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First stereocontrolled synthesis and biological evaluation of 1,6-dideoxy-L-nojirimycin

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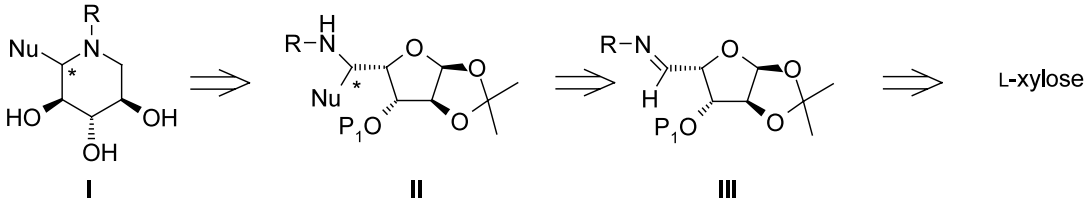
Abstract—The first synthesis of 1,6-dideoxy-L-nojirimycin in enantiomerically pure form has been achieved in nine steps from L-xylose in an overall yield of 15%. The biological activity of this compound as a glycosidase inhibitor provided useful information on structure–activity relationships in the family of 1,5-iminoalditols.

As potent glycosidase inhibitors,[1] iminosugars have been a subject of enduring scientific interest over the last three decades. An important new phase in the development of this dynamic field of research is starting to emerge. Recently, the scope of biological activities of iminoalditols has been extended to the inhibition of various carbohydrate-processing enzymes such as glycosyl transferases,[2] nucleoside[3] and glycogen[4] phosphorylases, and sugar nucleotide mutase.[5] Since these enzymes are involved in a number of essential physiological processes, iminosugars have tremendous potential as therapeutic agents[6] in a wide range of diseases including viral infections,[7] tumor metastasis[8] and lysosomal storage disorders.[9] Some iminoalditols are currently engaged in clinical trials and the first therapeutic applications seem now to be very close.[10] For example, initial clinical data have recently demonstrated the effectiveness of *N*-butyl-1-deoxynojirimycin against Gaucher's disease, a severe lysosomal storage disorder for which no chemotherapy is currently available.[9,11]

In order to gain rapid access to new iminosugars of biological interest, we have designed a general strategy, starting from D- or L-xylose, for the synthesis of 1,5-iminoxylitols analogs **I** bearing a diverse range of functionalities at C-5. Our retrosynthetic analysis hinges on the diastereocontrolled chain extension of the xylose-derived imine **III** (Scheme 1). Structural diversity may be introduced at C-5 by using the wide library of organometallic or heteroatomic nucleophiles available. Careful choice of reaction conditions can give selectively one or the other of the two possible epimers at C-5 in **II**.

Herein, we wish to report on our preliminary results concerning the first stereocontrolled synthesis of 1,6-dideoxy-L-nojirimycin. As this compound can be regarded as 4-*epi*-1-deoxy-L-fuconojirimycin or as 2-*epi*-1-deoxy-L-rhamnojirimycin, its biological evaluation as a glycosidase inhibitor may provide useful information on structure–activity relationships in the



Scheme 1.

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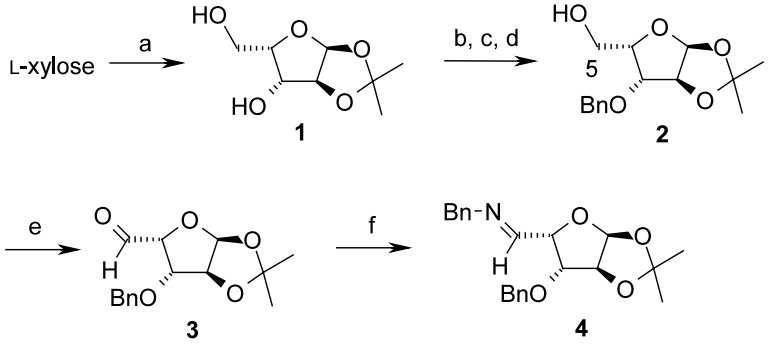
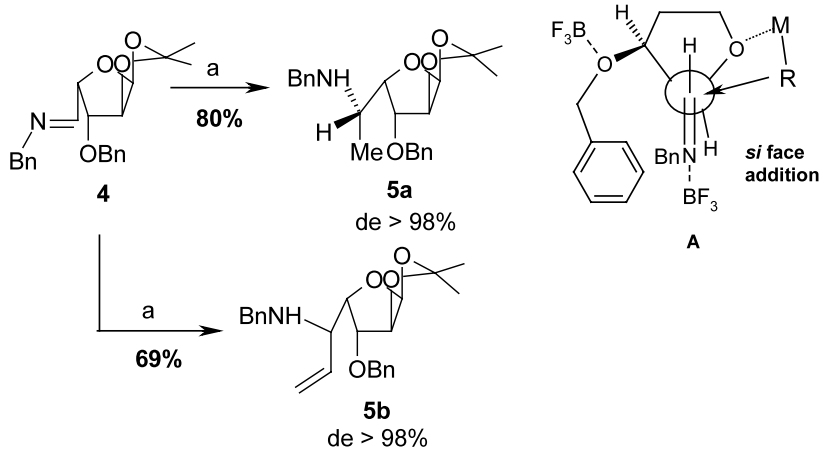
family of 1,5-iminohexitols. Five syntheses of 1,6-dideoxy-D-nojirimycin have been reported in the literature.[12] They have in common the fact that they are not stereospecific for a given sugar derivative except for the efficient approach described by Hollingsworth et al. from D-glucose.[12e] Nevertheless, considering the exorbitant cost of L-glucose, this approach would not be practical for the large scale preparation of L-nojirimycin derivatives.

The synthesis of the key imine intermediate **4** was performed in six steps and 45% overall yield from L-xylose following a protecting group strategy to isolate and then oxidize the hydroxyl group at C-5 (Scheme 2). Condensation of L-xylose with acetone catalyzed by H_2SO_4 in the presence of $CuSO_4$ afforded the diol **1**[13] in 94% yield after deprotection of the less stable isopropylidene group under aqueous acidic conditions. Regioselective tritylation of the primary alcohol in **1**, followed by benzylation of the 3-position and cleavage of the trityl group using HBr in glacial acetic acid provided the five-unprotected xylofuranose derivative **2**[14] in 73% yield for the three steps. Finally the imine **4** was cleanly prepared in quantitative yield by condensation of benzylamine with aldehyde **3** obtained by Dess–Martin periodinane oxidation of the corresponding primary alcohol.

Having the key imine **4** in hand, we first investigated the addition of methyllithium to the C=N bond in the presence of a monodentate Lewis acid ($BF_3{\cdot}Et_2O$) to obtain the precursor of 1,6-dideoxy-L-nojirimycin (Scheme 3). Previous studies[15] in our group on related L-sorbose-derived imines indicated that the absolute configuration of the newly created stereogenic center could be predicted according to the open transition state model A, with an antiperiplanar conformation due to electrostatic repulsion (Scheme 3).[16] Addition of MeLi at −78°C to the imine **4** thus preactivated provided after purification the expected amine **5a** as a single diastereoisomer in 80% yield. The absolute configuration of the stereogenic center was unambiguously established to be *S* at the stage of the piperidinol product. Addition of vinylmagnesium bromide to **4** was also found to be completely diastereoselective as judged by proton NMR spectroscopy of the crude product. It is noteworthy that the addition of methylmagnesium chloride to the *N*-benzyl nitrone analogue of imine **4** was found to be poorly diastereoselective (*si*-face addition, de <24%) with an improvement in the presence of 1 equiv. of TMSOTf (de = 74%).[17,18]



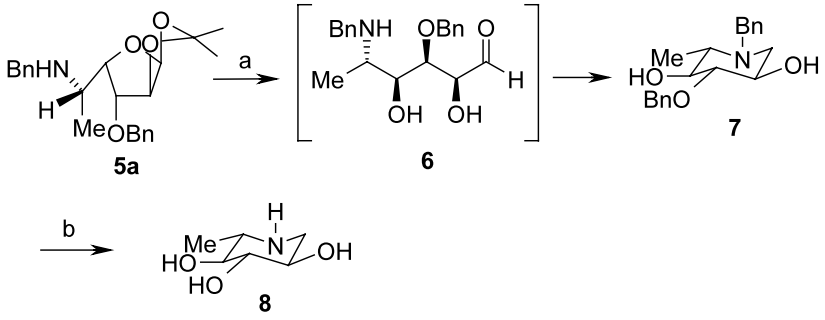
Scheme 2. *Reagents and conditions*: (a) dry acetone, $CuSO_4$ (1.9 equiv.), H_2SO_4 (0.3 equiv.), 22 h then aq. HCl (0.2%), 7 h, 94%; (b) TrCl (1.1 equiv.), pyridine, 50°C, 22 h, 93%; (c) BnBr (1.3 equiv.), NaH (1.6 equiv.), *n*-Bu_4NI (0.05 equiv.), THF, 4 h, 94%; (d) HBr/AcOH, 10°C, 1 min, 83%; (e) Dess–Martin periodinane (1.1 equiv.), CH_2Cl_2, 0°C to rt; 4 h, 67%; (f) $BnNH_2$ (1.05 equiv.), 4 Å molecular sieves, CH_2Cl_2, 4°C, 16 h, quant.



Scheme 3. *Reagents and conditions*: (a) MeLi (4 equiv.) or vinylMgBr (4 equiv.), $BF_3{\cdot}Et_2O$ (5 equiv.), Et_2O, −78°C, 4 h, 80% (R = Me), 69% (R = vinyl), de >98%.

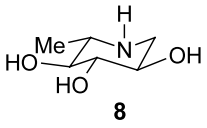
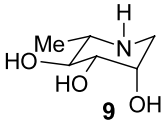
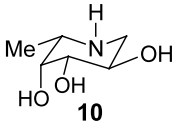
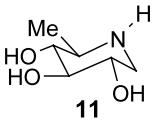
The last key step of our strategy was the formation of the piperidine ring by means of intramolecular reductive amination of the unmasked aminoxylose hemiketal derived from **5a** (Scheme 4). Surprisingly, this one-pot process was particularly difficult to optimize, in contrast to our observations in the sorbofuranose series.[15a] This result may be explained by the relative instability of the intermediate aldehyde **6** or of the related cyclic hemiaminal under aqueous acidic conditions. After extensive studies, the best experimental conditions were found to involve exposing **5a** to a mixture of glacial acetic acid and aq. HCl at room temperature for 5 h, followed by the addition of $NaBH_3CN$ to the reaction mixture. After purification by flash chromatography, the expected piperidinol **7** was obtained in 41% yield. The conversion of the allylic amine **5b** led to an untreatable mixture of products, and the configuration at C-5 was not firmly established. Finally, removal of the benzyl groups in **7** was conducted by hydrogenation in the presence of 10% Pd/C to provide 1,6-dideoxy-L-nojirimycin **8**[19] in high yield after purification by chromatography on ion-exchange resin [Dowex 1-X2, (OH^- form)].

The inhibitory effects of **8** on various glycosidases, as well as those of 1-deoxy-L-rhamnojirimycin **9**, 1-deoxy-L-fuconojirimycin **10** and 1,6-dideoxy-D-nojirimycin **11** for comparison, are gathered in Table 1. As was found for 1,6-dideoxy-D-nojirimycin **11**,[20] the L-iminosugar **8** showed no significant inhibition of α- or β-D-glucosi-



Scheme 4. *Reagents and conditions*: (a) AcOH/HCl 5N (10/1), 5 h, then $NaBH_3CN$ (9 equiv.), 96 h, 41%; (b) H_2, Pd/C, MeOH, HCl 5N cat., 24 h, quant.

Table 1. Inhibition values towards selected glycosidases

Enzyme	IC_{50} (μM)			
	 **8**	 **9**	 **10**	 **11**
α-L-Rhamnosidase				
Penicillium decumbens	52	(490)[c,d]	ND	ND
α-Fucosidase				
Bovine epididymis	94	ND[e]	0.09[f]	ND
Human placenta	29	ND	(0.0013)[c,g]	ND
α-Glucosidase				
Rice	(32%)[a]	ND	ND	NI[h]
Yeast	NI[b]	ND	ND	NI[h]
Rat intestinal maltase	(45%)[a]	ND	ND	NI[h]
Rat intestinal isomaltase	1000	ND	ND	NI[h]
Rat intestinal sucrase	(26%)[a]	ND	ND	NI[h]
β-Glucosidase				
Sweet almond	(38%)[a]	ND	ND	(780)[c,i]

[a] Inhibition rate at 1000 μM.
[b] NI: less that 50% inhibition at 1000 μM.
[c] Inhibition constant K_i in μM.
[d] Taken from Ref. 23.
[e] ND: not determined.
[f] Taken from Ref. 24.
[g] Taken from Ref. 25.
[h] Taken from Ref. 20.
[i] Taken from Ref. 12a.

dases. Comparison of the inhibition values between **8** and 1-deoxyfuconojirimycin **10** indicated that the α-L-fucosidase active site can discriminate by over three or four orders of magnitude inhibitors differing only by the relative orientation of the OH group at C-4. These results confirmed the conclusion of the study by Winchester et al. who suggested that the minimum structural requirement for inhibition of α-L-fucosidase is satisfied when the configurations at C-2, C-3 and C-4 correspond to those of L-fucose.[21] Interestingly, compound **8** (=2-*epi*-1-deoxy-L-rhamnojirimycin) is a good inhibitor of α-L-rhamnosidase of *Penicilium decumbens*, whereas 1-deoxy-L-rhamnojirimycin **9** showed no significant inhibition at 750 μM.[22] The weak inhibitory activity of **9** was confirmed by Wong et al. (K_i=490 μM).[23] On the basis of modelling and structure–activity studies, Fleet et al. suggested that potent inhibitors of rhamnosidase mimic the conformation of the relevant glycopyranosyl cation intermediate, postulated to be the $^4H_3$ half-chair form. For example the lowest energy conformation ($^4C_1$) of 5-*epi*-1-deoxy-L-rhamnojirimycin, a very good inhibitor of α-L-rhamnosidase (IC_{50}=5 μM), was found to be an excellent match with the $^4H_3$ half-chair structure of the rhamnopyranosyl cation, whereas the lowest energy conformation ($^1C_4$) of 1-deoxy-L-rhamnojirimycin **9** was not.[22] However, this hypothesis does not explain the good inhibitory activity of **8**, the $^1C_4$ conformation of which is a very poor mimetic of the $^4H_3$ half-chair structure of the rhamnopyranosyl cation.

In conclusion, we have achieved the first synthesis of 1,6-dideoxy-L-nojirimycin **8** in enantiomerically pure form in nine steps from L-xylose in an overall yield of 15%. The biological activity of this compound provided useful information on structure–activity relationships in the family of 1,5-iminoalditols. Future work will focus on the extension of this synthetic strategy to other 1,5-iminoxylitol derivatives bearing a diverse range of functionality at C-5.

Acknowledgements

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