^{-1}$ (ester C=O), 1674 $cm^{-1}$ and 1655 $cm^{-1}$ (amide C=O). The fraction with lower $R_f$ value gave $\nu_{max}$ (film) - 3427 $cm^{-1}$ (OH), 1750 $cm^{-1}$ (ester C=O), 1652 $cm^{-1}$ and 1636 $cm^{-1}$ (amide C=O). Both fractions decomposed readily so further characterisation was not possible.

## 3.6 Reduction of β-Hydroxy Ketones to 1,3-Diols

### 3.6.1 Reductions Using Sodium Borohydride

**General Procedure**[195]. A solution of $NaBH_4$ (0.4M equiv.) in water (2 ml) was added to an ice-cooled, stirred solution of the β-hydroxy ketone (80 mg, 1M equiv.) in an ethanol/water mixture (3:1, 4 ml). The resulting solution was stirred overnight while warming to room temperature. After removing the ethanol *in vacuo*, acetone (a few drops) was added to decompose any remaining reagent, and the solution concentrated. The ratio of diastereomers was measured by $^1H$ n.m.r. and the products purified by preparative t.l.c.

#### 3.6.1.1 Reduction of (178)

This was carried out using the general procedure outlined above to yield a 83:17 mixture of 1,3-diols in a combined yield of 76%. The major product, which was isolated as a colourless oil was identified as*8,12-anhydro-3-O-benzyl-6-deoxy-1,2-O-isopropylidene-α-D-*glycero-*L*-talo-*D*-gluco-*dodecofuranose* (**193**); $[\alpha]_D^{22}$:- 15.8° (c = 1.7, THF); $\delta_H$ (360 MHz), see Tables 30, 31 and 32; $\delta_C$ (50 MHz, $C_5D_5N$) - 137.9 (Ph quat.), 127.5, 126.8, 126.7 (5 x Ph CH), 110.5 (isopropyl. quat.), 104.6 ($C_1$), 83.4, 83.0, 81.9, 81.0, 79.3, 72.6, 72.4, 70.0, 68.3 ($C_2$, $C_3$, $C_4$, $C_5$, $C_7$, $C_8$, $C_9$, $C_{10}$. $C_{11}$), 71.3 (Ph$CH_2$), 70.2 ($C_{12}$), 35.7 ($C_6$), 25.9, 25.3 (2 x isopropyl. $CH_3$); *m/z* (FAB) - 457.20736 ($M^+$+1, $C_{22}H_{33}O_{10}$ requires 457.20735). The minor isomer, which was isolated as a crystaline solid m.p. = 183-184 °C (from acetone) was identified as*8,12-anhydro-3-O-benzyl-6-deoxy-1,2-O-isopropylidene-α-D-*glycero-*L*-galacto-*D*-gluco-*dodecofuranose* (**194**); $[\alpha]_D^{23}$:- 15.4° (c=0.28, THF); $\delta_H$ (360 MHz) see Tables 30, 31 and 32; $\delta_C$ (50 MHz, $C_5D_5N$) - 138.1 (Ph quat.), 128.1, 127.5, 127.3 (5 x Ph CH), 111.1 (isopropyl. quat.), 105.0 ($C_1$), 83.9, 83.5, 82.2, 81.7, 79.4, 70.4, 65.2, 64.8 ($C_2$, $C_3$, $C_4$, $C_5$, $C_7$, $C_8$, $C_9$, $C_{10}$, $C_{11}$), 71.7 (Ph$CH_2$), 70.4 ($C_{12}$), 39.6 ($C_6$), 26.3, 25.7 (2 x isopropyl. $CH_3$); *m/z* (FAB) - 457.20736 ($M^+$+1, $C_{22}H_{33}O_{10}$ requires 457.20735).

### 3.6.1.2 Reduction of (182)

This was carried out using the general procedure outlined above to yield a 51:49 inseparable mixture of 1,3-diols in a combined yield of 48%. The major isomer was identified as *8,12-anhydro-3-O-benzyl-6-deoxy-1,2-O-isopropylidene-α-D*-glycero-*D*-galacto-*D*-gluco-*dodecofuranose* (**194**) and the minor isomer was identified as *8,12-anhydro-3-O-benzyl-6-deoxy-1,2-O-isopropylidene-α-D*-glycero-*D*-talo-*D*-gluco-*dodecofuranose* (**193**); $\delta_H$ (360 MHz) - see Tables 30, 31 and 32; *m/z* (FAB) - 457.2092 ($M^+$+1, $C_{22}H_{33}O_{10}$ requires 457.20735).

**Table 30** - $^1$H n.m.r. Chemical Shift Values for 1,3-Diols in $CD_3COCD_3$

| Resonance | $\delta_H$ (ppm) | | |
|---|---|---|---|
| | **7S (193)** | **7R (194)** | **7S (195)** |
| $H_1$ | 5.85 | 5.85 | 5.84 |
| $H_2$ | 4.71 | 4.73 | 4.70 |
| $H_3$ | 4.04 | 4.08 | 4.05 |
| $H_4$ | 3.93 | 3.98 | 3.95 |
| $H_5$ | 4.15* | 4.22* | 4.19* |
| $H_{6a}$ | ~2.05[a] | 2.10[a] | 1.99 |
| $H_{6b}$ | 1.62 | 1.47 | nd |
| $H_7$ | 4.15* | 4.22* | 4.33 |
| $H_8$ | 3.13 | 3.02 | 3.05 |
| $H_9$ | 3.34* | 3.55 | nd |
| $H_{10}$ | 3.34* | 3.29 | nd |
| $H_{11}$ | 3.45 | 3.45 | nd |
| $H_{12a}$ | 3.85 | 3.86 | nd |
| $H_{12b}$ | 3.13 | 3.15 | nd |
| $PhCH_2$ | 4.68, 4.75 | 4.67, 4.75 | 4.69, 4.75 |
| Ph | 72.6-7.42 | 7.28-7.43 | 7.26-7.43 |
| Isopropyl $CH_3$ | 1.28, 1.43 | 1.28, 1.42 | 1.28, 1.43 |

* - Second Order Multiplet  a - Obscured by Acetone Peak

nd - Not Determined

**Table 31** - $^1H$ n.m.r. Chemical Shift Values for 1,3-Diols in $C_5D_5N$

| Resonance | $\delta_H$ (ppm) | | |
|---|---|---|---|
| | 7S (193) | 7R (194) | 7S (195) |
| $H_1$ | 6.16 | 6.16 | 6.16 |
| $H_2$ | 4.87 | 4.87 | 4.86 |
| $H_3$ | 4.47 | 4.53 | 4.49 |
| $H_4$ | 4.53 | 4.63 | 4.56 |
| $H_5$ | 4.82 | 5.12 | 4.81 |
| $H_{6a}$ | 2.80 | 2.97 | 2.65 |
| $H_{6b}$ | 2.41 | 2.17 | 2.54 |
| $H_7$ | 4.93 | 5.28 | nd |
| $H_8$ | 3.83 | 3.66 | 3.68 |
| $H_9$ | 4.07 | 4.51 | 4.85 |
| $H_{10}$ | 4.09* | 4.13* | 4.08 |
| $H_{11}$ | 4.09* | 4.16* | 4.26 |
| $H_{12a}$ | 4.34 | 4.38 | 4.28 |
| $H_{12b}$ | 3.61 | 3.67 | 3.57 |
| $PhCH_2$ | 4.82 | 4.75, 4.80 | 4.83 |
| Ph | 7.24-7.52 | 7.22-7.57 | 7.24-7.52 |
| Isopropyl $CH_3$ | 1.33, 1.51 | 1.34, 1.53 | 1.33, 1.52 |

* - Second Order Multiplet

nd - Not Determined

**Table 32** - $^1$H n.m.r. Coupling Constants for 1,3-Diols

| Coupling | *J* (Hz) | | |
|---|---|---|---|
| | **7S (193)** | **7R (194)** | **7S (195)** |
| 1,2 | 3.7 | 3.8 | 3.8 |
| 2,3 | 0 | 0 | 0 |
| 3,4 | 2.8 | 3.1 | 2.8 |
| 4,5 | 8.7 | 8.7 | 8.9 |
| 5,6a | 2.4 | 2.1 | 2.9 |
| 5,6b | 10.0 | 10.1 | 8.9 |
| 6a,6b | 14.4 | 13.8 | 14.3 |
| 6a,7 | 2.4 | 11.3 | 5.5 |
| 6b,7 | 10.0 | 2.1 | 8.4 |
| 7,8 | 3.3 | 1.7 | 2.1 |
| 8,9 | 9.6 | 9.4 | 9.5 |
| 9,10 | 8.4 | 8.8 | 9.4 |
| 10,11 | 8.7 | nd | 3.4 |
| 11,12a | 5.0 | 4.7 | 1.8 |
| 11,12b | 10.2 | 10.6 | 1.8 |
| 12a,12b | 10.9 | 10.6 | 12.2 |
| PhC$H_2$ | 11.7[a] | 11.6 | 11.7[a] |

nd - Not determined
a - 0Hz in $C_5D_5N$

### 3.6.2 Reductions Using L-Selectride

**General Procedure**[196]. 1M L-selectride in THF (1 ml) was added to a solution of the β-hydroxy ketone (~ 80 mg, 0.18 mmols) in THF (10 ml) at -78°C under nitrogen. After stirring for 30 mins at -78°C and room temperature for 45 mins the mixture was cooled to 0°C and the reaction quenched by successive slow additions of water (0.2 ml), ethanol (0.7 ml), 3M sodium hydroxide (1 ml) and 30% hydrogen peroxide (0.7 ml). The aqueous layer was saturated with potassium carbonate and then extracted with 3:1 THF/ethyl acetate (3 x 5 ml). The organics were dried ($MgSO_4$) and concentrated *in vacuo*.

#### 3.6.2.1 Reduction of 6-Deoxy-7-ulose (178)

This was carried out using the general procedure outlined above to afford a mixture of 1,3-diols (**193**) and (**194**) in a ratio of 35:65 and in a combined yield of 79%.

#### 3.6.2.2 Reduction of 6-Deoxy-7-ulose (182)

This was carried out using the general procedure outlined above to afford an inseparable mixture of 1,3-diols (**195**) and (**196**) in a ratio 82:18 and a yield of 93%.

## 3.7 Deprotection to Dipyranose *C*-disaccharides

1,3-Diol (**194**) (25 mg, 5.5 x $10^{-5}$ moles) was dissolved in TFA (2.7 ml) and water (0.3 ml) and stirred at room temperature for 20 mins. The solvent was evaporated *in vacuo*, water added and evaporated several times to afford a colourless glass. This was identified as an anomeric mixture (α:β 38:62, combined yield 92%) of *8,12-anhydro-3-*O*-benzyl-6-deoxy-*α*–D*-glycero-*L*-galacto-*D*-gluco-dodeco-pyranose* (**199**) and *8,12-anhydro-3-*O*-benzyl-6-deoxy-*β*–D*-glycero-*L*-galacto-*D*-gluco-dodecopyranose* (**200**); $\delta_H$ (600 MHz, $D_2O$) see Table 33; *m/z* (FAB) 418.1839 ($M^+$+2, $C_{19}H_{30}O_{10}$ requires 418.18388).

**Table 33** - $^1$H n.m.r. Data for Dipyranose *C*-disaccharides

| | $\delta_H$ (ppm) | | | *J* (Hz) | |
|---|---|---|---|---|---|
| **Resonance** | **β (200)** | **α (199)** | **Coupling** | **β (200)** | **α (199)** |
| $H_1$ | 4.56 | 5.11 | 1,2 | 8.7 | 3.9 |
| $H_2$ | 3.26 | 3.55 | 2,3 | 9.3 | 9.8 |
| $H_3$ | 3.42 | 3.63 | 3,4 | 9.3 | 9.2 |
| $H_4$ | 3.44* | 3.22 | 4,5 | nd | 9.8 |
| $H_5$ | 3.46* | 3.88* | 5,6a | nd | nd |
| $H_{6a}$ | 1.46 | 1.46 | 5,6b | nd | nd |
| $H_{6b}$ | 2.14 | 2.16 | 6a,6b | nd | nd |
| $H_7$ | 4.05 | 4.01 | 6a,7 | 3.4 | 3.4 |
| $H_8$ | 3.09 | 3.07 | 6b,7 | 9.8 | 9.8 |
| $H_9$ | 3.45* | 3.45* | 7,8 | 0 | 0 |
| $H_{10}$ | 3.34 | 3.34 | 8,9 | 9.3 | 9.8 |
| $H_{11}$ | 3.50 | 3.50 | 9,10 | 9.3 | 9.3 |
| $H_{12a}$ | 3.88* | 3.88* | 10,11 | 9.3 | 9.3 |
| $H_{12b}$ | 3.15 | 3.15 | 11,12a | 5.9 | 5.9 |
| Ph$CH_2$ | 4.79 | 4.79 | 11,12b | 10.2 | 10.2 |
| Ph | 7.31-7.4 | 7.31-7.4 | 12a,12b | 10.7 | 10.9 |
| | | | Ph$CH_2$ | nd | nd |

nd - Not determined

* - Second Order Multiplet

**Appendix** (X-Ray Crystallography Data for (**153**))

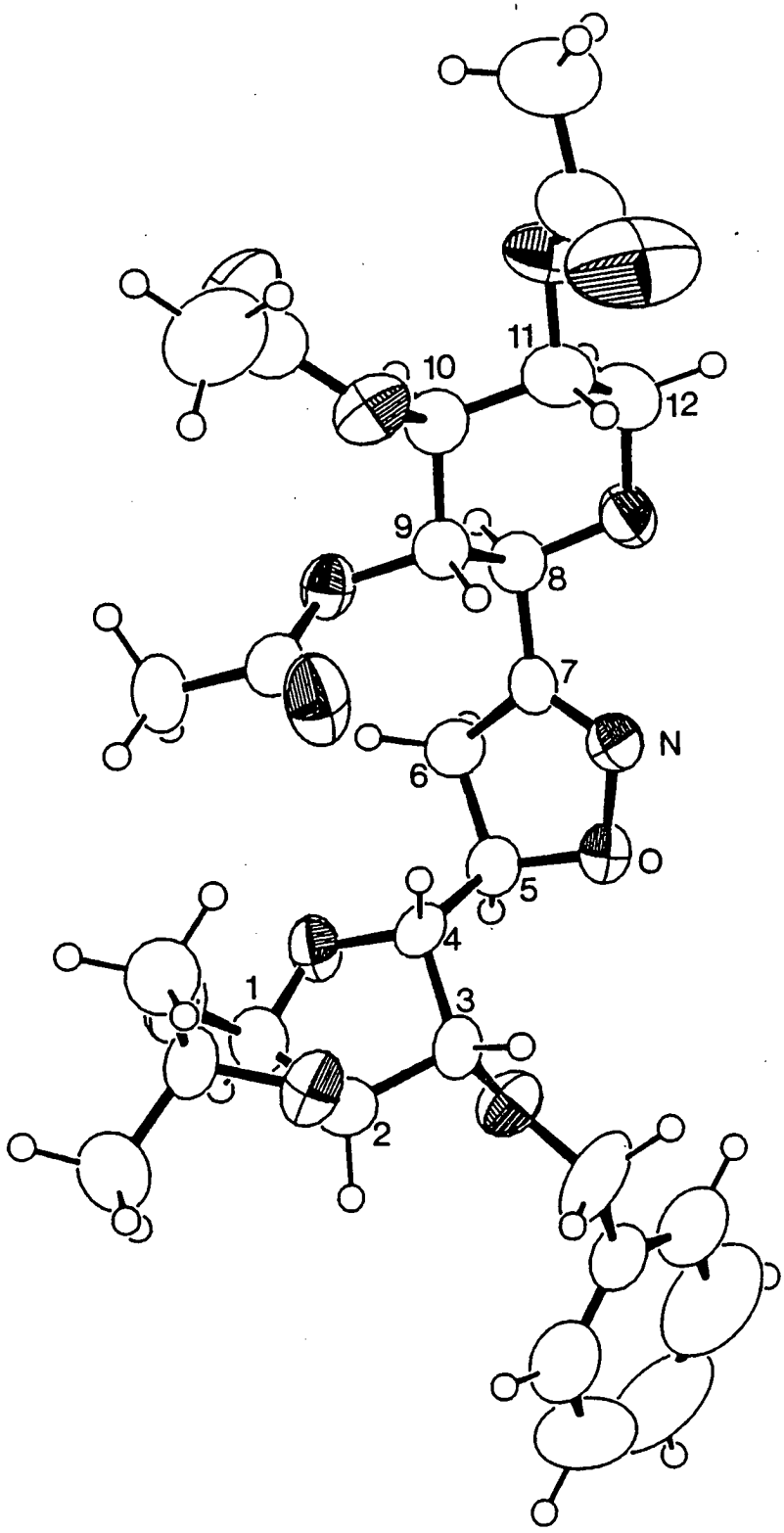


Table 1. Bond Lengths(Å) with standard deviations

| | | | |
|---|---|---|---|
| C(1) - C(2) | 1.533(10) | C(10) -O(101) | 1.443(11) |
| C(1) - O(4) | 1.401( 9) | C(11) -C(12) | 1.523(14) |
| C(1) - O(1) | 1.406( 9) | C(11) -O(111) | 1.438(12) |
| C(2) - C(3) | 1.522(12) | C(12) - O(8) | 1.427(12) |
| C(2) - O(2) | 1.411(11) | O(1) -C(01) | 1.434(12) |
| C(3) - C(4) | 1.500(11) | O(2) -C(01) | 1.418(11) |
| C(3) - O(3) | 1.428(10) | C(01) -C(02) | 1.544(14) |
| C(4) - O(4) | 1.459(10) | C(01) -C(03) | 1.514(14) |
| C(4) - C(5) | 1.504(11) | O(3) -C(31) | 1.404(14) |
| C(5) - C(6) | 1.521(11) | C(31) -C(32) | 1.481(14) |
| C(5) - O(5) | 1.456(10) | O(91) -C(91) | 1.372(11) |
| C(6) - C(7) | 1.510(11) | C(91) -O(92) | 1.176(12) |
| C(7) - N(7) | 1.261(11) | C(91) -C(92) | 1.468(13) |
| C(7) - C(8) | 1.505(12) | O(101)-C(101) | 1.342(12) |
| N(7) - O(5) | 1.429(10) | C(101)-O(102) | 1.192(13) |
| C(8) - C(9) | 1.537(12) | C(101)-C(102) | 1.486(16) |
| C(8) - O(8) | 1.427(11) | O(111)-C(111) | 1.354(14) |
| C(9) -C(10) | 1.530(12) | C(111)-O(112) | 1.176(16) |
| C(9) -O(91) | 1.436(10) | C(111)-C(112) | 1.439(17) |
| C(10) -C(11) | 1.498(13) | | |

Table 2. Angles(degrees) with standard deviations

| | | | |
|---|---|---|---|
| C(2) - C(1) - O(4) | 107.5( 6) | C(11) -C(10) -O(101) | 109.4( 7) |
| C(2) - C(1) - O(1) | 104.7( 6) | C(10) -C(11) -C(12) | 109.4( 8) |
| O(4) - C(1) - O(1) | 110.6( 6) | C(10) -C(11) -O(111) | 106.4( 7) |
| C(1) - C(2) - C(3) | 104.2( 6) | C(12) -C(11) -O(111) | 109.8( 8) |
| C(1) - C(2) - O(2) | 104.7( 6) | C(11) -C(12) - O(8) | 108.2( 8) |
| C(3) - C(2) - O(2) | 110.6( 7) | C(8) - O(8) -C(12) | 112.9( 7) |
| C(2) - C(3) - C(4) | 102.5( 6) | C(1) - O(1) -C(01) | 108.6( 6) |
| C(2) - C(3) - O(3) | 108.9( 6) | C(2) - O(2) -C(01) | 107.2( 7) |
| C(4) - C(3) - O(3) | 111.4( 6) | O(1) -C(01) - O(2) | 104.5( 7) |
| C(3) - C(4) - O(4) | 104.4( 6) | O(1) -C(01) -C(02) | 108.1( 7) |
| C(3) - C(4) - C(5) | 118.0( 7) | O(1) -C(01) -C(03) | 109.6( 8) |
| O(4) - C(4) - C(5) | 106.0( 6) | O(2) -C(01) -C(02) | 108.6( 7) |
| C(1) - O(4) - C(4) | 108.2( 6) | O(2) -C(01) -C(03) | 113.3( 8) |
| C(4) - C(5) - C(6) | 113.0( 7) | C(02) -C(01) -C(03) | 112.2( 8) |
| C(4) - C(5) - O(5) | 107.7( 6) | C(3) - O(3) -C(31) | 113.0( 7) |
| C(6) - C(5) - O(5) | 104.3( 6) | O(3) -C(31) -C(32) | 110.2( 9) |
| C(5) - C(6) - C(7) | 99.9( 6) | C(31) -C(32) -C(33) | 119.5( 8) |
| C(6) - C(7) - N(7) | 114.4( 7) | C(31) -C(32) -C(37) | 120.5( 8) |
| C(6) - C(7) - C(8) | 123.5( 7) | C(9) -O(91) -C(91) | 117.6( 7) |
| N(7) - C(7) - C(8) | 122.1( 7) | O(91) -C(91) -O(92) | 122.7( 8) |
| C(7) - N(7) - O(5) | 109.1( 7) | O(91) -C(91) -C(92) | 110.4( 7) |
| C(5) - O(5) - N(7) | 108.2( 6) | O(92) -C(91) -C(92) | 126.9( 9) |
| C(7) - C(8) - C(9) | 110.0( 7) | C(10) -O(101)-C(101) | 118.1( 7) |
| C(7) - C(8) - O(8) | 107.9( 7) | O(101)-C(101)-O(102) | 124.6( 9) |
| C(9) - C(8) - O(8) | 108.3( 7) | O(101)-C(101)-C(102) | 110.8( 9) |
| C(8) - C(9) -C(10) | 109.4( 7) | O(102)-C(101)-C(102) | 124.6(10) |
| C(8) - C(9) -O(91) | 108.3( 6) | C(11) -O(111)-C(111) | 117.7( 8) |
| C(10) - C(9) -O(91) | 108.5( 6) | O(111)-C(111)-O(112) | 122.0(11) |
| C(9) -C(10) -C(11) | 109.6( 7) | O(111)-C(111)-C(112) | 112.4(10) |
| C(9) -C(10) -O(101) | 108.4( 7) | O(112)-C(111)-C(112) | 125.4(12) |

Table 3. Non-H torsion angles(degrees) with standard deviations

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| O(4) | C(1) | C(2) | C(3) | -6.2( 8) | C(7) | C(8) | C(9) | -O(91) | -67.4( 8) |
| O(4) | C(1) | C(2) | O(2) | 109.9( 7) | O(8) | C(8) | C(9) | -C(10) | 56.9( 8) |
| O(1) | C(1) | C(2) | C(3) | -123.9( 6) | O(8) | C(8) | C(9) | -O(91) | 174.9( 6) |
| O(1) | C(1) | C(2) | O(2) | -7.8( 8) | C(7) | C(8) | O(8) | -C(12) | 177.6( 7) |
| C(2) | C(1) | O(4) | C(4) | -16.6( 7) | C(9) | C(8) | O(8) | -C(12) | -63.3( 9) |
| O(1) | C(1) | O(4) | C(4) | 97.2( 7) | C(8) | C(9) | -C(10) | -C(11) | -55.5( 9) |
| C(2) | C(1) | O(1) | -C(01) | -12.2( 8) | C(8) | C(9) | -C(10) | -O(101) | -174.9( 6) |
| O(4) | C(1) | O(1) | -C(01) | -127.8( 7) | O(91) | C(9) | -C(10) | -C(11) | -173.4( 7) |
| C(1) | C(2) | C(3) | C(4) | 25.5( 7) | O(91) | C(9) | -C(10) | -O(101) | 67.2( 8) |
| C(1) | C(2) | C(3) | O(3) | -92.6( 7) | C(8) | C(9) | -O(91) | -C(91) | 129.7( 7) |
| O(2) | C(2) | C(3) | C(4) | -86.5( 8) | C(10) | C(9) | -O(91) | -C(91) | -111.7( 8) |
| O(2) | C(2) | C(3) | O(3) | 155.5( 7) | C(9) | -C(10) | -C(11) | -C(12) | 56.9( 9) |
| C(1) | C(2) | O(2) | -C(01) | 25.1( 8) | C(9) | -C(10) | -C(11) | -O(111) | 175.4( 7) |
| C(3) | C(2) | O(2) | -C(01) | 136.8( 7) | O(101) | -C(10) | -C(11) | -C(12) | 175.6( 7) |
| C(2) | C(3) | C(4) | O(4) | -35.8( 7) | O(101) | -C(10) | -C(11) | -O(111) | -65.9( 9) |
| C(2) | C(3) | C(4) | C(5) | -153.1( 7) | C(9) | -C(10) | -O(101) | -C(101) | -120.5( 8) |
| O(3) | C(3) | C(4) | O(4) | 80.6( 7) | C(11) | -C(10) | -O(101) | -C(101) | 120.0( 8) |
| O(3) | C(3) | C(4) | C(5) | -36.8( 9) | C(10) | -C(11) | -C(12) | - O(8) | -59.9(10) |
| C(2) | C(3) | O(3) | -C(31) | -100.5( 9) | O(111) | -C(11) | -C(12) | - O(8) | -176.3( 7) |
| C(4) | C(3) | O(3) | -C(31) | 147.2( 8) | C(10) | -C(11) | -O(111) | -C(111) | 113.8( 9) |
| C(3) | C(4) | O(4) | C(1) | 33.5( 7) | C(12) | -C(11) | -O(111) | -C(111) | -128.0( 9) |
| C(5) | C(4) | O(4) | C(1) | 158.8( 6) | C(11) | -C(12) | - O(8) | - C(8) | 64.7( 9) |
| C(3) | C(4) | C(5) | C(6) | -173.6( 7) | C(1) | - O(1) | -C(01) | - O(2) | 27.8( 8) |
| C(3) | C(4) | C(5) | O(5) | -58.9( 9) | C(1) | - O(1) | -C(01) | -C(02) | 143.3( 7) |
| O(4) | C(4) | C(5) | C(6) | 69.9( 8) | C(1) | - O(1) | -C(01) | -C(03) | -94.0( 8) |
| O(4) | C(4) | C(5) | O(5) | -175.4( 6) | C(2) | - O(2) | -C(01) | - O(1) | -32.9( 9) |
| C(4) | C(5) | C(6) | C(7) | 97.8( 7) | C(2) | - O(2) | -C(01) | -C(02) | -148.1( 7) |
| O(5) | C(5) | C(6) | C(7) | -18.9( 7) | C(2) | - O(2) | -C(01) | -C(03) | 86.5( 9) |
| C(4) | C(5) | O(5) | N(7) | -100.5( 7) | C(3) | - O(3) | -C(31) | -C(32) | 162.3( 7) |
| C(6) | C(5) | O(5) | N(7) | 19.9( 8) | O(3) | -C(31) | -C(32) | -C(33) | -92.5(10) |
| C(5) | C(6) | C(7) | N(7) | 13.3( 9) | O(3) | -C(31) | -C(32) | -C(37) | 87.6(11) |
| C(5) | C(6) | C(7) | C(8) | -168.3( 7) | C(31) | -C(32) | -C(33) | -C(34) | -179.8( 8) |
| C(6) | C(7) | N(7) | O(5) | -1.4(10) | C(31) | -C(32) | -C(37) | -C(36) | 179.8( 8) |
| C(8) | C(7) | N(7) | O(5) | -179.8( 7) | C(9) | -O(91) | -C(91) | -O(92) | 2.5(12) |
| C(6) | C(7) | C(8) | C(9) | 90.2( 9) | C(9) | -O(91) | -C(91) | -C(92) | 179.7( 7) |
| C(6) | C(7) | C(8) | O(8) | -151.9( 7) | C(10) | -O(101) | -C(101) | -O(102) | -0.6(14) |
| N(7) | C(7) | C(8) | C(9) | -91.4( 9) | C(10) | -O(101) | -C(101) | -C(102) | -178.2( 8) |
| N(7) | C(7) | C(8) | O(8) | 26.5(11) | C(11) | -O(111) | -C(111) | -O(112) | 10.9(16) |
| C(7) | N(7) | O(5) | C(5) | -12.1( 9) | C(11) | -O(111) | -C(111) | -C(112) | -172.2( 9) |
| C(7) | C(8) | C(9) | -C(10) | 174.6( 7) | | | | | |

Table 4. H-atom torsion angles(degrees) with standard deviations

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| H(1) | C(1) | C(2) | H(2) | -7.8(11) | O(101) | C(10) | C(11) | H(11) | 55.7(11) |
| H(1) | C(1) | C(2) | C(3) | 114.2( 7) | H(10) | C(10) | O(101) | C(101) | 0.0(12) |
| H(1) | C(1) | C(2) | O(2) | -129.6( 7) | C(10) | C(11) | C(12) | H(12A) | -179.6(10) |
| O(4) | C(1) | C(2) | H(2) | -128.2( 9) | C(10) | C(11) | C(12) | H(12B) | 60.0(12) |
| O(1) | C(1) | C(2) | H(2) | 114.1( 9) | H(11) | C(11) | C(12) | H(12A) | -57.7(13) |
| H(1) | C(1) | O(4) | C(4) | -140.5( 6) | H(11) | C(11) | C(12) | H(12B) | -178.1(11) |
| H(1) | C(1) | O(1) | C(01) | 111.5( 7) | H(11) | C(11) | C(12) | O(8) | 62.0(11) |
| C(1) | C(2) | C(3) | H(3) | 148.0( 8) | O(111) | C(11) | C(12) | H(12A) | 64.0(12) |
| H(2) | C(2) | C(3) | H(3) | -86.6(11) | O(111) | C(11) | C(12) | H(12B) | -56.4(12) |
| H(2) | C(2) | C(3) | C(4) | 150.9( 8) | H(11) | C(11) | O(111) | C(111) | -8.0(13) |
| H(2) | C(2) | C(3) | O(3) | 32.9(10) | H(12A) | C(12) | O(8) | C(8) | -175.6( 9) |
| O(2) | C(2) | C(3) | H(3) | 36.0(11) | H(12B) | C(12) | O(8) | C(8) | -55.2(12) |
| H(2) | C(2) | O(2) | C(01) | -100.4( 9) | O(1) | C(01) | C(02) | H(02A) | 67.1(11) |
| C(2) | C(3) | C(4) | H(4) | 90.0( 8) | O(1) | C(01) | C(02) | H(02B) | -52.8(12) |
| H(3) | C(3) | C(4) | H(4) | -34.0(11) | O(1) | C(01) | C(02) | H(02C) | -172.9( 9) |
| H(3) | C(3) | C(4) | O(4) | -159.7( 8) | O(2) | C(01) | C(02) | H(02A) | -179.9( 9) |
| H(3) | C(3) | C(4) | C(5) | 82.9(10) | O(2) | C(01) | C(02) | H(02B) | 60.0(12) |
| O(3) | C(3) | C(4) | H(4) | -153.7( 8) | O(2) | C(01) | C(02) | H(02C) | -60.0(12) |
| H(3) | C(3) | O(3) | C(31) | 23.9(11) | C(03) | C(01) | C(02) | H(02A) | -53.9(12) |
| H(4) | C(4) | O(4) | C(1) | -84.3( 9) | C(03) | C(01) | C(02) | H(02B) | -173.9(10) |
| C(3) | C(4) | C(5) | H(5) | 65.3(10) | C(03) | C(01) | C(02) | H(02C) | 66.1(12) |
| H(4) | C(4) | C(5) | H(5) | -176.9( 9) | O(1) | C(01) | C(03) | H(03A) | 179.9(10) |
| H(4) | C(4) | C(5) | C(6) | -55.8( 9) | O(1) | C(01) | C(03) | H(03B) | 59.9(12) |
| H(4) | C(4) | C(5) | O(5) | 58.9( 9) | O(1) | C(01) | C(03) | H(03C) | -60.0(12) |
| O(4) | C(4) | C(5) | H(5) | -51.2( 9) | O(2) | C(01) | C(03) | H(03A) | 63.6(12) |
| C(4) | C(5) | C(6) | H(6A) | -20.6(11) | O(2) | C(01) | C(03) | H(03B) | -56.4(12) |
| C(4) | C(5) | C(6) | H(6B) | -143.8( 8) | O(2) | C(01) | C(03) | H(03C) | -176.4(10) |
| H(5) | C(5) | C(6) | H(6A) | 98.6(10) | C(02) | C(01) | C(03) | H(03A) | -59.8(12) |
| H(5) | C(5) | C(6) | H(6B) | -24.6(12) | C(02) | C(01) | C(03) | H(03B) | -179.8(10) |
| H(5) | C(5) | C(6) | C(7) | -143.0( 8) | C(02) | C(01) | C(03) | H(03C) | 60.2(12) |
| O(5) | C(5) | C(6) | H(6A) | -137.3( 8) | C(3) | O(3) | C(31) | H(31A) | -77.4(13) |
| O(5) | C(5) | C(6) | H(6B) | 99.5( 9) | C(3) | O(3) | C(31) | H(31B) | 42.3(14) |
| H(5) | C(5) | O(5) | N(7) | 140.6( 8) | H(31A) | C(31) | C(32) | C(33) | 147.3(11) |
| H(6A) | C(6) | C(7) | N(7) | 131.7( 9) | H(31A) | C(31) | C(32) | C(37) | -32.6(15) |
| H(6A) | C(6) | C(7) | C(8) | -49.8(11) | H(31B) | C(31) | C(32) | C(33) | 27.5(15) |
| H(6B) | C(6) | C(7) | N(7) | -105.1(10) | H(31B) | C(31) | C(32) | C(37) | -152.4(11) |
| H(6B) | C(6) | C(7) | C(8) | 73.3(11) | C(31) | C(32) | C(33) | H(33) | 0.2(13) |
| C(6) | C(7) | C(8) | H(8) | -30.2(12) | C(37) | C(32) | C(33) | H(33) | -180.0( 8) |
| N(7) | C(7) | C(8) | H(8) | 148.2( 9) | C(31) | C(32) | C(37) | H(37) | -0.1(13) |
| C(7) | C(8) | C(9) | H(9) | 53.9(10) | C(33) | C(32) | C(37) | H(37) | -179.9( 8) |
| H(8) | C(8) | C(9) | H(9) | 174.5( 9) | C(32) | C(33) | C(34) | H(34) | -179.9( 8) |
| H(8) | C(8) | C(9) | C(10) | -64.8(10) | H(33) | C(33) | C(34) | C(35) | 180.0( 8) |
| H(8) | C(8) | C(9) | O(91) | 53.3(10) | H(33) | C(33) | C(34) | H(34) | 0.0(13) |
| O(8) | C(8) | C(9) | H(9) | -63.8(10) | C(33) | C(34) | C(35) | H(35) | -180.0( 8) |
| H(8) | C(8) | O(8) | C(12) | 57.0(11) | H(34) | C(34) | C(35) | C(36) | 179.9( 8) |
| C(8) | C(9) | C(10) | H(10) | 64.5(10) | H(34) | C(34) | C(35) | H(35) | 0.0(13) |
| H(9) | C(9) | C(10) | H(10) | -174.8( 9) | C(34) | C(35) | C(36) | H(36) | 179.9( 8) |
| H(9) | C(9) | C(10) | C(11) | 65.2(10) | H(35) | C(35) | C(36) | C(37) | 179.9( 8) |
| H(9) | C(9) | C(10) | O(101) | -54.1(10) | H(35) | C(35) | C(36) | H(36) | -0.1(13) |
| O(91) | C(9) | C(10) | H(10) | -53.5(10) | C(35) | C(36) | C(37) | H(37) | 179.9( 8) |
| H(9) | C(9) | O(91) | C(91) | 9.0(11) | H(36) | C(36) | C(37) | C(32) | -179.9( 8) |
| C(9) | C(10) | C(11) | H(11) | -63.1(11) | H(36) | C(36) | C(37) | H(37) | 0.0(13) |
| H(10) | C(10) | C(11) | H(11) | 176.4(10) | O(91) | C(91) | C(92) | H(92A) | -180.0( 9) |
| H(10) | C(10) | C(11) | C(12) | -63.7(11) | O(91) | C(91) | C(92) | H(92B) | 60.0(12) |
| H(10) | C(10) | C(11) | O(111) | 54.8(10) | O(91) | C(91) | C(92) | H(92C) | -60.0(12) |

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O(92) -C(91) -C(92) -H(92A)  -3.0(15)
O(92) -C(91) -C(92) -H(92B)-122.9(12)
O(92) -C(91) -C(92) -H(92C) 117.1(12)
O(101)-C(101)-C(102)-H(102) 179.9(12)
O(101)-C(101)-C(102)-H(103)  59.9(15)
O(101)-C(101)-C(102)-H(104) -60.1(15)
O(102)-C(101)-C(102)-H(102)   2.4(18)
O(102)-C(101)-C(102)-H(103)-117.6(14)
O(102)-C(101)-C(102)-H(104) 122.4(14)
O(111)-C(111)-C(112)-H(112) 179.9(12)
O(111)-C(111)-C(112)-H(113)  59.9(15)
O(111)-C(111)-C(112)-H(114) -60.0(15)
O(112)-C(111)-C(112)-H(112)  -3.3(20)
O(112)-C(111)-C(112)-H(113)-123.3(15)
O(112)-C(111)-C(112)-H(114) 116.7(16)
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