Chiron approaches to polyhydroxylated piperidines: promising glycosidase inhibitors

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Dedicated to Prof. S. V. Kesser on the occasion of his 70th birthday
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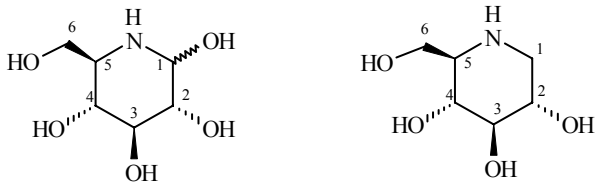
Abstract
New chiron approaches towards the syntheses of polyhydroxylated piperidine analogues are described. The methodologies involve 1,3-addition of methyl magnesium bromide and silyl ketene acetal to D-glucose derived nitrone, intramolecular Michael addition to D-glucose derived α,β-unsaturated ester and double reductive amination of 5-keto aldose as key steps.

Keywords: Alkaloids, piperidines, nitrone, reductive amination, conjugate addition, enzyme inhibitors

Introduction

In the last two decades, glycosidase inhibitors such as polyhydroxylated piperidines, commonly known as azasugars, have been attractive target molecules for synthetic chemists as well as biochemists not only because they serve as a useful tool for studying the biological function of oligosaccharides[1] but also because they have great potential as drugs in the treatment of a variety of carbohydrate mediated diseases.[2] Amongst these azasugars, nojirimycin (**1**) and 1-deoxynojirimycin (**2**) are the first naturally occurring alkaloids with promising glycosidase inhibitory activity.[3] In order to examine the structure-activity relationship, a number of synthetic analogues of **1** and **2** have been synthesized and evaluated for glycosidase inhibition in the treatment of various diseases such as diabetes, cancer, AIDS and viral infections.[4] This study established the correlation between the α/β-glycosidase inhibitory activity with the positions,and the configurations of –OH groups as well as various substituents (in lieu of –OH groups).[5] As a part of our continuing interest in sugar chemistry, we have developed new synthetic routes towards known and unknown analogues of polyhydroxylated piperidine alkaloids. An account of our studies is discussed herein.



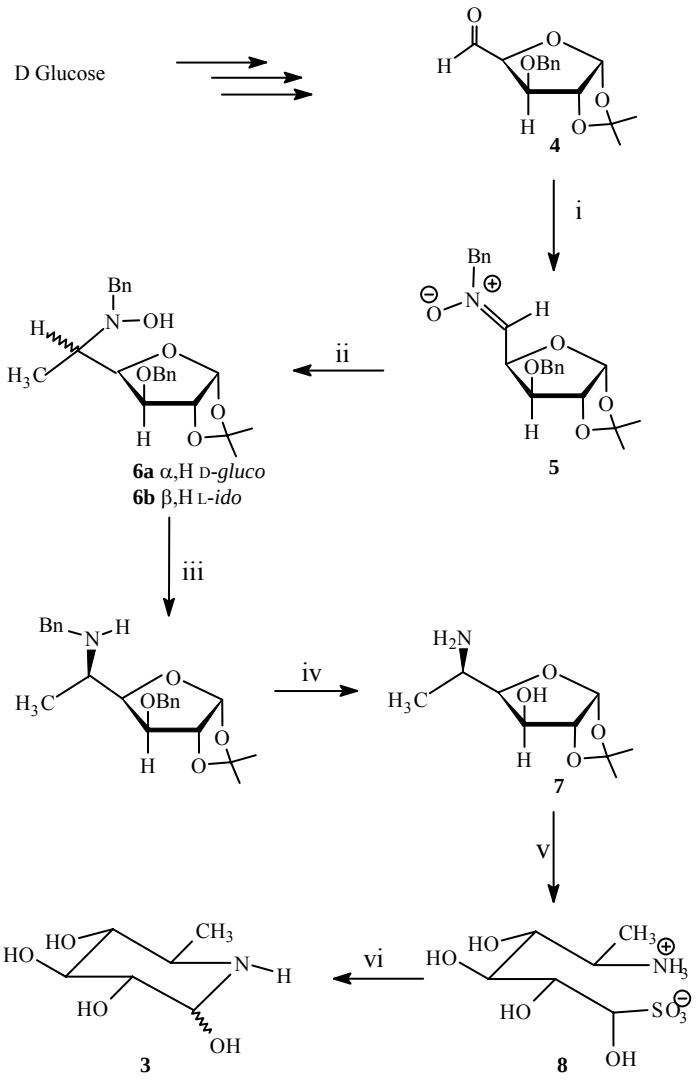
1 **2**

Figure 1

Review

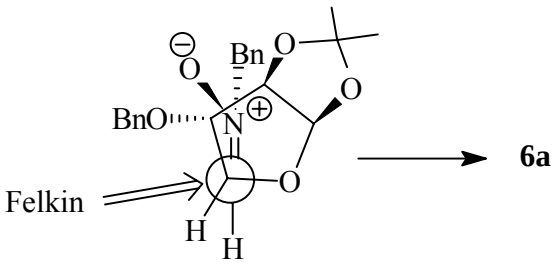
Synthesis of 6-deoxynojirimycin (3)

Our first approach involves synthesis of 6-deoxynojirimycin **3**. In this method, we have visualized the formation of piperidine ring skeleton in **3** by joining C-N bond between C-5 amino- and C-1 aldehyde functionality of D-*glucose* derivative. The C-5 amino sugar was therefore an apparent key intermediate that could be obtained from 1,3-addition of methylmagnesium bromide to D-*glucose* derived nitrone[6]. Thus, the reaction of 1,2-*O*-isopropylidene-3-*O*-benzyl-α-D-xylo-pentodialdose (**4**) with *N*-benzylhydroxylamine hydrochloride, in the presence of sodium acetate in methanol-water, afforded a nitrone **5** (Scheme 1). The 1,3-addition of methylmagnesium bromide to **5** gave a diastereomeric mixture of D-*gluco*- and L-*ido*-configurated *N*-hydroxylamines **6a** and **6b** in the ratio 61:39 respectively, which was separated by flash chromatography. The trimethylsilyl triflate catalyzed 1,3-addition of methylmagnesium bromide, however, gave a good diastereoselectivity in favor of D-*gluco*-isomer (D-*gluco*:L-*ido* = 88:12). The N-O bond reductive cleavage of **6a** with zinc-acetic acid followed by hydrogenolysis of benzyl groups afforded 1,2-*O*-isopropylidene-5,6-dideoxy-5-amino-α-D-*gluco*-furanose (**7**). Purging sulfur dioxide gas through a solution of **7** in methanol-water at 0 °C for 48 h gave a bisulphite adduct of 6-deoxynojirimycin **8** as a white solid. Compound **8** was passed through a basic resin and eluted with distilled water which afforded 6-deoxynojirimycin **3** as a pale yellow solid. The spectral and analytical data was in accordance with structure **3.** Shortly after our report Defoin *et al* reported the synthesis of 6–deoxynojirimycin[7].



Scheme 1. Reagents and conditions: (i) NH(OH)Bn-HCl, CH_3COONa, MeOH $-H_2O$, rt, 2h; (ii) MeMgCl, THF -30°C, 3h; (iii) Zn-AcOH, 70°C, 2h; (iv) $HCOONH_4$, 10% Pd/C, MeOH 12 h;(v) SO_2 Gas, MeOH, 35°C.

The observed facial diastereoselectivity in favor of product **6a**, arising from nucleophilic attack to the *Re* face of the nitrone, may be rationalized by assuming the preferred conformation **A** for nitrone **5** (Figure 2). According to the Felkin model the large substituent is perpendicular to the C=N bond. We believe that C-O bond will adopt this position; in fact it is known that nucleophilic attack seeks the LUMO of nitrone which may be stabilized through mixing of the $\pi^*_{C=N}$ orbital with the lowest energy σ^* orbital of a substituent that is generally associated with the most electronegative group. On these grounds, **A** offers the favorable trajectory to the incoming nucleophile and this is magnified after *O*-silylation by trimethylsilyl triflate leading to the formation of the D-*gluco* isomer as the major product.



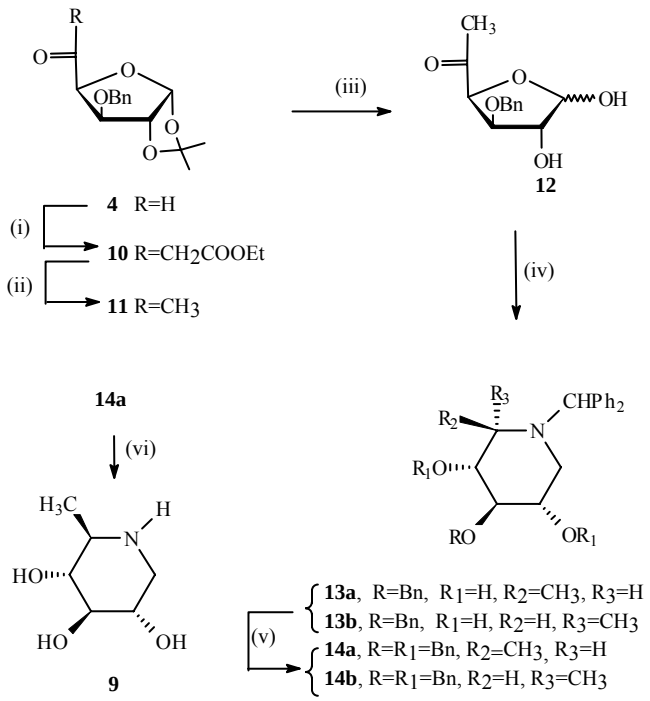
A

Figure 2

Synthesis of 1,6-dideoxy-nojirimycin (9)

In this approach, we have applied a double reductive amination of a C5-keto aldose as a key step in the formation of a target compound. Thus, the reaction of 1,2-*O*-isopropylidene-3-*O*-benzyl-α-D-xylo-pentodialdose (**4**) with ethyl diazoacetate in the presence of catalytic amounts of boron trifluoride ethyl etherate afforded sugar β-keto ester **10** in good yield (Scheme 2)[8]. Decarboxylation of **10** using sodium chloride in wet dimethylsulfoxide afforded C5-keto sugar **11**. Hydrolysis of 1,2-*O*-isopropylidene functionality in compound **11** gave 6-deoxy-3-*O*-benzyl-α-D-xylo-hexofuran-5-ulose (**12**). The critical double reductive amination reaction with benzhydrylamine, sodium cyanoborohydride and acetic acid in methanol at –78 °C afforded a diastereomeric mixture corresponding to D-*gluco*- and L-*ido*- configurations **13a** and **13b** in the ratio 86:14, respectively. The separation of diastereoisomers at this stage, by flash chromatography, was troublesome due to the close R_f values. However, perbenzylation of the diastereomeric mixture **13** with benzyl bromide and sodium hydride in tetrahydrofuran afforded an easy access for chromatographic purification, and the required D-*gluco*-isomer **14a** was obtained in good yield. One pot removal of diphenylmethyl and benzyl groups, in the D-*gluco* isomer **14a**, by hydrogenolysis using ammonium formate, 10% palladium on activated carbon in methanol at 70 °C for 30 min gave 1,6-dideoxynojirimycin (**9**) as a colorless resin. The ^{1}H- and ^{13}C-NMR data and specific rotation of **9** are known and were found to be parallel with those reported.[9]

The observed diastereoselectivity in the double reductive amination of **12** could be explained as follows. It is evident that sodium cyanoborohydride reductive amination of cyclic iminium ion intermediate is hydroxyl directed in which the –OH group at C-4 plays a significant stereo-directing effect. The substituent at C-3 is far away from the reactive site and therefore presumably has a lesser role in determining the stereochemistry of hydride addition.



Scheme 2. Reagents and Conditions: (i) N_2=CHCOOEt, $BF_3(EtO)_2$, CH_2Cl_2, 0-20 °C, 3h; (ii) DMSO, H_2O, NaCl, 135 °C, 2h; (iii) 3N HCl, THF, 70 °C, 2h; (iv) H_2NCHPh_2, $NaCNBH_3$, AcOH, MeOH - 78 °C to 20 °C, 22h; (v) Nah, BnBr, nBu_4NI, 0 to 20 °C, 5h; (vi) $HCOONH_4$, 10% Pd/C, MeOH, 70 °C, 30 min

Now, we feel that the complexation of the reagent with α-oriented C-4 hydroxy group favors the hydride attack from the α-face (axial orientation), leading to the formation of D-*gluco*-isomer as a major product (Figure 3).

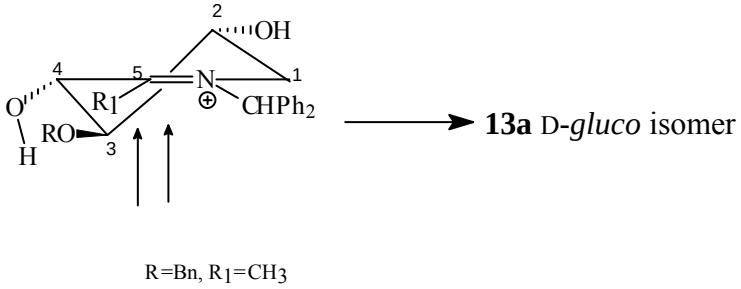


Figure 3

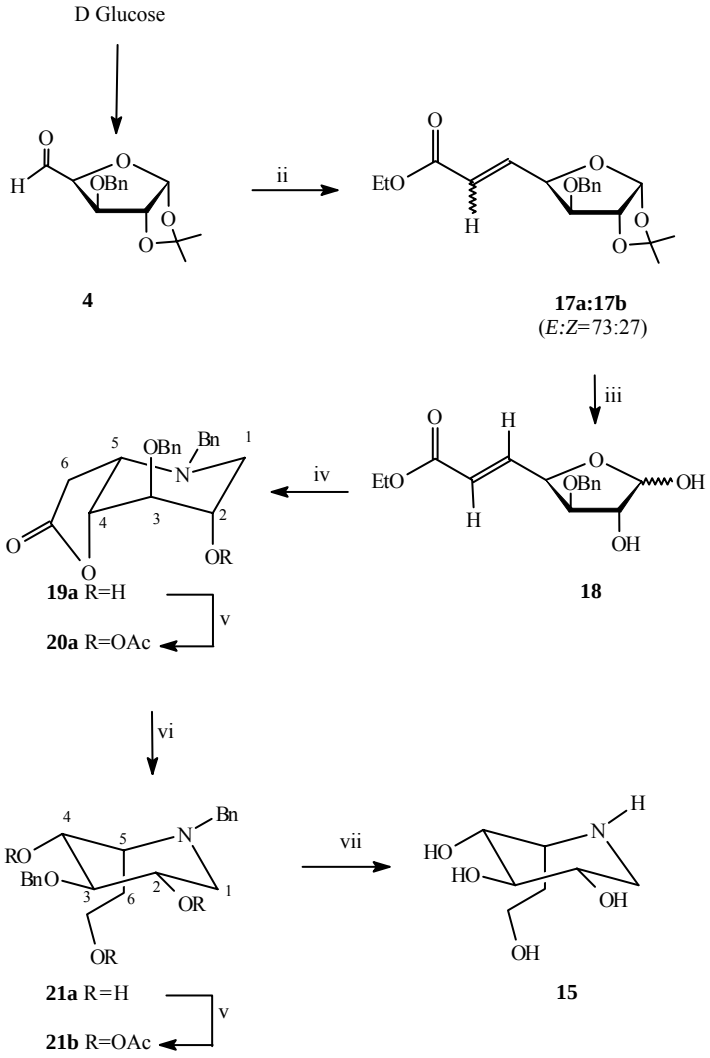
Synthesis of 1-deoxy-L-*ido*-homo-nojirimycin (15) and 1-deoxy-D-*gluco*-homo-nojirimycin (16)

In recent years, preparation and evaluation of homoazasugars with a -CH_2 homologation either at C-1 or at C-5 side chain as well as nojirimycin analogues with D- and/or L-configuration at C-5 have received much attention. In this connection, we are the first to report two independent pathways for the synthesis of **15** and **16**. The first pathway involves intramolecular Michael addition of *in situ* generated *N*-benzylamine to D-*glucose* derived α, β-unsaturated ester.[10] Thus, Wittig reaction of **4** with (carbethoxymethylene) triphenylphosphorane gave an isomeric mixture of α,β-unsaturated ester **17** (*E/Z* =73:27) that was separated by chromatography to afford **17a** (*E*-isomer) and **17b** (*Z*-isomer) in 64% and 24% yield, respectively (Scheme 3). The cleavage of acetonide functionality in the geometrical mixture of **17** afforded hemiacetal **18** (anomeric mixture α:β = 7:3) with an exclusive *E*-geometry at the double bond as indicated by the NMR spectra. One pot reaction of **18** with *N*-benzylamine (1.0 equiv.) in the presence of catalytic amounts of acetic acid in methanol followed by treatment with sodium cyanoborohydride afforded lactone **19a** as the only isolable product. Thus, the overall three-step transformation presumably involves amine as the primary reaction product (by reductive amination at C-1), which undergoes concomitant Michael addition and domino lactonization to yield diastereoselective formation of **19a** in 79% yield. The lactone **19a** was acetylated with acetic anhydride in pyridine to give **20a** (78%). The spectroscopic and analytical data obtained for **19a** and **20a** were in full accord with the assigned structures. The configuration at C-5 and the $^1C_4$ conformation of **19a** and **20a** were determined from their high field ^{1}H NMR spectra based on the coupling constant values. In the subsequent steps, lactone **20a** was reduced with lithium aluminum hydride in ether, and the primary alcohol **21a** (colorless solid, 84%) thus obtained was peracetylated to afford **21b** (80%). In the ^{1}H NMR spectra of **21a** and **21b**, H-3 showed a double doublet with large coupling constants ($J_{2,3}$ and $J_{3,4}$ ~8.8 Hz). This indicated the *axial-axial* relationship of H-3 with H-2 and

H-4, confirming the change in conformation of the piperidine ring from $^1C_4$ to $^4C_1$. Finally, removal of the benzyl groups in **21a** was achieved in one step using ammonium formate and 10% palladium on activated carbon in methanol to give 1-deoxy-L-*ido*-homo-nojirimycin **15** (90%). The ^{1}H- and ^{13}C-nmr spectra and analytical data were in good agreement with the proposed structure with the $^4C_1$ conformation.

The diastereoselective formation of **19a** can be explained by considering the transition states **A** and **B** (Figure 4). In general, the stereo-electronic and steric factors often play an integral role in affecting the stereochemical outcome of the intramolecular Michael addition reactions. However, we believe that under the reaction conditions of borohydride reductive amination and *in situ* Michael addition, the complexation of boron with nitrogen and the C-2 and C-4 hydroxyl groups determine the amine additions. Thus, the complexation of the boron with C-2 and C-4 hydroxyl groups and the amine functionality holds the nitrogen atom in such a way that the preferred *Si* face attack at the diastereotopic β-carbon atom, as shown in transition state **A**, leads to the formation of **19a**. However, transition state **B** in which *Re* face attack leads to the

formation of the other isomer, is destabilized due to the non-bonded interactions of the α-olefinic hydrogen with the C-1 *axial* hydrogen and 3-*O*-benzyl group, explains why D-*gluco* isomer is not obtained.



Scheme 3. Reagents and Conditions: (ii) $PPh_3CHCOOEt$, MeCN, reflux, 2h; (iii) TFA-H2O (3:2), rt, 2h; (iv) $BnNH_2$, $NaCNBH_3$, AcOH, MeOH, −78 °C, 2h, 30 °C, 24h; (v) Ac_2O, Pyridine, DMAP, 30 °C, 24 h; (vi) LAH, THF, 0 °C to rt, 2h; (vii) 10% Pd/C, $HCOONH_4$, MeOH, reflux, 1h.

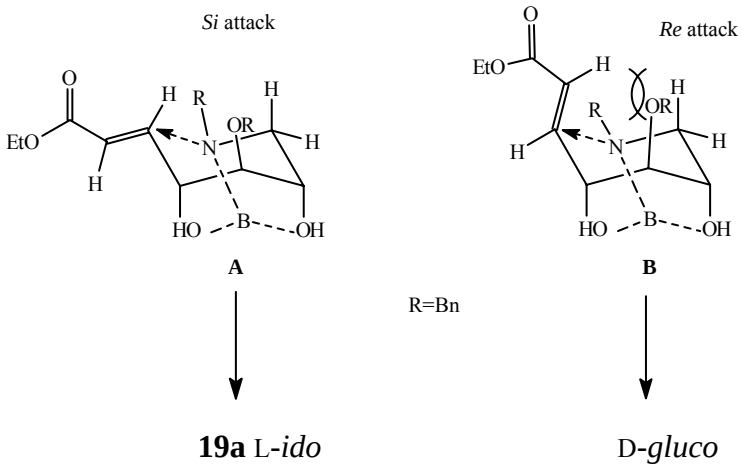


Figure 4

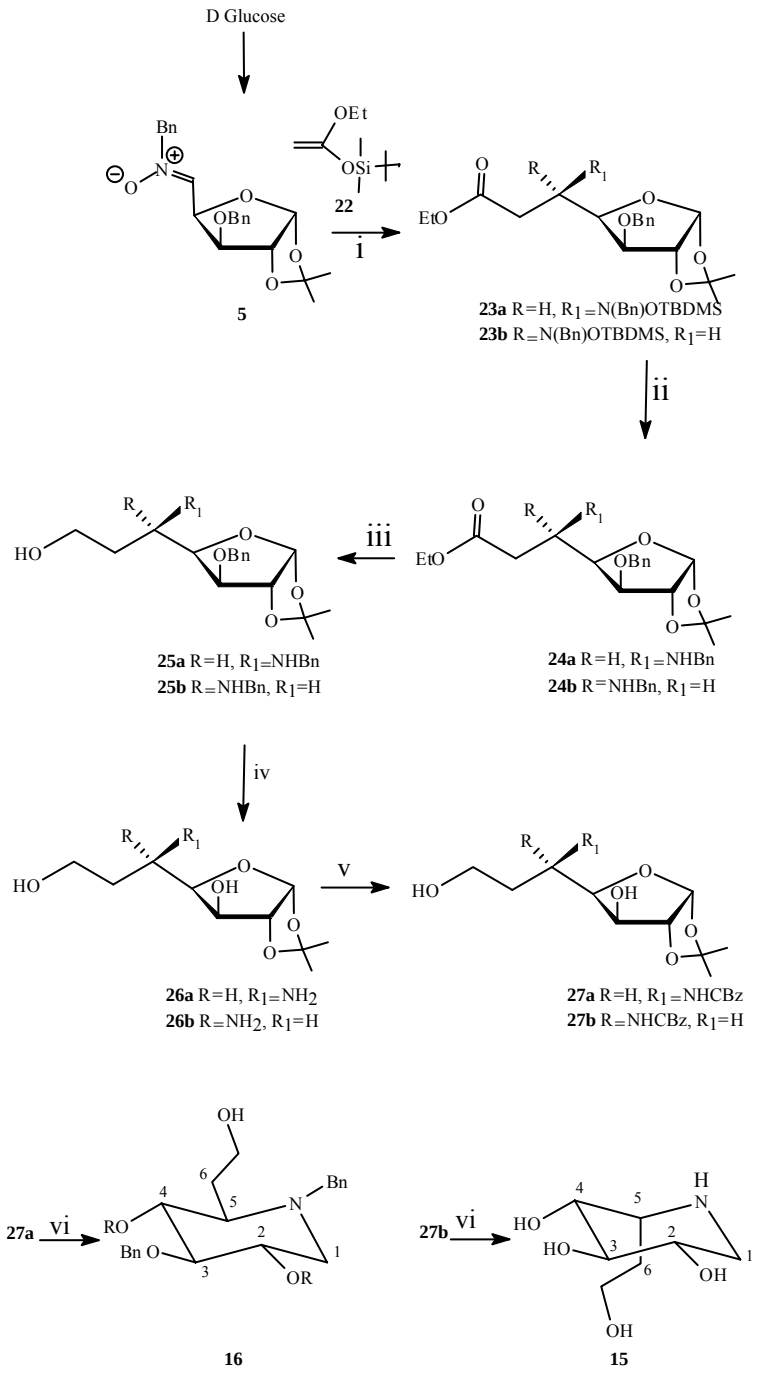
The second pathway towards the synthesis of homoazasugars **15** and **16** involves stereo controlled 1,3-addition reaction of silyl ketene acetal to D-*glucose* derived nitrone **5** as a key step[11]. The 1,3-addition reaction of silyl ketene acetal **22** to D-*glucose* derived nitrone **5** in dichloromethane at 25 °C for 24 h afforded an inseparable diastereomeric mixture of *O*-silyloxy-β-amino esters **23a** and **23b** (Scheme 4). Determination of diastereomeric ratio, at the newly generated C5 stereocentre, was difficult at this stage. Therefore, the crude mixture of *O*-silyloxy-β-amino esters **23** was subjected to N-O bond reductive cleavage by treatment with zinc/copper couple in acetic acid-water at 70 °C for 1 h and the diastereomeric mixture of *N*-benzyl β-amino esters **24a** and **24b** was separated by flash chromatography (D-*gluco*: L-*ido* = 36:64) in good yield. Although, β-amino esters **24a** and **24b** were isolated in the pure form, their ^{1}H NMR data could not clearly discriminate the D-*gluco* and L-*ido* isomers. As a result, the assignment of configuration at C5 was made in the next stage. Thus, the reduction of the ester functionality in the β-amino esters **24a** and **24b**, individually, with lithium aluminum hydride in tetrahydrofuran afforded β-amino alcohols **25a** and **25b**, respectively. The assignment of configuration at C5 was made on the basis of the comparison of the ^{1}H NMR spectra and the diastereomeric ratio was found to be D-*gluco*:L-*ido* = 36:64.

Attempts were made to improve the diasteoselectivity of the 1,3 addition reaction by changing the reaction conditions and Lewis acids. As shown in Table 1, performing the reaction using acetonitrile as a solvent at different reaction conditions (0 °C to reflux temperature) led to a moderate change of stereoselectivity in favor of L-*ido* isomer (Table 1 entry 2, 3). In order to increase or alter the diastereoselectivity, we have investigated the influence of various Lewis acids. In this respect, the effect of trimethylsilyl triflate was first examined. The individual reactions of **22** with **5** were performed in the presence of 0.1 or 1.2 equiv. of trimethylsilyl

triflate using either dichloromethane or acetonitrile as the solvent (Table 1, entry 4-7). Excellent yield with good diastereoselectivity (D-*gluco*: L-*ido*= 23:77), in favor of L-*ido* isomer, was achieved by using 1.2 equivalent of trimethylsilyl triflate in a binary mixture of dichloromethane and acetonitrile at –78 °C (entry 5). We presumed that this trimethylsilyl triflate promoted reaction proceeds with the formation of *O*-silyloxy intermediate leading to the product formation in a non-chelation controlled manner.

The sugar nitrone **5** possesses two alkoxy substituents namely the furanose ring oxygen at the α-position and benzyloxy group (at C3) at the β-position with respect to C=N bond. These alkoxy substituents are considered to be promising chelating groups prone to enhance or alter the stereoselectivity of the reactions. This promoted us to make use of metal chelating Lewis acids such as zinc chloride/zinc iodide and magnesium bromide in the subsequent reactions. The use of either zinc chloride or zinc iodide under various conditions of temperature, solvent and mole proportions did not alter the diastereoselectivity (preponderance of L-*ido* isomer **23b)** and stereoselectivity was also poor (Table 1, entry 8-15). Surprisingly, the replacement of zinc chloride with magnesium bromide altered the stereochemical course of the addition reaction (Table 1, entries 16-19). The best result was obtained by the use of 2.5 equiv. of magnesium bromide in a binary mixture of dichloromethane and acetonitrile at –10 °C which afforded **23a** (D-*gluco*-isomer) as the major product (**23a**:**23b** = 76:24), in 94% yield (entry 18). No significant effect was observed when the reaction was performed in acetonitrile as the solvent (entry 19).

The C5 amino alcohols **25a** and **25b,** with respective D-*gluco*- and L-*ido*- configurations, are the true intermediates for the synthesis of higher homologues of 1-deoxy-homo-nojirimycin. Thus, in subsequent steps, the one pot deprotection of *N*- and *O*-benzyl groups in **25a**, by treatment with 10% palladium on activated carbon in the presence of ammonium formate as a hydrogen donor in methanol, afforded amino alcohol **26a** in 91% yield. The C5-amino functionality in **26a** was selectively protected with Cbz group using benzyl chloroformate in the presence of sodium bicarbonate in ethanol-water to obtain *N*-Cbz protected amino alcohol **27a** in 95% yield. Hydrolysis of **27a** with trifluoroacetic acid-water at 0 °C to 25°C for 2 h afforded a hemiacetal which was directly subjected to hydrogenation using 10% palladium-carbon wherein deprotection of the *N*-Cbz group, intramolecular amine cyclization, imine formation and reduction of the imino group, in one pot, gave 1-deoxy-D-*gluco*-homonojirimycin **16** as a pale yellow solid. In the ^{1}H NMR spectra, appearance of two triplets with large coupling constants one at δ 3.08 corresponding to H-4 ($J_{4,5} = J_{3,4} = 9.5$ Hz) and other at δ 3.27 for H-3 ($J_{2,3} = J_{3,4} = 9.5$ Hz) indicated a *trans* diaxial relation with the adjacent protons. In the amino alcohol **25a**, the relative stereochemistry of the substituents at C2, C3, and C3, C4 is *trans* and the same stereochemistry is retained in the product formation. The appearance of eight line pattern (ddd) at 2.51 δ corresponding to H-5 with $J_{4,5} = 9.5$ Hz, $J_{5,6} = 8.8$ Hz, and $J_{5,6'} = 3.3$ Hz, confirmed the *trans* diaxial relative disposition of H-4 and H-5 protons. This confirms that the C5 substituent (-CH_2CH_2OH) is oriented equatorially [(5*R*)-configuration] and the compound **16** has the $^4C_1$ conformation.



Scheme 4. Reagents and conditions; (i) Silyl ketene acetal, Lewis acid, CH_2Cl_2, −78°C or −10°C, 1-24 h; (ii) Zn-AcOH, 70 °C, 2h; (iii) LAH, THF, 0°C to 25°C, 2h; (iv) $HCOONH_4$, 10% Pd/C, MeOH, 12 h; (v) CBzCl, $NaHCO_3$, EtOH-H_2O, 25 °C, 2h; (vi) TFA-H_2O °C to 25 °C, 2 h

Table 1. Lewis acid catalysed addition of silyl ketene acetal 6 to nitrone 7

Run	Lewis acid (equiv)	Solvent[b]	Conditions Temp. °C	time h	Yield[a] (%)	8a:8b
1	-	CH_2Cl_2	25	24	95	36:64
2	-	CH_3CN	25	20	95	34:66
3	-	CH_3CN	80	4	80	30:70
4	TMSOTf (1.2)	CH_2Cl_2	–78	1.5	94	34:66
5	TMSOTf (1.2)	CH_2Cl_2 + CH_3CN	–78	1.5	93	23:77
6	TMSOTf (0.1)	CH_2Cl_2 + CH_3CN	–78	15	96	31:69
7	TMSOTf (0.1)	CH_3CN	25	2.0	93	25:75
8	$ZnCl_2$ (1.2)	CH_2Cl_2	–78	24	No reaction	
9	$ZnCl_2$ (1.2)	CH_2Cl_2	–40	2.0	94	40:60
10	$ZnCl_2$ (1.2)	CH_2Cl_2 + CH_3CN	–40	2.0	96	42:58
11	$ZnCl_2$ (3.0)	CH_2Cl_2 + CH_3CN	–40	2.0	85	45:55
12	ZnI_2 (1.2)	CH_2Cl_2	–78	24	No reaction	
13	ZnI_2 (1.2)	CH_2Cl_2	–40	2.0	92	50:50
14	ZnI_2 (1.2)	CH_2Cl_2 + CH_3CN	–40	2.0	91	46:54
15	ZnI_2 (3.0)	CH_2Cl_2 + CH_3CN	–40	2.0	83	46:54
16	$MgBr_2$ (1.2)	CH_2Cl_2	–78	24	No reaction	
17	$MgBr_2$ (1.2)	CH_2Cl_2	–10	2.0	90	60:40
18	$MgBr_2$ (2.5)	CH_2Cl_2 + CH_3CN	–10	2.0	94	76:24
19	$MgBr_2$ (2.5)	CH_3CN	–10	2.0	90	74:26

[a] Yields refer to the isolated yields after column chromatography.
[b] CH_2Cl_2 + CH_3CN in the ratio 1:1.

In an analogous reaction sequence, the pure *N*-benzyl amino alcohol **25b** on hydrogenolysis gave **26b**, which on selective *N*-protection afforded *N*-Cbz-amino alcohol **27b**. In the next step, removal of the acetonide group followed by the hydrogenation afforded 1-deoxy L-*ido*-homo-nojirimycin **15** in 78% yield from **25**. Since the ^{1}H NMR spectrum of **15** is very different from **16**, it was thought that **15** could exist in the $^1C_4$ conformation. However, appearances of two distinct doublets of doublets for H-1a at δ 2.62 ($J_{1a,\ 1e}$ =13.3 Hz; J1a, 2 =8.2 Hz) and for H-1e at δ 2.88 ($J_{1a,\ 1e}$ =13.3 Hz; J_{1e}, 2 =4.2 Hz) were informative. The large coupling constant ($J_{\ 1a,\ 2}$ = 8.2 Hz) for the H-1 axial proton requires *trans* diaxial relationship with H-2 proton. This clearly requires H-2 proton to be *axial* and suggestive of the fact that compound **15** exits in $^4C_1$ conformation. The ^{1}H and ^{13}C NMR spectral and analytical data was also found to be in consonance with the data reported earlier by us thus conforming the $^4C_1$ conformation with (5*S*)-configuration.

Explanation for the observed diastereoselectivity

According to the Felkin-Anh model two conformations **C** and **D** (Figure 5) were considered for the trimethyl silyl triflate assisted nitrone addition reaction. Although, transition state **C** is preferred over **D**, the attack of the bulky silyl ketene acetal, along the Burgi-Dunitz trajectory from the *Re* face is disfavored by the C3-benzyloxy substituent. This explains why D-*gluco* isomer **23a** is obtained as a minor product. However, in the alternate transition state **D**, the attack of the silyl ketene acetal from the opposite face of the bulky C3-benzyloxy group (*Si* face) is strongly favored due to the minimized steric non-bonded interactions, leading to the preferential formation of the L-*ido*-isomer **23b** as a major product.

The stereochemical outcome in the bivalent metal assisted reaction could be explained by considering the chelated transition states involving the metal complexation with nitrone oxygen and proximate alkoxy groups. Two conformations **E** and **F** were therefore considered. The α-chelation of the nitrone oxygen with furanose ring oxygen, in a six membered transition state, is represented in **E** while the β-chelation with the C3-benzyloxy substituent resembles the model **F**. For the reaction in the presence of magnesium bromide, we assume that the reactive transition state that resemble the complexation of magnesium hydroxyl amine with the C3-benzyloxy group prevails (β-chelated model **F**) wherein; *Re* facial nucleophilic addition, from the small group, gives the observed D-*gluco* stereoselectivity (*anti* product). In case of zinc chloride or zinc iodide mediated addition reactions with nitrone, with α and β-alkoxy substituents in the proximity, earlier worker have shown that the α–chelation model explains the observed stereoselectivity. Thus, nucleophilic attack from the preferred *Si* face in conformer **E** affords the *syn*-adduct *albeit* in poor selectivity.

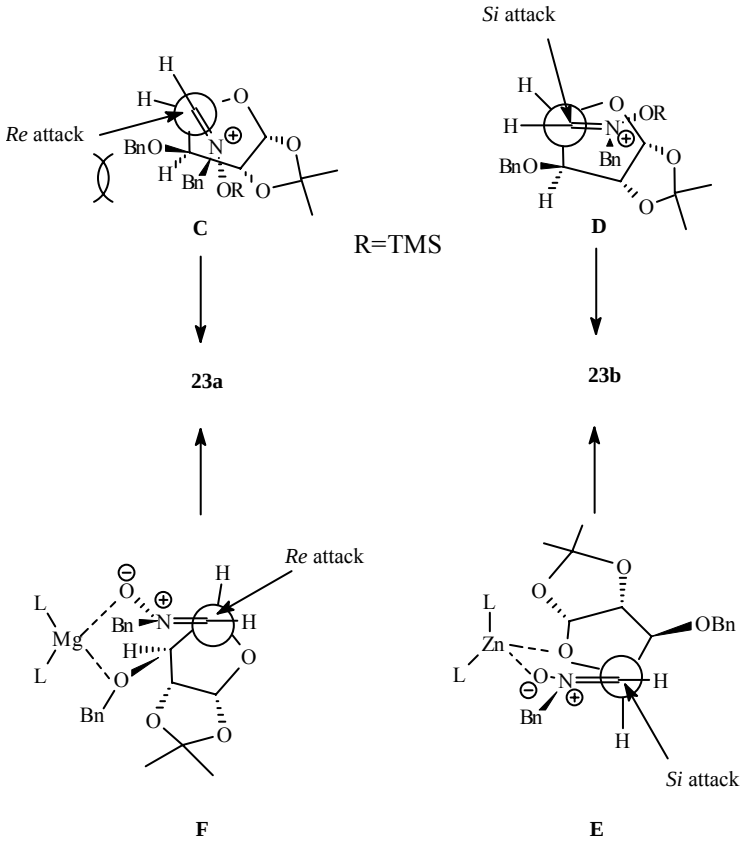


Figure 5

In conclusion, we have demonstrated various pathways to the synthesis of polyhydroxylated piperidine analogues. The easy and cheap availability of starting material, mild reaction conditions and simple reagents with good diastereoselectivity make our routes attractive which can be worked out on multigram scale.

Acknowledgements

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References

1. (a) Wong, C.-H.; Halcomb, R. L.; Ichikawa,Y.; Kajimoto,T. *Angew. Chem., Int. Ed.* **1995**, *34*, 412. (b) Wong, C.-H.; Halcomb, R. L.; Ichikawa,Y.; Kajimoto,T. *Angew. Chem., Int. Ed.* **1995**, *34*, 521. (c) Sinnott, M. L. *Chem. Rev.* **1990**, *90*, 1171. (d) Fleet, G. W. J.; Namgoong, S. K.; Barker, C.; Baines, S.; Jacob, G. S.; Winchester, B.; *Tetrahedron Lett*. **1989**, *30*, 4439

2. (a) Paulsen, H.; Todt, K. *Adv. Carbohydr. Chem*. **1968**, *23*, 115. (b) Fellows, L. E. *Chem. Ber*. **1987**, *23*, 842. (c) Truscheit, E.; Frommer, W. Junge, B.; Muller, L.; Schmith, D. D.; Wingender, W. *Angew. Chem., Int. Ed.* **1981**, *20*, 744. (d) Inouye, S.; Tsuruoka, T.; Ito, A.; Niida, T. *Tetrahedron* **1968**, *24*, 2125. (e) Muller, L. In *Biotechnology*; Rehn, H.-J.; Reed, G. Eds; VCH Verlagsgeselschaft: Weinheim, 1985; Vol. 4 Ch. 18. (f) Sinnott, M. L. *Chem Rev*. **1990**, *90*, 1171. (g) Winchester, B.; Fleet, G. W. J.; *Glycobiology*. **1992**, *2*, 199. (h) Wong, C.-H.; Halcomb, R. L.; Ichikawa,Y.; Kajimoto,T.; *Angew. Chem., Int. Ed.* **1995**, *34*, 412. (i) Wong, C.-H.; Halcomb, R. L.; Ichikawa,Y.; Kajimoto, T. *Angew. Chem., Int. Ed.* **1995**, *34*, 521 and references cited therein
3. Kajimoto, T.; Liu, K. K.-C.; Pederson,R. L.; Zhong, Z.; Ichikawa,Y.; Porco J. A., Jr.; Wong, C.-H. *J. Am. Chem. Soc.* **1991**, *113*, 6187 and references cited therein.
4. (a) Fellows, L. E.; Fleet, G. W. J. *Natural Product Isolation*; *Elsevier:Amsterdam*, 1988; Ch. 13, p 539. (b)Winchester, B.; Fleet, G. W. J.; *Glycobiology* **1992,** *2*, 199. (c) Looks, G. C.; Fotsch, C. H.; Wong, C.-H. *Acc. Chem. Res.* **1993**, *26*, 182. (d) Waynaroska, B.; Wilkiel, H.; Sharma, M.; Carpenter, N.; Fleet, G. W. J.; Bernacki, R. J. *Anticancer Res*. **1992**, *12*, 161. (e) 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.* **1998**, *85*, 9229. (f) Fleet, G. W. J.; Karpas, A.; Raymond A. D.; Fellows, L. E.; Tyms, A. S.; Petursson, S.; Namgoong, S. K.; Ramsden, N. G.; Smith, P. W.; Son, J. C.; Wilson, F.; Witty, D. R.; Jacob, G. S.; Rademacher, T. W. *FEBS Lett*. **1998**, *237*, 128. (g) Datema, R.; Olofsson, S.; Romero, P. A. *Pharmacol. Ther.* **1987**, *33*, 221. (h) Kino, N.; Inamura, N.; Nakahara, K.; Tsurumi, T.; Adachi, K.; Shibata, T.; Terano, H.; Kohsaka, M.; Aoki, H.; Imanaka, H. J. *Antibiot.* **1985**, *38*, 936.
5. (a) Truscheit, E.; Frommer, W. Junge, B.; Muller, L.; Schmith, D. D.; Wingender, W. *Angew. Chem., Int. Ed.* **1981**, *20*, 744. (b) Furneaux, R. H.; Gainsford, G. J.; Mason, J. M.; Tyler, P. C.; Hartley, O.; Wincheter, B. G. *Tetrahedron* **1997**, *57*, 245. (c) Humphires, M. J.; Matsumoto, K.; White, S. L.; Olden, K. *Cancer Res*. **1986**, *46*, 5215. (d) 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.* **1998**, *85*, 9229. (e) Walker, B. D.; Kowalski, M.; Goh, W. C.; Kozarsky, K.; Krieger, M.; Rosen, C.; Rohrschneider, L.; Heseltine,W. A.; Sodroski, J. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *84*, 8120. (f) Sunkara, P.S.; Sjoerdsma, A. *Biochem. Biophys. Res. Commun*. **1987**, *148*, 206. (g) Bernotas, R. C.; Papendreou, G.; Urbach, J.; Ganem, B. *Tetrahedron Lett*. **1990**, 3*1*, 3393.
6. Dhavale, D. D.;Desai, V. N.; Sindkhedkar, M. D.; Mali, R. S.; Castellari, C.; Trombini, C. *Tetrahedron: Asymmetry* **1997**, *8*, 1475 and references cited therein
7. Defoin, A.; Sarazin, H.; Streith, J. *Tetrahedron* **1997**, *53*, 13783
8. Dhavale, D. D.; Saha, N. N.; Desai, V. N. *J. Org. Chem.* **1997**, *62*, 7482.
9. (a) Kajimoto,T.; Liu, K. K.-C.; Pederson,R. L.; Zhong, Z.; Ichikawa,Y.; Porco J. A., Jr.; Wong, C.-H.; J *Am. Chem. Soc.* **1991**, *113*, 6187. (b) Defoin, A.; Sarazin, H.; Streith, J. *Helv. Chim. Acta* **1996**, *79*, 560.

10. Dhavale, D. D.; Desai, V. N.; Saha, N. N. *Chem. Commun.* **1999**, 1719.
11. Dhavale, D. D.; Saha, N. N.; Desai, V. N. *Tetrahedron* **2001**, *57*, 39.