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Graphical Abstract

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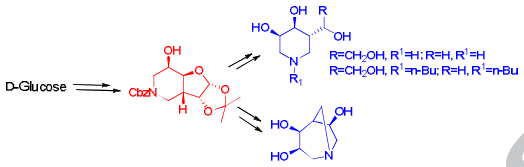

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Synthesis of L-3-*epi*-isofagomine, its homo-, n-butyl and bicyclic analogues from D-glucose as glycosidase inhibitors

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ABSTRACT

Synthesis of L-3-*epi*-isofagomine, its homo-, n-butyl derivatives and its bicyclic analogue as potent glycosidase inhibitor has been achieved from readily available D-glucose. Inhibiton of some commercially available glycosidases was also carried out with the newly synthesized inhibitors which showed reasonably good inhibitions (9.4-198.2 μM). One of them (compound **11**) showed selective inhibition of β–galactosidase.

In the recent past, azasugars (or iminosugars) and their analogues have shown enormous therapeutic applications[1,2] in diseases such as diabetes,[3] cancers,[4] HIV,[5] lysosomal storage disorders,[6] etc. Azasugars are polyhydroxylated compounds where anomeric carbon is replaced by a nitrogen atom, while if the ring oxygen is replaced by nitrogen atom then they are called iminosugars.[7] In 1966, Inouye *et al.* isolated nojirimycin **1** (Figure 1) from the strains of *Streptomyces*[8] as the first naturally occurring polyhydroxylated piperidine iminosugar which was found to be both an α- and a β-glucosidase inhibitor.[1a] Its stable congener 1-deoxynojirimycin (DNJ) **2a** was originally synthesized by Paulsen *et. al.*[9] in 1966. Later on in 1976, DNJ was isolated from the root of Mulberry trees by Murai *et al.*[10] The *N*-butyl derivative of DNJ (Zavesca) **2b** is being used as a drug for the Gaucher's disease whereas *N*-hydroxyethyl DNJ (Glyset) **2c** is used for the treatment of type II diabetes.[11] Isofagomine **3** is another important polyhydroxylated compound designed by Bols *et al.* which shows selective and strong inhibition against β-glucosidase (sweet almonds) with K_i of 110 nM.[12] It is known to rectify the conformation of misfolded β-glucocerebrosiadse and thus it could be useful in treating certain types of Gaucher's disease.[13] Furthermore, L-3-*epi*-isofagomine **4** has also been synthesized and it shows selective inhibition against β-galactosidase [IC_{50} = 469 μM, rat intestine lactase].[14] Similarly, polyhydroxylated indolizidine alkaloids such as (+)-swainsonine **5**, (+)-lentiginosine **6** and (+)-castanospermine **7** are also good targets for synthetic studies as they represent challenging bicyclic scaffolds and possess good therapeutic potential.[15-17] Considering the importance of isofagomine, and these bicyclic azasugars, newer approaches to procure such molecules and their analogues are still needed to facilitate the discovery of potential selective glycosidase inhibitors.

Recently, we reported the synthesis of isofagomine **3** and related biologically active molecules from carbohydrate based starting materials.[18] Likewise, we have also reported the synthesis of bicyclic azasugars such as L-(+)-swainsonine **5** and (+)-lentiginosine **6** from carbohydrate building blocks.[19] In continuation with our interest in developing newer approaches for the synthesis of glycosidase inhibitors,[20] we report in this paper the synthesis of L-3-*epi*-isofagomine and its homo-, n-butyl and bicyclic analogues from D-glucose.

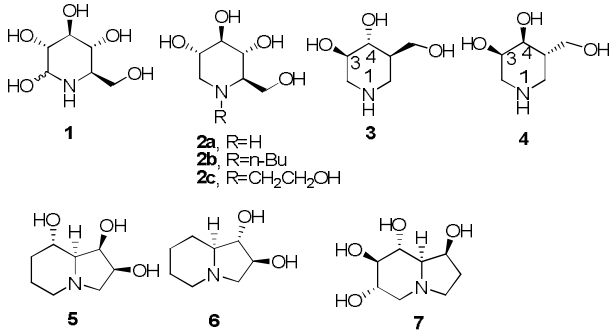

Figure 1. Monocyclic piperidine based and bicyclic indolizidine based imino / azasugars.

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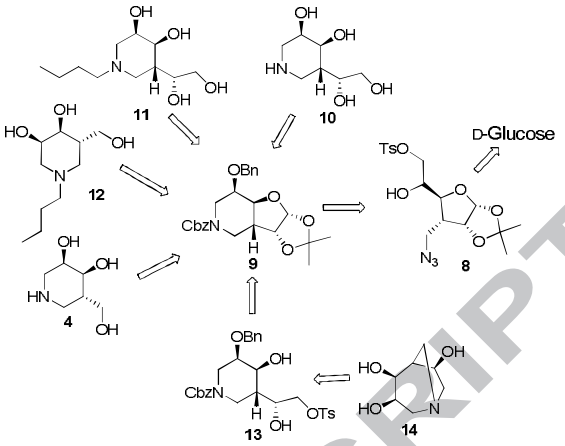
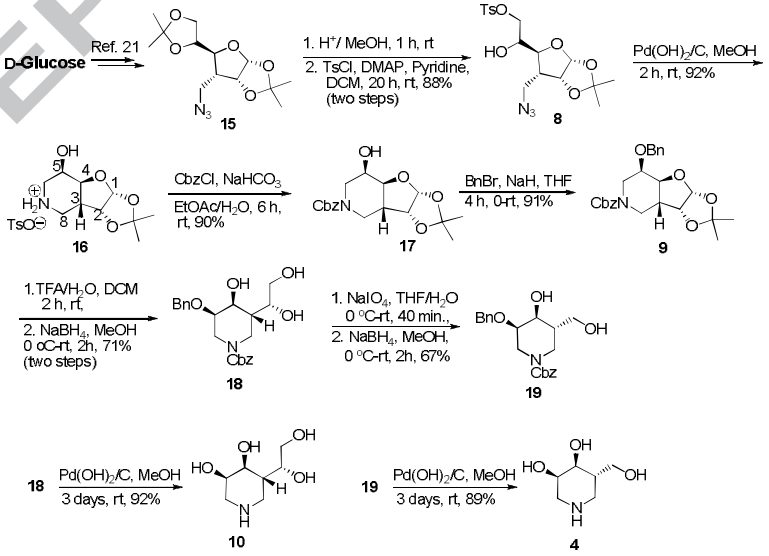
Our retrosynthetic analysis (Scheme 1) illustrates that these target monocyclic and bicyclic azasugar derivatives could be reduced to simpler intermediate **9** which could be obtained from D-glucose. Thus, our synthesis originated from compound **15** which was obtained from 1,2:5,6-di-*O*-isopropylidene protected glucose following a literature procedure[21] (Scheme 2). The 5,6-*O*-isopropylidene unit in compound **15** was selectively removed by the treatment with dilute acid at room temperature. The corresponding diol, so generated, was subjected to selective tosylation with TsCl, pyridine in the presence of DMAP to give compound **8** in 88% yield over two steps. The formation of compound **8** was ascertained by the appearance of a sharp singlet peak around δ2.42 corresponding to the tosyl group in its ^{1}H NMR spectrum. Reduction of azide group of compound **8**, to the corresponding amine followed by hydrogenolysis in presence of $Pd(OH)_2$/C in methanol that yielded the tosylate salt **16** as colourless crystals.[22] Typically, the formation of cyclic compound **16** was confirmed by the disappearance of the sharp band corresponding to azide at 2102 cm^{-1} in IR spectrum. As an additional proof, the stereochemical outcome of compound **16** was confirmed by X-ray crystal structure (cf. experimental section). This protonated amine salt **16** upon benzyl carbamate protection afforded the Cbz-protected amine **17** in 90% yield which typically showed a strong absorption peak at 1696 cm^{-1} in its IR spectrum and a peak at δ156.4 in the ^{13}C NMR spectrum for the carbamate group. The free hydroxyl group in compound **17** was converted to the benzyl ether functionality by treatment with benzyl bromide in presence of NaH to give compound **9** in 91% yield. Originally, we attempted to synthesize **19** from **9** by acetonide deprotection followed by oxidative cleavage with $NaIO_4$ and reduction with $NaBH_4$. But the overall yield was very poor in this series of reactions (22% yield over three steps). However, the yield was remarkably improved by changing the sequence of reactions. Thus, 1,2-*O*-isopropylidene ring was then removed by treatment with trifluoroacetic acid/water to give the corresponding hemiketal which upon reduction with $NaBH_4$ in methanol furnished the triol **18** in good yield. Formation of the triol was confirmed by the devoid of the peaks at δ1.50 and 1.31 (methyl groups of acetonide moiety) in ^{1}H NMR spectrum and appearance of $[M + Na]^+$ peak at 424.1739 (calculated)



Scheme 1. Retrosynthetic analysis of the various azasugars

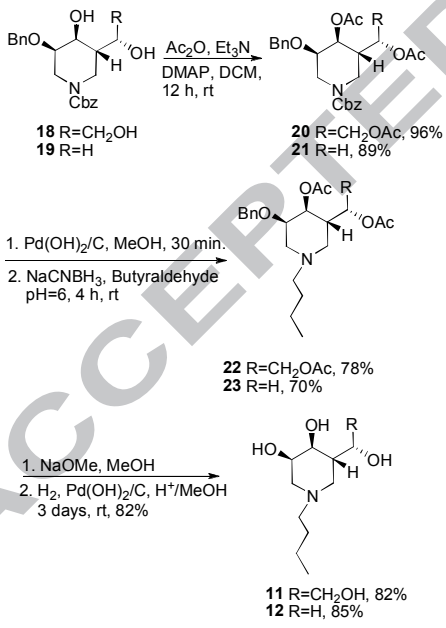
in its high resolution mass spectrum, along with other spectral characteristics. The 1,2-diol moiety in compound **18** was converted to the corresponding aldehyde by oxidative cleavage with $NaIO_4$, followed by reduction with $NaBH_4$ to yield compound **19**. The global deprotection of **18** and **19** by hydrogenolysis using $Pd(OH)_2$/C in methanol furnished tetra-ol **10** and triol **4**, respectively. The spectral data of compound **4** was found to be in agreement with the reported data.[14a] The triol **18** was converted to the corresponding acetate **20** (Scheme 3) in 96% yield which was characterized by a sharp absorption band at 1742 cm^{-1} in IR spectrum. The benzyl carbamate functionality was removed by hydrogenolysis to give the corresponding secondary amine which was converted to its *N*-butyl derivative by condensation with butyraldehyde in presence of $NaCNBH_3$ to afford **22**. The absence of an absorption band at 1702 cm^{-1} in its IR spectrum and the appearance of a peak at δ0.90 as a triplet (J = 7.3 Hz) for three hydrogens of the methyl group in ^{1}H NMR spectrum, apart from other spectral details (cf. experimental section), confirmed the formation of **22**. Furthermore, the stereochemical outcome of compound **22** was supported by COSY and NOE experiments. Thus, in NOE experiment (Fig. 2), no enhancement of signal for H-5 at δ2.16 was observed



Scheme 2. Synthesis of L-3-*epi*-isofagomine and its analogue

upon irradiation of signal for H-4 at around δ4.95 which suggests that H-5 and H-4 are in *trans* diaxial orientation. This was further proved by irradiation of proton from side chain (-C*H*OAc-) at δ5.28 which showed 0.9% of NOE enhancement of H-4 proton. No enhancement of signals in NOE was observed by irradiation of the signals for either H-3 at δ3.80 or H-5 for each other. This also indicated that H-3 and H-5 are *trans* oriented. Similar NOE observations were made for compound **23** also. The acetate functionalities in triacetate **22** were removed by treatment with NaOMe. Finally, the hydrogenolysis of the benzyl group furnished the final compound **11** in 82% yield. Similarly, the diol **19** was converted to **12** following the same sequence of reactions as employed for the synthesis of **11** from **18** in good yields (overall 53%). For the synthesis of bicyclic analogue **14**, the triol **18** was selectively converted to its primary tosyl derivative **13** (Scheme 4) by treatment with *p*-TsCl and n-Bu_2SnO in the presence of triethylamine.[23] The Cbz-deprotection and cyclization was achieved by hydrogenation in presence of $Pd(OH)_2$/C to get final compound **14** in 82% yield.

The biological activities of compounds **10**, **11**, **12** and **14** were tested against few commercially available glycosidases[24] and the results are shown in Table 1. None of these compounds showed significant inhibitory activity against α-glucosidase (rice). Compound **10** was found to be active against α-glucosidase, β-glucosidase, α-galactosidase and β-galactosidase in μM range. Compound **12** was also found to be active against α-glucosidase, β-galactosidase and α-mannosidase. Likewise, compound **14** also did not show much selectivity, though the inhibitions were in low micromolar range. However, compound **11** showed selective and potent inhibition against β-galactosidase with 158.5 μM IC_{50} value.



Scheme 3. Synthesis of n-butyl derivative of L-3-*epi*-isofagomine and its analogue

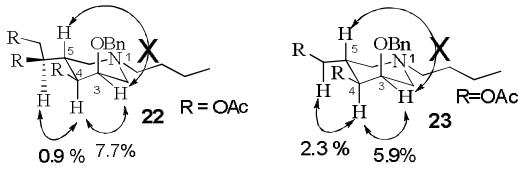
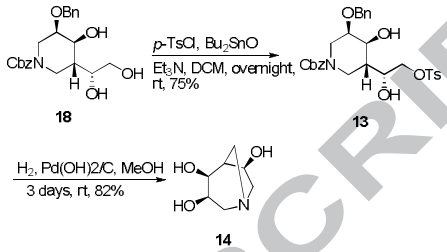


Figure 2. NOE enhancement signal for the compounds **22** and **23**.



Scheme 4. Synthesis of bicyclic analogue.

Table 1. IC_{50} (μM) values for synthesized polyhydroxylated compounds **10**, **11**, **12**and **14**.[a]

Enzyme	pH	10	11	12	14
α-Glucosidase (yeast)	6.5	l 198.2	NI	70.4	NI
β-Glucosidase (almonds)	4.6	64.5	NI	NI	86.0
α-Galacosidase (coffee beans)	6.5	14.4	NI	NI	9.4
β-Galactosidase (bovine liver)	7.3	25.2	158.5	22.6	31.4
α-Mannosidase (Jack beans)	4.6	NI	NI	61.5	NI
α-Glucosidase (rice)	4.6	NI	NI	NI	NI

[a] **NI:** no inhibition at 3 mM concentration; enzyme inhibition was carried out at optimal pH of the enzyme at 37 ^{0}C.

In conclusion, we have reported the synthesis of L-3-*epi*-isofagomine, its homo-, n-butyl derivatives and its bicyclic analogue as potential glycosidase inhibitors from chiral synthon 1,2:5,6-di-*O*-isopropylidene-α-glucofuranose via very effective pathways. Further variations in structural features of compound **11** could improve its inhibition potency against β-galactosidase. Also, further variations in structural features of compounds **10**, **12** and **14**, could lead to improve their selectivity.

Acknowledgments

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