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Design and Development of a Common Synthetic Strategy for a Variety of 1-*N*-Iminosugars

Ganesh Pandey* and Manmohan Kapur

Division of Organic Chemistry (Synthesis), National Chemical Laboratory, Pune 411008, India

pandey@ems.ncl.res.in

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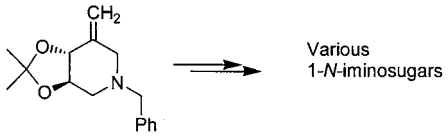
ABSTRACT



A new synthetic strategy has been developed for a general approach toward the synthesis of a variety of 1-*N*-iminosugar-type glycosidase inhibitors utilizing precursors developed by the PET-mediated cyclization of α-trimethylsilylmethylamine radical cation to a tethered π-functionality.

Glycosidase inhibitors, also called the "sugar-shaped alkaloids", are carbohydrate analogues in which one or more of the oxygen atoms have been substituted by a nitrogen and are found to be widespread in the plants and microorganisms.[1]

Due to the tremendous potential of these unique molecules in studying the biological functions of oligosaccharides[2] and by virtue of these being postulated as therapeutics for a variety of carbohydrate-mediated diseases such as HIV,[3] diabetes,[4] hepatitis,[5] cancer,[6] and Gaucher's disease[7] and viral infections such as influenza,[8] an interest in the chemistry, biochemistry, and pharmacology of these compounds has been sparked.[9] Although a plethora of natural as well as synthetic α-glycosidase inhibitors are known, the development of anomer-selective β-glycosidase inhibitors took place only in the past decade, pioneered by the studies from the groups of Bols[9f] and Ichikawa.[9g]

These carbohydrate mimics, in which the anomeric carbon is substituted by a nitrogen, have been termed 1-azasugars or 1-*N*-iminosugars. A variety of transition state analogues such as **1**−**4** have been designed and studied (Figure 1).

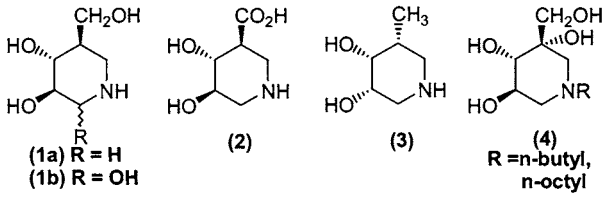


Figure 1. Some of the β-glycosidase inhibitors developed.

Isofagomine (**1a**) and noeuromycin (**1b**) (D-glucose-type 1-*N*-iminosugars) have been found to be extremely potent β-glucosidase inhibitors.[9f] Also notable is compound **4**, the 5-hydroxy analogue of isofagomine, which has been found to be an inhibitor of glycolipid biosynthesis.[10]

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(4) (a) Anzeveno, P. B.; Creemer, L. J.; Daniel, J. K.; King, C. -H. R.; Liu, P. S. J. *Org. Chem.* **1989**, *54*, 2539. (b) Balfour, J. A.; McTavish, D. *Drugs* **1993**, *46*, 1025.
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(8) Kim, C. U.; Lew, W.; Williams, M. A.; Liu, H.; Zhang, L; Swaminathan, S.; Bischofberger, N.; Chen, M. S.; Mendel, D. B.; Tai, C. Y.; Laver, W. G.; Stevens, R. C. *J. Am. Chem. Soc.* **1997**, *119*, 681.

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Although these molecules look relatively simple, their syntheses have not been straightforward. The greatest hurdle in the synthesis of these piperidines has been the introduction of the aminomethyl group next to a stereocenter. Although many intelligent approaches for the syntheses of these have been reported,[9f,g,11] a general synthetic strategy toward these is unknown. Approaches utilizing the chiral pool have had to change the starting material for each of these compounds. A close look at these 1-*N*-iminosugars reveals a general substitution pattern, as in **5**, varying only in the stereochemistry of the hydroxy groups at C-3 and C-4 and the nature of the R^1 and R^2 groups (Figure 2). Therefore, we wondered

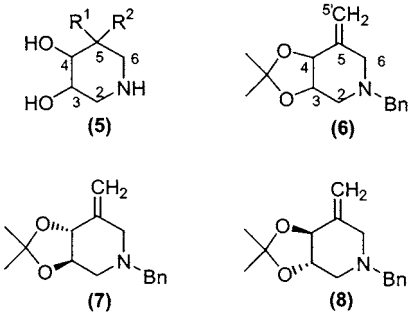


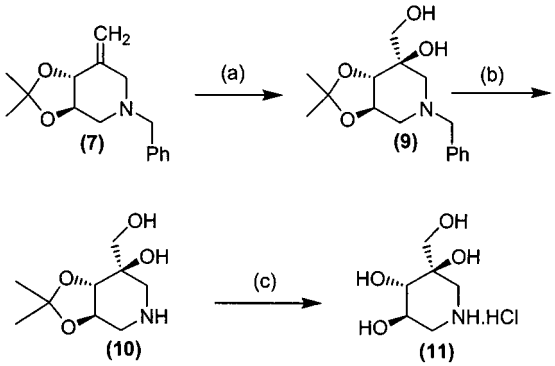
Figure 2. General precursors of D- and L-*threo* classes.

whether a precursor of the type **6** could be used for the design of a general route for the synthesis of these molecules. By having the correct stereochemistry at C-3 and C4 and by functionalizing the exocyclic double bond, one can have an access to a variety of these azasugars. In this context, we designed and successfully synthesized **7** and **8**, precursors of the D- and L-*threo* classes, respectively.[12] These precursors were obtained by utilizing our methodology[13] for synthesizing cyclic amines via PET (photoinduced electron transfer)-promoted cyclizations of α-trimethylsilylmethylamine radical cation to a tethered π-functionality.

We also synthesized (+)- and (−)-isofagomine (**1**) utilizing these precursors.[12] As a part of our continuing study in this area toward the development of new azasugars and also to broaden the scope of our strategy, we report herein the further development of this strategy for the synthesis of a variety of 1-*N*-iminosugars.

The successful synthesis of both isomers of isofagomine was followed by the synthesis of the 5-hydroxy analogue of 5-*epi*-isofagomine (Scheme 1).

Scheme 1[a]

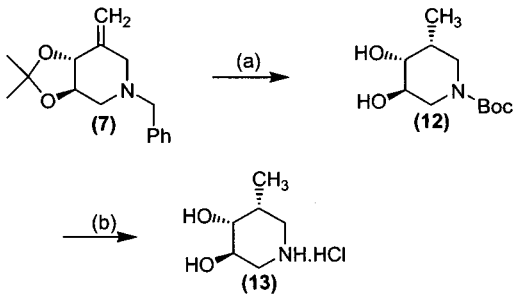


[a] Reagents and conditions: (a) OsO_4, NMO, pyridine, acetone−water (9:1), from 0 °C to room temperature, 24 h, 95%; (b) $Pd(OH)_2$, H_2, EtOH, 65 psi, 6 h, 90%; (c) HCl, MeOH, rt, 4 h, quant.

Osmium tetroxide dihydroxylation of **7** afforded **9** as a single diastereomer. The stereochemical outcome was adjudged by COSY, HETCOR, and NOESY experiments. The benzyl and acetonide protecting groups were removed to afford **11**.

We also synthesized 5′-deoxy-5-*epi*-isofagomine (**13**) from **7**. One-pot olefin reduction, N-debenzylation, and acetonide deprotection of **7** led to a 80:20 mixture of nonseparable diastereomers. These diastereomers, however, could be separated by careful column chromatography as their corresponding *N*-Boc derivatives. The stereochemistry at this stage was established by COSY. Removal of the *N*-Boc moiety afforded **13** (Scheme 2).

Scheme 2[a]



[a] Reagents and conditions: (a) (i) Pd/ C, MeOH, HCl, H_2, 1atm, rt, 12 h, 89%; (ii) $(Boc)_2O$, TEA, DCM, rt, 48 h, 75%. (b) HCl, MeOH, from 0 °C to room temperature, 4 h, quant.

(9) For some excellent accounts on glycosidases and their inhibitors, see: (a) Zechel, D. L.; Withers, S. G. *Acc. Chem. Res.* **2000**, *33*, 11. (b) Heightman, T. D.; Vasella, A. T. *Angew. Chem., Int. Ed.* **1999**, *38*, 750. (c) Ganem, B. *Acc. Chem. Res.* **1996**, *29*, 340. (d) Sears, P.; Wong, C. -H. *Angew. Chem., Int. Ed.* **1999**, *38*, 2300 (e) Stütz, A. E. *Iminosugars as Glycosidase Inhibitors: Nojirimycin and Beyond*; Wiley-VCH: Weinheim, Germany, 1999. (f) Lillelund, V. H.; Jensen, H. H.; Liang, X.; Bols, M. *Chem. Rev.* **2002**, *102*, 515. (g) Ichikawa, Y.; Igarashi, Y.; Ichikawa, M.; Suhara, Y. *J. Am. Chem. Soc.* **1998**, *120*, 3007.

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(11) For some recent syntheses, see: (a) Andersch, J.; Bols, M. *Chem. Eur. J.* **2001**, *7*, 3744 and references therein. (b) Zhao, G.; Deo, U. C.; Ganem, B. *Org. Lett.* **2001**, *3*, 201. (c) Kim, Y. J.; Ichikawa, M.; Ichikawa, Y. *J. Org. Chem.* **2000**, *65*, 2599. (d) Mehta, G.; Mohal, N. *Tetrahedron Lett.* **2000**, *41*, 5747. (e) Liu, H.; Liang, X.; Søhoel, H.; Bülow, A.; Bols, M. *J. Am. Chem. Soc.* **2001**, *123*, 5116. (f) Liang, X.; Lohse, A.; Bols, M. *J. Org. Chem.* **2000**, *65*, 7432. (g) Søhoel, H.; Liang, X.; Bols, M. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1584.

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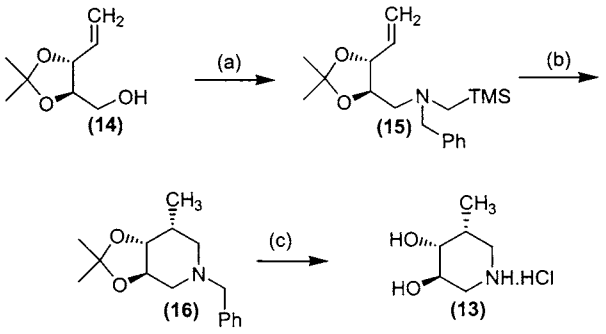
Although a fair degree of diastereoselection was obtained in the above case, we were not completely satisfied by the outcome. We decided to modify the approach for this molecule, utilizing our PET cyclization strategy[13] for the construction of this substituted piperidine. The modified synthesis began with alcohol **14**,[14] also derived from D-(−)-tartaric acid (Scheme 3).

Scheme 3[a]



[a] Reagents and conditions: (a)(i) TsCl, pyridine, DCM, rt, 24 h, 95%; (ii) $PhCH_2NHCH_2TMS$, Cs_2CO_3, TBAI, CH_3CN, reflux, 72 h, 58%. (b) *hν*, DCN, 2-PrOH, 2 h, 55%. (c) $Pd(OH)_2$ on C, HCl, MeOH, H_2, 1 atm, 28 h, quant.

Tosylation followed by nucleophilic substitution utilizing $PhCH_2NHCH_2TMS$ afforded **15**. To our pleasant surprise, amine **15**, when subjected to PET cyclization conditions, afforded **16** as a single diastereomer (>97%). Removal of the benzyl and acetonide groups afforded **13** in good yield.

The above successes led us to set our sight on the synthesis of some of the most important 3,4,5-piperidine triols (Figure 3). These trihydroxy piperidines are regarded as the derivatives of their parent deoxynojirimycin and have been shown to possess moderate to good glycosidase inhibitory activity. Careful consideration of these structural moieties reveals that these molecules can also be classified as 1-*N*-iminosugar-type glycosidase inhibitors, although they do not resemble any of the existing pyranose sugars.

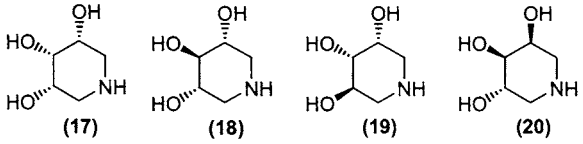
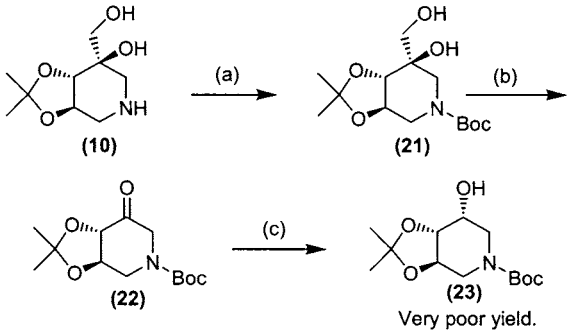


Figure 3. Some of the most important 3,4,5-piperidine triols.

Triols **17**, **18**, and **20** were isolated from *Eupatorium fortunei* TURZ by Kusano and co-workers[15] in 1995 and have been shown to be the active components of the extracts of this plant, traditionally used in Chinese and Japanese folk medicine as a diuretic, antipyretic, emmenagogue, and antidiabetic agent. Triols **17**−**20** have also been synthesized by Ganem[16] and others[17] and have been shown to be good selective inhibitors of glycosidases.

We realized that our precursors **7** and **8** could be ideal for the synthesis of these molecules. The synthesis of des(hydroxymethyl)deoxymannojirimycin (**19**) commenced with diol **9**, previously synthesized from **7**. In anticipation that the amine would be affected by periodate oxidation, we replaced the benzyl group in **9** by an *N*-Boc moiety (Scheme 4). However,

Scheme 4[a]

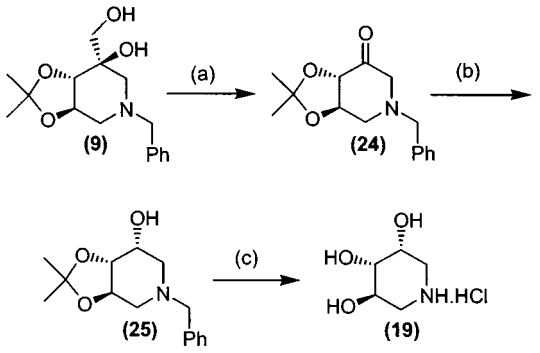


[a] Reagents and conditions: (a) $(Boc)_2O$, TEA, DCM, from 0 °C to room temperature, overnight, 80%; (b) $NaIO_4$, EtOH−H_2O (4:1), rt, 30 min, 70%; (c) $NaBH_4$, MeOH, rt, 36 h, then saturated NaCl, rt, 24 h, 25%.

to our surprise and for reasons unknown, the sodium borohydride reduction of the ketone **22** failed to give good yield, and therefore this route was abondoned.

The above failure forced us to revert back to diol **9**, which upon periodate oxidation, as shown in Scheme 5, gave **24**

Scheme 5[a]



[a] Reagents and conditions: (a) $NaIO_4$, EtOH−H_2O (4:1), rt, 1 h, 80%; (b) $NaBH_4$, MeOH, rt, 40 h, then saturated NaCl, rt, 24 h, 85%; (c) $Pd(OH)_2$ on C, HCl, MeOH, H_2, 1 atm, rt, 36 h, quant.

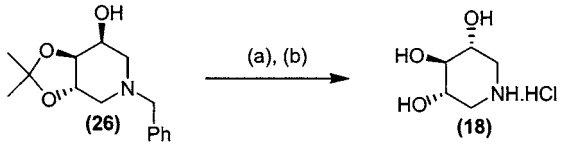
in 80% yield. However, since **24** was found to be extremely unstable, it was quickly subjected to sodium borohydride reduction, which afforded **25** in a 90:10 diastereomeric ratio.

(14) Kang, S. K.; Lee, S. B. *Chem. Commun.* **1998**, 761.
(15) Sekioka, T.; Shibano, M.; Kusano, G. *Nat. Med.* **1995**, *49*, 332.

One-pot N-debenzylation and acetonide removal afforded **19**, which could be purified completely by column chromatography as a free base and was converted back to its hydrochloride salt for spectral characterization. The stereochemistry of the newly formed hydroxy group was proved by COSY experiments. The spectral data and optical rotation for **19** were found to be in close agreement with those reported.[16]

We moved on further to synthesize des(hydroxymethyl)-deoxynojirimycin (**18)**. This was synthesized by inverting the stereochemistry of the hydroxy group of **26** (*ent*-**25**) using Mitsunobu conditions (Scheme 6). Removal of the benzyl and acetonide groups, followed by chromatographic purification yielded **18**, which was characterized as its hydrochloride salt. Spectral data for **18** were in excellent agreement with those reported.[16]

Scheme 6[a]



[a] Reagents and conditions: (a) (i) diisopropyl azodicarboxylate, PPh_3, *p*-nitrobenzoic acid, THF, rt, overnight; (ii) LiOH, MeOH, 60% over two steps. (b) $Pd(OH)_2$ on C, HCl, MeOH, H_2, 1 atm, rt, 20 h, quant.

In a similar manner, *ent*-**11**, *ent*-**13**, and des(hydroxymethyl)deoxygalactonojirimycin (**20)** were synthesized from the L-*threo* precursor **8**.

In summary, we have demonstrated the general nature of our approach by synthesizing various 1-*N*-iminosugars from a common precursor. It is obvious that the D- and L-*erythro* precursors (in which the C-3 and C-4 hydroxy groups are syn) would lead to other 1-*N*-iminosugars of the required stereochemistry. Currently, the new molecules **11** and **13** and their enantiomers are being studied for their inhibitory activity, and the results will be published in due course.

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Supporting Information Available: Spectral data and copies of ^1H and ^{13}C NMR spectra of compounds **11**, **13**, **15**, **16**, **18**, and **19**. This material is available free of charge via the Internet at http://pubs.acs.org.

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