Recent Advances in the Total Synthesis of Piperidine Azasugars

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Since the discovery of nojirimycin, a glycosidase inhibitor, polyhydroxylated piperidines (also called azasugars: the ring *O*-atom of a carbohydrate is replaced by nitrogen) have attracted considerable attention and have been the target of numerous synthetic strategies during the last decade. The efficient synthesis of naturally occurring azasugars and their analogs is of considerable importance due to their potential glycosidase inhibitor properties. Some of them have been widely investigated as candidates for drugs to treat a variety of carbohydrate-mediated diseases such as diabetes, viral infections, including HIV, cancer metastasis, hepatitis, and Gaucher's disease. This microreview focuses on recent syntheses of azasugars. In addition, the biology of these compounds is briefly considered.

Introduction

In 1966, nojirimycin (**1**; NJ) was discovered as the first alkaloid that mimics a sugar (Figure 1).[1] Almost forty years later, more than one hundred polyhydroxylated alkaloids have been isolated from plants and microorganisms and are arousing great interest both as tools to study cellular mechanisms and as potential therapeutic agents. In fact, these natural compounds, because of their structural resemblance to the sugar moiety of natural substrates of glycosidases, were believed to be potential inhibitors of the wide range of enzymes involved in important biological processes such as intestinal digestion, post-translational processing of glycoproteins or lysosomal catabolism of glycoconjugates. For this reason, sugar-mimic alkaloids were predicted to have a future as new drugs in antidiabetic therapy, as antiviral and anti-infective agents, or in lysosomal storage disease therapy.

Naturally occurring sugar mimics with a nitrogen in the ring are classified into five structural classes: polyhydroxylated piperidines, pyrrolidines, indolizidines, pyrrolizidines, and nortropanes. The main representatives of these different classes are respectively NJ (**1**), isolated from *Streptomycin* filtrate,[1] CYB 3 (**2**), found in the seeds and leaves of *Castanospermum australe*,[2] swainsonine (**3**), isolated from *Swainsona canescens* in 1979,[3] alexine (**4**), isolated from *Alexa leiopetala*,[4] and calystegines like **5** present in the roots of *Lycium chinense*[5] (Figure 1).

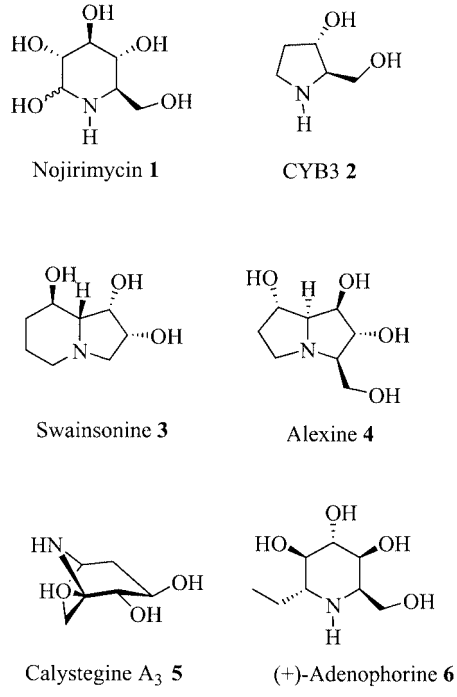

Figure 1. Main representatives of naturally occurring iminosugars.

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MICROREVIEWS: This feature introduces the readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.

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More information about the natural occurrence of these alkaloids and some of their analogs can be found in a recent review published by Nash and co-workers.[6] It can be noted that, since the year 2000, new deoxy-imino sugars like (+)-adenophorine (α-1-deoxy-1-*C*-methylhomonojirimycin; **6**) have been discovered in plants[7] and this explains why chemists must pursue their investigations in the synthesis of novel original imino sugar structures.

The distribution of naturally occurring imino sugars like NJ and their potential therapeutic applications will be considered here. A large number of polyhydroxylated piperidines and pyrrolidines have already been described and their syntheses reported in a number of articles. The chemistry part will summarize the more representative syntheses of 2-hydroxymethylpiperidines bearing at least two alcohol functions on the ring (Figure 2) published from 1999 to June 2004.

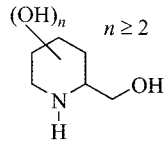


Figure 2. Polyhydroxylated 2-hydroxymethylpiperidines.

Natural Occurrence of Piperidinic Imino Sugars

As NJ was first described in the 1960′s as an antibiotic produced in bacterial cultures of *Streptomyces roseochromogenes* R-468 and *Streptomyces nojiriensis* SF-426,[8] and its isomers mannojirimycin[9] (**7**; MJ, nojirimycin B) and galactonojirimycin[10] (**8**; GJ, galactostatin) were isolated twenty years later from species of *Streptomyces* (Figure 3). NJ, like its isomers, is an unstable product because of its hemiacetal structure and therefore its corresponding 1-deoxy analog,

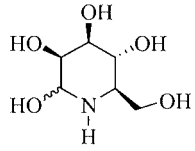
Morwenna S. M. Pearson (right) was born in Redhill (Great Britain) in 1979. During her undergraduate education, she worked in Professor Pierre Roger's group at Sanofi Synthelabo (Bagneux, France) under the guidance of Dr. Genevieve Estenne Bouhtou. In 2003, she received her M.Sc. degree in Chemistry from the University of Nantes, under the supervision of Professor Jean Claude Meslin and Dr. David Deniaud, for her work on the synthesis of pyrimidine nucleoside analogs by [4+2] cycloaddition reaction. In 2004, she joined Professor Jacques Lebreton's group at the University of Nantes where she has since been pursuing a Ph.D. in synthetic organic chemistry. Currently, her research interests involve the total synthesis of azasugars, potential glycosidase inhibitors, in enantiomerically pure form.

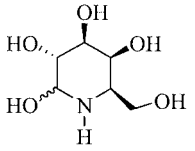
Monique Mathé-Allainmat (center) was born in Paimpol (France) in 1963. She studied chemistry at the University of Rennes and received her Ph.D. degree in 1990. During her thesis work under the guidance of Professor Daniel Plusquellec (Rennes), she developed novel reagents and new methodologies for selective protection of free mono- and disaccharides. After postdoctoral studies with Dr. Michel Langlois at the University of Paris XI (Châtenay-Malabry), she joined the CNRS in 1993. Here, she spent a few years working in the field of medicinal chemistry, particularly on the design and synthesis of serotoninergic and melatoninergic analogs, adapting some synthetic projects to solid- or solution-phase synthesis. In 2001, she joined Professor Jacques Lebreton's group at the University of Nantes. Her current research interests include the design and synthesis of analogs of bioactive molecules and the development of methodologies for solid or solution phase synthesis.

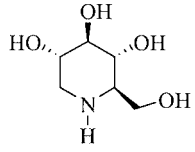
Valérie Fargeas (left), born in 1968 in Maisons-Alfort in France, completed her Ph.D. in organic chemistry at the Faculty of Pharmacy of Châtenay-Malabry (Paris XI) in 1997 for work in the field of the enantioselective synthesis of Tylonolide with Professor Janick Ardisson. She spent a postdoctoral year with Professor Philip Kocienski at the University of Glasgow (Glasgow, Scotland) working on the total synthesis of Rhizoxine. After carrying out another postdoctoral fellowship with Dr. David Grierson (Institut Curie, Orsay, France), she moved in 1998 to the University of Nantes to join Professor Jean-Paul Quintard's team, working on a project concerning the nitrodestannylation reaction. She then joined Professor Jacques Lebreton's group where she is currently a Senior Lecturer. She has research interests in various aspects of the stereoselective total synthesis of bioactive products and analogs (nucleosides, anticancer drugs).

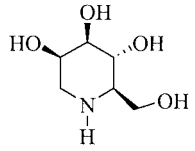
Jacques Lebreton (second row) was born in Guérande (France) in 1960. He received his Ph.D. degree (1986) from the University of Paris XI-Orsay under the supervision of Professor Eric Brown (Le Mans). His thesis work included the total synthesis of C-nor D-homosteroids. In 1986, he started his first postdoctoral fellowship with Professor James A. Marshall at the University of South Carolina working on the [2,3]-Wittig rearrangement and its application in total synthesis. Following a second post-doctoral fellowship with Professor Robert E. Ireland at the University of Virginia working on the total synthesis of monensine, he joined the laboratories of CIBA-GEIGY (Novartis) in Basle in 1990, where he worked in Dr. Alain De Mesmaeker's group in the field of antisense. In 1994, he joined the CNRS and spent a few years in the group of Dr. Jean Villiéras (UMR-CNRS 6513, Nantes) concerned with organometallic chemistry. In 1998, he was promoted to Professor at the University of Nantes. His major research interests are organometallic chemistry and medicinal chemistry. In 2000 with his friend and colleague A. Guingant, he set up a research group, named Symbiose, devoted to developing research at the interface between chemistry and biology. Most of his recent work has focused on the synthesis of bioactive molecules, such as steroids, nucleosides, alkaloids, and azasugars, for biological evaluation purposes in the fields of HIV, central nervous system diseases and cancer through academic and industrial collaborations. His research efforts also include the synthesis of labeled molecules to study biological processes.

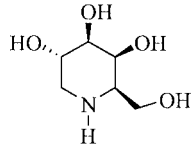
1-deoxynojirimycin (**9**; DNJ), was synthesized by reduction with $NaBH_4$ or from L-sorbofuranose by Paulsen and coworkers.[11] It is noteworthy that Paulsen was a pioneer in the development of monosaccharide analogs having nitrogen or sulfur in the ring and that few imino sugars had been synthesized prior to their identification from natural sources. Thus, DNJ (**9**) was later isolated from the roots of mulberry trees (Moracae) and was called moranoline.[6] Although 1-deoxymannojirimycin (**10**; DMJ) was also found to be produced by *Streptomyces lavandulae* SF-425 and recently extracted from *Adenophora triphylla*,[6] the corresponding 1-deoxygalactonojirimycin (**11**; DGJ) has not yet been reported from natural sources.

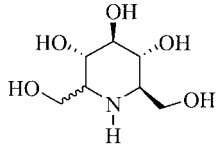

Mannojirimycin **7**


Galactonojirimycin **8**


1-Deoxynojirimycin **9**


1-Deoxymannojirimycin **10**


1-Deoxygalactonojirimycin **11**


α- or β-Homonojirimycin **12**

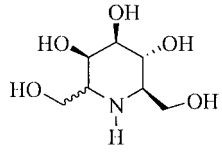
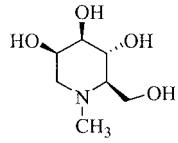
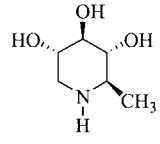

α- or β-Homomannojirimycin **13**

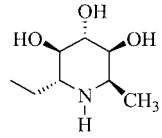
Figure 3. NJ, DNJ and HNJ isomers.

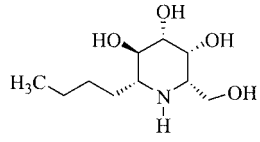
α- and β-Homonojirimycin (**12**; HNJ) and α- and β-homomannojirimycin (**13**; HMJ) are stable compounds found in the roots and leaves of *Aglaonema treubii*[12] and in bulbs of *Hyacynthus orientalis*.

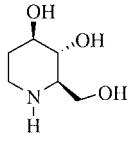
These plants also produce glycosides and isomers of these four compounds, like 7-*O*-β-D-glucopyranosyl of α-homonojirimycin (MDL, 25637) which was first designed and synthesized as a transition-state analog of sucrose by Liu.[13] A series of alkylated polyhydroxypiperidines are also produced by the tropical African legume *Angylocalyx pynaertii*, such as *N*-methyl-DMJ (**14**) or 1,6-dideoxynojirimycin (**15**; Figure 4).[14] Recently, novel polyhydroxylated piperidine alkaloids with a longer alkyl substituent branched on the cyclic moiety have been isolated from *Adenophorae radix*, such as (+)-adenophorine (**6**), 1-deoxyadenophorine (**16**), or β-1-*C*-butyl DGJ (**17**).[7]

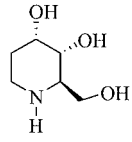

N-Me-DMJ **14**


1,6-Dideoxynojirimycin **15**


1-Deoxyadenophorine **16**


β-1-*C*-Butyl-1-deoxygalactonojirimycin **17**


Fagomine **18**


3-*epi*-fagomine **19**

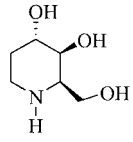

3,4-Di-*epi*-fagomine **20**

Figure 4. Alkylated and deoxy analogs of DNJ.

The dideoxynojirimycin analog fagomine (**18**; Figure 4) was first isolated from *Fagopyrum esculentum* (Polygonaceae). 3-*epi*-Fagomine (**19**) and 3,4-di-*epi*-fagomine (**20**) and their glucopyranosyl derivatives were found in leaves of *Xanthocercis zambesiaca* (Leguminoseae) in 1997.[15]

Target of Piperidinic Imino Sugars: Biological Activities and Therapeutic Applications

Carbohydrate branching or hydrolysis catalyzed by enzymes are widespread biological processes. These enzymes, named glycosyltransferases and glycosidases, are involved in the biosynthesis and degradation of oligosaccharides and glycoconjugates (glycoproteins, glycolipids, proteoglycans) that are found in nearly all forms of life. Their inhibition can affect the digestion of polysaccharides and the maturation, transport and secretion of glycoproteins. Because cell-surface carbohydrates are involved in various biological functions, such as cell-cell recognition, cell adhesion, and cell-growth regulation, their implication in the immune response, oncogenesis, tumor metastasis, and the differentiation of cells is no longer doubted. Therefore, searching for inhibitors of glycosidases that play an important role in the

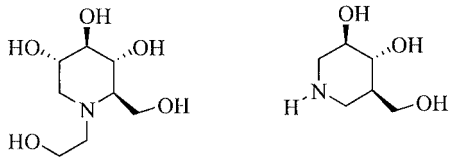
control of cell-surface carbohydrate structure and function could lead to the emergence of novel antiviral, anti-infective or anti-cancer agents.

Alkaloids mimicking sugars have now been proved to inhibit glycosidases because of their structural resemblance to the sugar moiety of the natural substrates of these enzymes.

Antidiabetic Agents

Digestive α-glucosidases, located in the small intestine, are enzymes that hydrolyze dietary carbohydrates to monosaccharides, which are absorbed through the intestinal wall. In 1995, it was thought that treatment of noninsulin-dependent diabetes (type II diabetes) could be achieved by means of these enzymes, thus regulating the absorption of carbohydrates.

DNJ **9**, described as having an inhibitory effect on mammalian α-glucosidases in vitro, was thought to be promising for diabetes, but its efficacy in vivo was not as good as expected. In order to optimize this natural compound, a series of DNJ derivatives was developed and *N*-alkylated-type analogs like Miglitol (**21**; BAY m1099; Figure 5) were characterized as potent inhibitors of the glycogenolysis induced by glucagon in studies with hepatocytes.[16] Today, Miglitol is commercially available in the USA and Canada for the treatment of type II diabetes (GLYSET™).



Miglitol **21** Isofagomine **22**

Figure 5. Promising antidiabetic imino sugars.

In this type II diabetes, an increase in hepatic glucose production and in blood glucose level is observed. Preventing this could be achieved by inhibition of hepatic glycogen phosphorylase. Isofagomine (**22**; Figure 5) was recently found to be a good inhibitor of liver glycogen phosphorylase, blocking glycogen degradation in hepatocytes in culture. Interestingly, some *N*-alkylated analogs of isofagomine retain the micromolar activity value, whereas experiments with fagomine (**18**) or DNJ (**9**) resulted in a dramatic loss of activity, thereby illustrating the specificity of some imino sugars.[17]

Processing Glycosidases and Quality Control in the Endoplasmic Reticulum

The oligosaccharide chains of *N*-linked glycoproteins are now believed to be involved in a large number of biological phenomena at the cell surface, like cell-cell adhesion, recognition, differentiation, and also infection processes by viruses and bacteria. The endoplasmic reticulum (ER) and Golgi apparatus are the center of the formation of complex *N*-glycan chains by the action of specific α-glycosidases as well as glycosyltransferases. The final *N*-glycan structures depend on the polypeptides and enzymes expressed in the cell.[18] In mammalian cells, removal of α-1,2-linked mannose residues from oligosaccharide precursors is essential for maturation to hybrid or complex oligosaccharides, while removal of α-1,3- or α-1,6-linked mannose residues is required for complex *N*-glycan synthesis. In the ER, the glycosidases are not only implicated in deglycosylation steps but are also closely involved in the quality control system designed to promote folding and oligomerization of novel mature proteins.[19] However, initiation of the biosynthesis of the oligosaccharide chains of *N*-linked glycoproteins is induced by insertion of a common oligosaccharide moiety ($Glc_3Man_9GlcNAc_2$) into the glycosylation site of the concerned polypeptide and successive removal of the glucose and mannose residues by ER glycosidases (Figure 6).

It is now clear that modification or alteration of one or more biological events during the biosynthesis of *N*-linked

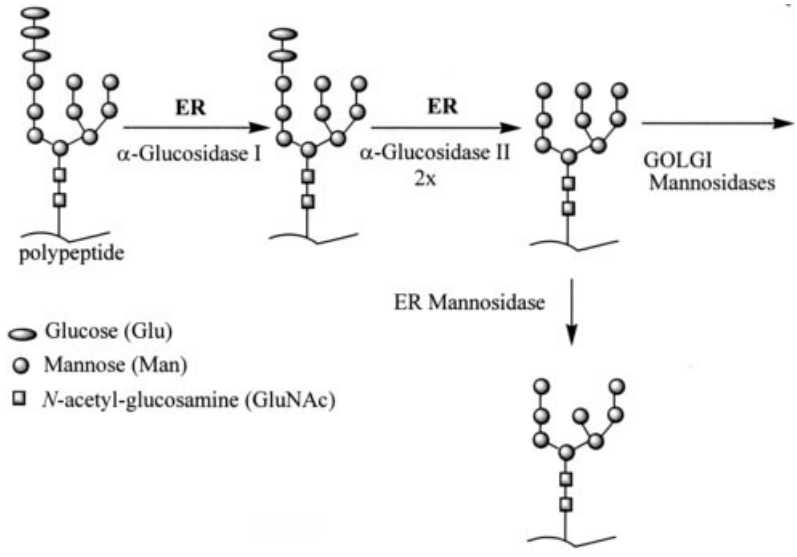
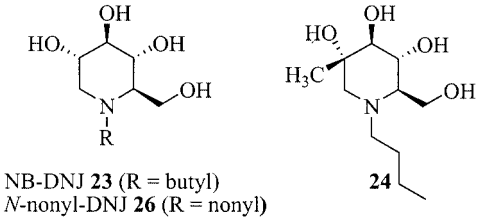


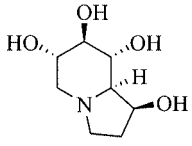
Figure 6. ER glycosidase pathways.

or asparagine-linked glycoproteins could have an impact, for instance, on viral infection or tumor invasion.[20] As an example, HIV viral infection of a cell is promoted by the participation of two key glycoproteins present on the membrane of the cell: gp120 and gp41. Compounds that interfere with correct glycoprotein glycosylation could prevent invasion by the virus. DNJ, as well as its *N*-butyl analog **23** (NB-DNJ) and peracylated *N*-butyl analog (Glycovir), have been found to be active at concentrations of around 0.5 mg mL^{-1} on HIV.[21] In the same piperidine series, many epimers or derivatives do not show anti-HIV activity, with compound **24**[22] and castanospermine **25** (Figure 7) being notable exceptions. In addition, *N*-nonyl-DNJ (**26**) has been shown to be 100–200 times more potent than NB-DNJ (**23**) in the inhibition of hepatitis B virus in cell-based assays.[23] It is now clear that the identification of inhibitors of classes of enzymes like α-glycosidases, α-L-fucosidases, and bacterial neuraminidases involved in viral and bacterial infections could be achieved by the design and synthesis of new original imino sugars.[20]



NB-DNJ **23** (R = butyl)
N-nonyl-DNJ **26** (R = nonyl)

24

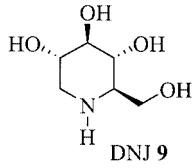


Castanospermine **25**

Figure 7. Potential agents targeting lysosomal storage disorders.

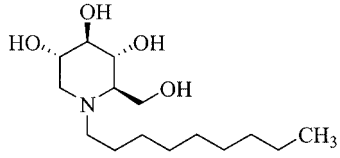
Lysosomal Storage Disorders

In a similar approach, disorders in the biosynthesis or catabolism of glycolipids in the cell (glycosphingolipids) have an impact on the so-called lysosomal storage diseases like type 1 Gaucher disease or Fabry disease.[24] In normal cells, there is a balance (homeostasis) between the degradation of glycosphingolipids (GSLs) in the lysosome and their biosynthesis in the ER/Golgi system. The rates of influx of GSLs and efflux of metabolites are in equilibrium. In a lysosomal storage disease cell, enzyme activity in the lysosome is so low that GSLs accumulate. However, although the catalytic activity of the enzymes is reduced, it is not totally eliminated. Thus, drugs that could regulate the biosynthesis of GSLs to a concentration that fits well in the residual enzymatic activity could prevent storage. Such a therapeutic strategy has been carried out with *N*-alkylated DNJs, which are inhibitors of ceramide-specific glucosyltransferases.[25] A structure–activity relationship study on the inhibition of α-glucosidase and ceramide glucosyltransferase has been performed with *N*-alkylated compounds like *N*-nonyl-DNJ (**26**) or *N*-7-oxadecyl-DNJ (**27**) and it was noted that the mode of action of these potential inhibitors might be markedly different with both enzymes (Figure 8).[26]



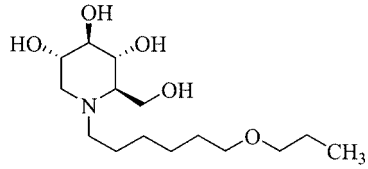
DNJ **9**

α-glucosidase I: IC_{50} = 1.44 μM
ceramide glucosyltransferase : no inhibition at 2 mM



N-nonyl-DNJ **26**

α-glucosidase I: IC_{50} = 0.48 μM
ceramide glucosyltransferase : 96 % (200 μM)



N-7-oxadecyl-DNJ **27**

α-glucosidase I: IC_{50} = 0.29 μM
ceramide glucosyltransferase : 97 % (200 μM)

Figure 8. Specificity of DNJ and original *N*-alkylated analogs.

The second experimental approach was the binding of lysosomal glycosidases (α- and β-galactosidases or β-glucosidase) with *N*-butyl-DNJ (**23**) or *N*-nonyl-DNJ (**26**), to favor the active three-dimensional structure of these lysosomal enzymes and induce correct catalysis (chemical chaperone).[27]

Tumor Metastasis

The membrane surfaces of malignant cells differ from normal ones in the structure and composition of their glycoproteins, glycolipids, and proteoglycans. Consequently, the nature of the carbohydrates that participate in the complex process of metastasis is also specific and these sugars are sometimes altered.[28] A study of the inhibitory effect of imino sugars like NJ, MJ, or DNJ has been carried out by

Tsuruoka and co-workers in a model of pulmonary metastasis of mouse B16 melanoma. In vitro treatment with 10 mg mL^{-1} of the tested compounds was 98% and 80% effective with NJ (**1**) and DNJ (**9**), respectively, and 57% effective with MJ (**7**), thus highlighting the participation of α-glycosidases in metastatic processes.[28]

Glycosidase Mechanisms and Nonnatural Glycosidase Piperidine Inhibitors

Glycosidases catalyze the same reaction − hydrolysis of a glycosidic bond − and to date more than two thousand glycoside hydrolases have been identified and classified into 97 different families. Structural information about these glycosidases is available at a specific website (http://afmb.cnrs-mrs.fr/CAZy). This enzymatic reaction can occur with one of two possible stereochemical controls − inversion or retention of configuration − leading to two different mechanisms (Figure 9).[29]

Two carboxylic residues at the enzymatic site are responsible for this specific cleavage, which also involves a molecule of water. In inverting glycosidases (Figure 9a), the two carboxylic groups playing the role of acid and base catalysts are suitably placed at an average distance of 10.5 Å to allow the substrate and the molecule of water to bind together.[30] The mechanism involves an oxocarbenium ion as the transition state. In retaining glycosidases (Figure 9b), a covalent glycosyl–enzyme bond is formed in the first step leading to the loss of the aglycon part. In the second step, the basic carboxylate group located on the opposite side of the pyranose plane reacts with the molecule of water to form a hydroxyl ion, which attacks the anomeric center and releases the sugar. In these currently accepted mechanisms, the oxocarbenium ion at the anomeric center is probably present in the transition states. Furthermore, structural information has been obtained by X-ray crystallography on trapped covalent intermediates. The role of substrate distortion, particularly in β-glycosidases, has also been evoked because this may favor sugar-bond cleavage.[30]

Considering that the enzyme should bind more strongly to the transition state than to the substrate, the design and synthesis of potential inhibitors of glycosidases must take these mechanisms into account. The relative importance of shape and charge in the design of new glycosidase inhibitors is still uncertain, as illustrated by the following question: why are neutral glyconolactones like **28** and protonable hydroxy piperidines like DNJ **9** equivalent inhibitors of β-glycosidases (Figure 10)? More information can be found in a complete and specific paper on the transition-state analog glycosidase inhibitors recently published by Bols and coworkers.[31] In this review, the authors concluded that, among all the glycosidase inhibitors considered, including those that emulate protonation of an exocyclic oxygen, like compound **29**, or are in favor of an oxocarbenium ion-like transition state, like DNJ (**9**), or that mimic charge at the anomeric site, like **30**, or at several positions, like **31**, and neutral inhibitors like **32** (Figure 10), the best ones seem to be the azasugars having a nitrogen in place of the exo- or endocyclic oxygen or in place of the anomeric carbon.

However, selectivity factors towards α- or β-glycosidases or a specific enzyme in one of these two groups remain unclear. It must also be remembered that introduction of a substituent other than a hydroxyl group on the six-membered ring, or attachment of one or more monosaccharides on the aza ring, could play an important role in enzyme specificity.

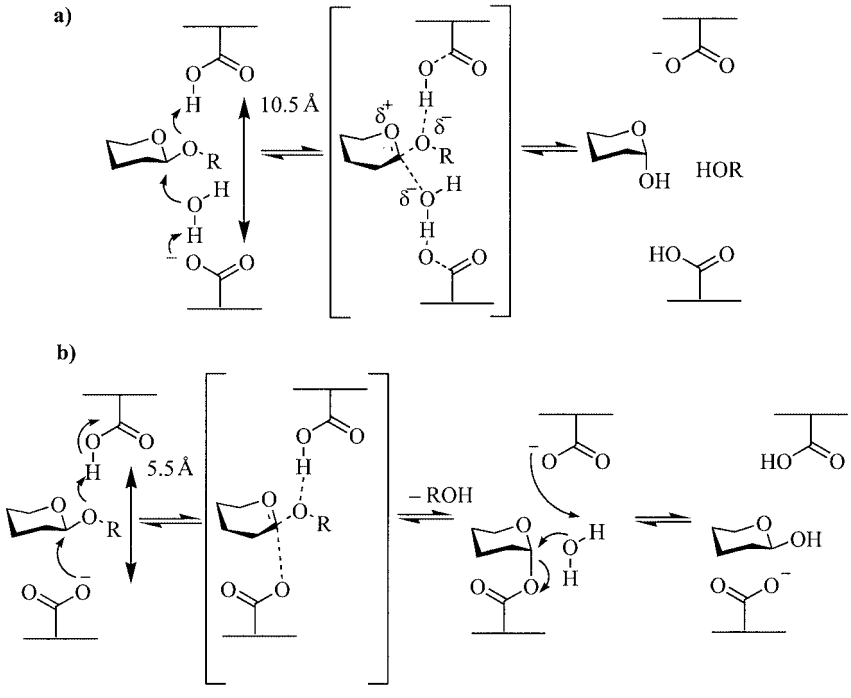


Figure 9. Mechanisms of inverting a) and retaining b) glycosidases.

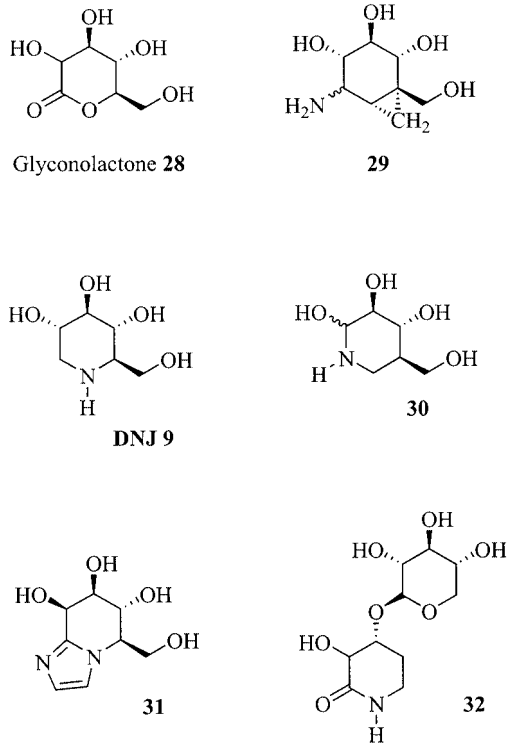


Figure 10. Various glycosidase inhibitors with different structures and protonable center.

The azasugars discussed in this review belong to those inhibitors that mimic a positively charged endocyclic oxygen. These polyhydroxylated piperidines must resemble the transition state of acidic glycoside hydrolysis, which is believed to be late. However, in their protonated form, the anomeric center is still sp^3 hybridized and they do not adopt a half-chair conformation as expected for oxocarbenium transition-state analogs of glycoside cleavage processes (Figure 11).

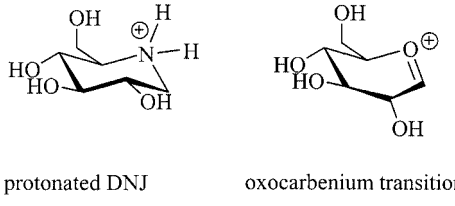


Figure 11. Protonated DNJ and oxocarbenium transition state.

Identification of protonated NJ or DNJ as transition-state analogs has been discussed and questions remain unanswered. However, their possible interaction with the catalytic carboxyl/carboxylate groups provides a rational explanation for their observed activity, even if it is not clear whether the basic piperidine deprotonates the catalytic acid carboxylic group or interacts in a protonated form with the catalytic nucleophile.

In α- and β-retaining glycosidases, the main differences lie in the relative positions of the catalytic acid and basic carboxyl groups. Whether the transition state is preferentially charged on the ring oxygen (Figure 12, state A) or on the anomeric carbon (Figure 12, state B) should induce a specific enzymatic hydrolysis. This has been clearly demonstrated with analogs with nitrogen in the anomeric position or in place of the oxygen ring. The first ones, like isofagomine (**22**), are good inhibitors of β-glycosidases in which the catalytic carboxylate is located beneath the sugar ring. α-Glycosidases, in which the catalytic carboxylate is located above this ring, are preferentially inhibited by DNJ analogs.[32] Even though isofagomine has been shown to be a potent inhibitor of β-glucosidases, DNJ (**9**) also binds these enzymes with micromolar affinity. A recent study published by Davies and co-workers has reinvestigated the binding of these two azasugars to β-glucosidases taking into account structural and thermodynamic requirements.[33]

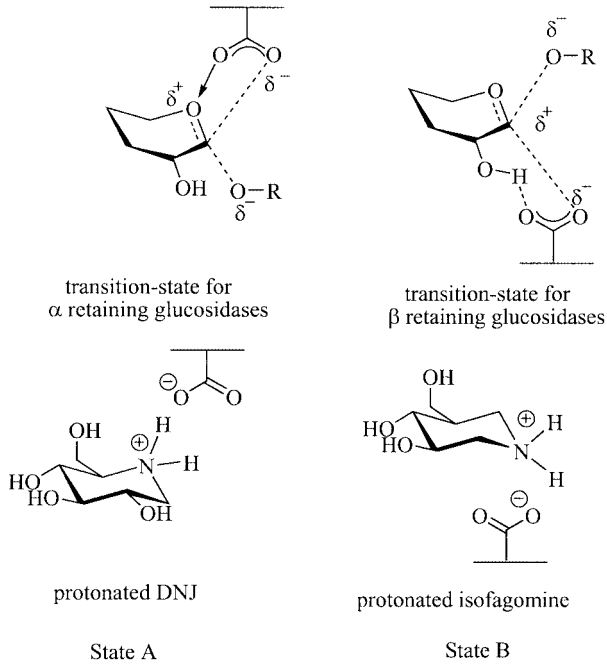


Figure 12. Transition states for α- and β-retaining glycosidases.

Aza inhibitors that mimic charge in several places have been developed, like amidine or amidoxime analogs (**33**) of DNJ or azasugars fused with heterocycles like imidazole **31** or triazole (Figure 13). The azoles, in particular, have led to a better understanding of α- and β-glucosidase mechanisms and have also shown good and specific inhibitory properties.[32]

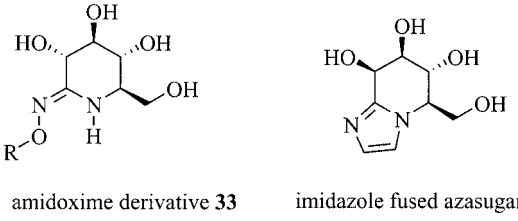


Figure 13. Amidoxime and MJ-imidazole derivatives.

Some authors have also prepared disaccharide analogs with the aglycon part of a natural substrate branched to the

designed azasugar inhibitor in order to increase potency and selectivity. As mentioned previously, *N*-alkylated compounds like Miglitol (**21**) or NB-DNJ (**23**) have been approved as potential therapeutic agents for lysosomal storage. It is now clear that the introduction of structural modifications on the natural glycosidase inhibitor NJ (**1**), in terms of epimerization or *C*- or *N*- substitutions, might open the way to the identification of novel azasugars with potential therapeutic applications.

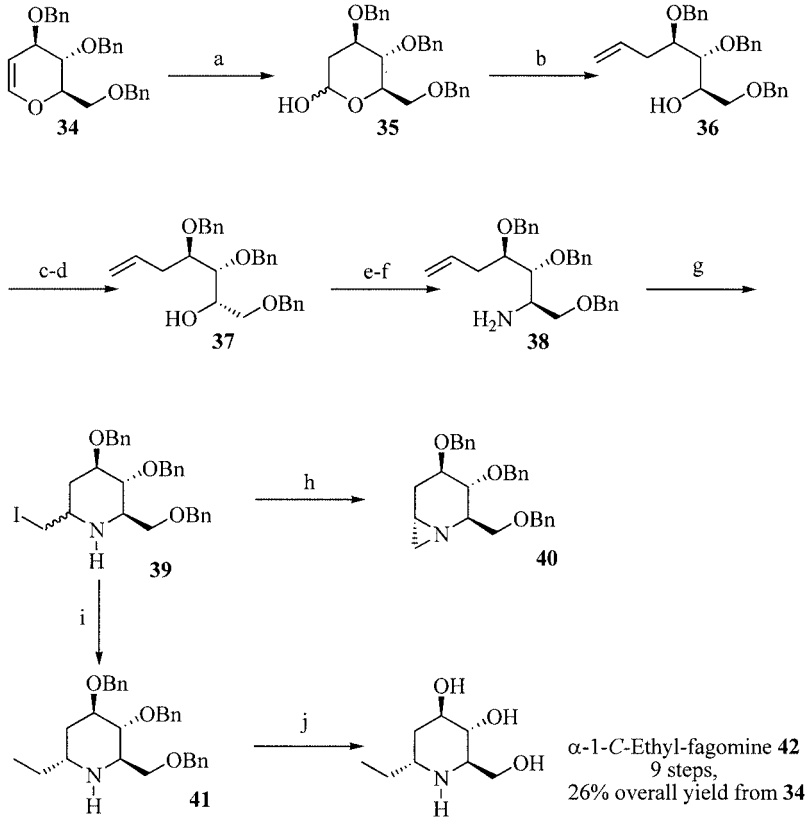
Synthesis of Azasugars

It is not surprising that the strong therapeutic potential of azasugars has generated a huge interest in their synthesis and structural modification and has stimulated many groups to develop short and stereoselective routes. In this context, many recent syntheses (from 1999 to June 2004) use readily available and inexpensive chiral-pool starting materials such as carbohydrates, amino acids, and tartaric acids. Furthermore, the obvious similar structural features between azasugars and carbohydrates have made them ideal starting materials. Sharpless asymmetric epoxidation and dihydroxylation reactions have found successful applications in the chiral synthesis of azasugars. In addition, chemoenzymatic synthesis has been used effectively in this field. The following chemistry part is organized according to the different synthetic strategies listed above.

Chiral-Pool Starting Materials: Carbohydrates

A wide range of carbohydrates is available providing excellent chirons.[34] Depending on the targets, the main challenge in this approach is the differentiation of the hydroxy groups and the conversion of one of them into an amino group or a precursor. In addition, the restructuring of the chiral pool with stereoselective chemical transformation is crucial to the efficiency and the viability of the syntheses. In this context, many azasugars have been obtained from carbohydrates, in most cases with an intramolecular cyclization reaction using a nucleophilic amine or an intramolecular reductive amination cyclization as the key step.

As the first example, an intramolecular electrophilic iodination of a terminal double bond with a nucleophilic amine has been skilfully used by Compain, Martin et al.[35] to synthesize various α-1-*C*-substituted derivatives of fagomine (**18**), as illustrated in Scheme 1. 3,4,6-Tri-*O*-benzyl-D-glucal (**34**) was treated with NIS followed by removal of the iodide by treatment with sodium dithionite in a one-pot procedure. The resulting 2-deoxysugar **35** was converted into the D-*xylo* heptenitol **36** by subsequent Wittig methyl-

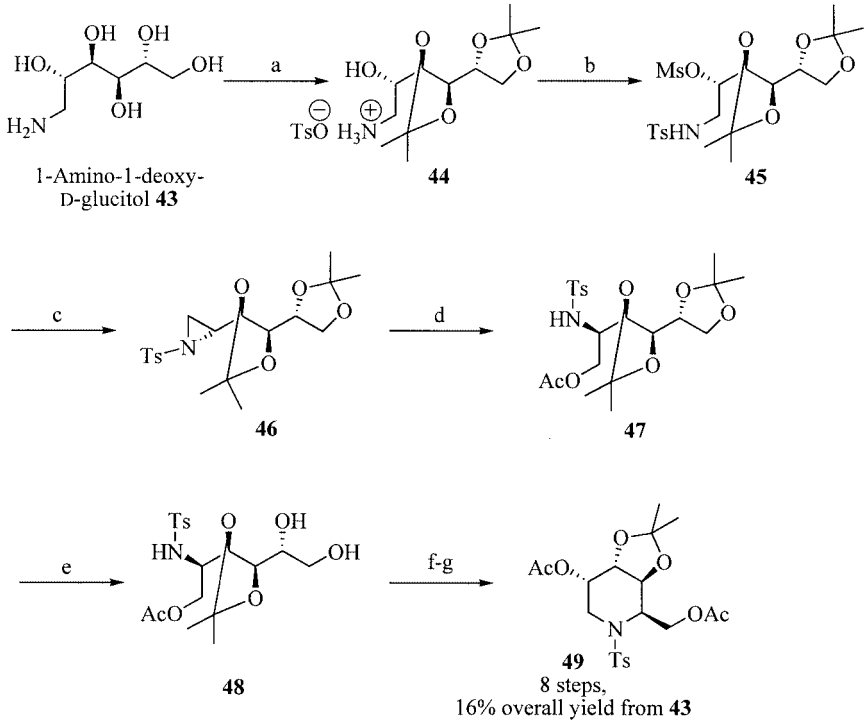


Scheme 1. Reagents and conditions: (a) NIS, CH_3CN/H_2O (95:5), 0 °C, 15 min. then $Na_2S_2O_4$, $NaHCO_3$, DMF/H_2O (1:1), 5 h; (b) [$Ph_3P^+CH_3Br^-$], *n*BuLi, THF, 0 °C to room temp., 16 h, 81% (2 steps); (c) PPh_3, *p*-nitrobenzoic acid, DIAD, toluene, 0 °C to room temp., 16 h; (d) Na, MeOH, 1 h, 79% (2 steps); (e) phthalimide, PPh_3, DIAD, toluene, 0 °C to room temp, 16 h; (f) ethylenediamine, EtOH, 80 °C, 5 h, 72% (2 steps); (g) NIS, DCM, 1 h; (h) DBU, THF, reflux, 6 h, 74% (2 steps); (i) Me_2CuLi, THF, –50 °C to room temp., 6 h, 65%; (j) H_2, Pd/C, EtOH, 4 N HCl, 24 h, 88%.

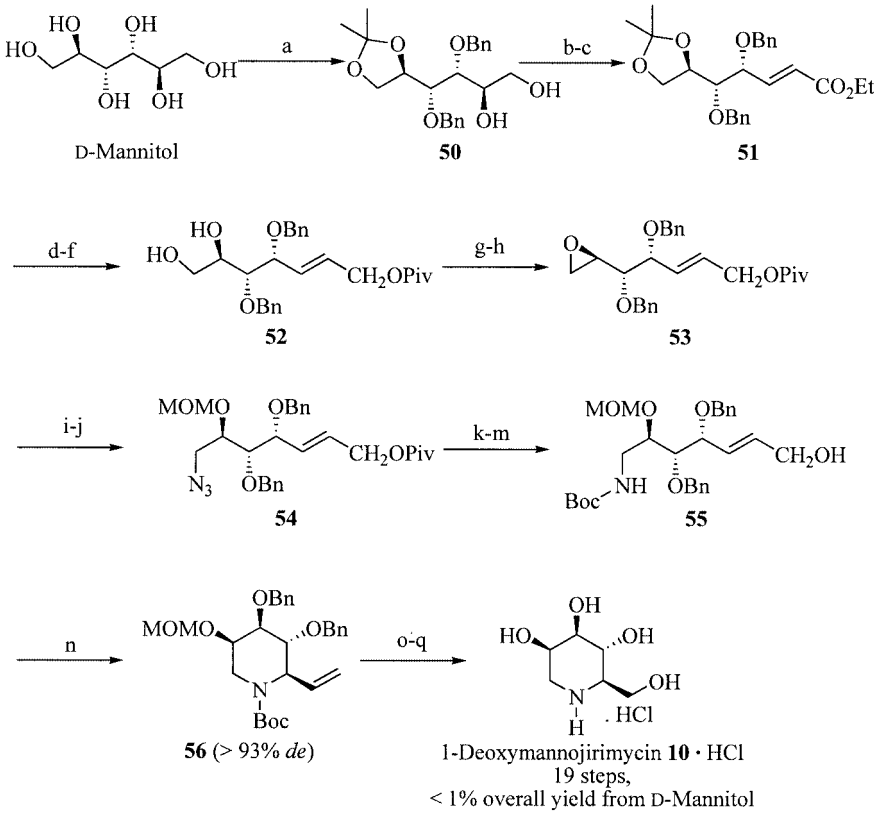
enation. A Mitsunobu reaction was then used to invert the alcohol **36** via the benzoate intermediate, which was cleaved under basic conditions to afford L-*arabino*-heptenitol (**37**). This material was treated once again under Mitsunobu conditions with phthalimide, and subsequent cleavage of the phthalimido group gave the desired D-*xylo*-amino sugar **38** in 78% yield for the whole process. The cyclization of **38** was promoted with NIS as an electrophile source to afford, with correct stereoselectivity (70% *de*), a mixture of α- and β-1-*C*-iodomethyl derivatives **39**. This was directly treated with DBU to give, after separation by flash chromatography, the aziridine **40** in 74% yield for the two steps. Unfortunately, all attempts to ring-open the aziridine with various organometallic species were unsuccessful. In contrast, this transformation carried out with various heteroatomic nucleophiles afforded the desired adducts in good yields. Moreover, to reach the target molecule **42**, the previous mixture of α- and β-1-*C*-iodomethyl intermediates **39** was treated with Me_2CuLi and, after separation of the isomers by flash chromatography, hydrogenolysis of the benzyl protecting groups in **41** led to the α-1-*C*-ethyl fagomine **42** in 57% overall yield for the two steps.

The potential offered by ring closure under Mitsunobu conditions for the synthesis of azasugars was demonstrated by Compernolle et al.[36] Thus, the synthesis of fully protected DMJ derivative **49** was achieved in 16% overall yield from 1-amino-1-deoxy-D-glucitol (**43**), as depicted in Scheme 2. The crystalline 3,4;5,6-di-*O*-isopropylidene ammonium salt derivative **44** [prepared in two steps with 71% overall yield from commercially available 1-aminoglucitol (**43**)][37] was sequentially treated with TsCl and MsCl to afford the intermediate **45**, which was isolated in 92% yield after chromatography. Formation of the aziridine **46** was promoted by treating **45** with NaH and then aziridine ring-opening with KOAc led to the corresponding *N*-tosylamide **47** in good yield for the two steps. Regioselective deprotection of the terminal isopropylidene group of **47** was then effected by treatment with an acidic ion-exchange resin to afford the 5,6-diol **48** in 80% yield. Finally, treatment of this diol under Mitsunobu conditions provided the unprotected piperidine intermediate. This was then directly converted into the less-polar corresponding acetate **49** to facilitate purification on silica gel chromatography from polar by-products arising from the reagents.

Hirai et al.[38] have completed an original synthesis of DMJ (**10**) using an intramolecular Pd-catalyzed cyclization as the key step (Scheme 3). Starting material **50** was prepared from D-mannitol in 25% overall yield following a known three-step procedure.[39] The diol **50** was then subjected to an oxidative cleavage followed by the Horner–Wadsworth–Emmons reaction to give the α,β-unsaturated ester **51** in 70% overall yield. Reduction of the ester group and protection of the corresponding alcohol as the pivaloyl ester gave an intermediate which, when treated with HCl, afforded the diol **52** in good yield. Tosylation of the primary alcohol of **52** followed by nucleophilic substitution in the presence of K_2CO_3 led to the epoxide **53**. Subsequent regioselective ring-opening of the epoxide **53** with azide anion followed by protection of the free alcohol as its MOM derivative afforded the azido intermediate **54** in 39% overall



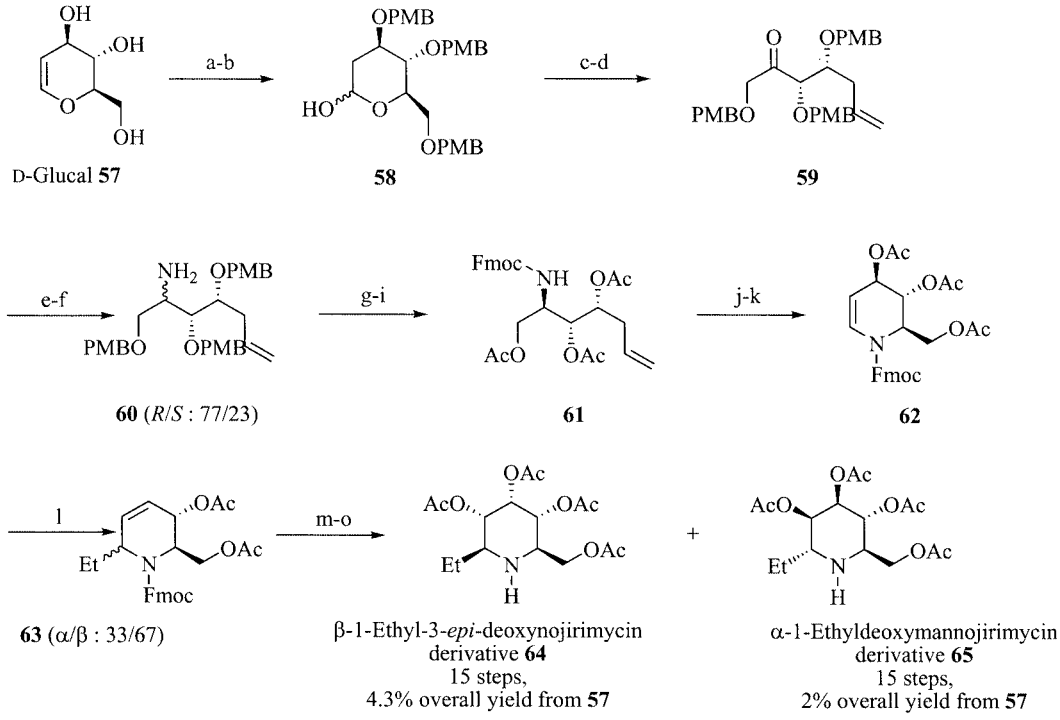
Scheme 2. Reagents and conditions: (a) ref. [37], 71% (2 steps); (b) TsCl, Et_3N, DCM, room temp., 30 min then MsCl, room temp., 1 h, 92%; (c) NaH, THF, room temp., 1 h, 90%; (d) KOAc, DMF, 90 °C, 18 h, 91%; (e) Dowex, MeOH/H_2O (9:1), room temp., 80%; (f) PPh_3, DEAD, THF, room temp.; (g) pyridine, Ac_2O, room temp., 2 h, 38% (2 steps).



Scheme 3. Reagents and conditions: (a) ref. [39], 25% (3 steps); (b) $NaIO_4$, Et_2O/H_2O (15:1), 0 °C to room temp., 2.5 h; (c) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, –78 °C to –20 °C, 3 h, 70% (2 steps); (d) DIBAL, THF, –78 °C to –20 °C, 4 h; (e) PivCl, pyridine/THF (1:1), 0 °C to room temp., 2.5 h; (f) 10% aq. HCl, THF, 40 °C, 5 h, 83% (3 steps); (g) TsCl, pyridine/DCM (1:5), room temp., 23 h; (h) K_2CO_3, MeOH, 0 °C, 2 h, 76% (2 steps); (i) NaN_3, NH_4Cl, 15-C-5, DMF, 55 °C, 10 h; (j) MOMCl, iPr_2NEt, 0 °C to room temp., 6.5 h, 39% (2 steps); (k) PPh_3, THF/H_2O, room temp., 16 h; (l) $(Boc)_2O$, Et_3N, DCM, room temp., 4 h; (m) K_2CO_3, MeOH, room temp., 14 h, 44% (3 steps); (n) $[PdCl_2(CH_3CN)_2]$ (14 mol%), THF, room temp., 3.5 h, 86%; (o) O_3, DCM/MeOH (4:1), –78 °C then $NaBH_4$, –78 °C to room temp., 21 h; (p) TFA, DCM, 0 °C to room temp., 21.5 h; (q) H_2, 10% Pd/C, conc. HCl, EtOH, room temp., 5 h, 30% (3 steps).

yield. The conversion of this latter azido ester **54** into the corresponding *N*-Boc protected amino alcohol **55** was carried out by subsequent reduction of the azide function with PPh_3 and treatment of the resulting amine with $(Boc)_2O$, followed by methanolysis of the pivaloyl ester. The intramolecular cyclization of **55** was achieved by treatment with Pd^{II} to afford the piperidine **56** in 86% yield and in excellent diastereoselectivity (up to 93% *de*). Conversion of **56** into DMJ (**10**) was effected by a three-step sequence involving ozonolysis and removal of the benzyl and *N*-Boc protecting groups. Following this approach, DMJ was synthesized in 19 steps and in less than 1% overall yield from D-mannitol.

An intramolecular cyclization of an amino aldehyde into an aza-hemiacetal intermediate has been developed by Shipman et al.[40] to synthesize the two other isomers of 1-*C*-ethyl-DNJ (**64** and **65**), as illustrated in Scheme 4. Starting with D-glucal (**57**), protection of the hydroxyl groups using PMB chloride followed by hydration of the dihydropyran ring with $Hg(OAc)_2$ and $NaBH_4$ led to the 3,4,6-*O*-protected-2-deoxyglucose **58** (51% yield). This lactol **58** was subjected to Wittig methylenation with $Ph_3P{=}CH_2$ to give, after oxidation of the resulting secondary alcohol with TPAP, the ketone **59** in 69% yield from **58**. Condensation of hydroxylamine with **59** in the presence of pyridine in EtOH produced an oxime intermediate, which was reduced with LAH in Et_2O to furnish the amine **60** as an inseparable 3:1 mixture of (*R*)- and (*S*)-isomers. This latter mixture was subjected to *N*-protection using Fmoc-Cl, followed by acidic cleavage of the PMB protecting groups and reprotection of the resulting triol as its acetate to afford, after purification by chromatography on silica gel, the desired (*R*)-diastereoisomer **61** in 54% yield for this five-step process. Under ozonolysis conditions, spontaneous intramolecular condensation of the amino function on the aldehyde group resulting from cleavage of the double bond of **61** generated an aza-hemiacetal intermediate, which was dehydrated into the iminoglucal **62** in 53% overall yield upon treatment with oxalyl chloride. This work provides an efficient preparation of the chiral key synthon **62** and opens up an access to a varied range of C1-substituted imino sugars via C–C bond-forming reactions at C1. Thus, addition of diethylzinc at –20 °C, in the presence of $BF_3{\cdot}Et_2O$, to a solution of **62** in DCM gave an α/β mixture of the tetrahydropyridines **63** in a ratio of 1:2. Without purification, this alkene was stereoselectively dihydroxylated according to Upjohn conditions. The crude resulting polyhydroxylated piperidine was successively treated with Ac_2O in pyridine to protect the



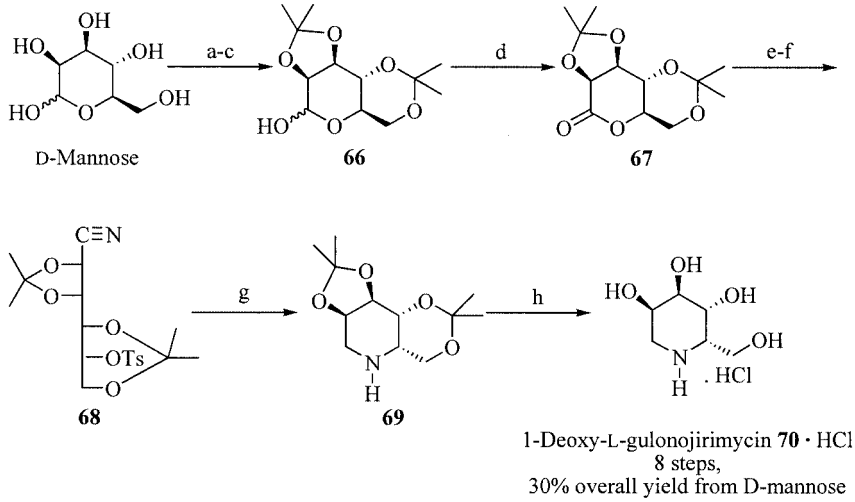
Scheme 4. Reagents and conditions: (a) NaH, PMBCl, DMF, room temp.; (b) $Hg(OAc)_2$, THF/H_2O, room temp., then $NaBH_4$, room temp., 51% (2 steps); (c) $Ph_3P{=}CH_2$, toluene, room temp.; (d) TPAP, NMO, MS, DCM, room temp., 69% (2 steps); (e) $HONH_2{\cdot}HCl$, pyridine, EtOH, 60 °C; (f) $LiAlH_4$, Et_2O, room temp.; (g) FmocCl, K_2CO_3, THF/H_2O (3:1), room temp.; (h) CF_3CO_2 H, DCM, room temp.; (i) Ac_2O, pyridine, room temp., 54% (5 steps); (j) O_3, DCM, –78 °C then Me_2S, room temp.; (k) $(COCl)_2$, Et_3N, DMF, DCM, room temp., 53% (2 steps); (l) $BF_3{\cdot}Et_2O$, Et_2Zn, DCM, –20 °C to room temp., 2 h; (m) OsO_4 cat., NMO, acetone/H_2O, room temp., 5 d; (n) Ac_2O, pyridine, room temp., 2 h; (o) piperidine, DCM, room temp., 1 h, 43% for **64** (4 steps), 19% for **65** (4 steps).

2,3-hydroxy groups and with piperidine in DCM to remove the Fmoc protecting group. After separation by chromatography on silica gel, 2,3,4,6-tetra-*O*-acetyl-β-1-ethyl-3-*epi*-DNJ (**64**) and 2,3,4,6-tetra-*O*-acetyl-α-1-ethyl-deoxymannojirimycin (**65**) were isolated in 43% and 19% yield, respectively, over four steps from the iminoglucal **62**. In summary, the synthesis of these 1-*C*-ethyl-imino sugars has been achieved in fifteen steps from D-glucal (**57**) in 4.3% yield for **64** and 2% yield for **65**.

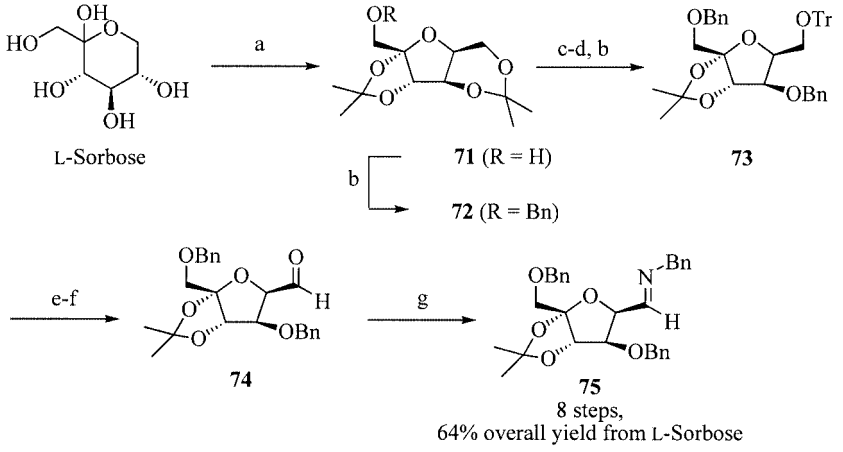
An efficient synthesis of 1-deoxy-L-gulonojirimycin (L-guloDNJ; **70**) from D-mannose by an intramolecular cyclization S_N2 reaction as the key step has been published by Chittenden et al.[41] and is shown in Scheme 5. Thus, the synthesis of L-guloDNJ (**70**) was initiated by the conversion of D-mannose into the known lactone **67**[42] via the diacetal **66**. A slight modification was made by the authors concerning the synthesis of the protected mannose derivative **66**. Instead of direct diisopropylidenation, which led to **66** with inconsistent yields, a three-step protocol consisting of anomeric hydroxyl protection as the benzyl ether followed by diisopropylidenation and debenzylation was performed (68% yield). Then, submission of the diacetal **66** to standard Swern oxidation gave the lactone **67** in 83% yield. Treatment with ammonia followed by protection of the resulting hydroxyl group as its tosyl ester afforded the nitrile **68** in 71% yield. Subsequent reduction of this nitrile function with LAH led to the piperidine structure **69**, in 83% yield, by a spontaneous cyclization with inversion of configuration at C5. Finally, removal of the protecting groups under acidic conditions yielded L-guloDNJ (**70**) as its hydrochloride salt in 90% yield (30% overall yield from D-mannose).

In the following syntheses, an intramolecular reductive amination cyclization of the appropriately amino-substituted sugar hemiacetal intermediate afforded the target azasugars in an efficient way.

A convenient and efficient route to synthesize other imino sugar C1-glycosides has been published by Martin et al.,[43] who accessed the α- and β-isomers of 1-*C*-ethyl-DNJ (**79** and **83**, respectively) and 1-*C*-butyl-DNJ (**78** and **82**, respectively) by a twelve-step sequence in excellent overall yield (22–29%; Scheme 6 and 7). The key intermediate of this approach is the imine **75**, which is easily prepared in eight steps from L-sorbose (an inexpensive sugar) in 64% overall yield (Scheme 6). 2,3;4,6-Di-*O*-isopropylidene-α-L-sorbofuranose (**71**) was obtained in one step from L-sorbose in 80% yield as reported earlier by Paulsen et al.[44] A judicious four-step protection–deprotection procedure gave the fully protected furanose **73** (91% yield from **71**), which was subsequently subjected to cleavage of the trityl group upon treatment with HBr in glacial AcOH. The resulting hydroxymethyl group was then oxidized by treatment with DM periodinane in DCM to afford the aldehyde **74** on a large scale (approx. 10 g). Conversion of **74** to the corre-



Scheme 5. Reagents and conditions: (a) BF_3·MeOH, BnOH, 75 °C, 12 h; (b) DMP, TsOH, acetone, room temp., 2 h; (c) H_2 (1 atm), 10% Pd/C, room temp., 48 h, 68% (3 steps); (d) Me_2SO/TFA, DCM, 83%; (e) NH_3, 25% aq. NH_3, MeOH, room temp., 30 min; (f) TsCl, pyridine, 0 °C to 5 °C, 5 d, 71% (2 steps); (g) $LiAlH_4$, DME, 0 °C, 4 h, 83%; (h) HCl, MeOH, room temp., 18 h, 90%.

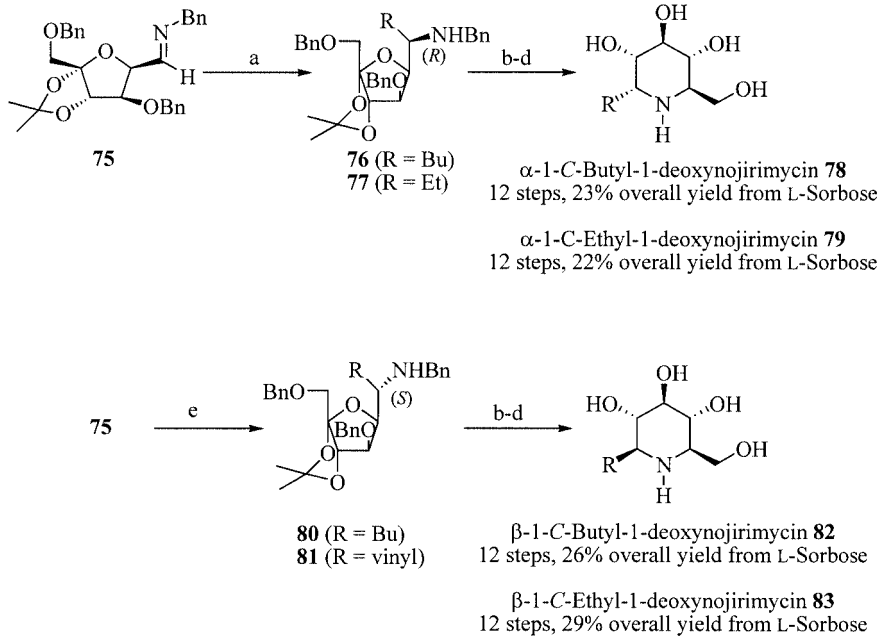


Scheme 6. Reagents and conditions: (a) ref. [44], 80% (1 step); (b) NaH, BnBr, nBu_4NI, THF, room temp., 3–4 h, 98% for **72**, 93% for **73** (3 steps); (c) H_2SO_4/H_2O, acetone, room temp., 3 h; (d) TrCl, pyridine, 55 °C, 48 h; (e) HBr/AcOH, 5 °C, 5 min.; (f) DM periodinane, DCM, room temp., 30 min, 87% (2 steps); (g) $BnNH_2$, mol. sieves, DCM, 4 °C, 3 h, 100%.

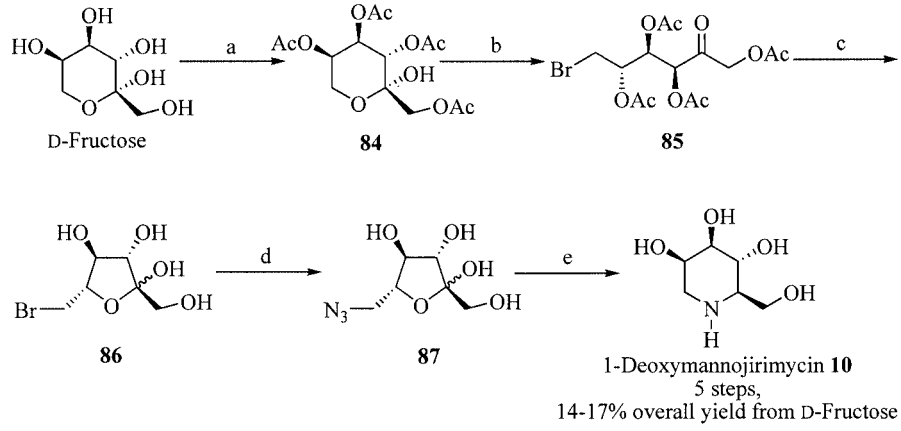
sponding imine was performed by quantitative condensation of $BnNH_2$ at 4 °C in DCM. Thus, this three-step process produced the imine **75** in 87% yield from **73**.

As illustrated in Scheme 7, diastereoselective addition of organometallic nucleophiles to **75**, followed by intramolecular reductive amination and deprotection of the benzyl groups, provided α- and β-1-*C*-butyl-DNJ (**78** and **82**, respectively) and α- and β-1-*C*-ethyl-DNJ (**79** and **83**, respectively). At first, the use of *n*BuLi and EtMgBr in Et_2O at –78 °C gave the 6-(*R*)-butyl and 6-(*R*)-ethyl derivatives **76** and **77** in 65% and 75% yield respectively. These latter aminosorbofuranoses were subsequently treated with a 9:1 solution of TFA and water with the aim of removing the 2,3-*O*-isopropylidene group. The hemiacetal intermediates, bearing a secondary amino group, were subjected to spontaneous intramolecular condensation under these acidic conditions and the resulting cyclic iminium structures were converted to piperidine derivatives by reduction with $NaBH_3CN$. Finally, hydrogenolysis of the protecting groups yielded α-1-*C*-butyl-DNJ (**78**) in 55% yield from **76** and α-1-*C*-ethyl-DNJ (**79**) in 45% yield from **77**. Similarly, the aminosorbofuranoses **80** and **81** were prepared in 69% and 72% yield from **75** by using *n*BuLi and vinylmagnesium bromide in Et_2O in the presence of $BF_3·Et_2O$ to reverse the addition stereoselectivity and thus obtain the (6*S*) derivatives. In the presence of $BF_3·Et_2O$, chelation effects were suppressed and the addition occurred to an opened transition state vs. a chelated intermediate without Lewis acid. Then, **80** and **81** were subjected to the same three-step procedure as **76** and **77** to provide β-1-*C*-butyl-DNJ (**82**) in 60% yield and β-1-*C*-ethyl-DNJ (**83**) in 62% yield (the hydrogenolysis step reducing the vinyl group to the ethyl substituent).

In this context, different syntheses of azasugars have also been reported starting from D-fructose. For example, Stütz et al.[45] have reported an efficient synthesis of DMJ (**10**) in five steps from D-fructose in 14–17% overall yield, as depicted in Scheme 8. Acetylated sugar **84**, prepared from D-



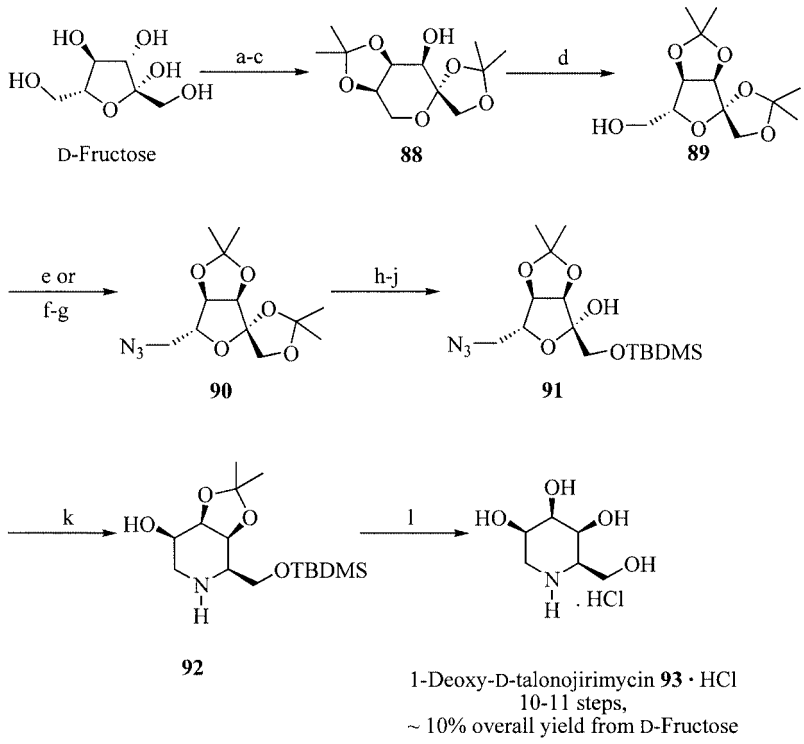
Scheme 7. Reagents and conditions: (a) for **76**: *n*BuLi, Et_2O, –78 °C to 0 °C, 3–12 h, 65%; for **77**: EtMgBr, Et_2O, 0 °C to room temp., 3–12 h, 75%; (b) TFA/H_2O (9:1), 0 °C to room temp., 30 h; (c) $NaBH_3CN$, AcOH, MeOH, 0 °C to room temp., 24 h; (d) H_2, Pd/C, HCl, MeOH, room temp., 48 h, 55% for **78** (3 steps), 45% for **79** (3 steps), 60% for **82** (3 steps), 62% for **83** (3 steps); (e) for **80**: *n*BuLi, $BF_3{\cdot}Et_2O$, –78 °C to 0 °C, 3 h, 69%; for **81**: vinylMgBr, $BF_3{\cdot}Et_2O$, –78 °C to 0 °C, 3 h, 72%.



Scheme 8. Reagents and conditions: (a) ref. [46], 55–60%; (b) $(Ph_3PBr)^+$ Br^-, DCM, pyridine, reflux, 3 h, 89%; (c) 1 M MeONa/MeOH, 0 °C, pH 8, 5 h, 70%; (d) NaN_3, DMF, room temp., 7 d, 66%; (e) H_2, 5% Pd/C, MeOH, room temp., 4 h, 60–70%.

fructose in 55–60% yield by partial acetylation,[46] was treated with commercially available dibromotriphenylphosphorane to give the expected open-chain bromosugar **85** in 89% yield (only 30% yield was obtained when using PBr_3). Cleavage of the acetyl groups led to the formation of the bromofuranose intermediate **86** which, when treated with NaN_3, gave the azidodeoxysugar **87**[47] in 46% overall yield for the two steps. Finally, reductive amination under hydrogen atmosphere and in the presence of a Pd/C catalyst furnished DMJ (**10**) in multigram quantities in 60–70% yield.

Using the same starting material, a synthesis of 1-deoxy-D-talonojirimycin (**93**; Scheme 9) was achieved by Chittenden et al.[41] in about 10% overall yield. Diketal **88** was obtained in a three-step diisopropylidenation–oxidation–selective reduction of known sequence.[48] Treatment of **88** with DMP in the presence of a catalytic quantity of 70% $HClO_4$ gave the thermodynamically more stable acetonide **89** in 93% yield. At this stage, two procedures were then studied by the authors to convert the C-6 primary hydroxyl group into the corresponding azido derivative **90**. Both procedures involved a nucleophilic attack by LiN_3[49] on a tosylate intermediate. Whichever method was applied − the one-pot procedure[50] using 1-methyl-2-fluoropyridinium or the classical two-step procedure[51] using TsCl and pyridine



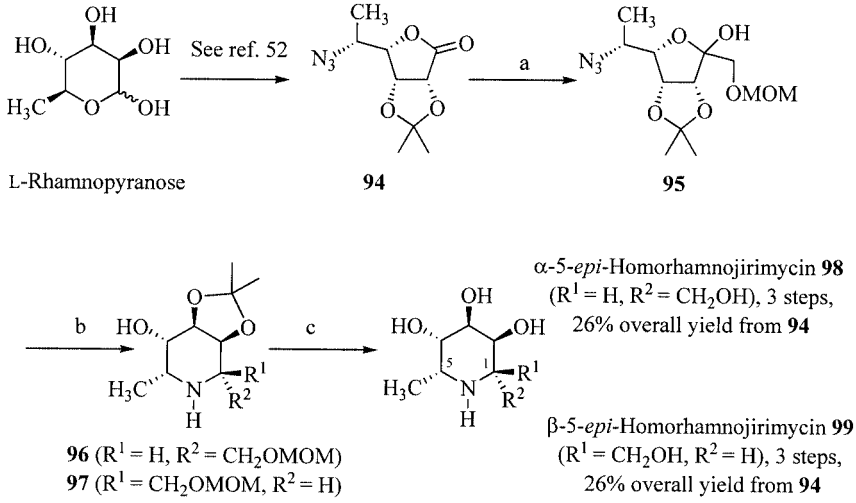
Scheme 9. Reagents and conditions: (a) acetone, I_2, room temp.; (b) Me_2SO/TFA, DCM; (c) $NaBH_4$, EtOH, yield not reported (3 steps); (d) DMP, acetone, $HClO_4$, 93%; (e) 1-methyl-2-fluoropyridinium toluenesulfonate, Et_3N, $CHCl_3$, room temp., 1 h, then LiN_3, NMP, 80 °C, 2 h, 82%; (f) TsCl, pyridine; (g) LiN_3, DMF, 40 °C, 6 d, 76% (2 steps); (h) $BF_3{\cdot}Et_2O$, Ac_2O, room temp., 2 h; (i) NaOMe, MeOH, room temp., 5 min, then Amberlite IR-120 (H^+ form); (j) TBDMSCl, imidazole, DMF, 0 °C to room temp., 35 min, 77% (3 steps); (k) H_2, 10% Pd/C, EtOH, room temp., 18 h, 86%; (l) HCl, MeOH, room temp., 18 h, yield not reported.

− the corresponding azido compound **90** was obtained in good yield (82% and 76% respectively). The 1,2-*O*-acetal group at the anomeric position was then removed under mild conditions, and subsequent Zemplén deacetalization and TBDMS protection afforded the furanose derivative **91** in 77% yield. After catalytic hydrogenation of the azido group, spontaneous intramolecular cyclization followed by hydrogenation of the cyclic imine intermediate gave piperidine **92** in 86% yield. Finally, the hydrochloride salt of 1-deoxy-D-talonojirimycin **93** was obtained by methanolysis under acidic conditions.

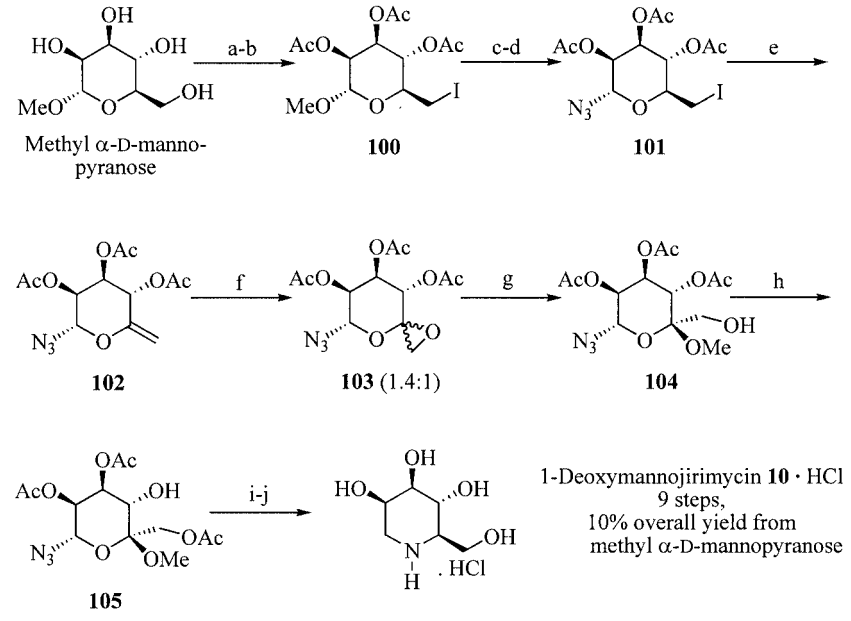
Starting with the 6-deoxy-5-azido-D-gulono-1,4-lactone (**94**) prepared from L-rhamnopyranose,[52] Fleet et al.[53] have reported a three-step strategy based on an intramolecular reductive amination to synthesize the α-homorhamnojirimycin (α-5-*epi*-HRJ, **98**) and α-1-methyl-DGJ (**99**; β-5-*epi*-HRJ), as outlined in Scheme 10. Thus, chain extension by hydroxymethylation[54] of **94** using tributyl-[(methoxymethoxy)methyl]stannane in the presence of *n*BuLi afforded the azido lactol **95** in 76% yield as a 14:1 mixture of anomers. Hydrogenation of the latter azide mixture then induced a reductive amination reaction to give the epimeric piperidines **96** and **97**, which were isolated in 46% and 44% yield, respectively, after separation by chromatography on silica gel. When treated with methanolic HCl, the latter compounds finally gave separately α-5-*epi*-HRJ (**98**) in 79% yield and β-5-*epi*-HRJ (**99**) in 73% yield.

An elegant nine-step synthesis of DMJ (**10**) by the catalytic hydrogenation of an azidoacetal intermediate **105** has been published by Murphy et al.,[55] as depicted in Scheme 11. The iodo derivative **100** was prepared from commercially available methyl α-D-mannopyranoside by exchange of iodine with the hydroxyl group at C-6[56] followed by acetylation of the other hydroxyl groups. From this latter intermediate, an acetolysis reaction followed by treatment with trimethylsilyl azide in the presence of tin(IV) chloride as catalyst yielded the azido derivative **101**. After elimination of hydrogen iodide by treatment with DBU, 1-azido-6-deoxyhex-5-enopyranoside (**102**) was isolated in 46% overall yield from methyl α-D-mannopyranoside. Exposure of this alkene to methyl(trifluoromethyl)dioxirane provided the unstable desired epoxide **103**, which was used for the next step without any purification. Thus, regioselective ring-opening of this crude epoxide with MeOH furnished the intermediate **104**, which underwent an acetate migration during purification by chromatography on silica gel to give the single product **105** in 98% yield from **103**. Finally, removal of the acetate protecting groups followed by catalytic hydrogenation under acidic conditions afforded DMJ (**10**) as its hydrochloride salt in 10% overall yield from methyl α-D-mannopyranoside.

In their continuing research, Fleet et al.[57] have described an original route to azasugars using a tandem Staudinger/aza-Wittig reaction as the pivotal step, as illustrated in

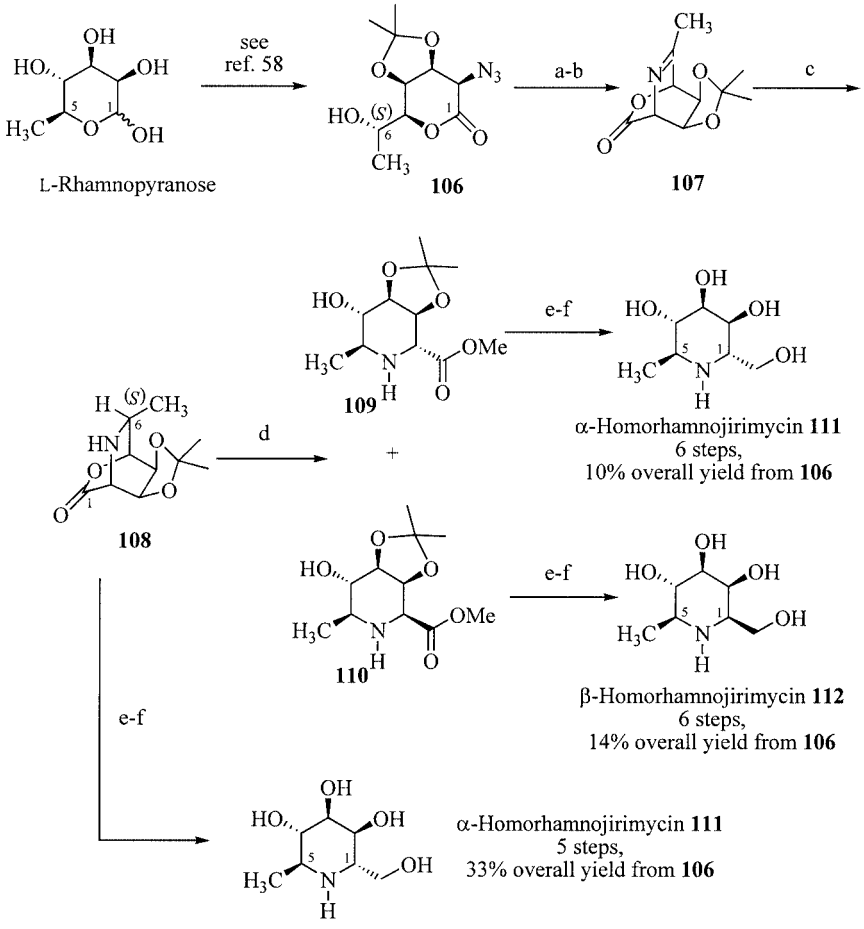


Scheme 10. Reagents and conditions: (a) nBu$_3$SnCH$_2$OMOM, nBuLi, THF, –78 °C, 30 min, 76%; (b) H_2, 10% Pd/C, EtOAc, room temp., 72 h, 46% for **96**, 44% for **97**; (c) HCl, MeOH, room temp., 24 h, 79% for **98**, 73% for **99**.



Scheme 11. Reagents and conditions: (a) PPh_3, imidazole, I_2, toluene, 80 °C, 2 h; (b) Ac_2O, pyridine, 12 h; (c) H_2SO_4/Ac_2O (1:50), room temp., 12 h; (d) $TMSN_3$, $SnCl_4$, DCM, room temp., 10 min; (e) DBU, toluene, 110 °C, 1.5 h, 46% (5 steps); (f) 1,1,1-trifluoroacetone, Oxone®, $NaHCO_3$, Na_2EDTA, CH_3CN, H_2O, 0 °C to room temp., 30 min, 97%; (g) MeOH, reflux, 12 h; (h) silica gel chromatography, 98% from **103**; (i) NaOMe, MeOH, room temp., 4 h; (j) Pd/C, EtOH, room temp., 12 h, then HCl, Et_2O, 23% (2 steps).

Scheme 12. α-HRJ (**111**) and its β-isomer **112**, both considered as aza-*C*-rhamnopyranosyl analogs, were separately obtained from the common bicyclic lactone **108**. The 2-azidoheptono-1,5-lactone **106** was prepared from L-rhamnopyranose following a known procedure.[58] The bicyclic lactone **108** intermediate was then prepared in 41% yield from **106** by a three-step process: oxidation of **106** with PCC in DCM produced a C6-ketone intermediate which, when subjected to an intramolecular Staudinger/aza-Wittig reaction using $P(OEt)_3$, gave the bicyclic imine **107** (50% overall yield). Reduction with $NaBH_3CN$ in AcOH occurred from the less-hindered face opposite the *O*-isopropylidene protecting group and only provided the aminolactone **108**, isolated in 82% yield. The high stereoselectivity of the latter reaction allowed the retention of configuration at C-6 (in comparison with **106**). Treatment of the lactone **108** with AcONa in refluxing MeOH afforded the axial α-methyl ester **109**, which then partially epimerized to the thermodynamic β-diastereoisomer **110** in a ratio of 1.8:1. After separation by chromatography on silica gel, both diastereoisomers **109** and **110** were isolated in 34% and 53% yields, respectively, and were subsequently subjected to the appropriate reduction–deprotection process to give α-HRJ (**111**) in 71% yield from **109** (10% overall yield from **106**) and β-HRJ (**112**) in 63% yield (14% overall yield from **106**). On the other hand, reduction of the lactone **108** with Super-

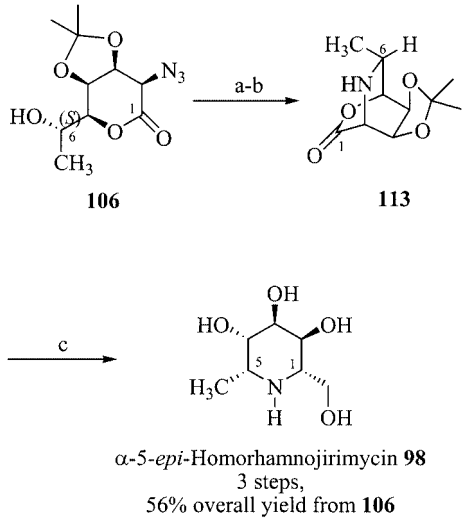


Scheme 12. Reagents and conditions: (a) PCC, MS, DCM, room temp., 2 h; (b) $P(OEt)_3$, THF, reflux, 4 h, 50% (2 steps); (c) $NaBH_3CN$, AcOH, room temp., 30 min, 82%; (d) NaOAc, MeOH, reflux, 6 h, 34% for **109**, 53% for **110**; (e) $LiBEt_3H$, THF, room temp., 5 min; (f) HCl, MeOH, room temp., 18 h, 71% for **111** from **109** (2 steps), 63% for **112** from **110** (2 steps), 80% for **111** from **108** (2 steps).

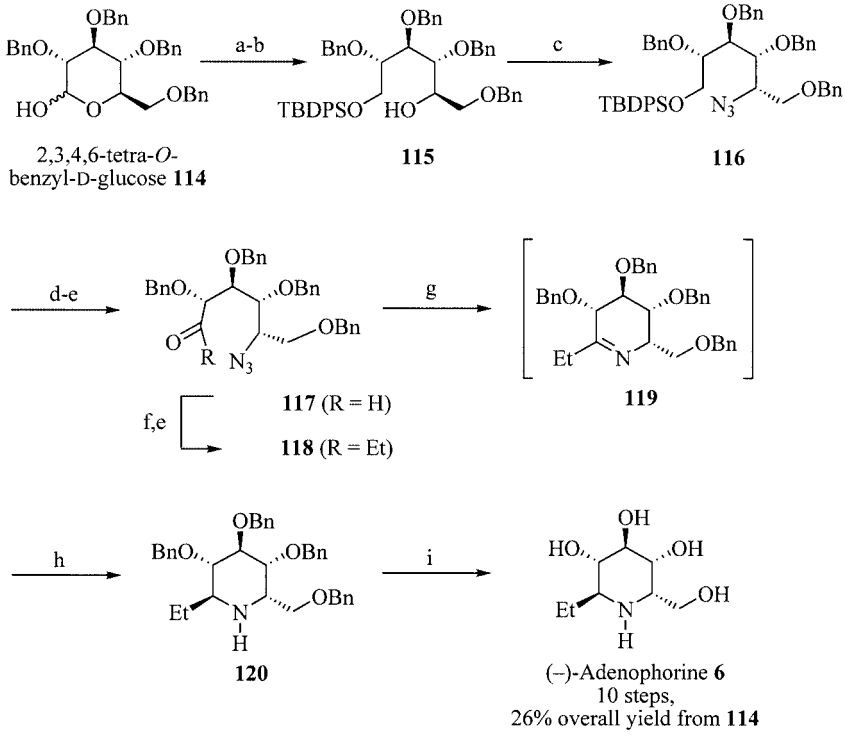
Hydride® followed by removal of the *O*-isopropylidene protecting group afforded, in straightforward fashion, α-HRJ in 80% yield from **108** (33% overall yield from **106**).

In the same paper, the 2-azidolactone **106** was used to access the 5-*epi*-rhamnopyranosyl analog **98** (Scheme 13). Activation of the hydroxy group of **106** at C-6 with Tf_2O, followed by conversion of the azido group to an amino group by hydrogenation, provided the bicyclic lactone **113** in 61% yield. The inversion of configuration at C-6 is due to the stereoselectivity of the intramolecular S_N2 reaction in the piperidine ring formation process. Finally, a lactone-opening reaction was achieved upon reduction of **113** with $LiBH_4$ in THF. Subsequent deprotection by treatment of the mixture with HCl afforded α-*epi*-HRJ (**98**) in 92% yield (56% for this three-step process).

The first synthesis of (–)-adenophorine (**6**)[7] (nonnatural enantiomer) was achieved in 26% yield in ten steps from the D-glucose derivative **114** by Davies et al.[59] using an intramolecular Staudinger/aza-Wittig reaction, as presented in Scheme 14. The opposite optical rotation of the synthetic compound allowed the authors to assign the absolute configuration of natural (+)-adenophorine. Following a known sequence,[60] reduction of the hemiacetal function of 2,3,4,6-



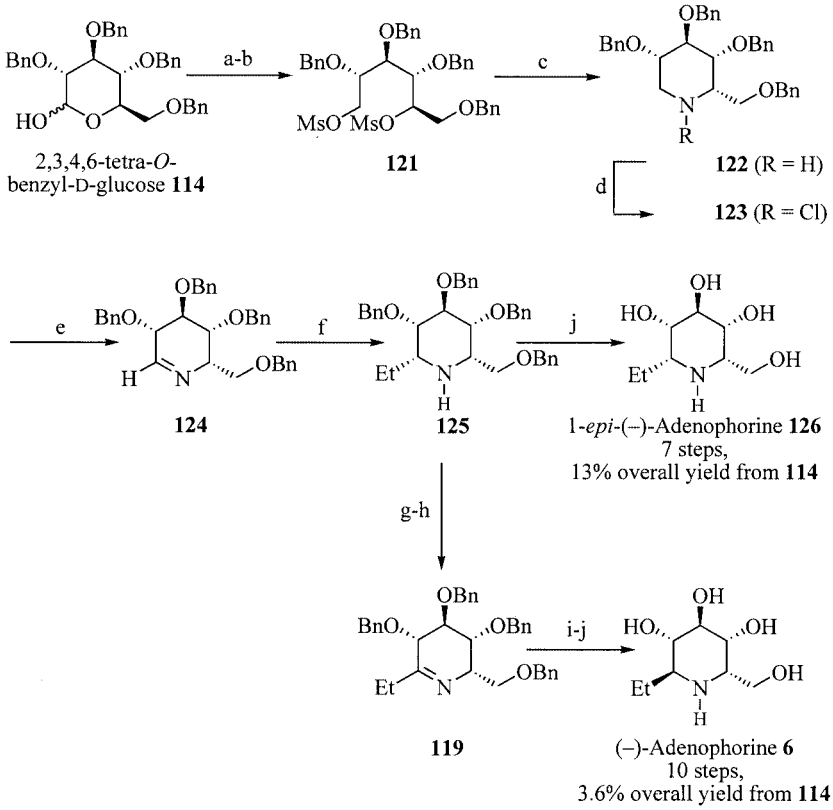
Scheme 13. Reagents and conditions: (a) Tf_2O, pyridine, DCM, –20 °C, 10 min; (b) H_2, Pd, NaOAc, EtOAc, room temp., 16 h, 61% (2 steps); (c) $LiBH_4$, THF, 0 °C to room temp., 1.5 h then HCl, 92%.



Scheme 14. Reagents and conditions: (a) $NaBH_4$, THF/H_2O, room temp., 24 h; (b) TBDPSCl, imidazole, DMF, room temp., 24 h, 99% (2 steps); (c) HN_3, DIAD, PPh_3, toluene, room temp., 3 h; (d) TBAF, THF, room temp., 3 h; (e) PCC, DCM, MS, room temp., 1.5–2 h, 76% for **117** (3 steps), 50% for **118** (2 steps); (f) EtMgBr, Et_2O, room temp., 1.5 h; (g) PPh_3, Et_2O, room temp., 3 h; (h) $LiAlH_4$, THF, room temp., 30 min, 69% (2 steps); (i) H_2, $PdCl_2$, EtOH, room temp., 1.5 h, 100%.

tetra-*O*-benzyl-D-glucose (**114**) with $NaBH_4$ followed by silylation of the primary alcohol with TBDPSCl in the presence of imidazole in DMF gave the 1,2,3,4,6-*O*-protected-D-glucitol **115** in 99% yield. Substitution of the hydroxy group by an azido group with inversion of configuration at C-5 was carried out by treatment of **115** with HN_3, DIAD, and PPh_3 in toluene. Cleavage of the silyl protecting group with TBAF in THF and oxidation of the resulting hydroxy group with PCC in DCM furnished the aldehyde **117** in 87% yield for the three-step process. Aldehyde **117** was then converted into the corresponding ethyl ketone **118** in 50% yield by addition of EtMgBr in Et_2O and oxidation of the resulting secondary alcohol with PCC, as described previously. With the aim of building the piperidine ring, intramolecular condensation of the azido and ketone groups was performed by adding PPh_3 to a solution of **118** in Et_2O. This Staudinger/aza-Wittig cyclization reaction gave the ethyl imine intermediate **119**, which was stereoselectively reduced by treatment with LAH in THF in order to install the asymmetric center at C-1. After purification by chromatography on silica gel, this one-pot procedure yielded **120** as the only diastereoisomer in 69% yield. Other reducing agents led to the degradation of the ethyl ketimine **119** or to low diastereoselectivity. Debenzylation by hydrogenation afforded (–)-adenophorine (**6**) in quantitative yield.

In the same paper, another strategy to access (–)-adenophorine (**6**) and also 1-*epi*-(–)-adenophorine (**126**) was described using, once again, the D-glucose derivative **114**, as outlined in Scheme 15. This original synthesis is based on a regioselective imine formation via an *N*-chlorinated intermediate, followed by organometallic addition. As previously described, treatment of **114** with $NaBH_4$ in a mixture of THF and water gave a glucitol intermediate, which was subsequently subjected to *O*-mesylation with MsCl at 0 °C in pyridine to afford **121** in 71% yield. Substitution of the 1-*C*-mesylate group by an amino group was carried out by treating **121** with NaN_3 in refluxing DMF and by adding PPh_3 to the solution five hours later. The spontaneous, intramolecular, S_N2 cyclization reaction of the resulting intermediate provided the piperidine derivative **122**, which was isolated in 61% yield after purification by chromatography on silica gel. Subsequent *N*-chlorination with NCS in DCM led to the *N*-chloropiperidine **123** in excellent yield (93%). A regioselective HCl elimination process developed by the authors[61] with DBU in refluxing Et_2O was carried out on **123** to prepare the crude imine **124**. This was then treated directly with EtMgBr in a mixture of Et_2O and dioxane. This two-step procedure furnished the ethylpiperidine **125** as the exclusive diastereoisomer in 47% yield after purification by chromatography on silica gel. Hydrogenolysis of this latter compound yielded the 1-*epi*-(–)-adenophorine **126** in 86% yield (13% overall yield from **114**). It was clear that at this point, due to the observed diastereoselectivity of the organometallic addition to imine **124**, an inversion of configuration at C-1 was required on the protected 1-*epi*-**125** intermediate to obtain (–)-adenophorine (**6**). Thus, subjection of **125** to a two-step *N*-chlorination followed by



Scheme 15. Reagents and conditions: (a) $NaBH_4$, THF/H_2O, room temp., 24 h; (b) MsCl, pyridine, 0 °C, 72 h, 71% (2 steps); (c) NaN_3, DMF, 80 °C, 5 h, then PPh_3, 80 °C, 17 h, 61%; (d) NCS, DCM, room temp., 16 h, 93%; (e) DBU, Et_2O, reflux, 7 h; (f) EtMgBr, Et_2O/dioxane, –78 °C to room temp., 2.5 h, 37% (2 steps); (g) NCS, DCM, room temp., 16 h; (h) LiTMP, Et_2O, –78 °C, 2 h; (i) $LiAlH_4$, THF, room temp., 30 min; (j) H_2, $PdCl_2$, EtOH, room temp., 1.5 h, 86% for **126**, 24% for (–)-**6** (4 steps).

elimination of HCl with LiTMP in Et_2O at –78 °C afforded the ethyl ketimine **119**. This gave, using the same sequence as described previously in Scheme 14, (–)-adenophorine (**6**) in ten steps and in 3.6% overall yield from the starting glucose derivative **114**.

Chiral-Pool Starting Materials: Amino Acids

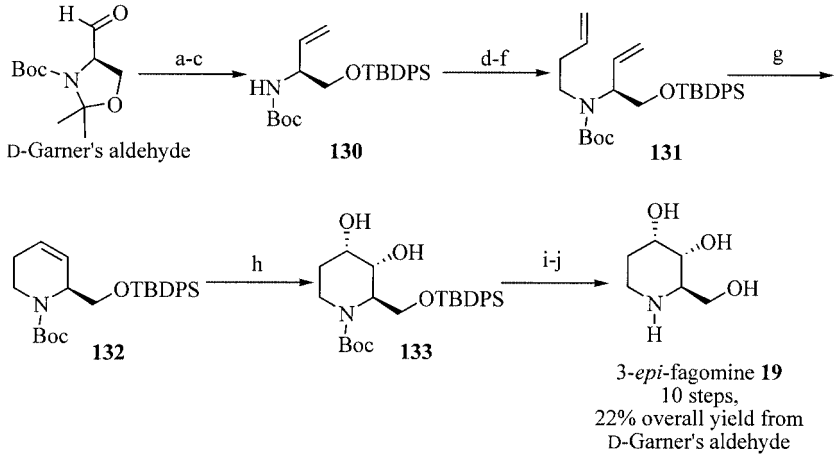
Commercially available Garner's aldehyde has been extensively used as a chiral building block in asymmetric synthesis[62] and has found successful application in the field of azasugars, as illustrated by the following examples.

A synthesis of fagomine **18** and analogs **19** and **20**,[63] as well as DGJ (**11**) and analogs **70** and **144**[64] from D-Garner's aldehyde (derived from D-serine) with a ring-closing metathesis (RCM) as the key step has been reported by Takahata et al., as shown in Schemes 16–19. In the last decade, the RCM reaction[65] has emerged as an extraordinarily powerful and general method for the construction of nitrogen heterocyclic compounds and has relevant application in the field of alkaloid synthesis. The success of this methodology is due to the development of stable and easy to handle commercial catalysts with a wide functional group tolerance. Of the several catalysts described in the literature, three of the most popular are the molybdenum- (**127**) and ruthenium-derived catalysts (**128** and **129**) developed by Schrock[66] and Grubbs,[67] respectively (see Figure 14).

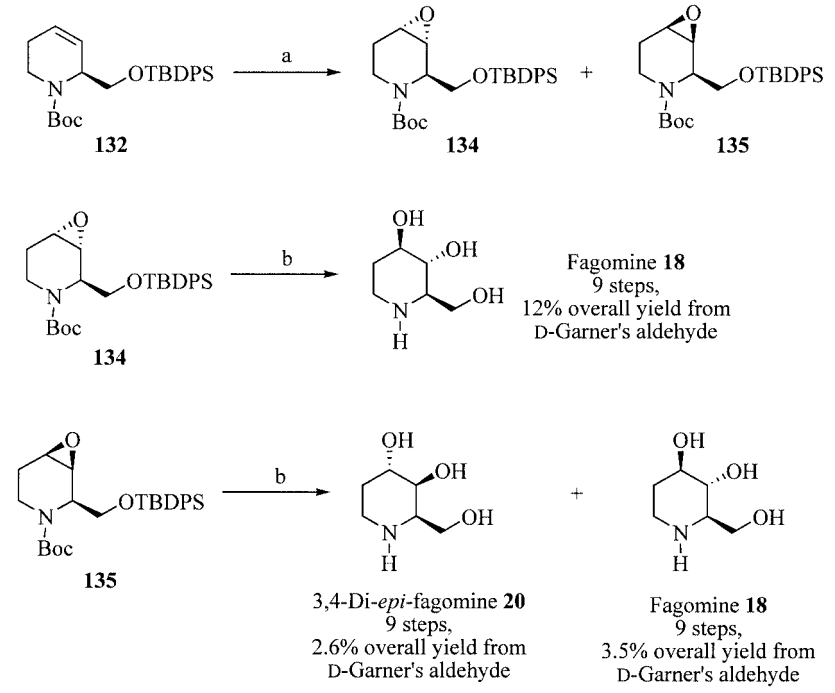
In the field of azasugar synthesis, the newly formed double bond has been found to be well-suited to install either a *cis* or *trans* vicinal diol functionality in the targets, using a dihydroxylation reaction or an epoxidation reaction followed by subsequent hydrolysis. The potential of the substituted tetrahydropyridine framework as a versatile building block for the synthesis of azasugars will be illustrated through many examples reported in this microreview.

Wittig methylenation of D-Garner's aldehyde followed by selective cleavage of the oxazolidine group and protection of the resulting alcohol as its silyl ether afforded **130** in 45% overall yield (Scheme 16).[63] All attempts to direct *N*-alkylation with 4-bromo-1-butene failed to convert **130** into **131**. This obstacle was overcome by cleavage of the *N*-Boc protecting group and subsequent mono N-alkylation of the resulting amine, followed by reprotection as a Boc derivative to give the desired RCM substrate **131** in 60% overall yield. Treatment of **131** with Grubbs' catalyst **129** produced the key intermediate **132** in high yield. Under modified Upjohn conditions,[68] dihydroxylation of **132** occurred at the less-hindered *anti*-side facing the siloxymethyl substituent, and furnished diol **133** as a single diastereoisomer in 92% yield. Removal of the protecting groups under acidic conditions followed by treatment with ion-exchange resin gave 3-*epi*-fagomine (**19**) in 91% yield.

Epoxidation of **132** with dioxirane, generated in situ from Oxone® and 1,1,1-trifluoroacetone, delivered both *anti*-



Scheme 16. Reagents and conditions: (a) $Ph_3P^+CH_3I^-$, NaHMDS, THF; (b) TsOH, MeOH; (c) TBDPSCl, DMAP, imidazole, DCM, 45% (3 steps); (d) TFA, DCM; (e) 4-bromo-1-butene, K_2CO_3, CH_3CN; (f) $(Boc)_2O$, Et_3N, DCM, 60% (3 steps); (g) [Ru]-**129**, DCM, 97%; (h) $K_2OsO_4 \cdot 2H_2O$, NMO, H_2O, acetone, 92%; (i) 10% HCl, dioxane; (j) Dowex 1X2 (OH^-) form, 91% (2 steps).

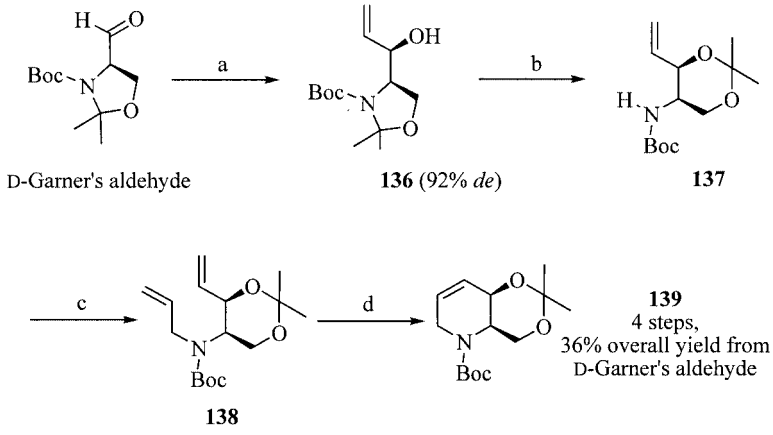


Scheme 17. Reagents and conditions: (a) Oxone®, CF_3COCH_3, $NaHCO_3$, 4×10^{-4} M Na_2EDTA, CH_3CN, 60% for **134**, 30% for **135**; (b) H_2SO_4, dioxane, H_2O, 75% for **18** from **134**, 44% for **18** from **135**, 33% for **20**.

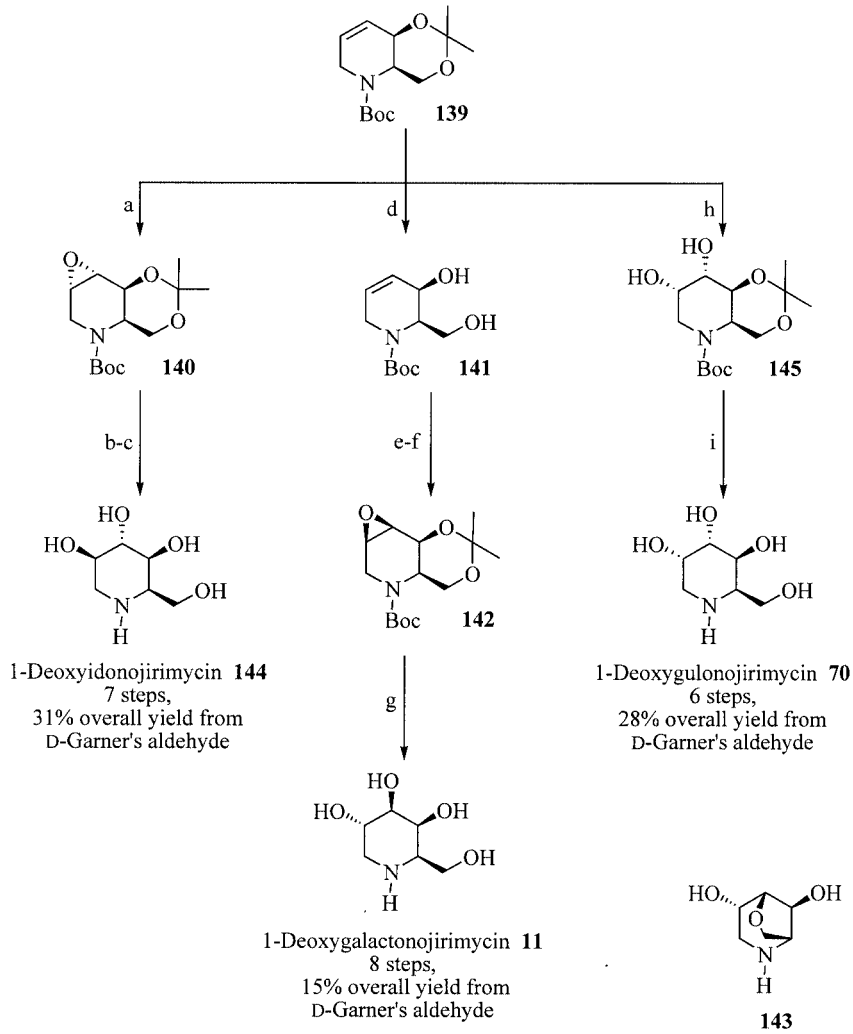
and *syn*-epoxides **134** and **135**, in 60% and 30% yield, respectively, after separation by chromatography (Scheme 17). Subsequent acidic hydrolysis of *anti*-epoxide **134** and removal of the protecting groups provided fagomine **18** in 75% yield. The complete selective hydrolysis of *anti*-epoxide **134** is consistent with a nucleophilic attack of water on C-4 at the more remote position *syn* with respect to the 2-substituent. In contrast, the same sequence applied with *syn*-epoxide **135** afforded a mixture of 3,4-*epi*-fagomine **20** and fagomine **18**, isolated in 33% and 44% yield, respectively, after purification by flash chromatography.

To demonstrate the efficiency of this approach to azasugars, the same authors described the synthesis of DGJ (**11**) and its congeners[64] **70** and **144** relying, in the first step, on the addition of a vinyl metal reagent to D-Garner's aldehyde (see Scheme 18 and 19).

Addition of vinylzinc bromide to D-Garner's aldehyde afforded the *syn*-vinyl alcohol **136** (see Scheme 18) with correct diastereoselectivity (69% *de*) in 91% yield after purification by chromatography. After one crystallization, the *de* was increased to 92% (72% yield). Treatment of **136** with HCl gas in chloroform led to the formation of the 1,3-acetonide **137** in 67% yield accompanied by 24% recovery of starting material. This *N*-Boc derivative **137** was then submitted to N-allylation, and an RCM reaction in the presence of Grubbs' catalyst **129** at room temperature provided



Scheme 18. Reagents and conditions: (a) vinylZnBr, Et_2O, –78 °C to room temp., 2 h, chromatography then recrystallization from *n*-hexane/EtOAc (5:1), 72%, 92% *de*; (b) HCl gas, $CHCl_3$, room temp., 12 h, 69%; (c) allyl iodide, NaH, THF, 0 °C, 12 h, 76%; (d) [Ru]-**129**, DCM, room temp., 2 h, 95%.



Scheme 19. Reagents and conditions: (a) Oxone®, CF_3COCH_3, $NaHCO_3$, aqueous Na_2EDTA, CH_3CN, 0 °C, 30 min, 99%; (b) 0.3 M KOH, 1,4-dioxane, H_2O, reflux, 36 h; (c) 6 N HCl, MeOH, reflux, 1 h, then Amberlite IRA-410 (OH^- form), 87% (2 steps); (d) TsOH, MeOH, room temp, 2 h, 97%; (e) *m*-CPBA, NaH_2PO_4, DCM, 0 °C to room temp., 12 h; (f) DMP, cat. PPTS, acetone, room temp., 12 h, 53% (2 steps); (g) H_2SO_4, 1,4-dioxane, H_2O, reflux, 3 h, then Dowex 1x2 (OH^- form), 83%; (h) $K_2OsO_4{\cdot}2H_2O$, NMO, acetone, H_2O, 0 °C to room temp., 12 h, 85%; (i) 6 N HCl, MeOH, reflux, 1 h, then Dowex 50Wx8 (H^+ form), 90%.

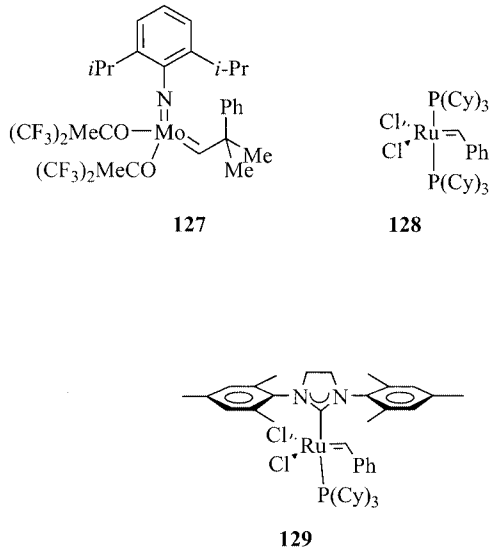


Figure 14. RCM catalysts.

the key tetrahydropyridine **139** in 36% overall yield from D-Garner's aldehyde.

From the key synthon **139**, both *syn*- and *anti*-epoxides **142** and **140** were obtained in diastereoselective fashion, as outlined in Scheme 19. Thus, treatment of **139** with fluorinated dioxirane led to the formation of the *anti*-epoxide **140** as the only diastereoisomer in nearly quantitative yield. The epoxidation took place exclusively from the less-hindered convex face, the concave face being shielded by a methyl group of the acetonide. The same diastereoselectivity was detected for the dihydroxylation step (compound **145**). However, the opposite stereochemical outcome was observed when epoxidation with *m*-CPBA was carried out on the diol **141**, obtained by acidic hydrolysis of the acetonide group of **139**. Under these conditions, the hydroxy-directed epoxidation provided the *syn*-diastereoisomer, which was re-protected as its acetonide to give **142** in 53% overall yield for the two steps. Concomitant acidic hydrolysis of the epoxy ring and acetonide of the *syn*-epoxide **142** provided, after further treatment on ion-exchange resin, the target molecule DGJ (**11**) in 83% yield. In sharp contrast to this result, applying the same acidic hydrolysis conditions to the *anti*-epoxide **140** resulted in the formation of an abnormal bicyclic product **143** in 83% yield. However, ring-opening of the epoxide **140** was efficiently performed under basic conditions, and subsequent removal of the protecting groups provided the 1-deoxyidonojirimycin **144** as the unique diastereoisomer in 87% overall yield from **140**. Finally, stereoselective dihydroxylation of tetrahydropyridine **139** under modified Upjohn conditions afforded the diol **145** as a single diastereoisomer in 85% yield, which was converted into 1-deoxygulonojirimycin (**70**) in good yield following the sequence previously described for other congeners. Thus, the three DNJ analogs **144**, **11**, and **70** were obtained in 31%, 15%, and 28% overall yield, respectively, from D-Garner's aldehyde.

As part of our effort towards the synthesis of azasugars, we became interested in the new 6-alkylimino sugars recently isolated from *Adenophora* spp by Asano and coworkers (see Figure 15).[7] These natural imino sugars have an unusual structure with hydrophobic α-1-*C*-substituents as the butyl or ethyl groups.

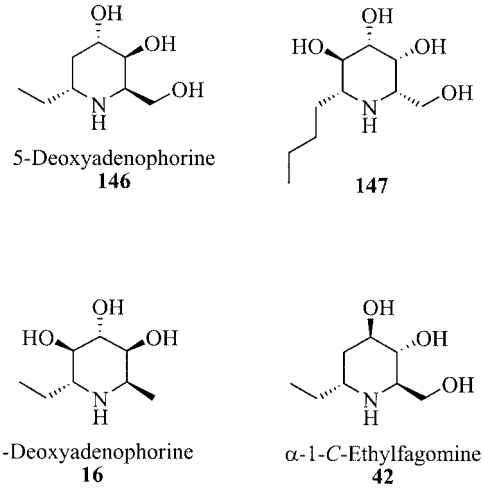
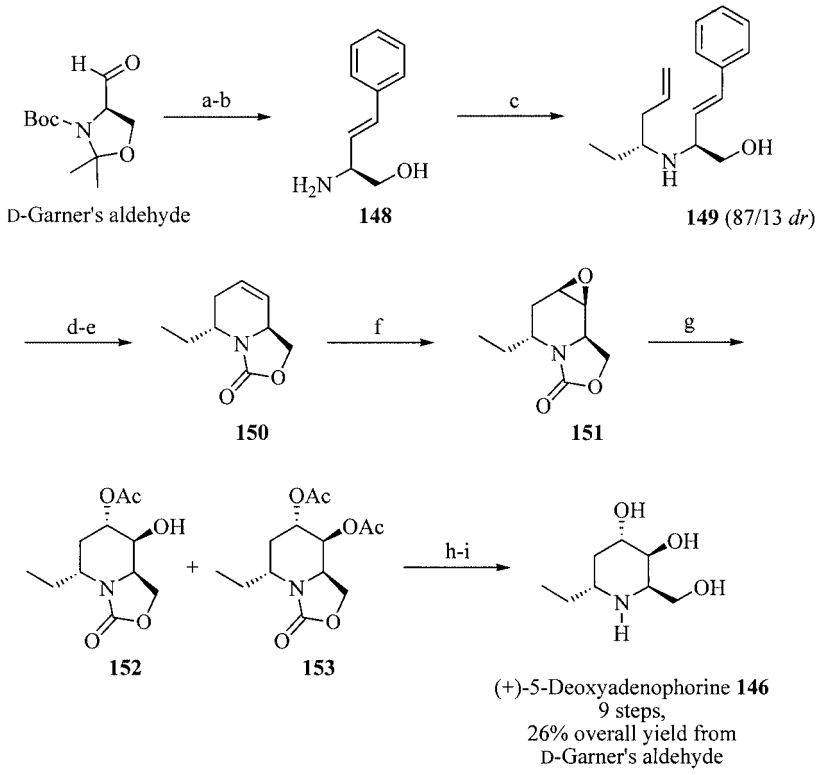


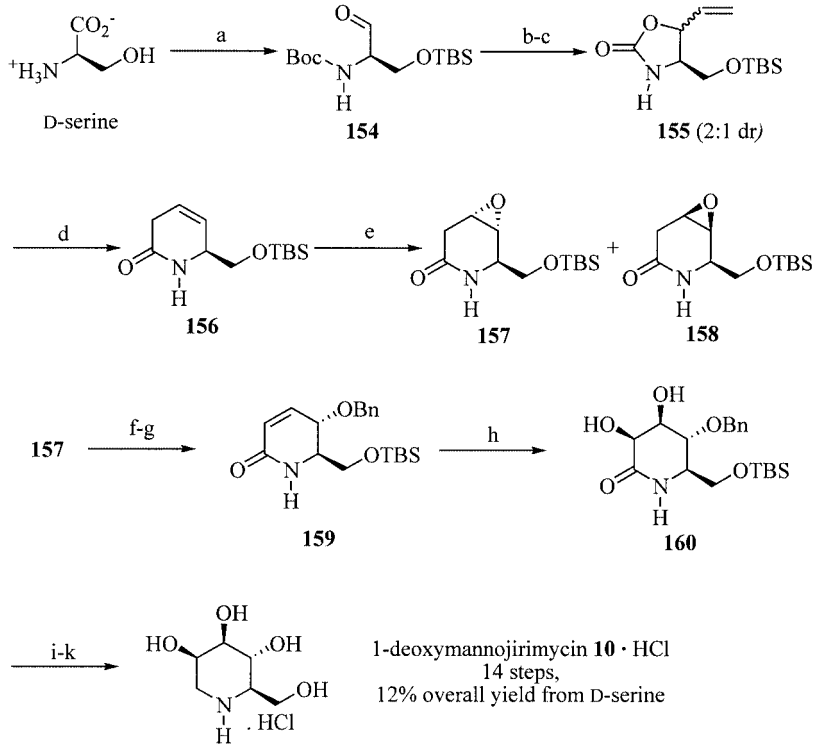
Figure 15. Structure of the alkaloids recently isolated by Asano and co-workers.

As a first step in this program, we have very recently described a synthesis of 5-deoxyadenophorine (**146**)[69] (Scheme 20) using a novel strategy[70] to build chiral *trans*-2,6-disubstituted-1,2,5,6-tetrahydropyridines.

Starting from D-Garner's aldehyde, Wittig olefination with the semi-stabilized benzylphosphonate followed by subsequent acidic deprotection of oxazolidine and *N*-Boc protecting groups gave exclusively the (*E*)-amino alcohol **148** in 74% overall yield with an *ee* of up to 96% (Scheme 20). In a one-pot, two-step procedure, the condensation of propanal with (*E*)-amino alcohol **148** in the presence of anhydrous $MgSO_4$ gave the corresponding imine, which was directly treated with an excess of allylmagnesium bromide to afford the desired product **149** and its epimer at C-1 as an inseparable mixture in an 87:13 ratio and 87% yield. This good stereoselectivity can be explained by an internal chelation of the magnesium atom of the Grignard reagent with the alkoxide and the imino nitrogen, which favors an addition of the Grignard reagent from the less-hindered face of the imine function and leads to the diastereoisomer **149**. It should be pointed out that the introduction of the bulky phenyl group is crucial to induce a good stereoselectivity in this step. Moreover, the styryl group is known to be a good substrate for the RCM reaction. Protection of the amino alcohol **149** as an oxazolidinone, followed by treatment with the Grubbs catalyst **129** in refluxing DCM, gave rise to the tetrahydropyridine **150** in good yield. At this stage, the *trans*- and *cis*-isomers were easily separated by flash chromatography and were isolated in 83% and 11% yield respectively. The required dihydroxyl functions were introduced by epoxidation of the double bond in intermediate **150**. Thus, the tetrahydropyridine **150** was treated with *m*-CPBA to afford the desired *endo* epoxide **151** with a good diastereoselectivity (9:1 *dr*). Separation



Scheme 20. Reagents and conditions: (a) diethyl benzylphosphonate, *n*BuLi, THF, –78 °C to room temp., 14 h; (b) conc. HCl, MeOH, reflux, 4 h, 74%; (c) propanal, $MgSO_4$, THF, room temp., 12 h, then allylmagnesium bromide, THF, Et_2O, –78 °C to –10 °C, 6 h, 87%; (d) CDI, Et_3N, DCM, 18 h, 83%; (e) [Ru]-**129** (5 mol-%), DCM, reflux, 1 h, 83%; (f) *m*-CPBA, DCM, 0 °C to room temp., 72 h, 86%; (g) AcOH, 100 °C, 17 h, 79% for **152** and 10% for **153**; (h) K_2CO_3, MeOH, room temp., 3 h, 95%; (i) 8 N NaOH, MeOH, 95 °C, 24 h, 88%.



Scheme 21. Reagents and conditions: (a) ref. [73], 79% (4 steps); (b) vinylMgBr, THF, –78 °C to room temp., 3 h; (c) *t*BuOK, THF, room temp., 3 h, 75% (2 steps); (d) $[PdCl_2(PPh_3)_2]$ (10 mol-%), CO (65 atm), EtOH, 60 °C, 32 h, 81%; (e) Oxone®, $NaHCO_3$, acetone/H_2O, room temp., 3 h, 76% for **157**, 19% for **158**; (f) DBU, DCM, reflux, 3 h; (g) NaH, DMF, BnBr, 0 °C to room temp., 3 h, 61% (2 steps); (h) OsO_4, NMO, *t*BuOH, room temp., 3 h, 89%; (i) $LiAlH_4$, Et_2O, room temp., 3 h; (j) Bu_4NF, THF, room temp., 1 h; (k) H_2, Pd/C, EtOH, HCl, room temp., 2 h, 61% (3 steps).

on a silica gel column gave the *endo* isomer **151** in 86% yield and the minor *exo* isomer in 5% yield. Total regioselective ring-opening of epoxide **151** was carried out in acetic acid at reflux to afford a mixture of monoacetate **152** and diacetate **153** in high yield and with an 86:14 ratio. The latter compound was formed by in situ esterification of monoacetate **152**. To reach our target molecule, the previous mixture was directly treated with K_2CO_3 in MeOH to give the corresponding diol essentially quantitatively, which was refluxed in MeOH with NaOH to remove the oxazolidinone function and form the 5-deoxyadenophorine **146** in 26% overall yield from D-Garner's aldehyde.

Knight et al. have reported the total synthesis of the hydrochloride salt of DMJ (**10**) from D-serine, with a palladium-catalyzed decarboxylative carbonylation[71] of the 5-vinyloxazolidin-2-one intermediate **155** to afford δ-lactam **156**, as outlined in Scheme 21, as the key step.[72] Synthesis of the serine derivative **154** was achieved in four steps in 79% yield from commercial D-serine.[73] Reaction of the chiral aldehyde **154** with vinyl Grignard reagent, followed by treatment of the resulting diastereomeric alcohol mixture with *t*BuOK, furnished the *anti*- and *syn*-5-vinyloxazolidin-2-ones **155** in 75% yield and in a 2:1 ratio. This mixture was then heated under CO pressure in the presence of a Pd catalyst to afford, via an π-allylpalladium intermediate, the unsaturated δ-lactam **156** in 81% yield. This key intermediate was treated with Oxone® to give a 4.1:1 mixture of *anti*- and *syn*-epoxides **157** and **158**, which were isolated after silica gel chromatography in 76% and 19% yield respectively. The *anti*-epoxide **157** was converted into the corresponding allylic alcohol by a base-mediated epoxide opening reaction in the presence of DBU. This allylic alcohol was protected as benzyl ether **159** and was then submitted to dihydroxylation to give the 4,5-*anti*-diol **160** in high selectivity. Only traces of the 4,5-*syn*-isomer were detectable by NMR spectroscopy. Reduction of the lactam function into the corresponding piperidine, followed by cleavage of all protecting groups, led to DMJ (**10**) as its hydrochloride salt in 12% overall yield from D-serine.

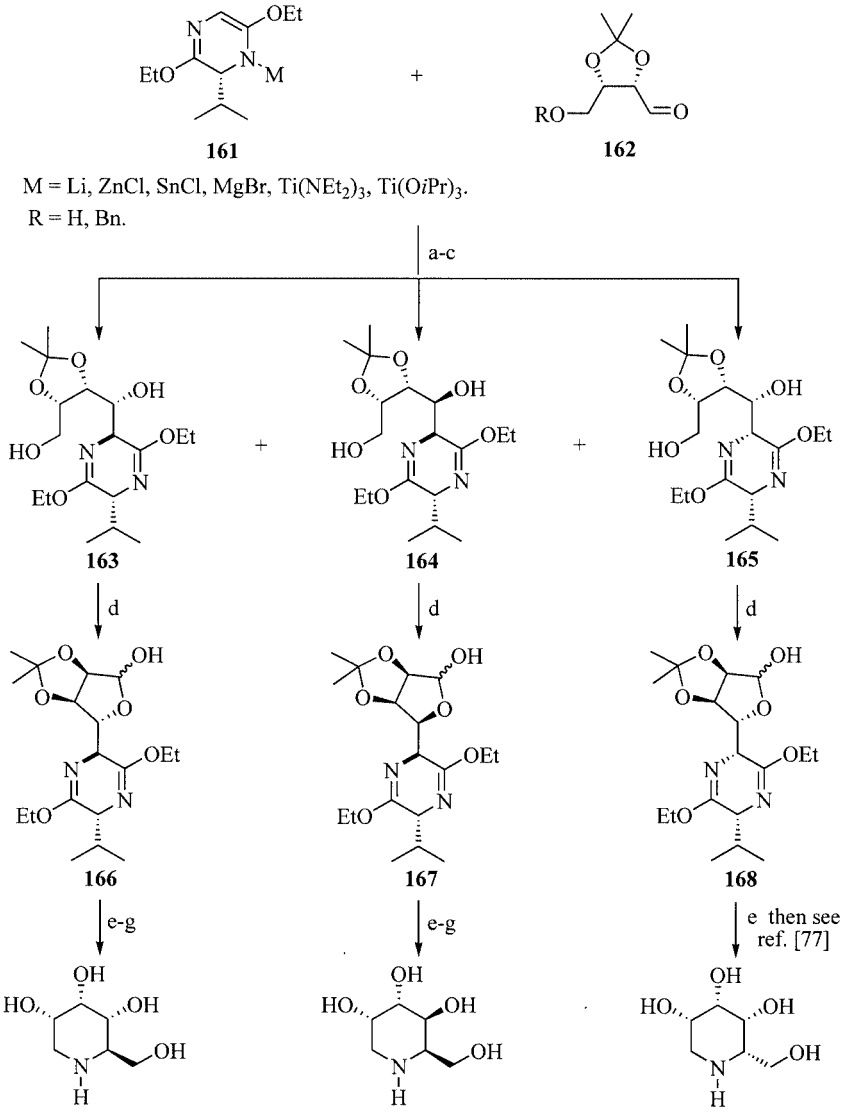
Chiral-Pool Starting Materials: (D)- and (L)-Tartaric Acids

Some syntheses of azasugars have been reported using carbon homologation from tartaric acid, which could be regarded as a four-carbon skeleton functionalized moiety disposed in a *threo* configuration.[74] In addition, syntheses of azasugars starting from 2,3-*O*-isopropylidene-L-erythrose (**162**), considered as diastereoisomers of tartaric acid derivatives, are included in this section.

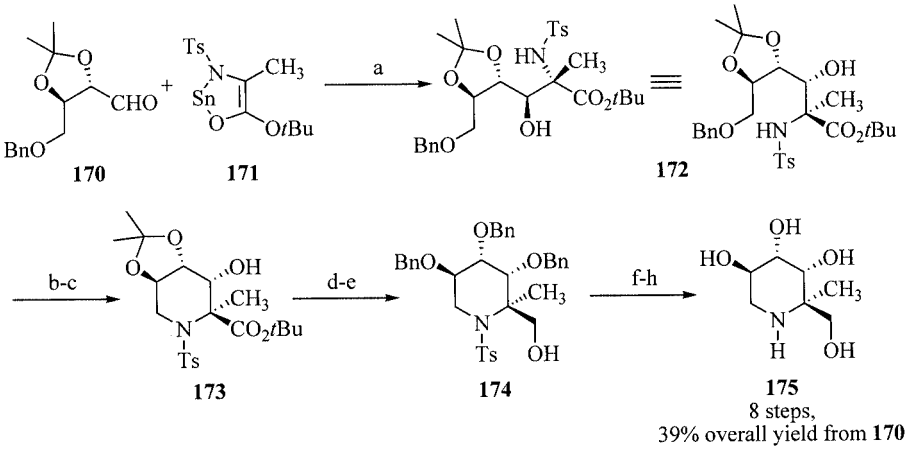
Ruiz et al.[75] have proposed an original approach to imino sugars by an aldol addition of metalated Schöllkop's bis-lactim ethers **161** to L-erythrose[76] derivatives **162** (diastereoisomers of tartaric acid derivatives; Scheme 22). The stereochemical outcome of this aldol-type reaction is strongly dependent on the nature of the metal counterpart. A highly (*anti*,*anti*)- and moderate (*syn*,*syn*)-selectivity was observed with Sn^{II} and Ti^{IV} azaenolates, respectively, with 2,3-*O*-isopropylidene-L-erythrose **162** (R = H). It should be pointed out that the condensation of stannous azaenolate with 2,3-*O*-isopropylidene-D-erythrose **162** forms a match pair, leading to the desired (*anti*,*syn*) adduct in high yield with excellent diastereoselectivity (*de* > 95%).[77] After separation, the adducts **163**, **164**, and **165** were converted in 82–86% yield into the γ-lactols **166**, **167**, and **168**, respectively, by chemoselective oxidation of the primary hydroxyl group with IBX. Reductive amination by Pd-catalyzed hydrogenation, followed by removal of the chiral auxiliary, gave the 1-deoxy-D-allonojirimycin **169**, 1-deoxy-D-gulonojirimycin **70**, and 1-deoxy-D-talonojirimycin **93**, respectively, in good yields.

Kazmaier et al.[78] have reported the synthesis of the imino sugar **175** from an aldol reaction[79] between the protected threose derivative **170** and the metal-chelated *N*-protected alanine *tert*-butyl ester **171** as the key step (Scheme 23). This aldol condensation provided a mixture of three diastereoisomers, wherein the desired 2,3-*anti*-3,4-*anti* isomer **172** was isolated in 62% yield. After removal of the benzyl group, a cyclization under Mitsunobu conditions gave the pipecolic acid derivative **173** in 72% yield. This compound was then easily converted into the *O*-benzyl-protected derivative **174** in two steps in 99% yield. After reduction of the ester function into a primary alcohol function with $LiAlH_4$, removal of the *N*-tosyl and *O*-benzyl protecting groups afforded the 1-deoxy-5-methyl imino sugar **175** in 89% yield for the three steps (39% overall yield from the protected threose derivative **170**).

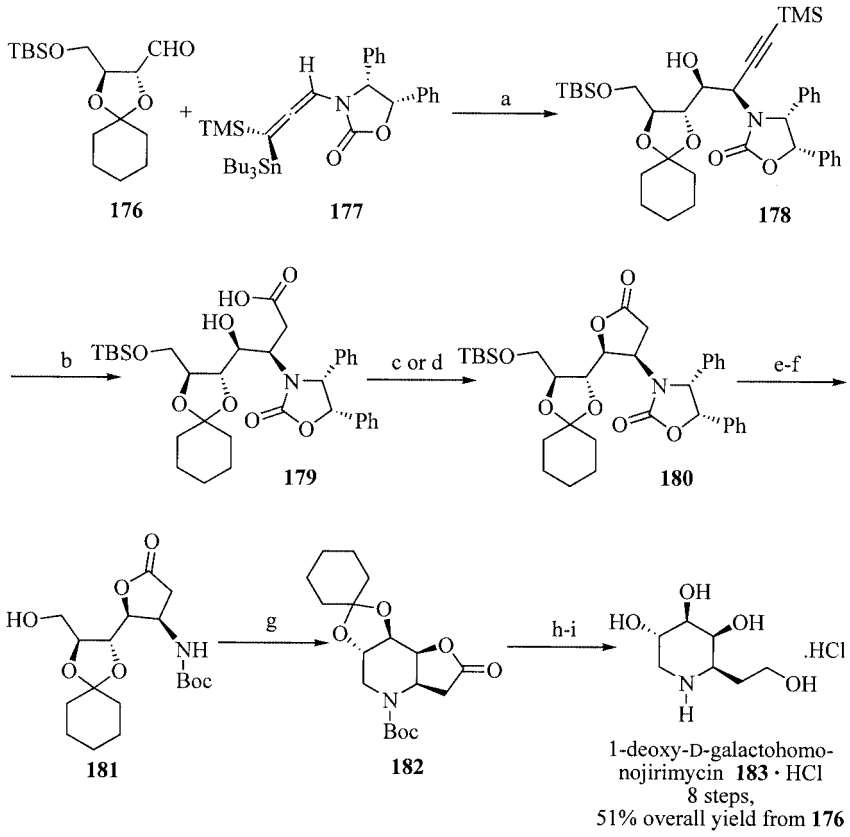
Hegedus et al.[80] have recently disclosed an original access to 1-deoxy-D-homogalactonojirimycin (**183**), with a Lewis acid-catalyzed aldol condensation of allenylstannane **177**, as depicted in Scheme 24, as the key step. Starting with the aldehyde **176**, which is available in 62% overall yield from diethyl L-tartrate in a four-step process, the aldolization reaction with the chiral diphenyloxazolidinone allenylstannane **177**[81] in the presence of $BF_3{\cdot}Et_2O$ afforded the *syn*-diastereoisomer **178** with high selectivity (up to 95%) in 86% yield. Conversion of the terminal alkyne function into a carboxylic acid function was easily performed by a hydroboration/oxidation sequence to provide 4-hydroxybutyric acid (**179**) in 88% yield (spontaneous lactonization was not observed). Then, the formation of the lactone **180** was achieved either by activation of the alcohol function under Mitsunobu conditions or by activation of the carboxylic acid using the Mukaiyama reagent (2-chloro-1-methylpyridinium iodide) to give the lactone **180** in good to excellent yield (85 to 99%). It should be noted that the intramolecular Mitsunobu reaction proceeded with retention of the absolute configuration of the alcohol: lactonization with retention of stereochemistry with hindered alcohols such as **179** has been studied and has been attributed to the preferential ring closure via an acyloxyphosphonium intermediate.[82] Removal of the oxazolidinone protection of **180** by hydrogenolysis in the presence of Boc_2O, followed by cleavage of the TBS protecting group with HF-pyridine, provided the carbamate intermediate **181** (2 steps, 98% yield), which was then subjected to Mitsunobu cyclization to fur-



Scheme 22. Reagents and conditions: (a) THF, –78 °C, 2 h for R = Bn, THF, –78 °C to 0 °C, 12 h for R = H; (b) NH_4Cl or phosphate buffer, 14–88% (2 steps); (c) H_2, Pd/C, THF, room temp., 6 h, 100% (for R = Bn only); (d) IBX, DMSO/THF (1:1), 8 °C, 24 h, 82% for **166**, 89% for **167**, 86% for **168**; (e) 0.25 M HCl/EtOH (1:2), H_2, Pd/C, room temp., 3 h, 51% from **166**, 75% from **167**, 67% from **168**; (f) $LiBEt_3$ H, THF, room temp., 5 h; (g) Dowex-H^+, room temp., 98% for **169** (2 steps), 93% for **70** (2 steps).



Scheme 23. Reagents and conditions: (a) THF, –78 °C, 62%; (b) H_2 (3 bar), Pd/C, MeOH, room temp.; (c) DEAD, PPh_3, THF, room temp., 72% (2 steps); (d) Dowex 50WX8, MeOH/H_2O room temp., 10 h; (e) NaH, BnBr, DMF, 0 °C to room temp., 99% (2 steps); (f) $LiAlH_4$, THF, room temp., 2 h; (g) sodium naphthalide, DME, –60 °C; (h) H_2 (1 bar), Pd/C, THF, room temp., 3 d, 89% (3 steps).



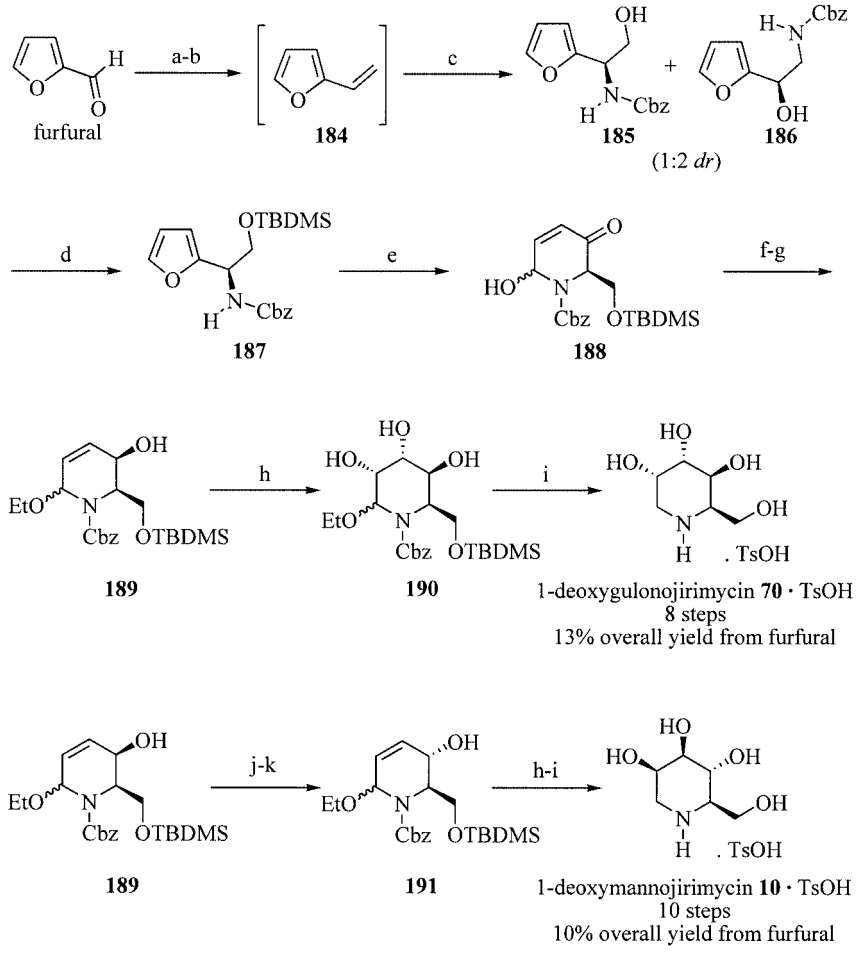
Scheme 24. Reagents and conditions: (a) $BF_3{\cdot}Et_2O$, DCM, –70 °C, 86%; (b) Cy_2BH, THF, 0 to 25 °C, and then H_2O_2, aq. $NaHCO_3$, 0 to 25 °C, 88%; (c) Mukaiyama reagent (2-chloro-1-methylpyridinium iodide), Et_3N, DCM, 25 °C, 99%; (d) DEAD, PPh_3, THF, –20 to +25 °C, 85%; (e) H_2 (80 psi), catalyst $Pd(OH)_2$, Boc_2O, THF, 25 °C; (f) HF-Py, MeCN, 25 °C, 98% (2 steps); (g) DEAD, PPh_3, THF, –20 to +25 °C, 82%; (h) $LiAlH_4$, THF, –20 °C; (i) HCl/MeOH, 25 °C, 84% (2 steps).

nish the bicyclic amino lactone **182** in 82% yield. Finally, reduction with $LiAlH_4$ followed by acidic hydrolysis of the protecting groups completed the synthesis of 1-deoxy-D-homogalactonojirimycin (**183**), as its hydrochloride salt, in 84% yield for the final two steps (32% yield for the twelve-step process from diethyl L-tartrate).

Sharpless Asymmetric Oxidations

The asymmetric epoxidation of allylic alcohols (Katsuki–Sharpless epoxidation),[83] the asymmetric dihydroxylation of olefins (Sharpless AD),[84] and the asymmetric aminohydroxylation of alkenes (Sharpless AA)[85] are the three most prominent catalytic asymmetric oxidations, and their efficiency has been fully demonstrated in the field of azasugar synthesis.

O'Doherty et al. have described an elegant access to various chiral azasugars based on the Sharpless AA and an aza-Achmatowicz rearrangement, as illustrated in Scheme 25 for the synthesis of 1-deoxygulonojirimycin (**70**).[86] Vinyl furan **184** was prepared by addition of furfural to an ethereal solution of TMSMgCl followed by acidic treatment of the resulting alcohol. After extraction, the solution of **184** was directly subjected (without further purification) to the Sharpless AA carried out with the $(DHQ)_2PHAL$ ligand system to give the formation of the regioisomers **185** and **186** in a 1:2 ratio. Both regioisomers **185** and **186** were efficiently separated by silica gel chromatography after selective protection of the primary alcohol function of regioisomer **187** as its silyl ether (*ee* up to 86%) in 21% overall yield from furfural. At this stage, after some experimentation, it was found that the aza-Achmatowicz rearrangement of **187** with *m*-CPBA under anhydrous conditions led to the formation of the desired hemiaminal **188** in 81% yield along with 7% of recovered starting material. Acid-catalyzed treatment of hemi-aminal **188** with ethyl orthoformate gave the corresponding ethylaminal, which was reduced under Luche conditions to afford the allylic alcohol **189** in 80% overall yield. Diastereoselective catalytic OsO_4 dihydroxylation of **189** from the less-hindered face led to the triol **190** in 96% yield. It should be noted that the epimeric mixture at C-1 has no influence on the stereochemical course of this reaction. Finally, classical hydrogenolysis of **190** in the presence of TsOH afforded the corresponding 1-deoxygulonojirimycin **70** salt in 99% yield and in 13% overall yield from furfural. A similar sequence applied to **191** (the C-4 epimer of **189**) obtained by Mitsu-



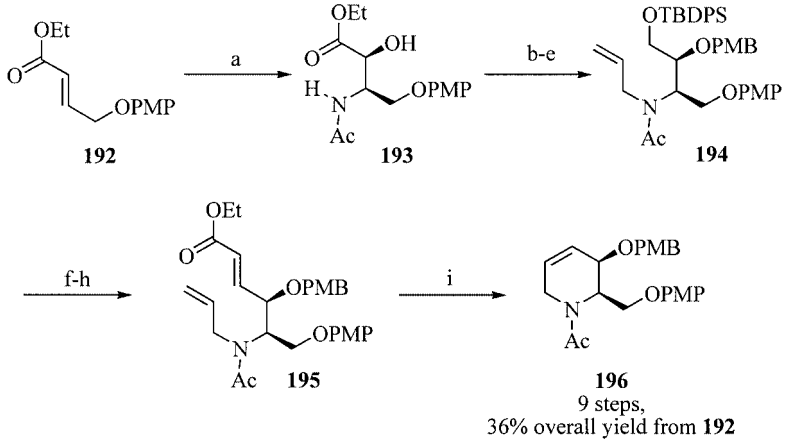
Scheme 25. Reagents and conditions: (a) Mg, $TMSCH_2Cl$, Et_2O, reflux, 12 h, then furfural, Et_2O, 0 °C, 12 h; (b) aq. HCl, Et_2O, 1 h; (c) $CbzNH_2$, *t*BuOH, *t*BuOCl, aq. NaOH, then $(DHQ)_2PHAL$, **184**, OsO_4, room temp., 1 h; (d) TBDMSCl, Et_3N, DMAP, DCM, room temp., 3 h, 21% from furfural; (e) *m*-CPBA, DCM, 0 °C, 3 h, 81%; (f) $(EtO)_3CH$, TsOH (5 mol%), DCM, room temp., 24 h; (g) $NaBH_4$, $CeCl_3$, DCM, –78 °C, 2 h, 80% (2 steps); (h) OsO_4, NMO/H_2O (1:1), DCM, 0 °C, 12 h, 96% for **190**; (i) H_2, Pd/C, MeOH, room temp., 12 h then TsOH, room temp., 3 h, 99% for **70**, 91% for **10** (2 steps); (j) PPh_3, *p*-$NO_2C_6H_4CO_2H$, DEAD, THF, 0 °C, 30 min; (k) Et_3N, MeOH, room temp., 8 h, 79% (2 steps).

nobu inversion gave DMJ (**10**) in diastereoselective fashion (10% overall yield from furfural).

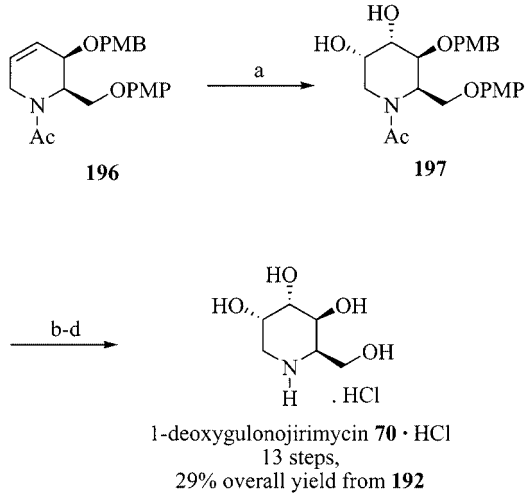
An elegant and efficient strategy for the synthesis of various chiral 1-deoxyimino sugars has been described by Singh and Han using Sharpless AA and RCM reactions, as illustrated below.[87] Regioselective asymmetric aminohydroxylation of olefin **192** (prepared from ethyl 4-bromocrotonate and *p*-methoxyphenol) afforded the amino alcohol **193** in 70% yield (>99% *ee*), after a single recrystallization of the chromatographed product (Scheme 26). The regiochemical course of this reaction could be attributed in part to the favorable interactions of the aromatic groups of the substrate and alkaloid ligand.[88] After protection of the alcohol **193** as a PMB ether, reduction of the ethyl ester gave the corresponding primary alcohol, which was then protected as a silyl ether. Finally, N-allylation led to the desired product **194** in 76% yield for the four steps. Fluoride-induced desilylation of **194** followed by oxidation of the liberated alcohol with DM periodinane afforded the corresponding aldehyde, which was treated with triethyl phosphonoacetate to afford the α,β-unsaturated ester **195** in 85% overall yield. The RCM reaction of **195** with [Ru]-**129** at elevated temperature (toluene at 90 °C) gave the key olefin intermediate **196** in good yield (36% overall yield from **192**).

With intermediate **196** in hand, the next stage was the functionalization of the double bond to reach the target molecules. It was found that the dihydroxylation of **196** occurred exclusively at the less-hindered *anti*-side to both substituents to give **197** in high yield (Scheme 27). Subsequent purification of the *cis*-vicinal diol **197** as its acetonide, followed by removal of all protecting groups, provided 1-deoxygulonojirimycin (**70**) as its hydrochloride salt in 81% overall yield from **196** (29% from **192**).

Conversion of the diol **197** into cyclic sulfate **198**[89] was carried out in two steps in 85% yield: first, formation of the cyclic sulfate by treatment with thionyl chloride then oxidation with $RuCl_3$ and $NaIO_4$, as outlined in Scheme 28. Regioselective ring-opening of the cyclic sulfate **198** with sodium benzoate as nucleophile occurred at the less steri-



Scheme 26. Reagents and conditions: (a) $K_2OsO_4 \cdot 2H_2O$ (5 mol-%), $(DHQD)_2PHAL$ (6 mol-%), LiOH, *N*-bromoacetamide, *t*BuOH/H_2O (3:2), 4 °C, 8 h, 70%, >99% *ee*; (b) NaH, PMBCl, DMF, 0 °C, 8 h; (c) $LiBH_4$, Et_2O, room temp., 15 min; (d) TBDPSCl, Et_3N, DMAP, DCM, room temp., 4 h; (e) KH, 18-C-6, allyl bromide, THF, room temp., 5 h, 76% (4 steps); (f) TBAF, THF, room temp., 1 h; (g) DM periodinate, DCM, room temp., 1 h; (h) $(EtO)_2P(O)CH_2CO_2Et$, LiBr, DBU, THF, room temp., 2 h, 85% (3 steps); (i) [Ru]-**129** (10 mol%), toluene, 90 °C, 2 h, 80%.



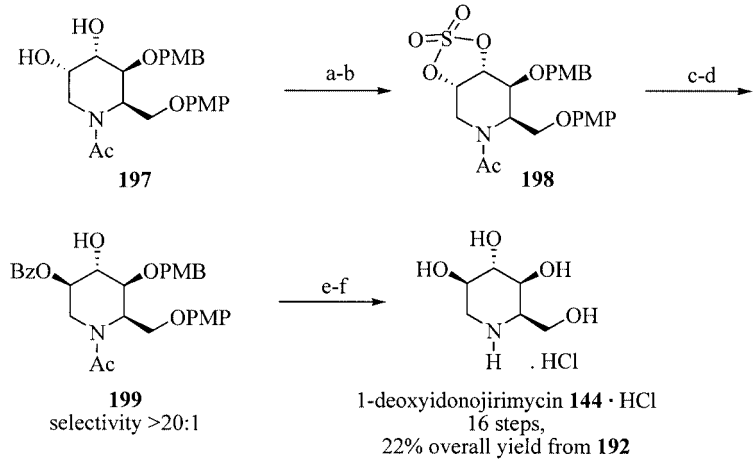
Scheme 27. Reagents and conditions: (a) OsO_4, NMO, *t*BuOH/H_2O (1:1), 12 h, 96%; (b) DMP, PPTS, DCM, room temp., 12 h; (c) CAN, MeCN/H_2O (4:1), 0 °C, 10 min; (d) 6 N HCl, 120 °C, 12 h, 85% (3 steps).

cally hindered C-2 to afford, with high selectivity (up to 20:1), the *trans*-diol derivative **199** in 85% yield. Cleavage of the protecting groups in **199** proceeded cleanly and 1-deoxyidonojirimycin (**144**) was isolated as its hydrochloride salt in 90% yield (22% yield from **192**).

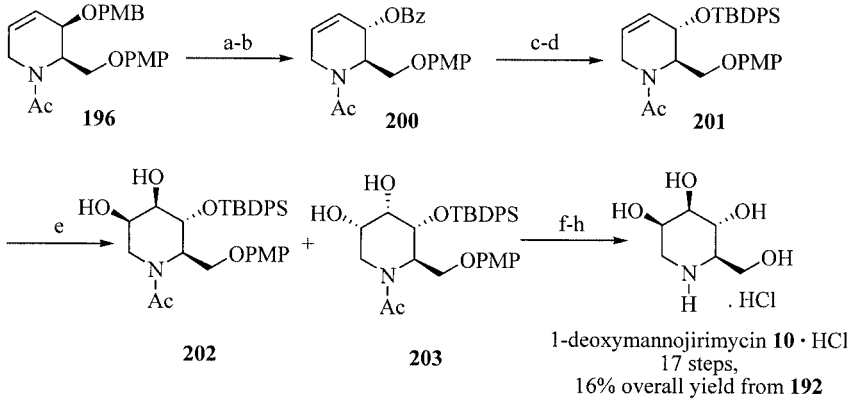
Olefin **196** was also considered as an intermediate for the synthesis of DMJ (**10**). Cleavage of the PMB group of **196** under acidic conditions proceeded smoothly and the corresponding allylic alcohol was subjected to standard Mitsunobu inversion to give the benzoate **200** (68% yield). This was submitted to dihydroxylation under Sharpless–Upjohn conditions to afford an inseparable 3:2 mixture of the 4-*O*-benzyl analogs of the *cis*-diols **202** and **203** (see Scheme 29). To overcome this lack of diastereoselectivity, the benzoate group was replaced by the much bigger silyl group. The use of the bulky TBDPS group to protect the C-4 hydroxyl group was found to be crucial for the diastereoisomeric outcome of the dihydroxylation reaction: the ratio was greatly improved so the diastereoisomers **202** and **203** were obtained with a good selectivity (10:1) and in 87% yield for this three-step process. The latter mixture was separated as their triacetate derivatives by column chromatography. Finally, hydrolysis of the protecting groups led to the hydrochloride salt of DMJ (**10**) in 44% overall yield over the eight steps from **196** and in 16% yield from the starting material **192**.

In order to obtain the last azasugar, 1-deoxyaltronojirimycin (**206**), the previous diols **202** and **203** were also converted into their cyclic sulfates and were separated at this stage on a silica gel column to give the intermediate **204** in 66% yield (Scheme 30). This was then submitted to the same sequence applied to compound **198** (Scheme 28) to afford 1-deoxyaltronojirimycin (**206**) as its hydrochloride salt in 10% yield from **192** (18 steps).

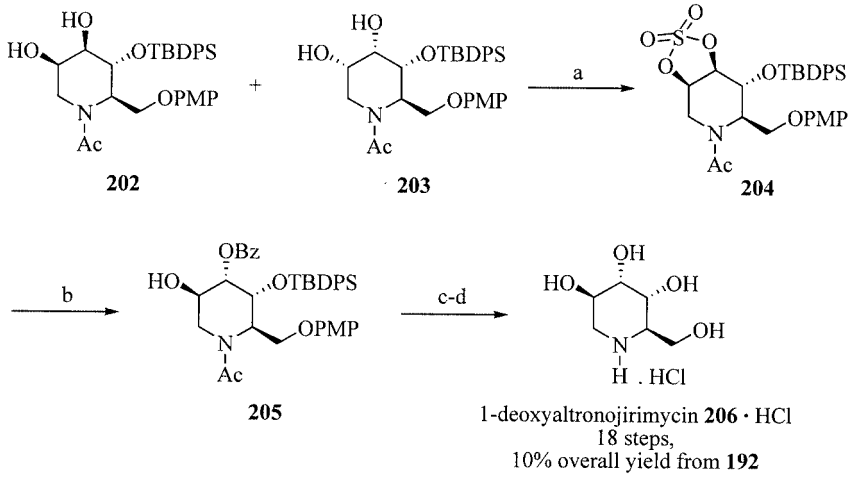
Somfai et al. have described an asymmetric synthesis of DNJ (**9**) in which the chiral synthon **209** was prepared by a Sharpless dihydroxylation and an epoxidation, as depicted in Scheme 31.[90] Asymmetric dihydroxylation of the 2,4-dienoic acid derivative **207** led to the formation of a 4,5-diol with 97% *ee* (99.5% *ee* after one crystallization). Subsequent protection of the diol gave the acetonide derivative **208** in 78% yield from **207**. Reduction of the ester function of **208** with DIBAL provided an allylic alcohol, which was submitted to stoichiometric Sharpless epoxidation to afford the desired diastereoisomer **209** in 74% yield with high diastereoselectivity (up to 95%). The catalytic protocol was found to be less efficient. Epoxy alcohol **209** was then protected as its silyl ether and the PMB group was removed. The resulting alcohol was converted into the mesylate derivative and subsequent nucleophilic displacement with azide anion led, without ring-opening of the epoxide, to the expected chiral azide **210** in 81% yield (4 steps). After reduction of the azide **210** under Staudinger conditions, the resulting amine was then refluxed in EtOH to afford, through a 6-*endo*-*tet* cyclization, the piperidine **211** in 75%



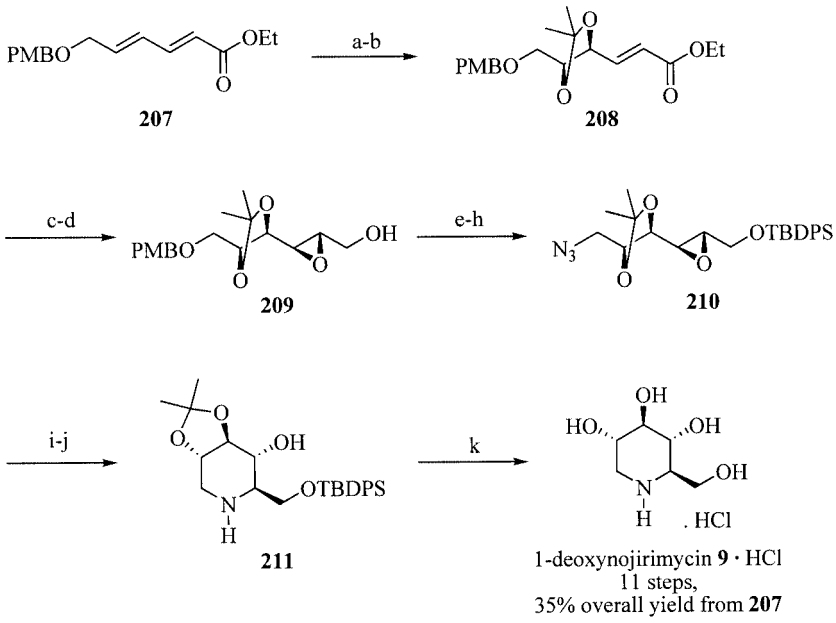
Scheme 28. Reagents and conditions: (a) $SOCl_2$, Et_3N, DCM, –15 °C, 30 min; (b) $RuCl_3$, $NaIO_4$, MeCN/DCM/H_2O (1:1:1), room temp., 1 h, 85% (2 steps); (c) NaOBz, DMF, 105 °C, 3 h; (d) 20% aq. H_2SO_4/DCM (1:1), room temp., 12 h, 85% (2 steps); (e) CAN, MeCN/H_2O (4:1), 0 °C, 10 min; (f) 6 N HCl, 120 °C, 12 h, 90% (2 steps).



Scheme 29. Reagents and conditions: (a) 5% TFA in DCM, room temp., 30 min; (b) DIAD, Ph_3P, PhCOOH, THF, 0 °C, 2 h, 68% (2 steps); (c) K_2CO_3, MeOH, room temp., 5 h; (d) TBDPSCl, imidazole, Et_3N, DMF, 60 °C, 12 h, 93% (2 steps); (e) $K_2OsO_4 \cdot 2H_2O$ or OsO_4, NMO, *t*BuOH/H_2O (1:1), 16 h, 94%; (f) Ac_2O, DMAP, Et_3N, DCM, room temp.; (g) CAN, MeCN/H_2O (4:1), 0 °C, 10 min; (h) 6 N HCl, 120 °C, 12 h, 74% (3 steps).



Scheme 30. Reagents and conditions: (a) $SOCl_2$, Et_3N, DCM, –15 °C, 30 min then $RuCl_3$, $NaIO_4$, MeCN/DCM/H_2O (1:1:1), room temp., 1 h, 66%; (b) BzONa, DMF, 105 °C, 5 h then 20% aq. H_2SO_4/DCM (1:1), 12 h, room temp., 80%; (c) CAN, MeCN/H_2O (4:1), 0 °C, 10 min; (d) 6 N HCl, 120 °C, 12 h, 88% (2 steps).

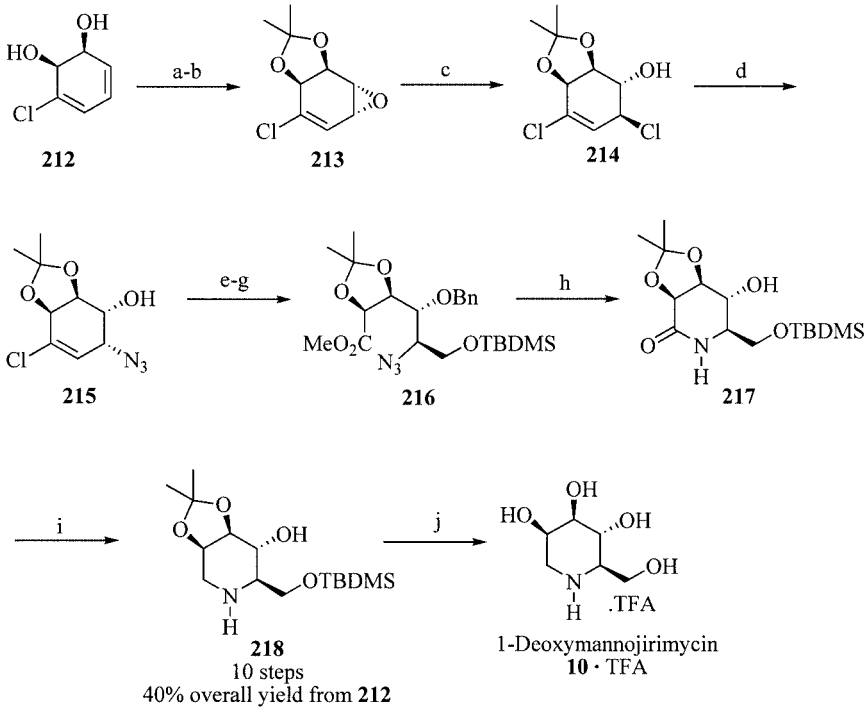


Scheme 31. Reagents and conditions: (a) AD-mix α, $CH_3SO_2NH_2$, *t*BuOH, H_2O, 0 °C, 46 h, 80%, 97% *ee*; (b) 2-methoxypropene, TsOH, DMF, room temp., 12 h, 78% (2 steps); (c) DIBAL, DCM, –78 °C, 30 min; (d) (+)-DIPT, Ti(O*i*Pr)$_4$, *t*BuOOH, DCM, –20 °C, 12 h, 74% (2 steps), > 95% *de*; (e) TBDPSCl, Et_3N, DMAP, DCM, room temp., 16 h; (f) DDQ, DCM, H_2O, room temp., 3 h; (g) MsCl, iPr_2EtN, DCM, 12 h; (h) NaN_3, DMF, 80 °C, 12 h, 81% (4 steps); (i) PPh_3, THF/H_2O (10:1), room temp., 12 h; (j) EtOH, reflux, 65 h, 75% (2 steps); (k) HCl (37%), MeOH, reflux, 4 h, 100%.

yield. Finally, removal of all protecting groups of intermediate **211** by acidic treatment in MeOH at reflux yielded the hydrochloride salt of DNJ (**9**) in quantitative yield (35% from **207**).

Chemoenzymatic Synthesis

The chemoenzymatic approach to chiral halogen-substituted cyclohexadienediols such as **212** (Scheme 32) by



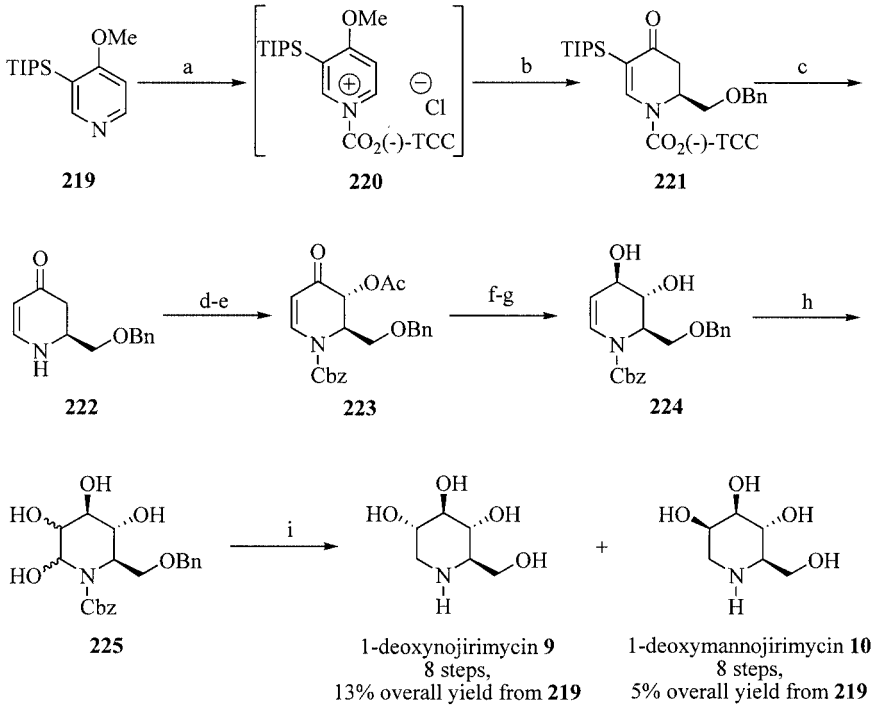
Scheme 32. Reagents and conditions: (a) DMP, TsOH, room temp., 1 h; (b) *m*-CPBA, DCM, 0 °C to room temp., 11 h, 81% (2 steps); (c) LiCl, NaH, AcOH, THF, room temp., 17 h, 98%; (d) LiN_3, DMF, room temp., 72 h, 91%; (e) BnBr, KI, NaH, THF, 0 °C to room temp., 24 h; (f) O_3, pyridine, MeOH, –78 °C, 1 h, then $NaBH_4$, –10 °C, 3 h; (g) TBDMSCl, imidazole, DCM, room temp., 2 h, 89% (3 steps); (h) H_2 (1 atm), 5% Pd/C, EtOAc, room temp., 36 h, 86%; (i) BH_3·Me_2S, THF, room temp., 4.5 h, then 10% Pd/C, MeOH, room temp., 38 h, 73%; (j) 80% aq. TFA/H_2O (1:1), room temp., 20 h.

whole-cell oxidation of aromatics by microbial dioxygenases has been exploited extensively in the syntheses of diverse natural products.[91] A combination of oxidative cleavage and reductive amination cyclization of functionalized cyclohexene intermediate **215** has been used by Banwell et al.[92] in the total synthesis of DMJ (**10**) depicted in Scheme 32. The *cis*-1,2-dihydrocatechol **212** was prepared in large quantity and in an enantiomerically pure form by microbial oxidation of chlorobenzene. This approach follows the early stages of Hudlicky's MJ **7** synthesis[93] with regard to the first four steps: epoxidation with *m*-CPBA of the acetonide of **212** followed by epoxide ring-opening with LiCl led, with a total regioselectivity, to the chlorohydrin **214**. This was then converted into the *cis*-azido alcohol (72% yield). Next, benzylation of the alcohol **215**, cleavage of the double bond with ozone in MeOH, followed by reductive work-up and subsequent protection of the primary alcohol as the TBDMS ether gave the desired intermediate **216** in 89% overall yield. Treatment of the azidomethyl ester **216** under hydrogen in the presence of Pd on carbon as catalyst allowed the hydrogenolysis of the benzyl protecting group and the reduction of the azide function into amine to give an intermediate. This later compound was then converted by spontaneous intramolecular cyclization to the expected lactam **217** in 86% yield. Next, reduction of the lactam with $BH_3{\cdot}Me_2S$ complex followed by one-pot addition of Pd on carbon as catalyst in MeOH to cleave the amine-borane complex intermediate[94] afforded the corresponding piperidine **218** in 73% yield (40% overall yield from **212**). To complete the synthesis, removal of the protecting groups under acidic conditions furnished DMJ (**10**) as a TFA salt (yield not reported).

Miscellaneous Approaches: Comins' Approach with Enantiopure 1-Acylpyridinium Salts

Comins has successfully explored with elegance the chemistry of enantiopure *N*-acyl-2,3-dihydro-4-pyridones as chiral building blocks for the stereocontrolled synthesis of various alkaloids.[95] In 2001, Comins' group[96] described an original approach to DNJ and DMJ from 4-methoxy-3-(triisopropylsilyl)pyridine (**219**), as outlined in Scheme 33.

The chiral 1-acylpyridinium salt **220**, prepared in situ by N-acetylation of the pyridine derivative **219** with the chloroformate of (1*R*,2*S*)-2-(1-phenyl-1-methylethyl)cyclohexanol [or (–)-*trans*-2-cumyl-cyclohexyloxycarbonyl chloride = (–)-TCCOCOCl], was directly treated with (benzyloxy)-methylcuprate to give the dihydropyridone **221** in 64% yield and 90% *de*. Removal of the chiral auxiliary (>95% recovery) and the C-5 TIPS group by treatment with sodium methoxide provided the enantiopure dihydropyridone **222** as a crystalline compound in 74% yield. This was then protected in high yield as the *N*-benzylcarbamate derivative by treatment with *n*BuLi followed by addition of Cbz-Cl. Subsequent treatment with $Pb(OAc)_4$ in refluxing toluene gave the *trans* enantiopure acetoxy derivative **223** in 77% yield for the two steps. Hydrolysis of the acetate protecting group under acidic conditions provided an alcohol intermediate, which was submitted to a stereoselective reduction of the



Scheme 33. Reagents and conditions: (a) (–)-TCCOCOCl; (b) $BnOCH_2(2\text{-Th})Cu(CN)Li_2$ then H_3O^+, 64%; (c) NaOMe then H_3O^+, 74%; (d) *n*BuLi then CbzCl; (e) $Pb(OAc)_4$, toluene, reflux, 22 h, 77% (2 steps); (f) 10% aq. HCl, EtOH; (g) $Me_4NBH(OAc)_3$, acetone, AcOH, 62% (2 steps); (h) OsO_4, NMO; (i) $Pd(OH)_2$, 10% HCl, 55% for **9** and 21% for **10** (2 steps).

carbonyl group by treatment with $Me_4NBH(OAc)_3$ to afford the *trans* diol **224** in 62% yield. Stereoselective introduction of a hydroxyl group at C-5 in **224** was found to be a more difficult task. At best, dihydroxylation of **224**, carried out with OsO_4 and NMO, led to the formation of a mixture of the corresponding unstable tetrahydroxypiperidines **225**. These were directly hydrogenated with $Pd(OH)_2$ and 10% HCl to remove the C6-OH and the *N*-protecting group. After chromatographic purification under neutral conditions, DNJ (**9**) and DMJ (**10**) were isolated in 55% and 21% yield respectively (13% and 5% overall yield from **219**).

Conclusions

It is now clearly the case that polyhydroxylated alkaloids, such as the hydroxy-substituted piperidines discussed in this microreview, have strong potential therapeutic applications, particularly in the pathologies involving glycosidases or glycosyltransferases. As an example, the efficiency of NB-DNJ in the inhibition of human immunodeficiency virus (HIV) or in type 1 Gaucher disease has prompted chemists to synthesize new original *C*- or *N*-substituted azasugars which could be more active and selective. Even though many successful and efficient routes to azasugars using a large variety of chemical techniques have been developed, as presented in this microreview, there is still lot of work remaining to improve these syntheses to give useful amounts of novel and original compounds in a short, flexible, and highly stereospecific fashion. Furthermore, application of combinatorial chemistry from already available chiral precursors could constitute a promising strategy to prepare libraries for structure–activity studies in some cases.

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[1] S. Inouye, T. Tsuruoka, T. Niida, *J. Antibiot.* **1966**, *19*, 288–292.
[2] R. J. Nash, E. A. Bell, G. W. J. Fleet, R. H. Jones, J. M. Williams, *J. Chem. Soc., Chem. Commun.* **1985**, *11*, 738–740.
[3] S. M. Colegate, P. R. Dorling, C. R. Huxtable, *Aust. J. Chem.* **1979**, *32*, 2257–2264.
[4] R. J. Nash, L. E. Fellows, J. V. Dring, G. W. J. Fleet, A. E. Derome, T. A. Hamor, A. M. Scofield, D. J. Watkin, *Tetrahedron Lett.* **1988**, *29*, 2487–2490.
[5] N. Asano, A. Kato, M. Miyauchi, H. Kizu, T. Tomimori, K. Matsui, R. J. Nash, R. J. Molyneux, *Eur. J. Biochem.* **1997**, *248*, 296–303.
[6] A. A. Watson, G. W. J. Fleet, N. Asano, R. J. Molyneux, R. J. Nash, *Phytochemistry* **2001**, *56*, 265–295 and references cited therein.
[7] K. Ikeda, M. Takahashi, M. Nishida, M. Miyauchi, H. Kizu, Y. Kameda, M. Arisawa, A. A. Watson, R. J. Nash, G. W. J. Fleet, N. Asano, *Carbohydr. Res.* **2000**, *323*, 73–80.
[8] S. Inouye, T. Tsuruoka, T. Ito, T. Niida, *Tetrahedron* **1968**, *24*, 2125–2144.
[9] T. Niwa, T. Tsuruoka, H. Goi, Y. Kodama, J. Itoh, S. Inoue, Y. Yamada, T. Niida, M. Nobe, Y. Ogawa, *J. Antibiot.* **1984**, *37*, 1579–1586.
[10] Y. Miyake, M. Ebata, *Agric. Biol. Chem.* **1988**, *52*, 661–666.
[11] a) H. Paulsen, I. Sangster, K. Heyns, *Chem. Ber.* **1967**, *100*, 802; b) H. Paulsen, K. Todt, *Adv. Carbohydr. Chem.* **1968**, *23*, 115–232.
[12] N. Asano, M. Nishida, H. Kizu, K. Matsui, A. A. Watson, R. J. Nash, *J. Nat. Prod.* **1997**, *60*, 98–101.
[13] P. S. Liu, *J. Org. Chem.* **1987**, *52*, 4717–4721.
[14] N. Asano, N. K. Yasuda, H. Kizu, A. Kato, J. Q. Fan, R. J. Nash, G. W. J. Fleet, R. J. Molyneux, *Eur. J. Biochem.* **2001**, *268*, 35–41.
[15] A. Kato, N. Asano, H. Kizu, K. Matsui, A. A. Watson, R. J. Nash, *J. Nat. Prod.* **1997**, *60*, 312–314.
[16] M. Bollen, W. Stalmans, *Eur. J. Biochem.* **1989**, *181*, 775–780.
[17] P. Jacobsen, J. M. Lundbeck, M. Kristiansen, J. Breinholt, H. Demuth, J. Pawlas, M. P. Torres Candela, B. Andersen, N. Westergaard, K. Lundgren, N. Asano, *Bioorg. Med. Chem.* **2001**, *9*, 733–744.
[18] A. Herscovics, *Biochim. Biophys. Acta* **1999**, *1473*, 96–107.
[19] A. J. Parodi, *Biochem. J.* **2000**, *348*, 1–13.
[20] For a review on this field, see: P. Greimel, J. Spreitz, A. E. Stütz, T. M. Wrodnigg, *Curr. Top. Med. Chem.* **2003**, *3*, 513–523.
[21] G. W. J. Fleet, A. Karpas, R. A. Dwek, L. E. Fellows, A. S. Tyms, S. Petursson, S. K. Namgoong, N. G. Ramsden, P. W. Smith, J. C. Son, F. Wilson, D. R. Witty, G. S. Jacob, T. W. Rademacher, *FEBS Lett.* **1988**, *237*, 128–132.
[22] I. S. Khanna, R. M. Weier, J. Julien, R. A. Muller, D. C. Lankin, L. Swenton, *Tetrahedron Lett.* **1996**, *9*, 1355–1358.
[23] A. Mehta, N. Zitzmann, P. M. Rudd, T. M. Block, R. A. Dwek, *FEBS Lett.* **1998**, *430*, 17–32.
[24] T. D. Butters, R. A. Dwek, F. M. Platt, *Curr. Top. Med. Chem.* **2003**, *3*, 561–574.
[25] F. M. Platt, T. D. Butters, *Exp. Rev. Mol. Med.* **2000**, 1–7.
[26] T. D. Butters, L. A. M. G. van den Broeck, G. W. J. Fleet, T. M. Krulle, M. R. Wormald, R. A. Dwek, F. M. Platt, *Tetrahedron: Asymmetry* **2000**, *11*, 113–124.
[27] A. R. Sawkar, W. C. Cheng, E. Beutler, C. H. Wong, W. E. Balch, J. W. Kelly, *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 15428–15433.
[28] Y. Nishimura, *Curr. Top. Med. Chem.* **2003**, *3*, 575–591 and references cited therein.
[29] B. Henrissat, G. Davies, *Curr. Opin. Struct. Biol.* **1997**, *7*, 637–644.
[30] D. L. Zechel, S. G. Withers, *Acc. Chem. Res.* **2000**, *33*, 11–18.
[31] V. H. Lillelund, H. H. Jensen, X. Liang, M. Bols, *Chem. Rev.* **2002**, *102*, 515–553.
[32] T. D. Heightman, A. T. Vasella, *Angew. Chem. Int. Ed.* **1999**, *38*, 750–770.
[33] D. L. Zechel, A. B. Boraston, T. Gloster, C. M. Boraston, J. M. McDonald, D. M. G. Tilbrook, R. V. Stick, G. J. Davies, *J. Am. Chem. Soc.* **2003**, *125*, 14313–14323.
[34] R. I. Hollingsworth, G. Wang, *Chem. Rev.* **2000**, *100*, 4267–4282 and references cited therein.
[35] J.-Y. Goujon, D. Gueyrard, P. Compain, O. R. Martin, N. Asano, *Tetrahedron: Asymmetry* **2003**, *14*, 1969–1972.
[36] G. J. Joly, K. Peeters, H. Mao, T. Brossette, G. J. Hoornaert, F. Compernolle, *Tetrahedron Lett.* **2000**, *41*, 2223–2226.

[37] F. Compernolle, G. J. Joly, K. Peeters, S. Toppet, G. J. Hoornaert, A. Kilonda, Babady-Bila, *Tetrahedron* **1997**, *53*, 12739–12754 and references cited herein.
[38] H. Yokoyama, K. Otaya, H. Kobayashi, M. Miyazawa, S. Yamaguchi, Y. Hirai, *Org. Lett.* **2000**, *2*, 2427–2429.
[39] S. Takano, K. Ogasawara, *J. Synth. Org. Chem. Jpn.* **1987**, 1156–1162.
[40] P. J. Dransfield, P. M. Gore, M. Shipman, A. M. Z. Slawin, *Chem. Commun.* **2002**, 150–151.
[41] C. C. Joseph, K. Regeling, B. Zwanenburg, G. J. F. Chittenden, *Carbohydr. Res.* **2002**, *337*, 1083–1087.
[42] A. Bandzouzi, M. Lakhrissi, Y. Chapleur, *J. Chem. Soc., Perkins Trans. 1* **1992**, 1471–1473.
[43] G. Godin, P. Compain, G. Masson, O. R. Martin, *J. Org. Chem.* **2002**, *7*, 6960–6970.
[44] H. Paulsen, I. Sangster, K. Heyns, *Chem. Ber.* **1967**, *100*, 802–811.
[45] J. Spreitz, A. E. Stütz, T. M. Wrodnigg, *Carbohydr. Res.* **2002**, *337*, 183–186.
[46] B. Helferich, R. Steinpreis, *Chem. Ber.* **1958**, *91*, 1794–1798.
[47] For a similar sequence with iodine as nucleophile, see: M. Fellahi, C. Morin, *Carbohydr. Res.* **1999**, *322*, 142–146.
[48] a) C. G. J. Verhart, B. M. G. Caris, B. Zwanenburg, G. J. F. Chittenden, *Recl. Trav. Chim. Pays-Bas* **1992**, *111*, 348–352; b) R. S. Tipson, R. F. Brady, B. F. West Jr., *Carbohydr. Res.* **1971**, *16*, 383–393.
[49] N. Hofmann-Bang, *Acta Chem. Scand.* **1957**, *11*, 581–582.
[50] K. Hojo, S. Kobayashi, K. Soai, S. Ikeda, T. Mukaiyama, *Chem. Lett.* **1977**, 635–636.
[51] E. J. Prisbe, J. Smejkal, J. P. H. Verheyden, J. G. Moffatt, *J. Org. Chem.* **1976**, *41*, 1836–1846.
[52] B. G. Davis, A. Hull, C. Smith, R. J. Nash, A. A. Watson, D. A. Winkler, R. C. Griffiths, G. W. J. Fleet, *Tetrahedron: Asymmetry* **1998**, *9*, 2947–2960.
[53] J. P. Shilvock, R. J. Nash, A. A. Watson, A. L. Winters, T. D. Butters, R. A. Dwek, D. A. Winkler, G. W. J. Fleet, *J. Chem. Soc., Perkin Trans. 1* **1999**, 2747–2754.
[54] a) G. W. J. Fleet, S. Petursson, A. L. Campbell, A. L. Mueller, J. R. Behling, K. A. Babiak, J. S. Ng, M. G. Scaros, *J. Chem. Soc., Perkin Trans. 1* **1989**, 665–666; b) D. M. Andrews, M. I. Bird, M. M. Cunningham, P. Ward, *Bioorg. Med. Chem. Lett.* **1993**, *3*, 2533–2536; c) G. W. J. Fleet, S. K. Namgoong, C. Barker, S. Baines, G. S. Jacob, B. Winchester, *Tetrahedron Lett.* **1989**, *30*, 4439–4442.
[55] J. L. O'Brien, M. Tosin, P. V. Murphy, *Org. Lett.* **2001**, *3*, 3353–3356.
[56] P. J. Garegg, B. Samuelsson, *J. Chem. Soc., Perkin Trans. 1* **1980**, 2866–2870.
[57] J. P. Shilvock, J. R. Wheatley, R. J. Nash, A. A. Watson, R. C. Griffiths, T. D. Butters, M. Müller, D. J. Watkin, D. A. Winkler, G. W. J. Fleet, *J. Chem. Soc., Perkin Trans. 1* **1999**, 2735–2745.
[58] a) J. R. Wheatley, A. R. Beacham, P. M. de Q. Lilley, D. J. Watkin, G. W. J. Fleet, *Tetrahedron: Asymmetry* **1994**, *5*, 2523–2534; b) J. C. Estevez, M. D. Smith, M. R. Wormald, G. S. Besra, P. J. Brennan, R. J. Nash, G. W. J. Fleet, *Tetrahedron: Asymmetry* **1996**, *7*, 391–394.
[59] M. A. T. Maughan, I. G. Davies, T. D. W. Claridge, S. Courtney, P. Hay, B. G. Davies, *Angew. Chem. Int. Ed.* **2003**, *42*, 3788–3792.
[60] P. A. Fowler, A. H. Haines, R. J. K. Taylor, E. J. T. Chystal, M. B. Gravestock, *Carbohydr. Res.* **1993**, *246*, 377–381.
[61] T. M. Chapman, S. Courtney, P. Hay, B. G. Davies, *Chem. Eur. J.* **2003**, *9*, 3397–3414.
[62] For a review, see: X. Liang, J. Andersch, M. Bols, *J. Chem. Soc., Perkin Trans. 1* **2001**, 2136–2157.
[63] Y. Banba, C. Abe, H. Nemoto, A. Kato, I. Adachi, H. Takahata, *Tetrahedron: Asymmetry* **2001**, *12*, 817–819.
[64] H. Takahata, Y. Banba, H. Ouchi, H. Nemoto, *Org. Lett.* **2003**, *5*, 2527–2529.
[65] For recent reviews on the olefin metathesis reaction, see: a) A. Deiters, S. F. Martin, *Chem. Rev.* **2004**, *104*, 2199–2238; b) F.-X. Felpin, J. Lebreton, *Eur. J. Org. Chem.* **2003**, 3693–3712; c) A. Fürstner, *Angew. Chem. Int. Ed.* **2000**, *39*, 3012–3043; d) R. R. Schrock, *Tetrahedron* **1999**, *55*, 8141–8153; e) D. L. Wright, *Curr. Org. Chem.* **1999**, *3*, 211–240; f) A. J. Philips, A. D. Abell, *Aldrichim. Acta* **1999**, *32*, 75–89.
[66] G. C. Bagan, J. H. Oskam, H.-N. Cho, L. Y. Park, R. R. Schrock, *J. Am. Chem. Soc.* **1991**, *113*, 6899–6907.
[67] E. L. Dias, S. T. Nguyen, R. H. Grubbs, *J. Am. Chem. Soc.* **1997**, *119*, 3887–3897.
[68] V. Van Rheenen, R. C. Kelly, D. Y. Cha, *Tetrahedron Lett.* **1976**, *17*, 1973–1976.
[69] a) F.-X. Felpin, K. Boubekeur, J. Lebreton, *J. Org. Chem.* **2004**, *69*, 1497–1503.
[70] a) F.-X. Felpin, J. Lebreton, *Tetrahedron Lett.* **2003**, *44*, 527–530; b) F.-X. Felpin, K. Boubekeur, J. Lebreton, *Eur. J. Org. Chem.* **2003**, 4518–4527.
[71] a) J. G. Knight, S. W. Ainge, A. M. Harm, S. J. Harwood, H. I. Maughan, D. R. Armour, D. M. Hollinshead, A. A. Jaxa-Chamiec, *J. Am. Chem. Soc.* **2000**, *122*, 2944–2945; b) J. G. Knight, K. Tchabanenko, *Tetrahedron* **2002**, *58*, 6659–6664.
[72] J. G. Knight, K. Tchabanenko, *Tetrahedron Lett.* **2003**, *59*, 281–286.
[73] M. Kang, J. Park, A. W. Konradi, S. F. Pederson, *J. Org. Chem.* **1996**, *61*, 5528–5531.
[74] For a review of the application of tartrates in the synthesis of bioactive molecules, see: A. K. Ghosh, E. S. Koltun, G. Bilcer, *Synthesis* **2001**, 1281–1301.
[75] M. Ruiz, V. Ojea, T. M. Ruanova, J. M. Quintela, *Tetrahedron: Asymmetry* **2002**, *13*, 795–799.
[76] P. Munier, A. Krusinski, D. Picq, D. Anker, *Tetrahedron* **1995**, *51*, 1229–1244.
[77] M. Ruiz, V. Ojea, J. M. Quintela, *Synlett* **1999**, 204–206.
[78] M. Kummeter, U. Kazmaier, *Eur. J. Org. Chem.* **2003**, 3330–3334.
[79] a) R. Grandel, U. Kazmaier, *Tetrahedron Lett.* **1997**, *38*, 8009–8012; b) R. Grandel, U. Kazmaier, F. Rominger, *J. Org. Chem.* **1998**, *63*, 4524–4528.
[80] M. Achmatowicz, L. S. Hegedus, *J. Org. Chem.* **2004**, *69*, 2229–2234.
[81] For the preparation of this chiral compound, see: P. B. D. Ranslow, L. S. Hegedus, C. de los Rios, *J. Org. Chem.* **2004**, *69*, 105–111.
[82] C. Ahn, P. DeShong, *J. Org. Chem.* **2002**, *67*, 1754–1759.
[83] a) T. Katsuki, K. B. Sharpless, *J. Am. Chem. Soc.* **1980**, *102*, 5976–5974; b) Review: T. Katsuki, V. S. Martin, *Org. React.* **1996**, *48*, 1–299.
[84] a) S. G. Hentges, K. B. Sharpless, *J. Am. Chem. Soc.* **1980**, *102*, 4263–4265; b) review: H. C. Kolb, M. S. Van Nieuwenhze, K. B. Sharpless, *Chem. Rev.* **1994**, *94*, 2483–2547.
[85] a) G. Li, H.-T. Chang, K. B. Sharpless, *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 451–454; b) review: H. C. Kolb, K. B. Sharpless, *Asymmetric Aminohydroxylation*, in *Transition Metals for Organic Synthesis: Building Blocks and Fine Chemicals* (Eds. M. Beller, C. Bolm), Wiley-VCH, Weinheim, **1998**.
[86] M. H. Haukaas, G. A. O'Doherty, *Org. Lett.* **2001**, *3*, 401–404.
[87] O. V. Singh, H. Han, *Tetrahedron Lett.* **2003**, *44*, 2387–2391. For previous work from this group on asymmetric synthesis of polyhydroxypiperidines, see: H. Han, *Tetrahedron: Asymmetry* **2001**, *12*, 1807–1809.
[88] For leading references, see: a) H. Han, C.-W. Cho, K. D. Janda, *Chem. Eur. J.* **1999**, 1565–1569; b) A. J. Morgan, C. E. Masse, J. S. Panek, *Org. Lett.* **1999**, *1*, 1949–1952.
[89] For a good review on cyclic sulfate chemistry, see: B. B. Lohray, *Synthesis* **1992**, 1035–1052.
[90] P. Somfai, P. Marchand, S. Torsell, U. M. Lindström, *Tetrahedron* **2003**, *59*, 1293–1299. A closely related synthesis of DNJ (**9**) was described previously by these authors, see: U. M. Lindström, P. Somfai, *Tetrahedron Lett.* **1998**, *39*, 7173–7176.

[91] For a review, see: T. Hudlicky, D. Gonzalez, D. T. Gibson, *Aldrichim. Acta* **1999**, *32*, 35–62.
[92] M. G. Banwell, X. Ma, N. Asano, K. Ikeda, J. N. Lambert, *Org. Biomol. Chem.* **2003**, *1*, 2035–2037.
[93] T. Hudlicky, J. Rouden, H. Luna, S. Allen, *J. Am. Chem. Soc.* **1994**, *116*, 5099–5107.
[94] M. Couturier, J. L. Tucker, B. M. Andresen, P. Dubé, J. T. Negri, *Org. Lett.* **2001**, *3*, 465–467.
[95] a) D. L. Comins, X. Zheng, R. R. Goehring, *Org. Lett.* **2002**, *4*, 1611–1613; b) D. L. Comins, S. P. Joseph, R. R. Goehring, *J. Am. Chem. Soc.* **1994**, *116*, 4719–4728.
[96] D. L. Comins, A. B. Fulp, *Tetrahedron Lett.* **2001**, *42*, 6839–6841.

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