

# Piperidine homoazasugars: natural occurrence, synthetic aspects and biological activity study

Dilip D. Dhavale\*<sup>a</sup> and Mohammed M. Matin<sup>b</sup>

<sup>a</sup> Department of Chemistry, Garware Research Centre, University of Pune, Pune-411 007, India

<sup>b</sup> Department of Chemistry, University of Chittagong, Chittagong 4331, Bangladesh

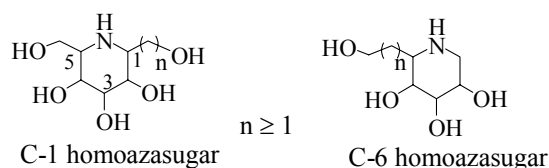
E-mail: [ddd@chem.unipune.ernet.in](mailto:ddd@chem.unipune.ernet.in)

Dedicated to Dr. A. V. Rama Rao on the occasion of his 70<sup>th</sup> birthday

(received 19 July 04; accepted 05 Nov 04; published on the web 11 Dec 04)

## Abstract

A number of natural and synthetic analogues of homoazasugars, known in the literature, are promising glycosidase inhibitors. The methodologies used for the synthesis of piperidine homoazasugars are: (i) intramolecular reductive amination, (ii) intermolecular double reductive amination, (iii) amino/amido mercuration, (iv) intramolecular nucleophilic substitution, (v) synthesis from non-carbohydrate building block and aza-heterocycles and (vi) enzyme catalyzed intramolecular reductive amination. Homoazasugars showed higher selectivity and potency in the glycosidase inhibitory activity. In this report, natural occurrence, synthetic methodologies and potential application to glycosidase inhibitory activity of homoazasugars will be reviewed.



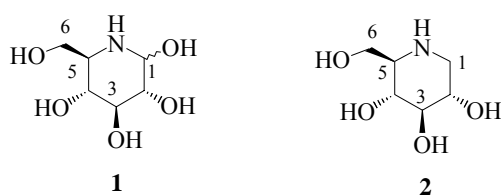
**Keywords:** Piperidine, azasugar, homoazasugar, glycosidase inhibitor

## Contents

1. Introduction
2. Natural occurrence
3. Synthesis of piperidine homoazasugars
4. Biological activity
5. Conclusion
6. References

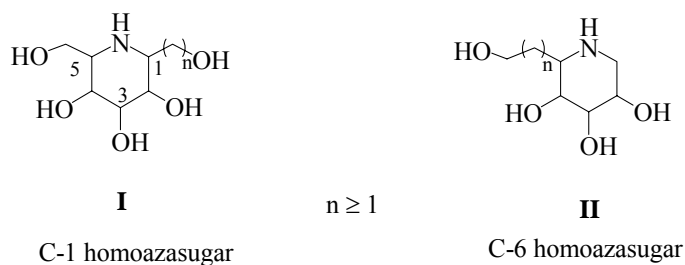
## 1. Introduction

The search for selective and effective inhibitors of oligosaccharide processing enzymes has promoted intense research over the last 20 years in the synthesis of stereochemically well-defined polyhydroxylated piperidines. This class of compounds, commonly called as azasugars or iminosugars, are known to be endowed with a remarkable therapeutic potential in the treatment of diabetes, viral infections (including HIV) and tumor metastasis<sup>1b</sup> due to their action as glycosidase inhibitors.<sup>1</sup> The polyhydroxylated piperidine namely nojirimycin (NJ **1**, Figure 1) was first isolated from a fermentation broth of *Streptomyces roseochromogenes* R-468.<sup>2a</sup> The more stable form of NJ is the 1-deoxynojirimycin (DNJ, **2**), also called as moranoline, was first prepared<sup>2b</sup> by catalytic hydrogenation of NJ and later on isolated from different species of the plant *Morus*.<sup>2c</sup>



**Figure 1**

The search for promising glycosidase inhibitors led to the discovery of homoazasugars. In general, the homoazasugars are classified in to two categories. In the first type, hydroxymethyl group/polyhydroxylated carbon chain is present at both the carbons (C-1 and C-5) adjacent to the ring nitrogen (type **I**, Figure 2) and is also known as aza-C-glycoside. While, in other the type carbon homologation is present at C-6 of the piperidine (type **II**).

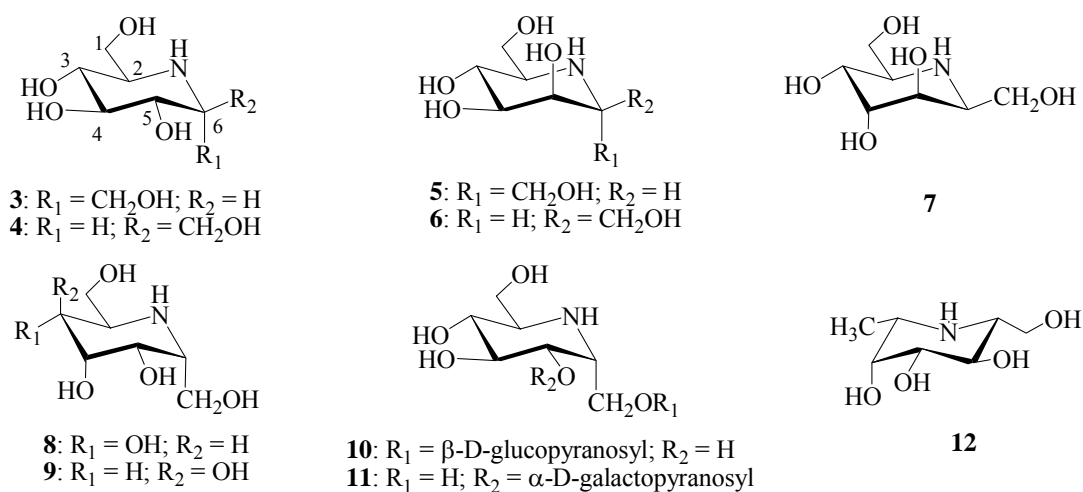


**Figure 2**

The homoazasugars are found to be more stable towards chemical and enzymatic degradation than azasugars, while retaining the powerful biological activity of the parent azasugars, the homoazasugars having substituents recognizing the aglycon-binding site of the enzyme are expected to further increase the selectivity. Due to their higher selectivity and potency in the glycosidase inhibitory activity, the homoazasugars are now gaining their own independent identity. A brief review of natural occurrence, synthetic aspects and biological activity of piperidine homoazasugars is described in this article.

## 2. Natural occurrence

Homoazasugars are natural alkaloids widely diffused in plants and microorganisms. Interestingly,  $\alpha$ -homonojirimycin ( $\alpha$ -HNJ **3**, Figure 3) was first synthesized in the protected form<sup>4</sup> just before its isolation in 1988.<sup>5</sup> The naturally occurring homoazasugars are listed in Figure 3 and their natural sources are summarized in Table 1.



**Figure 3.** Structures of naturally occurring piperidine homoazasugars.

**Table 1.** Polyhydroxylated piperidine homoazasugars isolated from natural sources

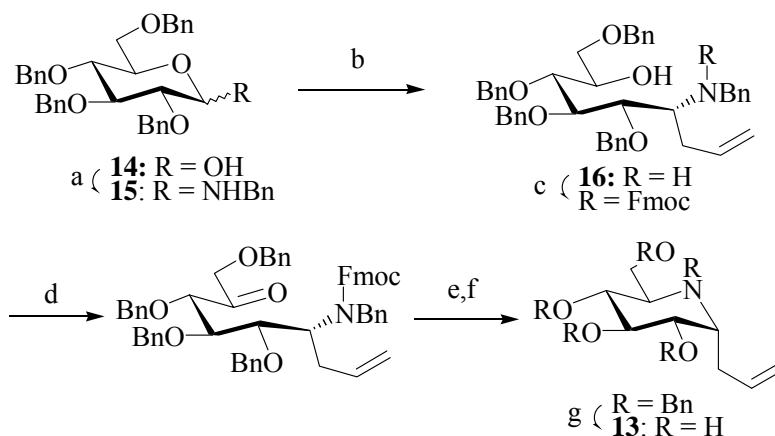
Sl. No.	Chemical/Common name	Plant/Organism name	Plant part	Ref.
1.	$\alpha$ -homonojirimycin ( <b>3</b> )	<i>Omphalea diandra</i> , <i>Urania Fulgens</i> , <i>Aglaonema treubii</i> , <i>Hyacinthus orientalis</i>	leaves whole plant bulbs	5, 6 7, 8, 9, 10
2.	$\beta$ -homonojirimycin ( <b>4</b> )	<i>Aglaonema treubii</i>	whole plant	8, 11
3.	$\alpha$ -homomannonojirimycin ( <b>5</b> )	<i>Aglaonema treubii</i>	whole plant	8, 11
4.	$\beta$ -homomannonojirimycin ( <b>6</b> )	<i>Aglaonema treubii</i>	whole plant	8, 11
5.	$\beta$ -homoaltronojirimycin ( <b>7</b> )	<i>Hyacinthus orientalis</i>	bulbs	10
6.	$\alpha$ -homoallonojirimycin ( <b>8</b> )	<i>Aglaonema treubii</i>	whole plant	11
7.	$\alpha$ -3,4-di- <i>epi</i> -homonojirimycin ( <b>9</b> )	<i>Aglaonema treubii</i>	whole plant	8
8.	7- <i>O</i> - $\beta$ -D-glucopyranosyl- $\alpha$ - homonojirimycin (MDL 25637) ( <b>10</b> )	<i>Aglaonema treubii</i>	whole plant	8
9.	5- <i>O</i> - $\alpha$ -D-galactopyranosyl- $\alpha$ - homonojirimycin ( <b>11</b> )	<i>Aglaonema treubii</i>	whole plant	8
10	$\beta$ -L-homofuconojirimycin ( <b>12</b> )	<i>Angylocalyx pynaertii</i>	bark	12

### 3. Synthesis of piperidine homoazasugars

A number of piperidine homoazasugars are known in the literature and are described in the review articles related to azasugars.<sup>1,13-17</sup> As the homoazasugars have a close resemblance with five or six carbon sugars, most of the synthetic strategies make use of sugars as the starting materials. The common methodologies used for the synthesis of piperidine homoazasugars are: (i) intramolecular reductive amination, (ii) intermolecular double reductive amination, (iii) amino/amido mercuration, (iv) intramolecular nucleophilic substitution, (v) synthesis from non-carbohydrate building block and aza-heterocycles and (vi) enzyme catalyzed intramolecular reductive amination.

#### (i) Intramolecular reductive amination strategy

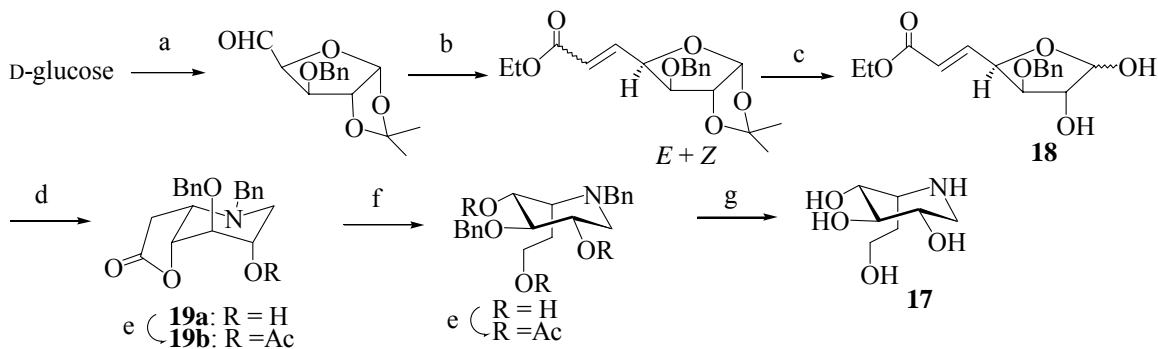
Cipolla and co-workers have synthesized the protected  $\alpha$ -allyl-C-glycoside of nojirimycin **13** by sequential reductive amination (Scheme 1).<sup>18</sup> Thus, reaction of perbenzylated D-glucose **14** with benzylamine afforded *N*,2,3,4,6-pentabenzyl-D-glucopyranosylamine **15**, that on allylation gave stereoselectively the open chain amino alcohol **16**. Protection of the amino functionality by Fmoc, oxidation of the free hydroxy group to ketone, hydrolysis of the Fmoc group and final intramolecular reductive amination with Na(OAc)<sub>3</sub>BH afforded the  $\alpha$ -allyl-C-glycoside nojirimycin **13**.



**Scheme 1.** Reagents and conditions: (a) PhCH<sub>2</sub>NH<sub>2</sub>, *p*-TSA, CH<sub>2</sub>Cl<sub>2</sub>, MS, 5 d, 80%; (b) CH<sub>2</sub>=CHCH<sub>2</sub>MgBr, Et<sub>2</sub>O, 81%, 90% de; (c) FmocCl, dioxane-10% aq. Na<sub>2</sub>CO<sub>3</sub>, 89%; (d) PCC, CH<sub>2</sub>Cl<sub>2</sub>, MS, 90%; (e) piperidine, DMF; (f) NaHB(OAc)<sub>3</sub>, AcOH, Na<sub>2</sub>SO<sub>4</sub>, 1,2-dichloroethane, -35°C, 78%, 90% de; (g) H<sub>2</sub>, Pd(OH)<sub>2</sub>, AcOH, AcOEt-EtOH (1:1).

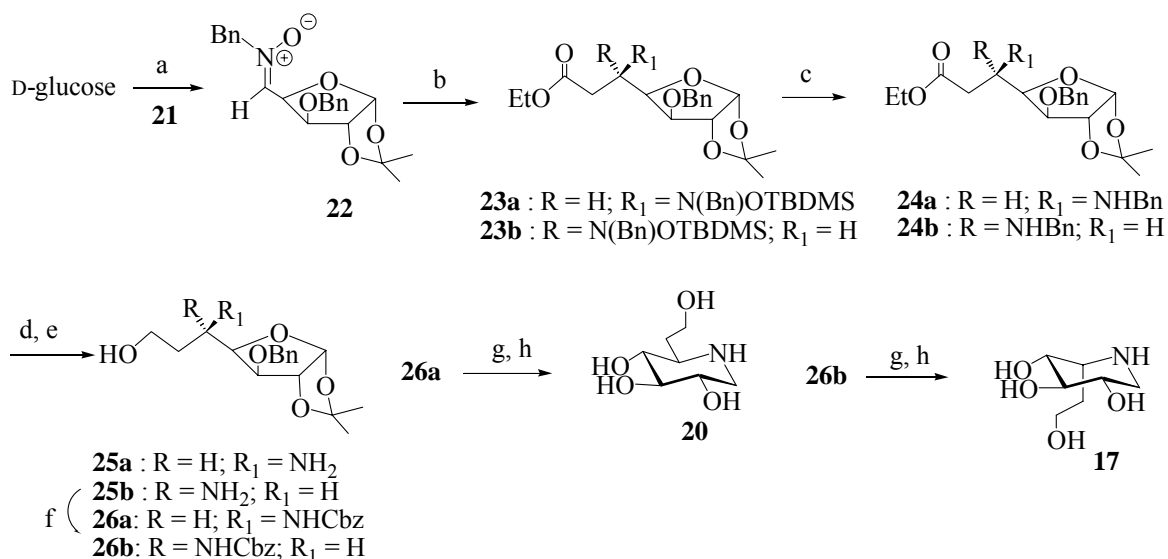
We have recently reported two different strategies for the synthesis of 6-homoazasugars **17** and **20**. The first method<sup>19a</sup> relies on the reductive amination followed by diastereoselective intramolecular conjugate addition of the *in situ* generated benzylamine in the formation of desired piperidine ring (Scheme 2). Thus, D-glucose was converted to  $\alpha,\beta$ -unsaturated ester that

on 1,2-acetonide cleavage afforded hemiacetal **18**. The reaction of **18** with benzylamine forms imine that was reduced to sugar benzylamine. The concomitant *in situ* addition of amine to  $\alpha,\beta$ -unsaturated ester followed by domino lactonization gave lactone **19a** with the required homoazasugar ring skeleton. Reduction of the lactone functionality and removal of the protecting group by hydrogenation afforded 1-deoxy-L-*ido*-homonojirimycin **17**.



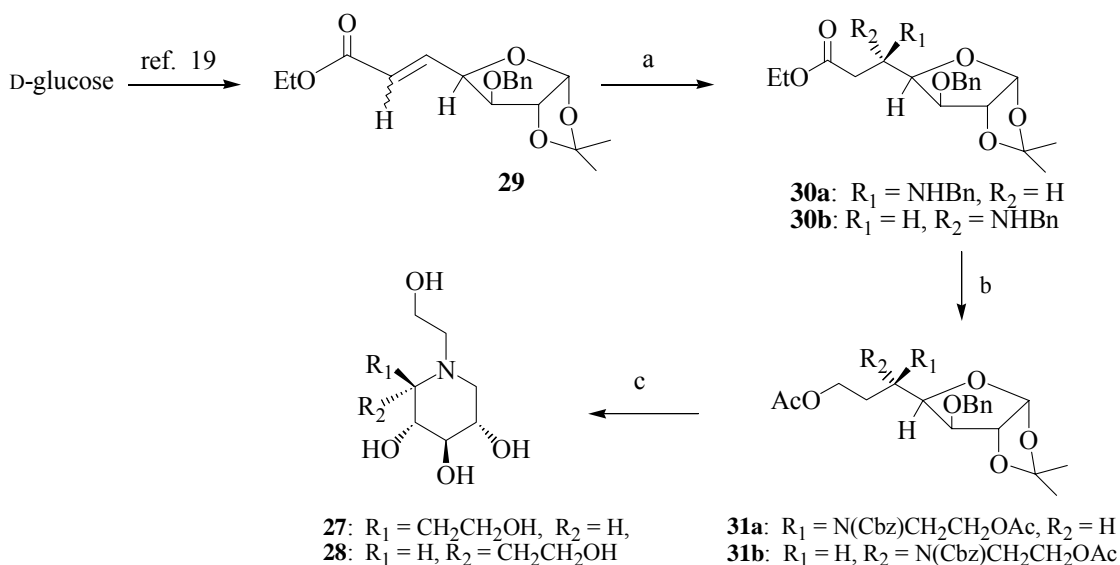
**Scheme 2.** Reagents and conditions: (a) ref. 19b (b)  $\text{PPh}_3\text{CHCO}_2\text{Et}$ , MeCN, reflux, 2 h; (c) TFA- $\text{H}_2\text{O}$  (3:2), rt, 2 h; (d)  $\text{BnNH}_2$ ,  $\text{NaCNBH}_3$ , AcOH, MeOH,  $-78^\circ\text{C}$ , 2 h, rt, 24 h; (e)  $\text{Ac}_2\text{O}$ , Py, DMAP, rt, 24 h; (f) LAH, THF,  $0^\circ\text{C}$ -rt, 2 h; (g) MeOH, 10% Pd/C,  $\text{HCO}_2\text{NH}_4$ , reflux, 1 h.

The second method<sup>20</sup> described the synthesis of homoazasugars **17** and **20**. The key step involved TMSOTf catalyzed 1,3-addition of silyl ketene acetal **21** to D-glucose derived nitrone **22**<sup>21</sup> which afforded a diastereomeric mixture of D-*gluco*- and L-*ido*- configured N-benzyl hydroxylamines **23a** and **23b** in a good diastereoselectivity in favor of required D-*gluco* isomer. Column chromatographic separation and N-O bond reductive cleavage afforded D-*gluco*- and L-*ido*- $\beta$ -amino esters **24a** and **24b**. Reduction of the ester group in **24a,b** followed by hydrogenolysis gave amino alcohol **25a,b** that on selective N-Cbz protection gave **26a,b**. The hydrolysis of 1,2-acetonide functionality in **26a,b** and intramolecular reductive amination afforded D-*gluco*-homo-1-deoxynojirimycin **20** and L-*ido*-homo-1-deoxynojirimycin **17**, respectively (Scheme 3).



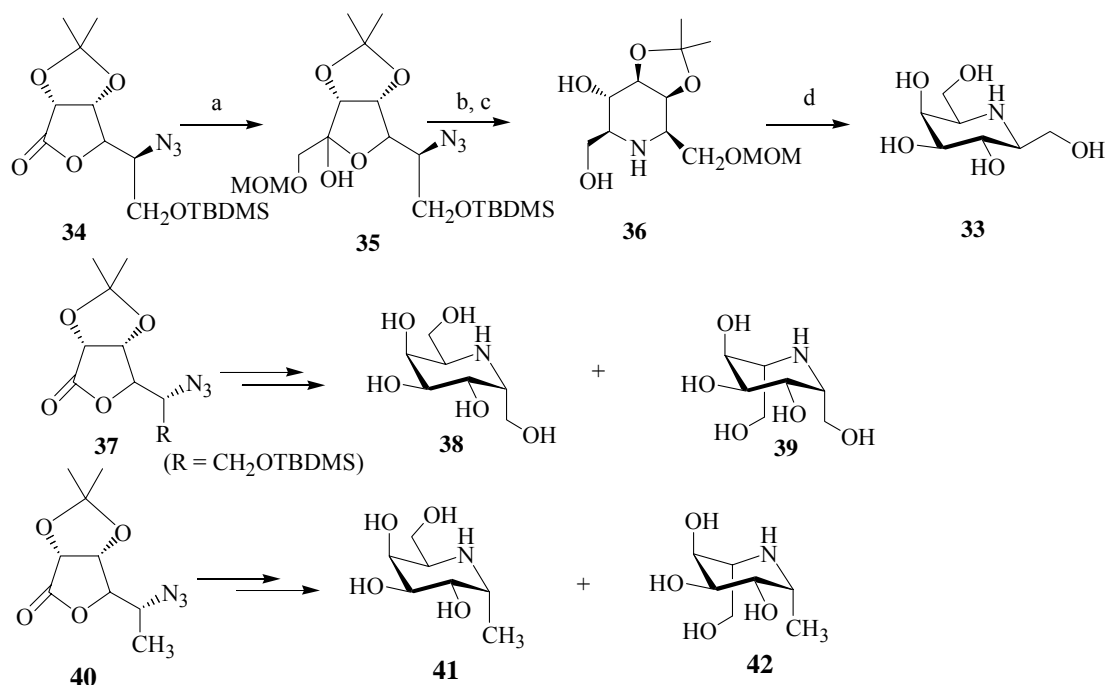
**Scheme 3.** *Reagents and conditions:* (a) ref. 21. (b) CH<sub>2</sub>Cl<sub>2</sub>, Lewis acid, -78°C, CH<sub>2</sub>=C(OEt)OTBDMS (21). (c) Cu(OAc)<sub>2</sub>, Zn dust, glacial AcOH, 70°C, EDTA, 1 h. (d) THF, LAH, 0°C-rt, 2 h; (e) MeOH, 10% Pd/C, HCOONH<sub>4</sub>, reflux, 1 h. (f) EtOH-H<sub>2</sub>O, NaHCO<sub>3</sub>, CbzCl, 6 h. (g) TFA-H<sub>2</sub>O (3:2), 25°C, 2 h. (h) MeOH, 10% Pd/C, H<sub>2</sub>, 70 psi, 16 h.

In the next report, we have described an efficient and practical strategy for the synthesis of *N*-hydroxyethyl-1-deoxy-homonojirimycins **27** and **28** with full stereocontrol (Scheme 4).<sup>23</sup> The key step involved is the intermolecular conjugate addition of benzylamine to D-glucose derived  $\alpha,\beta$ -unsaturated ester **29** to afford *D*-*gluco*- and *L*-*ido*- configured  $\beta$ -amino esters **30a** and **30b**. The sequential *N*-alkylation of **30a** and **30b** with ethyl bromoacetate, reduction with LAH, acetylation, hydrogenation and selective protection with -Cbz group afforded **31a** and **31b**, respectively. Separate removal of 1,2-acetonide functionality, hydrogenation and deacetylation of **30a** and **30b** afforded *N*-hydroxyethyl-*D*-*gluco*-1-deoxyhomonojirimycin (**27**) and *N*-hydroxyethyl-*L*-*ido*-1-deoxyhomonojirimycin (**28**), respectively. The glycosidase inhibition activity of compounds **27** and **28** was evaluated using sweet almond seed as a rich source of different glycosidases.



**Scheme 4.** Reagents and conditions: (a)  $\text{BnNH}_2$ , rt, 20 h (b) i.  $\text{BrCH}_2\text{COOEt}$ ,  $\text{K}_2\text{CO}_3$ , DMF, rt, 24-30 h; ii. LAH, THF,  $0^\circ\text{C}$ , 2 h; iii.  $\text{Ac}_2\text{O}$ , Py,  $0-25^\circ\text{C}$ , 43 h; iv. 10% Pd-C,  $\text{H}_2$ , 80 psi, MeOH, 12 h; v. CbzCl,  $\text{NaHCO}_3$ , EtOH- $\text{H}_2\text{O}$  (8:2),  $0^\circ\text{C}$ -rt, 4 h. (c) i. TFA- $\text{H}_2\text{O}$  (3:2),  $0-30^\circ\text{C}$ , 3 h; ii. 10% Pd-C,  $\text{HCOONH}_4$ , MeOH, reflux, 45 min; iii. NaOMe, MeOH,  $0-30^\circ\text{C}$ , 2 h.

Transmetalation of the hydroxy protected stannylmethanol derivative **32** with butyllithium is an effective source of the hydroxymethyl carbanion, which undergoes efficient nucleophilic addition to carbonyl compounds and has been utilized for one carbon chain extension of carbohydrate lactones.<sup>23</sup> Shilvock and co-workers have exploited this strategy for the synthesis of  $\beta$ -homogalactonojirimycin ( $\beta$ -HGJ) **33** (Scheme 5).<sup>24,25</sup> Thus, hydroxy-methylation of protected 5-azido-L-manno-1,4-lactone **34** gave **35**, which on hydrogenation afforded the piperidine derivative **36** as a single diastereomer. De-protection of the acetonide and MOM groups yielded **33** in good yield. The same strategy was extended for the synthesis of a variety of homoazasugars by changing the sugar lactones. For example, 5-azido-D-gulono-1,4-lactone **37** furnished  $\alpha$ -HGJ **38** and C-5 epimeric homoazasugar **39**, whereas 6-deoxy-5-azido-D-gulono-1,4-lactone **40** gave **41** and C-5 epimeric homoazasugar **42** (Scheme 5).

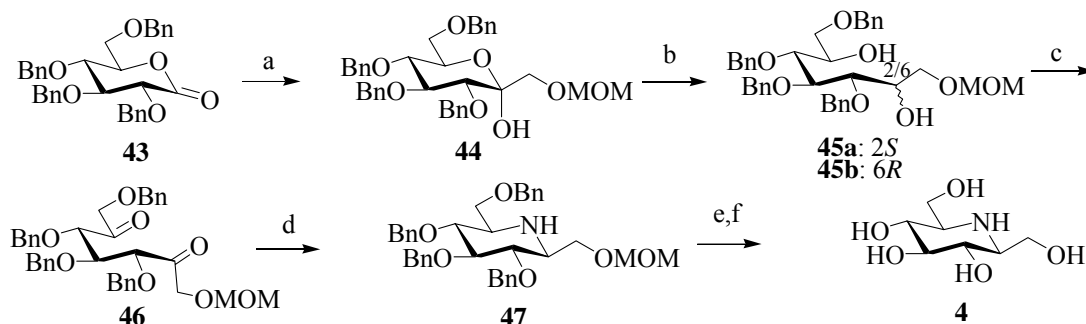


**Scheme 5.** Reagents and conditions: (a)  $\text{Bu}_3\text{SnCH}_2\text{OMOM}$  (32),  $n\text{-BuLi}$ , THF,  $-78^\circ\text{C}$ . (b) TBAF, THF, 81%. (c)  $\text{H}_2$ , 10% Pd/C, EtOAc, 94%. (d) HCl, MeOH, 85%.

### (ii) Intermolecular double reductive amination methodology

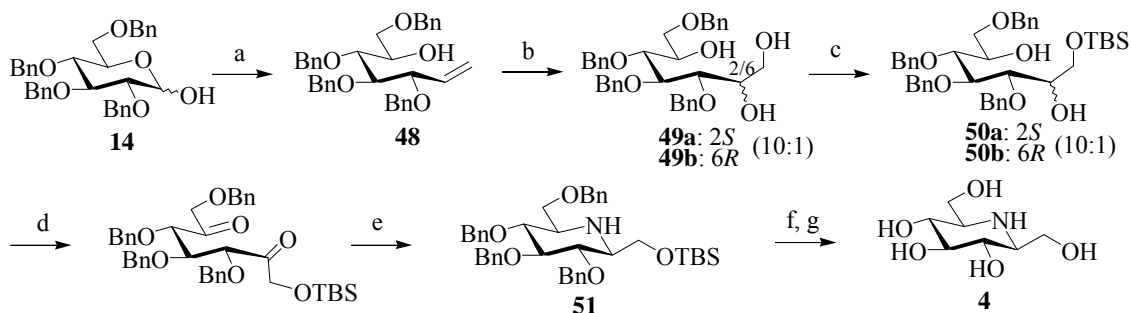
Saavedra and Martin<sup>26</sup> used two different approaches for the synthesis of  $\beta$ -homonojirimycin (**4**). In the first approach (Scheme 6), tetra-*O*-benzyl-D-glucono-1,5-lactone **43** was treated with (methoxymethoxy)methyl lithium and the resulting heptulopyranose derivative **44** was reduced to alcohols **45a** and **45b** (~1:1). The oxidation of the mixture of **45a** and **45b** using DMSO-TFAA gave heptodiulose **46**, which was immediately subjected to double reductive amination using  $\text{HCOONH}_4$  in the presence of  $\text{NaBH}_3\text{CN}$  to give **47** as a single stereoisomer. The high degree of stereoselectivity observed in this double reductive amination reaction, probably involves cyclic intermediate and the stereoselective hydride addition (axial attack) appeared due to torsional effects.<sup>27,28</sup> In the subsequent step, removal of the benzyl and MOM protecting groups provided **4**.





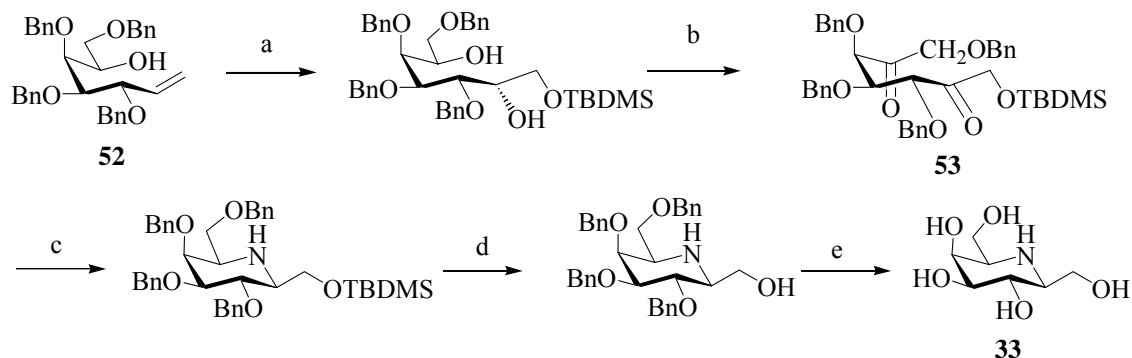
**Scheme 6.** Reagents and conditions: (a) LiCH<sub>2</sub>OMOM, THF, -78°C, 70%. (b) LAH, THF, 97%. (c) TFAA, DMSO-CH<sub>2</sub>Cl<sub>2</sub>, Et<sub>3</sub>N. (d) HCOONH<sub>4</sub>, NaBH<sub>3</sub>CN, MeOH, 50%. (e) aq. HCl, THF, 93%. (f) i. TMSI; ii. H<sub>2</sub>O, 70%.

In the second approach (Scheme 7),<sup>26</sup> one carbon extension by Wittig reaction of perbenzylated  $\alpha$ -D-glucopyranose **14** followed by dihydroxylation afforded **49a** and **49b** (10:1, the major isomer was predicted from Kishi's empirical rule<sup>29</sup>) in which the primary hydroxyl group was protected as silyl ether. Oxidation of secondary alcohol functionality in **50a/50b** afforded 1,5-diketone. Subsequently, double reductive amination using ammonium formate and sodium cyanoborohydride gave  $\beta$ -homonojirimycin derivative **51** that on removal of the protecting groups yielded **4**.



**Scheme 7.** Reagents and conditions: (a) Ph<sub>3</sub>P=CH<sub>2</sub>; (b) OsO<sub>4</sub>, NMO, 98%. (c) TBDMSCl, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, 70%. (d) TFAA, DMSO, Et<sub>3</sub>N. (e) NCOONH<sub>4</sub>, NaBH<sub>3</sub>CN, MeOH. (f) TBAF, THF, 88%. (g) i. TMSI; ii. H<sub>2</sub>O.

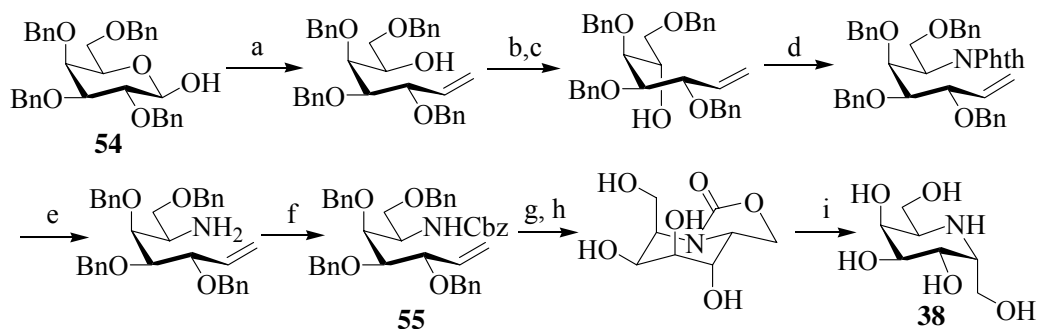
$\beta$ -Homogalactonojirimycin **33** was also synthesized in six steps from heptenitol **52** by Martin and co-workers.<sup>30</sup> The synthetic route consisted in forming the piperidine ring by way of double reductive amination process of diketone **53** using ammonium formate and sodium cyanoborohydride (Scheme 8).



**Scheme 8.** Reagents and conditions: (a) i.  $\text{OsO}_4$ , NMO (cat), 98% (de~90%). ii.  $\text{TBDMSCl}$ , 82%. (b) Swern oxidation. (c)  $\text{HCOONH}_4$ ,  $\text{NaBH}_3\text{CN}$ , 44%. (d)  $\text{AcOH-H}_2\text{O}$ ,  $\text{THF}$ , 78%. (e)  $\text{TMSI}$ , then  $\text{H}_2\text{O}$ .

### (iii) Amino/amido mercuration route

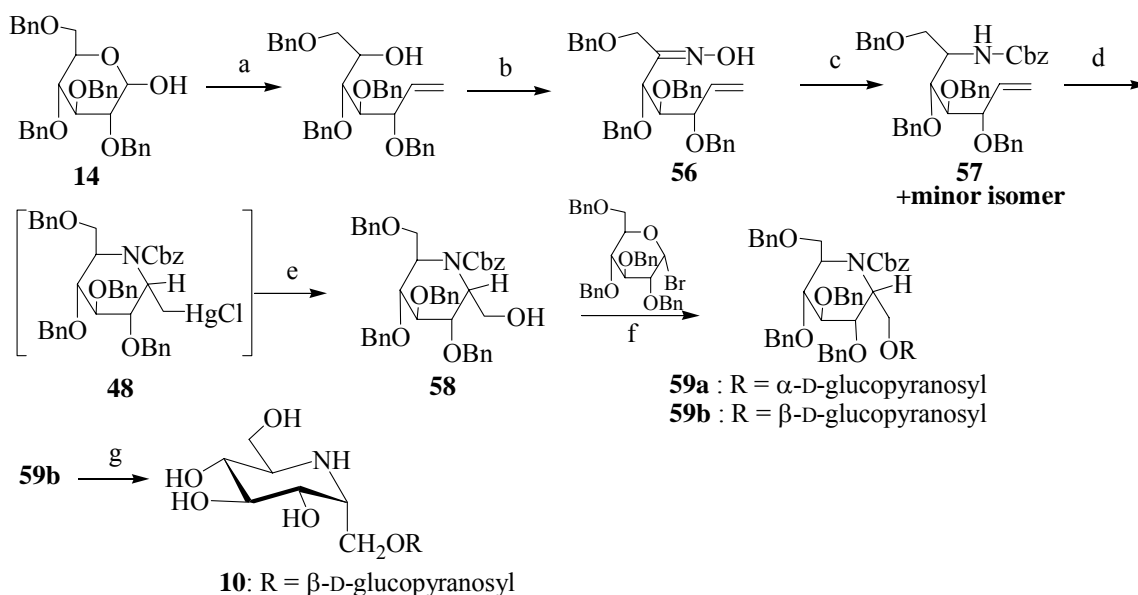
Martin and co-workers<sup>30</sup> synthesized  $\alpha$ -homogalactonojirimycin **38** in 10 steps from D-galactose derivative **54** by way of a chain extension-amination-cyclization sequence (Scheme 9). The key step involved the cyclization of D-galacto-configured aminoheptenitol **55** by intramolecular amidomercuration, which proceeded with 6-*exo*-trig cyclization with a high degree of diastereoselectivity (Scheme 9).



**Scheme 9.** Reagents and conditions: (a)  $[\text{Ph}_3\text{P=CH}_2]$ ,  $\text{PhMe}$ , 84%. (b)  $p\text{O}_2\text{NC}_6\text{H}_4\text{CO}_2\text{H}$ ,  $\text{Ph}_3\text{P}$ ,  $\text{DEAD}$ , 78%. (c)  $\text{MeONa}$ , 77%. (d) Phthalimide,  $\text{Ph}_3\text{P}$ ,  $\text{DEAD}$ , 79%. (e)  $\text{NH}_2\text{NH}_2\text{H}_2\text{O}$ ,  $\text{MeOH}$ . (f)  $\text{CbzCl}$ ,  $\text{THF}$ , 84%. (g) i.  $(\text{CF}_3\text{CO}_2)_2\text{Hg}$ ; ii.  $\text{I}_2$ ,  $\text{THF}$ , 71%. (h)  $\text{H}_2$ , 10%  $\text{Pd/C}$ , 75%. (i)  $\text{KOH}$ ,  $\text{MeOH-H}_2\text{O}$ , 81%.

The intramolecular amido mercuration strategy was also exploited by P.S. Liu in the total synthesis of 7-*O*- $\beta$ -D-glucopyranosyl- $\alpha$ -homonojirimycin **10** (MDL 25637).<sup>4</sup> The 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose **14** was converted to the oxime **56** (via Wittig olefination and oxidation of secondary hydroxyl group to ketone), which on reduction with LAH and Cbz protection gave D and L amino sugars in the ratio 6:1, respectively. The major D-*gluco*-isomer **57** on treatment with mercuric acetate in  $\text{THF}$  underwent stereospecific cyclization to give exclusively  $\alpha$ -

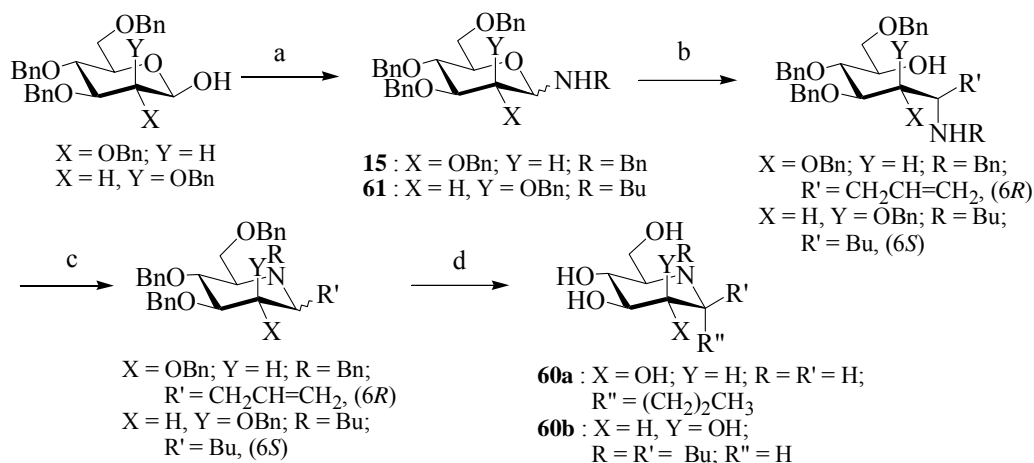
mercuriomethyl **48** that on demercuration oxygenation<sup>31</sup> gave **58**. The high stereoselectivity of the cyclization can be accounted for by the chelation effect of mercury with the vicinal  $\alpha$ -benzyloxy group, resulting in the preferential addition of the carbamate (nucleophile) from the opposite side of the olefin. The coupling with 2,3,4,6-tetra-*O*-benzyl- $\alpha$ -D-glucopyranosyl bromide furnished **59a** (19%) and **59b** (24%). Separation and de-protection in **59b** afforded  $\beta$ -glucoside **10** (Scheme 10).



**Scheme 10.** Reagents and conditions: (a)  $\text{Ph}_3\text{P}=\text{CH}_2$ . (b) i. DCC, DMSO. ii.  $\text{NH}_2\text{OHHCl}$ ,  $\text{KHCO}_3$ , 75%. (c) i. LAH; ii.  $\text{CbzCl}$ ,  $\text{K}_2\text{CO}_3$ , 67%. (d) i.  $\text{Hg}(\text{OAc})_2$ ; ii.  $\text{KCl}/\text{H}_2\text{O}$ . (e)  $\text{NaBH}_4$ -DMF- $\text{O}_2$ , 71%. (f)  $\text{CH}_2\text{Cl}_2$ ,  $\text{HgBr}_2$ , rt; (g)  $\text{CHCl}_3$ , EtOH, 5 *N*HCl, 10% Pd/C,  $\text{H}_2$ , 3 d, 74%.

#### (iv) Intramolecular nucleophilic substitution method

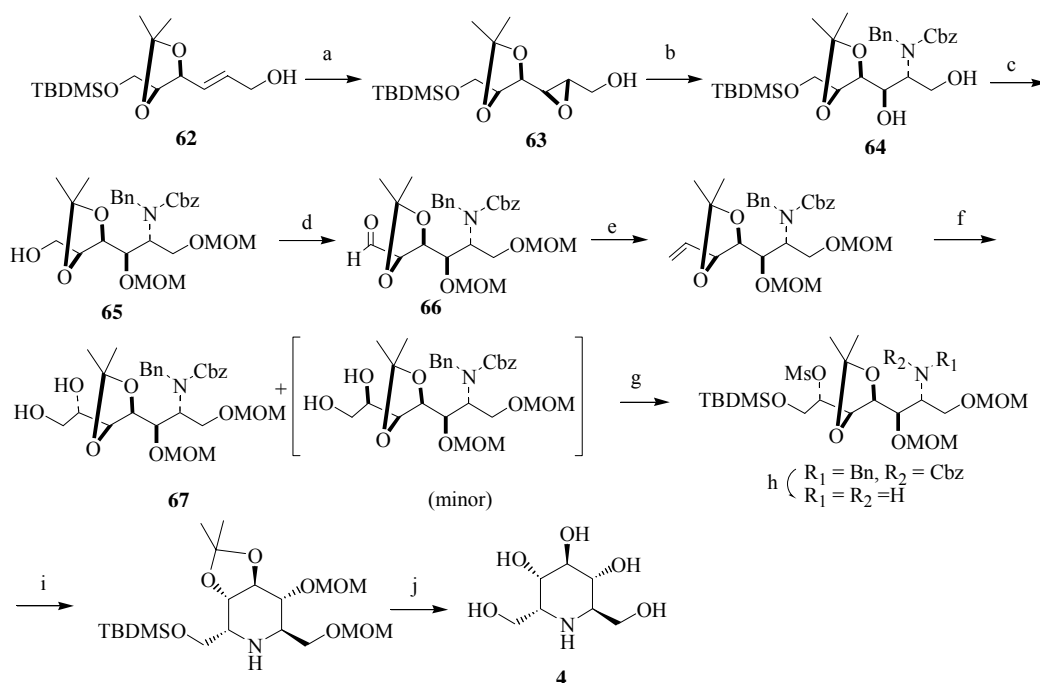
Cipolla and co-workers<sup>32</sup> have exploited the intramolecular nucleophilic displacement of *O*-triflate with amine to give piperidine ring skeleton in the synthesis of *N*-butyl homoazasugars **60a** and **60b** (Scheme 11). The *D*-gluco- and *D*-manno-pyranosylamine **15** and **61**, respectively, were reacted separately with allylmagnesium chloride to give allylated derivatives, which on treatment with  $\text{Tf}_2\text{O}$  led to the formation of  $-\text{OTf}$  derivative that undergoes intramolecular displacement of  $-\text{OTf}$  by amine giving piperidine ring that on removal of *O*-benzyl groups gave homoazasugars **60a** and **60b**, respectively.



**Scheme 11.** Reagents and conditions: (a)  $\text{RNH}_2$ ,  $\text{CH}_2\text{Cl}_2$ , MS. (b)  $\text{R}'\text{MgX}$ , THF, rt; (c)  $\text{Tf}_2\text{O}$ , Py. (d)  $\text{H}_2$ , 10% Pd/C, EtOH,  $\text{H}^+$ .

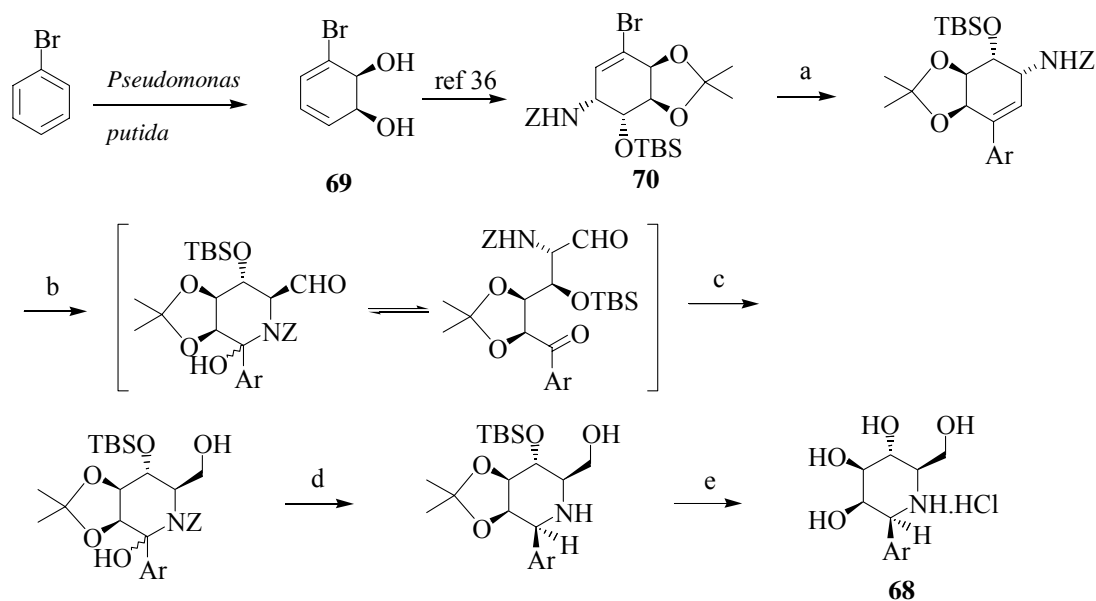
#### (v) Synthesis from non-carbohydrate building block and aza-heterocycles

The first synthesis of (+)- $\alpha$ -homojirimycin (**4**) was reported by S. Aoyagi et al.<sup>33</sup> via a non-carbohydrate based approach utilizing suitably protected allylic alcohol **62** (Scheme 12). The allylic alcohol **62** was converted to *syn* epoxide **63** by the Sharpless asymmetric epoxidation. Regio- and diastereoselective ring opening of the epoxide was effected by using dialkylaluminium amide followed by selective amino group protection to give amino alcohol **64** as a single diastereomer, which on MOM protection and desilylation furnished **65**. Swern oxidation of **65** gave the aldehyde **66** that on Wittig reaction followed by hydroxylation provided 2.5:1 diastereoselectivity in favor of the desired *anti*-diol **67**. Compound **67** was then converted to homojirimycin **4** (Scheme 12) by conversion of secondary alcohol to mesylate and hydrogenation wherein de-protection of *N*-Cbz lead to an amine that subsequently undergoes intramolecular nucleophilic substitution to give piperidine ring skeleton.



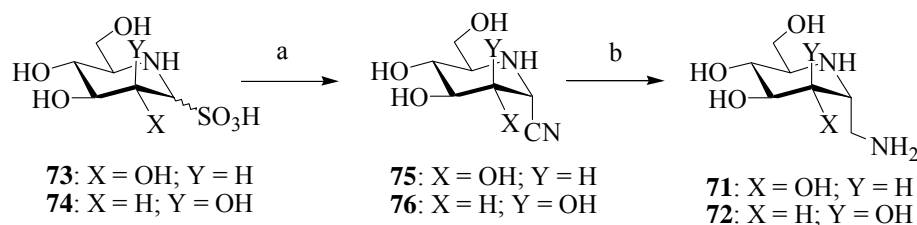
**Scheme 12.** Reagents and conditions: (a) (+)-DET,  $\text{Ti}(\text{OPr}^i)_4$ , TBHP. (b) i.  $\text{Et}_2\text{AlNHCH}_2\text{Ph}$ ,  $\text{CH}_2\text{Cl}_2$ ; ii.  $\text{CbzCl}$ , aq.  $\text{Na}_2\text{CO}_3$ ,  $\text{CH}_2\text{Cl}_2$ . (c)  $\text{MOMCl}$ ,  $(i\text{Pr})_2\text{Net}$ ,  $\text{CHCl}_3$ , then TBAF, THF; (d)  $(\text{COCl})_2$ , DMSO,  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$ ; (e)  $\text{Ph}_3\text{PCH}_3\text{Br}$ ,  $n\text{-BuLi}$ , THF; (f) NMO,  $\text{OsO}_4$ , aq.  $\text{Me}_2\text{CO}$ . (g)  $\text{TBDMSCl}$ , imidazole, DMF, then  $\text{MsCl}$ ,  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$ . (h)  $\text{H}_2$ ,  $\text{Pd}(\text{OH})_2$ ,  $\text{MeOH}$ ; (i)  $\text{Et}_3\text{N}$ ,  $\text{MeOH}$ , reflux; (j) conc.  $\text{HCl}$ ,  $\text{MeOH}$ , reflux.

Johnson and Johns<sup>34</sup> synthesized a number of  $\beta$ -1-C-aryl-mannonojirimycin analogues of type **68** using asymmetric strategy. The polyhydroxylated piperidine ring was constructed using vinyl bromide **70**, which was synthesized in six steps from bromobenzene by microbial oxidation to get bromo diol **69**.<sup>35</sup> A palladium-catalyzed Suzuki cross-coupling of vinyl bromide **70** and the corresponding arylboronic acid reaction served as the key pseudoanomeric C-C bond forming step. Ozonolysis and selective reduction of the resultant carbonyl functions followed by reductive amination produced the azasugar ring (Scheme 13). The stereochemical outcome of the reductive amination resulted into  $\beta$ -oriented aryl group as the hydrogen delivery resulted from the  $\alpha$ -face opposite to that of the adjacent  $\beta$ -oriented acetonide group.



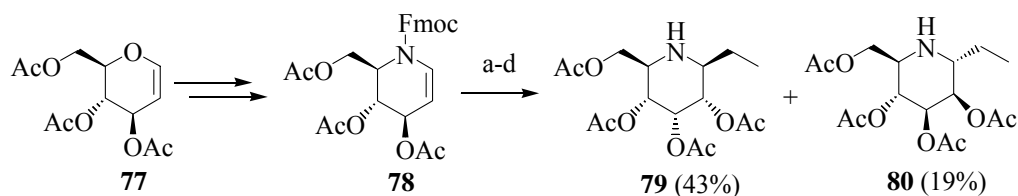
**Scheme 13.** Reagents and conditions: (a)  $\text{Arb(OH)}_2$ ,  $\text{PdCl}_2(\text{PPh}_3)_2$ , 2 M aq.  $\text{Na}_2\text{CO}_3$ , THF, reflux, 2-24 h. (b)  $\text{O}_3$ , DMS; (c)  $\text{NaBH}_3\text{CN}$ , pH 4 buffer, THF. (d) 10% Pd/C,  $\text{H}_2$ , MeOH/ $\text{H}_2\text{O}$ . (e) 6 N HCl, THF, rt, 12 h, 82-99%.

The homoaminozasugars **71** and **72** were synthesized by C.-H. Wong and co-workers<sup>36</sup> from commercially available nojirimycin bisulfite and mannonojirimycin bisulfite, respectively. The reaction of bisulfite adducts **73** and **74** with potassium cyanide in the presence of  $\text{Ba(OH)}_2$  and ethanolic HCl afforded the corresponding  $\alpha$ -nitriles **75** and **76**, which were converted to the homoaminozasugars **71** and **72** by a palladium-catalyzed reduction under acidic conditions (Scheme 14).



**Scheme 14.** Reagents and conditions: (a)  $\text{Ba(OH)}_2$ , KCN, HCl (>75%). (b)  $\text{H}_2$ , 10% Pd/C, HCl (71, 100%; 72, 78%).

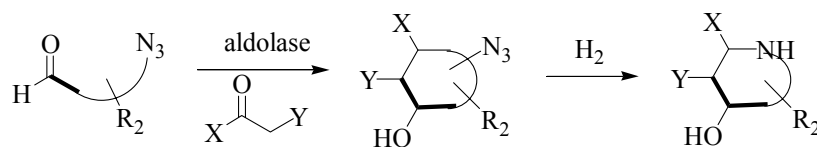
Tri-*O*-acetyl imino glucal **78**, prepared from D-glucal **77** was utilized for the synthesis of iminosugar *C*-glycosides.<sup>37</sup> Imino glucal **78** easily undergoes a variety of Lewis acid mediated C-C bond forming reactions at C-1 of the piperidine ring (e.g. **79** and **80**) giving major  $\beta$ -anomeric homoazasugars (Scheme 15)



**Scheme 15.** Reagents and conditions: (a)  $\text{BF}_3\text{Et}_2\text{O}$ ,  $\text{Et}_2\text{Zn}$ ,  $\text{CH}_2\text{Cl}_2$ ,  $-20^\circ\text{C}$ -rt. (b)  $\text{OsO}_4$  (cat.), NMO, actone- $\text{H}_2\text{O}$ , 5 d. (c)  $\text{Ac}_2\text{O}$ , Py, 2 h. (d) piperidine,  $\text{CH}_2\text{Cl}_2$ , 1 h.

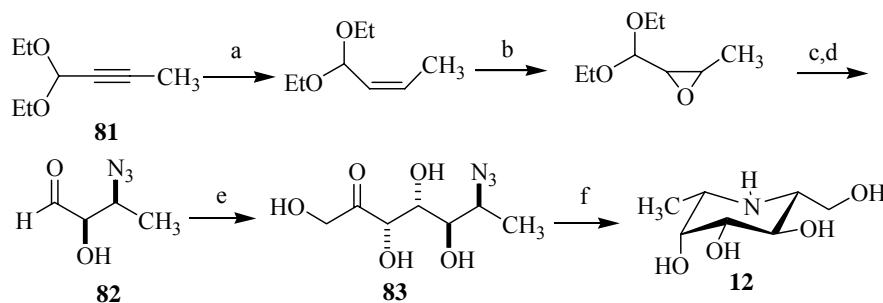
#### (vi) Enzyme catalyzed intramolecular reductive amination strategy

Enzymes are increasingly recognized as useful catalyst for the organic syntheses. The synthesis of monosaccharides and related compounds via enzymatic aldol addition reaction, catalyzed by aldolases, has been proven to be very useful and several successful examples have been described in recent years.<sup>38</sup> In addition, the use of enzyme aldolases with azido substrate followed by hydrogenation of the azido-sugar produces various five-, six- and seven-membered azasugars<sup>27,39,40</sup> (Figure 4). The same strategy is also extended for homoazasugars.



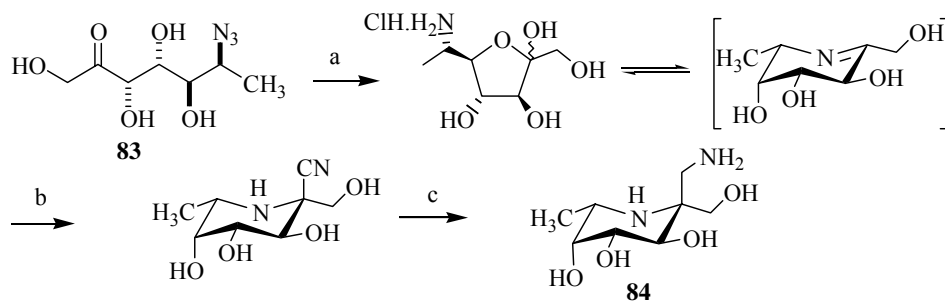
**Figure 4.** Preparation of azasugars using aldolases.

For example, Wong and co-workers prepared  $\beta$ -L-homofuconojirimycin ( $\beta$ -HFJ) **12** by an aldolase-based strategy.<sup>41</sup> The acceptor substrate ( $\pm$ )-*threo*-azidoaldehyde **82** was synthesized from commercially available 2-butyn-1-al diethyl acetal **81** (Scheme 16). Aldolase catalyzed aldol condensation of **82** with dihydroxyacetone phosphate (DHAP) followed by dephosphorylation with acid phosphatase afforded the desired enantiomerically pure azidoketose **83**. Hydrogenation of **83** in the presence of 10% Pd/C produced  $\beta$ -HFJ **12** as the only product. The complete diastereoselectivity is due to the delivery of hydrogen from the less hindered side of the possible cyclic imine intermediate during the reductive amination process.



**Scheme 16.** Reagents and conditions: (a)  $\text{Ni}(\text{OAc})_4 \cdot 4\text{H}_2\text{O}$ ,  $\text{NaBH}_4$ ,  $\text{NH}_2(\text{CH}_2)_2\text{NH}_2$ , then  $\text{H}_2$ , 1 atm, 81%. (b) *m*CPBA,  $\text{NaHCO}_3$ ,  $\text{CH}_2\text{Cl}_2$ , 71%. (c)  $\text{NaN}_3$ ,  $\text{NH}_4\text{Cl}$ ,  $\text{EtOH-H}_2\text{O}$ ,  $90^\circ\text{C}$ , 44%. (d) 0.1 *NHCl*,  $50^\circ\text{C}$ , 5 h. (e) i. DHAP, FDP aldolase, pH 6.7,  $25^\circ\text{C}$ ; ii. acid phosphatase, pH 4.7,  $37^\circ\text{C}$ , 66%. (f)  $\text{H}_2$ , (50 psi), Pd/C, 94%.

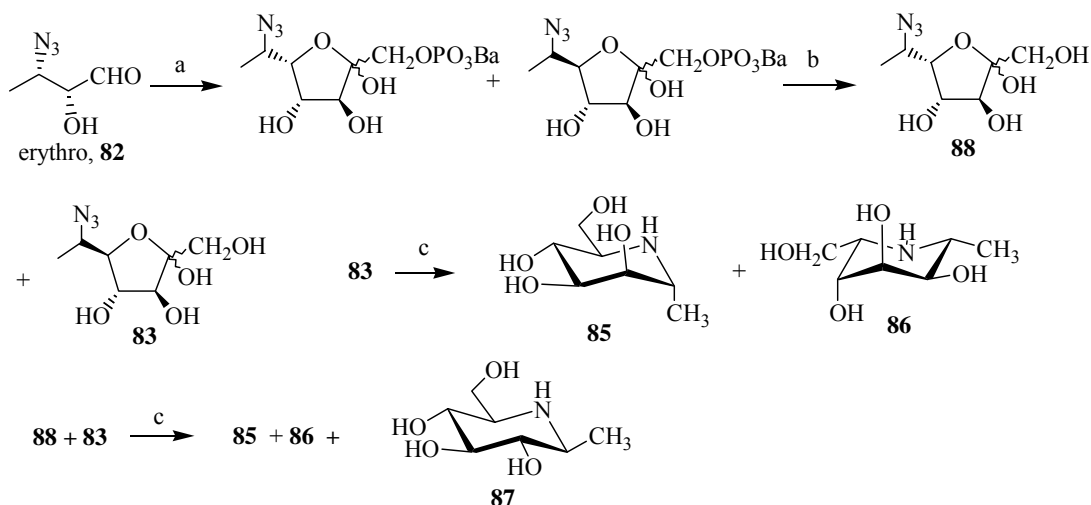
The same group also utilized the azidoketose **83** for the synthesis of 2-aminomethyl  $\beta$ -HFJ **84**.<sup>42</sup> Amino-homoazasugar was prepared by a novel chemoenzymatic strategy in which azido sugar **83** was constructed by enzymatic aldol reaction under acidic hydrogenation condition (Scheme 17).



**Scheme 17.** Reagents and conditions: (a)  $\text{H}_2$ , (1 atm), Pd/C, aq. HCl, quant. (b) KCN, dioxane,  $\text{H}_2\text{O}$ , 77%. (c)  $\text{H}_2$ ,  $\text{PtO}_2$ , conc. HCl, EtOH, 99%.

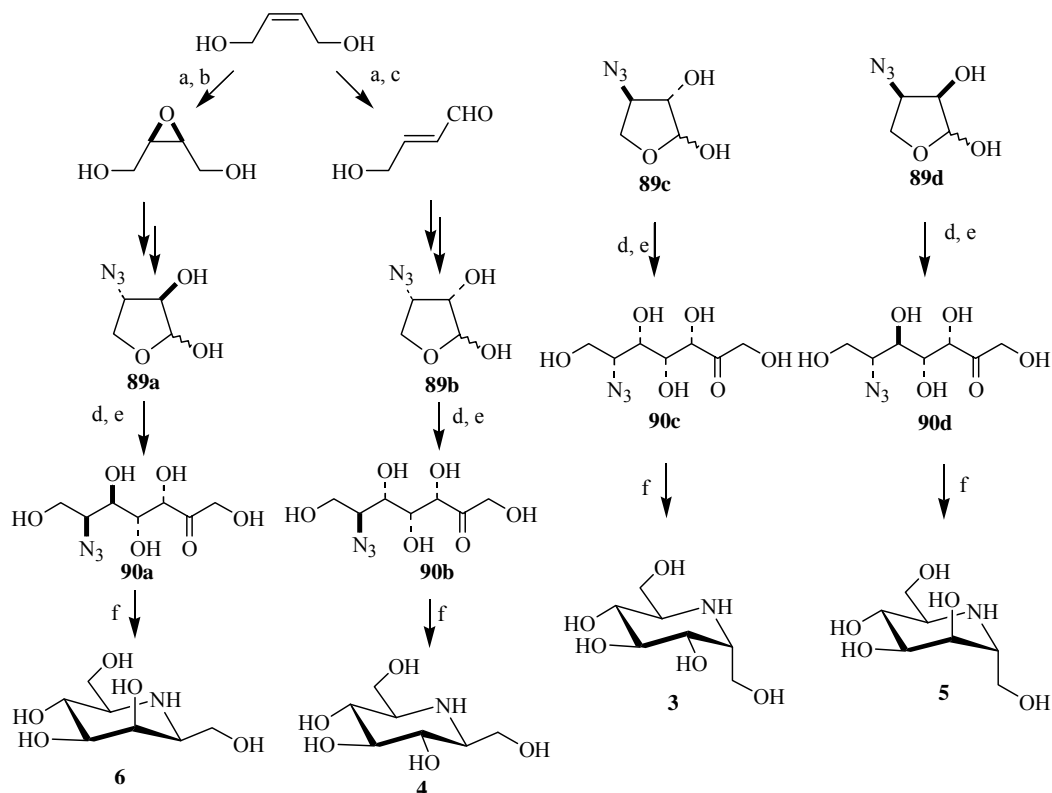
Homoazasugars **85**, **86** and **87** were prepared by A. Straub et al. by using rabbit muscle aldolase (RAMA).<sup>43</sup> Aldol addition of DHAP to 3-azido-2-hydroxybutanal **82** (*erythro:threo* = 92:8) afforded a mixture of **88** and **83** with major **83** (88%). After anion exchange chromatography **83** was isolated as a 18:82 mixture of the  $\beta/\alpha$  anomers. Reductive amination of **83** gave a mixture of homoazasugars **85** and **86** (3:2), whereas hydrogenation of a mixture of **88** and **83** provided **85**, **86** and **87** (Scheme 18).





**Scheme 18.** Reagents and conditions: (a) i. DHAP, rabbit muscle aldolase, BaCl<sub>2</sub>. (b) Wolfatit H<sup>+</sup>, Pase (EC 3.1.3.2), Dowex 1 x 8 HCO<sub>3</sub><sup>-</sup>. (c) PtO<sub>2</sub>/H<sub>2</sub>.

K. E. Holt et al.<sup>44</sup> and C.- H. Wong et al.<sup>45</sup> used RAMA for the synthesis of a number of naturally occurring homoazasugars. The four stereoisomers of the four-carbon azido sugar **89** have been stereoselectively synthesized by a route involving Sharpless epoxidation and these compounds were considered as substrates for rabbit muscle fructose 1,6-bisphosphate aldolase, giving (after treatment with phosphatase) 6-azido-6-deoxyheptuloses **90a-d**, respectively. Further hydrogenation gave corresponding homoazasugars **6**, **4**, **3** and **5** respectively (Scheme 19).



**Scheme 19.** Reagents and conditions: (a) BuLi, BDPSiCl. (b) DET, Ti(OPr)<sup>i</sup><sub>4</sub>, Bu<sup>t</sup>OOH. (c) PCC. (d) RAMA, DHAP. (e) acid phosphatase. (f) 10% Pd/C, H<sub>2</sub>, 40 psi.

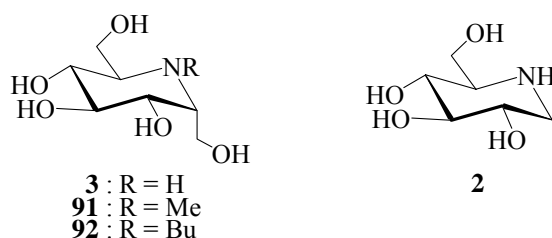
## 4. Biological activity

Glycosidases are involved in several important biological processes such as digestion, biosynthesis of glycoproteins and the lysosomal catabolism of glycoconjugates. Therefore, glycosidase inhibitors have many potential medical applications, for example, diabetes type 2,<sup>46</sup> cancers,<sup>47</sup> viral infection,<sup>48</sup> and heredity lysosomal storage diseases.<sup>49</sup> Homoazasugars are selective and in some cases better glycosidase inhibitors<sup>50</sup> and thus have been used for the treatment of a number of carbohydrate mediated diseases.

### 4.1. Glycosidase inhibition

The IC<sub>50</sub> values of a number of piperidine homoazasugars, shown in Table 2, was evaluated by Fleet and co-workers.<sup>9</sup>  $\alpha$ -HNJ **3** inhibited  $\alpha$ -glucosidases and trehalase to a similar extent as DNJ **2**, failing to have any activity toward other glycosidases tested. Thus, the hydroxymethyl group at the anomeric position of **2** contributed to a greater selectivity.  $\beta$ -HNJ **4** was very specific inhibitor of  $\alpha$ -glucosidase (IC<sub>50</sub> = ~10  $\mu$ M). Similar selectivity and potency was found in case of  $\alpha$ -HMJ (**5**) against human liver  $\alpha$ -mannosidases.<sup>51</sup>  $\beta$ -HMJ **6** is a potent inhibitor of rice and rat  $\alpha$ -

glucosidases and human  $\alpha$ -L-fucosidase ( $K_i = 4.5$  mM).<sup>51</sup>  $\beta$ -4,5-Di-*epi*-HNJ (**7**) showed potent inhibitory activity toward all  $\alpha$ -glucosidases tested and was found much better  $\alpha$ -galactosidase inhibitor than that of  $\beta$ -galactosidase. Thus, the epimerization at C-4 of **6** definitely enhances its inhibition toward  $\alpha$ -glucosidases and  $\alpha$ -galactosidase. *N*-alkylation of **3** enhances the potency and selectivity against the glycosidases tested. It has been proposed that the C-6 OH axial conformation of the *N*-alkyl derivatives of DNJ best fit the active site of ER  $\alpha$ -glucosidase I<sup>52</sup> or glucoamylase from *Aspergillus awamori*<sup>53</sup> and is responsible for strong inhibitory activity. In fact Me-HNJ **91** (Figure 5) with this preferred conformation is more potent inhibitor of  $\alpha$ -glucosidase I than **3**.



**Figure 5**

**Table 2.** IC<sub>50</sub> of piperidine homoazasugars

Enzyme	IC <sub>50</sub> ( $\mu$ M)							
	<b>3</b>	<b>4</b>	<b>5</b>	<b>6</b>	<b>7</b>	<b>8</b>	<b>91</b>	<b>92</b>
$\alpha$ -glucosidase								
rice	0.04	8.4	110	3.2	0.7	NI	0.06	4.2
rat intestinal maltase	0.34	15	46	4.6	1.6	NI	0.17	3.0
rat intestinal sucrase	0.17	7.2	27	3.0	0.8	410	0.02	3.0
rat liver lysosomal	0.26	8.2	NI	5.0	2.7	NI	1.0	2.2
trehalase (porcine kidney)	34	NI <sup>a</sup>	460	360	140	NI	-	-
$\alpha$ -galactosidase (coffee bean)	NI	NI	NI	NI	6.4	80	-	-
$\beta$ -galactosidase							-	-
bovine liver	NI	NI	NI	NI	86	160		
rat intestinal lactase	NI	NI	NI	NI	130	290		
$\alpha$ -L-fucosidase							-	-
bovine epididymis	NI	NI	30	2.6	38	NI		
rat epididymis	NI	NI	16	4.4	20	NI		

<sup>a</sup> NI = less than 50% inhibition at 1000  $\mu$ M.

Homoazasugars, due to the remarkable glycosidase inhibitory activity, were studied against diabetes. For example, compound **10** (MDL 25637) was reported to effectively reduce

postprandial elevations of blood glucose and plasma insulin in animals when administered 30-60 min before a sucrose load.<sup>54</sup>

#### 4.2. Antiviral activity

Glycoproteins are often essential proteins in that they are required in the viral life cycle, either in virion assembly and secretion and/or infectivity. As processing of these glycoprotein occurs through the cellular machinery, processing glycosidase inhibitors have been used to study the role of *N*-linked oligosaccharides in several viral systems including human immunodeficiency virus (HIV),<sup>55</sup> human hepatitis B virus (HBV),<sup>56</sup> human cytomegalovirus (HCMV),<sup>57</sup> influenza virus,<sup>58</sup> Sinvis virus<sup>59</sup> and VSV.<sup>60</sup>  $\alpha$ -Glucosidase inhibitors are potent inhibitors of HIV replication and HIV-mediated syncytium formation in vitro.<sup>55,61,62</sup> Whereas, *N*-linked oligosaccharide processing inhibitors have no effect on the secretion of infectious virus.<sup>62,63</sup>  $\alpha$ -HNJ **3** and its *N*-methyl derivative **91** are more potent against  $\alpha$ -glucosidase I both in vitro and in cell culture.<sup>64</sup> So it is expected that these homonojirimycins would show excellent anti-HIV activity. Surprisingly, both HNJ **3** and Me-HNJ **91** showed no significant anti-HIV activity even at concentrations of 500  $\mu$ g/mL.<sup>9</sup>

## 5. Conclusions

In conclusion, we have described the natural occurrence of piperidine homoazasugars. The synthetic aspects of homoazasugars using chiron, asymmetric approaches including chemo-enzymatic methods have been discussed. The structural basis for the specificity of glycosidase inhibition and biological applications are also discussed.

## 6. References

1. (a) Stütz, A. E., *Iminosugars as Glycosidase Inhibitors: Nojirimycin and Beyond*; Wiley-VCH: Weinheim, Germany, 1999. (b) Asano, N.; Nash, R. J.; Molyneux, R. J.; Fleet, G. W. *J. Tetrahedron: Asymmetry* **2000**, *11*, 1645.
2. (a) Ishida, N.; Kumagi, K.; Niida, T.; Tsuruoka, T.; Yumoto, H. *J. Antibiotics Ser. A* **1967**, *20*, 66. (b) Paulsen, H.; Sangster, I.; Heyns, K. *Chem. Ber.* **1967**, *100*, 802. (c) Hughes, A. B.; Rudge, A. J. *Nat. Prod. Rep.* **1994**, *11*, 135.
3. Martin, O. R., *Carbohydrate Mimics, Concepts and Methods*; Chapleur, Y., Ed.; Wiley-VCH: Weinheim, Germany, 1998, p 259.
4. Liu, P. S. *J. Org. Chem.* **1987**, *52*, 4717.
5. Kite, G. C.; Fellows, L. E.; Fleet, G. W. J.; Liu, P. S.; Scofield, A. M.; Smith, N. G. *Tetrahedron Lett.* **1988**, *29*, 6483.
6. Fellows, L. E.; Nash, R. J. *Sci. Progress Oxford* **1990**, *74*, 245.

7. Kite, G. C.; Horn, J. M.; Romero, J. T.; Fellows, L. E.; Lees, D. C.; Scofield, A. M.; Smith, N. G. *Phytochemistry* **1990**, *29*, 103.
8. Asano, N.; Nishida, M.; Kizu, H.; Matsui, K.; Watson, A. A.; Nash, R. J. *J. Nat. Prod.* **1997**, *60*, 98.
9. Asano, N.; Nishida, M.; Kato, A.; Kizu, H.; Matsui, K.; Shimada, Y.; Itoh, T.; Baba, M.; Watson, A. A.; Nash, R. J.; Lilley, P. M. de Q.; Watkin, D. J.; Fleet, G. W. J. *J. Med. Chem.* **1998**, *41*, 2565.
10. Asano, N.; Kato, A.; Miyauchi, M.; Kizu, H.; Kameda, Y.; Watson, A. A.; Nash, R. J.; Fleet, G. W. J. *J. Nat. Prod.* **1998**, *61*, 625.
11. Martin, O. R.; Compain, P.; Kizu, H.; Asano, N. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 3171.
12. Yasuda, K.; Kizu, H.; Yamashita, T.; Kameda, Y.; Kato, A.; Nash, R. J.; Fleet, G. W. J.; Molyneux, R. J.; Asano, N. *J. Nat. Prod.* **2002**, *65*, 198.
13. Lillelund, V. H.; Jensen, H. H.; Liang, X.; Bols, M. *Chem. Rev.* **2002**, *102*, 515.
14. Bols, M. *Acc. Chem. Res.* **1998**, *31*, 1.
15. Nash, R. J.; Watson, A. A.; Asano, N. *Alkaloids: Chem. Biol. Perspect.* **1996**, *11*, 345.
16. Legler, G. *Naturwissenschaften* **1993**, *80*, 397.
17. Vogel, P. *Chem. Oggi.* **1992**, *10*, 9.
18. Cipolla, L.; Ferla, B. L.; Peri, F.; Nicotra, F. *Chem. Comm.* **2000**, 1289.
19. (a) Desai, V. N.; Saha, N. N.; Dhavale, D. D. *Chem. Comm.* **1999**, 1719. (b) Wolform, M. L.; Hanessian, S. *J. Org. Chem.* **1972**, *27*, 1800.
20. Saha, N. N.; Desai, V. N.; Dhavale, D. D. *Tetrahedron* **2001**, *57*, 39.
21. Dhavale, D. D.; Desai, V. N.; Sindkhedkar, M. D. Mali, R. S. Castellari, C.; Trombini, C. *Tetrahedron: Asymmetry* **1997**, *8*, 1475.
22. Dhavale, D. D.; Matin, M. M.; Sharma, T.; Sabharwal, S. G. *Biorg. Med. Chem.* **2003**, *11*, 3295.
23. (a) Bols, M.; Grubbe, H.; Jaspersen, T. M.; Szarek, W. A. *Carbohydr. Res.* **1994**, *253*, 146. (b) Shiozki, M. *J. Org. Chem.* **1991**, *56*, 528.
24. Shilvock, J. P.; Fleet, G. W. J. *Synlett* **1998**, 554.
25. Shilvock, J. P.; Nash, R. J.; Watson, A. A.; Winters, A. L.; Butters, T. D.; Dwek, R. A.; Winkler, D. A.; Fleet, G. W. J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2747.
26. Saavedra, O. M.; Martin, O. R. *J. Org. Chem.* **1996**, *61*, 6987.
27. Baxter, E. W.; Reitz, A. B. *J. Org. Chem.* **1994**, *59*, 3175.
28. Look, G. C.; Fotsch, C. H.; Wong, C.-H. *Acc. Chem. Res.* **1993**, *26*, 182.
29. Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron Lett.* **1983**, *24*, 3943.
30. Martin, O. R.; Saavedra, O. M.; Xie, Fang.; Liu, L.; Picasso, S.; Vogel, P.; Kizu, H.; Asano, N. *Bioorg. Med. Chem.* **2001**, *9*, 1269.
31. (a) Bernotas, R. C.; Ganem, B. *Tetrahedron Lett.* **1985**, *26*, 1123. (b) Hill, C. L.; Whitesides, G. M. *J. Am. Chem. Soc.* **1984**, *96*, 870.
32. Cipolla, L.; Lay, L.; Nicotra, F.; Pangrazio, C.; Panza, L. *Tetrahedron* **1995**, *51*, 4679.
33. Aoyagi, S.; Fujimaki, S.; Kkibayashi, C. *J. Chem. Soc., Chem. Commun.* **1990**, 1457.

34. Johnson, C. R.; Johns, B. A. *J. Org. Chem.* **1997**, *62*, 6046.
35. Johns, B. A.; Pan, Y. T.; Elbein, A. D.; Johnson, C. R. *J. Am. Chem. Soc.* **1997**, *119*, 4856.
36. Wong, C.-H.; Provencher, L.; Porco, Jr. J. A.; Jung, S.-H.; Wang, Y.-F. *J. Org. Chem.* **1995**, *60*, 1492.
37. Dransfield, P. J.; Gore, P. M.; Shipman, M.; Salwin, A. M. *Z. Chem. Comm.* **2002**, 150.
38. Gijzen, H. J. M.; Qiao, L.; Fitz, W.; Wong, C.-H. *Chem. Rev.* **1996**, *96*, 443.
39. Moris-Varas, F.; Xin-Hua, Q.; Wong, C.-H. *J. Am. Chem. Soc.* **1996**, *118*, 7647.
40. Wong, C.-H.; Halcomb, R. L.; Ichikawa, Y.; Kajimoto, T. *Angew. Chem., Int. Ed.* **1995**, *34*, 412.
41. Qiao, L.; Murray, B. W.; Shimazaki, M.; Schultz, J.; Wong, C.-H. *J. Am. Chem. Soc.* **1996**, *118*, 7653.
42. Takayama, S.; Martin, R.; Wu, J.; Laslo, K.; Siuzdak, G.; Wong, C.-H. *J. Am. Chem. Soc.* **1997**, *119*, 8146.
43. Straub, A.; Effenberger, F.; Fischer, P. *J. Org. Chem.* **1990**, *55*, 3926.
44. Holt, K. E.; Leeper, F. J.; Handa, S. *J. Chem. Soc., Perkin Trans. 1* **1994**, 231.
45. Henderson, I.; Laslo, K.; Wong, C.-H. *Tetrahedron Lett.* **1994**, *35*, 359.
46. (a) Horii, S.; Fukase, H.; Matsuo, T.; Kameda, Y.; Asano, N.; Matsui, K. *J. Med. Chem.* **1986**, *29*, 1038. (b) Junge, B.; Heiker, F.-R.; Kurz, J.; Muller, L.; Schmidt, D. D.; Wunshe, C. *Carbohydr. Res.* **1984**, *128*, 235.
47. (a) Humpries, K. J.; Matsumoto, K.; White, S.; Olden, K. *Cancer Res.* **1986**, *46*, 5215. (b) Dennis, J. W. *Cancer Res.* **1986**, *46*, 5131. (c) Ostrander, G. K.; Scribner, N. K.; Rohrschneider, L. R. *Cancer Res.* **1988**, *48*, 1091.
48. (a) Ratner, L. *AIDS Res. Hum. Retroviruses* **1992**, *8*, 165. (b) Walker, B. D.; Kowalski, M.; Goh, W. C.; Kozarsky, K.; Sodroski, J. *Proc. Natl. Acad. Sci. U.S.A.* **1987**, *84*, 8120. (c) Gruters, R. A.; Neefjes, J. J.; Tersmette, M.; de Goede, R. E. Y.; Tulp, A.; Huisman, H. G.; Miedema, F.; Ploegh, H. L. *Nature* **1987**, *330*, 74.
49. (a) de Bello, C. I.; Dorling, P.; Winchester, B. *Biochem. J.* **1983**, *215*, 693. (b) de Bello, C. I.; Fleet, G.; Namgoong, S. K.; Tadano, K.; Winchester, B. *Biochem. J.* **1989**, *259*, 855. (c) Platt, F. M.; Neises, G. R.; Dwek, R. A.; Butters, T. D. *J. Biol. Chem.* **1994**, *269*, 8362.
50. Dondoni, A.; Giovannini, P. P.; Perrone, D. *J. Org. Chem.* **2002**, *67*, 7203.
51. Bruce, I.; Fleet, G. W. J.; de Bello, C. I.; Winchester, B. *Tetrahedron* **1992**, *48*, 10191.
52. Tan, A.; van den Broek, L.; van Boeckel, S.; Ploegh, H.; Bolscher, J. *J. Biol. Chem.* **1991**, *266*, 14504.
53. Harris, E. M. S.; Aleshin, A. E.; Firsov, L. M.; Honzatko, R. B. *Biochem.* **1993**, *32*, 1618.
54. Robinson, K. M.; Begovik, M. E.; Rhinehart, B. L.; Heineke, E. W.; Ducep, J. B.; Kastner, P. R.; Marshall, F. N.; Danzin, C. *Diabetes* **1991**, *40*, 825.
55. Karpas, A.; Fleet, G. W. J.; Dwek, R. A.; Petursson, S.; Namgoong, S. K.; Ramsden, N. G.; Jacob, G. S.; Rademacher, T. W. *Proc. Natl. Acad. Sci. U.S.A.* **1988**, *85*, 9229.
56. Block, T.; Platt, F.; Lu, X.; Gerlich, W.; Foster, G.; Blumberg, B.; Dwek, R. A. *Proc. Natl. Acad. Sci. U.S.A.* **1994**, *91*, 2235.

57. Taylor, D. L.; Fellows, L. E.; Farrar, G. H.; Nash, R. J.; Taylor-Robinson, D.; Mobberlay, M. A.; Ryder, T. A.; Jeffries, D. J.; Tyms, A. S. *Antiviral Res.* **1988**, *10*, 11.
58. Datema, R.; Olofsson, S.; Romero, P. *Pharmacol. Ther.* **1987**, *33*, 221.
59. Schlesinger, S.; Koyama, A. H.; Malfar, C.; Gee, S. L.; Schlesinger, M. J. *Virus Res.* **1985**, *2*, 139.
60. Schlesinger, S.; Miller, C.; Schlesinger, M. J. *J. Biol. Chem.* **1984**, *259*, 7597.
61. Fischer, P. B.; Collin, M.; Karlsson, G. B.; James, W.; Butters, T. D.; Davis, S. J.; Gordon, S.; Dwek, R. A.; Platt, F. M. *J. Virol.* **1995**, *69*, 5791.
62. Fu, Y.-K.; Hart, T. K.; Jonak, Z. L.; Bugelski, P. J. *J. Virol.* **1993**, *67*, 3818.
63. Sattentau, Q. J.; Zolla-Pazner, S.; Pognard, P. *Virology* **1995**, *206*, 713.
64. Zeng, Y.; Pan, Y. T.; Asano, N.; Nash, R. J.; Elbein, A. D. *Glycobiology* **1997**, *7*, 297.