Cyclic imine sugars: towards the synthesis of transition-state mimics as potential glycosyltransferase inhibitors

Michael A.T. Maughan

Cyclic Imine Sugars: Towards the Synthesis of Transition-State Mimics as Potential Glycosyltransferase Inhibitors

Michael A. T. Maughan

Ph.D Thesis

December 2003

COPYRIGHT

DECLARATION

The work discussed in this thesis was conducted in the Department of Chemistry at the University of Durham and Oxford Glycosciences Ltd, Milton Park Abingdon between October 1999 and December 2003. It is the work of the author and results generated in collaboration with other people are indicated. The work has not been submitted for a degree at any other university.

ABSTRACT

Michael A. T. Maughan

Ph.D December 2003

This thesis describes the development of methodology for the synthesis of cyclic imine-sugars, and their use in the synthesis of aza-sugars as potential sugar-processing enzyme inhibitors. Our goals include the synthesis of cyclic imines of L-rhamnose, D-glucose, and L-idose stereochemistry, and the introduction of functionality *via* nucleophilic addition reactions.

Work on the synthesis of cyclic imines commenced with the use of the simple model systems piperidine and 2-methylpiperidine. *N*-Chlorination of these systems was performed, and the products converted into their cyclic imine derivatives through elimination of HCl. Nucleophilic addition reactions to these systems were attempted, but the low stability and reactivity of the imines led to the isolation of only one adduct.

The synthesis of novel cyclic pyrrolidine imine-sugars of L-rhamnose stereochemistry was performed by a Staudinger aza-Wittig reaction. The aza-Wittig reaction of a known L-rhamnose derived azido-sugar gave a novel cyclic L-rhamnopyrrolidine aldimine. A novel synthesis of this azido-sugar was also devised. Successful nucleophilic additions to the cyclic L-rhamnopyrrolidine aldimine were performed with a range of Grignard reagents giving novel protected aza-sugars in good yields and with excellent diastereoselectivities. A novel cyclic L-rhamnopyrrolidine ketimine was also synthesised *via* a Staudinger aza-Wittig from a novel azido-sugar, although time constraints prevented screening this system with nucleophiles.

The synthesis of novel cyclic piperidine imine-sugars of D-glucose, and L-idose stereochemistry was performed, both *via* *N*-chlorination/elimination of the protected parent aza-sugars, and *via* the Staudinger aza-Wittig reaction of novel azido-sugars.

The elimination of HCl from six-membered *N*-chloro aza-sugars of D-glucose and L-idose stereochemistry was investigated, and methodology developed in the case of D-glucose system for the regioselective elimination of HCl to give either the aldimine or the ketimine derivative. Comparison of elimination reactions of the *N*-chloro aza-sugars of D-glucose, and L-idose stereochemistry allowed rationalisation of the observed regiocontrol.

Screening of the cyclic imines of D-glucose and L-idose stereochemistry with nucleophiles, followed by deprotection of the adducts, allowed the synthesis of novel aza-sugars *via* late-stage introduction of functionality. Low yields were obtained for these additions, but diastereocontrol was generally good, and could be rationalised by accepted stereoelectronic and steric approach control factors.

The formation of cyclic piperidine imines of L-idose, and D-glucose stereochemistry was also performed *via* the Staudinger aza-Wittig reaction. These systems were found to be identical to those synthesised by the *N*-chlorination/elimination protocol. We also performed the first synthesis of the enantiomer of the natural product (+)-adenophorine thereby allowing assignment of the absolute configuration of the natural product (+)-adenophorine. The key synthetic step in this synthesis was stereoselective reduction of a novel intermediate cyclic piperidine ketimine-sugar of L-idose stereochemistry.

Abbreviations

aq.	Aqueous
Bn	Benzyl
br	Broad
CI	Chemical ionisation
conc.	Concentrated
CSA	Camphor-10-sulfonic acid
d	Doublet
Dabco^{TM}	1,4-Diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo-[5.4.0]-undec-7-ene
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DEPT	Distortionless enhancement of polarization transfer
DIAD	Diisopropylazodicarboxylate
DMF	Dimethylformamide
DNJ	2-deoxynojirimycin
ES	Electrospray
Et	Ethyl
eq.	Molar equivalent(s)
EWG	Electron withdrawing group
GC	Gas chromatography
gCOSY	Correlated Spectroscopy
gHSQC	Heteronuclear single quantum coherence
h	Hour(s)
HOMO	Highest occupied molecular orbital
HRMS	High resolution mass spectroscopy
INJ	Idonojirimycin
IR	Infra red
LDA	Lithium diisopropylamine
LiTMP	Lithium 2,2,6,6-tetramethylpiperidide
LUMO	Lowest unoccupied molecular orbital
m	multiplet

Me	Methyl
Ms	Methanesulfonate
MS	Mass spectroscopy
NCS	*N*-Chlorosuccinimide
NJ	Nojirimycin
NMR	Nuclear magnetic resonance
nOesy	Nuclear Overhauser effect spectroscopy
PCC	Pyridinium chlorochromate
Ph	Phenyl
Py	Pyridine
q	Quartet
s	Singlet
satd.	Saturated
t	Triplet
TBAF	Tetra-*n*-butylammonium fluoride
TBAAZ	Tetra-*n*-butylammonium azide
TBDMS	*tert*-Butyldimethylsilyl
TBDPS	*tert*-Butyldiphenylsilyl
TFA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMP	2,2,6,6-Tetramethylpiperidine
TMS	Trimethylsilyl
UDP	Uridine diphosphate

Contents

Chapter 1. Introduction

1.1 Introduction

Polyhydroxylated piperidines and pyrrolidines, loosely classed as aza-sugars (sugars where the ring oxygen has been replaced by nitrogen), have long been recognised for their, sometimes highly potent, inhibition of sugar-processing enzymes.[1,2] Indeed alpha substituted piperidine and pyrrolidine alkaloids also have many applications in the treatment of disease.[3] There are countless syntheses of a wide variety of aza-sugars, and often, simple modification of aza-sugar scaffolds can dramatically change the specificity or potency of inhibition.[1] Nojirimycin (NJ) (**1.01**) (Figure 1),[4] an aza-sugar analogue of D-glucopyranose, first isolated from *Streptomyces roseochromogenes* R-468 is the archetypal aza-sugar, and many structural variants have been synthesised. NJ itself is a potent specific inhibitor of several glucose-processing enzymes,[4,5] which may be expected due to the simple stereochemical similarity between NJ and the pyranse form of D-glucose itself (**1.02**) (Figure 1).

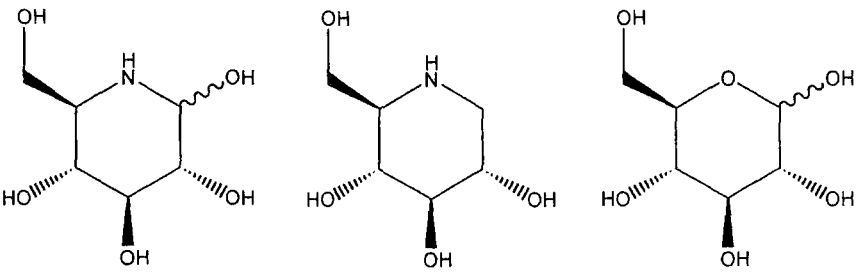


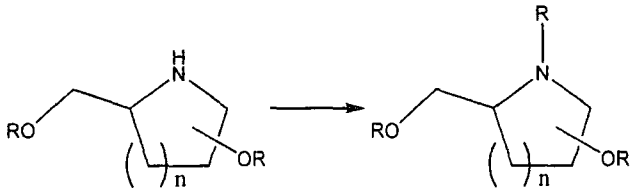
Figure 1. Comparison between NJ, DNJ and D-glucopyranose.

1-Deoxynojirimycin (DNJ) (**1.03**) is another glucose analogue found in nature (Figure 1).[6] It has also been found to inhibit specifically several glucose processing enzymes, although often with lower potency than NJ (**1.01**) itself.[7] As a general rule, aza-sugars mimicking the conformation of the sugar-processing enzyme substrate may show inhibitory activity toward that enzyme. This is not always the case, however, and inhibitory activity can be very sensitive to structure.[1] There are often many variants of

a particular sugar-processing enzyme present in a given organism, and indeed such variations occur between species. These isoenzymes can often show markedly different responses to a specific inhibitor, and this can allow the design of very enzyme specific inhibors as potential therapeutics.[1]

The introduction of hydrophobic functionality to an aza-sugar can not only potentially increase the inhibitory activity of an aza-sugar *in vitro*, but also increase the bioavailability of the inhibitor, and therefore its *in vivo* activity.[8] This is most likely to be due to the hydrophobic group improving the aza-sugar's ability to pass through cell walls.

In order to optimise the activity of enzyme inhibitors, and change their pharmacokinetic properties, it is important to have convenient access to large numbers of compounds with designed structural variations. The ideal situation is late-synthetic-stage introduction of functionality, allowing either the modification of existing inhibitors, or the facile synthesis of arrays or libraries of compounds from a single precursor in few chemical steps. In the case of aza-sugars late-stage introduction of functionality can be conveniently achieved through *N*-substitution (Scheme 1) by means of, for example reductive amination,[9] S_N2 reaction with suitable electrophiles,[10] condensation reactions[11] etc. This has allowed many *N*-substituted aza-sugars to be synthesised as potential inhibitors and mechanistic probes.

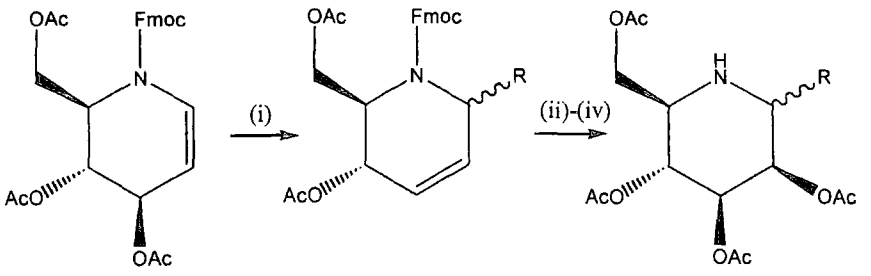


Scheme 1. *N*-fuctionalisation of aza-sugars.

Late-stage introduction of functionality at the α- nitrogen positions would be a valuable tool to the synthetic chemist in the synthesis of libraries of compounds for mechanistic studies and as potential therapeutics.

Dransfield *et al.*[12] reported the introduction of functionality to aza-sugars α- to nitrogen at an early synthetic stage by the use of S_N` additions to imino-glucal (**1.04**).

The addition reactions gave fair to good yields of C-1 functionalised unsaturated aza-sugars, with only moderate diasterocontrol (58 – 72 % de). Conversion into the peracetylated aza-sugar was also performed in the case of the ethyl adduct.

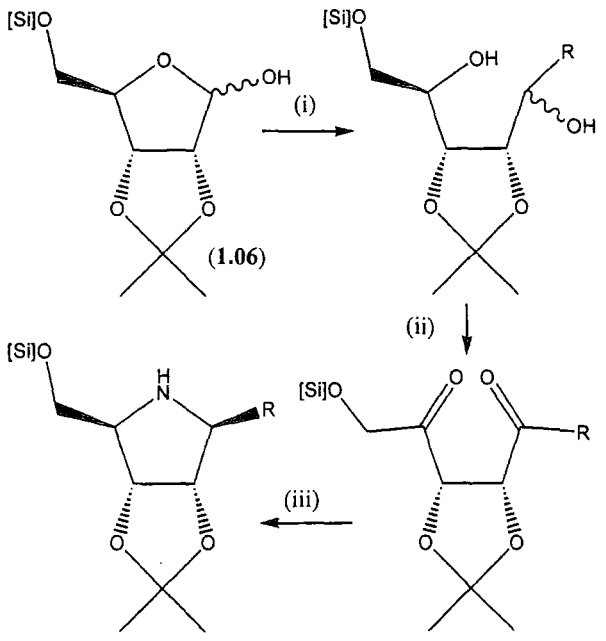


(1.04) R = Et (**1.05**)

(i)Et_2Zn, BF_3OEt_2, DCM, – 20 °C; (ii) OsO_4 (cat.), *N*-methylmorpholine *N*-oxide, acetone/H_2O; (iii) Ac_2O, Py; (iv) piperidine, DCM, R = Et, 62 % from (**1.04**) (1*R* : 1*S* 43 : 19).

Scheme 2. Early-synthetic stage introduction of functionality to aza-sugar scaffolds.[12]

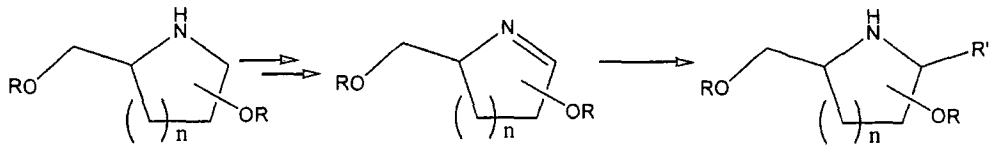
Yokoyama *et al.*[13] describe a convenient sysnthesis of C-1 substituted aza-nuleosides by the addition of organometallic reagents to the aldehyde function of a protected D-ribofuranose system (1.06 (Scheme 3). Subsequent oxidation to the dicarbonyl sugar, then a double reductive amination with ammonium formate gave the protected aza-sugars. Only one diastereoisomer was observed, but the stereocontrol of the reductive amination was not fully understood. The chemistry was performed with a range of aryllithium reagents.



(i) 2-Aryllithium, THF, 71-94 %; (ii) DMSO, TFAA, Et_3N, DCM, – 78 °C, 80-86 %; (iii) HCO_3NH_4, $NaBH_3CN$, MeOH, 75-98 %.

Scheme 3. Synthesis of α-substituted aza-sugars.[13]

Here we aim to address the necessity for convenient late-stage introduction of functionality at the α-nitrogen positions in the synthesis of aza-sugars, by the use of cyclic imines as substrates for addition reactions. We envisaged the conversion of existing aza-sugars into cyclic imine-sugars, and subsequent reaction with suitable nucleophiles (Scheme 4), and the synthesis of cyclic imines from chiral pool starting materials. This methodology also lends itself to the synthesis of C-1 branched aza-sugars, which may have applications as three component glycosyltransferase inhibitors.[2] Applications for this methodology will be investigated toward the synthesis of such three component transition-state mimics as potential rhamnosyltransferase inhibitors (see Section 1.6.2), and in the synthesis of piperidine aza-sugars of D-glucose and L-idose stereochemistry (see Section 1.6.3). Cyclic imine-sugars have previously been used as intermediates in the synthesis of aza-sugars, however they are relatively rare in the literature (see Section 1.5.3).



Scheme 4. Proposed introduction of functionality *via* irreversible additions to cyclic imine sugars.

In order to rationalise the structure-activity relationship of aza-sugar enzyme inhibitors, it is necessary to understand the mechanism of the target enzymes.

1.2 Sugar-Processing Enzymes

1.2.1 Background

Enzymes are biological catalysts, in that they have the ability to increase the rate of a given reaction, sometimes in a highly specific manner. Enzymes are proteins, made up of one or more chains of amino acids linked by covalent peptide bonds. Intra- and inter-chain bonding, both covalent and polar, hold the structure in the correct conformation.[14]

The site of catalysis, or active site, is shaped in order to accept the substrate(s), with which it interacts, exerting strong non-covalent attractive forces, such as hydrophobic/hydrophilic, hydrogen bonding, Van der Waals, ionic and dipolar interactions.[15] The specificity of many enzymes led to the lock-and-key theory of enzyme action, which compares the specificity of enzyme/substrate interaction to the interaction of a key with a lock.[16,17] This theory has been superseded by the concept of *transition-state stabilisation*,[17] whereby the enzyme is shaped so as to make maximum contact, and maximum stabilisation at the transition-state.

The micro-environment within the active site is optimised for the specific action of the enzyme, and contributions can be made by micro-pH change within the active site (general acid/base catalysis),[17] conformational changes, proximity of reactive groups on the protein surface, or proximity of other reactants held within the active site.[18] After the reaction is complete, the enzyme releases the product(s), and is ready to accept a new substrate(s).

If binding of the enzyme to the substrate or product is too favourable energetically, the action of the enzyme may be impaired, either due to slow product release, or product inhibition. This leads us to Pauling's suggestion that the enzyme must elicit tightest binding during the transition-state.[19] This theory has been supported by numerous examples of potent enzyme inhibitors synthesised as transition-state analogues, as well as crystal structures of enzyme/inhibitor complexes. Such transition-state analogues can be powerful mechanistic tools, as well as potential therapeutics.[2]

The catalytic process for a single substrate enzyme can be shown in terms of the two stages of the process, shown below in Equation 1.

1. Formation of the enzyme-substrate, or Michaelis complex ([ES]).
2. Reaction of [ES] to give free enzyme E, and product(s) P.

$$E + S \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} [ES] \xrightarrow{k_2} E + S \qquad K_M$$

Equation 1

The rate of the forward reaction can be seen to depend on [ES], which in turn is defined by the equilibrium constant for the binding of E to S, assuming that this equilibrium is not affected by the breakdown of [ES] to P, an assumption that is more accurate in the case of $k_{-1} >> k_2$.

1.2.2 Enzyme Inhibitors

Our target is the synthesis of compounds that effectively inhibit enzyme action. The mode of action of an enzyme inhibitor can be described by the use of the above model, and fall into four main classes;

1. Competitive
2. Non-competitive

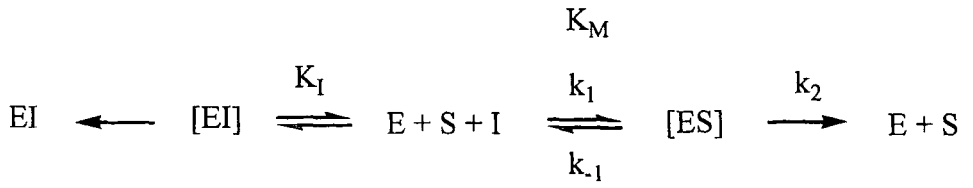
3. Mixed
4. Uncompetitive

In general there is an interaction between the enzyme and inhibitor to form a catalytically inactive enzyme-inhibitor complex ([EI]) (Equation 2).[17] Competitive inhibitors slow the catalysis of an enzyme by interacting with the active site, and as such both substrate and inhibitor cannot both bind simultaneously to the same enzyme. Such inhibitors *compete* with the substrate for the active site, and the efficiency of inhibition will be influenced by the concentration of substrate. Competitive inhibitors often share structural characteristics with the substrate as they usually both bind to the same site on the enzyme surface.

Non-competitive inhibitors can bind to the enzyme in conjunction with the substrate, and may bind specifically at a position removed from the active site, termed an *allosteric site*. The action of binding prevents catalytic turnover, possibly by causing a change in conformation of the enzyme. Such inhibitors do not need to compete for the active site, and can be very different structurally to the substrate. In some cases the action of the inhibitor (I) binding to the enzyme (E) can alter the equilibrium of binding of E to S (K_M, Equation 1), as well as reducing catalytic turnover (k_2, Equation 1), this is termed *mixed* inhibition.

Uncompetitive inhibitors bind to the enzyme only in association with the substrate, and inhibition is therefore dependent on both substrate and inhibitor concentration. Uncompetitive inhibitors are less common than the other types of inhibitor mentioned above.

In both the case of competitive and non-competitive inhibitors, there is some form of interaction between the inhibitor and enzyme; in many cases this is merely non-covalent bonding, and the enzyme can simply release the inhibitor, which is termed *reversible inhibition*. In certain cases, however, the enzyme may bind to the inhibitor, creating the inactive enzyme-inhibitor complex (EI), which may react further to form irreversibly a covalently bonded system EI (Equation 2), thereby rendering the enzyme permenantly inactive, this is termed *irreversible inhibition*, as both the inhibitor and the enzyme are rendered inactive.



Equation 2

Simplistically, competitive reversible inhibitors of enzymes can be designed in order to mimic the substrate, thereby increasing the possibility of tight binding to the inhibitor. This substrate-like inhibitor design is based around the lock-and-key theory of enzyme activity (see Section 1.2.1), in that the enzyme is specifically shaped to accept the substrate in its most stable conformation. Although this can be an effective method of inhibitor design, the lock-and-key theory over-simplifies the enzyme's activity.

Whilst in the active site, the micro-environment is very different for the substrate and non-bonding interactions can cause a change in preferred conformation. It is also postulated that enzymes elicit tightest binding during the transition-state (see Section 1.2.1). Much success has been achieved in the synthesis of transition-state mimics, compounds that mimic the shape and distribution of charge/bonding groups at the enzyme-transition state. Such inhibitor design not only has applications in the development of therapeutics, but can also be used to probe the mechanism of the enzyme.[2]

In order to describe the design of transition-state mimics, it is necessary to understand the mechanism of the enzyme in question. The two main classes of sugar-processing enzymes in which we are interested are glycosylhydrolases and glycosyltransferases. The general mechanism of action of glycosylhydrolase enzymes has been established by means of site-directed mutagenisis,[20] kinetic studies[21] and enzyme crystal structures.[21,22]

1.2.3 Glycosylhydrolases

Glycosylhydrolase, or glycosidase, enzymes are catalysts for the, often highly

specific, cleavage of glycosidic bonds.[21] There are two main classes of glycosylhydrolase enzymes, termed *retaining*, and *inverting*, referring to the stereochemical transformation at the anomeric carbon where the hydrolysis takes place.

Retaining glycosylhydrolases hydrolyse the glycosidic bond, with the product retaining the original stereochemistry, whereas inverting glycosylhydrolases cause an inversion of stereochemistry at the anomeric centre.

Retaining Glycosylhydrolases

The retention of configuration at the point of glycolysis has been postulated to be due to a double displacement at the anomeric centre, initially by an enzyme-bound nucleophile.[23] Crystal structures and sequencing of many glycosylhydrolases has shown that the active site of inverting glycosylhydrolases generally contain two carboxylate groups, and these are implicated in the catalytic activity of such enzymes. It is postulated that, upon binding of the substrate, the aglycon substituent is displaced by one of the enzyme carboxylates to form a covalently-enzyme-bound intermediate. Figure 2 shows schematic representations of the mechanisms of retaining and inverting glycosylhydrolase enzymes.[24] The presence of the second carboxylate was initially thought to be involved in the protonation of the anomeric substituent, increasing the lability of the glycosidic bond. However, there is some debate about the role of the second carboxylate, due to the ability of such enzymes to catalyse efficiently the hydrolysis of, for example, non-protonatable glycosylpyridinium ions.[25] It may be that the second carboxylate, in its deprotonated form, merely stabilises the developing positive charge during the hydrolysis. The active site of such enzymes have been likened to 'super-solvents',[21] allowing the finite existence of this otherwise very unstable intermediate species.

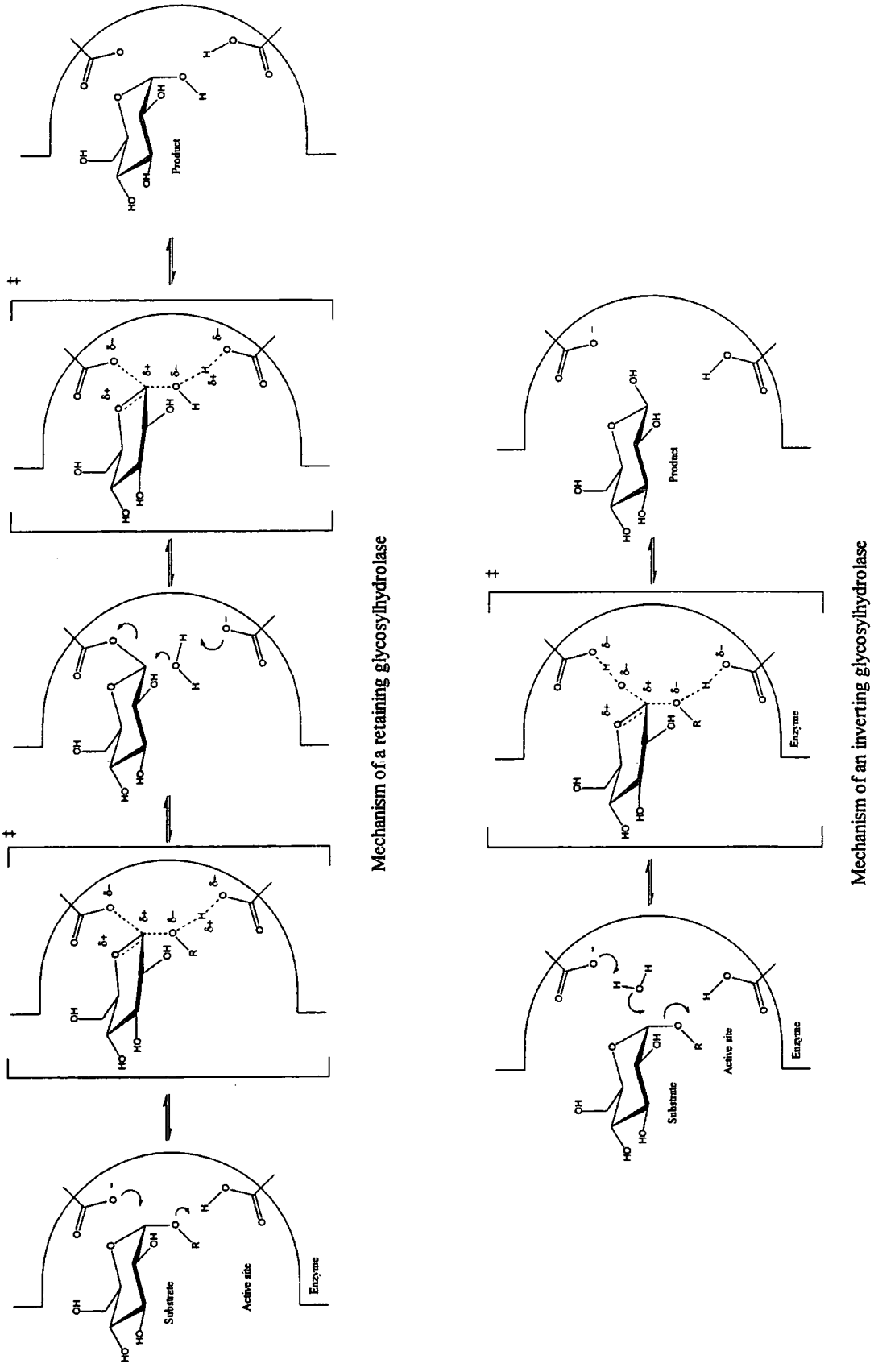


Figure 2. Schematic representation of the mechanism of inverting and retaining glycosylhydrolase enzymes.

The resulting enzyme-bound sugar is subsequently hydrolysed by water present in the active site. The overall transformation, *via* two S_N2 displacements, is replacement of the anomeric substituent with a hydroxyl group with retention of stereochemistry.
The transition-states of the reaction can therefore be simplified to a flattened system where positive charge develops both at the anomeric centre, and to some extent on the ring oxygen through conjugative stabilisation, and design of inhibitors based around structural mimics of such a transition-state has had much success (Figure 2).[2]

Inverting Glycosylhydrolases

Inverting glycosylhydrolases act in a similar manner to retaining glycosylhydrolases (see above), but lack the participation of the second carboxylate group in the active site, the cleavage of the anomeric linkage being performed by a water molecule.[21] As there is only one inversion the hydrolysis product has the opposite anomeric stereochemistry to the substrate. Again, a transition-state can be envisaged with flattening of the sugar ring, and developing positive charge at the anomeric centre and ring oxygen (Figure 2). Transition-state mimics for both inverting and retaining glycosylhydrolases may therefore be very similar.

1.2.4 Glycosyltransferases

Glycosyltransferases are catalysts for the formation of glycosidic bonds to molecules other than water. They have many and varied roles in nature, and are involved in the synthesis of all glycoconjugates, including glycosylation of proteins, lipids, and bacterial cell wall biosynthesis.[2] Inhibitors of such enzymes have applications as antibiotics, antiviral agents, anti-inflammatory agents, and may be important in enzyme folding, and activitiy, and biological encoding for processes such as metastasis, immune response and intercellular recognition.[2,26,27]
In general, glycosyltranferases are less well studied than their glycosylhydrolase counterparts, mainly due to the fact that the transferases are less stable, and usually

immobilised on the cell wall, making their handling and characterisation more difficult.[21]

Glycosyltransferase enzymes generally process either a glycosyl phosphonucleotide (Leloir type) or a glycosyl phosphate (non-Leloir type) as the glycosyl donor,[28,29] and form a new glycosidic bond selectively to another moiety. Leloir type glycosyltransferases, which we will be targeting, are responsible for glycosylation of proteins and formation of glycoconjugates in most mammalian systems. There are glycosyltransferases, which transfer to both *O*, and *N*-acceptors, and can be retaining or inverting, as discussed for glycosyl hydrolases above.

A proposed transition-state for a Leloir type glycosyltransferase (Figure 3), again involves the displacement of the anomeric substituent, with associated flattening of the sugar ring, and the development of a partial positive charge.[30]

Design of transition-state mimics as potential inhibitors of such enzymes can, once again again be based around incorporation of the develoment of positive charge on the ring oxygen, and flattening of the sugar ring. Due to the similarity in structure of the sugar ring during the transition-state of the glycosyltransferase to that of the glycosylhydrolase discussed above, inhibitors of such systems may have much in common with each other. Incorporation of structural features of both the donor and the acceptor, both of which are postulated to be present in the active site in the case of inverting glycosyltransferases, may increase potency or specificity of inhibition.[2]

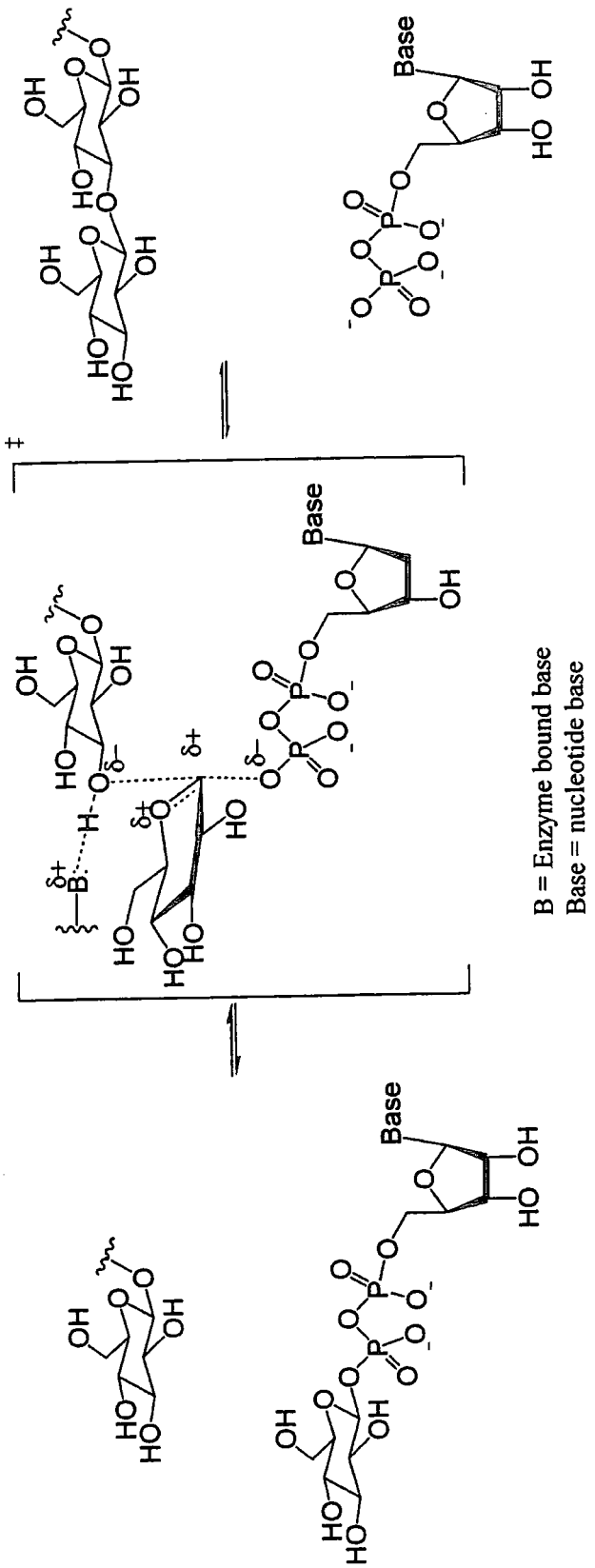
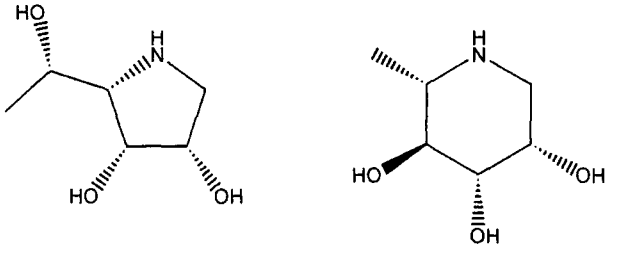


Figure 3. Proposed mechanism of a Leloir-type glycosyl transferase.[30]

1.3 Potential Sugar-Processing Enzyme Inhibitors

The discussion of the mechanism of glycoprocessing enzymes explains the inhibitory activity shown by many aza-sugars. The ring nitrogen, protonated at physiological pH,[31] is able to mimic the developing charge on the pyranose ring oxygen.

It has been observed that the 1,4-imino- (furanose) forms of aza-sugars can be more potent inhibitors of the corresponding pyrano-glycosylhydrolases[32,33,34] than their 1,5-imino (pyranose) forms. This inhibitory activity has been attributed to the similarity between the envelope conformation of the five-membered aza-sugar, and the proposed half-chair conformation of the pyranose sugar substrate in the glycosylhydrolase transition-state.[21] For example, rhamnopyrrolidine aza-sugar DRAM (**1.07**) (Figure 4), a furano-aza-sugar analogue of L-rhamnose, has been found to be a potent inhibitor of naringinase, an α-L-rhamnosidase,[35] whereas the pyranose aza-sugar analogue RNJ (**1.08**) has very low inhibitory activity.[36]



(**1.07**) (**1.08**)

Figure 4. DRAM (**1.07**), and RNJ (**1.08**), both potential rhamnosidase inhibitors.

The increase in positive charge postulated at the transition-state has prompted the synthesis of many C-1 aza-analogues of sugars.[1] Such systems have, in many cases, been found to be good inhibitors of the corresponding glycosylhydrolase enzyme, further reinforcing the accepted glycosylhydrolase mechanism.

Selectivity in enzyme inhibition may be increased by the introduction of functionality that mimics not only the central ring of the transition state, but also features of the donor/acceptor. Wong *et al.*[37] have synthesised an array of functionalised three-

component aza-sugars as potential transition-state mimics of a fucosyltransferase, incorporating features of the donor and acceptor (Figure 5).

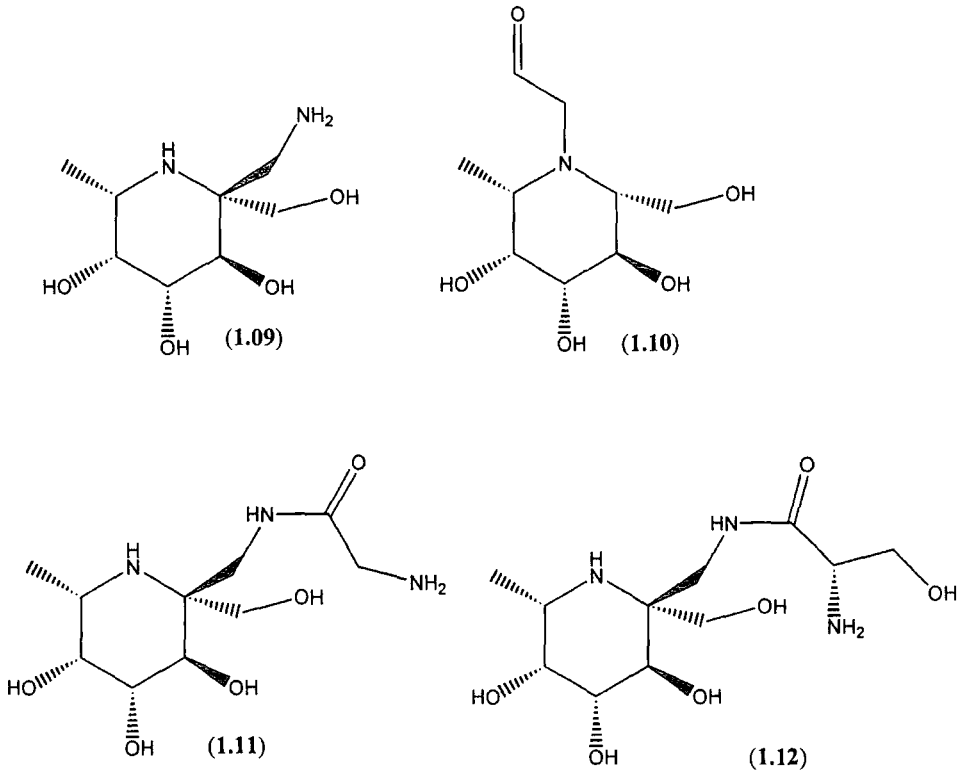
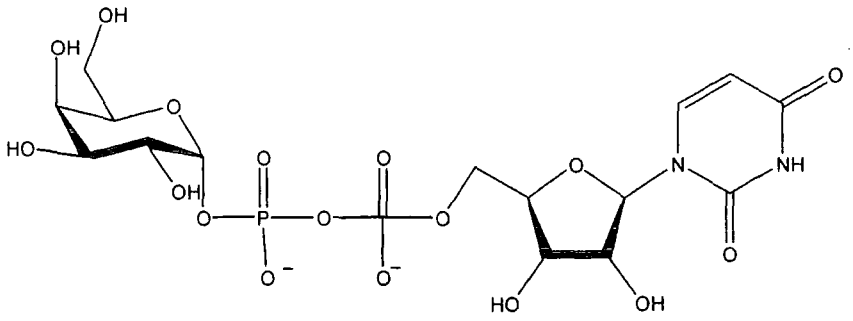


Figure 5. Three-component potential fucosyltransferase inhibitors.[37]

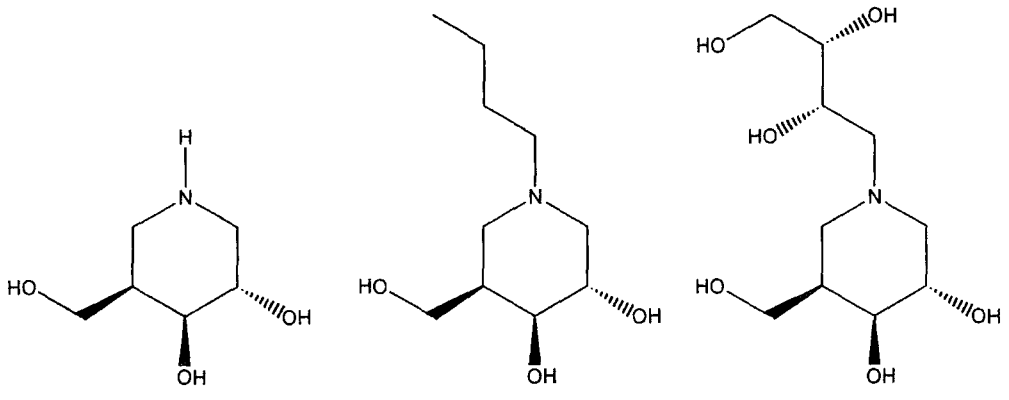
Kim *et al.*[38] describe the rational design, synthesis and biological testing of several compounds as potential inhibitors of human α-1,3-galactosyltransferase. The α-1,3-galactosyltransferase is a retaining glycosyltransferase utilising UDP-galactose as the glycosyl donor (Figure 6). The mechanism is expected to proceed *via* an enzyme-bound intermediate as discussed above for glycosylhydrolases.



UDP-Galactose

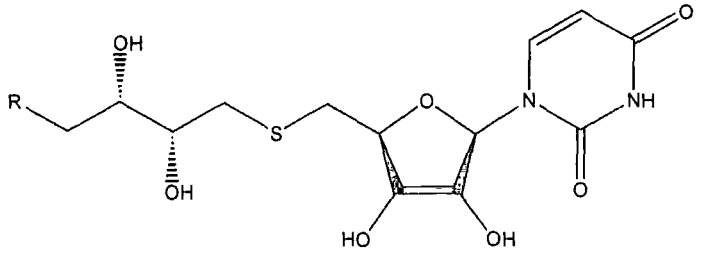
Figure 6. UDP-Galactose substrate for human α-1,3-galactosyltransferase.[38]

Potential inhibitors designed both around the aza-sugar analogues of the galactose segment (Figure 7) and the UDP segment (Figure 8) were synthesised. IC_{50} values in the micromolar region were obtained for these compounds.[38]



(1.13) **(1.14)** **(1.15)**

Figure 7. Aza-sugar analogues of the galactose segment of α-1,3-galactosyltransferase donor substrate.[38]



R = OH (**1.16**)
R = NH_2 (**1.17**)

Figure 8. UDP-segment mimics as potential glycosyltransferase inhibitors.[38]

The moderate inhibitory activity of these substrates indicates that the enzyme binds to both the sugar and the nucleotide segment of the donor.

1.4 Irreversible Nucleophilic Addition to Imines

1.4.1 Imines as Substrates for Irreversible Nucleophilic Addition Reactions

The structure of an imine has a great effect on its reactivity to nucleophiles.[49,50] Enolisable imines (see Figure 9), can be sensitive to basic nucleophiles, and may well form the aza-enolate in a competing reaction (B, Figure 9). Imines with a proton α- to the nitrogen may be susceptible to deprotonation, again competing with the addition reaction (C, Figure 9). The generally low electrophilicity of the imine carbon in such systems can mean these systems often favour deprotonation over addition.

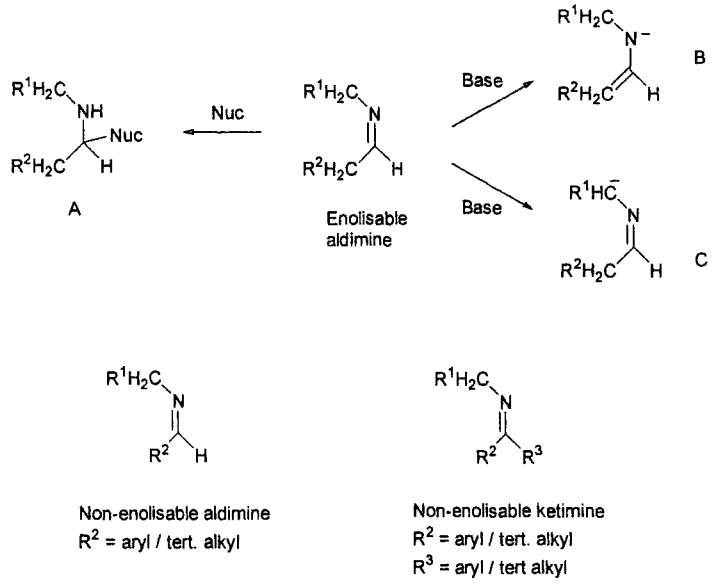


Figure 9. Types of imines and possible reactions with basic organometallics.

Many methods of increasing the electrophilicity of the imine carbon are possible. *N*-functionalisation can give more reactive species (Figure 10), such as highly reactive iminium ions, *N*-acyl iminium ions, nitrones, and *N*-sulfonyl imines, amongst others.[49,50] Although members of the general class of iminium ions are more reactive than their uncharged imine counterparts,[49] the *N*-substituent may be difficult to remove, and their formation and conversion back into the amine can add, possibly unnecessary, synthetic steps. Use of Lewis acids to increase the electrophilicity of the azomethine carbon can also be beneficial in nucleophilic addition reactions to imines.

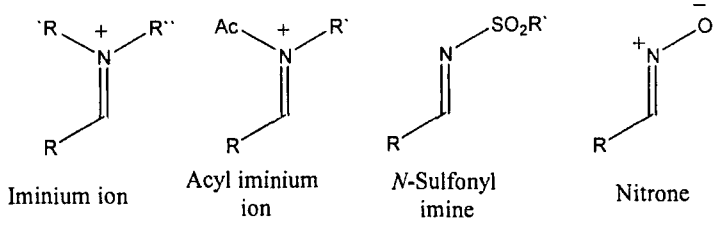


Figure 10. Examples of *N*-functionalised imines and iminiums.

The level of substitution of the azomethine carbon also has an effect on the reactivity of the imine bond towards nucleophiles. The less hindered aldimines (derived from an aldehyde) are, in general, more susceptible to nucleophilic attack than their ketimine equivalents (imines derived from a ketone), possibly due to a combination of lower steric hindrance and greater reactivity of the aldimine.[49,50]

The problems of acidity of enolisable imines can be overcome with the use of less basic nucleophiles. Metals such as zinc,[39,40] copper,[39,41,42,43] lead,[44] and cerium[45,46] are known to form less basic organometallics than their Grignard or alkyllithium counterparts. Recently Hou and co-workers[40] reported the addition of diethylzinc, in the presence of a trimethylsilyl Lewis acid, to both enolisable and non-enolisible aldimines. Hou observed an increased yield for non-enolisable aldimines, in particular those with an electron-withdrawing group present, consistent with both the generally poor electrophilicity of imines and side reactions associated with basic conditions.

Organocerium(III) reagents were first used due to their low basicity, for the addition of carbon nucleophiles to enolisable aldehydes and ketones,[47] but it was some years before they were used in addition to enolisable imines. Working independently, two groups began investigating the addition of organocerium reagents to enolisable aldimines[45,46] with good results. The author knows of no examples to date of the use of alkylcerium reagents with enolisible ketimines.

More recently, Oppolzer *et al.*[48] used organocerium(III) reagents derived from organolithiums and Grignard reagents in nucleophilic additions to simple five- and six-membered cyclic aldimines (Scheme 6, page 26). Slightly lower yields were obtained with organocerium reagents derived from Grignard reagents. This is in agreement with results observed within our group on the effect of magnesium based lewis acids on enolisable cyclic imines (see Chapter 2, Section 2.2).

1.4.2 Stereochemistry of Additions to Acyclic sp^2 Systems

Nucleophilic addition to acyclic imines in the synthesis of primary and secondary amines is well documented, and has been reviewed in the literature.[49,50] Additions to cyclic imine systems are less common.

Irreversible addition to such sp^2 systems is well understood, the nucleophile approaching at the Bürgi-Dunitz angle of around 105°.[51] Stereochemical induction in irreversible addition to aldehydes and ketones with an α-chiral centre has been the subject of much research, and can be predicted by use of Felkin-Anh[52] or Cram-chelate[53] models, often giving good correlation with experimental results.

In the case of the Felkin-Anh model, the likely stereochemical outcome of any given addition is determined by the steric size and orientation of the substituents adjacent to the carbonyl group. It is necessary to distinguish between each of the three substituents α- to the carbonyl in terms of their size, for example L, M, and S being the large, medium and small substituents respectively (Figure 11).[54] The analysis depends on the assumption that the most sterically demanding group (L) is perpendicular to the plane of the carbonyl. This leads us to two possible lowest energy conformations, A, and B (Figure 11). If we further assume that A and B are of similar energy, i.e. that there is no stereochemical preference for the position of S and M relative to the carbonyl group, we can see that the course of reaction is determined by steric interaction with the approaching nucleophile. In Figure 11 the more reactive conformation is A, where the nucleophile is in closest proximity to S.

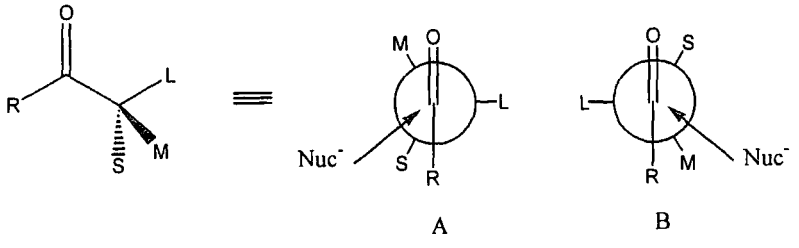
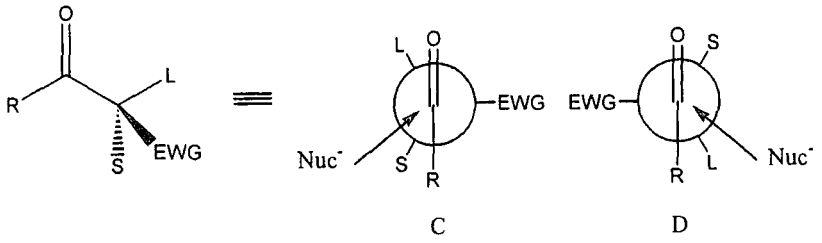


Figure 11. Felkin-Anh analysis of irreversible addition to a carbonyl compound.

There are notable exceptions to the Felkin-Anh model as it is described above. It has been observed that the presence of an electron-withdrawing group (EWG) α- to the carbonyl group can dictate the observed stereochemistry, giving the opposite stereochemistry from that expected by simple steric analysis when M is the EWG.[55] Strong EWGs (σ-acceptors) can interact with the carbonyl group, lowering the energy of the LUMO (π^*), and reducing the energy gap between the HOMO of the

nucleophile and the LUMO of the carbonyl, thereby favouring the addition. Such an interaction can only occur if the EWG lies perpendicular to the carbonyl group, and this leads us to two new favoured reactive conformations C, and D (Figure 12). Again interaction of the nucleophile, approaching from Bürgi-Duntiz angle, with the α-substituents, leads us to the most reactive conformation C.



C D

Figure 12. σ^*-π^*-Dominated Felhin-Anh analysis of irreversible addition to a carbonyl compound.

One further exception to the Felkin-Anh model as it is described above is in the case of systems containing a group α- to the carbonyl carbon capable of forming a cyclic chelate in the presence of a suitable Lewis acid. In this case the favoured reactive conformation of the carbonyl compound may be defined by the chelation, rather than simple steric considerations, as in the case of the Felkin-Anh model, or stereoelectronic considerations as in the case of the σ^*-π^*-dominated Felkin-Anh model. This chelation control can be accounted for by the Cram-chelate model,[53] and Figure 13 shows the formation of a five-membered chelate between a Lewis basic group (B:), a Lewis acid (LA), and the carbonyl oxygen. The stereochemistry of addition is predicted by consideration of the interactions between the approaching nucleophile and the non-chelating groups adjacent to the carbonyl group, indicating that in this case F is the favoured trajectory for the nucleophile.

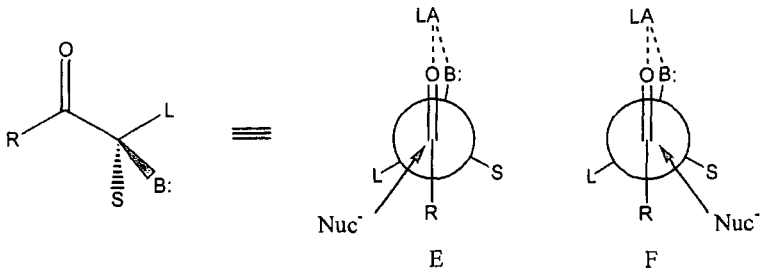


Figure 13. Chelation control in addition to carbonyl compounds.

The above considerations can easily be extended to imines with chiral centres α- to the azomethine carbon (derived from chiral aldehydes), and such analysis has given good agreement with experiment.[49,56] There is also the presence of a substituent on nitrogen, which may have an effect on the course of the addition. Yamamoto *et al.*[57] propose a further model to account for the presence of a chiral substituent at nitrogen (imines derived from chiral amines) (Figure 14). The model can be further extended to account for chelation contolled reactions (Figure 15).[49] Good diasterocontrol is often observed in chelation-controlled addition to acyclic imines due high Lewis basicity of nitrogen. There are relatively few examples of nonchelation-controlled additions to chiral imines.

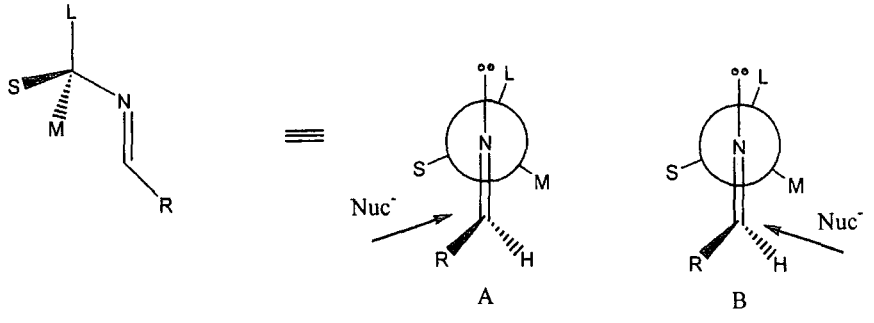


Figure 14. Stereocontrol of addition to non-chelation controlled addition to acyclic imines.[57]

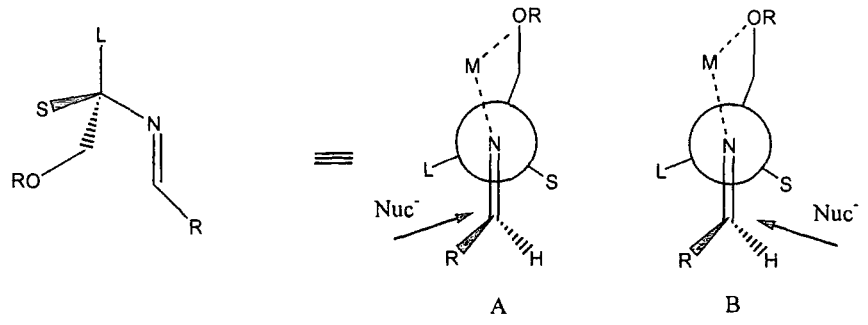


Figure 15. Stereocontrol of chelation controlled addition to acyclic imines.[49]

In the case of imines derived from chiral amines and chiral aldehydes, double induction reactions are possible and matched processes can lead to excellent diastereoselectivities.[49]

1.4.3 Stereochemistry of Additions to 6-Membered Cyclic sp^2 Systems

In irreversible additions to cyclic 6-membered sp^2 systems, steric approach considerations must be combined with the tortional and conformational energy barriers associated with possible cyclic transition-states.[58] In the case of six membered cyclic sp^2 systems, such as the example of 1,2,3,4-tetrahydropyridine (**1.18**) (Figure 16), the lowest energy conformation is that of the half-chair, as shown.

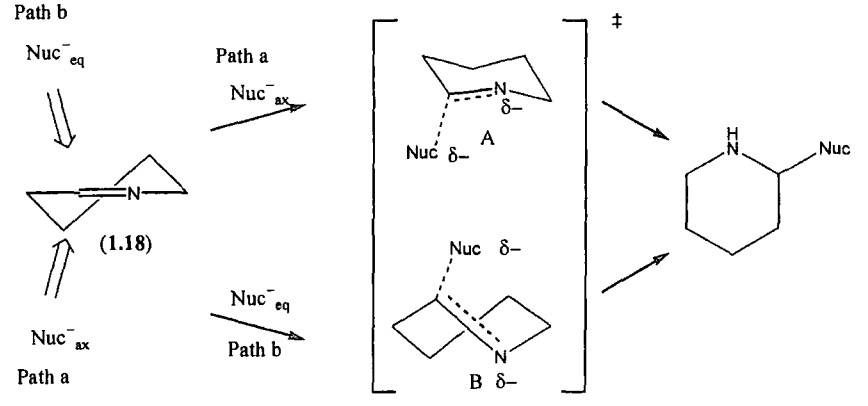


Figure 16. Proposed transtiton-states for addition reactions of 2,3,4,5-tetrahydropyridine (**1.18**).

Addition of a nucleophile to such an imine could occur from either above or below the

ring, giving two possible transition-states, which allow for the development of the tetrahedral sp^3 centre at the azomethine carbon, and maintain orbital overlap between the attacking nucleophile and the developing lone pair on nitrogen.

The chair-like transition-state (A, Figure 16) is energetically favoured over the boat-like transition-state (B, Figure 16); therefore, addition should proceed via **Path a** with pseudo-axial attack of the nucleophile. In the case of (**1.18**), **Path a**, and **Path b** lead to enantiomers of the same product, and determining transition-state of the reaction is not possible by analysis of the products. The introduction of functionality to the ring will allow us to observe the diastereocontrol of addition to such a system, and indeed prediction of diastereocontrol of additions to these systems by such stereoelectronic analysis is often in good agreement with experimental results.[58]

In the case of the cyclic iminium (**1.19**) for example, Bohlman *et al.*[59] observed reduction with borohydride to occur *via* a **Path a** reaction (Figure 17). Axial attack of hydride *via* chair-like transition-state A gave (**1.20**) as the only diastereoisomer (Figure 17).

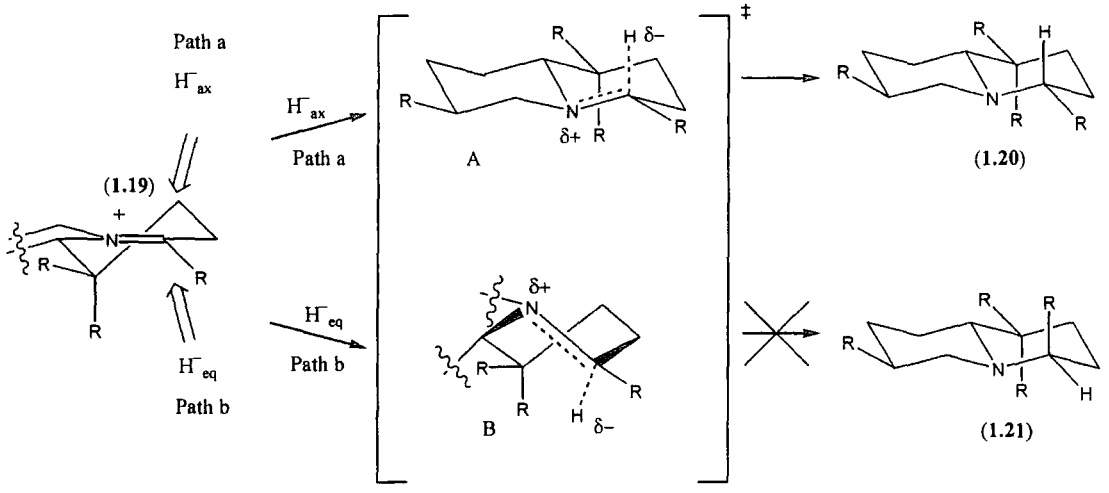
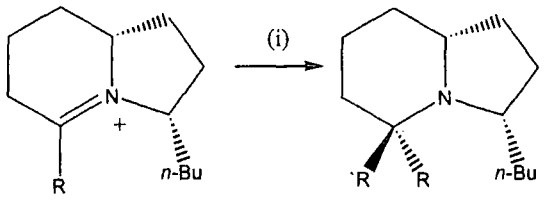


Figure 17. Reduction of cyclic iminium (**1.19**) with axial attack of hydride.[59]

Steric approach constraints may also influence the course of any addition reaction to such a system. In the case of the cyclic piperidine iminiums (**1.22**), and (**1.23**) (Scheme 5), Stevens and Lee observed nucleophilic addition of hydride to (**1.22**) (R` = H, Scheme 5, $NaBH_3CN$)[60] or a Grignard reagent to (**1.23**) (R` = Me, Scheme 5,

MeMgBr)[61] occurs to give a single diastereoisomer.



R = H (**1.23**)
R = Me (**1.22**)

R = H, R` = Me (**1.25**)
R = Me, R` = H (**1.26**)

(i) R` = H, $NaBH_3CN$; R` = Me, MeMgBr.

Scheme 5. Nucleophilic additions to cyclic piperidine iminium systems (**1.22**) and (**1.23**).[60,61]

Addition to such a system can occur to either of two half-chair conformers (conformer 1 and conformer 2, Figure 18), leading to proposed transition-states A, B, C, and D (Figure 18). Preffered addition is expected to occur *via* chair-like transition-states A, or C. In the case of C, however, unfavourable steric interactions of the incoming nucleophile with the hydrogen atom at C-8 are thought to disfavour this approach, and Stevens and Lee were thus able to rationalise the observed diastereocontrol, and synthesise stereoselectively (+/–)-monomorine (**1.26**), and the epimer (**1.25**).

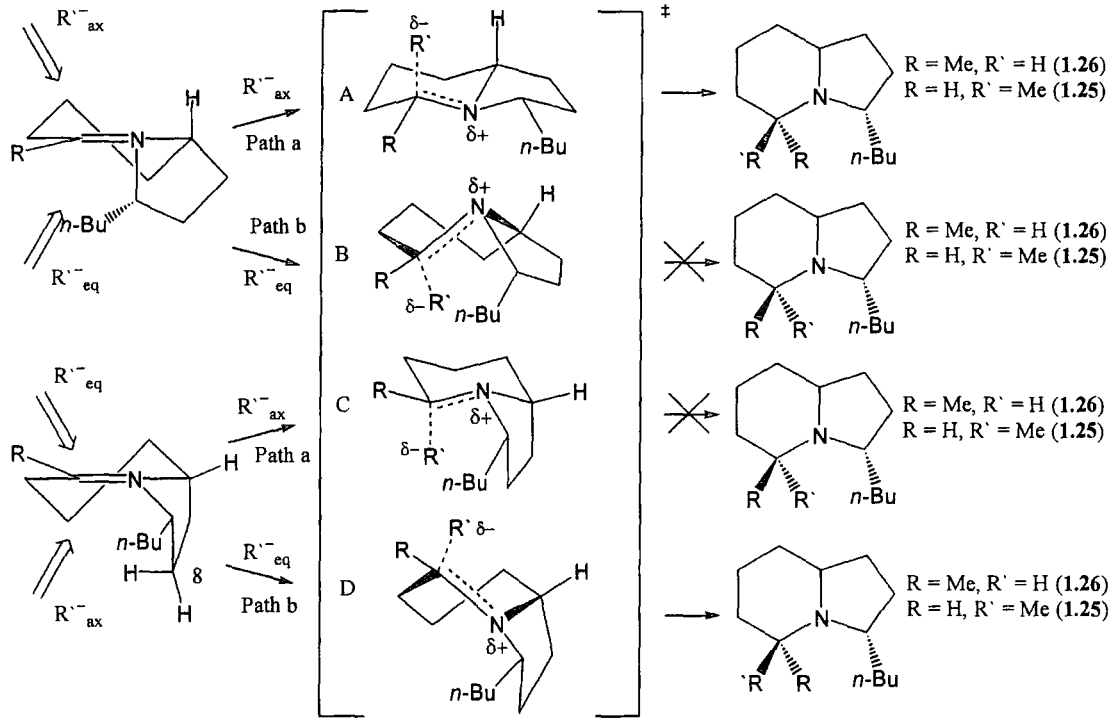
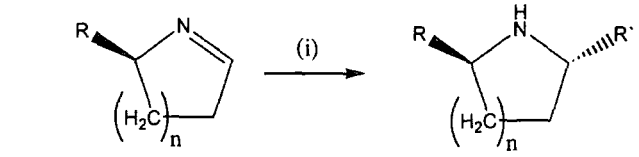


Figure 18. Possible nucleophilic additions of to cyclic piperidine iminium systems (**1.23**), and (**1.34**).[60,61]

In the case of five-membered imine systems, stereochemistry of addition reactions is often defined by simple steric approach considerations. There are relatively few examples of additions to cyclic five membered imines. Oppolzer *et al.*[48] reported addition of organocerium(III) reagents to cyclic pyrrolidine imines (**1.27**) and (**1.28**) (Scheme 6). Excellent diastereoselectivity (up to 98 % de) was attributed to steric approach control defined by large alkyl substituents α- to the imine nitrogen. The cyclic imines were generated *in-situ* from acylsultam precursors, and overall yields were moderate to fair (48 – 60 %).



n = 1, R` = C_7H_{15} (**1.27**)
n = 2, R` = $C_{11}H_{23}$ (**1.28**)

n = 1; R = C_7H_{15}, R` = *n*-butyl (**1.29**)
n = 1, R = C_7H_{15}, R` = 3-butenyl (**1.30**)
n = 2; R = $C_{11}H_{23}$, R` = Me (**1.31**)

(i) R`$CeCl_2$.

Scheme 6. Addition of organocerium(III) reagents to cyclic pyrrolidine imines.[48]

Horenstein *et al.*[62] describe the addition of Grignard reagents to a bicyclic five-membered imine-sugar (Scheme 12, page 33). The fused cup-like structure defines the stereochemistry of addition, the nucleophile approaching from the least-hindered face.

Bosco *et al.* [63] describe the addition of an organic phosphonate anion to a five-membered cyclic imine-sugar (**1.32**). Only one diastereoisomer was observed consistent with steric approach contol defined by the substituent α- to the azomethine carbon (Figure 19) (see Section 1.5.3).

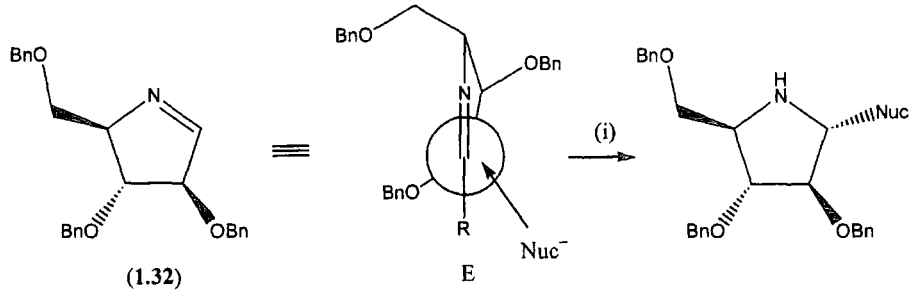
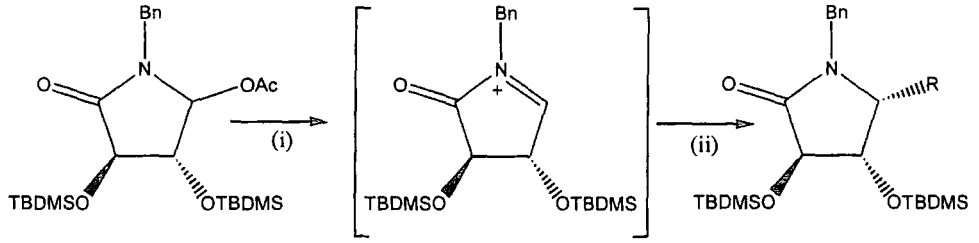


Figure 19. Steric approach control of addition to five-membered cyclic imine-sugar (**1.32**).[63]

Interestingly, Ryu and Kim[64] achieved organotin additions to the cyclic iminium (**1.33**) (Scheme 7), generated *in-situ* from the α-acetoxylactam (**1.34**), with steric control attributed to anchimeric delivery of the organometallic by the adjacent *tert*-butyldimethylsilyl ether, rather than steric approach control. Excellent yields and diastereoselectivities were observed for allyl-, propargyl- and allenyltin reagents (up to 100 % de, 97 % yield).



(1.34) (1.33)

$R=CH_2CHCH_2$
$R=CH_2CCH$
$R=CHCCH_2$

(i) $MgBr_2$; (ii) $R`_3SnR$.

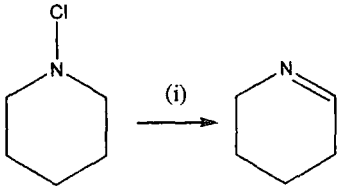
Scheme 7. Stereocontrol in addition to cyclic iminium (**1.33**) *via* anchimeric delivery of nucleophile.[64]

1.5 Synthesis of Cyclic Imines

1.5.1 *N*-Chlorination/Elimination Strategy

Our syntheses of cyclic imine-sugars are to be performed both from existing aza-sugars, and by synthesis from chiral pool starting materials. The conversion of existing aza-sugars into cyclic imine sugars can be achieved by the introduction of a suitable leaving group at nitrogen. Similar transformations are well known for *N*-chloro compounds, which can give the corresponding imines when treated with a suitable base.

Early examples of cyclic piperidine and pyrrolidine imines such as 2,3,4,5-tetrahydropyridine (**1.18**) (Scheme 8) have been synthesised from the corresponding *N*-chloro derivatives.[65]



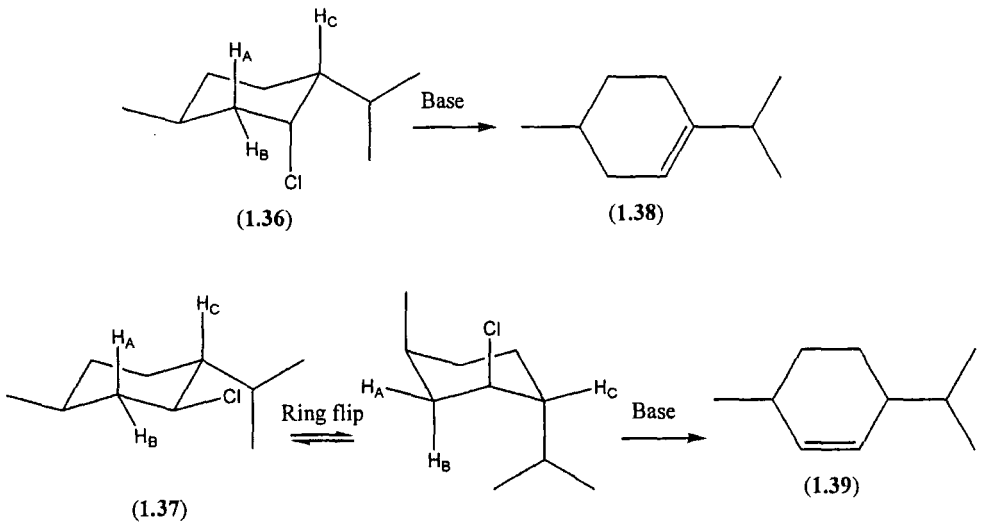
(1.35) (1.18)

(i) KOH, EtOH.

Scheme 8. Synthesis of a simple cyclic imine from *N*-chloropiperidine.[65]

Elimination reactions of *N*-chloro compounds with alkoxide bases are generally accepted to proceed *via* an E2 mechanism, and products are obtained according to Saytzev's rule.[66,67] Orbital alignment of the C-H and N-Cl bond being broken is required for the elimination to occur. To the best of the author's knowledge there has been no account of the regiochemistry of elimination of heterocyclic *N*-chloro compounds to give the corresponding cyclic imine. However, similar elimination reactions of cyclic haloalkanes have been studied. [68]

Alkyl halides with a β-hydrogen are, in general, expected to react with base to give the olefin with a concerted E2 mechanism.[68] This E2 mechanism dictates that there is some double bond character at the transition-state, which can be stabilised by the presence of alkyl substituents at the β-position. This stabilisation generally leads to Saytzev-rule products, i.e. the most substituted, or most stabile product is formed. Studies involving cyclic haloalkanes, in particular six-membered rings, have indicated that the elimination occurs with an anti-periplanar C-H, C-Cl conformation.[68]



Scheme 9. Elimination reactions of menthyl chloride (**1.36**) and neomenthyl chloride (**1.37**).[69,70]

Investigations into the elimination reactions of menthyl chloride (**1.36**), and neomenthyl chloride (**1.37**) have shown the preference for anti-periplanar elimination of HCl to give the olefin (Scheme 9).[69,70] In the case of menthyl chloride (**1.36**) the

Saytzev-rule product 3-menthene (**1.38**) is preffered (78 %) with loss of H_C and chloride *via* an E2 elimination. In the case of the neomenthyl chloride (**1.37**) 2-menthene (**1.39**) is the sole product obtained. Again the mechanism was determined as E2. The formation of a conformation that allows anti-periplanar elimination of H_B, and chloride is possible *via* a ring-flip to the alternative chair form with both alkyl groups axial. Due to the *cis*-configuration of H_C and Cl, in neomenthyl chloride, the elimination of H_C, and chloride is not possible *via* an anti-periplanar conformation. These two systems can be directly compared to a *N*-chloropiperidine system where inversion at nitrogen can allow chlorine to adopt either configuration.

The configurational lability of *N*-chloro compounds[71,72] dictates that elimination in similar six-membered ring systems should give the Saytzev-rule product in situations where there is a choice of two axial β-hydrogens (A, Figure 20). We can further speculate that in situations where there is only one axial β-hydrogen available, elimination by loss of this axial proton will occur (B, Figure 20). This situation may occur if the conformation of the ring is locked so as to disfavour ring-flip to the alternative chair form. This is as might be expected in A and B (Figure 20) due to the all-equatorial configuration of ring substituents.

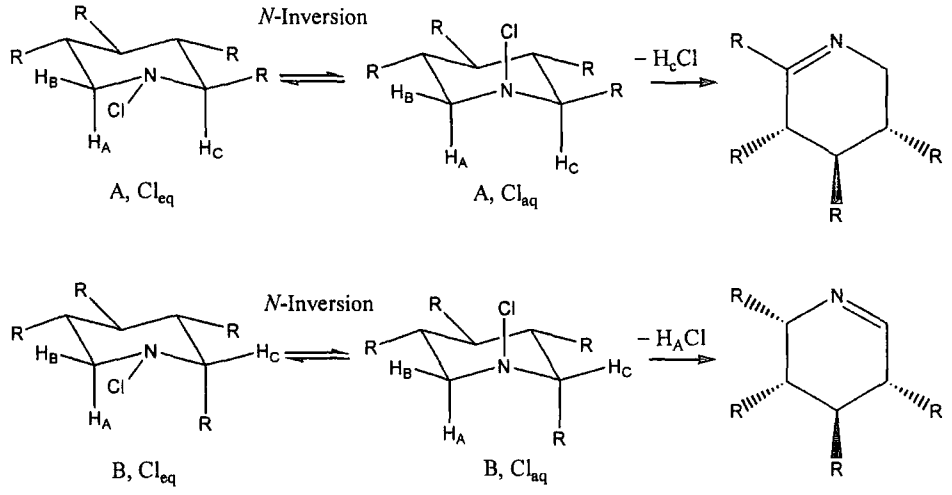


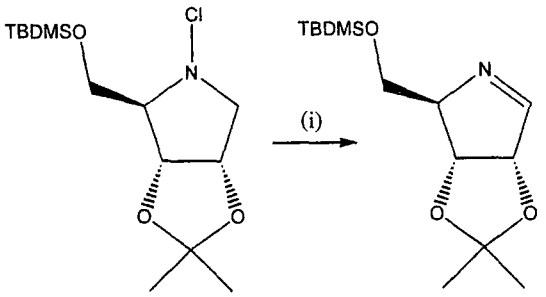
Figure 20. Proposed elimination reactions of six membered *N*-chloro piperidines of locked conformation.

By analogy to cyclic haloalkanes, the Saytzev-rule product should predominate in *N*-

chlorpiperidine systems where such a ring flip is energetically more favourable.

Swain and Thornton[73] postulated that the use of stronger bases in such E2 eliminations makes the transition-state less product-like, moving the mechanism toward E1cB. Partial development of negative charge on carbon at the transition-state favours the formation of the less stable Hoffman-rule, or least substituted product in such situations.

A functionalised sugar-imine system (**1.40**) has been synthesised by Horenstein *et al.*[62] from the *N*-chloro aza-sugar precursor. Elimination of HCl was performed with lithium 2,2,6,6-tetramethylpiperidide (LiTMP) at – 78 °C (Scheme 10). Only the aldimine was observed. The formation of the less stable aldimine (**1.41**), or Hoffman-rule product, is as would be expected in the case of an elimination of HCl with more E1cB character.



(**1.40**) (**1.41**)

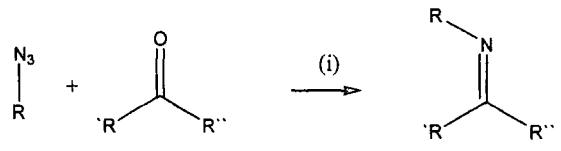
(i) Lithium tetramethyl piperidide, THF, -78°C, 30 min.

Scheme 10. Synthesis of cyclic pyrrolidine imine (**1.41**).[62]

Pyrimidal inversion in chloramines is slowed due to the presence of unshared electons on chlorine.[72] At low temperatures this inversion may be slowed or effectively halted, introducing a new factor, which may govern the regiochemistry of elimination. Our aim is to investigate elimination reactions of aza-sugars in order to develop methodology allowing the regioselective elimination of *N*-chlorinated aza-sugars.

1.5.2 The Staudinger Aza-Wittig Reaction.

Imines are conveniently synthesised by the Staudinger aza-Wittig reaction between an azide and carbonyl with a suitable phosphine (Scheme 11).[74] The intramolecular Staudinger reaction has rarely been performed in the synthesis of cyclic imine-sugars, and two examples are given in section 1.5.3 (see Scheme 14 and Scheme 16).



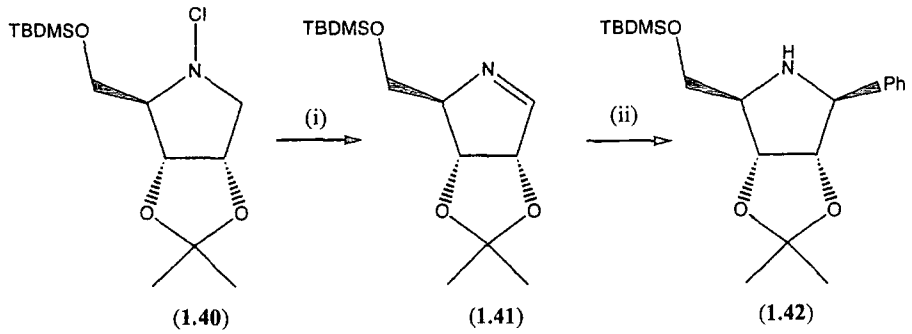
(i) PPh_3.

Scheme 11. Imine formation via the Staudinger aza-Wittig reaction.

The synthesis of the azido-sugars required as cyclic imine-sugar precursors will be approached *via* the introduction of azide by an S_N2 displacement of a suitable leaving group, such as a sulfonate ester. Such azido-sugars are well known in the literature.

1.5.3 Examples of Cyclic Imine-Sugars as Intermediates in the Synthesis of Aza-Sugars

Horenstein and co-workers[62] used an elaborate cyclic pyrrolidine imine-sugar (**1.41**) as a substrate for addition reactions. Excellent diastereocontrol was achieved in the addition of phenyl Grignard, attributed to steric approach control, in this case defined by the 'cup-like' shape of the bicyclic imine (Scheme 12). The imine was formed from the chloramine of the parent pyrrolidine, by treatment with the strong base lithium tetramethylpiperidide (LiTMP) (see Scheme 10, p 31). Further organometallic additions to this system have been reported in 20 - 66 % yield with the same observed diastereocontrol.[75,76,77] The resultant aza-sugars were designed as transition-state probes for protozoan nucleoside hydrolase and transferase enzymes.

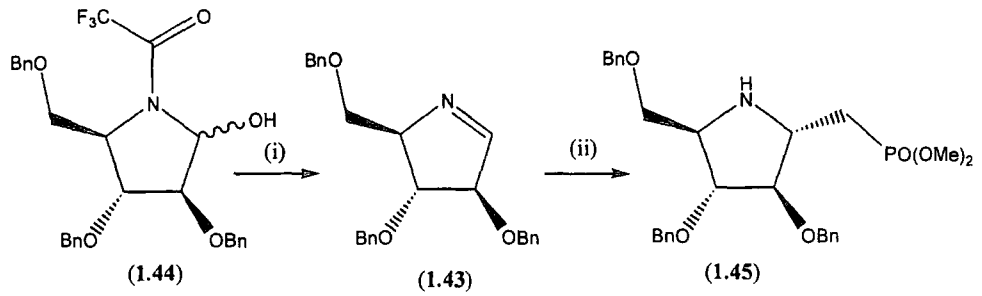


(1.40) (1.41) (1.42)

(i) Lithium tetramethyl piperidide, THF, -78°C, 30 min; (ii) 2 eq. PhMgBr, Et_2O, -78°C, 30 min.

Scheme 12. Nucleophilic addition to cyclic pyrrolidine imine (**1.40**).[62]

Bosco *et al.*[63] describe the synthesis of another pyrrolidine cyclic-sugar imine (**1.43**) as a substrate for the addition of an organic phosphonate anion (Scheme 13). The imine was synthesised by the hydrolysis of the trifluoroacetamide (**1.44**), then subsequent elimination of water from the cyclic hemi-aminal. Addition of lithiated dimethylmethylphosphate gave the adduct (**1.45**) in 32 % yield with only one diastereoisomer observed, consistent with steric approach control defined by the adjacent benzyloxy group.



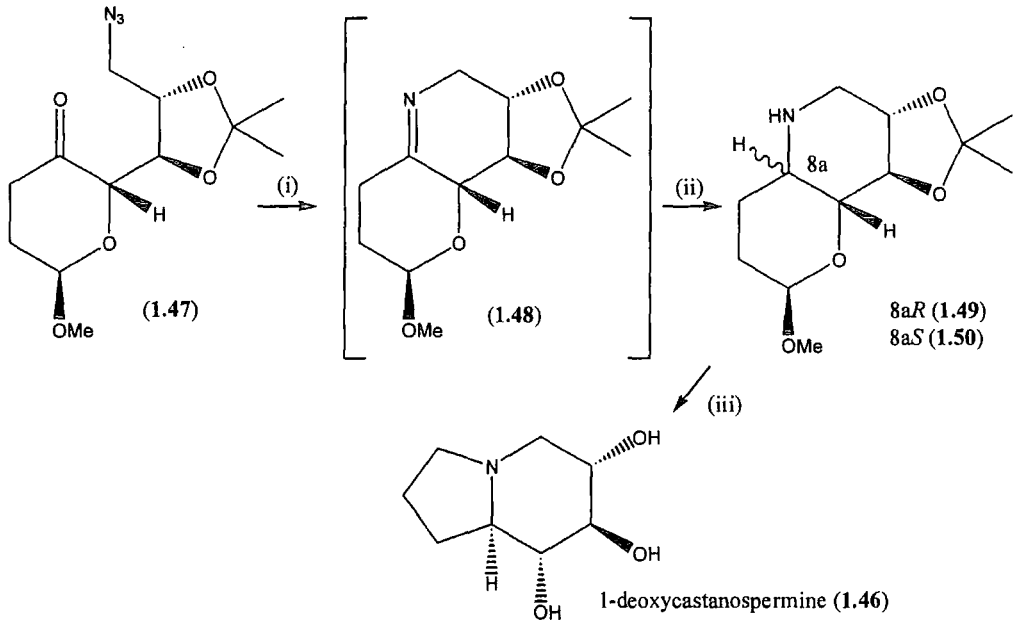
(1.44) (1.43) (1.45)

(i) LiOH, THF/MeOH/H_2O, 86 %; (ii) $LiCH_2PO(OMe)_2$, BF_3OEt_2, THF, – 78 °C, 32 %.

Scheme 13. Synthesis and addition to a cyclic pyrrolidine imine (**1.43**).[63]

Martin *et al.*[78] describe the total synthesis of 1-deoxycastanospermine (**1.46**) *via* the Staudinger reaction of a polyhydroxylated azido-sugar (**1.47**) (Scheme 14). The imine (**1.48**) was formed with triphenylphosphine in toluene at 70 °C and reduced to the amine with lithium aluminium hydride and a Lewis acid, without isolation. The desired 8a*R* diasteroisomer (**1.49**) was obtained in a 4.4 : 1 ratio with the the 8a*S*

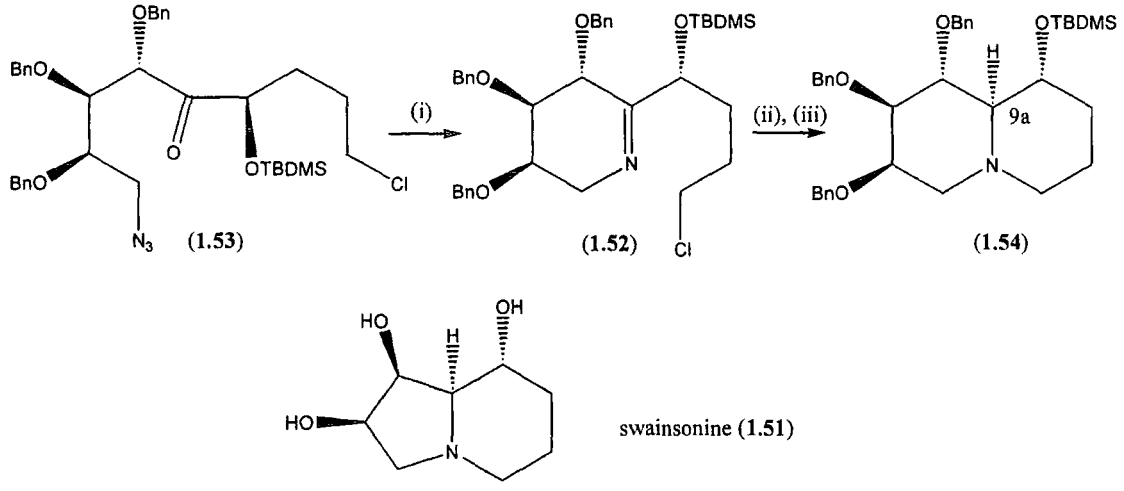
isomer (**1.50**). No discussion of the stereocontrol was given, other than the fact that 8a*S* isomer was obtained as the sole product when hydrogenation of the imine was performed.



(i) PPh_3, benzene, 70 °C; (ii) LAH, $TiCl_4$, Et_3N, DCM, 69 % over two steps; (iii) HCl, THF/H_2O, then H_2, Pd/C, MeOH, 81%.

Scheme 14. Synthesis of 1-deoxycastanospermine (**1.46**) *via* a Staudinger aza-Wittig reaction.[78]

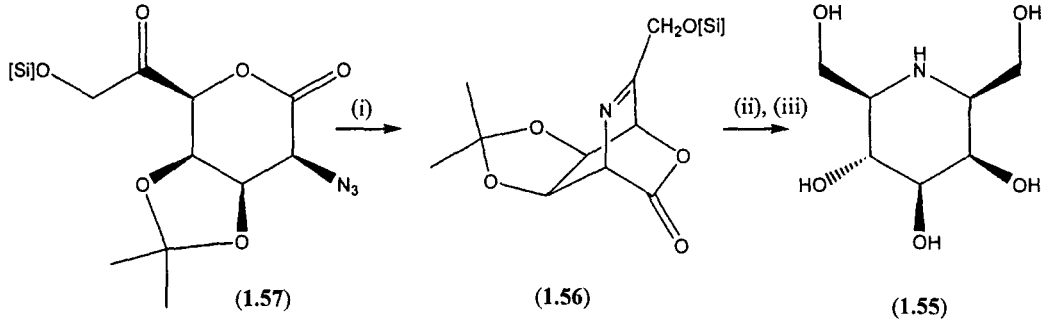
Pearson and Hembre[79] describe a synthesis of a similar fused aza-sugar as an analogue of the mannosidase II inhibitor swainsonine (**1.51**) (Scheme 15). The intermediate imine (**1.52**) was synthesised by hydrogenolysis of the azido-ketone (**1.53**). Subsequent reduction of the imine (**1.52**) with sodium borohydride in methanol, followed by cyclisation of the alkyl chloride, gave the desired 9a*R* isomer (**1.53**). The imine was not purified, and no account of the diastereocontrol of reduction was given.



(i) H_2, $Pd(OH)_2/C$; (ii) $NaBH_4$, MeOH; (iii) K_2CO_3, EtOH, 70 °C.

Scheme 15. Synthesis of a swainsonine analogue *via* an intermediate cyclic imine.[79]

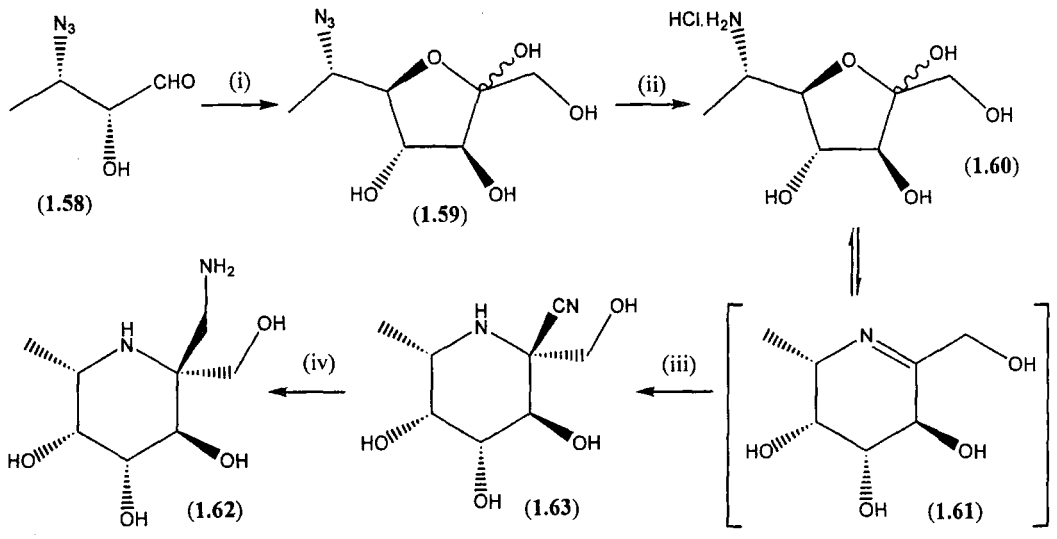
Bruce *et al.*[80] describe the synthesis of α-homomannojirimycin (**1.55**) *via* stereoselective reduction of an intermediate cyclic imine (**1.56**) synthesised by an aza-Wittig cyclisation of the azido-sugar precursor (**1.57**) (Scheme 16). Reduction of the imine function of (**1.56**) with lithium borohydride gave good diasterocontrol (23 : 1, isolated, 48 % overall yield). The lactone was also reduced under these conditions. Stereochemistry of reduction was attributed to reduction of the imine predominantly in the bicyclic form, prior to the lactone, from the least hindered face.



(i) $(EtO)_3P$, THF, 89 %; (ii) $LiBH_4$, THF, – 78 °C, 48 % (dr 23 : 1); (iii) CF_3COOH, H_2O, 92 %.

Scheme 16. Synthesis of α-homomannojirimycin (**1.55**) *via* intermediate cyclic imine-sugar (**1.56**).[80]

Wong *et al.*[81] describe the enzymatic synthesis of azido-sugars as cyclic imine-sugar precursors. The enzymatic condensation of azido-aldehyde (**1.58**) with dihydroxyacetone phosphate gave azido-sugar (**1.59**) (Scheme 17). Reduction of the azide functionality gave the sugar-amine (**1.60**), which was in equilibrium with the imine (**1.61**). The synthesis of the branched aza-sugar (**1.62**) is also described *via* addition of cyanide to intermediate cyclic imine (**1.61**), followed by reduction of the resultant cyano-sugar (**1.63**). No discussion of the observed stereocontrol of addition of cyanide was given. The observed stereocontrol is consistent with axial attack of cyanide on the half-chair conformer of (**1.61**). However, such Strecker-type reactions are reversible, and the product stereochemistry may be thermodynamically controlled.[82] The resultant branched aza-sugar (**1.62**) was later used in the synthesis of transition-state mimics by simple *N*-functionalisation (see Figure 5, page 15).[37]



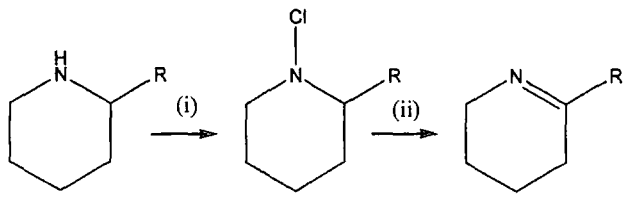
(i) DHAP, rabbit muscle aldolase, pH 6.7, 25 °C, then acid phosphatase, pH 5.0, 37 °C, 78 %; (ii) H_2, Pd/C, HCl, H_2O, 100 %; (iii) KCN, dioxane/H_2O, 77 %; ((iv) H_2, PtO_2, HCl, EtOH, 99 %.

Scheme 17. Synthesis of branched aza-sugar (**1.62**) *via* intermediate cyclic imine-sugar (**1.61**).[81]

1.6 Proposed Cyclic Imine Systems

1.6.1 Model Simple Cyclic Imines

Investigation into the synthesis and irreversible addition reactions of cyclic imines will start with the use of simple piperidine imines as model systems. *N*-Chlorination and elimination of HCl is expected to give the desired imines (see Section 1.5.1). The synthesis and evaluation of such simple piperidine systems are discussed in Chapter 2.



(i) "Cl^+"; (ii) Base.

Scheme 19. Proposed synthesis of simple piperidine imines.

1.6.2 Cyclic Imine-Sugars of L-Rhamnofuranose Stereochemistry

L-Rhamnose is a non-mammalian sugar residue that has been identified in the peptidoglycan region of the cell wall of certain mycobacteria, including *Mycobacterium tuberculosis* (Figure 21). [83] An L-rhamnopyranose unit is thought to be incorporated into the developing cell wall by a postulated rhamnosyltransferase enzyme. Selective inhibitors of such a non-mammalian biosynthetic pathway would present a novel therapeutic strategy for the treatment of diseases such as tuberculosis, and as such are a valuable synthetic target.

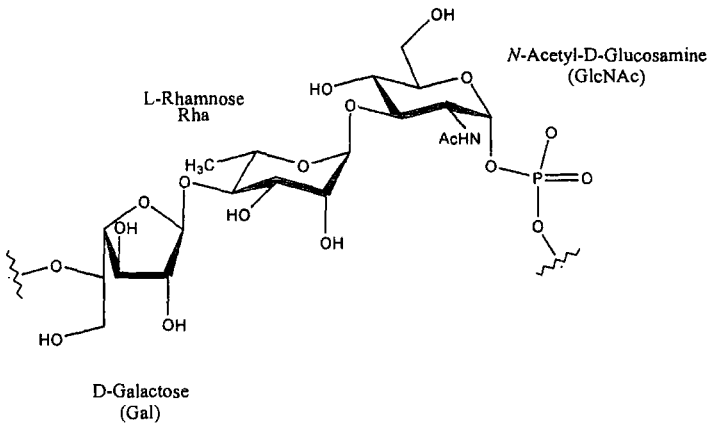


Figure 21. Postulated L-rhamnose unit present in the cell wall of *Mycobacterium tuberculosis*.[83]

The furanose form of an aza-sugar can, in many cases, show higher inhibitory activity towards the corresponding pyrano-glycosylhydrolase (see Section 1.3) than the pyranose form of the aza-sugar.[21]

The synthesis of a protected L-rhamnofuranose cyclic imine-sugar presents us with the possiblitiy of introduction of functionality at the C-1, pseudoanomeric position that mimics the shape of a proposed transition-state for the postulated L-rhamnosyl transferase enzyme (Figure 22).

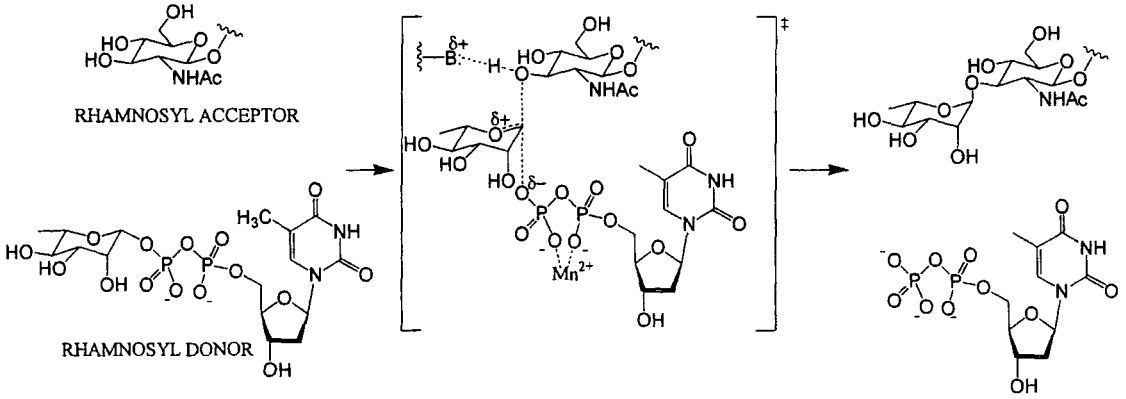


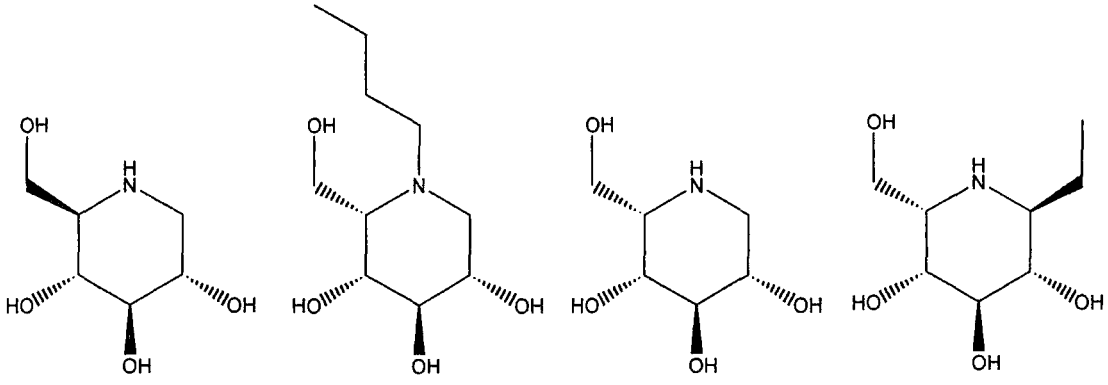
Figure 22. Proposed mechanism for the postulated rhamnosyltransferase enzyme (*Mycobacterim tuberculosis*).

Chapter 3 discusses the synthesis and nucleophilic addition reactions of such rhamnofuranose cyclic imine-sugars *via* a Staudinger aza-Wittig reaction.

1.6.3 Cyclic Imine-Sugars of DNJ (D-Glucopyranose) and DINJ (L-Idopyranose) Stereochemistry

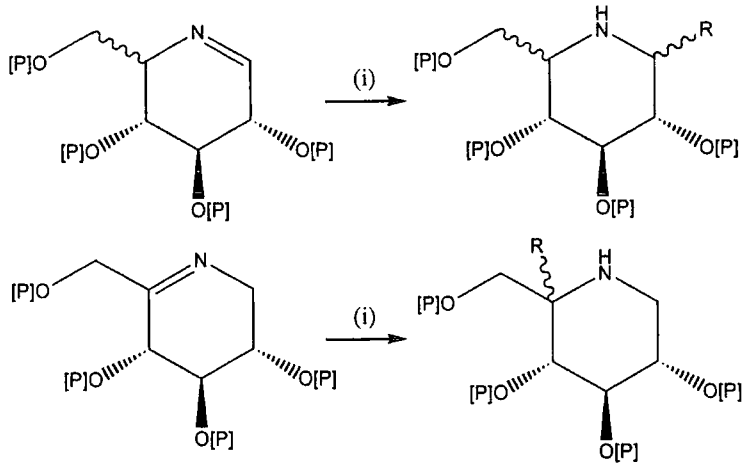
DNJ (**1.03**) (Figure 23) is a potent inhibitor of several glucose processing enzymes (see Section 1.1). *N*-Butyl DNJ (**1.64**) (Zavesca) (Figure 23) is a potent inhibitor of glucosylceramide synthase, and is approved for the treatement of Gaucher's disease, a glycolipid-storage disorder.[84] The introduction of hydrophobic functionality can increase the activity and improve the bioavailability of such systems.[8] The late stage introduction of functionality at the 1- and 5- positions of DNJ, as may be achieved by addition to 1-*N*, or 5-*N* dehydro derivatives, would therefore be of high potential utility in the generation of libraries of potentially biologically active compounds (Scheme 20).

1-Deoxyidonojirimycin (DINJ) (**1.65**), an L-idose analogue, is an isomer (C-5 epimer) of DNJ. It forms the central ring structure in the recently isolated natural product adenophorine (**1.66**) (Figure 23),[85] and as such is an interesting target skeleton. The use of systems with DINJ stereochemistry also allows a direct comparison of the effect of the C-5 stereochemistry on the regiochemistry of elimination of their *N*-chloro derivatives.



(**1.03**) (**1.64**) (**1.65**) (**1.66**)

Figure 23. DNJ (**1.03**), *N*-butyl-DNJ (**1.64**), DINJ (**1.65**) and the natural product adenophorine (**1.66**).



(i) RM.

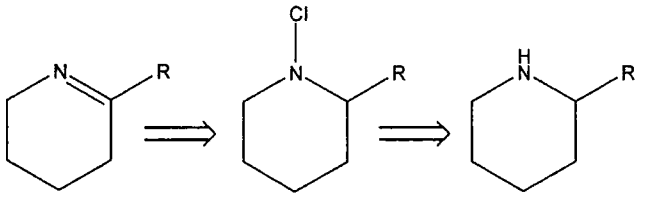
Scheme 20. Proposed late-stage introduction of functionality to DNJ and INJ aza-sugar systems.

Chapter 4 discusses the synthesis of cyclic imine sugars of DNJ (D-glucopyranose), and DINJ (L-idopyranose) stereochemistry by both Staudinger aza-Wittig methodology, and *N*-chlorination/elimination reactions.

Chapter 2. Synthesis and Evaluation of Simple Cyclic Imines as Substrates for Addition Reactions

In this chapter we discuss the synthesis, isolation, and nucleophilic addition reactions of simple cyclic piperidine imines. These systems are intended to model the cyclic imine sugars we will discuss in Chapters 3 and 4. Simple pyrrolidine imines were not studied due to time constraints and their reported low stability.[86]

2,3,4,5-Tetrahydropyridine (Δ^1piperideine) (**2.01**),[87] and 6-methyl-2,3,4,5-tetrahydropyridine (2-methyl-Δ^1piperideine) (**2.02**)[88] are proposed as model cyclic imine systems. The syntheses have been based upon the *N*-chlorination of simple piperidines, followed by elimination of HCl to give the desired imine. Scheme 20 shows a simple retrosynthetic analysis revealing piperidine (**2.03**) and 2-methylpiperidine (**2.04**) as readily available starting materials.

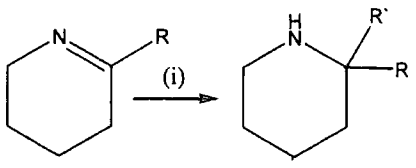


(**2.01**) R = H
(**2.02**) R= Me

(**2.03**) R = H
(**2.04**) R= Me

Scheme 20. Retrosynthetic analysis of simple piperidine imines (**2.01**), and (**2.02**).

Following the successful synthesis and isolation of imines (**2.01**), and (**2.02**), we will investigate their irreversible addition reactions with organometallic reagents.



(**2.01**) R = H
(**2.02**) R= Me

(i) R`M.

Scheme 21. Proposed addition reactions of imines (**2.01**), and (**2.02**).

The work in this chapter is divided into two main sections:

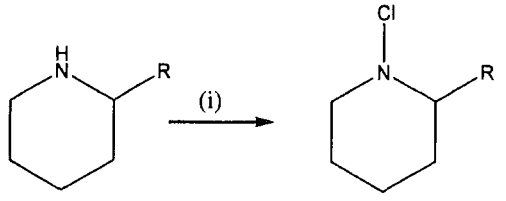
2.1 Synthesis of Simple Cyclic Imines

2.2 Nucleophilic Addition to Simple Cyclic Imines

2.1 Synthesis of Simple Cyclic Imines

2.1.1 *N*-Chlorination of Piperidines

Aqueous sodium hypochlorite has been used for *N*-chlorination of such piperidines. However, our requirement for anhydrous conditions prompted us to use a different chlorinating agent. *N*-chlorosuccinimide (NCS) was chosen as the chlorinating agent in forming the chloramines, as it is a convenient, solid source of electophilic chlorine. Formation of the desired chloramines (**2.05**), and (**2.06**) from the relevant piperidines proceeded smoothly in diethyl ether, following the procedure of Grundon and Reynolds for the chlorination of 2-butyl piperidine.[88] The use of diethyl ether as a solvent, however, proved quite inefficient with regards to reaction volume, due to the low solubility of NCS in diethyl ether. DCM was used as an alternative solvent, which overcame this problem.



(**2.03**) R = H
(**2.04**) R= Me

(**2.05**) R = H
(**2.06**) R= Me

(i) NCS, Et_2O, 70 % for (**2.05**), or NCS, DCM, 75 % for (**2.06**).

Scheme 22. Synthesis of imine precursors *N*-chloropiperidine (**2.05**) and *N*-chloro-2-methylpiperidine (**2.06**).

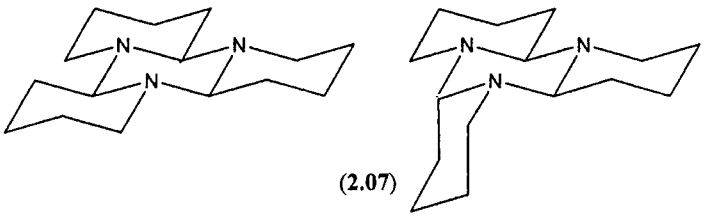
N-Chloro derivatives (**2.05**) and (**2.06**) were isolated as colourless oils by vacuum distillation in up to 70 % and 75 % yields, respectively (Scheme 22). *N*-Chloropiperidine (**2.05**) was found to be fairly stable, and can be stored for periods of weeks under nitrogen at – 18 °C without decomposition. The corresponding *N*-chloro-

2-methylpiperidine (**2.06**) is unstable and decomposes at – 18 °C under nitrogen in the dark over a period of days.

2.1.2 Elimination Reactions of *N*-Chloropiperidines

Synthesis of simple imine 2,3,4,5-tetrahydropyridine (**2.01**) was attempted by the treatment of *N*-chloropiperidine (**2.05**) with ethanolic potassium hydroxide followed by aqueous acid extraction then basification and re-extraction into diethyl ether, similar to a reported synthesis of the same compound.[65] Conversion of the starting material was observed by TLC, but formation of a further product was also observed. This was isolated as an off-white crystalline material in low yield. NMR analysis of the product suggested it may be a mixture of isomers of the trimerised imine, tripiperideine (**2.07**) (Figure 24).[87]

Attempts made to isolate imine (**2.01**) were largely unsuccessful. Continuous extraction of a basic aqueous solution of imine with both diethyl ether and THF, even over periods of days, resulted in negligible yields after drying and concentrating the solutions. The imine was observable by ^{1}H-NMR ($CDCl_3$, s, br, 7.8 ppm). However, the imine proton was observed to reduce in intensity over a period of hours, apparently forming the trimer (**2.07**).



(**2.07**)

Figure 24. Two possible isomers of tripiperideine (**2.07**).

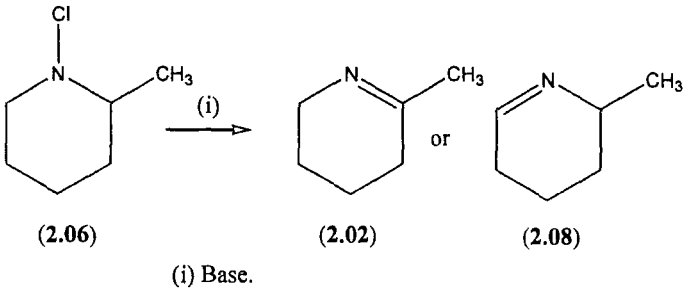
Whether the low yields were due to the inefficiency of the described continuous extraction methodology, or the formation of tripiperideine, is unclear. The investigation was, therefore, moved to the synthesis of the 2-methyl-Δ^1piperideine (**2.02**) system, which should show less tendency to trimerise due to the unfavourable steric interactions of the azomethine substituent in the trimer.[56]

The elimination of HCl from *N*-chloro-2-methylpiperidine (**2.06**) was attempted, as for (**2.05**) above. Again continuous extraction over a period of days gave

disappointing results, much of the imine formed remained in the aqueous layer (TLC), and problems were encountered removing the solvent by distillation - no distinct fraction was obtained as the imine azeotroped with diethyl ether.

Due to the need for the imine to be dry and free from protic solvents, and the difficulties encountered in isolation, the organic bases lithium diisopropylamide (LDA) and 1,8,diazabicyclo[5.4.0]undec-7-ene (DBU) were chosen as alternatives, and the reactions performed in dry THF.

It was anticipated that the elimination of HCl from chloramine (**2.06**) should form the most-substituted ketimine (**2.02**), rather than the aldimine (**2.08**) (Scheme 23). *N*-Chloro compounds are expected to give the most stable, most substituted imine when treated with base (see Chapter 1, Section 1.5.1).



(2.06) **(2.02)** **(2.08)**

(i) Base.

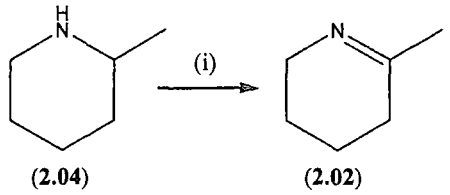
Scheme 23. Possible formation of cyclic imines from *N*-chloro-2-methylpiperidine **(2.06)**.

Treatment of *N*-chloro-2-methylpiperidine with LDA (1.1 eq.) at room temperature in THF gave a distinct change by TLC, but streaking of the products made ascertaining the extent of reaction difficult. A sample of the reaction mixture was concentrated. Crude NMR studies showed the presence of 2-methylpiperidine (**2.04**), and chloramine starting material (**2.06**), in the reaction mixture. The presence of the piperidine starting material suggests a possible metal-halogen exchange occurring instead of the desired elimination; no evidence of the desired imine was observed.

Treatment of chloramine (**2.06**) with DBU (1.1 eq) at room temperature in THF showed rapid consumption of starting material. A precipitate was observed to form, which could be isolated by filtration and was found to be the DBU hydrochloride salt. The product was found to azeotrope with THF, and the resultant THF solution was

analysed by GCMS, giving a single peak corresponding to the desired product (EI+, m/z 97, $[M]^+$).

In an attempt to isolate imine (**2.02**) the elimination reaction was performed in DCM with DBU (1.3 eq.). The product was purified by distillation, and could be isolated in 77 % yield from 2-methylpiperidine (**2.04**) with no problems associated with azeotropes, which had been encountered with THF. Analysis of the product revealed exclusive formation of the expected 6-methyl-2,3,4,5-tetrahydropyridine (**2.02**) (Scheme 24).



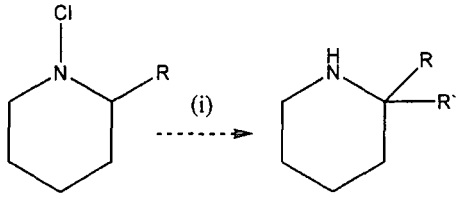
(2.04) **(2.02)**

(i) NCS, DCM, then DBU, DCM, 77 % over two steps.

Scheme 24. Formation of ketimine (**2.02**).

2.2 Nucleophilic Addition to Simple Cyclic Imines.

Initially, two types of nucleophilic addition reactions were used, Type A, and Type B. In a Type A reaction, the simple cyclic imine was synthesised from the chloramine, using DBU as a base to eliminate HCl, and was not isolated from THF solution. The HCl salt of DBU precipitated and was removed by filtration. Organometallic reagents were added to the resultant imine solution, assuming 100 % conversion of the chloramine to the imine (Scheme 25).

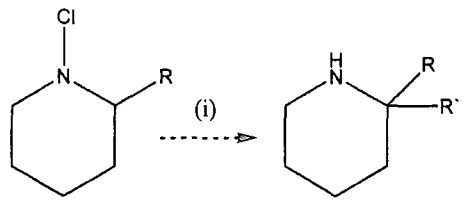


R = H (**2.05**)
R = Me (**2.06**)

(i) DBU, THF, filter, then R`M, THF.

Scheme 25. Proposed Type A addition to simple imines.

In an attempt to reduce trimerisation, in the case of cyclic aldimine (**2.01**), and the effects of residual base, a second method of forming the imine was employed. Excess of the organometallic reagent was added directly to the chloramine in an attempt to form the imine *in-situ*. This *in-situ* formation of the imine was termed a Type B addition (Scheme 26).

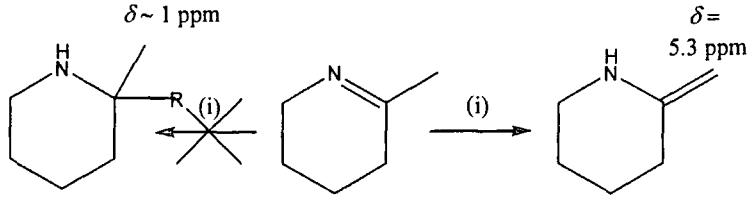


R = H (**2.05**)
R = Me (**2.06**)

(i) R`M.

Scheme 26. Proposed Type B addition to simple cylic imines.

Screening of 2-methyl-Δ^1piperideine with Type A reactions of alkyllithium and Grignard reagents (MeLi, *n*-BuLi, $TMSCH_2Li$, MeMgBr, EtMgBr and BnMgCl) was performed. Crude ^{1}H-NMR studies generally indicated the reaction had not followed the desired course and the expected methyl singlet at $\delta \sim 1.0$ ppm due to addition products was not seen in the crude reaction mixture, in fact the methyl peak generally stayed as a singlet and moved up from $\delta = 1.8$ ppm to 1.9 ppm. Both this, and the appearance of another multiplet peak at $\delta = 5.6$ ppm indicated the presence of an unsaturated compound, consistent with enamine formation through base catalysed tautomerisation (Scheme 27).



(**2.02**)

(i) RM.

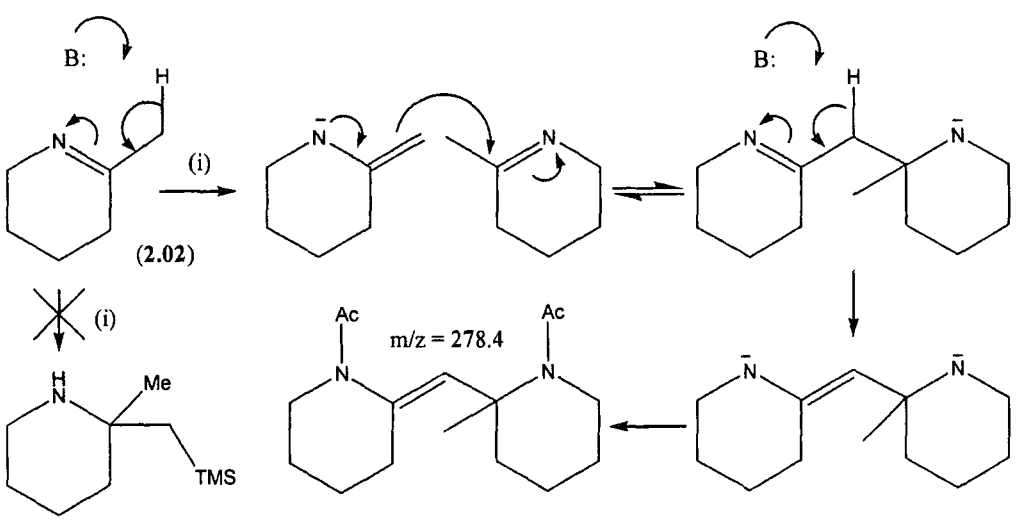
Scheme 27. Proposed base-catalysed tautomerisation of ketimine (**2.02**).

Purification of the products from Type A reactions of simple imines (**2.01**), and (**2.02**) was attempted initially by column chromatography. However this was not successful due to lack of separation and the large numbers of products formed. The presence of free amines would hamper attempts to separate by chromatography, and therefore in some cases an excess acetylating mixture of acetic anhydride and pyridine was added to completed reactions to form the corresponding amides. Column chromatography of these gave no isolable products. The final method of purification attempted was vacuum distillation. However this is difficult to achieve efficiently on the relatively small scales used, and with the large number of compounds formed.

Simple nucleophilic addition was not observed for ketimine (**2.02**) with any Grignard or alkyllithium employed under Type A conditions. GCMS and ^{1}H-NMR analysis indicated that aldol-type dimerisation and trimerisation reactions were occurring.

The proposed mechanism for the dimerisation of ketimine (**2.02**) with such basic nucleophiles is shown in Scheme 28 below, for the reaction with $TMSCH_2Li$, followed by per-acetylation of the reaction mixture to aid purification.

The presence of the condensation product of this reaction was established by a combination of GCMS and ^{1}H-NMR data. This product, although not isolated from the reaction mixture, is very similar to condensation products observed later for additions using dialkylmagnesium reagents (Scheme 29, page 48).



(i) $TMSCH_2Li$.

Scheme 28. Proposed dimerisation of ketimine (**2.02**) with $TMSCH_2Li$.

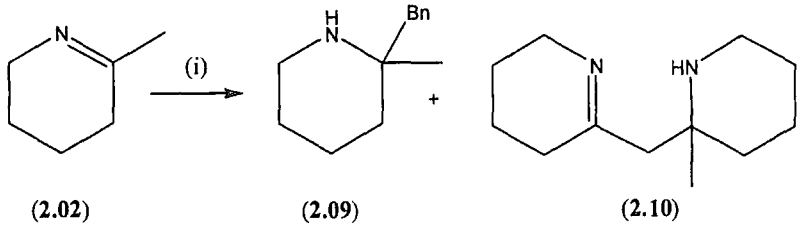
Treatment of ketimine (**2.02**) with Grignard reagents invariably led to intractable mixtures of many products. This was attributed to the high basicity of the Grignard reagent RMgX. The organomagnesium halide is in equilibrium with, amongst other components, the magnesium halide and a diorganomagnesium species, which are known to be less basic than the Grignards.[89] This equilibrium is known as the Schlenk equilibrium, and a simplified version is shown in Equation 3 below. Addition of dioxane to diethyl ether or THF solutions of Grignard reagents causes the magnesium halide/dioxane complex to precipitate, forcing the equilibrium infavour of diorganomagnesium R_2Mg.[89]

$$2RMgX \rightleftharpoons R_2Mg + MgX_2 \xrightarrow{\text{1,4-dioxane}} MgX_2.\text{dioxane}\downarrow$$

Equation 3. The Schlenk equilibrium is displaced by the presence of dioxane.

Methyl, ethyl, phenyl, and benzyl Grignard, in the presence of 1,4-dioxane (1.1 eq.) were used. Solutions of (**2.02**), isolated by distillation, were added slowly to the freshly prepared dialkylmagnesium solutions in diethyl ether solution at room temperature. In all cases the imine (**2.02**) dimerised (Scheme 29 below).

Where 1.1 eq. of Grignard reagent were used, between 50 and 60 % formation of dimer was consistently observed throughout the range of Grignards. Where an excess of Grignard reagent (1.5 eq.) was used with 1,4-dioxane (1.1 eq.), varying quantities of condensation products were observed, depending on the Grignard reagent.



(2.02) **(2.09)** **(2.10)**

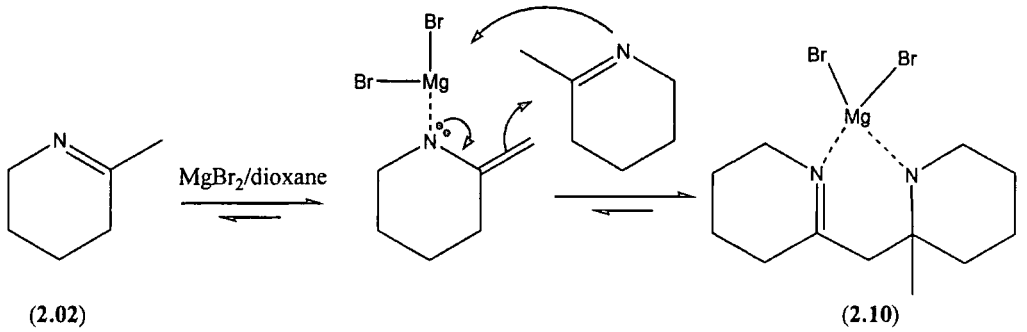
(i) BnMgCl, 1,4-dioxane, Et_2O, 39 % of (**2.09**) (7 % isolated), 52 % of (**2.10**).

Scheme 29. Addition to ketimine (**2.02**).

Only in the case of benzyl Grignard was any addition addition product seen, both with 1.1 eq. and 1.5 eq. of the reagent (Scheme 29). In the case of addition of 1.5 eq. of

BnMgCl with 1.1 eq. 1,4-dioxane, the mass recovery was good, being a mixture of 39 % benzyl adduct (**2.09**), and 52 % dimer (**2.10**) as determined by ^{1}H-NMR and GCMS analysis. The adduct was purified by flash chromatography.

Further investigation was made into the effect of such magnesium reagents on ketimine (**2.02**). It was found that similar condensation was observed for the treatment of (**2.02**) with magnesium bromide.dioxane complex in diethyl ether (Scheme 30). This indicates that, in this system, it is the Lewis acidity of magnesium that causes the dimerisation. This observation is supported by the formation of the dimer with the use of organocerium(III) reagents derived from Grignard reagents, as opposed to those derived from organolithium reagents, as described below.



(2.02) (2.10)

Scheme 30. Formation of dimer (**2.10**) of ketimine (**2.03**) with magnesium bromide.

In the absence of problems associated with Lewis acidity, the use of less basic organometallic reagents should reduce enolisation as a side reaction. Organocerium(III) reagents, made by transmetallation from Grignard or organo-lithium reagents,[90] were chosen due to their success in additions to enolisable acyclic and cyclic aldimines.[45,46]

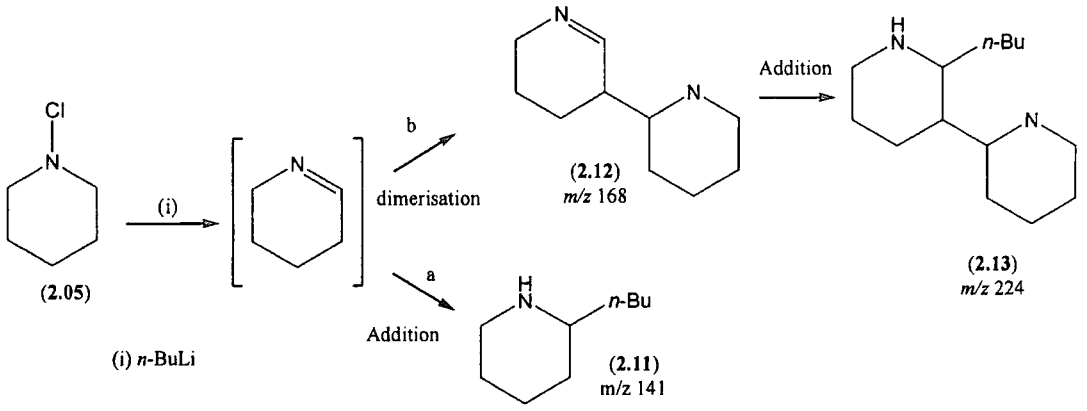
Use of organocerium(III) reagents derived from Grignard reagents led to dimerisation to give (**2.10**), similar to that observed for reactions performed with Grignards in the presence of 1,4-dioxane (see above). The transmetallation reaction of cerium(III) chloride in the presence of a Grignard reagent should yield a solution of the organocerium(III) reagent with a suspension of magnesium halide.[90] Again, this magnesium halide is likely to be the cause of the dimerisation observed in this case.

The use of methylcerium(III) dichloride, derived from methyllithium, for 12 h at ambient temperature gave very pure recovered starting material in low yield after aqueous work-up.[91] This result suggests that the organometallic is less basic, or less

Lewis acidic, but may also be less nucleophilic than the alkyllithium from which it is derived. The reaction may require longer, or the use of a Lewis acid to activate the C=N double bond.

Aldimine **(2.01)** has been reported to undergo nucleophilic addition of certain alkyllithium reagents.[92] Our investigations confirmed this with *n*-butyllithium, in a direct Type B reaction of *N*-chloropiperidine (**2.05**) with *n*-butyllithium, giving both addition and condensation products isolated by distillation (Scheme 31).

GCMS analysis of the product fractions obtained indicated that 2-*n*-butylpiperidine (**2.11**) had been formed (lower boiling point), together with dimer products (higher boiling point fraction) similar to that shown above (Scheme 29 above) with one notable exception: not only was the simple dimer (**2.12**) formed (m/e = 168), but the dimer butyl adduct (**2.13**) (m/e = 224). The proposed reaction scheme is shown below (Scheme 31).



Scheme 31. Type B reaction of *N*-chloropiperidine (**2.05**) with *n*-butyllithium.

The addition of butyllithium to the dimer (**2.12**) suggests that the absence of any 2-substituent on the imine makes the azomethine carbon more susceptible to nucleophilic attack, as might be expected due to simple steric effects.

The range of alkyl and aryl organometallics was chosen for their availability, simplicity and relevance to the future work of this project. The trimethylsilyl group introduced by $TMSCH_2Li$ could, for example be cleaved oxidatively to introduce a hydroxyl group.[93] This is similar to the use of methoxymethylmethyllithium ($MOMCH_2Li$) to introduce oxygen functionality into furanose ring systems.[94]

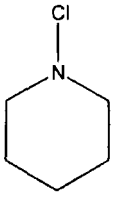
2.3 Summary and conclusions.

The simple cyclic imine systems studied in this chapter were intended to model the proposed use of functionalised cyclic imine-sugars as intermediates in the synthesis of functionalised aza-sugars (see Chapters 3 and 4). The methodology for the formation of *N*-chloro-compounds, and the successful use of DBU in the formation of cyclic imines, is transferable to the sugar systems (see Chapter 4, Section 4.3, and Section 4.5). Isolation of the imines by vacuum distillation, however, will not be possible for the higher molecular weight sugar-imines.

Addition reactions to the simple imines studied were largely unsuccessful, due to the tendency for dimerisation, and the low reactivity to nucleophiles. The reactions of the simple imines have, in general been uncontrolled and have in many cases give intractable mixtures of many products, probably oligomeric or polymeric aldol-like products. These simple imines themselves are not activated by the electron-withdrawing effect of oxygen ring functionality, as we might expect for cyclic imine-sugars, and enolisation of such systems will also no doubt be affected by substituents adjacent to the azomethine carbon. The methodology developed in this chapter does not present a convenient synthesis of 2- and 6- functionalised simple piperidines.

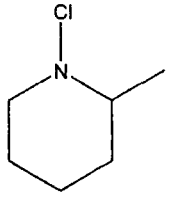
2.4 Experimental Section

N-Chloropiperidine (2.06) (Ref. 87):



NCS (1.1 eq., 55.8 mmol, 7.57 g) was stirred in dry diethyl ether (250 mL) under nitrogen. Piperidine (**2.03**) (1 eq., 50.4 mmol, 4.31 g, 5.0 mL) was added, and the reaction followed by TLC. After 4.5 h, TLC revealed complete conversion of starting material to a single product. The reaction was washed with water (3 × 50 mL) and the organic layer retained and concentrated *in vacuo*. The resultant colourless oil was purified by vacuum distillation, giving *N*-chloropiperidine (**2.05**) as a colourless liquid (4.25g, 70 %): bp 64 °C at 61 mb (lit.[87] 62-64 °C at 41 mmHg/62 mb); ν_{max} (film)/cm^{-1} 2941, 2850, 2830 cm^{-1} (aliphatic C–H stretch); δ_H ($CDCl_3$, 300 MHz) 1.39 (br, s, 2H), 1.63 (br, s, 4H), 2.6 - 3.6 (br, 4H); δ_C ($CDCl_3$, 125.7 MHz), 22.9 (C-4), 27.5 (C-3, C-5), 63.8 (C-2, C-6).

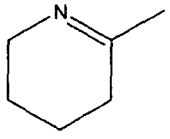
N-Chloro-2-methylpiperidine (2.06):



NCS (1.1 eq., 55.5 mmol, 7.50 g) was stirred with dry diethyl ether (250 mL), under nitrogen. 2-Methylpiperidine (**2.04**) (1.0 eq., 51.1 mmol, 5.06 g, 6.0 mL) was added and the reaction followed by TLC. After 20 h TLC showed complete consumption of starting material and formation of a new product. The reaction mixture was washed with water (3 × 50 mL) and the organic layer dried ($MgSO_4$), and concentrated *in vacuo*. The resultant yellow oil was distilled at reduced pressure to give *N*-chloro-2-methylpiperidine (5.09 g, 75 %) as a pale yellow oil; bp 74-79 °C at 62 mb; ν_{max} (film)/cm^{-1}: 2986, 2967, 2937, 2854, 2832 (aliphatic C–H stretch); δ_H ($CDCl_3$, 250 MHz), 1.22 (d, 1H, CH_3), 1.35 (m, br, 2H, CH_2), 1.65 (m, 4H, CH_2), 2.69 (s, br, 1H, H-6), 2.9 (m, br, 1H, H-6`), 3.50 (m, 1H, H-2); δ_C ($CDCl_3$, 62.9 MHz, DEPT) 21.6 (q,

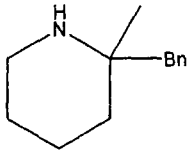
CH_3), 23.9 (t, $\underline{C}H_2$) 27.7, 35.3, 64.3 (3 × t, br, 3 × $\underline{C}H_2$), 66.4 (d, br, C-2).

*6-Methyl-2,3,4,5-tetrahydropyridine (**2.02**) (Ref. 88):*



NCS (1.1 eq., 55.5 mmol, 7.50 g) was stirred with dry DCM (150 mL), under nitrogen. 2-Methylpiperidine (**2.04**) (1.0 eq., 51.1 mmol, 5.06 g, 6.0 mL) was added and the reaction followed by TLC. After 20 h TLC showed complete consumption of starting material and formation of a new product. The reaction mixture was washed with water (4 × 50 mL). The aqueous layer was washed with DCM (2 × 50 mL) and the organic extracts combined dried ($MgSO_4$), and concentrated *in vacuo*. The resultant yellow oil (5.81 g) was dissolved in dry DCM (150 mL) under nitrogen. DBU (1.3 eq., 55.7 mmol, 8.50 g, 8.34 mL) was added with stirring. After 6.5 hours the solvent was removed and the residue distilled at reduced pressure yielding 6-methyl-2,3,4,5-tetrahydropyridine (**2.02**) (3.8 g, 77 %) as a colourless oil: (bp = 57 °C at 76 mb (lit.,[88] 78 °C at 222 Torr (295 mbar); *m/z* 99 (EI, GCMS, 273 seconds, $[M+H]^+$, 60 %, THF); ν_{max} (film)/cm^{-1}: 1664 (C=N stretch), 2987, 2932, 2852 (aliphatic C–H stretch); δ_H ($CDCl_3$, 500 MHz, COSY, gHSQC) 1.50 (m, 2H), 1.58 (m, 2H), 1.82 (s, br, 3H, H-9, CH_3), 2.04 (t, br, 2H, H-1,2, H-5, H-5`), 3.44 (s, br, 2H, H-2, H-2`); δ_C ($CDCl_3$, 125.7 MHz, DEPT, gHSQC), 19.8 (t, C-3), 21.8 (t, C-4), 27.7 (q, CH_3), 30.4 (t, C-5), 49.4 (t, C-2), 168.2 (s, C-6).

*2-Benzyl-2-methylpiperidine (**2.09**):*



6-Methyl-2,3,4,5-tetrahydropyridine (**2.02**) (1.0 eq., 1.86 mmol, 0.204 mL) in dry diethyl ether (10 mL), was added by cannular (nitrogen pressure) to a solution of benzylmagnesium chloride (1.1 eq., 2.02 mmol, 2.02 mL, 1 M solution in diethyl ether), dry 1,4-dioxane (1.1 eq., 2.02 mmol, 0.172 mL), and dry diethyl ether (2.8 mL). The mixture was stirred under nitrogen for 4.5 hours before quenching with methanol (1 mL). The reaction mixture was diluted with diethyl ether (20 mL), and

washed with HCl (3 M, aq., 2 × 20 mL). The aqueous layers were combined and basified with NaOH (3 M, aq.) to pH 13. The resultant cloudy solution was extracted with DCM (2 × 30 mL), and the organic layers combined, dried (Na_2SO_4), filtered and the solvent removed to yield a pale orange oil (191 mg) containing 39 % 2-benzyl-2-methylpiperidine (**2.09**) (^{1}H-NMR integration). The mixture was purified by column chromatography (5 : 95 - 1 : 9, methanol : $CHCl_3$, eluent) giving 2-benzyl-2-methyl piperidine (**2.09**) as an orange oil (19 mg, 7 % isolated): *m/z* 190 (ES, $[M+H]^+$, 100 %, MeOH); ν_{max} (film)/cm^{-1}: 2861, 2930 (aliphatic C–H stretch), 3027, 3062, 3090, (aromatic C–H stretch), 3305 (br, N–H stretch); δ_H ($CDCl_3$, 500 MHz, gHSQC) 0.95 (s, 3H, C$\underline{H}_3$), 1.3 - 1.6 (m, 6H, 3 × C$\underline{H}_2$), 2.57 (d, 1H, 1 of C$\underline{H}_2$Ph, J_{HH} 12.9 Hz), 2.70 (m, 1H, H-6), 2.77 (d, 1H, 1 of C$\underline{H}_2$Ph, J_{HH} 12.9 Hz), 2.86 (ddd, H-6`, $J_{6,6'}$ 12.7, J_{HH} 4.28 Hz, J_{HH} 5.86 Hz), 7.10 – 7.22 (m, 5H, aromatic CH); δ_C ($CDCl_3$, 125.7 MHz, DEPT, gHSQC) 24.7 (q, br, $\underline{C}H_3$), 20.7, 26.3, 36.7, 41.3 (4 × t, C-3, C-4, C-5, C-6), 46.5 (t, br, $\underline{C}H_2$Ph) 52.2 (s, C-2), 126.1, 128.0, 130.6 (3 × d, 3 × aromatic $\underline{C}$H), 138.0 (s, quarternary aromatic); HRMS found 190.1601 ($C_{13}H_{20}N$ ($[M+H]^+$) requires 190.1596).

*Type A nucleophilic addition to (**4.02**) (typical):*

To a stirred solution of 6-methyl-2,3,4,5-tetrahydropyridine (**4.02**) in dry THF under nitrogen was added a solution of the required organometallic (2 eq.) over 5 - 15 minutes. The reaction was followed by TLC (1 : 9 : 90, triethylamine : methanol : $CHCl_3$ eluent) and the consumption of starting imine observed. Upon completion the reaction mixture was either acetylated (a) or an aqueous work-up employed (b).

(a) Acetylation: An excess of acetic anhydride : pyridine (1 : 1) was added carefully to the reaction mixture. The resultant slurry was stirred for 1 h before washing with dilute HCl (0.1 M, aq.). The organic layer was separated and dried ($MgSO_4$), then concentrated. The resultant mixture was subjected to ^{1}H-NMR analysis then column chromatography, gas chromatography, GCMS analysis, distillation or a combination of these techniques.

(b) Aqueous work-up: The reaction mixture was quenched cautiously with water, diluted (diethyl ether), acidified (HCl, aq.) to pH 1, and the aqueous phase retained. The aqueous phase was basified (pH 13) and washed with diethyl ether. The organic

phases were combined, dried (Na_2SO_4), and the solvent removed. The resultant mixture was subjected to ^{1}H-NMR analysis then column chromatography, gas chromatography, GCMS analysis, distillation or a combination of these techniques.

*Type B elimination then addition to (**2.01**) and (**2.02**), (typical)*:

To a stirred solution of an *N*-chloropiperidine ((**2.01**) or (**2.02**)) in dry THF under nitrogen, a solution of the relevant organometallic (3 eq.) was added over 10 - 15 minutes. The solution was stirred and the reactions analysed by tlc. When complete, the reaction mixtures were subjected to the same analyses and work-up procedures as described above ((a) or (b)).

Reaction of cyclic imines with organocerium reagents (general):

Anhydrous cerium(III) chloride (1.1 eq. approx. 0.2 mmol) was stirred in dry diethyl ether (15 mL) under nitrogen. A solution of Grignard reagent was added (1.1 eq., 1-3 M in diethyl ether) with stirring. The suspension was stirred under nitrogen for 2.5 h before adding the imine reagent (1.0 eq.). The mixture was stirred for 16 h before diluting with diethyl ether (20 mL), and washing with sodium hydroxide (aq., 3 M, 2 × 20 mL). The organic layer was washed with HCl (aq., 3 M, 2 × 20 mL) and the aqeous extracts adjusted to pH 13 with sodium hydroxide (aq., 3 M). The resultant suspension was extracted with DCM (3 × 20 mL), dried (Na_2SO_3), filtered and the solvent removed *in vacuo*.

Reactions of cyclic imines with diorganomagnesium reagents (general):

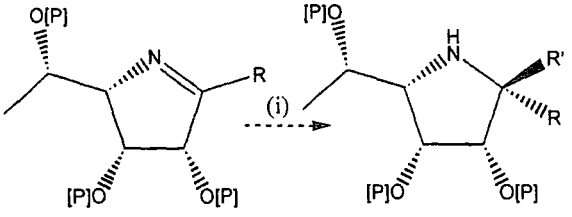
A solution of the cyclic imine (1.0 eq., approx 2 mmol) in dry diethyl ether (10 mL), was added by cannular (nitrogen pressure) to a solution of Grignard reagent (1.1 eq., 1-3 M solution in diethyl ether), dry 1,4-dioxane (1.1 eq.), and dry diethyl ether (2.8 mL). The mixture was stirred under nitrogen for 4.5 hours before quenching with methanol (1 mL). The reaction mixture was diluted with diethyl ether (20 mL), and washed with HCl (3 M, aq., 2 × 20 mL). The aqueous layers were combined and basified with NaOH (3 M, aq.) to pH 13. The resultant cloudy solution was extracted

with DCM (2 × 30 mL), and the organic layers combined, dried (Na_2SO_4), filtered and the solvent removed *in vacuo*.

Chapter 3. Synthesis and Evaluation of Rhamnopyrrolidine Imines as Substrates for Addition Reactions

Our target enzyme, inspiring the synthesis of aza-sugars of rhamno-stereochemistry, is a postulated rhamnosyl transferase enzyme in *Mycobacterium tuberculosis* (see Chapter 1, Section 1.6.2),[83] that incorporates an L-rhamnopyranose unit into the developing peptidoglycan region of the bacterial cell wall. Aza-sugars, sugar mimics with the ring oxygen replaced by nitrogen (see Introduction, Section 1.3), can be potent and specific inhibitors of sugar-processing enzymes.[95]

In this chapter we investigate the synthesis of cyclic imines of 1,4-dideoxy-1,4-imino-L-rhamnitol (L-rhamnofuranose) stereochemistry (Scheme 32), synthetic precursors of potential rhamnose-processing enzyme inhibitors (see Chapter 1, Section 1.6.2). The synthesis of novel rhamnopyrrolidine aza-sugars is to be based around the addition of nucleophiles to such cyclic imine sugars (Scheme 32). In the case of cyclic aldimines, potential access to 'two-component' aza-sugars is available (Scheme 32, R = H), where R' forms the second component).



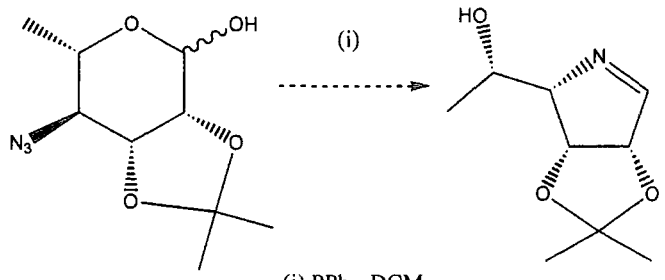
R = H, alkyl, aryl

R = H, alkyl, aryl
R' = H, alkyl, aryl

(i) R'.

Scheme 32. Proposed nucleophilic addition to cyclic rhamnopyrrolidine imines.

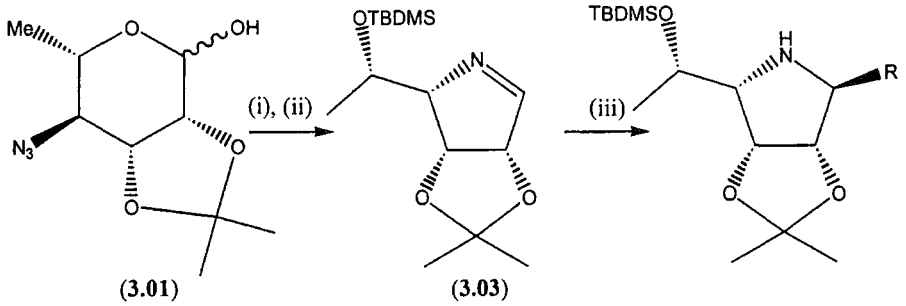
The synthesis of cyclic aldimines of the type shown above (Scheme 32) is to be approached from the known azido-sugar (**3.01**), the enantiomer of which is known. An intramolecular Staudinger aza-Wittig reaction[74] of the open chain aldehyde should afford the previously unknown cyclic imine (**3.02**) (Scheme 33) *via* the iminophosphorane intermediate, and elimination of triphenyphosphine oxide.



Scheme 33. Proposed formation of cyclic aldimine (**3.02**) *via* an intramolecular Staudinger aza-Wittig reaction.

The 2,3-*O*-ispopropylidine ketal protection of the *cis*-diol is ideally suited to our strategy, being stable to the reaction conditions employed, and conveniently removed by acidic hydrolysis.[96] A *tert*-butyldimethylsilyl ether is proposed to protect the free hydroxyl group of imine (**3.02**), again for the stability of such ethers to the reaction conditions used, and their ease of removal by acidic hydrolysis.[96] This should allow global deprotection of the final aza-sugar in one synthetic step.

Addition of suitable nucleophiles to imine (**3.03**) (Scheme 34) should afford the desired functionalised aza-sugar, with diastereoselectivity expected to be defined by steric approach control, often observed in such rigid bicyclic structures (see Chapter 1, Section 1.4). This methodology would allow the fast, convenient synthesis of libraries of compounds limited only by the availability of nucleophiles.

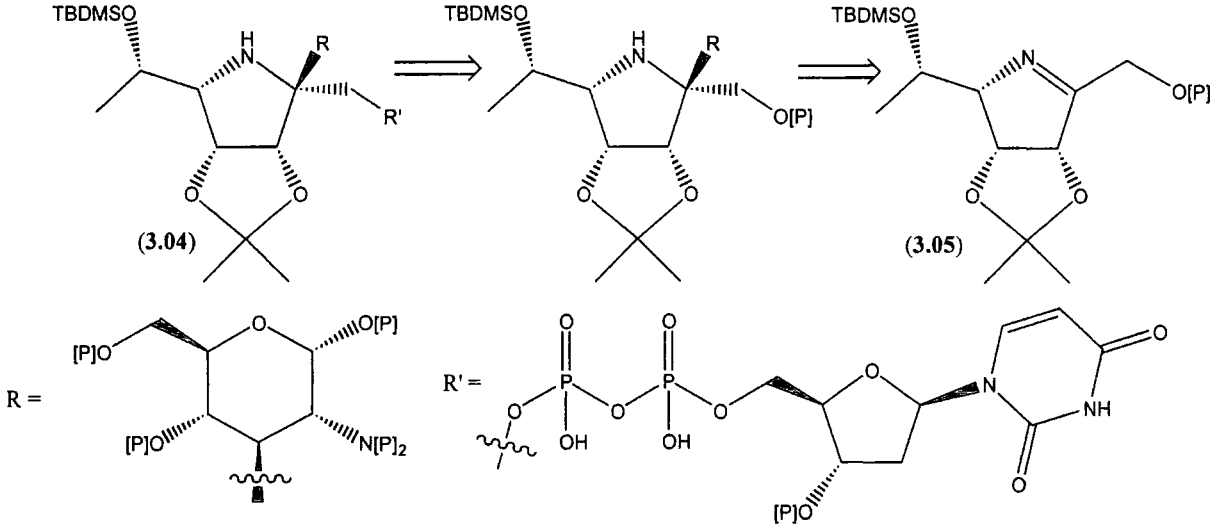


(i) PPh_3, DCM; (ii) TBDMSOTf, py; (iii) RMgX, Et_2O. TBDMS =$SiMe_2t$-Bu

Scheme 34. Proposed formation of functionalised cyclic imine (**3.03**), and subsequent nucleophilic addition.

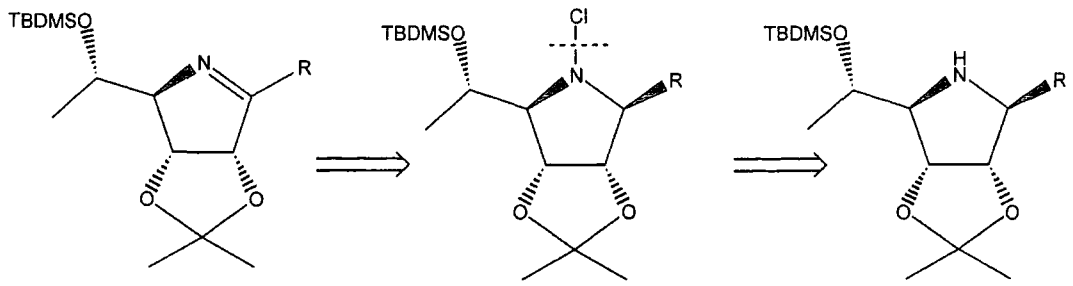
Use of a suitable hydroxymethyl anion equivalent such as, allyloxymethylmagnesium chloride[97] or benzyloxymethylmagnesium chloride[98] could also afford homologated, orthogonally protected aza-sugar products, allowing further functionalisation (Scheme 34, R = CH_2OBn, $CH_2Oallyl$).

In the case of addition to cyclic pyrrolidine ketimines (R ≠ H, Scheme 32, above), access to 'three-component' aza-sugars is available. A generalised retrosynthetic analysis for a potential rhamnosyltransferase inhibitor is shown below (Scheme 35), revealing the utility of such additions, the key synthetic step being nucleophilic addition to an intermediate cyclic ketimine (**3.05**). Stereochemistry of irreversible addition is again expected to be defined by steric approach control.



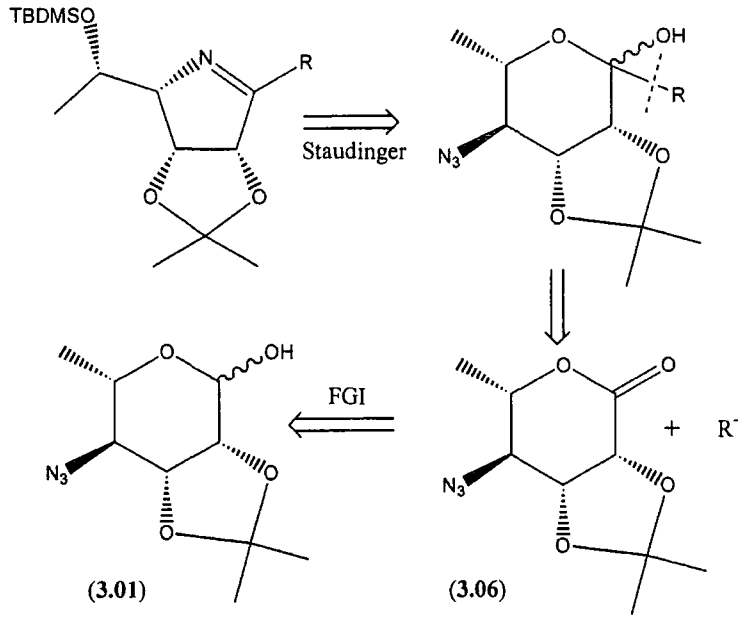
Scheme 35. Retrosynthetic analysis of a target inhibitor (**3.04**), showing the application of intermediate ketimine (**3.05**).

Two synthetic approaches to such cyclic ketimines are suggested, and the retrosyntheses are shown below. Aza-sugars formed by addition to aldimine (**3.03**) adducts (Scheme 34) could be *N*-chlorinated and elimination of HCl from these *N*-chloro compounds under basic conditions should afford a cyclic ketimine (Scheme 36) (cf. Chapter 2, and Chapter 4), although regiocontrol of elimination may be an issue (see Chapter 1, Section 1.5.1).



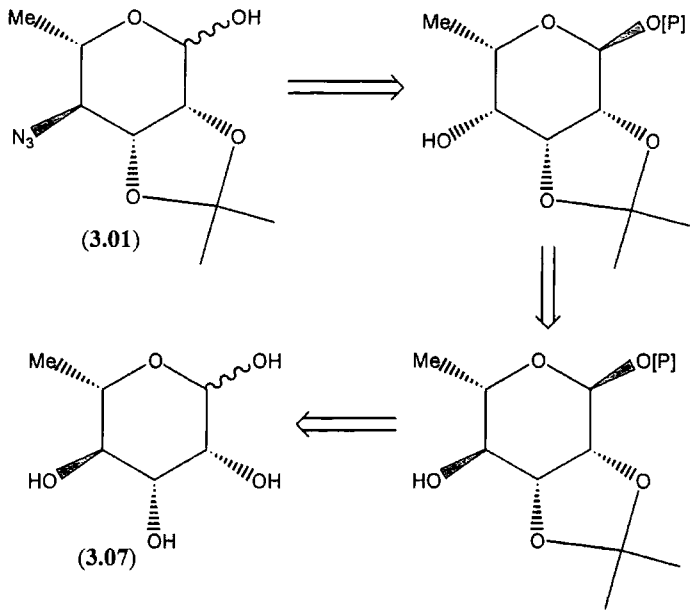
Scheme 36. Retrosynthetic analysis of cyclic ketimines, *via* a chlorination/elimination method.

A second approach to the synthesis of cyclic pyrrolidine ketimines is *via* the Staudinger aza-Wittig reaction of masked azido ketones (Scheme 37), analogous to that discussed for pyrrolidine aldimine (**3.02**) (Scheme 33). The synthesis depends upon the previously unknown nucleophilic addition to the known[99] azido lactone (**3.06**) to give the masked azido ketone.



Scheme 37. Retrosynthetic analysis of cyclic ketimines *via* a Staudinger aza Wittig reaction of masked azido ketones.

Scheme 38 shows the retrosynthetic analysis for the common intermediate azido-sugar (**3.01**), following the work of Fleet *et al.* ([P] = Me).[100] Commercially available L-rhamnose (**3.07**) is a convenient chiral pool starting material.



Scheme 40. Retrosynthetic analysis of azido lactol (**3.01**) (cf. Ref. 100).

The work performed in this chapter can be separated into five main sections:

3.1 The synthesis of 4-azido-4-deoxy-2,3-*O*-isopropylidene-α,β-L-rhamnose (**3.01**).

3.2 Alternative synthesis of 4-azido-4-deoxy-2,3-*O*-isopropylidene-α,β-L-rhamnose (**3.01**).

3.3 Synthesis of protected pyrrolidine aldimine (**3.03**) *via* an intramolecular Staudinger aza-Wittig reaction.

3.4 Nucleophilic addition to pyrrolidine aldimine (**3.03**).

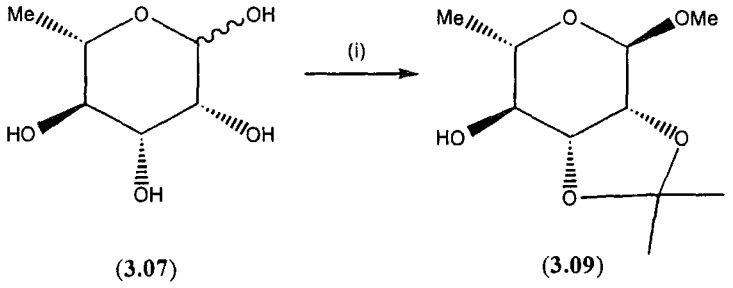
3.5 Synthesis of a cyclic pyrrolidine ketimine *via* an intramolecular Staudinger aza-Wittig reaction.

3.1 The Synthesis of 4-Azido-4-Deoxy-2,3-*O*-Isopropylidene-L-Rhamnose (3.03)

We have synthesised the known 4-azido-4-deoxy-2,3-*O*-isopropylidene-α,β-L-rhamnose (**3.03**) from L-rhamnose (**3.07**) by two separate synthetic routes. A known synthetic route (38 %, 7 steps)[100] to the deprotected azido lactol (**3.08**) was followed initially (Scheme 24, page 50), anomeric protection being afforded by the robust methyl glycoside.

Fischer glycosidation of L-rhamnose with methanol and acetyl chloride, as a source of acidic methanol, gave the α-methyl glycoside. Treatment of the methyl glycoside

with 2,2-dimethoxypropane and catalytic camphor-10-sulfonic acid (CSA) in acetone afforded methyl 2,3-*O*-isopropylidene-α-L-rhamopyranoside (**3.09**) in 85 % yield after chromatography (Scheme 41), according to literature methods,[100] on an 11 g scale.



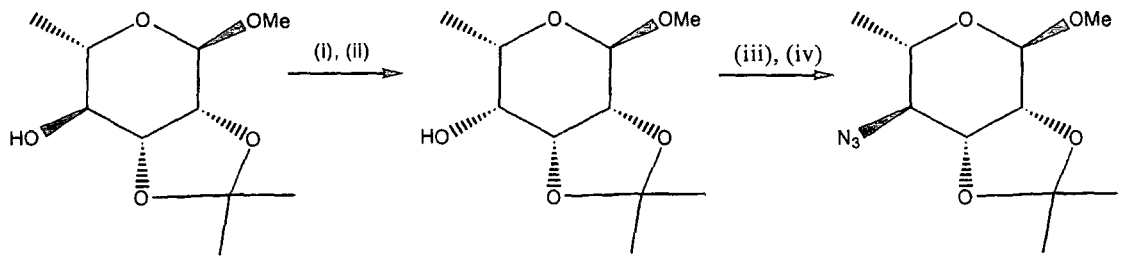
(3.07) (3.09)

(i) AcCl, methanol, then $Me_2C(OMe)_2$, CSA, acetone, 85 % over two steps.

Scheme 41. Formation of protected rhamnose derivative (**3.09**).

Oxidation of the free hydroxyl function with pyridinium chlorochromate (PCC) in DCM gave the intermediate ketone (Scheme 41), which was purified by passing through a silica plug, and immediately reduced with sodium borohydride in ethanol/water. Attack of hydride occurred, as expected, from the least hindered face to yield exclusively the L-talo-diastereoisomer, methyl 6-deoxy-2,3-*O*-isopropylidene-α-L-talopyranoside (**3.10**), in 75 % yield over two steps, on an 11 g scale, according to the literature method.[100]

Formation of the corresponding 4-trifluoromethylsulfonate (triflate) was achieved with trifluoromethanesulfonic anhydride and pyridine. After aqueous work-up, the resultant crude sugar triflate was treated with sodium azide in DMF. S_N2 displacement of the 4-triflate group gave methyl 4-azido-4-deoxy-2,3-*O*-isopropylidene-α-L-rhamnopyranoside (**3.11**) in 58 % yield over two steps. Side products with ^{1}H-NMR signals in the olefinic region were also obtained, corresponding to elimination occurring as a competing process.

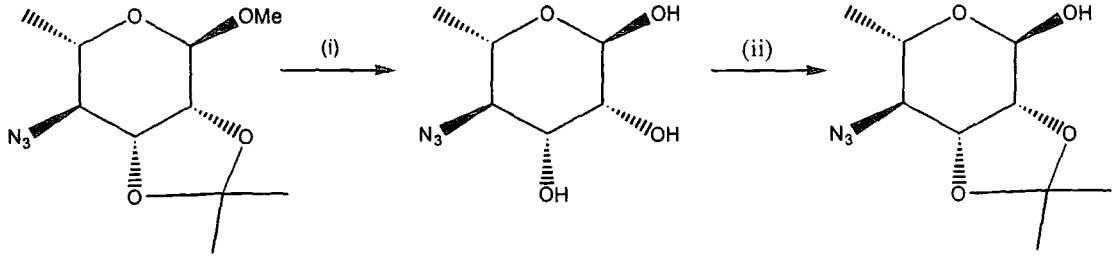


(3.09) (3.10) (3.11)

(i) PCC, sieves, DCM; (ii) $NaBH_4$, $EtOH/H_2O$, 75 % (two steps); (iii) Tf_2O, Py, DCM; (iv) NaN_3, DMF, 58 % over two steps.

Scheme 42. Synthesis of methyl 4-azido-4-deoxy-2,3-*O*-isopropylidene-α-L-rhamnopyranoside.

Hydrolysis of the methyl glycoside cannot be performed selectively in the presence of an isopropylidene-protected diol,[101] and it was therefore necessary to remove both protecting groups in one step, and then selectively reintroduce the 2,3-*O*-isopropylidene group. Acid-catalysed hydrolysis of the 2,3-*O*-isopropylidene and the methyl glycoside was achieved with degassed trifluoroacetic acid (TFA) and water (1 : 1) at 80 °C giving the fully deprotected 4-deoxy-4-azido-L-rhamnose (**3.08**) in up to 84 % yield.



(3.11) (3.08) (3.01)

(i) TFA : water (1 : 1), 80 °C, 84 %; (ii) $CuSO_4$(anhyd.), H_2SO_4, 94 %.

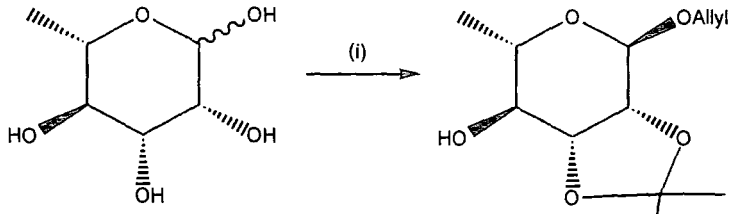
Scheme 43. Synthesis of protected azido-sugar (**3.01**).

Selective formation of the protected 4-azido-4-deoxy-2,3-*O*-isopropylidene-L-rhamnose (**3.01**) proceeded in high yield (94 %), by treatment with acetone, copper (II) sulfate, and catalytic sulfuric acid over molecular sieves. An overall yield of 35 % was obtained in the synthesis of the desired azido-sugar (**3.01**) from L-rhamnose, comparing well to the 38 % obtained in the literature preparation.[100]

3.2 Alternative Synthesis of 4-Azido-4-Deoxy-2,3-Isopropylidene-α,β-L-Rhamnose (3.01)

In order to synthesise larger quantities of the desired azido-lactol (3.01) a new synthesis was devised, which removes the need for global deprotection, then 2,3-reprotection at the stage of cleavage of the anomeric protecting group. Orthogonality at this stage was introduced by the use of an allyl glycoside. Simple isomerisation with a suitable catalyst or strong base,[102,103] followed by iodine-assisted cleavage of the resultant vinyl ether should allow selective cleavage of only the anomeric protecting group. The synthetic strategy followed that discussed in Section 3.1.

Fischer glycosidation to form the α-allyl glycoside was achieved in allyl alcohol, with catalytic conc. sulfuric acid. The crude allyl α-L-rhamnopyranoside was isolated then treated with 2,2-dimethoxypropane in acetone, again with catalytic conc. sulfuric acid, giving the known[104] allyl 2,3-*O*-isopropylidene-α-L-rhamnopyranoside (**3.12**) as a colourless oil in 88 % yield (Scheme 44).

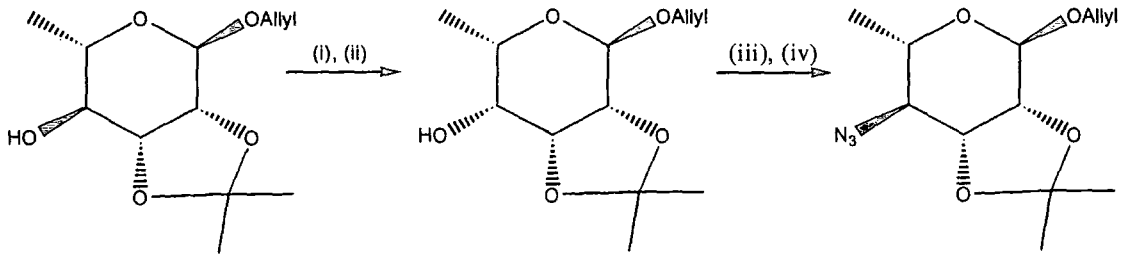


(3.07) (3.12)

(i) H_2SO_4, allyl alcohol, then H_2SO_4, $(CH_3)_2CO$, 88 %.

Scheme 44. Synthesis of allyl 2,3-*O*-isopropylidene-α-L-rhamnopyranoside (**3.12**).

Oxidation of the 4-hydroxyl group in allyl 2,3-*O*-isopropylidene-α-L-rhamnopyranoside (**3.12**) was achieved with PCC in DCM, as for the analogous compound (**3.09**) (Scheme 42) and the resultant ketone purified by passing through a silica plug. The ketone was immediately reduced with sodium borohydride in ethanol/water, giving the expected L-talo-diastereoisomer (**3.13**) in 93 % yield over two steps (cf. compound (**3.10**), p 46). This is a marked improvement over the parallel 2 step synthesis of (**3.10**) which was achieved in only 75 % yield.



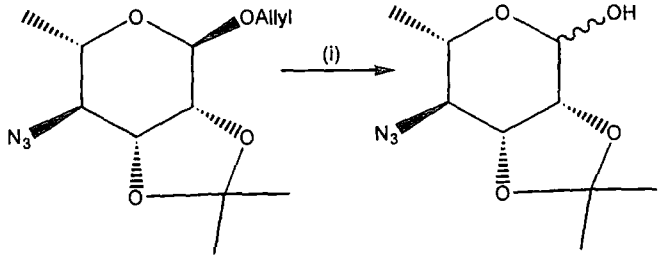
(3.12) (3.13) (3.14)

(i) PCC, sieves, DCM; (ii) $NaBH_4$, $EtOH/H_2O$, 93 % (two steps); (iii) Tf_2O Py, DCM; (iv) NaN_3, DMF, 37 %.

Scheme 45. Synthesis of allyl 4-azido-4-deoxy-2,3-*O*-isopropyilidine-α-L-rhamnopyranoside (**3.14**).

Introduction of nitrogen with inversion of configuration at C-4 was achieved by conversion of the free 4-hydroxyl into the corresponding triflate with triflic anhydride and pyridine in DCM, followed by aqueous work-up. Subsequent treatment with sodium azide in DMF, giving the desired azide (**3.14**) in 37 % yield (Scheme 45). The low yield is attributed to competing elimination of the triflate group, and impurities with additional ^{1}H-NMR signals in the olefinic region were obtained.

Removal of the allyl glycoside proved slightly problematic. Standard[102] use of Wilkinson's catalyst, with catalytic 1,4-diazabicyclo[2.2.2]octane (DABCO) in ethanol or THF gave, at best, only partial isomerisation (as judged by ^{1}H-NMR) even with extended reaction times at reflux. Variation of solvent, base and temperature gave no reproducible results. After several attempts, the use of the method of Corey and Suggs,[103] employing Wilkinson's catalyst, pre-treated with *n*-BuLi, at reflux in THF, gave reliable, reproducible results.



(3.14) (3.01)

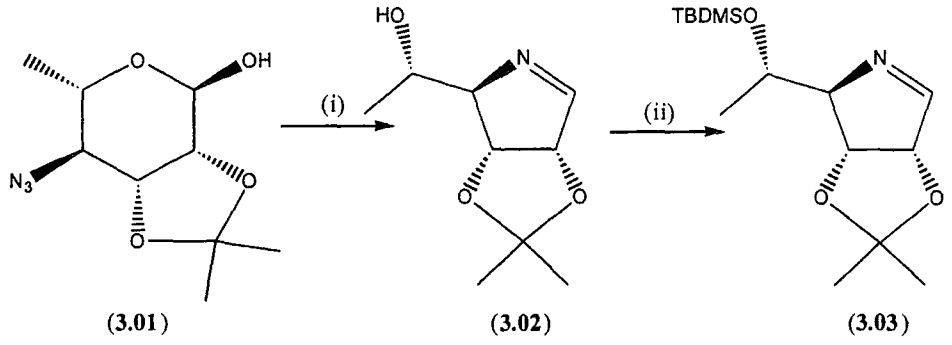
(i) $(PPh_3)_3RhCl$, BuLi, THF, reflux, then I_2, THF/water, rt, 76 %.

Scheme 46. Cleavage of the anomeric allyl ether with Wilkinson's catalyst and *n*-BuLi, and subsequent hydrolysis.

Pre-treatment of the Wilkinson's catalyst is thought to give the rhodium hydride species. The rhodium hydride species, synthesised separately, has also been found to isomerise allyl ethers.[102] Treatment of the intermediate vinyl glycoside with iodine in THF/water, gave the desired azido-sugar (**3.01**) in 76 % yield from the allyl glycoside (**3.14**) (Scheme 46).

3.6 Synthesis of Protected Pyrrolidine Aldimine (3.03) *via* an Intramolecular Staudinger Aza-Wittig Reaction

Staudinger aza-Wittig reaction of the azido-sugar (**3.01**) with triphenylphosphine gave the crystalline cyclic imine (**3.02**) in excellent yield (96 %) (Scheme 47). The resultant imine was stable enough to be purified by flash column chromatography on silica. Protection of the free hydroxyl group was achieved in DCM with either *tert*-butylchlorodimethylsilane/imidazole, or with *tert*-butyldimethylsilyltriflate/pyridine in good yield, giving protected imine (**3.03**) as a colourless liquid after chromatography (79 %, and 84 % respectively).



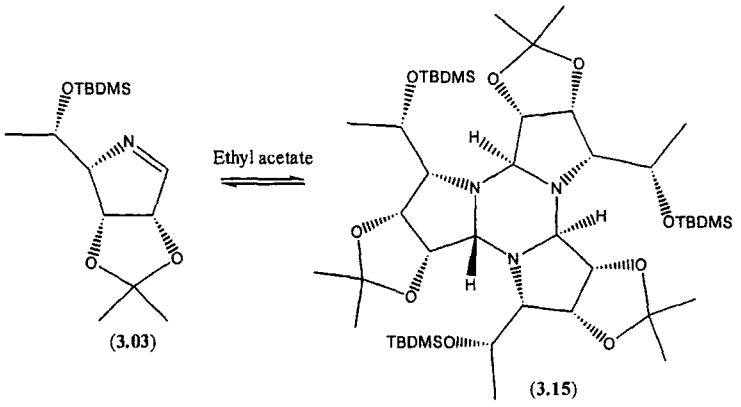
(**3.01**) (**3.02**) (**3.03**)

(i) PPh_3, DCM (96 %); (ii) TBDMSOTf, py, DCM (84 %), or TBDMSCl, imid, DCM (79 %).

Scheme 47. Intramolecular Staudinger reaction of azido sugar (**3.01**), and subsequent *O*-silylation.

Interestingly, attempts to recrystallise the protected imine (**3.03**) from ethyl acetate/hexane gave a mixture of compounds, including the trimer of (**3.15**) (c.f. tripiperidein Chapter 2, page 43), and the monomeric imine, which could be separated by flash chromatography giving the trimer and monomer in 29 % and 21 % yield respectively (Scheme 48 below). The trimer and monomer are apparently in

equilibrium in ethyl acetate solution at room temperature. Attempts to recrystallise the pure trimer from ethyl acetate failed. However, upon purification of initially pure trimer by column chromatography, a proportion of monomeric imine (**3.03**) was obtained, proving the equilibrium is active. Such equilibration was not observed in DCM, or deuterated chloroform.



Scheme 48. Reversible trimerisation of 5-*O*-*tert*-butyldimethylsilyl-1,*N*-dehydro-1,4-dideoxy-1,4-imino-2,3-*O*-isopropylidene-L-rhamnitol (**3.03**).

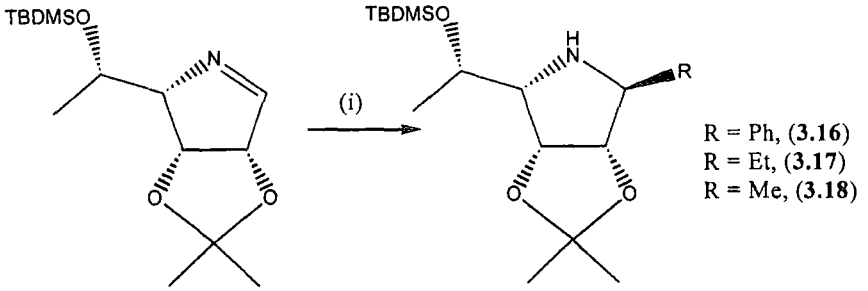
Trimer (**3.15**) was identified by mass spectroscopy (*m/z* 898, (ES, MeOH, $[M+H]^+$, 50 %), 921 ($[M+Na]^+$, 100 %). The trimer lacks a ^{13}C-NMR signal for the C-1 azomethine carbon, observed in (**3.03**) at 167 ppm. Three new major peaks at 110, 111, and 114 ppm may correspond to the C-1 geminal amines. Both the ^{1}H and ^{13}C NMR spectra are very complex, and it is possible that it may exist in more than one form. The stereochemistry shown is arbitrarily based on simple molecular model analysis.

Imine (**3.03**) was screened with a variety of commercial Grignard reagents (see Section 3.4, below).

3.4 Nucleophilic Addition to Pyrrolidine Aldimine (3.03)

Protected pyrrolidine imine (**3.03**) was treated with Grignard reagents in diethyl ether. Initially addition reactions were performed by addition of a solution of the appropriate Grignard (1.1 eq. in diethyl ether) to a diethyl ether solution of the imine at room temperature. Under these conditions an addition product was only isolated with

phenyl magnesium bromide (60 % yield, 37 % unreacted imine); Methyl and benzyl Grignard only gave unreacted starting material after 4.5 h under the same conditions. Using an alternative reverse addition strategy developed within our group,[105] a diethyl ether solution of the imine was added to the Grignard reagent (3.0 M in ether), and stirred at room temperature. This alternative strategy used an excess of the Grignard (15.0 eq.) and gave good to excellent yields of adducts (up to 100 %), with only one diasteroisomer observed in each the case of phenyl and ethyl Grignards. In the case of methyl Grignard a ratio of 69 : 2 was observed (NMR) with an overall yield of 86 %. The major diastereoisomer (**3.18**) could be isolated by flash chromatography. Stereochemistry was consistent with steric approach control due to the 'cup-like' shape of the fused system, with the smaller methyl nucleophile also able to access the opposite face.



(i) RMgBr, Et_2O, (R = Ph, 69 %, R = Et, 100 %, R = Me, 86 %, (dr 69:2))

Scheme 49. Nucleophilic addition to cyclic imine (**3.03**).

The stereochemistry of each adduct was established by NMR using nOesy experiments. The key interactions observed were as shown in Figure 25 below.

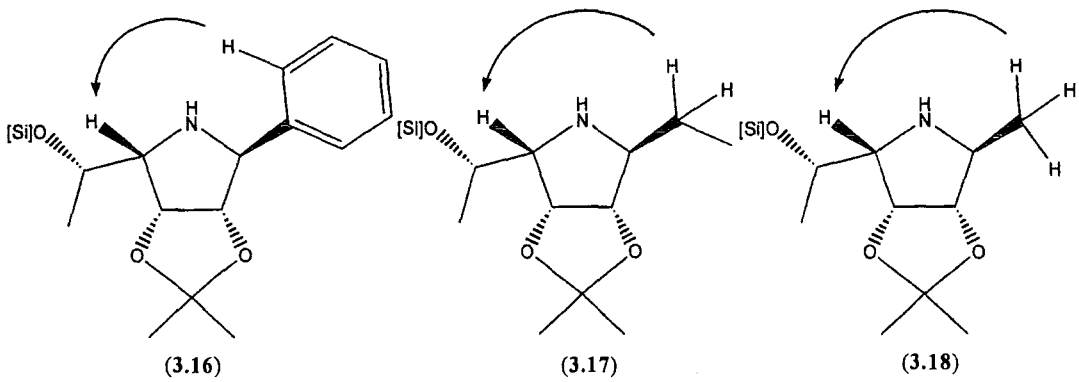
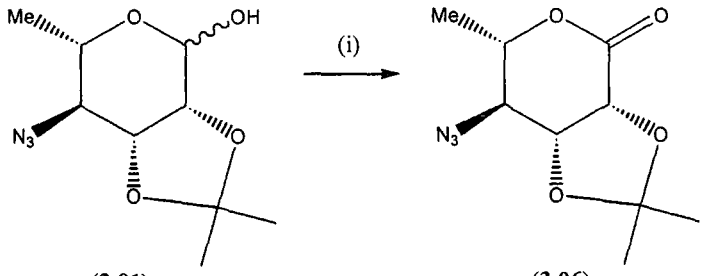


Figure 25. Stereochemical assignment of adducts by nOesy interactions.

3.5 Synthesis of a Pyrrolidine Ketimine *via* Nucleophilic Addition to L-Rhamnolactone (3.06)

For the formation of azido-lactone (**3.06**), protected azido-sugar (**3.01**) was treated with PCC in refluxing 1,2-dichloroethane (DCE), giving the desired lactone (**3.06**) in up to 76 % yield after chromatography (Scheme 50). The reaction was found to stop before completion at room temperature in DCM.



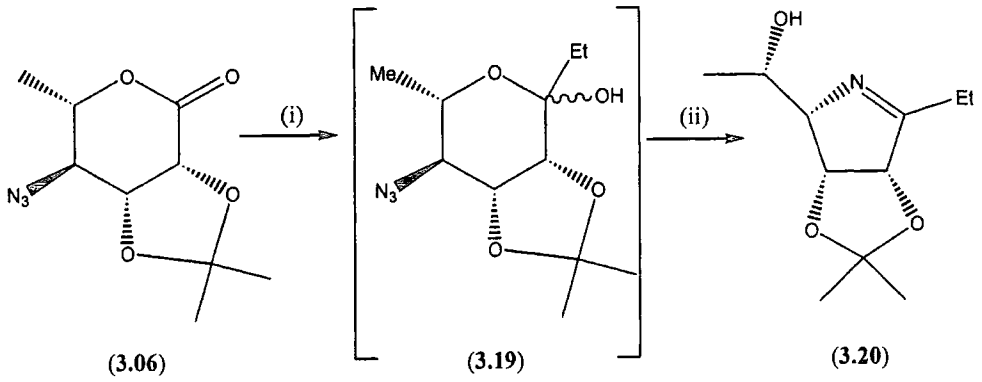
(3.01) (3.06)

(i) PCC, DCE, reflux, 76 %.

Scheme 50. Formation of azido-lactone (**3.06**).

4-Azido-4-deoxy-2,3-*O*-isopropylidene-L-rhamno-1,5-lactone (**3.06**) was treated with ethyl magnesium bromide at room temperature to form the azidocarbonyl-sugar (**3.19**), which exists as a mixture of anomers in 85 % crude yield. Azido-sugar (**3.19**) could be purified by flash chromatography, to give a single cyclic ketal anomer (17 %), however considerable decomposition was observed, and mixtures of several products with NMR signals in the olefinic region were obtained, together with the unanticipated spontaneous formation of cyclic ketimine (**3.20**), which was isolated in 26 % yield.

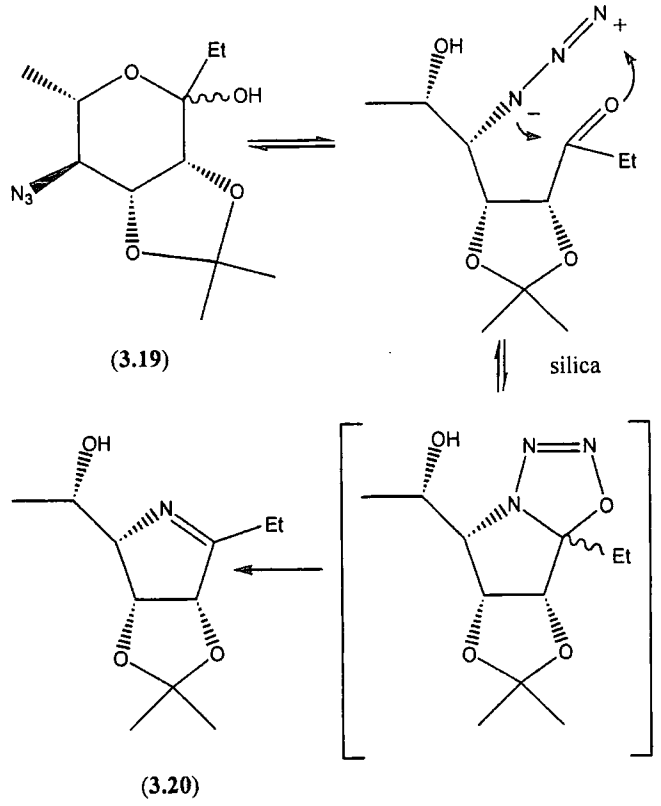
The absence of a reducing agent in the mixture suggests a, thermally allowed, [3+2] dipolar cycloaddition, possibly catalysed by silica, followed by spontaneous loss of N_2O, thereby forming the imine. Such cycloadditions are well known for nitriles with azides, and are a common way of forming cyclic tetrazoles. Indeed a similar cycloaddition has been observed in the formation of cyclic oxatriazoles[106] through a tandem substitution/cycloaddition reaction of 4-bromoalkyl aldehydes (Scheme 53). A suggested mechanism for the formation of imine (**3.20**) is shown in Scheme 50.



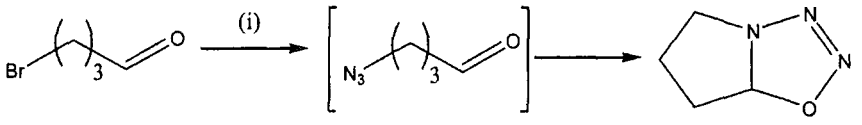
(i) EtMBr, Et_2O, rt; (ii) PPh_3, DCM, rt, 64 % from (**3.06**) over 2 steps.

Scheme 49. Synthesis of pyrrolidine ketimine (**3.20**) from azido lactone (**3.06**).

The crude addition product, when treated with triphenylphosphine in DCM at room temperature gave the same imine in 64 % yield from the lactone (Scheme 49), and this is the preferred method.



Scheme 50. Proposed mechanism for the formation of cyclic imine (**3.20**) upon chromatography.



(i) NaN_3, solvent temperature

Scheme 53. Synthesis of oxatriazoles from azido-aldehydes[106]

3.6 Summary and Future Directions

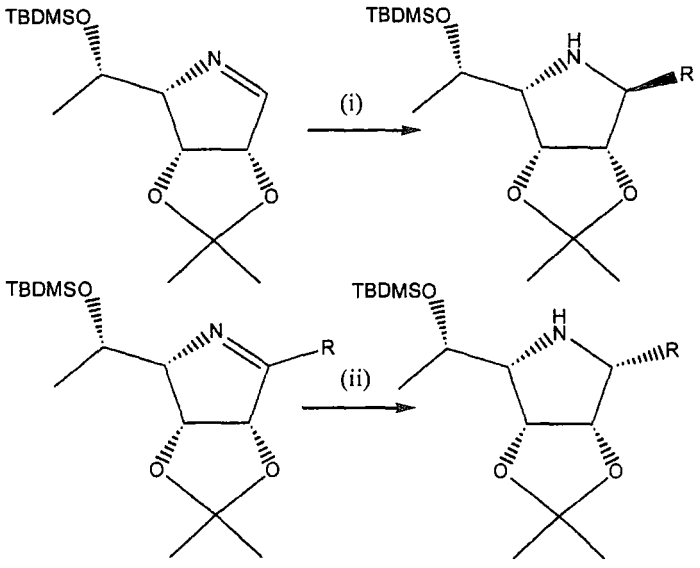
The successful synthesis of the previously unknown cyclic ketimine (**3.20**), and aldimine (**3.03**), *via* the common intermediate azido-sugar (**3.01**) presents us with our target enantiomerically pure cyclic imine sugar scaffolds as precursors to potential sugar-processing enzyme inhibitors. Both imines are synthesised from commercially available L-rhamnose in 28 % overall yield (9 steps, compound (**3.03**)), and 17 % overall yield (10 steps, compound (**3.20**)).

Successful irreversible addition of carbon nucleophiles to aldimine (**3.03**) in excellent yields and diastereoselectivities presents us with the possibility of the synthesis of arrays of aza-sugars, with late-stage introduction of functionality at the pseudoanomeric position.

The synthesis of pyrrolidine ketimine (**3.20**), *via* addition to the azido lactone (**3.06**) presents the possibility of the formation of three component aza-sugars. Protection of the free hydroxyl group as the *tert*-butyldimethylsilyl ether, followed by addition of a range of nucleophiles could lead to the synthesis of libraries of novel potentially biologically interesting compounds.

Use of hydroxymethyl anion equivalents, such as allyloxymethylmagnesium halides allows the introduction of new, orthogonally protected hydroxyl functionality. Deprotection and biological screening of these new compounds using both glycosylhydrolase and transferase assays could provide insight into enzyme mechanism, and possibly lead to novel therapeutic target compounds.

Reduction of cyclic ketimines with a suitable hydride source may also provide access to the C-1 epimers of adducts to the cyclic aldimine (**3.03**) as synthesised above, allowing the chemist to probe further the effect of stereochemistry on biological activity (Scheme 52).



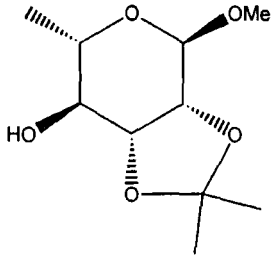
(i) RMgX, Et_2O; (ii) $LiAlH_4$, Et_2O.

Scheme 52. Proposed synthesis of C-1 functionalised epimers with cyclic imine sugars as intermediates.

The work presented above demonstates the synthetic utility of cyclic imine sugars as versitile intermediates in the synthesis of potential therapeutic compounds and mechanistic probes.

3.7 Experimental Section

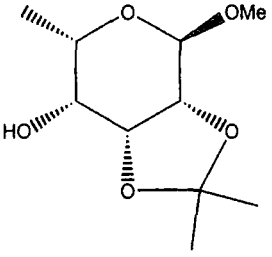
*Methyl 2,3-O-isopropylidene-α-L-rhamnopyranoside (**3.09**) (Ref. 109):*



Acetyl chloride (0.8 eq., 49.2 mmol, 3.86 g, 3.50 mL) was added to a solution of α-L-rhamnose monohydrate (**3.07**) (1.0 eq., 62.1 mmol, 11.31 g,) in methanol (anhydrous, 150 mL) and refluxed under nitrogen. After 45 h, TLC showed consumption of starting material, and formation of a major product. The reaction solution was cooled, neutralised with sodium bicarbonate and the solvent removed. The residue was dissolved in ethyl acetate, passed through a silica plug (ethyl acetate eluent), the

solvent removed and the residue dissolved in dry acetone (250 mL) under nitrogen. To the resulting solution, camphor-10-sulfonic acid (CSA) (0.2 g) and then 2,2-dimethoxypropane (40 mL) were added. After 22 h, TLC showed the formation of a major product, and consumption of starting material. The reaction solution was neutralised with concentrated aqueous ammonia solution, and the solvent removed. The residue was dissolved in $CHCl_3$ (200 mL) and washed with distilled water (50 mL). The aqueous layer was re-extracted (2 × 50 mL), the organic fractions combined, dried ($MgSO_4$), filtered and the solvent removed. The residue was purified by flash chromatography (1 : 3, ethyl acetate : hexane eluent) to give methyl 2,3-*O*-isopropylidene-α-L-rhamnopyranoside (**3.09**) (11.5 g, 85 %) as a pale yellow oil: $[\alpha]_D^{25.0}$ – 12.0 (c = 1.00, H_2O) (Lit.,[107] $[\alpha]_D^{23}$ –10.65 (c = 1.88, H_2O); δ_H ($CDCl_3$, 500 MHz, gCOSY) 1.30 (d, 3H, H-6, H-6`, H-6``, $J_{5,6}$ 6.4 Hz), 1.35, 1.52 (2 × s, 2 × 3H, $(CH_3)_2C$), 2.34 (s br, 1H, OH), 3.38 (m, 1H, H-4), 3.38 (s, 3H, OCH_3), 3.63 (1H, dq, H-5, $J_{4,5}$ 0.7 Hz, $J_{5,6}$ 6.4 Hz), 4.06 (dd, 1H, H-3, $J_{2,3}$ 5.8 Hz, $J_{3,4}$ 7.1 Hz), 4.12 (d, 1H, H-2, $J_{2,3}$ 5.8 Hz), 4.84 (s, 1H, H-1); δ_C ($CDCl_3$, 100.6 MHz, DEPT) 17.6 (q, C-6), 26.2, 28.1 (2 × q, $(\underline{C}H_3)_2C$), 55.1 (q, CH_3O), 65.9, 74.6, 75.9, 78.5 (4 × d, C-2, C-3, C-4, C-5), 98.3 (d, C-1), 109.6 (s, $(CH_3)_2\underline{C}$).

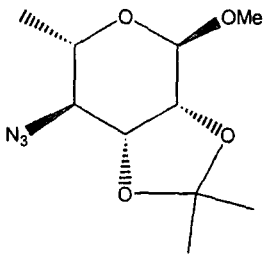
*Methyl 6-deoxy-2,3-O-isopropylidene-α-L-talopyranoside (**3.10**) (Ref.109):*



Methyl 2,3-*O*-isopropylidene-α-L-rhamnopyranoside (**3.09**) (1.0 eq., 52.7 mmol, 11.5 g), dried powdered molecular sieve (50.0 g) and pyridinium chlorochromate (3.7 eq., 195 mmol, 42.0 g) were stirred in dry DCM (500 mL) under nitrogen at room temperature for 20 h. At this point TLC showed complete conversion of starting material to a single product. The reaction mixture was triturated with diethyl ether (500 mL), and filtered through a silica plug topped with celite (diethyl ether eluent). The solvent was then removed to leave crude methyl 2,3-*O*-isopropylidene-α-L-rhamnopyran-4-uloside (**3.21**) (10.3 g): $[\alpha]_D^{25.9}$ – 110 (c = 1.00, $CHCl_3$) (lit.[108] $[\alpha]_D^{20}$

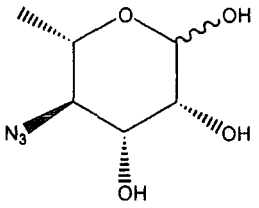
– 107 (c = 3.5, EtOH)); *m/z* 271.1 (ES, MeOH, $[M+MeOH+Na]^+$, 100 %), 239.1 ($[M+Na]^+$, 23 %); ν_{max} (film)/cm^{-1}: 1742 (C=O stretch), 2836, 2912, 2939, 2989 (aliphatic C-H stretch); δ_H ($CDCl_3$, 400 MHz, gCOSY, gHSQC) 1.36, 1.48 (2 × s, 2 × 3H, $(CH_3)_2C$), 1.40 (d, 3H, H-6, H-6`, H-6``, $J_{5,6}$ 6.8 Hz), 3.45 (s, 3H, CH_3O), 4.24 (q, 1H, H-5, $J_{5,6}$ 6.8 Hz), 4.42 (m, 2H, H-2, H-3), 4.84 (s, 1H, H-1); δ_C ($CDCl_3$, 100.6 MHz, DEPT) 16.0 (q, C-6), 25.6, 26.9 (2 × q, $(\underline{C}H_3)_2C$), 56.0 (q, CH_3O), 69.9, 76.0, 78.8 (3 × d, C-2, C-3, C-4), 98.3 (d, C-1), 111.6 (s, $(CH_3)_2\underline{C}$), 204.8 (s, C-4). (**3.21**) was immediately dissolved in ethanol : water (9 : 1, 600 mL) and cooled to 0 °C. Sodium borohydride (2.0 eq., 0.11 mmol, 4.0 g) was added and the solution stirred at 0 °C until TLC indicated the complete consumption of starting material, and formation of a single product. The reaction was quenched after 2 h by careful addition of solid ammonium chloride with stirring until effervescence ceased. The solvent was removed and the residue dissolved in $CHCl_3$ (350 mL), washed with distilled water (2 × 100 mL), brine (satd., 100 mL), then the organic layer dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to yield methyl 6-deoxy-2,3-*O*-isopropylidene-α-L-talopyranoside (**3.10**) (8.65 g, 75 % over two steps) as a pale yellow oil: $[\alpha]_D^{26.0}$ – 37.6 (*c* = 2.00, $CHCl_3$) (lit.[109] $[\alpha]_D^{20}$ – 38.3 (*c* = 2.73, $CHCl_3$); ν_{max} (film)/cm^{-1}: 2833, 2936, 2984 (aliphatic C-H stretch) 3547 (br, O-H stretch); δ_H ($CDCl_3$, 400 MHz, gCOSY) 1.31 (d, 3H, H-6, $J_{5,6}$ 6.7 Hz), 1.35, 1.56 (2 × s, 2 × 3H, $(CH_3)_2C$), 2.32 (s, br, 1H, OH), 3.38 (s, 3H, CH_3O), 3.53 (d, 1H, H-4, $J_{3,4}$ 4.7 Hz), 3.80 (q, 1H, H-5, $J_{5,6}$ 6.7 Hz), 4.00 (d, 1H, H-2, $J_{2,3}$ 6.4 Hz), 4.18 (dd, 1H, H-3, $J_{3,4}$ 5.2 Hz, $J_{2,3}$ 6.2 Hz,), 4.90 (s, 1H, H-1). δ_C ($CDCl_3$, 100.6 MHz, DEPT) 16.8 (q, C-6), 25.3, 25.9 (2 × s, $(\underline{C}H_3)_2C$), 55.2 (q, CH_3O), 64.4, 66.9, 73.0, 73.3 (4 × d, C-2, C-3, C-4, C-5), 98.5 (d, C-1), 109.3 (s, $(CH_3)_2\underline{C}$).

Methyl 4-azido-4-deoxy-2,3-O-isopropylidene-α-L-rhamnopyranoside (3.11):



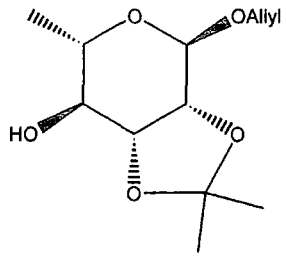
Methyl 6-deoxy-2,3-*O*-isopropylidene-α-L-talopyranoside (**3.10**) (1.0 eq., 39.6 mmol, 8.65 g) was dissolved in dry DCM (300 mL). Pyridine (3.1 eq., 121 mmol, 9.54 g, 9.75 mL) was added and the solution stirred at –20 °C under nitrogen. Trifluoromethanesulfonic anhydride (1.42 eq., 56.0 mmol, 15.8 g, 9.43 mL) was added slowly. After 7 h TLC indicated complete conversion of starting material into product. The reaction mixture was diluted with DCM (1 L), washed with dilute hydrochloric acid (3 M, 100 mL), saturated aqueous sodium bicarbonate (200 mL), brine (satd., 200 mL), then the organic layer dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. The residue was immediately dissolved in dry DMF (300 mL) and sodium azide added (1.8 eq., 71.1 mmol, 4.62 g). The reaction mixture was stirred vigorously under nitrogen at room temperature for 26 h. At the end of this time TLC indicated the complete consumption of starting material. The solvent was removed and the residue dissolved in DCM (500 mL). The DCM solution was washed consecutively with distilled water (100 mL), brine (satd., 200 mL) and dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. The residue was purified by flash chromatography (1 : 19, ethyl acetate : hexane eluent) to yield methyl 4-azido-4-deoxy-2,3-*O*-isopropylidene-α-L-rhamnopyranoside (**3.11**) (5.59 g, 58 % over 2 steps) as a colourless oil: $[\alpha]_D^{25.0}$ – 8.9 (c = 1.0, $CHCl_3$); δ_H ($CDCl_3$, 500 MHz, gCOSY, gHSQC) 1.24 (d, 3H, H-6, H-6`, H-6``, $J_{5,6}$ 6.2 Hz), 1.31, 1.50 (2 × s, 2 × 3H, $(CH_3)_2C$), 3.12 (dd, 1H, H-4, $J_{3,4}$ 8.2 Hz, $J_{4,5}$ 10.3 Hz), 3.31 (s, 3H, CH_3O), 3.47 (dq, 1H, H-5, $J_{5,6}$ 6.2 Hz, $J_{4,5}$ 10.3 Hz), 4.03 (d, 1H, H-2, $J_{2,3}$ 5.5 Hz), 4.09 (dd, 1H, H-3, $J_{2,3}$ 5.5 Hz, $J_{3,4}$ 8.2 Hz), 4.83 (s, 1H, H-1); δ_C ($CDCl_3$, 125.7 MHz, DEPT, gHSQC) 18.0 (q, C-6), 26.2, 28.2 (2 × q, $(\underline{C}H_3)_2C$), 54.9 (d, CH_3O), 64.2 (d, C-5), 66.7 (d, C-4), 75.0 (d, C-2), 76.6 (d, C-3), 98.0 (d, H-1), 109.8 (s, $(CH_3)_2\underline{C}$).

*4-Azido-4-deoxy-α,β-L-rhamnopyranose (**3.08**) (Ref. 99):*



Methyl 4-azido-4-deoxy-2,3-*O*-isopropylidene-α-L-rhamnopyranoside (**3.11**) (1.0 eq., 4.93 mmol, 1.20 g) was dissolved in 1,4-dioxane (12 mL), and aqueous trifluoroacetic acid (50 mL, 1 : 1 v/v) slowly added. The resulting solution was degassed by purging with nitrogen gas for 5 minutes. The mixture was stirred under nitrogen at 80 °C for 48 h, after which time TLC showed complete consumption of the starting material. The reaction mixture was cooled and the solvent removed *in vacuo*. The residue was purified by flash chromatography (1 : 1, ethyl acetate : hexane eluent) to give 4-azido-4-deoxy-α,β-L-rhamnopyranose (**3.08**) (780 mg, 84 %) as a white crystalline solid: m.p. 119-120 °C (ethyl acetate/hexane); $[\alpha]_D^{26.0}$ – 52.2 (equlibrium) (c = 1.00, H_2O) (lit.[99] $[\alpha]_D^{26.0}$ – 57.6 (equlibrium)(c = 1.07 in MeOH); ν_{max} (film)/cm^{-1}: 2119 (azide stretch), 2920, 2979 (aliphatic C-H stretch), 3431 (br, O-H stretch); *m/z* 212.4 (ES, MeOH, $[M+Na]^+$, 100 %); δ_H (D-6 DMSO, 500 MHz, gCOSY, gHSQC, ` denotes minor anomer) 1.17 (d, 2.1H, H-6, H-6', H-6'', $J_{5,6}$ 6.3 Hz), 1.19 (d, 0.9 H, H-6`, H-6``, H-6```, $J_{5`,6`}$ 6.0 Hz), 3.13 (dq, 0.3H, H-5`, $J_{5`,6`}$ 6.0 Hz, $J_{4`,5`}$ 10.1 Hz), 3.17-3.21 (m, 0.6H, H-2`, H-4`), 3.25 (t, 0.7H, H-4, $J_{3,4}$ 10.0 Hz, $J_{4,5}$ 10.0 Hz), 3.52 (H-3`, obscured by solvent signal), 3.55-3.61 (m, 1.4H, H-2, H-5), 3.68 (ddd, 0.7H, H-3, J_{HH} 3.2 Hz, J_{HH} 6.8 Hz, $J_{3,4}$ 10.0 Hz), 4.55 (d, 0.3H, H-1`, $J_{1,2}$ 8.0 Hz), 4.80 (0.3H, d, OH`, $J_{H`H`}$ 4.9 Hz), 4.85 (d, 0.7H, H-1, $J_{1,2}$ 3.5 Hz), 4.96 (d, 0.7H, OH, J_{HH} 4.4 Hz), 5.18 (d, 0.7H, OH, J_{HH} 7.1 Hz), 5.23 (d, 0.3H, OH`, $J_{H`H`}$ 7.3 Hz), 6.32 (d, 0.3H, OH`, $J_{H`H`}$ 7.8 Hz), 6.43 (d, 0.7H, OH, J_{HH} 4.2 Hz); δ_C (DMSO, 125.7 MHz, DEPT, gHSQC, ` denotes minor anomer) 19.56 (q, C-6`), 19.62 (q, C-6), 66.0, 72.3, 73.6 (3 × d, C-2`, C-3`, C-4`), 66.6, 66.7, 71.9 (3 × d, C-2, C-4, C-5), 70.4 (d, C-3), 70.5 (d, C-5`), 95.0 (d, C-1`), 95.1 (d, C-1).

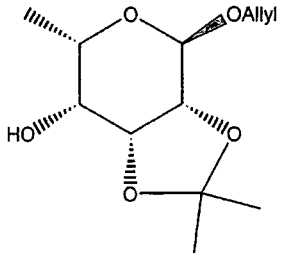
Allyl 2,3-O-isopropylidene-α-L-rhamnopyranoside (3.12) (Ref. 110):



L-Rhamnose monohydrate (**3.07**) (1.0 eq., 0.274 mol, 50.0 g), and allyl alcohol (400 mL) were stirred under nitrogen and H_2SO_4 added (4.0 mL, 98 %). The mixture was heated to reflux for 3 h, after which time TLC showed consumption of starting material. The reaction was cooled, and neutralised by addition of K_2CO_3 (0.77 eq., 0.210 mol, 29 g) with stirring. The mixture was concentrated *in vacuo* and the residue co-evaporated with toluene (2 × 100 mL). The residue was diluted with ethyl acetate and then dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resultant crude allyl α-L-rhamnopyranoside was dissolved in dry acetone (300 mL), and 2,2-dimethoxypropane (2.96 eq., 0.81 mol, 84.7 g, 100 mL) and H_2SO_4 (4.0 mL, 98 %) were added. TLC showed complete consumption of starting material after 2 h, and the reaction was adjusted to pH ~7 by portion-wise addition of NH_3 (aq., satd.). The resultant mixture was concentrated, and the residue dissolved in DCM (750 mL) then washed with water (3 × 500 mL). Aqueous washings were extracted with DCM (200 mL), and all organic washings combined and dried ($MgSO_4$), filtered and concentrated to give an orange oil. The oil was purified by flash chromatography through a silica plug (3 : 7, ethyl acetate : hexane eluent) to give allyl 2,3-*O*-isopropylidene-β-L-rhamnopyranoside (3.09 g, 5.1 %), and allyl 2,3-*O*-isopropylidene-α-L-rhamnopyranoside (**3.12**) (52.6 g, 88 %) as a colourless oil. A portion of allyl 2,3-*O*-isopropylidene-α-L-rhamnopyranoside (**3.12**) was purified further by flash chromatography on silica (1 : 3 ethyl acetate : hexane eluent) giving the desired product as a colourless oil: $[\alpha]_D^{25.8}$ - 35.0 (c = 0.50, $CHCl_3$) (lit.[110] $[\alpha]_D^{20}$ - 35.0 (c = 1, $CHCl_3$)); *m/z* 267.1 (ES, MeOH, $[M+Na]^+$, 100 %), 299.1 ($[M+MeOH+Na]^+$, 3 %); ν_{max} (film)/cm^{-1}: 1648 (C=C stretch), 2909, 2936, 2985 (aliphatic C-H stretch), 3470 (br, O-H stretch); δ_H ($CDCl_3$, 400 MHz, gCOSY, gHSQC) 1.26 (d, 3H, H-6, H-6`, H-6``, $J_{5,6}$ 6.3 Hz), 1.32, 1.50 (2 × s, 2 × 3H, $(CH_3)_2C$), 3.13 (s, br, 1H, OH), 3.34 (dd, 1H, H-4, $J_{3,4}$ 7.3 Hz, $J_{4,5}$ 9.3 Hz), 3.66 (dq,

1H, H-5, $J_{5,6}$ 6.3 Hz, $J_{4,5}$ 9.3 Hz), 3.97 (m, 1H, 1 of $OC\underline{H}_2CHCH_2$), 4.07 (dd, 1H, H-3, $J_{2,3}$ 5.7 Hz, $J_{3,4}$ 7.2 Hz), 4.15 (m, 2H, H-2, 1 of $OC\underline{H}_2CHCH_2$), 4.98 (s, 1H, H-1), 5.22 (m, 2H, $OCH_2CHC\underline{H}_2$), 5.87 (m, 1H, $OCH_2C\underline{H}CH_2$); δ_C ($CDCl_3$, 100.6 MHz, DEPT) 17.6 (q, C-6), 26.3, 28.1 (2 × q, $(\underline{C}H_3)_2C$), 66.1, 74.6, 76.0, 78.5 (4 × d, C-2, C-3, C-4, C-5), 68.1 (t, $O\underline{C}H_2CHCH_2$), 96.4 (d, C-1), 109.7 (s, $(CH_3)_2\underline{C}$), 118.0 (t, $OCH_2CH\underline{C}H_2$), 133.7 (d, $OCH_2\underline{C}HCH_2$).

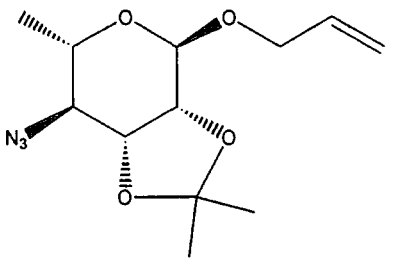
*Allyl 6-deoxy-2,3-O-isopropylidene-α-L-talopyranoside (**3.13**) (Ref. 111):*



A mixture of allyl 2,3-*O*-isopropylidene-α-L-rhamnopyranoside (**3.12**) (1.0 eq., 0.201 mol, 49.02 g) dissolved in dry DCM, sieves (100g, 4Å, powdered) and PCC (2.5 eq., 0.494 mol, 106.5 g), and the mixture stirred under argon. After 18 h, TLC indicated complete consumption of starting material and formation of a new product. The mixture was triturated with diethyl ether (700 mL), and filtered through a silica plug topped with celite (diethyl ether eluent). The resultant solution was concentrated to give crude allyl 2,3-*O*-isopropylidene-α-L-rhamnopyran-4-uloside (**3.22**), a portion of which was purified by flash chromatography on silica (3 : 20, ethyl acetate : hexane eluent) giving the desired product as a colourless oil: $[\alpha]_D^{26.5}$ – 79.1 (c = 1.00, $CHCl_3$) (lit.[111] optical rotation not quoted); *m/z* 297.1 (ES, MeOH, $[M+MeOH+Na]^+$, 100 %), 265.1 ($[M+Na]^+$, 10 %); ν_{max} (film)/cm^{-1}: 1647 (C=C stretch), 1743 (C=O stretch), 2884, 2937, 2988 (aliphatic C-H stretch); δ_H ($CDCl_3$, 400 MHz, gCOSY) 1.37, 1.49 (2 × s, 2 × 3H, $(CH_3)_2C$), 1.39 (d, 3H, H-6, H-6`, H-6``, $J_{5,6}$ 6.8 Hz), 4.08 (m, 1H, 1.37, 1 of $OC\underline{H}_2CHCH_2$), 4.24 (m, 1H, 1 of $OC\underline{H}_2CHCH_2$), 4.28 (q, 1H, H-5, $J_{5,6}$ 6.8 Hz), 4.46 (m, 2H, H-2, H-3), 5.00 (s, 1H, H-1), 5.22-5.34 (m, 2H, $OCH_2CHC\underline{H}_2$), 5.90 (m, 1H, $OCH_2C\underline{H}CH_2$); δ_C ($CDCl_3$, 100.6 MHz, DEPT) 16.0 (q, C-6), 25.6, 26.9 (2 × q, $(\underline{C}H_3)_2C$), 68.9 (t, $O\underline{C}H_2CHCH_2$), 70.2, 76.1, 78.9, (3 × d, C-2, C-3, C-5), 96.1 (d, C-1), 111.6 (s, $(CH_3)_2\underline{C}$), 118.5 (t, $OCH_2CH\underline{C}H_2$), 133.1 (d, $OCH_2\underline{C}HCH_2$), 204.8 (s, C-4); HRMS found 265.1043 ($C_{12}H_{18}O_5Na$ requires

265.1052). The resultant oil was dissolved in ethanol : water (9 : 1), and cooled to 0 °C, before careful, portion-wise addition of sodium borohydride (2.0 eq., 0.399 mol, 15.1 g), with stirring. After 2 h stirring at 0 °C TLC showed consumption of starting material and formation of a new product. The reaction was stopped by careful (exothermic) portion-wise, addition of NH_4Cl (s), until effervescence ceased. The resultant mixture was concentrated and diluted with DCM (1.25 L) and washed with water (2 × 250 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated *in vacuo* to give allyl 2,3-*O*-isopropylidene-α-L-talopyranoside (**3.13**) (45.45 g, 93 % crude yield), a sample of which was purified by flash chromatography on silica (1 : 3, ethyl acetate : hexane eluent): $[\alpha]_D^{25.9}$ -58.1 (c = 2.00, $CHCl_3$); *m/z* 267.1 (ES, MeOH, $[M+Na]^+$, 100 %), 299.1 ($[M+MeOH+Na]^+$, 3 %); ν_{max} (film)/cm^{-1}: 1650 (C=C stretch), 2936, 2985 (aliphatic C-H stretch), 3524 (br, O-H stretch); δ_H ($CDCl_3$, 400 MHz, gCOSY) 1.31 (d, 3H, H-6, H-6`, H-6``, $J_{5,6}$ 6.6 Hz), 1.37, 1.57 (2 × s, 2 × 3H, $(CH_3)_2C$), 2.19 (d, br, 1H, OH, J_{HH} 6.8 Hz), 3.54 (t, 1H, H-4, J_{HH} 5.6 Hz), 3.85 (q, 1H, H-5, $J_{5,6}$ 6.6 Hz), 3.99-4.07 (m, 2H, H-2, 1 of $OC\underline{H}_2CHCH_2$), 4.16-4.23 (m, 2H, H-3, 1 of $OC\underline{H}_2CHCH_2$), 5.07 (s, 1H, H-1), 5.25 (m, 2H, $OCH_2CHC\underline{H}_2$), 5.91 (m, 1H, $OCH_2C\underline{H}CH_2$); δ_C ($CDCl_3$, 100.6 MHz, DEPT) 16.8 (q, C-6), 25.4, 26.0 (2 × q, $(\underline{C}H_3)_2C$), 64.5, 67.0, 73.1, 73.4 (4 × d, C-2, C-3, C-4, C-5), 96.8 (d, C-1), 109.4 (s, $(CH_3)_2\underline{C}$), 117.9 (t, $OCH_2CH\underline{C}H_2$), 133.8 (d, $OCH_2\underline{C}HCH_2$); HRMS found 267.1229 ($C_{12}H_{20}O_5Na$ requires 267.1232).

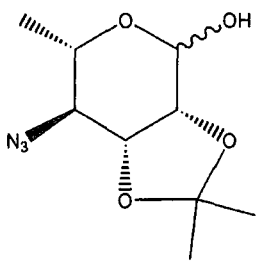
*Allyl 4-azido-4-deoxy-2,3-O-isopropylidene-α-L-talopyranoside (**3.14**):*



Allyl 6-deoxy-2,3-*O*-isopropylidene-α-L-talopyranoside (1.0 eq., 0.186 mol, 45.35 g) was dissolved in dry DCM (1.0 L) and dry pyridine added (3.17 eq., 0.589 mol, 46.6 g, 47.6 mL). The mixture was stirred under argon at −18 °C. Trifluoromethanesulfonic anhydride (1.41 eq., 0.262 mmol, 73.8 g, 44.0 mL) was added slowly, and the mixture stirred until TLC showed complete consumption of

starting material. After 150 minutes the mixture was diluted with DCM (500 mL) and washed with HCl (aq, 0.5 M, 2 × 200 mL) then $NaHCO_3$ (aq, satd, 400 mL), then brine (satd., 400 mL), and dried (Na_2SO_4), filtered, and evaporated. The crude oil was dissolved in dry DMF (1 L), and and sodium azide added (2.0 eq., 0.372 mol, 24.2 g). The mixture was stirred under argon. After 18.5 h TLC showed consumption of starting material, and the mixture was concentrated and the residue dissolved in DCM (1.25 L) and washed with water (2 × 400 mL), then brine (satd., 200 mL), and the organic layer dried (Na_2SO_4), filtered, and concentrated to give an orange oil, which was purified by flash chromatography (1 : 49 ethyl acetate : hexane to 1 : 20 ethyl acetate : hexane eluent) to give allyl 4-azido-4-deoxy-2,3-*O*-isopropylidene-α-L-talopyranoside (**3.14**) as a colourless oil (16.9 g, 37 %); $[\alpha]_D^{24.0}$ – 28.4 (c = 1.00, $CHCl_3$); *m/z* 292.3 (ES, MeOH, $[M+Na]^+$, 100 %); ν_{max} (film)/cm^{-1}: 1647 (C=C stretch), 2933, 2986 (aliphatic C-H stretch); δ_H ($CDCl_3$, 400 MHz, gCOSY) 1.39 (d, 3H, H-6, H-6`, H-6``, $J_{5,6}$ 6.3 Hz), 1.36, 1.56 (2 × s, 2 × 3H, $(CH_3)_2C$), 3.17 (dd, 1H, H-4, $J_{3,4}$ 7.9 Hz, $J_{4,5}$ 10.4 Hz), 3.58 (dq, 1H, H-5, $J_{5,6}$ 6.3 Hz), 3.98 (m, 1H 1 × $OC\underline{H}_2CHCH_2$),4.09-4.19 (m, 2H, H-2, H-3), 4.32 (m, 1H, 1 of $OC\underline{H}_2CHCH_2$), 5.04 (s, 1H, H-1) 5.18-5.37 (m, 2H, $OCH_2CHC\underline{H}_2$), 5.89 (m, 1H, $OCH_2C\underline{H}CH_2$); δ_C ($CDCl_3$, 100.6 MHz, DEPT) 18.1 (q, C-6), 26.4, 28.3 (2 × q, $(\underline{C}H_3)_2C$), 64.6, 66.9, 75.2, 76.7 (4 × d, C-2, C-3, C-4, C-5), 68.3 (t, $O\underline{C}H_2CHCH_2$), 96.2 (d, C-1), 110.0 (s, $(CH_3)_2\underline{C}$), 118.1 (t, $OCH_2CH\underline{C}H_2$), 133.6 (d, $OCH_2\underline{C}HCH_2$).

*4-Azido-4-deoxy-2,3-O-isopropylidene-α,β-L-rhamnopyranose (**3.01**):*



Method 1

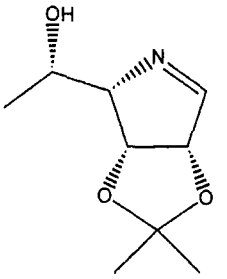
4-Azido-4-deoxy-α,β-L-rhamnopyranose (**3.08**) (1.0 eq., 4.23 mmol, 800 mg), powdered molecular sieves (1.78 g), anhydrous copper (II) sulfate (2.4 eq., 10.2 mmol, 1.62 g) and H_2SO_4 (0.2 mL, 98 %) were stirred in dry acetone (80 mL) under

nitrogen at room temperature. After 40 h TLC indicated complete consumption of starting material. The reaction mixture was neutralised with concentrated aqueous ammonia solution and silica (5 g) added. The resultant mixture was evaporated to dryness *in vacuo*. The resultant powder was deposited on a silica column and eluted with 1 : 3, ethyl acetate : hexane to give 4-azido-4-deoxy-2,3-*O*-isopropylidene-α,β-L-rhamnopyranose (**3.01**) (911.1 mg, 94 %) as a white crystalline solid.

Method 2:

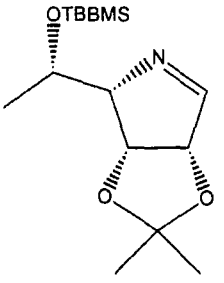
Allyl 4-azido-4-deoxy-2,3-*O*-isopropylidene-α-L-talopyranoside (**3.14**) (1.0 eq., 0.438 mmol, 118 mg) was dissolved in dry THF (2 mL) under nitrogen and heated to reflux. In a separate vessel Wilkinson's catalyst (0.1 eq., 0.044 mmol, 41 mg) was dissolved in dry THF (1 mL) under nitrogen and *n*-butyllithium (0.2 eq., 0.090 mmol, 56 μL, 1.6 M solution in hexanes) added. The mixture was stirred for 15 minutes befre addition to the solution of (**3.14**) at reflux. The mixture was heated at reflux for 3 h, after which time TLC indicated complete consumption of starting material. The reaction was concentrated *in vacuo* then the residue dissolved in THF (3.0 mL) and iodine (1.2 eq, 133 mg) added followed by water (0.2 mL). The mixture was stirred for 2 h after which time TLC indicated complete consumption of starting material. The reaction was stopped by dilution with water (20 mL), and the aqueous layer extracted with DCM (2 × 30 mL). The organic extracts were dried ($MgSO_4$) filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (1 : 3, ethyl acetate : hexane eluent) giving 4-azido-4-deoxy-2,3-*O*-isopropylidene-α,β-L-rhamnopyranose (**3.01**) (76 mg, 76 %) as a white crystalline solid: $[\alpha]_D^{24.1}$ (eq.) + 14.0 (c = 2.00, $CHCl_3$); *m/z* 252.4 (ES, MeOH, $[M+Na]^+$, 100 %), 284.4 ($[M+MeOH+Na]^+$, 83 %); ν_{max} (film)/cm^{-1}: 2112 (azide stretch), 2936, 2987 (aliphatic C-H stretch), 3450 (br, O-H stretch); δ_H ($CDCl_3$, 400MHz, gCOSY) 1.29 (d, 3H, H-6, H-6`, H-6``, $J_{5,6}$ 6.3Hz), 1.38, 1.56 (2 × s, 2 × 3H, $(CH_3)_2C$), 2.75 (s, br, 1H, OH), 3.18 (dd, 1H, H-4, $J_{3,4}$ 8.2 Hz, $J_{4,5}$ 10.3 Hz), 3.80 (dq, 1H, H-5, $J_{5,6}$ 6.3 Hz, $J_{4,5}$ 10.3 Hz), 4.14 (d, 1H, H-2, $J_{2,3}$ 5.5 Hz), 4.21 (dd, 1H, H-3, $J_{2,3}$ 5.5 Hz, $J_{3,4}$ 8.2 Hz), 5.42 (s, 1H, H-1); δ_C ($CDCl_3$, 100.6 MHz, DEPT, `denotes minor anomer) 18.2 (q, C-6), 18.6 (q, C-6`), 26.4, 28.3 (2 × q, $(\underline{C}H_3)_2C$), 26.5, 28.2 (2 × q, $(\underline{C}`H_3)_2C`$), 64.7, 66.8, 75.1, 76.8 (4 × d, C-2, C-3, C-4, C-5), 66.5, 70.1, 74.4, 78.3 (4 × d, C-2`, C-3`, C-4`, C-5`), 92.0 (d, C-1), 92.8 (d, C-1`), 110.1 (s, $(CH_3)_2\underline{C}$), 111.0 (s, $(C`H_3)_2\underline{C}`$).

*1,N-Dehydro-1,4-dideoxy-1,4-imino-2,3-O-isopropylidene-L-rhamnitol (**3.02**):*



4-Azido-4-deoxy-2,3-*O*-isopropylidene-α,β-L-rhamnopyranose (1.0 eq., 0.870 mmol, 200 mg) was stirred in dry DCM (2 mL) under nitrogen. Triphenylphosophine (1.1 eq., 0.954 mmol, 250 mg) was added and the reaction followed by TLC. After 20 h the reaction mixture was concentrated and purified by flash column chromatography (ethyl acetate eluent) to give 1,*N*-dehydro-1,4-dideoxy-1,4-imino-2,3-*O*-isopropylidene-L-rhamnitol (**3.02**) (154 mg, 96 %), as a white crystalline solid: mp 98-100 °C (ethyl acetate/hexane): $[\alpha]_D^{24.0}$ – 6.3 (c = 1.00, $CHCl_3$); *m/z* 186.1 (CI+, $[M+H]^+$, 60 %, NH_3), 94 (48 %), 76 (69 %), 68 (100 %); ν_{max} (KBr disc)/cm^{-1}: 1622 cm^{-1} (C=N stretch), 2873, 2901, 2932, 2959, 2987 (aliphatic C–H stretch), 3249 cm^{-1} (br, O–H stretch); δ_H ($CDCl_3$, 300 MHz) 1.48 (d, 3H, H-6, H-6`, H-6``, $J_{5,6}$ 6.3 Hz) 1.53, 1.36 (2 × s, 2 × 3H, $(CH_3)_2C$), 2.6 (s, br, 1H, OH), 3.75 (ddd, 1H, H-4, $J_{1,4}$ 3.1 Hz, $J_{3,4}$ 4.5 Hz, $J_{4,5}$ 8.2 Hz), 4.00 (dq, 1H, H-5, $J_{5,6}$ 6.4 Hz, $J_{4,5}$ 8.1 Hz), 4.83 (dd, 1H, H-3, $J_{3,4}$ 4.8 Hz, $J_{2,3}$ 5.7 Hz), 5.07 (d, 1H, H-2, $J_{2,3}$ 5.7 Hz), 7.60 (d, 1H, H-1, $J_{1,4}$ 3.1 Hz); δ_C ($CDCl_3$, 75.4 MHz) 21.0 (C-6), 25.7, 26.8 ($(\underline{C}H_3)_2C$), 67.8, 76.7, 80.1, 87.0 (C-2, C-3, C-4, C-5), 112.5 ($(CH_3)_2\underline{C}$), 165.5 (C-1); HRMS found 186.1125 ($C_9H_{16}NO_3$ requires 186.1130).

*5-O-tert-Butyldimethylsilyl-1,N-dehydro-1,4-dideoxy-1,4-imino-2,3-O-isopropylidene-L-rhamnitol (**3.03**):*



Method 1

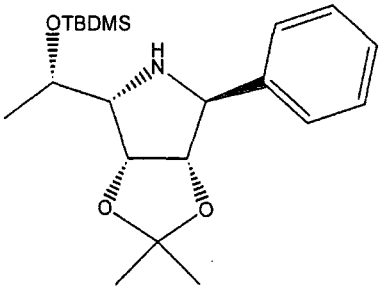
1,*N*-Dehydro-1,4-dideoxy-1,4-imino-2,3-*O*-isopropylidene-L-rhamnitol (**3.02**) (1.0 eq., 2.66 mmol, 493 mg) was dissolved in dry DCM (10 mL) in a dry round-bottomed flask under nitrogen. Dry pyridine (3.2 eq., 8.40 mmol, 665 mg, 0.650 mL), then *tert*-butyldimethylsilyl trifluoromethanesulfonate (1.5 eq., 4.02 mmol, 1.06 g, 0.923 mL) were added with stirring. After 10 h the mixture was diluted with DCM (30 mL), and the mixture washed with H_2O (2 × 10 mL). The aqueous layers were combined and extracted with a further portion of DCM (10 mL). The organic extracts were combined and dried ($MgSO_4$), filtered, then the solvent removed *in vacuo*. The resultant oil was purified by flash column chromatography (15 : 85, ethyl acetate : hexane eluent) giving 5-*O*-*tert*-butyldimethylsilyl-1,*N*-dehydro-1,4-dideoxy-1,4-imino-2,3-*O*-isopropylidene-L-rhamnitol (**3.03**) as a colourless oil (0.669 g, 84 %).

Method 2

1,*N*-Dehydro-1,4-dideoxy-1,4-imino-2,3-*O*-isopropylidene-L-rhamnitol (**3.02**) (1.0 eq., 0.950 mmol, 176 mg) was dissolved in dry DCM (5 mL) in a dry round-bottomed flask under nitrogen. Imidazole (2.2 eq, 142 mg, 2.09 mmol) was added, followed by *tert*-butylchlorodimethylsilane (1.5 eq, 1.43 mmol, 215 mg). The mixture was stirred for 15 h when TLC indicated complete consumption of starting material and formation of a new product. The reaction was diluted with DCM (50 mL), and the resultant solution washed with HCl (0.3 M, 2 × 40 mL), then brine (1 × 30 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated, and the residue purified by flash chromatography on silica (15 : 85, ethyl acetate : hexane eluant). The desired product 5-*O*-*tert*-butyldimethylsilyl-1,*N*-dehydro-1,4-dideoxy-1,4-imino-2,3-*O*-isopropylidene-L-rhamnitol (**3.03**) was obtained as a colourless oil (225 mg, 79 %): $[\alpha]_D^{21.0}$ + 12.9 (c = 1.0, $CHCl_3$); *m/z* 354.5 (ES, $[M+MeOH+Na]^+$, 100 %, MeOH), 332.5 ($[M+MeOH+H]^+$, 82 %), 300.5 ($[M+H]^+$, 10 %); ν_{max} (film)/cm^{-1}: 1620 (C=N

stretch), 2857, 2930, 2956, 2985 cm^{-1} (aliphatic C-H stretch); δ_H ($CDCl_3$, 500 MHz, gCOSY, gHSQC) 0.08, 0.07 (2 × s, 6H, $(CH_3)_2Si$), 0.896 (s, 9H, $(CH_3)_3CSi$), 1.34, 1.32 (2 × s, 2 × 3H, $(CH_3)_2C$), 1.45 (d, 3H, H-6, H-6`, H-6`` $J_{5,6}$ 6.1 Hz), 3.63 (ddd, 1H, H-4, $J_{1,4}$ 3.5 Hz), 3.98 (dq, 1H, H-5, $J_{4,5}$ 9.4 Hz, $J_{5,6}$ 6.1 Hz), 4.70 (dd, 1H, H-3, $J_{2,3}$ 4.9 Hz, $J_{3,4}$ 4.1 Hz), 5.0 (d, 1H, H-2, $J_{2,3}$ 5.0 Hz), 7.55 (d, H-1, $J_{1,4}$ 3.0 Hz); δ_C ($CDCl_3$, 125.7 MHz, DEPT, gHSQC) -4.3, -5.1 (2 × q, 2 × $(\underline{C}H_3)_2Si$), 18.0 (s, $(CH_3)_3\underline{C}Si$), 22.5 (q, C-6), 25.8 (s, $(\underline{C}H_3)_3CSi$), 27.1, 25.7 (2 × q, $(\underline{C}H_3)_2C$), 66.9 (d, C-5), 77.3 (d, C-3), 81.1 (d, C-4), 86.7 (d, C-2), 111.5 (s, $(CH_3)_2\underline{C}$), 166.6 (d, C-1); HRMS found 300.1990 ($C_{15}H_{29}NO_3SiH$ requires 300.1995).

*(1S)-5-O-tert-Butyldimethylsilyl-1,4-dideoxy-1,4-imino-2,3-O-isopropylidene-1-C-phenyl-L-rhamnitol (**3.16**):*



Method 1

5-*O*-*tert*-Butyldimethylsilyl-1,*N*-dehydro-1,4-dideoxy-1,4-imino-2,3-*O*-isopropylidene-L-rhamnitol (**3.02**) (1.0 eq., 0.184 mmol, 50.0 mg) was dissolved in dry diethyl ether (2.0 mL). Phenyl magnesium bromide (1.0 eq., 0.184 mmol, 0.184 mL, 1 M solution in diethyl ether) was added and the reaction mixture stirred under nitrogen for 3.5 h. The reaction was quenched with H_2O after 3.5 h, then the mixture diluted with diethyl ether (20 mL), and washed with H_2O (2 × 20 mL). The organic layer was isolated, dried (Na_2SO_4), filtered, and the solvent removed. The residue was purified by flash column chromatography (1 : 4, ethyl acetate : hexane eluent) to give recovered starting material (23 mg, 37 %), and (1*S*)-5-*O*-*tert*-butyldimethylsilyl-1,4-dideoxy-1,4-imino-2,3-*O*-isopropylidene-1-*C*-phenyl-L-rhamnitol (**3.16**) as a colourless oil (37 mg, 60 %).

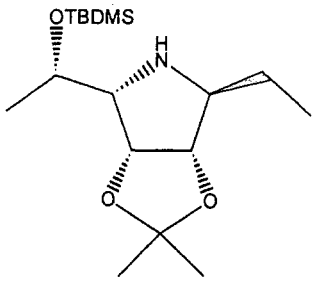
Method 2

5-*O*-*tert*-Butyldimethylsilyl-1,*N*-dehydro-1,4-dideoxy-1,4-imino-2,3-*O*-isopropylidene-L-rhamnitol (**3.03**) (1.0 eq., 0.0668 mmol, 20.0 mg) was dissolved in

dry diethyl ether (1.6 mL) and added to a stirred solution of phenyl magnesium bromide (15.0 eq., 0.334 mmol, 0.334 mL, 3.0 M solution in diethyl ether), and the reaction mixture stirred under nitrogen. After 1.5 h TLC indicated that the reaction was incomplete, so mixture was stirred for a further 24.5 h before quenching by careful addition of water (1 mL). The mixture was diluted with diethyl ether (30 mL), and washed with water (1 × 20 mL), then brine (satd., 1× 20 mL). The organic phase was dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The resultant colourless oil was purified by flash chromatography (1 : 9 ethyl acetate : hexane eluent), to give 1*S*)-5-*O*-*tert*-butyldimethylsilyl-1,4-dideoxy-1,4-imino-2,3-*O*-isopropylidene-1-*C*-phenyl-L-rhamnitol (**3.16**) as a colourless oil (17.3 mg, 69 %).

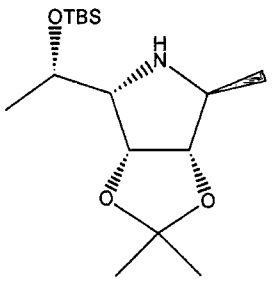
$[\alpha]_D^{19.0}$ + 12.3 (c = 1.00, $CHCl_3$); *m/z* 378 (ES, $[M+H]^+$, 100%, MeOH); ν_{max} (film)/cm^{-1}: 2856, 2930 (aliphatic C–H stretch), 3026, 3062, 3090 (aromatic C–H stretch), 3300 (br, N–H stretch); δ_H ($CDCl_3$, 500 MHz, gCOSY, gHSQC, nOoesy) 0.085, 0.087 (2 × s, 2 × 3H, $(CH_3)_2Si$), 0.88 (s, 9H, $(CH_3)_3CSi$), 1.33, 1.55 (2 × s, 2 × 3H, $(CH_3)_2C$), 1.35 (d, 3H, H-6, H-6`, H-6``, $J_{5,6}$ 6.4 Hz), 2.92 (dd, 1H, H-4, $J_{3,4}$ 3.9 Hz, $J_{4,5}$ 8.6 Hz), 4.02 (dq, 1H, H-5, $J_{5,6}$ 6.4 Hz, $J_{4,5}$ 8.6 Hz), 4.34 (s, 1H, H-1), 4.65 (dd, 1H, H-3, $J_{3,4}$ 3.9 Hz, $J_{2,3}$ 5.4 Hz), 4.82 (d, 1H, H-2, $J_{2,3}$ 5.5 Hz), 7.20 (t, 1H, aromatic CH, J_{HH} 7.3 Hz), 7.33 (t, 2H, aromatic CH, J_{HH} 7.9 Hz), 7.40 (pd, 2H, aromatic CH, J_{HH} 7.6 Hz); δ_C ($CDCl_3$, 125 MHz, DEPT, gHSQC) -5.10, -4.39 (2 × q, $(CH_3)_2Si$), 18.1 (s, $(CH_3)_3\underline{C}Si$), 22.6 (q, C-6), 24.0, 26.2 (2 × q, $(\underline{C}H_3)_2C$) , 25.8 (q, $(\underline{C}H_3)_3CSi$), 67.12 (d, C-1), 67.17 (d C-5), 68.4 (d, C-4), 81.5 (d, C-3), 88.4 (d, C-2), 110.6 (s, $(CH_3)_2C$), 126.6, 126.7, 128.4 (3 × d, 3 × aromatic CH), 140.2 (s, quarternary aromatic); HRMS found 378.2458 ($C_{21}H_{35}NO_3SiH$ requires 378.2464).

(1S)-5-O-tert-Butyldimethylsilyl-1,4-dideoxy-1-C-ethyl-1,4-imino-2,3-O-isopropylidene-L-rhamnitol (3.17):



5-*O*-*tert*-Butyldimethylsilyl-1,*N*-dehydro-1,4-dideoxy-1,4-imino-2,3-*O*-isopropylidene-L-rhamnitol (**3.03**) (1.0 eq., 0.0668 mmol, 20.0 mg) was dissolved in dry diethyl ether (1.6 mL) and added to a stirred solution of ethyl magnesium bromide (15.0 eq., 0.334 mmol, 0.334 mL, 3.0 M solution in diethyl ether) and the reaction mixture stirred under nitrogen. After 1.5 h TLC indicated complete consumption of starting material, and the reaction was stopped by careful addition of water (1 mL). The mixture was diluted with diethyl ether (30 mL), and washed with water (20 mL), then brine (satd., 20 mL). The organic phase was dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The resultant colourless oil was purified by flash chromatography (3 : 7, ethyl acetate : hexane eluent), to give (1*S*)-5-*O*-*tert*-butyldimethylsilyl-1,4-dideoxy-1-*C*-ethyl-1,4-imino-2,3-*O*-isopropylidene-L-rhamnitol (**3.17**) (21.9 mg, 100 %) as a colourless oil: $[\alpha]_D^{24.6}$ + 33.0 (c = 1.00, $CHCl_3$); *m/z* 330.2 (ES, $[M+H]^+$, 100%, MeOH); ν_{max} (film)/cm^{-1}: 2857, 2931, 2958 (aliphatic C–H stretch); δ_H ($CDCl_3$, 500 MHz, gCOSY, gHSQC, nOesy) 0.07 (s, 6H, $(CH_3)_2Si$), 0.88 (s, 9H, $(CH_3)_3CSi$), 0.94 (t, 3H, $CH_2C\underline{H}_3$), 1.24 (d, 3H, H-6, H-6`, H-6``, $J_{5,6}$ 6.2 Hz), 1.28, 1.44 (2 × s, 2 × 3H, $(CH_3)_2C$), 1.30-1.36 (m, 2H, $C\underline{H}_2CH_3$), 1.97 (s, br, 1H, NH), 2.79 (dd, 1H, H-4, $J_{3,4}$ 3.8 Hz, $J_{4,5}$ 8.6 Hz), 2.96 (t, 1H, H-1, J_{HH} 7.9 Hz), 3.92 (dq, 1H, H-5, $J_{5,6}$ 6.2 Hz, $J_{4,5}$ 8.6 Hz), 4.36 (d, 1H, H-2, $J_{2,3}$ 5.5 Hz), 4.60 (dd, 1H, H-3, $J_{3,4}$ 3.8 Hz, $J_{2,3}$ 5.5 Hz); δ_C ($CDCl_3$, 125 MHz, DEPT, gHSQC) -4.90, -4.27 (2 × q, $(CH_3)_2Si$), 11.3 (q, $CH_2\underline{C}H_3$), 18.2 (s, $(CH_3)_3\underline{C}Si$), 22.8 (q, C-6), 24.1, 26.3 (2 × q, $(\underline{C}H_3)_2C$), 24.8 (t, $\underline{C}H_2CH_3$), 26.0 (q, $(\underline{C}H_3)_3CSi$), 66.1 (d, C-1), 67.43, 67.45 (2 × d, C-4, C-5), 81.0 (d, C-3), 85.5 (d, C-2), 110.4 (s, $(CH_3)_2\underline{C}$); HRMS found 330.2457 ($C_{18}H_{35}NO_3SiH$ requires 330.2459).

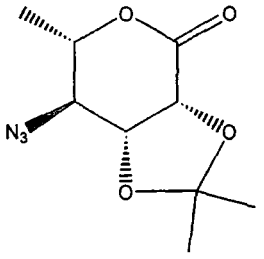
*(1S)-5-O-tert-Butyldimethylsilyl-1,4-dideoxy-1,4-imino-2,3-O-isopropylidene-1-C-methyl-L-rhamnitol (**3.18**):*



5-*O*-*tert*-Butyldimethylsilyl-1,*N*-dehydro-1,4-dideoxy-1,4-imino-2,3-*O*-isopropylidene-L-rhamnitol (**3.03**) (1.0 eq., 0.0668 mmol, 20.0 mg) was dissolved in diethyl ether (1.6 mL) and the resultant solution added to a stirred solution of methyl magnesium bromide (15 eq., 0.999 mol, 0.333 mL, 3 M solution in diethyl ether) under nitrogen. The reaction mixture was stirred for 10 minutes. At the end of this time TLC indicated the complete consumption of starting material and the reaction was cautiously quenched with water (1 mL). The resultant mixture was diluted with diethyl ether (30 mL), and washed with water (2 × 10 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated to give a colourless oil which was purified by flash chromatography on silica (1 : 1, ethyl acetate : hexane eluent). (1*S*)-5-*O*-*tert*-butyldimethylsilyl-1,4-dideoxy-1,4-imino-2,3-*O*-isopropylidene-1-*C*-methyl-L-rhamnitol (**3.18**) was isolated as a colourless oil (14.0 mg, 66 %) together with a mixture of adduct (**3.18**) and a similar compound tentatively assigned as the C-1 epimer (1*R*)-5-*O*-*tert*-butyldimethylsilyl-1,4-dideoxy-1,4-imino-2,3-*O*-isopropylidene-1-*C*-methyl-L-rhamnitol (**2.23**) (4.2 mg of a 7.2 : 1 mixture (NMR)) giving a total conversion to adduct of 86 %, and 69 : 2 overall diastereoselectivity. (**3.18**): $[\alpha]_D^{21}$ + 60.8 (c = 1.0, $CHCl_3$); *m/z* 316.2 (ES, MeOH, $[M+H]^+$, 100 %); ν_{max} (film)/cm^{-1}: 2857, 2931, 2958 (aliphatic C-H stretch); δ_H ($CDCl_3$, 400 MHz, gCOSY, gHSQC, nOesy) 0.07 (s, 6H, $(CH_3)_2Si$), 0.87 (s, 9H, $(CH_3)_3CSi$), 1.04 (d, 3H, C^1CH_3, J_{HH} 7.2 Hz), 1.25 (d, 3H, H-6, H-6`, H-6``, $J_{5,6}$ 6.2 Hz), 1.27, 1.44 (2 × s, 2 × 3H, $(CH_3)_2C$), 1.90 (s, br, 1H, NH), 2.88 (dd, 1H, H-4, $J_{3,4}$ 3.8 Hz, $J_{4,5}$ 8.5 Hz), 3.26 (q, 1H, H-1, J_{HH} 7.2 Hz), 3.93 (dq, 1H, H-5, $J_{5,6}$ 6.2 Hz, $J_{4,5}$ 8.4 Hz), 4.32 (d, 1H, H-2, $J_{2,3}$ 5.5 Hz), 4.62 (dd, 1H, H-3, $J_{3,4}$ 3.8 Hz, $J_{2,3}$ 5.5 Hz); δ_C ($CDCl_3$, 100.6 MHz, DEPT, gHSQC) – 4.9, – 4.3 (2 × q, $(CH_3)_2Si$), 17.9 (q, $C^1\underline{C}H_3$), 18.2 (s, $(CH_3)_3\underline{C}Si$), 22.8 (q, C-6), 24.0, 26.2 (2 × q, $(\underline{C}H_3)_2C$), 26.0 (q, $(\underline{C}H_3)_3CSi$), 59.6 (d, C-1), 67.2 (d, C-5),

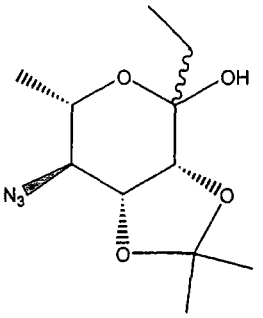
67.3 (d, C-4), 81.2 (d, C-3), 87.1 (d, C-2), 110.3 (s, $(CH_3)_2\underline{C}$); HRMS found 316.2296 ($C_{16}H_{34}NO_3Si$ requires 316.2302).

*4-Azido-4-deoxy-2,3-O-isopropylidene-L-rhamno-1,5-lactone (**3.06**) (Ref. 100):*



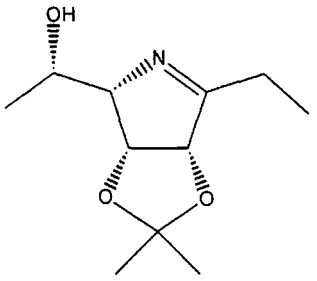
A mixture of 4-azido-4-deoxy-2,3-*O*-isopropylidene-α,β-L-rhamnopyranose (1.0 eq., 0.880 mmol, 200 mg) dissolved in dry DCE (5.0 mL), PCC (2.5 eq., 2.20 mmol, 474 mg), and molecular sieves (300 mg, 4 Å, powdered), was heated to reflux. The reaction was followed by TLC, which showed complete consumption of starting material after 16 h. The reaction was stopped by triturating with diethyl ether (30 mL), and filtered through a celite plug. The resultant brown oil was purified by flash chromatography (15 : 85, ethyl acetate : hexane eluent). 4-Azido-4-deoxy-2,3-*O*-isopropylidene-L-rhamno-1,5-lactone (**3.06**) was isolated as a white crystalline solid (151 mg, 76 %): mp 93-94 °C (ethyl acetate/hexane) (lit.[100] 93-95 °C (ethyl acetate/Hexane); $[\alpha]_D^{23.9}$ –114.7 (c = 1.00, $CHCl_3$) (lit.[100] $[\alpha]_D^{23.0}$ –104.8 (c = 1.27, $CHCl_3$); *m/z* 282.0 (ES, MeOH, $[M+MeOH+Na]^+$, 100 %); ν_{max} (KBr disc)/cm^{-1}: 1759 (s, C=O stretch), 2111 (azide stretch), 2919, 2940, 2985, 3001 (aliphatic C-H stretch); δ_H ($CDCl_3$, 400 MHz, gCOSY, gHSQC) 1.42, 1.52 (2 × s, 2 × 3H, $(CH_3)_2C$), 1.48 (d, 3H, H-6, H-6`, H-6`` $J_{5,6}$ 6.2 Hz), 3.44 (dd, 1H, H-4, $J_{3,4}$ 7.1 Hz, $J_{4,5}$ 10.3 Hz), 4.19 (dq, 1H, H-5, $J_{5,6}$ 6.2 Hz, $J_{4,5}$ 10.1 Hz), 4.50 (dd, 1H, H-3, $J_{3,4}$ 7.1 Hz, $J_{2,3}$ 8.1 Hz), 4.69 (d, 1H, H-2, $J_{2,3}$ 8.2 Hz); δ_C ($CDCl_3$, 100.6 Hz, DEPT, gHSQC) 18.1 (q, C-6), 25.3, 26.8 (2 × q, $(\underline{C}H_3)_2C$), 65.7 (d, C-4), 71.9 (d, C-3), 73.7 (d, C-5), 77.4 (d, C-2), 112.7 (s, $(CH_3)_2\underline{C}$), 168.4 (s, C-1).

*4-Azido-4-deoxy-1-C-ethyl-2,3-O-isopropylidene-α,β-L-rhamnopyranose(**3.19**):*



4-Azido-4-deoxy-2,3-*O*-isopropylidene-L-rhamno-1,5-lactone (**3.06**) (1.0 eq., 0.379 mmol, 86.0 mg) was dissolved in dry diethyl ether (5.0 mL) under nitrogen and ethyl magnesium bromide added (1.5 eq., 0.567 mmol, 189 μL, 3.0 M solution in diethyl ether). The mixture was stirred under nitrogen for 15 minutes when TLC indicated complete consumption of starting material. The reaction was stopped by addition of water (1 mL), and the mixture diluted with diethyl ether (30 mL), and washed with water (2 × 20 mL) then brine (satd., 20 mL), and the organic layer dried ($MgSO_4$), filtered, and the solvent removed *in vacuo*. The resultant colourless oil (83 mg, 85 % crude yield) was purified by flash chromatography (10 : 90, ethyl acetate : hexane eluent). The adduct (**3.19**) was isolated as a mixture of anomers (15.1 mg, 17 %). 5-*O*-*tert*-Butyldimethylsilyl-1,*N*-dehydro-1,4-dideoxy-1-*C*-ethyl-1,4-imino-2,3-*O*-isopropylidene-L-rhamnitol (**3.20**) (18.3 mg, 26 %) was also isolated by flushing the column with ethyl acetate. (**3.19**): $[\alpha]_D^{25.9}$ + 7.4 (c = 1.00, $CHCl_3$) ν_{max}(film)/cm^{-3}: 2110 (azide stretch), 2882, 2937, 2983 (aliphatic C-H stretch), 3441 (br, O-H stretch); δ_H ($CDCl_3$, 400 MHz, gCOSY, ` denotes minor anomer) 0.97 (t, 0.3H, CH`$_2$C<u>H`</u>$_3$, $J_{H`H`}$ 7.3 Hz), 1.00 (t, 3H, $CH_2C\underline{H}_3$, $J_{HH}$ 7.7 Hz), 1.26 (d, 3H, H-6, H-6', H-6'', $J_{5,6}$ 6.3 Hz), 1.34 (d, 0.3H, H-6`, H-6``, H-6```, $J_{5`,6`}$ 6.3 Hz), 1.37, 1.55 (2 × s, 2 × 3H, 2 × $(C\underline{H}_3)_2C$), 1.40, 1.55 (2 × s, 2 × 0.3H, 2 × $(C\underline{H`}_3)_2C$), 1.68 (dq, 1H, 1 of $C\underline{H}_2CH_3$, $J_{HH}$ 7.6 Hz, $J_{HH}$ 14.3 Hz), 1.90 (dq, 1H, 1 of $CH_2CH_3$, $J_{HH}$ 7.6 Hz, $J_{HH}$ 14.3 Hz), 1.90 (s, 1H, OH), 3.14 (dd, 1H, H-4, $J_{3,4}$ 8.6 Hz, $J_{4,5}$ 10.4 Hz), 3.31 (dq, 0.1H, H-5`, $J_{5`,6`}$ 6.2 Hz, $J_{4`,5`}$ 10.4 Hz), 3.48 (dd, 0.1H, H-4`, $J_{3`,4`}$ 8.3 Hz, $J_{4`,5`}$ 10.4 Hz), 3.77 (dq, 1H, H-5, $J_{5,6}$ 6.3 Hz, $J_{4,5}$ 10.4 Hz), 4.02 (d, 1H, H-2, $J_{2,3}$ 5.1 Hz), 4.06 (d, 0.1H, H-2`, $J_{2`,3`}$ 6.3 Hz), 4.12 (dd, 0.1H, H-3`, $J_{2`,3`}$ 6.4 Hz, $J_{3`,4`}$ 8.1 Hz), 4.20 (dd, 1H, H-3, $J_{2,3}$ 5.1 Hz, $J_{3,4}$ 8.5 Hz); δ_C ($CDCl_3$, 100.6 MHz, DEPT, minor anomer not observable) 7.0 (q, C-1), 18.4 (q, C-8), 26.4, 28.5 (2 × q, 2 × $(\underline{C}H_3)_2C$), 31.7 (t, C-2), 66.4, 66.9 (2 × d, C-6, C-7), 75.4 (d, C-5), 77.1 (d, C-4), 97.8 (s, C-3), 109.9 (s, $(CH_3)_2\underline{C}$).

*5-O-tert-Butyldimethylsilyl-1,N-dehydro-1,4-dideoxy-1-C-ethyl-1,4-imino-2,3-O-isopropylidene-L-rhamnitol (**3.20**):*

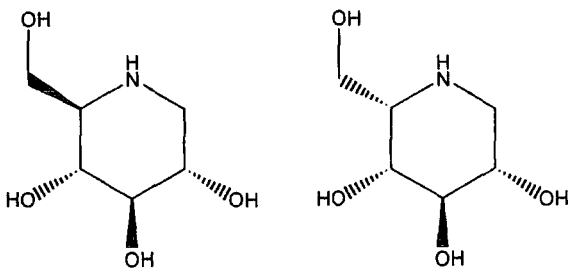


4-Azido-4-deoxy-2,3-*O*-isopropylidene-L-rhamno-1,5-lactone (**3.06**) (1.0 eq., 0.110 mmol, 25.0 mg) was dissolved in dry diethyl ether (1.0 mL). Ethyl magnesium bromide was added (1.5 eq., 0.165 mmol, 55 μL, 3.0 M solution in diethyl ether), and the mixture stirred under nitrogen. The reaction was stopped after 30 minutes, when TLC showed complete consumption of starting material, by addition of NH_4Cl (satd, 1.0 mL), and diluted with diethyl ether (25 mL). The solution was washed with water (20 mL), then brine (satd., 20 mL) then the organic layer dried ($MgSO_4$) and filtered. The solvent was removed *in vacuo* to give a colourless oil (24 mg), which was dissolved in $CDCl_3$ (0.6 mL), and triphenylphosphine added (1.1 eq., 0.121 mmol, 31.7 mg), and the mixture agitated. NMR analysis showed formation of one major product after 24 h, and the reaction was stopped by removal of the solvent *in vacuo*. The resultant pale yellow waxy solid was dissolved in diethyl ether (1 mL) and hexane (10 mL) added. The solution was cooled to –18 °C until triphenylphosphine oxide was observed to precipitate. The solution was filtered and the filtrate concentrated, then purified by repeated flash chromatography (ethyl acetate eluent), to give 5-*O*-*tert*-butyldimethylsilyl-1-*C*-ethyl-1,*N*-dehydro-1,4-dideoxy-1,4-imino-2,3-*O*-isopropylidene-L-rhamnitol (**3.20**) as a white crystalline solid (17 mg, 64 %): mp 47.5-53.0 °C (ethyl acetate); $[\alpha]_D^{24.0}$ -18.1 (c = 1.00, $CHCl_3$); *m/z* 236.1 (ES, $[M+Na]^+$, 100 %, MeOH), 214.2 ($[M+H]^+$, 30 %), 268.2 ($[M+MeOH+Na]^+$, 5 %); ν_{max}(KBr disc)/cm^{-3}: 1643 (C=N stretch), 2880, 2936, 2983 (aliphatic C-H stretch), 3406 (br, O-H stetch); δ_H ($CDCl_3$, 400 MHz, gCOSY) 1.18 (t, $CH_2\underline{CH_3}$, J_{HH} 7.6 Hz), 1.36 (s, 6H, $(CH_3)_2C$), 1.48 (d, 3H, H-6, H-6`, H-6``, $J_{5,6}$ 6.3 Hz), 2.34-2.56 (m, 2H, $\underline{CH_2}CH_3$), 3.68 (m, 1H, H-4), 4.00 (dq, 1H, H-5, $J_{4,5}$ 6.4 Hz, $J_{5,6}$ 14.1 Hz), 4.84 (t, 1H, H-3, $J_{2,3}$ 5.1 Hz, $J_{3,4}$ 5.1 Hz), 4.98 (d, 1H, H-2, $J_{2,3}$ 5.5 Hz); δ_C ($CDCl_3$, 100.6 MHz,

DEPT) 10.5 (q, $CH_2\underline{C}H_3$), 21.3, (q, C-6), 24.2 (t, $\underline{C}H_2CH_3$), 26.0, 27.0 (2 × q,$(\underline{C}H_3)_2C$), 68.4 (d, C-4), 78.2, 79.0, 86.7 (3 × d, C-2, C-3 C-5), 112.8 (s, $(CH_3)_2\underline{C}$), 178.1 (s, C-1); HRMS found 214.1447 ($C_{11}H_{20}NO_3$ requires 214.1443).

Chapter 4. Aza-sugar Piperidines: Tetra-*O*-benzyl DNJ, and DINJ, and their Cyclic Imine Derivatives

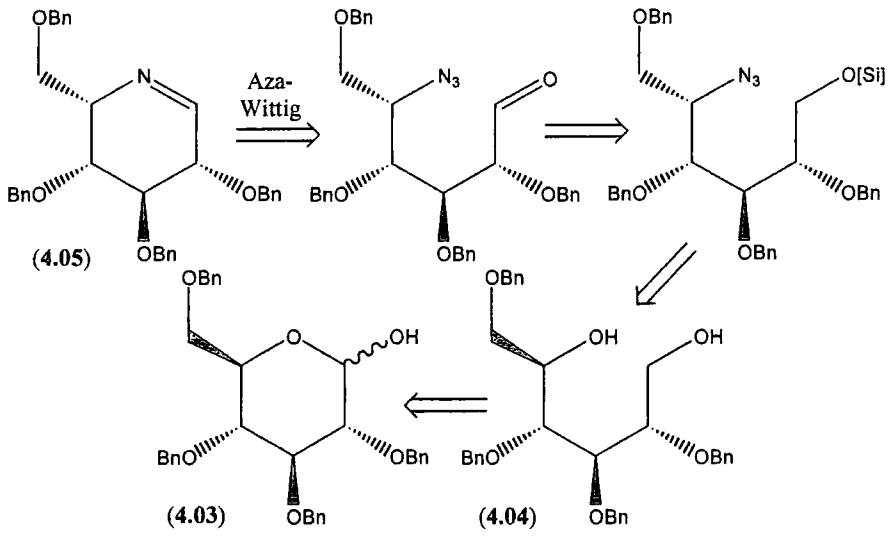
In this chapter we discuss the syntheses of cyclic imine derivatives with 1-deoxyidonojirimycin (DINJ) and 1-deoxynojirimycin (DNJ) stereochemistry (Figure 26, see also Chapter 1, Section 1.6.3), by both a chlorination/elimination procedure and by the use of the intramolecular Staudinger aza-Wittig reaction of azido-sugars (see Chapter 1, Section 1.5.2, and Chapter 3, Sections 3.3 and 3.5).[74]



DNJ DINJ

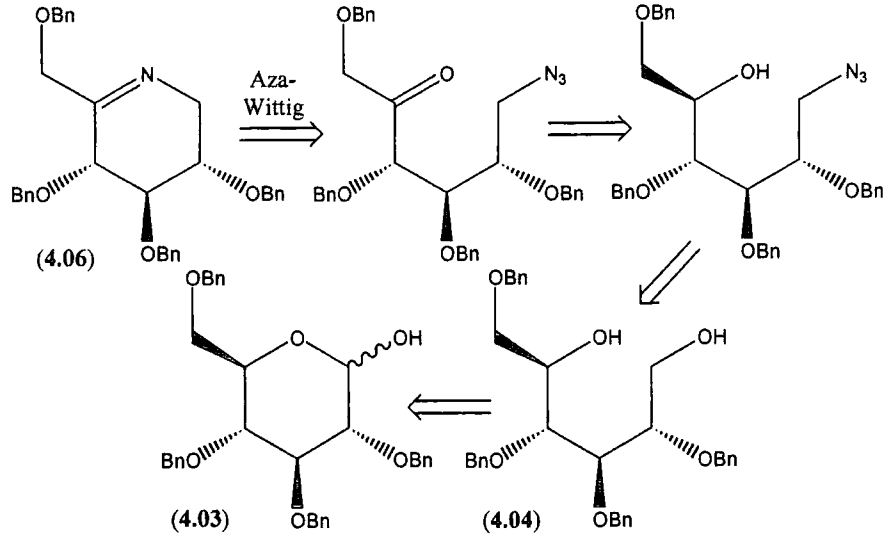
Figure 26. Naturally occurring aza-sugars DNJ and DINJ.

Benzyl ethers were chosen as suitable *O*-protecting groups due to the ease of introduction, their stability to the wide variety of reaction conditions employed throughout these syntheses, and their ease of removal by catalytic hydrogenation.[112] General strategies for the synthesis of cyclic imines derived from 2,3,4,6-tetra-*O*-benzyl-DINJ (TBDINJ) (**4.01**) and 2,3,4,6-tetra-*O*-benzyl-DNJ (TBDNJ) (**4.02**) are shown below (Scheme 53 to Scheme 55).



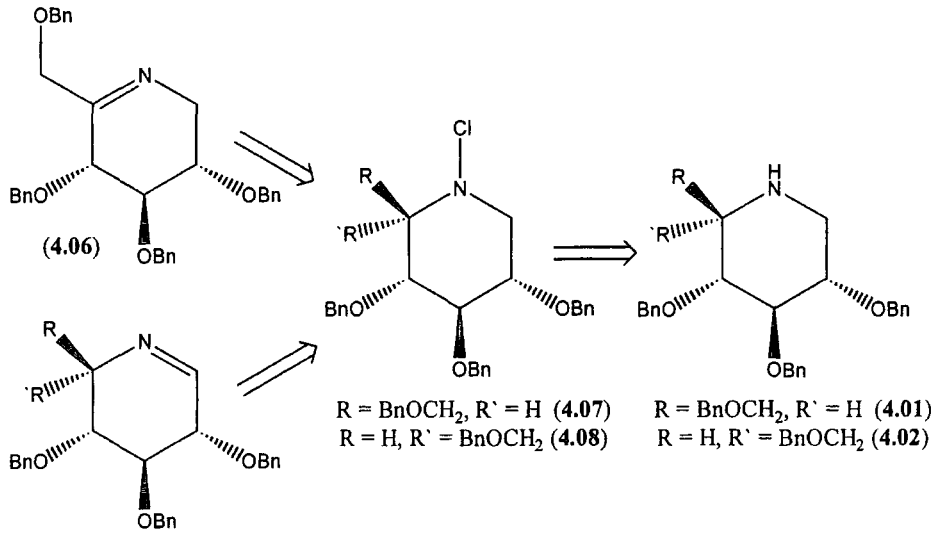
Scheme 53. Retrosynthetic analysis of protected cyclic sugar aldimine 1,*N*-dehydro-TBDINJ (**4.05**).

2,3,4,6-Tetra-*O*-benzyl-D-glucopyranose (**4.03**) is a convenient chiral pool starting material, which is commercially available or readily synthesised from D-glucose.[113] Reduction of the hemi-acetal function of (**4.03**) would afford the protected tetra-*O*-benzyl-D-glucitol (**4.04**).[114] We envisage the introduction of azide *via* an S_N2 displacement reaction at either the 1-, or 5-position allowing access to either the cyclic aldimine 1,*N*-dehydro-TBDINJ (**4.05**) (Scheme 53) or the cyclic ketimine 5,*N*-dehydro-TBDNJ (**4.06**) (Scheme 54).



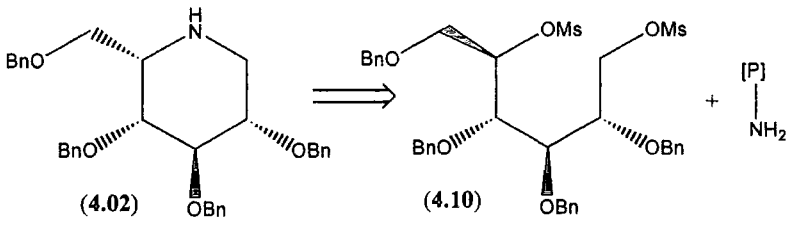
Scheme 54. Retrosynthetic analysis of cyclic sugar ketimine 5,*N*-dehydro-TBDNJ (**4.06**).

An alternative strategy involves the elimination of HCl from *N*-chloro-TBDNJ (**4.07**) and *N*-chloro-TBDINJ (**4.08**) (Scheme 39). Our goal wass successful regiocontrol of elimination, allowing selective formation of either the ketimine (**4.06**) or aldimine (**4.07**) by control of the reaction conditions. We expected regiocontrol of such eliminations to be governed by stereoelectronic and conformational factors (see Chapter 1, Section 1.5.1). However regiocontrol of elimination of HCl from such *N*-chlorinated piperidines had not, to the best of the author's knowledge, been previously investigated.



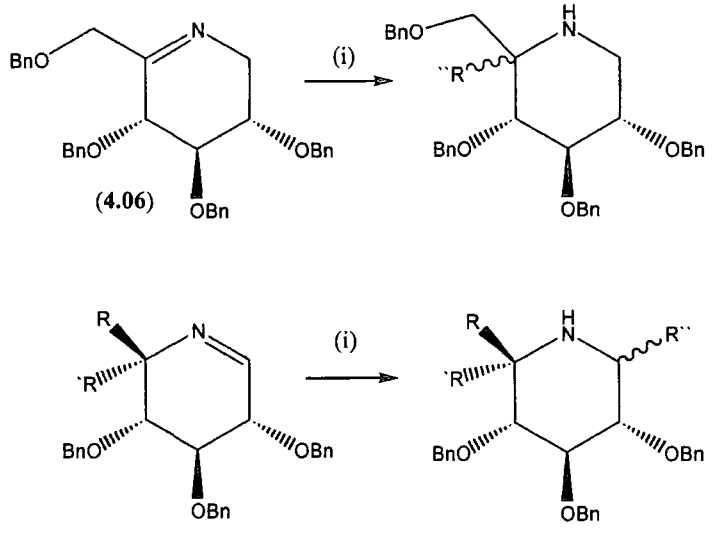
Scheme 55. Retrosynthetic analysis of protected cyclic imines from *N*-chloro-TBDNJ (**4.07**), and *N*-chloro-TBDINJ (**4.08**).

The *N*-chlorination methodology utilises fully *O*-protected aza-sugars TBDNJ (**4.01**) and TBDINJ (**4.02**). A synthesis of TBDINJ (**4.02**) *via* a double S_N2 displacement of di-*O*-methanesulfonyl glucitol derivative (**4.10**) is proposed (Scheme 56). This work follows from a similar literature synthesis of deprotected DINJ (see Section 4.4).[115] TBDNJ (**4.02**) was provided by Oxford Glycosciences Ltd., and although we achieved a small-scale synthesis (see Section 4.6), a large-scale synthesis was not performed.



Scheme 56. Retrosynthetic analysis of TBDINJ (**4.02**) (cf. ref. 115).

Following the successful synthesis of cyclic imines (**4.05**), (**4.06**), (**4.09**) we will investigate irreversible addition of organometallic reagents to give access to 1-, and 5-substituted aza-sugars (Scheme 57) (see Section 4.6, and 4.7). This late-stage introduction of functionality would be a valuable tool to the synthetic chemist for the creation of libraries of aza-sugars with potential biological activity. We will also illustrate the synthetic utility of our cyclic imine-sugar methodology with the first synthesis of the enantiomer of the natural product (–)-adenophorine[116] (**4.11**) ((1*S*)-1,5-dideoxy-1-*C*-ethyl-1,5-imino-L-iditol) (see Sections 4.8, and 4.9) and its C-1 epimer ((1*R*)-1,5-dideoxy-1-*C*-ethyl-1,5-imino-L-iditol) (**4.12**) (see Sections 4.8 and 4.9).



R = $BnOCH_2$, R` = H (**4.09**)
R = H, R` = $BnOCH_2$ (**4.05**)

(i) Organometallic, R``M.

Scheme 57. Addition reactions of cyclic imine derivatives of TBDNJ and TBDINJ.

The work in this Chapter can be separated into nine main sections:

4.1 Synthesis of Cyclic Ketimine 5,*N*-Dehydro-TBDNJ (**4.06**) by a Staudinger Aza-Wittig Reaction.

4.2 Synthesis of TBDINJ (**4.02**), and its Cyclic Aldimine 1,*N*-Dehydro-TBDINJ (**4.05**) by a Staudinger Aza-Wittig Reaction.

4.3 Synthesis of Cyclic Ketimine 5,*N*-dehydro-TBDNJ (**4.06**), and Cyclic Aldimine 1,*N*-Dehydro-TBDNJ (**4.09**) from TBDNJ (**4.01**) *via* a Chlorination/Elimination Strategy

4.4 Synthesis of TBDINJ (**4.02**) from Tetra-*O*-benzyl-D-glucitol (**4.04**) *via* a Double Displacement strategy

4.5 Synthesis of Cyclic Aldimine 1,*N*-Dehydro-TBDINJ (**4.05**) from TBDINJ (**4.02**) *via* a Chlorination/Elimination Strategy

4.6 Irreversible Addition Reactions of Cyclic Imines 5,*N*-Dehydro-TBDNJ (**4.06**) and 1,*N*-Dehydro-TBDNJ (**4.09**)

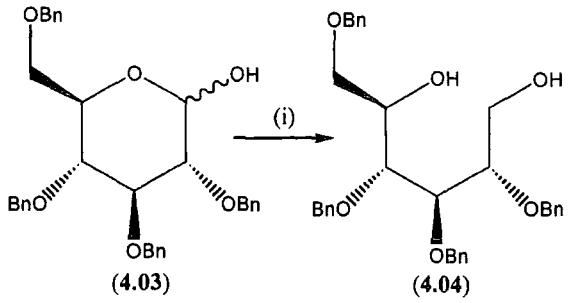
4.7 Synthesis of Protected (–)-1-*epi*-Adenophorine (**4.37**) by Nucleophilic Addition to 1,*N*-Dehydro-TBDINJ (**4.05**)

4.8 Synthesis of Protected (–)-Adenophorine (**4.43**) by Addition of Hydride to Cyclic Ketimine 1-*C*-Ethyl-1,*N*-dehydro-TBDINJ (**4.13**)

4.9 Deprotection of Aza-Sugars (**4.37**), (**4.43**), (**4.35**) and (**4.36**)

4.1 Synthesis of Cyclic Ketimine 5,*N*-dehydro-TBDNJ (4.06) by a Staudinger Aza-Wittig Reaction

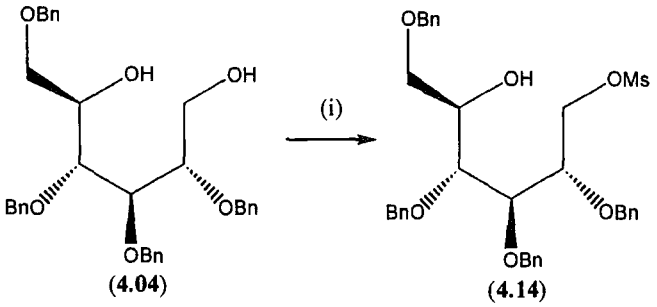
This strategy for the synthesis of the DNJ framework utilised the difference in reactivity of the two free hydroxyl groups in the known[114] 2,3,4,6-tetra-*O*-benzyl-D-glucitol (**4.04**) (Scheme 59), conveniently prepared by the reduction of commercially available 2,3,4,6-tetra-*O*-benzyl-α,β-D-glucose (**4.03**) (Scheme 58).



(i) $NaBH_4$, THF, H_2O, 100 %.

Scheme 58. Reduction of 2,3,4,6-tetra-*O*-benzyl-α,β-D-glucopyranose (**4.03**).

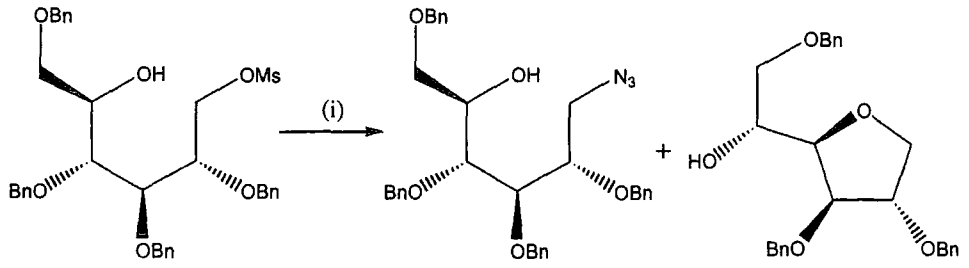
The previously unknown 1-mesyl-glucitol derivative (**4.14**) was obtained in 83 % yield by treatment of protected glucitol (**4.04**) with methanesulfonyl chloride at – 18 °C. Temperature was shown to have an effect in controlling the reaction selectivity, the dimesylate (**4.10**) (10 %) being obtained at 0 °C, together with the monomesylate in 73 % yield.



(i) MsCl, Py, – 18 °C, 83 %.

Scheme 59. Synthesis of primary mesylate (**4.14**).

Treatment of 1-mesyl-glucitol (**4.14**) with sodium azide in DMF at room temperature gave a mixture of 1,4-anhydro-sugar (**4.15**) (Scheme 60), and the desired azido-glucitol (**4.16**), which was isolated in 18 % yield. The anhydro-sugar (**4.15**) formed due to intramolecular participation of the benzyl ether at C-4. The synthesis of such tetrahydrofurans by intramolecular substitutions involving benzyl ethers has previously been reported.[117]



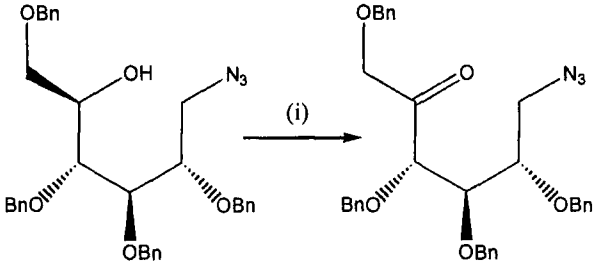
(4.14) (4.16) (4.15)

(i) NaN_3, DMF, rt, 18 % of (**4.16**), 14 % of (**4.15**) or TBAAZ, toluene, 21 % of (**4.16**).

Scheme 60. Unwanted cyclisation of 1-mesylate (**4.14**).

It was anticipated that the intramolecular side reaction might be disfavoured by a non-polar solvent, due to the polar nature of the transition-state, which presumably proceeds *via* a benzyl oxonium ion. In order to use the less polar solvent toluene, an organic-soluble azide source was necessary. One such source is tetra-*n*-butylammonium azide (TBAAZ).[118] TBAAZ was made from tetra-*n*-butylammonium hydroxide and sodium azide following a literature preparation.[119] The use of TBAAZ (10 eq.) in toluene gave only a moderate increase in yield of 1-azido glucitol (**4.16**) (21 %).

As the synthesis of 1-azido-tetra-*O*-benzyl-1-deoxy glucitol (**4.16**) was only achieved in very low yield (21 %), subsequent experiments were performed on a micromole scale.



(4.16) (4.17)

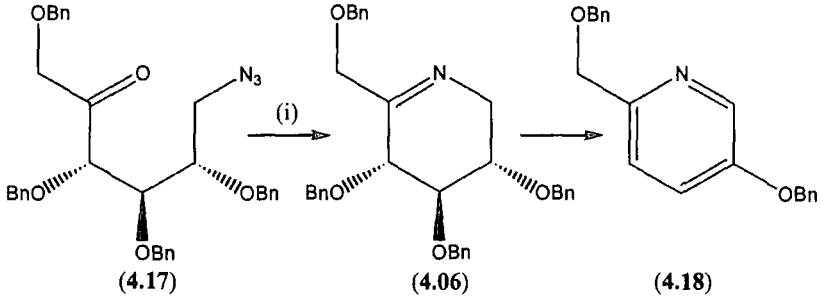
(i) PCC, DCM, sieves, 86 %.

Scheme 61. Oxidation of azido-glucitol (**4.16**) to give azido-sugar (**4.17**).

Oxidation of the free secondary hydroxyl group of azido glucitol (**4.16**) with pyridinium chlorochromate (PCC) in DCM (Scheme 61) on a 14 μmol scale gave the

previously unknown azido ketone (**4.17**) in 86 % yield. The structure of the ketone was tentatively assigned by its proton NMR.

Aza-Wittig cyclisation of (**4.17**) with triphenylphosphine in DCM, gave the desired imine (**4.06**) as identified by proton NMR, together with decomposition products notably substituted pyridine (**4.18**) (Scheme 62). The imine formed by this method was found to be identical to that formed by the *N*-chlorination/elimination of TBDNJ (**4.01**) (see Section 4.3).



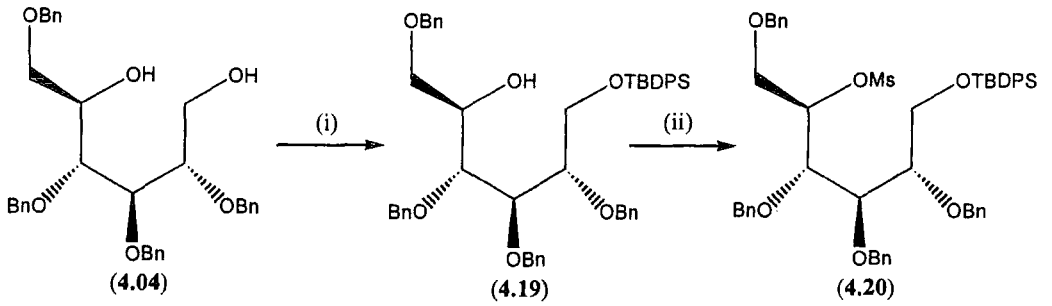
(i) PPh_3, DCM.

Scheme 62. Formation of ketimine (**4.06**) by a Staudinger aza-Wittig reaction.

In order to repeat this synthesis, a higher yielding synthesis of azide (**4.16**) must be developed. This was not achieved due to time constraints.

4.2 Synthesis of TBDINJ (4.02), and its Cyclic Aldimine 1,*N*-Dehydro-TBDINJ (4.05) by a Staudinger Aza-Wittig Reaction

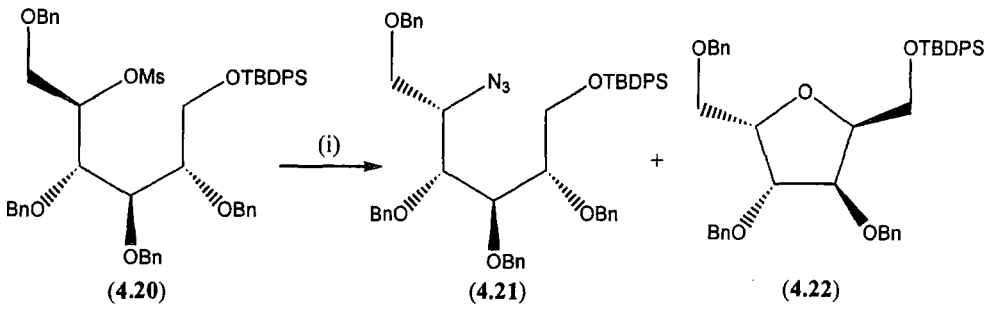
Selective protection of the primary hydroxyl function in tetra-*O*-benzyl-D-glucitol (**4.04**) (see Section 4.1) with *tert*-butylchlorodiphenylsilane (TBDPSCl) and imidazole, in DMF solution gave the previously unknown, orthogonally protected glucitol (**4.19**) in 99 % yield. The free secondary hydroxyl group, when treated with methanesulfonyl chloride in dry pyridine at room temperature, gave the previously unknown 5-mesyl-glucitol (**4.20**), in 95 % yield (Scheme 63).



(i) TBDPSCl, imidazole, DMF, 99 %; (ii) MsCl, Py, 95 %.

Scheme 63. Synthesis of protected mesylate (**4.20**) from 2,3,4,6-tetra-*O*-benzyl-D-glucitol (**4.04**).

S_N2 displacement of the secondary mesylate with azide to give the unknown protected 5-azido-5-deoxy-glucitol derivative (**4.21**) was only achieved in low yield (35 %) due to a competing side reaction (Scheme 64) similar to that observed for 1-mesyl glucitol derivative (**4.14**) (Scheme 60, page 98). The intramolecular cyclisation reaction giving the 2,5-anhydro-sugar (**4.22**) (Scheme 64) was found to predominate in all cases. Variation of reaction conditions and reagents was performed to optimise the yield of this reaction and the results are shown in Table 1.



(i) TBAAZ, xylene, 165 °C, 35 % of (**4.21**), 58 % of (**4.22**).

Scheme 64. Nucleophilic displacement of 5-mesylate (**4.20**) by azide, giving azido iditol (**4.21**), and unwanted 2,5-anhydro-sugar (**4.22**).

In the polar solvent DMSO, the desired azide (**4.21**) was only isolated when the azide source TBAAZ was used at high concentrations (typically 260 mg of TBAAZ per 1 mL solvent added) (Table 1 entry 11).

The use of less polar solvents such as toluene and xylene, high temperatures, and high concentration of azide favoured the intramolecular reaction. The use of less polar

solvents required the use of TBAAZ[119] (see Section 4.1), as a soluble source of azide. Optimum conditions on a 0.04 mmol scale were found to be refluxing xylene with 10 equivalents of azide for 1 h, giving only 35 % of the desired product (Table 1, entry 12).

Table 1. Formation of azido iditol (**4.21**) by S_N2 reaction with azide under varying reaction conditions (approx 0.04 mmol scale).

Entry	Solvent	Temperature / °C	Azide Source	Equivalents of Azide	Yield[a] (4.22) / %	Yield[a] (4.21) / %
1	DMF	30	NaN_3	3	64	0
2	DMF	50	NaN_3	3	75	0
4	DMF	50	LiN_3	3	79[b]	0
5	DMF	130	NaN_3	3	81	0
6	DMF	130	NaN_3	10	76	0
7	Toluene	110	Bu_4NN_3	10	37	23
8	DMSO	50	NaN_3	3	61	0
9	DMSO	130	NaN_3	3	75	0
10	DMSO	130	NaN_3	10	78	0
11	DMSO	130	Bu_4NN_3	10	69	11
12	Xylene	165	Bu_4NN_3	10	58	35

a) Isolated yields (flash chromatography) b) 10 % starting material (**4.20**) recovered.

All exploratory reactions shown above were performed on a small scale of approximately 40 mg (45 μmol). Upon proportional scale-up of the optimum reaction conditions in toluene to 0.5 g (0.58 mmol) the proportion of azido-iditol (**4.21**) formed was reduced (crude NMR). After repeated chromatography only 2 % of the desired azide (**4.21**) was isolated, together with 70 % of the unwanted 2,5-anhydro-sugar (**4.22**).

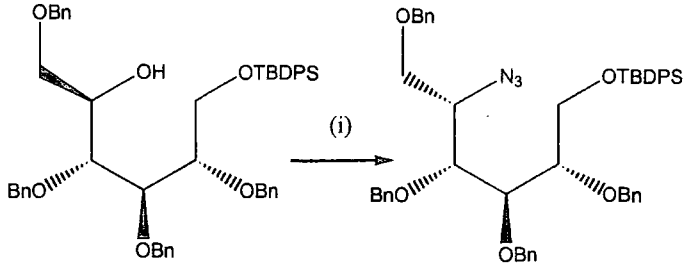
In an attempt to isolate azide (**4.21**) in sufficient yield to continue the synthesis, the 0.045 mmol scale reaction in xylene (entry 12, Table 1) was repeated twelve times in parallel using a Radley™ Reaction Carousel, and all reactions combined and purified.

This method gave an intractable mixture of the desired azido-iditol (**4.21**) and unidentified side products with proton NMR signals in the olefinic region, together with the unwanted 2,5-anhydro sugar (**4.22**) (53 %). The problems associated with the scale-up and parallel syntheses may be due to heat transfer through the reaction medium at larger scale, or in different vessels.

As a new strategy it was decided at this stage to explore the use of a Mitsunobu-type substitution reaction with hydrazoic acid.[120, 121]

4.2.2 Synthesis of Protected Azido-Iditol (4.21) *via* a Mitsunobu Reaction

The formation of alkyl azides *via* a Mitsunobu-type inversion using hydrazoic acid is well known, and a literature procedure for conversion of a secondary hydroxyl to azide was followed initially using diisopropylazodicarboxylate (DIAD) and triphenylphosphine.[120] Treatment of the protected glucitol derivative (**4.19**) with hydrazoic acid, DIAD and triphenylphosphine was expected to give the desired azido iditol (**4.21**) (Scheme 65).



(**4.19**) (**4.21**)

(i) HN_3, DIAD, PPh_3, toluene.

Scheme 65. Proposed synthesis of protected azido iditol (**4.21**) *via* a Mitsunobu-type reaction.

A solution of hydrazoic acid[122] in toluene was prepared from sodium azide according to a literature preparation,[123] and titrated against standard sodium hydroxide with phenolphthalein indicator. The standardised hydrazoic acid solution was then used directly. The Mitsunobu reaction with hydrazoic acid, DIAD, and triphenylphosphine gave clean conversion of glucitol (**4.19**) to the desired azide (**4.21**). The yield and

conversion, however, depended heavily upon the order of addition and quantities of reagents used.

Following a literature procedure[120] (Table 2, reaction type A, entry 1), DIAD (1.1 eq.), was added dropwise to a pre-mixed solution of hydrazoic acid (1.5 eq.), PPh_3 (1.1 eq.), and glucitol (**4.19**) (1.0 eq.). Under these conditions, the reaction was observed to stop before full consumption of starting material. Only 46 % of the desired product (**4.21**) was obtained, together with starting material (38 %). Pleasingly none of the unwanted 2,5-anhydro-sugar (**4.22**) was observed. Increased reaction times did not improve the yield.

Table 2. Optimisation of Mitsunobu reaction of glucitol (**4.19**).

Entry	HN_3 Eq.	DIAD Eq.	PPh_3 Eq.	Reaction Type[a]	Yield (4.19) (SM)[b]	Yield (4.21)[b]	Yield of (4.22)[b]
1	1.5	1.1	1.1	A	38	46	0
2	1.8	1.25	1.3	A	38	52	0
3	2.5	1.25	1.1	A	19	58	7
4	1.8	1.1	1.1	B	18[c]	73[c]	9[c]
5	2.5	2.5	2.2	C	0[c]	95[c]	5[c]
6	2.5	2.5	2.5	C	0	87	8

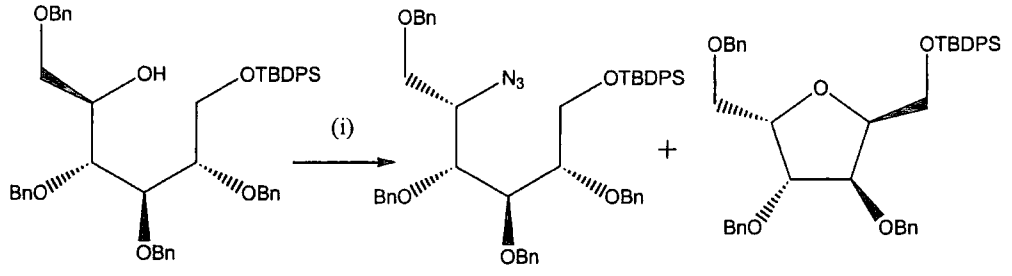
a) Reaction procedures defined as: A) PPh_3, hydrazoic acid, and glucitol (**4.19**) pre-mixed, DIAD added drop-wise; B) PPh_3, and glucitol (**4.19**) pre-mixed, DIAD added drop-wise, then hydrazoic acid added drop-wise to activated alcohol; C) PPh_3 stirred and DIAD added drop-wise, then premixed hydrazoic acid and glucitol (**4.19**) added drop-wise; b) Isolated yields (flash chromatography) unless otherwise stated; c) Yields determined by ^{1}H-NMR integration of the crude reaction mixture.

An array of experiments was performed (Table 2), and all reactions, unless complete by TLC, were allowed to run for 100 h before work up. In an attempt to increase conversion, the quantities of DIAD and hydrazoic acid were increased to 1.25 eq. and 2.5 eq. respectively (Table 2, entry 3). The reaction was again observed to stop before completion, and a proportion of 2,5-anhydro-sugar (**4.22**) was observed.

The order of addition of reagents was changed. DIAD (1.1 eq.), PPh_3 (1.1 eq.) and glucitol (**4.19**) were premixed and stirred for 15 minutes (Table 2, entry 4, reaction type B). Hydrazoic acid solution (1.8 eq) was added drop-wise to this solution. Again the reaction did not go to completion, and a greater proportion of furan was observed (9 %). This may be expected as the activated alcohol is formed in solution in the absence of the nucleophile.

During reaction type A (Table 2), as the DIAD is added last, the desired azido-iditol (**4.21**) is formed in solution with triphenylphosphine (Table 2, reaction type A), which could result in reduction of the desired product.

In order to circumvent both of these problems, pre-mixing of the DIAD and triphenylphosphine in toluene solution was performed, and a pre-mixed solution of HN_3 (2.5 eq) and glucitol (**4.19**) added drop-wise to the mixture (Table 2, reaction type C). Since equimolar quantities of DIAD and triphenylphosphine were used, their pre-mixing prevents *in situ* reduction of the desired product, and the use of an excess of both reagents was possible (2.5 eq.).



(**4.19**) (**4.21**) (**4.22**)

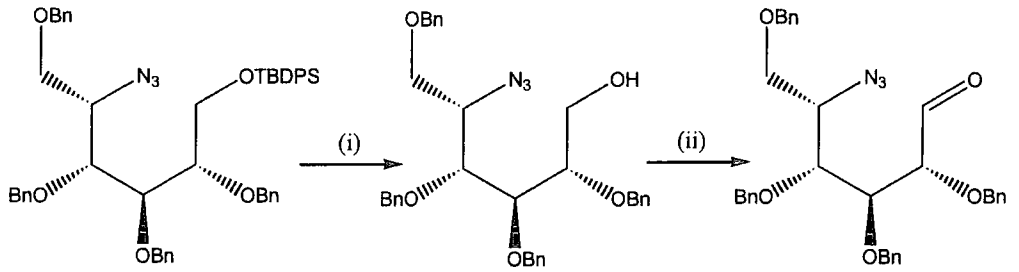
(i) HN_3, toluene, then DIAD, PPh_3, toluene, 87 % of (**4.21**), 8 % of (**4.22**)

Scheme 66. Synthesis of azido-iditol (**4.21**) by a Mitsunobu-type reaction of glucitol derivative (**4.19**).

On a small scale (0.06 mmol) the reaction proceeded to completion, and NMR analysis of the crude reaction mixture showed very little anhydro-sugar formation (Table 2, entry 5). Upon scale-up to 1.3 mmol, with the same procedure, column chromatography of the product gave the desired azide (**4.19**) in 87 % yield with a small quantity (8 %) of the anhydro-sugar (**4.22**) (Scheme 66).

4.2.3 Synthesis of 5-Azido-tetra-*O*-benzyl-5-deoxy-idose (4.24)

Treatment of protected azido-glucitol (**4.21**) with tetra-*N*-butyl ammonium fluoride (TBAF) in THF, afforded the 1-*O*-deprotected azido-glucitol (**4.23**) in quantitative yield (Scheme 67). Subsequent oxidation of the primary hydroxyl to the aldehyde was achieved with PCC in DCM, over 4Å molecular sieves, in up to 88 % yield (Scheme 67). Although evidence for the formation of the subsequent cyclic imine was not observed, it is possible that the azido aldehyde decomposes on silica in a similar fashion to that observed for azido-sugar (**3.19**) (see Chapter 3, section 3.5, page 69), and therefore minimum contact with silica is recommended.



(**4.21**) (**4.23**) (**4.24**)

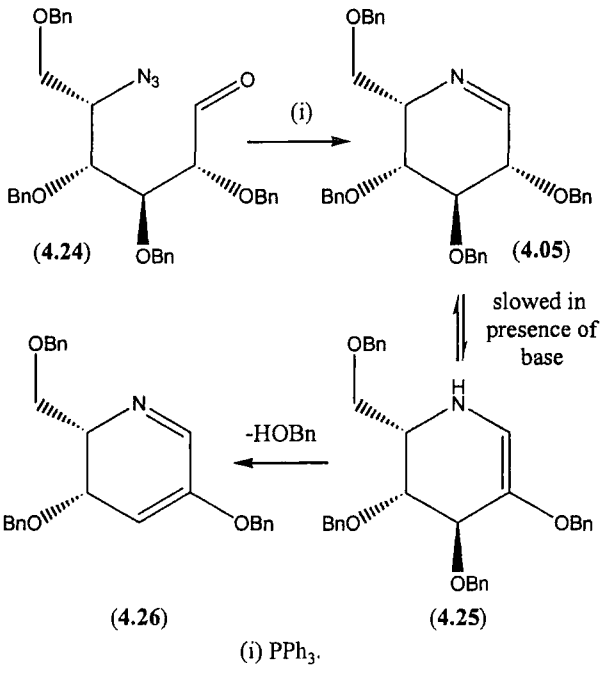
(i) TBAF, THF, 100 %; (ii) PCC, sieves, DCM, 88 %.

Scheme 67. Synthesis of 5-azido idose (**4.24**) from protected azido iditol (**4.21**).

4.2.4 Synthesis of 1,*N*-Dehydro-TBDINJ (4.05) *via* a Staudinger Aza-Wittig Reaction

The treatment of 5-azido-idose (**4.24**) with triphenylphosphine was expected to give the desired cyclic imine-sugar (**4.05**) (Scheme 68). The reaction was performed in $CDCl_3$, and monitored by ^{1}H-NMR using proton signals for the aldehyde (9.7 ppm), imine (**4.05**) (7.8 ppm), and a probable enamine tautomer (**4.25**) (6.0 ppm). It was found that the imine formed (as observed by NMR) but quickly tautomerised to the enamine, and further decomposed to the cyclic aza-diene (**4.26**) (Scheme 68). In fact treatment of azido idose (**4.24**) with triphenylphosphine in refluxing DCM gave direct conversion to aza-diene (**4.26**), which could be isolated by flash chromatography in 28 % yield.

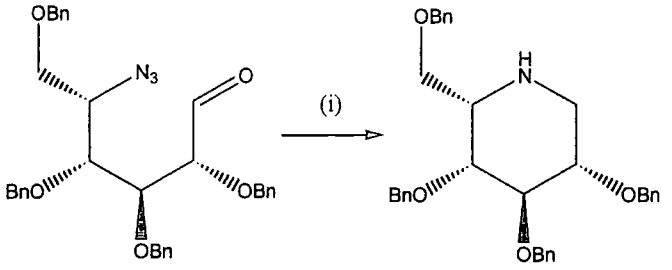
In order assess the effect of pH on tautomerisation, the Staudinger reaction was performed in $CDCl_3$ in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (0.1 eq). Further NMR experiments showed enolisation was indeed slowed by the presence of DBU, however, when performed with 1,4-diazabicyclo[2.2.2]octane (Dabco^{TM}), a weaker tertiary amine base, the imine again rapidly decomposed.



Scheme 68. Staudinger aza-Wittig reaction of azido idose (**4.24**) to form 1,*N*-dehydro-TBDINJ (**4.05**) and subsequent decomposition.

Use of diethyl ether as the solvent for the Staudinger reaction was found to reduce the formation of enamine/aza-diene, and optimum conditions were found to be excess triphenylphosphine (3.0 eq) in diethyl ether at room temperature, giving clean formation of the desired imine in 90 minutes (^{1}H-NMR).

NMR studies showed the imine synthesised by this methodology to be identical to that synthesised by the chorination/elimination protocol from TBDINJ (see Section 4.5), and reductive trapping of the aza-Wittig product (**4.05**) with sodium borohydride in methanol, gave TBDINJ (**4.02**) in 50 % yield (Scheme 69). Aldimine 1,*N*-dehydro-TBDINJ (**4.05**) was found to be unstable to silica, and was used without purification.



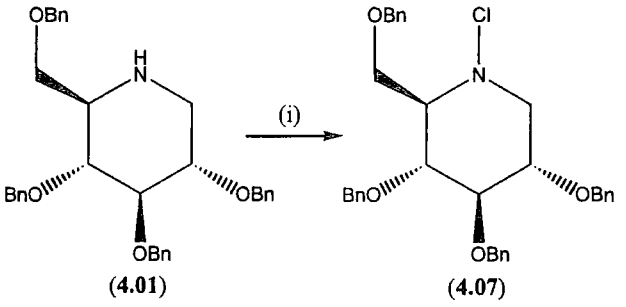
(4.24) (4.02)

(i) PPh_3, Et_2O, then $NaBH_4$ MeOH, 50 %.

Scheme 69. Reductive cyclisation of azido-idose (**4.24**).

4.3 Synthesis of Cyclic Ketimine 5,*N*-Dehydro-TBDNJ (4.06), and Cyclic Aldimine 1,*N*-Dehydro-TBDNJ (4.09) from TBDNJ (4.01) *via* a Chlorination/Elimination Strategy

N-Chlorination of TBDNJ (**4.01**) with *N*-chlorosuccinimide (NCS) in DCM gave *N*-chloro-TBDNJ (**4.07**) in up to 97 % yield (Scheme 70). *N*-Chloro-TBDNJ (**4.07**) was found to be stable at – 18 °C, and could be stored conveniently for several months without decomposition.

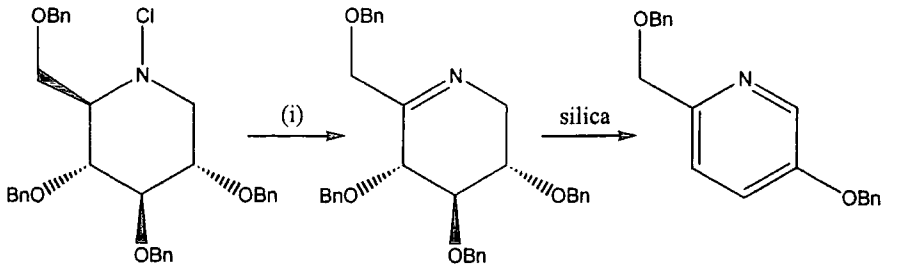


(4.01) (4.07)

(i) NCS, DCM, 97 %.

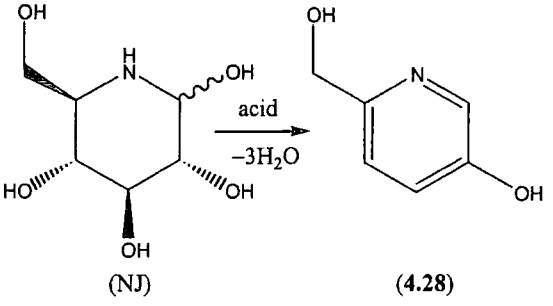
Scheme 70. *N*-Chlorination of TBDNJ (**4.01**).

Treatment of *N*-chloro-TBDNJ (**4.07**) with DBU in diethyl ether at room temperature gave elimination of HCl to form only ketimine (**4.06**) (Scheme 73). In diethyl ether and THF the DBU hydrochloride salt was found to precipitate from solution, and was conveniently removed by filtration. Ketimine 5,*N*-dehydro-TBDNJ (**4.06**) was found to be unstable to silica, eliminating benzyl alcohol to yield functionalised pyridine (**4.18**). It was therefore used without purification. The addition of nucleophiles to ketimine (**4.06**) is discussed in Section 4.6.



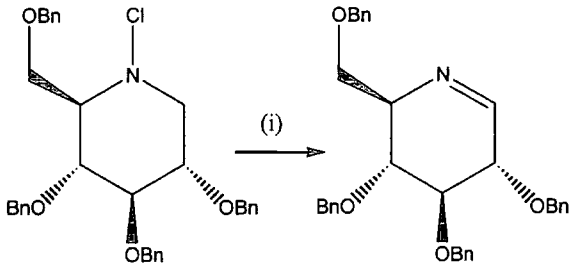
Scheme 71. Elimination of HCl from *N*-chloro-TBDNJ (**4.07**) at room temperature, and subsequent decomposition to pyridine (**4.18**).

Decomposition of imine (**4.06**) to the pyridine (**4.18**) is similar to the decomposition of nojirimycin (NJ) observed under acidic conditions (Scheme 72).[4] Indeed it has been observed that piperidinoses of 5-amino sugars are generally dehydrated in acidic media to give the 3-hydroxypyridine derivatives.[124]



Scheme 72. Decomposition of nojirimycin (NJ) under acidic conditions.[4]

Treatment of *N*-chloro-TBDNJ (**4.07**) with the stong base lithium 2,2,6,6-tetramethylpiperidide (LiTMP) at – 78 °C gave elimination of HCl to form exclusively the aldimine 1,*N*-dehydro-TBDNJ (**4.09**) (Scheme 73). Aldimine (**4.09**) was found to be slightly unstable, decomposing upon silica chromatography and storage at – 18 °C. The imine was identified by its characteristic spectroscopic data (HC=N, δ_H ($CDCl_3$) 7.60 ppm (s, H-1); C=N, δ_C ($CDCl_3$) 162.3 ppm (d, C-1); C=N stretch, ν_{max}/cm^{-1} (film) 1654).



(i) LiTMP, THF, – 78 °C.

Scheme 73. Elimination of HCl from *N*-chloro-TBDNJ at – 78 °C giving 1,*N*-dehydro-TBDNJ (**4.09**).

Elimination of HCl from *N*-chloro-TBDNJ (**4.07**) by an E2 mechanism, as would be expected in this case,[66,67] would require periplanar geometry of the N-Cl and C-H bonds being broken (see Section 1.5.1).[68] It is well known that amines undergo pyramidal inversion,[71,72] which is slowed in chloramines, due to the presence of unshared electrons on chlorine.[72] The all-equatorial configuration of *N*-chloro-TBDNJ (**4.07**) favours not only the $^4C_1$ conformation, but also a pseudoequatorial position for chlorine, giving the proposed favoured structure A (Figure 27).

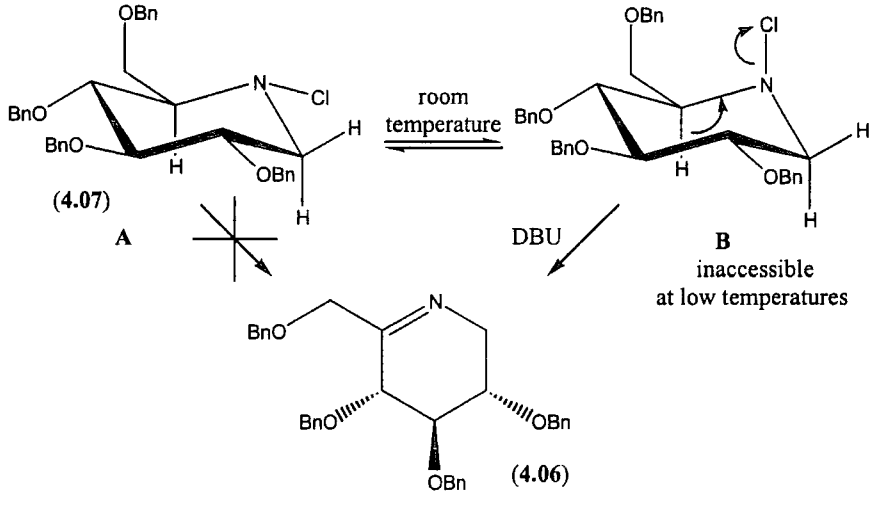


Figure 27. Simple conformational analysis of *N*-chloro-TBDNJ (**4.07**), and its relation to the formation of ketimine (**4.06**).

In adopting a axial configuration (NCl_{ax}) by pyramidal inversion, as in structure B (Figure 27), the chlorine atom gains an anti-periplanar relationship to the *β*-hydrogen atoms at C-1, and C-5, allowing formation of the more stable ketimine in a Zaitzev-

type elimination (see Chapter 1, Section 1.5.1). We speculate that the NCl_{ax} structure B is not accessible at – 78 °C, but is readily accessible at room temperature.

In general, elimination of HCl from *N*-chloro compounds in acyclic systems follows Zaitzev's rule in that the more substituted, imine is the expected product (see Chapter 1, section 1.5.1). This suggests that the reaction is product dependent or has a late product-like transition-state.

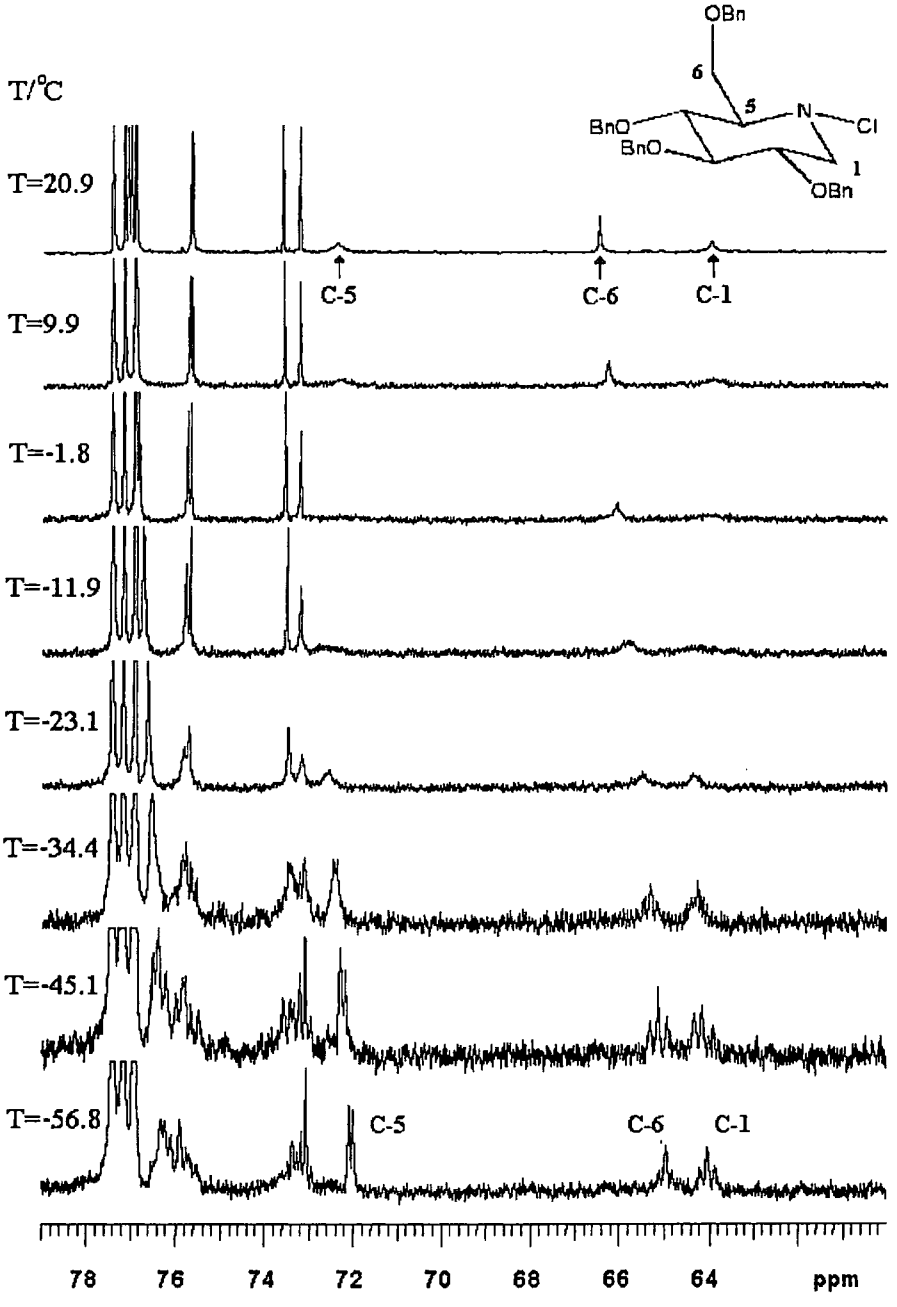


Figure 28. VT ^{13}C-NMR studies on *N*-chloro-TBDNJ (**4.07**) (T/°C).

type elimination (see Chapter 1, Section 1.5.1). We speculate that the NCl_{ax} structure B is not accessible at – 78 °C, but is readily accessible at room temperature.

In general, elimination of HCl from *N*-chloro compounds in acyclic systems follows Zaitzev's rule in that the more substituted, imine is the expected product (see Chapter 1, section 1.5.1). This suggests that the r eaction is product dependent or has a late product-like transition-state.

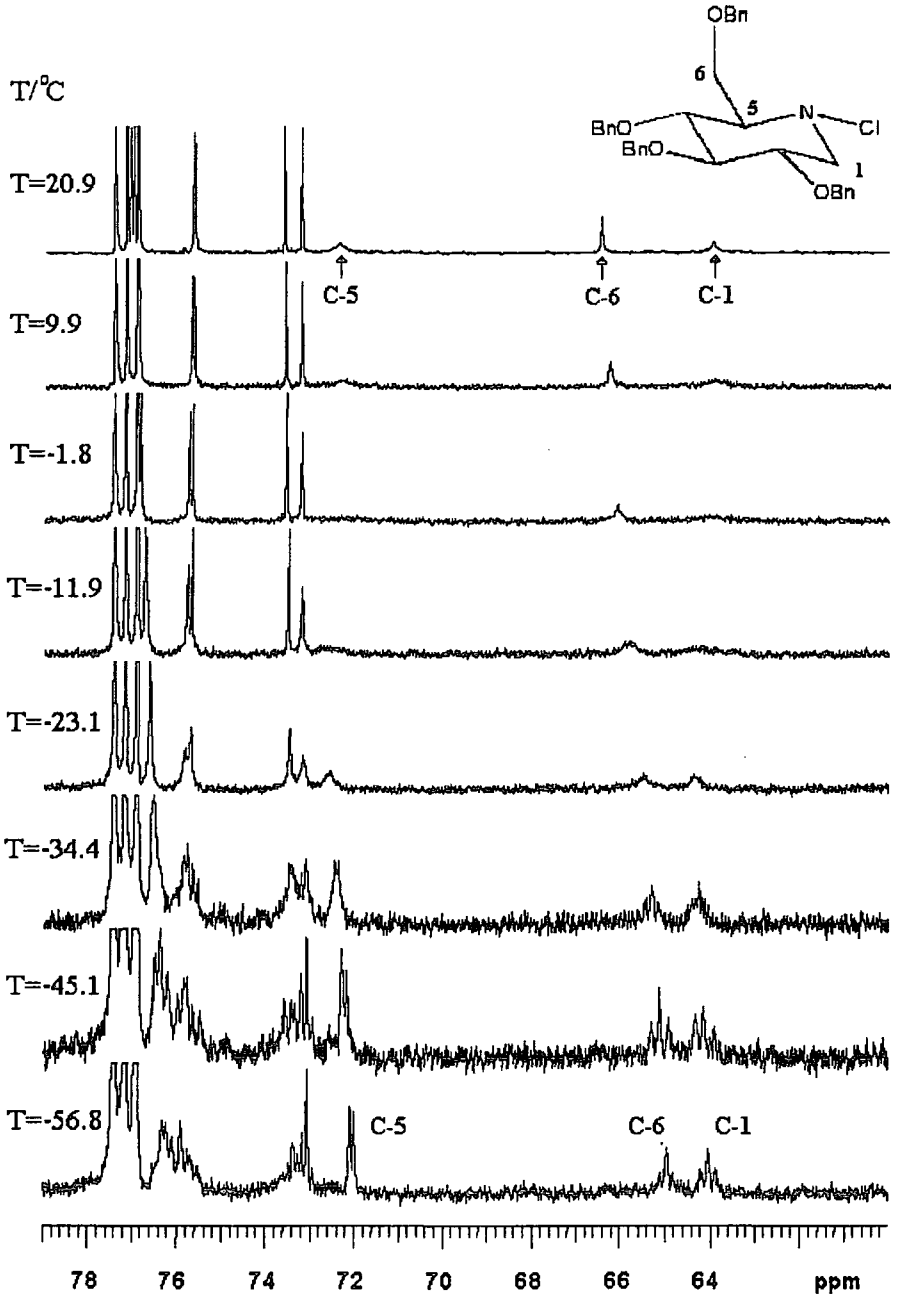


Figure 28. VT ^{13}C-NMR studies on *N*-chloro-TBDNJ (**4.07**) (T/°C).

The slow inversion of stereochemistry at nitrogen is observable by its effect on the room temperature ^{13}C-NMR of tetra-*O*-benzyl-*N*-chloro DNJ, causing a broadening of the carbon peaks adjacent to nitrogen in the ring. Preliminary variable temperature ^{13}C-NMR studies (Figure 28) have allowed us to observe the temperature dependence of this inversion.

In the case of TBDNJ (**4.01**) we can assume a preferential $^4C_1$ conformation, with all benzyl ethers adopting an equatorial position. This is supported by the large proton-proton NMR coupling constants ($^3J_{HH}$) in the ring, and is analogous to the $^4C_1$ conformation observed in similar D-glucose systems.[125] Pyrimidal inversion at nitrogen can be observed to slow upon cooling, by increased resolution in the ^{13}C-NMR spectrum, beginning around – 35 °C (Figure 28).

Once locked in the lowest energy NCl_{eq} orientation, anti-elimination of HCl to form the ketimine is not possible (Figure 27).

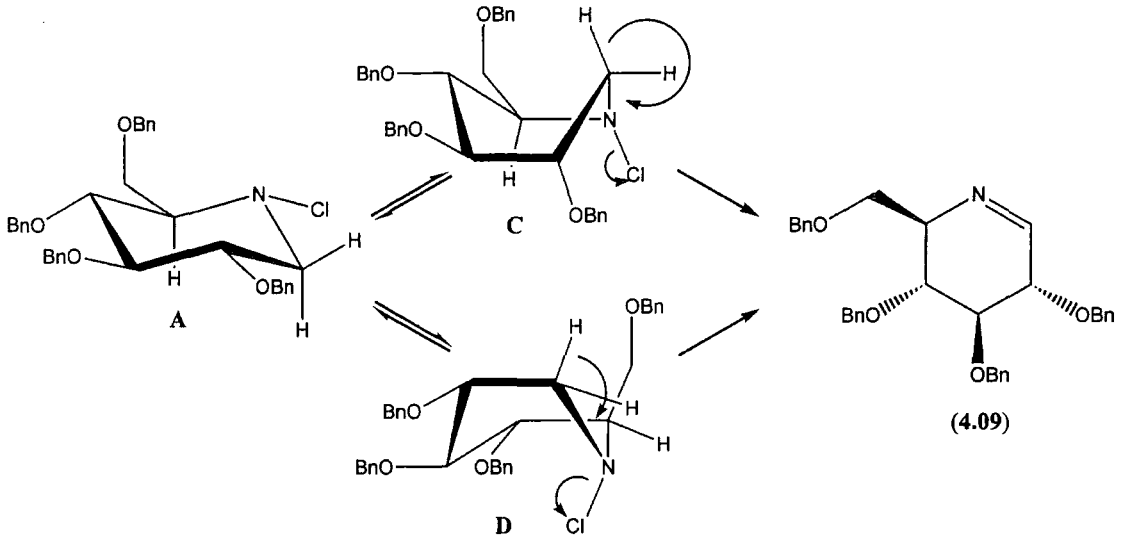


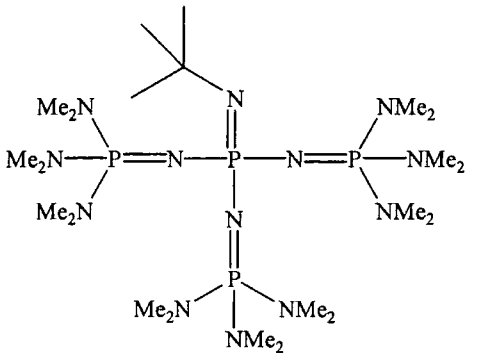
Figure 29. Conformations allowing anti-periplanar elimination of HCl in *N*-chloro-TNDNJ (**4.07**) at low temperatures.

We speculate that, at such low temperatures, only a few anti-periplanar conformers are accessible involving either of the two more stable boat forms of the system, conformations C (^{1,4}B), and D ($B_{N,3}$) as shown in Figure 29, above. Ring flip to the alternative $^1C_4$ chair with all substituents axial, which is unfavourable due to 1,3-diaxial interactions, also allows antiperiplanar alignment of H-1, and *N*-Cl.

Upon treatment of *N*-chloro-TBDNJ (**4.07**) with lithium tetramethylpiperidide (LiTMP) at – 78 °C, elimination to form exclusively the aldimine is observed, consistent with the rationalisation above (Scheme 73).

The other competing reaction in this case is a metal-halogen exchange, which we observed under certain conditions such as in the presence of Grignard reagents, with the use of LDA at low and elevated temperatures, and the use of LiTMP at room temperature. In such cases, reduction of the chloramines to the amine is observed, probably via metal/halogen exchange.

The low temperature elimination was also attempted with the strong phosphazene base P4-t-butyl phosphazene (**4.29**),[126] however no elimination was observed. Formation of TBDNJ (**4.01**), possibly through halogen exchange, occurred.



(**4.29**)

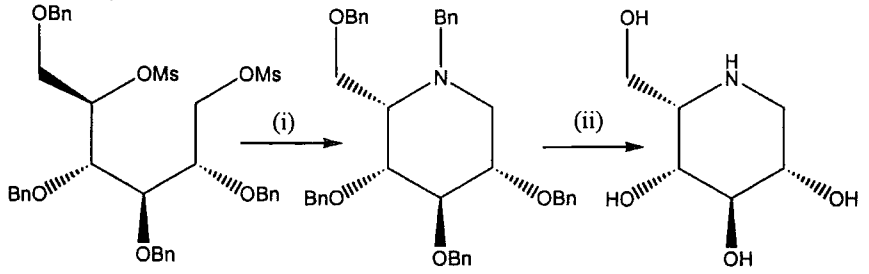
Figure 30. P4-t-butyl phosphazene (**4.29**).[126]

These stereochemical rationalisations are based on simple modelling studies, and are intended to explain the experimental data. Another possibility, in the case of stronger bases, is a more E1cB-like mechanism, with the partial formation of an anion at the more stable C-2 position, giving the aldimine (**4.09**) upon elimination of chloride. In order to assess the mechanism fully kinetic isotope and isotope exchange experiments would be required.[66,67]

These studies have allowed us access to both cyclic imines (**4.06**) and (**4.09**) derived from TBDNJ (**4.01**), and these have been screened with organometallic nucleophiles (see Section 4.6).

4.4 Synthesis of TBDINJ (4.02) from Tetra-*O*-benzyl-D-glucitol (4.04) *via* a Double Displacement Strategy

In this case, synthesis of TBDINJ (**4.02**) is based around a known strategy towards the synthesis of fully deprotected DINJ *via* a double displacement of two methanesulfonyl groups by a suitable 'bidentate' nitrogen nucleophile. Haines *et al.*[115] used benzylamine as the nucleophile, giving the intermediate *N*-benzyl-TBDINJ (**4.31**), and cleaved all *O*-benzyl ethers and the *N*-benzyl group in one step, giving fully deprotected DINJ (Scheme 74).

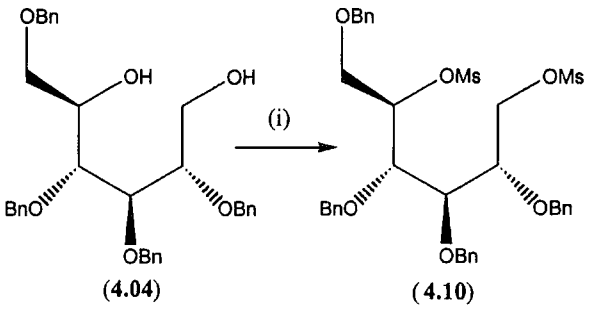


(**4.10**) (**4.31**) (**4.30**)

(i) $BnNH_2$, 55 °C, 56 %; (ii) H_2, Pd/C, HCl, EtOH, 97 %.

Scheme 74. Synthesis of 2-deoxy idonojirimycin *via* a double displacement reaction.[115]

Since we require the tetra-*O*-benzyl derivative of DINJ, we initially attempted introducing protecting groups orthogonally by use of aminodiphenylmethane as the amine source, giving the *N*-diphenylmethane derivative.

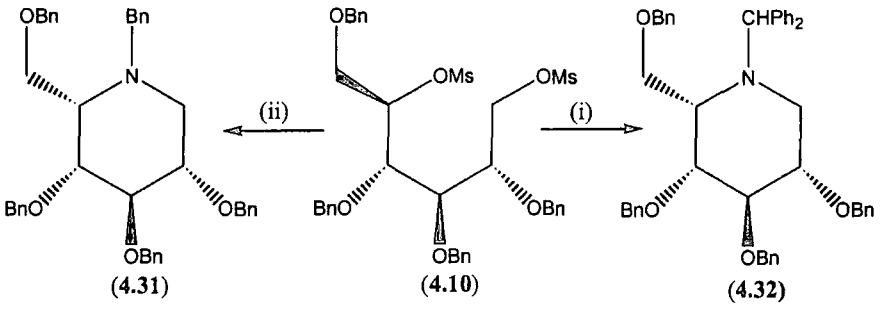


(**4.04**) (**4.10**)

(i) MsCl, Py, 0 °C, 71 %.

Scheme 75. Synthesis of dimesyl glucitol derivative (**4.10**).

Treatment of glucitol (**4.04**) (Scheme 75) with methanesulfonyl chloride gave the protected 1,5-dimesyl-glucitol (**4.10**) in 71 % yield. The previously unknown double displacement of this dimesylate by aminodiphenylmethane, without solvent, proceeded in low yield (4 % isolated), as may be expected for such a bulky nucleophile. Problems were also encountered in removing the aminodiphenylmethane, which has a high boiling point. Due to the low recovery, the product (**4.32**) was only identified by its mass spectrum. This strategy was abandoned due to the problems encountered during purification.

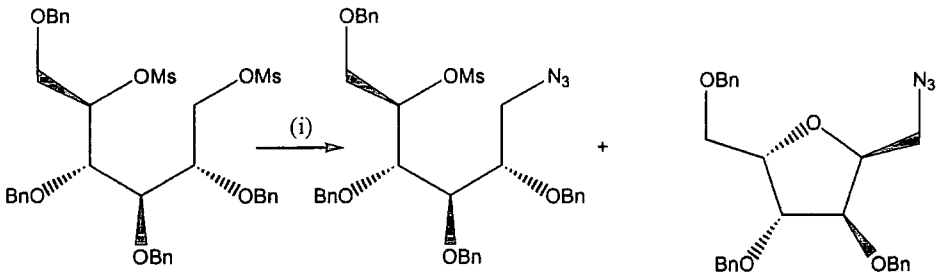


(i) H_2NCHPh, heat, 4 % isolated; (ii) $BnNH_2$, 80°C, 72 %.

Scheme 76. Synthesis of *N*-benzyl-TBDINJ (**4.31**), and *N*-diphenylmethyl-TBDINJ (**4.32**) from dimesylate (**4.10**).

In order to assess the double displacement reaction of dimesylate (**4.10**), benzyl amine was used, following the method of Haines *et al.*,[115] and pleasingly the protected *N*-benzyl-TBDINJ (**4.31**) could be isolated in 72 % yield after distillation of the excess benzylamine (Scheme 76). Subsequent selective deprotection of the *N*-benzyl group should be possible,[127] but was not attempted. An alternative synthesis of TBDINJ (**4.02**) was devised instead.

The low yields obtained with aminodiphenylmethane in this synthesis prompted us to investigate an alternative, novel strategy. The lower reactivity of the secondary mesylate in dimesyl-glucitol derivative (**4.10**) to nucleophilic addition of azide allowed selective formation the 1-azido-5-mesyl-glucitol (**4.33**) (Scheme 77).



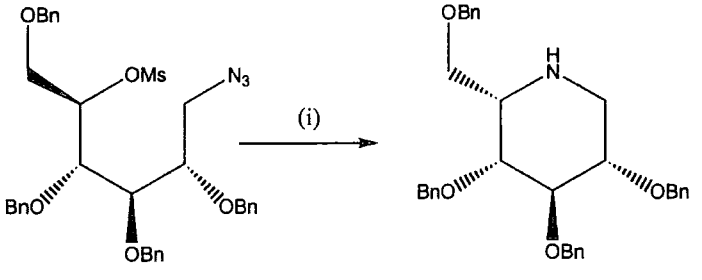
(4.10) (4.33) (4.34)

(i) NaN_3, DMF, 70 °C, 79 % of (**4.33**), 17 % of (**4.34**).

Scheme 77. Formation of azido-mesyl-glucitol (**4.33**).

Treatment of the dimesyl glucitol (**4.10**) with sodium azide in DMF at room temperature gave the 1-azido-5-mesyl-glucitol (**4.33**) in 48 % yield (78 % based on the recovery of the starting dimesylate (**4.10**)). However, the reaction did not proceed to completion even with extended reaction times. Elevated reaction temperatures improved this yield.

Optimum conditions were found to be sodium azide in DMF at 70 °C for 7 h, giving the desired azido mesylate in up to 79 % yield with 17 % of the unwanted 5-azido-1,4-anhydro-sugar (**4.34**) (Scheme 77). Cyclisation of the azido mesylate with triphenylphosphine in THF with dilute aqueous NaOH gave TBDINJ (**4.02**) in 92 % yield after purification by cationic ion exchange (Scheme 77).



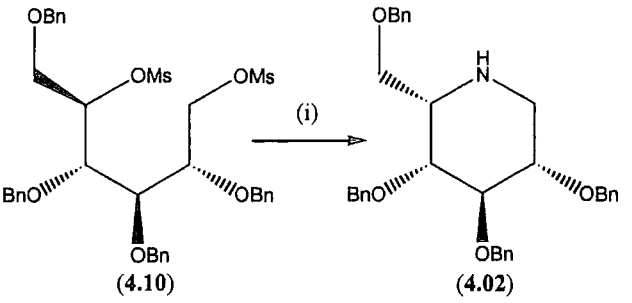
(4.33) (4.02)

(i) PPh_3, Et_2O, then THF, NaOH (aq.), 92 %.

Scheme 78. Synthesis of TBDINJ (**4.02**).

As an alternative large-scale approach to this synthesis of TBDINJ (**4.02**), the above reaction was performed in one pot (Scheme 79). Addition of triphenylphosphine and sodium hydroxide solution to the reaction mixture after formation of the azido

mesylate (**4.33**) gave TBDINJ in 61 % yield from dimesylate (**4.10**), an overall yield of 43 % from tetra-*O*-benzyl-D-glucose (**4.03**) over 4 steps.

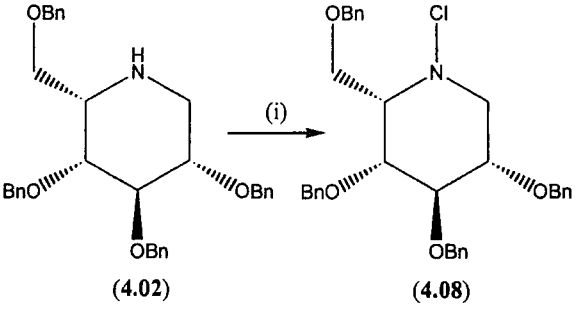


(i) NaN_3, DMF, then PPh_3, DMF/NaOH (aq), 80 °C, 61 %.

Scheme 79. One-pot synthesis of TBDINJ (**4.02**) from dimesylate (**4.10**).

4.5 Synthesis of Cyclic Aldimine 1,*N*-Dehydro-TBDINJ (4.05) from TBDINJ (4.02) *via* a Chlorination/Elimination Strategy

TBDINJ (**4.02**) (Section 4.4) undergoes *N*-chlorination efficiently (Scheme 80), as was observed for the TBDNJ analogue (see Section 4.3). The desired *N*-chloro-TBDINJ (**4.08**) was formed in up to 87 % yield by treatment of TBDINJ (**4.02**) with NCS in DCM, and could be stored at – 18 °C for several weeks without significant decomposition.



(i) NCS, DCM, 87 %.

Scheme 80. Chlorination of TBDINJ (**4.02**).

Studies of elimination reactions of *N*-chloro-TBDNJ (**4.07**) (Section 4.3) led us to expect that anti-elimination of HCl, *via* the $^4C_1$ conformation NCl_{ax} configuration, would be favoured at elevated temperatures (Figure 27, above). In the case of the analogous *N*-chloro-TBDINJ system (**4.08**) (the C-6 epimer of *N*-chloro-TBDNJ

(**4.07**)) elimination to form ketimine (**4.06**) *via* the $^4C_1$, NCl_{ax} structure (B, Figure 31) is not allowed. Using the same stereoelectronic considerations as applied to the DNJ system, only elimination to form the aldimine of TBDINJ can occur under such conditions (Figure 31, below).

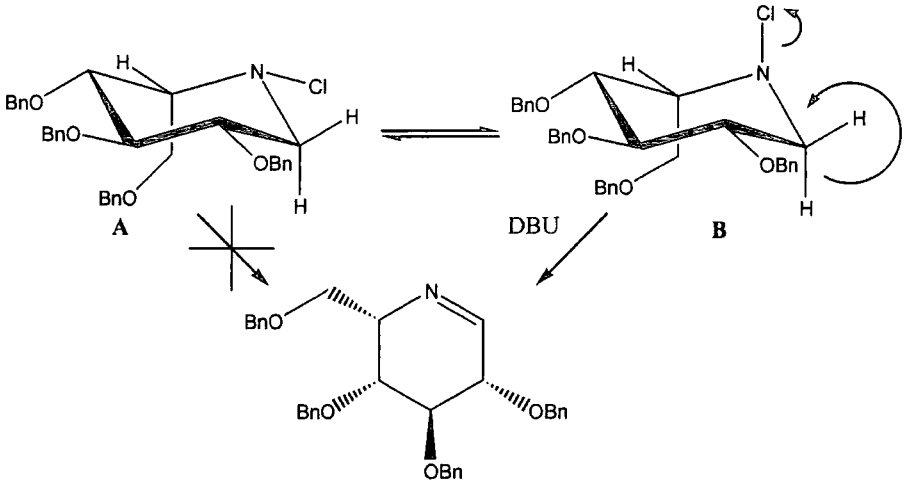
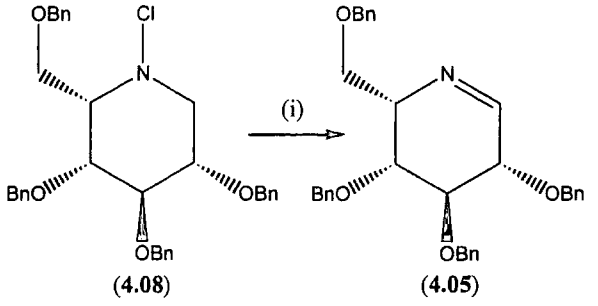


Figure 31. Conformational analysis of *N*-chloro-TBDINJ (**4.08**), and its relation to formation of 1,*N*-dehydro-TBDINJ (**4.05**).

It was found that treatment of *N*-chloro-TBDINJ (**4.08**) with DBU at room temperature gave the aldimine (**4.09**) as expected. The reaction was, however, slower than for the analogous *N*-chloro-TBDNJ (**4.07**) (Section 4.3), and evidence for enolisation of the imine (crude NMR) was observed before total consumption of the chloramine (**4.08**). Total consumption of starting material (TLC) was only observed after > 48h.

The reaction was performed in $CDCl_3$, and the progress monitored by ^{1}H-NMR. Slow formation of the desired imine could be observed (^{1}H, s, 7.85 ppm; ^{13}C, d, 164 ppm.) together with formation of another product, possibly the enamine (^{1}H, 5.56 ppm, ^{13}C 140.7, 126.3).

In refluxing THF the reaction was found to proceed faster. However, enolisation was again observed at the end-point. Optimum conditions were found to be 1.1 eq. DBU in refluxing diethyl ether for 7 h. After formation of the imine the hydrochloride salt of DBU was removed by filtration and the resultant solution was used directly in addition reactions (see section 4.7), as degradation of the imine was observed if stored for any length of time, even at low temperatures.



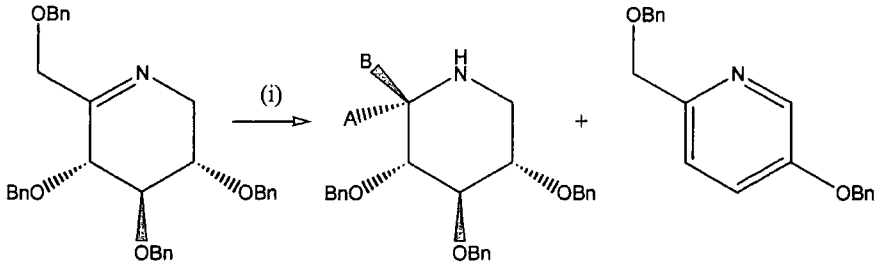
(i) DBU, Et_2O, reflux, 7 h.

Scheme 81. Formation of 1,*N*-dehydroTBDINJ (**4.05**).

The above observations are in agreement with the stereoelectronic factors discussed in Section 4.3 above with regard to elimination of HCl from *N*-chloro-TBDNJ (**4.07**).

4.6 Irreversible Addition Reactions of Cyclic Imines 5,*N*-Dehydro-TBDNJ (4.06) and 1,*N*-Dehydro-TBDNJ (4.09)

Ketimine (**4.09**) formed by the room temperature elimination of HCl from *N*-chloro-TBDNJ (see Section 4.3), was treated with various commercial Grignard reagents (MeMgBr, PhMgBr, EtMgBr and BnMgCl). Addition of the Grignard reagent to the imine in diethyl ether solution at room temperature led to decomposition of the imine, and no addition product was isolated for any of the Grignard reagents used. Addition of the nucleophile at low temperature (– 78 °C), followed by warming to room temperature gave isolable addition products in the case of methyl, and benzyl Grigards (see Table 3). In the case of phenyl and ethyl Grignards, only trace quantities of products arising from addition were isolated. Their identities were confirmed by mass spectroscopy.



(4.06) (4.18)

(i) R^-. A = H, B = $BnOCH_2$, (**4.01**)
A = Me, B = $BnOCH_2$, (**4.35**)
A = $BnOCH_2$,B = Bn, (**4.36**)

Scheme 82. Irreversible addiditon to ketimine 5,*N*-dehydro-TBDNJ (**4.06**).

In all cases significant decomposition of the imine was observed, and by-products, such as benzyl alcohol and the functionalised pyridine (**4.18**), were isolated. Treatment of the imine with 5 eq. of the desired Grignard reagent at – 78 °C for 1.5 h followed by warming to room temperature for a further 12 h and quenching with aq. NH_4Cl gave best yields of adducts, up to 19 % from *N*-chloro-TBDNJ (**4.07**) for benzylmagnesium chloride (Table 3).

Stereocontrol of addition to the cyclic ketimine (**4.06**) can be rationalised by accepted stereoelectronic and steric influences associated with such systems (see Chapter 1, Section 1.4).[58] The addition of a nucleophile to a 6-membered cyclic sp^2 system, in the absence of steric approach effects, should afford preferentially the product corresponding to the lower energy transition-state. The conformation of the transition-state is defined by the requirement for the reactive electron pair of the nucleophile to maintain orbital alignment with the breaking double bond, and the change in stereochemistry forced by the sp^2 to sp^3 transition. For example, Figure 32 shows the approach of a nucleophile to ketimine (**4.06**). **Path a** (Nuc^-_{ax}) leads to a chair-like $^4C_1$ transition-state (conformation A, Figure 32), and **Path b** (Nuc^-_{eq}) to a higher energy boat-like transition-state (conformation B, Figure 32).

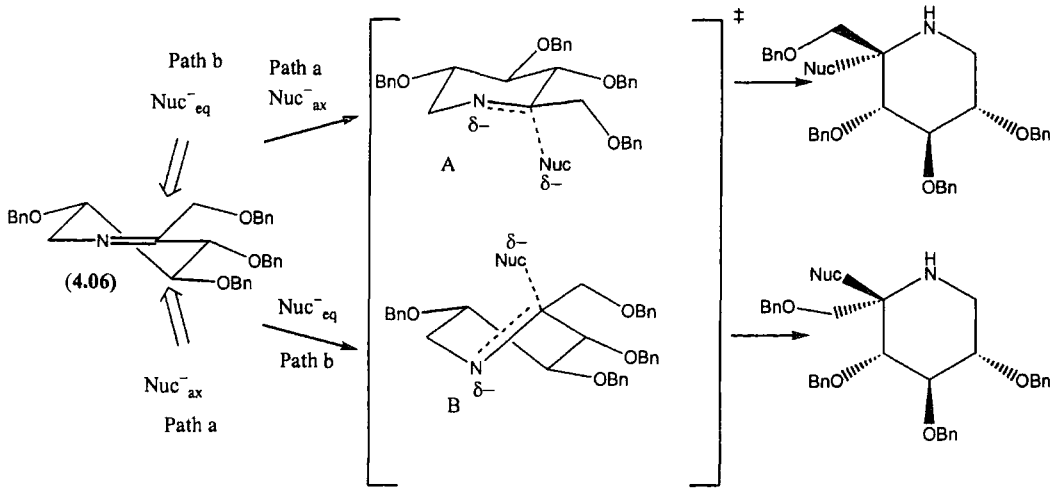


Figure 32. Proposed transition-states in addition to cyclic ketimine 1,*N*-dehydro-TBDNJ (**4.06**).

Path a reactions are generally observed to be favoured, and products corresponding to such pseudo-axial attack are generally isolated in such cases (see Chapter 1, Section 1.4). In our case the less bulky Grignard reagent, methyl, approached in a **Path a** type reaction, whereas the larger benzyl Grignard gave only the product corresponding to equatorial addition. In the case of benzyl Grignard we must therefore assume that the size of the nucleophile is introducing a new controlling factor to the addition. Simple steric approach control analysis of the imine shows that, when steric approach factors dominate, the preferred approach of the nucleophile is from the least hindered face, equating to **Path b** by our nomenclature (Figure 33).

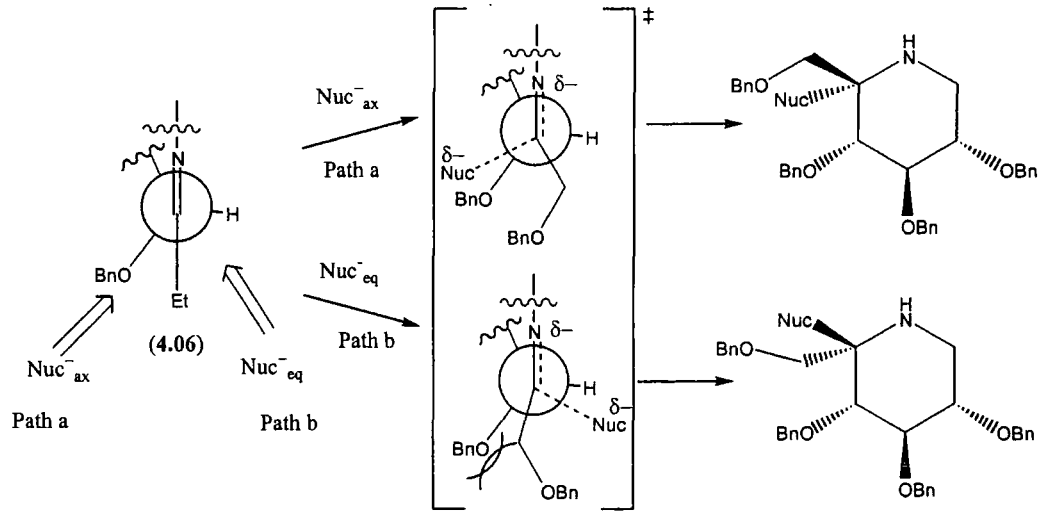
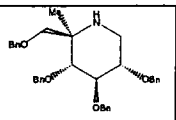
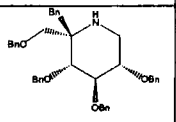
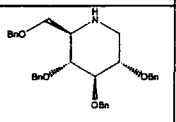


Figure 33. Steric approach control analysis of addition to ketimine (**4.06**).

In order to probe further the stereochemistry of addition to the cyclic ketimine (**4.06**), nucleophilic addition of hydride was attempted in diethyl ether, with $LiAlH_4$ as the hydride source. Reduction gave only the DNJ diasteroisomer (87 % from *N*-chloro-TBDNJ (**4.07**)).[128] The observations are consistent with axial attack of hydride, as might be expected for a small nucleophile. The results are also consistent with the reduction of 5,*N*-dehydro-1-*C*-ethyl-TBDINJ (**4.38**) (Section 4.9) in the synthesis of the (–)-adenophorine skeleton.

Table 3. Optimised results of addtition reactions to DNJ ketimine (**4.06**).

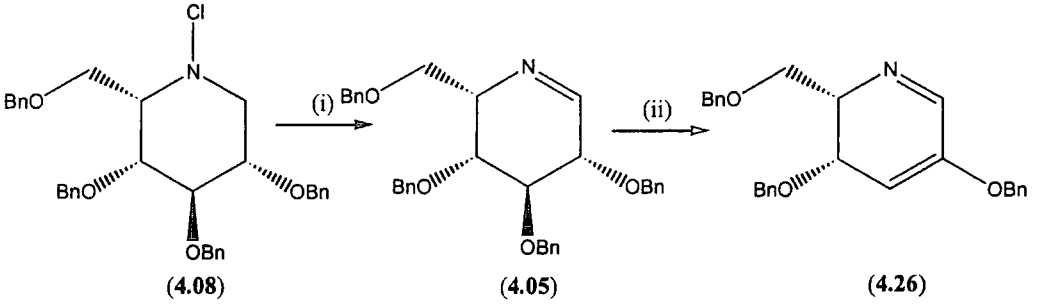
Nucleophile	**Conditions**	**Product**		**Yield[b] / %**
MeMgBr	Et_2O, – 78 °C – rt		**(4.35)**	**10**
PhMgBr	Et_2O, – 78 °C – rt	-	-	-
BnMgCl	Et_2O, – 78 °C – rt		**(4.36)**	**19**
$LiAlH_4$	Et_2O, rt, 10 min		**(4.01)**	**87**
Et_2Mg	–78 °C - rt, 2h	-	-	-
EtMgBr	rt, reverse addition	-	-	-

a) Isolated yields over two steps from *N*-chloro-TBDNJ (**4.07**).

Addition reactions were attempted with aldimine (**4.09**), as synthesised by the low temperature elimination of *N*-chloro-TBDNJ (**4.07**) (see Section 4.3). Screening with methyl, phenyl, benzyl Grignards at – 78 °C, then warming to room temperature before quenching gave no isolable adducts. In some cases formation of TBDNJ (**4.01**) was observed, possibly due to metal/halogen exchange of unreacted *N*-chloro-TBDNJ (**4.07**), together with intractable mixtures of degradation products.

4.7 Synthesis of (–)-1-*epi*-Adenophorine (4.12) by Nucleophilic Addition to 1,*N*-Dehydro-TBDINJ (4.05)

Nucleophilic addition to 1,*N*-dehydro-TBDINJ (**4.05**) as formed by the chlorination/elimination of TBDINJ (see section 4.5) was attempted with the aim of synthesising the natural product adenophorine. Attempts at additions were therefore based around ethyl nucleophiles. Simple addition of ethylmagnesium bromide at room temperature led to decomposition of the imine and formation of the elimination product (**4.26**), through loss of benzyl alcohol (Scheme 83). Interestingly, complete elimination to form the pyridine was not observed, unlike the case of the formation of pyridine (**4.18**) from 5,*N*-dehydro-TBDNJ (**4.06**) ketimine under similar conditions (see Section 4.6). Performing the reactions at low temperature (– 78 °C), as was successful for 5,*N*-dehydro-TBDNJ (**4.06**) (Section 4.6), gave no isolable adducts in this system.



(i) DBU, Et_2O, reflux, 7h; (ii) EtMgBr, rt, Et_2O.

Scheme 83. Decomposition of 1,*N*-dehydro-TBDINJ (**4.05**) in the presence of Grignard reagents.

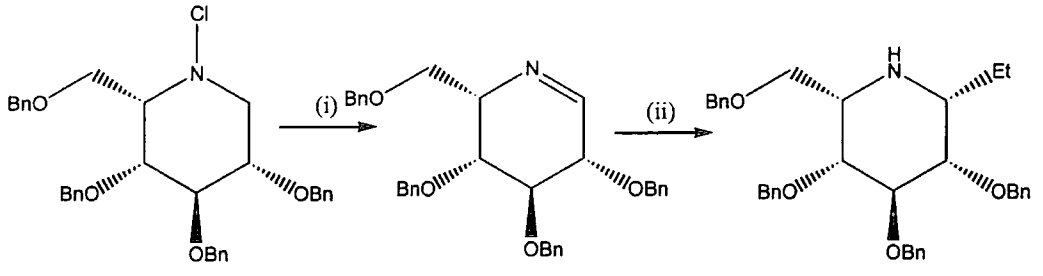
It is possible that the basicity of the nucleophile contributed to the elimination. However, the same product was observed by the spontaneous decomposition of the imine in solution as formed either by the Staudinger approach or by the chlorination/elimination method (Sections 4.2, and 4.5 respectively). In order to change the properties of the nucleophile several factors were employed.

Initially, use of catalytic copper(I) iodide was attempted in order to 'soften' the nucleophile, possibly making it more compatible with the azomethine electrophile,[49]

however, no incorporation of the ethyl nucleophile was observed under the conditions used.

Dialkyl zincs have been observed to add to imines with and without activators such as amino-alcohols or Lewis acids.[56] Treatment of imine (**4.05**) with diethyl zinc at room temperature in diethyl ether gave no incorporation of the nucleophile.

Use of the less basic dialkylmagnesium reagent in diethyl ether solution at – 78 °C was attempted by use of 1,4-dioxane to displace the Schlenk equilibrium in favour of the dialkyl nucleophiles.[89] Pleasingly addition to the imine was observed under these conditions, and up 35 % of desired adduct (**4.37**) was isolated (Scheme 84). Varying quantities of TBDINJ, were also formed during such reactions, probably formed by halogen exchange of *N*-chloro-TBDINJ (**4.08**) during the elimination or residual *N*-chloro-TBDINJ (**4.08**) after the addition of the Grignard reagent. Decomposition of the imine was also observed, with aza-diene (**4.26**) being formed.



(**4.08**) (**4.05**) (**4.37**)

(i) DBU, Et_2O, reflux, 7 h; (ii) EtMgBr, 1,4-dioxan , – 78 °C, Et_2O, 35 % from (**4.08**).

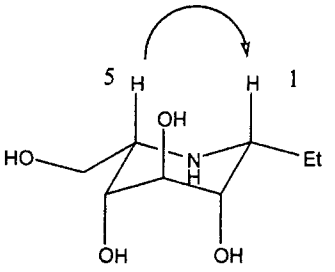
Scheme 84. Addition to 1,*N*-dehydro-TBDINJ (**4.05**).

The addition product was found to have broad room temperature ^{1}H- and ^{13}C-NMR spectra, suggesting that more than one conformational state was readily accessible. The equatorial nature of the majority of substituents in the desired product adenophorine would suggest that the $^4C_1$ chair form would be favoured as this allows four pseudoequatorial substituents, reducing diaxial interactions.[129]

Proton-proton coupling constants for (**4.37**) were not observable, and the relative stereochemistry at C-1 could not be determined by this means. NOe interactions were observed but were inconclusive, possibly due to the conformational lability. In order to assign the C-1 stereochemistry of adduct (**4.37**) it was decided to remove the benzyl

protecting groups and compare the sample to an authentic sample of adenophorine supplied by Assano *et al.*[116]

Deprotection of (**4.37**) by hydrogenation over with palladium(II) chloride gave the hydrochloride salt of the fully deprotected aza-sugar, which could be converted into the free base by ion exchange (see Section 4.9). The NMR spectrum of the deprotected aza-sugar showed it to be different to the authentic sample of adenophorine, indicating that the C-1 epimer had been formed, and the stereochemistry of (**4.37**) was assigned accordingly. NOe experiments showed through-space interactions between H-1, and H-5 (Figure 34) suggesting that the preferred conformation of the deprotected sugar in water was the opposite $^1C_4$ chair, with three axial hydroxyl groups.



(**4.12**)

Figure 34. NOesy interactions of deprotected aza-sugar (**4.12**) in D_2O.

The conformational analysis of the deprotected sugar allowed analysis of the stereochemistry of addition to the cyclic imine (**4.05**), with axial attack of the nucleophile, as might have been expected under stereoelectronic consideration of the transition state (see Section 4.6). Under our nomenclature, addition could occur by one of two paths, **Path a** or **Path b** (Figure 35).

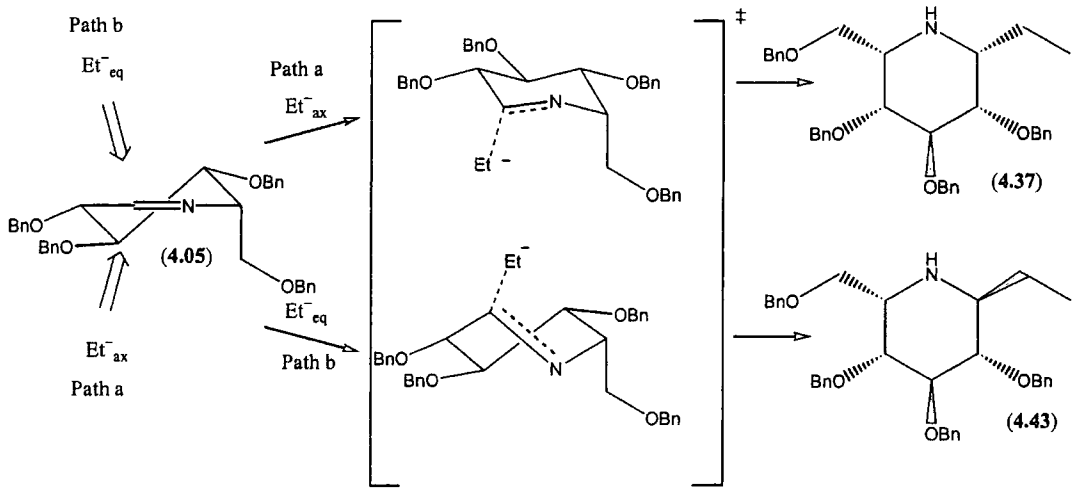
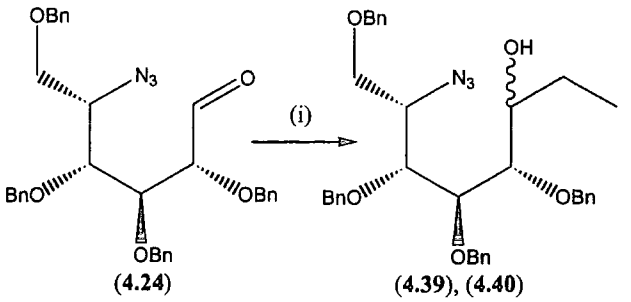


Figure 35. Proposed transition-states for addition to cyclic imine (**4.05**).

As we reasoned earlier (see Section 4.6), addition of a small nucleophile such as diethylmagnesium, to such an imine system should preclude formation of a favourable chair-like transition-state (**Path a**, Figure 26). Steric-approach-controlled additions, such as may be expected with large nucleophiles, should proceed by **Path b**. Retrospective analysis of the transition-state allows us to rationalise the observed addition *via* **Path a**, and propose another synthesis of the desired natural product by reduction of the cyclic ethyl ketimine (**4.13**) with a small hydride source (see Section 4.8).

4.8 Synthesis of (–)-Adenophorine by Addition of Hydride to Cyclic Ketimine 1-Ethyl-1,*N*-dehydro-TBDINJ (4.13).

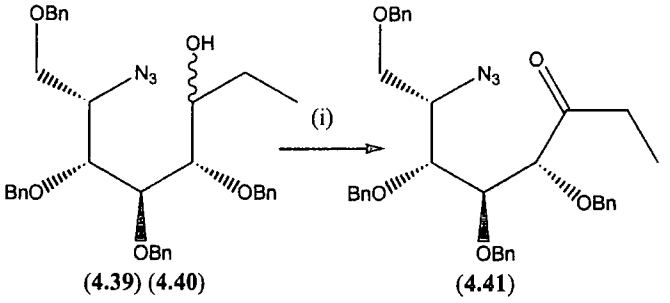
Ethyl ketimine 1,*N*-dehydro-1-C-ethyl-TBDINJ (**4.13**) was our target molecule, and retrosynthetic analysis gave a convenient synthesis from the azido-sugar (**4.24**), synthesised earlier (see Section 4.2). Nucleophilic addition to the aldehyde function was achieved with ethylmagnesium bromide in diethyl ether at room temperature, giving an inseparable mixture of diastereoisomers (**4.39**), and (**4.40**) (dr 1 : 3) in up to 70 % yield (Scheme 85).



(i) EtMgBr, Et_2O, rt, 70 %, (dr 1 : 3).

Scheme 85. Nucleophilic addition to azido-sugar (**4.24**).

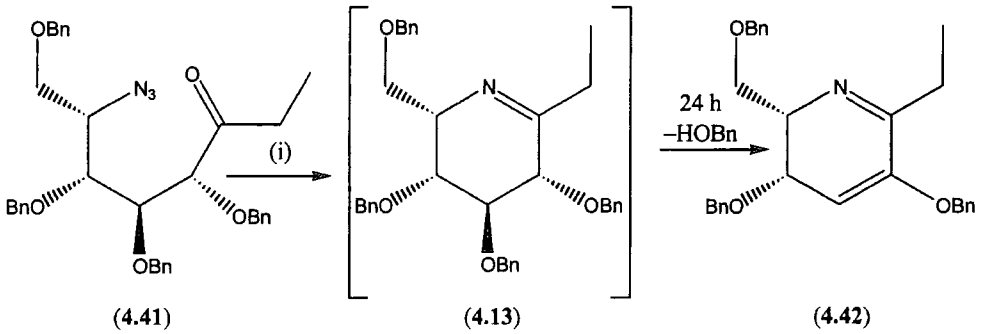
The resultant mixture of azido alcohols (**4.39**), and (**4.40**), was treated with PCC in DCM, giving the azido ketone (**4.41**) in up to 72 % yield (Scheme 86). The azido ketone is a direct precursor to the desired ketimine (**4.13**) *via* a Staudinger aza-Wittig cyclisation.[74]



(i) PCC, DCM, sieves, 72 %.

Scheme 86. Oxidation of azido-alcohols (**4.39**), and (**4.40**).

The Staudinger reaction of ketone (**4.41**) was performed initially in DCM with triphenylphosphine. It was found that considerable decomposition of the imine occurred in DCM or $CDCl_3$, similar to that observed during the formation of aldimine 1,*N*-dehydro-TBDINJ (**4.05**) by a Staudinger reaction (see Section 4.2). Imine (**4.05**) decomposed by elimination of benzyl alcohol, and the aza-diene (**4.42**) (Scheme 87) could be isolated after extended reaction times. This decomposition was less pronounced in diethyl ether solution, and optimium conditions for the formation of ketimine (**4.13**) were found to be treatment with excess triphenylphosphine (3.0 eq.) in diethyl ether for 3 h at room temperature. Ketimine (**4.13**) could not be purified by flash chromatography, and was therefore used immediately in all subsequent reactions.



(4.41) (4.13) (4.42)

(i) PPh_3, Et_2O, 3h

Scheme 87. Formation of 1,*N*-dehydro-1-*C*-ethyl-TBDINJ (**4.13**) and subsequent decomposition with extended reaction times.

Treatment of ketimine (**4.13**) with a suitable nucleophilic hydride source was expected to give the desired adenophorine stereochemistry, by analogy with nucleophilic addition to the similar 1,*N*-dehydro-TBDINJ (**4.06**) (Section 4.7). Formation of the proposed lower energy chair-like transition-state (conformation A, Figure 36), by pseudo-axial attack of hydride (**Path a**), should be favoured over the more strained boat-like transition-state (conformation B, Figure 36) formed by pseudo-equatorial attack of the nucleophile (**Path b**).

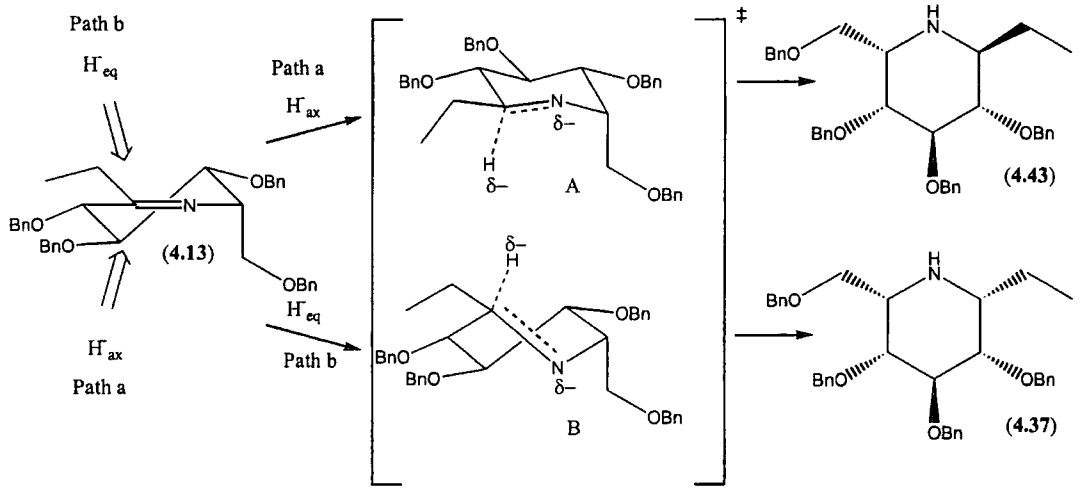


Figure 36. Proposed transition states for nucleophilic addition of hydride to ketimine (**4.13**).

Steric approach control analysis of the addition (Figure 37) shows the least hindered approach for the nucleophile to be pseudo-equatorial (H^-_{eq}), and as such would lead to the 1-*epi*-adenophorine. In this model, however, no consideration is given to the energetic barriers associated with change of conformation in the ring. Again, the stereochemistry may be defined by the size of the nucleophile, larger nucleophiles being directed by steric approach control.

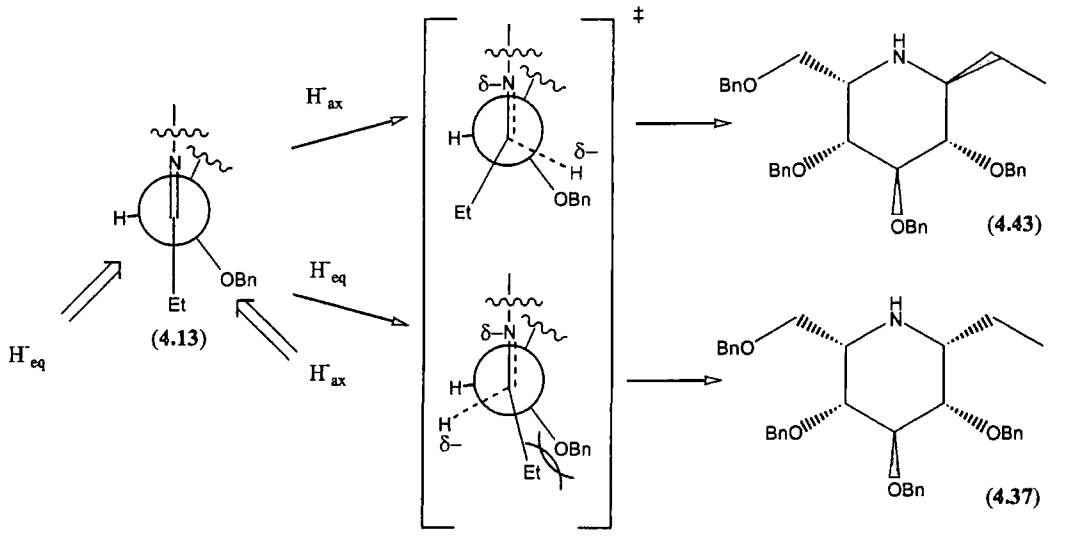
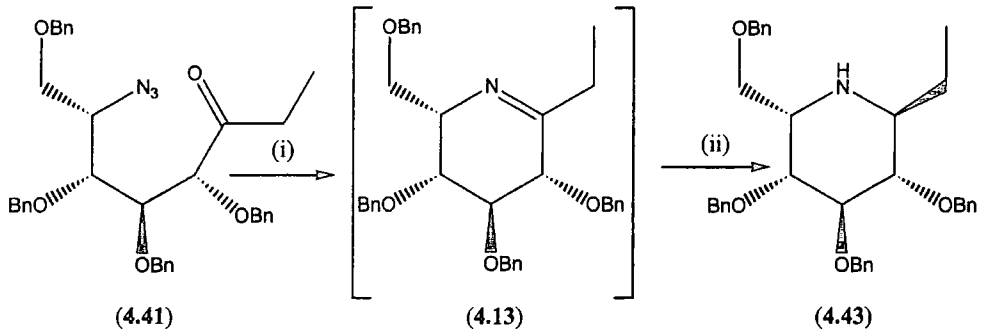


Figure 37. Steric approach control analysis of addition to the cyclic ketimine (**4.13**).

Initially methanolic sodium borohydride was chosen as the hydride source. The ketimine (**4.13**) was synthesised by the Staudinger reaction of azido-sugar (**4.41**) in diethyl ether. The reaction mixture was immediately concentrated and redissolved in methanol with sodium borohydride (5.0 eq.). The borohydride reduction led to formation of a mixture of the desired (1*S*) isomer, tetra-*O*-benzyl-adenophorine (**4.43**) (16 %), and the (1*R*) isomer (**4.37**) (32 %), (dr 1 : 2).

As an alternative approach, diethyl ether was used as the solvent, consistent with additions to the corresponding 1,*N*-dehydro-TBDINJ (**4.05**) (see Section 4.7). Lithium aluminium hydride (LAH) was chosen as a nucleophilic hydride source. Addition of LAH to the Staudinger reaction mixture after imine formation gave only the adenophorine isomer (**4.43**), isolated in 68 % yield, together with the unsaturated piperidine (**4.42**) (13 %) (Scheme 88). None of the *epi*-adenophorine isomer was observed.



(4.41) (4.13) (4.43)

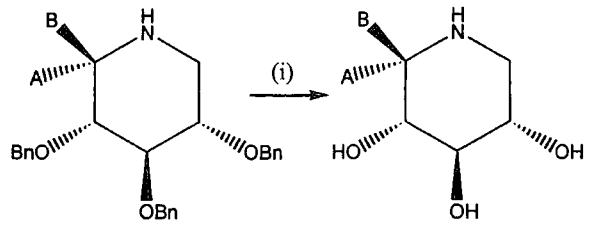
(i) PPh_3, Et_2O, 3h; (ii) LAH, Et_2O, 68 %.

Scheme 88. Reduction of ketimine (**4.13**).

In order to assess the effect of the size of the hydride source in diethyl ether, reduction of the imine was attempted with K-selectride, however, no reduction at all was observed, and only the aza-diene (**4.42**) was isolated even with extended reaction times and excess reagent.

4.9 Deprotection of Aza-Sugars (4.37), (4.43), (4.35) and (4.36)

In order to demonstrate the utility of the above methodology in the synthesis of potentially biologically active compounds, removal of protecting groups from protected aza-sugars adducts (**4.37**), (**4.43**), (**4.35**) and (**4.36**) was attempted by catalytic hydrogenation.



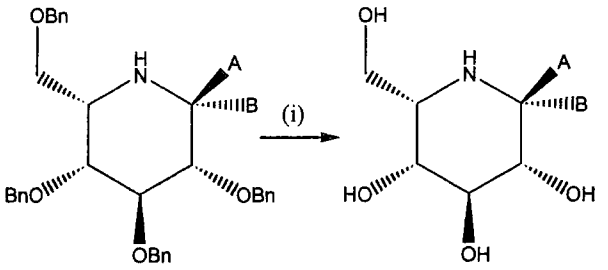
A = Me, B = $BnOCH_2$, (**4.35**) A = Me, B = $HOCH_2$, (**4.45**)
A = $BnOCH_2$,B = Bn, (**4.36**) A = $HOCH_2$,B = Bn, (**4.46**)

(i)H_2, $PdCl_2$, methanol, 93 % for (**4.45**), (**4.46**) not isolated.

Scheme 89. Hydrogenation of protected aza-sugars (**4.35**), and (**4.36**).

Treatment of (**4.35**) with hydrogen in the presence of palladium(II) chloride in methanolic solution gave the desired aza-sugar (**4.45**) in 93 % yield. Under similar

conditions, however, decomposition of (**4.36**) was observed, and no isolable product was obtained.



A = H, B = Et, (**4.37**)
A = Et, B = H, (**4.43**)

A = H, B = Et, (**4.12**)
A = Et, B = H, (**4.11**)

(i)H_2, $PdCl_2$, ethanol, 87 % for (**4.12**), 100 % for (**4.11**).

Scheme 90. Synthesis of (–)-adenophorine (**4.11**), and (–)-1-*epi*-adenophorine (**4.12**).

Hydrogenation of (**4.37**) in the presence of palladium(II) chloride gave the desired (–)-1-*epi*-adenophorine (**4.12**) in 87 % yield. The stereochemistry was assigned by nOesy interactions (see Section 4.7, Figure 34, p 124). Similarly, removal of protecting groups from (**4.43**) gave the desired (–)-adenophorine (**4.11**) in quantitative yield. The sample was found to be identical in all respects to the authentic (+)-adenophorine supplied by Assano *et al.*,[116] except for the sense of its optical rotation ((**4.11**): $[\alpha]_D^{22.0}$ = - 52.3 (c = 0.20, H_2O); (+)-adenophorine: $[[\alpha]_D$ = + 59.7 (c = 1.0, H_2O)). It was by this means we were able to assign the absolute configuration of (+)-adenophorine.

4.10 Summary and Conclusions

In this chapter we have investigated the formation and reactivity of several functionalised cyclic piperidine imines. Such imines have been shown to be versatile intermediates in the synthesis of novel aza-sugars as potential sugar-processing enzyme inhibitors via nucleophilic addition reactions.

We have observed, and rationalised, good diastereoselectivity in such additions, and have used the methodology to acheive the first synthesis of the natural product enantiomer (–)-adenophorine (**4.11**), and its C-1 epimer (**4.12**).

The use of such imines has allowed the late-stage introduction of functionality to aza-sugar scaffolds α- to the ring nitrogen. Through careful control of reaction conditions

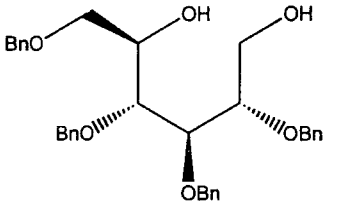
we have also controlled the regiochemistry of formation of imines from their *N*-chloro precursors.

In order to increase the utility of this methodology, commercially available nucleophiles have been used throughout, with a particular emphasis on Grignard reagents, also found to be very successful in the case of rhamnopyrrolidine imine (**3.03**) (Chapter 3, Section 3.4). Future work in this field may concentrate on other carbon nucleophiles (see Chapter 1, Section 1.4), which may help to increase further the yields of additions to such systems.

We have achieved good yields and excellent diastereoselectivites in the reduction of cyclic ketimine (**4.13**) (Section 4.8), and as such have developed methodology allowing potential access to a wide variety of aza-sugars with late-stage introduction of functionality and conveniently defined stereochemistry.

4.11 Experimental Section

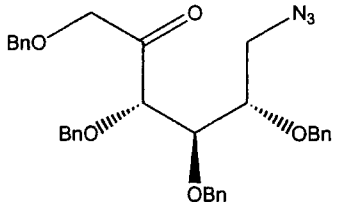
*2,3,4,6-Tetra-O-benzyl-D-glucitol (**4.04**) (Ref. 114):*



2,3,4,6-Tetra-*O*-benzyl-D-glucose (**4.03**) (1.0 eq, 9.24 mmol, 5.00 g) was dissolved in THF (70 mL). Distilled water (35 mL) was added, and nitrogen bubbled through the solution for 30 seconds. Sodium borohydride was added (10 eq, 0.0924 mol, 3.50 g) in one portion, and the reaction stirred under nitrogen for 24 h. At the end of this time TLC analysis (5 : 4, ethyl acetate : hexane) revealed complete consumption of starting material. The reaction was stopped after 24 h by addition of NH_4Cl (aq, satd.) until effervescence ceased. The THF was removed *in vacuo*, diethyl ether (150 mL) was added, and the organic layer washed with H_2O (3 × 50 mL). The organic layers were isolated, dried ($MgSO_4$), filtered, and the solvent removed to give a colourless oil which was purified by flash chromatography to yield 2,3,4,6-tetra-*O*-benzyl-D-glucitol (**4.04**) as a colourless oil (4.98 g, 99.7 %)l: $[\alpha]_D^{26}$ + 11.8 (c = 1.00, $CHCl_3$) (lit.[114] $[\alpha]_D^{19}$ + 10.3 (c = 4.54, $CHCl_3$); *m/z* 565.2 (ES, $[M+Na]^+$, 100 %, MeOH), 1107 ($[2M+Na]^+$, 40 %); ν_{max} (film)/cm^{-1}: 2867, 2923 (aliphatic C-H stretch), 3028,

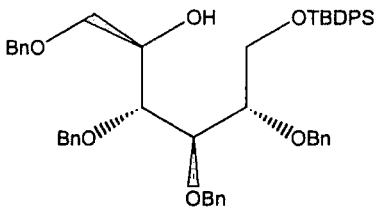
3061 (aromatic C-H stretch), 3447 (br, O-H stretch); δ_H ($CDCl_3$, 500 MHz, gCOSY, gHSQC) 2.13 (t, 1H, C^1OH, J_{HH} 4.8 Hz), 2.97 (d, 1H, C^5OH, J_{HH} 5.5 Hz), 3.57 (pdt, 1H, H-1, J_{HH} 5.0 Hz, $J_{1,1'}$ 11.4 Hz), 3.65 (m, 2H, H-6, H-6') 3.71-3.83 (m, 3H, H-1, H-2, H-4), 3.90 (dd, 1H, H-3, J_{HH} 3.70 Hz, J_{HH} 6.4 Hz), 4.04 (m, 1H, H-5), 4.52 (d, 1H, 1 × $PhC\underline{H}_2O$, J_{HH} 11.8 Hz), 4.55 (d, 1H, 1 × $PhC\underline{H}_2O$, J_{HH} 11.6 Hz), 4.56 (d, 1H, 1 × $PhC\underline{H}_2O$, J_{HH} 11.8 Hz), 4.60 (d, 1H, 1 × $PhC\underline{H}_2O$, J_{HH} 11.6 Hz), 4.64 (d, 1H, 1 × $PhC\underline{H}_2O$, J_{HH} 11.6 Hz), 4.67 (d, 1H, 1 × $PhC\underline{H}_2O$, J_{HH} 11.3 Hz), 4.68 (d, 1H, 1 × $PhC\underline{H}_2O$, J_{HH} 11.6 Hz), 4.73 (d, 1H, 1 × $PhC\underline{H}_2O$, J_{HH} 11.3 Hz), 7.21-7.39 (m, 20H, aromatic CH); δ_C ($CDCl_3$, 125.7 MHz, DEPT, gHSQC) 62.0 (t, C-1), 70.8, (d, C-5), 71.2 (t, C-6), 73.2, 73.4, 73.6, 74.6 (4 × t, 4 × $Ph\underline{C}H_2O$), 77.4, 79.2 (2 × d, C-2, C-4), 79.6 (d, C-3), 127.9, 127.98, 128.04, 128.07, 128.12, 128.3, 128.55, 128.57, 128.59, 128.60, 128.61 (d, 11 of 20 aromatic CH, others coincident), 137.93, 137.97, 138.10, 138.27 (4 × s, 4 × quaternary aromatic); HRMS found 565.2596 ($C_{34}H_{38}NaO_6$ ($[M+Na]^+$) requires 565.2566).

*6-Azido-1,3,4,5-tetra-O-benzyl-6-deoxy-L-sorbose (**4.17**):*



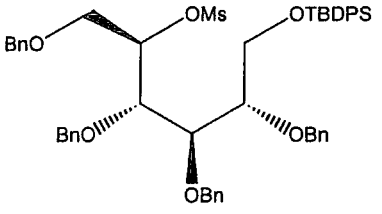
1-Azido-2,3,4,6-tetra-*O*-benzyl-1-deoxy-D-glucitol (**4.16**) (1.0 eq, 14.4 μmol, 8.2 mg) was dissolved in DCM (1.5 mL) with molecular sieves (4 Å, powdered, 200 mg) and PCC (3.1 eq, 44.6 μmol, 9.6 mg). The mixture was stirred under nitrogen for 3 days before filtering through a plug of silica (1 : 1, ethyl acetate : hexane eluent). The solvent was removed *in vacuo* to give 6-azido-1,3,4,5-tetra-*O*-benzyl-6-deoxy-L-sorbose (**4.17**) as a colourless oil (7.0 mg, 86 %): δ_H ($CDCl_3$, 300 MHz) 3.22 (dd, 1H, H-1, $J_{1,2}$ 6.7 Hz, $J_{1,1'}$ 13.1 Hz), 3.34 (dd, 1H, H-1`, $J_{1',2}$ 3.7 Hz, $J_{1,1'}$ 13.1 Hz), 3.75 (ddd, 1H, H-2, $J_{1',2}$ 3.7 Hz, $J_{2,3}$ 6.0 Hz, $J_{1,2}$ 6.7 Hz), 3.94 (dd, 1H, H-3, $J_{3,4}$ 3.7 Hz, $J_{2,3}$ 6.0 Hz), 4.09-4.21 (m, 3H, H-4, H-6, H-6`), 4.35-4.63 (m, 8H, 8 × $PhC\underline{H}_2O$), 7.17-7.35 (m, 20 H, aromatic CH).

2,3,4,6-Tetra-O-benzyl-1-O-tert-butyldiphenylsilyl-D-glucitol (4.19):



2,3,4,6-Tetra-*O*-benzyl-D-glucitol (**4.04**) (1.0 eq, 2.04 mmol, 1.11 g) was dissolved in dry DMF (3.0 mL), and imidazole (2.2 eq, 4.50 mmol, 306 mg) added with stirring under nitrogen. *tert*-Butylchlorodiphenylsilane (1.3 eq., 2.66 mmol, 0.689 mL) was added dropwise with stirring. The reaction was stirred under nitrogen for 24 h. At the end of this period TLC analysis (1 : 1, ethyl acetate : hexane eleunt) revealed complete conversion of starting material into product. The reaction was stopped after 24 h by removal of the solvent *in vacuo* and the residue purified by flash chromatography (15 : 85, ethyl acetate : hexane eluent) to yield 2,3,4,6-tetra-*O*-benzyl-1-*O*-*tert*-butyldiphenylsilyl-D-glucitol (**4.19**) as a colourless oil (1.58 g, 99 %): $[\alpha]_D^{20.0}$ + 19.5 (c = 1.00, $CHCl_3$); *m/z* 803.2 (ES, $[M+Na]^+$, 100 %, MeOH); ν_{max} (film)/cm^{-1}: 3490 (br, O-H stretch), 3806, 3065, 3029 (aromatic C-H stretch), 2929, 2857 (aliphatic C-H stretch); δ_H ($CDCl_3$, 400 MHz, gCOSY, gHSQC) 1.06 (s, 9H, $(CH_3)_3CSi$), 2.94 (d, 1H, OH, J_{HH} 4.8 Hz), 3.60-3.63 (m, 2H, H-6, H-6'), 3.76-3.82 (m, 2H, H-1, H-2), 3.85 (dd, 1H, J_{HH} 4.9 Hz, J_{HH} 9.6 Hz), 3.91 (dd, 1H, H-1, $J_{1,2}$ 4.6 Hz, $J_{1,1'}$ 10.1 Hz), 3.96 (dpt, 1H, H-5, J_{HH} 4.4 Hz, J_{HH} 10.7 Hz), 4.00 (t, 1H, J_{HH} 4.4 Hz), 4.47-4.56 (m, 5H, 5 × $PhC\underline{H}_2O$), 4.64-4.67 (m, 3H, 3 × $PhCH_2O$), 7.10-7.42 (m, 26H, aromatic CH), 7.63-7.66 (m, 4H, aromatic CH); δ_C ($CDCl_3$, 100.6 MHz, DEPT, gHSQC) 19.2 (s, $(CH_3)_3\underline{C}Si$), 27.0 (q, $(\underline{C}H_3)_3CSi$), 63.2 (t, C-1), 71.1 (d, C-5), 71.3 (t, C-6), 73.1, 73.4, 73.5, 74.3 (4 × t, 4 × $Ph\underline{C}H_2O$), 77.5 (d, C-2), 78.0, 79.7 (2 × d, C-3, C-4), 127.7, 127.76, 127.81, 127.83, 127.9, 128.07, 128.37, 128.40, 128.42, 128.5, 128.6, 129.80, 129.82, 135.8 (14 × d, 14 of 25 aromatic CH, others coincident), 133.4, 133.5 (2 × s, 2 × quaternary aromatic $\underline{C}Si$), 138.20, 138.24, 138.3, 138.5 (4 × s, 4 × quaternary aromatic); HRMS found 798.4186 ($C_{50}H_{60}NO_6Si$ ($[M+NH_4]^+$) requires 798.4190).

2,3,4,6-Tetra-O-benzyl-1-O-tert-butyldiphenylsilyl-5-O-methanesulfonyl-D-glucitol (4.20):



2,3,4,6-Tetra-*O*-benzyl-1-*O-tert*-butyldiphenylsilyl-D-glucitol (**4.19**) (1.0 eq., 1.28 mmol, 1.00 g) was dissolved in dry pyridine (20 mL) under nitrogen. Methanesulfonyl chloride (1.5 eq., 1.92 mmol, 0.149 mL) was added, and the mixture stirred under nitrogen for 72 h. No change in R_f by TLC (ethyl acetate/hexane eluent) was observed. The reaction mixture was diluted with $CHCl_3$ (500 mL) and washed washed with water (2 × 250 mL) and the aqueous washings extracted with $CHCl_3$ (100 mL). The organic layers were combined, dried ($MgSO_4$), filtered, and the solvent removed *in vacuo*. The resultant oil was purified by flash chromatography (15 : 85, ethyl acetate : hexane eluent) to yield 2,3,4,6-tetra-*O*-benzyl-1-*O-tert*-butyldiphenylsilyl-5-*O*-methanesulfonyl-D-glucitol (**4.20**) as a colourless oil (1.08 g, 97 %): $[\alpha]_D^{25}$ + 15.7 (c = 1.00, in $CHCl_3$); *m/z* 881.0 (ES, $[M+Na]^+$, 100%, MeOH); ν_{max} (film)/cm^{-1}: 2857, 2929, 2953 (aliphatic C-H stretch), 3030, 3066 (aromatic C-H stretch); δ_H ($CDCl_3$, 500 MHz, gHSQC) 1.06 (s, 9H, $(CH_3)_3CSi$), 2.87 (s, 3H, CH_3SO_3), 3.75-3.81 (m, 3H, H-1, H-2, H-6), 3.83 (t, 1H, J_{HH} 5.2 Hz), 3.86 (dd, 1H, H-6`, $J_{5,6'}$ 2.5 Hz, $J_{6,6'}$ 11.2 Hz), 3.89-3.94 (m, 1H, H-1`), 4.04 (dd, 1H, H-4, $J_{4,5}$ 2.7 Hz, J_{HH} 5.7 Hz), 4.41 (d, 1H, 1 × $PhC\underline{H}_2O$, J_{HH} 11.7 Hz), 4.44 (d, 1H, 1 × $PhC\underline{H}_2O$, J_{HH} 11.7 Hz), 4.50 (d, 1H, 1 × $PhC\underline{H}_2O$, J_{HH} 11.2 Hz), 4.57 (d, 1H, 1 × $PhC\underline{H}_2O$, J_{HH} 11.6 Hz), 4.60 (s, 2H, 2 × $PhC\underline{H}_2O$), 4.68 (m, 2H, 2 × $PhC\underline{H}_2O$, J_{HH} 11.2 Hz), 4.98 (dpt, 1H, H-5, $J_{5,6'}$ 2.6 Hz, J_{HH} 7.9 Hz, J_{HH} 7.9 Hz), 7.14-7.43 (m, 26H, aromatic CH), 7.65 (t, 4H, aromatic CH, J_{HH} 8.2 Hz); δ_C ($CDCl_3$, 125.7 MHz, DEPT, gHSQC) 19.3 (s, $(CH_3)_3\underline{C}Si$), 27.0 (q, $(\underline{C}H_3)_3CSi$), 38.5 (q, CH_3SO_3), 63.3 (t, C-1), 69.2 (t, C-6), 73.3, 73.4, 74.7, 74.8 (4 × t, 4 × $Ph\underline{C}H_2O$), 78.7, 80.0, 80.1 (3 × d, C-2, C-3, C-4), 83.6 (d, C-5), 127.7, 127.79, 127.83, 127.9, 128.0, 128.1, 128.2, 128.41, 128.44, 128.45, 128.5, 128.6, 129.8, 129.9, 135.78, 135.82 (16 × d, 16 of 30 aromatic CH, others coincident), 133.4, 133.5 (2 × s, 2 × quaternary aromatic CSi), 137.8, 137.9, 138.1, 138.5 (4 × s, 4 × quaternary aromatic).

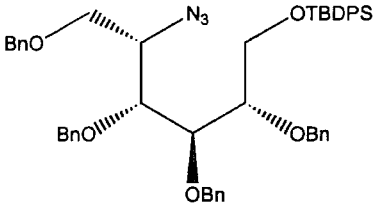
Tetra-n-butylammonium azide (Ref. 119):

Caution![118] Sodium azide (1.0 eq., 15.4 mmol, 1.00 g) was dissolved in water (40 mL), and tetra-*N*-butyl ammonium hydroxide (1.1 eq, 16.9 mmol, 11.0 g, 11.1 mL, 40 % aq.) added. The resultant mixture was extracted with DCM (4 × 50 mL), and the organic layers dried ($MgSO_4$), filtered, and evaporated. Toluene was added to the residue and the solvent removed *in vacuo* at low bath temperature to give tetra-*n*-butylammonium azide (TBAAZ) as a waxy solid (4.12 g, 95 %).

Hydrazoic acid (Ref. 123):

Caution![122] Sodium azide (1.0 eq, 25.1 mmol, 1.63 g) was placed in a two-necked round-bottom flask with distilled water (1.6 mL). The slurry was cooled to 0 °C then 98 % sulfuric acid (0.5 eq, 12.5 mmol, 1.23 g) added dropwise over 20 minutes (exothermic), maintaining the temperature between 5-10 °C throughout the addition. The mixture was stirred at 0 °C for a further 30 minutes then the organic layer dried (Na_2SO_4) and filtered to give hydrazoic acid (1.30-1.79 M in toluene). The concentration of the solution was determined by titration in the following manner: Hydrazoic acid solution (2.0 mL) and phenolphthalein indicator (3 drops) were added to distilled water (20 mL) and mixed. The resultant solution was titrated agaist standard sodium hydroxide (approx 0.1 M). The procedure was repeated until consecutive consistent titres were obtained.

5-Azido-2,3,4,6-tetra-O-benzyl-1-O-tert-butyldiphenylsilyl-5-deoxy-L-iditol (4.21):



Method 1

Caution![118] 2,3,4,6-Tetra-*O*-benzyl-1-*O*-*tert*-butyldiphenylsilyl-5-*O*-methanesulfonyl-D-glucitol (**4.20**) (1.0 eq., 0.0439 mmol, 37.7 mg) was placed in dry flask under nitrogen and a solution of tetra-*n*-butylammonium azide (TBAAZ) (10 eq., 0.439 mmol, 125 mg) in dry toluene (1.0 mL) was added and the mixture stirred briefly at

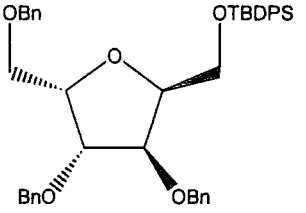
room temperature to dissolve all reactants. The mixture was then refluxed at 130 °C for 90 minutes until TLC indicated full consumption of starting material. The solution was cooled to room temperature, diluted with DCM (40 mL), washed with water (2 × 20 mL), and the organic phase dried ($MgSO_4$), filtered, and the solvent removed to give a pale yellow oil. Repeated flash column chromatography of the crude mixture (5 : 95, ethyl acetate : hexane and 1 : 9, diethyl ether : hexane eluent) gave 5-azido-2,3,4,6-tetra-*O*-benzyl-1-*O*-*tert*-butyldiphenylsilyl-5-deoxy-L-iditol (**4.21**) (8.1 mg, 23 %).

Method 2

Caution![122] 1-*O*-*tert*-butyldiphenylsilyl-2,3,4,6-tetra-*O*-benzyl-D-glucitol (**4.19**) (1.0 eq., 1.28 mmol, 1.00 g) was placed in a round bottomed flask with dry toluene (20 mL), and freshly prepared HN_3 solution added (2.5 eq., 3.21 mmol, 1.79 mL, 1.79 M solution in toluene) and the solution stirred under nitrogen for 10 minutes. In a separate flask triphenylphosphine (2.5 eq., 3.20 mmol, 840 mg) was dissolved in dry toluene (20 mL) under nitrogen. DIAD was added slowly (2.5 eq., 3.20 mmol, 647 mg, 630 μl) and the resultant mixture stirred under nitrogen for 15 minutes. The pre-prepared solution of hydrazoic acid and 1-*O*-*tert*-butyldiphenylsilyl-2,3,4,6-*O*-benzyl-D-glucitol (**4.19**) was added over 5 minutes. A white precipitate formed. The resultant mixture was stirred under nitrogen for 3 h after which time TLC indicated complete consumption of starting material. The reaction was stopped by addition of NaOH (aq., 3 M, 4 mL), then diluted with diethyl ether (250 mL) and washed with NaOH (aq.) (0.5 M, 2 × 150 mL). The organic extract was dried ($MgSO_4$), filtered, and the solvent removed to give a colourless oil which was purified by flash chromatography (5 : 95, diethyl ether : hexane). 2,5-Anhydro-3,4,6-tri-*O*-benzyl-1-*O*-*tert*-butyldiphenylsilyl-L-iditol (**4.22**), (69 mg, 8.0 %) was obtained as a colourless oil, and 5-azido-2,3,4,6-tetra-*O*-benzyl-1-*O*-*tert*-butyldiphenylsilyl-5-deoxy-L-iditol (**4.21**) as a colourless oil (894 mg, 87 %): $[\alpha]_D^{23.9}$ + 23.9 (c = 1.00, $CHCl_3$); *m/z* 828.4 (ES, $[M+Na]^+$, 100 %, MeOH), 785.4 ($[M-HN_3+Na]^+$, 15 %); ν_{max} (film)/cm^{-1}: 2097 (azide stretch), 2857, 2929, 2955 (aliphatic C-H stretch), 3030, 3066, 3088 (aromatic C-H stretch); δ_H ($CDCl_3$, 500 MHz, gCOSY, gHSQC) 1.06 (s, 9H, $(C\underline{H}_3)_3CSi$), 3.21 (ddd, 1H, H-5, $J_{4,5}$ 3.0 Hz $J_{5,6}$ 4.6 Hz, $J_{5,6'}$ 7.7 Hz), 3.31 (dd, (1H, 1H, H-6, $J_{5,6}$ 4.7 Hz, $J_{6,6'}$ 9.5 Hz), 3.50-3.56 (m, 2H, H-2, H-6'), 3.79 (dd, 1H, H-4, $J_{4,5}$ 3.0 Hz, $J_{3,4}$ 7.7 Hz), 3.84 (dd, 1H, H-1, $J_{1,2}$ 5.6 Hz, $J_{1,1'}$ 10.5 Hz), 3.91 (dd, 1H, H-1', $J_{1',2}$ 6.5 Hz, $J_{1,1'}$ 10.5

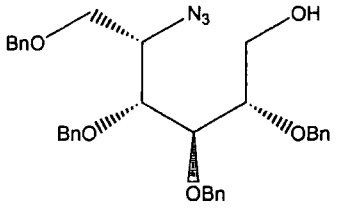
Hz), 4.00 (dd, 1H, H-3, $J_{2,3}$ 2.8 Hz, $J_{3,4}$ 7.7 Hz), 4.28 (d, 1H, 1 × PhC$\underline{H}_2$O, J_{HH} 12.0 Hz), 4.36 (d, 1H, 1 × PhC$\underline{H}_2$O, J_{HH} 11.8 Hz), 4.39 (d, 1H, 1 × PhC$\underline{H}_2$O, J_{HH} 11.8 Hz), 4.51 (d, 1H, 1 × PhC$\underline{H}_2$O, J_{HH} 11.5 Hz), 4.59 (d, 1H, 1 × PhC$\underline{H}_2$O, J_{HH} 11.8 Hz), 4.63 (d, 1H, 1 × PhC$\underline{H}_2$O, J_{HH} 11.1 Hz), 4.74 (t, 2H, 2 × PhC$\underline{H}_2$O, J_{HH} 11.8 Hz), 7.15-7.24 (m, 26H, aromatic), 7.63-7.70 (m, 4H, aromatic); δ_C ($CDCl_3$, 125.7 MHz, DEPT, gHSQC) 19.3 (s, $(CH_3)_3\underline{C}Si$), 27.0 (q, $(\underline{C}H_3)_3CSi$), 61.4 (d, C-5), 62.4 (t, C-1), 70.0 (t, C-6), 72.5, 73.3, 75.0, 75.4 (4 × t, 4 × Ph$\underline{C}H_2$O), 77.9 (d, C-2), 78.5 (d, C-4), 79.1 (d, C-3), 127.7, 128.0, 128.1, 128.5, 129.9, 130.0, 135.7, 135.9 (8 × d, 8 of 30 aromatic CH, others coincident), 133.4 (s, aromatic CSi), 137.9, 138.0, 138.3, 138.4 (4 × s, 4 × quaternary aromatic); HRMS found 828.3877 ($C_{50}H_{55}N_3O_5NaSi$ ($[M+Na]^+$) requires 828.3809).

2,5-Anhydro-3,4,6-tri-O-benzyl-1-O-tert-butyldiphenylsilyl-L-iditol ***(4.22)****:*



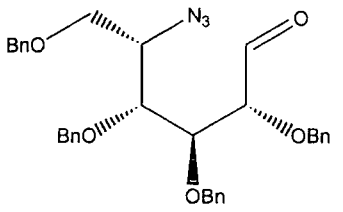
δ_H ($CDCl_3$, ppm, 499.8 MHz, gCOSY, gHSQC) 1.10 (s, 9H, $(C\underline{H}_3)_3CSi$), 3.73 (m, 2H, H-1, H-1'), 3.90 (dd, 1H, H-6, $J_{5,6}$ 5.3 Hz, $J_{6,6'}$ 9.8 Hz), 4.01 (dd, 1H, H-6', $J_{5,6'}$ 8.3 Hz, $J_{6,6'}$ 9.8 Hz), 4.09 (d, 1H, H-4, $J_{3,4}$ 3.6 Hz), 4.12 (d, 1H, H-3, $J_{3,4}$ 3.6 Hz), 4.37 (m, 2H, H-2, H-5), 4.51-4.58 (m, 3H, 3 × PhC$\underline{H}_2$O), 4.60 (s, 2H, 2 × PhC$\underline{H}_2$O), 4.65 (d, 1H, 1 × PhC$\underline{H}_2$O, J_{HH} 12.1 Hz), 7.48-7.28 (m, 21H, aromatic), 7.71 (d, 4H, aromatic C-H); δ_C ($CDCl_3$, 125.7 MHz, DEPT, gHSQC) 19.3 (s, $(CH_3)_3\underline{C}SiO$), 27.0 (q, $(C\underline{H}_3)_3CSiO$), 61.6 (t, C-1), 68.8 (t, C-6), 72.4, 72.6, 73.5 (t, 3 × Ph$\underline{C}H_2$O), 79.1 (d, C-2), 80.5 (d, C-5), 81.3 (d, C-3), 81.7 (d, C-4),127.69, 127.73, 127.9, 128.4, 128.50, 128.6, 129.67, 129.72, 135.66, 135.72 (d, 10 of 25 aromatic CH, others coincident), 133.7, 133.5 (s, 2 × quaternary aromatic CSi), 137.1, 138.2, 138.4 (3 × s, 3 × quaternary aromatic).

5-Azido-2,3,4,6-tetra-O-benzyl-5-deoxy-L-iditol (4.23):



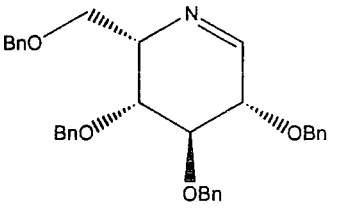
5-Azido-2,3,4,6-*O*-benzyl-1-*O*-*tert*-butyldiphenyl-silyl-5-deoxy-L-iditol (**4.21**) (1.0 eq., 0.689 mmol, 555 mg) was dissolved in THF (14 mL), and TBAF was added (1.5 eq., 1.03 mmol, 1.03 mL of a 1 M solution in THF). The resultant solution was stirred under nitrogen for 3 h, after which time TLC showed complete consumption of starting material. The reaction mixture was concentrated and the residue dissolved in DCM (150 mL) and washed with water (2 × 50 mL). Then the organic layer dried ($MgSO_4$), filtered, and concentrated to give a colourless oil which was purified by flash chromatography (1 : 4, ethyl acetate : hexane eluent) to give 5-azido-2,3,4,6-*O*-benzyl-5-deoxy-L-iditol (**4.23**) as a colourless oil (390 mg, 99 %): $[\alpha]_D^{25.7}$ + 18.3 (c, 1.00, $CHCl_3$); *m/z* 590.0 (ES, $[M+Na]^+$, 100 %, MeOH); ν_{max}/cm^{-1} (film): 2098 (azide stretch) 2866, 2926 (aliphatic C-H stretch) 3030, 3062, 3088 (aromatic C-H stretch) 3440 (br, O-H stretch); δ_H ($CDCl_3$, 500 MHz, gCOSY, gHSQC) 1.91 (s, br, 1H, OH), 3.46 (dd, 1H, H-6, $J_{5,6}$ 5.0 Hz, $J_{6,6'}$ 9.3 Hz), 3.54 (dd, 1H, H-6', $J_{5,6'}$ 7.2 Hz, $J_{6,6'}$ 9.3 Hz), 3.56-3.59 (m, 2H, H-2, H-5), 3.64 (m, 1H, H-1), 3.75 (m, 1H, H-1'), 3.88 (dd, 1H, H-3, $J_{2,3}$ 3.0 Hz, $J_{3,4}$ 7.0 Hz), 3.86 (dd, 1H, H-4, $J_{4,5}$ 4.2 Hz, $J_{3,4}$ 7.0 Hz), 4.38 (d, 1H, 1 × PhC$\underline{H}_2$O, J_{HH} 11.9 Hz), 4.42 (d, 1H, 1 × PhC$\underline{H}_2$O, J_{HH} 11.9 Hz), 4.54-4.60 (m, 3H, 3 × PhC$\underline{H}_2$O), 4.62 (d, 1H, 1 × PhC$\underline{H}_2$O, J_{HH} 11.3 Hz), 4.67 (d, 1H, 1 × PhC$\underline{H}_2$O, J_{HH} 11.3 Hz), 4.47 (d, 1H, 1 × PhC$\underline{H}_2$O, J_{HH} 11.6 Hz), 7.22-7.33 (m, 20H, aromatic CH); δ_C ($CDCl_3$, 125.7 MHz, DEPT, gHSQC) 61.1 (d, C-5), 61.5 (t, C-1), 69.6 (t, C-6), 72.5, 73.4, 74.8, 74.9 (4 × t, 4 × Ph$\underline{C}H_2$O), 78.0 (d, C-2), 78.1, 79.1 (2 × d, C-3, C-4), 127.8, 127.92, 127.93, 128.1, 128.4, 128.55, 128.57, 128.63, 128.64 (9 × d, 9 of 20 aromatic CH, others coincident), 137.8, 137.88, 137.90, 138.0 (4 × s, 4 × quaternary aromatic); HRMS found 568.2813 ($C_{34}H_{38}N_3O_5$ ($[M+H]^+$) requires 568.2811).

5-Azido-2,3,4,6-tetra-O-benzyl-5-deoxy-D-idose (4.24):



5-Azido-2,3,4,6-*O*-benzyl-5-deoxy-L-iditol (**4.23**) (1.0 eq., 0.074 mmol, 42 mg) was placed in a round-bottom flask with dried powdered molecular sieves (4Å, 100 mg) and PCC (4.0 eq., 0.297 mmol, 62 mg), and dry DCM added (3.0 mL). The mixture was stirred under nitrogen for 1.5 h. At the end of this period TLC indicated complete consumption of starting material. The reaction was stopped by addition of diethyl ether (10 mL), and the mixture filtered through a celite plug, then concentrated, and the resultant brown/orange oil purified by flash chromatography (1 : 9, ethyl acetate : hexane eluent) to give 5-azido-2,3,4,6-*O*-benzyl-5-deoxy-L-idose (**4.24**) as a colourless oil (36 mg, 87 %): $[\alpha]_D^{23}$ + 20.7 (c = 1.00, in $CHCl_3$); *m/z* 588.3 (ES, $[M+Na]^+$, 100%, MeCN); ν_{max} (film)/cm^{-1}: 1729 (C=O stretch), 2098 (azide stretch), 2863, 2922 (aliphatic C-H stretch), 3031, 3063, 3088 (aromatic C-H stretch); δ_H ($CDCl_3$ 400 MHz, gCOSY, gHSQC) 3.44 – 3.57 (m, 3H, H-5, H-6, H-6'), 3.87 (t, 1H, H-4, $J_{3,4}$ 5.0 Hz, $J_{4,5}$ 5.0 Hz), 3.93 (d, 1H, H-2, $J_{2,3}$ 4.8 Hz), 3.97 (t, 1H, H-3, $J_{2,3}$ 4.8 Hz, $J_{3,4}$ 4.8 Hz), 4.42 (m, 2H, 2 × $PhC\underline{H}_2O$), 4.50 (d, 1H, 1 × $PhC\underline{H}_2O$, J_{HH} 11.9 Hz), 4.55 (m, 3H, 3 × $PhC\underline{H}_2O$), 4.64 (d, 1H, 1 × $PhC\underline{H}_2O$, J_{HH} 11.2 Hz), 4.83 (d, 1H, 1 × $PhC\underline{H}_2O$, J_{HH} 11.9 Hz), 7.18 (m, 2H, 2 × aromatic CH), 7.25-7.37 (m, 18H, 18 × aromatic CH), 9.67 (s, 1H, H-1); δ_C (100.6 MHz, $CDCl_3$, DEPT, gHSQC), 61.6 (d, C-5), 69.3 (t, C-6), 73.2, 73.4, 74.2, 74.6 (4 × d, 4 × $Ph\underline{C}H_2O$), 77.4 (d, C-4), 79.3 (d, C-3), 80.9 (d, C-2), 127.8, 127.95, 127.99, 128.3, 128.4, 128.46, 128.48, 128.52, 128.58, 128.64, 128.75 (11 × d, 11 of 20 aromatic CH, others coincident), 136.9, 137.2, 137.6, 137.7 (4 × s, 4 × quaternary aromatic), 200.9 (d, C-1).

*2,3,4,6-Tetra-O-benzyl-1,N-dehydro-1,5-dideoxy-1,5-imino-L-iditol (**4.05**):*



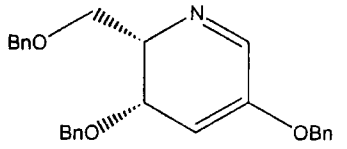
Method 1

5-Azido-2,3,4,6-tetra-*O*-benzyl-5-deoxy-D-idose (**4.24**) (1.0 eq., 0.0725 mmol, 41.0 mg) was dissolved in dry diethyl ether (1.5 mL) together with triphenylphosphine (3.0 eq., 0.217 mmol, 57.0 mg). The mixture was stirred under nitrogen at room temperature for 90 minutes after which time TLC indicated complete consumption of starting material. The solvent was removed *in vacuo* to give 2,3,4,6-tetra-*O*-benzyl-1,5-dideoxy-1,*N*-dehydro-1,5-imino-L-iditol (**4.05**), with residual phosphines, as a waxy white solid (97 mg) which was used directly.

Method 2

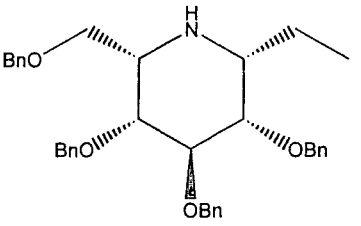
2,3,4,6-Tetra-*O*-benzyl-*N*-chloro-1,5-dideoxy-1,5-imino-L-iditol (**4.08**) (1.0 eq., 0.0842 mmol, 47.0 mg) was dissolved in dry diethyl ether (2 mL) and DBU (1.1 eq., 0.0926 mmol, 14.1 mg, 13.8 μL) added. The mixture was stirred at reflux for 7.5 h after which time TLC indicated complete consumption of starting material. The reaction was filtered under nitrogen and the filter washed with diethyl ether (1.0 mL). The solvent was removed *in vacuo* giving 2,3,4,6-tetra-*O*-benzyl-1,5-dideoxy-1,*N*-dehydro-1,5-imino-L-iditol (**4.05**) (45 mg) as a pale yellow oil which was used directly: $[\alpha]_D^{25.1}$ – 14.7 (c = 2, $CHCl_3$); ν_{max} (film)/cm^{-1}: 1647 (C=N stretch), 2863, 2921 (aliphatic C-H stretch), 3029, 3062, 3086 (aromatic C-H stretch); δ_H ($CDCl_3$, 400 MHz, gCOSY) 3.77-3.87 (m, 4H), 3.98 (dd, 1H, J_{HH} 4.0 Hz, J_{HH} 8.7 Hz), 4.00 (t, 1H, J_{HH} 5.3 Hz), 4.47-4.57 (m, 3H, 3 × $PhC\underline{H}_2O$), 4.60 (d, 1H, 1 × $PhC\underline{H}_2O$, J_{HH} 11.5 Hz), 4.62 (d, 1H, 1 × $PhC\underline{H}_2O$, J_{HH} 11.8 Hz), 4.63 (d, 1H, 1 × $PhC\underline{H}_2O$, J_{HH} 11.4 Hz), 4.68 (d, 1H, 1 × $PhC\underline{H}_2O$, J_{HH} 11.8 Hz), 4.70 (d, 1H, 1 × $PhC\underline{H}_2O$, J_{HH} 11.5 Hz), 7.24-7.37 (aromatic C-H), 7.80 (s, 1H, H-1); δ_C ($CDCl_3$, 100.6 MHz, DEPT) 60.2 (d, C-5), 69.6 (t, C-6), 74.4, 72.5, 72.8, 73.4 (4 × t, 4 × $Ph\underline{C}H_2O$), 75.0, 77.8, 78.6 (3 × d, C-2, C-3, C-4), 127.8-128.8 (aromatic CH), 137.8, 138.2, 138.4 (3 × s, 3 of 4 quaternary aromatic, 2 coincident), 164.0 (d, C-1).

*2,3,4,6-Tetra-O-benzyl-1,3,5-trideoxy-1,N-dehydro-2,3-dehydro-1,5-imino-L-iditol, ((2S,3S)2-benzyloxymethyl-3,5-dibenzyloxy-2,3-dihydro-pyridine) (**4.26**):*



5-Azido-2,3,4,6-tetra-*O*-benzyl-5-deoxy-D-idose (**4.24**) (1.0 eq., 0.0716 mmol, 40.5 mg) was dissolved in dry DCM (2.5 mL) with triphenylphosphine (3.0 eq., 0.215 mmol, 56.3 mg), and the mixture heated to reflux for 12 h under nitrogen, after which time TLC indicated formation of a new product. The solvent was removed *in vacuo*, and the crude orange oil purified by flash chromatography (15 : 85, ethyl acetate : hexane eluent), to give 2,3,4,6-tetra-*O*-benzyl-1,3,5-trideoxy-1,*N*-dehydro-2,3-dehydro-1,5-imino-L-iditol (**4.26**) as a colourless oil (11.3 mg, 28 %) as the only isolable product: $[\alpha]_D^{25.1}$ + 64.4 (c = 0.55, $CHCl_3$); *m/z* 436.1 (ES, $[M+Na]^+$, 100 %, MeOH), 306.2 ($[M-BnOH+H]^+$, 20 %), 328.1 ($[M-BnOH+Na]^+$, 10 %); ν_{max} (film)/cm^{-1}: 1603 (C=C stretch), 1654 (C=N stretch), 2855, 2919 (aliphatic C-H stretch), 3030, 3062, 3088 (aromatic C-H stretch); δ_H ($CDCl_3$, 500 MHz, gCOSY, gHSQC) 3.58 (m, 1H, H-5), 4.05-4.07 (m, 2H, H-6, H-6`), 4.21 (dd, 1H, H-4, $J_{4,5}$ 5.5 Hz, $J_{3,4}$ 6.3 Hz), 4.41 (d, 1H, 1 × $PhC\underline{H}_2O$, J_{HH} 11.9 Hz), 4.45 (d, 1H, 1 × $PhCH_2O$, J_{HH} 11.9 Hz), 4.61 (d, 1H, 1 × $PhCH_2O$, J_{HH} 11.9 Hz), 4.68 (d, 1H, 1 × $PhCH_2O$, J_{HH} 11.9 Hz), 4.80 (s, 2H, 2 × $PhCH_2O$), 5.37 (dd, 1H, H-3, $J_{1,3}$ 2.7 Hz, $J_{3,4}$ 6.3 Hz), 7.22-7.40 (m, 15H, aromatic CH), 7.91 (dd, 1H, H-1, $J_{1,3}$ 2.7 Hz, $J_{1,5}$ 3.5 Hz); δ_C ($CDCl_3$, 125.7, DEPT, gHSQC) 61.7 (d, C-5), 67.9 (d, C-4), 69.4, 70.4, 73.6 (3 × t, 3 × $Ph\underline{C}H_2O$), 70.2 (t, C-6), 99.6 (d, C-3), 127.7, 127.76, 127.80, 128.0, 128.4, 128.5, 128.8 (7 × d, 7 of 15 aromatic CH, others coincident), 135.9, 138.4, 138.8 (3 × s, 3 × quaternary aromatic), 149.6 (s, C-2), 156.4 (d, C-1); HRMS found 414.2080 ($C_{27}H_{28}NO_3$ ($[M+H]^+$) requires 414.2069).

(1R)-2,3,4,6-Tetra-O-benzyl-1,5-dideoxy-1-C-ethyl-1,5-imino-L-iditol (4.37):



2,3,4,6-Tetra-*O*-benzyl-*N*-chloro-1,5-dideoxy-1,5-imino-L-iditol (**4.08**) (1.0 eq., 0.111 mmol, 62 mg) was placed in a round-bottom flask with dry diethyl ether (2.0 mL) and DBU added (1.1 eq., 0.122 mmol, 18.6 mg). The mixture was immediately heated to reflux under nitrogen for 7 h. At the end of this period TLC showed complete consumption of starting material. The mixture was then filtered under nitrogen to remove the white precipitate of DBU.HCl, and the flask and precipitate washed with dry ether (1 mL) under nitrogen. The combined colourless filtrate was used immediately. It was added dropwise to a freshly prepared, cooled (– 78 °C) solution of Et_2Mg (see below). The mixture was stirred at – 78 °C for 2 h then allowed to warm to room temperature for 30 minutes before quenching with HCl (aq., 3.0 M, 1 mL). The mixture was diluted with DCM (30 mL) and basified with NaOH (aq., 3.0 M, to pH 13). The organic layer was washed with NaOH (aq., 0.1 M, 2 × 15 mL), dried (Na_2SO_4), filtered and the solvent removed to give a colourless oil. Column chromatography (1 : 3, ethyl acetate : hexane) gave (1*R*)-2,3,4,6-tetra-*O*-benzyl-1,5-dideoxy-1-*C*-ethyl-1,5-imino-L-iditol (**4.37**) as a colourless oil (21 mg, 34 %) together with recovered 2,3,4,6-tetra-*O*-benzyl-1,5-dideoxy-1,5-imino-L-iditol (**4.02**) (16 mg, 27 %).

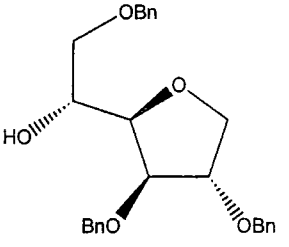
Preparation of Et_2Mg reagent.

Dry diethyl ether (5.0 mL) was placed in a dry round-bottomed flask under nitrogen, and ethylmagnesium bromide added (5.4 eq. based on *N*-chloro-2,3,4,6-tetra-*O*-benzyl-1,5-dideoxy-1,5-imino-L-iditol (**4.08**), 0.60 mmol, 0.2 mL of a 3 M solution in diethyl ether). The mixture was stirred under nitrogen and dry 1,4-dioxane was added (5.4 eq., 53 mg, 51 μL). A white precipitate formed immediately, and the mixture was stirred under nitrogen for 15 minutes at room temperature, before cooling to – 78 °C.

(**4.37**): $[\alpha]_D^{24.6}$ + 2.33 (c = 0.67, in $CHCl_3$); *m/z* 552.3 (ES, $[M+H]^+$, 100 %, MeOH), 574.3 ($[M+Na]^+$, 15 %); ν_{max} (film)/cm^{-1}: 2866, 2922, 2958 (aliphatic C-H stretch), 3028, 3 062, 3 086 (aromatic C -H stretch); δ_H ($CDCl_3$, 5 00 M Hz, g COSY, g HSQC)

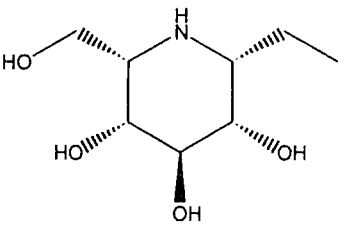
0.78 (t, 3H, C$\underline{H}_3CH_2$, $J_{1,2}$ 7.5 Hz), 1.49-1.56 (m, 2H, $CH_3C\underline{H}_2$), 1.90 (s, br, 2H, NH), 2.78 (m, br, 1H, H-1), 3.26 (t, br, 1H, H-5, J_{HH} 6.5 Hz), 3.28 (s, br, 1H, H-2), 3.48 (t, 1H, H-6, $J_{6,6'}$ 8.6 Hz), 3.50 (s, br, 1H, H-4`), 3.60 (dd, 1H, H-6`, $J_{5,6'}$ 7.3 Hz, $J_{6,6'}$ 8.6 Hz), 3.74 (t, 1H, H-3, J_{HH} 2.5 Hz), 4.32 (d, 1H, 1 × PhC$\underline{H}_2$O, J_{HH} 12.0 Hz), 4.36 (d, 1H, 1 × PhC$\underline{H}_2$O, J_{HH} 12.2 Hz), 4.42 (d, 1H, 1 × PhC$\underline{H}_2$O, J_{HH} 12.3 Hz), 4.45 (d, 1H, 1 × PhC$\underline{H}_2$O, J_{HH} 12.3 Hz), 4.47 (d, 1H, 1 × PhC$\underline{H}_2$O, J_{HH} 11.8 Hz), 4.50-4.54 (m, 2H, 2 × PhC$\underline{H}_2$O), 4.56 (d, 1H, 1 × PhC$\underline{H}_2$O, J_{HH} 12.0 Hz), 7.21-7.37 (m, 20H, 20 × aromatic CH); δ_C ($CDCl_3$ 125.7 Hz, DEPT, gHSQC) 10.7 (q, $\underline{C}H_3CH_2$), 24.7 (t, $CH_3\underline{C}H_2$), 55.5 (d, C-5), 57.3 (d, C-1), 70.8 (t, br, C-6), 70.9 (d, C-3), 72.0, 72.1, 72.5, 73.4 (4 × t, 4 × Ph$\underline{C}H_2$O), 72.9 (d, C-4), 74.0 (d, br, C-2), 127.66, 127.73, 127.8, 127.9, 128.0; 128.35, 128.37, 128.5, 128.6 (9 × d, 9 of 20 aromatic CH, others coincident), 138.3, 138.55, 138.60, 138.7 (4 × s, 4 × quaternary aromatic); HRMS found 552.3192 ($C_{36}H_{42}NO_4$ ([M+H]$^+$) requires 552.3114).

*1,4-Anhydro-2,3,6-tetra-O-benzyl-D-glucitol (**4.15**) (Ref. 117):*



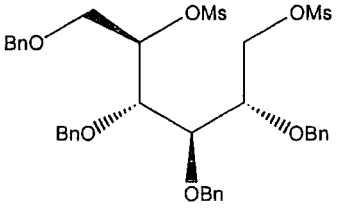
$[\alpha]_D^{19}$ – 9.1 (c = 1.00, $CHCl_3$) (lit.[117] $[\alpha]_D^{19}$ – 6 (c = 1.0, $CHCl_3$)); *m/z* 891.2 (ES, $[2M+Na]^+$, 100 %, MeOH), 457.1 ($[M+Na]^+$, 83 %); δ_H ($CDCl_3$, 500 MHz, gCOSY, gHSQC) 2.75 (s, br, 1H, O$\underline{H}$), 3.63 (dd, 1H, H-1, $J_{1,2}$ 6.3 Hz, $J_{1,1'}$ 9.7 Hz), 3.76 (dd, 1H, H-1`, $J_{1',2}$ 3.2, $J_{1,1'}$ 9.7 Hz), 3.83 (dd, 1H, H-6, $J_{5,6}$ 1.5 Hz, $J_{6,6'}$ 9.8 Hz), 3.99 (dd, 1H, H-4, $J_{3,4}$ 3.6 Hz, $J_{4,5}$ 8.2 Hz), 4.08 (m, 1H, H-3), 4.13-4.19 (m, 3H, H-2, H-5, H-6'), 4.47 (d, 1H, 1 × PhC$\underline{H}_2$O, J_{HH} 12.0 Hz), 4.51 (d, 1H, 1 × PhC$\underline{H}_2$O, J_{HH} 12.0 Hz), 4.56 (d, 1H, 1 × PhC$\underline{H}_2$O, J_{HH} 11.8 Hz), 4.57 (d, 1H, 1 × PhC$\underline{H}_2$O, J_{HH} 11.8 Hz), 4.61 (d, 1H, 1 × PhC$\underline{H}_2$O, J_{HH} 11.8 Hz), 4.62 (d, 1H, 1 × PhC$\underline{H}_2$O, J_{HH} 11.8 Hz), 7.28-7.39 (m, 15H, 15 × aromatic); δ_C ($CDCl_3$, 125.7 MHz, DEPT, gHSQC) 68.5 (d, C-5), 71.8, (t, C-6), 72.21 (t, C-1), 71.3, 72.25, 73.5 (3 × t, 3 × Ph$\underline{C}H_2$O), 80.3(d, C-4), 81.9 (d, C-3), 82.0 (d, C-2), 127.6, 127.7, 127.8, 127.86, 127.87, 127.9, 128.4, 128.47, 128.51 (9 × d, 9 of 15 aromatic $\underline{C}$H, others coincident), 137.6, 138.1 (2 × s, 2 × quaternary aromatic, two coincident).

(1R)-1,5-dideoxy-1-C-ethyl-1,5-imino-L-iditol (4.11):



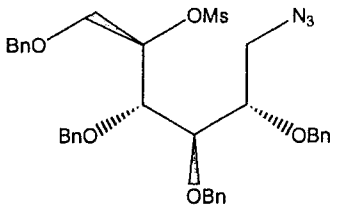
(1*R*)-2,3,4,6-Tetra-*O*-benzyl-1,5-dideoxy-1-*C*-ethyl-1,5-imino-L-iditol (**4.37**) (1.0 eq., 0.0254 mmol, 14.0 mg) was dissolved in ethanol (2.0 mL), and $PdCl_2$ (2.2 eq., 0.0564 mmol, 10.0 mg) added. The flask was evacuated and purged with hydrogen four times before stirring under hydrogen at atmospheric pressure for 1.5 h. At the end of this period all the starting material had been consumed and a single product was visible by TLC (ethyl acetate/hexane). The mixture was filtered through celite and the solvent removed *in vacuo*. The residue was purified by loading on to a column of Dowex^{TM} 50W acidic exchange resin, washing with methanol, then eluting the product with methanol : ammonia (aq., satd.) (9 : 1) The solvent was removed *in vacuo* to give (1*R*)-1,5-dideoxy-1-*C*-ethyl-1,5-imino-L-iditol (**4.11**) as a colourless oil (4.2 mg, 86 %); $[\alpha]_D^{25.8}$ – 26.4 (c = 0.18, H_2O); *m/z* 214.2 (ES, $[M+Na]^+$, 100 %, MeOH), 192.2 ($[M+H]^+$, 40 %); ν_{max} (film)/cm^{-1}: 2860, 2934, 2956 (aliphatic C-H stretch), 3410 (br, O-H stretch); δ_H (D_2O, 500 MHz, nOesy) 0.83 (t, 3H, $C\underline{H}_3CH_2$, $J_{1,2}$ 7.5 Hz) 1.38-1.49 (m, 2H, $CH_3C\underline{H}_2$), 2.72 (dpt, 1H, H-3, $J_{3,4}$ 1.42 Hz, $J_{2,3}$ 7.3 Hz), 2.95 (dpt, 1H, H-7, $J_{6,7}$ 1.6 Hz, $J_{7,8}$ 6.6 Hz), 3.54 (dd, 1H, H-8, $J_{7,8}$ 6.6 Hz, $J_{8,8'}$ 11.1), 3.60 (dd, 1H, H-8', $J_{7,8}$ 6.7 Hz, $J_{8,8'}$ 11.1 Hz), 3.63 (m, 1H, H-4), 3.68 (m, 1H, H-6), 3.94 (t, 1H, H-5, $J_{4,5}$ 3.1Hz, $J_{5,6}$ 3.1 Hz); δ_C (D_2O, 125.7 MHz) 9.83 (C-1), 23.8 (C-2), 55.4, 55,5, 62.2, 68.6, 69.0, 69.4 (C-3, C-4, C-5, C-6, C-7, C-8); HRMS found 192.1253 ($C_8H_{18}NO_4$ ($[M+H]^+$) requires 192.1236).

*2,3,4,6-Tetra-O-benzyl-1,5-di-O-methanesulfonyl-D-glucitol (**4.10**) (Ref. 130):*



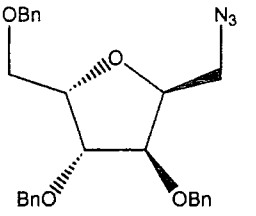
2,3,4,6-Tetra-*O*-benzyl-D-glucitol (**4.03**) (1.0 eq., 3.97 mmol, 2.15 g) was dissolved in dry pyridine (20 mL), under nitrogen and cooled to 0 °C. A cooled (0 °C) solution of methanesulfonyl chloride (2.45 eq., 9.70 mol, 1.11 g) in dry pyridine (10 mL) was added with stirring. The reaction was stirred at 0 °C for 72 h. TLC analysis then showed complete consumption of starting material and formation of a new product. The mixture was diluted with $CHCl_3$ (50 mL), and washed with HCl (aq., 1 M, 20 mL), water (20 mL) and $NaHCO_3$ (aq., satd., 20 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (4 : 5, ethyl acetate : hexane) to yield 2,3,4,6-tetra-*O*-benzyl-1,5-di-*O*-methanesulfonyl-D-glucitol (**4.10**) as a pale yellow oil (1.95 g, 71 %): $[\alpha]_D^{23.4}$ + 4.8 (c = 1.00, $CHCl_3$) (lit.[130] + 7.6 (C = 0.91 $CHCl_3$); *m/z* 721.2 (ES, $[M+Na]^+$, 100 %, MeOH); ν_{max} (film)/cm^{-1}: 1175, 1356 (SO_2 stretch) 2873, 2936 (aliphatic C-H stretch), 3031, 3063, 3094 (aromatic C-H stretch); δ_H ($CDCl_3$, 500 MHz, gCOSY, gHSQC) 2.83 (s, 3H, C$\underline{H}_3SO_3$), 2.95 (s, 3H, C$\underline{H}_3SO_3$), 3.72 (t, 1H, H-3, $J_{2,3}$ 5.0 Hz, $J_{3,4}$ 5.0 Hz), 3.78 (dd, 1H, H-6, $J_{5,6}$ 7.8 Hz, $J_{6,6'}$ 11.0 Hz), 3.87 (dd, 1H, H-6`, $J_{5,6}$ 2.7 Hz, $J_{6,6'}$ 11.0 Hz), 3.93 (m, 1H, H-2), 4.05 (dd, 1H, H-4, $J_{4,5}$ 2.8 Hz, $J_{3,4}$ 4.9 Hz), 4.26 (dd, 1H, H-1, $J_{1,2}$ 6.9 Hz, $J_{1,1'}$ 10.7 Hz), 4.47 (s, 2H, 2 × PhC$\underline{H}_2$O), 4.49 (m, 1H, H-1`) 4.56 (s, 2H, 2 × PhC$\underline{H}_2$O), 4.53 (d, 1H, 1 × PhC$\underline{H}_2$O, J_{HH} 11.6 Hz), 4.57 (d, 2H, 2 × PhC$\underline{H}_2$O, J_{HH} 11.1 Hz), 4.71 (d, 1H, 1 × PhC$\underline{H}_2$O, J_{HH} 11.6 Hz), 4.83 (d, 1 × 1H, PhC$\underline{H}_2$O, J_{HH} 11.1 Hz), 5.05 (ddd, 1H, H-5, $J_{5,6'}$ 2.7 Hz, $J_{4,5}$ 2.8 Hz, $J_{5,6}$ 7.8 Hz), 7.21-7.38 (m, 20H, aromatic CH); δ_C ($CDCl_3$, 125.7 MHz, gHSQC, DEPT) 36.9, 38.3 (q, 2 × CH_3SO_3), 68.9 (t, C-6), 70.2 (t, C-1), 73.3, 73.5, 74.2, 74.6 (4 × t, 4 × Ph$\underline{C}H_2$O), 76.6 (d, C-2), 77.8 (d, C-3), 79.0 (d, C4), 82.9, (d, C-5), 127.7, 127.89, 127.94 128.0, 128.09, 128.1, 128.2, 128.4, 128.5 (9 of 20 aromatic CH, others coincident), 137.2, 137.32, 137.37, 137.44 (3 × quaternary aromatic); HRMS found 716.2564 ($C_{36}H_{46}S_2NO_{10}$ ($[M+NH_4]^+$) requires 716.2563).

1-Azido-2,3,4,6-tetra-O-benzyl-1-deoxy-5-O-methanesulfonyl-D-glucitol (4.33):



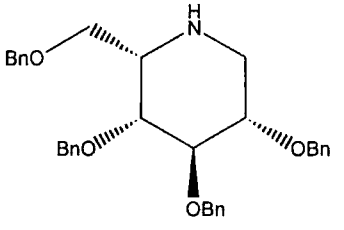
2,3,4,6-Tetra-*O*-benzyl-1,5-dimethanesulfonyl-D-glucitol (**4.10**) (1.0 eq., 0.249 mmol, 174 mg) was dissolved in dry DMF (4.0 mL). Sodium azide was added (1.8 eq., 0.448 mmol, 29 mg) and the reaction stirred under nitrogen for 72 h after which time TLC showed partial conversion of starting material to product. The reaction mixture was concentrated *in vacuo*, and the residue dissolved in $CHCl_3$ (50 mL) and washed with water (2 × 30 mL). The aqueous layers were combined and extracted with $CHCl_3$ (30 mL). The organic extracts were combined, dried ($MgSO_4$), filtered, and the solvent removed *in vacuo*. The residue was purified by flash chromatography (15 : 85, ethyl acetate : hexane) to give recovered 2,3,4,6-tetra-*O*-benzyl-1,5-di-*O*-methanesulfonyl-D-glucitol (**4.10**) (75 mg, 43 %), and 1-azido-2,3,4,6-tetra-*O*-benzyl-1-deoxy-5-*O*-methanesulfonyl-D-glucitol (**4.33**) (56 mg, 42 %) as a colourless oil: $[\alpha]_D^{23.5}$ + 25.2 (c = 1.00, $CHCl_3$); *m/z* 668.2 (ES, $[M+Na]^+$, 100 %, MeOH), 1313.5 ($[2M+Na]^+$, 5 %); ν_{max} (film)/cm^{-1}: 2099 (azide stretch), 2854, 2922, 2952 (aliphatic C-H stretch), 3026, 3060, 3094 (aromatic C-H stretch); δ_H ($CDCl_3$, 500 MHz, gCOSY, gHSQC) 2.91 (s, 3H, $C\underline{H}_3SO_2$), 3.31 (dd, 1H, H-1, $J_{1,2}$ 7.4 Hz, $J_{1,1'}$ 13.1 Hz), 3.35 (dd, 1H, H-1`, $J_{1',2}$ 3.4 Hz, $J_{1,1'}$ 13.1 Hz) 3.62 (t, 1H, H-3, $J_{2,3}$ 5.5 Hz, $J_{3,4}$ 5.5 Hz), 3.68 (ddd, 1H, H-2, $J_{1',2}$ 3.4 Hz, $J_{2,3}$ 5.4 Hz, $J_{1,2}$ 7.4 Hz), 3.75 (dd, 1H, H-6, $J_{5,6}$ 7.8 Hz $J_{6,6'}$ 11.1 Hz), 3.80 (dd, 1H, H-6`, $J_{5,6'}$ 2.9 Hz, $J_{6,6'}$ 11.1 Hz), 3.95 (dd, 1H, H-4, $J_{4,5}$ 2.6 Hz, $J_{3,4}$ 5.6 Hz), 4.40 (s, 2H, 2 × $PhC\underline{H}_2O$), 4.51-4.62 (m, 5H, 5 × $PhC\underline{H}_2O$), 4.72 (d, 1H, 1 × $PhC\underline{H}_2O$), 5.00 (pdt, 1H, H-5, $J_{4,5}$ 2.9Hz, $J_{5,6'}$ 2.9 Hz, $J_{5,6}$ 7.8 Hz), 7.20-7.33 (m, 20H, aromatic CH): δ_C ($CDCl_3$, 125.7 MHz, DEPT, gHSQC) 38.6 (q, $C\underline{H}_3SO_3$), 51.5 (t, C-1), 69.2 (t, C-6), 73.6, 73.7, 74.8, 74.9 (4 × t, 4 × $PhC\underline{H}_2O$), 78.5 (d, C-3), 78.6 (d, C-2), 79.8 (d, C-4), 83.4 (d, C-5), 128.0, 128.16, 128.22, 128.25, 128.30, 128.4, 128.5, 128.65, 128.71, 128.73, 128.8 (11 × d, 11 of 20 aromatic CH, others coincident), 137.69, 137.73, 137.76 (3 × s, 3 of 4 quaternary aromatic, two coincident); HRMS found 663.2850 ($C_{35}H_{43}SN_4O_7$ ($[M+NH_4]^+$) requires 663.2852).

2,5-Anhydro-1-azido-3,4,6-tetra-O-benzyl-1-deoxy-D-glucitol (4.34):



m/z 482.2 (ES, $[M+Na]^+$, 100 %, MeOH), 460.2 ($[M+H]^+$, 15 %); ν_{max} (film)/cm^{-1}: 2099 (azide stretch), 2852, 2866, 2920 (aliphatic C-H stretch), 3028, 3064, 3088 (aromatic C-H stretch); δ_H ($CDCl_3$, 500 MHz, gCOSY, gHSQC) 3.45 (dd, 1H, H-1, $J_{1,2}$ 6.6 Hz, $J_{1,1'}$ 12.4 Hz), 3.51 (dd, 1H, H-1`, $J_{1',1}$ 6.8 Hz, $J_{1,1'}$ 12.4 Hz), 3.68 (dd, 1H, H-6, $J_{5,6}$ 6.3 Hz, $J_{6,6'}$ 9.7 Hz) 3.72 (dd, 1H, H-6`, $J_{5,6'}$ 6.2 Hz), 3.98 (dd, 1H, H-3, $J_{3,4}$ 1.3 Hz, $J_{2,3}$ 4.2 Hz), 4.04 (dd, 1H, H-4, $J_{3,4}$ 1.3 Hz, $J_{4,5}$ 3.9 Hz), 4.28 (dpt, 1H, H-2, $J_{2,3}$ 4.2 Hz, $J_{1,2}$ 6.7 Hz, $J_{1',2}$ 6.7 Hz), 4.36 (dpt, 1H, H-5, $J_{4,5}$ 3.9 Hz, $J_{5,6}$ 6.2 Hz, $J_{5,6'}$ 6.2 Hz), 4.42 (d, 1H, 1 × $PhC\underline{H}_2O$, J_{HH} 11.7 Hz), 4.47-4.45 (m, 4H, 4 × $PhC\underline{H}_2O$), 4.61 (d, 1H, 1 × $PhC\underline{H}_2O$, J_{HH} 11.7 Hz), 7.24-7.37 (m, 15H, 15 × aromatic CH); δ_C ($CDCl_3$, 125.7 Hz, DEPT, gHSQC) 50.2 (t, C-1), 68.4 (t, C-6), 72.2, 72.5, 73.6 (3 × t, 3 × $PhC\underline{H}_2O$), 78.9 (d, C-2), 79.4 (d, C-5), 81.2 (d, C-4), 81.4 (d, C-3), 127.78, 128.16, 127.9, 128.0, 128.1, 128.2, 128.5, 128.7 (8 × d, 8 of 15 aromatic CH, others coincident), 137.6, 137.9, 138.3 (3 × s, 3 × quaternary aromatic).

*2,3,4,6-Tetra-O-benzyl-1,5-dideoxy-1,5-imino-L-iditol (**4.02**):*



Method 1

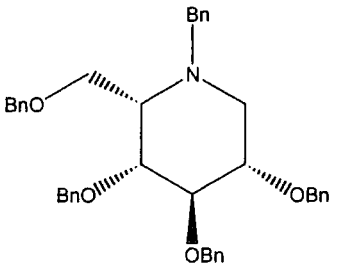
1-azido-1-deoxy-2,3,4,6-tetra-*O*-benzyl-5-*O*-methanesulfonyl-D-glucitol (**4.33**) (1.0 eq., 0.0542 mmol, 35.0 mg) was dissolved in dry diethyl ether (2.0 mL) under nitrogen. Triphenylphosphine was added (1.1 eq., 0.0595 mmol, 15.6 mg), and the reaction stirred. The reaction was monitored by TLC. After 18 h the mixture was diluted with diethyl ether (30 mL), washed with brine (20 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated. The residue was dissolved in THF (3.0 mL), and NaOH (aq., 0.1 M, 1 mL) added. The mixture was refluxed for 18 h, then diluted with diethyl ether (30 mL). The solution was washed with brine (20 mL), then the organic layer dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was

purified by adsorbing onto Dowex™ 50W acidic exchange resin (MeOH eluent), and eluting with methanol : ammonia (conc., aq.) (4 : 1). The solvent was removed *in vacuo* to give 2,3,4,6-tetra-*O*-benzyl-1,5-dideoxy-1,5-imino-L-iditol (**4.02**) as a colourless oil (26 mg, 92 %).

Method 2

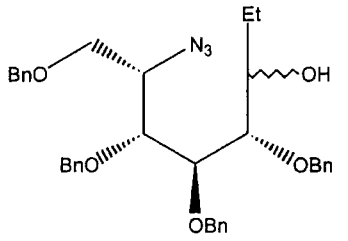
2,3,4,6-Tetra-*O*-benzyl-1,5-di-*O*-methanesulfonyl-D-glucitol (**4.10**) (1.0 eq., 2.98 mmol, 2.09 g), and sodium azide (3.0 eq, 8.97 mmol, 583 mg) were dissolved in dry DMF under nitrogen, and the mixture stirred at 80 °C. After 5 h the reaction mixture was cooled to room temperature and triphenylphosphine added (860 mg, 3.28 mmol, 1.1 eq.). The mixture was heated to 80 °C for a further 17 h. The reaction mixture was diluted with diethyl ether (200 mL), washed with water (100 mL), dried (Na_2SO_4), filtered, and the solvent removed *in vacuo*. The crude oil was passed through a column of Dowex™ 50W acidic exchange resin (10 g) and washed with methanol (100 mL) then the desired product eluted with methanol : ammonia (aq., satd.) (4 : 1), 100 mL, and the solvent removed *in vacuo*. The resultant oil was purified by flash chromatography (3 : 1, ethyl acetate : hexane eluent) to give 2,3,4,6-tetra-*O*-benzyl-1,5-dideoxy-1,5-imino-L-iditol (**4.02**) as a colourless oil (958 mg, 61 %): *m/z* 524.0 (ES, $[M+H]^+$, 100%, MeOH), 546.0 ($[M+Na]^+$, 35 %); δ_H ($CDCl_3$, 500 MHz, gCOSY, gHSQC) 2.47 (s, br, 1H, NH), 2.93 (dd, 1H, H-1, $J_{1,2}$ 6.6 Hz, $J_{1,1'}$ 12.8 Hz), 3.07 (dd, 1H, H-1`, $J_{1',2}$ 3.8 Hz, $J_{1,1'}$ 12.8 Hz), 3.45 (m, 1H, H-5), 3.51 (m, 1H, H-2), 3.61 (dd, H-6, $J_{5,6}$ 5.2 Hz, $J_{6,6'}$ 9.5 Hz), 3.67-3.71 (m, 2H, H-3, H-4), 3.74 (t, 1H, H-6`, $J_{5,6}$ 9.2 Hz, $J_{6,6'}$ 9.2 Hz), 4.56-4.73 (m, 8H, 8 × PhC$\underline{H}_2$O), 7.30-7.41 (m, 20H, aromatic CH); δ_C (100.6 MHz, $CDCl_3$, DEPT, gHSQC) 44.3, (t, C-1), 54.7 (d, C-5), 67.2 (t, C-6), 72.1, 72.6, 73.4, 74.1 (4 × t, 4 × Ph$\underline{C}H_2$O), 76.9 (d, br, C-2), 77.4, 78.0 (2 × d, br, C-3, C-4), 127.6, 127.68, 127.74, 127.8, 127.9, 128.0, 128.37, 128.41, 128.5 (9 × d, 9 of 20 aromatic CH, others coincident), 138.34, 138.46, 138.57, 138.63 (4 × s, 4 × quaternary aromatic); HRMS found 524.2801 ($C_{34}H_{38}NO_4$ ($[M+H]^+$) requires 524.2801).

*N-Benzyl-2,3,4,6-tetra-O-benzyl-1,5-dideoxy-1,5-imino-L-iditol (**4.31**):*



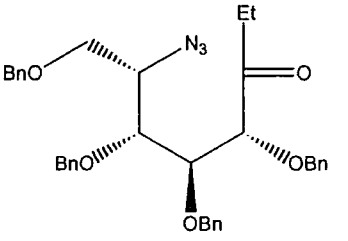
2,3,4,6-Tetra-*O*-benzyl-1,5-di-*O*-methanesulfonyl-D-glucitol (**4.10**) (1.0 eq., 0.869 mmol, 607 mg) was dissolved in benzylamine (5.0 mL), and the mixture heated to 80 °C under nitrogen for 24 h. The benzylamine was removed *in vacuo*, and the residue purified by flash chromatography (1 : 9, ethyl acetate : hexane eluent) to give *N*-benzyl-2,3,4,6-tetra-*O*-benzyl-1,5-dideoxy-1,5-imino-L-iditol (**4.31**) as a colourless oil (386 mg, 72 %): δ_H ($CDCl_3$, 500 MHz, gCOSY, gHSQC) 2.63 (m, 1H, H-1), 2.88 (m, 1H, H-1`), 3.46 (m, 1H, H-5), 3.60 (m, 2H, H-2, H-3), 3.75-3.81 (m, 3H, H-4, H-6`, 1 × $PhCH_2N$), 3.97 (dd, 1H, H-6, $J_{5,6}$ 7.2 Hz, $J_{6,6'}$ 10.0 Hz), 4.02 (d, 1H, 1 × $PhC\underline{H}_2N$, J_{HH} 14.1 Hz), 4.53-4.69 (m, 6H, 6 × $PhC\underline{H}_2O$), 4.84 (d, 1H, J_{HH} 10.9 Hz), 4.90 (d, 1H, J_{HH} 10.9 Hz), 7.24-7.42 (m, 25H, aromatic CH); δ_C (100.6 MHz, $CDCl_3$, DEPT, gHSQC) 48.9 (t, C-1), 59.2 (t, C-6), 59.9 (d, C-5), 64.8 (t, $Ph\underline{C}H_2N$), 72.6, 72.9, 73.4, 75.6 (4 × t, 4 × $PhCH_2O$), 79.1, 83.2 (2 × d, C-2, C-3), 80.4 (d, C-4), 126.9, 127.5, 127.61, 127.64, 127.7, 127.8, 128.0, 128.3, 128.35, 128.37, 128.41, 128.43, 128.5 (13 × d, 13 of 25 aromatic CH, others coincident), 138.62, 138.63, 138.65, 139.3, 139.8 (5 × q, 5 × quaternary aromatic); HRMS found 614.3275 ($C_{41}H_{44}NO_4$ ($[M+H]^+$) requires 614.3270).

(1S)-5-Azido-2,3,4,6-tetra-O-benzyl-1,5-dideoxy-1-C-ethyl-L-iditol ***(4.39)****, and (1R)-5-azido-2,3,4,6-tetra-O-benzyl-1,5-dideoxy-1-C-ethyl-L-iditol* ***(4.40)*** *(mixture of isomers):*



5-Azido-2,3,4,6-*O*-benzyl-5-deoxy-L-idose (**4.24**) (1.0 eq., 0.437 mmol, 247 mg) was dissolved in dry diethyl ether (10 mL), and ethylmagnesium bromide added (1.5 eq., 0.655 mmol, 218 μL, 3.0 M solution in THF). The reaction was stopped after 90 minutes by addition of NH_4Cl (aq., satd., 1 mL). The mixture was diluted with diethyl ether (50 mL), washed with water (30 mL), and brine (satd., 30 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated. The resultant colourless oil was purified by flash chromatography (1 : 9, ethyl acetate : hexane eluent) to give as an intractable mixture of isomers (1*S*)-5-azido-2,3,4,6-tetra-*O*-benzyl-1,5-dideoxy-1-*C*-ethyl-L-iditol (**4.39**) and (1*R*)-5-azido-2,3,4,6-tetra-*O*-benzyl-1,5-dideoxy-1-*C*-ethyl-L-iditol (**4.40**) (dr = 1 : 3 (NMR)) (183 mg, 70 %): *m/z* 618.3 (ES, $[M+Na]^+$, 100%, MeOH); ν_{max} (film)/cm^{-1}: 2098 (azide stretch), 2869, 2925, 2959 (aliphatic C-H stretch), 3030, 3063, 3090 (aromatic C-H stretch), 3436 (br, O-H stretch); HRMS found 596.3122 ($C_{36}H_{42}N_3O_5$ ($[M+H]^+$) requires 596.3124).

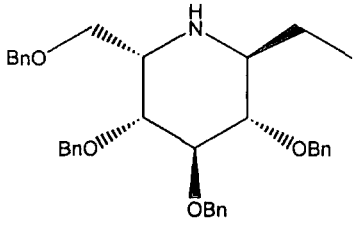
5-Azido-2,3,4,6-tetra-O-benzyl-1,5-dideoxy-1-C-ethyl-L-idose ***(4.41)****:*

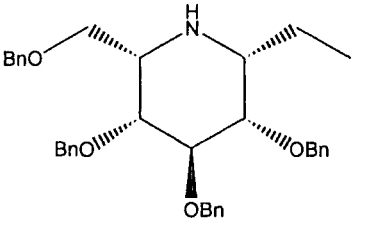


(1*S*)-5-Azido-2,3,4,6-tetra-*O*-benzyl-1,5-dideoxy-1-*C*-ethyl-L-iditol (**4.39**) and (1*R*)-5-azido-2,3,4,6-tetra-*O*-benzyl-1,5-dideoxy-1-*C*-ethyl-L-iditol (**4.40**) (mixture of isomers) (1.0 eq., 0.307 mmol, 183 mg), PCC (2.5 eq., 0.766 mmol, 165.2 mg), and molecular sieves (4 Å, powdered, 200 mg), were dissolved in dry DCM (6.0 mL) and stirred under nitrogen. The reaction was stopped after 2 h by triturating with diethyl ether (30 mL), and filtering through celite. The mixture was concentrated and the

resultant brown oil purified by flash chromatography (7.5 : 93.5, ethyl acetate : hexane eluent) to give 5-azido-2,3,4,6-tetra-*O*-benzyl-1,5-dideoxy-1-*C*-ethyl-L-idose (**4.41**) (132 mg, 72 %): $[\alpha]_D^{21.6}$ + 33.8 (c = 1.00, in $CHCl_3$); *m/z* 616.2 (ES $[M+Na]^+$, 100 %, MeOH), 1209.7 ($[2M+Na]^+$, 40 %); ν_{max}/cm^{-1}(film), 1713 (C=O stretch), 2098 (azide stretch), 2852, 2920 (aliphatic C-H stretch), 3030, 3064, 3088 (aromatic C-H stretch); δ_H ($CDCl_3$, 500 MHz, gCOSY, gHSQC) 0.85 (t, 3H, $C\underline{H}_3CH_2$, J_{HH} 7.2 Hz), 2.40 (dq, 1H, 1 × $CH_3C\underline{H}_2$, J_{HH} 7.2 Hz, J_{HH} 18.8 Hz), 2.47 (dq, 1H, 1 × $CH_3C\underline{H}_2$, J_{HH} 7.2 Hz, J_{HH} 18.8 Hz), 3.23 (ddd, 1H, H-5, $J_{4,5}$ 3.6 Hz, $J_{5,6}$ 5.1 Hz, $J_{5,6'}$ 7.4 Hz), 3.38 (dd, 1H, H-6, $J_{5,6}$ 5.1 Hz, $J_{6,6'}$ 9.7 Hz), 3.47 (dd, 1H, H-6`, $J_{5,6'}$ 7.4 Hz, $J_{6,6'}$ 9.6 Hz), 3.78 (dd, 1H, H-4, $J_{4,5}$ 3.6 Hz, $J_{3,4}$ 7.2 Hz), 3.89 (d, 1H, H-2, $J_{2,3}$ 3.5 Hz), 3.97 (dd, 1H, H-3, $J_{2,3}$ 3.5 Hz, $J_{3,4}$ 7.2 Hz), 4.26 (d, 1 × $PhC\underline{H}_2O$, J_{HH} 11.8 Hz), 4.31 (d, 1H, 1 × $PhC\underline{H}_2O$, J_{HH} 11.9 Hz), 4.35 (d, 1H, 1 × $PhC\underline{H}_2O$, J_{HH} 11.9 Hz), 4.38 (d, 1H, 1 × $PhC\underline{H}_2O$, J_{HH} 11.2 Hz), 4.47 (d, 1H, 1 × $PhC\underline{H}_2O$, J_{HH} 11.5 Hz), 4.58 (d, 1H, 1 × $PhC\underline{H}_2O$, J_{HH} 11.2 Hz), 4.64 (m, 2H, 2 × $PhC\underline{H}_2O$, J_{HH} 11.8 Hz), 7.10-7.28 (m, 20H, aromatic CH); δ_C ($CDCl_3$, 125.7 MHz, DEPT, gHSQC) 7.16 (q, $\underline{C}H_3CH_2$), 33.6 (t, $CH_3\underline{C}H_2$), 61.1 (d, C-5), 69.5 (t, C-6), 73.3, 73.4, 75.0, 75.1 (4 × t, 4 × $Ph\underline{C}H_2O$), 78.1 (d, C-4), 80.7 (d, C-3), 82.9 (d, C-2), 127.8, 127.9, 128.0, 128.10, 128.4, 128.45, 128.49, 128.52, 128.56, 128.59, 128.7 (11 × d, 11 of 20 aromatic CH, others coincident), 136.8, 137.7, 137.8, 138.0 (4 × s, 4 × quaternary aromatic), 211.5 (s, C-1); HRMS found 611.3237 ($C_{36}H_{43}N_4O_5$ ($[M+NH_4]^+$) requires 611.3233).

(1R)-2,3,4,6-Tetra-O-benzyl-1,5-dideoxy-1-C-ethyl-1,5-imino-L-iditol ***(4.37)****, and (1S)-2,3,4,6-tetra-O-benzyl-1,5-dideoxy-1-C-ethyl-1,5-imino-L-iditol* ***(4.43)****:*

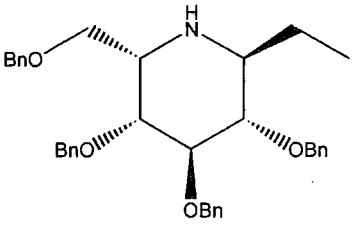




5-azido-2,3,4,6-tetra-*O*-benzyl-1,5-dideoxy-1-*C*-ethyl-L-idose (**4.41**) (1.0 eq., 0.0337 mmol, 20.0 mg) and triphenylphosphine (1.5 eq., 0.0507 mmol, 13.3 mg) were dissolved in dry diethyl ether (1.0 mL) and stirred under nitrogen. The reaction was followed by TLC, and stopped after 6 h, after which time complete consumption of starting material was observed. The mixture was concentrated *in vacuo* and the

residue dissolved in methanol (2.5 mL). Sodium borohydride was added (5.0 eq., 0.167 mmol, 6.3 mg) and the mixture stirred. After a further 16 h the reaction mixture was concentrated *in vacuo*. The residue was dissolved in DCM (30 mL), washed with NaOH (aq., pH 13) (2 × 20 mL), then brine (satd., 20 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (1 :3, ethyl acetate : hexane eluent) to give (1*S*)-2,3,4,6-tetra-*O*-benzyl-1,5-dideoxy-1-*C*-ethyl-1,5-imino-L-iditol (**4.43**) (3.0 mg, 16 %), (1*R*)-2,3,4,6-tetra-*O*-benzyl-1,5-dideoxy-1-*C*-ethyl-1,5-imino-L-iditol (**4.37**) (5.9 mg, 32 %), and 2,3,4,6-Tetra-*O*-benzyl-1,3,5-trideoxy-1,*N*-dehydro-2,3-dehydro-1-*C*-ethyl-1,5-imino-L-iditol (**4.42**) (3.1 mg, 20 %), together with other intractable decomposition products.

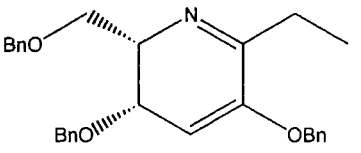
*(1S)-2,3,4,6-Tetra-O-benzyl-1,5-dideoxy-1-C-ethyl-1,5-imino-L-iditol (**4.43**):*



5-Azido-2,3,4,6-tetra-*O*-benzyl-1,5-dideoxy-1-*C*-ethyl-L-idose (**4.41**) (1.0 eq., 0.0185 mmol, 11.0 mg), was dissolved in dry diethyl ether (1.5 ml) and triphenylphosphine added (3.5 eq., 0.0656 mmol, 17.2 mg). The mixture was stirred under nitrogen for 3 h after which time TLC showed consumption of starting material. Lithium aluminium hydride was added (4.0 eq., 0.074 mmol 74 μL, 1.0 M solution in THF). The mixture was stirred for 30 minutes before quenching with NH_4Cl (satd., aq., 1 mL). The mixture was diluted with diethyl ether (30 mL), and washed with water (2 × 10 mL). The organic layer was dried (Na_2SO_4), filtered, and the solvent removed *in vacuo*. The resultant colourless oil was purified by flash column chromatography (15 : 85, ethyl acetate : hexane eluent) to yield (1*S*)-2,4,6-tri-*O*-benzyl-1,3,5-trideoxy-2,3-dehydro-1-*C*-ethyl-1,5-imino-L-iditol (**4.44**) (1.1 mg, 13 %) and, as the only diastereoisomer (1*S*)-2,3,4,6-tetra-*O*-benzyl-1,5-dideoxy-1-*C*-ethyl-1,5-imino-L-iditol (**4.43**) (7.0 mg, 68 %): $[\alpha]_D^{25.1}$ – 34.1 (c = 1.00, in $CHCl_3$); *m/z* 552.3 (ES, $[M+H]^+$, 100 %, MeOH), 574.5 ($[M+Na]^+$, 20 %); ν_{max}/cm^{-1}(film), 2856, 2919, 2959 (aliphatic C-H stretch), 3030, 3063, 3088 (aromatic C-H stretch); δ_H ($CDCl_3$, 500 MHz, gCOSY, gHSQC) 0.85 (t, 3H, $C\underline{H}_3CH_2$), 1.18-1.29 (m, 1H, 1 × $CH_3C\underline{H}_2$), 1.79-1.88

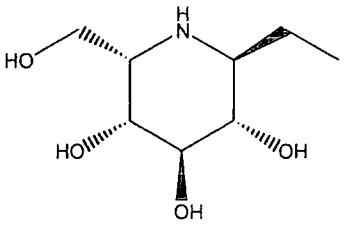
(m, 1H, 1 × $CH_3C\underline{H}_2$), 2.60 (dpt, 1H, H-1, J_{HH} 2.6 Hz, $J_{1,2}$ 9.1 Hz), 3.07 (t, 1H, H-2, $J_{1,2}$ 9.1 Hz, $J_{2,3}$ 9.1 Hz), 3.46-3.59 (m, 3H, H-3, H-5, H-6) 3.69 (t, 1H, H-4, $J_{3,4}$ 10.0 Hz, $J_{4,5}$ 10.0 Hz), 3.72 (dd, 1H, H-6`, $J_{5,6'}$ 5.8 Hz, $J_{6,6'}$ 9.6 Hz); δ_C ($CDCl_3$, 125.7 MHz, DEPT, gHSQC) 10.3 (q, $\underline{C}H_3CH_2$), 29.8 (t, $CH_3\underline{C}H_2$), 54.0, 54.2 (2 × d, C-1, C-5), 65.4 (t, C-6), 72.8, 73.7, 75.6, 75.7 (4 × t, 4 × $PhC\underline{H}_2O$), 80.8, 83.9 (2 × d, C-3, C-4), 83.5 (d, C-2), 127.7, 127.9, 128.49, 128.54, 128.57, 128.63 (6 × d, 6 of 20 aromatic C-H, others coincident), 138.3, 138.4, 138.6, 139.0 (4 × s, 4 × quaternary aromatic); HRMS found 552.3151 ($C_{36}H_{42}NO_4$ ($[M+H]^+$) requires 552.3114).

2,4,6-Tri-O-benzyl-1,3,5-trideoxy-1,N-dehydro-2,3-dehydro-1-C-ethyl-1,5-imino-L-iditol, ((2S,3S)1-benzyloxymethyl-3,5-dibenzyloxy-2,3-dihydro-6-ethyl-pyridine) ***(4.44)****:*



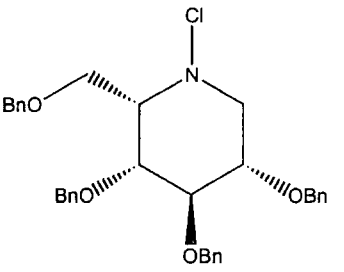
δ_H ($CDCl_3$, 500 MHz, gCOSY, gHSQC) 1.14 (t, 3H, $C\underline{H}_3CH_2$, J_{HH} 7.7 Hz), 2.52-2.59 (m, 2H, $CH_3C\underline{H}_2$), 3.51 (m, 1H, H-5), 4.04 (d, 2H, H-6, H-6`, $J_{5,6}$ 8.0 Hz), 4.21 (dd, 1H, H-4, $J_{4,5}$ 5.1 Hz, $J_{3,4}$ 6.5 Hz), 4.62 (d, 1H, 1 × $PhC\underline{H}_2O$, J_{HH} 12.0 Hz), 4.66 (d, 1H, 1 × $PhC\underline{H}_2O$, J_{HH} 12.0 Hz), 4.71 (s, 2H, 2 × $PhCH_2O$), 4.78 (s, 2H, $PhC\underline{H}_2O$), 5.36 (d, 1H, H-3, $J_{3,4}$ 6.5 Hz), 7.19-7.37 (m, 15H, aromatic CH); δ_C ($CDCl_3$, 125.7 MHz, DEPT, gHSQC) 11.3 (q, $\underline{C}H_3CH_2$), 27.9 (t, $CH_3\underline{C}H_2$), 60.9 (d, C-5), 68.5 (d, C-4), 69.2, 70.3, 73.7 (3 × t, 3 × $Ph\underline{C}H_2O$), 70.8 (t, C-6), 100.1 (d, C-3), 127.3, 127.4, 127.7, 127.8, 127.9, 128.1, 128.3, 128.5, 128.6, 128.8 (10 × d, 10 × aromatic CH), 136.5, 138.7, 139.3 (3 × s, 3 × quaternary aromatic), 150.6 (s, C-2), 165.8 (s, C-1).

*(1S)-1,5-dideoxy-1-C-ethyl-1,5-imino-L-iditol, (–)-adenophorine (**4.11**) (Ref. 116):*



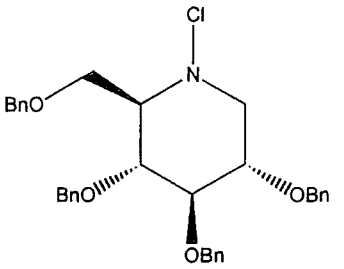
(1*S*)-2,3,4,6-Tetra-*O*-benzyl-1,5-dideoxy-1-*C*-ethyl-1,5-imino-L-iditol (**4.43**) (1.0 eq., 0.014 mmol, 7.9 mg) was dissolved in absolute ethanol (2.0 mL) which had been degassed by boiling under reduced pressure, and $PdCl_2$ (2 eq., 0.028 mmol, 5 mg) and HCl (aq., 3.0 M, 0.25 mL) added. The mixture was stirred under an atmosphere of hydrogen at atmospheric pressure for 1.5 h before filtering through celite. The resultant solution was passed through a plug of Dowex^{TM} 550A anionic exchange resin, and eluted with methanol. The eluent was then passed over Dowex^{TM} 50W acidic echange resin, and the resin washed with methanol (25 ml). The desired product was eluted with methanol : ammonia (conc., aq.) (4 : 1) (10 mL) and the solvent removed *in vacuo* to give as a colourless oil (1*S*)-1,5-dideoxy-1-*C*-ethyl-1,5-imino-L-iditol (**4.11**) (2.7 mg, 100 %). $[\alpha]_D^{22.0}$ – 52.3 (c = 0.2, H_2O) (lit.[116] for enantiomer $[\alpha]_D^{19}$ + 59.7 (c = 1, H_2O); ν_{max} (film)/cm^{-1}: 2860, 2935, 2957 (aliphatic C-H stretch), 3405 (br, O-H stretch); *m/z* 192.1 (ES, $[M+H]^+$, 100 %, MeOH), 214.1 ($[M+Na]^+$, 5 %); δ_H (D_2O, 500 MHz, gCOSY) 0.94 (t, 3H, $C\underline{H}_3CH_2$), 1.30-1.39 (m, 1H, 1 × $CH_3C\underline{H}_2$), 1.80-1.89 (m, 1H, 1 × $CH_3C\underline{H}_2$), 2.64 (dpt, 1H, H-1, J_{HH} 3.0 Hz, J_{HH} 8.9 Hz, $J_{1,2}$ 8.9 Hz), 3.11 (t, 1H, H-2, $J_{1,2}$ 9.5 Hz, $J_{4,5}$ 9.5 Hz), 3.23-3.28 (m, 1H, H-5), 3.45 (t, 1H, H-3, $J_{2,3}$ 9.4 Hz, $J_{3,4}$ 9.4 Hz), 3.75 (dd, 1H, H-4, $J_{4,5}$ 6.0 Hz, $J_{3,4}$ 10.0 Hz), 3.77-3.84 (m, 2H, H-6, H-6`); δ_C (D_2O, 125.7 MHz, DEPT) 11.7 (q, $\underline{C}H_3CH_2$), 26.8 (t, $CH_3\underline{C}H_2$), 56.2 (d, C-1), 59.1 (t, C-6), 59.7 (d, C-5), 74.4 (d, C-4), 77.2 (d, C-3), 77.6 (d, C-2); HRMS found 192.1229 ($C_8H_{18}NO_4$ ($[M+H]^+$) requires192.1236.

*2,3,4,6-Tetra-O-benzyl-N-chloro-1,5-dideoxy-1,5-imino-L-iditol (**4.08**):*



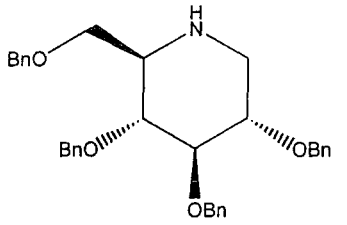
2,3,4,6-Tetra-*O*-benzyl-1,5-dideoxy-1,5-imino-L-iditol (**4.02**) (1.0 eq., 1.91 mmol, 1.00 g) was placed in a round-bottomed flask with dry DCM (20 mL), and *N*-chlorosuccinimide added (1.2 eq., 2.30 mmol, 311 mg). The mixture was stirred under nitrogen and followed by TLC until complete conversion of starting material into product had occurred. After 16 h the reaction mixture was diluted with DCM (80 mL), and washed with water (2 × 50 mL), then the organic layer dried (Na_2SO_4), filtered, and the solvent removed to give a pale yellow oil which was purified by passing through a plug of silica (1 : 4, ethyl actetate : hexane eluent). Removal of the solvent *in vacuo* gave 2,3,4,6-tetra-*O*-benzyl-*N*-chloro-1,5-dideoxy-1,5-imino-L-iditol (**4.08**) as a colourless oil (987 mg) (93 %): $[\alpha]_D^{25.3}$ + 9.9 (c = 1.00, $CHCl_3$); *m/z* 580.0 (ES, $[M+Na]^+$,^{35}Cl, 100 %, MeOH), 524.0 ($[M-Cl+2H]^+$, 90 %), 582 ($[M+Na]^+$, ^{37}Cl, 24 %); ν_{max} (film)/cm^{-1}: 2865 (br, aliphatic C-H stretch), 3029, 3062, 3090 (aromatic C-H stretch); δ_H ($CDCl_3$, 500 MHz, COSY) 3.35-3.45 (m, 2H, H-1, H-1`), 3.54 (pdd, 1H, H-5, $J_{4,5}$ 4.8 Hz, $J_{5,6}$ 9.6 Hz, $J_{5,6'}$ 9.6 Hz), 3.75 (t, 1H, H-3, $J_{2,3}$ 8.0 Hz, $J_{3,4}$ 8.0 Hz), 3.81 (m, 2H, H-2, H-6), 3.91 (dd, 1H, H-6`, $J_{5,6'}$ 4.4 Hz, $J_{6,6'}$ 10.1 Hz), 4.0 (dd, 1H, H-4, $J_{4,5}$ 5.3 Hz $J_{3,4}$ 7.8 Hz,), 4.57 (s, 2H, 2 × PhC$\underline{H}_2$O), 4.59-4.73 (m, 5H, 5 × PhC$\underline{H}_2$O), 4.76 (d, 1H, 1 × $PhCH_2O$, J_{HH} 11.3 Hz), 7.27-7.37 (m, 20H, aromatic CH); δ_C (125.7 MHz, $CDCl_3$, DEPT, gHSQC) 59.3 (t, br, C-1), 67.3 (t, C-6), 68.2 (d, C-5), 73.0, 73.4, 73.5, 74.9 (4 × t, 4 × Ph$\underline{C}H_2$O), 76.9 (d, C-2), 77.7 (d, C-4), 80.1 (d, br, C-3), 127.7, 127.8, 127.87, 127.93, 128.08, 128.10, 128.49, 128.51, 128.54 (9 × d, 9 of 20 aromatic $\underline{C}$H, others coincident), 138.17, 138.24, 138.3, 138.7 (4 × s, 4 × quaternary aromatic); HRMS found 558.2416, ($C_{34}H_{37}ClNO_4$ ($[M+H]^+$) requires 558.2411).

*2,3,4,6-Tetra-O-benzyl-N-chloro-1,5-dideoxy-1,5-imino-D-glucitol (**4.07**):*



2,3,4,6-Tetra-*O*-benzyl-1,5-dideoxy-1,5-imino-D-glucitol (**4.01**) (1.0 eq., 0.573 mmol, 300 mg) was placed in a dry round bottomed flask with dry DCM (5.0 mL) under nitrogen with stirring. NCS (1.1 eq., 0.632 mmol, 84.4 mg) was added. The reaction was followed by TLC, revealing consumption of starting material after 22 h. The reaction mixture was diluted with DCM (20 mL) and washed with distilled water (2 × 30 mL). The organic layer was dried (Na_2SO_4), filtered, and the solvent removed *in vacuo* to give a colourless oil, which was flushed though a silica plug (1 : 1, ethyl acetate : hexane eluent) and the solvent removed *in vacuo* to give 2,3,4,6-tetra-*O*-benzyl-*N*-chloro-1,5-dideoxy-1,5-imino-D-glucitol (**4.07**) as a colourless oil which forms a white crystalline solid on standing (310 mg, 97 %); mp 168-169 °C (dec., ethyl acetate/hexane): $[\alpha]_D^{25.3}$ + 8.0 (c = 1.00, $CHCl_3$); *m/z* 558 (ES, $[M+H]^+$,^{35}Cl, 12 %, MeOH), 580 ($[M+Na]^+$, 20 %, ^{35}Cl), 582 ($[M+Na]^+$, 7 %, ^{37}Cl), 524 ($[M-Cl+2H]^+$, 100 %); ν_{max} (KBr disc)/cm^{-1}: 2900 - 2930 (aliphatic C-H stretch), 3027 (aromatic C-H stretch); δ_H ($CDCl_3$, 500 MHz, gCOSY) 2.75 (d, br, 1H, J_{HH} 8.0 Hz), 2.9 (t, 1H, J_{HH} 11.7 Hz), 3.55 (t, 1H, J_{HH} 9.1 Hz), 3.75 (m, 4H), 3.85 (dd, 1H, J_{HH} 2.0 Hz J_{HH} 10.6 Hz), 4.4 – 4.95 (m, 8H, 8 × $PhC\underline{H}_2O$), 7.1 (m, 2H, 2 × aromatic CH), 7.3 (m, 18H, 18 × aromatic CH); δ_C ($CDCl_3$, 100.5 MHz, DEPT) 64 (t, br, C-1), 66.3 (t, C-6), 72 (d, br, C-5), 73.1, 73.5, 75.5, 75.6 (4 × t, 4 × $Ph\underline{C}H_2O$), 76.9, 77.0, 86.3 (3 × d, C-2, C-3, C-4), 127.6, 127.7, 127.8, 127.9, 127.95, 127.98, 128.1, 128.35, 128.36, 128.41, 128.5 (11 × d, 11 of 20 aromatic CH, others coincident), 137.81, 137.84, 138.0, 138.5 (4 × s, 4 × quarternary aromatic); HRMS found 580.2224 ($C_{34}H_{36}NaClNO_4$ ($[M+Na]^+$) requires 580.2231); Found: C, 72.93; H, 6.45; N, 2.46 % ($C_{34}H_{36}ClNO_4$ requires C, 73.17; H, 6.50; N, 2.51 %).

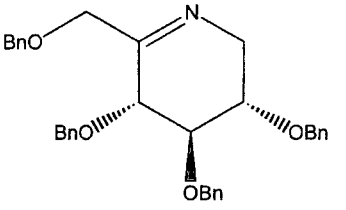
*2,3,4,6-Tetra-O-benzyl-1,5-dideoxy-1,5-imino-D-glucitol (**4.01**):*



2,3,4,6-Tetra-O-benzyl-*N*-chloro-1,5-dideoxy-1,5-imino-D-glucitol (**4.07**) (1.0 eq., 0.0896 mmol, 50 mg), was placed in a dry round-bottomed flask. Dry diethyl ether (2.0 mL) was added under nitrogen with stirring, followed by DBU (4.2 eq., 0.375 mmol, 57.1 mg) was added. After 2 h the reaction mixture was filtered through a glass sinter under nitrogen and concentrated in vacuo to give crude 2,3,4,6-tetra-*O*-benzyl-1,5-dideoxy-5,*N*-dehydro-1,5-imino-D-glucitol (**4.06**), with residual DBU as a pale orange oil (98 mg). The residue was dissolved in dry $CDCl_3$, and analysed by NMR. Analysis confirmed the identity of (**4.06**) and showed no remaining starting material (**4.07**). The sample was concentrated *in vacuo* and the residue dissolved in dry ether (2.0 mL). $LiAlH_4$ was added (5.0 eq., 0.448 mmol, 0.448 mL, 1.0 M solution in THF). The reaction was stopped after 10 minutes by addition of NH_4Cl (aq., satd., 1 mL), and the mixture diluted with diethyl ether (30 mL), washed with water (20 mL). The organic layer was dried (Na_2SO_4), filtered and the solvent removed *in vacuo* to give a colourless oil. Column chromatography of the crude product (3 : 7 ethyl acetate : hexane) gave 2,3,4,6-tetra-*O*-benzyl-1,5-dideoxy-1,5-imino-D-glucitol (**4.01**) as a colourless oil (41 mg, 87 %) which could be recrystallised to give white needles from ethyl acetate/hexane; mp 64.0 - 65.0 °C (ethyl acetate/hexane); *m/z* 524.2 (ES, $[M+H]^+$, 100 %, MeOH), 546.2 ($[M+Na]^+$, 35 %), 1069.7 ($[2M+Na]^+$, 15 %); ν_{max} (KBr disc)/cm^{-1}: 2848, 2902, 2948 (aliphatic C-H stretch), 3028, 3062, 3086 (aromatic C-H stretch), 3320 (N-H stretch) δ_H ($CDCl_3$, 400 MHz, gCOSY) 1.86 (br, 1H, NH), 2.51 (dd, 1H, H-1, $J_{1,2}$ 10.2 Hz, $J_{1,1'}$ 12.1 Hz), 2.73 (ddd, 1H, H-5, $J_{5,6'}$ 2.7 Hz, $J_{5,6}$ 6.3 Hz, $J_{4,5}$ 9.4 Hz), 3.25 (dd, 1H, H-1`, $J_{1',2}$ 4.88 Hz, $J_{1,1'}$ 12.1 Hz), 3.36 (dd, 1H, H-4, $J_{3,4}$ 8.8 Hz, $J_{4,5}$ 9.5 Hz), 3.47-3.55 (m, 2H, H-2, H-6), 3.56 (t, 1H, H-3, $J_{2,3}$ 9.0 Hz, $J_{3,4}$ 9.0 Hz), 3.68 (dd, 1H, H-6`, $J_{5,6'}$ 2.5 Hz, $J_{6,6'}$ 8.9 Hz), 4.43 (d, 1H, 1 × $PhC\underline{H}_2O$, J_{HH} 11.8 Hz), 4.47 (d, 1H, 1 × $PhC\underline{H}_2O$, J_{HH} 11.8 Hz), 4.50 (d, 1H, 1 × $PhC\underline{H}_2O$, J_{HH} 11.1 Hz), 4.67 (d, 1H, 1 × $PhC\underline{H}_2O$, J_{HH} 11.6 Hz), 4.71 (d, 1H, 1 × $PhC\underline{H}_2O$, J_{HH} 11.6 Hz), 4.86 (t, 2H, 2 × $PhC\underline{H}_2O$, J_{HH} 10.5 Hz), 4.99 (d, 1H, 1 × $PhC\underline{H}_2O$, J_{HH} 10.9 Hz), 7.19-7.22 (m, 2H, 2 × aromatic CH), 7.27-7.38 (m, 18H, 18

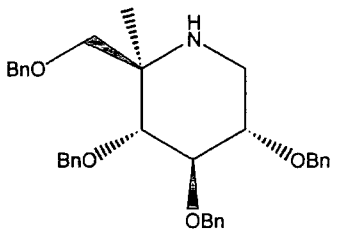
× aromatic); δ_C ($CDCl_3$, 125.7 MHz, DEPT) 48.1 (t, C-1), 59.7 (d, C-5), 70.2 (t, C-6), 72.8, 73.3, 75.2, 75.7 (4 × t, 4 × Ph<u>C</u>H_2O), 80.0, 80.6, 87.3 (3 × d, C-2, C-3, C-4), 127.5, 127.6, 127.65, 127.72, 127.74, 127.8, 127.9, 127.99, 128.3, 128.35, 128.37, 128.38 (12 × d, 12 of 20 aromatic CH, others coincident), 137.9, 18.3, 138.4, 138.8 (4 × s, 4 × quaternary aromatic).

2,3,4,6-Tetra-O-benzyl-1,5-dideoxy-5,N-dehydro-1,5-imino-D-glucitol ***(4.06)****:*



2,3,4,6-Tetra-*O*-benzyl-*N*-chloro-1,5-dideoxy-1,5-imino-D-glucitol (**4.07**) (1.0 eq., 0.179 mmol, 100 mg), was placed in a dry round-bottomed flask with dry diethyl ether (4 mL) under nitrogen with stirring. DBU (1.05 eq., 0.188 mmol, 28.5 mg, 28 µl) was added, and the reaction followed by TLC, which revealed consumtion of starting material and formation of a new product. A white precipitate of DBU.HCl was seen to form quickly. After 135 minutes, the reaction mixture was filtered through a glass sinter under nitrogen and concentrated *in vacuo* to give 2,3,4,6-tetra-*O*-benzyl-1,5-dideoxy-5,*N*-dehydro-1,5-imino-D-glucitol (**4.06**) as a pale orange oil (97 mg, 95 %); ν_{max} (film)/cm^{-1}: 1667 (C=N stretch), 2953, 2850 (aliphatic C-H stretch), 3030, 3088 (aromatic C-H stretch); δ_H ($CDCl_3$, 400 MHz, gCOSY, gHSQC) 3.60 (ddd, 1H, H-1, $J_{1,4}$ 1.4 Hz, $J_{1,2}$ 8.4 Hz, $J_{1,1'}$ 16.8 Hz,), 3.70 (ddd, 1H, H-2, $J_{1',2}$ 4.6 Hz, $J_{1,2}$ 8.4 Hz, $J_{2,3}$ 8.4 Hz), 3.90 (dd, 1H, H-3, $J_{3,4}$ 7.1 Hz, $J_{2,3}$ 8.6 Hz), 4.05 (dd, 1H, H-1`, $J_{1',2}$ 4.6 Hz, $J_{1,1'}$ 16.8 Hz), 4.10 (d, 1H, H-6, $J_{6,6'}$ 13.1 Hz), 4.13 (dd, 1H, H-4, $J_{1,4}$ 1.4 Hz, $J_{3,4}$ 7.1 Hz), 4.40 (d, 1H H-6`, $J_{6,6'}$ 13.1 Hz), 4.5-4.9 (m, 8H, 8 × Ph<u>C</u>H_2O), 7.23-7.40 (m, 20H, 20 × aromatic CH); δ_C ($CDCl_3$, 75 MHz, DEPT, gHSQC) 53.2 (t, C-1), 71.9 (t, C-6), 72.4, 73.0, 74.3, 74.9 (4 × t, 4 × Ph<u>C</u>H_2O), 75.7 (d, C-2), 78.5 (d, C-4), 81.7 (d, C-3), 127.65, 127.66, 127.68, 127.76, 127.78, 127.84, 127.87, 128.0, 128.1, 128.16, 128.24, 128.27, 128.32, 128.34, 128.5 (15 × d, 15 of 20 aromatic CH, others coincident), 137.6, 137.8, 138.0, 138.2 (4 × s, 4 × quaternary aromatic), 168.5 (s, C-6).

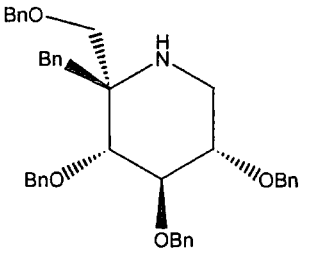
*(5R)-2,3,4,6-Tetra-O-benzyl-1,5-dideoxy-1,5-imino-5-C-methyl-D-glucitol (**4.35**):*



To a cooled (– 78 °C) freshly prepared solution of 2,3,4,6-tetra-*O*-benzyl-1,5-dideoxy-5,*N*-dehydro-1,5-imino-D-glucitol (**4.06**) (1.0 eq., 0.112 mmol, 3.33 mL, 0.0340 M solution in dry diethyl ether) under nitrogen, was added methylmagnesium bromide (3.0 eq., 0.112 mmol, 0.112 mL, 3.0 M solution in diethyl ether) with stirring. After 2 h at – 78 °C the mixture was warmed to room temperature and stirred for a further 12 h. The reaction was stopped by the addition of water (5 mL), then diluted with diethyl ether (10 mL), and washed with water (2 × 20 mL). The organic layer was dried (Na_2SO_4), filtered, and the solvent removed *in vacuo*. The resultant oil was separated by flash column chromatography (1 : 4, ethyl acetate : hexane eluent) to yield (5*R*)-2,3,4,6-tetra-*O*-benzyl-1,5-dideoxy-1,5-imino-5-*C*-methyl-D-glucitol (**4.35**) (6.0 mg, 10 %): $[\alpha]_D^{21.5}$ + 22.2 (c = 0.65, $CHCl_3$); *m/z* 192.1 (ES, $[M+H]^+$, 100 %, MeOH), 538.4 ($[M+H]^+$, 100 %, MeOH), 560.3 ($[M+Na]^+$, 80%), 1097.7 ($[2M+Na]^+$, 10%); ν_{max} (film)/cm^{-1}: 2854, 2918 (aliphatic C-H stretch), 3030, 3062 (aromatic C-H stretch); δ_H ($CDCl_3$, 500 MHz, gCOSY, gHSQC nOesy) 1.09 (s, 3H, CH_3), 1.96 (s, br, 1H, NH), 2.72 (1H, dd, H-1, $J_{1,2}$ 11.0 Hz, $J_{1,1'}$ 13.6 Hz), 3.09 (dd, 1H, H-1`, $J_{1,2}$ 5.6 Hz, $J_{1,1'}$ 13.6 Hz), 3.18 (d, 1H, H-6, $J_{6,6'}$ 8.8 Hz), 3.44 (ddd, 1H, H-2, $J_{1',2}$ 5.5 H, $J_{2,3}$ 9.1 Hz, $J_{1,2}$ 10.8 Hz), 3.53 (d, 1H, H-6`, $J_{6,6'}$ 8.7 Hz), 3.62 (d, 1H, H-4, $J_{3,4}$ 9.6 Hz), 3.72 (t, 1H, H-3, $J_{2,3}$ 9.2 Hz, $J_{3,4}$ 9.2 Hz), 4.37 (d, 1H, 1 × PhC$\underline{H}_2$O, J_{HH} 11.8 Hz), 4.44 (d, 1H, 1 × PhC$\underline{H}_2$O, J_{HH} 11.8 Hz), 4.51 (d, 1H, 1 × PhC$\underline{H}_2$O, J_{HH} 11.2 Hz), 4.61 (d, 1H, 1 × PhC$\underline{H}_2$O, J_{HH} 11.6 Hz), 4.72 (d, 1H, 1 × PhC$\underline{H}_2$O, J_{HH} 11.6 Hz), 4.81 (d, 1H, 1 × PhC$\underline{H}_2$O, J_{HH} 10.6 Hz), 4.90 (d, 1H, 1 × PhC$\underline{H}_2$O, J_{HH} 11.3 Hz), 4.93 (d, 1H, 1 × PhC$\underline{H}_2$O, J_{HH} 10.7 Hz), 7.21-7.37 (m, 20H, aromatic); δ_C ($CDCl_3$, 125.7 MHz, DEPT, gHSQC) 15.4 (q, CH_3), 43.3 (t, C-1), 57.7 (s, C-5), 73.1, 73.3, 75.4, 75.9 (4 × t, 4 × Ph$\underline{C}H_2$O), 75.0 (t, C-6), 81.2 (d, C-4), 82.0 (d, C-2), 84.2 (d, C-3), 127.5, 127.7, 127.8, 127.86, 127.92, 127.94, 128.1, 128.4, 128.50, 128.52, 128.6 (11 × d, 11 × aromatic CH, others coincident), 138.1, 138.7, 139.1, 139.2 (4 × s, 4 ×

quaternary aromatic); HRMS found 538.2959 ($C_{35}H_{40}NO_4$ ($[M+H]^+$) requires 538.2957).

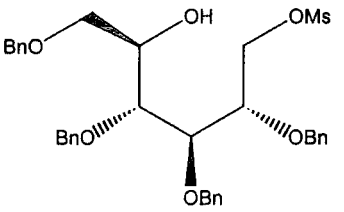
(5S)-2,3,4,6-Tetra-O-benzyl-5-C-benzyl-1,5-dideoxy-1,5-imino-L-iditol ***(4.36)****:*



To a cooled (– 78 °C) freshly prepared solution of 2,3,4,6-tetra-*O*-benzyl-1,5-dideoxy-5,*N*-dehydro-1,5-imino-D-glucitol (**4.06**) (1.0 eq., 0.112 mmol, 3.33 mL, 0.0340 M solution in dry diethyl ether) under nitrogen was added benzylmagnesium chloride (3.0 eq., 0.336 mmol, 0.336 mL, 1 M solution in diethyl ether) with stirring. After 2 h at – 78 °C the mixture was warmed to room temperature and stirred for a further 12 h. The reaction was stopped by the addition of water (5 mL). The solution was diluted with diethyl ether (10 mL), and washed with water (2 × 20 mL). The organic layer was isolated, dried (Na_2SO_4), filtered, and the solvent removed *in vacuo*. The resultant oil was separated by flash column chromatography (1 : 4, ethyl acetate : hexane eluent) to yield (5*S*)-2,3,4,6-tetra-*O*-benzyl-5-*C*-benzyl-1,5-dideoxy-1,5-imino-L-iditol (**4.36**) (13.2 mg, 19 %); $[\alpha]_D^{20.0}$ + 14.6 (c = 1.00, $CHCl_3$); *m/z* 614 (ES, $[M+H]^+$,100 %, MeOH), 636 ($[M+Na]^+$, 10 %); ν_{max} (film)/cm^{-1}: 2916 (aliphatic C-H stretch) 3029, 3062, 3090 (aromatic C-H stretch), 3348 (N-H stretch); δ_H ($CDCl_3$, 500 MHz, gCOSY, nOesy) 2.74 (dd, 1H, H-1, $J_{1,2}$ 10.1 Hz, $J_{1,1'}$ 12.0 Hz), 2.90 (d, 1H, 1 × PhC$\underline{H}_2$C, J_{HH} 13.6 Hz), 3.10 (d, 1H, PhCH_2C, J_{HH} 13.6 Hz), 3.12 (dd, 1H, H-1`, $J_{1,2}$ 5.4 Hz, $J_{1,1'}$ 12.0 Hz), 3.37 (d, 1H, H-4, $J_{3,4}$ 9.0 Hz), 3.43 (ddd, 1H, H-2, $J_{1',2}$ 5.4 Hz, $J_{2,3}$ 8.9 Hz, $J_{1,2}$ 10.1 Hz), 3.61 (d, 1H, H-6, $J_{6,7}$ 9.8 Hz), 3.83 (t, 1H, H-3, $J_{2,3}$ 9.1 Hz, $J_{3,4}$ 9.1 Hz), 3.96 (d, 1H, H-6`, $J_{6,6'}$ 9.6 Hz), 4.53 (d, 1H, 1 × PhC$\underline{H}_2$O, J_{HH} 11.9 Hz), 4.56 (d, 1H, 1 × PhC$\underline{H}_2$O, J_{HH} 11.9 Hz), 4.63 (s, 2H, 2 × PhC$\underline{H}_2$O), 4.66 (d, 1H, 1 × PhC$\underline{H}_2$O, J_{HH} 11.9 Hz), 4.69 (d, 1H, 1 × PhC$\underline{H}_2$O, J_{HH} 10.2 Hz), 4.95 (d, 1H, 1 × PhC$\underline{H}_2$O, J_{HH} 10.2 Hz), 5.02 (d, 1H, 1 × PhC$\underline{H}_2$O, J_{HH} 11.9 Hz), 7.20-7.35 (m, 25H, 25 × aromatic CH); δ_C ($CDCl_3$, 125.7 MHz, DEPT, gHSQC) 42.1 (t, PhCH_2C), 43.4 (t, C-1), 60.6 (s, C-5), 69.4 (t, C-6), 72.5, 73.5, 74.8, 75.4 (4 × t, 4 × Ph$\underline{C}H_2$O), 81.0 (d, C-2), 82.0 (d, C-4), 84.8 (d, C-3), 126.3, 126.8, 127.3, 127.6, 128.0, 128.3,

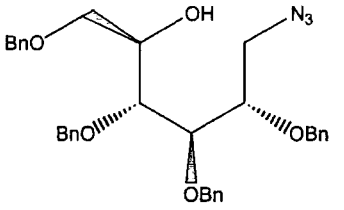
130.8 (7 × d, 7 of 25 aromatic CH, others coincident), 137.2, 138.4, 138.5, 138.6, 139.3 (5 × s, 5 × quaternary aromatic); HRMS found 614.3269 ($C_{41}H_{43}NO_4$ ([M+H]$^+$) requires 614.3270).

2,3,4,6-Tetra-O-benzyl-1-O-methanesulfonyl-D-glucitol (4.14):



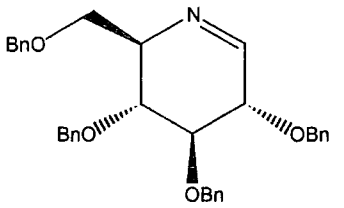
2,3,4,6-Tetra-*O*-benzyl-D-glucitol (**4.04**) (1.0 eq., 0.111 mmol, 600 mg) was dissolved in dry pyridine (20 mL) under nitrogen at 0 °C. Methanesulfonyl chloride (1.1 eq, 1.22 mmol, 139 mg, 94.3 μL) was added. The solution was stirred at 0 °C for 24 h after which time TLC indicated almost complete consumption of starting material and formation of a major product. The solvent was removed *in vacuo* at low bath temperature. The residue was diluted with $CHCl_3$ (50 mL), and washed with water (30 mL). The organic layer was dried ($MgSO_4$), filtered, and the solvent removed *in vacuo*. The resultant pale yellow oil was purified by repeated flash chromatography (3 : 7, ethyl acetate: hexane eluent) giving 2,3,4,6-tetra-*O*-benzyl-1,5-*O*-di-*O*-methanesulfonyl-D-glucitol (**4.10**) (81 mg, 10 %), and 2,3,4,6-tetra-*O*-benzyl-1-*O*-methanesulfonyl-D-glucitol (**4.14**) as a colourless oil (502 mg, 73 %): $[\alpha]_D^{21.2}$ + 3.55 (c = 1.00, $CHCl_3$); *m/z* 457.2 (ES, [M–CH_3SO_3–$PhCH_2$+Na]$^+$,100 %, MeOH), 643.2 ([M+Na]$^+$, 95 %), 891.4 ([2(M–CH_3SO_3–$PhCH_2$)+Na]$^+$, 45 %); ν_{max} (film)/cm^{-1}: 2867, 2932 (aliphatic C-H stretch), 3029, 3062, 3084 (aromatic C-H stretch); δ_H ($CDCl_3$, 400 MHz, gCOSY) 2.60 (s, br, 1H, OH), 2.63 (s, 3H, CH_3SO_3), 3.53-3.56 (m, 2H, H-1, H-1`), 3.71 (dd, 1H, H-3, $J_{3,4}$ 3.2 Hz, $J_{2,3}$ 6.9 Hz), 3.79 (dd, 1H, H-4, $J_{3,4}$ 3.2 Hz, $J_{4,5}$ 5.7 Hz), 3.87 (m, 1H, H-5), 3.93 (m, 1H, H-2), 4.13 (dd, 1H, H-6, $J_{5,6}$ 6.5 Hz, $J_{6,6'}$ 11.2 Hz), 4.25-4.69 (m, 9H, H-6, 8 × $PhC\underline{H}_2O$) 7.14-7.29 (m, 20 H, aromatic CH); δ_C ($CDCl_3$, 125.7 MHz, DEPT, gHSQC) 37.2 (q, $\underline{C}H_3SO_3$), 70.4 (d, C-2), 70.9 (t, C-6), 71.1 (t, C-1), 73.4, 73.6, 74.3 (3 × d, 3 of 4 $Ph\underline{C}H_2O$, two coincident), 77.1, 77.2 (2 × d, C-3, C-5), 77.7 (d, C-4), 128.00, 128.02, 128.07, 128.08, 128.22, 128.30, 128.59, 128.62, 128.64, 128.7 (10 × d, 10 of 20 aromatic CH, others coincident), 137.6, 137.8, 137.9, 137.9 (4 × s, 4 × quaternary aromatic).

*1-Azido-2,3,4,6-tetra-O-benzyl-1-deoxy-D-glucitol (**4.16**):*



2,3,4,6-Tetra-*O*-benzyl-1-*O*-methanesulfonyl-D-glucitol (**4.14**) (1.0 eq., 0.248 mmol, 154 mg) was dissolved in DMF (6.0 mL) and sodium azide (1.8 eq., 0.45 mmol, 29 mg) added. The mixture was stirred at room temperature under nitrogen. TLC anaysis after 20 h indicated the presence of starting material. The mixture was stirred for a total of 6 days. The solvent was removed *in vacuo*, and the residue dissolved in $CHCl_3$ (50 mL) and washed with water (50 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The mixture was purified by repeated column chromatography (1 : 4, ethyl acetate : hexane eluent, then 15 : 85, ethyl acetate : hexane eluent) giving 1,4-anhydro-2,3,6-tetra-*O*-benzyl-D-glucitol (**4.15**) (16 mg, 14 %), and 1-azido-2,3,4,6-tetra-*O*-benzyl-1-deoxy-D-glucitol (**4.16**) (25.2 mg, 18 %): $[\alpha]_D^{24.3}$ + 4.3 (c = 1.00, $CHCl_3$); *m/z* 590.2 (ES, $[M+Na]^+$,100 %, MeOH); ν_{max} (film)/cm^{-1}: 2099 (azide stretch), 2864, 2924 (aliphatic C-H stretch), 3030, 3064, 3088 (aromatic C-H stretch); δ_H ($CDCl_3$, 500 MHz, gCOSY) 2.83 (d, 1H, O-H, $J_{H,H}$ 5.5 Hz), 3.25 (dd, 1H, H-1, $J_{1,2}$ 6.0 Hz, $J_{1,1'}$ 13.0 Hz), 3.40 (dd, 1H, H-1`, $J_{1',2}$ 3.5 Hz, $J_{1,1'}$ 13.0 Hz), 3.63 (m, 2H, H-6, H-6`), 3.71 (dd, 1H, H-4, J_{HH} 3.0 Hz, J_{HH} 7.0 Hz), 3.84 (m, 2H, H-2, H-3), 4.00 (m, 1H, H-5) 4.50-4.59 (m, 4H, 4 × $PhC\underline{H}_2O$), 4.63-4.69 (m, 4H, 4 × $PhCH_2O$), 7.22-7.36 (m, 20H, 20 × aromatic CH); δ_C ($CDCl_3$, 125.7 MHz, DEPT, gHSQC) 51.8 (t, C-1), 70.7 (d, C-5), 71.2 (t, C-6), 73.2, 73.61, 73.62, 74.7 (4 × t, 4 × $PhC\underline{H}_2O$), 77.2 (d, C-4), 78.4, 78.8 (2 × d, C-2, C-3), 128.0, 128.2, 128.3, 128.6 (4 × d, 4 of 20 aromatic CH, others coincident), 137.87, 137.93, 138.0 (3 × s, 3 of 4 quaternary aromatic, two coincident).

*2,3,4,6-Tetra-O-benzyl-1,5-dideoxy-1,N-dehydro-1,5-imino-D-glucitol (**4.09**):*



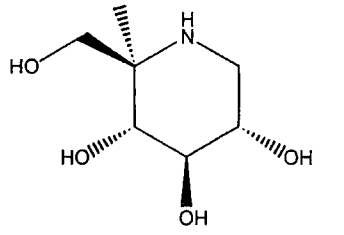
2,3,4,6-Tetra-*O*-benzyl-*N*-chloro-1,5-dideoxy-1,5-imino-D-glucitol (**4.07**) (1.0 eq, 0.104 mmol, 58.0 mg) was dissolved in dry THF (5.0 mL), and the mixture cooled to – 78 °C under nitrogen. LiTMP (1.1 eq, 0.11 mmol, 960 μL, 0.12 M solution in THF) was added with stirring. After 1 h the reaction was stopped by the addition of water (5 mL), then the mixture warmed to room temperature. Diethyl ether was added (20 mL) and the solution washed with water (10 mL). The organic layer was dried (Na_2SO_4), filtered, and the solvent removed *in vacuo*. 2,3,4,6-Tetra-*O*-benzyl-1,5-dideoxy-1,*N*-dehydro-1,5-imino-D-glucitol (**4.09**) was obtained as an orange oil (62 mg). The imine was found to be unstable and was used immediately in any subsequent reactions.

Preparation of LiTMP reagent.

2,2,6,6-Tetramethylpiperidine (1.0 eq., 0.594 mmol, 100 μL) was dissolved in THF (4.0 mL) under nitrogen. *n*-BuLi (1.0 eq., 0.59 mmol, 371 μL, 1.6 M solution in hexanes) was added dropwise with agitation. The resultant solution was made up to 5.0 mL with dry THF, and agitated for 15 minutes under nitrogen before use.

(**4.09**): ν_{max} (film)/cm^{-1}: 1654 (C=N stretch); δ_H ($CDCl_3$, 200 MHz) 7.60 (s, br, H-1), δ_C ($CDCl_3$, 50.3 Hz, DEPT) 162.3 (d, C-1).

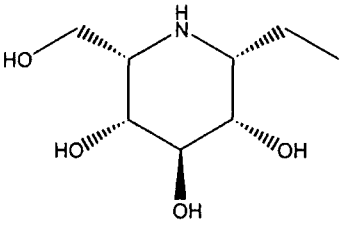
*(5R)-1,5-Dideoxy-1,5-imino-5-C-methyl-D-glucitol (**4.45**):*



(5*R*)-2,3,4,6-Tetra-*O*-benzyl-1,5-dideoxy-1,5-imino-5-*C*-methyl-D-glucitol (**4.35**) (1.0 eq., 0.0260 mmol, 14.0 mg) was stirred in methanol (1.0 mL) with palladium chloride (1.5 eq, 0.0395 mmol, 7 mg). The flask was purged with hydrogen, and the mixture stirred under hydrogen for 1 h after which time TLC indicated complete conversion of starting material into a single product. The reaction mixture was filtered through

celite and concentrated *in vacuo* to give a colourless oil (4.3 mg). The oil was dissolved in methanol (10 mL) and passed through a plug of Dowex™ 550A anionic exchange resin. The mixture was concentrated *in vacuo* to give (5*R*)-1,5-dideoxy-1,5-imino-5-*C*-methyl-D-glucitol (**4.45**) as a colourless oil (4.3 mg, 93 %): $[\alpha]_D^{24.3}$ + 4.3 (c = 0.52, MeOH); *m/z* 178.1 (ES, $[M+H]^+$,100 %, MeOH), 200.1 ($[M+Na]^+$, 10%); δ_H (D_2O, 400 MHz, gCOSY, gHSQC) 1.25 (s, 3H, CH_3), 3.05 (dd, 1H, H-1, $J_{1,2}$ 11.5 Hz, $J_{1,1'}$ 12.8 Hz), 3.35 (dd, 1H, H-1`, $J_{1,2}$ 5.5 Hz, $J_{1,1'}$ 12.8 Hz), 3.55-3.59 (m, 2H, H-4, H-6), 3.64 (t, 1H, H-3, $J_{2,3}$ 9.3 Hz, $J_{3,4}$ 9.3 Hz), 3.73 (ddd, 1H, H-2, $J_{1',2}$ 5.5 Hz, $J_{2,3}$ 9.3 Hz, $J_{1,2}$ 11.5 Hz), 3.79 (d, 1H, H-6`, $J_{6,6'}$ 12.6 Hz); δ_C (D_2O, 100.6 MHz, DEPT, gHSQC) 11.7 (q, CH_3), 41.8 (t C-1), 62.4 (s, C-5), 63.3 (t, C-6), 67.4 (d, C-2), 69.2 (d, C-3), 72.8 (d, C-4); HRMS found 178.1078 ($C_7H_{16}NO_4$ ($[M+H]^+$) requires 178.1079).

*(1R)-1,5-dideoxy-1-C-ethyl-1,5-imino-L-iditol, (–)-1-epi-adenophorine (**4.12**):*



(1*R*)-2,3,4,6-tetra-*O*-benzyl-1,5-dideoxy-1-*C*-ethyl-1,5-imino-L-iditol (**4.37**) (1.0 eq., 25.4 μmol, 14.0 mg) was dissolved in ethanol (2.0 mL) and palladium(II) chloride (2.2 eq., 56.4 μmol, 10 mg) added. The vessel was purged with hydrogen and the mixture stirred under an atmosphere of hydrogen for 1.5 h. The mixture was filtered through celite and the solvent removed *in vacuo*. The residue was dissolved in methanol and loaded on to Dowex™ 50W acidic exchange resin, washed with methanol, and the product eluted with methanol : ammonia (conc., aq.) (95 : 5). The solvent was removed *in vacuo* to give (1*R*)-1,5-dideoxy-1-*C*-ethyl-1,5-imino-L-iditol (**4.12**) (4.2 mg, 87 %): $[\alpha]_D^{24.3}$ – 26.4 (c = 0.18, H_2O); *m/z* 214.2 (ES, $[M+Na]^+$,100 %, MeOH), 191.2 ($[M+H]^+$, 40 %); ν_{max} (film)/cm^{-1}: 2099 (azide stretch), 2864, 2924 (aliphatic C-H stretch), 3030, 3064, 3088 (aromatic C-H stretch); δ_H (D_2O, 400 MHz, gCOSY, gHSQC) 0.86 (t, 3H, $C\underline{H}_3CH_2$, J_{HH} 7.5 Hz), 1.46 (m, 2H, $CH_3C\underline{H}_2$), 2.73 (ddd, 1H, H-1, J_{HH} 1.5 Hz, J_{HH} 6.5 Hz, J_{HH} 8.1 Hz), 2.98 (ddd, 1H, H-5, J_{HH} 1.7 Hz, J_{HH} 6.5 Hz, J_{HH} 8.3 Hz), 3.57 (dd, 1H, H-6, $J_{5,6}$ 6.5 Hz, $J_{6,6'}$ 11.1 Hz), 3.63 (dd, 1H, H-6`, $J_{5,6'}$ 6.7 Hz, $J_{6,6'}$ 11.1 Hz), 3.65 (s, 1H, H-2), 3.70 (m, 1H, H-4), 3.96 (t, 1H, H-3, $J_{2,3}$ 3.2 Hz, $J_{3,4}$ 3.2 Hz); δ_C (D_2O, 125.7 MHz) 9.8 ($\underline{C}H_3CH_2$), 23.8 ($CH_3\underline{C}H_2$), 55.4,

55.5 (C-1, C-5), 62.2 (C-6), 68.6, 69.0, 69.4 (C-2, C-3, C-4); HRMS found 192.1253 ($C_8H_{18}NO_4$ ($[M+H]^+$) requires 192.1236).

General Experimental.

^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on Varian Gemini 200, Unity 300, VXR 400, Bruker 400 or Varian Inova 500 NMR spectrometers at the frequencies indicated. Where indicated, NMR peak assignments were made using COSY, DEPT, gHSQC or nOesy experiments; all others are subjective. All chemical shifts are quoted on the δ-scale and were referenced to residual solvent as an internal standard. Combinations of the following abbreviations are used to describe NMR spectra: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Infra-red spectra were recorded on a Perkin-Elmer Fourier Transform spectrophotometer. The following abbreviations are used to describe infra-red absortion bands: br, broad; s, strong. Mass spectra were recorded by the University of Durham mass spectrometry service using electron impact, chemical ionisation or electrospray ionisation techniques on a Micromass LCT time-of-flight mass spectrometer; high resolution electrospray spectra were recorded by the University of Durham mass spectrometry service or EPSRC mass spectrometry service at Swansea, UK. Microanalyses were performed by the University of Durham analytical service. Melting-point determination was performed on a Gallenkamp melting-point apparatus with a Zeal mercury-filled thermometer.

Thin layer chromatography (TLC) was carried out on aluminium sheets coated with silica gel $60F_{254}$ (Merck, 1.05554). Plates were visualised under ultra-violet light or developed using an ethanolic phosphomolybdic acid or aqueous basic potassium permanganate dip. Flash column chromatography was performed using silica gel (Merck, 60A, 230-400 Mesh). Diethyl ether, tetrahydrofuran, and DCM were dried immediately prior to use according to standard procedures: diethyl ether and tetrahydrofuran were distilled under nitrogen from metallic sodium with benzophenone indicator. DCM was distilled under nitrogen from calcium hydride. Toluene was distilled under nitrogen from metallic sodium and stored over 4Å molecular sieves under nitrogen. Methanol and ethanol were distilled from magnesium/iodine, and stored over 4Å molecular sieves under nitrogen. Acetone was distilled from calcium sulfate immediately prior to use. Other dry solvents used were commercial, and stored and handled under dry nitrogen. All solvents were removed by evaporation under reduced pressure.

References.

[1] B. Winchester, G. W. J. Fleet, *Glycobiology*, 1992, **2**, 199.

[2] P. Compain, O. R. Martin, *Bioorg. Med. Chem.*, 2001, **9**, 3077.

[3] G. A. Cordell, *The Alkaloids, Chemistry and Biology*, Academic Press, San Diego, 1988, vol. 50.

[4] S. Inoue, T. Tsuruoka, T. Niida, *J. Antibiot.*, 1966, 19, 288.

[5] S. Inouye, T. Tsuruoka, T. Ito, T. Niida, *Tetrahedron*, 1968, **24**, 2125.

[6] S. Mourao, S. Miyata, *Agric. Biol. Chem.* 1980, **44**, 219.

[7] A. Donodoni, P. Merino, D. Perrone, *Tetrahedron*, 1993, **49**, 2939; Y. Tsuda, Y. Okuno, K. Kanemitsu, *Heterocycles*, 1998, **27**, 63; N. Chida, Y. Furuno, H. Ikemoto, S. Ogawa, *Carbohydr. Res.*, 1992, **237**, 185.

[8] T. D. Butters, R. A. Dwek, F. M. Platt, *Chem. Rev.*, 2000, **100**, 4683.

[9] M. Bols, *Acc. Chem. Res.*, 1998, **31**, 1, 1.

[10] N. Asano, H. Kisu, K. Oseki, K. E. Tomioka, K. Matsui, M. Okamoto, M. Baba, *J. Med. Chem.*, 1995, **38**, 13, 2349.

[11] A. R. Beacham, K. H. Smelt, K. Biggadike, C. J. Britten, L. Hacket, B. G. Winchester, R. J. Nash, R. C. Griffiths, G. W. J. Fleet, *Tetrahdron Lett.*, 1998, **39**, 151.

[12] P. J. Dransfield, P. M. Gore, M. Shipman, A. M. Z. Slawin, *Chem. Commun.*, 2002, 150.

[13] M. Yokoyama, T. Akiba, Y. Ochiai, A. Momotake, H. Togo, *J. Org. Chem.*, 1996, **61**, 6079.

[14] M. I. Page in *New Comprehensive Biochemistry*, Elsevier, Amsterdam, 1984 (6th edition) Ch. 1.

[15] N. C. Price, L. Stevens, *Fundamentals of Enzymology*, Oxford University Press, Oxford, 1999, Ch. 3.

[16] E. Fisher, *Ber. Dt. Chem. Ges.*, 1894, 2985.

[17] A. R. Ferscht, *Structure and Mechanism in Protein Science*, Freeman, New York, 1999, Ch 2.

[18] W. P. Jencks, M. I. Page, *Biochem. Biophys. Res. Commun.*, 1974, **57**, 887.

[19] L. Pauling, *Nature*, 1948, **161**, 4097, 707.

[20] M. Muraki, Y. Jigami, M. Morikawa, H. Tanaka, *Biochim. Biophys. Acta.*, 1987, **991**, 376; M. Muraki, M. Morikawa, Y. Jigami, H. Tanaka, *Eur. J. Biochem.*, 1989, **179**, 573.

[21] M. L. Sinnot, *Chem. Rev.*, 1990, **90**, 1171.

[22] W. F. Anderson, M. G. Grütter, S. J. Remington, L. H. Weaver, B. W. Mathews, *J. Mol. Biol.*, 1981, **147**, 523.

[23] D. E. Koshland, *Biol. Rev.*, 1953, **28**, 416.

[24] D. E. Koshland, *Angew. Chem. Int. Ed. Engl.* 1994, **33**, 2375.

[25] M. L. Sinnot, In *Enzyme Mechanisms*, M. I. Page, A. Williams (editors), Royal Society of Chemistry, London, 1987, 259.

[26] A. Varki, *Glycobiology*, 1993, **3**, 97.

[27] R. A. Dwek, *Chem. Rev.*, 1996, **96**, 683.

[28] L. F. Leloir, *Science*, 1971, **172**, 1299.

[29] C. H. Wong, R. Halcomb, Y. Ichikawa, T. Kajimoto, *Angew. Chem. Int. Ed. Engl.*, 1995, **34**, 412.

[30] O. Hindsgaul, K. J. Kaur, G. Ssrivastava, M. Blaszczyk-Thurin, C. C. Crawley, L. D. Heerze, and M. M. Palcic, *J. Biol. Chem.*, 1991, **266**, 27, 17858.

[31] G. Hanozet, H. P. Pircher, P. Vanni, B. Oesch, G. J. Semenza, *J. Biol. Chem.*, 1981, **256**, 3703.

[32] C. Saotome, Y. Kanie, O. Kanie, C. H. Wong, *Bioorg. Med. Chem.*, 2000, **8**, 2249.

[33] B. G. Davis, A. A. Bell, R. J. Nash, A. A. Watson, R. C. Griffiths, M. G. Jones,; C. Smith, G. W. J. Fleet, *Tetrahedron Lett.*, 1996, **37**, 8565.

[34] G. W. J. Fleet, P. W. Smith, S. V. Evans, L. E. Fellows, *Chem. Commun.*, 1984, 1240.

[35] B. G. Davis, A. A. Bell, R. J. Nash, A. A. Watson, R. C. Griffiths, M. G. Jones, C. Smith, G. W. J. Fleet, *Tetrahedron Lett.*, 1996, **37**, 8565.

[36] A. J. Fairbanks, N. M. Carpenter, G. W. J. Fleet, N. G. Ramsden, I. Cenci de Bello, B. G. Winchester, S. S. Al-Daher, G. Nagahashi, *Tetrahedron*, 1992, **48**, 3365.

[37] R. Wischnat, R. Martin, S. Takayama, C. H. Wong, *Bioorg. Med. Chem. Lett.*, 1998, **8**, 3353.

[38] Y. J. Kim, M. Ichikawa, Y. Ichikawa, *J. Am. Chem. Soc.*, 1999, **121**, 5829.

[39] M. Bandini, P. G. Cozzi, A. Umani-Ronchi, M. Villa, *Tetrahedron*, 1999, **55**, 8103.

[40] X. L. Hou, X. L. Zheng, L. X. Dai, *Terahedron Lett*, 1998, **39**, 6949.

[41] G. Alvaro, D. Savoia, M. R. Valentinetti, *Tetrahedron*, 1996, **52**, 12571.

[42] C. Boga, D. Savoia, A. Umani-Ronchi, *Tetrahedron: Asymmetry*, 1990, **1**, 291.

[43] M. Wada, Y. Sakurai, K. Akiba, *Tetrahedron Lett.*, 1984, **25**, 10, 1079.

[44] J. Yamada, H. Satô, Y. Yamamoto, *Tetrahedron Lett.*, 1989, **30**, 5611.

[45] T. Matsumoto, Y. Kobayashi, Y. Takemoto, Y. Ito, T. Kamijo, H. Harada, S. Terashima, *Tetrahedron Lett.*, 1990, **31**, 4175.

[46] M. T. Reetz, R. Jaeger, R. Drewlies, M. Hübel, *Angew. Chem. Int. Ed. Engl.*, 1991, **30**, 103.

[47] T. Imamoto, T. Kusumoto, Y. Tawarayama, Y. Sugiura, T. Mita, Y. Hatanaka, M. Yokoyama, *J. Org. Chem.*, 1984, **49**, 3904.

[48] W. Oppolzer, C. G. Bochet, E. Merifield, *Tetrahedron Lett.*, 1994, **35**, 38, 7015.

[49] R. Bloch, *Chem. Rev.*, 1998, **98**, 1407.

[50] R. V. Stevens, In *Strategies and Tactics in Organic Synthesis*, T. Lindberg (editor), Academic Press, San Diego, 1984, pp 275-298.

[51] H. B. Bürgi, J. D. Dunitz, *Acc. Chem. Res.*, 1983, **16**, 153.

[52] M. Cherest, H. Felkin, N. Prudent, *Tetrahedron. Lett.*, 1968, **18**, pp 2199; N. T. Anh, O. Eisenstein, *Nouv. J. Chem.*, 1977, **1**, 61; E. P. Lodge, C. H. Heathcock, *J. Am. Chem. Soc.*, 1987, **109**, 3353.

[53] D. J. Cram, K. R. Kopecky, *J. Am. Chem. Soc.*, 1959, **81**, 2748.

[54] R. S. Atkinson, *Stereoselective Synthesis*, Wiley, Chichester, 1999, p 297.

[55] J. W. Cornforth, R. H. Cornforth, K. K. Mathew, *J. Chem. Soc.*, 1959, pp 112.

[56] R.A. Volkmann, In *Comprehensive Organic Synthesis: Additions to C=X Bonds, Part 1,* S.L. Schreiber (editor), Pergamon, Oxford, 1991, vol. 1, pp 355-396.

[57] Y. Yamamoto, T. Komatsu, K. Maruyama, *J. Am. Chem. Soc.*, 1986, **108**, 7778.

[58] P. Deslongchamps, *'Stereoelectronic Effects in Organic Chemistry'*, J. E. Baldwin (editor), Pergamon, Oxford, 1983, 209.

[59] F. Bohlman, E. Winterfeldt, P. Studt, H. Laurent, G. Boroschewski, K. M. Klein, *Chem. Ber.*, 1961, **94**, 3151.

[60] R. V. Stevens, A. W. M. Lee, *J. Chem. Soc., Chem. Commun.*, 1982, 102.

[61] R. V. Stevens, A. W. M. Lee, *J. Chem. Soc., Chem. Commun.*, 1982, 103.

[62] B. A. Horenstein, R. F. Zabinski, V. L. Schramm, *Tetrahedron Lett.*, 1993, **34**, 7213.

[63] M. Bosco, P. Bisseret, C. Bouix-Peter, J. Eustache, *Tetrahedron Lett.*, 2001, **42**, 7949.

[64] Y. Ryu, G. Kim, *J. Org. Chem.*, 1995, **60**, 103.

[65] G. P. Claxton, L. Allen, J. M. Grisar, *Org. synth.*, 1977 ,**56**, 118.

[66] B. R. Cho, S. K. Namgoong, T. R. Kim, *J. Chem. Soc. Perkin Trans. II*, 1987, 853.

[67] X. L. Armesto, M. Canle L., M. V. Garcia, M. Losada, J. A. Santaballa, *J. Phys. Org. Chem.*, 1996, **9**, 552.

[68] W. H. Saunders, A. F. Cockerill, *Mechanisms of Elimination Reactions*, Wiley, New York, 1973.

[69] E. D. Hughes, C. K. Ingold, J. B. Rose, *J. Chem. Soc.*, 1953, 3839.

[70] E. D. Hughes, J. Wilby, *J. Chem. Soc.*, 1960, 4094.

[71] Lambert, *Top. Stereochem.*, 1971, 6, 19.

[72] A. Rauk, L. C. Allen, K. Mislow, *Angew. Chem. Int. Ed*, 1970, **9**, 6, 400.

[73] C. G. Swain, E. R. Thornton, *J. Am. Chem. Soc.*, 1962, **84**, 817; E. R. Thornton, *J. Am. Chem. Soc.*, 1967, **89**, 2915.

[74] H. Staudinger, J. Meyer, *Helv. Chim. Acta.*, 1919, **2**, 635; W. H. Pearson, D. P. Szura, M. J. Postich, *J. Am. Chem. Soc.*, 1992, **114**, 4, 1329.

[75] R. H. Furneaux, G. Limberg, P. C. Tyler, *Tetrahedron*, 1997, **53**, 8, 2915.

[76] R. H. Furneaux, V. L. Schramm, P. C. Tyler, *Bioorg. Med. Chem.*, 1999, **7**, 2599.

[77] G. B. Evans, R. H. Furneaux, G. J. Gainsford, V. L. Schramm, P. C. Tyler, *Tetrahedron*, 2000, **56**, 3053.

[78] S. F. Martin, H. J. Chen, C. P. Yang, *J. Org. Chem.*, 1993, **58**, 2867.

[79] W. H. Pearson, E. J. Hembre, *J. Org. Chem.*, 1996, **61**, 5537.

[80] I. Bruce, G. W. J. Fleet, I. Cenci di Bello, B. Winchester, *Tetrahedron*, 1992, **48**, 46, 10191.

[81] S. Takayama, R. Martin, J. Wu, K. Laslo, G. Siuzdak, C. H. Wong, *J. Am. Chem. Soc.*, 1997, **119**, 8146.

[82] Bloomfield, *Org. React.*, 1967, **15**, 1.

[83] M. R. McNeil, M. Daffé, P. J. Brennan, *J. Biol. Chem.*, 1990, **265**, 18200; M. R. McNeil, P. J. Brennan, *Res. Microbiol.*, 1991, **142**, 451.

[84] M. A. T. Maughan, I. G. Davies, T. D. W. Claridge, S. Courtney, P. Hay, B G. Davis, *Angew. Chem. Int. Ed.*, 2003, **42**, 3788.

[85] K. Ikeda, M. Takahashi, M. Nishidaa, M. Miyauchi, H. Kizu, Y. Kameda, M. Arisawa, A. A. Watson, R. J. Nash, G. W. J. Fleet, N. Asano, *Carbohydr. Res.*, 2000, **323**, 73.

[86] D. W. Fulhage, C. A. VanderWerf, *J. Am. Chem. Soc.*, 1958, **80**, 6249.

[87] Schoepf, *Justus Liebigs Ann. Chem.*, 1948, **559**, 1, 22.

[88] M. F. Grundon, B. E. Reynolds, *J. Chem. Soc.*, 1964, 2445.

[89] M. S. Karasch, O. Reinmuth, *Grignard reactions of non-metallic substances*, Prentice-Hall, New York, 1954.

[90] Cerium(III) organometallics are accessible from organolithiums (see T. Imamoto, *Pure & appl. Chem.*, 1990, **62**, 747.), and Grignard reagents (see B. A. Narayanan, W. H. Bunnelle, *Tetrahedron Lett.*, **20**, 1987, 6261.)

[91] The low yield of starting imine was attributed to the fact that 2-methyl-Δ^1piperideine azeotroped with THF and diethyl ether during the concentration of the crude reaction mixture.

[92] F. C. Scully, *J. Org. Chem.*, 1980, **45**, 1515.

[93] S. R. Wilson, C. E. Augelli-Szafran, *Tetrahedron*, 1998, **44**, 13, 3983.

[94] G. W. J. Fleet, and Co-workers, *J. Chem. Soc., Perkin Trans. 1*, 1999, 2747.

[95] B. Winchester, G. W. J. Fleet, *Glycobiol.*, 1992, **2**, 3, 199.

[96] T. W. Greene, *Protective Groups in Organic Synthesis*, 2nd ed., Wiley, New York, 1991.

[97] B. Grzeszczyk, A. Zamojski, *Carbohydr. Res.*, 2001, **332**, 225

[98] K. Dziewiszek A. Banaszec, A. Zamojski, *Tetrahedron Lett.*, 1987, **28**, 14, 1569.

[99] B. G. Davis, R. J. Nash, A. A. Watson, C. Smith, G. W. Fleet, *Tetrahedron*, 1999, **55**, 14, 4501.

[100] B. G. D. Davis, T. W. Brandstetter, C. Smith, L. HackettB. G. Winchester, G. W. J. Fleet, *Tetrahedron Lett.* 1995, **36**, 41, 7507.

[101] P. Collins, R. Ferrier, *Monosacharides*, John Wiley and sons, Chichester, 1995, p 321.

[102] G. J Boons, S. Isles, *J. Org. Chem.*, 1996, **61**, 13, 4262.

[103] E. J. Corey, J. W. Suggs, *J. Org. Chem.*, 1973, **38**, 18, 3224.

[104] B. M. Pinto, D. G. Morissette, *J. Chem. Soc Perkin Trans. I*, 1987, **1**, 9.

[105] T. M. Chapman, S. Courtney, P. Hay, B. G. Davis, *Chem. Eur. J.*, 2003, **9**, 14, 3397.

[106] Y. Ma, *Heteroatom Chemistry*, 2002, **13**, 4, pp 307.

[107] J. Jary, K. Cabeck, J. Covar, *Czech. Chem. Commun.* 1963, 28, 2171.

[108] P. M. Collins, W. G. Overend, *J. Chem. Soc.*, 1965, 1912.

[109] J. Defaye, A. Gadelle, S. J. Angyal, *Carbohydr. Res.*, 1984, **126**, 165.

[110] D. R. Chatterjee, S. N. Cho, P. J. Brennan, G. O. Aspinall, *Carbohydr. Res.*, 1986, **156**, 39.

[111] G. O. Aspinall, N. K. Khare, R. K. Sood, D. R. Chatterjee, B. Brennan, J. Patrick, *Carbohydr. Res.*, 1991, **216**, 1, 357.

[112] T. W. Greene, *Protective Groups in Organic Synthesis*, 2nd edition, Wiley, New York, 1991.

[113] D. J. Hardick, D. W. Hutchinson, S. J. Trew, E. M. H. Wellington, *Tetrahedron*, 1992, **48**, 30, 6285.

[114] Y. Rabinsohn, H. G. Fletcher, *J. Org. Chem.*, 1967, 32, 3452.

[115] P.A. Fowler, A.H. Haines, R.J.K. Taylor, E.J.T. Chrystal, M.B. Gravestock, *Carb. Res.* 1993, **246**, 377.

[116] K. Ikeda, M. Takahashi, M. Nishida, M. Miyauchi, H. Kizu, Y. Kameda, M. Arisawa, A. A. Watson, R. J. Nash, G. W. J. Fleet, N. Assano, *Carbohydr. Res.*, 2000, **323**, 73.

[117] G. A. Shotorbani, J. G. Buchannan, A. R. Edgar, C. T. Shanks, G. C. Williams, *J. Chem. Soc. Perkin Trans. I*, 1981, 2267.

[118] Alkyl ammonium azides are potentially explosive and suitable safety precautions should be employed. (*Bretherick's Handbook of Reactive Chemical Hazards*, Butterworth-Heinemann, Oxford, 1999, volume 6, P. G. Urben (editor), 1685.

[119] J. B. Hendrickson, D. A. Judelson, T. Chancellor, *Synth. Commun.*, 1984, 320.

[120] H. Loibner, E. Zbiral, *Helv. Chim. Acta.*, 1976, **59**, 2100.

[121] D. S. Coffey, A. I. McDonald, L. E. Overman, M. H. Rabinowitz, P. A. Renhowe, *J. Am. Chem. Soc.*, 2000, **122**, 20, 4893.

[122] Hydrazoic acid is potentially explosive and suitable safety precautions should be employed. Solutions of the acid should be disposed immediately as evaporation of volatile solvent leading to increased concentration increases shock-sensitivity.

(*Bretherick's Handbook of Reactive Chemical Hazards*, Butterworth-Heinemann, Oxford, 1999, volume 6, P. G. Urben (editor), pp 1602-1603.

[123] H. Wolf, *Org. React.*, 1946, **3**, 327.

[124] H. Paulsen, *Leibigs Ann. Chem.*, 1963, **665**, 166.

[125] P. L. Durette, D. Horton, *Adv. Carbohydr. Chem. Biochem.*, 1971, **26**, 49.

[126] R. Schwesinger, H. Schlemper, *Angew. Chem. Int. Ed. Eng.*, 1987, **26**, 1167; R. Schwesinger, C. Hasenfratz, H. Schlemper, L. Walz, E. M. Peters, H. G. Von Schnering, *Angew. Chem. Int. Ed.*, 1993, **32**, 1361.

[127] S. D. Bull, S. G. Davies, G. Fenton, A. W. Mulvaney, R. S. Prasad, A. D. Smith, *Chem. Commun.*, 2000, 337.

[128] The formation of the intermediate imine was confirmed by NMR and IR, proving that simple reduction or metal halogen exchange of the chloramine had not been achieved.

[129] F. C. McQuillin, M. S. Baird, *Alicyclic Chemistry*, Cambridge University Press, Cambridge, 1983, 2nd edition, Chapter 2.

[130] V. S. Rao, A. S. Perlin, *Can. J. Chem.*, 1981, **59**, 333.