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Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 16 (2005) 1239–1287

TETRAHEDRON: ASYMMETRY REPORT NUMBER 81

Recent advances in the chemistry of azapyranose sugars

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Received 5 January 2005; accepted 8 February 2005

Abstract—This report covers the natural occurrence and recent (1998 to 2004) reported syntheses of azapyranose sugars.

Contents

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0957-4166/$ - see front matter
doi:10.1016/j.tetasy.2005.02.020

1. Introduction

Azasugars (also known as iminosugars) are structural analogues of 'true' sugars in which the ring oxygen atom is replaced by a nitrogen atom. Recent years have seen an increasing interest in synthetic and naturally occurring azasugars as biological tools and potential therapeutics culminating in the launch of the first azasugar medicine, Zavesca®.[1] The biological properties of azasugars arises because they interfere with the function of carbohydrate handling enzymes and carbohydrate recognizing receptors, which are widely found in all organisms.

Like true sugars, both five membered ring (azafuranose) analogues and six membered ring (azapyranose) analogues are known. In this review we cover the recent advances in the preparation of azapyranose sugars. The subject of azasugars has been comprehensively reviewed previously and older synthetic approaches to them can be ascertained from the references cited here and in the main body of the review.[2–8]

Over the last 40 years, a very large number of azapyranose sugars have been isolated from various plant and animal sources. Nearly all these naturally occurring azasugars as well as the majority of synthetic azapyranose sugars elicit some sort of biological response. In order to frame the synthetic efforts in context, an overview of the naturally occurring azapyranose sugars and their potential biological application is also presented.

2. Natural occurrence

Azasugars, strictly speaking, belong to the polyhydroxylated alkaloid super-family of natural products. In fact, the azapyranose motif can be recognised in three of the main structural groups of alkaloids: piperidines, indolizidines and nortropanes.

2.1. Piperidine azasugars

In 1966, Inouye et al.[9] discovered the first natural polyhydroxylated alkaloid, nojirimycin (NJ) **1**. Isolated from a *Streptomyces* filtrate, it was shown to actively inhibit α- and β-glucosidase and was therefore the first natural glucose mimic. Nojirimycin B (commonly called mannonojirimycin)[10] **2** and galactostatin (galactonojirimycin)[11] **3** were isolated soon after.

Azasugars bearing a hydroxyl group at C-1 were found to be relatively difficult to isolate and handle due to the unstable aminal functionality. The first deoxy-derivative, 1-deoxynojirimycin (DNJ) [(2*S*)-hydroxymethyl]-(3*R*,4*R*,5*S*)-trihydroxy-piperidine or 1,5-dideoxy-1,5-imino-D-glucitol **4** was synthesised by Inouye et al. by the reduction of the anomeric hydroxyl group.[12] However DNJ was soon afterwards isolated from Mulberry trees[13] as well as *Streptomyces* cultures.[14]

1-Deoxymannonojirimycin (DMJ) **5** was first found in *Lonchocarpus sericeus*[15] and is thought to come from the biosynthetic reduction of mannojirimycin.[16] Epimerisation of DNJ to DMJ is also thought to be a possible biosynthetic origin of the latter.[17]

N-Substituted piperidines also occur naturally. *N*-Methyl DNJ **6** was extracted from the roots of the Mulberry tree (*Morus alba*).[18] Higher order azaglycosides, 1-deoxynojirimycin-2-*O*-, 3-*O*-, 4-*O*-α-D-glucopyranosides, 2-*O*-, 6-*O*-α-D-galactosides and 2-*O*-, 3-*O*-, 4-*O*-, 6-*O*-β-D-glucopyranosides have also been isolated from the *Morus* genus.[18,19]

Kite et al. reported on the isolation of the NJ homologue, α-homonojirimycin (α-HNJ) **7**.[20] Isolated from the leaves of *Omphalea diandra* (Euphorbiaceae) it was the first example of a piperidine azasugar with a carbon group at C-1. Subsequent discoveries of HNJ isomers followed. These included the isomers α-4-e*pi* homonojirimycin (α-homoallonojirimycin) **8**, β-HNJ **9**, α-homomannonojirimycin **10**, β-homomannonojirimycin **11**[21] and β-4,5-di*epi*homonojirimycin (β-homoaltronojirimycin) **12**[22] from the leaves and roots of *Aglaonema treubii* (Araceae). Naturally occurring azaglycosides of α-HNJ include 5-*O*-α-D-galactopyranoside and 7-*O*-β-D-glucopyranoside, which is a potent inhibitor of porcine kidney trehalase.[21,23]

More recently, other naturally occurring HNJ analogues have been discovered by Asano et al.[23] The deoxyHNJ homologue, adenophorine **13**, 1-deoxyadenophorine **14**, 5-deoxyadenophorine **15**, as well as the glycosides adenophorine-1-*O*-β-D-glucopyranoside and 5-deoxyadenophorine-1-*O*-β-D-glucopyranoside, were all extracted from the roots of *Adenophora* spp. (Campanulaceae). The absolute configuration of adenophorine has not yet been established, however it is believed that its pseudoanomeric substituent (depending on the absolute configuration at either C-1 or C-5 can be viewed as the pseudoanomeric position) makes it a highly potent inhibitor of α-glucosidase, intestinal sucrase and α-galactosidase. 5-Deoxyadenophorine has inhibitory properties against the coffee bean α-galactosidase and bovine liver β-galactosidase enzymes. Another interesting α-galactosidase inhibitor isolated from *Adenophora* spp. is the derivative β-1-*C*-butyl-deoxygalactonojirimycin, also known as 1-*C*-(5-amino-5-deoxy-β-D-galactopyranosyl)butane **16**.[23]

A further DNJ analogue is the 1,2-dideoxynojirimycin, fagomine **17**. Initially found in the seeds of *Fagopyrum esculentum* (Polygonaceae) seeds,[24] it was later discovered in the leaves and roots of *Xanthocercis zambesiaca* (Leguminosae) together with 3-*epi*fagomine **18**, 3,4-di*epi*fagomine **19**, fagomine-4-*O*-β-D-glucopyranoside, and fagomine-3-*O*-β-D-glucopyranoside.[25] Fagomine analogues, 6-deoxy-fagomine 20 and α-1-*C*-ethyl-fagomine 21 were isolated from *Lycium chinense* (Solanaceae) roots[26] and Campanulaceae, respectively.[23,27]

In 1984, Cenci di Bello et al. extracted from the seeds of *Baphia racemosa* the first naturally occurring azaglucoronic acid, (2*S*)-carboxy-(3*R*,4*R*,5*S*)-trihydroxypiperidine **22**, which was found to inhibit the

human liver β-D-glucuronidase and α-L-iduronidase (Fig. 1).[28]

2.2. Indolizidine azasugars

Indolizidines are bicyclic alkaloids where the azapyranose ring is fused to a pyrrolidine ring via an *N*-bridge. The first example was swainsonine **23**, isolated in 1979 from the leaves of *Swainsona canescens* (Leguminosae).[29] Later the same molecule was found in *Astragalus* spp. (Leguminosae), together with swainsonine *N*-oxide.[30] The discovery of lentiginosine **24** and 2-*epi*lentiginosine **25** soon followed.[31] Interestingly swainsonine and 2-*epi*lentiginosine are two of the few azapyranoside based alkaloids that are known to be produced by fungi.[3] Another indolizidine, castanospermine **26** is a bicyclic equivalent of DNJ having an ethylene bridge between the hydroxymethyl group and nitrogen atom.[2] Isolated from the seeds of *Castanospermum australe*, its structure was confirmed by X-ray crystallography.[32] Also from *C. australe* are the isomers 6-*epi*castonospermine **27** (DMJ derivative),[33] 6,7-di*epi*castoanospermine **28**[34] and 7-deoxy-6-*epi*castanospermine **29**.[35] 6-*epi*Castonospermine **27** has inhibitory properties against human neutral *a*-mannosidase.[33,36] 6,7-Di*epi*castoanospermine **28** and 7-deoxy-6-*epi*castanospermine **29** both inhibit fungal amyloglucosidase weakly (Fig. 2).[34]

There have been extensive studies into the toxicity of swainsonine[29] and castanospermine[32] containing legumes *S. canescens* and *C. australe*, respectively. In fact swainsonine was also found in locoweeds (*Astragalus* spp. and *Oxytropis* spp.), which causes the disorder 'locoism' in Western United States.[30]

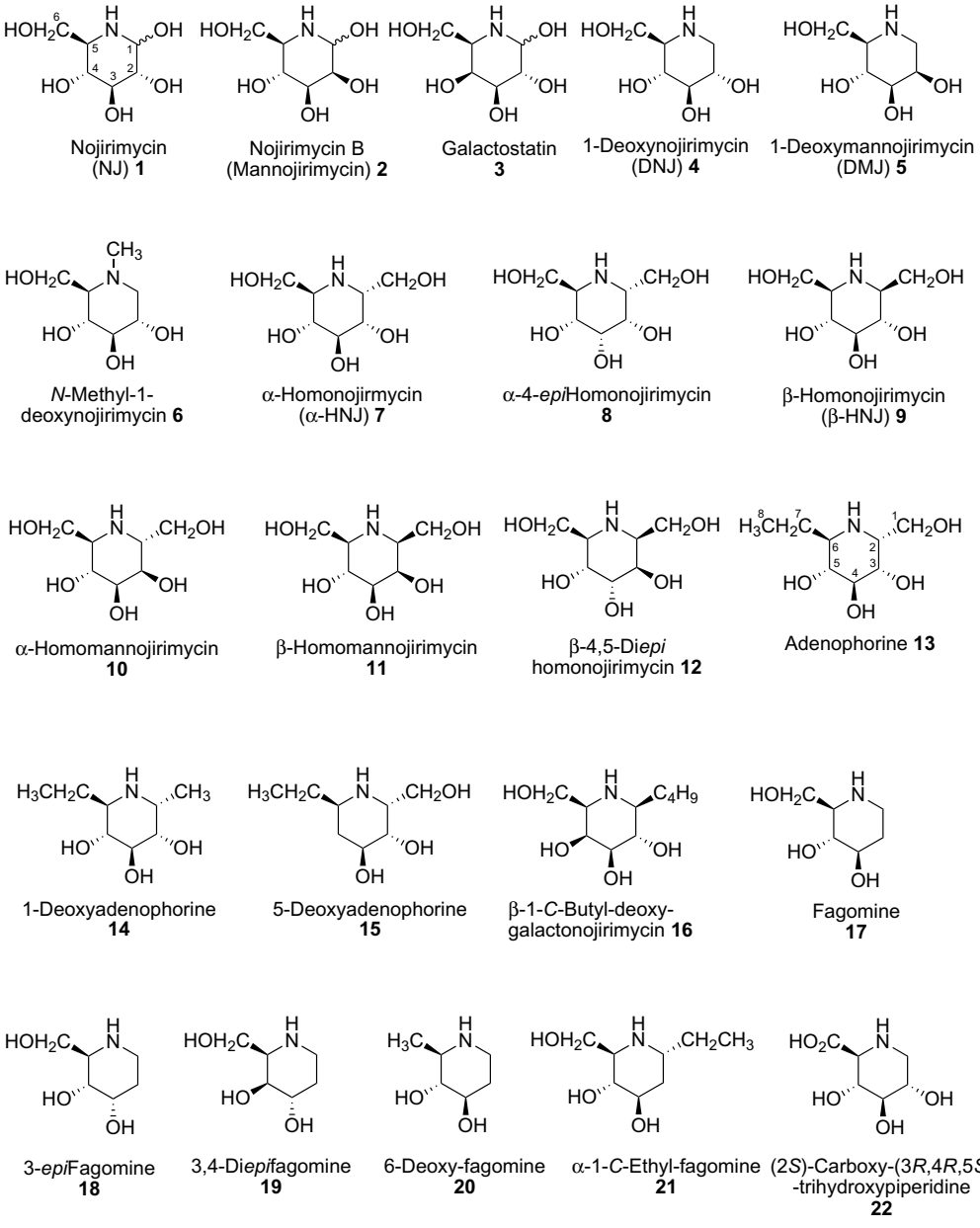


Figure 1. Some naturally occurring polyhydroxylated piperidine alkaloids.

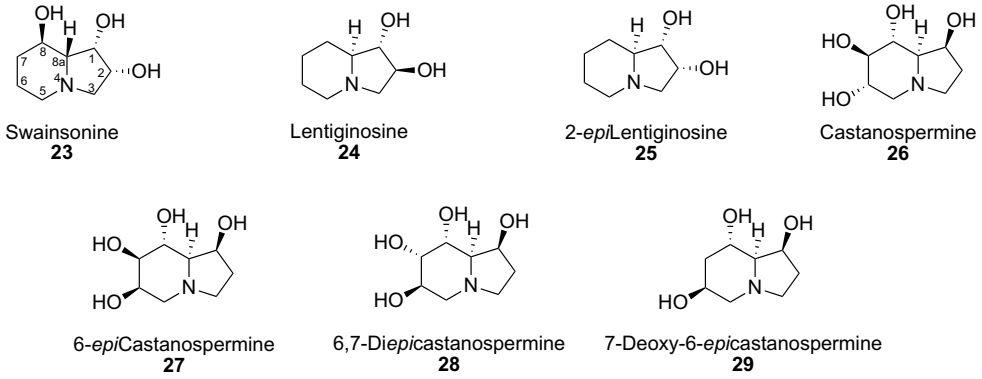


Figure 2. Some naturally occurring polyhydroxylated indolizidine alkaloids.

2.3. Nortropane azasugars

Nortropanes are a relatively new division of polyhydroxylated alkaloids that contain an azapyranose ring, which are isolated primarily from the *Atropa belladonna* (Solanaceae) and *Convolvulus arvensis* (Convolvulaceae) but also from the Moraceae families.[18] These azasugar analogues, called calystegines are interesting because they contain a tertiary hydroxyl group at the bicyclic bridgehead[2] with the exception of one (see calystegine N_1 **30**).[3] Based on electrophoresis separation they were divided into two groups, calystegines A and calystegines B.[37] The major component of the A group was calystegine A_3 **31**, which was spectroscopically determined to be 1α,2β,3α-trihydroxynortropane. Similarly the two major components of B are calystegine B_1, 1α,2β,3α,6α-tetrahydroxynortropane **32** and calystegine B_2, 1α,2β,3α,4β-tetrahydroxynortropane **33**.[38] The *M. alba* (Moraceae) roots yielded calystegine C_1 **34** identified to be 1α,2β,3α,4β,6α-pentahydroxynortropane.[18] Calystegine C_2 **35** was extracted from the leaves of *Duboisia leichhardtii*.[39] Soon afterwards, calystegine A_5 **36** and B_3 **37** were also isolated.[40] The roots of *Scopolia japonica* gave calystegine B_4 **38**.[41] *Hyoscyamus niger* yielded calystegines A_6 **39** and N_1. Calystegine N_1 (1α-amino-2β,3α,4β-trihydroxynortropane) **30** is particularly interesting as it has an amino group in place of the quaternary hydroxyl group.[42] Recent discoveries

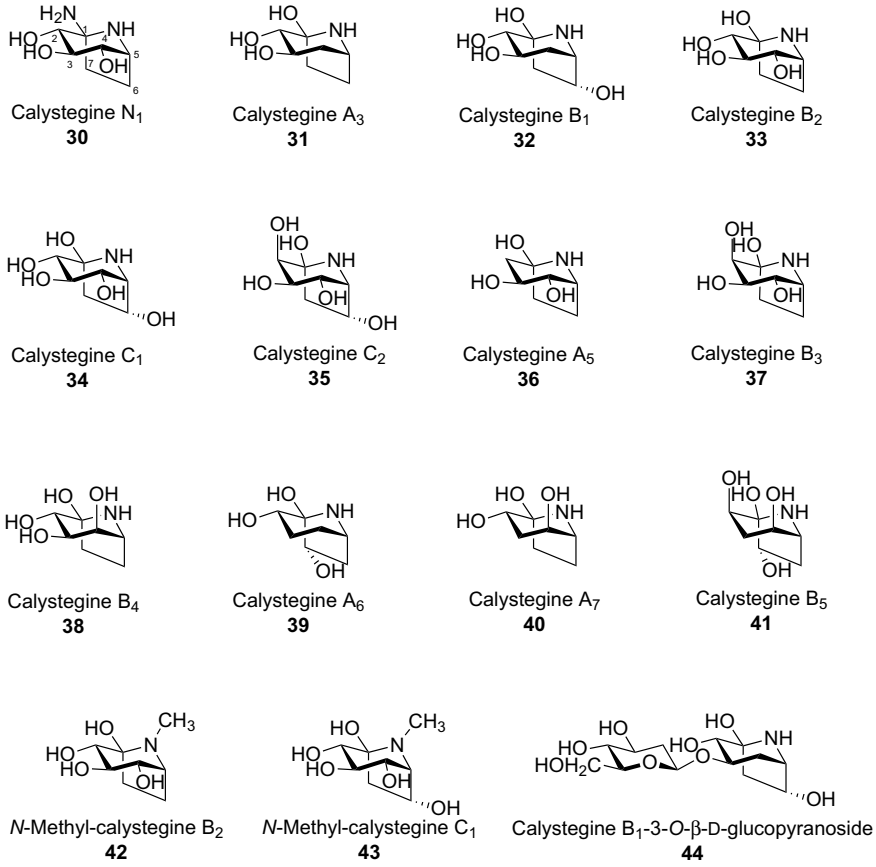


Figure 3. Some naturally occurring polyhydroxylated nortropane alkaloids.

from *L. chinense* have led to calystegines A_7 **40**, B_5 **41** as well as the *N*-substituted *N*-methyl-calystegine B_2 **42** and *N*-methyl-calystegine C_1 **43**.[26] An example of a nortropane glycoside has also been reported, calystegine B_1-3-*O*-β-D-glucopyranoside **44**.[43] Asano et al. have reported that many calystegines can be found in edible fruits and vegetables (Fig. 3).[44]

3. Therapeutic applications

Carbohydrate sugars have a range of in vivo functions. Of course, their best known function is as an energy source. Complex carbohydrates, which form part of the diet, are broken up during digestion into individual carbohydrate units, which are then recombined to form glycans and stored in the body until needed for rapid energy release. However, the biological roles of carbohydrates are much more diverse. In particular, cell surface glycoconjugates (e.g., glycolipids and glycoproteins) are responsible for a host of functions involving interaction and communication between the cell and its environment. These functions are essential for the workings of cells, which therefore heavily rely on the biosynthesis and maintenance of these glycoconjugates. It has been estimated that genes, which regulate the glycosylation of the glycoproteins make up to 2% of the human genome thus making this the most important post-translational modification to proteins in the human body. Not surprisingly, defects in their biosynthesis and function is implicated in the pathology of a host of diseases ranging from cancer to neurodegenerative diseases.[45–50]

The collective names of the enzymes, which are responsible for the biosynthesis and maintenance of the glycolipid and glycoprotein units, are glycosyltransferases and glycosidases.[51,52] Their inhibition can significantly modulate the function or response of the cell, and therefore they make excellent targets for medicinal intervention.[53] This approach has been particularly important in the treatment of diabetes mellitus, cancer, viral and bacterial infections and neurological diseases resulting from the mishandling of sphingolipid storage in the body.

3.1. Anti-diabetic

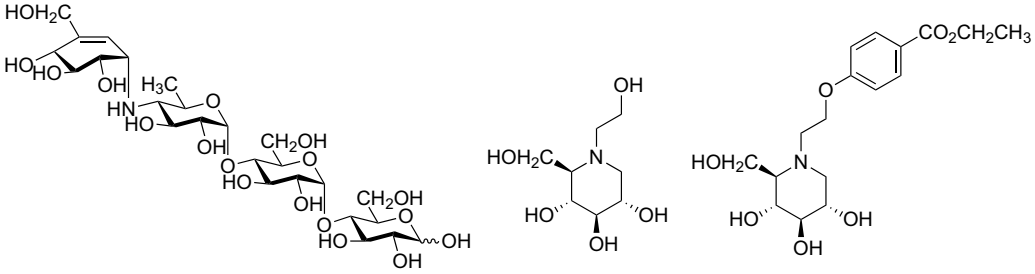
Diabetes mellitus (DM) is a disease that occurs when the body cannot remove circulating blood glucose properly. The epithelial cell of the brush border region of the small intestine is lined with oligosaccharides and disaccharides. It is these enzymes that breakdown dietary carbohydrates to monosaccharides, which are absorbed through the intestinal wall. Therefore the enzymes are directly responsible for the level of glucose found in the blood and inhibition of some or all of these enzyme activities and can lead to the regulation of the carbohydrate adsorption.

The Bayer group in the late 1960s isolated the pseudotetrasaccharide acarbose **45** from the fermentation broth of the *Actinoplanes* strain SE 50 and was found to be a potent inhibitor of pig intestinal sucrase. In the 1990s, acarbose was released in the German drug market under the name Glucobay™. The structure consists of an imino-linked trihydroxy(hydroxymethyl)cyclohexene moiety and a 4-amino-4,6-dideoxy-D-glucopyranose moiety.[2,54]

Many azasugars have been found to inhibit various α-glucosidase specific disaccharidases involved in mammalian digestion, for example, sucrase, maltase, isomaltase, etc. Mulberry leaves, which are used in traditional Chinese medicine for the treatment of diabetes ('Xiao-ke') were found to contain DNJ. The use of DNJ for the treatment of type II diabetes has been considered, based on its strong in vitro inhibition of α-glucosidases, however its in vivo efficacy was only moderate. As a result, the anti-diabetic potential activity of many synthetic DNJ derivatives have been investigated.[2,3]

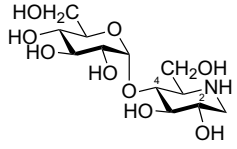
Some of the azasugars, that have been tried for the antihyperglycemic effects in diabetic mice, include fagomine, 3-*epi*fagomine, castanospermine and HNJ. Of these, fagomine significantly reduced blood glucose levels.[2,3] Castanospermine also showed strong activity, however its toxicity was too great. DNJ and HNJ however showed no antihyperglycemic effects. DNJ/HNJ being strong inhitors of mammalian α-glucosidases, suggests that α-glucosidase inhibition does not contribute to the antihyperglycemic role of sugar mimics.[2,3]

N-Substituted azasugars were found to be more active. *N*-Hydroxyethyl-DNJ (Miglitol®) **46** reduced the postprandial rise in blood glucose in the sucrose loading tests of rats. *N*-Hydroxyethyl-DNJ and the analogous Miglitate **47** both had good lasting times in vivo, however *N*-hydroxyethyl-DNJ absorbed appreciably from the gut into the bloodstream, where additional affects were noticed.



Acarbose **45** Miglitol **46** Miglitate **47**

The aza-disaccharide 4-*O*-α-D-glucopyranosyl-1-DNJ **48** inhibited rabbit sucrase with a greater affinity than its DNJ monomer.[55] The naturally occurring glycoside, 2-*O*-α-D-galactopyranosyl-DNJ has been shown to have strong antihyperglycemic effects in isolated pancreases of diabetic mice.[56]



4-*O*-α-D-glucopyranosyl-DNJ

48

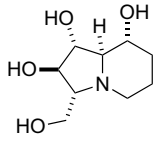
3.2. Anti-cancer

It is believed that glycosylation plays a key role in the formation and migration of tumour cells (metastasis).[57] It has been shown that high levels of many glycosidase enzymes are present in some tumour cells and interstitial fluids. Furthermore, many tumour cells show abnormal glycosylation due to an altered expression of glycosyltransferases.[58] This can manifest either as a shortening of the carbohydrate chain of glycoproteins or as an alteration to their structures.[5]

Since glycosidases are involved in the formation of cancer cells and migration of tumour cells, a line of treatment could involve the specific inhibition of catabolic glycosidases associated with cancer. Castanospermine and *N*-methyl-1-DNJ have been shown to have antimetastatic activity by inhibiting platelet aggregation as well as reducing vascular endothelium adhesion of tumour cells.[2]

The extensively studied swainsonine was found to be an excellent inhibitor of Golgi α-mannosidase II with low toxicity and good oral accessibility. However due to co-inhibition of lysosomal mannosidase, swainsonine caused the accumulation of high-mannose oligosaccharides in tissues (swainsonine induced mannosidosis). Therefore synthetic analogues of swainsonine were investigated. Pearson et al. have shown analogue **49** to be a potent inhibitor (IC_{50} 150 μM) of jack bean α-mannosidase, a commercially available model for mammalian α-mannosidases.[59,60]

Other target enzymes for anticancer chemotherapy include the mammalian β-*N*-acetylglucosaminidase for which the *N*-acetyl-D-glucosamine mimic **50**, showed good activity.[61]



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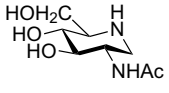

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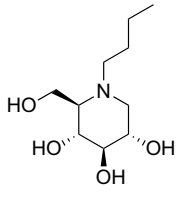
3.3. Anti-viral

Many mammalian viruses have a heavily glycosylated lipoprotein envelope. They use carbohydrates to recognise and interact with preferred hosts. For instance, the influenza virus gains access to a cell by binding with a sugar (sialic acid) that protrudes from a cell surface glycoprotein. This allows a cellular pathway to be opened, allowing the virus to penetrate the cell and to replicate within them. These viruses use the host cells glycosylation machinery to modify their envelope proteins, which is essential in the viruses' life cycle, assembly, secretion and infectivity of the virus.[4,2]

The *Helicobacter pylori* virus attaches itself to the sugars on the cell surface of the stomach lining, causing conditions such as stomach ulcers and inflammation. A possible opportunity for the prevention of viral infectivity is to target the glycosidase enzymes involved. The endoplasmic reticulum α-glucosidase is an important enzyme used in protein folding. The *H. pylori* virus is sensitive to the inhibitors of ER α-glucosidase. In fact, *N*-butyl-DNJ **51** is shown to have in vitro activity towards endoplasmic reticulum α-glucosidase.[4]

Alternatively azasugars can be used to target viruses directly.[62] The HIV virus primarily infects cells of the immune system. Key to infection, is the interaction of the glycosylated viral envelope, to the CD-4 receptor of the T-lymphocyte glycoprotein membrane. However in the presence of DNJ, the glycosylation patterns of the viral coat change. This results in the virus not being able to bind to the CD-4 receptors, making them non-infectious. *N*-Butyl-DNJ reached phase II clinical trials as an anti-HIV agent. However the high concentrations required make it unsuitable as a drug. *N*-Benzyl-DNJ **52** also showed similar activities.[3]



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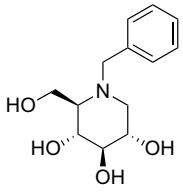

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3.4. Sphingolipid storage diseases

Sphingolipid storage diseases are hereditary disorders in which the control of sphingolipid biosynthesis or degradation is lost. Glycosylated sphingolipid can be divided into two groups: glucosphingolipids (GSL) and galactosphingolipids.[4] GSLs are especially important during embryonic development and therefore this disease is fatal in early infancy. Tay-Sachs disease is a typical example, in which lipids build up in the lysosomes of cells due to a degradation disorder.[63–65] Similarly, accumulation in neurons leads to neurological disorders, such as Gaucher's disease.[66] Most research in the treatment of sphingolipid storage diseases has

focused on direct enzyme replacement, bone marrow transplantation or gene therapy. Therefore a more conventional method of treatment was needed. Only recently, was it found that drugs could be used to regulate the biosynthesis of glycosphingolipid, so that the amount of substrate matches the activity of the residual enzyme. This 'balancing' of synthesis with degradation in order to prevent storage, is referred to as *substrate deprivation*.

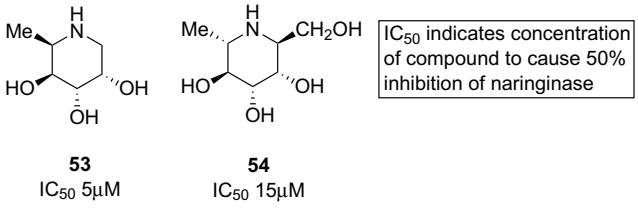
N-Alkylated azasugars of glucose or galactose stereochemistry are found to inhibit GSL biosynthesis. *N*-Butyl-DNJ **51**, originally developed as an anti-viral agent, was found to inhibit *N*-acylsphingosine D-glucosyltransferase (CerGlcT), which catalyses the transfer of glucose to ceramide, the first step in the biosynthesis of glucospingolipid (Scheme 1).[4,66] It was established that the *N*-alkyl chain must be at least three carbons long for it to actively mimic the ceramide chain.

Gauchers disease is the most common glycosphingolipid lysosomal storage disorder. It was the first to be treated by enzyme replacement therapy. Deficiency of the lysosomal enzyme glucocerebrosidase leads to the build up of glucocerebroside, especially in the mononuclear phagocyte cell system. *N*-Butyl-DNJ is a potent inhibitor of the ceramide-specific glucosyltransferase, which is involved in the glycosphingolipid biosynthetic pathway and catalyses the formation of glucocerebroside. After successful clinical trials, *N*-butyl-DNJ **51** (OGT 918, Zavesca®) was released for the treatment of Gauchers disease by Oxford Glycosciences.[1]

3.5. Anti-bacterial

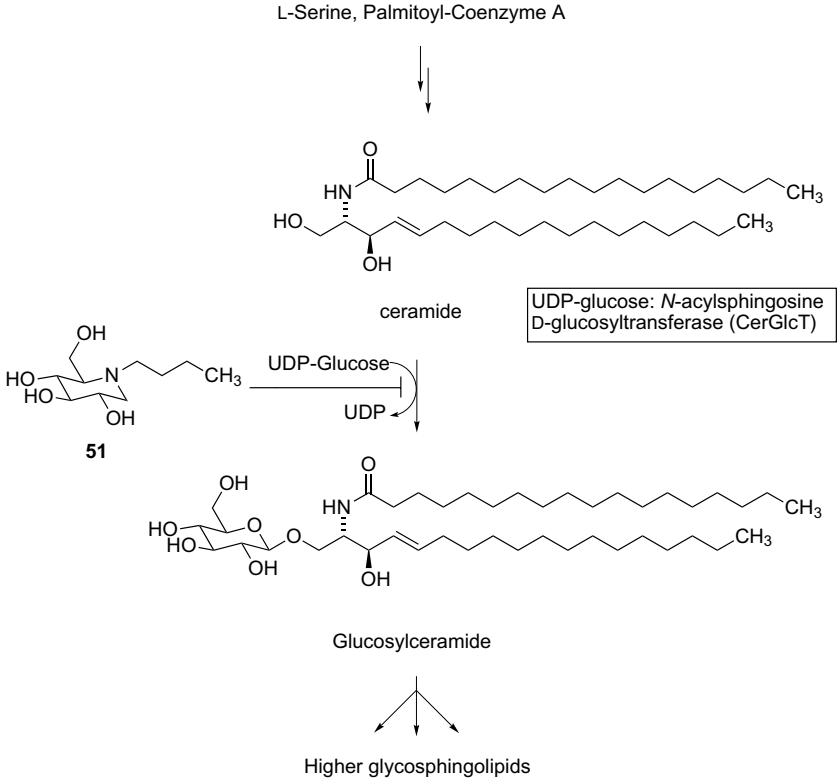
A new line of research is the use of polyhydroxylated alkaloids in the treatment of complications involved with human-pathogenic micro-organism infections. This is achieved by targeting the enzymes involved in the biosynthesis of the cell walls of such organisms, such as *Mycobacterium tuberculosis*, the causative agent in tuberculosis (TB).[3] Recent studies have shown the structure of the cell wall to have a disaccharide linker between the arabinogalactin polysaccharides and peptidoglycan contains L-rhamnopyranose.[67] Since rhamnose has no role in mammalian metabolism, compounds, which are specific inhibitors for rhamnose metabolism, it should have no effect on the animal host. It is hoped that diseases induced by mycobacteria such as TB and leprosy (*Mycobacterium leprae*) can be treated this way.

In 1996, Fleet et al. reported piperidine analogues of L-rhamnopyranose; 5-*epi*-L-deoxyrhamnojirimycin **53** and **54** are powerful inhibitors of naringinase (L-rhamnosidase).[68]



53 IC_{50} 5μM

54 IC_{50} 15μM



Scheme 1. Component of the biosynthesis of sphingolipid. The site of inhibition of **51**.[66]

Unlike their 'true' sugar counterparts, very few polyhydroxylated alkaloids are commercially available; DNJ, DMJ, castanospermine and swainsonine. Therefore many groups have sought after a good synthetic strategy for the preparation of this important class of molecules. Herein we report some recent and interesting chemical strategies towards naturally occurring as well as synthetic azapyranose sugars.

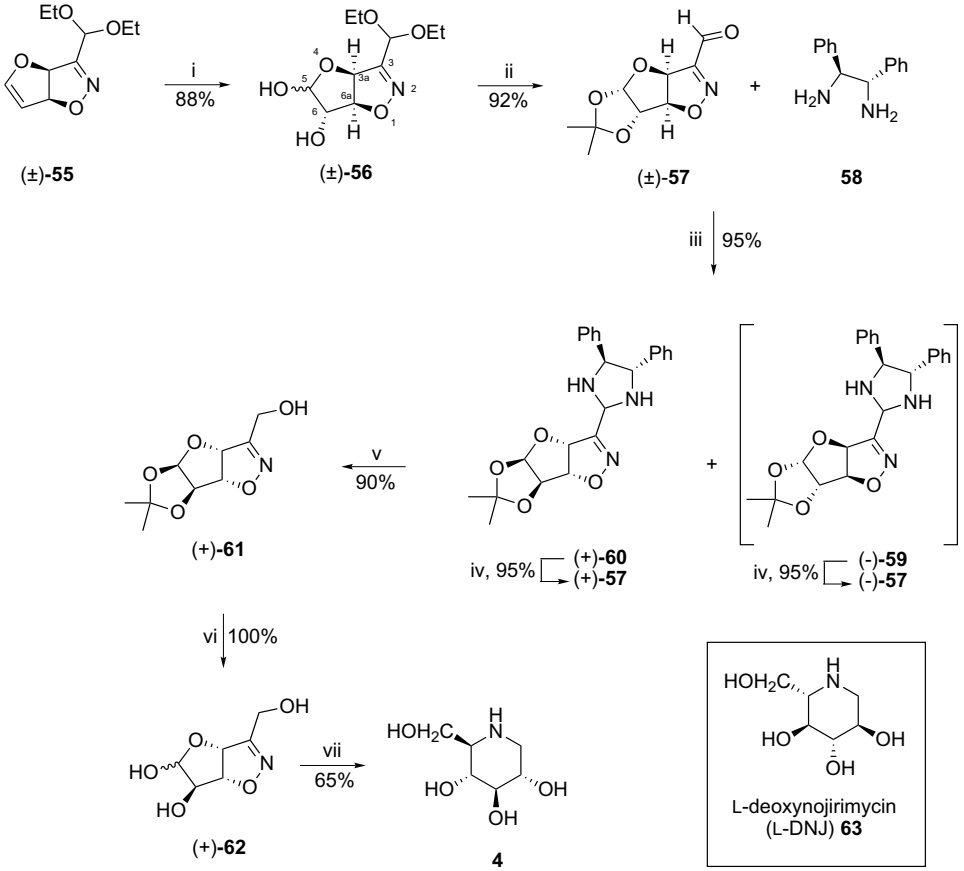
4. The synthesis of nojirimycin (NJ) and deoxynojirimycin (DNJ)

The synthesis of DNJ and DMJ can be divided into two sections. Syntheses that utilise extensively available carbohydrates as their starting reagents and those that use alternative starting reagents.

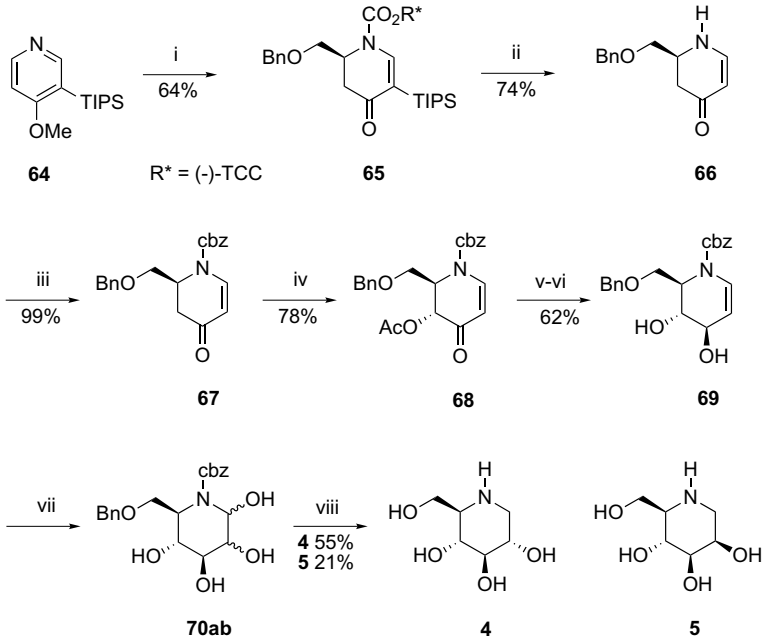
4.1. Noncarbohydrate routes to 1-deoxynojirimycin (DNJ)

The first reported synthesis of NJ and DNJ was by Paulsen et al. in 1967.[69,70] Since then many novel routes have been devised. An asymmetric synthesis using a chiral resolution was reported by Vogel et al. (Scheme 2).[71] Isoxazoline (±)-**55** was derived from 2-nitroethanal diethyl acetal and furan via a [2+3] di-polar cycloaddition (75%).[72] Using osmium tetraoxide and *N*-methylmorpholine *N*-oxide, bis-hydroxylation was achieved to give the 6-*exo* isomers (±)-**56** (88%) as a 3:1 mixture of anomers. Diol protection of (±)-**56** was achieved via transacetalation with concd H_2SO_4 and acetone to furnish the racemic aldehyde (±)-**57** (92%). Its reaction with (−)-(1*S*,2*S*)-1,2-diphenylethane-1,2-diamine **58** gave the separable mixture of imidazolidines (−)-**59** (40%) and (+)-**60** (45%). The diastereomeric purity of both were greater than 98% (determined by HPLC). A selective hydrolysis using 1 M H_2SO_4, gave the aldehydes (−)-**57** and (+)-**57** (95%) with recovery of **58**. Enantiomeric purity of both compounds were determined by HPLC and found to be greater than 99:1. Reduction of the isoxazoline-3-carbaldehyde (+)-**57** with sodium borohydride gave alcohol (+)-**61** (90%). Deprotection was achieved with aqueous trifluoroacetic acid to give a 3.4:1 mixture of anomers of (+)-**62** (100%). Pd/C hydrogenation yielded **4** in a 65% yield. The same operation starting with (−)-**57** gave 1-deoxy-L-nojirimycin **63**.

A chiral auxiliary mediated asymmetric synthesis of DNJ has been reported by Comins and Fulp (Scheme 3).[73] The reaction of 4-methoxy-3-(triisopropylsilyl)pyridine **64**[74] with the acyl-chloroester of (1*R*,2*S*)-2-(1-methyl-1-phenylethyl)cyclohexanol [(−)-TCC][75] generated a 1-acylpyridinium salt in situ. To this, a (ben-

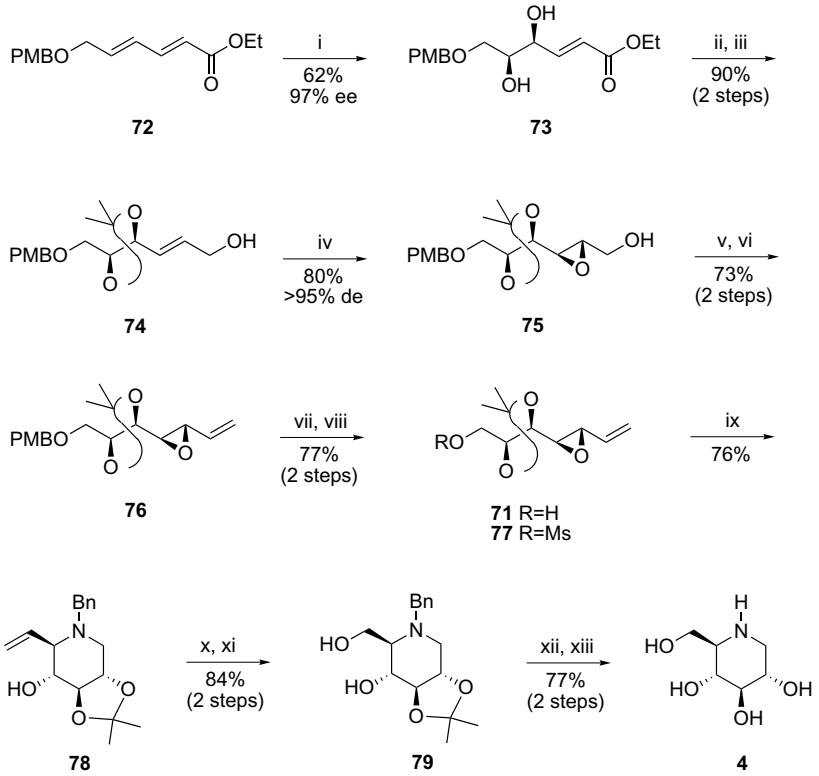


Scheme 2. Reagents and conditions: (i) OsO_4, NMO, acetone/H_2O, 60 °C, 3 h; (ii) concd H_2SO_4, acetone, 25 °C, 3 h; (iii) (1*S*,2*S*)-(−)-1,2-diphenylethane-1,2-diamine **58**, Et_2O, 25 °C, 10 h; (iv) Et_2O, 1 M H_2SO_4, 25 °C, 30 min; (v) $NaBH_4$, MeOH, 5 °C; (vi) TFA/H_2O, 4 °C, 15 h; (vii) Pd/C (10%), H_2, MeOH, 25 °C, 15 h.



Scheme 3. Reagents and conditions: (i) (a) R*OCOCl, (b) $BnOCH_2[2\text{-(Th)Cu(CN)}]Li_2$, (c) aq HCl; (ii) NaOMe, aq HCl; (iii) *n*-BuLi, cbzCl; (iv) $Pb(OAc)_4$, toluene, reflux; (v) aq HCl/EtOH; (vi) $Me_4NBH(OAc)_3$, acetone/AcOH; (vii) OsO_4, NMO; (viii) $Pd(OH)_2$, H_2, 10% aq HCl.

zyloxy)methylcuprate was added to give the dihydropyridone **65**. The cuprate was prepared from the benzyl chloromethyl ether via the corresponding tributyl stannane. Lithium-tin exchange with *n*-BuLi, followed by the addition of lithium 2-trienylcyano cuprate, gave the cuprate. One pot removal of the chiral auxiliary and the C-5 TIPS group fashioned enantiopure **66** (74% yield). Treatment with *n*-BuLi and benzyl chloroformate gave carbamate



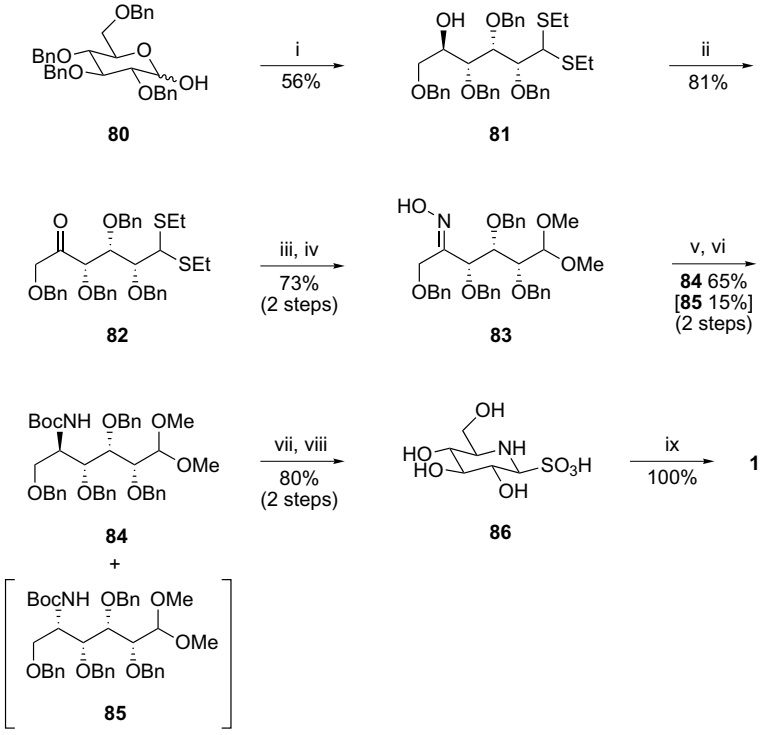
Scheme 4. Reagents and conditions: (i) $K_2OsO_4{\cdot}2H_2O$, $(DHQ)_2PHAL$, *t*-BuOH, H_2O; (ii) $(MeO)_2CMe_2$, DMF; (iii) DIBAL, CH_2Cl_2, −78 °C; (iv) (+)-DIPT, $Ti(Oi\text{-}Pr)_4$, TBHP, CH_2Cl_2, −20 °C; (v) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C; (vi) Ph_3PCH_3Br, KHMDS, THF, toluene; (vii) DDQ, CH_2Cl_2, H_2O; (viii) MsCl, $i\text{-}Pr_2NEt$, CH_2Cl_2, 0 °C; (ix) $BnNH_2$, TsOH, DMSO, 120 °C; (x) (a) OsO_4, NMO, *t*-BuOH, THF, H_2O, (b) $NaIO_4$, THF, H_2O; (xi) $LiAlH_4$, THF, 0 °C; (xii) TFA, MeOH; (xiii) H_2, Pd/C, EtOH.

67. Selective acetoxylation was achieved using $Pb(OAc)_4$ (acetate delivery from the axial direction of a chair like transition state)[74] to give dihydropyridone **68** in 74% yield. The acetate group was subsequently removed using 10% HCl in ethanol and reduction achieved with tetramethylammonium triacetoxyborohydride to give diol **69** stereoselectively. Treatment of **69** with osmium tetraoxide and *N*-methylmorpholine *N*-oxide yielded the unstable tetrahydroxy piperidines **70ab**. Hydrogenation with $Pd(OH)_2$ catalyst and 10% aq HCl afforded DNJ **4** in a 55% yield. Its epimer DMJ **5** was also isolated as a side product in a 21% yield.

In 1998, Somfai and Lindström reported an asymmetric synthesis of DNJ (Scheme 4).[76,77] Utilising the fact that their key intermediate, vinyl epoxide **71**, is known to be attacked by amine nucleophiles with regio- and stereoselectivity at the allylic position, opening of the epoxide moiety in **71** via a primary amine and subsequent ring closure was expected to give an azasugar type structure. The synthesis of vinyl epoxide **71** starts from the *p*-methoxybenzyl ether (PMB) protected diene **72**. Treating with the AD-mix-α reagent [$K_2OsO_4{\cdot}2H_2O$ + $(DHQ)_2$-PHAL], diol **73** was achieved with a 62% yield and 97% enantioselectivity. Diol protection and ester reduction gave allylic alcohol **74**, which was converted to epoxide **75**. Swern oxidation, and Wittig olefination of the resulting aldehyde gave vinyl epoxide **76**. Deprotection furnished the key intermediate **71** to give the corresponding mesylate **77**. Using benzyl amine and a catalytic amount of *p*-toluene sulfonic acid in DMSO at 120 °C resulted in the ring opening of the epoxide moiety. Intramolecular displacement of the mesylate gave **78** in 76% yield. Vinyl piperidine **78** was treated with OsO_4 and the resulting diol cleaved with $NaIO_4$ to give the corresponding aldehyde. $LiAlH_4$ reduction yielded the protected azasugar **79**. Sequential removal of the protecting groups gave **4**.

4.2. Carbohydrate based routes to nojirimycin (NJ) and 1-deoxynojirimycin (DNJ)

Due to their close structural similarity to true monosaccharides, many groups have used carbohydrate precursors as their chiral pool starting material. Shipman and Moutel demonstrated a synthesis of nojirimycin starting from the protected monosaccharide, 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose **80** (Scheme 5).[78] Opening of the ring and subsequent aldehyde protection was achieved by a previously published procedure.[79] The resulting alcohol **81** was oxidised to ketone **82** using tetra-*n*-propylammonium perruthenate (TPAP).[80] Transacetalation of the thioacetal group to the more acid-labile dimethylacetal was achieved with mercury(II) salts and methanol. The ketone was further converted to oxime **83** (a 1:1 mixture of geometric isomers) using hydroxyl amine hydrochloride and pyridine. Lithium aluminium hydride reduction followed by reaction of the amine mixture with di-*tert*-butyl dicarbonate gave the separable urethanes **84** and **85** in 65% and 15% overall yields from oxime **83**. Deprotection of the major compound **84** was achieved by debenzylation using Pearlman's catalyst and urethane and dimethylacetal cleavage using sulfurous acid generated in situ from gaseous sulfur dioxide under acidic conditions. Under these conditions the cyclised 1-deoxynojirimycin-1-sulfonic



Scheme 5. Reagents and conditions: (i) EtSH, HCl, dioxane; (ii) TPAP, NMO, CH_2Cl_2; (iii) HgO, $HgCl_2$, MeOH; (iv) $NH_2OH{\cdot}HCl$, py, EtOH; (v) $LiAlH_4$, Et_2O; (vi) $(Boc)_2O$, Et_3N, MeCN; (vii) $Pd(OH)_2$, H_2, EtOH; (viii) SO_2, H_2O; (ix) DOWEX® 1X2 (HO^-), H_2O.

acid **86** was achieved. Treatment with DOWEX® 1X2 (HO^-) furnished (+)-nojirimycin **1**.

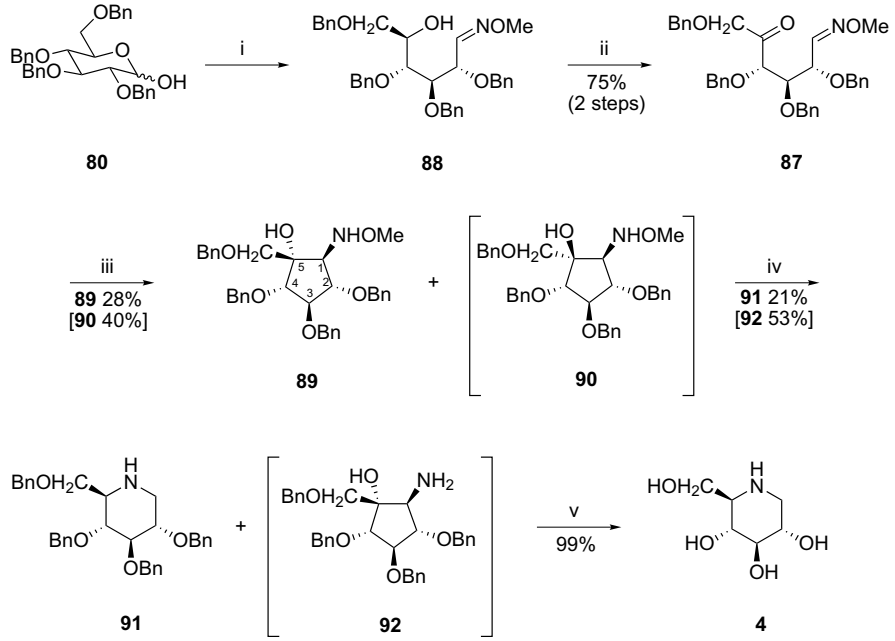
Naito et al. have developed a route to 1-deoxynojirimycin via a radical cyclisation of oxime ethers derived from sugars (Scheme 6).[81] From the commercially available 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose **80**, the oxime ether **87** was readily prepared via the corresponding alcohol **88**. Compound **87** was obtained as a mixture of *E*- and *Z*-isomers at the oxime ether moieties with a 5:1 ratio, respectively. Since the geometry of the oxime ether group does not influence the *trans*/*cis* selectivity of the product in the radical cyclisation,[82] the mixture of oxime ethers was used without isolation. The key radical cyclisation furnished products **89** and **90** in a 28% and 40% yield, respectively. The isomers were separated by medium-pressure column chromatography (MCC). Treatment of the 1,5-*trans* methoxyamine **89** with lithium aluminium hydride gave a ca. 1:2 mixture of the ring expanded product **91** and the demethoxylated amino alcohol **92**. The ring expanded piperidine product **91** was converted to 1-deoxynojirimycin **4** under typical debenzylation methods. (Compound **92** was used in the preparation of 5-membered aminocyclopentitols.)

En route to the synthesis of an aza-disaccharide heparanase inhibitor, Takahashi et al. devised a synthesis of 1-deoxynojirimycin **4** (Scheme 7).[83] The 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose **93** was converted into the 6-*O*-benzoyl-5-*O*-mesyl derivative **94** over three steps. The first step was an *O*-allylation achieved with sodium hydride and allylbromide. The benzoyl and mesyl groups were introduced by selective hydrolysis of the 5,6-*O*-isopropylidene group with 90% acetic acid. One-pot addition of benzoyl chloride followed by methanesulfonyl chloride, furnished **94** in 70% overall yield. This was treated with methanolic sodium methoxide and potassium *tert*-butoxide to afford epoxide **95** (78%). The action of sodium azide in the presence of NH_4Cl, followed by benzylation gave benzyl ether **96**. This was treated with 3% HCl in methanol to yield the anomeric mixture of methyl glycosides **97** and **98**. Silica gel chromatography allowed separation of the isomers in 50% and 47% yields, respectively. The β-isomer **98** can again be equilibrated under the same conditions to the anomeric mixture to yield a further 52% yield of the α-isomer **97**. By repetition of this procedure, a total of 80% conversion of **96** to **97** was obtained. Treatment of **97** with triflic anhydride gave the unstable 2-*O*-triflate derivative. Reduction of the azide group with triphenylphoshine followed by intramolecular cyclisation (via displacement of the trifluoromethanesulfonyl group) and benzyloxycarbonyl (cbz) protection, yielded **99**. Acidic hydrolysis followed by sodium borohydride reduction gave diol **100** in 71% yield. The conversion of β-isomer **98** to diol **100** under the same conditions proved very poor yielding. The intermediary triflate would decompose under the reaction conditions. The primary alcohol was protected as the *tert*-butyldiphenylsilyl ether. The secondary hydroxyl group was benzylated to yield a fully protected nojirimycin derivative **101** (key intermediate). Cleavage of the allyl group with palladium(II) chloride gave **102** in 72% yield. The azasugar **4** was obtained after typical deprotection steps.

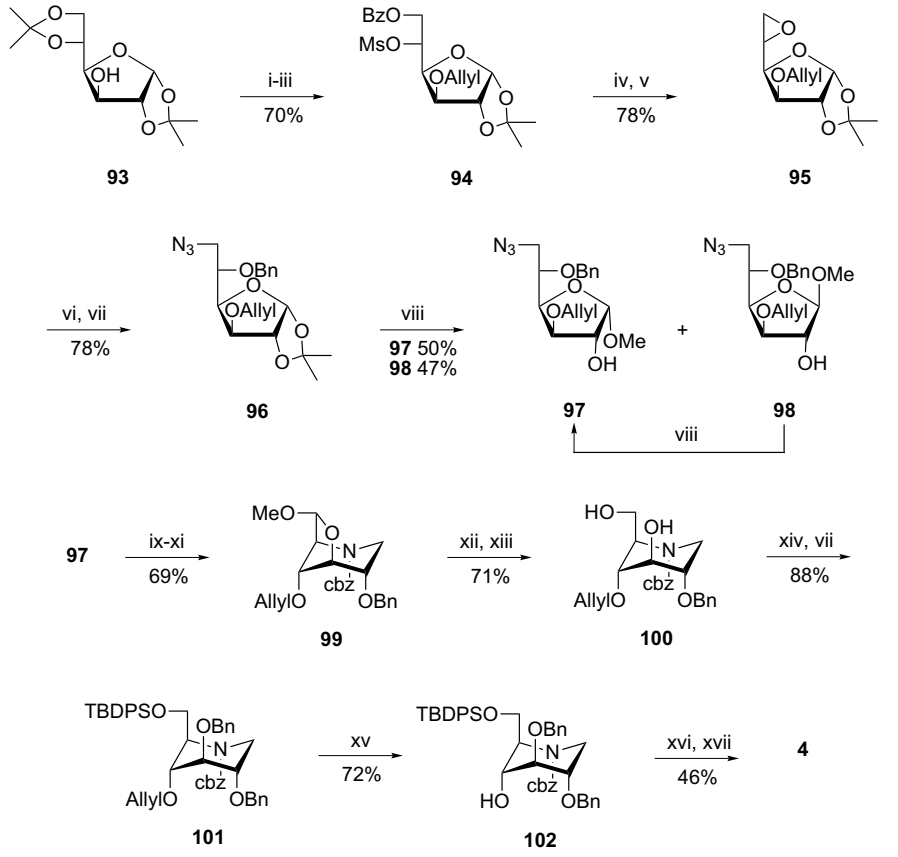
5. The synthesis of deoxymannojirimycin (DMJ)

5.1. Noncarbohydrate based routes to 1-deoxymannojirimycin (DMJ)

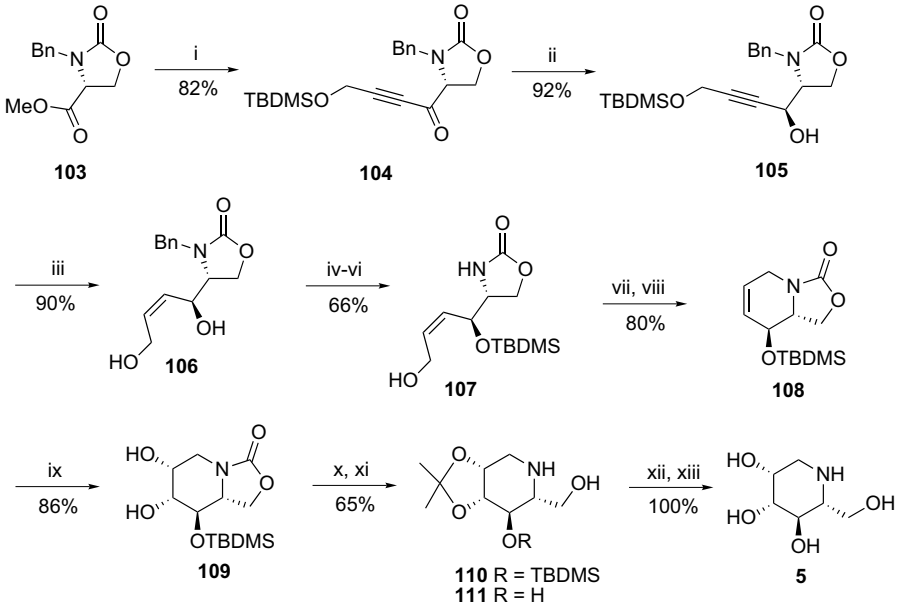
Katsumura et al. have designed an asymmetric synthesis of 1-deoxymannojirimycin **5** starting from the chiral building block (*R*)-(+)-4-carbomethoxyoxazolidinone



Scheme 6. Reagents and conditions: (i) $NH_2OMe{\cdot}HCl$, py, 80 °C, 3 h; (ii) CrO_3, py, CH_2Cl_2, rt, 2 h; (iii) Bu_3SnH, AIBN, C_6H_6, reflux, 5 h; (iv) $LiAlH_4$, THF, reflux, 4 h; (v) (a) Pd/C (10%), H_2, EtOH, rt, 1–3 d, (b) DOWEX® 1X8.



Scheme 7. Reagents and conditions: (i) NaH, $H_2C{=}CHCH_2Br$, 0 °C; (ii) aq AcOH, 60 °C; (iii) BzCl, then MsCl, py/CH_2Cl_2, −15 to 0 °C; (iv) NaOMe, MeOH, rt; (v) *t*-BuOK, THF/DMF, 0 °C to rt; (vi) NaN_3, NH_4Cl, aq DMF, 80 °C; (vii) BnBr, NaH, *n*-Bu_4NI, DMF, 0 °C; (viii) 3% HCl in MeOH, rt; (ix) Tf_2O, py, CH_2Cl_2, −60 °C; (x) Ph_3P, CH_2Cl_2, rt to 45 °C; (xi) K_2CO_3, H_2O, dioxane, MeOH, THF, rt; then cbzCl, 0 °C; (xii) TFA, H_2O/dioxane, rt; (xiii) $NaBH_4$, EtOH, 0 °C; (xiv) TBDPSCl, imidazole, DMF, rt; (xv) $PdCl_2$, NaOAc, aq AcOH, 50 °C; (xvi) TBAF, AcOH, THF, rt; (xvii) Pd/C (10%), H_2, AcOH/EtOH/H_2O, rt.



Scheme 8. Reagents and conditions: (i) $TBDMSOCH_2C{\equiv}CLi$, THF, −100 °C; (ii) diisobutylaluminium 2,6-di-*tert*-butyl-4-methylphenoxide, toluene, 0 °C; (iii) Lindlar's cat., H_2, MeOH; (iv) Na, liquid NH_3, −78 °C; (v) TBDMSCl, imidazole, DMF; (vi) 55% aq HF, MeCN, −20 °C; (vii) MsCl, Et_3N, DMAP, DMF, (viii) NaH, DMF, 0 °C; (ix) OsO_4, NMO, *t*-BuOH, H_2O; (x) $(MeO)_2C(Me)_2$, PPTS, acetone; (xi) 6 M NaOH, dioxane, reflux, 24 h; (xii) concd HCl, MeOH, reflux, 4 h; (xiii) basic ion-exchange resin.

103 (Scheme 8).[84,85] The reaction of **103** with the lithium anion of propargyl alcohol silyl ether gave ketone **104**. A stereoselective reduction with diisobutylaluminium 2,6-di-*tert*-butyl-4-methylphenoxide produced the desired *anti* alcohol **105** in 92% yield. (The *anti:syn* selectivity was 11:1 ratio determined by ^{1}H NMR.) Curiously the same reduction with $NaBH_4$ proceeded with no significant selectivity (5:3 ratio). The stereoselectivity can be understood by considering the postulated reaction intermediates (Fig. 4). It is believed that the steric interaction between the bulky diisobutyl groups and the methylene group of the oxazolidinone ring disfavours the *syn* product. This steric interaction would not exist with $NaBH_4$. Reduction of **105** with Lindlar's catalyst produced the *cis*-allyl alcohol **106**. Treatment with liquid ammonia yielded the corresponding diol (67% for two steps). The secondary hydroxyl group of **106** was protected with TBDMS. The terminal silyl group was selectively removed by treatment with aq HF to give allyl alcohol **107**. Treatment of **107** with MsCl followed by NaH produced the cyclised product **108**. Oxazolidinonylpiperidine **108** proved a key intermediate in the synthesis of other azasugars (see Scheme 27). Oxidation with osmium tetraoxide gave the diol **109** as the sole product. Acetonide formation followed by cleavage of the oxazolidinone ring with aqueous NaOH gave a mixture of monosilyl ether **110** and diol **111**. Upon acid treatment followed by basic ion-exchange purification, 1-deoxymannojirimycin **5** was obtained quantitatively.

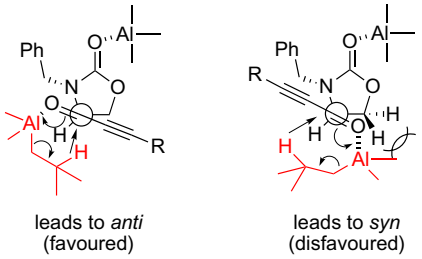
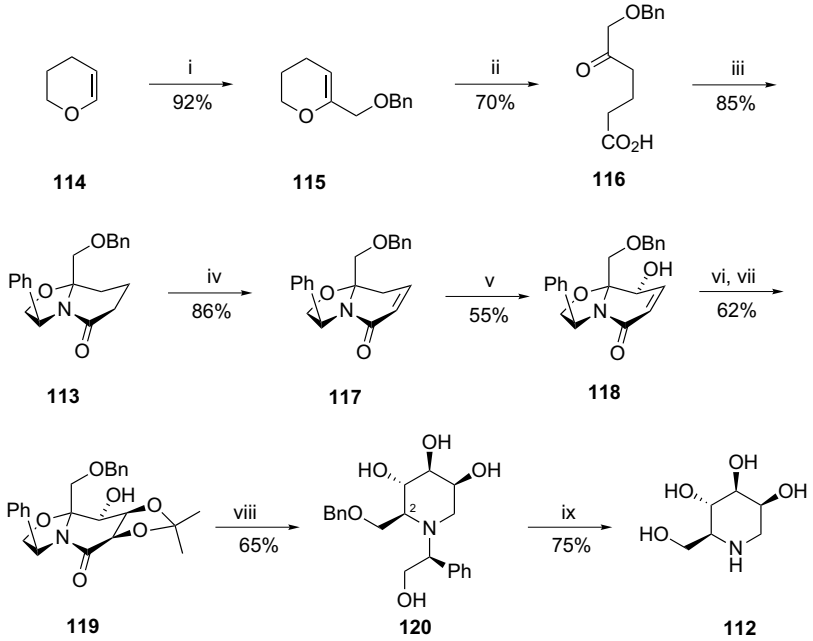
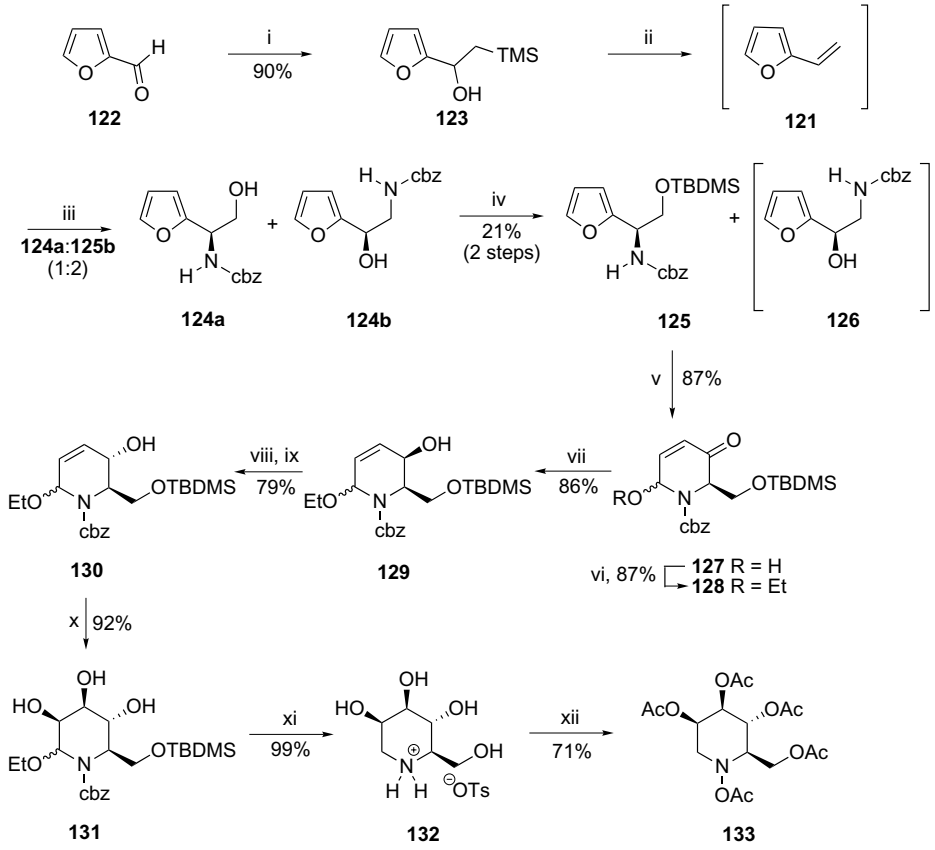


Figure 4. The *anti*-selectivity of diisobutylaluminium 2,6-di-*tert*-butyl-4-methylphenoxide.

An asymmetric route to 1-deoxy-L-mannonojirimycin **112** was developed by Meyers et al. using the chiral bicyclic lactam **113** as a key (Scheme 9).[86] The initial task was the construction of the bicyclic lactam. Starting from 2,3-dihydropyran **114**, hydroxymethyl-2,3-dihydropyran was formed using *t*-BuLi and paraformaldehyde. Ether **115** was formed by the treatment of benzyl chloride and sodium hydride. Keto acid **116** was prepared by Jones oxidation in 70% yield. Cyclodehydration in the presence of (*S*)-phenylglycinol then afforded the key intermediate **113**. Treatment of **113** with methyl phenylsulfinate and KH followed by thermal elimination gave **117**. A selective allylic oxidation introduced the first hydroxyl group to yield **118** as a single diastereomer in 64% yield. The diol functionality was introduced by oxidation with osmium tetraoxide under standard conditions. Only a single diastereoisomer was detected, although the absolute stereochemistry could not be determined at this stage. Diol protection gave acetonide **119**, which when subjected to the reduction conditions (BH_3), gave piperidine **120** as a 20:1 mixture of diastereoisomers at the angular position (C-2). Catalytic hydrogenolysis and treatment with TFA gave the L-azasugar **112**.



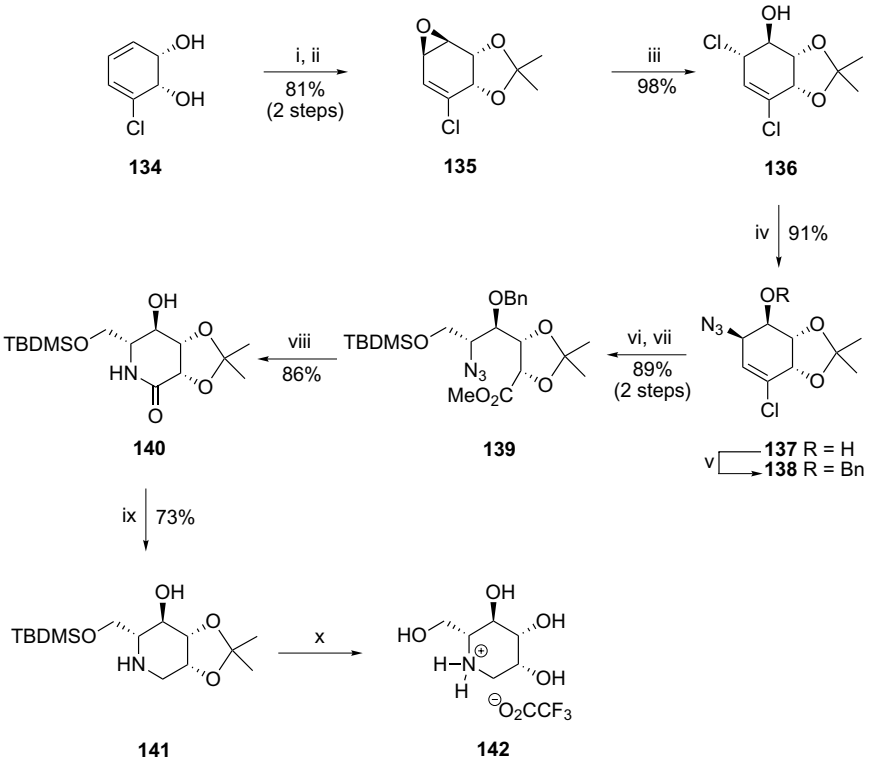
Scheme 9. Reagents and conditions: (i) (a) *t*-BuLi, trioxane, THF, −78 °C to rt, 2 h, (b) NaH, BnCl, DMF, rt, 16 h; (ii) CrO_3, H_2SO_4, THF; (iii) (*S*)-phenylglycinol, toluene, reflux, 18 h; (iv) KH, $PhSO_2$ Me, THF/toluene, reflux, 4 h; (v) SeO_2, dioxane, reflux, 10 h; (vi) OsO_4, NMO, aq acetone, rt, 2 d; (vii) $(MeO)_2CMe_2$, CH_2Cl_2, TsOH, rt, 30 min; (viii) (a) BH_3/THF, reflux, 30 min, (b) NaOH, H_2O_2, 0 °C, 30 min; (ix) (a) $Pd(OH)_2$, H_2, EtOH, rt, 12 h, (b) TFA, MeOH, rt, 15 min, (c) DOWEX® 50WX2.



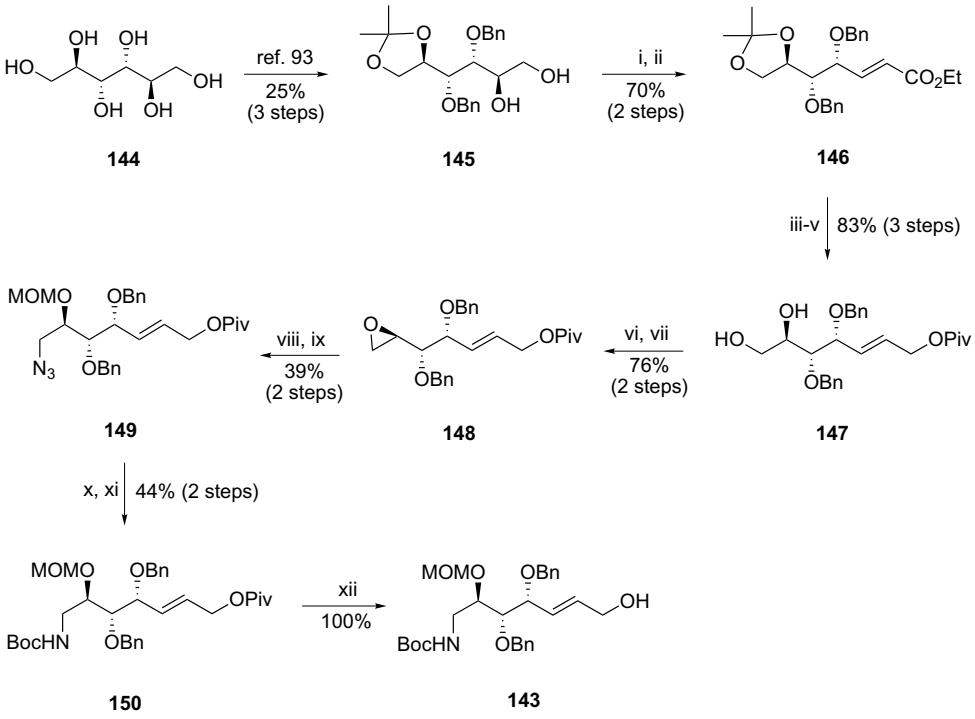
Scheme 10. Reagents and conditions: (i) TMSCl, Mg, Et_2O, 0 °C, 12 h; (ii) 1 M HCl, Et_2O, rt, 1 h; (iii) $cbzNH_2$, NaOH, *tert*-butyl hypochlorite, OsO_4, $(DHQ)_2PHAL$, *t*-BuOH, rt, 1 h; (iv) DMAP, TBDMSCl, Et_3N, CH_2Cl_2, rt, 3 h; (v) *m*-CPBA, CH_2Cl_2, 0 °C, 3 h; (vi) $HC(OEt)_3$, $TsOH{\cdot}H_2O$, CH_2Cl_2, rt, 1 d; (vii) $CeCl_3$, $NaBH_4$, CH_2Cl_2/MeOH, −78 °C, 2 h; (viii) PPh_3, DEAD, *p*-nitrobenzoic acid, THF, 0 °C, 30 min; (ix) Et_3N, MeOH, rt, 8 h; (x) OsO_4, NMO, CH_2Cl_2, 0 °C, 12 h; (xi) Pd/C (10%), H_2, MeOH, $TsOH{\cdot}H_2O$, rt; 12 h; (xii) Ac_2O, DMAP, py, CH_2Cl_2, rt, 12 h.

Both Ciufolini et al.[87] (1998) and Haukaas and O'Doherty[88] (2001) have reported on an azasugar synthesis via an asymmetric aminohydroxylation/aza-Achmatowicz approach. In O'Doherty's synthesis, vinyl-furan **121** was fashioned from furfural **122** (Scheme 10). First furfural was treated with a Grignard generated from magnesium and chloromethyltrimethylsilane to give 1-(2′-furyl)-2-(trimethylsilyl)-ethanol **123**. 2-Vinyl-furan was generated on addition of 1 M HCl. Enantiomerically enriched *N*-cbz-protected amino alcohols **124** and **125** were obtained by the Sharpless asymmetric aminohydroxylation (AA) chemistry. This was achieved by treating furan **121** with the sodium salt of *N*-chlorobenzylcarbamate and a 4% OsO_4/5% $(DHQ)_2PHAL$ mixture (AD-mix-α). Regioisomers **124a** and **124b** were formed in a 1:2 ratio and were inseparable at this stage. Purification was achieved after selective TBDMS protection of the primary alcohol followed by silica gel chromatography. The highest enantiomeric excess of **124** was achieved with the $(DHQ)_2PHAL$ ligand system, which gave **125** (which was separable from **126**) in a 21% yield from furfural **122** (>86% ee). The enantiomer of **125** could also be prepared from this sequence, using the $(DHQD)_2PHAL$ ligand (AD-mix-β). Treatment of **125** with NBS gave **127** via the aza-Achmatowicz rearrangement. Compound **127** was a mixture of hemiaminal diastereomers in an 87% yield. Treatment with triethyl chloroformate and TsOH gave ethylaminal **128**. This set up the Luche[89] reduction to furnish **129**. The allylic alcohol was introduced with complete stereochemical control. However manno-stereochemistry was brought into effect by a Mitsunobu inversion via the 4-nitrobenzoate ester (84% yield), hydrolysis of which gave the C-4 epimer **130** (94% yield). Exposure of **130** to OsO_4 catalysed dihydroxylation gave **131**. After deprotection (TBAF) and hydrogenolysis, a single diastereomer of DMJ was isolated as the TsOH salt **132**, which was converted to the penta-acetate **133** for characterisation.

On route to a DMJ-disaccharide, Banwell et al. presented a synthesis of DMJ.[90] Following up a synthesis proposed by Hudlicky et al.[91] the synthesis starts from *cis*-1,2-dihydrocatechol **134** (Scheme 11). *cis*-1,2-Dihydrocatechol is derived from microbial oxidation of chlorobenzene in large quantities in its enantiomerically pure form.[91] Subjecting **134** to *m*-CPBA gave epoxide **135** (81%), which was regioselectively converted to chlorohydrin **136**. Treatment with lithium azide resulted in *cis*-azido-alcohol **137** by an S_N2-type displacement. *O*-Benzylation gave ether **138**, quantitatively. Ozonolytic cleavage followed by sodium borohydride reduction and TBDMS protection furnished azido-ether **139**. Hydrogenolysis resulted in the formation of lactam **140**. This was reduced and converted into borane–amine complex using borane-dimethyl sulfide, cleavage of



Scheme 11. Reagents and conditions: (i) $(MeO)_2CMe_2$, $TsOH{\cdot}H_2O$ (cat.), 18 °C, 1 h; (ii) *m*-CPBA, CH_2Cl_2, 0–18 °C, 11 h; (iii) LiCl, AcOH, THF, 18 °C, 17 h; (iv) LiN_3, DMF, 18 °C, 72 h; (v) BnBr, KI, NaH, THF, 0–18 °C, 24 h; (vi) O_3, py, MeOH, −78 °C, 1 h then $NaBH_4$, −10 °C, 3 h; (vii) TBDMSCl, imidazole, CH_2Cl_2, 18 °C, 2 h; (viii) Pd/C (5%), H_2, EtOAc, 18 °C, 36 h; (ix) $BH_3{\cdot}DMS$, THF, 18 °C, 4.5 h then Pd/C (5%), MeOH, 18 °C, 38 h; (x) TFA/H_2O, 18 °C, 20 h.



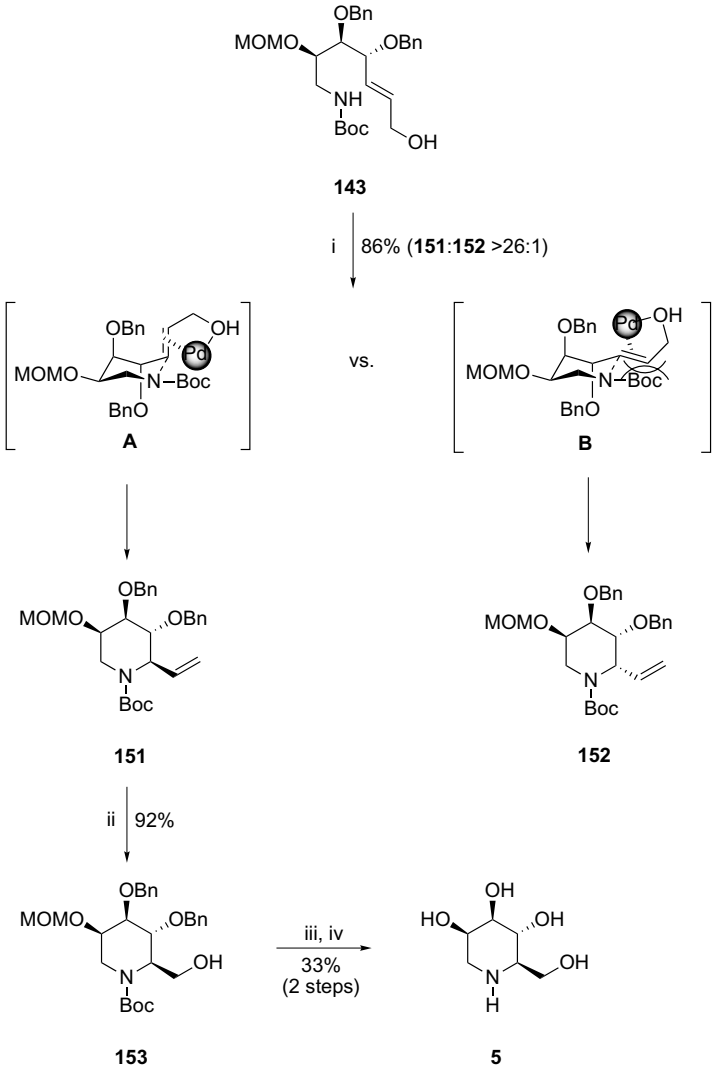
Scheme 12. Reagents and conditions: (i) $NaIO_4$, H_2O/Et_2O, 0 °C; (ii) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, 0 °C; (iii) DIBAL, THF, −78 °C; (iv) PivCl, py, THF, 0 °C; (v) 10% aq HCl, THF, 40 °C; (vi) TsCl, py, CH_2Cl_2, 0 °C; (vii) K_2CO_3, MeOH, 0 °C; (viii) NaN_3, NH_4Cl, 15-crown-5, DMF, rt; (ix) MOMCl, *i*-Pr_2NEt, 0 °C; (x) PPh_3, THF, rt; (xi) $(Boc)_2O$, Et_3N, CH_2Cl_2, rt; (xii) K_2CO_3, MeOH, rt.

which, under Pd/C (5%) conditions gave **141**. Treatment of **141** with TFA gave DMJ salt **142**.

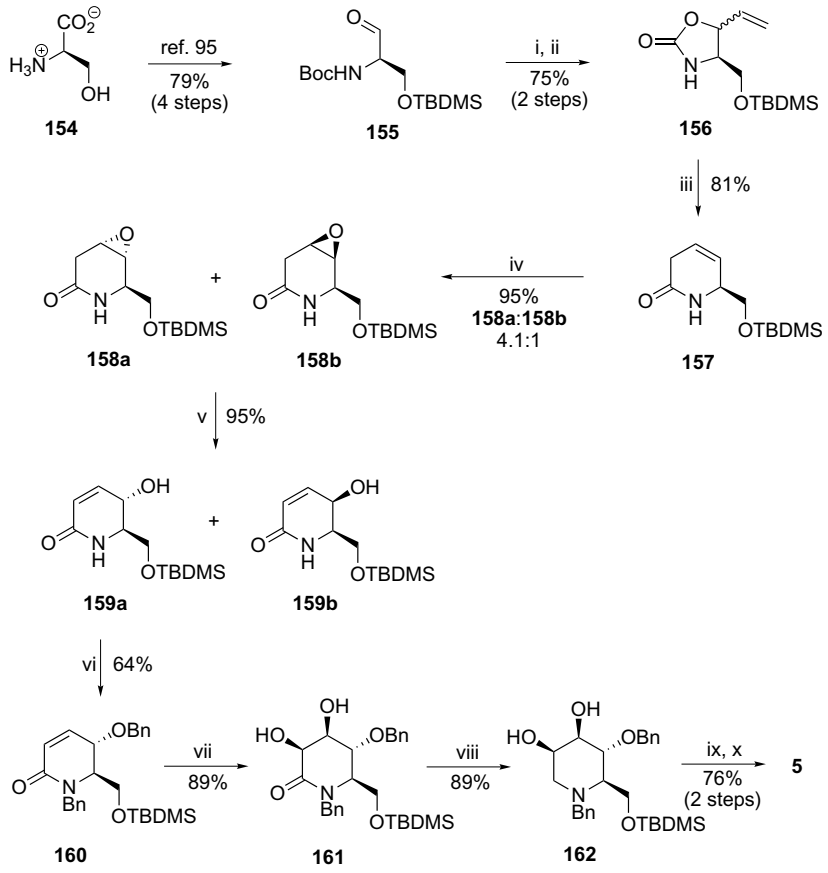
Hirai et al. reported on a palladium catalysed cyclisation of urethane **143** as a route to DMJ (Scheme 12).[92] The synthesis starts from the readily available D-mannitol **144**. This was converted to 3,4-di-benzyl-5,6-*O*-isopropylidene-D-mannitol **145** according to a known procedure.[93] Oxidative cleavage followed by Horner–Wadsworth–Emmons olefination gave α,β-unsaturated ester **146**. Reduction followed by pivaloyl (Piv) protection gave the pivaloyl ester in 88% yield. Treatment with HCl gave the diol **147**. Tosylation of **147**, then treatment with potassium carbonate gave the epoxide **148**. Ring opening with sodium azide was regioselective and the alcohol formed was protected with a methoxy methyl group (MOM). The resulting azide **149** was reduced by PPh_3, and the amine protected to give pivaloyl ester **150**. Deprotection afforded the key allyl alcohol **143**.

Ring cyclisation was achieved using 15 mol % $PdCl_2(MeCN)_2$ to give primarily one compound (**151**:**152**, >26:1 ratio) in an 86% yield (Scheme 13). The stereoselectivity was explained by assuming the cyclisation proceeding via the sterically favoured transition state **A**. Compound **151** was converted to DMJ **5** via deprotection of **153**.

Knight and Tchabanenko reported a DMJ synthesis using a palladium-catalysed 'decarboxylative carbonylation' as a key step (Scheme 14).[94] Starting from the amino acid D-serine **154**, aldehyde **155** (79%, >98 ee) was synthesised according to a previously reported procedure.[95] Addition of vinyl magnesium bromide followed by *N*-Boc deprotection with potassium *tert*-butoxide gave a mixture of vinyloxazolidinone **156** (*anti:syn* 2:1). Synthesis of the δ-lactam **157** was achieved under carbonylation conditions. Stereoselective epoxidation with Oxone® gave the *anti* **158a** and *syn* **158b** epoxides in a 4.1:1 ratio; the relative stereochemistries were unambiguously assigned at this stage. The α,β-unsaturated lactams **159a** and **159b** were formed on treatment with DBU. Benzyl protection of the free hydroxyl group of **159a** gave **160**. It was



Scheme 13. Reagents and conditions: (i) 15 mol % $PdCl_2(MeCN)_2$, THF, rt; (ii) (a) O_3, CH_2Cl_2/MeOH, −78 °C, (b) $NaBH_4$, −78 °C; (iii) TFA, CH_2Cl_2, 0 °C to rt; (iv) H_2, Pd/C, concd HCl, EtOH, rt.

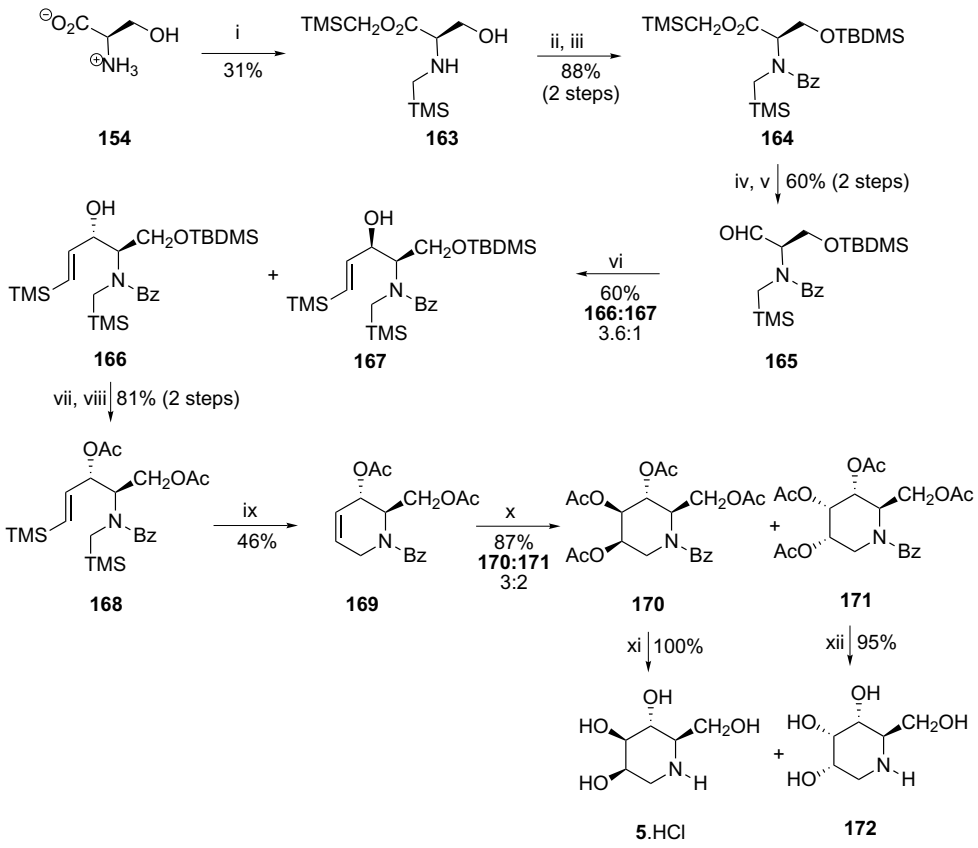


Scheme 14. Reagents and conditions: (i) $H_2C{=}CHMgBr$, THF, −78 °C to rt, 3 h; (ii) *t*-BuOK, THF, rt, 3 h; (iii) $PdCl_2$ $(PPh_3)_2$ (10 mol %), CO (65 atm), EtOH, 60 °C, 32 h; (iv) Oxone®, $NaHCO_3$, acetone/H_2O, rt; 3 h; (v) DBU (2 equiv), CH_2Cl_2, reflux, 3 h; (vi) NaH (2 equiv), DMF, BnBr, 0 °C to rt, 3 h; (vii) OsO_4, NMO, *t*-BuOH, rt; 3 h; (viii) $LiAlH_4$, Et_2O, rt, 3 h; (ix) Bu_4NF, THF, rt; 1 h; (x) Pd/C (10%), H_2, EtOH, HCl, rt, 2 h.

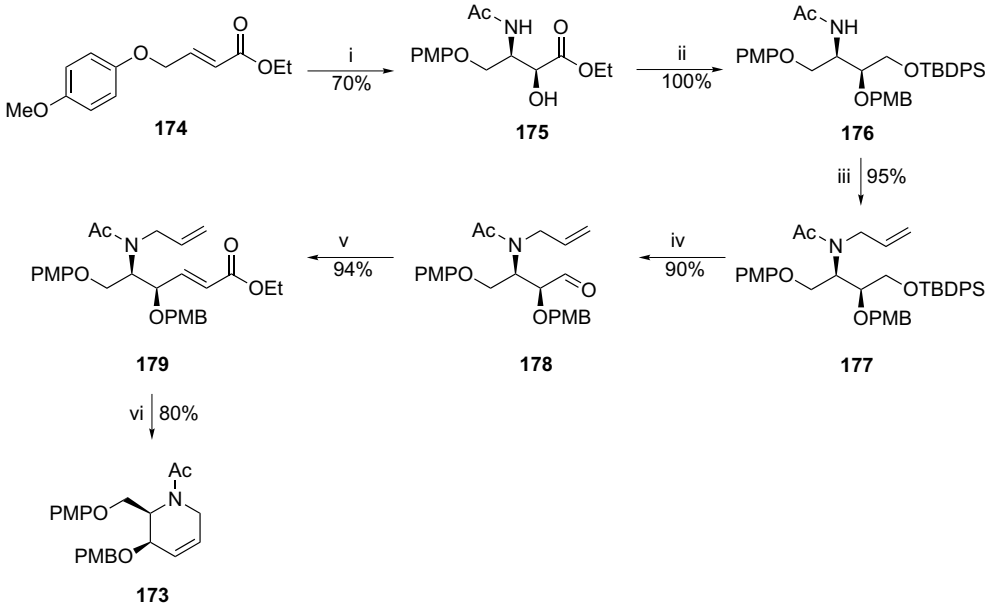
believed that this would lead to higher selectivity upon dihydroxylation compared to **159a**. Indeed 4,5-*anti*-diol **161** was formed in high stereoselectivity with only traces of the *syn*-isomer. $LiAlH_4$ reduction furnished piperidine **162**, which was readily converted to DMJ **5**.

Another DMJ synthesis using D-serine **154** was described by Mariano et al. demonstrating an oxidative Mannich cyclisation (Scheme 15).[96] D-Serine was converted to α-silylamido ester **163** by treatment with (trimethylsilyl)methyl iodide. Protection of the primary alcohol, followed by *N*-benzoylation provided **163**. $NaBH_4$ reduction proceeded by a Swern oxidation to give aldehyde **165** (70% ee). Reaction of the aldehyde with *E*-[(trimethylsilyl)vinyl]lithium yielded two separable diastereomeric alcohols **166** and **167** (3.6:1 ratio). Initially, assignment of the configuration of alcohol **166** as the major isomer was presumed according to the Felkin–Ahn model. This was later confirmed by X-ray crystallography of the diacetoxy compound **168**. Synthesis of the ring cyclised tetrahyropyridine **169** was achieved using cerric ammonium nitrate. Treatment with OsO_4 in aqueous acetone followed by treatment with acetic anhydride gave a mixture of tetraacetates **170** and **171** in a 3:2 ratio. The major isomer **170** was readily converted to DMJ **5**. (The minor isomer having the allo-configuration led to 1-deoxyallonojirimycin **172**, see Section 7.3 for further syntheses.)

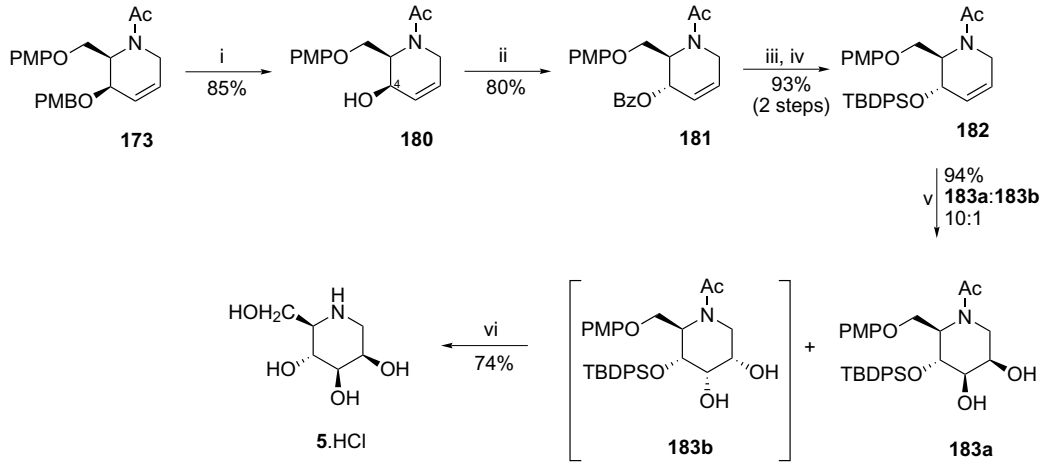
A general synthesis of 1-deoxyazasugars (including DMJ) was developed by Singh and Han, via the common olefin intermediate **173** (Scheme 16).[97] The preparation of the key compound began with olefin **174** (readily prepared from 4-bromocrotonate and *p*-methoxyphenol). The aryl substituents were chosen, as it was believed that aryl–aryl stacking interactions between **174** and the Sharpless asymmetric aminohydroxylation catalyst would proceed with improved selectivity. In fact the reaction proceeded with excellent regioselectivity (>20:1) to furnish the amino alcohol **175** (>99% ee after recrystallisation). *para*-Methoxyphenyl (PMP) protection of the free hydroxyl group followed by reduction and subsequent TBDPS protection gave **176**. *N*-Allylation was best achieved with allyl bromide and KH in THF (95%) to yield **177**. Deprotection of the TBDPS group followed by a Dess–Martin oxidation gave aldehyde **178**. Olefination via the Horner–Wadsworth–Emons protocol furnished the α,β-unsaturated ester **179** in 94% yield. A ring closing metathesis (RCM) led to the synthetically useful olefin **173**. The key olefin **173** was used to synthesise 1-deoxymannonojirimycin **5** as outlined in Scheme 17.[98] Inversion of the 4-hydroxy group of **180** was required and achieved under Mitsunobu conditions to give benzoate ester **181**. The benzyl group was converted to the bigger TBDPS group **182** to drive the diastereoselectivity. Dihydroxylation gave the two diastereoisomers **183a** and **183b** in good



Scheme 15. Reagents and conditions: (i) $TMSCH_2I$, K_2CO_3, DMF, 100 °C, 17 h; (ii) imidazole, TBDMSCl, DMF, 25 °C, 18 h; (iii) BzCl, Et_3N, CH_2Cl_2, 0 °C, 15 min; (iv) $NaBH_4$, EtOH, 25 °C, 6 h; (v) DMSO, $(COCl)_2$, CH_2Cl_2, −78 °C, 2.5 h; (vi) (*E*)-1-(trimethylsilyl)-2-(tri-*n*-butylstannyl)ethene, *n*-BuLi, THF, −78 to 25 °C 6.5 h; (vii) 48% HF/H_2O, MeCN, 25 °C, 0.5 h; (viii) DMAP, Ac_2O, py, 25 °C, 17 h; (ix) CAN, MeCN, 25–40 °C, 20 h; (x) (a) OsO_4, NMO, acetone/H_2O, 0 °C, 17 h, (b) DMAP, Ac_2O, 25 °C, 17 h; (xi) 6 N HCl, reflux, 2 h; (xii) (a) 6 M HCl, reflux, 5 h, (b) ion-exchange chromatography.



Scheme 16. Reagents and conditions: (i) $K_2OsO_4{\cdot}2H_2O$, $(DHQD)_2PHAL$, LiOH, *N*-bromoacetamide, *t*-BuOH/H_2O, 4 °C, 8 h; (ii) (a) NaH, PMBCl, DMF, 0 °C, 8 h, (b) $LiBH_4$, Et_2O, 15 min, (c) TBDPSCl, Et_3N, DMAP, CH_2Cl_2, 25 °C, 4 h; (iii) KH, 18-crown-ether, $H_2C{=}CHCH_2Br$, THF, 25 °C, 5 h; (iv) (a) TBAF, THF, 25 °C, 1 h, (b) periodinane, CH_2Cl_2, 25 °C, 1 h; (v) $(EtO)_2P(O)CH_2CO_2Et$, LiBr, DBU, THF, 25 °C, 2 h; (vi) Grubbs' cat. (10 mol %), toluene, 90 °C, 2 h.



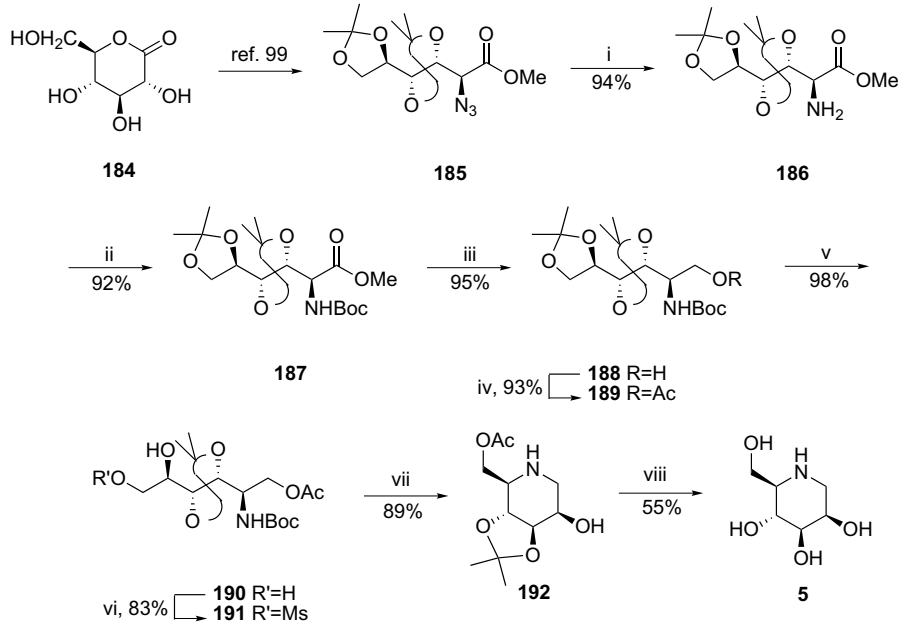
Scheme 17. Reagents and conditions: (i) 5% TFA in CH_2Cl_2, 25 °C, 30 min; (ii) DIPAD, Ph_3P, BzOH, THF, 0 °C, 2 h; (iii) K_2CO_3, MeOH, 25 °C, 5 h; (iv) TBDPSCl, imidazole, Et_3N, DMF, 60 °C, 12 h; (v) OsO_4, NMO, *t*-BuOH/H_2O, 16 h; (vi) (a) Ac_2O, DMAP, Et_3N, CH_2Cl_2, 25 °C, (b) CAN, MeCN/H_2O, 0 °C, 10 min; (c) 6 N HCl, 120 °C, 12 h.

selectivity (10:1). Deprotection of **183a**, furnished **5** as the hydrogen chloride salt.

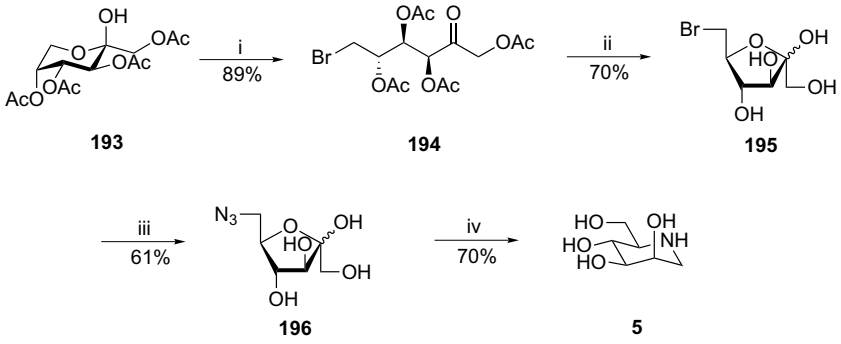
5.2. Carbohydrate based routes to 1-deoxymannojirimycin (DMJ)

Lee et al. reported a DMJ synthesis starting from D-glucurono-δ-lactone **184** (Scheme 18).[98] Manno-azide **185** was prepared from a known method[99] and converted to amine **186** followed by protection with di-*tert*-butyl carbonate to give **187**. A lithium aluminium hydride reduction gave **188**, and the derived alcohol was protected with an acetyl group furnishing **189**. Alcohol **190** was obtained from the regioselective deprotection of **189** and readily converted to mesyl **191**. The deprotection of the *tert*-butyl carbamate and acetyl groups was achieved with 3 M hydrochloric acid. The resulting amine underwent intramolecular nucleophilic amination to give piperidine **192** in an 89% yield. Treatment with methanolic ammonia yielded DMJ **5**.

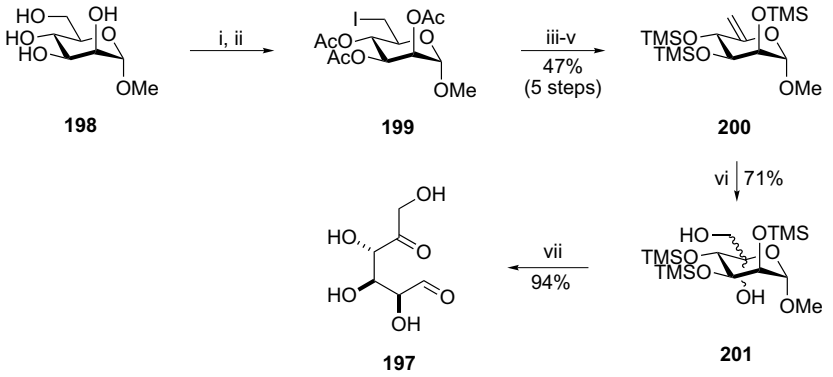
A short synthesis of DMJ has been reported by Stütz et al.[100] He proposed a novel synthesis starting with the easily available tetra-*O*-acetyl derivative of D-fructose **193** (Scheme 19).[101] Reaction with the commercially available triphenylphosphane dibromide gave the open-chain bromosugar **194** in a 90% yield after purification. Its deprotection gave 6-bromo-6-deoxy-D-fructofuranose **195** as a syrup, which was then transformed into azide **196**. Hydrogenation of azidodeoxysugar **196** gave DMJ **5** as a crystalline compound with an overall yield of ca. 27%.



Scheme 18. Reagents and conditions: (i) Pd/C (10%), H_2, EtOAc, rt; (ii) di-*tert*-butyl carbonate, MeOH, Et_3N, rt; (iii) $LiAlH_4$, THF, 0 °C; (iv) Ac_2O, py, rt; (v) DOWEX® 50WX8, MeOH; (vi) MsCl, Et_3N, CH_2Cl_2, −10 °C; (vii) 3 M HCl, EtOAc, rt; (viii) 50% NH_3/MeOH, rt.



Scheme 19. Reagents and conditions: (i) Ph_3PBr_2, py, CH_2Cl_2, reflux, 3 h; (ii) (a) NaOMe, MeOH, 0 °C, 5 h, (b) Amberlite® IR 120 (H^+); (iii) NaN_3, DMF, rt, 7 d; (iv) Pd/C (5%), H_2, MeOH, rt, 4 h.



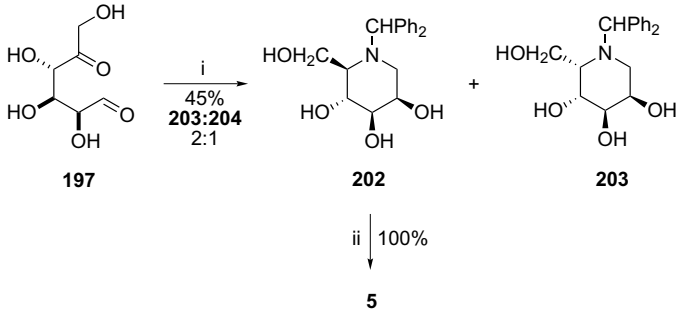
Scheme 20. Reagents and conditions: (i) PPh_3, imidazole, I_2, toluene, reflux; (ii) Ac_2O, py; (iii) DBU, toluene, reflux; (iv) NaOMe, MeOH; (v) TMSCl, py; (vi) CF_3COCH_3, Oxone®, $NaHCO_3$, Na_2EDTA, MeCN, H_2O, 1 h; (vii) MeOH, rt.

Murphy et al. also mention a strategy for the synthesis of DMJ on a multigram scale (Scheme 20).[102] DMJ was prepared from the double amination of 5-ketomannose **197** as already reported by Baxter and Reitz (Scheme 21).[103] To get to 5-keto-mannose, Murphy et al. started from the commercially available methyl-α-D-mannopyranoside **198**. Treatment with PPh_3 and iodine, followed by acetyl protection gave the iodo-derivative **199**. Elimination of hydrogen iodide using DBU, followed by exchange of the protecting groups to TMS gave **200**. Treatment of **200** with methyl(trifluoromethyl)-dioxirane (generated in situ) gave hemiketal derivative **201**. The TMS groups were easily removed by stirring in methanol with the desired 1,5-dicarbonyl product **197** isolated in good yield (94%).

The double amination was achieved using benzhydrylamine to give a 2:1 mixture of the piperidines **202** and **203**. Hydrogenolysis of **202** gave **5** (29% overall yield) (Scheme 21).

6. The synthesis of homomannojirimycin (HMJ) and adenophorine

Syntheses of the naturally occurring homoazasugars have rarely been reported. Of the ones described, peculiarly both α- and β-homomannojirimycin **7** and **9** were synthesised before their isolation as natural products.[104,105] Indeed, before their isolation,[15] Liu had shown that azasugars with additional carbon

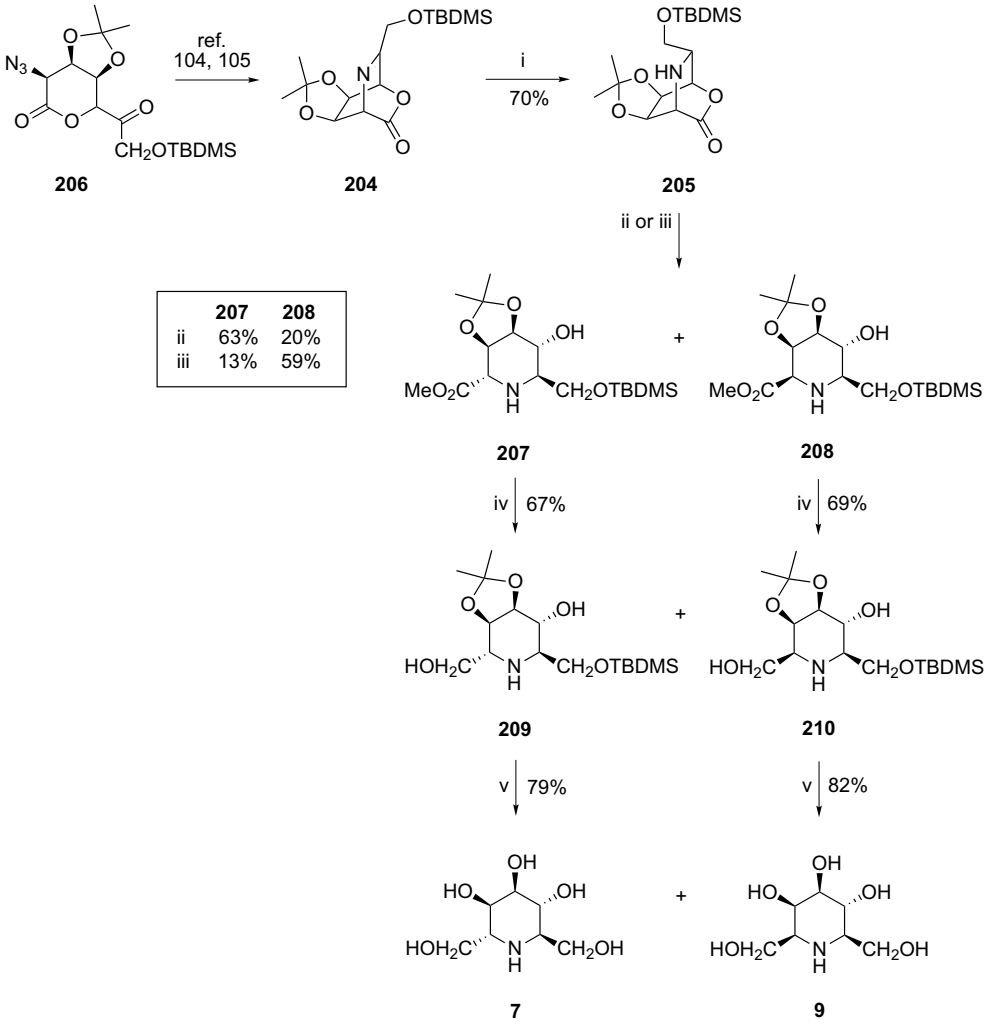


Scheme 21. Reagents and conditions: (i) Ph_2CHNH_2, AcOH, $NaBH_3CN$, MeOH, −78 °C to rt; (ii) $Pd(OH)_2$, H_2, EtOH.

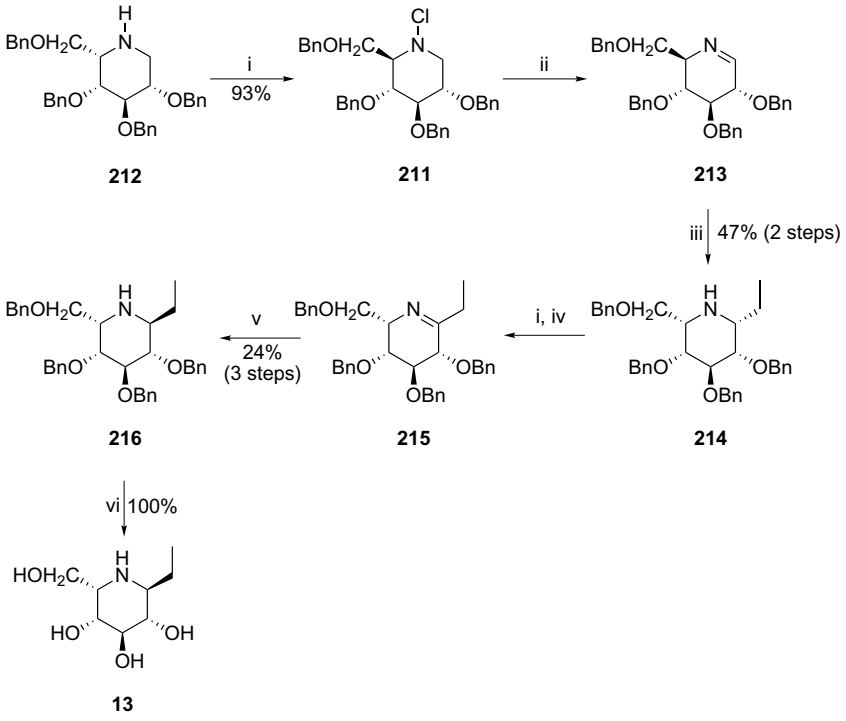
substituents at the anomeric position are more potent and specific inhibitors of glycosidases, and therefore have significant advantages over DNJ. For example, it was found that α-HMJ inhibited α-glucosidases selectively, with the same efficacy as DNJ but did not inhibit any other glycosides.[106] Enzyme specificity is an important factor in treating disease, which laments the need for a good synthetic strategy of homoazasugars.

Interestingly Fleet et al. reports that the synthesis of α- and β-homomannojirimycin **7** and **9** can be achieved from the stereoselective and chemoselective sodium cyanoborohydride reduction of a [2.2.2]-bicyclic-imino-lactone **204** to give a single isomer of [2.2.2]-bicyclic-amino-lactone **205** (Scheme 22).[107] Reduction of azido-ketone **206**, followed by an aza-Wittig reaction gives the formation of the bicyclic imine lactone **204**. Reduction of **204** by hydrogenation was unsuccessful, however treatment with sodium cyanoborohydride in acetic acid (a solvent that does not open the lactone bridge) was both chemo- and stereoselectively giving **205**. The lactone was opened with sodium acetate in methanol to give the α-amino-ester **207** (63%) plus the unexpected β-epimer **208** (20%) from racemisation. Ester **207** has an axial ester group, which is believed to assist epimerisation, whereas **208** has a thermodynamically stable 2,6-diequitorially substituted ring system. Intriguingly, it was found that ring opening under basic conditions (sodium carbonate in methanol) gave the esters **207** and **208** in yields of 13% and 59%, respectively. Reduction of the esters **207** and **208** were achieved with $LiBHEt_3$ to yield **209** and **210**, respectively. The azasugars **7** and **9** were formed on treatment with aqueous HCl.

Adenophorine **13** is a naturally occurring azasugar with a hydrophobic alkyl substituent at the anomeric position. Such azasugars are believed to show increased enzyme inhibition and enhanced bioavailability[108] (cf. *N*-butyl-DNJ **51**). Davis et al. have claimed the first synthesis of adenophorine (Scheme 23) although the absolute stereochemistry of adenophorine is not yet determined.[109] From tetrabenzylidonojirimycin-*N*-chloride **211** (prepared from tetrabenzylidonojirimycin **212**) elimination with DBU gave idonojirimycin-aldimine **213**. Addition of EtMgBr to imine **213** gave the tetrabenzyl-epimer of adenophorine **214**. To obtain the correct stereochemistry, ethyl ketimine **215** was formed from a two-step chlorination–elimination process. It was found



Scheme 22. Reagents and conditions: (i) $NaBH_3CN$, AcOH; (ii) NaOAc, MeOH, reflux; (iii) Na_2CO_3, MeOH, reflux; (iv) $LiBHEt_3$, THF, −60 °C; (v) aq HCl.



Scheme 23. Reagents and conditions: (i) NCS, CH_2Cl_2; (ii) DBU, Et_2O, reflux; (iii) EtMgBr, Et_2O/dioxane; (iv) LiTMP, −78 °C, Et_2O; (v) $LiAlH_4$, THF; (vi) $PdCl_2$, H_2, EtOH.

that by using a small nucleophilic hydride (from $LiAlH_4$) the correct sense was obtained in product **216**. Adenophorine **13** was obtained on typical deprotection.

7. The synthesis of synthetic azasugars (non-naturally occurring)

In comparison to the true pyranose monosaccharides, the 1-deoxy-aza-analogues of D-galacto-, D-altro-, D-ido-, D-gulo-, D-talo- and D-allopyranose sugars are not naturally occurring or are yet to be isolated from nature. However in search of new and specific glycosidase inhibitors their syntheses have been pursued by many groups. This section covers the recent syntheses of the piperidine azasugars that are not naturally occurring namely; 1-deoxygalactostatin (1-deoxygalactonojirimycin) **217**, 1-deoxyaltronojirimycin **218**, 1-deoxyidonojirimycin **219**, 1-deoxygulonojirimycin **220**, 1-deoxytalonojirimycin **221** and 1-deoxyallonojirimycin **172** (Fig. 5).

7.1. The synthesis of 1-deoxygalactostatin and 1-deoxyaltronojirimycin

Although galactostatin (galactonojirimycin) **3** is found in nature, 1-deoxygalactostatin (1-deoxygalactonojirimycin) **217**, is yet to be isolated. The reduced form of the natural product has generated great interest as it

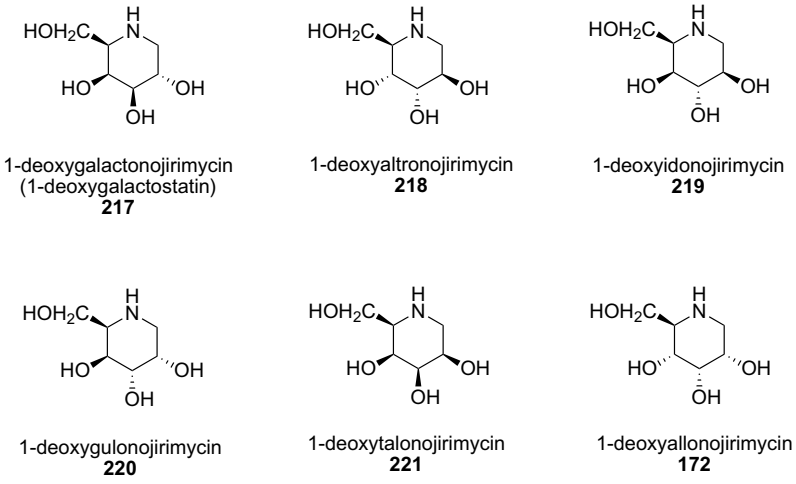
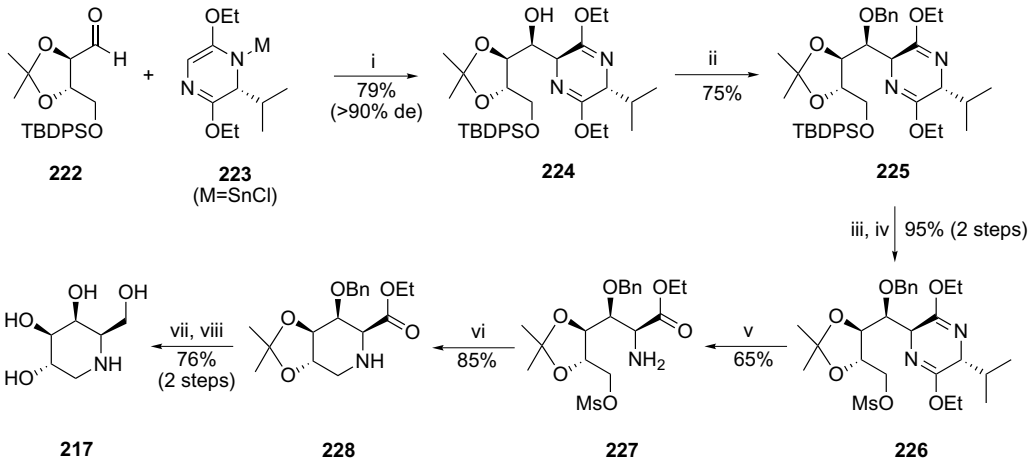


Figure 5. Synthetic piperidine azasugars (non-naturally occurring).



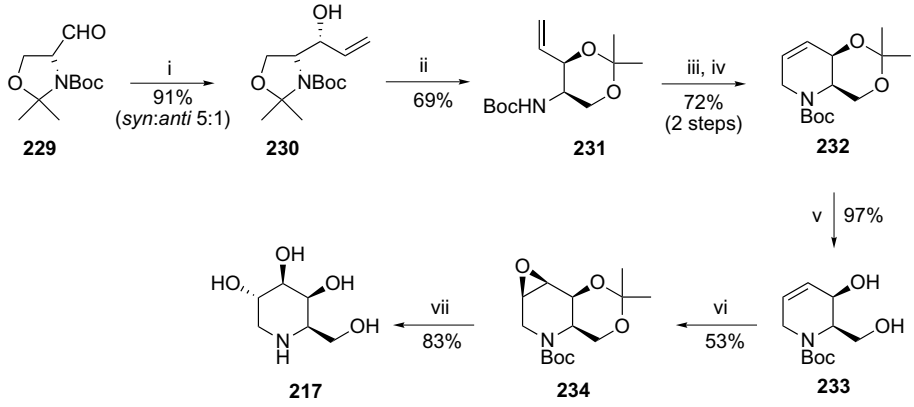
Scheme 24. Reagents and conditions: (i) (a) THF, −78 °C, 1 h, (b) aq NH_4Cl; (ii) NaH, BnBr, Bu_4NI, 24 h, rt; (iii) Bu_4NF, THF, rt, 4 h; (iv) MsCl, Et_3N, DMAP, CH_2Cl_2, rt, 1 h; (v) 0.25 M HCl/EtOH, 9 h; (vi) DMSO, Et_3N, 70 °C, 2 h; (vii) $LiBHEt_3$, THF, rt; 2 h; (viii) (a) 0.25 M HCl/THF, Pd/C (10%), H_2, rt, 9 h, (b) DOWEX® (H^+).

has been reported that 1-deoxygalactostatin has shown potent and specific inhibition of many α- and β-galactosidases.[110,111]

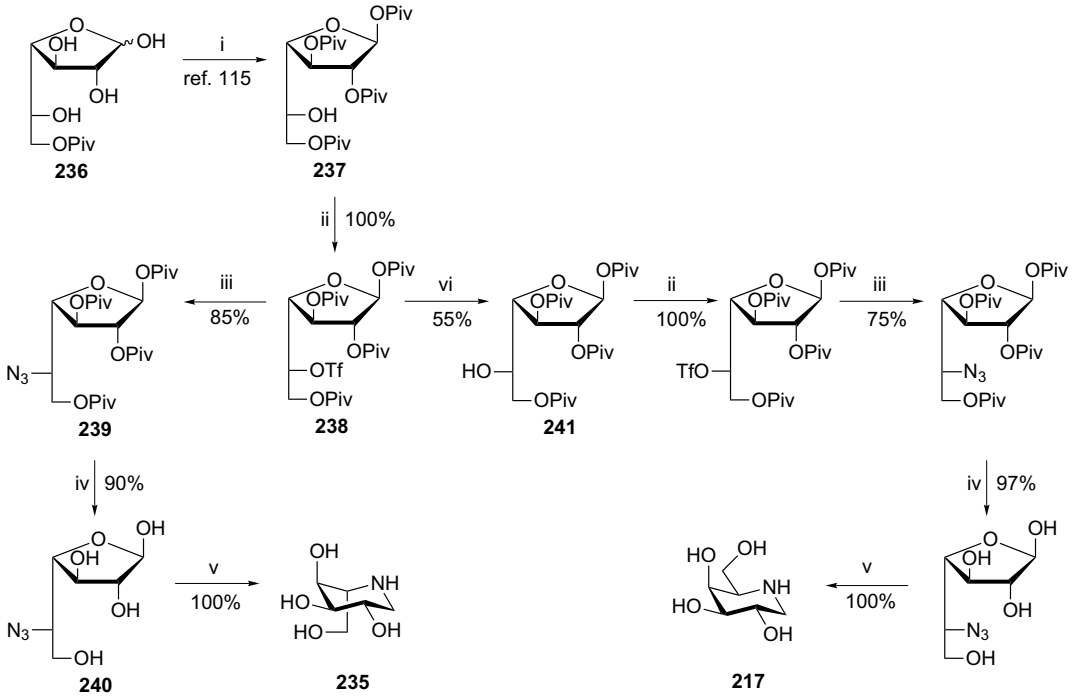
A recent synthesis by Quintela et al. utilises a noncarbohydrate based approach to **217** (Scheme 24).[112] Starting with the chiral L-tartaric acid derivative, 4-*O*-(*tert*-butyldiphenylsilyl)-2,3-*O*-isopropylidene-L-threose **222**, reaction with the tin(II) azaenolate **223** gave **224** in good yield and high diastereomeric excess (79%, >90% de). Treatment of **224** with sodium hydride and benzyl bromide furnished the benzyl ether **225**. The mesyl group was introduced after deprotection to give **226**. Hydrolysis of the pyrazino moiety of **226** led to the amino ester **227**. Efficient cyclisation was accomplished by heating in dimethylsulfoxide with triethylamine as an auxiliary base. Reduction of the piperidine ester **228**, followed by catalytic hydrogenation yielded the azasugar **217**.

It is possible to prepare 1-deoxygalactostatin from the Garner aldehyde **229** (Scheme 25).[113] The diastereoselective vinyl addition led to *syn*-vinyl alcohol **230** (67% de). It was then converted to the 1,3-acetonide **231**. *N*-Allylation followed by a Grubb's RCM yielded **232**. To generate the epoxide; the first hydrolysis of **232** was achieved with TsOH to give **233**. Hydroxyl-directed epoxidation with *m*-CPBA, followed by diol protection furnished the *syn*-epoxide **234**. Acid hydrolysis followed by treatment with ion-exchange resin gave **217** in only an 83% yield.

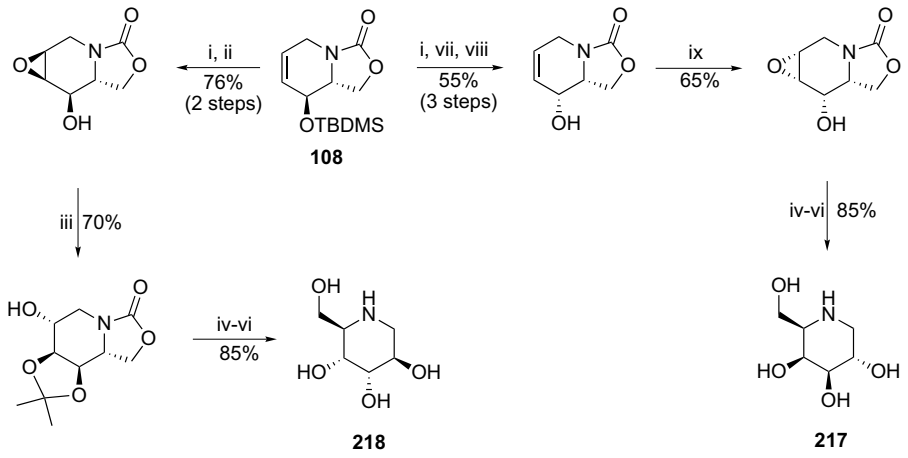
Uriel and Santoyo-González have reported the synthesis of 1-deoxygalactostatin **217** and L-deoxyaltronijrimycin **235** from D-galactose **236** (Scheme 26).[114,115] From D-galactose, the partly protected galactofuranoside **237** was derived. Triflation of the free hydroxyl gave **238** quantitatively. Treatment with NaN_3 gave the 5-azido-L-altrofuranose derivative **239**. Pivaloyl deprotection furnished 5-azido-5-deoxy-L-altrofuranose **240**. Catalytic hydrogenation gave the azasugar **235**. For the synthesis of 1-deoxygalactostatin, an inversion of the 5-OH was required. This was achieved by treating **238** with sodium nitrite in DMF yielding **241** in a 55% yield from **237**. Using the same sequence previously outlined, 1-deoxygalactostatin **217** was formed.



Scheme 25. Reagents and conditions: (i) (a) $H_2C{=}CHCH_2$ ZnBr, Et_2O, −78 °C to rt; (ii) (a) recrystallisation from *n*-hexanes/EtOAc, (b) HCl (g), $CHCl_3$, rt; (iii) $H_2C{=}CHCH_2I$, NaH, THF, 0 °C; (iv) Grubbs' cat., CH_2Cl_2, rt; (v) $TsOH{\cdot}H_2O$, MeOH, rt; (vi) (a) *m*-CPBA, NaH_2PO_4, CH_2Cl_2, 0 °C to rt, (b) $(MeO)_2CMe_2$, cat. PPTS, acetone, rt; (vii) (a) H_2SO_4, dioxane, H_2O, reflux, (b) Amberlite® IRA-410 (HO^-), (c) DOWEX® 1X2 (HO^-).



Scheme 26. Reagents and conditions: (i) Piv-imidazole, DMF, 60 °C, 24 h; (ii) Tf_2O, py, CH_2Cl_2; (iii) NaN_3, DMF; (iv) NaOMe, MeOH; (v) Pd/C (10%), H_2, MeOH, 12 h; (vi) $NaNO_2$, DMF.

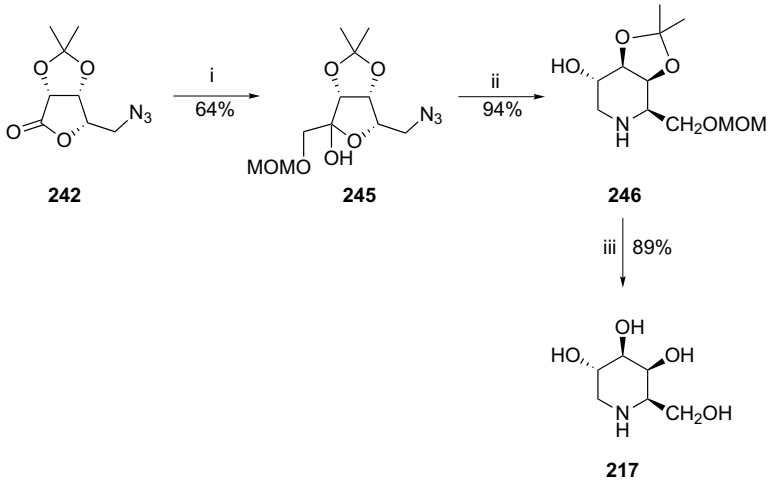


Scheme 27. Reagents and conditions: (i) TBAF, THF; (ii) *m*-CPBA, CH_2Cl_2; (iii) $BF_3{\cdot}OEt_2$, acetone, 0 °C; (iv) 6 M aq NaOH, dioxane, reflux, 24 h; (v) concd HCl, MeOH, reflux, 4 h; (vi) basic ion-exchange resin; (vii) PDC, molecular sieves 4 Å, CH_2Cl_2; (viii) L-Selectride®, $CeCl_3$, THF; (ix) *m*-CPBA, $CHCl_3$, 3 d.

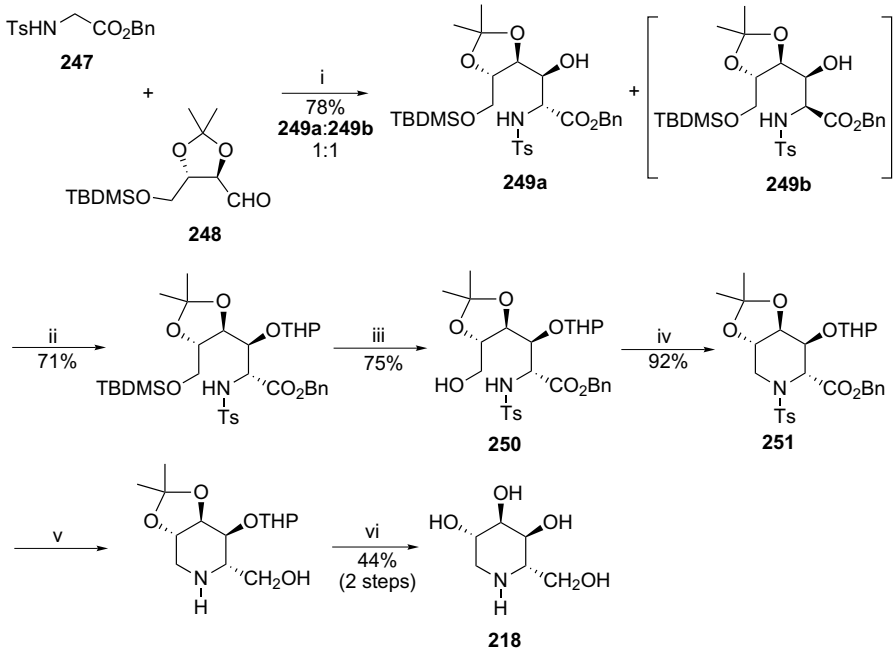
Katsumura et al. also outlined the syntheses for both 1-deoxygalactostatin **217** and 1-deoxyaltronojirimycin **218** from the key bicyclic oxazolidinylpiperidine intermediate **108** (Schemes 8 and 27).[84]

Shilvock and Fleet reported the synthesis of 1-deoxygalactostatin via a stannane mediated hydroxymethylation of 5-azido-L-lyxono-1,4-lactone **242** (Scheme 28).[116] From the transmetallation of the stannylmethanol species **243**, the hydroxymethyllithium compound **244** was derived. Nucleophilic addition to **244** gave azido lactol **245** in a 64% yield. Subsequent hydrogenation allowed the formation of the protected D-galactopiperidine **246** as a single diastereomer. Methanolic hydrogen chloride deprotection furnished azasugar **217**.

It is possible to prepare the synthetic azasugar 1-deoxyaltronojirimycin **218** by an aldol reaction of a chelated amino acid ester enolate (Scheme 29).[117] Starting from the protected amino acid glycine **247**, the aldol reaction with chiral aldehyde **248** led to the aldol product **249** in excellent β,γ-diastereoselectivity (>95% de) although the α-centre was obtained as a 1:1 epimeric mixture. The β-hydroxyl group of **249a** was protected as a THP ether, and subsequent deprotection of the primary alcohol led to compound **250**. Ring cyclisation was achieved



Scheme 28. Reagents and conditions: (i) [$LiCH_2OMOM$ **244**] (generated in situ, from Bu_3SnCH_2OMOM **243**, BuLi, THF, −78 °C); (ii) Pd, H_2, EtOH; (iii) HCl, MeOH.



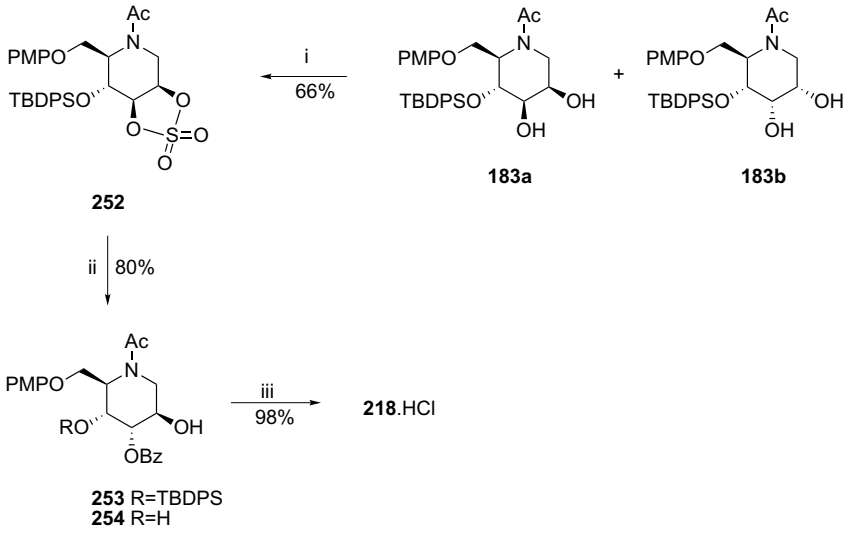
Scheme 29. Reagents and conditions: (i) LDA (2.5 equiv), $SnCl_2$ (2.5 equiv), THF, −78 °C, 30 min; (ii) DHP, CSA cat., CH_2Cl_2, 0 °C to rt, 90 min; (iii) TBAF, THF, rt, 2 h; (iv) PPh_3, DEAD, THF, rt, 30 min; (v) Red-Al®, THF, reflux, 4 h; (vi) DOWEX® 50WX8, 2 N NH_3, reflux, 1 h.

using an excess of Mitsunobu reagent and gave **251**. Subsequent reduction and deprotection steps gave rise to **218**.

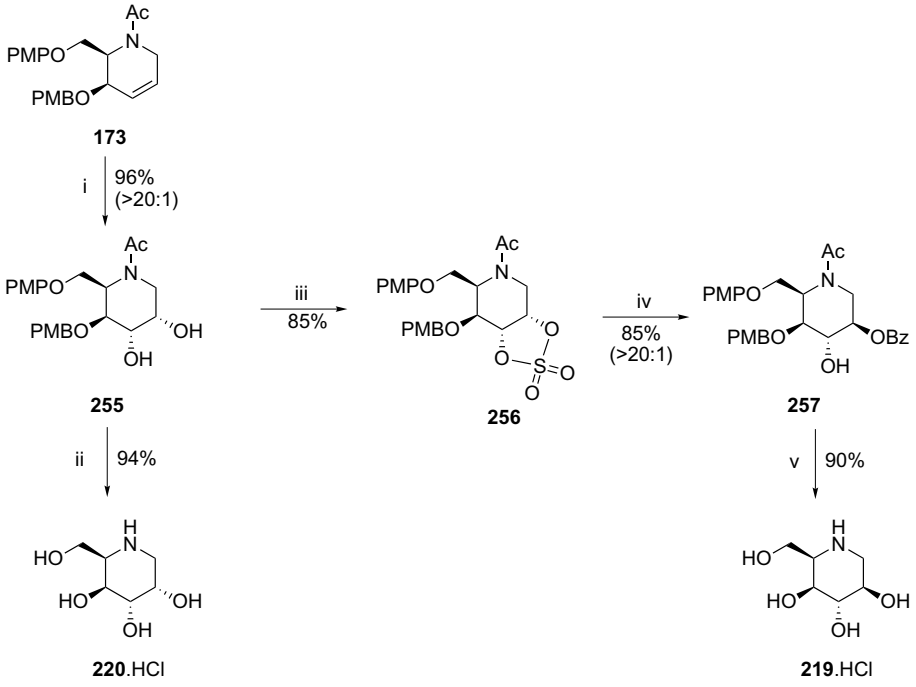
Singh and Han also demonstrated a synthesis of 1-deoxyaltronojirimycin **218** (Scheme 30).[97] The major cyclic sulfate **252** was isolated cleanly after column chromatography from the mixture of diastereoisomers **183a** and **183b** (10:1 ratio) (see Scheme 16). On subjecting **252** to ring opening, alcohol **253**, as well as the partially deprotected diol **254**, were obtained. A final deprotection by CAN and acid hydrolysis gave azasugar **218**.

7.2. The synthesis of 1-deoxyidonojirimycin and 1-deoxygulonojirimycin

The azasugars, 1-deoxygulonojirimycin **220** and 1-deoxyidonojirimycin **219** were also synthesised (Scheme 31) via the common olefin intermediate **173** (see Schemes 16 and 17).[97] Dihydroxylation of **173** furnished the deoxygulonojirimycin precursor **255** as the sole product, deprotection of which led to azasugar **220**. *trans*-Diol stereochemistry at C-2 and C-3 was introduced using cyclic sulfate chemistry. Treatment of **255** with thionyl chloride followed by oxidation using $RuCl_3$ and $NaIO_4$ gave the cyclic sulfate **256**. Using sodium benzoate, the



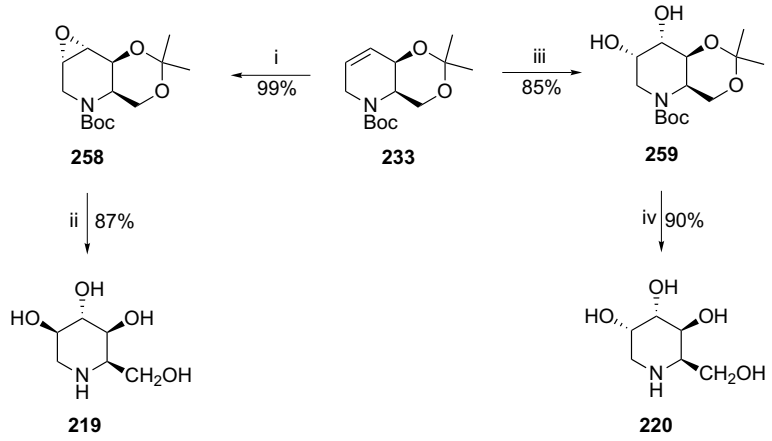
Scheme 30. Reagents and conditions: (i) $SOCl_2$, Et_3N, CH_2Cl_2, −15 °C, 30 min, then $RuCl_3$, $NaIO_4$, MeCN/CH_2Cl_2/H_2O, 25 °C, 1 h; (ii) NaOBz, DMF, 105 °C, 5 h, then 20% aq H_2SO_4/CH_2Cl_2, 12 h, 25 °C; (iii) (a) CAN, MeCN/H_2O, 0 °C, 10 min, (b) 6 N HCl, 120 °C, 12 h.



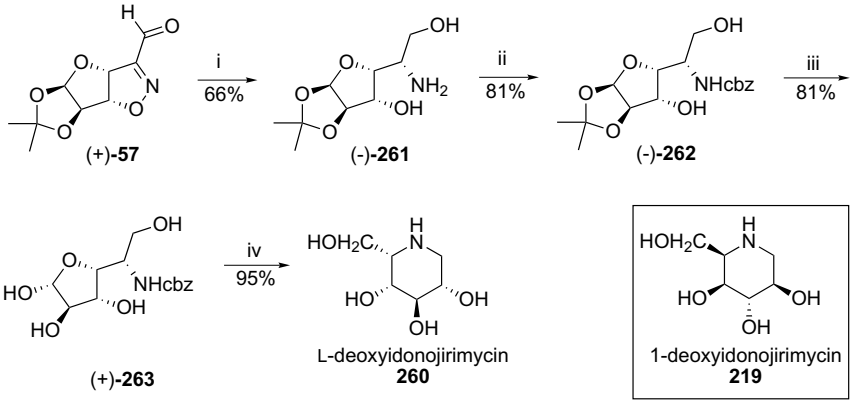
Scheme 31. Reagents and conditions: (i) OsO_4, NMO, *t*-BuOH/H_2O, 12 h; (ii) (a) $(MeO)_2CMe_2$, PPTS, CH_2Cl_2, 25 °C, 12 h, (b) CAN, MeCN/H_2O, 0 °C, 10 min, (c) 6 N HCl, 120 °C, 12 h; (iii) (a) $SOCl_2$, Et_3N, CH_2Cl_2, −15 °C, 30 min, (b) $RuCl_3$, $NaIO_4$, MeCN/CH_2Cl_2/H_2O, 25 °C, 1 h; (iv) (a) NaOBz, DMF, 105 °C, 3 h, (b) aq H_2SO_4/CH_2Cl_2, 25 °C, 12 h; (v) (a) CAN, MeCN/H_2O, 0 °C, 10 min, (b) 6 N HCl, 120 °C, 12 h.

cyclic sulfate was opened almost exclusively at C-2 (according to the *trans*-diaxial ring opening rule) due to steric influences at C-3. The resulting compound **257**, led to azasugar **219** after exhaustive deprotection methods.

Takahata et al. also demonstrated the use of their dioxanylpiperidine **233**, as a precursor for more than one azasugar.[113] Having already demonstrated the synthesis of 1-deoxygalactostatin (see Scheme 25), stereochemically controlled dihydroxylation of **233** was also shown to lead to the azasugars 1-deoxyidonojirimycin **219** and 1-deoxygulonojirimycin **220** (Scheme 32). The *anti*-epoxide **258** was generated as a single isomer by the reaction of **233** with the dioxirane generated in situ from Oxone® and 1,1,1-trifluoroacetone. Chem 3D MOPAC calculations indicated that epoxidation occurred from the less hindered convex face, the concave face being hindered by a methyl substituent. Basic cleavage of the epoxide, followed by deprotection and desalting gave azasugar **219**. Osmylation of **233**, again occurred from the convex face giving diol **259**, deprotection of which, followed by



Scheme 32. Reagents and conditions: (i) Oxone®, CF_3COCH_3, $NaHCO_3$, aq Na_2 EDTA, MeCN, 0 °C; (ii) (a) 0.3 M KOH, dioxane, H_2O, reflux; (b) 6 N HCl, MeOH, rt; (c) Amberlite® IRA-410 (HO^-); (iii) $K_2OsO_4{\cdot}2H_2O$, NMO, acetone, H_2O, rt; (iv) (a) DOWEX® 50WX8 (H^+).



Scheme 33. Reagents and conditions: (i) $LiAlH_4$, Et_2O, 25 °C, 4 d; (ii) $NaHCO_3$, cbzCl, aq EtOH, 25 °C, 1.5 h; (iii) TFA/H_2O, 4 °C, 15 h; (iv) Pd/C (10%), H_2, MeOH, 25 °C, 15 h.

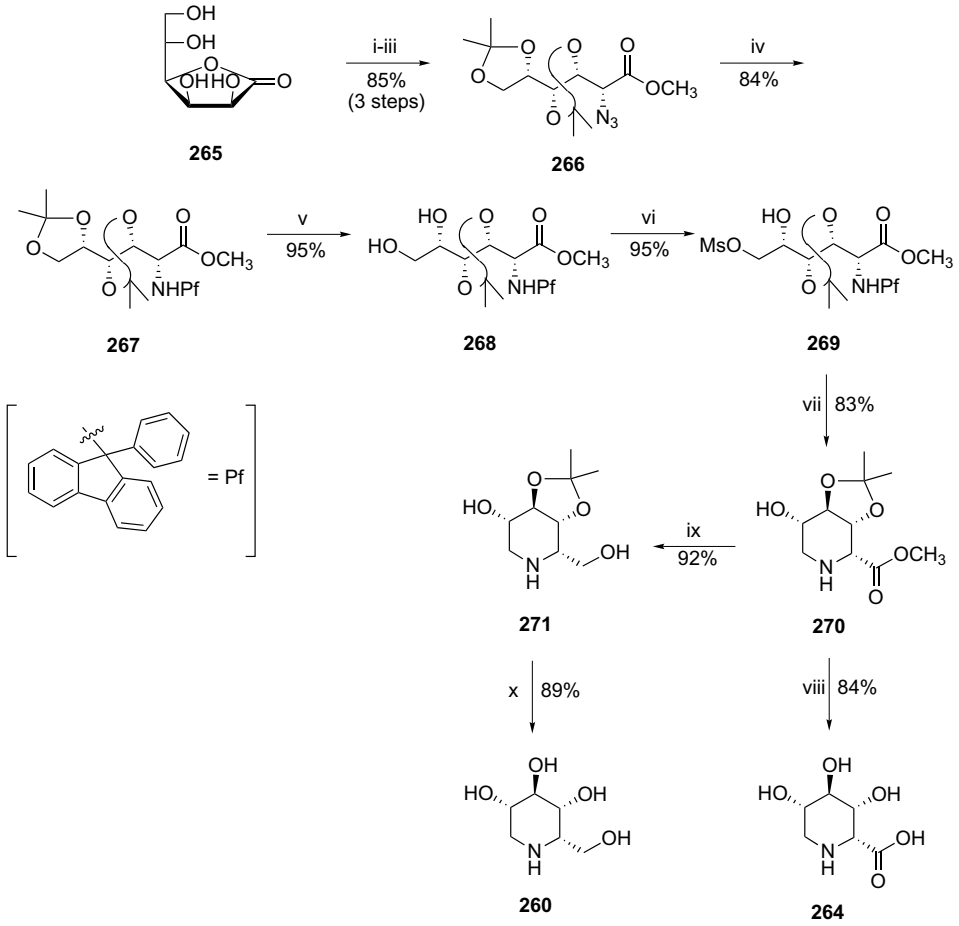
treatment with an ion-exchange resin furnished azasugar **220**.

Vogel et al. have adapted their DNJ synthesis towards the synthesis of 1-deoxyidonojirimycin **219**, and its enantiomer 1-deoxy-L-idonojirimycin **260**, utilising their enantiomerically pure aldehydes (−)-**57** and (+)-**57** (see Scheme 2).[71] From (+)-**57**, a hydride reduction led to the aminodiol (−)-**261** (Scheme 33). *N*-Protection led to carbamate (−)-**262**. Deprotection gave furanose (−)-**263** and catalytic hydrogenation furnished 1-deoxy-L-idonojirimycin **260**. The same operations with (−)-**57** produced 1-deoxyidonojirimycin **219**.

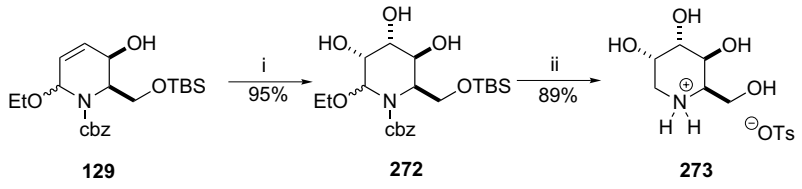
In a follow-up to the DMJ synthesis (see Scheme 18),[98] Park et al. reported the synthesis of 1-deoxy-L-idonojirimycin **260** and the acid analogue **264** (Scheme 34).[118] Starting from L-gulonic acid γ-lactone **265**, azido iodonate **266** was synthesised over three steps. The free amine was generated by catalytic hydrogenation, and then subsequently protected with 9-phenylfluoren-9-yl (Pf) bromide to give **267**. Using an ion-exchange resin (DOWEX® 50WX8 [H^+]) the isopropylidene group was selectively cleaved to furnish **268**. The primary alcohol of **268** was selectively mesylated with mesyl chloride producing **269**. Hydrogenolysis of the *N*-Pf group proceeded with intramolecular amination yielded the piperidine **270**. The resulting L-idonate **270** was readily converted to (+)-(2*R*,3*R*,4*R*,5*S*)-3,4,5-trihydroxypipecolic acid **264**. Reduction of **270** gave L-iditol **271**, which then led to azasugar **260**.

The synthesis of 1-deoxygulonojirimycin **220** was outlined by Haukaas and O'Doherty (Scheme 35).[88] Starting from the allyl alcohol **129** (see Scheme 10), triol **272** was achieved by osmylation. Hydrogenolysis, followed by treatment with *p*-toluene sulfonic acid monohydrate led to the characterisable tosylate salt (**273**) of 1-deoxygulonojirimycin.

Independently, Liao et al. reported a similar synthesis of 1-deoxygulonojirimycin via the allyl alcohol **274** (Scheme 36).[119] $NaBH_4$ reduction of the protected compound **275** yielded **276** in an 86% yield. Sharpless asymmetric dihydroxylation however led to a mixture of diols **277**, acetylation of which gave compounds **278** and **279** (4:1, respectively). Deprotection of the major isomer led to 1-deoxygulonojirimycin **220**. [Deprotection of the minor isomer gave 1-deoxytalonojirimycin **221** (46% from **279**). For further **221** syntheses see Section 7.3.]



Scheme 34. Reagents and conditions: (i) $(MeO)_2CMe_2$, TsOH, acetone, MeOH, rt, 7 h; (ii) py, Tf_2O, CH_2Cl_2, −15 °C, 10 min; (iii) NaN_3, DMF, rt, 1 h; (iv) (a) Pd/C (10%), H_2, EtOAc, rt, 5 h, (b) PfBr, $Pb(NO_3)_2$, Et_3N, CH_2Cl_2, rt, 48 h; (v) DOWEX® 50WX8, MeOH, rt, 20 h; (vi) MsCl, Et_3N, CH_2Cl_2, 40 °C, 10 min; (vii) Pd/C (10%), H_2, NaOAc, MeOH, 40 °C to reflux, 14 h; (viii) DOWEX® 50WX8, THF, H_2O, reflux, 9 h; (ix) $LiAlH_4$, THF, 0 °C, 10 min; (x) DOWEX® 50WX8, THF, H_2O, reflux, 3 h.

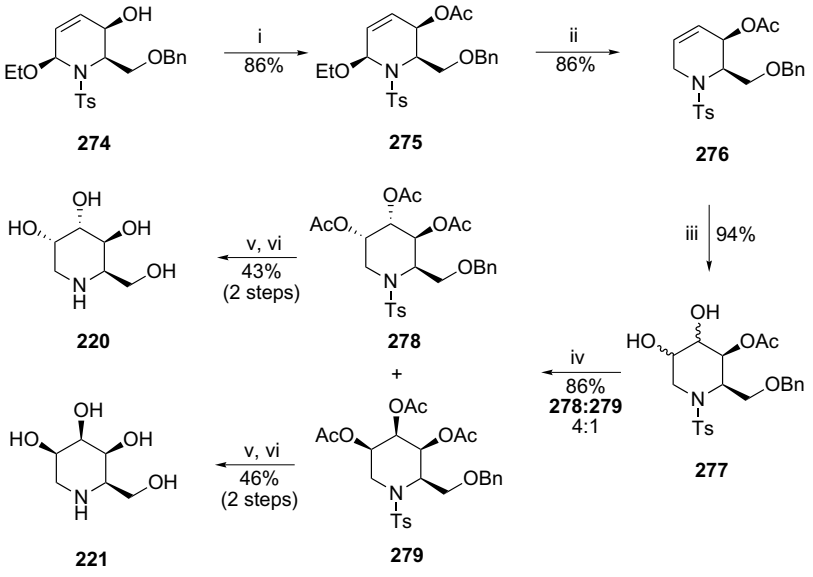


Scheme 35. Reagents and conditions: (i) OsO_4, NMO, CH_2Cl_2, 0 °C, 12 h; (ii) (a) Pd/C (10%), H_2, MeOH, rt, 12 h, (b) $TsOH{\cdot}H_2O$, MeOH, rt, 3 h.

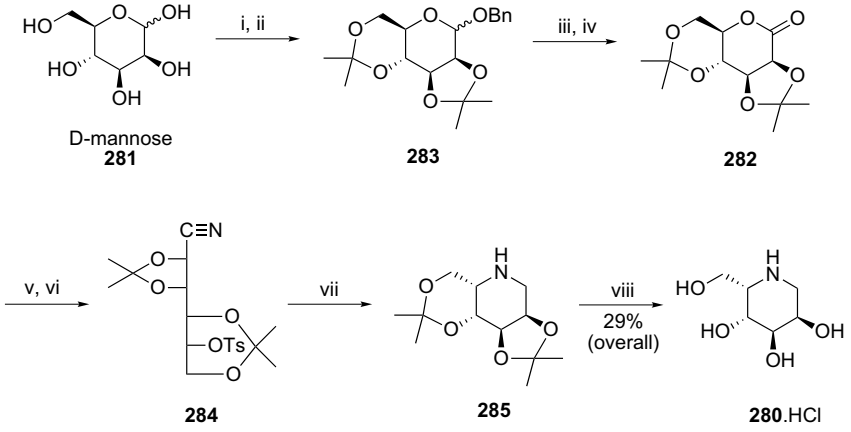
An interesting synthesis of 1-deoxy-L-gulonojirimycin **280** was developed by Chittenden et al. starting from the monosaccharide D-mannose **281** (Scheme 37).[120] To obtain the known lactone **282**, product **283** was debenzylated and oxidised. Treatment of **282** with ammonia in methanol, followed by treatment with *p*-toluenesulfonyl chloride led to derivative **284**. The protected aza-sugar **285** was obtained from concomitant cyclisation obtained after $LiAlH_4$ reduction of species **284**. Acidic hydrolysis then afforded **280**.

Altenbach et al. have also reported a (±)-1-deoxygulonojirimycin **220** synthesis from their synthetically useful aza-analogue of *iso*-levoglucosenone (±)-**286**.[121] Starting from the well-known furyl-glycine **287**, *N*-tosylation followed by reduction gave amino alcohol **288**. Treatment with NBS, resulted in oxidative ring expansion yielding dihydropyridone **289** with complete diastereoselective control. A catalytic amount of TsOH in benzene under reflux gave the desired bicyclic acetal (±)-**286** (Scheme 38).

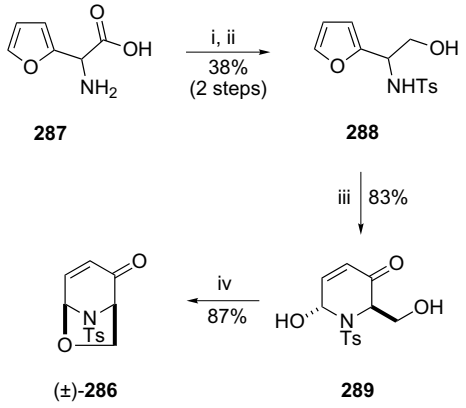
Reduction of (±)-**286** under Luche conditions with $NaBH_4$ and $CeCl_3$ led to allylic alcohol **290** as the main product with $NaBH_4$ reduction occurring from the less hindered face. Alcohol protection followed by *cis*-dihydroxylation furnished diastereomer **291**, exclusively. Cleavage of the aminal was achieved by reductive



Scheme 36. Reagents and conditions: (i) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 0 °C, 2 h; (ii) $NaBH_4$, HCO_2H, 0 °C; (iii) $K_2OsO_4{\cdot}2H_2O$, $(DHQD)_2PHAL$, $K_3Fe(CN)_6$, K_2CO_3, *t*-BuOH/H_2O, 0 °C; (iv) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 0 °C, 2 h; (v) Pd/C, H_2, EtOAc, rt; 4 h; (vi) Na/NH_3 (l), −78 °C, 4 h.

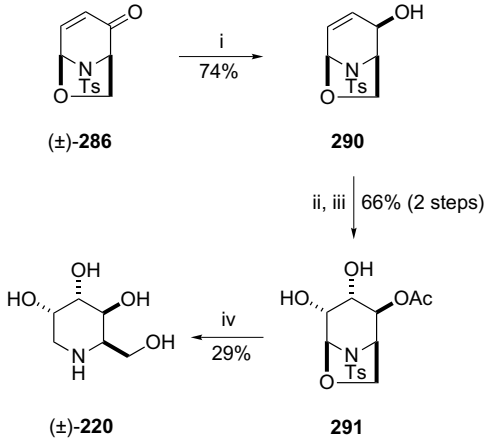


Scheme 37. Reagents and conditions: (i) $BnOH{\cdot}BF_3$, MeOH; (ii) $(MeO)_2CMe_2$/acetone, TsOH; (iii) Pd/C (10%), H_2; (iv) DMSO/TFA, CH_2Cl_2; (v) NH_3/NH_4OH, MeOH; (vi) TsCl, py; (vii) $LiAlH_4$, H_2, DME, 0 °C; (viii) HCl.

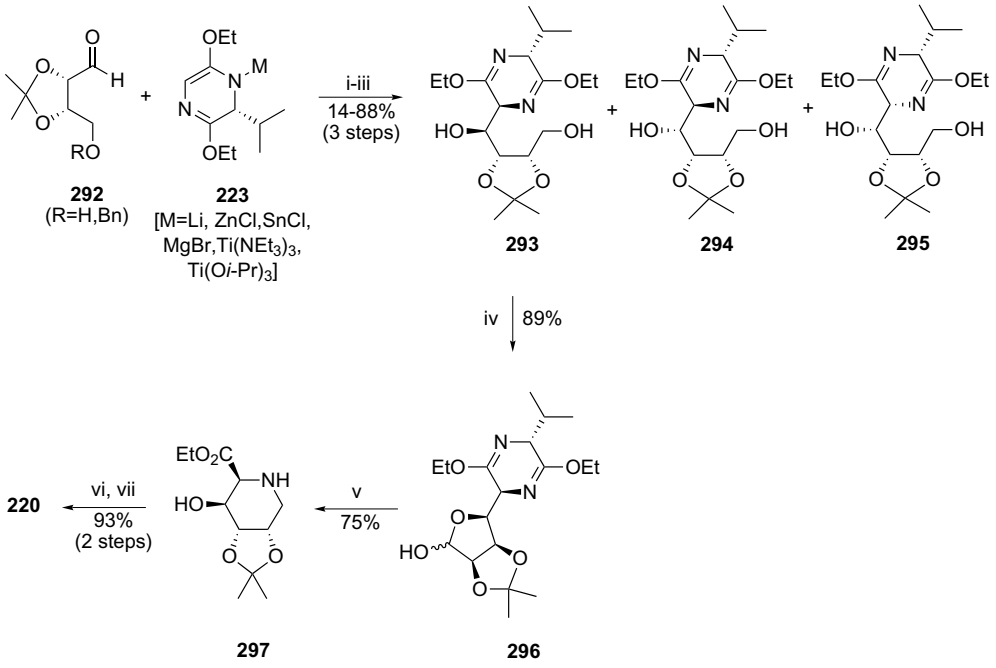


Scheme 38. Reagents and conditions: (i) *i*-Pr_2NEt, TsCl, 8 h, rt; (ii) $LiAlH_4$; (iii) NBS, 0 °C, 4 h; (iv) TsOH, benzene, reflux, 30 min.

removal of the amino protecting group with Red-Al®, yielding azasugar (±)-**220** (Scheme 39).



Scheme 39. Reagents and conditions: (i) (a) MeOH, $CeCl_3$, $NaBH_4$, (b) H_2O; (ii) Ac_2O, DMAP, 2 h; (iii) (a) $RuCl_3$, $NaIO_4$, MeCN, 10 min, (b) $Na_2S_2O_3$; (iv) (a) Red-Al®, DME, reflux, 24 h, (b) HCl, H_2O, (c) DOWEX® 50X8.



Scheme 40. Reagents and conditions: (i) THF, −78 °C, 2 h; or THF, −78 to 0 °C, 12 h; (ii) NH_4Cl or phosphate buffer; (iii) Pd/C, H_2, THF, rt, 6 h; (iv) *o*-iodobenzoic acid, DMSO/THF, 8 °C, 24 h; (v) 0.25 M HCl/EtOH, H_2, Pd/C, rt, 3 h; (vi) $LiBHEt_3$, THF, rt, 5 h; (vii) DOWEX® (H^+).

As a follow up to the 1-deoxygalactostatin synthesis (see Scheme 24),[112] Ruiz et al. demonstrated the synthesis of enantiopure 1-deoxygulonojirimycin **220** and other isomers (see Section 7.3). Using their established chemistry, aldol addition of azaenolate **223** to 2,3-*O*-isopropylidene-L-erythrose **292** led to the polyhydroxylated amino acid precursors **293**, **294** and **295** (Scheme 40).[122] The selectivity of the diastereomers can be varied depending on the substituents (M and/or R) used. To form the gulo-azasugar, chemoselective oxidation of **293** led to the γ-lactol **296**. Selective hydrolysis of the bis-lactim ether followed by intramolecular reductive amination gave piperidine **297**. This was converted to the azasugar **220** in 93% yield.

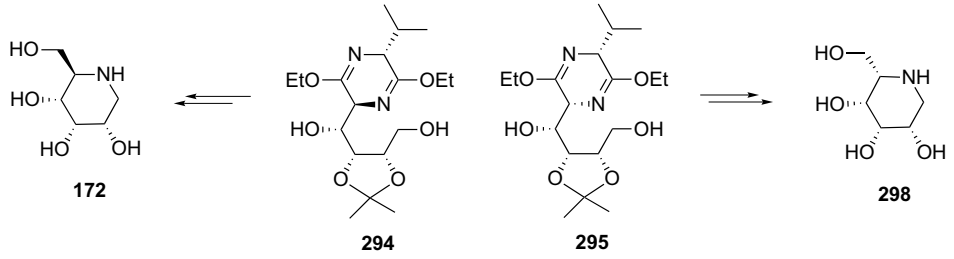
7.3. The synthesis of 1-deoxytalonojirimycin and 1-deoxyallonojirimycin

From the other two polyhydroxylated amino acid adducts previously described (**294** and **295**, Scheme 40).[112,122] Ruiz et al. conveniently formed the azasugars 1-deoxyallonojirimycin **172** and 1-deoxy-L-talonojirimycin **298** (the enantiomer of 1-deoxytalonojirimycin **221**) according to the previously described method (Scheme 41). In a separate paper, Ruiz et al. describe a diastereoselective (>95% de) route to 1-deoxytalonojirimycin **221**, utilising the D-erythrose derivative **299** and the *bis*-lactim ether **223** (Scheme 42).[123] 1-Deoxytalonojirimycin **221**, was synthesised in a total yield of 38%, via the γ-lactam **300** after deprotection of **301**.

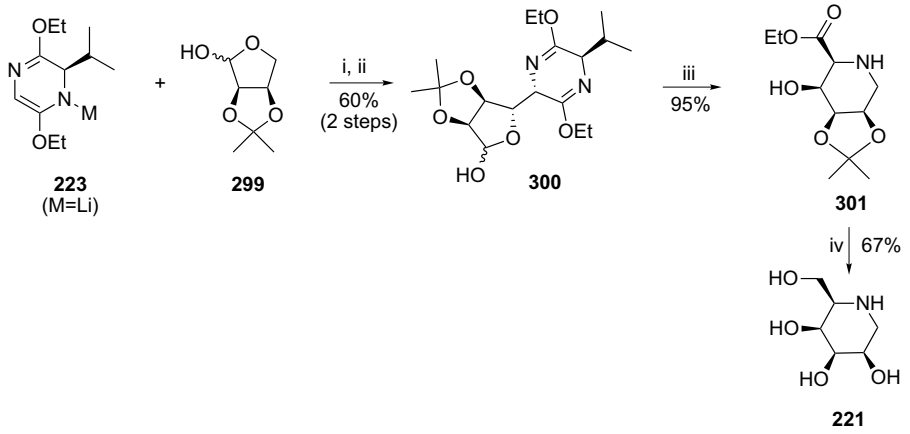
8. The synthesis of dideoxyazasugar analogues

8.1. 1,3-Dideoxyazasugars and 1,2-dideoxyazasugars (fagomine)

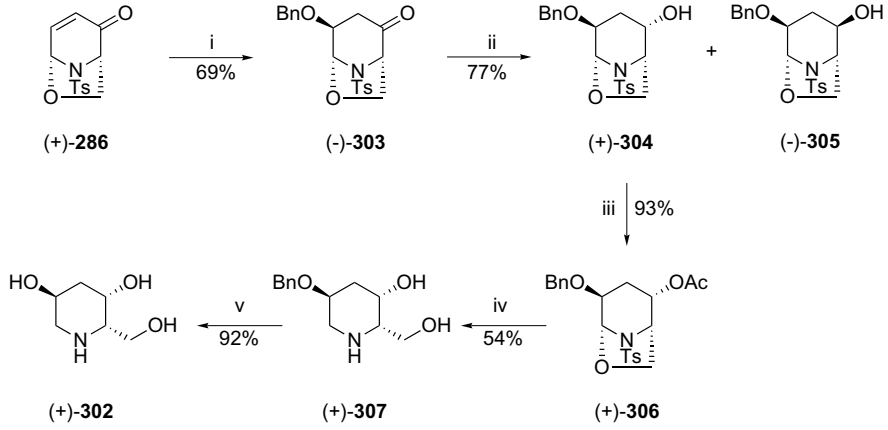
The synthesis of 1,3-dideoxyazasugars have scarcely been described.[124] From the aza-analogue of *iso*-levoglucosenone (+)-**286** (Scheme 38), Altenbach et al. have demonstrated the synthesis of (+)-1,3-dideoxygulonojirimycin **302** (Scheme 43).[121] Treatment of (+)-**286** with benzyl alcohol in the presence of triethylamine gave (−)-**303** via Michael addition from the less hindered face. Reduction under Luche conditions resulted in a mixture of diastereoisomers (+)-**304** and (−)-**305** in a 5.2:1 ratio. Protection of the free alcohol of (+)-**304** gave (+)-**306** in 93% yield. Aminal cleavage was readily



Scheme 41.



Scheme 42. Reagents and conditions: (i) (a) THF, −78 to 10 °C, 5 h, (b) aq NH_4Cl; (ii) *o*-iodobenzoic acid, DMSO/THF, 8 °C, 24 h; (iii) 0.25 M HCl, Pd/C, H_2, EtOH, rt, 3 h; (iv) (a) $LiBHEt_3$, THF, rt, 5 h, (b) DOWEX® (H^+).



Scheme 43. Reagents and conditions: (i) BnOH, Et_3N, 24 h; (ii) (a) $CeCl_3{\cdot}7H_2O$, MeOH, −5 °C, (b) aq HCl; (iii) Ac_2O, DMAP, 2 h; (iv) (a) Red-Al®, DME, reflux, 24 h, (b) aq HCl, (c) DOWEX® 50X8; (v) Pd/C (10%), H_2, 24 h.

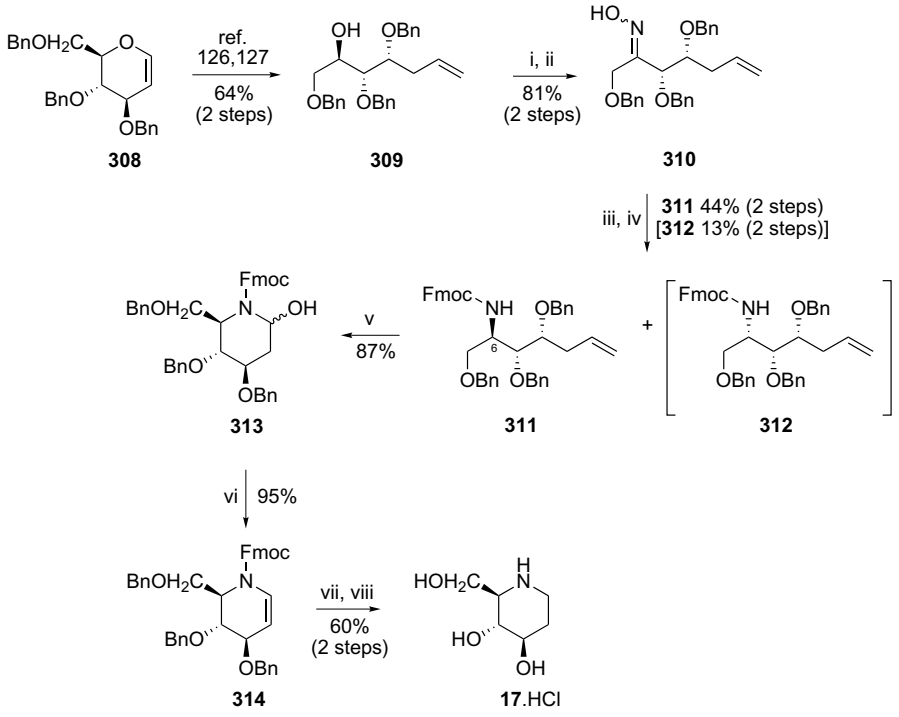
achieved to give (+)-**307**, debenzylation of which yielded (+)-**302**. For further syntheses of 1,3-dideoxyazasugars see Scheme 66.

Fagomines are a family of naturally occurring 1,2-dideoxyazasugars. The synthesis of fagomine **17** was reported by Shipman et al. starting from tri-*O*-benzyl-D-glucal **308** (Scheme 44).[125] Alkene **309** was prepared over two steps according to reported procedures.[126,127] The free alcohol was successfully converted to oxime **310** via oxidation with tetra-*n*-propylammonium perruthenate (TPAP) followed by treatment with hydroxylamine hydrochloride. Lithium aluminium hydride reduction proceeded with a 2.5:1 selectivity in favour of the required (6*R*)-diastereomer. After *N*-protection, the two isomers, **311** and **312** were separated. Compound **311** cyclised to give **313** upon ozonolysis in good yield (87%). Imino glucal **314** was formed upon treatment of **313** with oxalyl chloride. Reduction of the olefin and subsequent deprotection gave fagomine **17** in 60% yield from **314**.

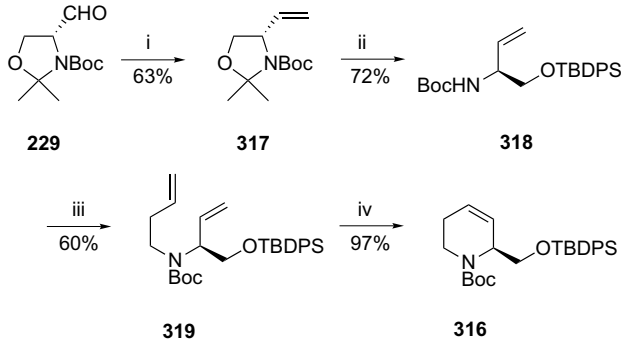
The synthesis of fagomine **17**, 3-*epi*fagomine **18**, 3,4-di*epi*fagomine **19** and the non-naturally occurring 4-*epi*fagomine (1,2-dideoxygalactostatin) **315** was reported by Takahata et al., from the common intermediate **316** (Scheme 46).[128,129] Synthesis of **316** started from the Garner aldehyde **229** (Scheme 45). A Wittig reaction furnished olefin **317**, which was readily converted to **318** via hydrolysis followed by subsequent *O*-silylation. *N*-Alkylation of **318** with 4-bromo-1-butene was best achieved via an *N*-deprotection, alkylation, *N*-protection sequence affording **319**. An RCM of **319** using Grubbs' catalyst gave the desired intermediate **316**.

Epoxidation of **316** was achieved using a dioxirane generated in situ from Oxone® and 1,1,1-trifluoroacetone to give the separable stereoisomeric epoxides **320** and **321** in a 2:1 ratio. Acid hydrolysis of **320** gave fagomine **17** as a single product. Basic cleavage of **321** using a mixture of KOH/dioxane/water gave 3,4-di*epi*fagomine **19** preferentially (**17**:**19**, 1:5 ratio).

3-*epi*Fagomine **18** was obtained stereoselectively from the treatment of **316** with $K_2OsO_4{\cdot}2H_2O$ and 4-methylmorpholine *N*-oxide, where dihydroxylation occurred exclusively from the *anti* side of the siloxymethyl substituent. Subsequent deprotection of the resulting diol



Scheme 44. Reagents and conditions: (i) TPAP, NMO, CH_2Cl_2, 4 Å molecular sieves; (ii) $NH_2OH{\cdot}HCl$, py, EtOH, 60 °C; (iii) $LiAlH_4$, Et_2O; (iv) FmocCl, K_2CO_3, THF/H_2O, 0 °C; (v) O_3, CH_2Cl_2, −78 °C then PPh_3; (vi) $(COCl)_2$, CH_2Cl_2, DMF; (vii) Pd/C, H_2, morpholine, EtOH; (viii) Pd/C, H_2, HCl, EtOH.



Scheme 45. Reagents and conditions: (i) Ph_3PCH_3I, $NaN(TMS)_2$, THF; (ii) (a) $TsOH{\cdot}H_2O$, MeOH, (b) TBDPSCl, DMAP, imidazole, CH_2Cl_2; (iii) (a) TFA, CH_2Cl_2, (b) 4-bromo-1-butene, K_2CO_3, MeCN, (c) $(Boc)_2O$, Et_3N, THF; (iv) Grubbs' cat., CH_2Cl_2.

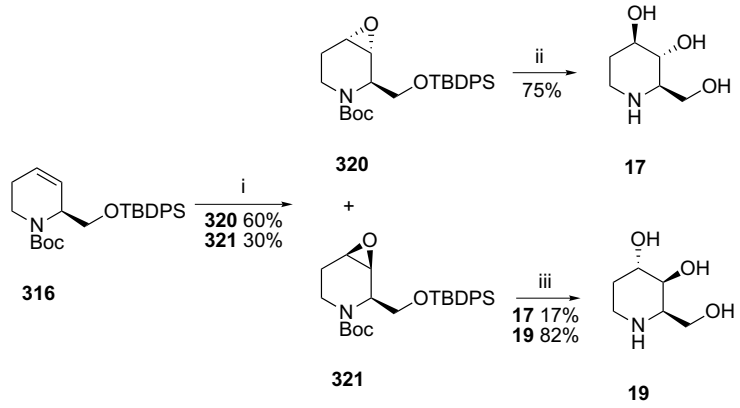
322 furnished **18** in good yield (84% from **316**). Interestingly, a *syn* directed dihydroxylation of compound **323** was achieved using an OsO_4/TMEDA complex. Dihydroxylation of the homoallylic alcohol was achieved with moderate selectivity (2:1 ratio). *N*-Deprotection under acidic conditions gave 4-*epi*fagomine **315** (Scheme 47).

8.2. 1,6-Dideoxyazasugars (rhamnojirimycin and fuconojirimycin analogues)

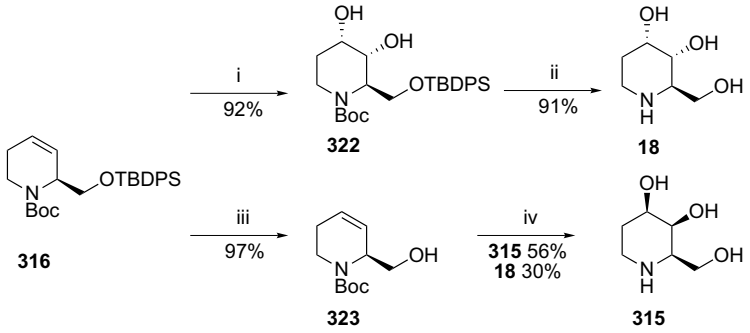
There have been many reports on the synthesis of DNJ and its analogues, however synthetic procedures towards the synthesis of 1,6-dideoxyazasugars have scarcely been described. The preparation of 1,6-dideoxy-DNJ **324** and 1,6-dideoxy-galactostatin **325** have been described by Pistia and Hollingsworth (Scheme 48).[130] From the tetraacetate of methyl β-D-glucopyranoside **326**, the corresponding keto-ester **327** was formed by a selective oxidation using CrO_3 as oxidant. A reduction of the oxime to the lactam was best achieved using the more nucleophilic hydroxylamine, furnishing **328** as a mixture of *syn* and *anti* isomers. Under hydrogenolysis conditions, reduction of the lactam was achieved followed by immediate cyclisation led to δ-lactam **329**. Under these conditions, the cleavage of the acetoxy group to form a 6-deoxy function was also achieved. The reduction was also selective giving none of the L-isomer despite being a mixture of *syn* and *anti* oximes. Reduction and deacetylation with borane furnished the azasugar. The same procedure with the tetraacetate of methyl β-D-galactopyranoside **330** gave **325**.

L-Rhamnojirimycin (LRJ) **331** is the aza-analogue of L-rhamnose. A very similar approach to the one used in the synthesis of 1-deoxy-L-mannonojirimycin **112** (see Scheme 9) was used by Meyers et al. towards the synthesis of LRJ (Scheme 49).[86] Starting from the known bicyclic lactam **332**, oxidation at the allylic position using SeO_2 gave alcohol **333** as a single diastereomer. Treatment with OsO_4 afforded the triol, the *syn* hydroxyl group of which was protected as the acetonide **334**. Again, BH_3 reduction gave piperidine **335** with good stereoselectivity at the C-2 angular position (20:1 ratio). Deprotection steps led to LRJ **331**.

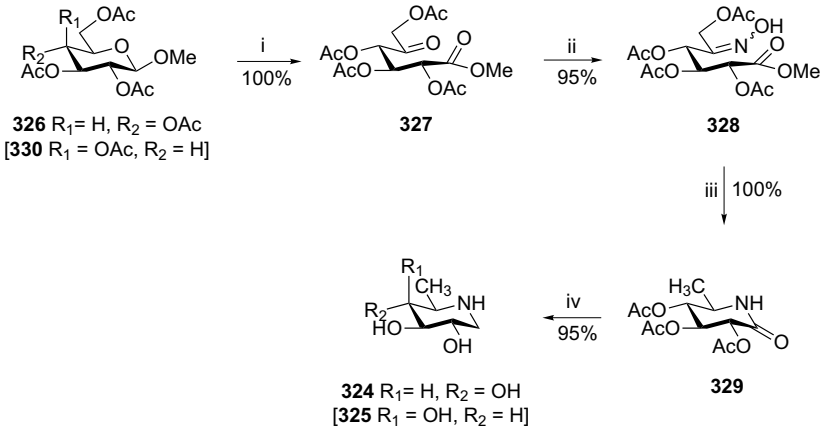
Fleet et al. described the synthesis of the potent inhibitor of α-L-rhamnosidase, 5-*epi*-deoxyrhamnojirimycin **53**



Scheme 46. Reagents and conditions: (i) Oxone®, CF_3COCH_3, $NaHCO_3$, aq Na_2EDTA, MeCN; (ii) H_2SO_4, dioxane, H_2O; (iii) KOH, dioxane, H_2O.



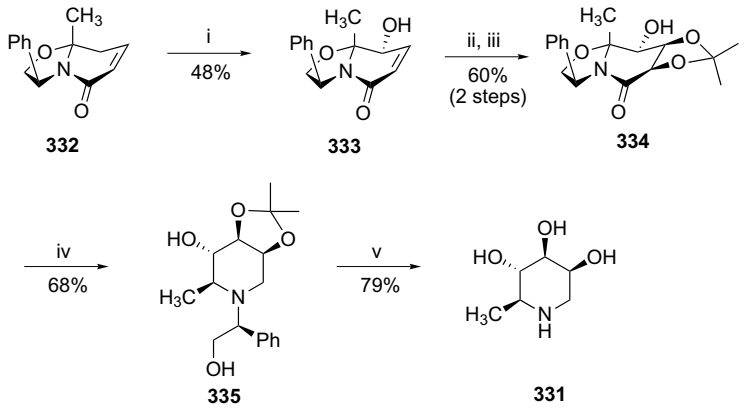
Scheme 47. Reagents and conditions: (i) $K_2OsO_4{\cdot}2H_2O$, NMO, H_2O, acetone; (ii) 10% aq HCl, dioxane; (iii) TBAF, THF; (iv) (a) OsO_4, TMEDA, CH_2Cl_2, (b) 35% HCl, MeOH.



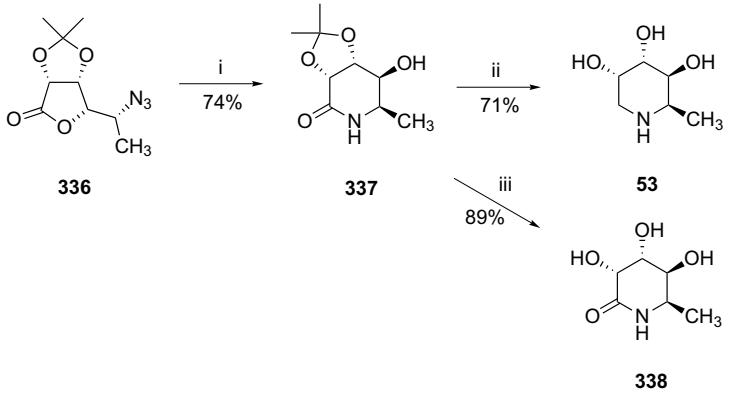
Scheme 48. Reagents and conditions: (i) CrO_3, Ac_2O, AcOH, 50 °C, 2 h; (ii) $NH_2OH{\cdot}HCl$, py, 0 °C to rt, 2 h; (iii) Pd/C (10%), H_2 (300–400 psi), AcOH, 55 °C, 40 h; (iv) (a) 1 M $BH_3{\cdot}THF$, THF, rt to reflux, 3 h, (b) HCl, MeOH, reflux, 30 min.

(Scheme 50).[131] Compound **336**, a homologue of azide **242** (see Scheme 28), was converted to lactam **337** by cyclisation after hydrogenation. One pot treatment with borane followed by methanolic hydrogen chloride allowed both reduction and acetonide deprotection furnishing **53**. Lactam **338**, formed from the deprotection of **337**, is also a potential glycosidase inhibitor (see Section 10.2).

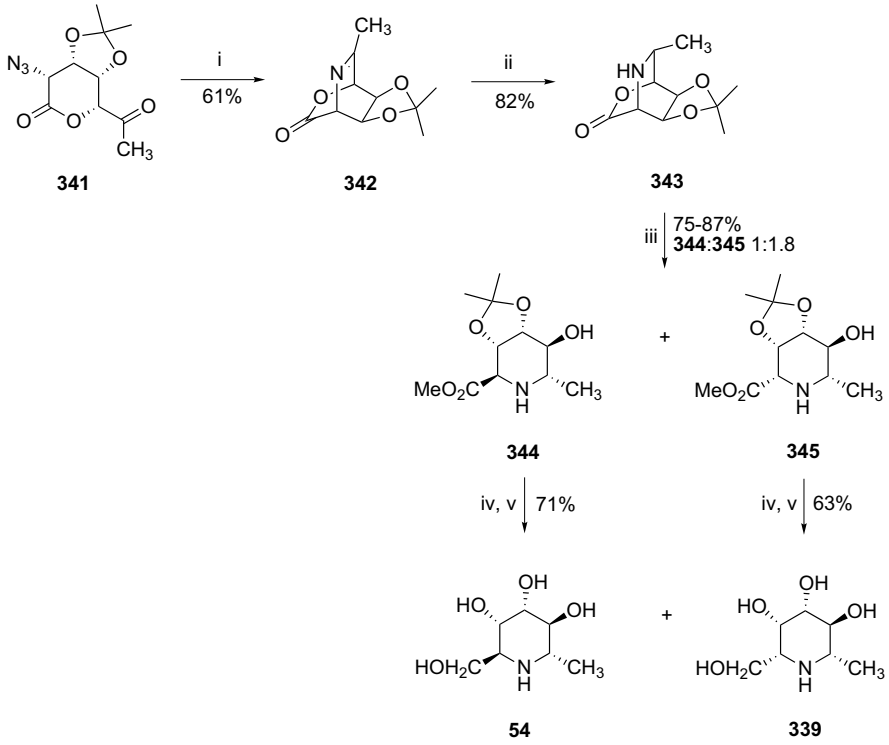
In the search for more potent L-rhamnosidase inhibitors, Fleet also described a synthesis for the homorhamnojirimycin-type (HRJ) analogues **54**, **339** and **340** (Schemes 51 and 52).[132] The azido-ketone **341**, a similar azido-ketone to **206** (see Scheme 22) was treated with triethyl phosphite. The product of the aza-Wittig reaction was the bicyclic imine **342**. A stereoselective reduction gave bicyclic amino lactone **343**, from which



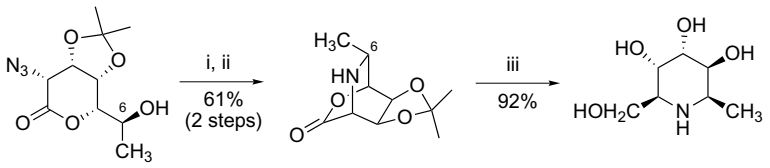
Scheme 49. Reagents and conditions: (i) SeO_2, dioxane, reflux; (ii) OsO_4, NMO, aq acetone; (iii) $(MeO)_2CMe_2$, CH_2Cl_2, TsOH; (iv) BH_3, THF, reflux; (v) (a) Pd/C, H_2, MeOH, (b) TFA, MeOH.



Scheme 50. Reagents and conditions: (i) Pd/C (10%), H_2, MeOH; (ii) (a) $Me_2S.BH_3$/THF, (b) HCl, EtOH; (iii) TFA/H_2O.



Scheme 51. Reagents and conditions: (i) $P(OEt)_3$, THF, reflux; (ii) $NaBH_3CN$, AcOH; (iii) NaOAc, MeOH, reflux; (iv) $LiBHEt_3$, THF; (v) HCl, MeOH.



Scheme 52. Reagents and conditions: (i) Tf_2O, py, CH_2Cl_2, −20 °C; (ii) Pd, H_2, NaOAc, EtOAc; (iii) (a) $LiBH_4$, THF, (b) HCl.

54 and **339** were accessed via their corresponding methyl esters **344** and **345**. The synthesis of the HRJ analogue of 5-*epi*-L-rhamnopyranose **340** was achieved starting from azido-ketone **346**. To achieve the inversion of configuration at C-6, **346** was treated with trifluoromethanesulfonic anhydride to give an azide-triflate, hydrogenation of which yielded the cyclised bicyclic amino lactone **347**. A ring opening/reduction led to **340** with a 92% yield (Scheme 52).

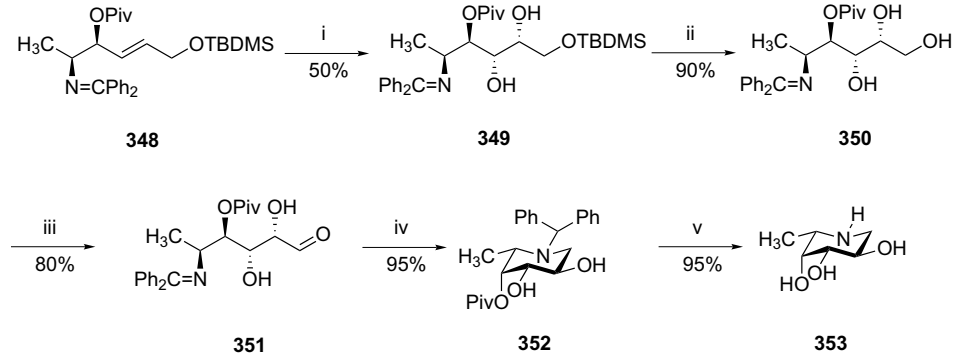
The synthesis of an aza-analogue of L-fucose has been reported by Polt et al.[133] Starting from compound **348** (Scheme 53), diol **349** was obtained after osmylation. Desilylation of **349** gave triol **350**, which was oxidised by a TEMPO/NaOCl system to the fucose derivative **351**. Imine reduction proceeded with cyclisation to furnish piperidine **352**. Deprotection of the pivalate followed by hydrogenolysis yielded L-fuco-1-deoxynojirimycin **353**.

A method has also been developed towards the homologue of **353**. Fleet et al. reported that α-homofuconojiimycin **354** is the most powerful inhibitor of fucosidases (Scheme 54).[134] Azidolactol **355** (derived from L-gulonolactone) was the key intermediate used, the hydrogenation of which gave the equilibrium mixture of hemiaminal **356** and imine **357**. Hydrogenation in the presence of Adam's catalyst, followed by acid hydrolysis furnished the inhibitor **354**.

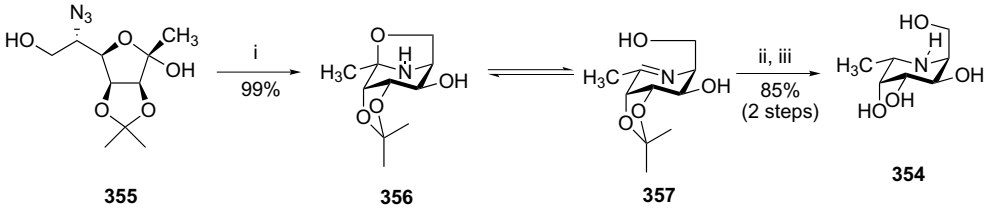
9. The synthesis of homoazasugar analogues

9.1. Homogalactonojirimycin and related analogues

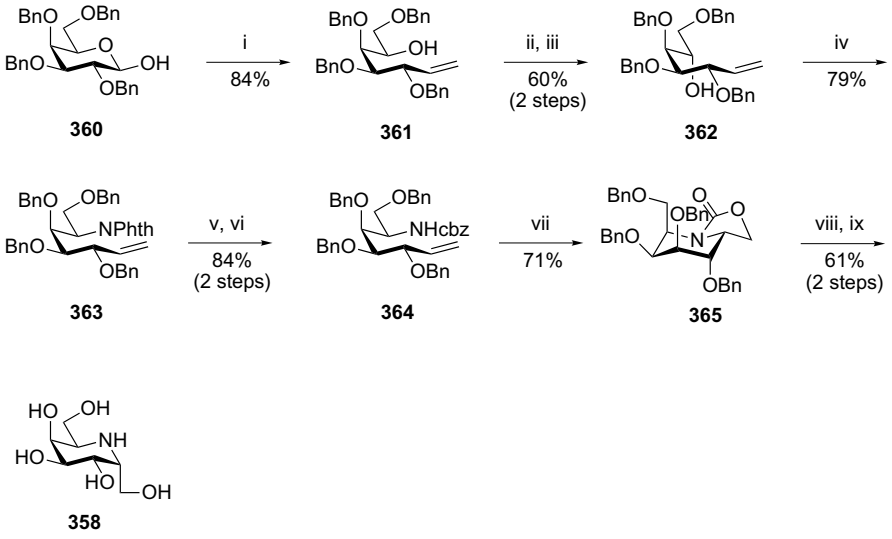
One modification of the archetypal azasugar motif is the addition of a hydroxymethylene group at the anomeric position. A number of such homoazasugars are naturally occurring (see Section 6) but they also have received particular attention due to the potential enzyme specificity that they invoke. The preparation of the synthetic homoazasugars, α-homogalactonojirimycin (α-HGJ) and β-homogalactonojirimycin (β-HGJ) **358** and **359**, respectively, have been described by Martin et al. (Schemes 55 and 56).[135] Starting from tetra-*O*-benzyl-D-galactopyranoside **360**, the corresponding heptenitol



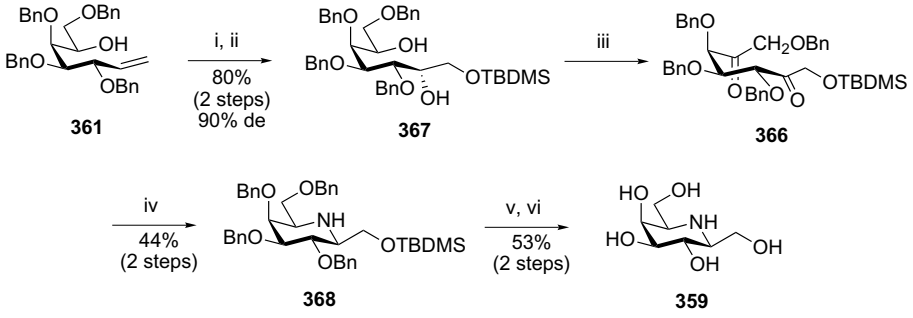
Scheme 53. Reagents and conditions: (i) $K_2OsO_4{\cdot}2H_2O$, $K_3Fe(CN)_6$, $MeSO_2NH_2$ (additive), *t*-BuOH/H_2O, rt; (ii) TBAF, THF, rt, 3 h; (iii) TEMPO, NaOCl, CH_2Cl_2, −5 °C, 15 min; (iv) $NaBH_3CN$, MeCN/AcOH, rt, 10 min; (v) (a) *n*-Bu_4NOH, dioxane, 0 °C, (b) Pd/C (5%), H_2, MeOH, EtOAc, rt, 3 h.



Scheme 54. Reagents and conditions: (i) Pd/C, H_2, EtOH; (ii) PtO_2, H_2, EtOH; (iii) TFA, H_2O.



Scheme 55. Reagents and conditions: (i) Ph_3PCH_3Br, *n*-BuLi, toluene, rt, 2 h; (ii) PPh_3, 4-nitrobenzoic acid, DEAD, THF, rt, 12 h; (iii) (a) NaOMe, MeOH, rt, 5 h, (b) Amberlite® IR-120 (H^+); (iv) PPh_3, phthalamide (Phth), DEAD, THF, rt, 12 h; (v) $NH_2NH_2{\cdot}H_2O$, MeOH, 70 °C, 1 h; (vi) cbzCl, THF, 0 °C 1 h; (vii) (a) $(TFA)_2$ Hg, THF, rt, 48 h, (b) I_2, THF, rt, 45 min; (viii) Pd/C (10%), H_2 (90 psi), AcOH/EtOH, 50 °C, 12 h; (ix) (a) aq KOH, rt to 60 °C, 14 h, (b) Amberlite® IR-120 (H^+).

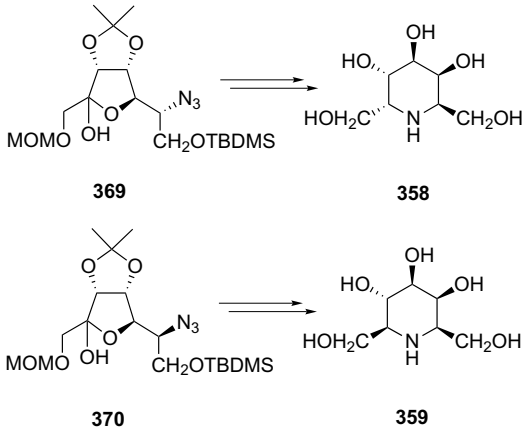


Scheme 56. Reagents and conditions: (i) OsO_4, NMO, acetone/H_2O, rt, 14 h; (ii) DMAP, Et_3N, TBDMSCl, rt, 1 h; (iii) $(COCl)_2$, DMSO, −78 °C to rt, 2 h; (iv) HCO_2NH_4, molecular sieves 3 Å, $NaBH_3CN$, MeOH, rt, 1 h; (v) AcOH, THF/H_2O, 55 °C, 12 h; (vi) (a) TMSI, CH_2Cl_2, 0 °C to rt, 12 h, (b) DOWEX® 1X2-200 (HO^-), H_2O.

361 was produced. Compound **361**, was first subjected to a Mitsunobu inversion of the free alcohol to afford **362** which then underwent a nucleophilic displacement under Mitsunobu conditions to afford D-galacto amino heptenitol derivative **363**. Exchange of the amine protecting groups led to benzoylcarbonyl derivative **364**, which was subjected to an intra-amidomercuration using mercury(II) acetate. Iododemercuration led to the cyclic carbamate **365**, from which α-HGJ **358** was derived.

Compound **361** was also used in the synthesis of β-HGJ **359**, from which diketone **366** was formed via diol **367**. A double reductive amination led to a single piperidine derivative **368**, from which **359** was obtained (Scheme 56).

Shilvock and Fleet also demonstrated the synthesis of 2,6-iminoheptitols via their hydrogenation of the azidolactol chemistry previously demonstrated (see Schemes 22 and 47).[116,136] α-HGJ **358** was acquired from azido lactol **369**. The β-HGJ **359** was derived from its epimer **370** (Scheme 57).

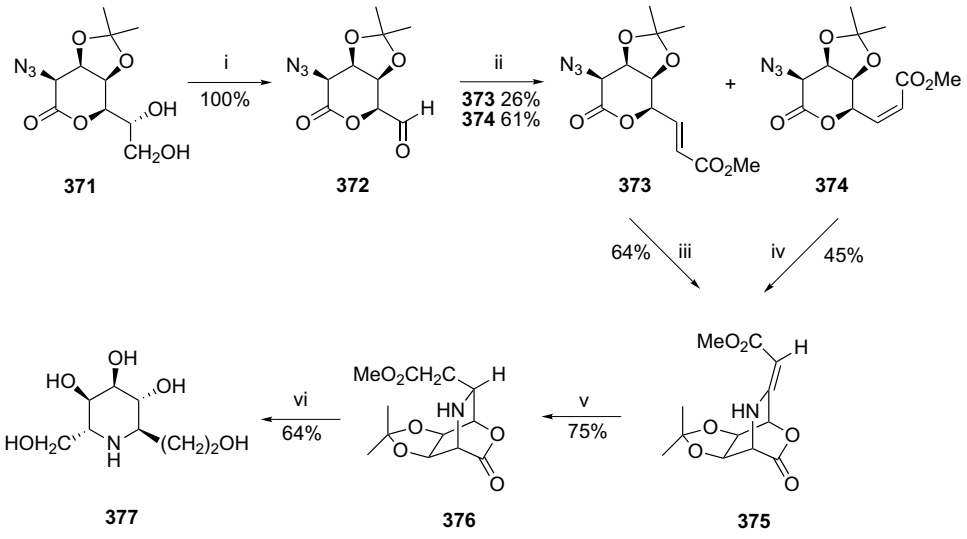


Scheme 57.

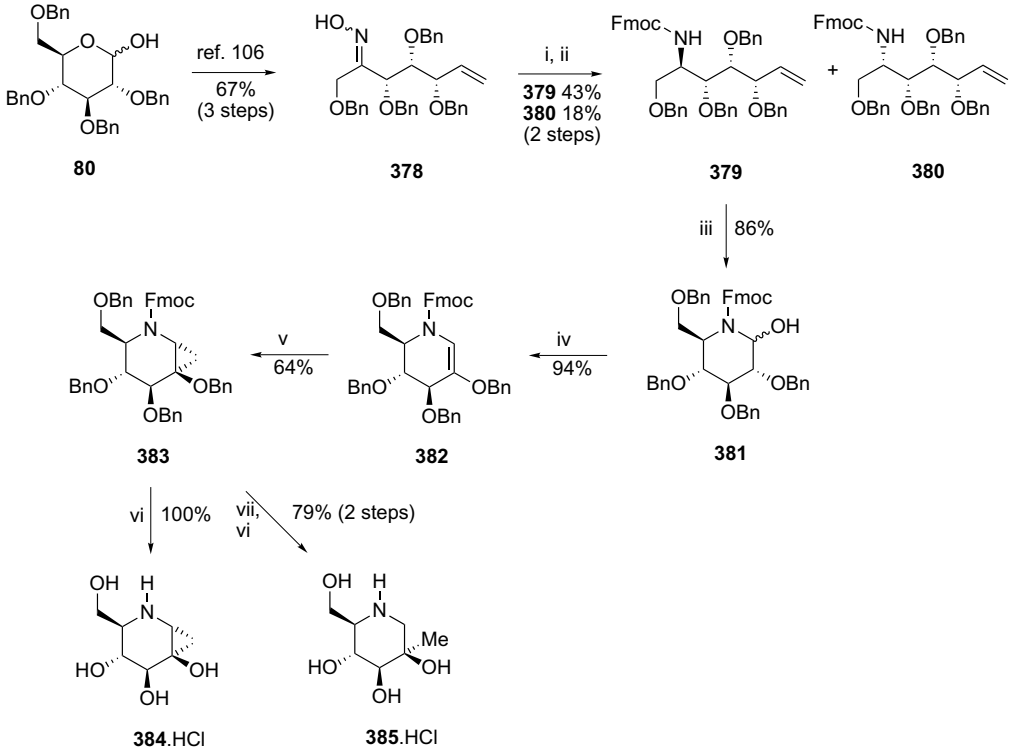
9.2. Miscellaneous homologues

An eight carbon homologue of α-HMJ was described by Fleet et al. (Scheme 58).[137] Starting from diol **371**, aldehyde **372** was readily prepared. A Wittig olefination provided α,β-unsaturated esters **373** and **374** in yields of 26% and 61%, respectively. When the *E*-acrylate was heated in toluene at 100 °C, the *Z*-vinylogous urethane **375** was obtained. Interestingly the same product could also be obtained from the *Z*-acrylate. A selective reduction using sodium triacetoxyborohydride afforded the bicyclic amino lactone **376**. Reduction with $LiBHEt_3$ followed by deprotection of the isopropylidene group with methanolic hydrogen chloride gave the mannose analogue **377**.

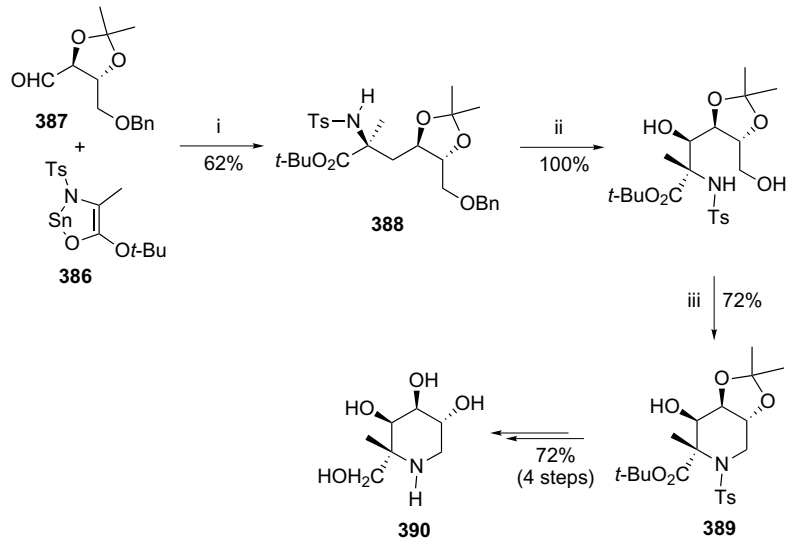
The synthesis of a 2-methyl azasugar has been proposed by Désiŕe and Shipman (Scheme 59).[138] In a separate paper by Khanna, it was postulated that such conformationally restrained azasugars would still retain the



Scheme 58. Reagents and conditions: (i) H_5IO_6, THF; (ii) $Ph_3P{=}CHCO_2Me$; (iii) Toluene, 100 °C; (iv) xylenes, 140 °C; (v) $NaBH_3CN$, AcOH; (vi) (a) $LiBHEt_3$, THF, −60 °C, (b) HCl, MeOH.



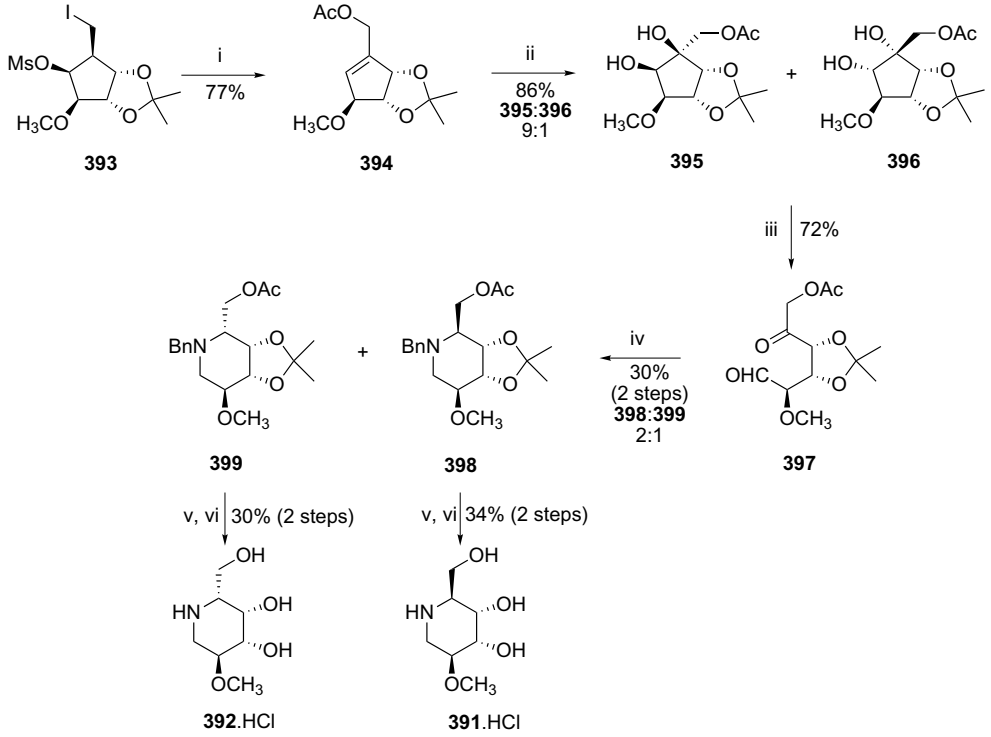
Scheme 59. Reagents and conditions: (i) $LiAlH_4$, Et_2O; (ii) FmocCl, K_2CO_3, THF/H_2O, 0 °C; (iii) O_3, CH_2Cl_2, −78 °C then PPh_3; (iv) $(COCl)_2$, CH_2Cl_2, DMF; (v) (a) Et_2 Zn, CH_2I_2, toluene, (b) morpholine; (vi) Pd/C, H_2, HCl, EtOH; (vii) $Pd(OH)_2$, H_2, EtOH.



Scheme 60. Reagents and conditions: (i) THF, −78 °C; (ii) Pd/C, H_2 (3 bar), MeOH, rt; (iii) DEAD, PPh_3, THF, rt.

H-binding ability of the C-2 OH while imparting a stability to the azasugar against oxidative metabolism.[139] Starting from tetra-*O*-benzyl-D-glucopyranoside **80**, oxime **378** was readily obtained.[106] Reduction of the imine furnished the amine, which was protected as the Fmoc group **379** and **380**. The selectivity of the reduction was in favour of the (6*R*)-diastereomer in a 2.4:1 ratio. Ozonolysis of **379**, followed by treatment with PPh_3 gave the cyclised piperidine **381**. Treatment with oxalyl chloride resulted in elimination giving the structurally interesting imino glucal **382**. Cyclopropanation was achieved using excess diiodomethane and diethyl zinc. Basic deprotection of Fmoc gave **383** from which deoxymannojirimycin analogues **384** and **385** were derived.

Kummeter and Kazmaier have developed a route to 5-Me azasugars (Scheme 60).[140] The aldol reaction between the metal chelated *N*-protected alanine *tert*-butyl ester **386** and the protected *threose* derivative **387** (see Scheme 24) gave three diastereoisomers with the desired *anti* isomer **388** was isolated in a 62% yield. After debenzylation, a Mitsunobu cyclisation gave the pipecolinic acid derivative **389**. A series of deprotection and reduc-

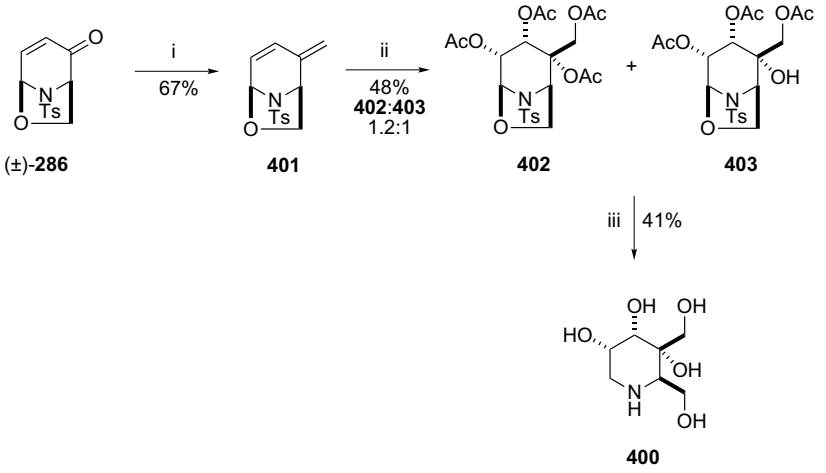


Scheme 61. Reagents and conditions: (i) NaOAc, DMF, 105 °C, 6 h; (ii) OsO_4, NMO, acetone/H_2O; (iii) $NaIO_4$, CH_2Cl_2, 0 °C; (iv) $BnNH_2$, AcOH, $NaBH_3CN$, −10 °C to rt, 20 h; (v) KOH, MeOH, 2 h; (vi) (a) Pd/C (10%), H_2, EtOH, 18 h, (b) 2.5 M HCl/Et_2O.

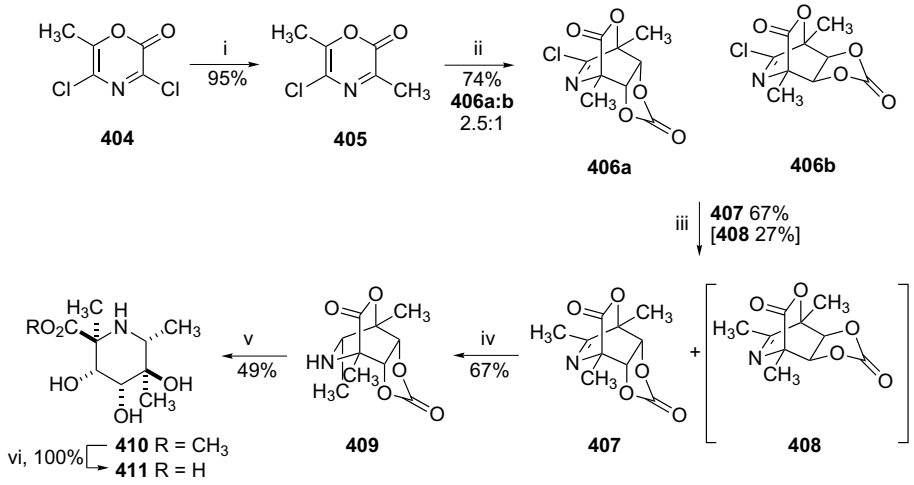
tion steps yielded the 5-methyl-1-deoxyaltronojirimycin azasugar **390**.

Mehta and Mohal demonstrated the synthesis of methyl ethers of 1-deoxyaltronojirimycin **391** and galactostatin **392** (Scheme 61).[141] Iodocyclopentane **393** (developed from a norbonyl system) was used to generate the acetoxycyclopentene **394**. Osmylation gave diols **395** and **396** in a 9:1 ratio. Glycol cleavage of the diol mixture with sodium periodate gave keto-aldehyde **397**. The key step involved a double reductive amination with $NaBH_3CN/BnNH_2$ to furnish **398** and **399** as a mixture of two diastereoisomers (2:1 ratio), which were seperated. Hydrolysis followed by deprotection gave the azasugars.

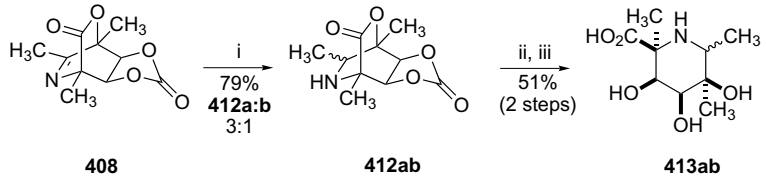
Altenbach described the synthesis of 2-hydroxymethyl-1-deoxyallonojirimycin **400** (Scheme 62) from the aza-analogue of *iso*-levoglucosenone (±)-**286** (see Schemes 38 and 39).[121] Generation of diene **401** was achieved



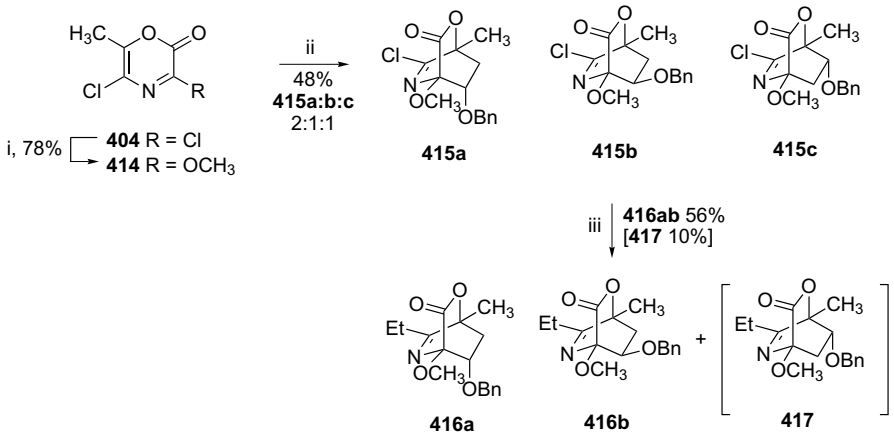
Scheme 62. Reagents and conditions: (i) (a) Ph_3PCH_3Br, *n*-BuLi, −78 °C to rt, 5 h, (b) H_2O; (ii) (a) OsO_4, NMO, 4 d, (b) $Na_2S_2O_3$, (c) Ac_2O, py, 24 h; (iii) (a) Red-Al®, DME, reflux, 24 h, (b) aq HCl, (c) DOWEX® 50X8.



Scheme 63. Reagents and conditions: (i) $SnMe_4$, $Pd(PPh_3)_4$, toluene, reflux, 1 d; (ii) vinylene carbonate, toluene, reflux, 1 d; (iii) $SnMe_4$, $Pd(PPh_3)_4$, toluene, reflux, 1 d; (iv) $NaBH(OAc)_3$, AcOH, rt, 1 d; (v) NaOMe, MeOH, reflux, 30 min; (vi) 2 M NaOH, rt, 1 h.



Scheme 64. Reagents and conditions: (i) $NaBH(OAc)_3$, AcOH, rt, 1 d; (ii) NaOMe, MeOH, reflux, 30 min; (iii) 2 M NaOH, rt, 1 h.



Scheme 65. Reagents and conditions: (i) HCl, MeOH, rt, 2 h; (ii) benzyl vinyl ether, toluene, reflux, 2 d; (iii) $SnEt_4$, $Pd(PPh_3)_4$, toluene, reflux, 1 d.

by a Wittig olefination. A double *cis* dihydroxylation followed by acetylation gave a mixture of acetylated product **402** and partially acetylated **403** in a 1.2:1 ratio. Deprotection and reduction of the compound mixture led to the azasugar **400**.

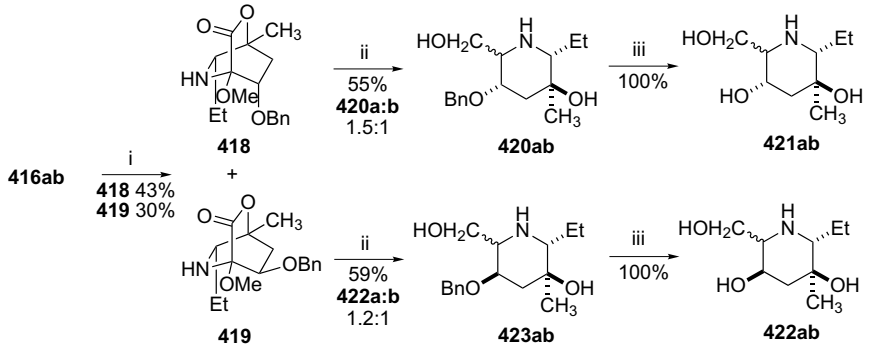
Afarinkia and Bahar have reported a new synthesis of densely substituted azasugar homologues via the Diels–Alder cycloadditions of substituted 1,4-oxazin-2-ones (Schemes 63, 64 and 66).[142] The key advantage of this approach is the diversity of substituents, which can be introduced on every position of the piperidine nucleus. From 3,5-dichloro-6-methyl-1,4-oxazin-2-one **404**, previously described by Meerpoel and Hoornaert,[143] the 5-chloro-3,6-dimethyl-1,4-oxazin-2-one **405** was derived. Cycloaddition with vinylene carbonate afforded cycloadduct **406ab** as a 2.5:1 ratio (*endo:exo*). The chloro substituents of the cycloadducts were replaced with methyl groups under Stille cross coupling conditions. At this stage, the two isomers could be separated by silica gel chromatography yielding **407** and **408** in 65% and 27% yields. Hydride reduction of the imine bond of **407** gave **409** stereoselectively. Methanolysis of **409** to the methyl ester **410** proceeded with deprotection of the diol functionality. Basic hydrolysis under typical conditions gave 1,2,5-trimethyl azaglucoronic acid analogue **411**, with an altro-configuration (Scheme 63).

Hydride reduction of *exo* adduct **408** gave a mixture of amines **412ab** in a 3:1 ratio (79% yield). Similarly methanolysis followed by basic hydrolysis furnished azasugars **413ab** (Scheme 64).

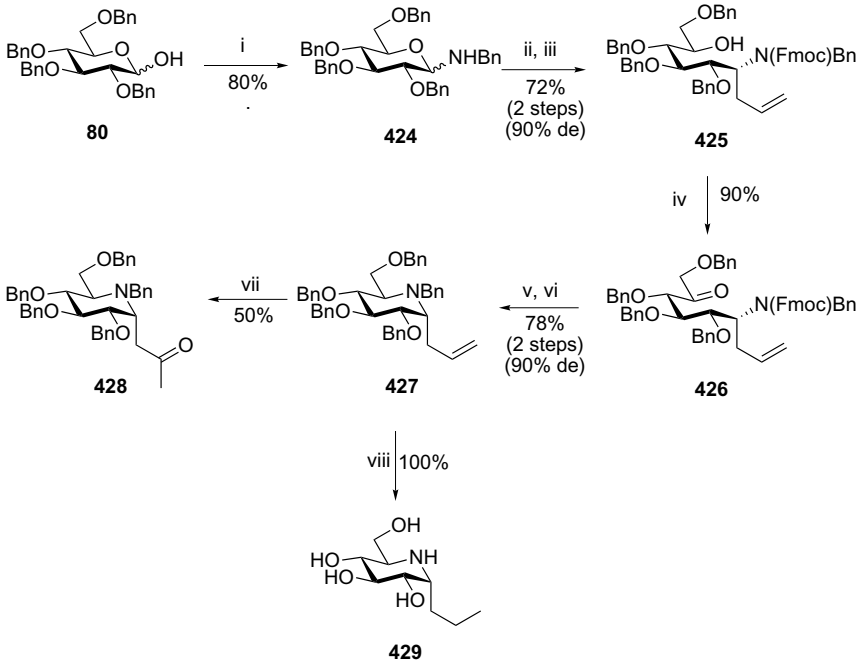
Afarinkia et al. have also applied this method in the synthesis of 1,3-dideoxy-1-*C*-ethyl-azasugars, which are deoxy-analogues of adenophorine (Scheme 66).[142b] The 3-methoxy-1,4-oxazin-2-one **414** was prepared from **404** for efficient elimination of the methoxy group at a later stage (Scheme 65). Cycloaddition with benzyl vinyl ether gave three cycloadducts as a mixture, with a 2:1:1 ratio (**415a**:**b**:**c**). Stille coupling with tetraethyltin yielded **416ab** and **417** in 56% and 10% yields. Stereoselective reduction of **416ab** was again achieved with sodium triacetoxyborohydride in acetic acid to afford the separable isomers **418** and **419** (Scheme 66). Treatment of **418** with lithium aluminium hydride proceeded with the elimination of the methoxy substituent to give the monoprotected azasugars **420ab**. Debenzylation under palladium catalysed conditions gave 1,3-dideoxyazasugars **421ab** (1.5:1 ratio). The same procedure with **419** furnished azasugars **422ab** via **423ab**.

9.3. C-Glycosides

Nicotra et al. have developed a method of synthesising a range of 1-substituted azasugars (Scheme 67).[144] Start-



Scheme 66. Reagents and conditions: (i) $NaBH(OAc)_3$, AcOH, rt, 1 d; (ii) $LiAlH_4$, THF, reflux, 1 d; (iii) $PdCl_2$, H_2, MeOH, 1 d.

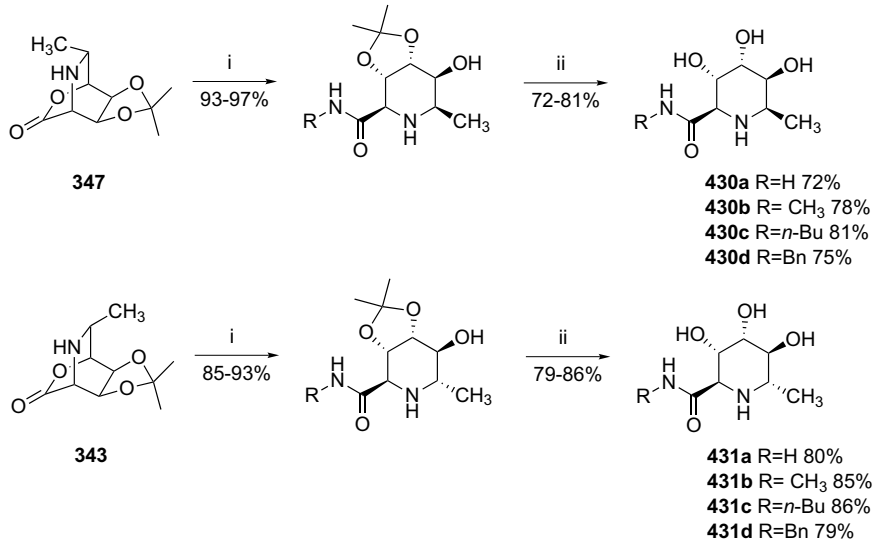


Scheme 67. Reagents and conditions: (i) $PhCH_2NH_2$, $TsOH{\cdot}H_2O$, CH_2Cl_2, 5 d; (ii) $H_2C{=}CHCH_2MgBr$, Et_2O; (iii) FmocCl, dioxane, aq Na_2CO_3; (iv) PCC, CH_2Cl_2, molecular sieves 4 Å; (v) py, DMF; (vi) $NaBH(OAc)_3$, AcOH, Na_2SO_4, DCE, −35 °C; (vii) Na_2PdCl_4, $CuCl_2$, DMF/THF/H_2O; (viii) $Pd(OH)_2$, H_2, AcOH, EtOAc/EtOH.

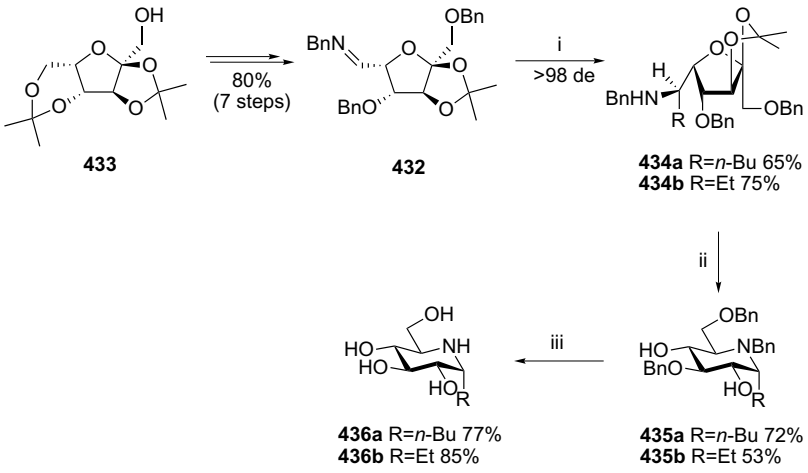
ing from tetra-*O*-benzyl-glucopyranoside **80**, the glycosyl amine **424** was derived. The key allylic appendage was introduced by a Grignard reaction via a Cram chelated intermediate giving a single *threo* isomer, protection of which gave **425**. A PCC oxidation gave ketone **426**. *N*-Deprotection, followed by a reductive amination furnished the protected allyl-α-*C*-glycoside of nojirimycin **427** in 78% and 90% de. Wacker–Tsuji oxidation of the allylic appendage with catalytic Na_2PdCl_4 and $CuCl_2$ in DMF/THF/H_2O gave **428**. Deprotection of **427** by hydrogenolysis afforded **429** in quantitative yield.

In search of potent naringinase inhibitors, Fleet et al. also produced a range of aza-*C*-glycosyl analogues **430a–d** and **431a–d** from their common intermediates (Schemes 68, 22, 51 and 52).[132]

Martin et al. also demonstrated a novel procedure for the synthesis of *C*-glycosides (Scheme 69).[145] Key intermediate **432**, was produced from the commercially available 2,3:4,6-di-*O*-isopropylidene-α-L-sorbofuranose **433** over seven steps (overall yield 80%). Stereocontrolled addition to imine **432**, with organometallic nucleophiles



Scheme 68. Reagents and conditions: (i) RNH_2, THF; (ii) HCl, MeOH.



Scheme 69. Reagents and conditions: (i) *n*-BuLi or EtMgBr, Et_2O, −78 °C to rt or 0 °C to rt, 3–12 h; (ii) $NaBH_3CN$, AcOH, MeOH, 24 h; (iii) Pd/C (10%), H_2, HCl, MeOH, 48 h.

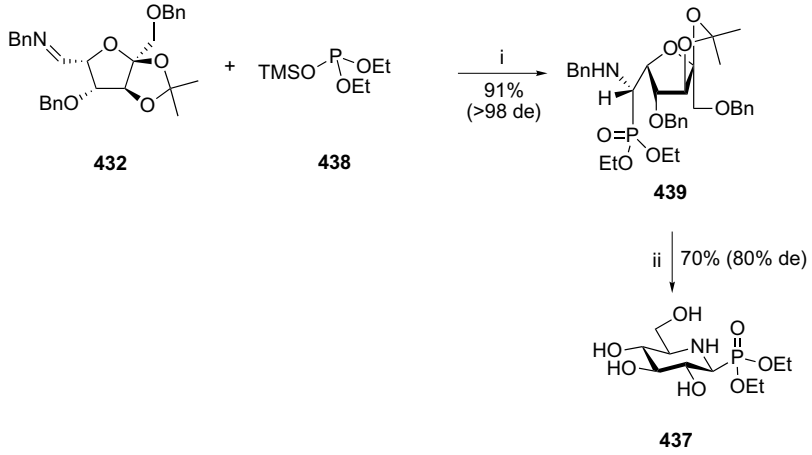
provided 6*R*-aminosorbose derivatives **434**. The diastereomerically pure diols **435** were obtained on deprotection of the isopropylidene group followed by a reductive amination. The diols were readily converted to the substituted azasugars **436** upon deprotection.

10. Other azasugar analogues

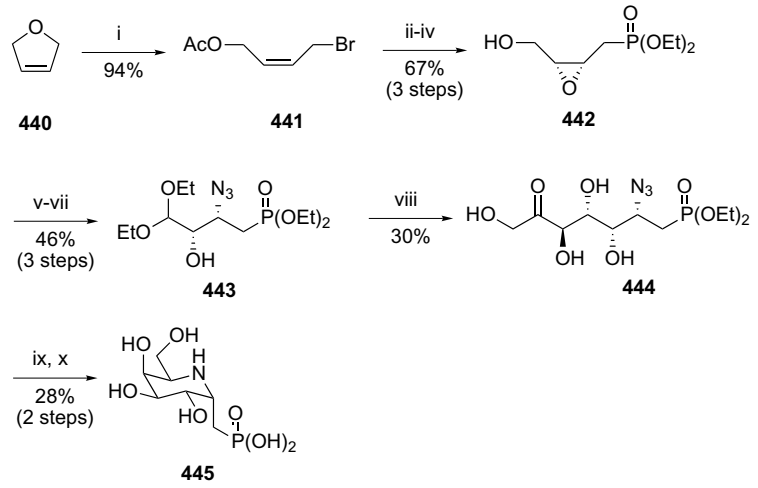
10.1. Analogues of DNJ-1-phosphates

Martin et al. also applied a previous strategy (see Scheme 69) towards the synthesis of azasugar 1-phosphonate **437** (Scheme 70). From imine **432**, treatment with trimethylsilyloxy phosphine derivative **438** (generated in situ from diethyl phosphite) gave the α-aminophosphonate **439**. The (*S*)-configuration at the newly generated stereocentre is thought to result from a combination of steric and electrostatic repulsion factors in the postulated approach trajectory. Interestingly, the stereoselectivity of this addition could be reversed with a diastereomeric excess of 85% upon addition of $ZrCl_4$, which forms a chelated intermediate imine. A one-pot deprotection furnished **437**.

Wong postulated 1-methylphosphonic acid derivatives of azasugars would make specific glycosyl transferase inhibitors. He demonstrated a chemoenzymatic approach starting from the readily available 2,5-dihydrofuran **440** (Scheme 71).[146] Reaction with acetyl bromide provides 1-bromo-4-*O*-acetoxy-2-*cis*-butene **441**. Epoxy alcohol **442** was formed over three steps: reaction with triethyl phosphite, hydroxyl group deprotection and Sharpless asymmetric epoxidation. A Swern oxidation followed by protection of the aldehyde as the diethyl acetal allowed for a regioselective epoxide opening using diethylaluminium azide (generated in situ) to furnish azido acetal **443**. Aldehyde deprotection followed by fuculose-1-phosphate aldolase-catalysed aldol condensation with DHAP and dephosphorylation with acid phosphatase gave azido-sugar **444**. Reduction of the azide by hydrogenation led to intramolecular cycli-



Scheme 70. Reagents and conditions: (i) TMSCl, $(EtO)_2POH$, Et_3N, CH_2Cl_2, 0–40 °C, 45 min; (ii) (a) TFA/H_2O, Pd/C (10%), H_2, 70 h; (b) Amberlyst® IRA-400 (HO^-), H_2O.



Scheme 71. Reagents and conditions: (i) AcBr; (ii) $P(OEt)_3$, NaI; (iii) EtOH, TsOH; (iv) (−)-DIPT, $Ti(O\textit{i}\text{-}Pr)_4$, $PhC(Me)_2OOH$; (v) $(COCl)_2$, DMSO, Et_3N; (vi) $HC(OEt)_3$, TsOH; (vii) Et_2AlCl, LiN_3; (viii) (a) TFA, (b) DHAP, FucA, pH 6.7, (c) acid phosphatase, pH 4.8; (ix) Pd/C, H_2 (50 psi); (x) (a) TMSBr, (b) H_2O, THF.

sation to yield the azasugar phosphonate. Deprotection of the diethyl phosphonate groups gave the D-galactonojirimycin phosphonic acid **445**.

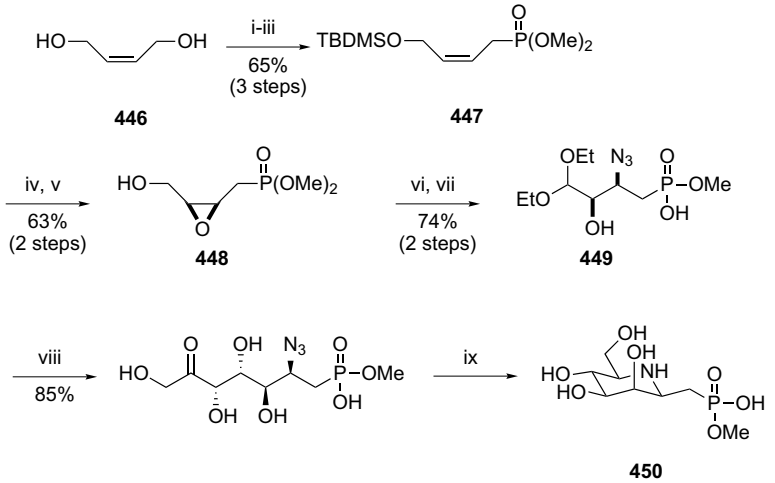
For the D-mannose configuration (Scheme 72), diol **446** was monoprotected with a *tert*-butyldimethylsilyl ether group. The free hydroxyl group was converted to the trimethyl phosphonate **447** via the iodide. Deprotection followed by epoxidation gave epoxy alcohol **448**. A Dess–Martin oxidation of the hydroxyl group, protection of the resulting aldehyde followed by regioselective epoxide opening by sodium azide gave compound **449**. The same chemo-enzymatic approach as previously described, followed by chemical manipulation led to **450**.

10.2. Lactams

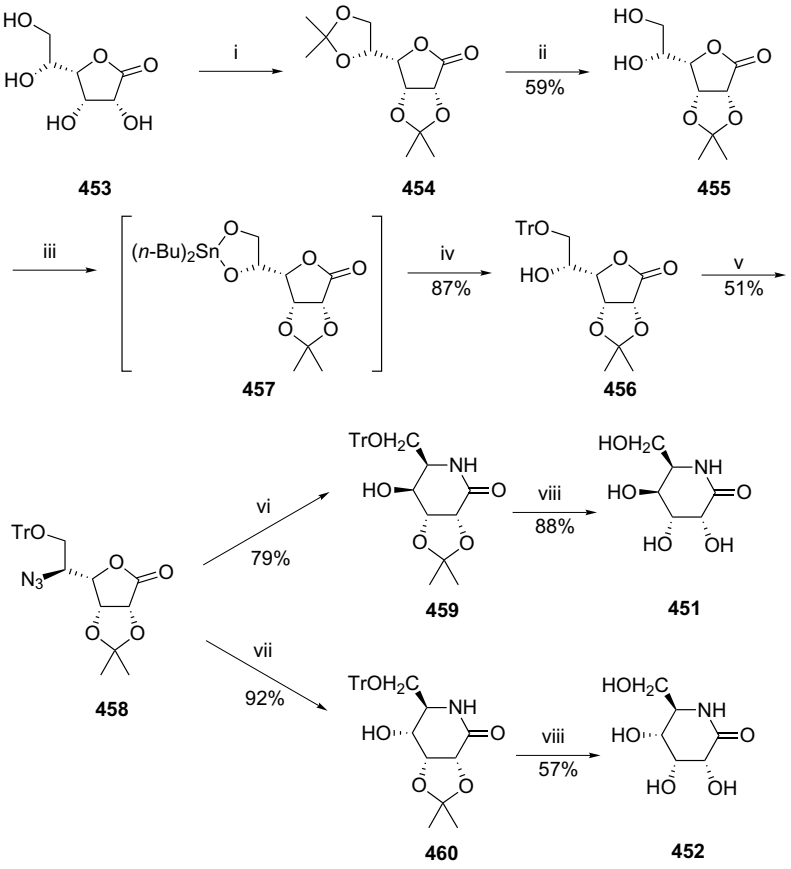
Nishimura et al. have reported the syntheses of all eight stereoisomeric D-glycono-δ-lactams (Schemes 73–76).[147]

For instance the D-gulono- and D-allono-δ-lactams **451** and **452** were derived from L-mannonic acid δ-lactone **453** (Scheme 73). Isopropyl protection gave the 2,3:5,6-di-*O*-isopropylidene-L-mannonic acid δ-lactone **454**. Selective removal of the 5,6-*O*-isopropylidene group was achieved with acetic acid, furnishing **455**. Compound **455** was transformed into 6-*O*-trityl-protected lactone **456** via the cyclic stannoxane **457**. The free alcohol was readily converted to the *O*-triflate and displaced by sodium azide to give the key intermediate **458**. From the azide, the Raney Nickel catalytic reduction produced the protected D-guluno-δ-lactam **459**, the deprotection of which led to **451**. Alternatively, treatment of **458** with triphenylphosphine followed by hydrogenolysis gave the D-allono-derivative **460**.

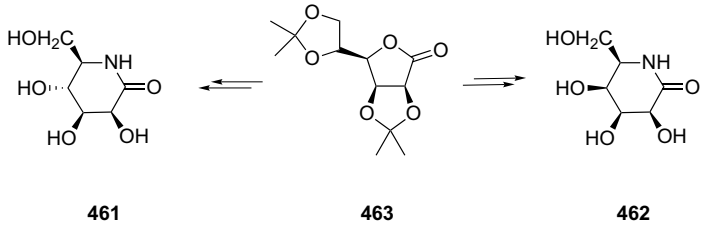
In a similar procedure D-manno- and D-talo-δ-lactams **461** and **462** were prepared from the 2,3:5,6-di-*O*-isopropylidene-L-gulonic acid δ-lactone **463** (Scheme 74).



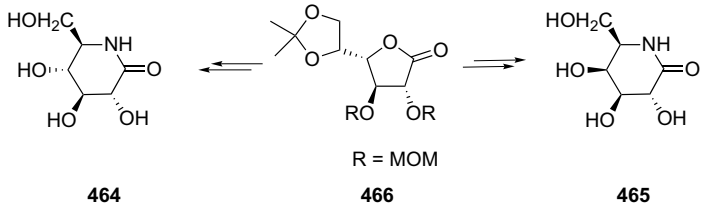
Scheme 72. Reagents and conditions: (i) TBDMSCl, Et_3N; (ii) PPh_3, I_2, imidazole; (iii) $P(OMe)_3$, NaI; (iv) AcOH; (v) *m*-CPBA; (vi) (a) $(COCl)_2$, DMSO, Et_3N, (b) $HC(OEt)_3$, TsOH; (vii) NaN_3, NH_4Cl; (viii) (a) 0.1 N HCl, (b) DHAP, FDP aldolase, pH 6.7, (c) acid phosphatase, pH 4.8; (ix) Pd/C, H_2 (50 psi).



Scheme 73. Reagents and conditions: (i) $(MeO)_2CMe_2$, acetone, TsOH, rt; (ii) aq AcOH, 30 °C; (iii) *n*-Bu_2SnO, molecular sieves 4 Å, benzene, 80 °C; (iv) Ph_3CCl, *i*-Pr_2NEt, DMF, rt; (v) (a) Tf_2O, py, CH_2Cl_2, −40 °C, (b) NaN_3, DMF, rt; (vi) Raney Ni, H_2, MeOH, rt; (vii) (a) PPh_3, MeCN, rt, (b) H_2O, rt; (viii) 4 M HCl/dioxane.



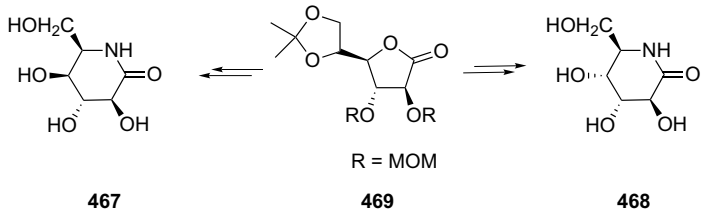
Scheme 74.



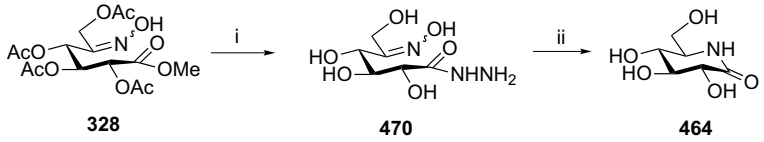
Scheme 75.

D-Gluco- and D-galactono-δ-lactams **464** and **465** were prepared from the D-galactonic acid δ-lactone derivative **466** (Scheme 75) and D-altrono- and D-idono-δ-lactams **467** and **468** from L-galactonic acid δ-lactone **469** (Scheme 76).

Pistia and Hollingsworth have synthesised **464** from their key intermediate **328** (see Scheme 48).[130] Treatment with hydrazine, followed by deacetylation yielded acyl hydrazide **470**. Catalytic hydrogenation led to the product **464** (Scheme 77).



Scheme 76.

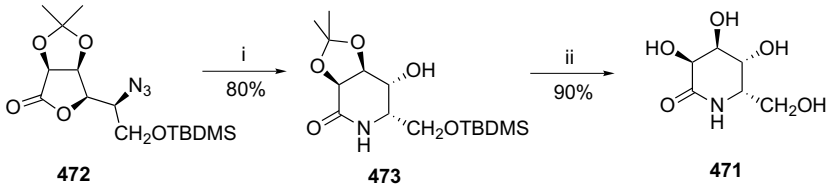


Scheme 77. Reagents and conditions: (i) NH_2NH_2, (ii) Pd/C, H_2.

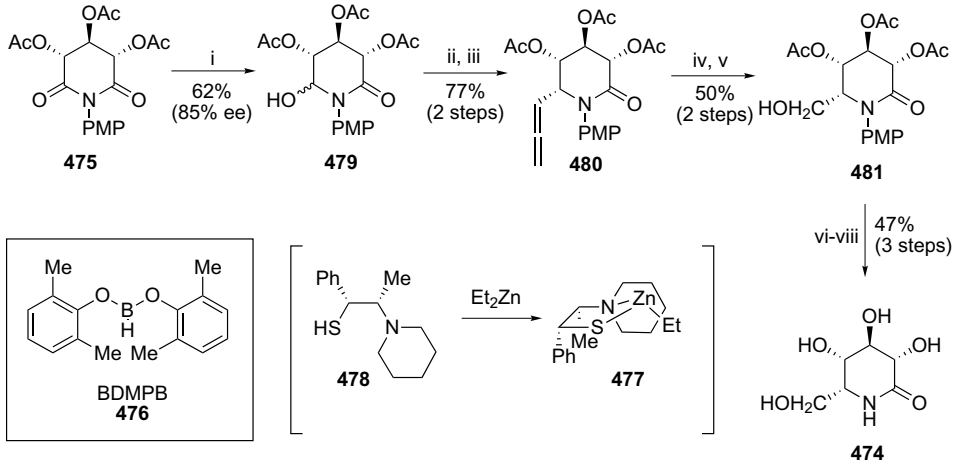
Fleet et al. obtained the corresponding δ-lactam of 5-*epi*DMJ **471** (Scheme 78).[131] Hydrogenation of azide **472**, followed by deprotection of the resulting L-gulono-1,5-lactam **473** produced the target material.

Kang et al. reported the synthesis of 5-*epi*NJ-δ-lactam **474** (Scheme 79).[148] Enantioselective reduction of the cyclic triacetyloxy *meso* imide **475** using bis(2,6-dimethylphenoxy)borane (BDMPB) **476** in the presence of a catalytic amount of complex **477** (generated from amino thiol ligand **478**) furnished **479**. The allenic compound **480** was generated via the tetraacetate of compound **479** using propargyltrimethylsilane. Nucleophilic addition of propargyl silane on the acyliminium ion centre occurred exclusively from the axial direction. Ozonolysis followed by $NaBH_4$ reduction gave the hydroxylmethyl product **481**. Deprotection steps involving the oxidative cleavage of the *p*-methoxyphenyl (PMP) group and deacetylation gave the azasugar **474**.

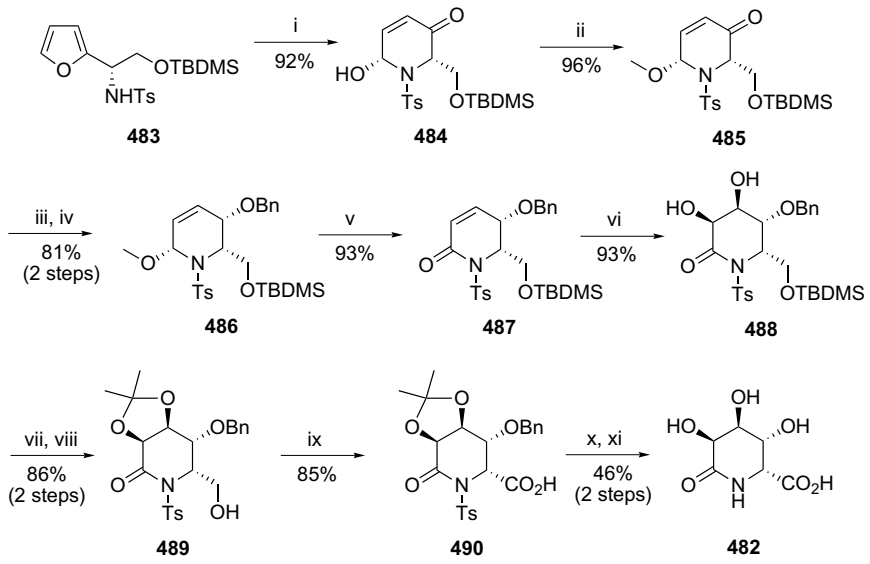
A synthesis of the D-glucaro-δ-lactam **482** was described by Haroutounian et al. (Scheme 80).[149] This compound



Scheme 78. Reagents and conditions: (i) Pd/C (10%), H_2, EtOH; (ii) TFA/H_2O.



Scheme 79. Reagents and conditions: (i) BDMPB, **477**, toluene, −10 °C, 16 h; (ii) Ac_2O, py, CH_2Cl_2, rt; (iii) $HC{\equiv}CCH_2OTMS$, $BF_3{\cdot}OEt_2$, TBSOTf, MeCN; (iv) O_3, CH_2Cl_2, −78 °C; (v) $NaBH_4$, EtOH, 0 °C; (vi) Ac_2O, py, CH_2Cl_2, rt; (vii) CAN, MeCN/H_2O, rt; (viii) 2 N NaOH, MeOH, 0 °C.



Scheme 80. Reagents and conditions: (i) *m*-CPBA, CH_2Cl_2; (ii) $HC(OMe)_3$, $BF_3{\cdot}OEt_3$, molecular sieves 4 Å, THF, 0 °C; (iii) $NaBH_4$, $CeCl_3{\cdot}H_2O$, MeOH, −30 °C; (iv) NaH, BnBr, Bu_4NI, THF; (v) *m*-CPBA, $BF_3{\cdot}Et_2O$, THF; (vi) OsO_4, NMO, *t*-BuOH/acetone; (vii) $(MeO)_2CMe_2$, $TsOH{\cdot}H_2O$, acetone; (viii) TBAF, THF; (ix) $RuCl_3$, $NaIO_4$, H_2O/CCl_4/MeCN; (x) (a) Pd/C, H_2, EtOH, (b) $TsOH{\cdot}H_2O$, MeOH; (xi) Na, napthalene, THF.

was an active inhibitor of β-glucurodinase with 98.5% inhibition at 0.1 nM and antimetastatic activity on mouse melanoma B16 with 91.8% metastatic inhibition at 10 μg/mL. From the protected furyl glycinol derivative **483** subsequent hydrogenation and oxidative cyclisation produced the (2*S*)-hydroxymethyldihydropyridin-3-one **484**, which was further protected to give the key compound **485**. A Luche reduction yielded the alcohol as a single diastereomer, which was subsequently benzylated as **486**. Oxidation of compound **486** by *m*-CPBA led to the α,β-unsaturated lactam **487**. Typical osmium tetraoxide dihydroxylation gave diol **488** as a single diastereomer through approach of the oxidant from the less sterically hindered face. Diol protection and hydroxymethylene deprotection gave compound **489**. Oxidation was achieved with ruthenium tetraoxide to furnish the protected pipecolic acid-δ-lactam derivative **490**, from which **482** was obtained.

11. Conclusion

Methods for the asymmetric synthesis of azapyranose sugars have continued to expand over the past 6 years. Although using starting materials from chiral pool, particularly hexose sugars, tetrose sugars (e.g., Schemes 24, 29, 40–42 and 60), dihydrobenzene (Scheme 11) and α-amino acids (e.g., Schemes 14, 15, 25 and 45, 46, 47) are the most popular.

The use of a chiral auxiliary (e.g., Schemes 3, 9 and 49), resolution (e.g., Scheme 2) and the use of chiral reagents in particular Sharpless aminohydroxylation (e.g., Scheme 16), dihydroxylation (e.g., Schemes 4, 10 and 53) and epoxidation (Schemes 71 and 72) continue to grow.

Manipulation of carbohydrates remains the main strategy for the synthesis of azapyranose sugars with reductive amination and intramolecular displacement (Schemes 7, 8, 12, 13, 24, 29, 34, 37, 52 and 60) being the two main methodologies for the construction of the piperidine (azapyranose) ring.

In the context of the reductive amination, the amine required for the reductive amination/cyclisation is typically unmasked by a reduction of an azide, which is the most popular route (see Schemes 19, 22, 26, 54, 58, 71 and 72). However, reduction of the nitrile (Scheme 37), ketimine (Scheme 53), oxime (Scheme 2) and double reductive amination/cyclisation of a 1,5-diketone with an external amine (e.g., Schemes 20, 21 and 56) have also been used. Aminomercuration (Scheme 55) and nitrene insertion (Scheme 58) add to the versatility of the synthetic routes to azapyranose sugars. Addition of bislactimes to tetroses (Schemes 24 and 40–42) and nonasymmetric synthesis of azasugars from the oxidation of (1-aminomethyl)furan (e.g., Scheme 38) are the two other extensively used methodologies.

Moreover, strategies based on ring closure metathesis (RCM) continues to play an increasingly important role in the synthesis of piperidines and azapyranose sugars (see Schemes 16, 17, 25, 31, 32 and 45–47).

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