The Nitrile Oxide/Isoxazoline Approach to Higher Sugars

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University of Edinburgh
1990

The chymists are a strange class of mortals
impelled by an almost insane impulse
to seek their pleasures amoung
smoke and vapour, soot and flame,
poisons and poverty,...

J.J. Brechner, Mainz, 1669.

Acknowledgements

I should like to thank Dr R.M. Paton, my supervisor during the course of this work, for the conception of the project and his advice and encouragement over the last three years. I am greatful to Dr I.H. Sadler and Dr D. Reed for n.m.r. advice and to Dr A.J. Blake and Dr R.O. Gould for the X-ray structure determinations. Thanks to Ken Penman who patiently proofread this thesis. Special thanks to Douglas Hutton who spent many hours helping me with the typing and presentation of this thesis. Finally I should like to extend my gratitude to all the other people, academic and technical staff and fellow students, who have helped me during my time in Edinburgh.

Post Graduate Lectures

The following lecture courses were attended during 1987-1990.

Departmental Seminars, three years attendance.

Free Radicals (Dr I. Gosney), 5 lectures.

Industrial Processes (various lecturers), 5 lectures.

Introduction to Management (various lecturers), 5 lectures.

Medicinal Chemistry (Prof. R. Baker and Dr P. Leeson, MSD), 10 lectures.

Recent Advances in Organic Chemistry (various lecturers), 10 lectures.

Departmental German course passed (1988).

Abstract

The application of nitrile oxide/isoxazoline chemistry towards the synthesis of higher sugars (monosaccharides containing seven or more contiguous carbon atoms) has been investigated. This convergent approach, involving the cycloaddition of sugar derived alkene and nitrile oxide fragments and subsequent manipulation of the resulting isoxazoline, has much of the product stereochemistry preselected. Three ω-unsaturated monosaccharides were chosen for study: the D-glucose-derived six carbon unit (**94**), its C-3 epimer (**102**) and a seven carbon alkene, (**97**), prepared from D-galactose. Benzonitrile oxide was employed in preliminary studies as a model 1,3-dipole to probe the π-facial selectivity of cycloaddition to these alkenes. Cycloadditions with the carbohydrate derived nitrile oxides (**117**), (**121**) and (**125**) were subsequently examined.

For alkenes (**94**) and (**97**) a high degree of stereoselectivity (typically *ca* 85:15) favouring the formation of the *erythro* 2-isoxazoline was obtained. This observation can be rationalised in terms of the "inside alkoxy effect" proposed by Houk in which the allylic oxygen occupies the *inside* position in the transition state. D-*Ribo*-alkene (**102**) proved to be an exception; cycloaddition with ethoxycarbonylformonitrile oxide (**117**) occurred with negligible stereoselectivity (51:49). This result demonstrates the role played by the homoallylic oxygen in determining the stereoselectivity.

Pd/C mediated reductive hydrolytic cleavage of the 2-isoxazolines unmasked the β-hydroxy ketone functionality of the deoxy-ulose derivatives. Subsequent reduction furnished a pair of separable diastereomeric 1,3-diols, whose stereochemistry was determined by examination of the ^{1}H n.m.r. spectra of the corresponding isopropylidene ketals. A series of deoxy -octose, -nonose, -decose, -dodecose and -tridecose monosaccharides have been thus prepared.

Finally, other aspects of isoxazoline chemistry have been investigated. The reduction of isoxazoline (**123**) by lithium aluminium hydride afforded the *syn*-γ-amino alcohol (**176**) as the only isolated product. *Trans* α-enones (**174**) and (**175**) were synthesised stereospecifically by dehydration of the corresponding β-hydroxy ketones.

Contents

1 Introduction

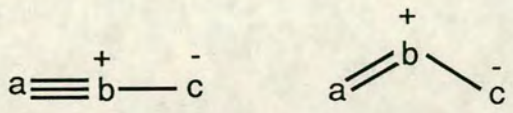
1.1 Foreword

This thesis is concerned with the nitrile oxide/isoxazoline approach to higher sugars. The introduction section addresses the background to these topics. The nitrile oxide/isoxazoline part is discussed first, then, after a brief introduction, other approaches to higher sugars will be described as there is no published review on this topic.

Examples of 1,3-dipoles have been known for over 100 years, but it was Huisgen[1] who, in 1958, first classified them as such and appreciated their great potential in synthesis. Thus, 1,3-dipolar cycloaddition has been transformed from a little known phenomenon into a major reaction type. It is now one of the most general methods for the synthesis of five-membered heterocycles and its versatility may be regarded as comparable to that of the Diels-Alder reaction. The field is now too large to be reviewed comprehensively here so, after a brief introduction to 1,3-dipoles, only nitrile oxides, the 1,3-dipole used in this work, will be discussed further. More information can be obtained in Padwa's two extensive volumes entitled "1,3-Dipolar Cycloaddition Chemistry"[2] and about nitrile oxides in particular from Grundman and Grünanger's text "The Nitrile Oxides"[3] and Torssell's more recent "Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis".[4]

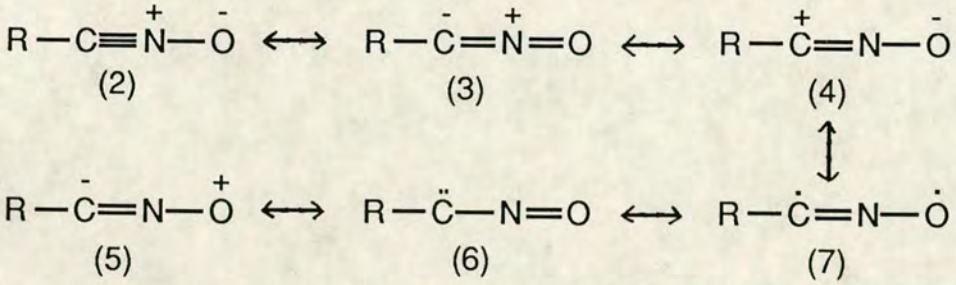
1.2 1,3-Dipoles

A system **a-b-c**, with four electrons in three π-orbitals, which can be represented by zwitterionic octet structures (**1**), and undergoes 1,3-cycloaddition ([3+2] cycloaddition) to dipolarophiles, is defined as a 1,3-dipole.[5]



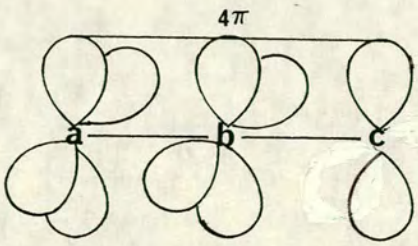
(1)

They may be regarded as heteroallyl anions since they are isoelectronic with the allyl anion; however, in contrast, the 1,3-dipole bears no net charge. The central atom (b) has a lone pair of electrons, which is said to confer "internal octet stabilisation" on the species. The true structure of the 1,3-dipole is that of a hybrid of all the possible resonance forms, illustrated for a nitrile oxide in Scheme 1.



Scheme 1

These include the full octet structures (**2**) and (**3**), which most likely represent the ground state electron distribution; the sextet structures (**4**) and (**5**), which best symbolise the 1,3-dipolar character; the carbene form (**6**) and the diradical species (**7**) about which there has been much debate (see section 1.3.1). The octet and sextet structures illustrate that the 1,3-dipoles are ambivalent nucleophiles and electrophiles (i.e. both termini can display both nucleophilic and electrophilic character). 1,3-Dipoles are subdivided into two classes: the *propargyl-allenyl type* (**8**), i.e. those containing an additional π-bond in the plane perpendicular to the heteroallyl anion molecular orbital, thus conferring a linear geometry upon the structure,[6] and the bent *allyl type* (**9**), which do not contain an additional bond.



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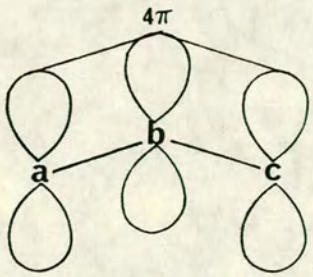


(9)

The most common 1,3-dipoles are shown in Table 1, represented in one of the full octet forms.

Propargyl-Allenyl Type

large Nitrilium Betaines		Diazonium Betaines	
$RC\equiv\overset{+}{N}\text{-}\overset{-}{C}R_2$	Nitrile Ylides	$N\equiv\overset{+}{N}\text{-}\overset{-}{C}R_2$	Diazoalkanes
$RC\equiv\overset{+}{N}\text{-}\overset{-}{N}R$	Nitrile Imines	$N\equiv\overset{+}{N}\text{-}\overset{-}{N}R$	Azides
$RC\equiv\overset{+}{N}\text{-}\overset{-}{O}$	Nitrile Oxides	$N\equiv\overset{+}{N}\text{-}\overset{-}{O}$	Nitrous Oxide
$RC\equiv\overset{+}{N}\text{-}\overset{-}{S}$	Nitrile Sulphides		

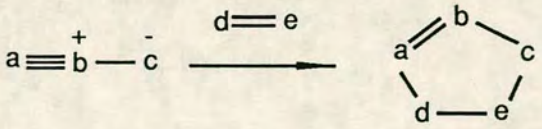
Allyl Type

Central Atom N		Central Atom O	
$R_2C{=}\overset{+}{N}R\text{-}\overset{-}{C}R_2$	Azomethine Ylides	$R_2C{=}\overset{+}{O}\text{-}\overset{-}{C}R_2$	Carbonyl Ylides
$R_2C{=}\overset{+}{N}R\text{-}\overset{-}{N}R$	Azomethine Imines	$R_2C{=}\overset{+}{O}\text{-}\overset{-}{N}R$	Carbonyl Imines
$R_2C{=}\overset{+}{N}R\text{-}\overset{-}{O}$	Nitrones	$R_2C{=}\overset{+}{O}\text{-}\overset{-}{O}$	Carbonyl Oxides
$RN{=}\overset{+}{N}R\text{-}\overset{-}{N}R$	Azimines	$RN{=}\overset{+}{O}\text{-}\overset{-}{N}R$	Nitrosimines
$RN{=}\overset{+}{N}R\text{-}\overset{-}{O}$	Azoxy Compounds	$RN{=}\overset{+}{O}\text{-}\overset{-}{O}$	Nitrosoxides
$O{=}\overset{+}{N}R\text{-}\overset{-}{O}$	Nitro Compounds	$O{=}\overset{+}{O}\text{-}\overset{-}{O}$	Ozone

Table 1.

1.3 1,3-Dipolar Cycloaddition

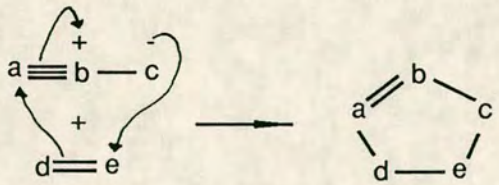
The most common reaction of 1,3-dipoles is their addition to a multiple bond system (a dipolarophile) to form a 5-membered heterocycle. This [3+2→5] cycloaddition has the π electronic description [π4s + π2s] as illustrated in Scheme 2.



Scheme 2

1.3.1 Reaction Mechanism

The mechanism of the 1,3-dipolar cycloaddition, which occurs with retention of alkene stereochemistry, has been the subject of much debate.[7] The more widely accepted view is that proposed by Huisgen,[8] which involves a concerted mechanism, and formation of the two new σ-bonds in one step as shown in Scheme 3.



Scheme 3

It is envisaged that the reactants approach each other in parallel planes to form a two plane orientation complex[9] as depicted in Figure 1. In order for the propargyl-allenyl type to achieve this arrangement, the orthogonal π-bond must break to allow bending to occur.

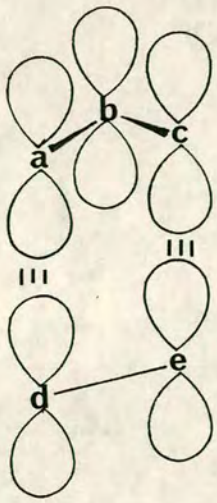
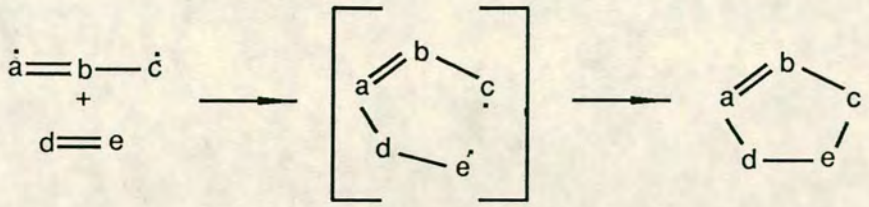


Figure 1.

The factors which favour the concerted mechanism[7] are: the conservation of alkene stereochemistry, the large negative $\Delta S^{\#}$ values obtained experimentally, and the very small effect that solvent polarity has on the rate of the cycloaddition reaction. Moreover, the 1,3-dipolar cycloaddition obeys the Woodward and Hoffmann selection rules for conservation of orbital symmetry[10] as would be expected for a concerted process. It should be noted that, although the reactions are concerted, the formation of the two new σ-bonds may not be perfectly synchronous. Due to the unsymmetrical nature of the reactants the formation of one bond may be more advanced than the other at a given point in the transition state. A 1,3-dipole is comparable to the Diels-Alder diene except that it has 4π electrons spread across 3 atoms not 4.

The alternative, less widely accepted, mechanism is that proposed, and defended, by Firestone.[11] He suggests a radical mechanism, involving the formation of a spin-paired diradical intermediate as shown in Scheme 4. Firestone explains the retention of stereochemistry by assuming that the activation energy for bond rotation at the intermediate stage is much greater than that for either the second bond formation to yield the product, or decomposition to reactants. Hence, if the intermediate is not generated in the correct conformation for ring closure it simply reverts to starting materials. The regioselectivity is explained by the reaction proceeding *via* the most stabilised diradical.



Scheme 4

1.3.2 Frontier Molecular Orbital Theory of 1,3-Dipolar Cycloadditions

Consideration of the Frontier Molecular Orbitals (FMO)[12] of the reactants offers a satisfactory explanation of the reactivity and regiochemistry of a concerted 1,3-dipolar cycloaddition.

When reactants approach each other, the occupied molecular orbitals of each interact with the unoccupied ones of the same symmetry of the other. The major interactions come from the FMO - the Highest Occupied Molecular Orbital (HOMO) and the Lowest Unoccupied Molecular Orbital (LUMO) of each.

The addition of the allyl anion to ethene is considered to be the prototype for 1,3-dipolar cycloaddition reactions.[9] The FMO interactions are shown in Figure 2.

The HOMO/LUMO interaction which gives the greatest stabilisation energy (ΔE) is the dominant one:[13] LUMO ethene/HOMO allyl anion in this case.

The allyl anion case is a very simple model since it is symmetrical. Removing the molecular symmetry by introducing heteroatoms and substituents alters the orbital coefficients (related to electronegativities), but the overall molecular orbital symmetry is retained; thus, the same selection rules apply.

Sustman[14] classified 1,3-dipolar cycloadditions into three types, based on the HOMO/LUMO interactions (Figure 3). Generally, electron-poor dipolarophiles favour type 1, and electron-rich dipolarophiles favour type 3 controlled reactions.

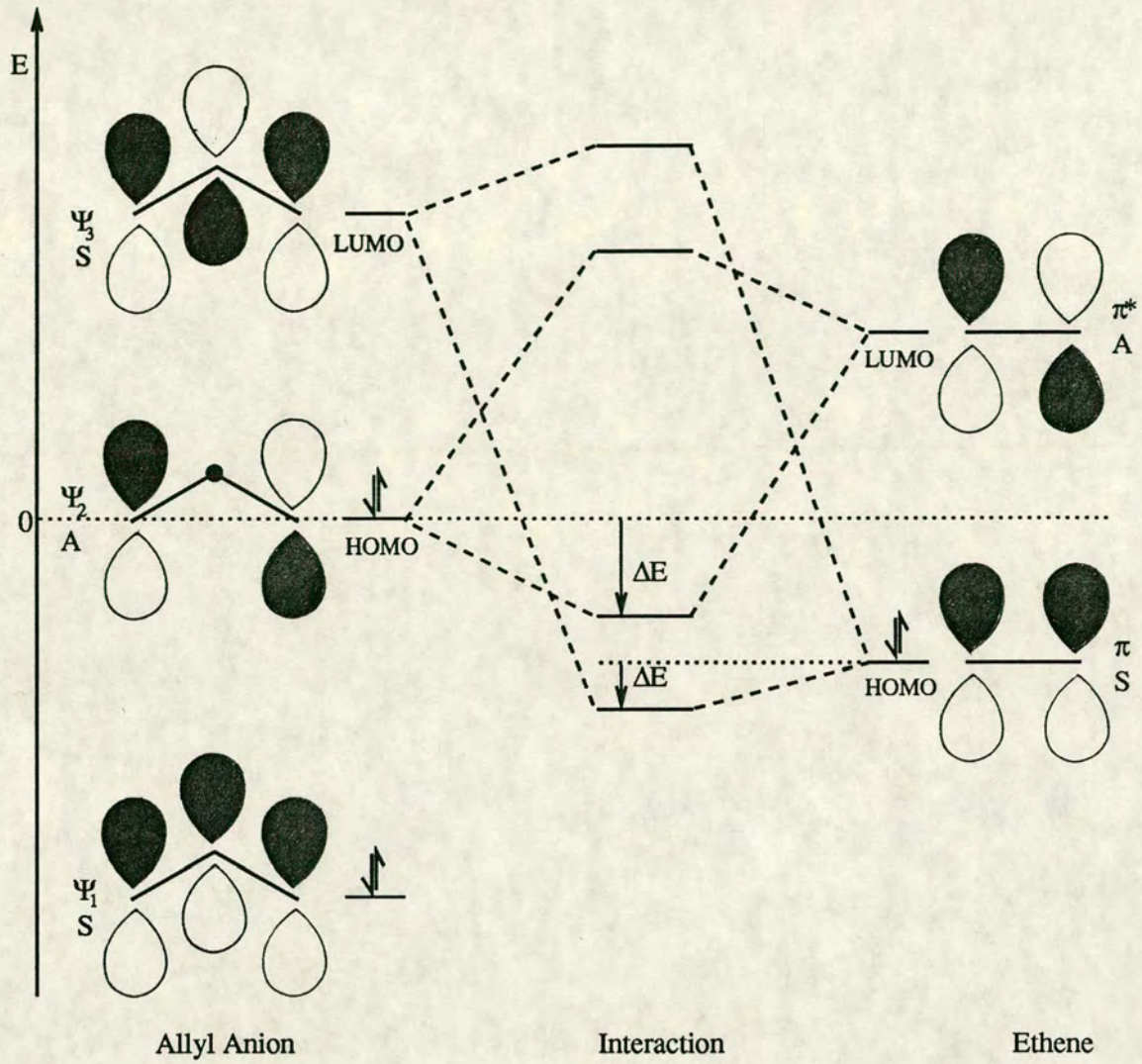
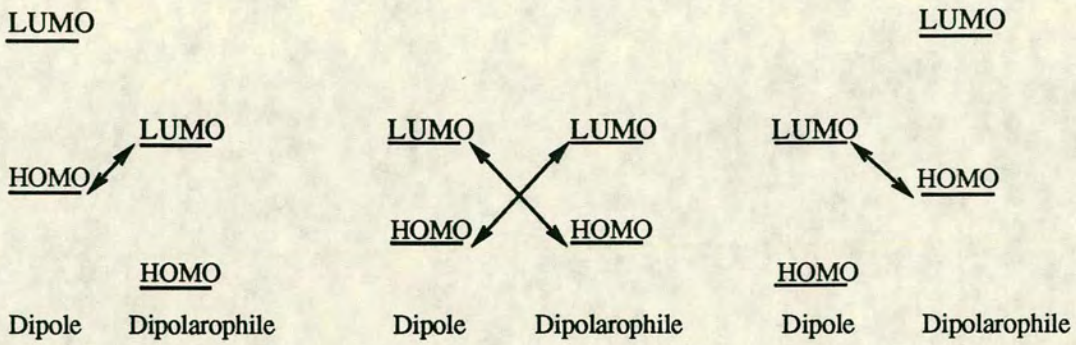


Figure 2.

The regioselectivity of the cycloaddition is often explained by invoking the rule[15] which says that the orientation is such that maximum orbital overlap is obtained. This is achieved by overlapping orbitals of the same relative size, i.e. large/large plus small/small overlap is better than 2× large/small overlap (Figure 4).

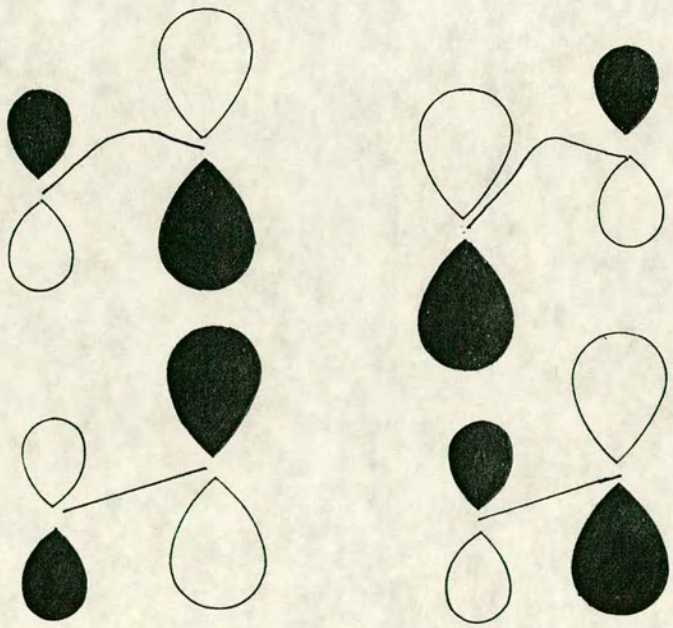


Type I
Dipole HOMO controlled
(nucleophilic dipole)

Type II
Dipole HOMO-LUMO controlled
(ambiphilic dipole)

Type III
Dipole LUMO controlled
(electrophilic dipole)

Figure 3.

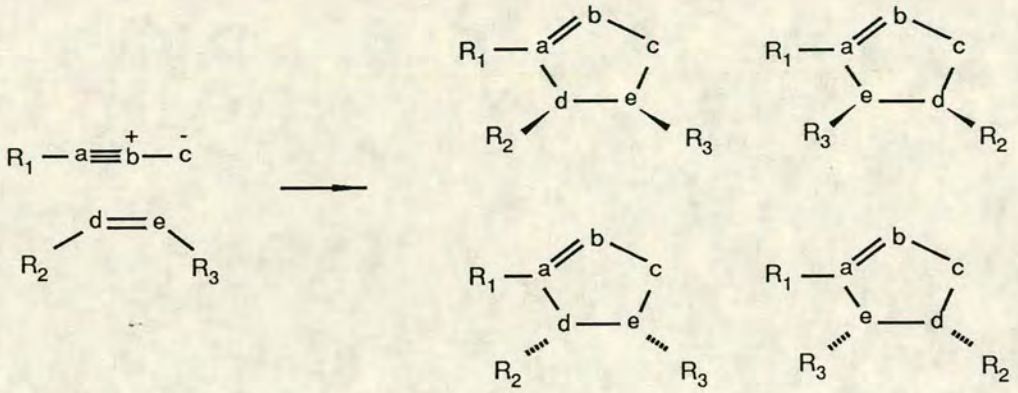


$$LL + SS > 2 \times LS$$

Figure 4.

1.3.3 Stereoselectivity

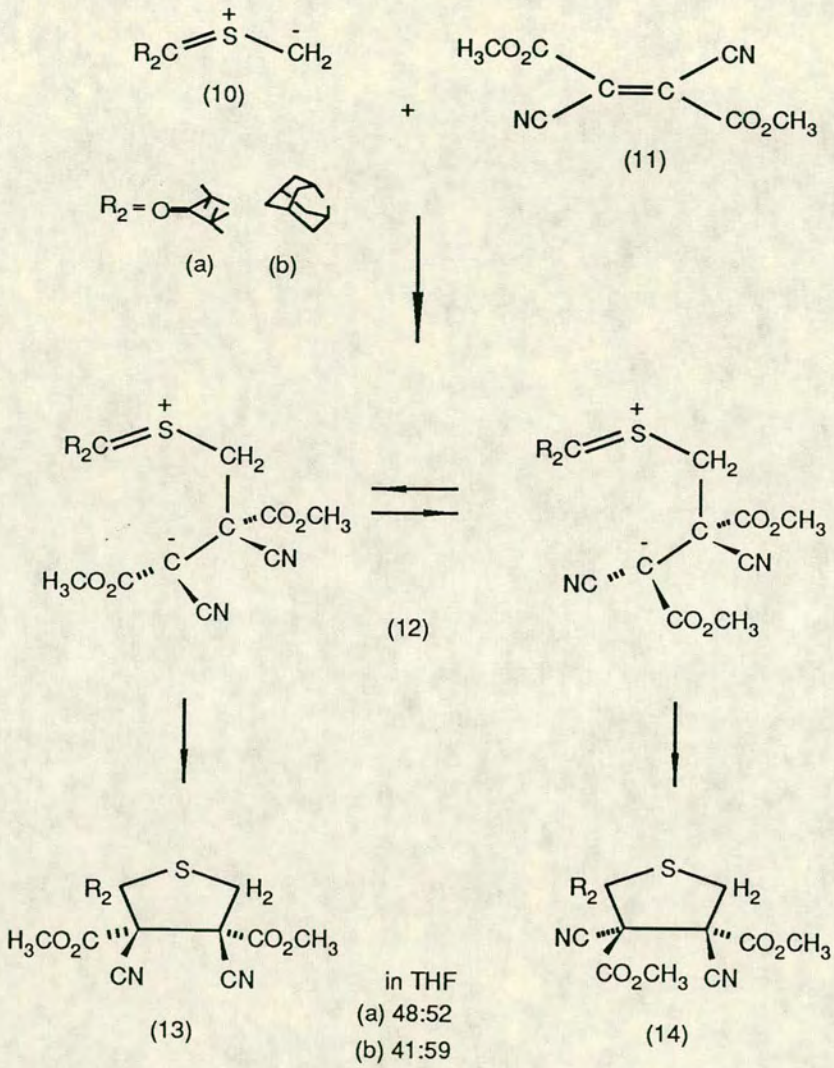
The dipole can approach the dipolarophile from two distinct faces; hence there are two possible stereoisomers for each regioisomer, as illustrated for a *cis*-1,2-disubstituted dipolarophile in Scheme 5. The experimentally obtained stereoselectivity in such cases can frequently be explained by approach of the dipole from the less sterically hindered face.[16]



Scheme 5

1.3.4 Stepwise 1,3-Dipolar Cycloaddition

Huisgen has recently found that under certain extreme conditions, a non-concerted, stepwise 1,3-dipolar cycloaddition may occur.[17] The reaction of thiocarbonyl ylide (**10**) with 2,3-dicyanofumarate (**11**) afforded the isomeric cycloadducts (**13**) and (**14**) (Scheme 6). Huisgen rationalises this observation by explaining that, since the reactants have very different FMO energies (those of the dipole very high, and those of the dipolarophile very low), the transition state will be dominated by one interaction, i.e. HOMO (dipole)-LUMO (dipolarophile). Hence, electron flow from dipole to dipolarophile results in the formation of one new bond generating a zwitterionic intermediate (**12**), which may undergo rotation before ring closure. The ratio of products changes with solvent polarity; this is consistent with a highly charged intermediate. It is also believed that steric factors may also play a role in favouring the stepwise route over the concerted one.

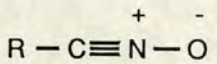


Scheme 6

1.4 Nitrile Oxides

Although formonitrile oxide and benzonitrile oxide had been generated in the 19^{th} century, little was known about nitrile oxides and there was much debate about their structure, before the one that is known today (**2**) was accepted.[18] The chemistry of nitrile oxides has only been investigated in depth since the mid 20^{th} century.

Nitrile oxides are a member of the propargyl-allenyl type of 1,3-dipoles and it is noteworthy that, in general, they contain two equivalent sets of 4π- electrons. This is not the case, however, for benzonitrile oxide since only one set can conjugate with the aromatic ring. They are isomeric with cyanates (**15**) and isocyanates (**16**).



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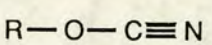

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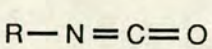


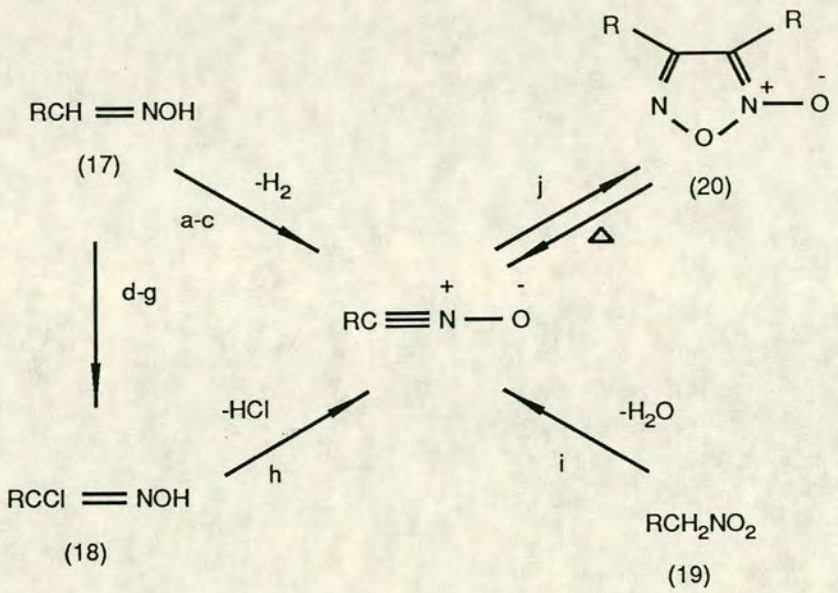
(16)

The majority of nitrile oxides have the functional group (-CNO) bonded to a carbon atom. Exceptions include formonitrile oxide (HCNO) and bromonitrile oxide (BrCNO). Formonitrile oxide, the parent of the series, is an unstable, explosive species. Its chemistry will not be dealt with here, but may be found by consulting the appropriate literature.[3]

1.4.1 Generation of Nitrile Oxides

Nitrile oxides are reactive species which are seldom isolated due to their tendency to dimerise (see later). More often they are generated *in situ*, either by dehydrogenation of the appropriate aldoxime (**17**),[19–21] dehydrochlorination of the hydroximoyl chloride (**18**), dehydration of a primary nitro compound (**19**),[22] or thermal cleavage of the furoxan-dimer (**20**),[23] The hydroximoyl chloride may be prepared by direct chlorination of the aldoxime using chlorine gas at low temperature,[24] but this is not satisfactory where functional groups which are reactive to chlorine are present. In such cases there are alternative, milder routes available which involve chlorination *in situ*.[25–27]

The generation of nitrile oxides is summarised in Scheme 7.

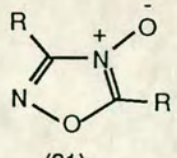


Scheme 7

(a) $NaOBr/OH^-$ (ref 19) (b) $Pb(OAc)_4$, -78°C (ref 20) (c) NCBT (ref 21) (d) Cl_2, -60°C (ref 24) (e) NCS (ref 25) (f) NOCl (ref 26) (g) chloramine-T (ref27) (h) Et_3N (i) PhNCO, Et_3N (ref 22) (j) (ref 23)

1.4.2 Reactions of Nitrile Oxides

Nitrile oxides are reactive species which undergo a range of reactions, [28] summarised in Scheme 8. Dimerisation to furoxans (**20**) (1,2,5-oxadiazole-2-oxides) is the characteristic nitrile oxide mode of decay in the absence of a dipolarophile. The furoxan is frequently obtained as a by-product in cycloaddition reactions. Under certain conditions, the isomeric dimers 1,2,4-oxadiazole-4-oxide (**21**) and 1,4,2,5-dioxadiazine (**22**) may be obtained.



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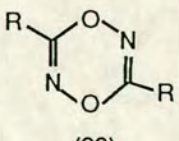
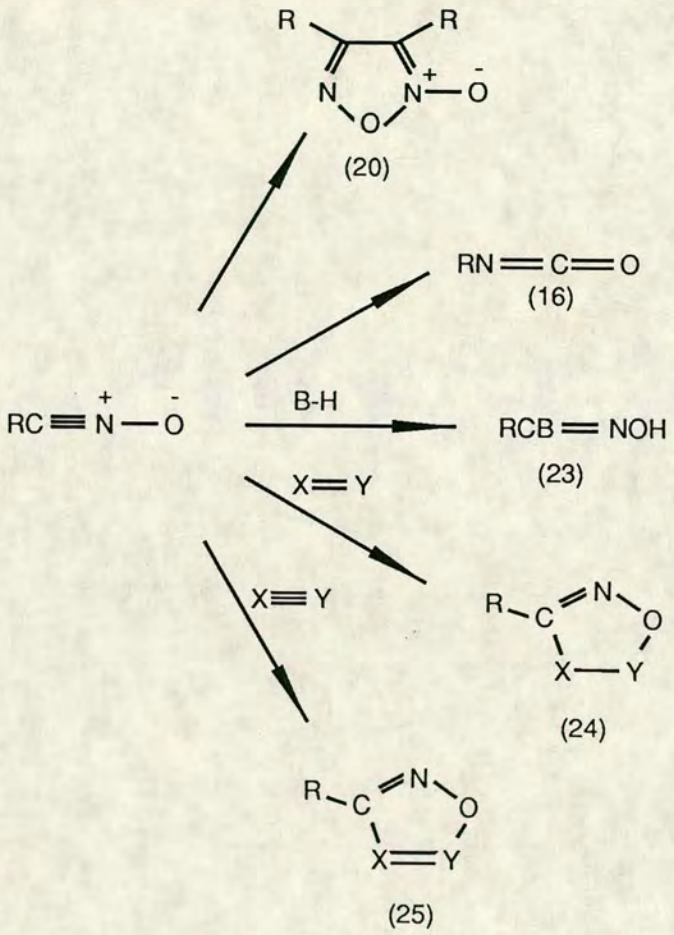


(22)

At temperatures in excess of 110°C thermal rearrangement to isocyanates (**16**) is observed, and with nucleophiles containing an acidic proton nitrile oxides undergo 1,3-addition to the corresponding substituted oxime (**23**). Probably the

most important of all the nitrile oxide reactions is 1,3-dipolar cycloaddition with dipolarophiles to yield a five-membered heterocycle (**24**), (**25**), containing the (-C=N-O-) moiety. Intramolecular nitrile oxide cycloadditions are a useful route to polycyclic compounds. The dipolarophile may be doubly bonded X=Y (e.g. C=C, C=S, C=O, C=N), or the less reactive triple bonded species X≡Y (e.g. C≡C, C≡N). It is the 1,3-dipolar cycloaddition of nitrile oxides to alkenes to form 2-isoxazolines (4,5-dihydroisoxazoles) which is of direct relevance to this work and this topic is discussed more fully in the next section.

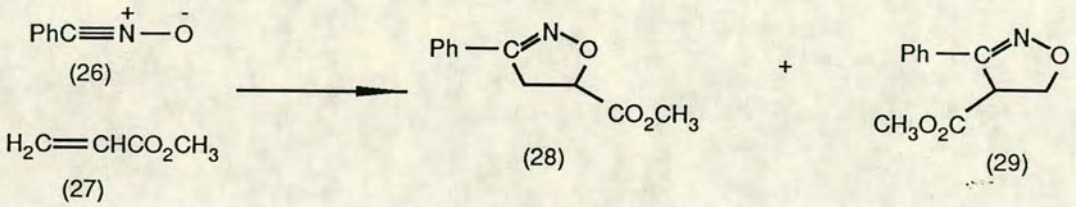


Scheme 8

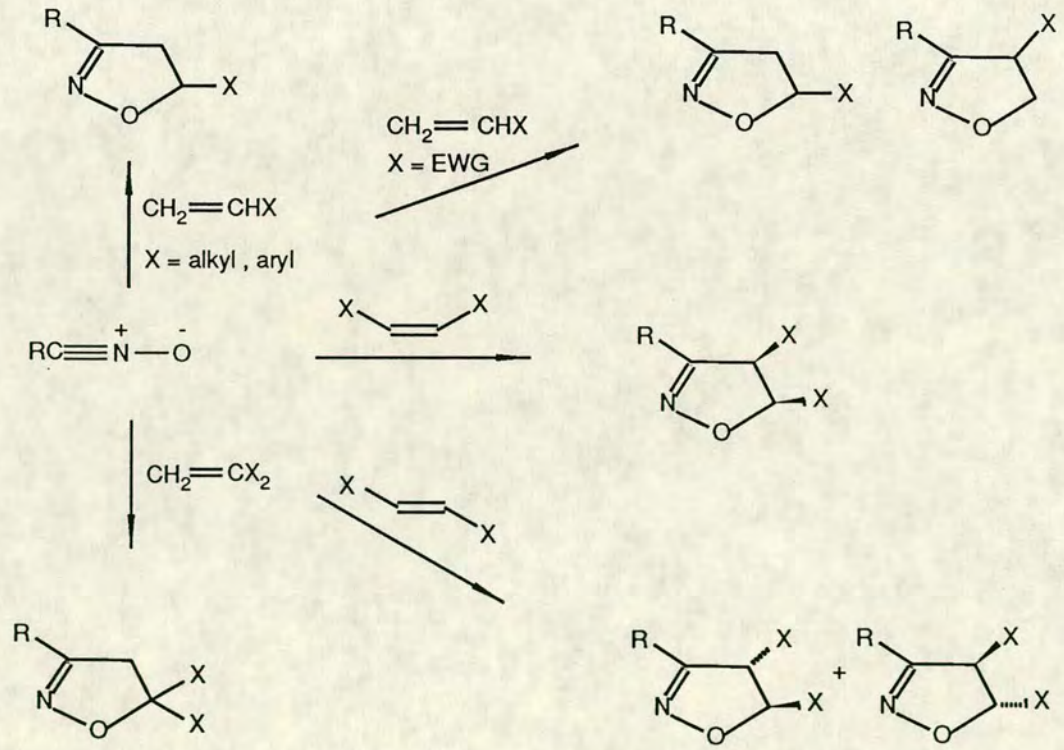
1.4.3 Nitrile Oxide Cycloaddition to Alkenes

The most general synthesis of 2-isoxazolines is *via* the 1,3-dipolar cycloaddition of nitrile oxides to alkenes. The reaction, which occurs with retention of alkene stereochemistry, is slower with highly substituted compounds, while the reac-

tivity of the dipolarophile is enhanced by conjugation. With monosubstituted alkenes the addition is almost completely regiospecific, and affords 5-substituted 2-isoxazolines. An exception occurs when the dipolarophile is very electron deficient, i.e. the substituent is a strongly electron withdrawing group. In such cases varying amounts of the 4-substituted 2-isoxazoline are obtained; this effect is increased by electron donating substituents on the dipole. In the cycloaddition of benzonitrile oxide (**26**) to methyl acrylate (**27**) the 5- and 4-substituted isoxazolines, (**28**) and (**29**) respectively, were obtained in the ratio[28] 96.4:3.6 (Scheme 9). Nitrile oxide 1,3-dipolar cycloaddition to alkenes is summarised in Scheme 10.



Scheme 9



Scheme 10

The regioselectivity can be explained[13] by considering the FMOs (Figure 5). Nitrile oxide cycloadditions to alkenes are Sustman type III (dipole LUMO controlled) for electron-rich and conjugated dipolarophiles. In the case of electron-poor dipolarophiles, however, the dipolarophile HOMO and LUMO energy levels are lowered such that dipole HOMO-dipolarophile LUMO interaction is no longer negligible and the situation is more that of a Sustman type II cycloaddition. This is especially the case where the dipole has electron donating substituents which raise dipole HOMO and LUMO energy levels. It should be noted that in intramolecular nitrile oxide cycloadditions steric constraints may necessitate the formation of the 4-substituted product.[29]

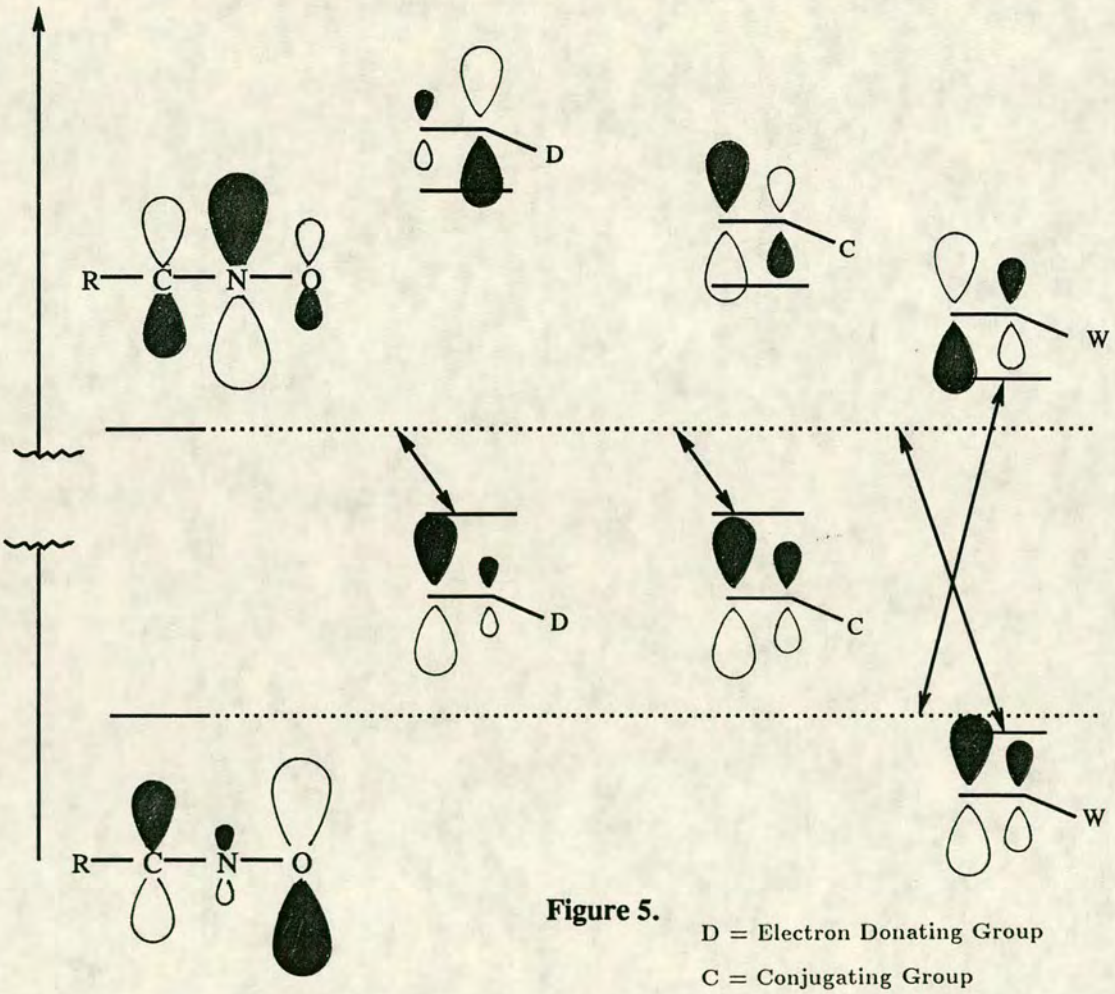


Figure 5.

D = Electron Donating Group

C = Conjugating Group

W = Electron Withdrawing Group

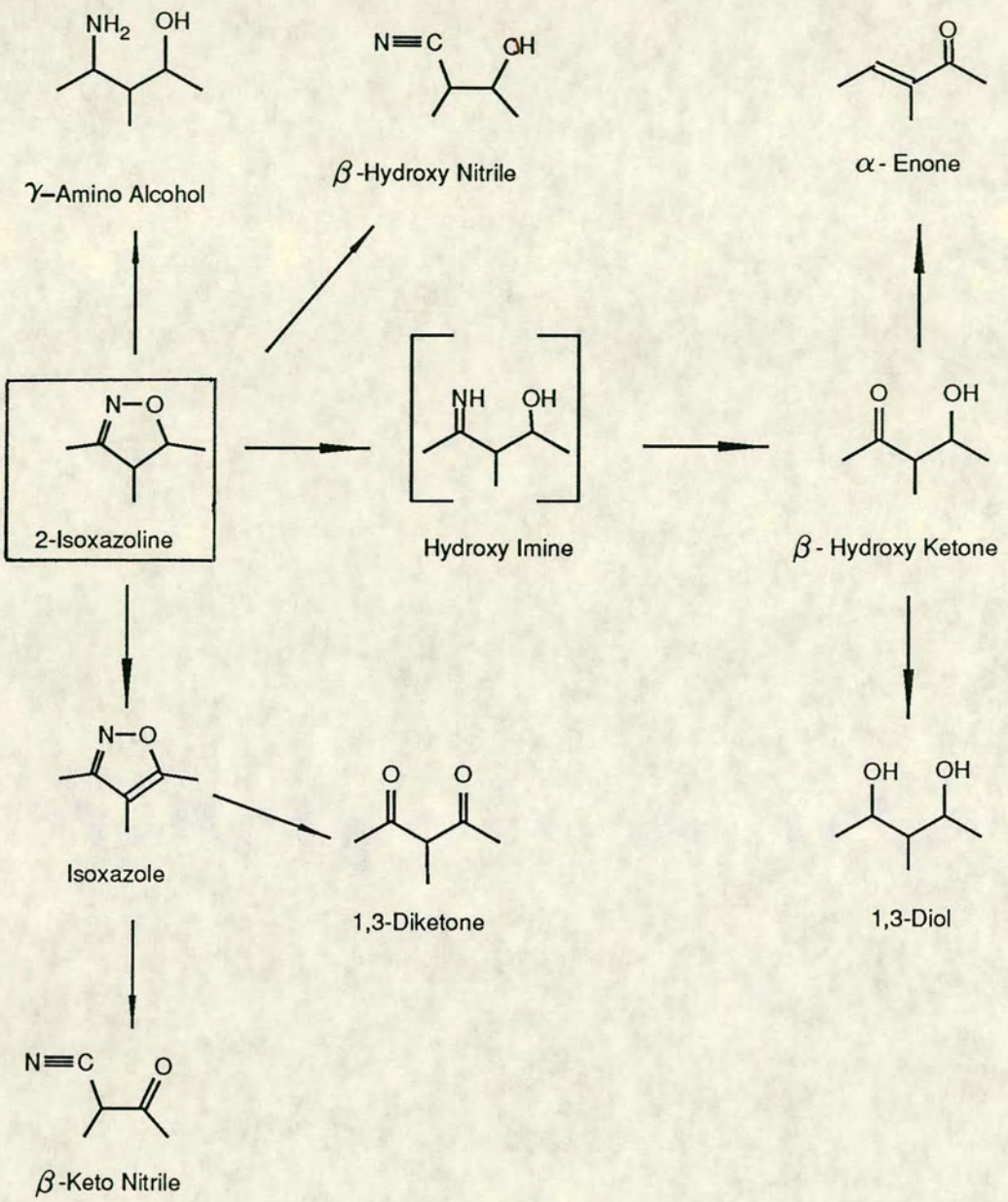
1.5 Applications of Nitrile oxide/Isoxazoline Chemistry in Synthesis

In the last 25 years 1,3-dipolar cycloaddition chemistry has been extensively investigated, and it is now acknowledged as being one of the most general methods for the synthesis of five-membered heterocyclic rings.[2] The application of these heterocycles as synthetic intermediates, however, is a more recent phenomenon.[30]

2-Isoxazolines have proved to be particularly useful in this respect, since they are readily prepared from easily accessible starting materials with predictable regio- and stereo-chemistry. Moreover, the 2-isoxazoline ring system is stable to a wide range of reaction conditions, allowing the side chains to be modified leaving the heterocycle intact but, when subjected to selective reagents which cleave the ring, a number of previously latent functionalities are obtained.[31,32] The range of products available from 2-isoxazolines is outlined in Scheme 11.

Dehydrogenation of the 2-isoxazoline (with e.g. potassium permanganate) provides a route to isoxazoles and hence to e.g. 1,3-diketones and β-keto nitriles. This is especially useful since cycloaddition is easier to the more readily available olefins than acetylenes. The β-hydroxy nitrile is obtained from an isoxazoline unsubstituted at the 3-position by treatment with sodium methoxide. Alternatively, saponification of an ester group to the free acid followed by heating results in a decarboxylative ring opening affording the same β-hydroxy nitrile. Lithium aluminium hydride mediated reduction of both the N-O and C=N bonds produces γ-amino alcohols. Work carried out by Jäger and co-workers[33] indicates fair to excellent diastereoselectivity, depending on the substituents on the isoxazoline.

One of the most noteworthy features of the isoxazoline is that it can be cleaved to a β-hydroxy ketone and hence to enone and 1,3-diol. This reaction, occurring *via* hydrogen addition across the N-O bond to the imine and subsequent hydrolysis, offers an alternative to the aldol reaction.[34] A range of conditions have been used, including catalytic hydrogenation with either Raney-nickel or palladium/charcoal in acidic conditions,[34] and ozonolysis.[35]



Scheme 11

The major difference between the cycloaddition and the classical aldol approach to β-hydroxy ketones is that a different carbon-carbon bond is formed during the reaction (Figure 6).

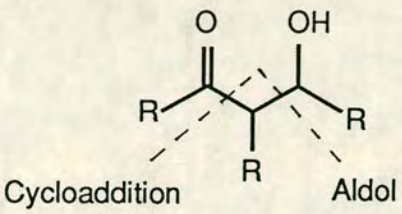
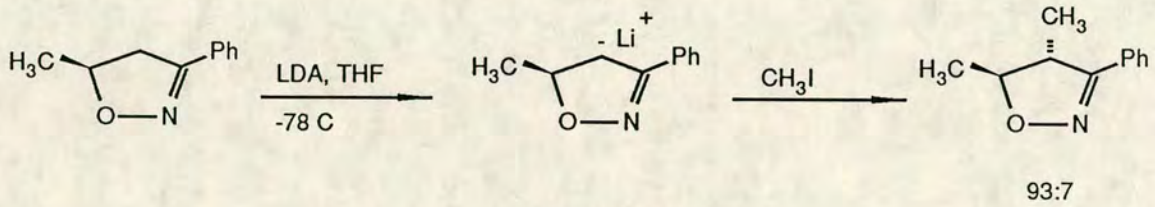


Figure 6.

The cycloaddition route offers several advantages: the traditional aldol problems, such as reversibility, selective enolate formation, cross- and self-aldol product mixtures, are avoided; functional groups sensitive to aldol conditions are usually tolerated, and better control of the *syn/anti* stereochemistry at C_2-C_3 is obtained since the olefin geometry is retained in the product (see Scheme 10).

The range of available products is further increased by selective substitution at the 4- position of the isoxazoline ring. Jäger has shown[36] that isoxazolines may be selectively deprotonated at this position and the resulting anion reacted with an electrophile to afford the 4-substituted product. The predominant approach of the incoming electrophile is *trans* to the existing 5-substituent, as illustrated in Scheme 12 for 4-methylation of 5-methyl-3-phenyl-isoxazoline.



Scheme 12

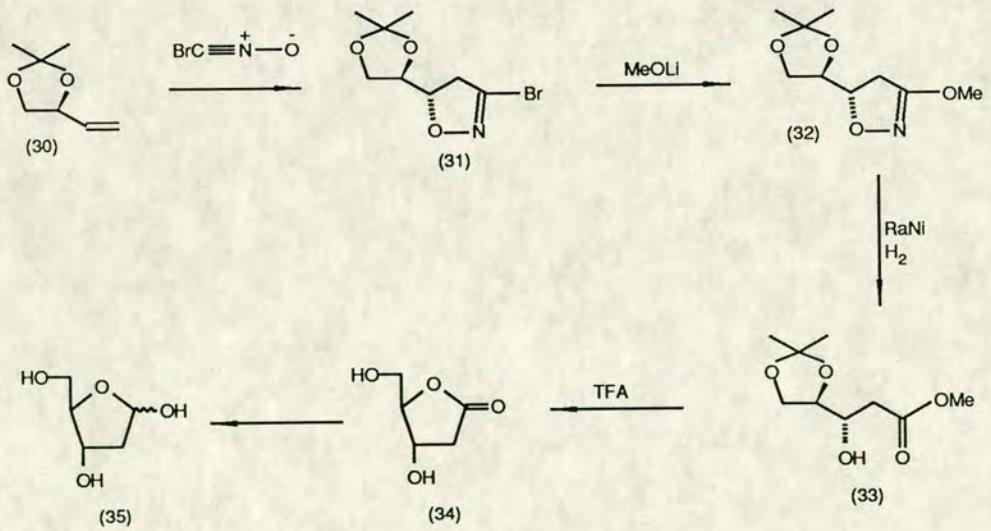
In summary, the isoxazoline route, which is based on three steps; cycloaddition, modification, and ring opening, is an excellent method for building polyfunctionalised structures by the combination of dipole and dipolarophile functionalities with those derived from unmasking the isoxazoline.

This methodology has been used in the synthesis of a vast range of natural products, a few examples of which will be illustrated in the next section.

1.5.1 Examples of Synthesis Using the Nitrile Oxide/Isoxazoline Approach

1.5.1.1 2-Deoxy-D-ribose

There have been several syntheses of 2-deoxy-D-ribose using nitrile oxide/isoxazoline methodology.[37–39] Scheme 13 illustrates one such example, by De Micheli and co-workers,[37] in which the key steps are the formation of a 3-bromoisoxazoline and its transformation into a β-hydroxy ester. The dipolarophile, (+)-(S)-isopropylidene-3-buten-1,2-diol (**30**), is prepared from 1,2-isopropylidlene-D-glyceraldehyde *via* a Wittig olefination. Cycloaddition with bromonitrile oxide, generated *in situ* by dehydrobromination of dibromoformaldoxime, afforded a diastereomeric mixture of isoxazolines in the ratio 86:14. The major cycloadduct (**31**), obtained in the pure form by chromatography, was refluxed in excess lithium methoxide to yield the 3-methoxy derivative (**32**). The hydroxy ester (**33**) was the product of hydrogenation-hydrolysis. It was transformed into the lactone (**34**), and subsequent reduction afforded 2-deoxy-D-ribose (**35**) in good overall yield. The cycloaddition step is particularly efficient (96%); this is attributed to the nitrile oxide being generated extremely slowly, hence the concentration is kept low and the competing dimerisation to furoxan is minimised. This technique is especially useful for unreactive dipolarophiles.

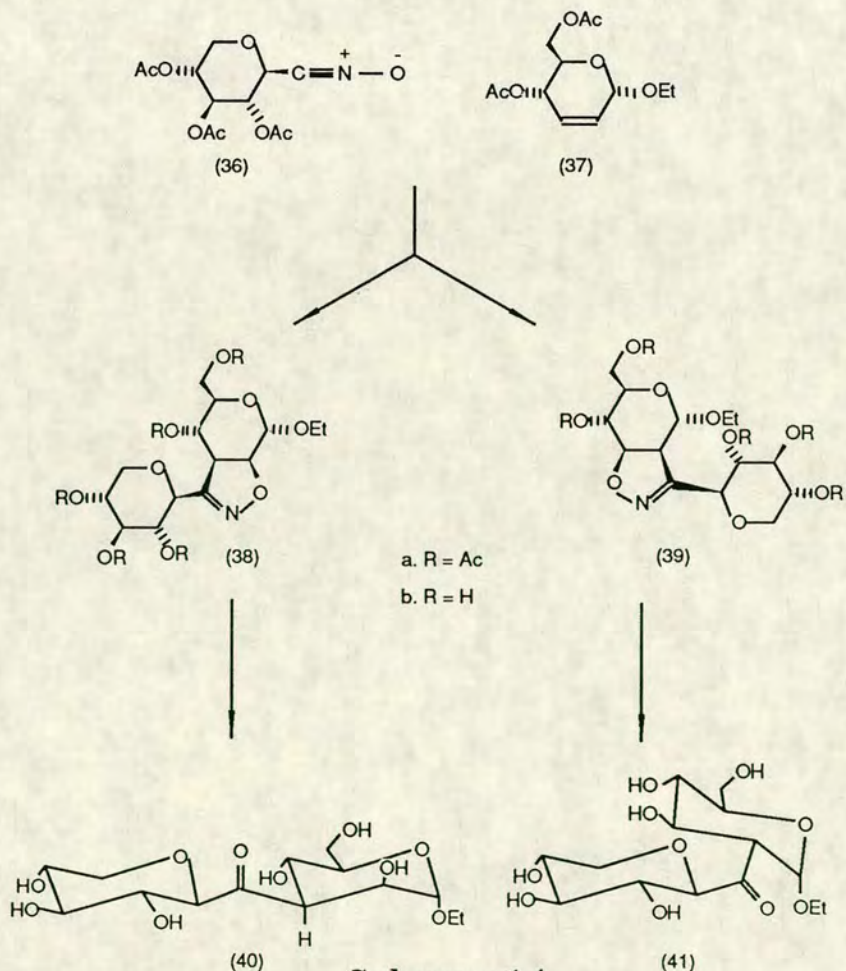


Scheme 13

1.5.1.2 C-Disaccharides

C-Disaccharides have been the subject of great interest due to their possible inhibitory action of enzymes such as glycosidase.

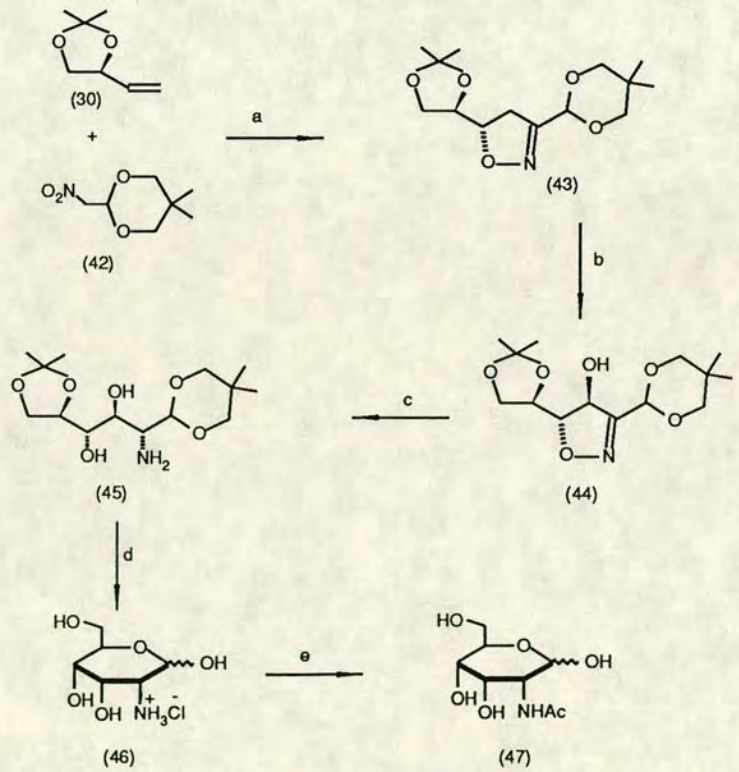
One route to such compounds which involves nitrile oxide/isoxazoline chemistry, reported by Paton[40] *et al*, is outlined in Scheme 14. Cycloaddition of β-D-xylose nitrile oxide (**36**) to the cyclic glucose-derived alkene (**37**) afforded the pair of regioisomers (**38**) and (**39**) in equimolar amounts. Thus the cycloaddition is face selective, attributed to attack from the less hindered face, but not regioselective. Deacetylation followed by hydrogenolysis-hydrolysis afforded the carbonyl derivatives (**40**) and (**41**). For isoxazoline (**38**) this occurred smoothly and the predicted product was obtained. The product from isoxazoline (**39**), however, shows complete epimerisation at C-2. This is believed to occur at either the intermediate imine step or in the final product itself. It probably occurs for energetic reasons to allow the bulky C-2 substituent to occupy the sterically less demanding equatorial position.



Scheme 14

1.5.1.2 D-Allosamine

Jäger and co-workers have conducted a detailed study of synthesis using the nitrile oxide/isoxazoline route,[33] and the formation of amino sugars in particular. These are of special interest on account of their potential biological activity.[41] This approach is illustrated in Scheme 15 for the synthesis of D-allosamine. Cycloaddition of nitroacetaldehyde derivative (**42**) with (+)-(S)-isopropylidlene-3-buten-1,3-diol (**30**) under Mukaiyama conditions afforded the *erythro* adduct (**43**) in preference over the *threo* isomer in a ratio of 78:22. The major cycloadduct was *trans* hydroxylated at the 4-position with excellent selectivity (> 95:5); none of the *cis* isomer was detected. Reduction of the resulting isoxazoline (**44**) with lithium aluminium hydride occurred stereoselectively yielding (**45**). This was attributed to the presence of the *syn* directing hydroxyl group in the 4-position. Hydrolysis of the ketal and acetal protecting groups afforded the hygroscopic ammonio-pyranose hydrochloride (**46**), which in turn, was *N*-acetylated to yield the product (**47**) in 31% overall yield.



Scheme 15

(a) PhNCO, Et_3N (b) LDA; $B(OR)_3$; H_2O_2/NH_3 (c) $LiAlH_4$ (d) 6N HCl (e) Ac_2O

1.6 Higher Carbon Sugars

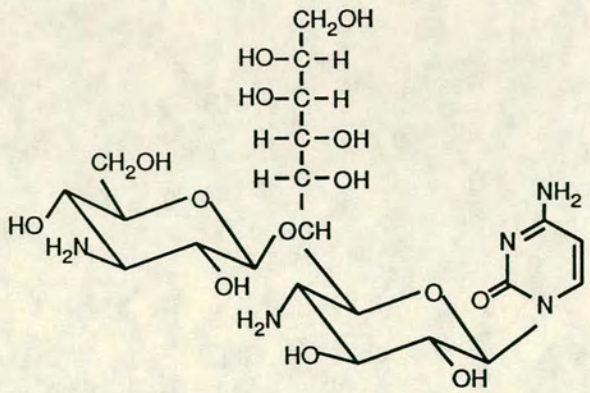
1.6.1 Introduction

A higher carbon sugar is a monosaccharide with seven or more consecutive carbon atoms i.e. heptoses, octoses, nonoses etc. They are seldom found in the free form but have been discovered as structural subunits of larger molecules with significant biological activity. Some examples are noted below.

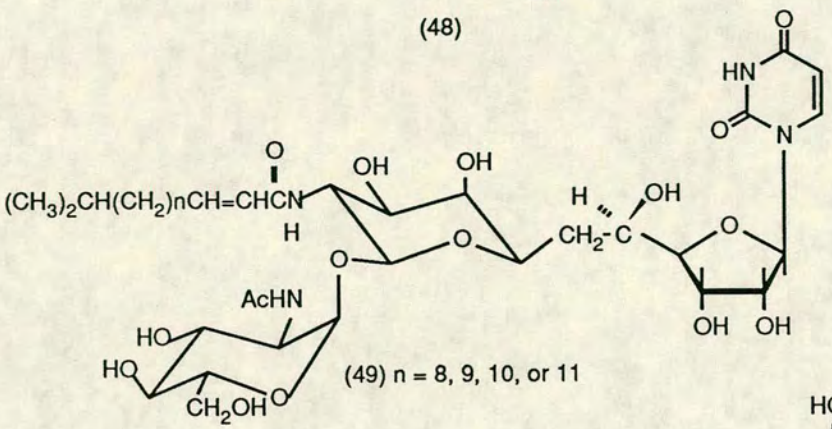
Hikizimycin (**48**), isolated from *Streptomyces longissimus*, contains an amino-undecose unit named hikosamine.[42] It is an anthelmintic agent and prevents protein synthesis by inhibiting the peptide bond forming step. The C_{11} dialdose unit tunicamine is found in the antiviral agent tunicamycin (**49**),[43] produced by *Streptomyces lysosuperificus*. It inhibits the biosynthesis of complex glycoconjugates. The mode of action is believed to involve inhibition of the enzyme UDP-galactose transferase. The D- and L-*glycero*-D-*manno*-heptoses[44](**50**) and (**51**) are found in many bacterial polysaccharides and their function is thought to be related to immunological reactions. Apramycin,[45] (**52**), a broad spectrum antibiotic obtained from a strain of *Streptomyces tenebrarius* contains an amino-octodialdose unit held in a rigid bicyclic system. The commercially important antibiotic lincomycin (**53**), isolated from *Streptomyces lincomycin*, contains the amino-octose unit lincosamine.[46]

Various ulosonic acids, e.g. KDO[47] (**54**) and neuraminic acids[48] such as NANA (**55**) also have important biological consequences and may be categorised under the broad definition of higher monosaccharides.

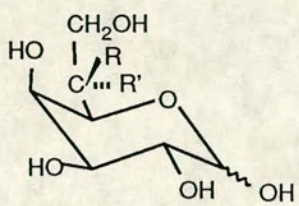
As a result of the discovery of these compounds and the realisation that such polyhydroxylated aldehydes are also useful chiral precursors for natural product synthesis,[49] there has been widespread interest in the preparative routes to higher carbon sugars. Their synthesis presents a challenging problem, involving the formation of carbon-carbon bonds and the creation of new chiral centres. It is of paramount importance that only reactions with predictable regio- and stereochemistry be employed lest mixtures of compounds be obtained and identification of the products becomes a formidable task.



(48)

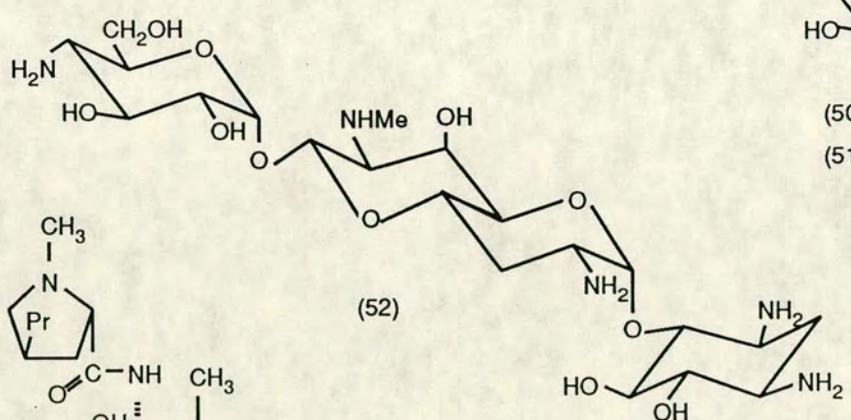


(49) n = 8, 9, 10, or 11



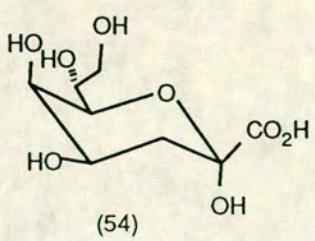
(50) R = OH, R' = H

(51) R = H, R' = OH

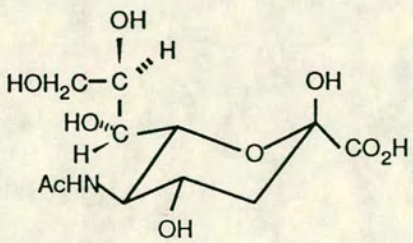


(52)

(53)



(54)



(55)

The classic approach for ascending the series is the Fischer-Kiliani cyanohydrin synthesis.[50] This iterative process involves the addition of hydrogen cyanide to the carbonyl bond followed by hydrolysis, lactonization and reduction to the new aldoses. This method is not very efficient for the synthesis of long chain sugars since each cycle produces diastereomers and only increases the length by one unit. Nitromethane[51] and diazomethane[52] have also been used as one-carbon nucleophiles for chain elongation.

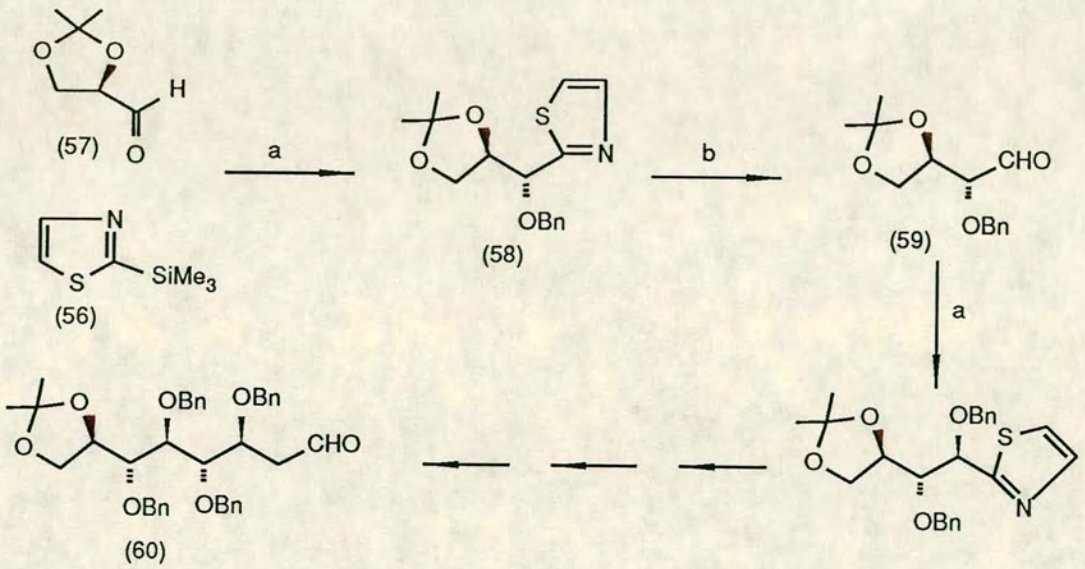
Recently a number of more efficient methods for the synthesis of higher carbon sugars has been reported. Some of these will be discussed in the following section.

1.6.2 The Synthesis of Higher Carbon Sugars

1.6.2.1 The Thiazole Route

Dondoni[53] and co-workers have established a method for the iterative, diastereoselective homologation of sugar aldehydes using 2-trimethylsilylthiazole (2-TST) (**56**) as a formyl anion equivalent. The synthesis, which results in the formation of higher sugars with *anti*-configuration of vicinal hydroxyl groups owes its success to two main steps: the diastereoselective addition of 2-TST to a chiral α-hydroxy aldehyde, and the conversion of the thiazole ring to the formyl group without racemisation. The process is illustrated in Scheme 16 for the elongation of 2,3-*O*-isopropylidlene-D-glyceraldehyde (**57**). Diastereofacial addition of 2-TST to the aldehyde followed by desilylation and subsequent benzylation afforded the (R, R)-thiazole (**58**) as a single diastereomer. The aldose (**59**) is obtained by a thiazole-formyl conversion which involves *N*-methylation to the thiazolium halide, reduction to the thiazolidene and subsequent metal assisted hydrolysis. This sequence has been shown to be equally efficient on the fifth cycle resulting in the octose derivative (**60**). The observed diastereoselectivity is consistent with the reaction proceeding *via* a Felkin-Anh type transition state[54] as shown in Figure 7.

This reaction sequence has been performed with good diastereoselectivity on other sugar α-hydroxy aldehydes.[54,55] Since the hydroxyl groups may be selectively protected, a whole array of carbohydrates are potentially available *via* this route by suitable functional group manipulation.



Scheme 16

(a)(i) CH_2Cl_2, 25°C (ii) THF/F^- (iii) NaH, BnBr, $^nBu_4NI$, THF, 25°C (b)(i) MeI, acetonitrile, reflux (ii) $NaBH_4$, MeOH, -10°C (iii) $HgCl_2$, acetonitrile/H_2O, 25°C

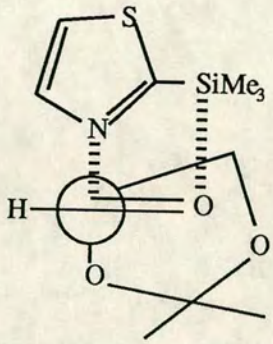


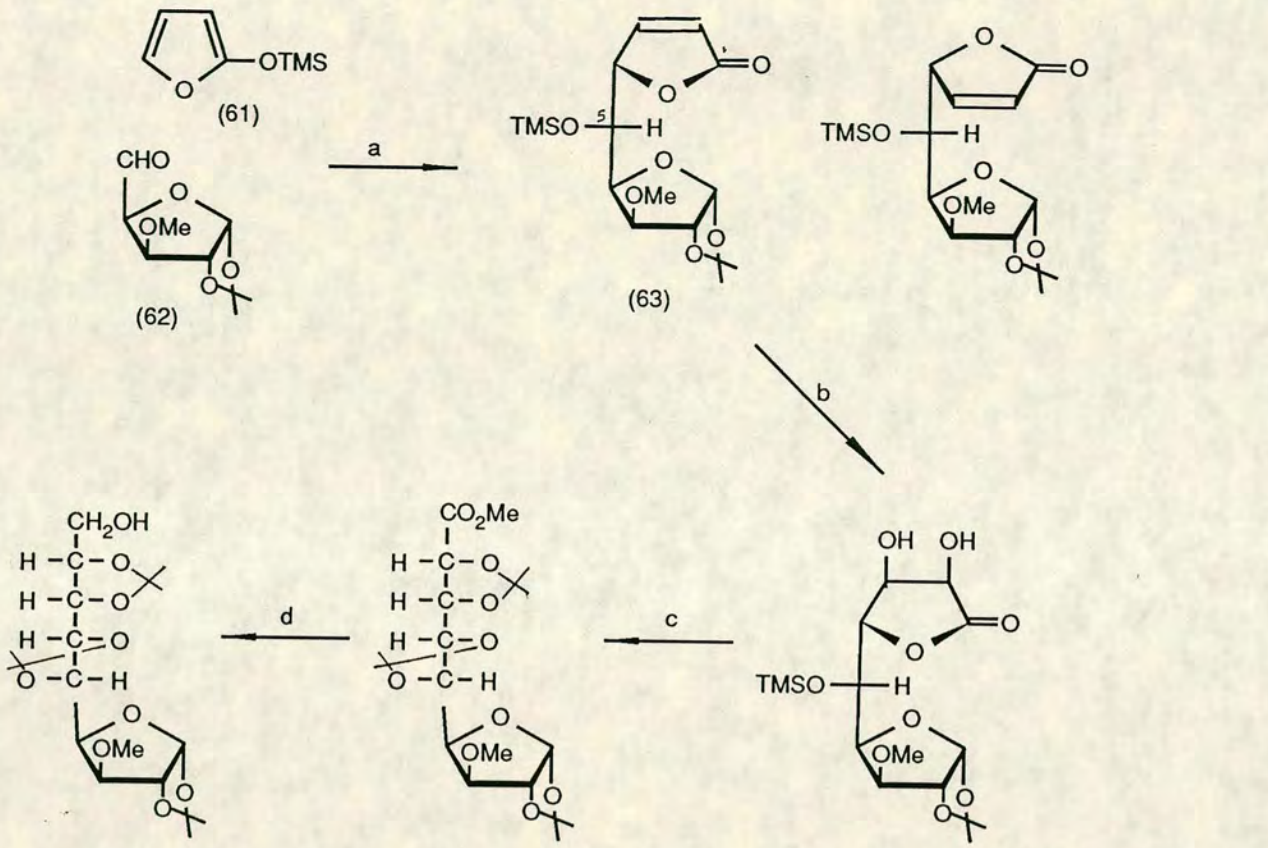
Figure 7.

1.6.2.2 Chain Extension *via* Butenolides

2-(Trimethylsiloxy)furan (TMSOF) (**61**) is a four carbon unit nucleophile which affords substituted butenolides upon reaction with aldehydes in the presence of boron trifluoride etherate.[56–58] The butenolide subunit is a versatile synthon which can be converted to a range of compounds.[59]

Casiraghi[60] *et al* have applied this chemistry to the synthesis of higher monosaccharides *via* the four-carbon elongation of sugar aldehydes with excep-

tional diastereoselectivity. Scheme 17 illustrates the synthesis of β-L-*ribo*-D-*gluco*-nonofuranose (**64**) from *xylo*-dialdofuranose (**62**). Reaction of TMSOF in the presence of $BF_3.Et_2O$ with the aldehyde afforded a mixture of the 9-carbon butenolide epimers, with a strong preference (94:6) for the 4,5-*threo*:5,6-*erythro* compound (**63**).



(a) $BF_3.Et_2O$, CH_2Cl_2, -80°C
(b) DCH-18-C-6/$KMnO_4$,CH_2Cl_2, -5°C
(c) DMP/TSOH, 20°C
(d) DIBAL-H, Toluene, 20°C

Scheme 17

The 5,6-*erythro* stereochemistry can be rationalised by a Felkin-Selective approach of the nucleophile, while the 4,5-*threo* relationship is consistent with the previously observed *threo*-selective behaviour of Lewis acid mediated reactions of TMSOF with aldehydes.[56–58] *Anti*-selective *cis*-hydroxylation of the double bond, followed by lactone ring opening, desilylation, protection and subsequent reduction, afforded the nonose (**64**) as a single compound. TMSOF has been added to other aldehydes and in all cases reported[60] the ratio of diastereomers was >95:5.

1.6.2.3 Catalytic Osmylation of Carbohydrate Alkenes

Brimacombe and co-workers have conducted a lengthy study[61] into the synthesis of higher carbon sugars, concentrating their efforts mainly on the catalytic osmylation of unsaturated sugars prepared by Wittig olefination of appropriate aldehydic precursors. Catalytic osmylation[62] tends to be a little less stereospecific than the stoichiometric procedure, but the cost of the latter becomes prohibitive for large scale work.

A number of seven-,[63] eight-,[64] nine-,[65] and ten-[66]carbon sugars have been prepared. A range of selectivities have been obtained (see later), but in the majority of cases formation of the major isomer complies with Kishi's empirical rule[67] which predicts an *erythro* relationship between a pre-existing hydroxyl (or alkoxyl) group and the new hydroxyl group introduced at an adjacent carbon. This diastereoselectivity is explained by the osmium tetroxide approaching the double bond from the face opposite that of the pre-existing hydroxyl (or alkoxyl) group, when the molecule adopts the least sterically crowded position (Figure 8). Osmium tetroxide is a large electrophile and a bulky R^1 group may hinder the preferred approach.

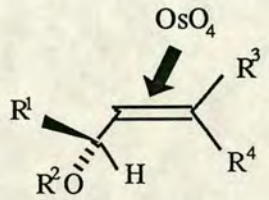
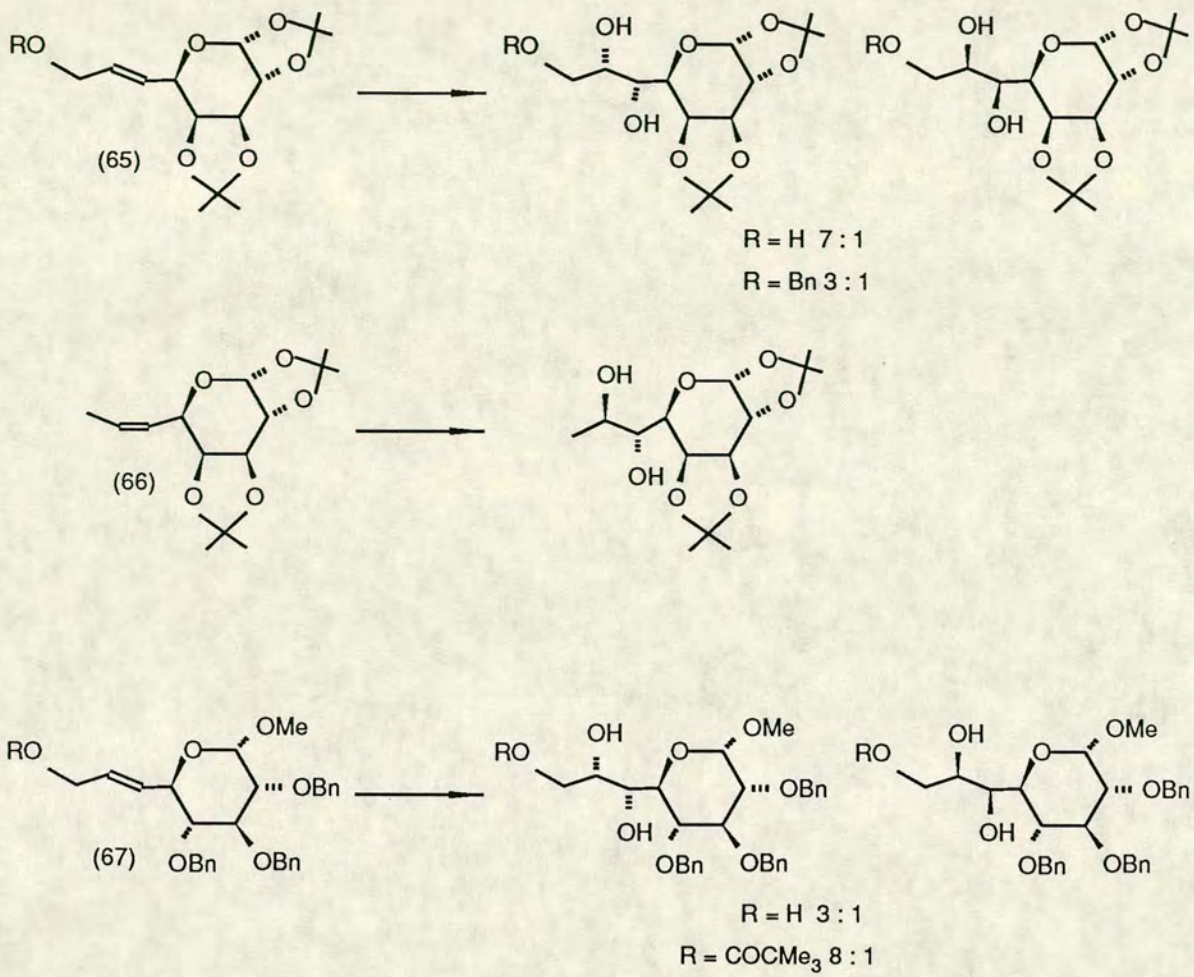


Figure 8.

The acyclic allylic systems studied may be classified into four groups:[68]

(1) Osmylation Directed by a Pyranose Ring Oxygen.

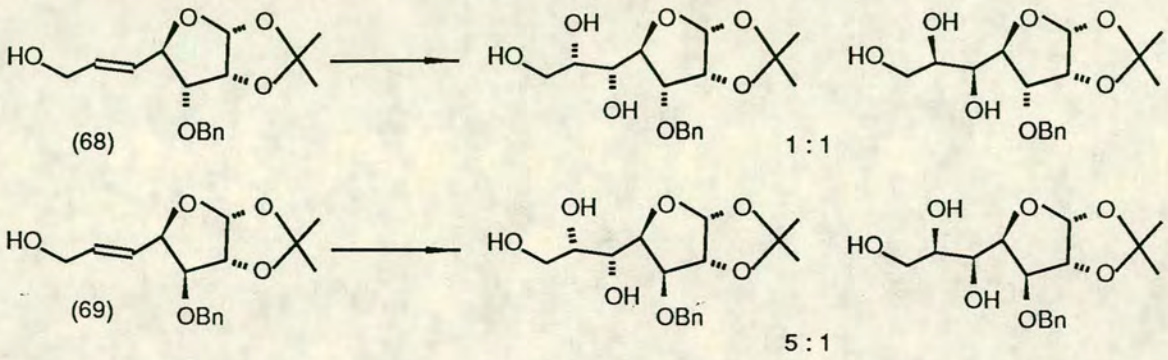
A range of 6-enopyranose compounds were prepared by Wittig olefination of a dialdopyranose system followed by functional group manipulation. As can be seen from the examples illustrated in Scheme 18, the pyranose ring oxygen is effective at directing *anti*-osmylation. It is interesting that benzylation of the hydroxyl group in (**65**) decreases the ratio; however, esterification of the glucose derivative (**67**) has the opposite effect. Catalytic osmylation of the *cis*-olefin (**66**) affords only the Kishi-predicted product.



Scheme 18

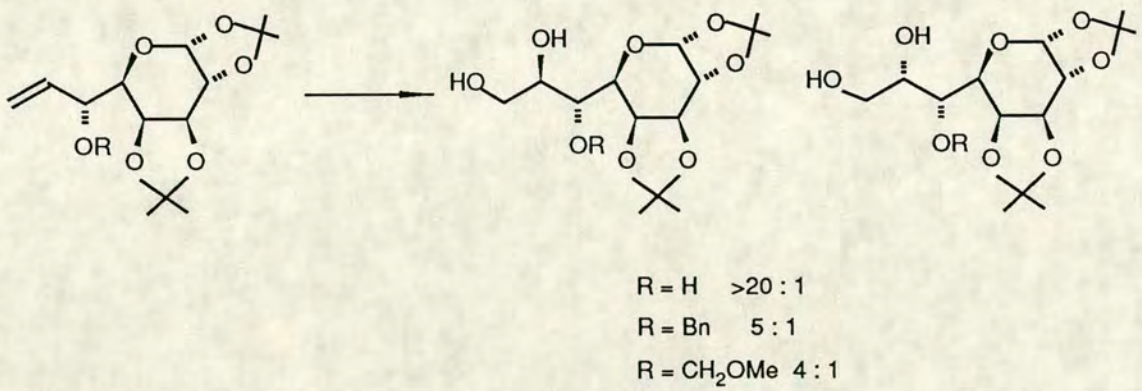
(2) Osmylation Directed by a Furanose Ring Oxygen.

5-Enofuranoses were prepared by an analogous route to the pyranose compounds, and subjected to catalytic osmylation. Again the reaction was found to be *anti*-stereoselective with respect to the ring oxygen; however, some protecting groups on the furanose ring result in poor selectivity. It is believed that the total lack of selectivity in the case of (**68**) is attributable to the bulky benzyl group at O(3) hindering the *anti*-approach of the electrophile, since (**69**), which is epimeric at the 3-position, yields the expected product preferentially.



(3) Osmylation Directed by an Exocyclic Hydroxyl or Alkoxyl Group.

This group of compounds conform to Kishi's empirical rule, as illustrated in Scheme 19.



Scheme 19

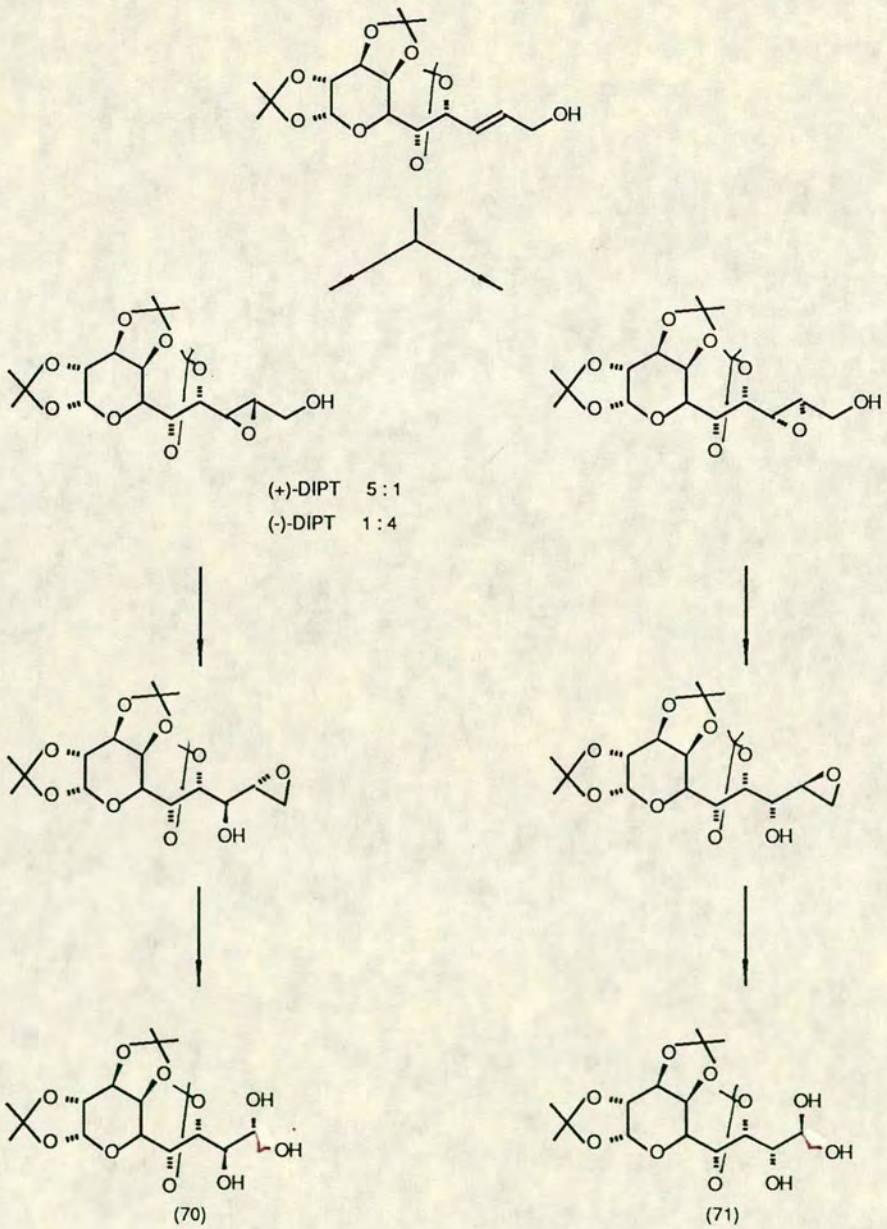
(4) Osmylation of Compounds Containing a Conjugated Carbonyl Group.

Several exceptions to Kishi's rule have been observed with *cis*-α,β-unsaturated carbonyl compounds. Those with *trans*-geometry yielded the predicted major stereoisomer, but with a range of stereoselectivities. It is believed that these anomalous results are attributed to the differences in the preferred conformation of the conjugated ester compared to the corresponding olefinic compound.

The synthesis of decitol derivatives, *via* Wittig olefination of previously prepared octose products and subsequent osmylation, met with very little selectivity, which led to the conclusion that this is an effective route to 7-, 8-, and 9- carbon

sugars, but unsatisfactory for the synthesis of 10-carbon analogues. However, it was subsequently found that the titanium-catalysed asymmetric epoxidation[69] of the same unsaturated precursors, using either di-isopropyl-L-(+)-tartrate [(+)-DIPT] or di-isopropyl-D-(-)-tartrate [(-)-DIPT] as the chiral auxiliary, followed by Payne rearrangement,[70] afforded a viable stereoselective route to such decoses[71] and others.[72] The stereoselectivity may be rationalised by using the Sharpless model,[73] assuming the reaction is reagent controlled.

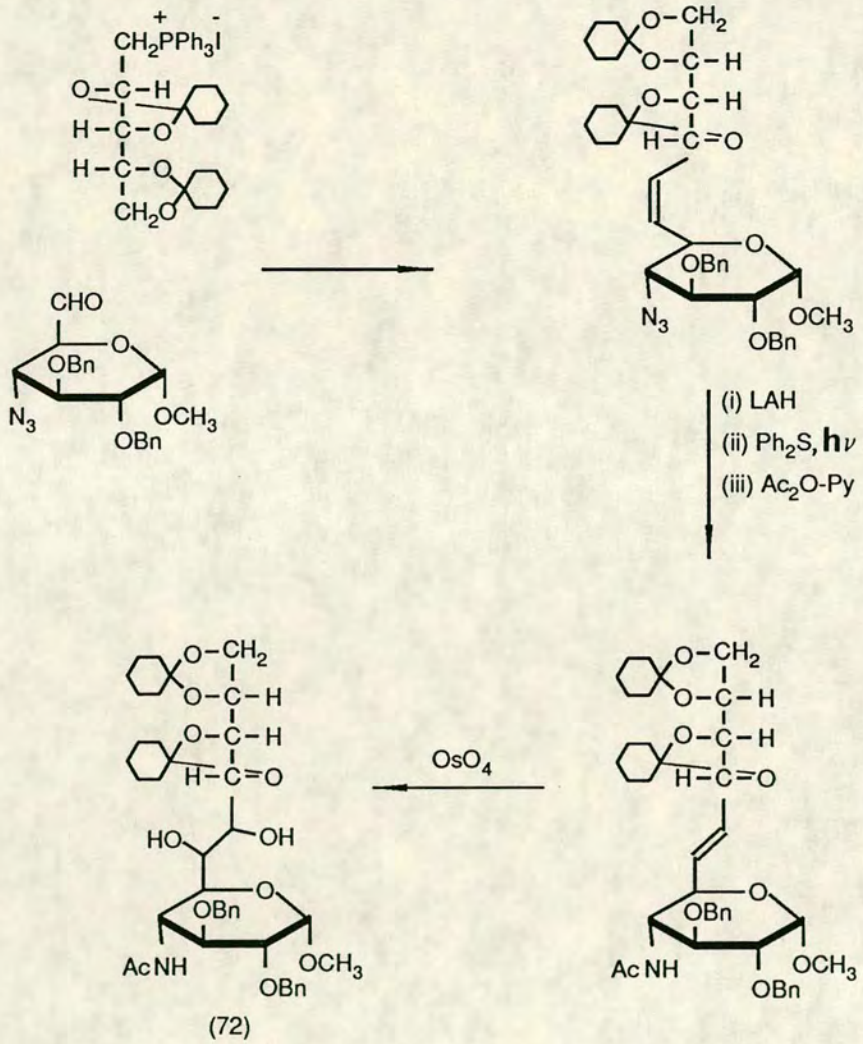
This methodology is illustrated in Scheme 20 for the formation of decose derivatives (**70**) and (**71**).[71]



Scheme 20

1.6.2.4 Convergent Wittig Approach

The condensation of a simple Wittig reagent with a sugar aldehyde has been used to extend the chain by one to three carbons (see previous section). However, a convergent approach involving both a carbohydrate Wittig reagent and a carbohydrate aldehyde is a much more direct synthesis of a higher sugar, since much of the stereochemistry is already built in and the double bond produced is suitable for further elaboration.



Scheme 21

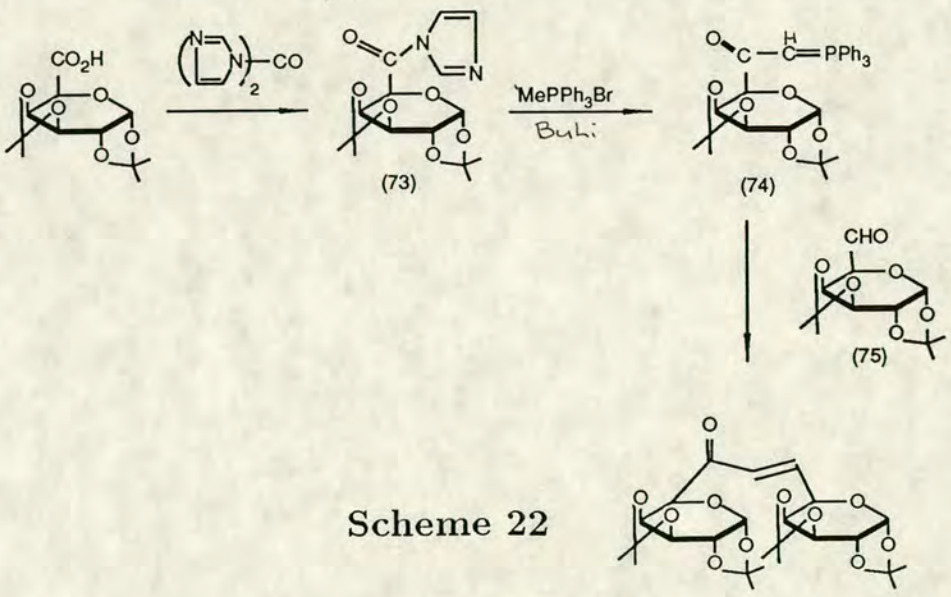
The method used by Secrist[74] and co-workers involves a non-stabilised ylide as an intrinsic part of the carbohydrate. This introduces the possibility of β-elimination, producing a vinyl phosphonium salt, since there is an oxygen leaving

group β to the ylide carbon. Reversible β-elimination was in fact only found to occur in one case, resulting in what was believed to be the more thermodynamically stable isomer; however, it is imperative that the β-oxygen be attached to the molecule *via* another bond lest elimination recur. This phenomenon was not observed in other cases which implies that the thermodynamically most stable ylide was chosen.

The same group successfully carried out several condensations, and discovered that the *cis*-isomer was highly favoured (the only one isolated in most cases reported). However, the geometry of the product alkene could be reversed by photochemical means if required. Catalytic osmylation was found to be a very effective method for the stereospecific introduction of the remaining hydroxyl groups.

This methodology is illustrated[42] in Scheme 21 for the synthesis of the undecose portion (**72**) of hikizimycin (**48**).

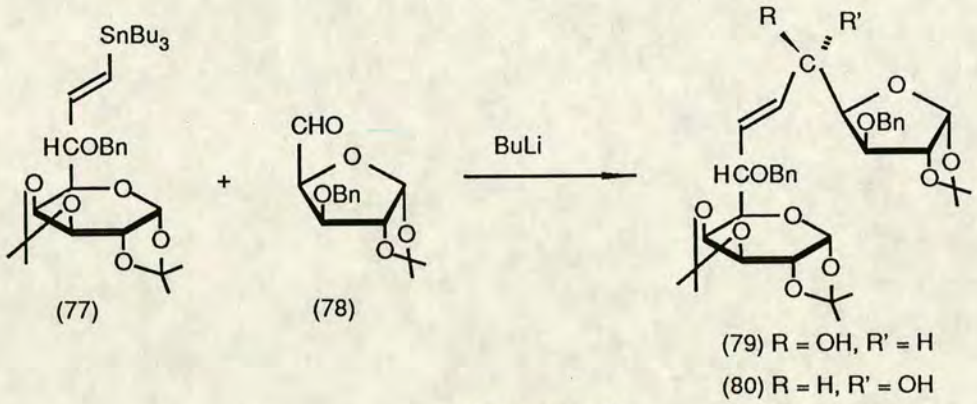
Fraser-Reid[75] and co-workers have also investigated the possibility of condensing two monosaccharide units *via* Wittig technology. They chose to use a carbonyl-stabilised Wittig reagent to avoid the potential β-elimination . It was also anticipated that the sugar groups would confer some degree of asymmetric induction on subsequent manipulations of the enone produced by the condensation. Scheme 22 shows an example of this approach. The phosphorane (**74**) was obtained from the corresponding acid *via* the imidazole (**73**) and subsequent reaction with methylenetriphenylphosphorane. Only the *trans* isomer (**76**) was obtained upon reaction with the aldehyde (**75**) in refluxing benzene.



Scheme 22

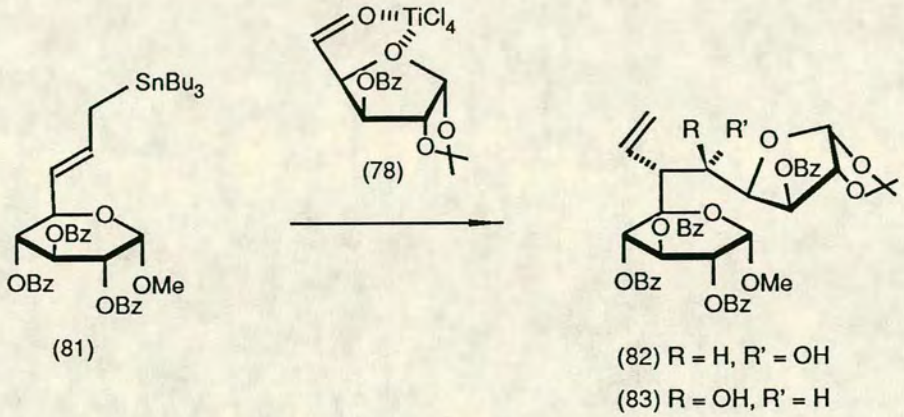
1.6.2.5 Organo-Tin Chemistry

Another method for coupling two sugar units together is to use organo-tin chemistry. The addition of tributyltin hydride to an acetylene affords a mixture of the *cis* and *trans* vinyltin derivatives. *Cis* to *trans* isomerisation can be effected, however, by heating the compound in the presence of a catalytic amount of tributyltin hydride. Displacement of the tributylstannyl moiety with butyl lithium on the *trans* isomer affords the vinyl anion equivalent, which readily reacts with aldehydes to produce allylic alcohols. Jarosz[76] has applied this methodology to the synthesis of higher sugars as illustrated in Scheme 23 for the reaction of D-galactose-derived vinyltin compound (**77**) with the *xylo*-dialdo-1,4-furanose derivative (**78**). It was observed that the diastereofacial selectivity for the formation of alcohols (**79**) and (**80**) was temperature dependent: at -78°C the R:S ratio of the newly created chiral centre is 3:1; however, by increasing the reaction temperature to 0°C the ratio decreases to 1.5:1.



Scheme 23

An alternative approach using allyltin derivatives has been reported by Fraser-Reid and Jarosz.[77] It was known[78] that homoallylic alcohols could be obtained with high *syn* selectivity by the Lewis acid catalysed reaction of allyltin derivatives with α-hydroxy aldehydes. The application of this chemistry for carbohydrates is demonstrated in Scheme 24. The titanium tetrachloride catalysed reaction of the glucose derived allyltin compound (**81**) with the xylo-dialdofuranose (**78**) afforded homoallylic higher sugar derivatives (**82**) and (**83**) in the ratio 3.5:1. The major isomer has the expected 6,7-*syn* configuration. It is assumed that the titanium complexes to both the carbonyl and α-oxygens (as shown in Scheme 24); the predominant attack of the nucleophile is from behind the ring.

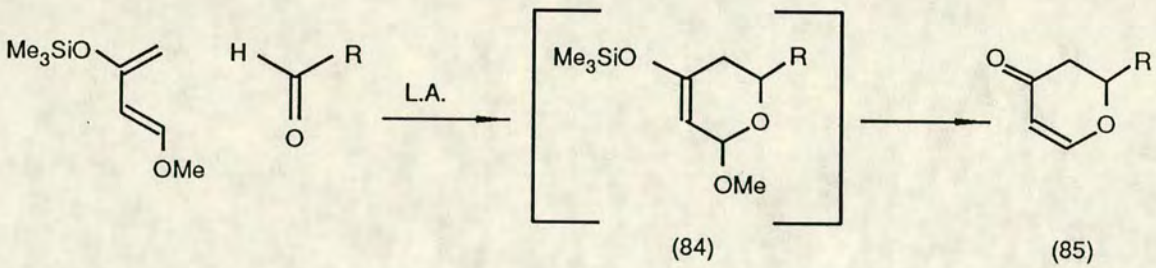


Scheme 24

1.6.2.6 Total Synthesis by Hetero Diels-Alder Cycloaddition

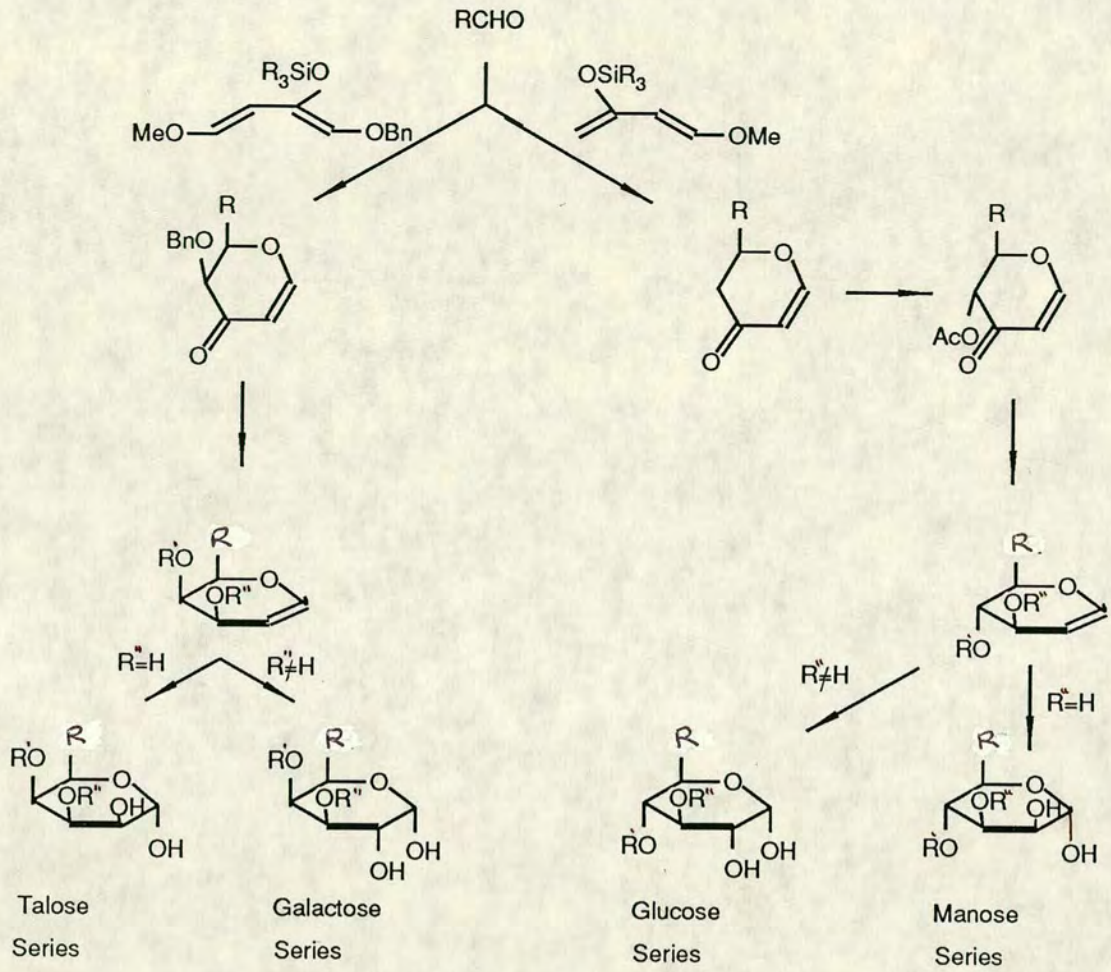
Danishefsky[79] *et al* have developed a very elegant method for the total synthesis of higher sugars based on the construction of a pyranoid matrix and its subsequent stereoselective manipulation.

The pyran is formed *via* Lewis acid catalysed hetero Diels-Alder reaction of highly functionalised and highly activated siloxydienes and aldehydes. The overall reaction is a cyclocondensation since the cycloadduct (**84**) is not isolated and only the dihydropyrone compound (**85**) is obtained (Scheme 25).



Scheme 25

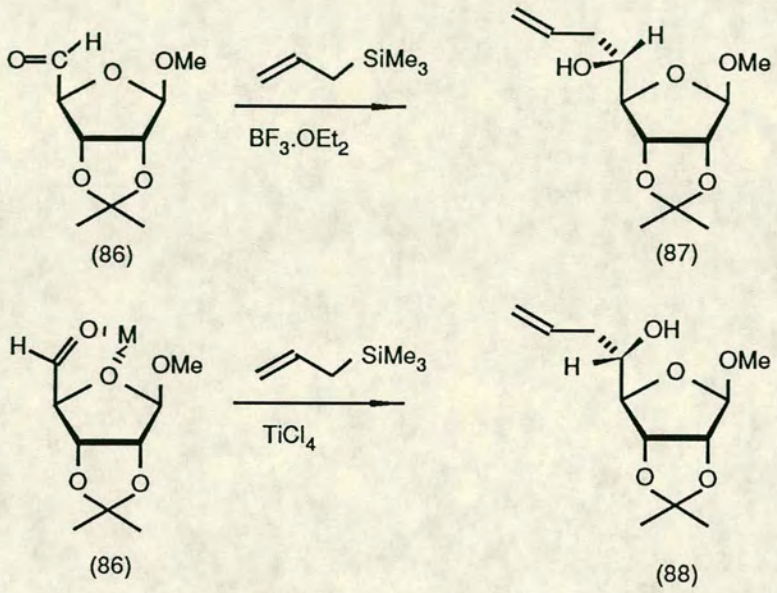
The total regiospecificity of the reaction is attributed to the electron donating oxygen atoms at the 1- and 3- positions of the diene. By careful exploitation of stereoselective reactions the pyranose moiety can be elaborated and the additional oxygens incorporated to yield a range of hexoses as shown in Scheme 26.



Scheme 26

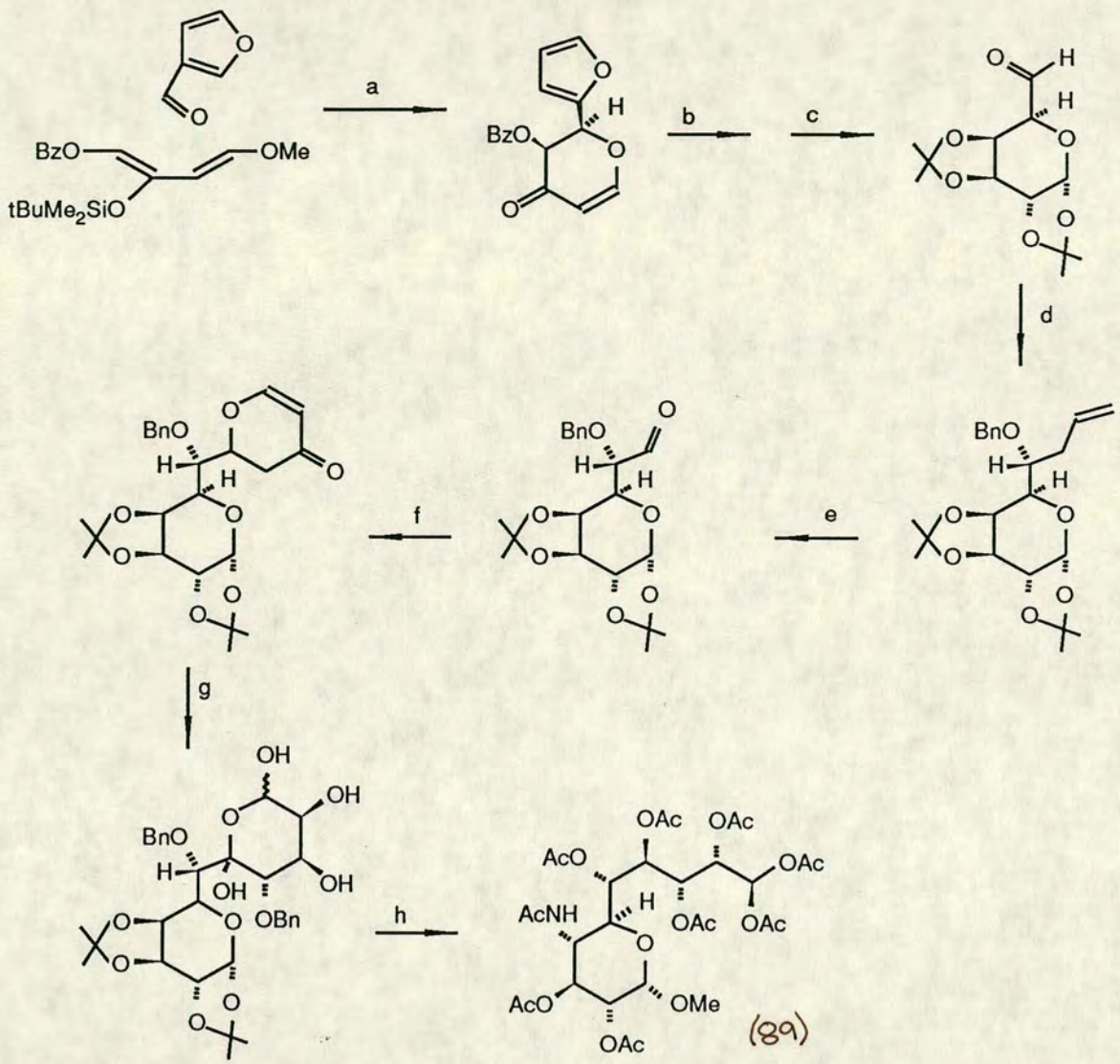
The next challenge was to extend the side chain. Two options were investigated, both involving the use of an aldehyde group. The first was to repeat the process *via* a second cyclocondensation. The alternative approach was to utilise the Sakurai reaction,[80] which involves the Lewis acid catalysed addition of allyltrimethylsilane to the dialdose. This highly stereoselective process is dependent on the catalyst used. As an example (Scheme 27), the *ribo*-dialdose (**86**) gives the 5R-epimer (**87**) under the influence of $BF_3.Et_2O$, corresponding to Cram-Felkin[81,82] attack. The 5S-epimer (**88**), however, is obtained with titanium tetrachloride catalysis. In this case, the metal is assumed to complex to both

aldehyde and ring oxygens, and the nucleophile attacks from the less hindered face.



Scheme 27

An example[83] of the aforementioned methodology can be seen in the total synthesis of peracetyl-β-methylhikosamide (**89**), Scheme 28. A number of other natural products have also been synthesised by this route, including Lincosamine[84] and peracetyltunicaminyluracil.[85] Jarosz[86] has reported similar work, using high pressure to bring about the Diels-Alder cyclocondensation of 1-methoxybuta-1,3-diene with sugar aldehydes.



Scheme 28

(a)(i) $Eu(fod)_3$ (ii) TFA (b)(i) $NaBH_4$-$CeCl_3$ (ii) BzCl-Py (iii) hydrolysis (c)(i) Me_2CO, H_2SO_4 (cat) (ii) K_2CO_3, MeOH (iii) Me_2CO, H_2SO_4 (cat) (iv) O_3, CH_2Cl_2, MeOH, -78°C (v) BH_3.THF (vi) reduction (d)(i) $BF_3.Et_2O$, $CH_2{=}CHCH_2SiMe_3$ (ii) BnBr, NaH, DMF (e)(i)O_3, CH_2Cl_2, -78°C (ii) Zn, AcOH (iii) Ac_2O, Et_3N, DMAP, CH_2Cl_2 (iv) O_3, CH_2Cl_2, -78°C (v) Zn, AcOH (f) $MgBr_2$, CH_2Cl_2, $PhCH_3$, 0°C (g)(i) TFA (ii) $NaBH_4$-$CeCl_3$ (iii) epoxidation (iv) K_2CO_3, MeOH (h)(i) $LiBH_4$, THF, reflux (ii) BnBr, NaH, DMF (iii) MeOH, HCl (iv) BzCl-Py (v) MsCl-Py (vi) $^nBu_4NN_3$ (vii) K_2CO_3, MeOH (viii) Ac_2O-Py (ix) Ph_3P (x) Ac_2O-Py (xi) H_2Pd-$(OH)_2$/C (xii) Ac_2O-Py

1.6.2.7 Other Approaches

A variety of other approaches towards the synthesis of higher sugars have been reported. These include the use of aldol chemistry to couple two monosaccharide units together[87] *via* the enolate of one unit. A cross-aldolization has been used[88] with 7-oxanobornan-2-one derivatives and sugar aldehydes, followed by functional group manipulation to afford a chain extended sugar.

Carbohydrate nitrosugars have been added to sugar aldehydes in a base catalysed reaction,[89] thus creating 2 new chiral centres and the possibility of 4 stereoisomers. The nitro group is subsequently converted to the hydroxyl or amino group. This route has been applied towards the synthesis of Tunicamycin (**63**).

An alternative convergent approach has been proposed[90] involving the condensation of β-hydroxysulphonyl sugars with sugar aldehydes. This results in an extended monosaccharide with some degree of selectivity.

2 Results and Discussion

2.1 Aim and Outline

Higher sugars, monosaccharides with more than seven carbon atoms, pose a challenge to the synthetic chemist owing to the number of chiral centres present. However, it is as a result of the potential biological activity of molecules containing a higher sugar fragment, such as tunicamycin,[43] and the use of such complex monosaccharides as valuable chiral precursors,[49] that the interest of so many chemists has been aroused in the last few years (see 1.6).

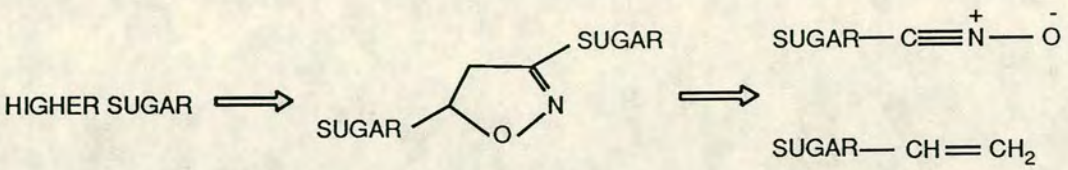
A variety of approaches have been used, from iterative through convergent to total synthesis, applying a wide range of chemical reactions, and obtaining good to excellent stereoselectivities (see 1.6.2). Much of the reported work is orientated towards the synthesis of specific target molecules. The objective of the present work has been to establish a general, convergent approach, with predictable regio- and stereo-chemistry, using inexpensive, readily available starting materials, and exploiting reactions of acknowledged stereochemical control.

The method chosen involves the use of nitrile oxide/isoxazoline chemistry. Nitrile oxides[2–4] are readily obtained by straightforward routes from accessible precursors. They undergo 1,3-dipolar cycloaddition to terminal alkenes, in good yield, to form 2-isoxazolines with predictable regiochemistry and there is precedent for expecting some degree of stereoselectivity.[33] 2-Isoxazolines are useful synthons; they are relatively stable towards a range of reaction conditions, therefore substituents may be modified leaving the heterocyclic ring intact. However, when subjected to the appropriate reagents, the isoxazoline ring can be cleaved thus unmasking a variety of structural units (see 1.4). This methodology has been employed to synthesise a range of complex molecules including natural products and analogues (see 1.5).

Examples of both sugar derived nitrile oxides and alkenes can be found in the literature. Tronchet[91] studied the cycloaddition of sugar nitrile oxides and sugar alkenes in the synthesis of novel *C*-glycosides. Jäger[33] has used smaller carbohydrate-related nitrile oxides and alkenes in the synthesis of, for example, amino-sugars. Good stereoselectivity resulting from the combination of these chiral fragments was reported in both cases.

The methodology proposed for the present work is summarised in the ret-

rosynthetic analysis illustrated in Scheme 29. By choosing to combine both a sugar derived nitrile oxide and a sugar alkene, much of the product stereochemistry is preordained.

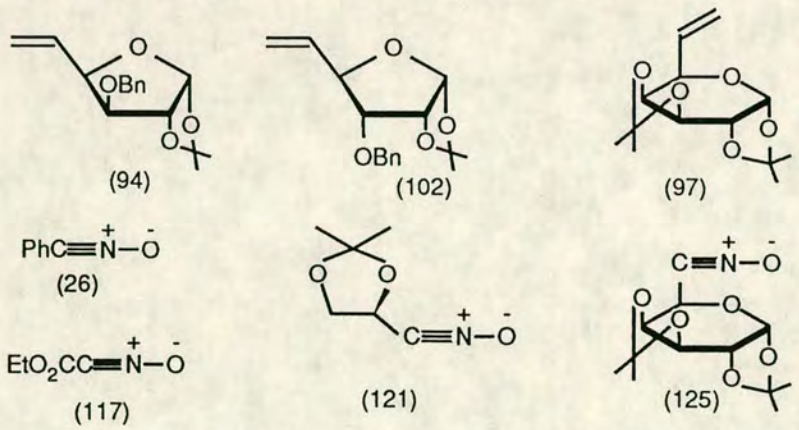


Scheme 29

This approach requires the synthesis of appropriate sugar substituted nitrile oxides and monosaccharide units containing a terminal alkene. The combination of these chiral precursors *via* 1,3-dipolar cycloaddition is expected to yield a 3,5-disubstituted 2-isoxazoline with some degree of stereoselectivity. Subsequent steps involve exploiting the well established isoxazoline chemistry to release the desired functionality, followed by functional group manipulation to afford the target higher sugar.

The alkenes selected were the six-carbon xylose and ribose units (**94**) and (**102**) respectively, and the seven-carbon D-galactose derived unit (**97**). Benzonitrile oxide (**26**) was employed as a model dipole and the carbohydrate derived analogues (**117**), (**121**) and (**125**) were also used.

In the following sections the results obtained during the course of this work will be presented and discussed.

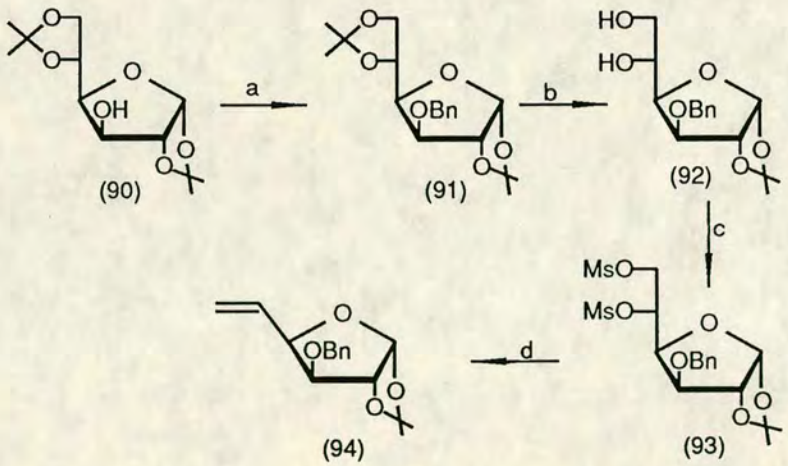


2.2 Synthesis of Alkenes

Three alkenes were chosen for study; all are known compounds and were prepared by literature methods or slight modifications thereof. In each case the structures of the products were confirmed by ^{1}H n.m.r. spectroscopy.

2.2.1 3-*O*-Benzyl-5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hex-5-enofuranose (94)

This six-carbon unit[92] (**94**) was prepared from commercially available diacetone-D-glucose (**90**) in four steps according to Scheme 30. The free hydroxyl group in the 3-position was benzylated[93] before selectively hydrolysing the isopropylidene protection from the 5,6-positions[94] to afford the diol (**92**). Treatment with methanesulphonyl chloride[95] afforded the dimesylate derivative (**93**) as a crystalline solid in 57% overall yield from diacetone-D-glucose. It was found to be unnecessary to purify the products at the intermediate steps, so the crude reaction mixture was carried through to (**93**) which was easily purified by recrystallisation. This compound can be stored indefinitely and provides an ideal precursor to the alkene (**94**), which shows slight signs of decomposition if stored for prolonged periods. Reduction of (**93**) mediated by a zinc/copper couple results in the formation[96] of (**94**) in 80% yield after chromatography.

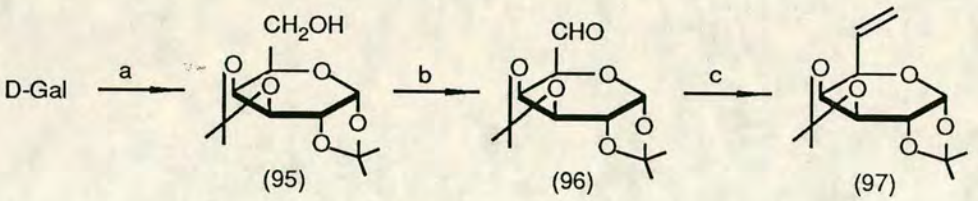


Scheme 30

(a) NaH, BnCl (b) AcOH, H_2O, 40°C, 16h (c) MsCl, Pyridine, 0°C, 12h (d) Zn/Cu couple, NaI, 133°C

2.2.2 6,7-Dideoxy-1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-hept-6-enopyranose (97)

This seven-carbon unit,[63] (**97**), was prepared from D-galactose as outlined in Scheme 31. The acid catalysed reaction[97] of D-galactose with acetone selectively yielded the α-anomer protected by isopropylidene groups at the 1,2 and 3,4 positions, in a pyranose ring. ^{1}H n.m.r. coupling constants for $J_{1,2}$, $J_{2,3}$, $J_{3,4}$ and $J_{4,5}$ of 5.1, 2.4, 7.8, and 1.8Hz respectively are observed indicating that the pyran ring in compound (**95**) does not adopt the chair conformation which would give the characteristically large diaxial and small axial-equatorial and diequatorial values. This is attributed to distortion caused by fusing two 1,3-dioxolane rings to the pyranose moiety.



Scheme 31

(a) $CuSO_4$, H_2SO_4, $(CH_3)_2CO$, 24hr (b) PCC, CH_2Cl_2, 12hr (c) $Ph_3P^+MeI^-$, THF, K^tBuO

Oxidation of alcohol(**95**) using pyridinium chlorochromate (PCC) resulted in a mixture of the dialdose (**96**) and unreacted (**95**) which was removed by chromatography. Subsequent Wittig olefination of the aldehyde using methyl triphenylphosphonium iodide afforded alkene (**97**) in 34% overall yield from D-galactose.

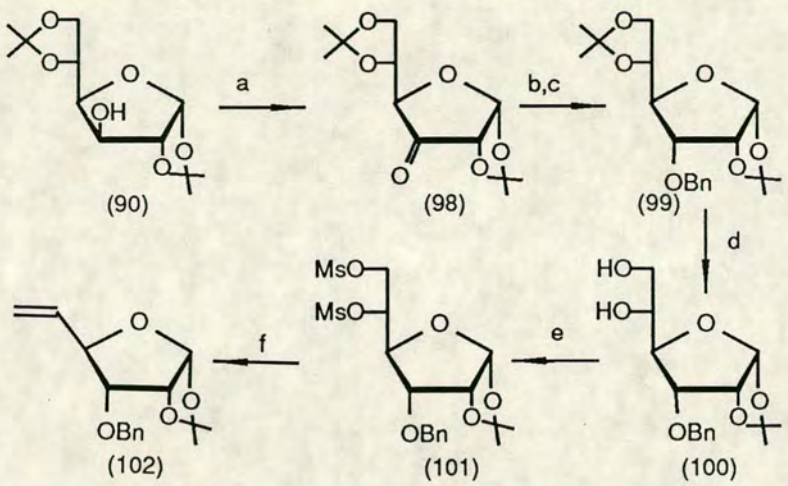
The Wittig reaction was accomplished using milder conditions than previously reported.[63] Potassium *tert*-butoxide was used as a base in the place of sodium amide in liquid ammonia and carried out in comparable yield.

2.2.3 3-*O*-Benzyl-5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*ribo*-hex-5-enofuranose (102)

This alkene,[98] which is epimeric with (**94**) at the 3-position, was obtained from diacetone-D-glucose (Scheme 32) by reversing the stereochemistry at C-3, and then following an analogous route to that used for the synthesis of (**94**). The

epimerisation was achieved[99] by oxidation using acetic anhydride in DMSO and selective reduction of the resulting keto compound (**98**) with sodium borohydride. Subsequent benzylation afforded the allose derivative (**99**) as a crystalline compound in 69% yield. Selective removal of the 5,6-isopropylidene group and mesylation occurred as for the glucose derivative, as did the formation of the alkene (**102**) which was obtained in 84% yield from (**101**).

The ^{1}H n.m.r. spectra of the *xylo-* and *ribo-* alkenes (**94**) and (**102**) respectively show some similar characteristics (see Tables 14 and 16). The major differences are those expected for with the reversal of the 3-position stereochemistry; no $J_{2,3}$ is observed for (**94**) consistent with a dihedral angle approaching 90°; by contrast, a $J_{2,3}$ value of 4.3Hz is observed for (**102**).



Scheme 32

(a) Ac_2O, DMSO (b) $NaBH_4$, EtOH (c) NaH, BnCl (d) AcOH, H_2O, 40°C, 16h
(e) MsCl, Pyridine,0°C, 12h (f) Zn/Cu couple, NaI, 133°C

2.3 Synthesis of Nitrile Oxide Precursors

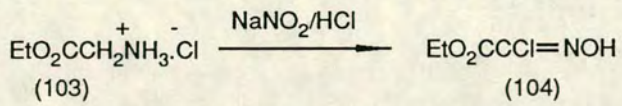
The nitrile oxides, which are all known literature compounds, were generated *in situ* by dehydrochlorination of the corresponding hydroximoyl chloride with triethylamine. These precursors were characterised by FAB mass spectrometry.

2.3.1 Benzohydroximoyl Chloride

Benzohydroximoyl chloride, prepared[100] from benzaldehyde *via* benzaldoxime and subsequent chlorination, was supplied by Mr Ewan Boyd.

2.3.2 Ethyl Chloro-oximino-acetate (104)

Nitrosation, using hydrochloric acid and sodium nitrite, of glycine ethyl ester hydrochloride (**103**) afforded[101] the crystalline hydroximoyl chloride (**104**) in 46% yield (Scheme 33). The product is readily storable for prolonged periods if kept in a sealed container in the fridge.



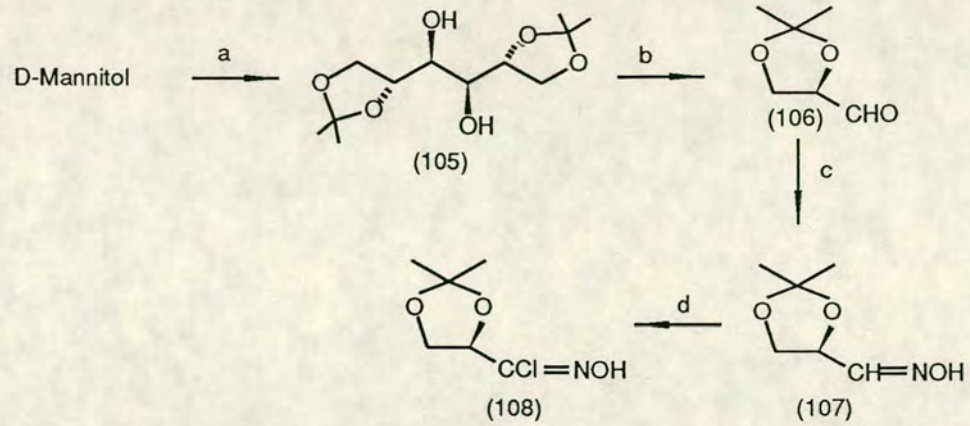
(103) (104)

Scheme 33

2.3.3 2,2-Dimethyl-4-formyl-1,3-dioxolane Chloro-oxime (108)

This was prepared in four steps from D-mannitol following literature procedures (Scheme 34).

The zinc chloride mediated reaction of D-mannitol with acetone resulted in the 1,2:5,6-di-*O*-isopropylidene derivative[102] (**105**) in low yield (29%) after recrystallisation. This low yield can be attributed to the formation of by-products involving formation of mono-, tri, and alternative di- acetone derivatives which are removed by recrystallisation. Cleavage of the 3,4-diol with periodate[103] gives two molar equivalents of the protected glyceraldehyde (**106**), which was immediately reacted with hydroxylamine to afford the oxime[104] (**107**) in 72% yield after Kugelrhor distillation. The i.r. spectrum shows the disappearance of the C=O absorption at 1735cm^{-1} of the aldehyde and the formation of the C=N band at 1650cm^{-1} for the oxime. The ^{1}H n.m.r. shows the oxime to be a 1:1.5 mixture of the *syn* and *anti* isomers as expected from the literature.[105]

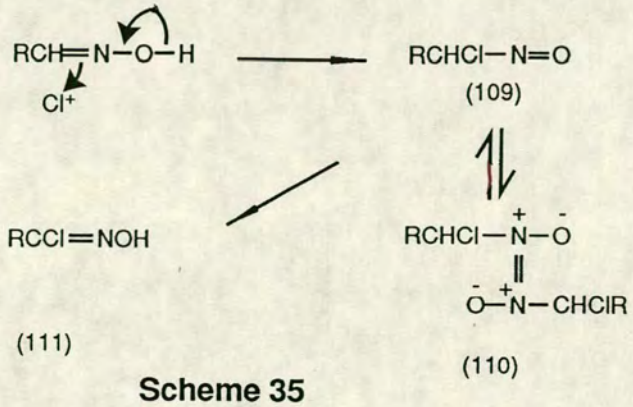


Scheme 34

(a) $ZnCl_2$, $(CH_3)_2CO$ (b) $NaIO_4$, H_2O, THF (c) $NH_2OH.HCl$, $NaCO_3$, H_2O (d) Cl_2, Et_2O, -60°C

The hydroximoyl chloride was obtained by a modification of the procedure reported by Thomas[105] *et al.* The yield of the product was very sensitive to the conditions of the reaction. Chlorine gas was slowly bubbled through a dilute ether solution of the oxime at -60°C. The colour of the reaction mixture was carefully monitored, and chlorination stopped when it became an opaque turquoise colour. After warming to room temperature, the ether was evaporated *in vacuo* at room temperature to afford a blue solid which became white upon cooling in the freezer. Benzene was added and evaporated several times until a white solid, insoluble in benzene, was obtained. With careful reaction procedure near quantitative yields could be obtained.

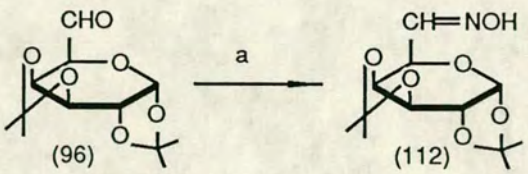
The mechanism of the reaction has been described by Tronchet[106] *et al* (Scheme 35). The chlorination is believed to occur *via* an S_E 2' mechanism to give the *gem*-chloronitroso derivative (**109**) which is in a temperature controlled equilibrium with the dimer (**110**). *gem*-Chloronitroso compounds are characteristically blue and the associated dimers are white. The mixture gradually isomerises to the hydroximoyl chloride (**111**). If the oxime is over-chlorinated no isolable hydroximoyl chloride is obtained. The product may be stored for limited periods of time in the freezer, but it is found to decompose on prolonged storage.



Scheme 35

2.3.4 1,2:3,4-Di-*O*-isopropylidene-α-D-*galacto*-hexodialdo-1,5-pyranose-6-oxime (112)

This six carbon unit nitrile oxide precursor differs from the others in that it was prepared from a dialdose. Reaction of the *galacto*-hexodialdose derivative (**96**) with hydroxylamine hydrochloride in pyridine, according to the method of Tronchet[107] *et al* (Scheme 36), resulted in the formation of an oil and not a solid as previously reported. This compound was not chlorinated directly, the milder *in situ* method using NCS[84] was chosen instead.



Scheme 36

(a) $NH_2OH.HCl$, MeOH, Pyridine

2.4 Nitrile Oxide Cycloaddition Reactions

The cycloaddition reactions were performed by the slow addition of a dilute ether solution of the hydroximoyl chloride, *via* a syringe pump, to a chilled ether solution of the alkene (1.5 equivalents) and triethylamine (1.1 equivalents). These conditions ensured the generation of a low concentration of the nitrile oxide in

the presence of an excess of dipolarophile, thereby reducing the formation of furoxan *via* the competing dimerisation reaction. Triethylamine hydrochloride is insoluble in ether and it is therefore easily removed by filtration after the reaction is complete.

The only exception to the above procedure was in the case of the D-galactose-derived nitrile oxide (**125**) for which the alternative method reported by Torssell[25] *et al* was adopted. This involves chlorination of the oxime *in situ* with *N*-chlorosuccinimide (NCS) and subsequent slow addition of triethylamine to generate the nitrile oxide.

It should be noted that the aforementioned reaction conditions were selected from the wide range of established procedures (see 1.4.1). No attempt was made to investigate any of the others with a view to optimising yields or altering product ratios.

After reaction the products were purified by chromatography. The excess alkene was recoverable and reusable. The cycloaddition products were characterised by ^{1}H and ^{13}C n.m.r., optical rotation, i.r., and FAB mass spectra measurements. The chemical formulae were verified by either elemental analysis or high resolution FAB mass spectrometry. In some cases an X-ray structure was also determined. The ratio of the diastereomeric 2-isoxazolines was obtained from the integrals for the anomeric protons, which are well resolved, in the ^{1}H n.m.r. spectrum of the crude mixture after removing the excess alkene.

2.4.1 Cycloaddition of Nitrile Oxides to 3-*O*-Benzyl-5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hex-5-enofuranose (94)

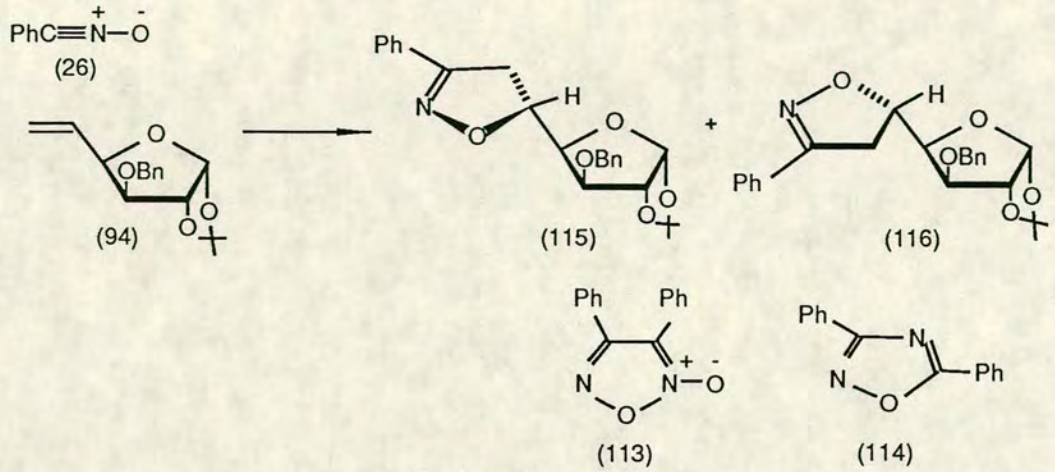
2.4.1.1 Benzonitrile Oxide

At the outset of this work Tronchet[108] had reported the 1,3-dipolar cycloaddition of substituted aromatic nitrile oxides to *xylo*-alkene (**94**). He obtained 3,5-disubstituted 2-isoxazolines with good stereoselectivity, but was unable to identify the configuration of the new chiral centre.

Benzonitrile oxide was therefore chosen as a model system for cycloaddition to probe the π-facial selectivity. It was anticipated that crystalline products would be obtained and the stereochemistry of the newly created chiral centre could be determined by X-ray crystallography.

The cycloaddition was carried out as outlined above and illustrated in Scheme

37. After chromatography four products were obtained: small amounts of the furoxan (**113**) and oxadiazole (**114**) (nitrile oxide dimers which are characteristic by-products of their reactions) and a pair of diastereomeric 2-isoxazolines (**115**) and (**116**) in the ratio of 90:10 and overall yield of 95%.



Scheme 37

The major isoxazoline (**115**) was isolated as a crystalline solid. X-Ray crystal structure analysis revealed that the new chiral centre at C(5) has R configuration which bestows the *erythro* arrangement upon the C(4)-C(5) bond, as depicted in Figure 9. The H(2)-C(2)-C(3)-H(3) torsion angle of 86.3° is consistent with no coupling being observed between these protons. The H(4)-H(5) coupling constant of 8.2Hz is in accord with the dihedral angle of 179°. The best plane containing four atoms in the isoxazoline ring encompasses ONC(7)C(6) and the corresponding torsion angle is 1.2°; C(5) is situated 0.12Å below the plane. Full X-ray data are presented in Appendix A.

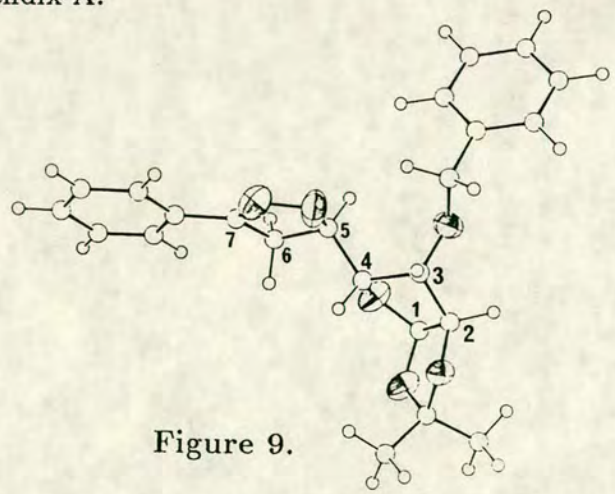
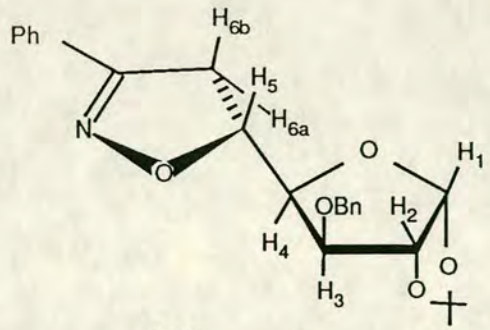
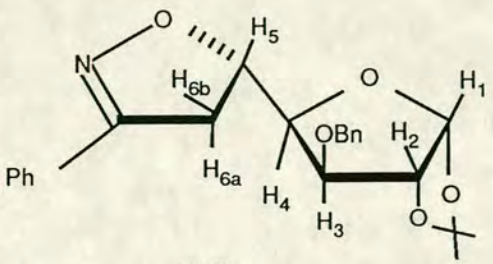


Figure 9.



(115)



(116)

^{1}H N.O.e. difference spectra were obtained for both isoxazolines. They did not provide conclusive evidence for the stereochemistry of the adducts. However, they did show some features compatible with the observed structures:

Irradiation of H(4) shows an n.O.e. of < 1% for H(6a) and H(6b) on the major isomer whereas, the minor isomer gives a 1% difference for H(6a) and < -1% for H(6b). This indicates that H(4) is closer to H(6a) in the minor isomer than in the major isomer.

No enhancement is observed for either H(3) or H(4) on the 5R epimer as a result of irradiating H(6a), but a small effect is observed on both these protons in the case of the 5S epimer. This suggests H(6a) is closer in space to both H(3) and H(4) in the latter than in the former.

Irradiation of H(5) shows < 1% increase for H(4) of the major isomer; on the other hand the effect is 2.5% in the case of the minor isomer, implying that the H(4)-H(5) spatial separation is significantly less in this case.

It should be noted that these results alone are not sufficient to determine the stereochemistry of the newly created chiral centre, although the observed effects are in accord with the structure obtained by X-ray crystallography.

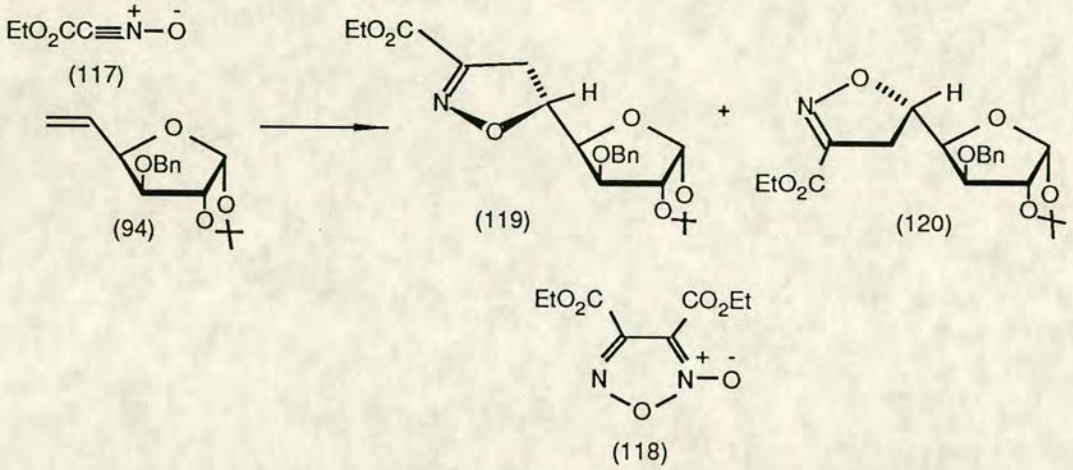
2.4.1.2 Ethoxycarbonylformonitrile Oxide (117)

This nitrile oxide was chosen because it would increase the length of the chain by two carbons after reduction of the ester functionality to a hydroxymethyl group. It is a highly reactive dipole which readily dimerises[4] to form the furoxan (**118**). This compound was found to be a severe skin irritant after sensitisation. Both the hydroximoyl chloride and furoxan should therefore be treated with utmost care.

Cycloaddition (Scheme 38) resulted in the formation of furoxan (**118**), and a

pair of diastereomeric cycloadducts, (**119**) and (**120**), in the ratio of 86:14 and a combined yield of 75%. The i.r. spectra of the isoxazolines show a peak at 1695cm^{-1} for the C=N group in conjugation with the C=O at 1720cm^{-1}. The C=N band for the nonconjugated species such as (**123**) occurs at 1655cm^{-1}.

The major isoxazoline (**119**) was isolated as a crystalline solid, but X-ray analysis was considered unnecessary. It was assigned the 5R configuration on the basis of comparison of its properties (see later), particularly ^{1}H n.m.r., with those of (**115**) for which the stereochemistry was unambiguously ascertained (Figure 9).



Scheme 38

2.4.1.3 4-Cyano-2,2-dimethyl-1,3-dioxolane-N-oxide (121)

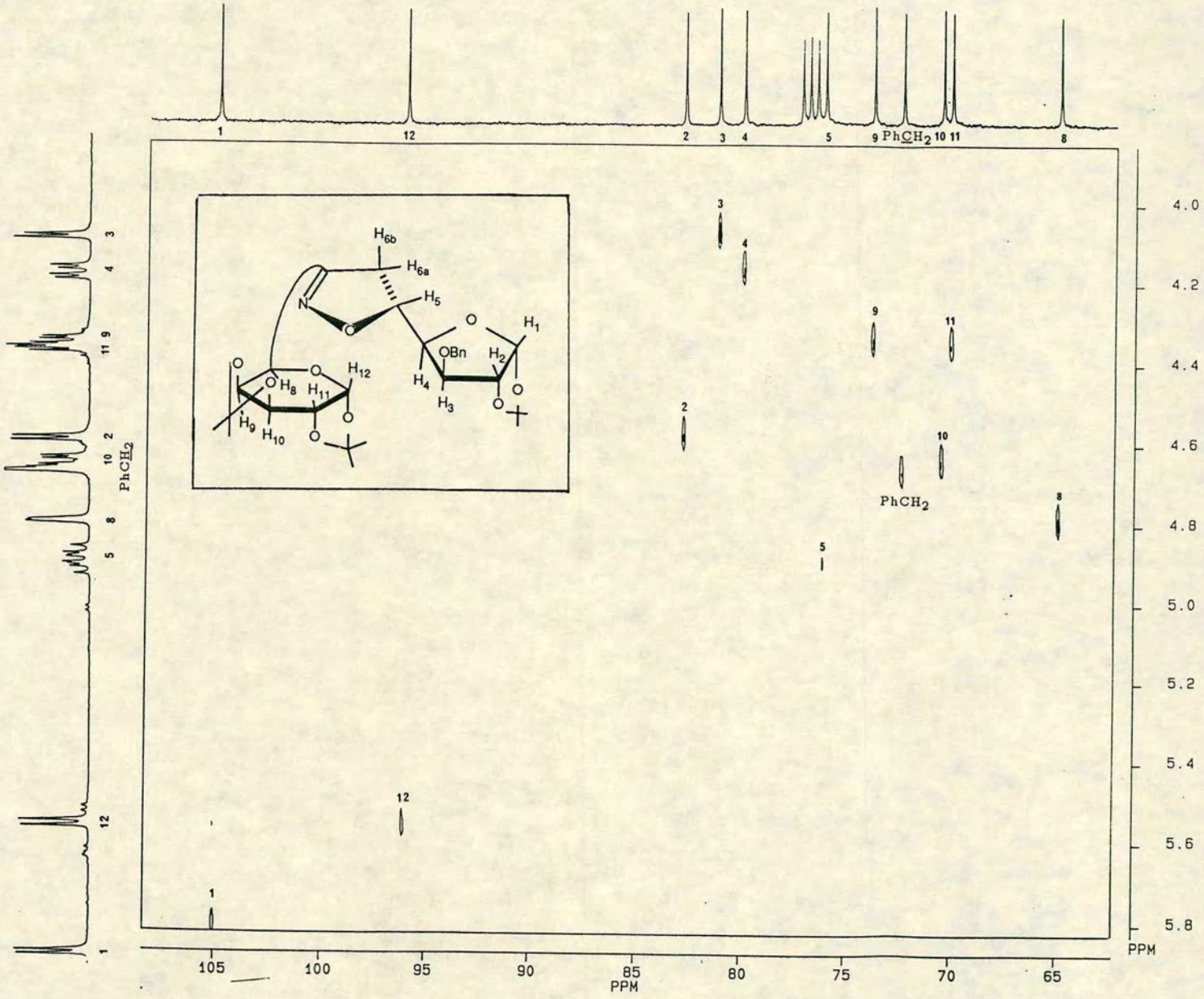
This chiral nitrile oxide (**121**) extends the chain by three carbon units incorporating the D-*glycero* configuration.

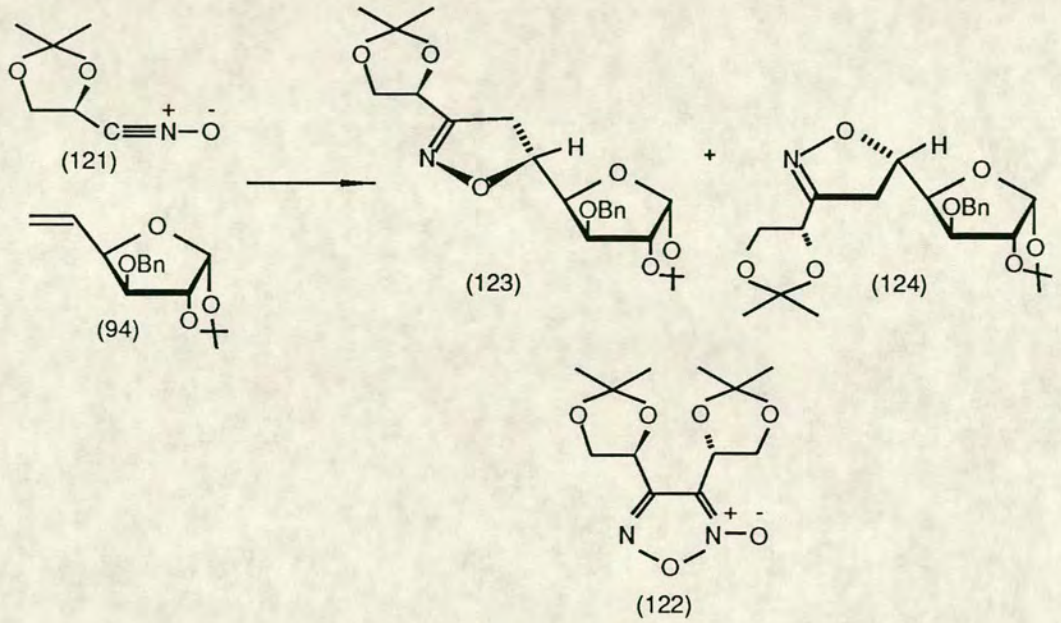
Cycloaddition afforded furoxan (**122**) and a pair of C(5) epimeric isoxazolines, (**123**) and (**124**), in the ratio of 85:15 and the modest yield of 44% (Scheme 39). The major isoxazoline was assigned the 5R configuration by comparison of its properties with those of (**115**).

Thomas[105] has reported the cycloaddition of this nitrile oxide (**121**) to achiral alkenes. The yields reported are comparable to that obtained here, although the selectivity reported is considerably lower. For example, cycloaddition of nitrile oxide (**121**) to styrene afforded furoxan (**122**) and a mixture of diastereomers in equimolar quantities and 52% yield.

Figure 11.

2-D C-H correlation spectrum of compound (**126**) (inset) with 1-D ^{13}C n.m.r. spectrum (X-axis) and 1-D ^{1}H n.m.r. spectrum (Y-axis) plotted on the same scale. The H(1)-C(1) cross peak is observed as a fold-back peak since $\delta_{H(1)}$ is just outside the spectral width.

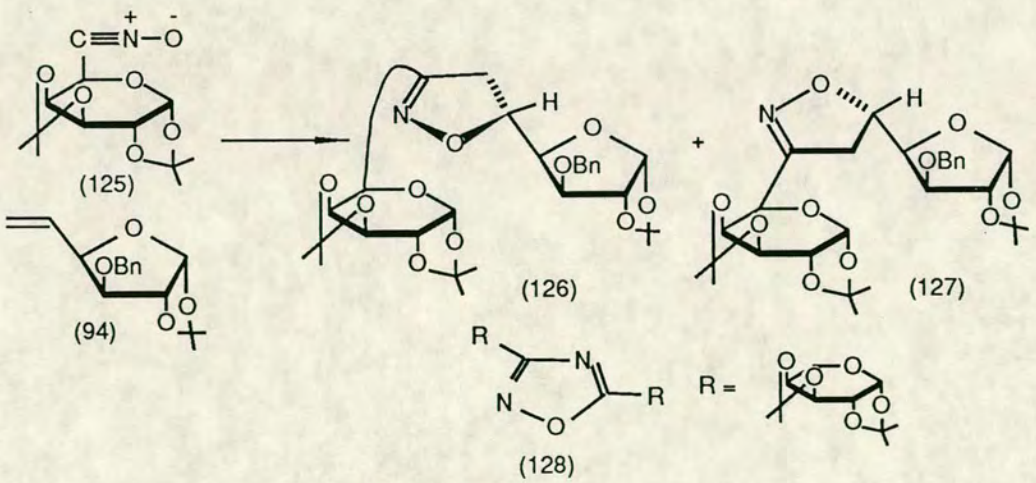




Scheme 39

2.4.1.4 1,2:3,4-Di-*O*-isopropylidene-α-D-*galacturono*-nitrile oxide (125)

This nitrile oxide (**125**) contributes six carbon atoms to the growing monosaccharide chain and it differs from the others in that it was formed from a dialdose, therefore leading to a higher dialdose (see 2.6). The protected D-*galacto*-pyranose ring proffers substantial bulk upon the nitrile oxide and the effect of this on stereoselectivity was of interest.



Scheme 40

Cycloaddition (Scheme 40) resulted in the formation of the 2-isoxazolines (**126**) and (**127**) in the ratio of 85:15 (30% yield). A significant amount of an impure oil, which is believed to contain oxadiazole (**128**) (from FAB high resolution mass spectrometry), was also obtained. The major isoxazoline (**126**) was isolated as a crystalline solid and the structure verified by X-ray analysis (Appendix B). Figure 10 shows (**126**) has the 5R configuration and C(4)-C(5) *erythro* relationship as in previous cases.

As previously observed, the galactose derived fragment does not adopt a chair conformation as a result of the strain caused by the 1,2 and 3,4-*O*-isopropylidene protecting groups. For the pyranose ring the ^{1}H n.m.r. coupling constants and corresponding torsion angles [H(x)-C(x)-C(y)-H(y)] are as follows: H(8)-H(9) 1.8Hz (36°), H(9)-H(10) 8.0Hz (21°), H(10)-H(11) 2.3Hz (71°), H(11)-H(12) 4.9Hz (18°). The changes in coupling constants from those which would be expected for a chair are broadly paralleled by the changes in torsion angle. The $J_{2,3}$ and $J_{4,5}$ values of 0 and 8.8Hz are compatible with the observed dihedral angles of 85 and 175° respectively. The isoxazoline ring shows a C(6)-C(7)-N-O torsion angle of 0.7°. Drawing the best-fit plane through these atoms shows the ring to exist in an envelope-type arrangement with C(5) 0.33Å below the plane.

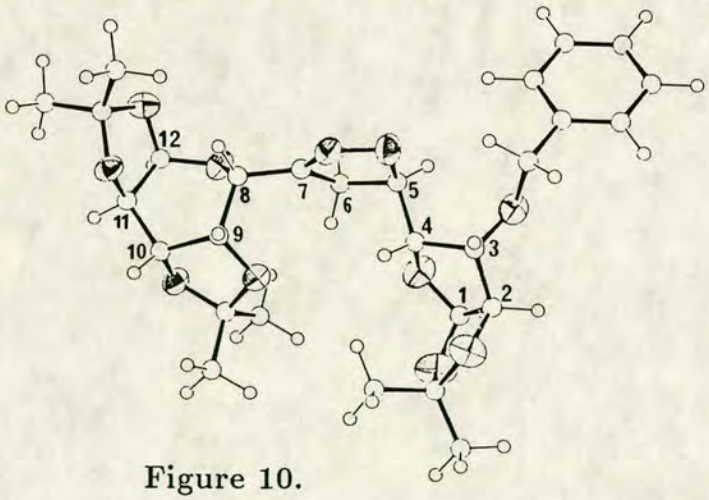


Figure 10.

The ^{13}C n.m.r. spectrum of (**126**) was assigned using the carbon-hydrogen correlation spectrum illustrated in Figure 11. The ^{1}H n.m.r. spectrum is plotted on the Y-axis and the ^{13}C spectrum on the X-axis. The proton spectrum can be assigned by coupling constant correlation and hence the carbons are identified by the cross peaks as marked.

2.4.1.5 General Comparisons

The assignment of C(5) stereochemistry as R for the major isomer and S for the minor was achieved by comparison of the properties with those of (**115**) and (**126**) whose structures were verified by X-ray analysis.

Optical Rotation. Although optical rotation measurements cannot be regarded as proof of configuration it is noteworthy that in all cases the major diastereomer has a large negative $[\alpha]_D^{21}$ value, while the minor isomer has a small positive value. The only exception is minor isomer (**127**), which has a small negative value.

T.l.c. The minor isomer is always the more polar, having the smaller R_f value on silica.

^{1}H n.m.r. Chemical Shifts. The δ_H-value for the anomeric proton of the minor isomer is higher than that of major.

The benzyl C$\underline{H}_2$ protons have very similar chemical shift values for the major isomer, coinciding in the cases of (**115**) and (**126**), whereas they have well separated chemical shift values for the minor isomer.

A characteristic pattern is also observed for the methylene group of the isoxazoline (H(6a) and H(6b)). They occur close together in the 5R epimer, but are well separated in the 5S epimer.

These differences are shown in Table 2 below. Full ^{1}H n.m.r. data can be found in Table 17.

Compound	H(1)	Ph-C$\underline{H}$(2)	H(6a)	H(6b)
(115)	5.94	4.71	3.55	3.45
(116)	6.05	4.44, 4.73	2.87	3.20
(119)	5.87	4.52, 4.64	3.34	3.19
(120)	6.00	4.41, 4.61	2.82	3.14
(123)	5.90	4.67, 4.62	3.22	3.13
(124)	5.98	4.41, 4.70	2.62	3.02
(126)	5.87	4.65	3.29	3.20
(127)	5.98	4.42, 4.66	2.71	3.24

Table 2.

^{13}C n.m.r. Chemical Shifts. The δ_C values are similar in both isomers, with the exception of the epimeric centre C(5). At this carbon there is a marked

difference; for example (**126**) and (**127**) give C(5) resonances at 76.2 and 79.0ppm respectively. The signal for C(5) of the minor isomer always occurs at the higher chemical shift. The assignment for this carbon atom was on the basis of the carbon-hydrogen correlation spectrum illustrated in Figure 11.

2.4.1.6 Rationalisation of Stereoselectivity

There are a number of reports in the literature concerning the diastereoselectivity of nitrile oxide cycloadditions to various alkenes.[4] Of particular relevance to the present work are monosubstituted alkenes with an oxygen bearing stereocentre. Allylic ethers are reported[109] to show marked π-facial selectivity favouring the *erythro* product. Allylic alcohols, by contrast, exhibit little stereoselectivity, but marginally favour the *threo* product.

The factors influencing this experimentally observed phenomenon and the nature of the preferred transition state are the subject of some disagreement. The general opinion, however, lies with the view first proposed by Houk[109] in which the stereoselectivity is rationalised by the so-called "inside alkoxy effect".

In the transition state for nitrile oxide cycloaddition, the allylic substituents are staggered[110] with respect to the newly forming bonds (Figure 12)

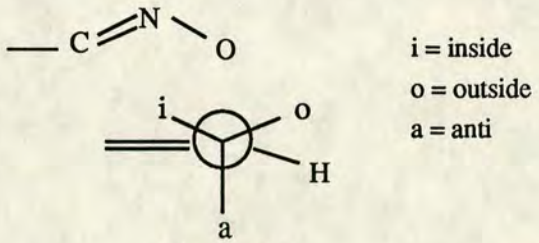


Figure 12.

Therefore, there are six possible transition states for cycloaddition to chiral allyl ethers (Figure 13): three (**A**, **B** and **C**) lead to the formation of the *erythro* product, and the remaining three (**A'**, **B'** and **C'**) result in *threo* products.

The results of theoretical calculations[109] revealed that the relative energies of these transition states, in ascending order, are: **A<A'<B<B'<C'<C**. This indicates that in the lowest energy state the ether group prefers the *inside* position, the bulky alkyl group adopts the least sterically crowded *anti* position and the hydrogen atom takes up the *outside* position. It was therefore concluded that arrangement **A** is responsible for the formation of the favoured product and **A'** for the minor isomer formation. In contrast, for allylic alcohols the hydroxyl group

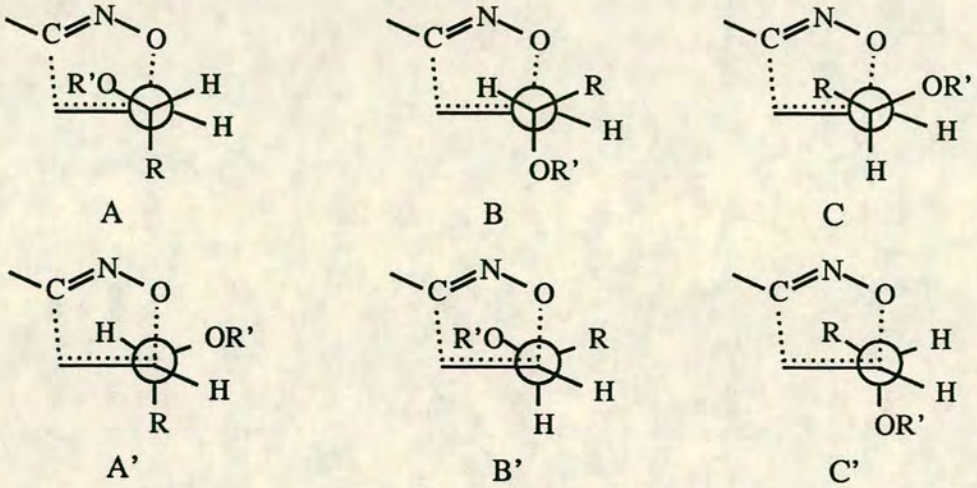


Figure 13.

prefers to exist in the *outside* position in order to maximise hydrogen bonding. This increases the proportion of **A'** resulting in the low, but reversed, stereoselectivity obtained.

This "inside alkoxy effect" is related to the transition state proposed by Felkin[82] and Anh[111] for nucleophilic attack on carbonyl groups.

The increase in diastereoselectivity as the alkyl group, R, increases in size is consistent with transition state **A**. As R increases in size the C=CCR dihedral angle, θ, increases (Figure 14). This stabilises **A** by reducing the interaction between the alkoxy and nitrile oxide oxygens. However, it has the opposite effect on **A'**; the interaction is increased and hence the transition state is destabilised.

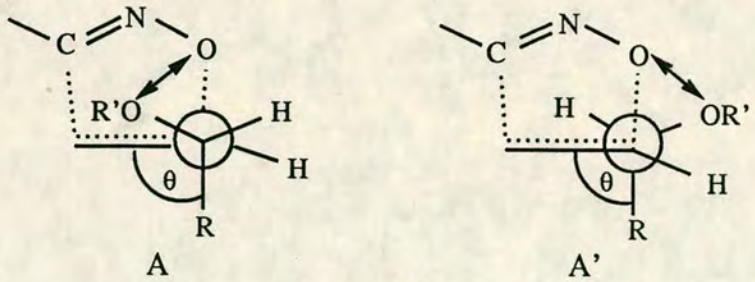


Figure 14.

Houk's rationalisation[109] for the preference of the alkoxy group for the *inside* position is based on secondary orbital interaction considerations. The nitrile oxide cycloaddition reaction may be regarded as a mildly electrophilic process; thus the π-bond becomes electron deficient in the transition state. This will be stabilised by electron donating substituents, but destabilised by those that are electron withdrawing. The alkoxy group is electron withdrawing in the *anti* position as a

result of σ^*_{CO} and alkene π orbital overlap. However, when in the *inside* position, this unfavourable interaction is minimised and the stabilising interaction of σ_{CH} and σ_{CR} orbitals with the π-orbital is maximised.

This model has been extended[112] to include chiral vinyl alkenes with substituents differing in size. The favoured transition state has the large group (L) *anti*, the medium group (M) *inside* with the smallest group (S) *outside*. The opposite stereochemistry is obtained by reversing the positions of the small and medium groups (Figure 15). It should be noted that selectivities are lower in the absence of an alkoxy group.

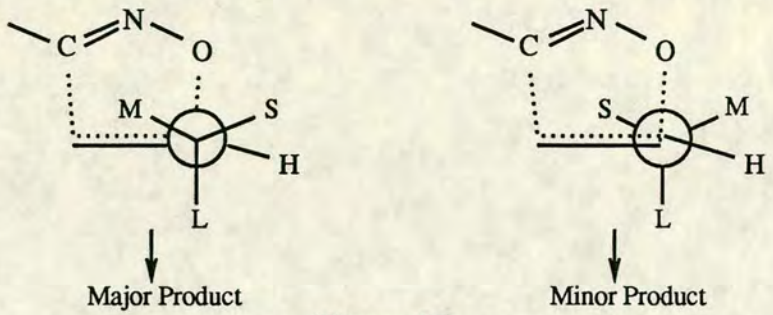
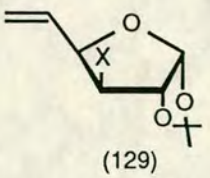


Figure 15.

The alternative view, proposed by Kozikowski,[113] suggests that the alkoxy group should be antiperiplanar to the forming C-O bond. This corresponds to transition state **B** in the Houk analysis. Kozikowski states that this minimises secondary antibonding orbital interactions, and contradicts Houk's view that in this position the destabilising interactions are maximised.

During the course of the present work some complimentary results were published by De Micheli[114] *et al.* They reported the cycloaddition of benzonitrile oxide, ethoxycarbonylformonitrile oxide and mesitonitrile oxide to *xylo*-alkene (**129**) with a variety of substituents at the 3-position. Similar stereoselectivities to those discussed here were reported and rationalised in terms of a modified Houk view (see 2.4.3).



(129)

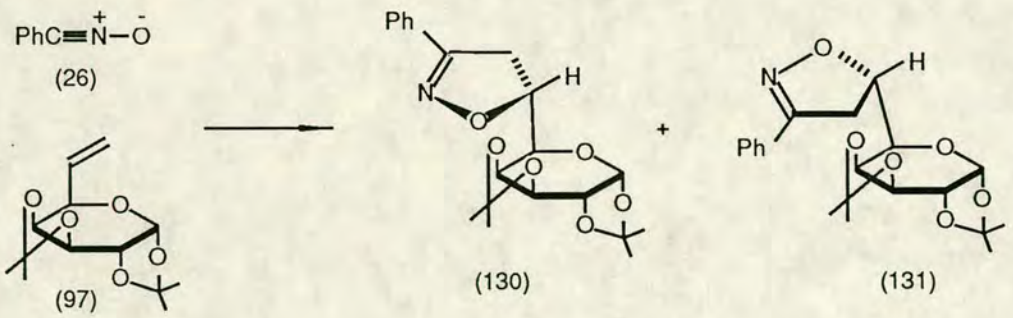
X = H; OH; OCH_3; OBn;
OCH_2-2,6-$Cl_2C_6H_3$; $OCOCH_3$;
OSO_2CH_3; $OCONH_2$

2.4.2 Cycloadditions of Nitrile Oxides to 6,7-Dideoxy-1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-hept-6-enopyranose (97)

There are no previous reports of nitrile oxide cycloadditions to this alkene. It was selected for two reasons: firstly it would contribute seven carbons to the higher sugar, and with some different stereocentres from the *xylo*-alkene (**94**); and secondly to investigate and compare the stereoselectivities of a pyranose substituted vinyl group *versus* a furanose substituted one. The latter was especially important in the light of Jäger's findings[115] (albeit with non-carbohydrate molecules) that a five-membered ring substituent on a vinyl group gave optimum stereoselectivity. Furthermore, this D-galactose derived alkene could be considered a more efficient synthon in the proposed route to higher sugars as it retains all of its original stereochemistry. By contrast, the C(5) stereocentre of D-glucose is destroyed in the synthesis of alkene (**94**), only to be recreated upon formation of the major isoxazoline.

2.4.2.1 Benzonitrile Oxide (26)

Benzonitrile oxide was again chosen as a model system. The cycloaddition (Scheme 41) with alkene (**97**) afforded diphenylfuroxan (**113**) and a separable pair of isoxazoline C(6)-epimers, (**130**) and (**131**), in the ratio of 87:13 and in 64% yield.



Scheme 41

The major isomer was isolated as a crystalline solid and the stereochemistry determined by X-ray analysis (Appendix C). This revealed the C(5)-C(6) *erythro* relationship and R configuration at the newly created chiral centre, C(6). The pyranose ring is distorted as a result of the isopropylidene protecting groups as

X-ray Structure of Compound (**132**)

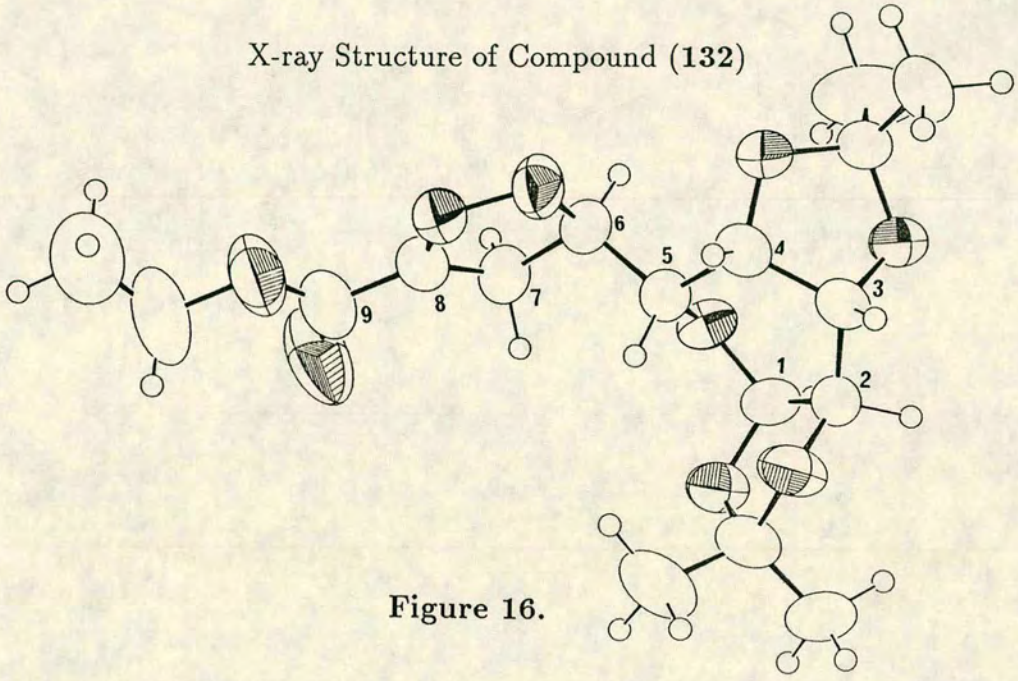


Figure 16.

X-ray Structure of Compound (**133**)

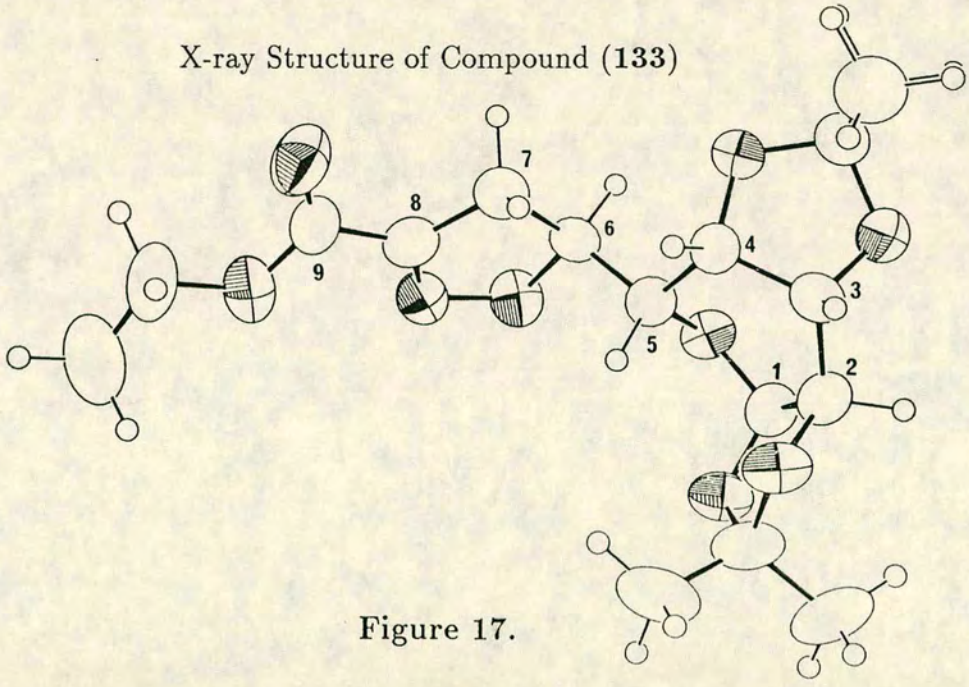
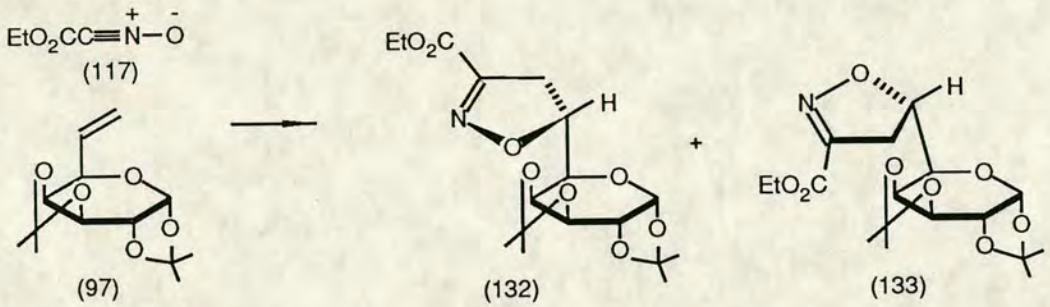


Figure 17.

observed for (**126**). The H(5)-C(5)-C(6)-H(6) torsion angle of 177° is consistent with the H(5)-H(6) coupling constant of 8.3Hz and the isoxazoline ring is fairly planar. The dihedral angles round the ring range from 0.9-2.9° (see Appendix C). Two best-fit planes of four atoms are possible: the first encompasses ONC(8)C(7), with C(6) situated 0.05Å above the plane and the second contains C(6)ONC(8), with C(7) 0.05Å above the plane.

2.4.2.2 Ethoxycarbonylformonitrile Oxide (117)

Cycloaddition of this nitrile oxide to D-*galacto*-alkene (**97**) (Scheme 42) resulted in the formation of carbethoxyfuroxan (**118**) and a pair of separable, crystalline diastereomeric 2-isoxazolines (**132**) and (**133**) in 62% yield and ratio of 91:9.



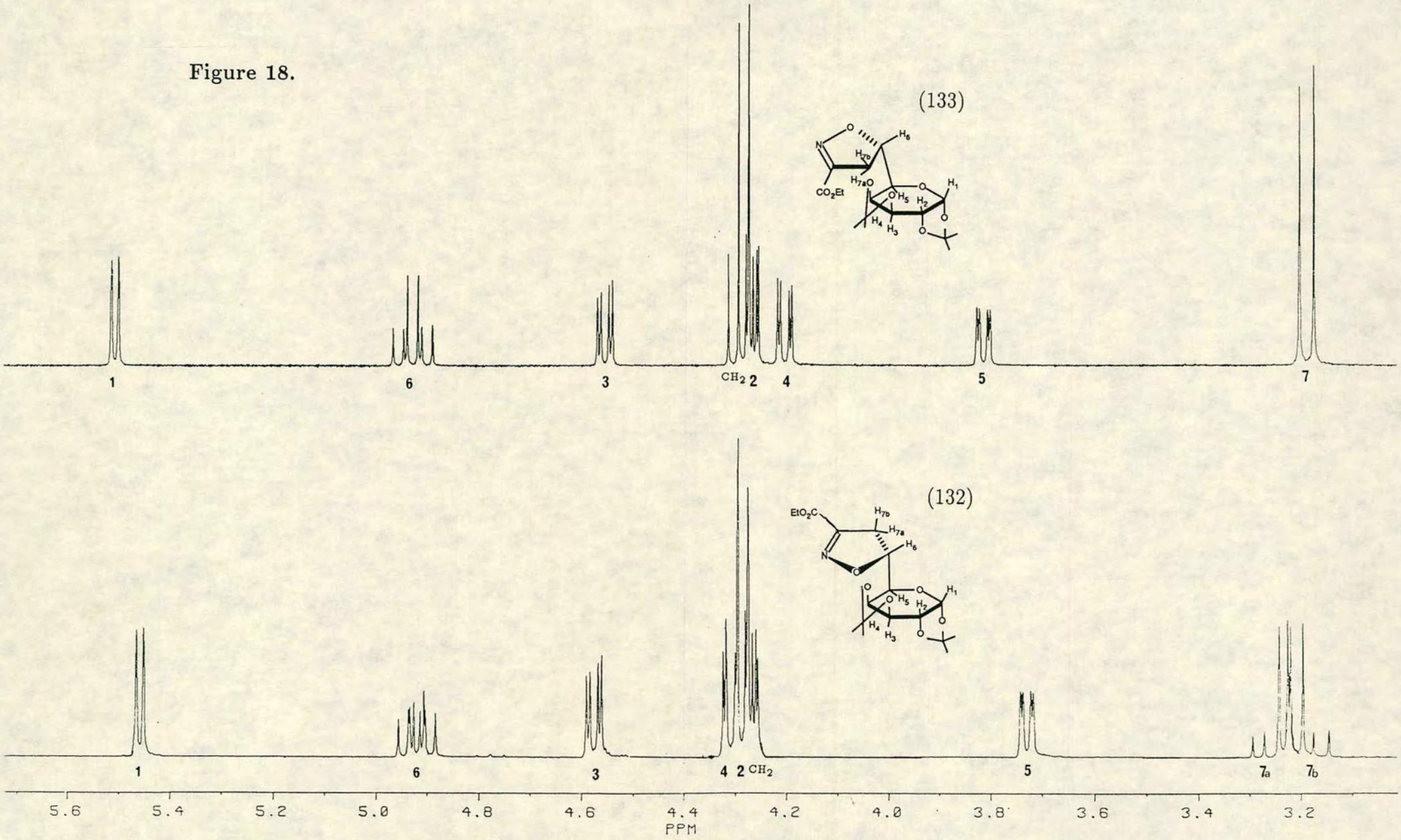
Scheme 42

The stereochemistry was determined for each by X-ray analysis, as depicted in Figures 16 and 17 (and in Appendices D and E). This reveals, as in previous cases, that the major isomer (**132**) has 6R configuration accompanied by the C(5)-C(6) *erythro* arrangement. Conversely, the minor isomer (**133**) exhibits 6S configuration and corresponding *threo* C(5)-C(6) arrangement.

The X-ray structures illustrate some noteworthy features. The ester and imine functionalities are trans-coplanar in both epimers with corresponding dihedral angles of 170° in each case. H(5)-H(6) coupling constants of 7.1 and 7.5Hz in the major and minor isomer respectively are in accord with the observed dihedral angles of 175 and 179°.

In each isomer the best-fit plane containing four atoms from the isoxazoline ring encompasses the C(7)C(8)NO group. In the case of the 6R epimer (**132**) the torsion angle is 1.2° and it is 0.4° for the 6S epimer. Thus, the isoxazoline

Figure 18.


(133)
1
6
3
CH2
2
4
5
7
(132)
1
6
3
4
2
CH2
5
7a
7b
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

adopts an envelope-type arrangement with C(6) situated 0.08Å below the plane in (**132**) and 0.09Å below the plane in (**133**). The galactose ring is distorted in accord with previous observations

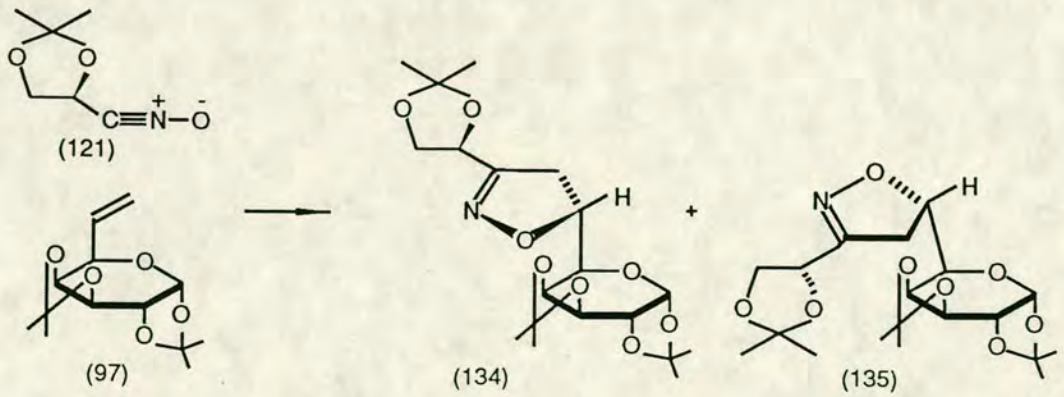
The ^{1}H n.m.r. spectra of compounds (**132**) and (**133**) are shown in Figure 18. By comparison of the spectra several distinctions can be made. The chemical shifts of the anomeric protons are separated by 0.1ppm. This allows an accurate isomer ratio to be determined from the product mixture by measuring the integral of this region of the spectrum.

The protons of methylene group, H(7a) and H(7b), from the isoxazoline ring displays the most marked distinction between the C(6)-epimers. In the minor isomer they are coincident, appearing as a doublet due to coupling to H(6). In the major isomer they are distinct; they are coupled to each other and to H(6), and they thus each appear as a doublet of doublets.

Full ^{1}H n.m.r. data for (**132**) and (**133**) can be found in Table 18.

2.4.2.3 4-Cyano-2,2-dimethyl-1,3-dioxolane-N-oxide (121)

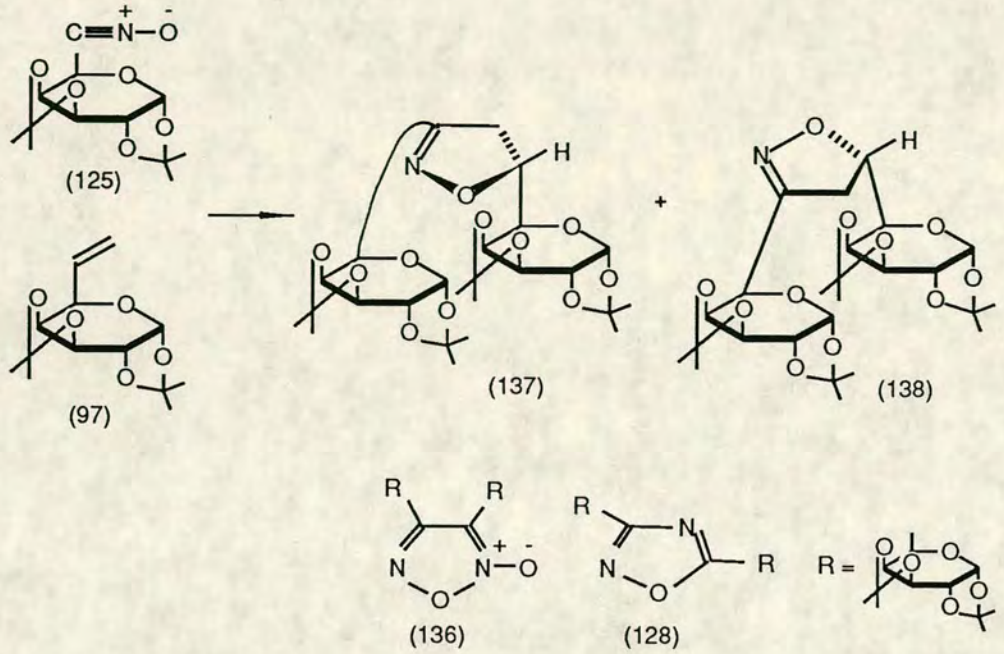
Cycloaddition of the glyceraldehyde nitrile oxide derivative (**121**) with *galacto*-alkene (**97**) (Scheme 43) furnished a 87:13 mixture of isoxazolines (**134**) and (**135**) in 40% yield. The stereochemistry of the major cycloadduct (**134**) was assigned as 6R on the basis of comparison of its properties (see 2.4.2.5) with those of (**130**) and (**132**) whose structure was determined by X-ray crystallography. The furoxan (**122**) was also formed. The yield of isoxazolines is marginally lower than that obtained for cycloaddition of the same dipole to alkene (**94**). It may be assumed that this nitrile oxide participates in other reactions leading to products which are not isolated, since the yields reported in the literature[105] for reactions involving this compound are also relatively low.



Scheme 43

2.4.2.4 1,2:3,4-Di-*O*-isopropylidene-α-D-*galacturono*-nitrile oxide (125)

This cycloaddition (Scheme 44) involved coupling two D-galactose derived units which differ in the C(5) functionality. Compound (**97**) has a vinyl substituent, whereas (**125**) contains a nitrile oxide group.



Scheme 44

Cycloaddition resulted in two chromatographically separable components: the first an oil, believed to contain both the furoxan (**136**) and oxadiazole (**128**) (by FAB exact mass measurements consistent with the expected formulae); and a white crystalline solid. This latter compound was found to contain the diastereomers (**137**) and (**138**) in the ratio 78:22. In this case the ratio was determined by ^{13}C n.m.r. spectroscopy on account of the anomeric protons (two from each isomer) occurring very close together in the ^{1}H n.m.r. spectrum. The combined yield was 33% based on nitrile oxide, but 91% if based on recovered alkene. This indicates that the oxime, which is chlorinated and subsequently dehydrochlorinated *in situ*, may be participating in other reactions leading to products which are not isolated.

Although the cycloadducts proved to be inseparable by chromatography, however, a sample of the major isomer (**137**) was obtained by repeated recrystallisation. The stereochemistry was unequivocally determined by X-ray analysis (Appendix F) demonstrating that, in accord with the other major isoxazoline isomers, it has R configuration at the newly created chiral centre. As in previous cases the galactose rings are distorted by the fused 1,3-dioxolane rings. The large H(5)-H(6) coupling constant (8.7Hz) is ascribable to the near *anti* alignment of these protons. The N-O bond is 0.048Å longer in this case than that measured for the carbethoxy-analogue (**132**). The shorter bond in the latter compound may be a result of conjugation with the carbonyl group.

The ^{1}H n.m.r. spectrum was assigned (Table 18) by comparison with that for the corresponding β-hydroxy ketone (**155**) (section 2.5.2).

2.4.2.5 General Comparisons

The assignment of the C(6)-C(7) configuration as *erythro* for the major cycloadduct and *threo* for the minor isomer was achieved by X-ray crystallography in the cases of compounds (**130**), (**132**), (**133**) and (**137**) (Appendices C, D, E, and F) and by comparison of their properties with (**134**) and (**135**) in order to determine the stereochemistry of the latter pair of C(6)-epimers.

As for the *xylo*-alkene (**94**) derived cycloadducts, those resulting from the *galacto*-alkene show some characteristics which distinguish between the *erythro* and *threo* diastereomers.

Optical Rotation. The *erythro* isomer has a large negative $[\alpha]_D^{21}$ value, with the exception of (**134**) which has a small negative value. The *threo* isomers, by contrast, give a small and positive $[\alpha]_D^{21}$ value.

T.l.c. The *threo* isomer is more polar and has the smaller R_f value on silica.

^{1}H n.m.r. Chemical Shifts. The anomeric proton of the *threo* isomer resonates at higher chemical shift in all cases examined, as shown in Table 3. Full ^{1}H n.m.r. data can be found in Table 18.

Compound	δ_{H_1} (ppm)
130	5.51
131	5.58
132	5.46
133	5.56
134	5.47
135	5.53
137	5.45

Table 3.

^{13}C n.m.r. Chemical Shifts. The δ_C values are similar for both the *erythro* and *threo* isomers, with the exception of the epimeric centre C(6). At this carbon there is a marked difference between the diastereomers. For example (**130**) and (**131**) give C(6) resonances at 78.1 and 80.1ppm respectively. The C(6) signal for the *threo* isomer occurs at the higher chemical shift in all cases examined.

In conclusion, the *xylo*-alkene (**94**) and *galacto*-alkene (**97**) are equally effective at promoting stereoselectivity in cycloaddition reactions with the chosen nitrile oxides. In every case the *erythro* isomer is formed preferentially. This can be rationalised in terms of the reaction occurring *via* a transition state involving the "inside alkoxy effect" proposed by Houk.[109] It should be noted that, for both alkene (**94**) and (**97**), the alkoxy (OR') and alkyl (R) groups are linked together, in a furanose and pyranose ring respectively (Figure 19).

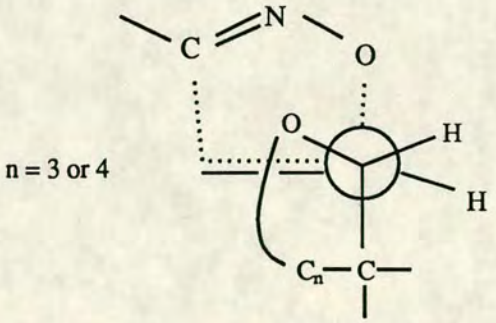


Figure 19.

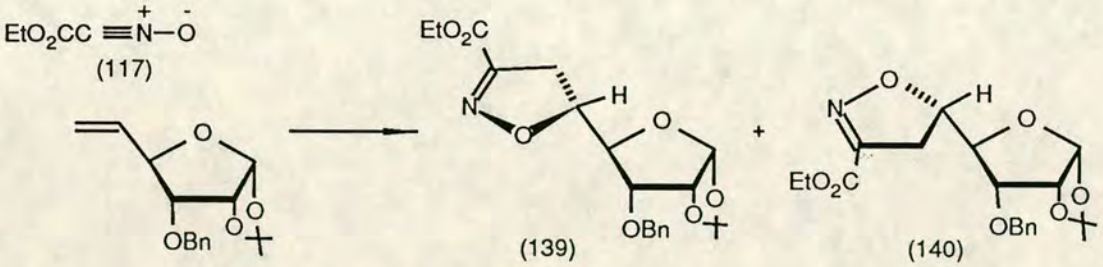
Assignment of the stereochemistry of the products was possible by comparison of their properties with those of analogous compounds whose structure was unambiguously determined by X-ray crystallography.

The yields of isoxazolines from the *galacto*-alkene (**97**) were generally poorer than from the *xylo*-alkene (**94**), indicating that it may not be as reactive a dipolarophile.

2.4.3 Cycloaddition of Nitrile Oxides to 3-*O*-Benzyl-5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*ribo*-hex-5-enofuranose (102)

Encouraged by the high levels of diastereoselectivity obtained with both alkene (**93**) and (**97**), which can be attributed to the directing effect of the allylic alkoxy group, the corresponding reactions with alkene (**102**), which has inverted stereochemistry at the homoallylic position, were investigated.

The cycloaddition of ethoxycarbonylformonitrile oxide (**117**) to this alkene (Scheme 45) resulted in the formation of carbethoxyfuroxan (**118**) and a pair of chromatographically inseparable diastereomers, (**139**) and (**140**), in almost equimolar quantities (51:49 by ^{1}H n.m.r.) and in a yield of 47%. The cycloadducts were isolated as an oil and therefore could not be separated by crystalisation.

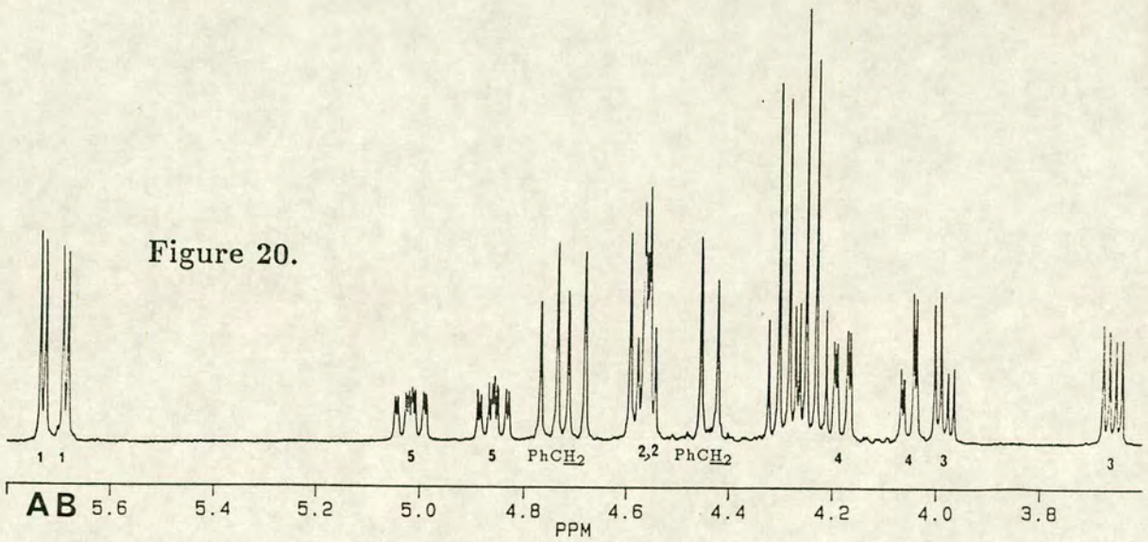


Scheme 45

The ^{1}H n.m.r. spectrum (Figure 20) of the isoxazolines did, however, show two distinct patterns for each proton, i.e. one for each isomer. The spectrum can be assigned by coupling constant correlation. However, since the two signals for each proton were of equal intensity, the connectivity cannot be determined. Distinguishing one isomer from the other is achieved with the aid of the TOCSY spectra shown in Figures 21 and 22.

The distinctive anomeric protons, H(1), are nominally labelled; that at higher chemical shift **A**, and the other **B**. The connectivity is illustrated in Figure 21 (dashed lines for isomer **A** and solid lines for isomer **B**) for protons 1 to 4. The

Figure 20.



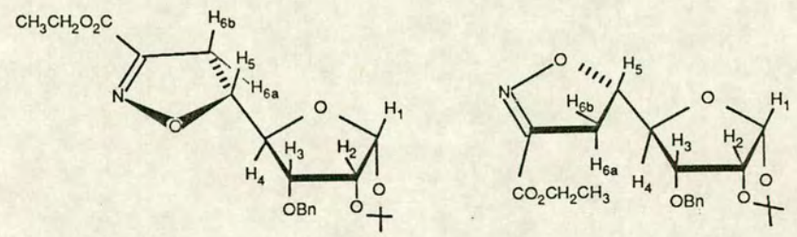
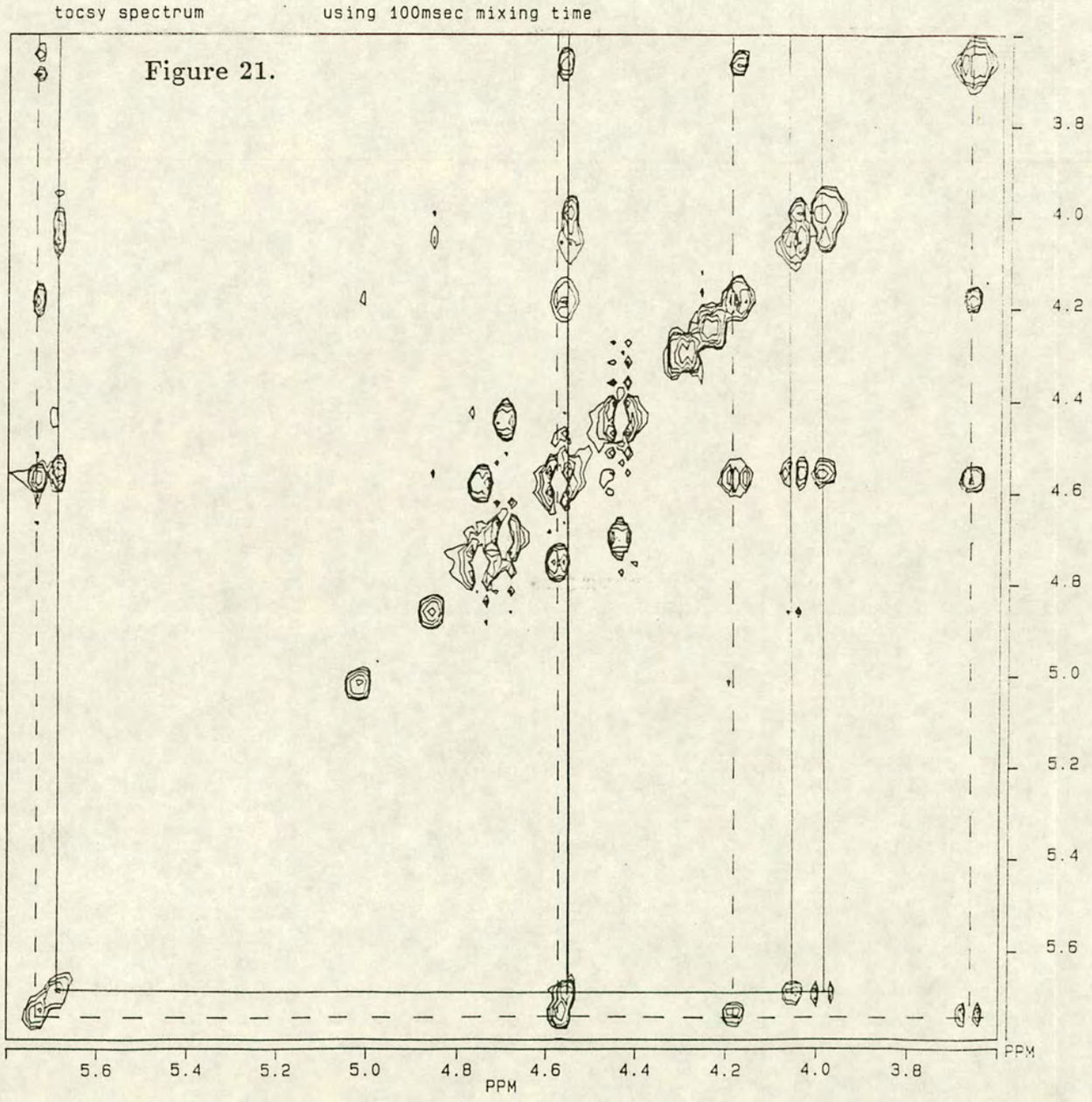
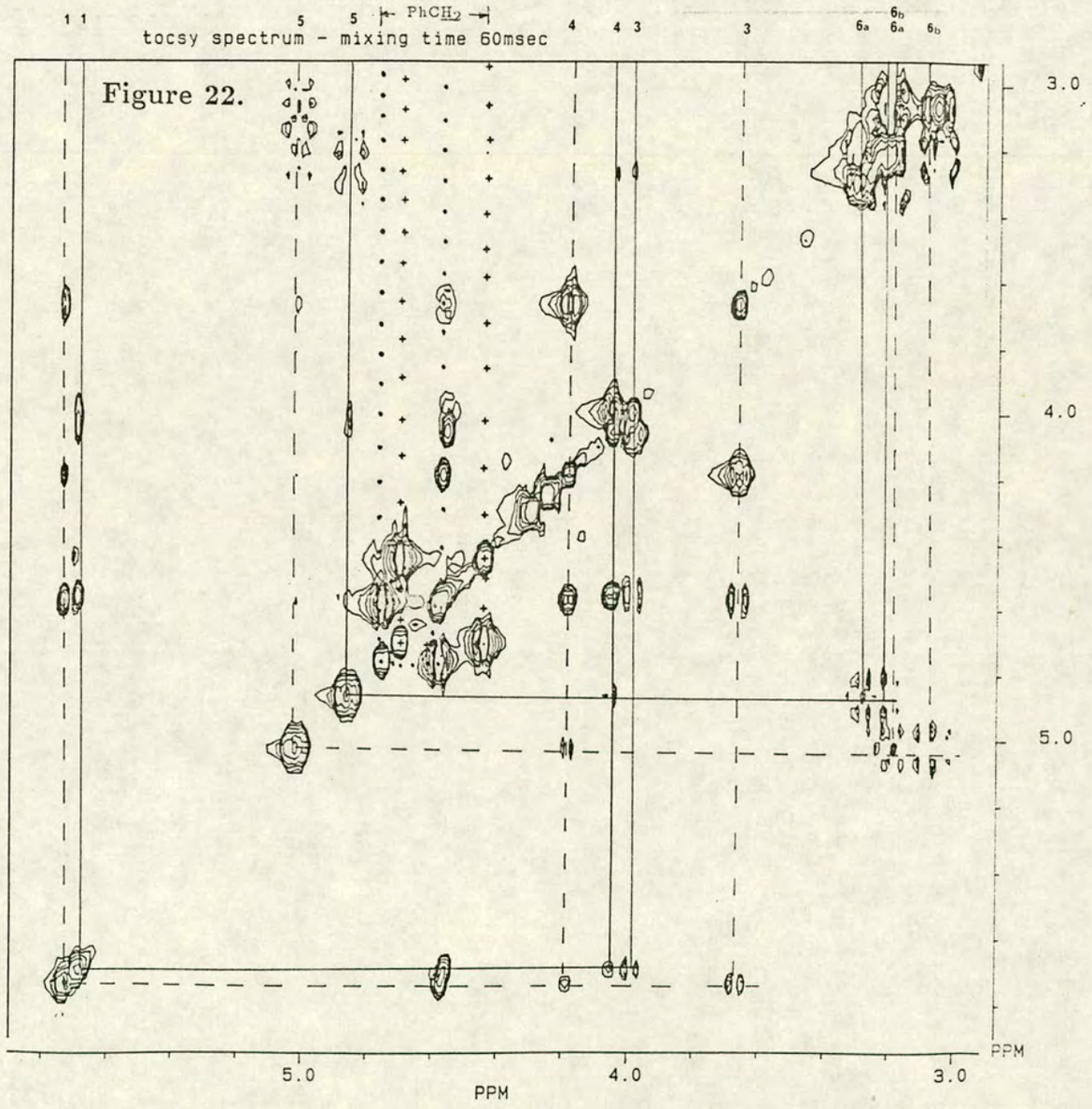


Figure 21.



AB

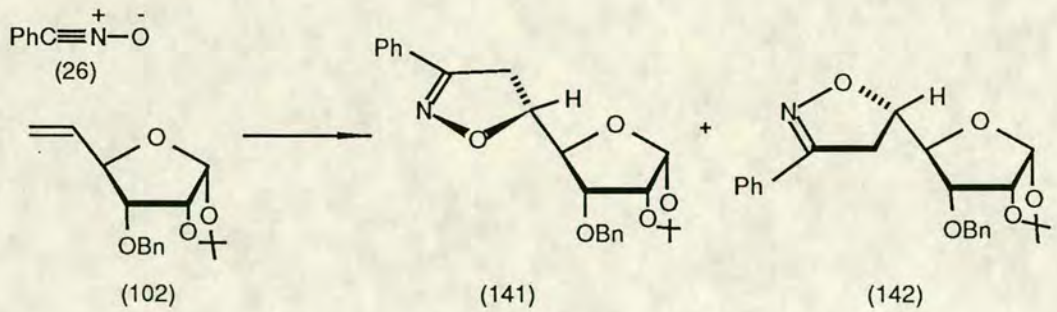
Figure 22.



signals for protons H(2) for each isomer are not well separated and lie very close to the signal for one of the benzyl protons $PhC\underline{H}_2$. From the TOCSY spectrum in Figure 22 the connectivity to H(5), H(6a) and H(6b) can be established *via* the previously observed connectivity to H(4). The benzyl protons, $PhC\underline{H}_2$, cannot be assigned to individual isomers, but can be paired as illustrated by the dotted and crossed lines.

Thus, from a mixture of isomers, the ^1H n.m.r. spectrum for each contiguous chain can be distinguished. However, this does not give any indication of the stereochemistry of the respective species. The ^1H n.m.r. spectra of compounds (**139**) and (**140**) show the expected differences, when compared to their *xylo*-alkene derived analogues, arising as a result of the inverted C(3) stereochemistry. However, the most significant difference is in the size of the H(4)-H(5) coupling constant. It is 8.2Hz for compound (**119**) but only 2.1Hz for *ribo*-alkene derived (**139**). This indicates a substantial change in the orientation of the isoxazoline and furanose rings with respect to each other.

To investigate further the lack of stereoselectivity obtained with *ribo*-alkene (**102**), Karen M^{c}Ghie[116] studied the cycloaddition of benzonitrile oxide (**26**) to the same alkene as her final year honours project (Scheme 46). Once again a chromatographically inseparable pair of diastereomeric isoxazolines was obtained. Some diphenylfuroxan (**113**) was also isolated.



(102) (141) (142)

Scheme 46

In this instance the product ratio was found to be 60:40 and both isomers were obtained as crystalline solids. The ^1H n.m.r. spectrum of the mixture showed two distinct patterns for each proton, one for each isomer, and because of the difference in intensity, the connectivity was readily established.

By repeated recrystalisations a crystal of the minor isomer was obtained. It

was identified as the *erythro* isomer (**141**) by X-ray analysis. This remarkable result has no parallels in the literature. Although the effect is small, it violates the "inside alkoxy" hypothesis by reversing the stereoselectivity from that predicted. By comparison of the ^{1}H n.m.r. spectra of the phenyl (**141**), (**142**) and carbethoxy isoxazolines (**139**), (**140**) isomer **A** from the TOCSY spectrum corresponds to the *erythro* compound (**139**) and **B** to the *threo* isomer (**140**). There was no discernible stereoselectivity in the latter case (measured ratio 51:49).

These results demonstrate the importance of the stereochemistry at the homoallylic position. The effect of a homoallylic oxygen has been highlighted by De Micheli.[114] Alkenes (**94**) and (**97**) both have this group in such a position that, in transition states **A** and **A'**, the oxygen lone pair may interact with the π-bond of the alkene, thus having a destabilising effect (Figure 23). As a consequence, transition state **B**, in which this interaction cannot occur, becomes relatively more important. De Micheli[114] uses this argument to explain why the observed stereoselectivity is higher than that calculated theoretically for compounds containing a homoallylic ether.

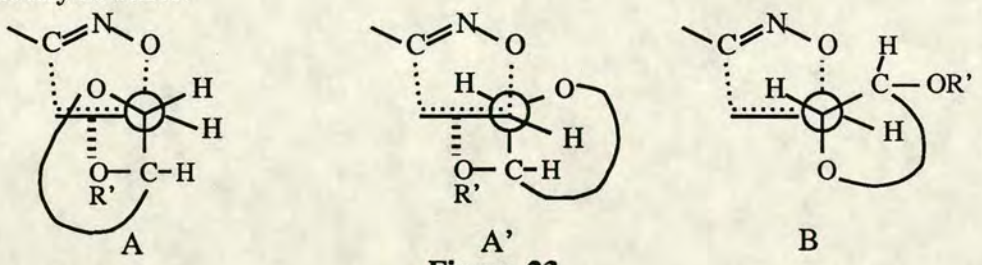


Figure 23.

It may be postulated that for alkene (**102**) the homoallylic oxygen is in such a position (Figure 24) that it cannot play a role in promoting the stereoselectivity of the reaction, thus leading to decreased isomer ratios. This does not, however, account for the slight reversal of stereoselectivity observed for cycloaddition between alkene (**102**) and benzonitrile oxide (**26**). This remains unexplained and inconsistent with any literature reports on other systems.

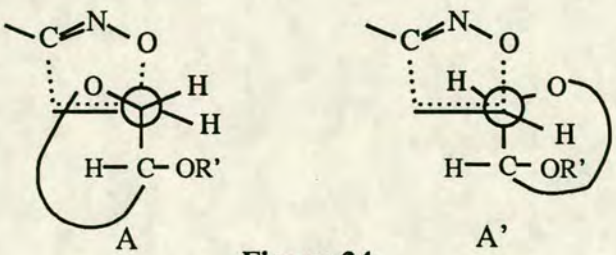


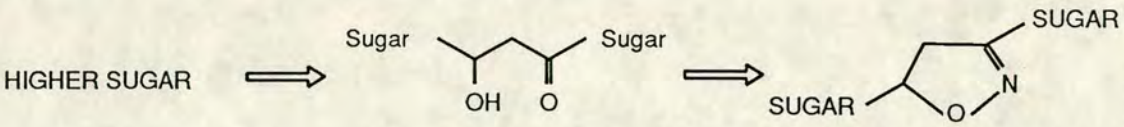
Figure 24.

In conclusion, these results have shown that alkene (**102**) is not an efficient synthon for higher sugars due to both the lack of stereoselectivity and the chromatographically inseparable nature of the products.

2.5 Hydrolytic Reduction of Isoxazolines to β-Hydroxy Ketones

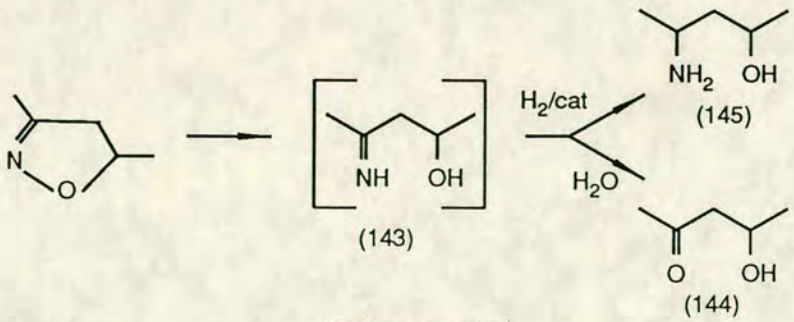
In the previous section it has been shown that, by careful choice of precursors, sugar nitrile oxides can undergo 1,3-dipolar cycloaddition with ω-unsaturated monosaccharides affording the *erythro* 2-isoxazolines preferentially. The diastereoselectivity is typically *ca* 85:15.

The next step along the proposed pathway to higher sugars is to gain access to one of the hidden functionalities of the isoxazoline, namely the β-hydroxy ketone (Scheme 47).



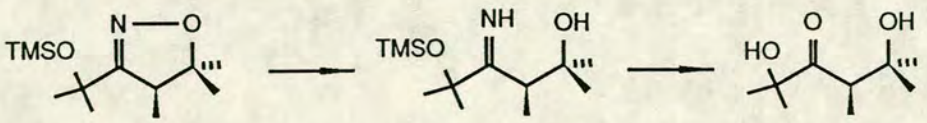
Scheme 47

The direct unmasking of a 2-isoxazoline to yield a β-hydroxy ketone was first reported in 1978 by Torssell[117] *et al.* The mechanism is believed to involve hydrogen addition across the N-O bond to afford the imine (**143**), which is either hydrolysed to the β-hydroxy ketone (**144**) or further reduced to the γ-amino alcohol (**145**) (Scheme 48). To ensure that hydrolysis proceeds at a much greater rate than reduction, appropriate conditions must be selected.[34] It has been reported that mildly acidic conditions (pH 5.5-6.0) and a metal supported catalyst are most favourable. These catalysts facilitate relatively easy cleavage of weak inter-heteroatom bonds. On the other hand, reduction of carbon-heteroatom multiple bonds is frequently slow, thus allowing hydrolysis to occur.



Scheme 48

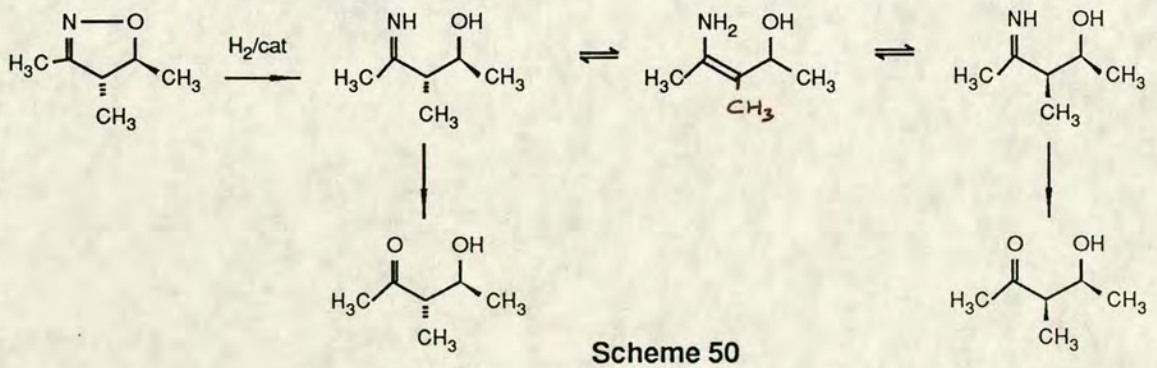
As a rule imine hydrolysis under these conditions is rapid and they cannot therefore be detected as intermediates. Curran[118] *et al*, however, have reported the isolation of one such species (**146**) (Scheme 49). The imine (**146**) was subsequently hydrolysed when resubjected to the reaction conditions. This provides strong evidence for the proposed mechanism. The slow rate of hydrolysis in this case was attributed to steric hindrance by the bulky tertiary trimethylsilyl ether, which was also cleaved in the second step.



(146)

Scheme 49

In some instances epimerisation is observed and a mixture of diastereomers is obtained. Curran[34] proposes that this occurs at the imine stage in cases where the rate of tautomerism is comparable to that of hydrolysis (Scheme 50).



Scheme 50

For the work presented here the chosen catalyst was 10% palladium-on-charcoal (Pd/C). Raney-nickel is the most common alternative, but the former is easier to handle and generally equally efficient. The appropriate pH was provided by 6 molar equivalents of boric acid in a methanol/water (5:1) solution. Other acids may be employed, but boric acid is considered to be especially effective at minimising epimerisation. This is attributed[34] to hydrolysis of the imine *via* a cyclic borate ester of the type illustrated in Figure 25, although no proof of this has been obtained.

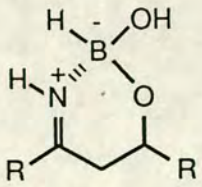
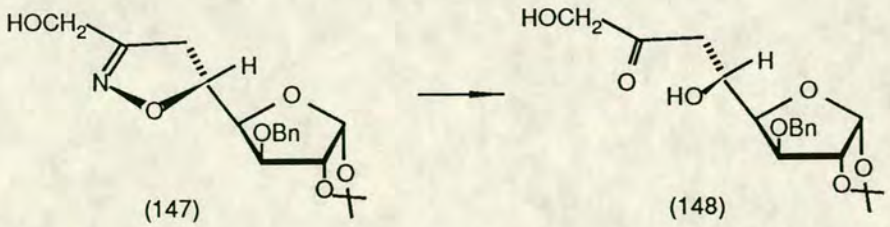


Figure 25.

The isoxazoline to β-hydroxy ketone transformations were conducted by following the same general procedure. The reaction mixture was degassed, flushed with hydrogen and then left to stir vigorously in an atmosphere of hydrogen at ambient temperature for 16 hours. After removal of the catalyst by filtration the solvent was evaporated. Methanol was added and evaporated several times to remove excess boric acid as the more volatile trimethylborate. The product is readily observed on t.l.c. by staining with Brady's reagent. It is more polar than the corresponding isoxazoline and so has a smaller R_f value on silica. In most cases it was found unnecessary to purify the crude product since the purity was estimated to be $> 90\%$ by ^{13}C n.m.r. Furthermore, on attempted purification by preparatory t.l.c. some of the material was not recovered.

2.5.1 Ring Opening of Isoxazolines Derived from *Xylo*-Alkene (94)

No reaction occurred upon subjecting carbethoxy-substituted isoxazoline (**119**) to the aforementioned conditions, the isoxazoline being recovered in quantitative yield. To overcome this problem, it was first converted to the 3-hydroxymethyl-substituted isoxazoline (**147**) by reduction[119] with sodium borohydride in ethanol. The latter isoxazoline was subsequently converted (Scheme 51) to the 6-deoxy-octosulose derivative (**148**)in 81% yield using the procedure outlined above.



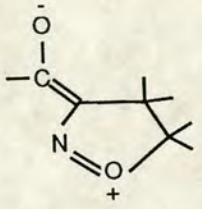
(147) (148)

Scheme 51

The product was characterised by its spectral properties. It shows a carbonyl absorption band in the i.r. spectrum at $1720cm^{-1}$. The presence of the carbonyl

group is also evident from the ^{13}C n.m.r. spectra which shows a peak at 209.6ppm. The ^{1}H n.m.r. spectrum is very similar to that of isoxazoline (**147**) except that the methylene protons, which are very close together in the isoxazoline, are now well separated. The chemical formula was verified by high resolution FAB mass spectrometry.

Difficulties in ring opening 3-carbethoxy-substituted isoxazolines to γ-amino alcohols have been reported[120] previously. The problem was attributed to the presence of the resonance form (**149**) acting to strengthen the N-O bond. It may therefore be assumed that the same effect operates in the present case and prevents the formation of the β-hydroxy ketone.

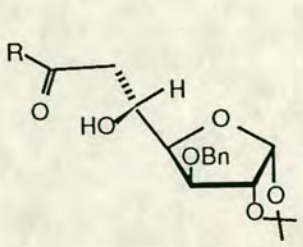


(149)

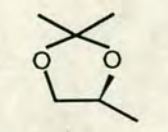
3-Phenyl-substituted isoxazolines, which may have similar resonance contributions, are reported[34] to produce the γ-amino alcohol rather than a β-hydroxy ketone on hydrogenation with a Pd/C catalyst. In contrast, hydrogenation catalysed by Raney-nickel affords the β-hydroxy ketone.

Since it was intended that the ester group would be reduced to hydroxymethyl in a subsequent step, it was decided not to investigate the ring opening of (**119**) with Raney-nickel catalysed hydrogenation.

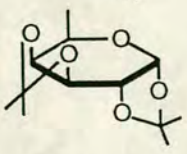
1,3-Dioxolane-substituted isoxazoline (**123**) was smoothly converted to β-hydroxy ketone (**150**) in 89% yield. The compound, which is a 6-deoxy-7-nonosulose derivative, was isolated as an oil. It was identified by its spectral properties and the chemical formula confirmed by high resolution FAB mass spectrometry. The presence of the carbonyl group is readily seen by the band in the i.r. spectrum at 1710cm^{-1} and in the ^{13}C n.m.r. spectrum at 210.8ppm.



(150) R =



(151) R =

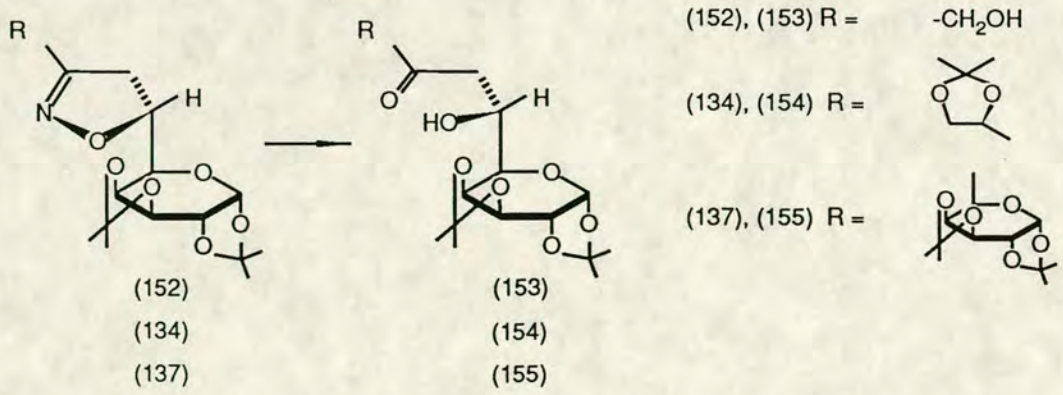


The corresponding dodecosulose derivative (**151**) was obtained by ring-opening of isoxazoline (**126**). Since the isoxazoline (**126**) was insoluble in the methanol/water solvent mixture, THF was added to aid dissolution. The rate of the reaction was much lower than in previous cases, and even after 24 hours some isoxazoline was still detectable by t.l.c. The product was separated from unreacted starting material by preparatory t.l.c. resulting in an isolated yield of 58%. The reason for the slower reaction rate is not known, but it may be associated with the increased bulk of the substituent at the 3-position of the isoxazoline ring. The β-hydroxy ketone (**151**) was identified by its spectral properties. In parallel with compounds (**148**) and (**150**) the presence of the carbonyl group was identified by its characteristic band in the i.r. spectrum at 1715cm^{-1} and in the ^{13}C n.m.r. spectrum at 209.4ppm.

The traditional method for removing a benzyl protecting group from a hydroxyl is by Pd/C-catalysed hydrogenation. There was no evidence of debenzylation occurring during any of the above isoxazoline ring-cleavage reactions. It maybe that the boric acid acts as a partial catalyst poison, thus lowering its ability to cleave the Bn-O bond.

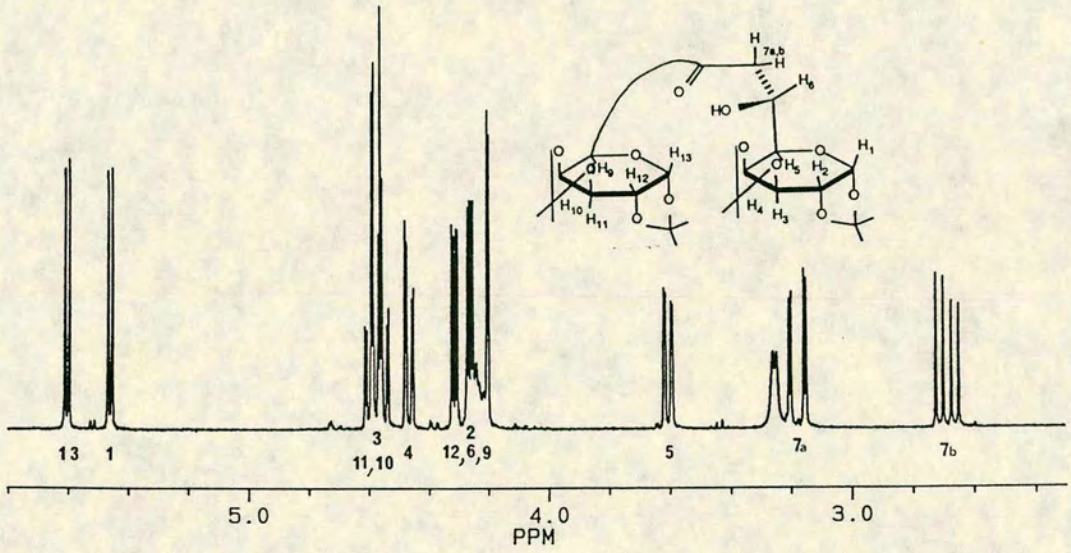
2.5.2 Ring Opening of Isoxazolines Derived from *Galacto*-Alkene (97)

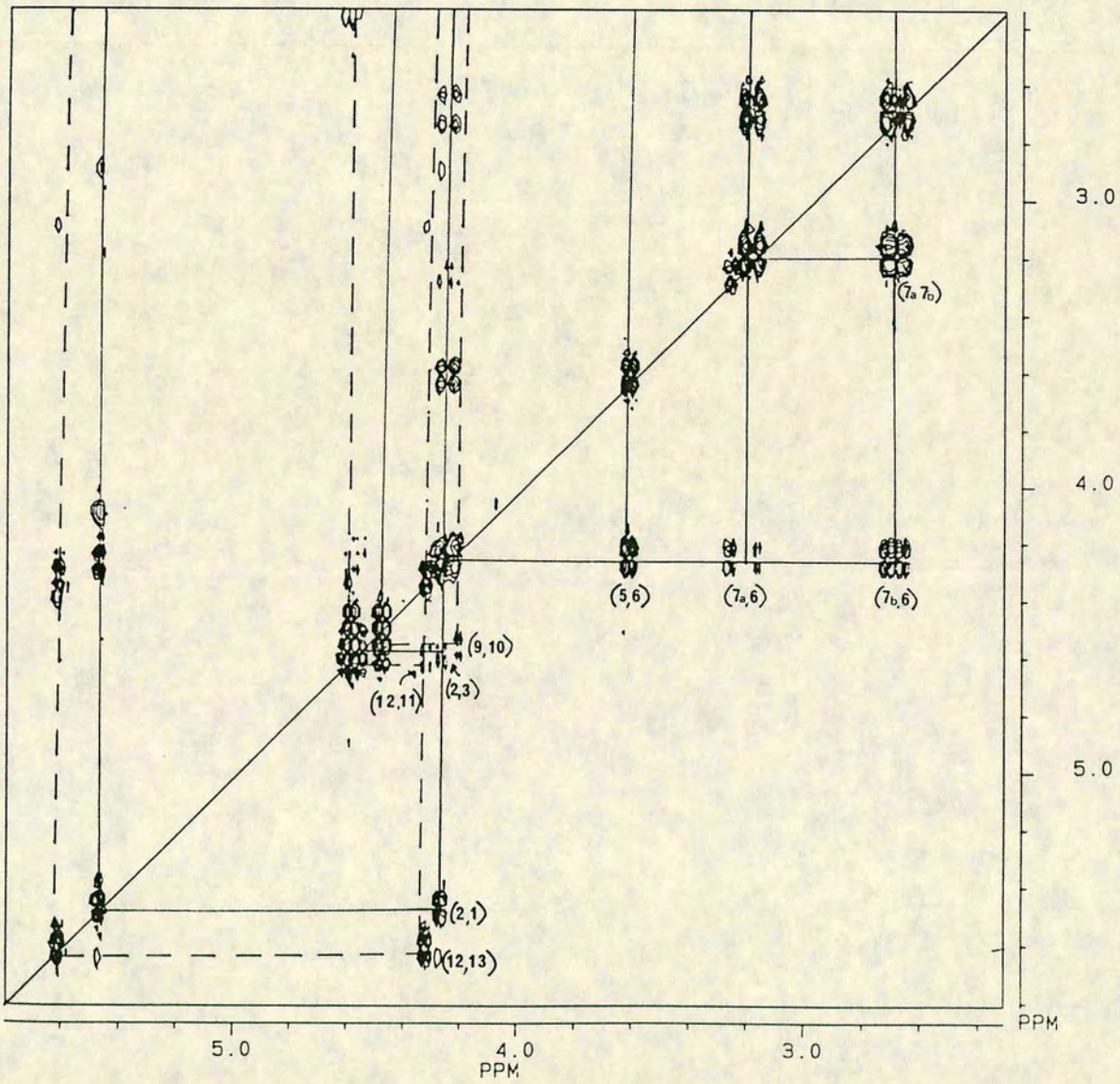
The reduction of the D-*Galacto*-alkene-derived isoxazolines (**152**), (**134**) and (**137**) to form the β-hydroxy ketones (7-deoxy-8-uloses) (**153**), (**154**) and (**155**) (Scheme 52) followed a similar pattern to the D-*xylo*-alkene-derived analogues.



Scheme 52

Figure 26.


13
1
3
11,10
4
2
12,6,9
5
7a
7b
5.0
4.0
3.0
PPM


(7a 7b)
(5,6)
(7a,6)
(7b,6)
(9,10)
(12,11)
(2,3)
(2,1)
(12,13)
3.0
4.0
5.0
PPM
5.0
4.0
3.0
PPM

They were identified by their spectral properties which all show the presence of the carbonyl group as discussed above.

The ester substituent at the 3-position of carbethoxy-isoxazoline (**132**) was first reduced to hydroxymethyl using sodium borohydride in ethanol. Subsequent ring opening to β-hydroxy ketone (**153**) resulted in 83% yield.

The 1,3-dioxolane-substituted isoxazoline (**134**) was smoothly converted to the corresponding 7-deoxy-8-decosulose derivative (**154**).

As with its *xylo*-alkene derived counterpart, isoxazoline (**137**) was insoluble in the reaction solvent. Therefore, THF was added as a co-solvent. Again the rate of reaction was much slower than for other cases. Even after 24 hours some remaining isoxazoline could be detected by t.l.c. β-Hydroxy ketone (**155**) was separated from unreacted starting material in 72% yield. The ^{1}H n.m.r. spectrum of (**155**) was assigned with the aid of the COSY spectrum shown in Figure 26. The methylene protons, H(7a) and H(7b), are easily identifiable as they occur in the same region of the spectrum and with the same pattern as other compounds in the series. The anomeric protons, H(1) and H(13), are assigned by comparison with the analogous protons in compounds (**151**), (**153**) and (**154**). Hence, H(13) is assigned to the peak at higher chemical shift and H(1) to the lower peak. Coupled protons are identified by off-diagonal (cross) peaks as indicated in Figure 26. The solid lines join protons from the alkene derived portion of the molecule and those from the nitrile oxide fragment are shown by dashed lines.

2.5.3 General Comparisons

The above results show that sugar substituted 2-isoxazolines may be unmasked affording the corresponding β-hydroxy ketones (deoxy-ulose derivatives) in good yield (58-89%). The compounds discussed share some notable characteristics.

IR. Each shows a strong carbonyl absorption in the region 1710-1720cm^{-1}. This value is consistent with that reported[117] for other β-hydroxy ketones.

^{13}C n.m.r. Chemical Shifts. The ^{13}C spectrum of each β-hydroxy ketone bears a close resemblance to that of the corresponding isoxazoline, except in the region shown in Figure 27. Table 4 compares typical δ_C values (ppm) for the carbons of the isoxazoline with those of the corresponding β-hydroxy ketone, showing the characteristic changes in chemical shift (illustrated by compounds (**126**) and (**151**)).

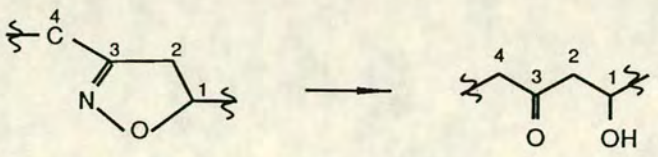


Figure 27.

Carbon	1	2	3
Isoxazoline (**126**)	76.2	39.2	158.6
β-Hydroxy Ketone (**151**)	64.5	44.4	209.4

Table 4.

The chemical shift for C(4) increases by *ca* 10ppm from the isoxazoline to β-hydroxy ketone, but the actual position varies according to the substituent (see experimental section).

^{1}H n.m.r. Spectra. The only significant differences between the ^{1}H n.m.r. spectra of the isoxazolines and the corresponding β-hydroxy ketones occur in the region associated with the moiety shown in Figure 28. This parallels the findings from the ^{13}C n.m.r. spectra. Table 5 illustrates the differences in both δ_H value (ppm) and coupling constant (J/Hz) for H(1), H(2a) and H(2b). Isoxazoline (**126**) which resulted from the combination of D-galactose-derived nitrile oxide (**125**) and *xylo*-alkene (**94**), and the corresponding β-hydroxy ketone derivative (**151**) represent typical examples.

Figure 28.

	H(1)	H(2a)	H(2b)	$J_{1,2a}$	$J_{1,2b}$	$J_{2a,b}$
Isoxazoline (**126**)	4.88	3.29	3.20	6.4	10.1	17.9
β-Hydroxy Ketone (**151**)	4.47	3.18	2.77	2.6	9.4	18.4

Table 5.

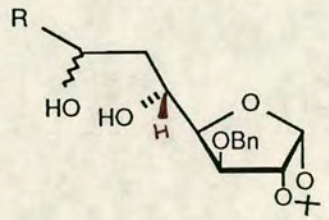
2.6 Reduction of β-Hydroxy Ketones to 1,3-Diols

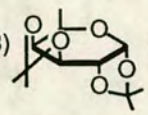
In the previous section it has been shown that the sugar substituted isoxazolines readily undergo Pd/C-catalysed hydrogenation-hydrolysis to afford β-hydroxy ketones (deoxy-uloses) in good yield. The next step towards the target higher sugar molecules is to reduce the carbonyl group to a secondary alcohol. In the process a new chiral centre is created. This provides two challenges: the first to carry out the reduction stereoselectively; and secondly to identify the stereochemistry of the products.

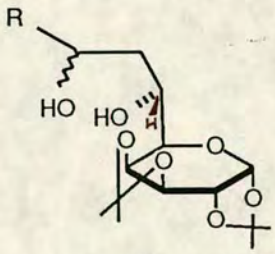
2.6.1 Using Sodium Borohydride

Sodium borohydride in an ethanol/water solvent mixture was the first reagent chosen. The products were purified by chromatography and characterised by ^{1}H n.m.r. spectroscopy. Verification of the chemical formulae were obtained by high resolution FAB mass spectrometry. The diastereomers were labelled **A** and **B** according to their order of elution on t.l.c.

The 1,3-diols obtained by the reduction of the corresponding β-hydroxy ketones are shown below with their yield and isolated ratios **A**:**B**.



	R	A : B, Yield (%)
(156)	$HOCH_2$-	2 : 1, 65
(157)		2 : 3, 73
(158)		5 : 1, 86



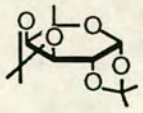
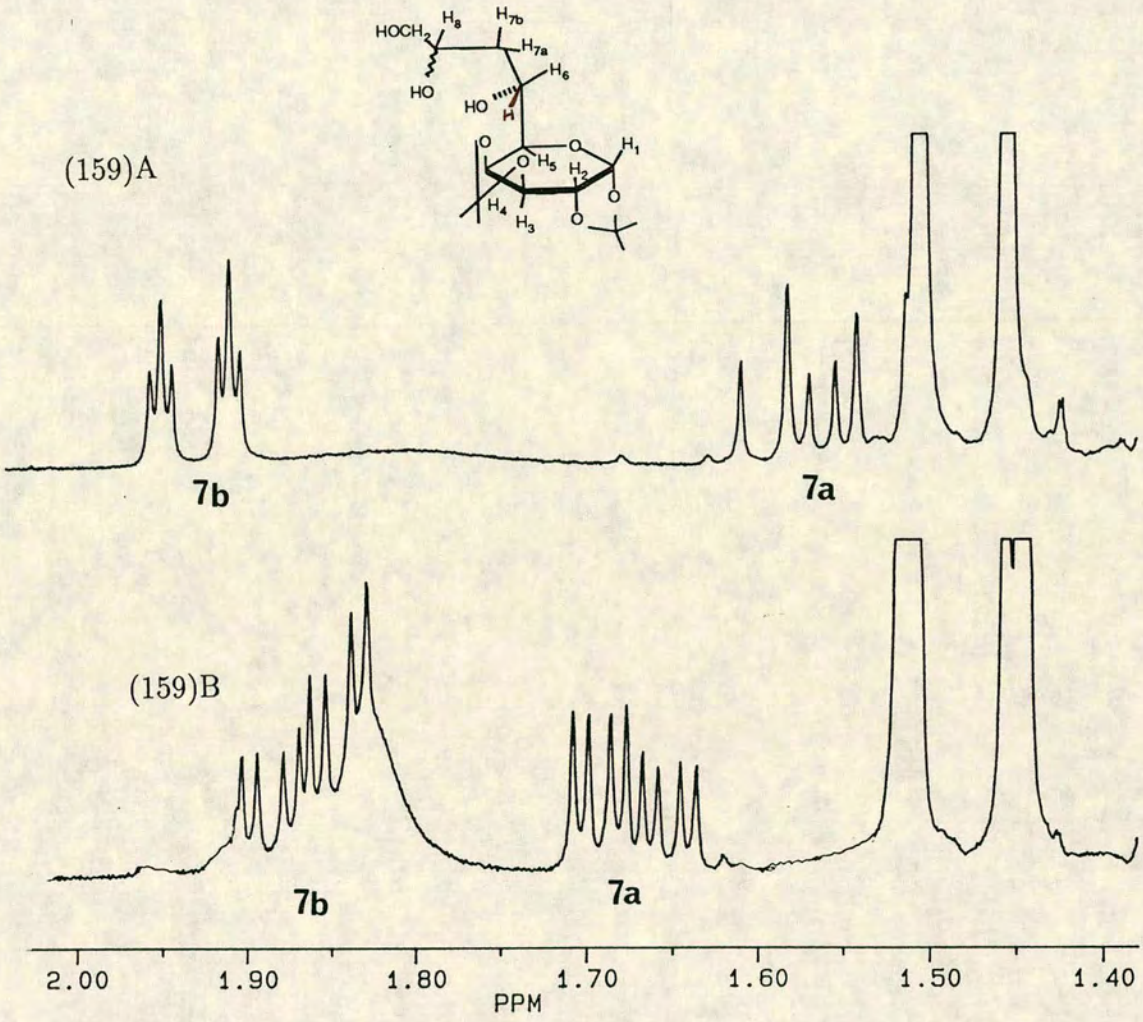
	R	A : B, Yield (%)
(159)	$HOCH_2$-	4 : 5, 33
(160)		4 : 5, 60
(161)		1 -, 62

Figure 30.



The 6-deoxy-dodecosulose (**151**) and 7-deoxy-tridecosulose (**155**) derivatives were insoluble in the ethanol/water solvent system. THF was therefore added as a co-solvent. In the case of the latter compound, only one of the two possible diastereomers, (**161**)**A**, was detected. This compound contains a number of pairs of similar protons since the 1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-pyranose ring is the substituent at both ends of the 1,3-diol system. The ^{1}H n.m.r. spectrum of this compound shows distinct characteristics for both the alkene and nitrile oxide derived portions. The spectrum was assigned with the aid of a COSY spectrum and by comparison with analogous compounds. Full ^{1}H n.m.r. data for all the 1,3-diols can be found in Tables 24 and 25.

2.6.2 General Comparisons

Sodium borohydride achieves a degree of stereoselectivity, if somewhat random in nature, in the reduction of the β-hydroxy ketones to afford deoxy-higher sugars. In the case of compound (**155**) the reagent was stereoselective with only one 1,3-diol, (**161**)**A**, being detected.

The most noteworthy differences in the ^{1}H n.m.r. spectra in changing from β-hydroxy ketone to 1,3-diol are in the signals associated with H(2a) and H(2b) of the fragment illustrated in Figure 29. Replacement of the carbonyl functionality with a -CHOH- group results in the methylene protons being less deshielded. Consequently, they move to a lower δ-value. They also exhibit an additional coupling to H(3). H(4) is similarly affected and the spectra show an extra multiplet, corresponding to H(3).

Figure 29.

The diastereomeric 1,3-diols were arbitrarily labelled **A** and **B** relating to their order of elution on t.l.c. However, from the ^{1}H n.m.r. spectra a characteristic pattern can be seen in the region associated with H(2a) and H(2b) (Figure **30**), which allows the two types to be distinguished. For type **A** these protons both appear as a doublet of triplets; H(2a) has a small triplet coupling, whereas that for H(2b) is large. The pattern for type **B** 1,3-diols, by contrast, consists of two

multiplets of eight lines, one for H(2a) and the other representing H(2b). This characteristic difference between the diastereomeric 1,3-diols is illustrated in the region of the ^{1}H n.m.r. spectra shown in Figure 30. Table 6 shows the position (ppm) and coupling constants (J/Hz) of H(2a) and H(2b) as a comparison of the epimeric 1,3-diols (**159**)A and (**159**)B and the corresponding β-hydroxy ketone (**153**).

	H(2a)	H(2b)	$J_{2a,b}$	$J_{2a,1}$	$J_{2b,1}$	$J_{2a,3}$	$J_{2b,3}$
(153)	2.56	2.80	16.5	3.4	8.1	-	-
(159)A	1.93	1.56	14.5	2.3	10.1	2.3	10.1
(159)B	1.87	1.67	14.5	3.3	7.9	8.9	3.3

Table 6.

The coupling constants for isomer **A** are consistent with those expected for a chair conformation, i.e. axial-axial (10-13Hz) and axial-equatorial or equatorial-equatorial (2-5Hz). This indicates that the 1,3-diol system forms a hydrogen bonded six-membered ring in a chair conformation (Figure 31). In the case of isomer **A**, both substituents (R and R') can occupy the sterically less crowded equatorial positions. This accounts for the observed pattern: H(2b) has two large axial-axial couplings, and H(2a) has two small axial-equatorial couplings. In order for isomer **B** to exist in a chair conformation, one of the substituents must occupy the axial position. This is energetically unfavourable and, as the coupling constants shown in Table 6 indicate, the conformation is distorted from that shown in Figure 31.

On this basis, the stereochemistry at the new chiral centre is assigned as S for isomers **A** and R for isomers **B**.

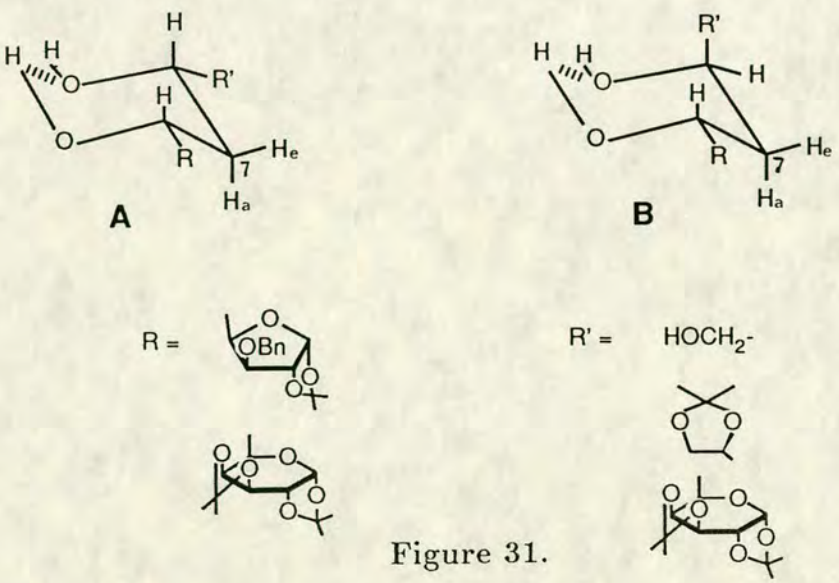
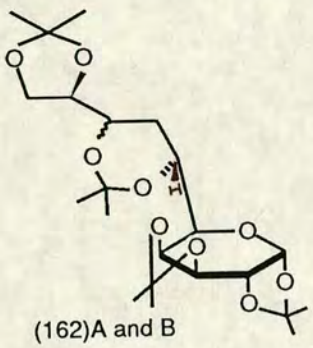


Figure 31.

2.6.3 Determination of the Stereochemistry at the New Chiral Centre

In order to confirm the above assignments it was necessary to link the free hydroxyl groups together, thus forming a six-membered ring. This was achieved by preparation of the corresponding isopropylidene ketal, a technique which has previously been employed[77] to determine the configuration of other carbohydrate derived 1,3-diols.

The 7-deoxy-decose derivatives (**160**)**A** and **B** were reacted with an acetone/dimethoxy propane mixture in the presence of a catalytic amount of *p*-toluenesulphonic acid to afford the isopropylidene ketals (**162**) **A** and **B** respectively.



(162)A and B

A pure sample of each was obtained by chromatography and studied by ^1H n.m.r. spectroscopy. The region of interest is the 1,3-dioxan ring. The coupling constants (Table 7) for isomer **A** are consistent with the six-membered ring adopting a chair conformation having both substituents (R and R') equatorially positioned (Figure 32). This confirms the S configuration at C(8) since the C(6) stereochemistry is known to be R. Isomer **B**, correspondingly, must have R configuration at C(8). The coupling constants of this latter compound indicate that it does not adopt the chair conformation shown in Figure 32 in which one group would be forced into the energetically unfavourable axial position.

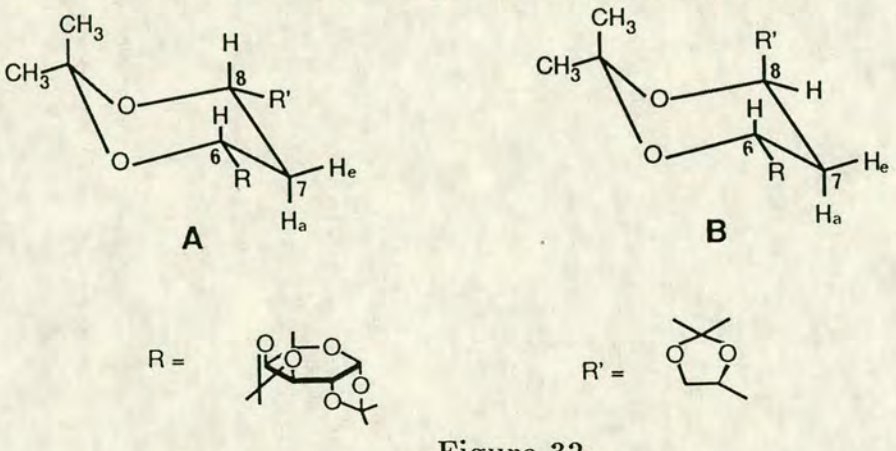


Figure 32.

	$J_{6,7a}$	$J_{6,7e}$	$J_{7a,7e}$	$J_{7a,8}$	$J_{7e,8}$
A	11.6	2.5	13.1	11.6	2.5
B	9.2	6.1	13.0	6.3	9.8

Table 7.

NOe measurements provide additional evidence in support of the chair conformation for isomer **A**. The percentage enhancements are shown in Table 8.

Proton Irradiated	7a	7e	8	6	Me
7a	-	21	-	-	-
7e	21	-	6	4	-
8	-	4	-	4	1
6	-	3.5	2	-	1

Table 8.

These results demonstrate that H(7e), H(8) and H(6) are relatively close in space, and hence must be on the same side of the molecule. Irradiation of both H(8) and H(6) result in an enhancement of a methyl group. This is consistent with the structure shown in Figure 32. An indication of the orientation of groups R and R' is also obtained. Both H(5) and H(9) are enhanced as a result of irradiation of H(7a). By contrast, no effect is observed on either H(5) or H(9) by irradiation of H(7e), H(8), or H(6). This suggests a molecular geometry in which H(5) and H(6) are antiperiplanar. A similar relationship exists between H(8) and H(9).

The results of an analogous nOe study for isomer **B** are shown in Table 9.

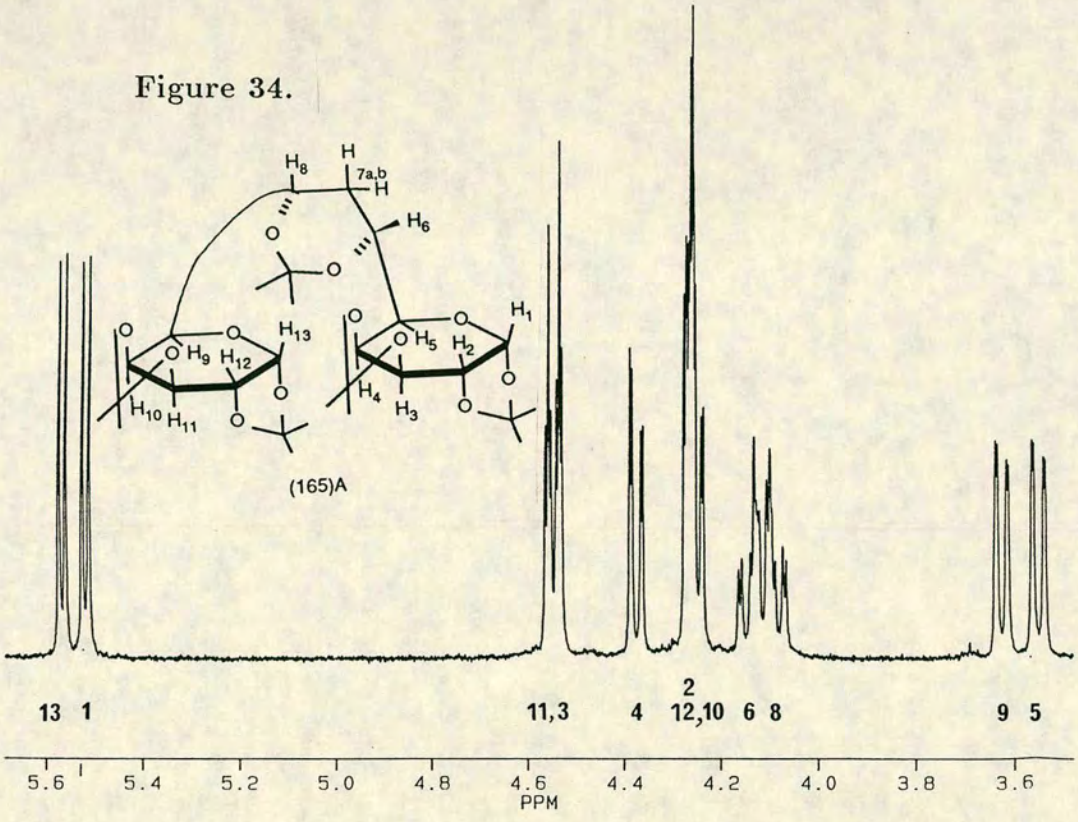
Proton Irradiated	7a	7b*	6	8	Me
7a	-	-	7.5	-	-
7b	14	-	-	7	-
6	6	-	-	-	-
8	-	-	-	-	1

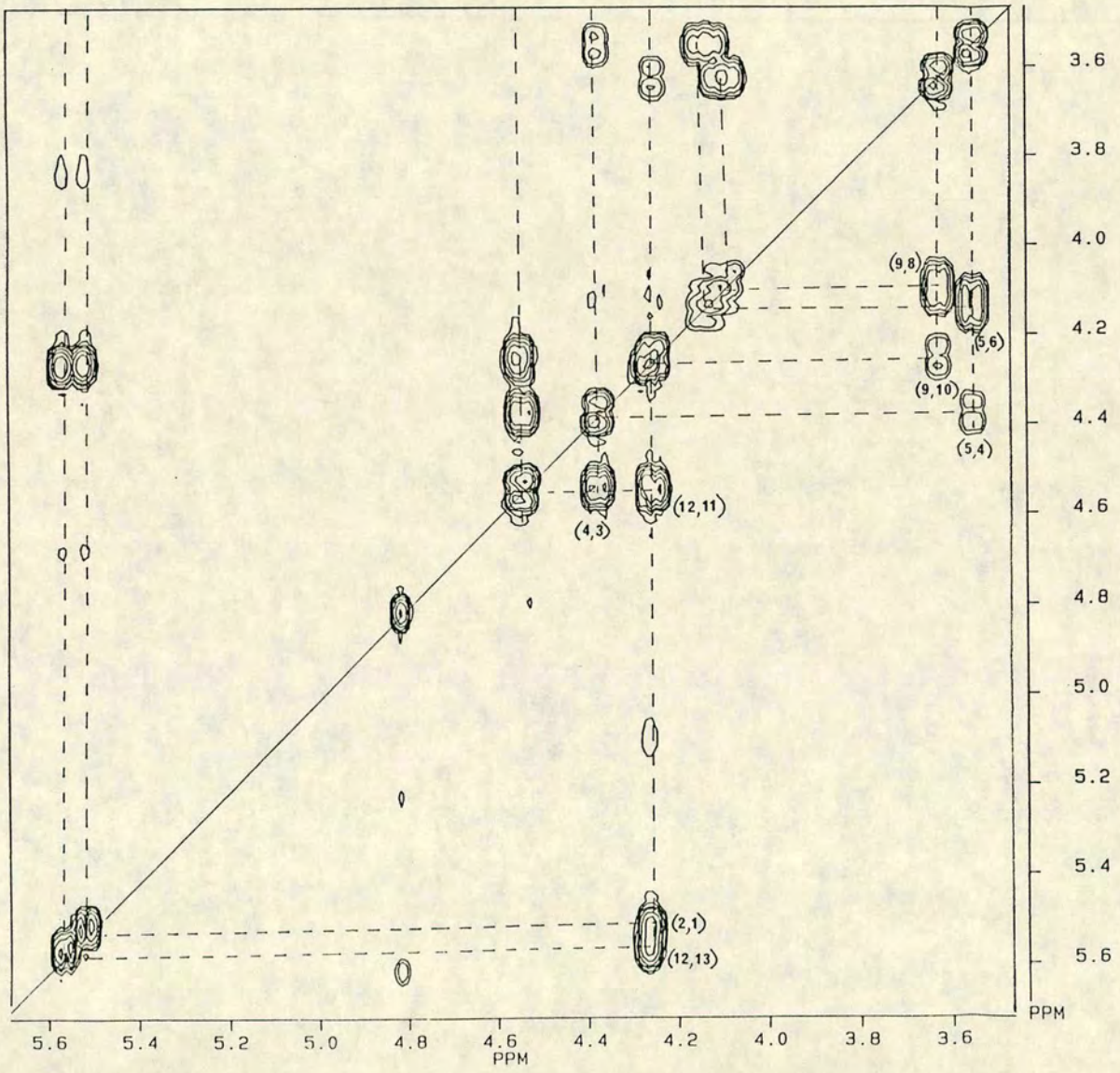
Table 9.

* no enhancements are detectable due to the proximity to methyl groups

From these results, it appears that H(7a) is on the same side of the molecule as H(6), whereas H(7b) is close in space to H(8) and a methyl group. this indicates

Figure 34.


(165)A
13 1
11,3
4
2
12,10
6 8
9 5
5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6
PPM


(9,8)
(5,6)
(9,10)
(5,4)
(12,11)
(4,3)
(2,1)
(12,13)
3.6 3.8 4.0 4.2 4.4 4.6 4.8 5.0 5.2 5.4 5.6
PPM
5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6
PPM

a boat-type arrangement (Figure 33), in which the two substituent groups, R and R', adopt pseudo equatorial positions.

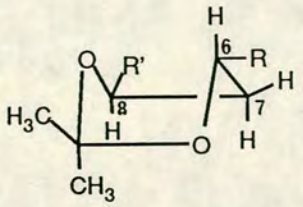


Figure 33.

Isopropylidene ketals (**163**)**A** and **B**, (**164**)**A** and (**165**)**A** were synthesised from the corresponding 1,3-diols. The ^{1}H n.m.r. spectrum of (**165**)**A** was assigned by comparing the chemical shift values with those of (**164**)**A** which has the same nitrile oxide derived moiety and (**162**)**A** which was synthesised from the same alkene. Thus the signal associated with H(4) was identified. Using the COSY spectrum illustrated in Figure 34 coupled protons can be identified *via* the cross peaks as marked. The anomeric proton at higher chemical shift was assigned to H(13) by comparison with the analogous proton in other compounds in the series.

The coupling constants (J/Hz)for the protons in the 1,3-dioxan ring are shown in Table 10. They parallel the findings discussed above; those of type **A**, having S configuration at the new chiral centre, adopt a chair conformation with the two substituents equatorially positioned. Correspondingly, type **B** isomers have R configuration at the new chiral centre and prefer to exist in a more boat-like arrangement.

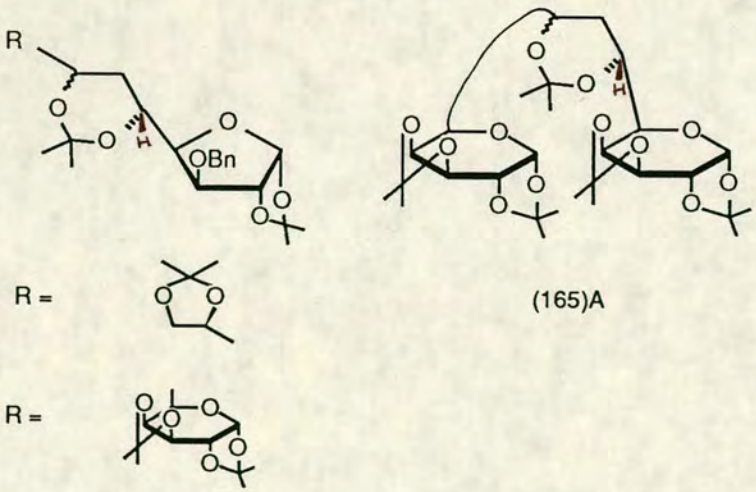
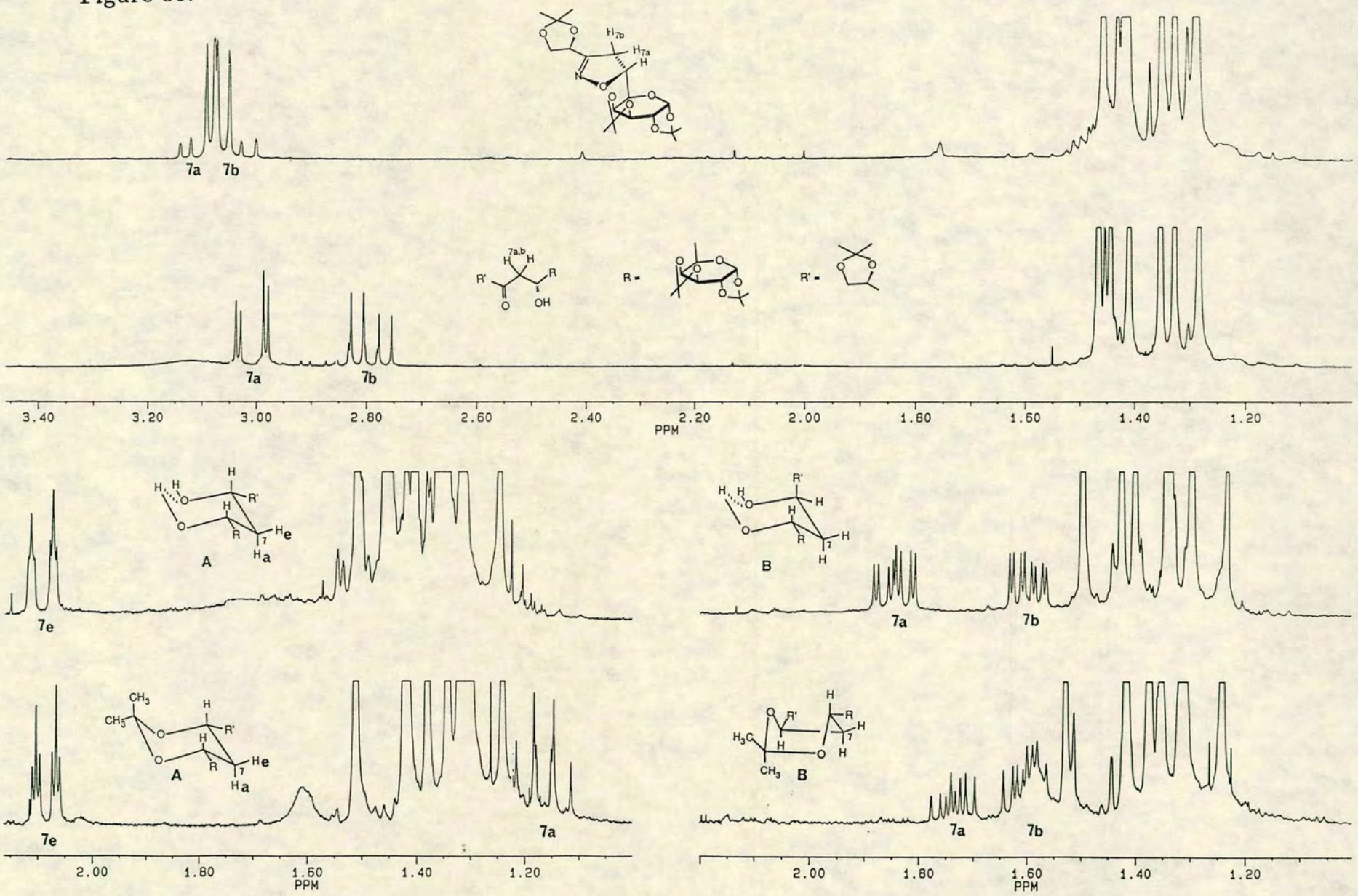
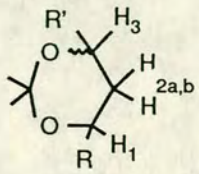


Figure 35.


7a
7b
7a,b
R' =
R =
OH
3.40
3.20
3.00
2.80
2.60
2.40
2.20
2.00
1.80
1.60
1.40
1.20
PPM
A
B
7e
7a
7b
2.00
1.80
1.60
1.40
1.20
PPM



	$J_{1,2a}$	$J_{1,2b}$	$J_{2a,2b}$	$J_{2a,3}$	$J_{2b,3}$
(162)A	11.6	2.5	13.1	11.6	2.5
(162)B	9.2	6.1	13.0	6.3	9.8
(163)A	11.6	2.5	13.1	11.6	2.5
(163)B	8.9	6.3	13.1	6.5	9.4
(164)A	12.0	2.6	12.7	12.0	2.6
(165)A	11.7	2.5	12.5	11.7	2.5

Table 10.

Full ^{1}H n.m.r. data for all the isopropylidene ketals discussed above can be found in Tables 28 and 29.

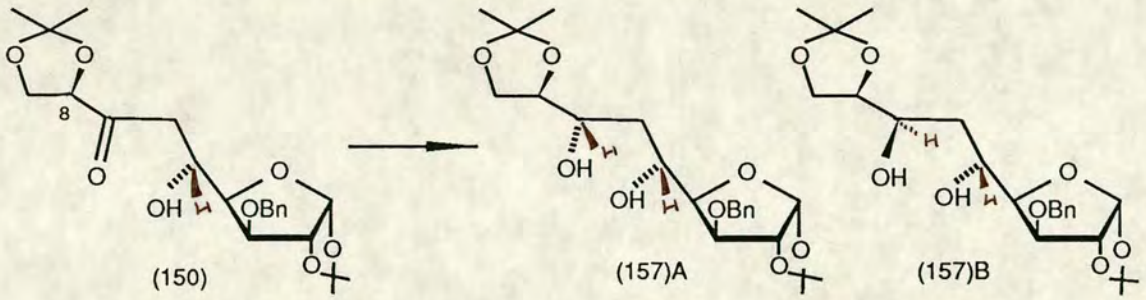
The foregoing results have demonstrated that a sugar substituted isoxazoline may be transformed into a β-hydroxy ketone, which in turn can be reduced to furnish a pair of epimeric 1,3-diols. As a result of intramolecular hydrogen bonding, the ^{1}H n.m.r. spectra of these epimers gives an indication of the stereochemistry at the new chiral centre and proof of the configuration is provided by examining the ^{1}H n.m.r. spectra of the corresponding isopropylidene ketals.

Figure 35 highlights the characteristic changes in the ^{1}H n.m.r. pattern of the methylene protons going from isoxazoline, through β-hydroxy ketone and epimeric 1,3-diols, to the isopropylidene ketals. The isoxazoline (**134**) formed by addition of glyceraldehyde derived nitrile oxide (**121**) to *galacto*-alkene (**97**) and its subsequent products are used as a typical example.

Triol derivatives (**156**)**A** and (**159**)**A** are assigned S stereochemistry at the new chiral centre by comparison of their ^{1}H n.m.r. spectra with those of others of type **A**. Correspondingly R configuration is assigned to (**156**)**B** and (**159**)**B**.

2.6.4 Investigation of Stereocontrol in Reduction of Nonosulose Derivative (150)

In an attempt to introduce a measure of stereocontrol into the carbonyl reduction reaction, a range of reducing reagents were examined. β-Hydroxy ketone (**150**) was the first substrate chosen. It was thought that the chiral centre at C(8) and the bulk of the 1,3-dioxolane substituent may influence the stereoselectivity of the reduction. The ratio of the 7S and 7R epimers, (**157**)**A** and **B** respectively, was obtained by h.p.l.c. analysis. Table 11 shows the ratio obtained for each reagent. Although the degree of stereoselectivity varies significantly, from 5:95 with L,S-selectride to 42:58 with DIBAL-H, formation of isomer **B** is favoured in every case.



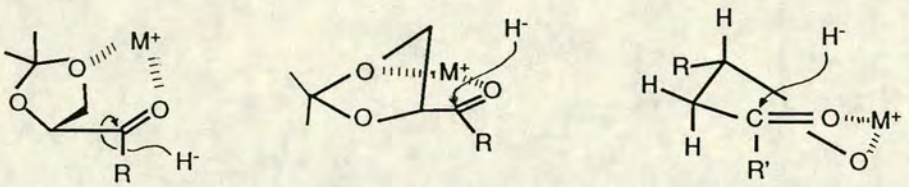
Reagent	(157)A		(157)B
$NaBH_4$	28	:	72
$LiAlH_4$	30	:	70
Borane	39	:	61
$ZnBH_4$	32	:	68
DIBAL-H	42	:	58
L-selectride	6	:	94
L,S-selectride	5	:	95

Table 11.

2.6.5 Rationalisation of Stereoselectivity

Reduction of the carbonyl group of the 6-deoxy-nonosulose derivative (**150**) resulted in preferential formation of (**157**)**B** with each reagent investigated. The favoured 1,3-diol has R stereochemistry at the new chiral centre. This imparts the C(5)-C(7) *anti* and C(7)-C(8) *threo* configurations upon the compound.

The asymmetric reduction of chiral carbonyl compounds is of great synthetic interest and a number of theoretical models[121] have been postulated to explain the observed outcome. The principal two are the chelate model and the Felkin-Anh model. The former involves complexation of a metal counter ion to both the oxygen of the carbonyl and another suitably placed ligand to form a cyclic arrangement. In compounds where there are a number of such ligands, several chelate structures are feasible. Possible arrangements for compound (**150**) are shown in Figure 36 together with the preferred direction of attack.



(i) α-chelation (ii) β-chelation (iii) β-chelation

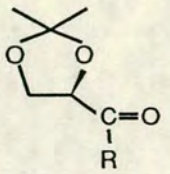
Figure 36.

Only one of these, (ii), would result in the formation of the observed product in the present case. However, not all of the reagents used are known to chelate. For example, L-selectride (lithium tri-s-butylborohydride) is a bulky reagent and owes its high stereoselectivity simply to approaching from the less hindered face.

The alternative, non-chelate, Felkin-Anh[82,111] model involves hydride attack on a staggered orientation of the substituents, and favours the *threo* (*anti*) product. The stereoselectivity observed for the reduction of (**150**) can therefore be attributed to a process occurring *via* a Felkin-Anh type transition state as shown in Figure 37.

Figure 37.

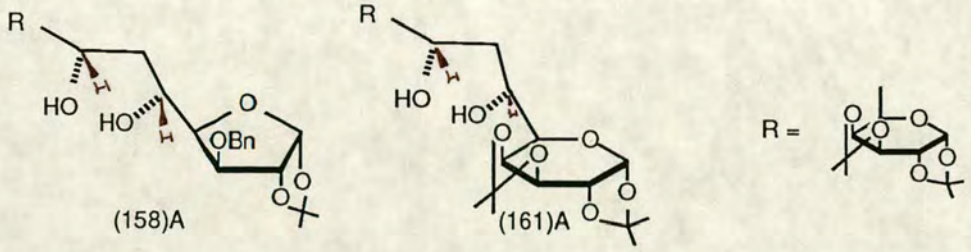
This is in accord with analogous results reported[121] for the reduction of glyceraldehyde derivatives (**106**) and (**166**) to the corresponding secondary alcohols, for which the formation of the *anti* (*threo*) product was ascribed to hydride addition *via* the Felkin-Anh model.



(106) R = H

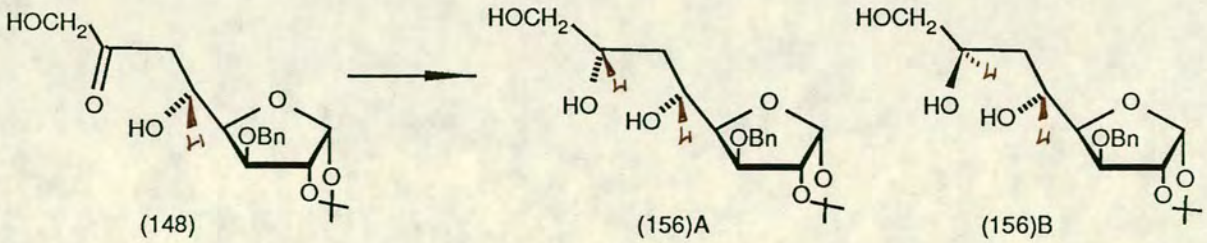
(166) R = CH_3

The high stereoselectivities obtained from the sodium borohydride mediated reduction of the *galacto*-nitrile oxide derived dodecosulose and tridecosulose derivatives, (**151**) and (**155**) respectively, may also be rationalised using this model. The 7,8-*anti* (*threo*) isomer (**158**)**A** was favoured 5:1 over its C(7) epimer and the 8,9-*anti* (*threo*) compound (**161**)**A** was the only isomer detected upon reduction of the corresponding β-hydroxy ketone (**155**).



2.6.6 Investigation of Stereocontrol in Reduction of Octosulose Derivative (148)

For comparison, the reduction of β-hydroxy ketone (**148**) was subjected to further study. In contrast to (**150**), (**151**), (**154**), and (**155**) it contains a free hydroxyl group α to the carbonyl. There is therefore, neither a chiral centre nor bulky group to influence the direction of reduction, but the adjacent hydroxyl group could provide an alternative mode of complexation. Three reagents were chosen for study: L-selectride which was the most selective in the previous case, DIBAL-H which was least selective, and sodium borohydride. The diastereomeric mixture was analysed by h.p.l.c. and the ratios are shown in Table 12.



Reagent	(156)A		(156)B
$NaBH_4$	70	:	30
L-selectride	69	:	31
DIBAL-H	38	:	62

Table 12.

For sodium borohydride and L-selectride, isomer **A**, which has the 5,7-*syn* configuration, is the major product. In contrast for DIBAL-H the 5,7-*anti* arrangement is favoured. The formation of isomer **A** may be visualised as occurring *via* hydride attack on the carbonyl group in the hydrogen bonded arrangement illustrated in Figure 38. In this the bulky furanose substituent occupies the less sterically demanding equatorial position.

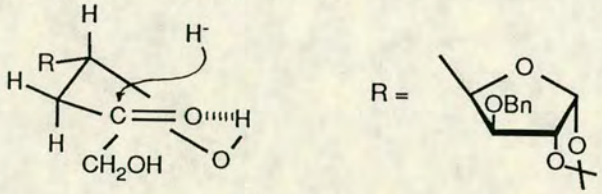
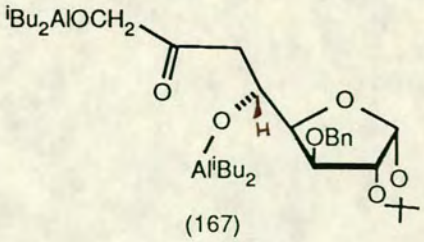


Figure 38.

DIBAL-H is reported to co-ordinate to oxygen;[122,123] however, in the presence of free hydroxyl groups it may react to form oxygen-aluminium bonds. For the present work two molar equivalents of DIBAL-H were used and it may be proposed that it all reacts with the hydroxyl groups to give compound (**167**).



(167)

Reduction may then occur *via* a mechanism similar to that proposed for TRIBAL (tri-isobutylaluminium), involving intramolecular transfer of hydride[124] (Figure 39) from the isobutyl group.

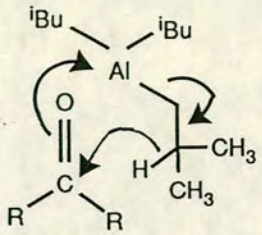


Figure 39.

If the hydride transfer occurs from a group attached to the β-oxygen, delivery of hydride would be expected to be from the more hindered face,[125] *syn* to the β-oxygen, resulting in the *anti* 1,3-diol. By contrast, if the hydride originated from the group bonded to the terminal oxygen then no directional preference would be predicted (Figure 40). Therefore, in this latter case approximately equal amounts of the *syn* and *anti* products would be obtained. A process occurring *via* both the above routes would account for the observed preference for the *anti* product but the relatively low levels of selectivity.

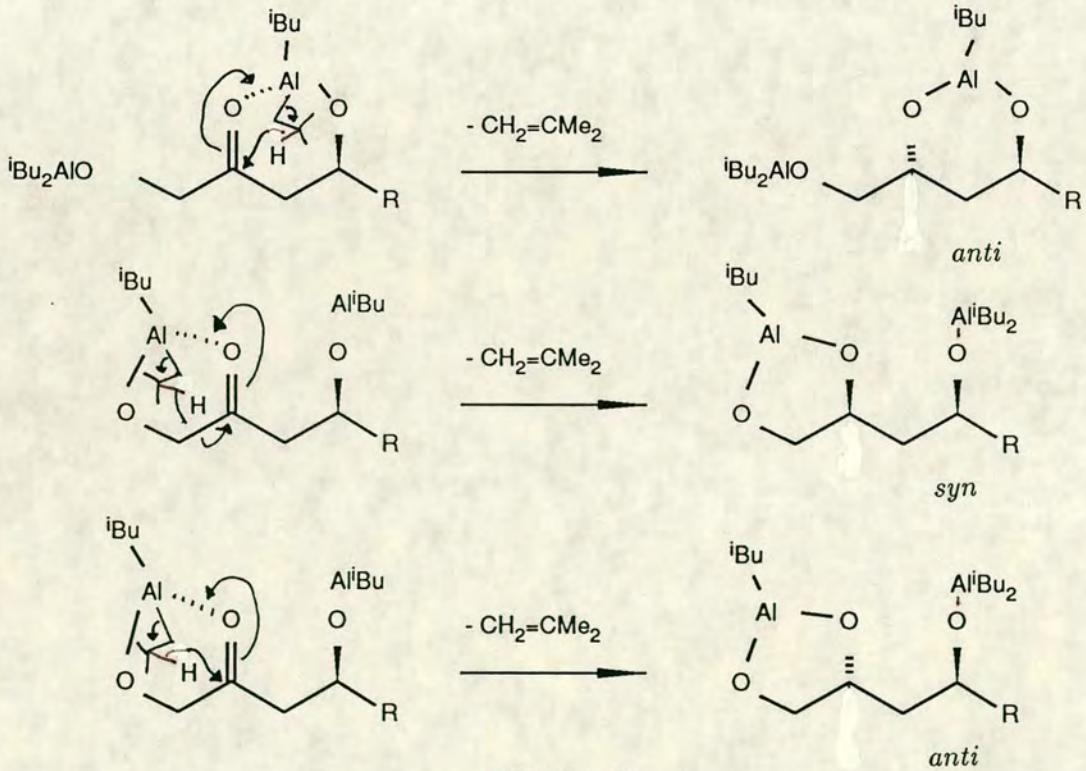
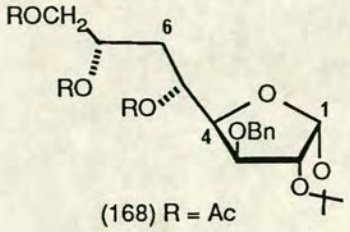


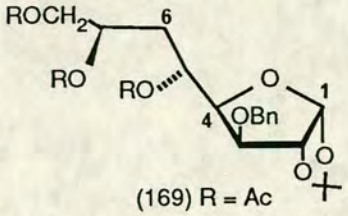
Figure 40.

2.7 Synthesis of Tri-*O*-mesylate and Tri-*O*-acetate Derivatives of Compounds (156)A and B

The 5,7,8-tri-*O*-acetate derivatives (**168**) and (**169**) and the mesylate analogues (**170**) and (**171**) were prepared by conventional routes from the corresponding triols (**156**)**A** and **B**.



(168) R = Ac
(170) R = Ms
(156)A R = H



(169) R = Ac
(171) R = Ms
(156)B R = H

They were characterised by ^{1}H n.m.r. and ^{13}C n.m.r. and the formulae were verified by high resolution FAB mass spectrometry, but since non of the compounds were solids X-ray structure determination was not possible.

The ^{1}H n.m.r. spectra of compounds (**168**) and (**170**) do not show the two large diaxial type couplings for H(6b) and the small axial-equatorial couplings for H(6a) which were characteristic of the associated triol (**156**)**A**. This is further evidence of the hydrogen bonding present in the latter compound, between the 5- and 7-position hydroxyl groups as illustrated in Figure 31. This intramolecular hydrogen bonding is no longer possible after derivatisation.

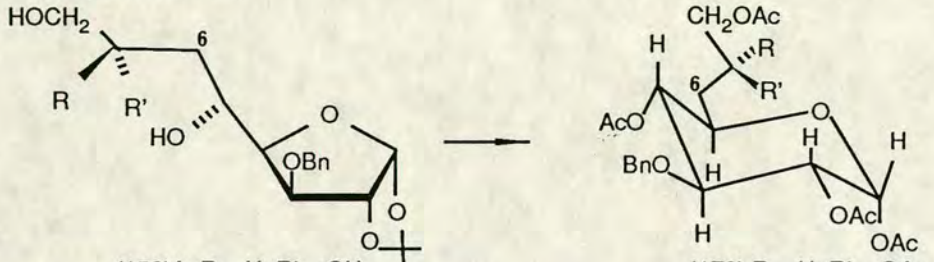
The chemical shifts of the protons on the furanose ring are not altered significantly compared to the corresponding triol. The protons on the carbons 5 to 8 have moved to higher δ values, consistent with their proximity to the electron withdrawing groups. Table 13 shows the δ_H value (ppm) of selected protons, as a comparison with the free triol species.

Compound	H(1)	H(5)	H(6a)	H(6b)	H(7)	H(8a)	H(8b)
(156)A	5.91	4.18	1.82	1.56	3.97	3.42	3.58
(168)	5.88	5.14	2.37	2.37	5.14	4.25	4.45
(170)	5.88	5.25	2.19	1.98	5.15	4.00	4.24

Table 13.

2.8 Conversion of Octofuranose Compounds (156)A and B to Penta-acetate Derivatives

To investigate further the stereochemistry at C(5), the chiral centre created in the nitrile oxide cycloaddition step, the octofuranose derivatives (**156**)**A** and **B** were converted into their penta-acetate derivatives. The 1,2-*O*-isopropylidene protecting group in (**156**)**A** was removed by hydrolysis with trifluoroacetic acid and water and the residue acetylated using zinc chloride as a catalyst to afford the penta-acetate (**172**) as an oil after chromatography. The C(7) epimer (**173**) was obtained as a white solid by similar treatment of the corresponding triol (**156**)**B** (Scheme 53).



(156)A R = H, R' = OH
(156)B R = OH, R' = H

(172) R = H, R' = OAc
(173) R' = OAc, R = H

Scheme 53

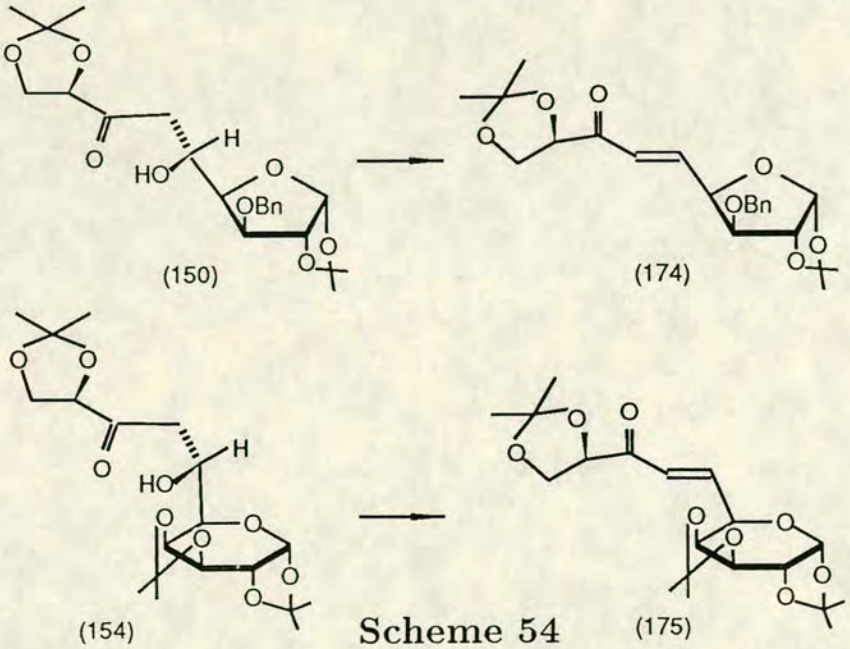
The products were identified by their spectral properties. The ^{1}H n.m.r. spectra were assigned with the aid of some proton decoupling experiments. The spectra for the two isomers are very similar with the exception of the signals associated with the methylene protons H(6a) and H(6b). In (**172**) they each appear as an eight line doublet-of-doublet-of-doublets; however, in compound (**173**) the chemical shift values for these protons are very close and a second order multiplet is observed. The ^{1}H n.m.r. coupling constants are consistent with both molecules having formed a pyranose ring. The large $J_{2,3}$, $J_{3,4}$, and $J_{4,5}$ values (all 9.8Hz in each epimer) indicate that H(2), H(3), H(4) and H(5) are all axial and the bulky acetoxy and benzyl ether groups occupy the sterically less demanding equatorial positions. The small $J_{1,2}$ value (3.8Hz for each epimer) is evidence that the α-anomer has been formed in each case. These coupling constants confirm the α-D-*gluco* stereochemistry of the pyranose ring and hence R configuration at C(5).

2.9 Synthesis of α-Enones

The previous sections have addressed the formation of β-hydroxy ketones by hydrogenation-hydrolysis of sugar substituted isoxazolines. Subsequent reduction furnished diastereomeric 1,3-diols which are deoxy-higher sugars. However, as indicated in the Introduction (1.5), this is only one of a number of latent functionalities that may be derived from an isoxazoline.

An α-enone may be obtained directly[126] from the isoxazoline by treatment with titanium chloride and hydrochloric acid in DMF. Alternatively, dehydration of the isolated β-hydroxy ketone affords the same product. The dehydration is carried out most simply by acetylation which is followed by spontaneous elimination of acetic acid.[4] For this reason β-hydroxy ketones require mild selective protection. The resulting α-enones are versatile synthons as they can undergo a variety of reactions including osmylation and Michael additions which allow the introduction of new functionalities.

β-Hydroxy ketones (**150**) and (**154**) were dehydrated by stirring with acetic anhydride in pyridine at room temperature for 48 hours to yield the α-enones (**174**) and (**175**) respectively (Scheme 54). The products were identified by their spectral properties and the chemical formulae verified by high resolution FAB mass spectrometry. The large vicinal coupling constants (15.8Hz) for the alkene protons is evidence for the formation of the *trans* isomer; the *cis* isomers were not detected. These observations parallel literature reports[4] for the dehydration of β-hydroxy ketones.



(150) (174)

(154) (175)

Scheme 54

On changing from the β-hydroxy ketone to α-enone, the characteristic pair of doublet of doublets representing the methylene protons, H(6a) and H(6b) for (**150**) and H(7a) and H(7b) for (**154**), at *ca* 3ppm have been replaced by the alkene proton pattern at 6.7-7.0ppm. The enone proton, H(3) in Figure 41, shows a small coupling (1.5 and 1.8Hz for (**174**) and (**175**) respectively) to the allylic proton H(1).

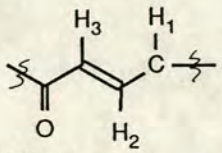


Figure 41.

In the ^{13}C n.m.r. spectra the carbonyl peak is at 298ppm, typical of α-β-unsaturated carbonyl groups. The olefinic carbons, C(2) and C(3) in Figure 41, resonate at 126 and 142ppm respectively. These are higher than for typical alkene carbon atoms, an effect attributable to conjugation to the carbonyl group. The C=C peak at 1630cm^{-1} in the i.r. spectrum of each compound is also indicative of conjugation to the carbonyl group; the non-conjugated absorption appears at *ca* 1670cm^{-1}.

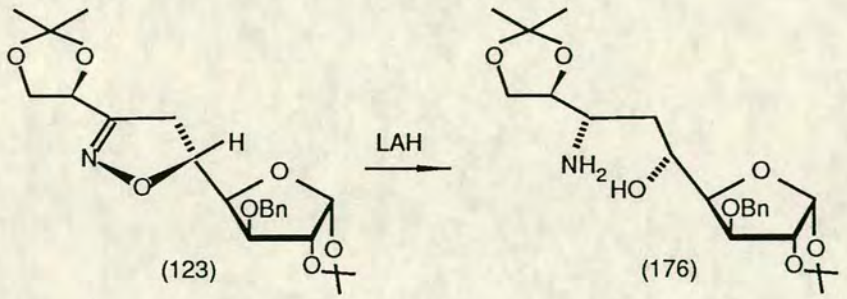
2.10 Conversion of Carbohydrate Isoxazoline to γ-Amino Higher Sugar

The γ-amino alcohol unit is present in a variety of natural products, including amino polyols, amino sugars and amino acids, many of which exhibit biological activity. Jäger[33] *et al* have shown that this functionality may be obtained easily and in good stereoselectivity by reaction of the 2-isoxazoline ring with lithium aluminium hydride (LAH). Using nitrile oxide/isoxazoline methodology they have synthesised a number of natural products containing the γ-amino alcohol moiety, e.g. D-allosamine (see 1.5.1.2).

In contrast to the formation of β-hydroxy ketones, which involves initial hydrogen addition to the N-O bond, in the LAH mediated synthesis of γ-amino alcohols the C=N bond is reduced first, followed by cleavage of the N-O bond of the resulting isoxazolidine.

Isoxazoline (**123**) was subjected to LAH reduction (Scheme 55). The ^1H n.m.r. spectrum of the crude product revealed that it was mainly (>90%) one compound. A sample was purified by chromatography affording a single isomer, (**176**), which

was characterised by ^{1}H and ^{13}C n.m.r. spectroscopy and the chemical formula verified by FAB high resolution mass spectrometry.



Scheme 55

The ^{1}H n.m.r. spectrum of (**176**) was assigned with the aid of decoupling experiments. It is very similar to that of 1,3-diol analogue (**157**)**A** in which C(7) has a hydroxyl substituent in the place of the amino group. The most noteworthy feature is the pattern for H(6a) and H(6b) which both appear as a doublet of triplets. One has a large geminal coupling (14.2Hz) and two small vicinal couplings (2.0Hz each), typical of axial-equatorial arrangements; the other also displays the large geminal coupling, but has two large vicinal couplings (10.6Hz each) associated with axial-axial arrangements. This indicates that (**176**) has the same C(7) stereochemistry as (**157**)**A**, i.e. 7S, and that it adopts an intramolecular hydrogen bonded chair conformation with the sugar substituents in the equatorial positions (Figure 42).

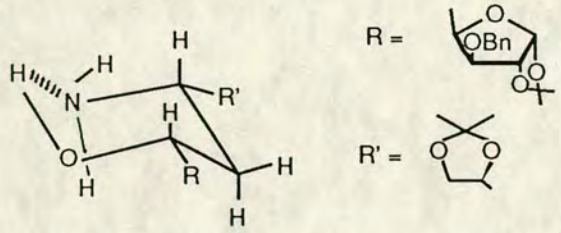


Figure 42.

Jäger[33] has used a similar argument to establish the stereochemistry of reduction products. He found that in most cases the major diastereomer has a 1,3-*syn* arrangement of amino and hydroxyl groups. To rationalise the stereochemistry of the LAH-mediated reduction, it was proposed that the lithium ion co-ordinates to the ring oxygen in the transition state and hydride delivery occurs from the face opposite the 5-position substituent (Figure 43).

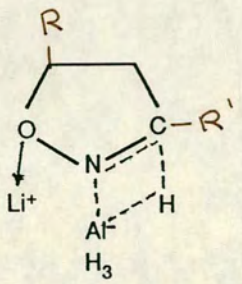


Figure 43.

For isoxazoline (**176**) the predominant direction of hydride delivery must therefore be *anti* to the furanose ring, as shown in Figure 44. The ^{13}C n.m.r. spectra for 1,3-diol (**157**)**A** and γ-amino alcohol (**176**) are similar. The only exceptions to this are in the position for C(5) and C(7). The C(5) peak appears at 72.5ppm in the 1,3-diol but has a lower δ-value, 69.6ppm, for the γ-amino alcohol. A larger difference is observed in the position of C(7); this carbon resonates at 70.2ppm in (**157**)**A** and 53.6ppm for the amino compound. These are typical values for a hydroxyl and amino substituted carbon atom respectively.

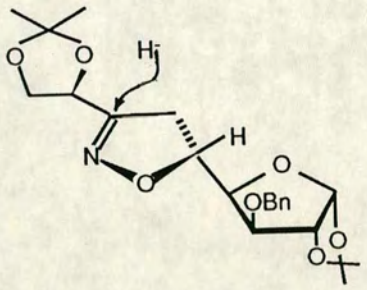
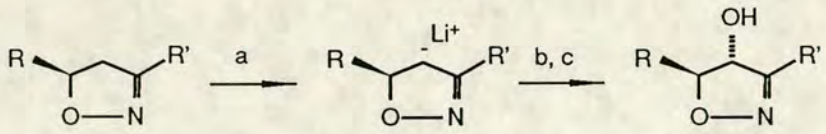


Figure 44.

2.11 Conclusions and Further Work

The work described in this thesis demonstrates that nitrile oxide/isoxazoline methodology is an effective route to higher carbon monosaccharides. Cycloaddition of a sugar derived nitrile oxide and an ω-unsaturated monosaccharide furnishes a 2-isoxazoline in good yield (typically 70%) and with high stereoselectivity (typically 85:15 in favour of the *erythro* isomer). The dipole and dipolarophile are easily prepared from a wide range of readily available, inexpensive monosaccharides, thus allowing the inclusion of a variety of stereochemistries in the final product. The Pd/C catalysed hydrogenation-hydrolysis facilitates the unmasking of the β-hydroxy ketone functionality, which is subsequently reduced to the 1,3-diol with excellent stereoselectivity in some cases.

The compounds synthesised during the course of this work are deoxy-higher sugars. To obtain the fully oxygenated species a hydroxyl functionality needs to be introduced at the 6-position for D-glucose derived products or the 7-position for D-galactose derived products. The most efficient method of achieving this would be to apply the methodology developed by Jäger[127] *et al*, whereby the hydroxyl is introduced at the 4-position of the isoxazoline ring. This involves deprotonation using LDA followed by an oxidative work-up(Scheme 56). Good to excellent stereoselectivities have been reported favouring the 4,5-*anti* configuration.



Scheme 56

(a) LDA -65 → -78°C (b) $B(OCH_3)_2$ (c) oxidation

It may be, however, that less efficient approaches such as epoxidation or osmylation of the α-enone would give alternative product stereochemistry, thus further extending the scope of this route. The limitations of the cycloaddition stereochemistry require to be investigated, especially in the light of the poor stereoselectivity obtained with *ribo*-alkene (**102**).

In summary, this work has generated some promising results regarding the stereoselective synthesis of higher carbon monosaccharides employing nitrile oxide/isoxazoline chemistry.

3 Experimental

3.1 General

3.1.1 Glossary of Terms, Symbols and Abbreviations

atm.	atmosphere
BNO	benzonitrile oxide
b.p.	boiling point
COSY	COrrelation SpectroscopY
DEPT	Distortionless Enhancement by Polarisation Transfer
DMF	N,N-dimethylformamide
DMSO	dimethylsulphoxide
ether	diethyl ether
FAB	Fast Atom Bombardment
FAB, g	Fast Atom Bombardment using glycerol matrix
FAB, t	Fast Atom Bombardment using thioglycerol matrix
FMO	Frontier Molecular Orbital
g	gram
g.c.	gas chromatography
h	hour
HOMO	Highest Occupied Molecular Orbital
h.p.l.c.	high performance liquid chromatography
Hz	Hertz
INOC	Intramolecular Nitrile Oxide Cycloaddition
i.r.	infra-red
J	coupling constant
LAH	Lithium Aluminium Hydride
lit.	literature value
LUMO	Lowest Unoccupied Molecular Orbital
M	Moles per litre
M^+	molecular ion
M equiv.	Molar 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
NOC	Nitrile Oxide Cycloaddition
n.O.e.	nuclear Overhauser enhancement
PCC	pyridinium chlorochromate
p.s.i.	pounds per square inch
TFA	trifluoroacetic acid
THF	tetrahydrofuran
t.l.c.	thin layer chromatography
TMS	tetramethylsilane
TOCSY	TOtal Correlation SpectroscopY
U.V.	Ultra Violet
$[\alpha]$	optical rotation
δ	chemical shift
$\nu_{max.}$	wave number of absorbance maximum

3.1.2 Instrumentation

3.1.2.1 Elemental Analysis

Elemental analyses were performed by Mrs E. McDougall using a Carlo Erba elemental analyser model 1106.

3.1.2.2 Infra-red Spectroscopy

Infra-red spectra were recorded as films, nujol mulls or solutions on a Perkin Elmer 781 spectrometer.

3.1.2.3 Mass Spectrometry

FAB spectra and exact mass measurements were recorded by Mr A. Taylor on a Kratos MS50TC instrument using either a glycerol (g) or thioglycerol (t) matrix.

3.1.2.4 Melting Points

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

3.1.2.5 Nuclear Resonance Spectroscopy

All ^{1}H and ^{13}C n.m.r. spectra were recorded on Bruker WP200SY and WH360 or Varian VSX600 instruments by Miss H. Grant, Mr J.R.A. Millar, Dr D. Reed and Dr I. Sadler. Two-dimensional and n.O.e. spectra were recorded on the WH360 machine.

Chemical shifts (δ) in all spectra are measured in parts per million using tetramethylsilane (δ=0.0) as a reference signal.

Unless stated otherwise the solvent was deuterated chloroform ($CDCl_3$).

3.1.2.6 Optical Rotation

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

3.1.2.7 X-ray Crystallography

The X-ray diffraction analyses were performed on a Stoë STADI-4 four circle diffractometer by Dr A. Blake and Dr R.O. Gould and in part (Appendix F) by David Cooper.

3.1.3 Chromatography

3.1.3.1 High Performance Liquid Chromatography

H.p.l.c. analyses were performed using a Cecil Instruments CE 212 variable wavelength U.V. monitor at 254nm and an Altex model 110A pump.

3.1.3.2 Gas Liquid Chromatography

G.l.c analyses were carried on a Pye Unicam Series 204 chromatograph fitted with a flame ionisation detector. The nitrogen carrier gas flow rate was 60ml/min, the hydrogen at 70ml/min and the air at a pressure of 16psi.

3.1.3.3 Thin Layer Chromatography

Preparative t.l.c. was carried out on glass plates (20cm×20cm) coated with a layer (0.5mm) of Kieselgel GF_{254} silica 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} (0.2mm).

Detection was achieved by U.V. irradiation (254nm), iodine vapour staining, Brady's reagent staining or acid-charring using 10% sulphuric acid solution and a hotplate.

3.1.3.4 Dry Flash Chromatography

Dry flash column chromatography was performed using a variety of sinters with different diameters filled with Kieselgel 60 silica and eluted under a vacuum suplied by a water pump.

3.1.4 Solvents and Reagents

All reagents were standard laboratory grade and were used as supplied unless specifically stated in the text.

Solvents for general use were standard laboratory grade and used as supplied unless specifically stated in the text.

Dry ether and benzene were analar grade solvents and dried over sodium wire.

Dry acetone was analar grade acetone stored over type 4A molecular sieve.

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

Dry dichloromethane was freshly distilled from calcium hydride.

Dry THF was always freshly distilled from sodium and benzophenone.

Methanol was dried by distillation from calcium hydride and stored over molecular sieve.

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

Dry DMSO was prepared by allowing the solvent to stand over activated calcium sulphate for 24h, filtering and distilling from calcium hydride under water pump vacuum. The distilled solvent was stored over molecular sieve.

Dry chloroform was obtained by distillation from phosphorus pentoxide and stored over molecular sieve.

H.p.l.c. solvents were h.p.l.c. grade and were degassed before use by applying a water pump vacuum to the solvent contained in a flask.

3.2 Synthesis of Sugar Alkenes

3.2.1 3-*O*-Benzyl-1,2-*O*-isopropylidene-5-deoxy-α-D-*xylo*-furanose-5,6-ene (94)

This alkene was prepared in four steps from commercially available diacetone-D-glucose according to Scheme 30.

3.2.1.1 3-*O*-Benzyl-1,2:5,6-di-*O*-isopropylidene-α-D-*gluco*-furanose (91)

This was prepared by the method of Iwashige and Saeki.[93] Sodium hydride (80% dispersion in mineral oil, 5.16g) in DMSO (60ml) was stirred at room temperature under nitrogen. A solution of diacetone-D-glucose (22.5g, 8.7mmol) in DMSO (60ml) was added dropwise and the resulting mixture stirred for 45min before adding benzyl chloride (25ml) dropwise and continuing stirring for 1h. The mixture was poured onto an ice/water slurry (300ml) and extracted into ether (3×250ml). The solvent was removed *in vacuo* to yield an oil which was dissolved in petrol (b.p. 60-80°C, 200ml) and washed with water (4×100ml) to remove any unreacted diacetone-D-glucose. The organic layer was dried over $MgSO_4$ and the solvent removed *in vacuo* to yield an oil as the crude product. *m/z* (FAB, g) 351 (M^++1), 335, 273.

3.2.1.2 3-*O*-Benzyl-1,2-*O*-isopropylidene-α-D-*gluco*-furanose (92)

This was prepared according to the literature.[94] The crude product from the previous stage, in a mixture of water (40ml) and glacial acetic acid (60ml), was stirred at 40°C for 16h. The solution was neutralised by the dropwise addition of a saturated aqueous solution of potassium carbonate. The product was extracted into chloroform (3×100ml), dried over $MgSO_4$ and the solvent evaporated *in vacuo* to yield an oil. This crude product was used for the next step.

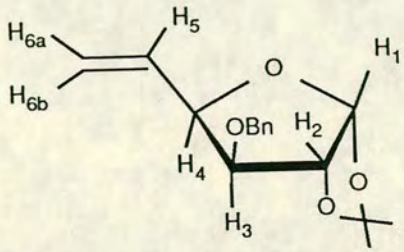
3.2.1.3 3-*O*-Benzyl-1,2-*O*-isopropylidene-5,6-bis-*O*-methanesulphonyl-α-D-glucofuranose (93)

Prepared according to the method of Paulsen and Stoye.[95] Methanesulphonyl chloride (11ml) was added to a solution of the crude product from 3.2.1.2 in pyridine (35ml), cooled in an ice/salt bath and left to stir for 16h, forming

a brown solid. This was dissolved in a mixture of water (50ml) and chloroform (50ml). The aqueous layer was extracted with chloroform (3×25ml), the combined organic layers washed with 1M sulphuric acid (50ml) then saturated sodium hydrogen carbonate solution (50ml) and dried over $MgSO_4$. The volume was reduced to half by evaporation *in vacuo*, and decolourising charcoal added. The solution was refluxed for 30min, filtered and the solvent removed to yield a yellow solid. Recrystallisation from ethanol afforded fine white needles (23.0g, 57% from diacetone-D-glucose), m.p. 123.5-125°C, lit.,[95] 124-125°C; *m/z* (FAB, g) 467 (M^++1), 465, 451.

3.2.1.4 3-*O*-Benzyl-1,2-*O*-isopropylidene-5-deoxy-α-D-*xylo*-furanose-5,6-ene (94)

This was prepared by reduction[96] of (**93**). The dimesyl compound (**93**) (12.8g, 27.5mmol), sodium iodide (20.6g, 137.5mmol, dried over P_2O_5), Zn/Cu couple (freshly prepared from 9.0g zinc powder[128]), DMF (130ml), and dimethoxyethane (22ml) were stirred together under reflux for 70min. After cooling to 50°C the mixture was poured onto water (500ml) with rapid stirring. Toluene (200ml) was added and the mixture filtered through celite. The filter pad was washed with toluene (2×200ml) and the washes used to extract the aqueous phase. The combined organic extracts were washed with water (2×100ml), dried over $MgSO_4$, filtered and evaporated *in vacuo* to a syrup, which was purified by dry flash chromatography on silica using 30% ether/hexane as eluent, to afford an oil (6.05g, 80%); δ_H(360Mz) see Table (14); *m/z* (FAB, g) 277 (M^++1), 261, 219.



Resonance	δ_H(ppm)	Coupling	J/Hz
H(1)	5.97	1,2	3.8
H(2)	4.63	2,3	-
H(3)	3.89	3,4	3.2
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
$PhC\underline{H}_2$	4.55, 4.65	$PhC\underline{H}_2$	12.1
Ph	7.26-7.36		
CH_3	1.32, 1.52		

Table 14.

3.2.2 6,7-Di-deoxy-1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-hept-6-enopyranose (97)

This alkene was prepared in three steps from D-galactose, according to Scheme 31

3.2.2.1 1,2;3,4-Di-*O*-isopropylidene-α-D-*galacto*-pyranose (95)

This was prepared according to the literature.[97] Powdered D-galactose (20.0g, 0.11mol), anhydrous copper sulphate (43.7g, 0.27mol) , concentrated sulphuric acid (2.2ml) and dry acetone (440ml) were vigorously stirred together for 24h. The copper sulphate was removed by filtration and powdered calcium hydroxide (20.0g, 0.35mol) added to the filtrate and stirred for 4h, before removing by filtration through celite. The filter pad was washed with acetone and the acetone fractions combined. The solvent was removed on a rotary evaporator firstly at 15-20mmHg and latterly at 1mmHg to remove the final traces of solvent. The

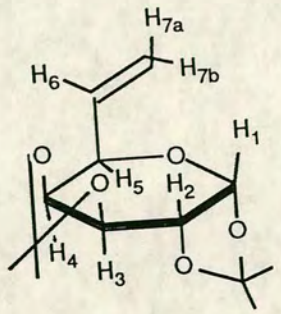
resulting yellow oil was purified by Kugelrhor distillation to yield a colourless oil (23g, 79%); b.p. 140°C, 0.05mmHg (lit.,[97] 135°C, 0.01mmHg); *m/z* (FAB, g) 261 (M^++1), 245, 127.

3.2.2.2 1,2:3,4-Di-*O*-isopropylidene-α-D-*galacto*-hexodialdo-1,5-pyranose (96)

1,2:3,4-Di-*O*-isopropylidene-D-*galacto*-pyranose (**95**) (11.0g, 40mmol) in dry dichloromethane (20ml) was added to a suspension of PCC (18g) in dry dichloromethane (500ml). The resulting mixture was stirred overnight, before the addition of ether (500ml). The solution was filtered through celite and the solvent removed *in vacuo* to yield a brown oil, which was purified by wet flash chromatography on silica using 45% ether/hexane as eluent and a pressure of 5psi. The fractions were monitored by g.c. analysis at 150°C, using a 1m long column packed with OV1 2.5% and a gas flow rate of 60cm/min. The pure aldehyde was obtained as a colourless oil (5.5g, 51%); $\nu_{max.}$ (film) 1740cm^{-1} (C=O); *m/z* (FAB, t), 259 (M^++1), 243, 233, 201, 159, 143.

3.2.2.3 6,7-Di-deoxy-1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-hept-6-enopyranose (97)

Potassium t-butoxide (7.3g, 65mmol) in dry THF (50ml) was added to a suspension of methyl triphenylphosphonium iodide (17.4g, 40mmol) in dry THF (100ml) under nitrogen. After 30min, a solution of the aldehyde (**96**) (5.5g, 20mmol) in dry THF (50ml) was added dropwise. The resulting solution was left to stir at room temperature overnight under nitrogen before pouring onto water (100ml) and extracting with chloroform (4×100ml). The combined chloroform extracts were dried over $MgSO_4$ and the solvent removed *in vacuo*. The resulting oil was purified by dry flash chromatography on silica, using 25% ether/hexane as eluent to yield the pure alkene (**97**) as an oil (4.5g, 83%); δ_H (360Mz) see Table (15); *m/z* (FAB, g) 257 (M^++1), 241, 199, 185, 141.



Resonance	δ_H(ppm)	Coupling	J/Hz
H(1)	5.51	1,2	5.1
H(2)	4.25	2,3	2.4
H(3)	4.55	3,4	7.8
H(4)	4.15	4,5	1.8
H(5)	4.22	5,6	6.0
H(6)	5.86	6,7a	10.6
H(7a)	5.19	6,7b	17.3
H(7b)	5.29	7a,7b	1.5
CH_3	1.47, 1.39		
	1.27		

Table 15.

3.2.3 3-*O*-Benzyl-1,2-isopropylidene-5-deoxy-α-D-*ribo*-furanose-5,6-ene (102)

This alkene was prepared in six steps from commercially available diacetone-D-glucose according to Scheme 32[93–96]

3.2.3.1 1,2:5,6-Di-*O*-isopropylidene-5-deoxy-α-D-*allo*-furanose

This was prepared by the literature route.[99] Diacetone-D-glucose (10g, 38.5mmol) was added to a stirred mixture of dry DMSO (80ml) and dry acetic anhydride (20ml) at 70°C under nitrogen. Stirring was continued for 1h before removing the solvent *in vacuo* at *ca* 70°C to an oil. The oil was dissolved in ethanol (60ml), cooled on an ice bath, and sodium borohydride (1.2g, 31.6mmol) added in portions. The solution was stirred overnight while warming to room temperature. The solvent was removed *in vacuo* and the resulting oil dissolved

in a mixture of chloroform (20ml) and water (60ml). The layers were separated, the aqueous layer extracted with chloroform (3×20ml), and each extract washed with the same portion of water (15ml). The combined extracts were washed with water (40ml), dried over $MgSO_4$ and the solvent evaporated *in vacuo* to afford an oil which slowly crystallised on standing (7.1g, 71%), white prisms, m.p. 77-78°C (lit.,[99] 77-78°C); m/z (FAB, g) 261 (M^++1), 245, 203, 101.

3.2.3.2 3-*O*-Benzyl-1,2:5,6-di-*O*-isopropylidene-α-D-*allo*-furanose (99)

Diacetone-D-*allo*-furanose, from 3.2.3.1 (2.8g, 10.8mmol) in DMSO (15ml) was added dropwise to a stirred suspension of sodium hydride (80% dispersion in mineral oil, 0.7g) in DMSO (15ml) under nitrogen, at room temperature. After stirring for 45min, benzyl chloride (3.5ml) was dripped in and stirring continued for 1h before pouring onto an ice/water slurry (70ml) and extracting into ether (3×40ml). The ether layers were combined, dried over $MgSO_4$ and the solvent removed *in vacuo* to yield an oil, which crystallised on standing, and was recrystallised from hexane to afford the product (2.5g, 69%), white needles, m.p. 65-67°C; m/z (FAB, g) 351 (M^++1), 349, 335, 293, 233, 101.

3.2.3.3 3-*O*-Benzyl-1,2-*O*-isopropylidene-α-D-*allo*-furanose (100)

A solution of the 3-*O*-benzyl-1,2:5,6-di-*O*-isopropylidene-α-D-*allo*-furanose (**99**) (4.0g, 11.4mmol) in a mixture of glacial acetic acid (12ml) and water (8ml) was stirred for 16h at 40°C. The acid was neutralised by the addition of aqueous saturated potassium carbonate solution, and the mixture extracted into chloroform (3×20ml). The combined organic layers were washed with 10% sodium chloride solution (20ml), dried over $MgSO_4$, and the solvent removed *in vacuo* to afford an oil, which was not purified but used immediately for the next step.

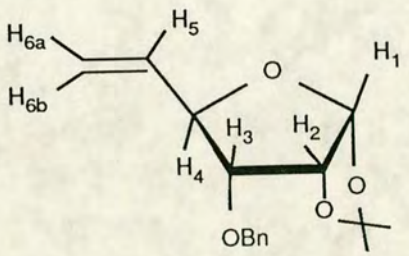
3.2.3.4 3-*O*-Benzyl-1,2-*O*-isopropylidene-5,6-bis-*O*-methanesulphonyl-α-D-*allo*-furanose (100)

Methanesulphonyl chloride (2.2ml) was added to a solution of the crude product from 3.2.3.3 in pyridine (7ml) chilled on an ice bath. The resulting mixture was stirred overnight, while warming to room temperature. After pouring onto water (10ml), the product was extracted into chloroform (3×10ml). The combined chloroform layers were washed with 1M sulphuric acid (10ml), saturated

sodium bicarbonate solution (10ml), dried over $MgSO_4$ and the solvent removed *in vacuo* to yield a solid, which was recrystallised from 1:1 ethanol:methanol to afford the product as fine white needles (3.4g, 63% from (**99**)), m.p. 111-112°C; m/z (FAB, t) 467 (M^++1), 465, 451, 359.

3.2.3.5 3-*O*-Benzyl-1,2-*O*-isopropylidene-5-deoxy-α-D-*ribo*-furanose-5,6-ene (102)

The dimesyl compound (**101**) (2g, 4.3mmol), sodium iodide (3.2g, 21mmol), dimethoxyethane (3.5ml), DMF (21ml) and Zn/Cu couple (freshly prepared from 1.4g powdered zinc[128]), were stirred together under reflux for 70min. After cooling to 50°C the mixture was poured onto water (80ml) with rapid stirring. Toluene (30ml) was added and the mixture filtered through celite. The filter pad was washed with toluene (2×30ml) and the washes used to extract the aqueous phase. The combined organic extracts were washed with water (2×20ml), dried over $MgSO_4$ and the solvent removed *in vacuo* to a syrup which was purified by dry flash chromatography on silica , using 30% ether/hexane as eluent, to afford the product as an oil (1.0g, 84%); δ_H (200Mz) see Table (16); m/z (FAB, g) 277 (M^++1), 275, 261, 217,129.



Resonance	δ_H(ppm)	Coupling	J/Hz
H(1)	5.65	1,2	3.7
H(2)	4.47	2,3	4.3
H(3)	3.41	3,4	9.0
H(4)	4.42	4,5	6.6
H(5)	5.77	5,6a	10.4
H(6a)	5.18	5,6b	17.1
H(6b)	5.38	6a,6b	1.2
$PhC\underline{H}_2$	4.50, 4.66	$PhC\underline{H}_2$	12.2
Ph	7.17-7.33		
CH_3	1.34, 1.57		

Table 16.

3.3 Synthesis of Nitrile Oxide Precursors

The nitrile oxides were generated *in situ* by dehydrochlorination of the parent hydroximoyl chloride with triethylamine.

3.3.1 Benzohydroximoyl Chloride

This was prepared by Mr Ewan Boyd from benzaldehyde according to the method of Chiang.[100]

3.3.2 Ethyl Chloro-oximinoacetate (104)

This was prepared by from glycine ethyl ester hydrochloride according to the method of Skinner.[101] Hydrochloric acid (35%, 31.8ml) was added dropwise to a stirred, ice-cooled solution of glycine ethyl ester hydrochloride (50.0g, 0.36mol) in water (150ml); a solution of sodium nitrite (25.0g, 0.36mol) in water (100ml) was then dripped in slowly. A further portion of hydrochloric acid (31.8ml) and aqueous sodium nitrite (25.0g in 100ml water) were added with stirring. The resulting mixture was extracted with ether (2×200ml). The combined ether layers were dried over $MgSO_4$ and the solvent evaporated *in vacuo* to yield an oil, which was added to hexane (50ml) with just enough ether to allow dissolution to occur, and placed in the freezer. The white crystals formed were removed and the filtrate concentrated to an oil, which was again dissolved in a hexane/ether mixture and placed in the freezer, thus affording a second crop of crystals (24.6g, 46%), m.p. 78-79 °C (lit.,[101] 79-80°C).

3.3.3 2,2-Dimethyl-4-formyl-1,3-dioxolane Chloro-oxime (108)

This was prepared in four steps from D-mannitol, according to scheme 34.

3.3.3.1 1,2:5,6-Di-*O*-isopropylidene-D-mannitol (105)

Prepared using the method of Tipson and Cohen.[102] Anhydrous zinc chloride (70.4g, 0.52mol) in dry acetone (425ml) was stirred vigorously under a dry atmosphere for 1h before adding powdered D-mannitol (36.4g, 0.2mol), and stirring continued for a further 3h. Undissolved D-mannitol was removed by filtration, and the filtrate poured into aqueous potassium carbonate (88.0g in 88ml

water) and left overnight in the fridge. The solids were filtered off, and the aqueous layer extracted with chloroform (3×100ml). The filtered solids were slurried with chloroform and filtered (3×200ml). The chloroform phases were washed with aqueous ammonia (5% v/v, 250ml), water (250ml), dried over $MgSO_4$, and the solvent removed *in vacuo* to yield an off-white solid (24.7g). The product was purified by recrystallisation from a mixture of hot chloroform (25ml) and n-heptane (247ml), and cooled on an ice-bath for 2h before filtering. The solid was washed firstly with the mother liquor and then cold heptane (25ml), and dried *in vacuo* affording the product as a white fluffy solid (12.5g, 29% based on recovered D-mannitol); m.p. 119.5-121.4°C (lit.,[102] 120-122°C); m/z (FAB, g) 263 (M^++1), 247, 245, 205.

3.3.3.2 1,2-*O*-Isopropylidene-D-glyceraldehyde (106)

Prepared using the method of Mann *et al.*[103] 1,2:5,6-Di-*O*-isopropylidene-D-mannitol (**105**) (5.0g, 20mmmol) in THF (48ml) was added to a stirred solution of water (7ml), THF (10ml) and sodium periodate (4.56g, 21.3mmol). The resulting mixture was shaken for 2h before adding ether (70ml) and filtering. The filtrate was concentrated and extracted into dichloromethane (2×25ml), dried over $MgSO_4$ and the solvent removed *in vacuo* to afford the crude product as a brown oil (4.2g, 84%); $\nu_{max.}$(film) 1735cm^{-1} (C=O). The product was not purified but used immediately to form the oxime (**107**).

3.3.3.3 1,2-*O*-Isopropylidene-D-glyceraldehyde-3-oxime (107)

Prepared using the method of Hoffman *et al.*[104] Sodium carbonate (3.0g, 27.5mmol) was added in portions to a stirred solution of hydroxylamine hydrochloride (3.74g, 54mmol) in water (40ml). The crude aldehyde (**106**) (4.15g, 31.9mmol) was added and the resulting mixture stirred overnight at room temperature. After saturating with sodium chloride, the mixture was extracted with ether (3×40ml). The combined organic phases were dried over $MgSO_4$, and concentrated *in vacuo* to an oil, which was purified by Kugelrhor distillation to afford the oxime (**107**) (3.3g, 72%), b.p. 90°C at 1mmHg (lit.,[104] 80°C at 0.5mmHg); $\nu_{max.}$(film) 3390 (OH), 1650cm^{-1} (C=N); m/z (FAB, t) 146 (M^++1), 130, 102, 74, 43.

3.3.3.4 2,2-Dimethyl-4-formyl-1,3-dioxolane Chloro-oxime (108)

This was obtained using a modification of the procedure outlined by Thomas *et al.*[105] Dry chlorine gas was slowly bubbled through a stirred solution of the oxime (**107**) (0.68g, 4.66mmol) in dry ether (100ml) at -60°C for approximately 5min (until the solution became an opaque turquoise colour). After warming to room temperature the solvent was evaporated *in vacuo* without heating. Dry benzene was added and evaporated *in vacuo* several times until the chloro-oxime (**108**) was obtained as a white solid (0.82g, 98%); m/z (FAB, t) 180 (M^++1), 164, 122, 102, 94, 61.

3.3.4 1,2:3,4-Di-*O*-isopropylidene-α-D-*galacto*-hexodialdo-1,5-pyranose-6-oxime (112)

Prepared by the method of Tronchet *et al.*[106] Hydroxylamine hydrochloride (0.95g, 13.7mmol) in water (7ml) and pyridine (7ml) was added to a stirred solution of the dialdose (**96**) (3.4g, 13.2mmol) in methanol (35ml) and left to stir overnight. The mixture was concentrated *in vacuo*, the resultant syrup was dissolved in benzene (300ml), and washed successively with water (150ml), 10% sulphuric acid (150ml), 5% sodium hydrogen carbonate (150ml) and water (150ml). The organic layer was dried over $MgSO_4$ and the solvent removed *in vacuo* to afford the oxime (**112**) as an oil (2.74g, 76%); $\nu_{max.}$(film) 3420 (OH), 1650cm^{-1} (C=N); m/z (FAB, t) 274.12904 (M^++1, $C_{12}H_{20}NO_6$ requires 274.12905), 258, 243, 229.

3.4 Nitrile Oxide Cycloaddition Reactions

3.4.1 Cycloadditions of Nitrile Oxides to 3-*O*-Benzyl-5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hex-5-enofuranose (94)

3.4.1.1 Benzonitrile Oxide (26)

A solution of benzohydroximoyl chloride (0.34g, 2.2mmol) in dry ether (15ml) was added dropwise over 2.5h to a stirred solution of the *xylo*- alkene (**97**) (0.9g, 3.3mmol) and triethylamine (0.24g, 2.4mmol) in dry ether (35ml) at room temperature and the resulting mixture stirred overnight. The precipitate of triethylamine hydrochloride was removed by filtration and 10% of the crude mixture retained for isomer ratio determination. The solvent was removed from

the remainder to afford an oil, which was purified by wet flash chromatography on silica using a 10-20% ether/hexane gradient as the eluent, to afford, in order of elution, traces of 3,5-diphenyl-1,2,4-oxadiazole (**114**) and 3,4-diphenyl furoxan (**113**), characterised by comparison (t.l.c.) with authentic samples, unreacted alkene (0.35g) and a pair of diastereomeric isoxazoline cycloadducts in the ratio 90:10 as determined by the ratio of the integral of the anomeric protons in ^{1}H n.m.r. (200MHz, $CDCl_3$). The major cycloadduct was identified as *5R-5-(3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*xylo*-furanos-4-yl)-3-phenyl-2-isoxazoline* (**115**) (0.77g, 89%), white needles, m.p. 121-124°C (from 1:1 ether:hexane); $[\alpha]_D^{21}$ -128.0° (c=2.0, $CHCl_3$); (Found: C, 69.9; H, 6.3; N, 3.5. $C_{23}H_{25}NO_5$ requires C, 69.9; H, 6.3; N, 3.5%); δ_H (360MHz) see Table 17; δ_C (50MHz) 156.8 (C_7), 137.3 (Ph), 130.0 (Ph), 129.3 (C_8), 128.6, 128.4, 127.9, 127.8, 126.7 (9×Ph), 111.8 ($C_{11'}$), 105.1 (C_1), 82.8, 81.4, 80.5, (C_2, C_3, C_4), 77.1 (C_5), 72.6 (Ph$\underline{C}H_2$), 38.2 (C_6), 26.7, 26.1 (2×CH_3); *m/z* (FAB, g) 396.18107 (M^++1, $C_{23}H_{26}NO_5$ requires 396.18108), 380, 338, 146. The identity was confirmed by x-ray crystallography (Appendix A). The minor cycloadduct, which was obtained as an oil, was identified as *5S-5-(3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*xylo*-furanos-4-yl)-3-phenyl-2-isoxazoline* (**116**) (50mg, 6%); δ_H (360MHz) see Table 17; δ_C (50MHz) 156.1 (C_7), 136.7 (Ph), 129.9 (Ph), 129.2 (C_8), 128.5, 128.1, 127.9, 126.5 (9×Ph), 112.0 ($C_{11'}$), 105.6 (C_1), 81.9, 81.8, 81.6 (C_2, C_3, C_4), 79.6 (C_5), 71.6 (Ph$\underline{C}H_2$), 37.0 (C_6), 26.8, 26.3 (2×CH_3); *m/z* (FAB, g) 396.18107 (M^++1, $C_{23}H_{26}NO_5$ requires 396.18108), 380, 338, 146.

3.4.1.2 Ethoxycarbonylformonitrile Oxide (117)

A solution of hydroximoyl chloride (**104**) (3.7g, 24.4mmol) in dry ether (45ml) was added, over 14h using a motorised syringe pump, to an ice-cooled, stirred, solution of alkene (**94**) (10.1g, 36.6mmol) and triethylamine (2.7g, 26.7mmol) in dry ether (150ml). The mixture was stirred for a further 3h before removing the precipitated triethylamine hydrochloride. The solvent was removed *in vacuo* to yield a syrup, which was purified by dry flash chromatography on silica using 15% ether/hexane as the eluent to afford, in order of elution, unreacted alkene (2.9g), 3,4-diethoxycarbonylfuroxan (**118**) (0.2g, 14% identified by comparison (t.l.c.) with authentic sample) and a pair of diastereomeric isoxazoline cycloadducts in the ratio 86:14. The major cycloadduct

was identified as *5R-5-(3-O-benzyl-1,2-O-isopropylidene-α-D-xylo-furanos-4-yl)-3-carbethoxy-2-isoxazoline* (**119**), (6.0g, 63%), white needles, m.p. 63-65°C; $[\alpha]_D^{21}$ -110.6° (c=1.53, $CHCl_3$); (Found: C, 61.3; H, 6.7; N, 3.5. $C_{20}H_{25}NO_7$ requires C, 61.4; H, 6.4; N, 3.6%); $\nu_{max.}$(nujol mull) 1720 (C=O), 1695cm^{-1} (C=N); δ_H (200MHz) see Table 17; δ_C (50MHz), 160.2 (C_8), 151.8 (C_7), 136.9 (Ph), 128.2, 127.7, 127.4 (5×Ph), 111.7 ($C_{11'}$), 104.9 (C_1), 82.1, 81.2, 79.9 (C_2, C_3, C_4), 79.8 (C_5), 72.0 (Ph$\underline{C}H_2$), 61.6 (C_9), 36.0 (C_6), 26.5, 25.9 (2×CH_3), 13.7 (C_{10}); *m/z* (FAB, g) 392 (M^++1), 376, 334, 306, 142. The minor cycloadduct, obtained as an oil, was identified as *5S-5-(3-O-benzyl-1,2-O-isopropylidene-α-D-xylo-furanos-4-yl)-3-carbethoxy-2-isoxazoline* (**120**) (1.2g, 12%); $[\alpha]_D^{21}$ +13.4° (c=2.54, $CHCl_3$); (Found: C, 61.6; H, 6.6; N, 3.5. $C_{20}H_{25}NO_7$ requires C, 61.1; H, 6.4; N, 3.6%); $\nu_{max.}$(film) 1730 (C=O), 1695cm^{-1} (C=N); δ_H (200MHz) see Table 17; δ_C (50MHz) 160.3 (C_8), 151.3 (C_7), 136.9 (Ph), 128.4, 128.1, 127.9, 127.7 (5×Ph), 112.1 ($C_{11'}$), 105.6 (C_1), 82.1, 81.9, 81.7 (C_2, C_3, C_4), 81.2 (C_5), 71.7 (Ph$\underline{C}H_2$), 61.8 (C_9), 35.7 (C_6), 26.8, 26.3 (2×CH_3), 13.9 (C_{10}); *m/z* (FAB, g) 392 (M^++1), 341, 306, 289, 167.

3.4.1.3 4-Cyano-2,2-dimethyl-1,3-dioxolane-N-oxide (121)

The hydroximoyl chloride (**108**) (3.6g, 20.1mmol) in dry ether (45ml) was added, using a motorised syringe pump over 10h, to an ice-chilled, stirred, solution of the alkene (**94**) (8.9g, 32.2mmol) and triethylamine (2.2g, 21.8mmol) in dry ether (100ml). The solution was stirred for a further 6h before removing the precipitate of triethylamine hydrochloride and concentrating the mixture *in vacuo*. The resulting oil was purified by dry flash chromatography on silica using a 10-40% ether/hexane gradient as eluent, to yield, in order of elution, unreacted alkene (5.56g), the furoxan (**122**) (dimer of the nitrile oxide, 0.46g, 32%) *m/z* (FAB, t) 287.12429 (M^++1, $C_{12}H_{19}N_2O_6$ requires 287.12430) and a pair of diastereomeric isoxazoline cycloadducts in the ratio of 85:15. The major isomer, which was obtained as an oil, was identified as *5R-5-(3-O-benzyl-1,2-O-isopropylidene-α-D-xylo-furanos-4-yl)-3-(4R-2,2-dimethyl-1,3-dioxolan-4-yl)-2-isoxazoline* (**123**) (3.3g, 40%); $[\alpha]_D^{21}$ -103.9° (c=2.19, $CHCl_3$); (Found: C, 62.9; H, 7.1; N, 3.2. $C_{22}H_{29}NO_7$ requires C, 63.0; H, 6.9; N, 3.3%); δ_H (360MHz) see Table 17; δ_C (50MHz) 158.4 (C_7), 137.3 (Ph), 128.3, 128.1, 127.8, 127.5 (5×Ph), 111.8, 110.2 ($C_{11'}$,

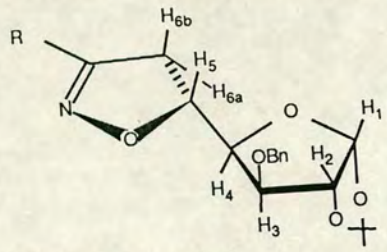
$C_{81'}$), 105.1 (C_1), 82.6, 81.4, 80.5 (C_2, C_3, C_4), 76.9 (C_5), 72.4 (Ph$\underline{C}H_2$), 70.9 (C_8), 66.9 (C_9), 37.0 (C_6), 26.7, 26.1, 25.1 (4×CH_3); *m/z* (FAB, g) 420 (M^++1), 404, 362, 304, 196, 181. The minor cycloadduct was identified as *5S-5-(3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*xylo*-furanos-4-yl)-3-(4R-2,2-dimethyl-1,3-dioxolan-4-yl)-2-isoxazoline* (**124**) (0.36g, 4%), white needles, m.p. 109.5-110°C (from ethanol); $[\alpha]_D^{21}$ +15.3° (c=0.87, $CHCl_3$); (Found: C, 62.9; H, 7.0; N, 3.4. $C_{22}H_{29}NO_7$ requires C, 63.0; H, 6.9; N, 3.3%); δ_H (360MHz) see Table 17; δ_C (50MHz) 157.5 (C_7), 136.7 (Ph), 128.4, 128.1, 127.9 (5×Ph), 112.1, 110.1 ($C_{11'}$, $C_{81'}$), 105.5 (C_1), 82.0, 81.5, (C_2, C_3, C_4), 79.1 (C_5), 71.6 (Ph$\underline{C}H_2$), 70.8 (C_8), 66.7 (C_9), 35.7 (C_6), 26.8, 26.3, 26.1, 24.9 (4×CH_3); *m/z* (FAB, g) 420 (M^++1), 362, 196, 181.

3.4.1.4 1,2:3,4-Di-*O*-isopropylidene-α-D-*galacturono*-nitrile oxide (125)

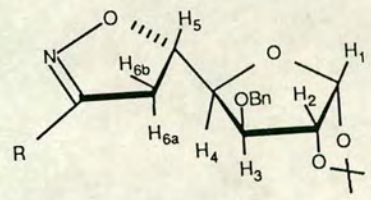
The oxime (**112**) (2.74g, 10.0mmol) in dry chloroform (10ml) was added to a suspension of NCS[25] (1.34g, 10.0mmol) in dry chloroform (10ml) and pyridine (0.1ml) and stirred for 30min at room temperature. The solution was then cooled in an ice bath, alkene (**94**) (4.2g, 15.2mmol) added and a solution of triethylamine (1.07g, 10.6mmol) in dry chloroform (25ml) pumped in, using a motorised syringe, over 8h. After stirring for a further 6h, the solution was washed with water (2×15ml), dried over $MgSO_4$, and the solvent removed *in vacuo* to afford a syrup. 5% of the crude mixture was retained for isomer ratio determination. The remainder was purified by dry flash chromatography on silica using 15-40% ether/hexane as eluent to afford unreacted alkene (2.6g), an oil (1.12g), believed to contain an inseparable mixture of oxadiazole (**128**) *m/z* (FAB, t) 527.22409 (M^++1, $C_{24}H_{35}N_2O_{11}$ requires 527.22406) and some unidentified species, and a pair of diastereomeric isoxazoline cycloadducts in the ratio 85:15. The major product was identified as *5R-5-(3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*xylo*-furanos-4-yl)-3-(1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-pyranos-5-yl)-2-isoxazoline* (**126**) (1.32g, 25%), white needles, m.p. 133-133.5°C (from ethanol); $[\alpha]_D^{21}$ -142.3° (c=0.76, CH_3); (Found: C, 61.2; H, 6.8; N, 2.6. $C_{28}H_{37}NO_{10}$ requires C, 61.4; H, 6.8; N, 2.6%); δ_H (360MHz) see Table 17; δ_C (50MHz) 158.6 (C_7), 137.4 (Ph), 128.3, 127.7, 127.6 (5×Ph), 111.6, 109.5, 108.8 ($C_{111'}$, $C_{91'}$, $C_{11'}$), 105.0 (C_1), 96.1 (C_{12}), 82.8 (C_2), 81.2 (C_3), 80.0 (C_4), 76.2 (C_5), 73.8 (C_9), 72.4 (Ph$\underline{C}H_2$),

70.5 (C_{10}), 70.1 (C_{11}), 65.0 (C_8), 39.1 (C_6), 26.8, 26.2, 25.8, 24.7, 24.1 (6×CH_3); *m/z* (FAB, g) 548 (M^++1), 501, 127. The identity was confirmed by x-ray crystallography (Appendix B). The minor cycloadduct, which was obtained as an oil, was identified as *5S-5-(3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*xylo*-furanos-4-yl)-3-(1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-pyranos-5-yl)-2-isoxazoline* (**127**) (0.26g, 5%); $[\alpha]_D^{21}$ -50.5° (c=1.8, $CHCl_3$); δ_H (360MHz) see Table 17; δ_C (90MHz) 157.4 (C_7), 136.9 (Ph), 128.4, 127.9, 127.6 (5×Ph), 111.9, 109.4, 108.9 ($C_{11'}$, $C_{91'}$, $C_{121'}$), 105.6 (C_1), 96.0 (C_{12}), 82.2 (C_2), 82.0 (C_3), 81.7(C_4), 79.0 (C_5), 73.7 (C_9), 71.6 (Ph$\underline{C}H_2$), 70.5 (C_{10}), 70.2 (C_{11}), 64.8 (C_8), 37.8 (C_6), 26.8, 26.3, 25.9, 25.8, 24.7, 24.0 (6×CH_3); *m/z* (FAB, g) 548.24953 (M^++1, $C_{28}H_{38}NO_6$ requires 548.24955), 501, 127.

Table 17. ^{1}H n.m.r. Data for *Xylo*-alkene (94) Cycloadducts

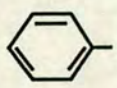
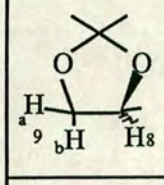
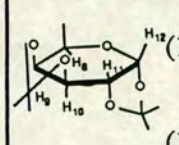


Major Isomer (A)

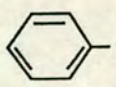
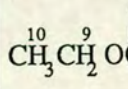
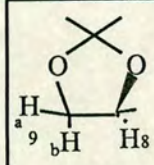
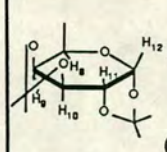


Minor Isomer (B)

δ_H(ppm)

Proton No -> Substituent R		1	2	3	4	5	6a	6b	$PhC\underline{H}_2$	Ph	CH_3	Others
	A (115)	5.94	4.64	4.14	4.23	5.10	3.55	3.45	4.71	7.2-7.8	1.25, 1.31	
	B (116)	6.05	4.70	4.05	4.34	4.99	2.87	3.20	4.44, 4.73	7.3-7.6	1.27, 1.35	
	A (119)	5.87	4.57	4.01	4.22	5.01	3.34	3.19	4.52, 4.64	7.2-7.4	1.42, 1.25	4.27 (CH_2), 1.29 (CH_3)
	B (120)	6.00	4.65	4.00	4.27	5.03	2.82	3.14	4.41, 4.61	7.2-7.4	1.31, 1.46	4.26 (CH_2), 1.31 (CH_3)
	A (123)	5.90	4.60	4.07	4.18	4.92	3.22	3.13	4.67, 4.62	7.2-7.4	1.30, 1.39, 1.44, 1.47	4.92 (H-8), 3.99 (H-9a), 4.20 (H-9b)
	B (124)	5.98	4.67	3.99	4.24	4.87	2.62	3.02	4.41, 4.70	7.2-7.4	1.32, 1.35, 1.39, 1.46	4.86 (H-8), 3.80 (H-9a), 4.06 (H-9b)
	A (126)	5.87	4.57	4.06	4.15	4.88	3.29	3.20	4.65	7.2-7.4	1.28, 1.32, 1.45, 1.46, 1.53	4.78 (H-8), 4.32 (H-9), 4.63 (H-10) 4.34 (H-11), 5.55 (H-12)
	B (127)	5.98	4.62	3.95	4.25	4.89	2.71	3.24	4.42, 4.66	7.25-7.34	1.30, 1.32, 1.40, 1.47, 1.51	4.78 (H-8), 4.30 (H-9), 4.61 (H-10), 4.31 (H-11), 5.51 (H-12)

J/Hz

Proton No -> Substituent R		1,2	3,4	4,5	5,6a	5,6b	$PhC\underline{H}_2$	Others
	A (115)	3.7	3.1	8.2	7.5	9.8	- 17.2	
	B (116)	3.9	3.9	7.6	8.3	10.9	11.8 16.8	
	A (119)	3.7	3.4	6.7	7.8	11.0	11.7 18.2	7.1 (9,10)
	B (120)	3.6	3.9	7.7	8.9	11.5	11.6 17.8	7.1 (9,10)
	A (123)	3.7	3.2	8.0	7.6	10.7	11.6 17.9	6.2 (8, 9a), 6.6 (8, 9b), 8.6 (9a, 9b)
	B (124)	3.9	4.1	7.2	8.7	10.8	11.8 17.3	6.8 (8, 9a), 6.8 (8, 9b), 8.7 (9a, 9b)
	A (126)	3.7	3.1	8.8	6.4	10.1	- 17.9	1.9 (8, 9), 7.9 (9, 10), 2.6 (10, 11), 5.0 (11, 12)
	B (127)	3.9	3.8	8.2	8.3	11.0	11.8 17.8	1.8 (8, 9), 8.0 (9, 10), 2.3 (10, 11), 4.9 (11, 12)

3.4.2 Cycloaddition of Nitrile Oxides to 6,7-Di-deoxy-1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-hept-6-enopyranose (97)

3.4.2.1 Benzonitrile Oxide (26)

A solution of benzohydroximoyl chloride (0.37g, 2.4mmol) in dry ether (30ml) was added, using a motorised syringe pump, over 5h to a stirred, ice-chilled solution of alkene (**97**) (0.9g, 3.6mmol) and triethylamine (0.26g, 2.6mmol) in dry ether (50ml). After stirring for a further 16h the precipitate of triethylamine hydrochloride was removed and the solvent evaporated *in vacuo*. 10% of the crude reaction mixture was retained for isomer ratio determination, the remainder was purified by dry flash chromatography on silica using 20% ether/hexane as eluent, to afford, in order of elution, 3,4-diphenylfuroxan (**113**) (82mg, 29%), unreacted alkene (0.12g) and a pair of diastereomeric cycloadducts in the ratio 87:13. The major product was identified as *6R-6-(1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-pyranos-5-yl)-3-phenyl-2-isoxazoline* (**130**)) (0.50g, 56%), white needles, m.p. 139-140.5°C (from 1:1 ether:hexane); $[\alpha]_D^{21}$ -198.8° (c=1.13, $CHCl_3$); (Found: C, 64.0; H, 6.9; N, 3.7. $C_{20}H_{25}NO_6$ requires C, 64.0; H, 6.7; N, 3.7%); δ_H (200MHz) see Table 18; δ_C (50MHz) 156.7 (C_8), 129.9 (Ph), 129.2 (C_9), 128.5, 126.6 (5×Ph), 109.2, 108.5 ($C_{11'}$, $C_{31'}$), 96.1 (C_1), 78.1 (C_6), 70.6, 70.2, 67.8 (C_2, C_3, C_4, C_5), 37.9 (C_7), 25.7, 24.7, 24.0 (4× CH_3); *m/z* (FAB, g) 376 (M^++1), 360, 318, 260, 146. The identity was confirmed by x-ray crystallography (Appendix C). The minor cycloadduct, which was isolated as an oil, was identified as *6S-6-(1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-pyranos-5-yl)-3-phenyl-2-isoxazoline* (**131**) (78mg, 8%); $[\alpha]_D^{21}$ +11.8° (c=1.24, $CHCl_3$); (Found: C, 63.8; H, 7.0; N, 3.6. $C_{20}H_{25}NO_6$ requires C, 64.0; H, 6.7; N, 3.7%); δ_H (200MHz) see table 18; δ_C (50MHz) 156.7 (C_8), 129.8 (Ph), 129.5 (C_9), 128.4, 126.5, 126.4 (5×Ph), 109.4, 108.6 ($C_{11'}$, $C_{31'}$), 96.1 (C_1), 80.1 (C_6), 70.6, 70.5, 70.3, 68.2 (C_2, C_3, C_4, C_5), 36.6 (C_7), 25.9, 25.7, 24.7, 24.1 (4× CH_3); *m/z* (FAB, g) 376 (M^++1), 360, 318, 260, 146.

3.4.2.2 Ethoxycarbonylformonitrile Oxide (117)

A solution of ethyl chloro-oximinoacetate (**104**) (0.5g, 3.3mmol) in dry ether (30ml) was added, using a motorised syringe pump, over 5h to a stirred, ice-chilled solution of alkene (**97**) (1.5g, 5.9mmol) and triethylamine (0.33g, 3.3mmol) in dry ether (50ml). The mixture was then stirred for a further 16h at room temperature before removing the precipitate of triethylamine hydrochloride and concentrating

the solution *in vacuo*. 10% of the crude mixture was retained for isomer ratio determination, the remainder was purified by dry flash chromatography on silica using 30% ether/hexane as eluent, to afford, in order of elution, unreacted alkene (1.11g), 3,4-diethoxycarbonylfuroxan (**118**) (25mg, 14%) and a pair of diastereomeric isoxazoline cycloadducts in the ratio 91:9. The major product was identified as *3-carbethoxy-6R-6-(1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-pyranos-5-yl)-2-isoxazoline* (**132**) (0.69g, 56%), white needles, m.p. 131-132°C (from 1:1 ether:hexane); $[\alpha]_D^{21}$ -181.7° (c=1.06, $CHCl_3$); (Found: C, 55.0; H, 6.8; N, 3.7. $C_{17}H_{25}NO_8$ requires C, 55.0; H, 6.7; N, 3.8%); $\nu_{max.}$ (nujol) 1715 (C=O), 1595 cm^{-1} (C=N); δ_H (360MHz) see Table 18; δ_C (50MHz) 160.4 (C_9), 151.9 (C_8), 109.3, 108.6 ($C_{11'}$, $C_{31'}$), 96.0 (C_1), 81.0 (C_6), 70.4, 70.3, 70.2, 67.5 (C_2, C_3, C_4, C_5), 61.8 (C_{10}), 36.0 (C_7), 25.8, 25.6, 24.7, 24.0 (4× CH_3), 13.9 (C_{11}); *m/z* (FAB, t) 372 (M^++1), 356, 314, 256, 210. The identity was confirmed by x-ray crystallography (Appendix D). The minor cycloadduct was identified as *3-carbethoxy-6S-6-(1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-pyranos-5-yl)-2-isoxazoline* (**133**) (75mg, 6%), white needles, m.p. 107-109°C (from 1:1 ether:hexane); $[\alpha]_D^{21}$ -84.2° (c=0.84, $CHCl_3$); (Found: C, 55.1; H, 6.8; N, 3.8. $C_{17}H_{25}NO_8$ requires C, 55.0; H, 6.7; N, 3.8%); $\nu_{max.}$ (nujol) 1715 (C=O), 1595 cm^{-1} (C=N); δ_H (360MHz) see Table 18; δ_C (50MHz) 160.5 (C_9), 151.8 (C_8), 109.6, 108.7 ($C_{11'}$, $C_{31'}$), 96.2 (C_1), 82.6 (C_6), 70.7, 70.4, 70.3, 68.1 (C_2, C_3, C_4, C_5), 61.9 (C_{10}), 35.3 (C_7), 26.0, 25.7, 24.8, 24.2 (4× CH_3), 14.0 (C_{11}); *m/z* (FAB, t) 372 (M^++1), 356, 314, 256, 210. The identity was confirmed by x-ray crystallography (Appendix E).

3.4.2.3 4-Cyano-2,2-dimethyl-1,3-dioxolane-N-oxide (121)

The hydroximoyl chloride (**108**) (2.3g, 12.8mmol) in dry ether (40ml) was added over 12h, using a motorised syringe pump, to an ice-chilled, stirred solution of alkene (**97**) (5.0g, 19.5mmol) and triethylamine (1.4g, 13.9mmol) in dry ether (100ml). After stirring for a further 4h the precipitate of triethylamine hydrochloride was removed, and the filtrate reduced *in vacuo* to an oil which was purified by dry flash chromatography on silica using a 10-40% ether/hexane gradient as eluent, to afford, in order of elution, unreacted alkene (2.4g), furoxan (**122**) (0.13g, 14%, *m/z* (FAB, t) 287.12429 (M^++1, $C_{12}H_{19}N_2O_6$ requires 287.12430)) and a pair of diastereomeric isoxazoline cycloadducts in the ratio of 83:13. The major cycloadduct, which was obtained as an oil,

was identified as *6R-6-(1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-pyranos-5-yl)-3-(4R-2,2-dimethyl-1,3-dioxolan-4-yl)-2-isoxazoline* (**134**) (1.95g, 38%); $[\alpha]_D^{21}$ -6.24° (c=0.63, $CHCl_3$); δ_H (360MHz) see Table 18; δ_C (50MHz) 158.3 (C_8), 110.1, 109.2, 108.6 ($C_{11'}$, $C_{31'}$, $C_{91'}$), 96.0 (C_1), 77.9 (C_6), 70.8, 70.6, 70.2, 67.4 (C_2, C_3, C_4, C_5, C_9), 66.8 (C_{10}), 36.5 (C_7), 26.0, 25.8, 25.7, 24.9, 24.7, 24.1 (6×CH_3); *m/z* (FAB, g) 400.19713 (M^++1, $C_{19}H_{30}NO_8$ requires 400.197212), 384, 284, 162.The minor cycloadduct was identified as *6S-6-(1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-pyranos-5-yl)-3-(4R-2,2-dimethyl-1,3-dioxolan-4-yl)-2-isoxazoline* (**135**) (65mg, 2%), white needles, m.p. 141-142°C (from ethanol); $[\alpha]_D^{21}$ +3.4° (c=1.52, $CHCl_3$); δ_H (360MHz) see Table 18; δ_C (90MHz) 158.2 (C_8), 110.1, 109.4, 108.6 ($C_{11'}$, $C_{31'}$, $C_{91'}$), 96.3 (C_1), 79.6 (C_6), 71.0, 70.7, 70.6, 70.5, 67.4 (C_2, C_3, C_4, C_5, C_9), 66.9 (C_{10}), 35.1 (C_7), 26.1, 26.0, 25.8, 25.0, 24.8, 24.2 (6×CH_3); *m/z* (FAB, t) 400.19713 (M^++1, $C_{19}H_{30}NO_8$ requires 400.19712), 384, 284, 112.

3.4.2.4 1,2:3,4-Di-*O*-isopropylidene-α-D-*galacturono*-nitrile oxide (125)

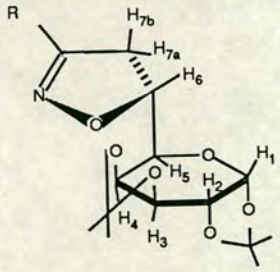
The oxime (**112**) (2.2g, 8.1mmol) in dry chloroform (10ml) was added to a stirred suspension of NCS[25] (1.13g, 8.5mmol) in dry chloroform (10ml) and dry pyridine (0.1ml) and the mixture stirred at 25°C for 20min, before adding alkene (**97**) (3.1g, 12.1mmol) and cooling on an ice-bath. A solution of triethylamine (0.89g, 8.8mmol) in dry chloroform (25ml) was added, using a motorised syringe pump, over 8h. After stirring for a further 8h the organic layer was washed with water (2×15ml), dried over $MgSO_4$ and the solvent removed *in vacuo* to afford an oil. 5% of the crude mixture was retained for isomer ratio determination. The remainder was purified by dry flash chromatography on silica using a 10-50% ether/hexane gradient as eluent to afford, in order of elution, unreacted alkene (2.19g), an oil (0.35g) believed to contain an inseparable mixture of furoxan (**136**), *m/z* (FAB, t) 543.21895 (M^++1, $C_{24}H_{35}N_2O_{12}$ requires 543.21898), and oxadiazole (**128**), *m/z* (FAB, t) 527.22409 (M^++1, $C_{24}H_{35}N_2O_{11}$ requires 527.22406), and a pair of chromatographically inseparable diastereomeric isoxazoline cycloadducts in the ratio 78:22 (1.7g, 33% based on oxime, 91% based on recovered alkene). A pure sample of the major cycloadduct was obtained by several recrystallisations from ethanol. This was identified as *3,6R-6-di-(1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-pyranos-5-yl)-2-isoxazoline* (**137**) (0.94g); m.p.

162-163°C; $[\alpha]_D^{21}$ -204.2° (c=0.70, $CHCl_3$); (Found: C, 56.8; H, 7.2; N, 2.6. $C_{25}H_{37}NO_{11}$ requires C, 56.9; H, 7.0; N, 2.7%); δ_H (360MHz) see Table 18; δ_C (50MHz) 157.8 (C_8), 109.5, 109.1, 108.8, 108.3 ($C_{11'}$, $C_{31'}$, $C_{101'}$, $C_{121'}$),96.1 (C_1, C_{13}), 77.1 (C_6), 73.6 (C_{10}), 70.7, 70.6, 70.3, 70.2, 68.0, 65.0 (C_2, C_3, C_4, C_5, C_9, C_{11}, C_{12}), 38.9 (C_7), 26.1, 25.9, 25.8, 24.8, 24.7, 24.3, 24.2 ($8\times CH_3$); *m/z* (FAB, g) 528 (M^++1), 512, 470, 171. The identification was confirmed by x-ray crystallography (Appendix F). The minor isomer was not isolated.

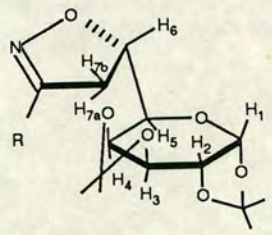
3.4.3 Cycloaddition of Ethoxycarbonylformonitrile Oxide (117) to 3-*O*-Benzyl-1,2-*O*-Isopropylidene-5-deoxy-α-D-*ribo*-furanose-5,6-ene (102)

A solution of ethyl chloro-oximinoacetate (**104**)(0.3g, 2.0mmol) in dry ether (15ml)was added over 10h, using a motorised syringe pump, to a stirred ice-chilled solution of alkene (**102**) (0.78g, 2.8mmol) and triethylamine (0.22g, 2.2mmol) in dry ether (15ml). After stirring for a further 6h the precipitated triethylamine hydrochloride was removed and the solvent evaporated *in vacuo* to afford an oil. 10% of the crude reaction mixture was retained for isomer ratio determination and the remainder was purified by dry flash chromatography on silica using 30% ether/hexane as eluent, to afford, in order of elution, unreacted alkene (0.28g), 3,4-diethoxycarbonylfuroxan (**118**) (89mg) and a pair of inseparable diastereomeric isoxazoline cycloadducts (**139**) and (**140**) in the ratio of 51:49%, isolated as an oil. δ_H (360MHz) see Table 19; *m/z* (FAB, g) 392.17088 (M^++1, $C_{20}H_{26}NO_7$ requires 392.17091), 376, 341, 311, 147. The compounds were identified as *5R-* and *5S-5-(3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*ribo*-furanos-4-yl)3-carbethoxy-2-isoxazoline.*

Table 18. ^{1}H n.m.r. Data for D-*Galacto*-alkene (97) Cycloadducts

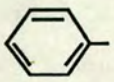
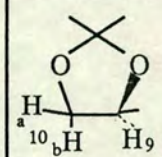
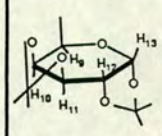


Major Isomer (A)

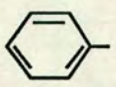
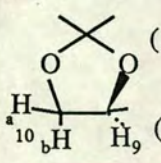
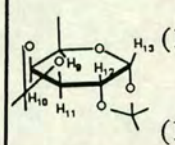


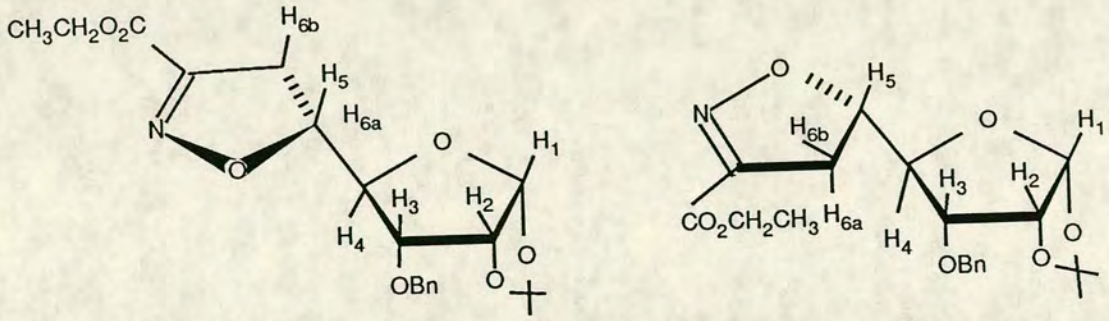
Minor Isomer (B)

δ_H (ppm)

Proton No -> Substituent R		1	2	3	4	5	6	7a	7b	CH_3	Others
	A (130)	5.51	4.30	4.61	4.45	3.73	4.92	3.40		1.28, 1.37, 1.47	7.3-7.7 (Ph)
	B (131)	5.58	4.31	4.60	4.32	3.91	4.93	3.38		1.24, 1.31, 1.38, 1.49	7.2-7.7 (Ph)
$CH_3CH_2OC(=O)-$	A (132)	5.46	4.27	4.57	4.31	3.73	4.92	3.26	3.19	1.27, 1.31, 1.40, 1.43	4.28 (CH_2), 1.30 (CH_3)
	B (133)	5.56	4.32	4.61	4.25	3.87	4.99	3.24		1.29, 1.32, 1.42, 1.49	4.33 (CH_2), 1.35 (CH_3)
	A (134)	5.47	4.27	4.58	4.36	3.66	4.76	3.11	3.04	1.29, 1.33, 1.35, 1.41, 1.42, 1.46	4.88 (H-9), 3.95 (H-10a), 4.17 (H-10b)
	B (135)	5.53	4.28	4.57	4.27	3.83	4.84	3.14	3.07	1.28, 1.30, 1.36, 1.42, 1.43, 1.48	4.92 (H-9), 3.97 (H-10a), 4.16 (H-10b)
	A (137)	5.45	4.25	4.56	4.37	3.62	4.70	3.22	3.15	1.24, 1.27, 1.29 1.32, 1.41, 1.42 1.44, 1.49	4.71 (H-9), 4.28 (H-10), 4.59 (H-11), 4.30 (H-12), 5.51 (H-13)
	B (138)	NOT ISOLATED									

J/Hz

		1,2	2,3	3,4	4,5	5,6	6,7a	6,7b	7a,7b	Others
	A (130)	4.9	2.4	8.0	1.8	8.3	8.5		-	
	B (131)	5.0	2.4	8.0	2.0	7.5	9.5		-	
$CH_3^{10}CH_2^{9}OC(=O)-$	A (132)	4.9	2.5	7.9	1.8	7.1	8.1	10.7	18.2	7.2 (9,10)
	B (133)	5.0	2.5	7.9	1.9	7.5	10.1		-	7.2 (9,10)
	A (134)	4.9	2.4	8.0	1.8	8.0	7.0	9.5	17.6	6.0 (9,10a), 6.7 (9,10b), 8.7 (10a,10b)
	B (135)	4.9	2.3	7.9	1.7	7.1	8.2	10.8	17.4	6.1 (9,10a), 6.8 (9,10b), 8.5 (10a,10b)
	A (137)	4.9	2.4	8.0	1.8	8.7	7.2	10.1	18.1	2.0 (9,10), 7.9 (10,11), 2.6 (11,12), 5.1 (12,13)
	B (138)	NOT ISOLATED								



Resonance	δ_H (ppm) A	δ_H (ppm) B	Coupling	(J/Hz) A	(J/Hz) B
H(1)	5.72	5.68	1,2	3.6	3.6
H(2)	4.56	4.56	3,4	8.9	8.9
H(3)	3.65	3.98	4,5	2.1	2.2
H(4)	4.17	4.05	5,6a	7.7	7.8
H(5)	5.01	4.85	5,6b	12.0	11.7
H(6a)	3.19	3.29	6a.6b	18.0	18.0
H(6b)	3.05	3.21			
	X	Y		X	Y
$PhC\underline{H}_2$	4.57, 4.74	4.43, 4.69	$PhC\underline{H}_2$	11.6	11.6
$CH_3C\underline{H}_2$	4.28, 4.23		9,10	7.1	7.1
$C\underline{H}_3CH_2$	1.27				
$C\underline{H}_3$	1.31				
	1.32				
	1.33				

Table 19.

3.5 Reductive Hydrolytic Cleavage of 2-Isoxazolines to β-Hydroxyketones

β-Hydroxyketones were prepared from a number of the major diastereomers, obtained in the cycloaddition reactions, using the general procedure described below.

General Procedure. The isoxazoline (1M equiv.), boric acid (6M equiv.) and 10% palladium on charcoal (100mg per mmol isoxazoline) in a mixture of methanol and water (5:1) *ca* 15ml per 100mg of isoxazoline, were degassed using a water pump and flushed with hydrogen several times before leaving to stir vigorously under a balloon filled with hydrogen for 18h. After removing the

Pd/C by filtration through a celite pad, the mixture was concentrated *in vacuo* (*ca* 22°C, 1mmHg). Methanol was added and evaporated several times, to remove the remaining boric acid as the volatile trimethyl borate, to afford the product as an oil. In most cases further purification was not required, as judged by ^{13}C n.m.r.

3.5.1 Reduction of Ethyl Ester to alcohol

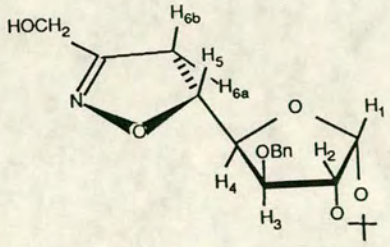
General Procedure.[119] The isoxazoline (0.5g) was stirred in ethanol (20ml) and THF added dropwise until it had completely dissolved. Sodium borohydride (6M equiv.) was added in portions and the resulting mixture stirred at room temperature overnight. After pouring into water (30ml) and extracting with chloroform (3×20ml), the organic phase was dried over $MgSO_4$ and the solvent removed *in vacuo* to afford the product. No further purification was necessary.

3.5.1.1 *5R-5-(3-*O*-Benzyl-1,2-*O*-isopropylidene-α-D-*xylo*-furanos-4-yl)-3-hydroxymethyl-2-isoxazoline* (**147**)

Obtained from (**119**) using the general procedure above (yield 93%); $[\alpha]_D^{21}$ -97.3° (c=0.99, $CHCl_3$); δ_H (200MHz) see Table 20; δ_C (50MHz) 159.0 (C_7), 137.2 (Ph), 128.3, 127.8, 127.5 (5×Ph), 111.8 ($C_{11'}$), 105.0 (C_1), 82.5, 81.4, 80.4 (C_2, C_3, C_4), 77.1 (C_5), 72.3 ($Ph\underline{C}H_2$), 57.8 (C_8), 37.9 (C_6), 26.6, 26.0 (2×CH_3); *m/z* (FAB, t) 350.16037 (M^++1, $C_{18}H_{24}NO_6$ requires 350.16035), 292, 190, 154.

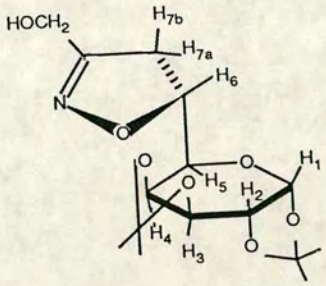
3.5.1.2 *6R-6-(1,2:3,4-Di-*O*-isopropylidene-α-D-*galacto*-pyranos-5-yl)-3-hydroxymethyl-2-isoxazoline* (**152**)

Obtained from (**32**) using the general procedure above (yield 96%); $[\alpha]_D^{21}$ -136.3° (c=2.03, $CHCl_3$); δ_H (200MHz) see Table 21; δ_C (50MHz) 158.9 (C_8), 109.2, 108.6 ($C_{11'}$, $C_{31'}$), 96.1 (C_1), 78.1 (C_6), 77.5, 70.6, 70.3, 67.6 (C_2, C_3, C_4, C_5), 57.8 (C_9), 37.7 (C_7), 25.8, 25.7, 24.7, 24.0 (4×CH_3); *m/z* (FAB, t) 330.15525 (M^++1, $C_{15}H_{24}NO_7$ requires 330.15526), 314, 214, 113, 97.



Resonance	δ_H(ppm)	Coupling	J/Hz
H(1)	5.89	1,2	3.8
H(2)	4.59	2,3	-
H(3)	4.05	3,4	3.2
H(4)	4.19	4,5	7.3
H(5)	4.92	5,6a	7.1
H(6a)	3.19	5,6b	10.1
H(6b)	3.11	6a,6b	17.5
HOC$\underline{H}_2$	4.37		
PhC$\underline{H}_2$	4.58, 4.66	PhC$\underline{H}_2$	11.7
C$\underline{H}_3$	1.46, 1.29		
O$\underline{H}$	2.8		
Ph	7.25-7.36		

Table 20



Resonance	δ_H(ppm)	Coupling	J/Hz
H(1)	5.48	1,2	5.08
H(2)	4.28	2,3	2.4
H(3)	4.58	3,4	8.0
H(4)	4.35	4,5	1.8
H(5)	3.66	5,6	7.7
H(6)	4.78	6,7a	8.5
H(7a)	3.09	6,7b	8.5
H(7b)	3.09	7a,7b	-
HOC$\underline{H}_2$	4.36		
C$\underline{H}_3$	1.29, 1.33		
	1.42, 1.45		
O$\underline{H}$	2.5		

Table 21

3.5.2 β-Hydroxyketones Derived from *Xylo*-Alkene (94) Cycloadducts

3.5.2.1 *3*-O-*Benzyl-6-deoxy-1,2*-O-*isopropylidene-α-D*-gluco-*7-octosulose-(1,4)* (148)

This was obtained from (**147**) as an oil following the general procedure (yield 81%); $[\alpha]_D^{21}$ -35.1° (c=0.73, $CHCl_3$); $\nu_{max.}$ (film) 3400 (OH), 1720cm^{-1} (C=O); δ_H (200MHz) see Table 22; δ_C (50MHz) 209.6 (C_7), 136.9 (Ph), 128.6, 128.1, 127.8 (5×Ph), 111.8 ($C_{11'}$), 104.9 (C_1), 82.1, 81.7, 80.9 (C_2, C_3, C_4), 72.0 (Ph$\underline{C}H_2$), 68.7 (C_8), 65.1 (C_5), 42.4 (C_6), 26.6, 26.1 (2×CH_3); *m/z* (FAB, g) 353.16002 (M^++1, $C_{18}H_{25}O_7$ requires 353.16001), 277, 245, 141.

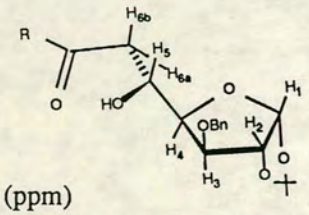
3.5.2.2 *3*-O-*Benzyl-6-deoxy-1,2:8,9-di*-O-*isopropylidene-D*-glycero-*α-D*-gluco-*7-nonosulose-(1,4)* (150)

Obtained from (**123**) as an oil following the general procedure (yield 89%); $[\alpha]_D^{21}$ -4.9° (c=0.84, $CHCl_3$); $\nu_{max.}$ (film) 3490 (OH), 1710cm^{-1} (C=O); δ_H (360MHz) see Table 22; δ_C (50MHz) 210.8 (C_7), 137.3 (Ph), 128.5, 127.9, 127.7 (5×Ph), 111.7, 111.0 ($C_{11'}$, $C_{91'}$), 105.0 (C_1), 82.4, 81.8, 81.3, 80.3 (C_2, C_3, C_4, C_8), 72.3 (Ph$\underline{C}H_2$), 66.0 (C_9), 64.8 (C_5), 42.8 (C_6), 26.7, 26.1, 25.9, 24.9 (4×CH_3); *m/z* (FAB, g) 423.20191 (M^++1, $C_{22}H_{31}O_8$ requires 423.20188), 420, 406, 362, 330.

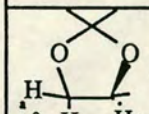
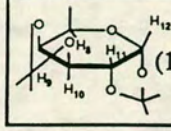
3.5.2.3 *3*-O-*Benzyl-6-deoxy-1,2:9,10:11,12-tri*-O-*isopropylidene-α-D*-galacto-*α-D*-gluco-*7,12-dodecosulose-(1,4),(12,8)* (151)

Obtained from (**126**) following the general procedure, except that THF (3ml) was added as a co-solvent to aid dissolution, and stirring was continued for 24h. The product was purified by preparative t.l.c. on silica in 50% ether/ hexane to remove unreacted isoxazoline (yield 58%, based on reacted isoxazoline); $[\alpha]_D^{21}$ -77.5° (c=0.60, $CHCl_3$); $\nu_{max.}$ (film) 3550 (OH), 1715cm^{-1} (C=O); δ_H (200MHz) see Table 22; δ_C (50MHz) 209.4 (C_7), 137.4 (Ph), 128.4, 127.8, 127.7 (5×Ph), 111.5, 109.6, 108.8, ($C_{11'}$, $C_{91'}$, $C_{111'}$), 104.9 (C_1), 96.2 (C_{12}), 82.4, 81.6, 81.2 (C_2, C_3, C_4), 73.6, 72.2, 70.5, 70.2, 64.5 (C_5, C_8, C_9, C_{10}, C_{11}), 60.2 (Ph$\underline{C}H_2$), 44.4 (C_6), 26.6, 26.1, 25.7, 24.6, 24.1 (6×CH_3); *m/z* (FAB, t) 551.24910 (M^++1, $C_{28}H_{39}O_{11}$ requires 551.24921), 548, 533, 493, 309, 275, 149.

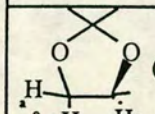
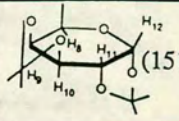
Table 22. ^{1}H n.m.r. Data for D-*Gluco*-derived β-hydroxy Ketones



δ_H (ppm)

Proton No -> Substituent R	1	2	3	4	5	6a	6b	$PhCH_2$		Ph	CH_3	OH	Others
$HOCH_2$ (148)	5.89	4.61	4.07	4.00	4.42	2.81	2.58	4.53	4.72	7.25-7.38	1.30, 1.46	2.9, 3.2	4.22 (CH_2)
 (150)	5.87	4.59	4.07	4.03	4.42	3.03	2.82	4.57	4.69	7.25-7.37	1.29, 1.36, 1.44, 1.46	2.86	4.43 (H-8), 3.99 (H-9a), 4.16 (H-9b)
 (151)	5.87	4.57	4.08	4.02	4.47	3.18	2.77	4.62	4.69	7.25-7.34	1.27, 1.29, 1.31, 1.41, 1.46, 1.47	3.03	4.19 (H-8), 4.55 (H-9), 4.61 (H-10), 4.33 (H-11), 5.60 (H-12)

J/Hz

	1,2	3,4	4,5	5,6a	5,6b	$PhCH_2$	6a,6b	Others
$HOCH_2$ (148)	3.8	3.3	8.2	3.0	8.9	11.8	16.6	
 (150)	3.8	3.2	8.4	2.8	9.0	11.8	18.1	5.6 (8,9a), 7.7 (8,9b), 8.7 (9a, 9b)
 (151)	3.8	3.1	8.5	2.6	9.4	11.6	18.4	2.1 (8,9), 7.9 (9,10), 2.4 (10,11) 5.0 (11,12)

3.5.3 β-Hydroxyketones Derived from D-*Galacto*-Alkene (97) Cycloadducts

3.5.3.1 *7-Deoxy-1,2:3,4-di*-O-*isopropylidene-D*-glycero-α-*D*-galacto-*8-nonosulose-(1,5)* (153)

Obtained from isoxazoline (**152**), as an oil, following the general procedure (yield 86%); $[\alpha]_D^{21}$ -47.2° (c=0.78, $CHCl_3$); $\nu_{max.}$ (film) 3350 (OH), 1720cm^{-1} (C=O); δ_H (360MHz) see Table 23; δ_C (50MHz) 210.2 (C_8), 109.2, 108.6 ($C_{11'}$, $C_{31'}$), 96.2 (C_1), 70.5, 70.1, 69.4 (C_2, C_3, C_4, C_5), 68.7 (C_9), 66.2 (C_6), 41.7 (C_7), 25.7, 24.7, 24.2 (4×CH_3); *m/z* (FAB, g) 334.16275 (M^++1, $C_{15}H_{25}O_8$ requires 334.16276).

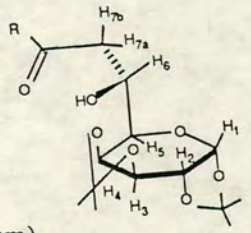
3.5.3.2 *7-Deoxy-1,2:3,4:9,10-tri*-O-*isopropylidene-D*-glycero-*D*-glycero-α-*D*-galacto-*8-decosulose-(1,5)* (154)

Obtained from isoxazoline (**134**), as an oil, following the general procedure. The product was purified by preparative t.l.c. on silica using 70% ether/hexane as eluent (yield 67%); $[\alpha]_D^{21}$ -18.0° (c=0.31, $CHCl_3$); $\nu_{max.}$ (film) 3460 (OH), 1722cm^{-1} (C=O); δ_H (360MHz) see Table 23; δ_C (50MHz) 211.2 (C_8), 110.9, 109.1, 108.6 ($C_{11'}$, $C_{31'}$, $C_{91'}$), 96.2 (C_1), 80.2 (C_9), 70.5, 70.4, 70.1, 69.0 (C_2, C_3, C_4, C_5), 66.0 (C_{10}), 65.9 (C_6), 42.0 (C_7), 25.8, 24.9, 24.8, 24.2 (6×CH_3); *m/z* (FAB, g) 404.20464 (M^++2, $C_{19}H_{32}O_9$ requires 404.20461), 400, 327, 207, 147.

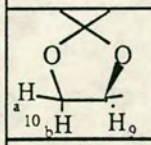
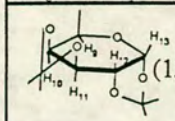
3.5.3.3 *7-Deoxy-1,2:3,4:10,11:12,13-tetra*-O*isopropylidene*-α-*D*-galacto-*D*-glycero-α-*D*-galacto-*8,13-tridecosulose-(1,5),(13,9)* (155)

Obtained from isoxazoline (**137**), as an oil, following the general procedure, except that THF (3ml) was added as a co-solvent to aid dissolution and stirring was continued for 24h. The product was purified by preparative t.l.c. with ether as eluent, to remove unreacted isoxazoline (yield 72%); $[\alpha]_D^{21}$ -91.0° (c=1.09, $CHCl_3$); $\nu_{max.}$ (film) 3500 (OH), 1715cm^{-1} (C=O); δ_H (360MHz) see Table 23; δ_C (50MHz) 209.8 (C_8), 109.7, 109.1, 108.8, 108.5 ($C_{11'}$, $C_{31'}$, $C_{101'}$, $C_{121'}$), 96.2 (C_1, C_{13}), 73.8, 72.1, 70.5, 70.2, 70.1, 68.8, 66.0 (C_2, C_3, C_4, C_5, C_6,C_9, C_{10}, C_{11}, C_{12}), 25.8, 24.9, 24.8, 24.2 (8×CH_3); *m/z* (FAB, t) 531.24411 (M^++1, $C_{19}H_{32}O_9$ requires 531.24413), 528, 243, 113, 97.

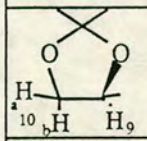
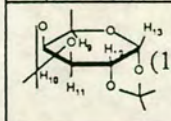
Table 23. ^{1}H n.m.r. Data for D-*Galacto*-derived β-hydroxy Ketones



δ_H (ppm)

Proton No -> Substituent R	1	2	3	4	5	6	7a	7b	CH_3	OH	Others
$HOCH_2$ (153)	5.43	4.25	4.56	4.39	3.53	4.21	2.80	2.56	1.26, 1.30, 1.38, 1.45	3.27, 3.36	4.23 (CH_2)
 (154)	5.45	4.27	4.58	4.44	3.62	4.21	3.01	2.79	1.28, 1.33, 1.35, 1.41, 1.44, 1.47	3.15	4.40 (H-9), 4.03 (H-10a), 4.15(H-10b)
 (155)	5.46	4.26	4.58	4.47	3.60	4.24	3.18	2.68	1.26, 1.28, 1.29 1.33, 1.39, 1.41 1.46, 1.48	3.25	4.20 (H-9), 4.55 (H-10), 4.60 (H-11), 4.31 (H-12), 5.60 (H-13)

J/Hz

	1,2	2,3	3,4	4,5	5,6	6,7a	6,7b	7a,7b	Others
$HOCH_2$ (153)	5.0	2.4	7.9	1.9	8.7	3.4	8.1	16.5	-
 (154)	5.0	2.4	8.0	1.9	8.7	3.0	8.1	18.2	5.5 (9,10a), 7.7 (9,10b), 8.7 (10a,10b)
 (155)	5.0	2.3	7.9	1.8	8.8	2.8	8.5	18.4	2.3 (9,10), 8.1 (10,11), 2.4 (11,12) 5.0 (12,13)

3.6 Reduction of β-Hydroxyketones using Sodium Borohydride

General Procedure.[129] A solution of sodium borohydride (0.4M equiv.) in water (2ml) was added slowly to an ice-chilled, stirred solution of the β-hydroxy ketone (*ca* 100mg, 1M equiv.) in an ethanol/water mixture (3:1, 4ml). 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 extracted with chloroform (5×0.5ml). The combined organic fractions were dried over $MgSO_4$ and the solvent removed *in vacuo* to afford the crude mixture of diastereomeric alcohols.

3.6.1 Reduction of D-Glucose Derived β-Hydroxyketones

3.6.1.1 Reduction of (148)

This was achieved using the above general procedure. The crude product was purified by preparatory t.l.c. on silica using ether as eluent, to afford, in order of elution *3-O-benzyl-6-deoxy-1,2-O-isopropylidene-L*-glycero-α-*D*-gluco-*octose-(1,4)* (**156**)**A** (43%); $[\alpha]_D^{21}$ -42.1° (c= 1.31, $CHCl_3$); δ_H (360MHz) see Table 24; δ_C (50MHz) 136.9 (Ph), 128.6, 128.2, 127.9 (5×Ph), 111.7 ($C_{11'}$), 104.9 (C_1), 82.3, 82.0, 81.5 (C_2, C_3, C_4), 72.2 (C_5), 72.0 (Ph$\underline{C}H_2$), 69.3 (C_7), 66.5 (C_8), 36.4 (C_6), 26.6, 26.1 (2×CH_3); *m/z* (FAB, g) 355.17565 (M^++1, $C_{18}H_{27}O_7$ requires 355.17566), 297, 261, 171, 149; and *3-O-benzyl-6-deoxy-1,2-O-isopropylidene-D*-glycero-α-*D*-gluco-*octose-(1,4)* (**156**)**B** (22%); $[\alpha]_D^{21}$ -44.3° (c= 0.54, $CHCl_3$); δ_H (360MHz) see Table 24; δ_C (50MHz) 136.9 (Ph), 128.6, 128.2, 127.9 (5×Ph), 111.7 ($C_{11'}$), 104.9 (C_1), 82.0, 81.7 (C_2, C_3, C_4), 71.9 (Ph$\underline{C}H_2$), 69.2 (C_5), 66.7 (C_8), 66.4 (C_7), 36.5 (C_6), 26.7, 26.2 (2×CH_3); *m/z* (FAB, g) 355.17565 (M^++1, $C_{18}H_{27}O_7$ requires 355.17566), 297, 261, 171, 149.

3.6.1.2 Reduction of (150)

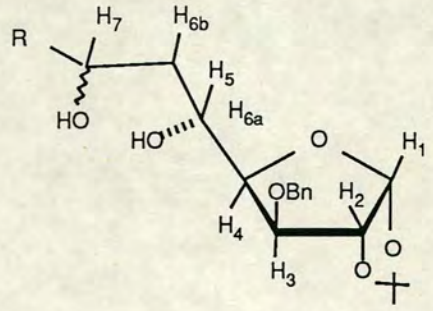
Carried out using the above procedure. The crude product was purified by preparatory t.l.c. on silica using 80% ether/hexane as eluent, to afford, in order of elution *3-O-benzyl-6-deoxy-1,2:8,9-di-O-isopropylidene-D*-erythro-α-*D*-gluco-*nonose-(1,4)* (**157**)**A** (32%); $[\alpha]_D^{21}$ -31.9° (c= 0.69, $CHCl_3$); δ_H (360MHz) see Table 24; δ_C (50MHz) 137.0 (Ph), 128.6, 128.2, 127.9 (5×Ph), 111.7, 109.0 ($C_{11'}$, $C_{81'}$), 104.9 (C_1), 82.2, 82.1, 81.7 (C_2, C_3, C_4), 78.4 (C_8), 72.5

(C_5), 72.1 ($PhCH_2$), 70.2 (C_7), 65.5 (C_9), 36.5 (C_6), 26.7, 26.4, 26.2, 25.1 ($4\times CH_3$); *m/z* (FAB, t) 425.21750 (M^++1, $C_{22}H_{33}O_8$ requires 425.21752), 367, 201; and *3-O-benzyl-6-deoxy-1,2:8,9-di-O-isopropylidene-D*-threo-*α-D*-gluco-*nonose-(1,4)* (**157**)**B** (51%); $[\alpha]_D^{21}$ -36.1° (c=1.48, $CHCl_3$); δ_H (360MHz) see Table 24; δ_C (50MHz) 137.2 (Ph), 128.6, 128.1, 127.9 ($5\times$Ph), 111.6, 109.4 ($C_{11'}$, $C_{81'}$), 105.0 (C_1), 82.2, 81.8, 79.0 (C_2, C_3, C_4, C_8), 72.0 (C_5), 69.3 ($PhCH_2$), 66.2 (C_7), 65.9 (C_9), 37.3 (C_6), 26.7, 26.5, 26.2, 25.2 ($4\times CH_3$); *m/z* (FAB, t) 425.21750 (M^++1, $C_{22}H_{33}O_8$ requires 425.21752), 400, 274, 257.

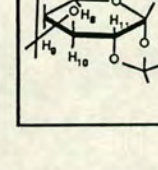
3.6.1.3 Reduction of (151)

This was achieved using the above procedure except that THF (0.5ml) was added to the ethanol/water solvent to aid dissolution. The crude product was purified by preparatory t.l.c. using 65% ether/hexane as eluent, to afford, in order of elution *3-O-benzyl-6-deoxy-1,2:9,10:11,12-tri-O-isopropylidene-α-D*-galacto-*L*-glycero-*α-D*-gluco-*dodecdialdose-(1,4),(12,8)* (**158**)**A** (72%); $[\alpha]_D^{21}$ -36.3° (c= 0.57, $CHCl_3$); δ_H (360MHz) see Table 24; δ_C (50MHz) 137.7 (Ph), 128.3, 127.7, ($5\times$Ph), 111.5, ($C_{11'}$), 109.4, 108.7 ($C_{91'}$, $C_{111'}$), 104.9 (C_1), 96.3 (C_{12}), 82.7, 81.5 (C_2, C_3, C_4), 72.6 ($PhCH_2$), 71.9 ,71.5 (C_5, C_7), 70.7, 70.5, 70.4, 68.6 (C_8, C_9, C_{10}, C_{11}), 35.8 (C_6), 26.6, 26.1, 25.9, 25.7, 24.8, 24.0 ($6\times CH_3$); *m/z* (FAB, t) 553.264861 (M^++1, $C_{28}H_{41}O_{11}$ requires 553.26486), 369, 311, 227, 161, 141; and *3-O-benzyl-6-deoxy-1,2:9,10:11,12-tri-O-isopropylidene-α-D*-galacto-*D*-glycero-*α-D*-gluco-*dodecdialdose-(1,4),(12,8)* (**158**)**B** (14%); $[\alpha]_D^{21}$ -60.0° (c=0.90, $CHCl_3$); δ_H (360MHz) see Table 24; δ_C (50MHz) 136.8 (Ph), 128.6, 128.2, 128.0 ($5\times$Ph), 111.6 ($C_{11'}$), 109.2, 108.5 ($C_{91'}$, $C_{111'}$), 105.0 (C_1), 96.4 (C_{12}), 82.2, 82.0, 81.9 (C_2, C_3, C_4), 71.9 ($PhCH_2$), 70.9, 66.9, 70.6, 70.4, 69.2, 68.0 (C_5, C_7, C_8, C_9, C_{10}, C_{11}), 37.3 (C_6), 26.7, 26.2, 25.8, 24.8, 24.3 ($6\times CH_3$); *m/z* (FAB, t) 553.264861 (M^++1, $C_{28}H_{41}O_{11}$ requires 553.26486), 369, 311, 227, 169, 141.

Table 24. ^{1}H n.m.r. Data for D-*Gluco*-Derived 1,3-Diols



δ_H (ppm)

Proton No -> Substituent R		1	2	3	4	5	6a	6b	7	$PhCH_2$		Ph	OH	CH_3	Others
$HOCH_2$-	A (156)	5.91	4.60	4.08	3.97	4.18	1.82	1.56	3.97	4.56	4.71	7.25-7.38	2.32 2.34	1.30 1.46	3.42 (H-8a) 3.58 (H-8b)
	B (156)	5.91	4.59	4.08	4.03	4.19	1.76	1.52	3.98	4.52	4.69	7.25-7.37	3.25	1.30 1.46	3.43 (H-8a) 3.56(H-8b)
	A (157)	5.92	4.61	4.10	❄	4.21	2.02	†	❄	4.57	4.72	7.25-7.39	3.29	1.31 1.34 1.39 1.47	❄(H-8), (H-9a), (H-9b)
	B (157)	5.92	4.61	4.09	4.03	4.23	1.83	1.53	3.85	4.53	4.72	7.25-7.38	2.54, 2.79	1.31 1.33 1.41 1.46	3.71 (H-8), 3.98 (H-9a), 3.99 (H-9b)
	A (158)	5.90	4.57	3.99	3.98	4.12	2.10	1.69	4.18	4.57	4.67	7.26-7.37	4.24	1.29, 1.31 1.46, 1.48 1.50	3.58 (H-8), 4.27 (H-9) 4.55 (H-10), 4.31 (H-11) 5.57 (H-12)
	B (158)	5.73	4.62	4.11	4.05	4.47	1.90	1.90	4.08	4.54	4.71	7.25-7.36	2.86 3.13	1.30, 1.31 1.34, 1.44 1.47, 1.49	3.64 (H-8), 4.49 (H-9), 4.62 (H-10), 4.30 (H-11), 5.52 (H-12)

† hidden under resonance for methyl groups

❄ complex multiplet 3.89-4.05ppm

J/Hz

Proton No -> Substituent R		1,2	3,4	4,5	5,6a	5,6b	6a,6b	7,6a	7,6b	$PhCH_2$	Others
$HOCH_2$-	A (156)	3.8	3.2	7.7	2.4	10.0	14.5	2.4	10.0	11.8	6.6 (8a,7), 11.2 (8a,8b), 3.4 (8b,7)
	B (156)	3.8	3.2	7.7	2.9	8.7	14.4	9.2	3.0	11.8	7.2 (8a,7), 11.2 (8a,8b), 3.1 (8b,7)
	A (157)	3.8	3.2	✠	2.1	✠	14.4	✠	2.1	11.8	(7,8),✠ (8,9a),✠ (8,9b)✠
	B (157)	3.8	3.2	7.9	2.8	8.9	14.5	2.8	9.5	11.9	(7,8),✠ (8,9a),✠ (8,9b)✠
	A (158)	3.8	2.8	8.5	2.8	10.2	14.2	2.8	10.2	11.8	6.3 (7,8), 1.8 (8,9), 8.0 (9,10), 2.4 (10,11), 5.0 (11,12)
	B (158)	3.9	3.4	7.3	5.9	5.9	-	5.9	5.9	11.6	8.1 (7,8), 1.8 (8,9), 8.0 (9,10), 2.4 (10,11), 5.1 (11,12)

✠ not determined

3.6.2 Reduction of D-Galactose Derived β-Hydroxyketones

3.6.2.1 Reduction of (153)

This was carried out using the above procedure. The crude product was purified by preparatory t.l.c. on silica with ether as eluent, to afford, in order of elution, *7-deoxy-1,2:3,4-di*-O-*isopropylidene-L*-glycero-α-*D*-glycero-α-*D*-galacto-*nonose-(1,5)* (**159**)**A** (19%); $[\alpha]_D^{21}$ -50.5° (c=0.48, $CHCl_3$), δ_H (360MHz) see Table 25; δ_C (50MHz) 109.2, 108.5 ($C_{11'}$, $C_{31'}$), 96.2 (C_1), 72.4, 70.6, 70.4, 70.3, 70.0 (C_2, C_3, C_4, C_5, C_6, C_8), 66.6 (C_9), 35.8 (C_7), 25.8, 24.7, 24.2 (4×CH_3); *m/z* (FAB, t) 335.17060 (M^++1, $C_{15}H_{27}O_8$ requires 335.17058), 219, 97, 85; and *7-deoxy-1,2:3,4-di*-O-*isopropylidene-D*-glycero-α-*D*-glycero-α-*D*-galacto-*nonose-(1,5)* (**159**)**B** (14%); $[\alpha]_D^{21}$ -45.6° (c=0.52, $CHCl_3$), δ_H (360MHz) see Table 25; δ_C (50MHz) 109.2, 108.5 ($C_{11'}$, $C_{31'}$), 96.3 (C_1), 70.7, 70.5, 70.4, 69.4, 67.9 (C_2, C_3, C_4, C_5, C_6, C_8), 66.7 (C_9), 35.9 (C_7), 25.8, 24.7, 24.3 (4×CH_3); *m/z* (FAB, t) 335.17060 (M^++1, $C_{15}H_{27}O_8$ requires 335.17058), 219, 201, 97.

3.6.2.2 Reduction of (154)

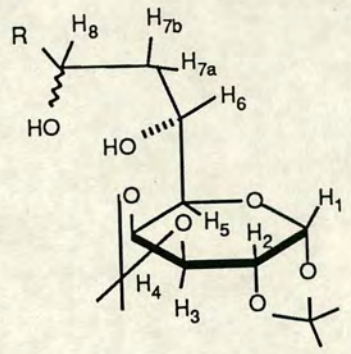
This was carried out using the above procedure. The product was purified by dry flash chromatography using a mini-column packed with silica and 50% ether/hexane as eluent, to afford, in order of elution, *7-deoxy-1,2:3,4:9,10-tri*-O-*isopropylidene-D*-erythro-*D*-glycero-α-*D*-galacto-*decose-(1,5)* (**160**)**A** (26%); $[\alpha]_D^{21}$ -31.1° (c=0.82, $CHCl_3$), δ_H (360MHz) see Table 25; δ_C (50MHz) 109.2, 109.0, 108.5 ($C_{11'}$, $C_{31'}$, $C_{91'}$), 96.3 (C_1), 78.3 (C_9), 72.3, 71.2, 70.4, 69.7 (C_2, C_3, C_4, C_5, C_6, C_8), 65.1 (C_{10}), 35.6 (C_7), 26.3, 25.9, 25.8, 25.1, 24.8, 24.2 (6×CH_3); *m/z* (FAB, t) 405.21243 (M^++1, $C_{19}H_{33}O_9$ requires 405.21244), 349, 329, 85; and *7-deoxy-1,2:3,4:9,10-tri*-O-*isopropylidene-D*-threo-*D*-glycero-α-*D*-galacto-*decose-(1,5)* (**160**)**B** (34%); $[\alpha]_D^{21}$ -30.2° (c=0.59, $CHCl_3$), δ_H (360MHz) see Table 25; δ_C (50MHz) 109.4, 109.1, 108.4 ($C_{11'}$, $C_{31'}$, $C_{91'}$), 96.4 (C_1), 78.9 (C_9), 70.6, 70.5, 69.8, 69.0, 67.4 (C_2, C_3, C_4, C_5, C_6, C_8), 65.9 (C_{10}), 35.6 (C_7), 26.5, 25.8, 25.3, 24.8, 24.3 (6×CH_3); *m/z* (FAB, t) 405.21243 (M^++1, $C_{19}H_{33}O_9$ requires 405.21244), 349, 329, 85.

3.6.2.3 Reduction of (155)

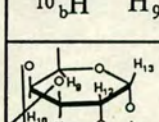
This was carried out using the general procedure except that THF (1ml) was added to the water/ethanol solvent to aid dissolu-

tion. The crude product was purified by preparatory t.l.c. using 80% ether/hexane as eluent, to afford only one product which was identified as *7-deoxy-1,2:3,4:10,11:12,13-tetra*-O-*isopropylidene*-α-*D*-galacto-*L*-glycero-*D*-glycero-α-*D*-galacto-*tridecdialdose-(1,4),(13,9)* (**161**)**A** (62%); $[\alpha]_D^{21}$ -78.0° (c=1.27, $CHCl_3$); δ_H (360MHz) see Table 25; δ_C (90MHz) 109.5, 108.9, 108.7, 108.4 ($C_{11'}$, $C_{31'}$, $C_{101'}$, $C_{121'}$), 96.3, 96.2 (C_1, C_{13}), 71.5, 71.3, 70.7, 70.6, 70.5, 70.4, 70.1, 70.0, 69.6 (C_2, C_3, C_4, C_5, C_6, C_8, C_9, C_{10}, C_{11}, C_{12}), 34.9 (C_7), 26.0, 25.9, 25.8, 25.7, 24.9, 24.8, 24.2, 24.1 ($8\times CH_3$); m/z (FAB, t) 533.25975 (M^++1, $C_{25}H_{41}O_{12}$ requires 533.25978), 517, 123, 113, 97, 85.

Table 25. ^{1}H n.m.r. Data for D-*Galacto*-derived 1,3 Diols



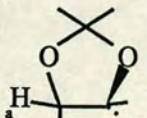
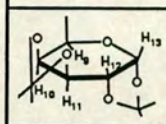
δ_H (ppm)

Proton No -> Substituent R		1	2	3	4	5	6	7a	7b	8	OH	CH_3	Others
$HOCH_2$-	A (159)	5.51	4.31	4.61	4.46	3.55	4.04	1.93	1.56	4.00	1.80, 2.43, 3.60	1.31, 1.36, 1.45, 1.50	3.47 (H-9a), 3.63 (H-9b)
	B (159)	5.51	4.31	4.62	4.47	3.64	4.06	1.87	1.67	4.06	1.85, 2.51	1.31, 1.35, 1.44, 1.51	4.06 (H-8), 3.52 (H-9a), 3.64(H-9b)
	A (160)	5.51	4.30	4.61	4.47	3.56	❄	2.09	†	❄	3.18, 3.50	1.31, 1.34, 1.36, 1.40, 1.46, 1.51	(H-9),❄(H-10a),❄(H-10b) ❄
	B (160)	5.49	4.29	4.60	4.48	3.63	4.07	1.84	1.60	3.91	2.69, 3.18	1.30, 1.33, 1.34, 1.40, 1.42, 1.50	3.71 (H-9), 3.99 (H-10a), 3.99 (H-10b)
	(161)	5.52	4.28	4.57	4.52	3.55	4.14	2.15	†	4.06	3.35	1.32, 1.37, 1.44, 1.47, 1.50, 1.52	3.57 (H-9), 4.28 (H-10), 4.59 (H-11), 4.31 (H-12). 5.56 (H-13)

❄resonance hidden under resonances for methyl groups

† complex multiplet 3.69-4.07ppm

J/Hz

Proton No -> Substituent R		1,2	2,3	3,4	4,5	5,6	6,7a	6,7b	7a,7b	7a,8	7b,8	Others
$HOCH_2$-	A (159)	5.0	2.4	8.0	1.9	8.2	2.3	10.1	14.5	2.3	10.1	6.6 (8,9a), 3.4 (8,9b), 11.1 (9a,9b), 11.1 (9a,9b)
	B (159)	5.1	2.4	8.0	2.0	8.3	3.3	7.9	14.6	8.9	3.3	7.8 (8,9a), 11.2 (9a,9b), (8,9b)⊠
	A (160)	5.0	2.4	8.0	1.9	8.1	2.1	⊠	14.4	⊠	2.1	(8,9), (9,10a), (9,10b), (10a,10b)⊠
	B (160)	5.1	2.4	8.0	1.8	8.7	3.1	7.3	14.5	9.7	2.6	(8,9), (9,10a), (9,10b), (10a,10b)⊠
	(161)	5.1	2.2	7.9	1.7	6.7	2.2	9.9	14.2	2.2	8.3	1.6 (8,9), 4.6 (9,10), 8.3 (10,11) 2.3 (11,12), 5.1 (12,13)

⊠ not determined

3.7 Reduction of (150) Using Various Reducing Reagents

The diastereomeric ratio was measured by h.p.l.c. using an ODS reverse phase column, (particle size 5 microns) with a solvent system of 55% methanol/45% water and a flow rate of 1.5ml/min.

3.7.1 Sodium Borohydride[129]

As for section 3.6.1.2

% A:B = 28:72

3.7.2 Lithium Aluminium Hydride[130]

Lithium aluminium hydride (83mg, 2.2mmol) was added to a stirred solution of β-hydroxy ketone (**150**) (0.23g, 0.5mmol) in THF (10ml) at 0°C under nitrogen. After stirring at 0°C for 4h the mixture was stirred at room temperature for 16h before adding water (2.5ml), 1M hydrochloric acid (10ml), and extracting with dichloromethane (3×15ml). The combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo* to afford the crude mixture of diastereomeric alcohols (0.20g, 86%).

% A:B = 30:70

3.7.3 Borane[130]

A solution of borane in THF (0.9M, 2.9ml, 2.6mmol) was added to a stirred solution of β-hydroxy ketone (**150**) (0.22g, 0.52mmol) in THF (10ml) at 0°C. After stirring at 0°C for 15min then room temperature for 90min no starting material could be detected by t.l.c. 1M aqueous potassium hydroxide (10ml) was added and the mixture extracted into dichloromethane (3×15ml).The combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo* to yield the crude mixture of diastereomeric alcohols (0.21g, 95%).

% A:B = 39:61

3.7.4 Zinc Borohydride[131]

β-Hydroxyketone (**150**) (0.21g, 0.5mmol) in ether (5ml) was added to 0.15M zinc borohydride in ether (13ml) and stirred at 0°C for 2h then at room temperature

for 16h. Water (30ml)was added and stirred until the effervescence had ceased before extracting into dichloromethane (4× 20ml). The combined extracts were dried over $MgSO_4$ and then concentrated *in vacuo* to the crude mixture of diastereomeric alcohols (0.20g, 94%).

$$\% \text{ A:B} = 32:68$$

3.7.5 L-Selectride[132]

1M L-selectride in THF (0.8ml) was added to a solution of the β-hydroxy ketone (**150**) (0.25g, 0.58mmol) in THF (12ml) at -78°C under nitrogen. The mixture was stirred at -78°C for a further 30min, at room temperature for 45min, then cooled to 0°C where the reaction was quenched by the successive slow addition of water (0.15ml), ethanol (0.61ml), 3M sodium hydroxide (0.8ml) and 30% hydrogen peroxide (0.61ml). The aqueous layer was saturated with potassium carbonate then extracted with 1:1 ether:THF (3×6ml), dried over $MgSO_4$ and concentrated *in vacuo* to the crude mixture of diastereomeric alcohols (0.19g, 76%).

$$\% \text{ A:B} = 6:94$$

3.7.6 L,S-Selectride

As for L-selectride, section 3.7.5, except using L,S-selectride (crude yield 77%)

$$\% \text{ A:B} = 5:95$$

3.7.7 Di-Isobutylaluminium Hydride[122]

1M DIBAL-H in hexane (1.4ml) was added to a stirred solution of β-hydroxy ketone (**150**) (0.30g, 0.7mmol) in dichloromethane (10ml) at 0°C. The mixture was stirred for 16h while warming to room temperature. Methanol (0.5ml) was added then 5% aqueous hydrochloric acid (2ml) and the mixture extracted into dichloromethane (3×10ml). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to the crude mixture of diastereomeric alcohols (0.11g, 37%).

$$\% \text{ A:B} = 42:58$$

3.8 Reduction of (148) Using Various Reducing Reagents

The diastereomeric ratio was determined by h.p.l.c. as in section 3.7 except that the solvent system was 65% water/35% methanol.

3.8.1 Sodium Borohydride[129]

As for section 3.6.1.1.

% A:B = 70:30

3.8.2 L-Selectride[132]

1M L-selectride in THF (0.8ml) was added to a solution of β-hydroxy ketone (**148**) (0.17g, 0.48mmol) in THF (8ml) at -78°C under nitrogen. After stirring for 30min at -78°C and at room temperature for 45min, the mixture was cooled to 0°C and quenched by the successive slow addition of water (0.15ml), 3M aqueous sodium hydroxide (0.8ml) and 30% hydrogen peroxide. The aqueous layer was saturated with potassium carbonate and extracted with 1:1 ether/THF (3×5ml). The combined organic layers were dried over $MgSO_4$ and evaporated *in vacuo* to afford the crude mixture of diastereomers (93mg, 54%).

% A:B = 69:31

3.8.3 Di-Isobutylaluminium Hydride[122]

1M DIBAL-H in hexane (1ml) was added to a stirred solution of β-hydroxy ketone (**148**) (0.17g, 0.48mmol) in dichloromethane (8ml) at 0°C. The solution was stirred for 16h while warming to room temperature. Methanol (0.5ml) was added, then 5% aqueous hydrochloric acid (2ml) and the mixture extracted into dichloromethane (3×10ml). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to the crude mixture of diastereomeric alcohols (96mg, 56%).

% A:B = 39:62

3.9 Preparation of Derivatives

3.9.1 Tri-*O*-Mesylate Derivatives of Compounds (156)A and B

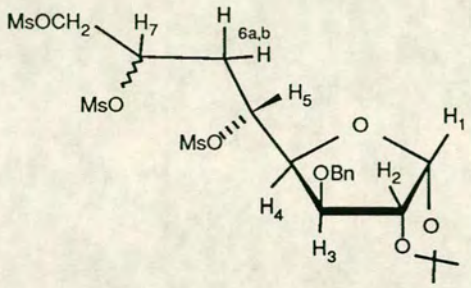
General Method. Methane sulphonyl chloride (3 drops) was added to a stirred solution of the alcohol (23mg, 0.06mmol) in pyridine (0.4ml) at 0°C. After stirring for 2h at 0°C the solution was stirred overnight while warming to room temperature. Water (0.5ml) was added and the solution extracted with chloroform (3×1ml). The combined organic layers were washed with 5% v/v aqueous sulphuric acid (1.5ml), saturated sodium bicarbonate solution (1.5ml), dried over $MgSO_4$ and the solvent removed *in vacuo* to an oil which was purified by preparatory t.l.c. on silica with ether as eluent to afford the tri-mesylate compound as an oil.

3.9.1.1 From (156)A

Obtained from (**156**)**A** using the above procedure (28mg, 73%); δ_H (200MHz) see Table 26; δ_C (90MHz) 136.9 (Ph), 128.5, 128.2, 128.1 (5×Ph), 112.2 ($C_{11'}$), 105.0 (C_1), 81.4, 81.1, 80.5 (C_2, C_3, C_4), 75.4, 72.6 (C_5, C_7), 72.1 (Ph$\underline{C}H_2$), 69.4 (C_8), 38.8, 38.5, 37.5 (3×CH_3, Ms), 34.3 (C_6), 26.6, 26.1 (2×CH_3); *m/z* (FAB, t) 589.10829 (M^++1, $C_{21}H_{33}O_{13}S_3$ requires 589.10831), 587, 493, 357, 307, 249, 231, 211. This was identified as *3*-O-*benzyl-6-deoxy-1,2*-O-*isopropylidene-5,6,8-tri*-O-*methanesulphonyl-L*-glycero-*α-D*-gluco-*octose-(1,4)*(**170**).

3.9.1.2 From (156)B

Obtained from (**156**)**B** using the above procedure (15mg, 39%); δ_H (200MHz) see Table 26; δ_C (50MHz) 136.9 (Ph), 128.4, 128.0, (5×Ph), 112.1 ($C_{11'}$), 104.8 (C_1), 81.3, 81.1, 80.0 (C_2, C_3, C_4), 74.8, 73.3 (C_5, C_7), 71.9 (Ph$\underline{C}H_2$), 69.6 (C_8), 38.6, 37.4, (3×CH_3, Ms), 33.0 (C_6), 26.6, 26.1 (2×CH_3); *m/z* (FAB, t) 589.10829 (M^++1, $C_{21}H_{33}O_{13}S_3$ requires 589.10831), 587, 493, 357, 307, 249, 231, 211. This was identified as *3*-O-*benzyl-6-deoxy-1,2*-O-*isopropylidene-5,6,8-tri*-O-*methanesulphonyl-D*-glycero-*α-D*-gluco-*octose-(1,4)*(**171**).



Resonance	δ_H (ppm)		Coupling	J/Hz	
	A	B		A	B
H(1)	5.88	5.89	1,2	3.8	3.7
H(2)	4.63	4.62	2,3	-	-
H(3)	4.1	4.14	3,4	3.1	3.2
H(4)	4.33	4.42	4,5	7.5	6.1
H(5)*	5.14	5.23	5,6a	‡	2.9
H(6a)†	2.37	2.49	5,6b	‡	8.7
H(6b)†	2.37	2.12	6a,6b	‡	15.8
H(7)*	5.14	5.09	7,6a	‡	9.2
H(8a)	4.25	4.26	7,6b	‡	3.3
H(8b)	4.45	4.47	7,8a	5.4	5.1
PhC$\underline{H}_2$	4.59	4.60, 4.64	7,8b	2.8	3.3
Ph	7.25-7.39	7.25-7.38	8a,8b	11.8	11.6
Ms	2.95, 3.02	3.03, 3.04, 3.08	PhC$\underline{H}_2$	-	11.0
C$\underline{H}_3$	1.31, 1.50	1.32, 1.50			

Table 26

* complex multiplet

† unresolved - second order

‡ not determined

3.9.2 Tri-*O*-Acetate Derivatives of Compounds (156)A and B

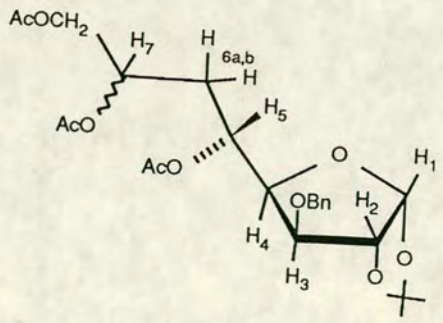
3.9.2.1 From (156)A

Dry acetic anhydride (0.15ml) was added to a stirred solution of the alcohol (**156**)**A** (47mg, 0.13mmol) in dry pyridine (3ml). After stirring at room temperature for 16h the mixture was concentrated *in vacuo* and purified by

preparatory t.l.c. on silica using 70% ether/hexane as eluent, to afford (in reverse order of elution), a mixture of the mono-acetate derivatives (6mg, 11%), m/z (FAB, t) 397.18625 (M^++1, $C_{20}H_{29}O_8$ requires 397.18623), a mixture of the di-acetate derivatives (21mg, 44%), m/z (FAB, t) 439.19680 (M^++1, $C_{22}H_{31}O_9$ requires 439.19679), and *3-O-benzyl-6-deoxy-1,2-O-isopropylidene-5,6,8-tri-O-acetyl-L-*glycero-*α-D-*gluco-*octose-(1,4)* (**168**) (47mg, 74%); δ_H (200MHz) see Table 27; δ_C (90MHz) 170.4, 170.0, 169.6 ($C_{51'}$, $C_{71'}$, $C_{81'}$), 136.8 (Ph), 128.4, 128.1, 128.0 (5×Ph), 111.6 ($C_{11'}$), 105.0 (C_1), 81.7, 81.0, 80.5 (C_2, C_3, C_4), 71.9 (Ph$\underline{C}H_2$), 68.7, 67.9 (C_5, C_7), 64.8 (C_8), 32.7 (C_6), 26.6, 26.1 (2×CH_3), 20.9, 20.8, 20.5 (3×CH_3, Ac); m/z (FAB, t) 481.20736 (M^++1, $C_{24}H_{33}O_{10}$ requires 481.20735), 479, 465, 373, 331, 213.

3.9.2.2 From (156)B

Dry acetic anhydride (0.1ml) was added to a stirred solution of the alcohol (**156**)**B** (24mg, 0.07mmol) in dry pyridine (2ml). After stirring at room temperature for 16h, the mixture was concentrated *in vacuo* and purified by preparatory t.l.c. on silica using 75% ether/hexane as eluent, to afford (in reverse order of elution), a mixture of the di-acetate derivatives (16mg, 59%), m/z (FAB, t) 439.19680 (M^++1, $C_{22}H_{31}O_9$ requires 439.19679), and *3-O-benzyl-6-deoxy-1,2-O-isopropylidene-5,6,8-tri-*O*-acetyl-D-*glycero-*α-D-*gluco-*octose-(1,4)* (**169**) (15mg, 46%); δ_H (200MHz) see Table 27; δ_C (50MHz) 170.6, 170.4, 169.8 ($C_{51'}$, $C_{71'}$, $C_{81'}$), 136.8 (Ph), 128.3, 128.0, (5×Ph), 111.7 ($C_{11'}$), 104.8 (C_1), 81.5, 81.2, 80.7 (C_2, C_3, C_4), 71.9 (Ph$\underline{C}H_2$), 67.3, 66.9 (C_5, C_7), 65.2 (C_8), 31.9 (C_6), 26.6, 26.0 (2×CH_3), 20.8, 20.6, (3×CH_3, Ac); m/z (FAB, t) 481.20736 (M^++1, $C_{24}H_{33}O_{10}$ requires 481.20735), 465, 373, 331.



Resonance	δ_H (ppm)		Coupling	J/Hz	
	A	B		A	B
H(1)	5.88	5.90	1,2	3.8	3.8
H(2)	4.58	4.58	2,3	-	-
H(3)	3.89	3.94	3,4	3.3	3.2
H(4)	4.13	4.20	4,5	8.0	6.5
H(5)	5.25	5.33	5,6a	3.7	2.9
H(6a)	2.19	2.24	5,6b	7.7	9.7
H(6b)	1.98	1.91	6a,6b	15.2	15.0
H(7)	5.15	5.13	7,6a	6.0	10.4
H(8a)	4.00	3.98	7,6b	6.3	3.4
H(8b)	4.24	4.24	7,8a	6.0	6.2
PhC$\underline{H}_2$	4.41, 4.59	4.47, 4.61	7,8b	3.4	3.6
Ph	7.25-7.37	7.25-7.38	8a,8b	12.0	12.1
Ac	1.91, 2.00, 2.01	1.96, 2.00, 2.02	PhC$\underline{H}_2$	11.6	11.5
C$\underline{H}_3$	1.30, 1.47	1.31, 1.49			

Table 27

3.10 Synthesis of Isopropylidene Ketals

General Procedure. The 1,3-diol (45-60mg) was dissolved in dry acetone (2ml) and 2,2-dimethoxypropane (2ml) and stirred for 16h with a TsOH (cat) at room temperature. The solvent was evaporated *in vacuo* and the product purified by preparatory t.l.c. on silica.

3.10.1 5,7-Isopropylidene Ketals of D-Glucose Derived Products

3.10.1.1 5,7-Isopropylidene Ketal of (157)A

This was obtained following the general procedure. The product was purified by preparatory t.l.c. on silica using 35% ether/hexane as eluent to afford *3-O-benzyl-6-deoxy-1,2:5,7:8,9-tri-O-isopropylidene-D*-erythro-α-*D*-gluco-*nonose-(1,4)* (**163**)**A** as an oil (36%); $[\alpha]_D^{21}$ -31.5° (c= 0.94, $CHCl_3$); δ_H (360MHz) see Table 28; δ_C (90MHz) 137.6 (Ph), 128.3, 127.7, 127.5 (5×Ph), 111.7, 109.2

($C_{11'}$, $C_{81'}$), 104.8 (C_1), 98.4 ($C_{51'}$), 82.9, 82.3, 80.6 (C_2, C_3, C_4), 78.2 (C_8), 72.2 (Ph$\underline{C}H_2$), 70.0 (C_5), 66.7 (C_9), 65.5 (C_7), 31.8 (C_6), 30.8, 29.8, 26.6, 26.1, 25.1 (6×CH_3); *m/z* (FAB, t) 465.24884 (M^++1, $C_{23}H_{31}O_6$ requires 465.24882), 449, 447, 425, 407, 327, 207.

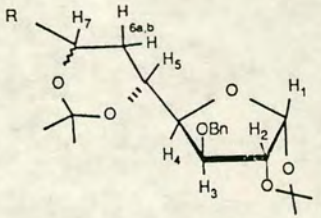
3.10.1.2 5,7-Isopropylidene Ketal of (157)B

This was obtained following the general procedure. The product was purified by preparatory t.l.c. on silica using 35% ether/hexane as eluent to afford *3-O-benzyl-6-deoxy-1,2:5,7:8,9-tri-O-isopropylidene-D*-threo-*α-D*-gluco-*nonose-(1,4)* (**163**)**B** as an oil (42%); $[\alpha]_D^{21}$ -31.5° (c= 0.87, $CHCl_3$); δ_H (360MHz) see Table 28; δ_C (90MHz) 137.3 (Ph), 128.6, 128.2, 127.9 (5×Ph), 111.6, 109.6 ($C_{11'}$, $C_{81'}$), 104.8 (C_1), 100.5 ($C_{51'}$), 82.7, 82.1, 81.1 (C_2, C_3, C_4), 77.8 (C_8), 72.2 (Ph$\underline{C}H_2$), 69.2 (C_5), 65.4 (C_9), 62.9 (C_7), 31.3 (C_6), 26.7, 26.4, 26.1, 25.2, 24.8, 24.5 (6× CH_3); *m/z* (FAB, t) 465.24884 (M^++1, $C_{25}H_{37}O_6$ requires 465.24882), 425, 385, 349, 309.

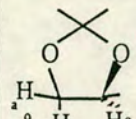
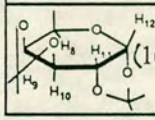
3.10.1.3 5,7-Isopropylidene Ketal of (158)A

This was obtained following the general procedure. The product was purified by preparatory t.l.c. on silica using 50% ether/hexane as eluent to afford *3-O-benzyl-6-deoxy-1,2:5,7:9,10:11,12-tetra-O-isopropylidene-α-D*-galacto-*L*-glycero-*α-D*-gluco-*dodecdialdose-(1,4),(12,8)* (**164**)**A** as an oil (85%); $[\alpha]_D^{21}$ -42.4° (c= 2.39, $CHCl_3$); δ_H (360MHz) see Table 28; δ_C (90MHz) 137.5 (Ph), 128.3, 127.7, 127.5 (5×Ph), 111.7, 109.0, 108.4 ($C_{11'}$, $C_{91'}$, $C_{111'}$), 104.9 (C_1), 98.6 ($C_{51'}$), 96.2 (C_{12}), 83.1, 82.3, 80.6 (C_2, C_3, C_4), 72.3 (Ph$\underline{C}H_2$), 71.4, 70.4, 70.3, 70.0 (C_8, C_9, C_{10}, C_{11}), 68.6 (C_5), 65.1 (C_7), 30.3 (C_6), 26.7, 26.1, 25.9, 25.8, 24.9, 24.1 (8× CH_3); *m/z* (FAB, t) 593.29618 (M^++1, $C_{31}H_{45}O_{11}$ requires 593.29616), 577, 477, 419, 197, 169, 155.

Table 28. ^{1}H n.m.r. Data for D-*Gluco*-derived Isopropylidene Ketals

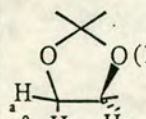
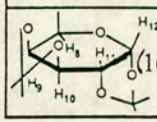


δ_H (ppm)

Proton No -> Substituent R	1	2	3	4	5	6a	6e	7	$PhCH_2$		Ph	CH_3	Others
A  (163)	5.88	4.56	4.04	3.97	4.24	†	2.04	3.78	4.57	4.64	7.25-7.36	1.30, 1.32, 1.34, 1.37, 1.38, 1.47	3.90 (H-8), 3.86 (H-9a), 4.02 (H-9b)
B (163)	5.87	4.54	4.00	4.06	4.21	1.81	1.23	3.87	4.55	4.63	7.25-7.35	1.29, 1.30, 1.35, 1.37, 1.41, 1.48	4.10 (H-8), 3.67 (H-9a), 3.98 (H-9b)
 (164A)	5.89	4.56	4.05	3.98	4.30	†	2.05	4.08	4.57	4.63	7.25-7.35	1.26, 1.29, 1.37, 1.41, 1.47, 1.51	3.63 (H-8), 4.22 (H-9), 4.54 (H-10), 4.26 (H-11), 5.55 (H-12)

† resonance hidden under methyl resonances

J/Hz

	1,2	3,4	4,5	5,6a	5,6e	6a,6e	6a,7	6e,7	$PhCH_2$	Others
A  (163)	3.8	2.9	8.7	11.6	2.5	13.1	11.6	2.5	12.0	7.0 (7,8), 5.2 (8,9a), 6.1 (8,9b), 8.4 (9a, 9b)
B (163)	3.8	3.1	8.6	8.9	6.3	13.1	6.5	9.4	11.5	7.3 (7,8), 6.6 (8,9a), 6.6 (8,9b), 8.4 (9a,9b)
 (164A)	3.8	2.9	8.6	12.0	2.6	12.7	12.0	2.6	11.8	7.8 (7,8), 1.6 (8,9), 8.1(9,10), 2.5 (10,11), 5.0 (11,12)

3.10.2 6,8-Isopropylidene Ketals From D-Galactose Derived Products

3.10.2.1 6,8-Isopropylidene Ketal of (160)A

This was obtained following the general procedure. The product was purified by preparatory t.l.c. on silica using 80% ether/hexane as eluent to afford *7-deoxy-1,2:3,4:6,8:9,10-tetra*-O-*isopropylidene*-α-*D*-erythro-*D*-glycero-α-*D*-galacto-*decose-(1,5)* (**162**)**A** as an oil (39%); $[\alpha]_D^{21}$ -47.9° (c=0.66, $CHCl_3$) ; δ_H (360MHz) see Table 29; δ_C (90MHz) 109.2, 108.7, 108.4 ($C_{11'}$, $C_{31'}$, $C_{91'}$),98.5 ($C_{61'}$), 96.1 (C_1), 78.2 (C_9), 71.0, 70.5, 70.4, 70.3 (C_2, C_3, C_4, C_5), 69.6 (C_6), 66.9 (C_{10}), 66.3 (C_8), 31.6 (C_7), 26.6, 26.1, 25.9, 25.1, 24.9, 24.3 (8×CH_3); *m/z* (FAB, t) 445.24377 (M^++1, $C_{22}H_{37}O_9$ requires 445.24374), 429, 387, 329, 313, 271, 227.

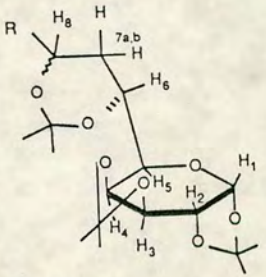
3.10.2.2 6,8-Isopropylidene Ketal of (160)B

This was obtained following the general procedure. The product was purified by preparatory t.l.c. on silica using 80% ether/hexane as eluent to afford *7-deoxy-1,2:3,4:6,8:9,10-tetra*-O-*isopropylidene*-α-*D*-threo-*D*-glycero-α-*D*-galacto-*decose-(1,5)* (**162**)**B** as an oil (32%); $[\alpha]_D^{21}$ -28.1° (c=0.14, $CHCl_3$) ; δ_H (360MHz) see Table 29; δ_C (90MHz) 109.7, 108.8, 108.4 ($C_{11'}$, $C_{31'}$, $C_{91'}$), 100.8 ($C_{61'}$), 96.2 (C_1), 78.0 (C_9), 70.8, 70.4, 70.3, 70.0 (C_2, C_3, C_4, C_5), 68.3 (C_6), 65.4 (C_{10}), 63.9 (C_8), 31.5 (C_7), 26.6, 26.1, 25.9, 25.3, 24.8, 24.4, 24.3 (8×CH_3); *m/z* (FAB, t) 445.24377 (M^++1, $C_{22}H_{37}O_9$ requires 445.24374),429, 387, 329, 313, 271, 227.

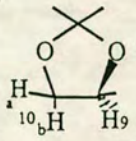
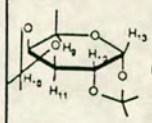
3.10.2.3 6,8-Isopropylidene Ketal of (161)A

This was obtained following the general procedure. The product was purified by preparatory t.l.c. on silica using 70% ether/hexane as eluent to afford unreacted starting material (40%) and a compound which was identified as *7-deoxy-1,2:3,4:6,8:10,11:12,13-penta*-O-*isopropylidene*-α-*D*-galacto-*L*-glycero-α-*D*-glycero-α-*D*-galacto-*tridecdialdose-(1,4),(13,9)* (**165**)**A** as an oil (35%); $[\alpha]_D^{21}$ -50.5° (c=1.80, $CHCl_3$) ; δ_H (360MHz) see Table 29; δ_C (90MHz) 109.1, 108.6, 108.4, 108.2 ($C_{11'}$, $C_{31'}$, $C_{101'}$, $C_{121'}$), 98.7 ($C_{61'}$), 96.3, 96.1 (C_1, C_{13}), 71.4, 70.9, 70.4, 70.3, 70.2, 70.0, 69.5 (C_2, C_3, C_4, C_5, C_9, C_{10}, C_{11}, C_{12}), 68.5 (C_6), 65.9 (C_8), 29.7 (C_7), 26.1, 25.9, 25.8, 24.8, 24.7, 24.3, 24.1 (10×CH_3); *m/z* (FAB, t) 573.29104 (M^++1, $C_{28}H_{45}O_{12}$ requires 573.29108), 557, 457, 439, 109.

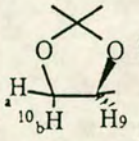
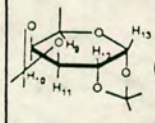
Table 29. ^{1}H n.m.r. Data for D-*Galacto* -derived Isopropylidene Ketals



δ_H (ppm)

Proton No -> Substituent R	1	2	3	4	5	6	7a	7e	8	CH_3	Others
A (162) 	5.47	4.25	4.54	4.35	3.55	4.07	1.16	2.08	3.75	1.30, 1.32, 1.34, 1.38, 1.42	3.89 (H-9), 3.85 (H-10a), 4.04 (H-10b)
B (162)	5.48	4.27	4.55	4.33	3.62	4.07	1.74	1.60	3.85	1.31, 1.32, 1.35, 1.38, 1.42	4.10 (H-9), 3.68 (H-10a), 4.00 (H-10b)
(161) 	5.51	4.26	4.56	4.37	3.55	4.12	1.09	2.03	4.09	1.29, 1.30, 1.32, 1.33, 1.39, 1.43, 1.44, 1.46, 1.52, 1.54	3.62 (H-9), 4.24 (H-10), 4.55 (H-11), 4.26 (H-12), 5.56 (H-13)

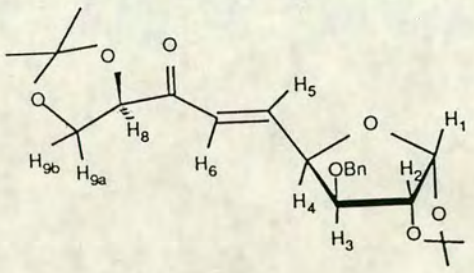
J/Hz

	1,2	2,3	3,4	4,5	5,6	6,7a	6,7e	7a,7e	7a,8	7e,8	Others
A (162) 	4.9	2.2	8.0	1.7	8.8	11.6	2.5	13.1	11.6	2.5	7.3 (8,9), 5.2 (9,10a), 5.9 (9,10b), 8.0 (10a,10b)
B (162)	5.0	2.3	8.0	1.8	9.2	9.2	6.1	13.0	6.3	9.8	7.5 (8,9), 6.5 (9,10a), 6.5 (9,10b), 8.3 (10a, 10b)
(161) 	5.0	2.2	8.0	1.6	8.7	11.6	2.5	12.5	11.6	2.5	8.0 (8,9), 1.6 (9,10), 8.0 (10,11), 2.2 (11,12), 5.0 (12,13)

3.11 Synthesis of Enones

3.11.1 Enone Derived From β-Hydroxy Ketone (150)

β-Hydroxy ketone (**150**) (82mg, 0.19mmol) was dissolved in pyridine (3ml) and dry acetic anhydride (0.1ml) and stirred at room temperature for 48h. The solvent was evaporated *in vacuo* and the residue purified by preparative t.l.c. on silica with 80% ether/hexane as eluent to afford the enone (**174**) identified as *(E)-3-O-benzyl-5,6-dideoxy-1,2:8,9-di-O-isopropylidene-D*-glycero-α-*D*-xylo-*7-non-5-enosulose-(1,4)*, as an oil. This was the only product isolated (45mg, 55%); $[\alpha]_D^{21}$ -15.8° (c=1.29, $CHCl_3$); $\nu_{max.}$ (solution, $CHCl_3$) 1725 (C=O), 1630cm^{-1} (C=C, conj); δ_H (200MHz) see Table 30; δ_C (90MHz) 197.3 (C_7), 141.7 (C_6), 136.9 (Ph), 128.4, 128.0, 127.6 (5×Ph), 126.0 (C_5), 111.9, 111.0 ($C_{11'}$, $C_{81'}$), 105.0 (C_1), 83.0, 82.8, 79.8, 79.5 (C_2, C_3, C_4, C_8), 72.2 (Ph$\underline{C}H_2$), 66.3 (C_9), 26.7, 26.1, 25.9, 25.2 (4× CH_3); *m/z* (FAB, t) 405.19132 (M^++1, $C_{22}H29O_7$ requires 405.19131), 347, 289, 239.

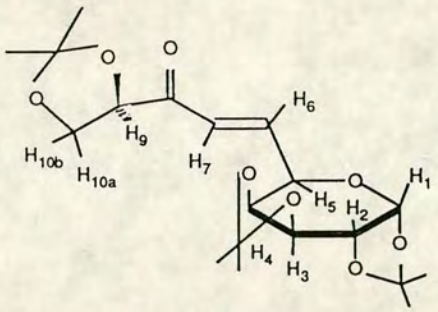


Resonance	δ_H(ppm)	Coupling	J/Hz
H(1)	6.00	1,2	3.8
H(2)	4.64	2,3	-
H(3)	4.00	3,4	3.2
H(4)	4.83	4,5	4.5
H(5)	7.01	5,6	15.8
H(6)	6.78	4,6	1.5
H(8)	4.02	8,9a	8.6
H(9a)	4.21	8,9b	5.8
H(9b)	4.61	9a,9b	7.5
Ph$\underline{C}H_2$	4.46, 4.60	Ph$\underline{C}H_2$	12.1
Ph	7.21-7.35		
CH_3	1.31, 1.39		
	1.43, 1.48		

Table 30.

3.11.2 Enone Derived From β-Hydroxy Ketone (154)

β-Hydroxy ketone (**154**) (87mg, 0.22mmol) was dissolved in dry pyridine (3ml) and dry acetic anhydride (0.1ml) and stirred at room temperature for 48h. The solvent was removed *in vacuo* and the residue purified by preparative t.l.c. on silica using 50% ether/hexane as eluent, to afford the enone (**175**) identified as *(E)-6,7-dideoxy-1,2:3,4:9,10-tri*-O-*isopropylidene-D*-glycero-α-*D*-galacto-*8-dec-6-enosulose-(1,5)* as an oil. This was the only product isolated (38mg, 46%); $[\alpha]_D^{21}$ -59.7° (c=1.54, $CHCl_3$), $\nu_{max.}$ (solution, $CHCl_3$) 1730 (C=O), 1630cm^{-1} (C=C, conj); δ_H (360MHz) see Table 31; δ_C (90MHz) 197.8 (C_8), 143.1 (C_7), 125.0 (C_6), 110.9, 109.6, 108.6 ($C_{11'}$, $C_{31'}$, C_{91}), 96.3 (C_1), 79.6 (C_9), 72.5, 70.8, 70.4, 67.7 (C_2, C_3, C_4, C_5), 66.4 (C_{10}), 25.9, 25.8, 25.7, 25.3, 24.7, 24.4 (6×CH_3); *m/z* (FAB, t) 385.18621 (M^++1, $C_{19}H_{29}O_8$ requires 385.18623), 369, 342, 311, 225, 129.



Resonance	δ_H(ppm)	Coupling	J/Hz
H(1)	5.58	1,2	5.0
H(2)	4.34	2,3	2.6
H(3)	4.63	3,4	7.7
H(4)	4.59	4,5	5.7
H(5)	4.30	5,6	4.0
H(6)	6.93	6,7	15.8
H(7)	6.78	5,7	1.8
H(9)	4.46	9,10a	5.6
H(10a)	4.06	9,10b	7.5
H(10b)	4.19	10a,10b	8.5
CH_3	1.29, 1.32		
	1.38, 1.39		
	1.43, 1.49		

Table 31.

3.12 Synthesis of Penta-Acetate Derivatives

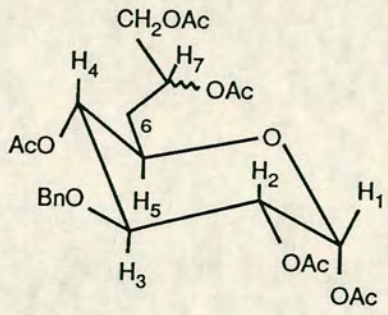
3.12.1 From Octosofuranose (156)A

Alcohol (**156**)**A** (0.127g, 0.36mmol) was dissolved in TFA (2.7ml) and water (0.3ml) and stirred at room temperature for 20min. The solvent was evaporated *in vacuo*. Water was added and evaporated several times before a mixture of anhydrous zinc chloride (90mg) and acetic anhydride (1.5ml), which had been heated at 100°C for 5min, was added. The temperature was retained at 100°C for 1h before adding to an ice/water slurry (10ml) and extracting into chloroform. After drying over $MgSO_4$ the solvent was removed *in vacuo* and the residue purified by preparatory t.l.c. on silica using ether as the eluent to yield the penta-acetate (**172**) as an oil. This was identified as *3-O-benzyl-6-deoxy-1,2,4,7,8-penta-O-acetyl-L-glycero-α-D-gluco-octose-(1,5)* (64mg, 36%); $[\alpha]_D^{21}$ +48.2° (c=2.59, $CHCl_3$); $\nu_{max.}$ (film) 1745cm^{-1} (C=O); δ_H (360MHz) see Table 32; δ_C (90MHz) 170.4, 169.3 ($C_{11'}$, $C_{21'}$, $C_{41'}$, $C_{71'}$, $C_{81'}$), 137.8 (Ph), 128.3, 127.6, 127.3 (5×Ph), 88.6 (C_1), 74.6 (C_8), 76.9, 72.6, 71.3, 69.2, 69.0 (C_2, C_3, C_4, C_5, C_7), 64.3 (Ph$\underline{C}H_2$), 32.1 (C_6), 20.8, 20.6, 20.5, 20.4 (5×CH_3); *m/z* (FAB, g) 525.197 (M^++1, $C_{25}H_{33}O_{12}$ requires 525.19719), 494, 465, 417.

3.12.2 From Octofuranose (156)B

Alcohol (**156**)**B** (0.147g, 0.42mmol) in a mixture of TFA (2.7ml) and water (0.3ml) was stirred at room temperature for 20min. The solvent was evaporated *in vacuo*. Water was added and evaporated several times before adding to a mixture of anhydrous zinc chloride (0.1g) in dry acetic anhydride (2ml) which had been heated to 100°C for 5min. The temperature was retained at 100°C for 30min before adding to an ice/water slurry (10ml). The resulting solid was obtained by filtration and purified by recrystalisation twice from ethanol, to afford the penta-acetate (**173**) as a white fluffy solid. This was identified as *3-O-benzyl-6-deoxy-1,2,4,7,8-penta-O-acetyl-D-glycero-α-D-gluco-octose-(1,5)* (86mg, 40%), m.p. 161-162°C (ethanol); $[\alpha]_D^{21}$ +28.0° (c=0.20, $CHCl_3$); $\nu_{max.}$ (nujol mull) 1740cm^{-1} (C=O); δ_H (360MHZ) see Table 32; δ_C (90MHz) 170.3, 169.8, 169.5, 169.4, 168.7 ($C_{11'}$, $C_{21'}$, $C_{41'}$, $C_{71'}$, $C_{81'}$), 138.0 (Ph), 127.7, 127.3 (5×Ph), 88.8 (C_1), 74.6 (C_8), 77.2, 72.7, 71.5, 68.2, 68.1 (C_2, C_3, C_4, C_5, C_5, C_7), 65.0 (Ph$\underline{C}H_2$), 32.9 (C_6), 20.7, 20.6, 25.5, 20.4 (5×CH_3); *m/z* (FAB, g) 525.19719

(M^++1, $C_{25}H_{33}O_{12}$ requires 525.19719), 494, 465, 417.



Resonance	δ_H (ppm)		Coupling	J/Hz	
	A	B		A	B
H(1)	6.22	6.23	1,2	3.8	3.8
H(2)	4.98	5.01	2,3	9.8	9.8
H(3)	3.88	3.90	3,4	9.8	9.8
H(4)	4.87	4.89	4,5	9.8	9.8
H(5)	3.90	3.80	5,6a	9.5	8.2
H(6a)	1.79	1.97*	5,6b	2.8	4.3
H(6b)	1.71	1.97*	6a,6b	14.9	†
H(7)	5.16	5.17	7,6a	6.8	†
H(8a)	5.16	4.17	7,6b	5.8	†
H(8b)	4.00	3.97	7,8a	3.3	3.6
PhC$\underline{H}_2$	4.00, 4.66	4.68, 4.6	7,8b	6.3	6.5
Ph	7.19-7.32	7.22-7.34	8a,8b	12.1	11.9
Ac	2.15, 2.02, 1.99	2.13, 2.03, 2.01	PhC$\underline{H}_2$	11.8	11.8
	1.95	1.98, 1.97			

Table 32

* second order multiplet.

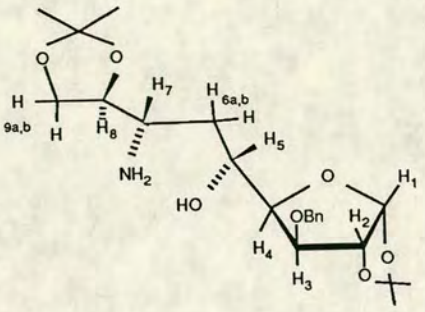
† not determined.

3.13 Synthesis of γ-Amino Alcohols

3.13.1 γ-Amino Alcohol From Isoxazoline (123)

Isoxazoline (**123**) (0.11g, 0.26mmol), in dry THF (3ml) was added to an ice-chilled, stirred suspension of lithium aluminium hydride[33](0.02g, 0.53mmol) in THF (7ml) under nitrogen. The mixture was allowed to stir overnight while warming to room temperature. Water (0.02ml), 20% aqueous sodium hydroxide (0.015ml) then more water (1ml) were sequentially added and the mixture

stirred until the precipitate became granular. The solvent was decanted and evaporated *in vacuo*. The resultant oil was purified by preparative t.l.c. on silica using 90% ethyl acetate/hexane as eluent. Only one product, an oil, was isolated. This was identified as *7-amino-6,7-dideoxy-1,2:8,9-di*-O-*isopropylidene-D*-erythro-*α*-*D*-gluco-*nonose-(1,4)*, (**176**) (yield 52mg, 49%); $[\alpha]_D^{21}$ -10.6° (c=1.71, $CHCl_3$); δ_H (360MHz) see Table 33; δ_C (90MHz) 137.9 (Ph), 128.3, 127.6, 127.5 (5 × Ph), 111.5, 109.0 ($C_{11'}$, $C_{81'}$), 104.9 (C_1), 83.4, 82.7, 81.4 (C_2, C_3, C_4), 79.2 (C_8), 72.5 ($Ph\underline{C}H_2$), 69.5 (C_5), 64.5 (C_9), 53.6 (C_7), 35.8 (C_6), 26.6, 26.2, 26.1 (4×CH_3); *m/z* (FAB, g) 424.23350 (M^++1, $C_{22}H_{34}NO_7$ requires 424.23351), 384, 366.



Resonance	δ_H(ppm)	Coupling	*J*/Hz
H(1)	5.87	1,2	3.7
H(2)	4.55	2,3	-
H(3)	4.09	3,4	2.9
H(4)	3.92	4,5	8.5
H(5)	4.16	5,6a	10.6
H(6a)	1.19	5,6b	2.0
H(6b)	1.99	6a,6b	14.2
H(7)	3.11	7,6a	10.6
H(8)	3.95*	7,6b	2.0
H(9a)	3.95*	8,7	4.7
H(9b)	3.70	8,9a	†
$PhC\underline{H}_2$	4.72, 4.67	8,9b	†
Ph	7.25-7.37	9a,9b	†
CH_3	1.28, 1.32, 1.46	$PhC\underline{H}_2$	11.8
OH	2.78		
NH_2	2.78		

Table 33.

* second order multiplet.

† not determined.

Appendices

X-Ray Crystallography Data

Crystal structure analyses were carried out in the Department of Chemistry at the University of Edinburgh by Dr A.J. Blake and Dr R.O. Gould and in part (Appendix F) by David Cooper. Diffraction data were collected at ambient temperature on Stoë STADI-2 two-circle and STOë STADI-4 four circle diffractometers using Mo-Kα X-radiation. Structures were solved by direct methods and refined by least-squares. Illustrations were produced using ORTEPII or PLUTO and molecular geometry calculations utilised CALC.

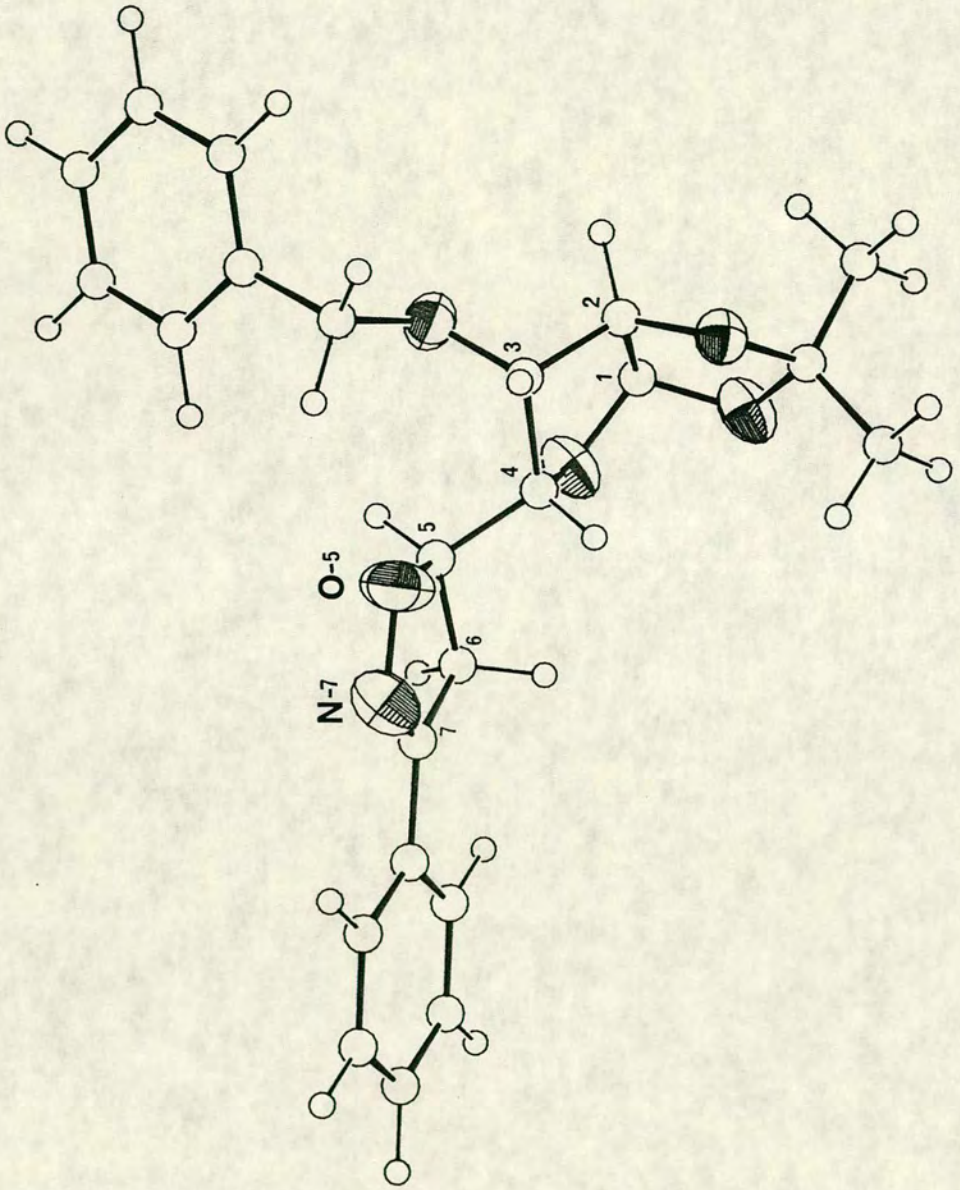
References

ORTEPII, interactive version, P.D. Mallinson & K.W. Muir, *J. Appl. Cyst.*, 1985, **18**, 51.

PLUTO, program for molecular and crystal structure illustrations, W.D.S. Motherwell, University of Cambridge, England, 1976.

CALC, program for molecular geometry calculations, R.O. Gould & P. Taylor, University of Edinburgh, Scotland, 1985.

Appendix A - X-Ray Crystallography Data for Compound (115)



Torsion angles(degrees) with standard deviations

O(4) - C(1) - C(2) - C(3)	-4.5(10)	C(1) - O(1) -C(11) -C(12)	-94.5(9)
O(4) - C(1) - C(2) - O(2)	109.0(8)	C(1) - O(1) -C(11) -C(13)	140.8(8)
O(1) - C(1) - C(2) - C(3)	-122.8(8)	C(1) - O(1) -C(11) - O(2)	23.6(10)
O(1) - C(1) - C(2) - O(2)	-9.2(9)	O(1) -C(11) - O(2) - C(2)	-30.0(9)
C(2) - C(1) - O(4) - C(4)	-19.8(10)	C(12) -C(11) - O(2) - C(2)	87.1(9)
O(1) - C(1) - O(4) - C(4)	95.5(9)	C(13) -C(11) - O(2) - C(2)	-146.4(8)
C(2) - C(1) - O(1) -C(11)	-9.0(10)	C(3) - O(3) -C(30) -C(31)	-176.3(7)
O(4) - C(1) - O(1) -C(11)	-125.2(8)	O(3) -C(30) -C(31) -C(32)	85.3(10)
C(1) - C(2) - C(3) - C(4)	24.2(9)	O(3) -C(30) -C(31) -C(36)	-91.7(10)
C(1) - C(2) - C(3) - O(3)	-91.0(8)	C(30) -C(31) -C(32) -C(33)	-177.0(8)
O(2) - C(2) - C(3) - C(4)	-85.2(8)	C(30) -C(31) -C(36) -C(35)	176.9(8)
O(2) - C(2) - C(3) - O(3)	159.6(7)	C(4) - C(5) - C(6) - C(7)	121.5(9)
C(1) - C(2) - O(2) -C(11)	24.0(9)	O(5) - C(5) - C(6) - C(7)	7.5(10)
C(3) - C(2) - O(2) -C(11)	134.0(8)	C(4) - C(5) - O(5) - N(7)	-125.7(8)
C(2) - C(3) - C(4) - O(4)	-36.6(9)	C(6) - C(5) - O(5) - N(7)	-7.6(10)
C(2) - C(3) - C(4) - C(5)	-153.6(9)	C(5) - C(6) - C(7) - N(7)	-5.8(12)
O(3) - C(3) - C(4) - O(4)	72.5(9)	C(5) - C(6) - C(7) -C(71)	174.3(9)
O(3) - C(3) - C(4) - C(5)	-44.5(11)	C(6) - C(7) - N(7) - O(5)	1.2(13)
C(2) - C(3) - O(3) -C(30)	-147.0(7)	C(71) - C(7) - N(7) - O(5)	-178.9(8)
C(4) - C(3) - O(3) -C(30)	105.2(8)	C(6) - C(7) -C(71) -C(72)	3.6(14)
C(3) - C(4) - O(4) - C(1)	35.9(9)	C(6) - C(7) -C(71) -C(76)	-175.8(9)
C(5) - C(4) - O(4) - C(1)	159.8(8)	N(7) - C(7) -C(71) -C(72)	-176.3(9)
C(3) - C(4) - C(5) - C(6)	-178.0(8)	N(7) - C(7) -C(71) -C(76)	4.3(14)
C(3) - C(4) - C(5) - O(5)	-63.9(11)	C(7) - N(7) - O(5) - C(5)	4.1(11)
O(4) - C(4) - C(5) - C(6)	66.1(10)	C(7) -C(71) -C(72) -C(73)	-179.4(8)
O(4) - C(4) - C(5) - O(5)	-179.8(7)	C(7) -C(71) -C(76) -C(75)	179.4(8)

Selected Torsion Angles (degrees) Involving Hydrogen with Standard Deviation.

H(1)-C(1)-C(2)-H(2)	-9.0(1.4)
H(2)-C(2)-C(3)-H(3)	-86.3(1.2)
H(3)-C(3)-C(4)-H(4)	-38.4(1.2)
H(4)-C(4)-C(5)-H(5)	178.8(1.1)
H(5)-C(5)-C(6)-H(6a)	124.3(1.1)
H(5)-C(5)-C(6)-H(6b)	1.7(1.4)

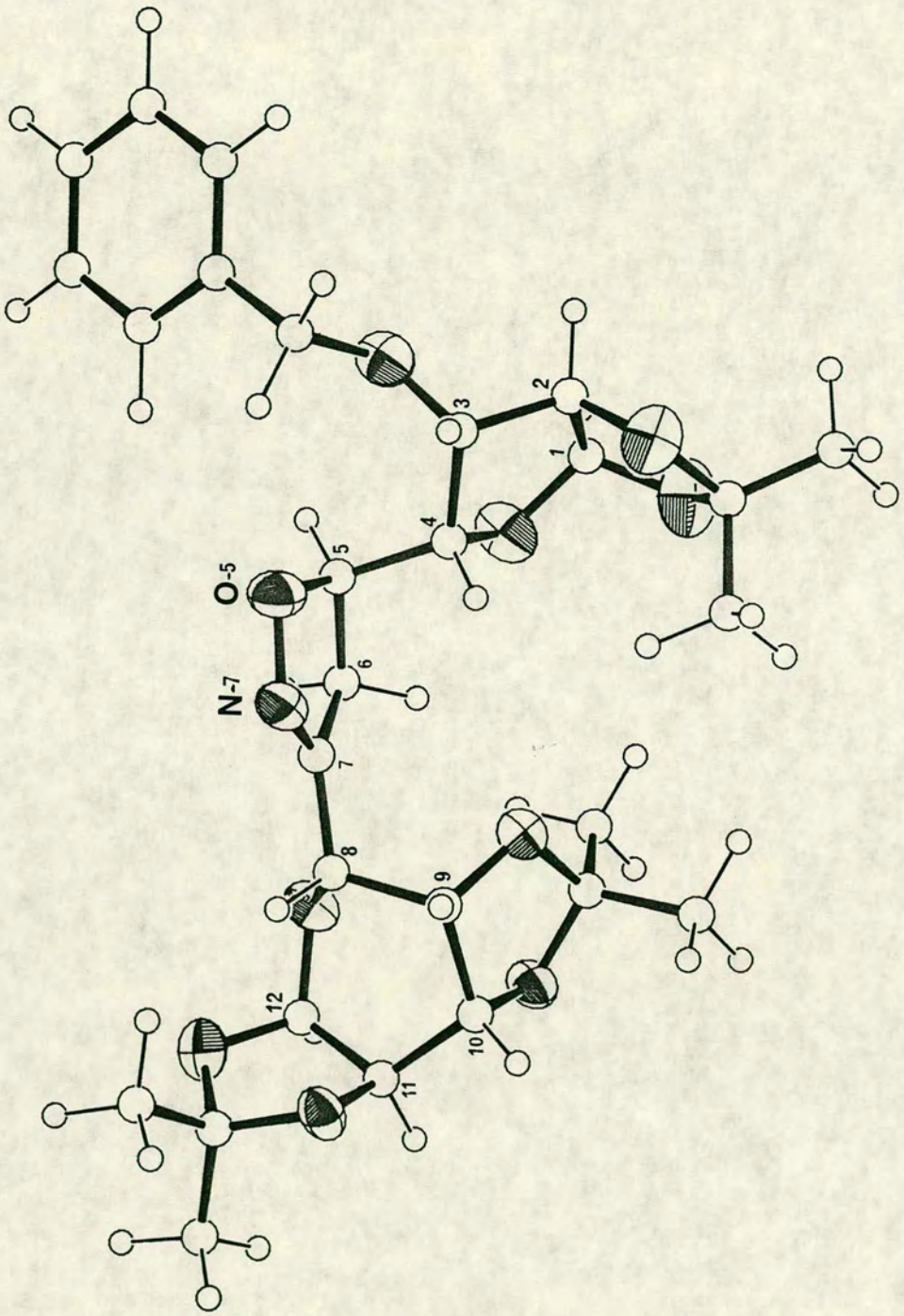
Bond Lengths(Å) with standard deviations

C(1) - C(2)	1.544(14)	C(11) -C(13)	1.474(14)
C(1) - O(4)	1.408(12)	C(11) - O(2)	1.439(12)
C(1) - O(1)	1.399(12)	O(3) -C(30)	1.444(11)
C(2) - C(3)	1.535(13)	C(30) -C(31)	1.500(13)
C(2) - O(2)	1.416(11)	C(5) - C(6)	1.513(14)
C(3) - C(4)	1.549(14)	C(5) - O(5)	1.489(13)
C(3) - O(3)	1.440(11)	C(6) - C(7)	1.475(15)
C(4) - O(4)	1.419(12)	C(7) - N(7)	1.285(14)
C(4) - C(5)	1.523(15)	C(7) -C(71)	1.502(14)
O(1) -C(11)	1.424(13)	N(7) - O(5)	1.414(11)
C(11) -C(12)	1.514(14)		

Angles(degrees) with standard deviations

C(2) - C(1) - O(4)	107.4(8)	C(12) -C(11) - O(2)	110.5(8)
C(2) - C(1) - O(1)	106.1(8)	C(13) -C(11) - O(2)	109.9(8)
O(4) - C(1) - O(1)	110.6(8)	C(2) - O(2) -C(11)	108.6(7)
C(1) - C(2) - C(3)	104.0(8)	C(3) - O(3) -C(30)	113.1(7)
C(1) - C(2) - O(2)	103.1(7)	O(3) -C(30) -C(31)	108.2(7)
C(3) - C(2) - O(2)	108.8(7)	C(30) -C(31) -C(32)	118.6(8)
C(2) - C(3) - C(4)	101.2(7)	C(30) -C(31) -C(36)	121.4(8)
C(2) - C(3) - O(3)	103.2(7)	C(4) - C(5) - C(6)	111.5(9)
C(4) - C(3) - O(3)	111.2(7)	C(4) - C(5) - O(5)	105.4(8)
C(3) - C(4) - O(4)	104.3(8)	C(6) - C(5) - O(5)	105.6(8)
C(3) - C(4) - C(5)	116.6(8)	C(5) - C(6) - C(7)	100.6(8)
O(4) - C(4) - C(5)	106.4(8)	C(6) - C(7) - N(7)	116.4(10)
C(1) - O(4) - C(4)	108.9(7)	C(6) - C(7) -C(71)	123.4(9)
C(1) - O(1) -C(11)	109.6(7)	N(7) - C(7) -C(71)	120.2(10)
O(1) -C(11) -C(12)	109.0(8)	C(7) - N(7) - O(5)	108.6(8)
O(1) -C(11) -C(13)	108.6(8)	C(5) - O(5) - N(7)	108.2(7)
O(1) -C(11) - O(2)	104.4(8)	C(7) -C(71) -C(72)	120.4(8)
C(12) -C(11) -C(13)	113.9(8)	C(7) -C(71) -C(76)	119.6(8)

Appendix B - X-Ray Crystallography Data for Compound (126)



. Torsion angles(degrees) with standard deviations

O(4) - C(1) - C(2) - C(3)	11.9(11)	C(8) - O(8) -C(12) -C(11)	40.6(11)
O(4) - C(1) - C(2) - O(2)	-102.3(9)	C(8) - O(8) -C(12) -O(12)	-75.9(10)
O(1) - C(1) - C(2) - C(3)	131.8(9)	C(8) - C(9) -C(10) -C(11)	19.1(12)
O(1) - C(1) - C(2) - O(2)	17.6(10)	C(8) - C(9) -C(10) -O(10)	-95.8(9)
C(2) - C(1) - O(4) - C(4)	9.3(11)	O(9) - C(9) -C(10) -C(11)	139.9(9)
O(1) - C(1) - O(4) - C(4)	-105.4(10)	O(9) - C(9) -C(10) -O(10)	24.9(9)
C(2) - C(1) - O(1) -C(1A)	-16.6(12)	C(8) - C(9) - O(9) -C(9A)	114.0(9)
O(4) - C(1) - O(1) -C(1A)	98.4(11)	C(10) - C(9) - O(9) -C(9A)	-7.0(10)
C(1) - C(2) - C(3) - C(4)	-26.8(10)	C(9) -C(10) -C(11) -C(12)	-45.5(12)
C(1) - C(2) - C(3) -O(30)	89.7(10)	C(9) -C(10) -C(11) -O(11)	68.5(11)
O(2) - C(2) - C(3) - C(4)	82.7(10)	O(10) -C(10) -C(11) -C(12)	67.2(11)
O(2) - C(2) - C(3) -O(30)	-160.8(8)	O(10) -C(10) -C(11) -O(11)	-178.8(8)
C(1) - C(2) - O(2) -C(1A)	-13.1(11)	C(9) -C(10) -O(10) -C(9A)	-34.3(10)
C(3) - C(2) - O(2) -C(1A)	-125.1(9)	C(11) -C(10) -O(10) -C(9A)	-154.2(8)
C(2) - C(3) - C(4) - O(4)	32.1(10)	C(10) -C(11) -C(12) - O(8)	16.1(13)
C(2) - C(3) - C(4) - C(5)	147.7(9)	C(10) -C(11) -C(12) -O(12)	135.2(9)
O(30) - C(3) - C(4) - O(4)	-81.3(10)	O(11) -C(11) -C(12) - O(8)	-100.4(10)
O(30) - C(3) - C(4) - C(5)	34.3(13)	O(11) -C(11) -C(12) -O(12)	18.8(10)
C(2) - C(3) -O(30) -C(30)	143.8(9)	C(10) -C(11) -O(11) -C(11A)	-153.5(8)
C(4) - C(3) -O(30) -C(30)	-105.8(10)	C(12) -C(11) -O(11) -C(11A)	-31.8(10)
C(3) - C(4) - O(4) - C(1)	-26.7(11)	O(8) -C(12) -O(12) -C(11A)	122.4(9)
C(5) - C(4) - O(4) - C(1)	-150.9(9)	C(11) -C(12) -O(12) -C(11A)	0.8(11)
C(3) - C(4) - C(5) - O(5)	68.3(12)	C(1) - O(1) -C(1A) - O(2)	8.8(12)
C(3) - C(4) - C(5) - C(6)	-179.1(9)	C(1) - O(1) -C(1A) -C(1B)	-107.9(11)
O(4) - C(4) - C(5) - O(5)	-176.2(8)	C(1) - O(1) -C(1A) -C(1C)	129.3(10)
O(4) - C(4) - C(5) - C(6)	-63.6(11)	C(2) - O(2) -C(1A) - O(1)	3.7(12)
C(4) - C(5) - O(5) - N	96.2(9)	C(2) - O(2) -C(1A) -C(1B)	119.9(10)
C(6) - C(5) - O(5) - N	-21.2(10)	C(2) - O(2) -C(1A) -C(1C)	-114.6(10)
C(4) - C(5) - C(6) - C(7)	-94.5(10)	C(3) -O(30) -C(30) -C(31)	171.6(9)
O(5) - C(5) - C(6) - C(7)	19.3(10)	O(30) -C(30) -C(31) -C(32)	93.8(13)
C(5) - O(5) - N - C(7)	14.2(11)	O(30) -C(30) -C(31) -C(36)	-85.6(14)
O(5) - N - C(7) - C(6)	-0.7(12)	C(33) -C(32) -C(31) -C(30)	-179.4(12)
O(5) - N - C(7) - C(8)	-178.6(8)	C(35) -C(36) -C(31) -C(30)	179.4(12)
C(5) - C(6) - C(7) - N	-12.3(12)	C(9) - O(9) -C(9A) -O(10)	-13.8(10)
C(5) - C(6) - C(7) - C(8)	165.5(10)	C(9) - O(9) -C(9A) -C(9B)	-131.3(9)
N - C(7) - C(8) - O(8)	-148.2(9)	C(9) - O(9) -C(9A) -C(9C)	105.2(9)
N - C(7) - C(8) - C(9)	89.5(12)	C(10) -O(10) -C(9A) - O(9)	30.7(10)
C(6) - C(7) - C(8) - O(8)	34.2(13)	C(10) -O(10) -C(9A) -C(9B)	147.6(9)
C(6) - C(7) - C(8) - C(9)	-98.1(12)	C(10) -O(10) -C(9A) -C(9C)	-88.0(10)
C(7) - C(8) - O(8) -C(12)	168.2(8)	C(11) -O(11) -C(11A) -O(12)	32.6(10)
C(9) - C(8) - O(8) -C(12)	-68.7(10)	C(11) -O(11) -C(11A) -C(11B)	148.3(9)
C(7) - C(8) - C(9) -C(10)	154.3(8)	C(11) -O(11) -C(11A) -C(11C)	-85.6(10)
C(7) - C(8) - C(9) - O(9)	38.0(11)	C(12) -O(12) -C(11A) -O(11)	-20.1(11)
O(8) - C(8) - C(9) -C(10)	35.1(11)	C(12) -O(12) -C(11A) -C(11B)	-136.2(9)
O(8) - C(8) - C(9) - O(9)	-81.2(9)	C(12) -O(12) -C(11A) -C(11C)	99.1(10)

Angles(degrees) with standard deviations

C(2) - C(1) - O(4)	105.7(9)	C(10) -C(11) -O(11)	107.3(8)
C(2) - C(1) - O(1)	105.4(9)	C(12) -C(11) -O(11)	103.2(8)
O(4) - C(1) - O(1)	113.1(9)	O(8) -C(12) -C(11)	113.1(9)
C(1) - C(2) - C(3)	106.0(9)	O(8) -C(12) -O(12)	109.4(9)
C(1) - C(2) - O(2)	102.3(8)	C(11) -C(12) -O(12)	104.9(9)
C(3) - C(2) - O(2)	109.0(8)	C(1) - O(1) -C(1A)	110.9(9)
C(2) - C(3) - C(4)	102.0(9)	C(2) - O(2) -C(1A)	112.6(8)
C(2) - C(3) -O(30)	106.7(9)	O(1) -C(1A) - O(2)	105.6(9)
C(4) - C(3) -O(30)	110.9(9)	O(1) -C(1A) -C(1B)	108.3(10)
C(3) - C(4) - O(4)	104.6(8)	O(1) -C(1A) -C(1C)	108.8(10)
C(3) - C(4) - C(5)	117.5(9)	O(2) -C(1A) -C(1B)	109.0(10)
O(4) - C(4) - C(5)	104.8(8)	O(2) -C(1A) -C(1C)	112.1(10)
C(1) - O(4) - C(4)	111.2(8)	C(1B) -C(1A) -C(1C)	112.7(10)
C(4) - C(5) - O(5)	106.1(9)	C(3) -O(30) -C(30)	113.4(8)
C(4) - C(5) - C(6)	111.2(9)	O(30) -C(30) -C(31)	108.3(10)
O(5) - C(5) - C(6)	104.2(9)	C(30) -C(31) -C(32)	119.6(11)
C(5) - O(5) - N	107.9(8)	C(30) -C(31) -C(36)	120.4(11)
O(5) - N - C(7)	109.3(9)	C(9) - O(9) -C(9A)	108.9(7)
C(5) - C(6) - C(7)	100.8(9)	C(10) -O(10) -C(9A)	106.9(8)
N - C(7) - C(6)	113.2(9)	O(9) -C(9A) -O(10)	105.7(8)
N - C(7) - C(8)	120.0(9)	O(9) -C(9A) -C(9B)	108.6(9)
C(6) - C(7) - C(8)	126.8(9)	O(9) -C(9A) -C(9C)	109.9(9)
C(7) - C(8) - O(8)	106.1(8)	O(10) -C(9A) -C(9B)	109.6(9)
C(7) - C(8) - C(9)	112.8(8)	O(10) -C(9A) -C(9C)	110.3(9)
O(8) - C(8) - C(9)	111.4(8)	C(9B) -C(9A) -C(9C)	112.5(9)
C(8) - O(8) -C(12)	113.0(8)	C(11) -O(11) -C(11A)	107.0(8)
C(8) - C(9) -C(10)	112.0(8)	C(12) -O(12) -C(11A)	110.0(8)
C(8) - C(9) - O(9)	111.6(8)	O(11) -C(11A) -O(12)	104.1(8)
C(10) - C(9) - O(9)	104.1(8)	O(11) -C(11A) -C(11B)	109.1(9)
C(9) -C(10) -C(11)	113.6(9)	O(11) -C(11A) -C(11C)	111.3(9)
C(9) -C(10) -O(10)	102.9(8)	O(12) -C(11A) -C(11B)	108.5(9)
C(11) -C(10) -O(10)	106.7(8)	O(12) -C(11A) -C(11C)	109.8(9)
C(10) -C(11) -C(12)	114.9(9)	C(11B) -C(11A) -C(11C)	113.5(10)

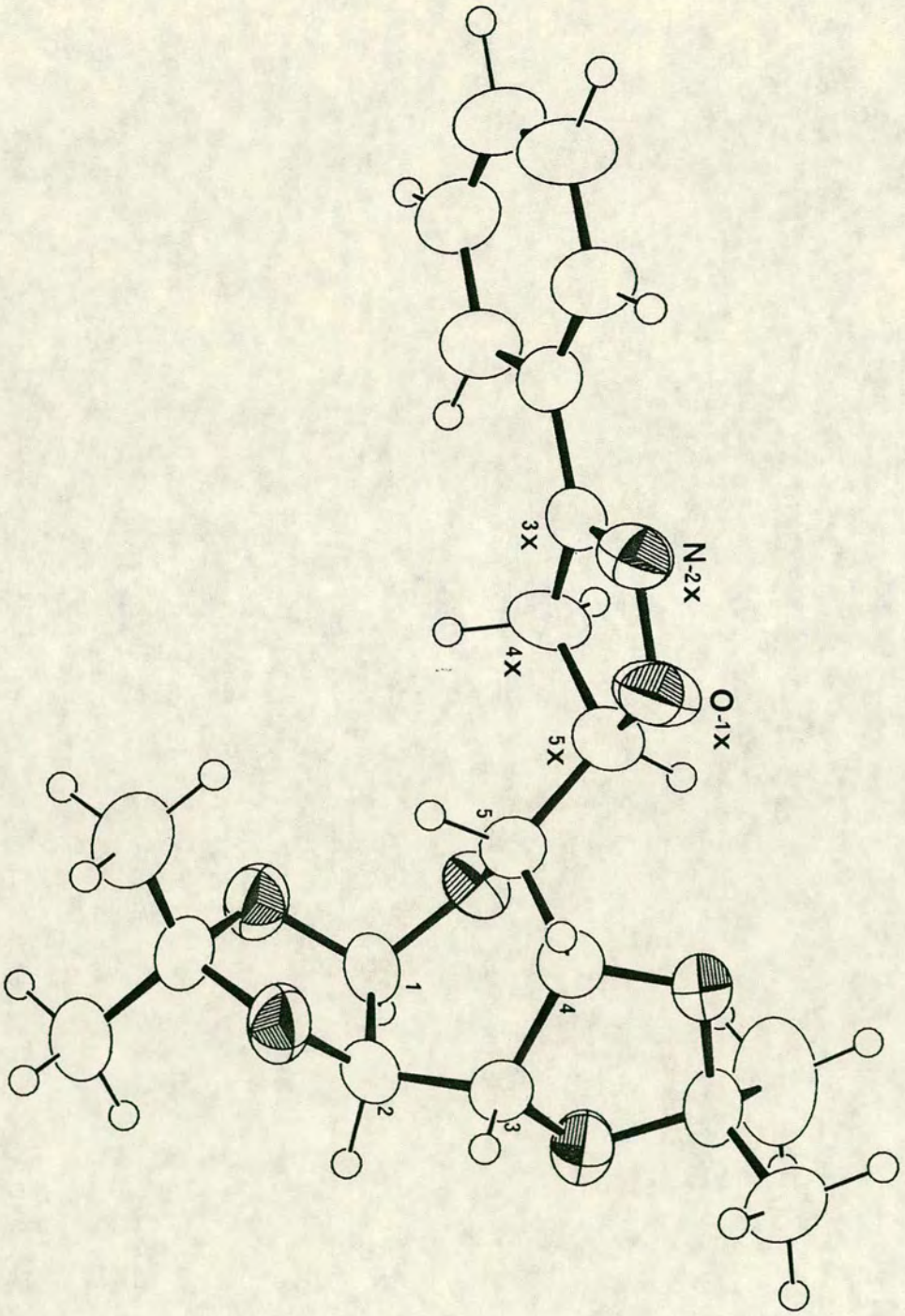
Bond Lengths(A) with standard deviations

C(1) - C(2)	1.543(16)	C(10) -C(11)	1.517(15)
C(1) - O(4)	1.418(14)	C(10) -O(10)	1.426(13)
C(1) - O(1)	1.390(14)	C(11) -C(12)	1.529(16)
C(2) - C(3)	1.528(15)	C(11) -O(11)	1.433(13)
C(2) - O(2)	1.417(13)	C(12) -O(12)	1.414(14)
C(3) - C(4)	1.533(15)	O(1) -C(1A)	1.426(15)
C(3) -O(30)	1.425(14)	O(2) -C(1A)	1.403(15)
C(4) - O(4)	1.461(13)	C(1A) -C(1B)	1.501(18)
C(4) - C(5)	1.536(16)	C(1A) -C(1C)	1.482(17)
C(5) - O(5)	1.465(14)	O(30) -C(30)	1.455(14)
C(5) - C(6)	1.507(16)	C(30) -C(31)	1.487(18)
O(5) - N	1.433(12)	O(9) -C(9A)	1.453(13)
N - C(7)	1.271(14)	O(10) -C(9A)	1.420(13)
C(6) - C(7)	1.522(15)	C(9A) -C(9B)	1.486(16)
C(7) - C(8)	1.493(14)	C(9A) -C(9C)	1.515(16)
C(8) - O(8)	1.429(12)	O(11) -C(11A)	1.433(13)
C(8) - C(9)	1.526(14)	O(12) -C(11A)	1.440(14)
O(8) -C(12)	1.435(13)	C(11A)-C(11B)	1.493(17)
C(9) -C(10)	1.543(14)	C(11A)-C(11C)	1.493(17)
C(9) - O(9)	1.430(12)		

Selected Torsion Angles (degrees) Involving Hydrogen with Standard Deviation.

H(1)-C(1)-C(2)-H(2)	14.4(1.7)
H(2)-C(2)-C(3)-H(3)	84.5(1.5)
H(3)-C(3)-C(4)-H(4)	31.0(1.5)
H(4)-C(4)-C(5)-H(5)	-175.3(1.2)
H(5)-C(5)-C(6)-H(6a)	-96.4(1.4)
H(5)-C(5)-C(6)-H(6b)	26.5(1.6)
H(8)-C(8)-C(9)-H(9)	36.5(1.3)
H(9)-C(9)-C(10)-H(10)	20.6(1.5)
H(10)-C(10)-C(11)-H(11)	71.5(1.4)
H(11)-C(11)-C(12)-H(12)	17.6(1.6)

Appendix C - X-Ray Crystallography Data for Compound (130)



Angles(degrees) with standard deviations

C(2) - C(1) - O(1)	103.5(5)	C(121)-C(12) -C(122)	113.6(6)
C(2) - C(1) - O(5)	114.5(5)	O(3) -C(34) - O(4)	104.9(5)
O(1) - C(1) - O(5)	110.9(5)	O(3) -C(34) -C(341)	111.6(6)
C(1) - C(2) - C(3)	113.9(5)	O(3) -C(34) -C(342)	109.7(6)
C(1) - C(2) - O(2)	103.8(5)	O(4) -C(34) -C(341)	108.6(6)
C(3) - C(2) - O(2)	108.1(5)	O(4) -C(34) -C(342)	108.7(6)
C(2) - C(3) - C(4)	114.1(6)	C(341)-C(34) -C(342)	113.0(6)
C(2) - C(3) - O(3)	105.9(5)	N(2X) -O(1X) -C(5X)	109.8(5)
C(4) - C(3) - O(3)	103.9(5)	O(1X) -N(2X) -C(3X)	108.4(5)
C(3) - C(4) - C(5)	112.4(5)	N(2X) -C(3X) -C(4X)	115.2(6)
C(3) - C(4) - O(4)	103.9(5)	N(2X) -C(3X) -C(1P)	118.4(6)
C(5) - C(4) - O(4)	111.9(5)	C(4X) -C(3X) -C(1P)	126.3(5)
C(4) - C(5) - O(5)	111.1(5)	C(3X) -C(4X) -C(5X)	101.5(5)
C(4) - C(5) -C(5X)	113.1(5)	C(5) -C(5X) -O(1X)	108.5(5)
O(5) - C(5) -C(5X)	105.5(5)	C(5) -C(5X) -C(4X)	114.3(5)
C(1) - O(1) -C(12)	110.5(4)	O(1X) -C(5X) -C(4X)	105.0(5)
C(2) - O(2) -C(12)	106.7(5)	C(3X) -C(1P) -C(2P)	121.7(6)
C(3) - O(3) -C(34)	107.3(5)	C(3X) -C(1P) -C(6P)	118.7(6)
C(4) - O(4) -C(34)	111.4(5)	C(2P) -C(1P) -C(6P)	119.7(6)
C(1) - O(5) - C(5)	113.0(5)	C(1P) -C(2P) -C(3P)	119.3(7)
O(1) -C(12) - O(2)	104.4(5)	C(2P) -C(3P) -C(4P)	120.9(8)
O(1) -C(12) -C(121)	109.7(5)	C(3P) -C(4P) -C(5P)	119.4(8)
O(1) -C(12) -C(122)	108.1(5)	C(4P) -C(5P) -C(6P)	121.5(8)
O(2) -C(12) -C(121)	111.8(6)	C(1P) -C(6P) -C(5P)	119.4(7)
O(2) -C(12) -C(122)	108.8(6)		

Selected Torsion Angles (degrees) Involving Hydrogen with Standard Deviation.

H(1)-C(1)-C(2)-H(2)	-18.9(9)
H(2)-C(2)-C(3)-H(3)	-74.2(9)
H(3)-C(3)-C(4)-H(4)	-19.7(9)
H(4)-C(4)-C(5)-H(5)	-37.1(8)
H(5)-C(5)-C(5X)-H(5X)	-176.8(7)
H(41X)-C(4X)-C(5X)-H(5X)	120.8(8)
H(42X)-C(4X)-C(5X)-H(5X)	-1.8(9)

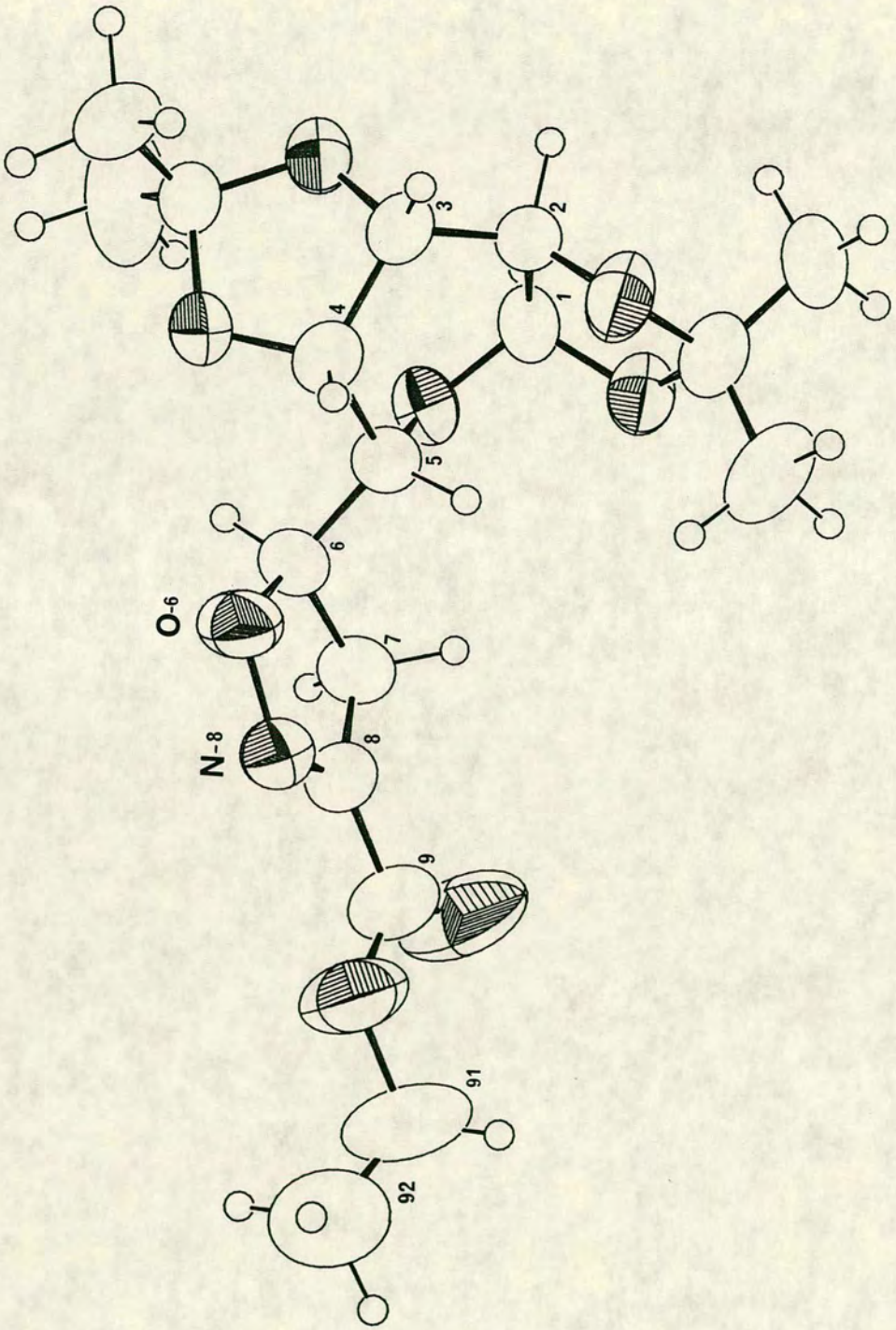
Torsion angles(degrees) with standard deviations

O(1)	C(1)	C(2)	C(3)	-137.5(5)	
O(1)	C(1)	C(2)	O(2)	-20.1(6)	
O(5)	C(1)	C(2)	C(3)	-16.7(8)	
O(5)	C(1)	C(2)	O(2)	100.6(6)	
C(2)	C(1)	O(1)	C(12)	0.6(6)	
O(5)	C(1)	O(1)	C(12)	-122.6(5)	
C(2)	C(1)	O(5)	C(5)	-39.0(7)	
O(1)	C(1)	O(5)	C(5)	77.6(6)	
C(1)	C(2)	C(3)	C(4)	44.1(8)	
C(1)	C(2)	C(3)	O(3)	-69.6(7)	
O(2)	C(2)	C(3)	C(4)	-70.7(7)	
O(2)	C(2)	C(3)	O(3)	175.6(5)	
C(1)	C(2)	O(2)	C(12)	32.7(6)	
C(3)	C(2)	O(2)	C(12)	154.0(5)	
C(2)	C(3)	C(4)	C(5)	-16.8(8)	
C(2)	C(3)	C(4)	O(4)	-138.0(6)	
O(3)	C(3)	C(4)	C(5)	98.1(6)	
O(3)	C(3)	C(4)	O(4)	-23.2(6)	
C(2)	C(3)	O(3)	C(34)	150.6(5)	
C(4)	C(3)	O(3)	C(34)	30.0(7)	
C(3)	C(4)	C(5)	O(5)	-37.0(7)	
C(3)	C(4)	C(5)	C(5X)	-155.5(5)	
O(4)	C(4)	C(5)	O(5)	79.5(6)	
O(4)	C(4)	C(5)	C(5X)	-39.0(7)	
C(3)	C(4)	O(4)	C(34)	8.4(7)	
C(5)	C(4)	O(4)	C(34)	-113.2(6)	
C(4)	C(5)	O(5)	C(1)	68.3(6)	
C(5X)	C(5)	O(5)	C(1)	-168.8(5)	
C(4)	C(5)	C(5X)	O(1X)	-57.1(7)	
C(4)	C(5)	C(5X)	C(4X)	-173.8(5)	
O(5)	C(5)	C(5X)	O(1X)	-178.7(5)	
O(5)	C(5)	C(5X)	C(4X)	64.6(6)	
C(1)	O(1)	C(12)	O(2)	19.1(6)	
C(1)	O(1)	C(12)	C(121)	-100.8(6)	
C(1)	O(1)	C(12)	C(122)	134.8(5)	
C(2)	O(2)	C(12)	O(1)	-32.5(6)	
C(2)	O(2)	C(12)	C(121)	85.9(6)	
C(2)	O(2)	C(12)	C(122)	-147.8(6)	
C(3)	O(3)	C(34)	O(4)	-25.1(7)	
C(3)	O(3)	C(34)	C(341)	92.3(7)	
C(3)	O(3)	C(34)	C(342)	-141.7(6)	
C(4)	O(4)	C(34)	O(3)	9.8(7)	
C(4)	O(4)	C(34)	C(341)	-109.7(6)	
C(4)	O(4)	C(34)	C(342)	127.0(6)	
C(5X)	O(1X)	N(2X)	C(3X)	0.9(7)	
N(2X)	O(1X)	C(5X)	C(5)	-125.1(5)	
N(2X)	O(1X)	C(5X)	C(4X)	-2.5(7)	
O(1X)	N(2X)	C(3X)	C(4X)	1.3(7)	
O(1X)	N(2X)	C(3X)	C(1P)	-177.2(5)	
N(2X)	C(3X)	C(4X)	C(5X)	-2.7(7)	
C(1P)	C(3X)	C(4X)	C(5X)	175.7(6)	
N(2X)	C(3X)	C(1P)	C(2P)	6.1(9)	
N(2X)	C(3X)	C(1P)	C(6P)	-174.8(6)	
C(4X)	C(3X)	C(1P)	C(2P)	-172.2(7)	
C(4X)	C(3X)	C(1P)	C(6P)	6.8(10)	
C(3X)	C(4X)	C(5X)	C(5)	121.7(6)	
C(3X)	C(4X)	C(5X)	O(1X)	2.9(6)	
C(3X)	C(1P)	C(2P)	C(3P)	178.8(7)	
C(6P)	C(1P)	C(2P)	C(3P)	-0.3(11)	
C(3X)	C(1P)	C(6P)	C(5P)	-178.6(6)	
C(2P)	C(1P)	C(6P)	C(5P)	0.5(10)	
C(1P)	C(2P)	C(3P)	C(4P)	-0.5(12)	
C(2P)	C(3P)	C(4P)	C(5P)	1.1(13)	
C(3P)	C(4P)	C(5P)	C(6P)	-0.9(13)	
C(4P)	C(5P)	C(6P)	C(1P)	0.1(12)	

Bond Lengths(A) with standard deviations

C(1)	C(2)	1.534(9)	
C(1)	O(1)	1.411(7)	
C(1)	O(5)	1.406(8)	
C(2)	C(3)	1.517(10)	
C(2)	O(2)	1.415(8)	
C(3)	C(4)	1.516(9)	
C(3)	O(3)	1.431(9)	
C(4)	C(5)	1.529(9)	
C(4)	O(4)	1.399(8)	
C(5)	O(5)	1.423(8)	
C(5)	C(5X)	1.507(9)	
O(1)	C(12)	1.433(7)	
O(2)	C(12)	1.419(8)	
O(3)	C(34)	1.423(9)	
O(4)	C(34)	1.432(8)	
C(12)	C(121)	1.489(10)	
C(12)	C(122)	1.507(10)	
C(34)	C(341)	1.479(10)	
C(34)	C(342)	1.478(12)	
O(1X)	N(2X)	1.408(8)	
O(1X)	C(5X)	1.446(8)	
N(2X)	C(3X)	1.299(8)	
C(3X)	C(4X)	1.454(9)	
C(3X)	C(1P)	1.483(9)	
C(4X)	C(5X)	1.531(9)	
C(1P)	C(2P)	1.376(10)	
C(1P)	C(6P)	1.393(10)	
C(2P)	C(3P)	1.390(12)	
C(3P)	C(4P)	1.382(12)	
C(4P)	C(5P)	1.343(12)	
C(5P)	C(6P)	1.386(11)	

Appendix D - X-Ray Crystallography Data for Compound (132)



Bond Lengths(Å) with standard deviations

C(1) - C(2)	1.523(8)	C(31) -C(33)	1.473(10)
C(1) - O(1)	1.412(6)	C(31) - O(3)	1.420(7)
C(1) - O(5)	1.409(6)	C(5) - O(5)	1.420(6)
C(2) - O(2)	1.424(6)	C(5) - C(6)	1.505(7)
C(2) - C(3)	1.502(8)	C(6) - C(7)	1.532(8)
O(2) -C(11)	1.432(7)	C(6) - O(6)	1.475(6)
C(11) -C(12)	1.494(10)	C(7) - C(8)	1.488(8)
C(11) -C(13)	1.509(9)	C(8) - N(8)	1.264(7)
C(11) - O(1)	1.412(7)	C(8) - C(9)	1.467(9)
C(3) - C(4)	1.526(7)	N(8) - O(6)	1.392(6)
C(3) - O(3)	1.421(7)	C(9) - O(9)	1.182(9)
C(4) - O(4)	1.401(6)	C(9) -O(91)	1.307(9)
C(4) - C(5)	1.533(7)	O(91) -C(91)	1.457(12)
O(4) -C(31)	1.426(7)	C(91) -C(92)	1.304(15)
C(31) -C(32)	1.493(8)		

Angles(degrees) with standard deviations

C(2) - C(1) - O(1)	104.0(4)	O(4) -C(31) - O(3)	104.6(4)
C(2) - C(1) - O(5)	113.7(4)	C(32) -C(31) -C(33)	111.5(5)
O(1) - C(1) - O(5)	109.8(4)	C(32) -C(31) - O(3)	112.0(4)
C(1) - C(2) - O(2)	104.1(4)	C(33) -C(31) - O(3)	109.9(5)
C(1) - C(2) - C(3)	115.1(4)	C(3) - O(3) -C(31)	108.2(4)
O(2) - C(2) - C(3)	108.6(4)	C(4) - C(5) - O(5)	111.2(4)
C(2) - O(2) -C(11)	105.6(4)	C(4) - C(5) - C(6)	113.9(4)
O(2) -C(11) -C(12)	111.6(5)	O(5) - C(5) - C(6)	104.7(4)
O(2) -C(11) -C(13)	107.7(5)	C(1) - O(5) - C(5)	113.9(4)
O(2) -C(11) - O(1)	104.5(4)	C(5) - C(6) - C(7)	113.7(4)
C(12) -C(11) -C(13)	113.3(5)	C(5) - C(6) - O(6)	107.9(4)
C(12) -C(11) - O(1)	110.6(5)	C(7) - C(6) - O(6)	104.4(4)
C(13) -C(11) - O(1)	108.6(5)	C(6) - C(7) - C(8)	100.3(4)
C(1) - O(1) -C(11)	110.3(4)	C(7) - C(8) - N(8)	115.9(5)
C(2) - C(3) - C(4)	114.8(4)	C(7) - C(8) - C(9)	121.1(5)
C(2) - C(3) - O(3)	107.4(4)	N(8) - C(8) - C(9)	123.0(5)
C(4) - C(3) - O(3)	103.9(4)	C(8) - N(8) - O(6)	109.4(4)
C(3) - C(4) - O(4)	104.2(4)	C(6) - O(6) - N(8)	109.7(4)
C(3) - C(4) - C(5)	111.6(4)	C(8) - C(9) - O(9)	121.5(7)
O(4) - C(4) - C(5)	110.6(4)	C(8) - C(9) -O(91)	113.7(6)
C(4) - O(4) -C(31)	111.4(4)	O(9) - C(9) -O(91)	124.8(7)
O(4) -C(31) -C(32)	108.8(4)	C(9) -O(91) -C(91)	115.3(6)
O(4) -C(31) -C(33)	109.8(5)	O(91) -C(91) -C(92)	112.2(9)

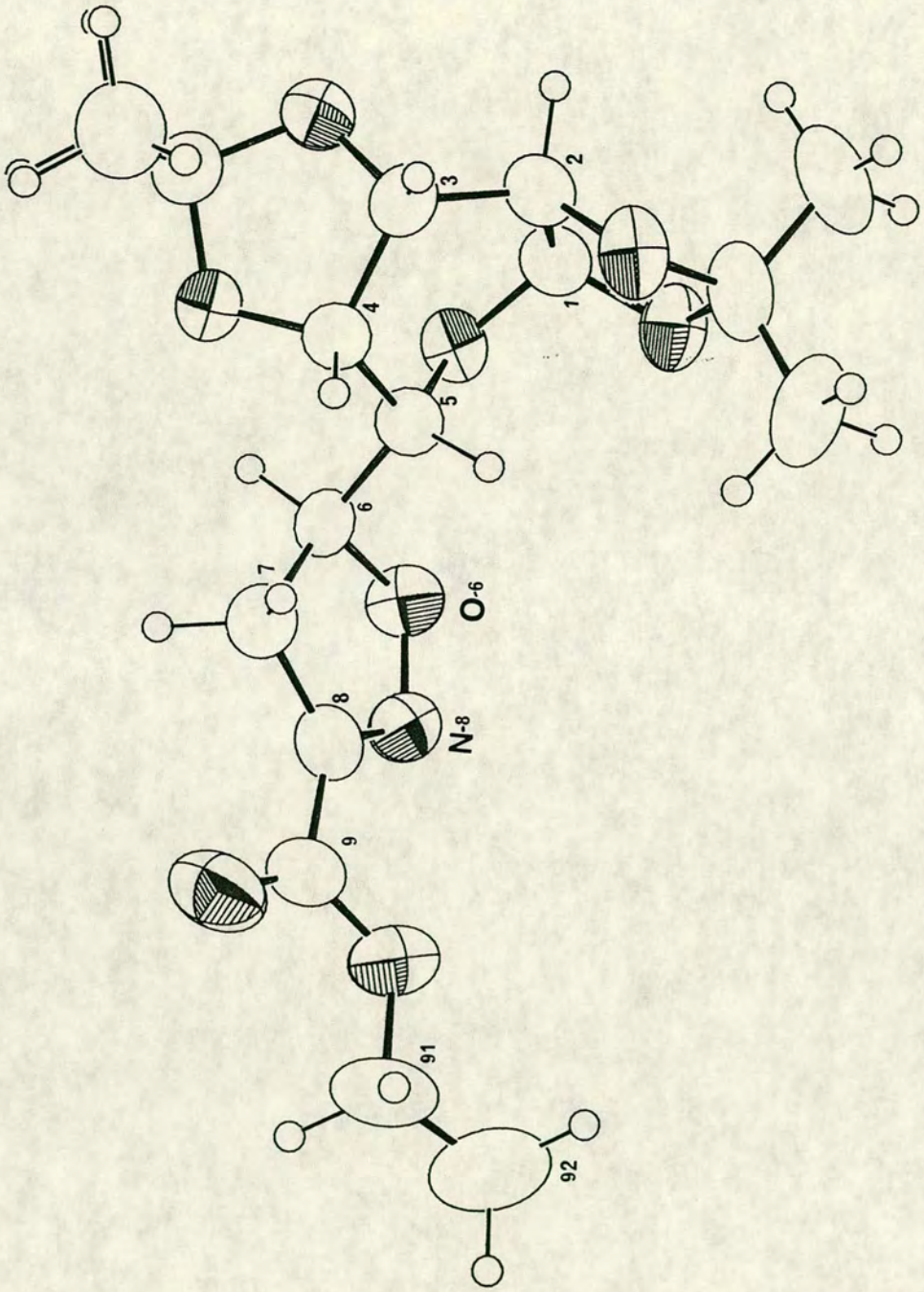
Torsion angles(degrees) with standard deviations

O(1)	C(1)	C(2)	O(2)	-17.3(5)	O(4)	C(4)	C(5)	O(5)	78.4(5)
O(1)	C(1)	C(2)	C(3)	-136.0(4)	O(4)	C(4)	C(5)	C(6)	-39.7(6)
O(5)	C(1)	C(2)	O(2)	102.1(5)	C(4)	O(4)	-C(31)	-C(32)	-105.4(5)
O(5)	C(1)	C(2)	C(3)	-16.6(6)	C(4)	O(4)	-C(31)	-C(33)	132.4(5)
C(2)	C(1)	O(1)	-C(11)	-3.6(5)	C(4)	O(4)	-C(31)	O(3)	14.5(5)
O(5)	C(1)	O(1)	-C(11)	-125.6(4)	O(4)	-C(31)	O(3)	C(3)	-26.6(5)
C(2)	C(1)	O(5)	C(5)	-38.7(5)	C(32)	-C(31)	O(3)	C(3)	91.2(5)
O(1)	C(1)	O(5)	C(5)	77.3(5)	C(33)	-C(31)	O(3)	C(3)	-144.3(5)
C(1)	C(2)	O(2)	-C(11)	31.6(5)	C(4)	C(5)	O(5)	C(1)	67.9(5)
C(3)	C(2)	O(2)	-C(11)	154.6(4)	C(6)	C(5)	O(5)	C(1)	-168.6(4)
C(1)	C(2)	C(3)	C(4)	43.2(6)	C(4)	C(5)	C(6)	C(7)	-171.0(4)
C(1)	C(2)	C(3)	O(3)	-71.8(6)	C(4)	C(5)	C(6)	O(6)	-55.7(5)
O(2)	C(2)	C(3)	C(4)	-72.9(6)	O(5)	C(5)	C(6)	C(7)	67.3(5)
O(2)	C(2)	C(3)	O(3)	172.1(4)	O(5)	C(5)	C(6)	O(6)	-177.4(4)
C(2)	O(2)	-C(11)	-C(12)	85.4(6)	C(5)	C(6)	C(7)	C(8)	112.4(5)
C(2)	O(2)	-C(11)	-C(13)	-149.6(5)	O(6)	C(6)	C(7)	C(8)	-5.0(5)
C(2)	O(2)	-C(11)	O(1)	-34.2(5)	C(5)	C(6)	O(6)	N(8)	-116.4(4)
O(2)	-C(11)	O(1)	C(1)	23.1(5)	C(7)	C(6)	O(6)	N(8)	4.9(5)
C(12)	-C(11)	O(1)	C(1)	-97.1(5)	C(6)	C(7)	C(8)	N(8)	4.1(6)
C(13)	-C(11)	O(1)	C(1)	137.9(5)	C(6)	C(7)	C(8)	C(9)	-177.0(5)
C(2)	C(3)	C(4)	O(4)	-134.9(5)	C(7)	C(8)	N(8)	O(6)	-1.2(6)
C(2)	C(3)	C(4)	C(5)	-15.6(6)	C(9)	C(8)	N(8)	O(6)	179.9(5)
O(3)	C(3)	C(4)	O(4)	-17.9(5)	C(7)	C(8)	C(9)	O(9)	10.8(10)
O(3)	C(3)	C(4)	C(5)	101.4(5)	C(7)	C(8)	C(9)	-O(91)	-169.0(5)
C(2)	C(3)	O(3)	-C(31)	149.7(4)	N(8)	C(8)	C(9)	O(9)	-170.4(6)
C(4)	C(3)	O(3)	-C(31)	27.7(5)	N(8)	C(8)	C(9)	-O(91)	9.9(9)
C(3)	C(4)	O(4)	-C(31)	2.1(5)	C(8)	N(8)	O(6)	C(6)	-2.5(5)
C(5)	C(4)	O(4)	-C(31)	-117.9(4)	C(8)	C(9)	-O(91)	-C(91)	-178.7(6)
C(3)	C(4)	C(5)	O(5)	-37.1(5)	O(9)	C(9)	-O(91)	-C(91)	1.6(11)
C(3)	C(4)	C(5)	C(6)	-155.2(4)	C(9)	-O(91)	-C(91)	-C(92)	-153.5(8)

Selected Torsion Angles (degrees) Involving Hydrogen with Standard Deviation.

H(1)-C(1)-C(2)-H(2)	-16.4(7)
H(2)-C(2)-C(3)-H(3)	-76.7(7)
H(3)-C(3)-C(4)-H(4)	-15.6(7)
H(4)-C(4)-C(5)-H(5)	-36.9(6)
H(5)-C(5)-C(6)-H(6)	-175.5(6)
H(6)-C(6)-C(7)-H(7a)	-112.9(7)
H(6)-C(6)-C(7)-H(7b)	-10.1(8)

Appendix E - X-Ray Crystallography Data for Compound (133)



Bond Lengths(Å) with standard deviations

C(1) - C(2)	1.528(7)	C(31) -C(33)	1.472(9)
C(1) - O(1)	1.405(6)	C(31) - O(3)	1.429(7)
C(1) - O(5)	1.412(6)	C(5) - O(5)	1.427(5)
C(2) - O(2)	1.408(6)	C(5) - C(6)	1.503(6)
C(2) - C(3)	1.511(7)	C(6) - C(7)	1.518(7)
O(1) -C(11)	1.433(7)	C(6) - O(6)	1.472(6)
C(11) -C(12)	1.497(10)	C(7) - C(8)	1.487(7)
C(11) -C(13)	1.492(9)	C(8) - N(8)	1.267(7)
C(11) - O(2)	1.426(7)	C(8) - C(9)	1.476(8)
C(3) - C(4)	1.535(7)	N(8) - O(6)	1.387(5)
C(3) - O(3)	1.403(6)	C(9) - O(9)	1.204(7)
C(4) - O(4)	1.429(6)	C(9) -O(91)	1.319(7)
C(4) - C(5)	1.520(6)	O(91) -C(91)	1.449(8)
O(4) -C(31)	1.409(6)	C(91) -C(92)	1.439(12)
C(31) -C(32)	1.511(9)		

Angles(degrees) with standard deviations

C(2) - C(1) - O(1)	104.2(4)	O(4) -C(31) - O(3)	103.5(4)
C(2) - C(1) - O(5)	113.9(4)	C(32) -C(31) -C(33)	112.8(5)
O(1) - C(1) - O(5)	110.7(4)	C(32) -C(31) - O(3)	110.0(5)
C(1) - C(2) - O(2)	104.4(4)	C(33) -C(31) - O(3)	109.9(5)
C(1) - C(2) - C(3)	115.5(4)	C(3) - O(3) -C(31)	107.1(4)
O(2) - C(2) - C(3)	108.6(4)	C(4) - C(5) - O(5)	110.6(4)
C(1) - O(1) -C(11)	109.2(4)	C(4) - C(5) - C(6)	113.3(4)
O(1) -C(11) -C(12)	110.7(5)	O(5) - C(5) - C(6)	105.2(4)
O(1) -C(11) -C(13)	109.0(5)	C(1) - O(5) - C(5)	113.3(3)
O(1) -C(11) - O(2)	103.7(4)	C(5) - C(6) - C(7)	115.2(4)
C(12) -C(11) -C(13)	113.0(5)	C(5) - C(6) - O(6)	108.9(4)
C(12) -C(11) - O(2)	111.6(5)	C(7) - C(6) - O(6)	104.0(4)
C(13) -C(11) - O(2)	108.4(5)	C(6) - C(7) - C(8)	101.3(4)
C(2) - O(2) -C(11)	105.8(4)	C(7) - C(8) - N(8)	114.8(5)
C(2) - C(3) - C(4)	114.6(4)	C(7) - C(8) - C(9)	122.7(5)
C(2) - C(3) - O(3)	109.0(4)	N(8) - C(8) - C(9)	122.5(5)
C(4) - C(3) - O(3)	103.8(4)	C(8) - N(8) - O(6)	109.6(4)
C(3) - C(4) - O(4)	103.7(4)	C(6) - O(6) - N(8)	110.0(3)
C(3) - C(4) - C(5)	112.6(4)	C(8) - C(9) - O(9)	121.7(5)
O(4) - C(4) - C(5)	109.5(4)	C(8) - C(9) -O(91)	113.5(5)
C(4) - O(4) -C(31)	109.3(4)	O(9) - C(9) -O(91)	124.7(5)
O(4) -C(31) -C(32)	110.1(5)	C(9) -O(91) -C(91)	116.8(5)
O(4) -C(31) -C(33)	110.1(5)	O(91) -C(91) -C(92)	107.4(6)

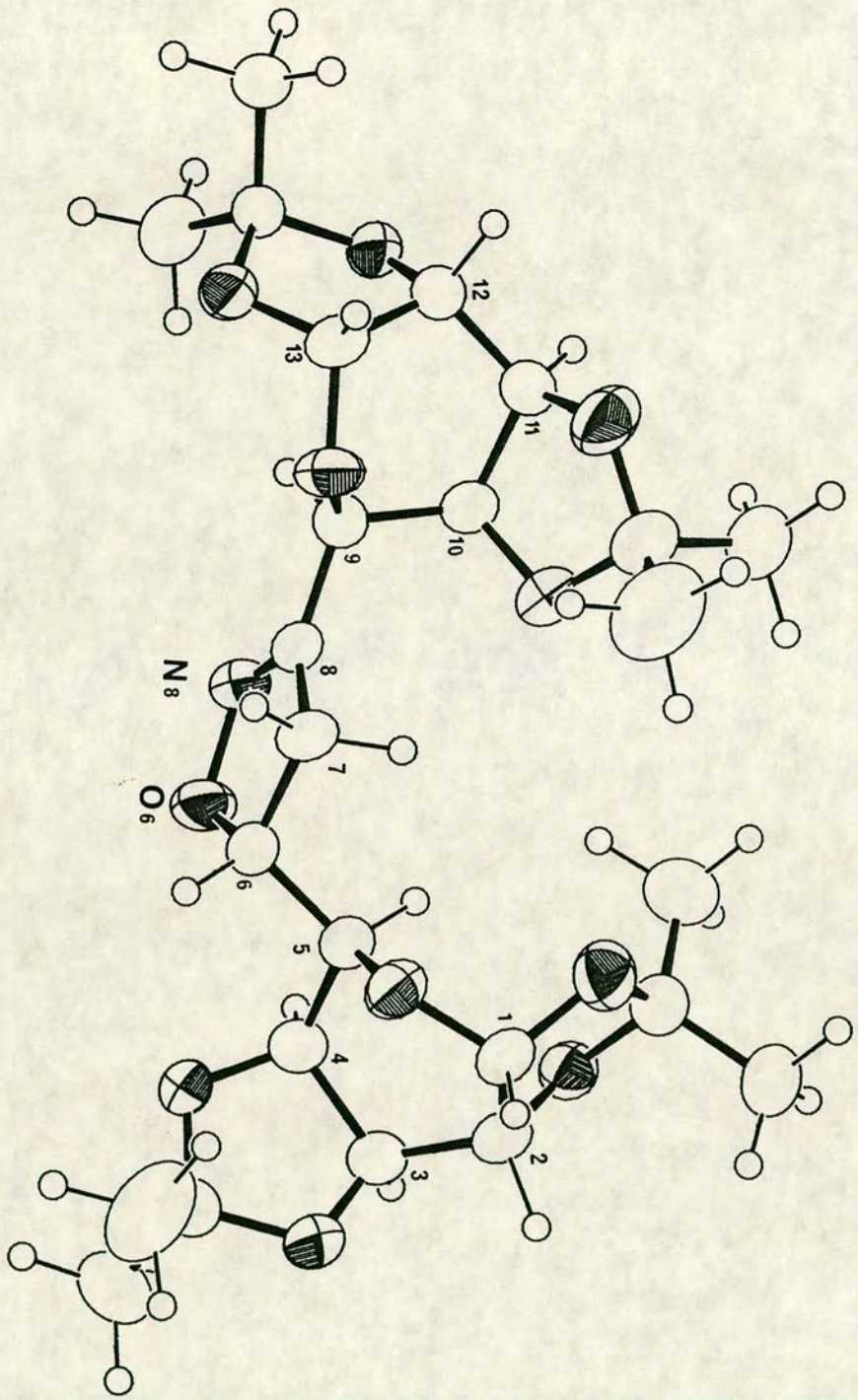
Torsion angles(degrees) with standard deviations

O(1)	C(1)	C(2)	O(2)	-14.8(5)	O(4)	C(4)	C(5)	O(5)	75.9(4)
O(1)	C(1)	C(2)	C(3)	-134.0(4)	O(4)	C(4)	C(5)	C(6)	-41.9(5)
O(5)	C(1)	C(2)	O(2)	105.9(4)	C(4)	O(4)	-C(31)	-C(32)	-89.3(5)
O(5)	C(1)	C(2)	C(3)	-13.3(6)	C(4)	O(4)	-C(31)	-C(33)	145.7(5)
C(2)	C(1)	O(1)	-C(11)	-7.5(5)	C(4)	O(4)	-C(31)	O(3)	28.2(5)
O(5)	C(1)	O(1)	-C(11)	-130.3(4)	O(4)	-C(31)	O(3)	C(3)	-36.6(5)
C(2)	C(1)	O(5)	C(5)	-40.9(5)	C(32)	-C(31)	O(3)	C(3)	81.0(5)
O(1)	C(1)	O(5)	C(5)	76.0(5)	C(33)	-C(31)	O(3)	C(3)	-154.2(5)
C(1)	C(2)	O(2)	-C(11)	31.7(5)	C(4)	C(5)	O(5)	C(1)	69.2(5)
C(3)	C(2)	O(2)	-C(11)	155.4(4)	C(6)	C(5)	O(5)	C(1)	-168.0(4)
C(1)	C(2)	C(3)	C(4)	39.3(6)	C(4)	C(5)	C(6)	C(7)	-59.0(5)
C(1)	C(2)	C(3)	O(3)	-76.5(5)	C(4)	C(5)	C(6)	O(6)	-175.3(4)
O(2)	C(2)	C(3)	C(4)	-77.5(5)	O(5)	C(5)	C(6)	C(7)	-179.9(4)
O(2)	C(2)	C(3)	O(3)	166.7(4)	O(5)	C(5)	C(6)	O(6)	63.7(4)
C(1)	O(1)	-C(11)	-C(12)	-93.0(6)	C(5)	C(6)	C(7)	C(8)	-113.8(4)
C(1)	O(1)	-C(11)	-C(13)	142.2(5)	O(6)	C(6)	C(7)	C(8)	5.2(5)
C(1)	O(1)	-C(11)	O(2)	26.8(5)	C(5)	C(6)	O(6)	N(8)	117.8(4)
O(1)	-C(11)	O(2)	C(2)	-36.4(5)	C(7)	C(6)	O(6)	N(8)	-5.5(5)
C(12)	-C(11)	O(2)	C(2)	82.8(6)	C(6)	C(7)	C(8)	N(8)	-3.8(6)
C(13)	-C(11)	O(2)	C(2)	-152.1(5)	C(6)	C(7)	C(8)	C(9)	176.8(5)
C(2)	C(3)	C(4)	O(4)	-130.9(4)	C(7)	C(8)	N(8)	O(6)	0.4(6)
C(2)	C(3)	C(4)	C(5)	-12.6(6)	C(9)	C(8)	N(8)	O(6)	179.9(4)
O(3)	C(3)	C(4)	O(4)	-12.1(5)	C(7)	C(8)	C(9)	O(9)	9.6(8)
O(3)	C(3)	C(4)	C(5)	106.1(4)	C(7)	C(8)	C(9)	-O(91)	-166.8(5)
C(2)	C(3)	O(3)	-C(31)	152.5(4)	N(8)	C(8)	C(9)	O(9)	-169.8(5)
C(4)	C(3)	O(3)	-C(31)	29.9(5)	N(8)	C(8)	C(9)	-O(91)	13.8(8)
C(3)	C(4)	O(4)	-C(31)	-10.1(5)	C(8)	N(8)	O(6)	C(6)	3.4(5)
C(5)	C(4)	O(4)	-C(31)	-130.6(4)	C(8)	C(9)	-O(91)	-C(91)	176.0(5)
C(3)	C(4)	C(5)	O(5)	-38.9(5)	O(9)	C(9)	-O(91)	-C(91)	-0.2(9)
C(3)	C(4)	C(5)	C(6)	-156.8(4)	C(9)	-O(91)	-C(91)	-C(92)	-178.2(6)

Selected Torsion Angles (degrees) Involving Hydrogen with Standard Deviation.

H(1)-C(1)-C(2)-H(2)	-13.5(7)
H(2)-C(2)-C(3)-H(3)	-81.2(6)
H(3)-C(3)-C(4)-H(4)	-11.5(7)
H(4)-C(4)-C(5)-H(5)	-38.6(6)
H(5)-C(5)-C(6)-H(6)	-177.8(5)
H(6)-C(6)-C(7)-H(7a)	-112.1(6)
H(6)-C(6)-C(7)-H(7b)	10.6(7)

Appendix F - X-Ray Crystallography Data for Compound (137)



Torsion angles(degrees) with standard deviations

C(2) - C(1) - O(1) -C(21)	-1.6(6)	C(6) - C(7) - C(8) - N(8)	7.1(7)
O(5) - C(1) - O(1) -C(21)	-124.3(5)	C(6) - C(7) - C(8) - C(9)	-176.5(6)
O(1) - C(1) - C(2) - O(2)	-18.4(6)	C(7) - C(8) - N(8) - O(6)	-1.3(7)
O(1) - C(1) - C(2) - C(3)	-135.3(5)	C(9) - C(8) - N(8) - O(6)	-178.1(5)
O(5) - C(1) - C(2) - O(2)	101.6(5)	C(7) - C(8) - C(9) - O(9)	-32.3(8)
O(5) - C(1) - C(2) - C(3)	-15.4(7)	C(7) - C(8) - C(9) -C(10)	88.7(7)
O(1) - C(1) - O(5) - C(5)	76.4(6)	N(8) - C(8) - C(9) - O(9)	144.0(5)
C(2) - C(1) - O(5) - C(5)	-40.3(6)	N(8) - C(8) - C(9) -C(10)	-95.0(7)
C(1) - O(1) -C(21) - O(2)	21.0(6)	C(8) - C(9) - O(9) -C(13)	-164.4(5)
C(1) - O(1) -C(21) -C(22)	135.7(6)	C(10) - C(9) - O(9) -C(13)	71.8(6)
C(1) - O(1) -C(21) -C(23)	-98.6(6)	C(8) - C(9) -C(10) -O(10)	-42.0(7)
C(1) - C(2) - O(2) -C(21)	31.5(6)	C(8) - C(9) -C(10) -C(11)	-156.2(5)
C(3) - C(2) - O(2) -C(21)	154.1(5)	O(9) - C(9) -C(10) -O(10)	76.7(6)
C(1) - C(2) - C(3) - O(3)	-73.8(6)	O(9) - C(9) -C(10) -C(11)	-37.6(6)
C(1) - C(2) - C(3) - C(4)	41.4(7)	C(9) - O(9) -C(13) -C(12)	-43.7(6)
O(2) - C(2) - C(3) - O(3)	170.9(5)	C(9) - O(9) -C(13) -O(13)	73.1(5)
O(2) - C(2) - C(3) - C(4)	-73.9(6)	C(9) -C(10) -O(10) -C(41)	-118.9(5)
C(2) - O(2) -C(21) - O(1)	-32.8(6)	C(11) -C(10) -O(10) -C(41)	0.7(6)
C(2) - O(2) -C(21) -C(22)	-148.5(5)	C(9) -C(10) -C(11) -O(11)	100.7(5)
C(2) - O(2) -C(21) -C(23)	86.3(6)	C(9) -C(10) -C(11) -C(12)	-17.3(7)
C(2) - C(3) - O(3) -C(31)	141.0(5)	O(10) -C(10) -C(11) -O(11)	-18.4(6)
C(4) - C(3) - O(3) -C(31)	19.6(6)	O(10) -C(10) -C(11) -C(12)	-136.5(5)
C(2) - C(3) - C(4) - O(4)	-135.0(5)	C(10) -O(10) -C(41) -O(11)	17.3(7)
C(2) - C(3) - C(4) - C(5)	-12.6(7)	C(10) -O(10) -C(41) -C(42)	133.7(6)
O(3) - C(3) - C(4) - O(4)	-18.1(6)	C(10) -O(10) -C(41) -C(43)	-102.2(6)
O(3) - C(3) - C(4) - C(5)	104.3(6)	C(10) -C(11) -O(11) -C(41)	29.8(6)
C(3) - O(3) -C(31) - O(4)	-13.5(7)	C(12) -C(11) -O(11) -C(41)	152.2(5)
C(3) - O(3) -C(31) -C(32)	105.8(6)	C(10) -C(11) -C(12) -O(12)	-71.8(6)
C(3) - O(3) -C(31) -C(33)	-132.0(6)	C(10) -C(11) -C(12) -C(13)	43.8(7)
C(3) - C(4) - O(4) -C(31)	10.7(7)	O(11) -C(11) -C(12) -O(12)	172.3(5)
C(5) - C(4) - O(4) -C(31)	-111.4(6)	O(11) -C(11) -C(12) -C(13)	-72.1(6)
C(3) - C(4) - C(5) - O(5)	-40.2(7)	C(11) -O(11) -C(41) -O(10)	-29.7(6)
C(3) - C(4) - C(5) - C(6)	-158.6(5)	C(11) -O(11) -C(41) -C(42)	-144.6(6)
O(4) - C(4) - C(5) - O(5)	77.0(6)	C(11) -O(11) -C(41) -C(43)	90.3(6)
O(4) - C(4) - C(5) - C(6)	-41.6(7)	C(11) -C(12) -O(12) -C(51)	151.4(5)
C(4) - O(4) -C(31) - O(3)	1.0(7)	C(13) -C(12) -O(12) -C(51)	29.4(6)
C(4) - O(4) -C(31) -C(32)	-119.6(6)	C(11) -C(12) -C(13) - O(9)	-13.5(7)
C(4) - O(4) -C(31) -C(33)	117.8(6)	C(11) -C(12) -C(13) -O(13)	-133.2(5)
C(4) - C(5) - O(5) - C(1)	70.4(6)	O(12) -C(12) -C(13) - O(9)	104.8(5)
C(6) - C(5) - O(5) - C(1)	-166.3(5)	O(12) -C(12) -C(13) -O(13)	-14.9(6)
C(4) - C(5) - C(6) - O(6)	-57.9(6)	C(12) -O(12) -C(51) -O(13)	-32.7(5)
C(4) - C(5) - C(6) - C(7)	-174.3(5)	C(12) -O(12) -C(51) -C(52)	84.7(5)
O(5) - C(5) - C(6) - O(6)	-178.6(4)	C(12) -O(12) -C(51) -C(53)	-149.3(5)
O(5) - C(5) - C(6) - C(7)	64.9(6)	O(9) -C(13) -O(13) -C(51)	-127.2(5)
C(5) - C(6) - O(6) - N(8)	-110.8(5)	C(12) -C(13) -O(13) -C(51)	-5.0(6)
C(7) - C(6) - O(6) - N(8)	10.0(6)	C(13) -O(13) -C(51) -O(12)	22.9(5)
C(5) - C(6) - C(7) - C(8)	107.9(5)	C(13) -O(13) -C(51) -C(52)	-95.6(5)
O(6) - C(6) - C(7) - C(8)	-9.8(6)	C(13) -O(13) -C(51) -C(53)	139.8(5)
C(6) - O(6) - N(8) - C(8)	-5.8(6)		

Angles(degrees) with standard deviations

O(1) - C(1) - C(2)	104.3(5)	C(10) -C(11) -O(11)	104.4(5)
O(1) - C(1) - O(5)	109.9(5)	C(10) -C(11) -C(12)	114.6(5)
C(2) - C(1) - O(5)	114.0(5)	O(11) -C(11) -C(12)	108.1(5)
C(1) - O(1) -C(21)	110.1(5)	C(11) -O(11) -C(41)	107.3(5)
C(1) - C(2) - O(2)	104.1(5)	C(11) -C(12) -O(12)	108.7(5)
C(1) - C(2) - C(3)	115.3(5)	C(11) -C(12) -C(13)	114.2(5)
O(2) - C(2) - C(3)	107.1(5)	O(12) -C(12) -C(13)	104.0(5)
C(2) - O(2) -C(21)	105.6(4)	C(12) -O(12) -C(51)	107.0(4)
C(2) - C(3) - O(3)	107.4(5)	O(9) -C(13) -C(12)	113.5(5)
C(2) - C(3) - C(4)	113.9(5)	O(9) -C(13) -O(13)	109.8(5)
O(3) - C(3) - C(4)	104.4(5)	C(12) -C(13) -O(13)	104.7(5)
C(3) - O(3) -C(31)	110.0(5)	C(13) -O(13) -C(51)	109.8(4)
C(3) - C(4) - O(4)	103.9(5)	O(1) -C(21) - O(2)	104.7(5)
C(3) - C(4) - C(5)	112.4(5)	O(1) -C(21) -C(22)	108.9(6)
O(4) - C(4) - C(5)	112.9(5)	O(1) -C(21) -C(23)	110.4(5)
C(4) - O(4) -C(31)	112.0(5)	O(2) -C(21) -C(22)	107.5(5)
C(4) - C(5) - O(5)	109.9(5)	O(2) -C(21) -C(23)	111.1(5)
C(4) - C(5) - C(6)	113.8(5)	C(22) -C(21) -C(23)	113.9(6)
O(5) - C(5) - C(6)	105.9(5)	O(3) -C(31) - O(4)	105.8(5)
C(1) - O(5) - C(5)	112.6(4)	O(3) -C(31) -C(32)	111.6(6)
C(5) - C(6) - O(6)	108.0(5)	O(3) -C(31) -C(33)	108.1(6)
C(5) - C(6) - C(7)	112.6(5)	O(4) -C(31) -C(32)	109.6(6)
O(6) - C(6) - C(7)	105.8(5)	O(4) -C(31) -C(33)	110.6(6)
C(6) - O(6) - N(8)	108.9(4)	C(32) -C(31) -C(33)	110.9(6)
C(6) - C(7) - C(8)	100.2(5)	O(10) -C(41) -O(11)	105.4(5)
C(7) - C(8) - N(8)	114.9(5)	O(10) -C(41) -C(42)	107.4(6)
C(7) - C(8) - C(9)	127.6(5)	O(10) -C(41) -C(43)	111.0(6)
N(8) - C(8) - C(9)	117.4(5)	O(11) -C(41) -C(42)	109.3(6)
O(6) - N(8) - C(8)	109.0(5)	O(11) -C(41) -C(43)	110.3(6)
C(8) - C(9) - O(9)	105.7(4)	C(42) -C(41) -C(43)	113.1(6)
C(8) - C(9) -C(10)	114.3(5)	O(12) -C(51) -O(13)	104.2(4)
O(9) - C(9) -C(10)	109.9(5)	O(12) -C(51) -C(52)	110.8(5)
C(9) - O(9) -C(13)	111.8(4)	O(12) -C(51) -C(53)	109.5(5)
C(9) -C(10) -O(10)	111.0(5)	O(13) -C(51) -C(52)	109.2(5)
C(9) -C(10) -C(11)	111.6(5)	O(13) -C(51) -C(53)	109.1(5)
O(10) -C(10) -C(11)	102.9(5)	C(52) -C(51) -C(53)	113.5(5)
C(10) -O(10) -C(41)	110.8(5)		

Bond Lengths(A) with standard deviations

C(1) - O(1)	1.415(8)	C(9) -C(10)	1.524(8)
C(1) - C(2)	1.524(8)	O(9) -C(13)	1.419(7)
C(1) - O(5)	1.399(7)	C(10) -O(10)	1.427(8)
O(1) -C(21)	1.424(8)	C(10) -C(11)	1.538(9)
C(2) - O(2)	1.431(7)	O(10) -C(41)	1.414(8)
C(2) - C(3)	1.510(9)	C(11) -O(11)	1.415(8)
O(2) -C(21)	1.437(8)	C(11) -C(12)	1.509(9)
C(3) - O(3)	1.419(8)	O(11) -C(41)	1.419(8)
C(3) - C(4)	1.527(9)	C(12) -O(12)	1.417(8)
O(3) -C(31)	1.418(8)	C(12) -C(13)	1.531(9)
C(4) - O(4)	1.404(8)	O(12) -C(51)	1.433(7)
C(4) - C(5)	1.524(9)	C(13) -O(13)	1.410(7)
O(4) -C(31)	1.415(8)	O(13) -C(51)	1.433(7)
C(5) - O(5)	1.438(7)	C(21) -C(22)	1.503(10)
C(5) - C(6)	1.514(9)	C(21) -C(23)	1.497(10)
C(6) - O(6)	1.437(8)	C(31) -C(32)	1.478(10)
C(6) - C(7)	1.540(9)	C(31) -C(33)	1.495(12)
O(6) - N(8)	1.430(7)	C(41) -C(42)	1.502(12)
C(7) - C(8)	1.486(8)	C(41) -C(43)	1.494(10)
C(8) - N(8)	1.283(8)	C(51) -C(52)	1.498(8)
C(8) - C(9)	1.477(8)	C(51) -C(53)	1.492(9)
C(9) - O(9)	1.443(7)		

Selected Torsion Angles (degrees) Involving Hydrogen with Standard Deviation.

H(11)-C(1)-C(2)-H(21)	-16.8(8)
H(21)-C(2)-C(3)-H(31)	-78.0(8)
H(31)-C(3)-C(4)-H(41)	-16.8(9)
H(41)-C(4)-C(5)-H(51)	-39.2(8)
H(51)-C(5)-C(6)-H(61)	-177.7(7)
H(61)-C(6)-C(7)-H(71)	109.7(8)
H(61)-C(6)-C(7)-H(72)	-13.5(9)
H(91)-C(9)-C(10)-H(101)	-38.0(8)
H(101)-C(10)-C(11)-H(111)	-17.0(9)
H(111)-C(11)-C(12)-H(121)	-76.3(8)
H(121)-C(12)-C(13)-H(131)	-14.7(9)

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