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Aziridine carboxylate from D-glucose: synthesis of polyhydroxylated piperidine, pyrrolidine alkaloids and study of their glycosidase inhibition†

Dilip D. Dhavale,*[a] K. S. Ajish Kumar,[a] Vinod D. Chaudhari,[a] Tarun Sharma,[b] Sushma G. Sabharwal[b] and J. PrakashaReddy[c]

[a] *Garware Research Centre, Department of Chemistry, University of Pune, Pune, 411 007, India*
[b] *Division of Biochemistry, Department of Chemistry, University of Pune, Pune, 411 007, India*
[c] *Division of Organic Chemistry, National Chemical Laboratory, Pune, 411 008, India.*
E-mail: ddd@chem.unipune.ernet.in

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The D-glucose derived aziridine carboxylate **5** was obtained from (*E*)-ethyl-6-bromo-1,2-*O*-isopropylidene-3-*O*-benzyl-5-deoxy-α-D-*xylo*-5-eno-heptofuranuronate **4** through conjugate addition of benzylamine and *in situ* intramolecular nucleophilic expulsion of bromine. The regioselective aziridine ring-opening, using water as a nucleophile, resulted in the α-hydroxy-β-aminoester **6**, which was exploited in the synthesis of six and five membered azasugars **1b/1c** and **2b/2c**, respectively. The glycosidase inhibitory activity of the title compounds was evaluated.

Introduction

The aziridine carboxylic esters of type **A** (R^1 = alkyl, aryl) play a vital role in the synthetic sequence due to their inherent capability to undergo nucleophilic ring opening either at C3 or C2 giving an access to differentially substituted α- or β-amino esters, respectively[1] (Fig. 1). The weak electrophilic nature of the aziridine carboxylate **A** is overpowered either by incorporation of an electron-withdrawing group (*e.g.*, R^3 = sulfonyl) on the aziridinic nitrogen atom and/or by the use of acidic reaction conditions. In general, nucleophiles such as alcohols,[2] Wittig reagents,[3] thiols,[4] indoles[4,5] and amines[6] attack at the C3 carbon leading to the aziridine ring opening in the usual conjugate addition pathway, thus yielding α-amino esters. A few examples are known wherein organocuprates,[7] malonates[8] and some indole derivatives[9] react at both C3 and C2 of **A** to give a mixture of products. However, azidotrimethylsilane[10] and lithium dimethylcuprate[1] undergo regioselective aziridine ring opening at the C2–N bond to give β-amino esters.[11] In this context, we noticed an interesting observation in the reaction of D-glucose-derived aziridine carboxylate **A** (R^1 = sugar), with water as a nucleophile. Under acidic conditions, the aziridine ring opening took place at the C2 position leading to the exclusive formation of α-hydroxy-β-aminoesters, which represents promising chiral precursor to the synthesis of six and five membered azasugars. Although, aziridines have been widely exploited as intermediates in the synthesis of a number of biologically important compounds,[12] only a few examples are known with sugar aziridines[13] and, to the best of our knowledge, no report is available with D-glucose derived aziridine carboxylate of type **A** (R^1 = D-*gluco*-furanose) in the synthesis of azasugars.

Nitrogen-incorporated polyhydroxylated carbocylic ring systems, commonly known as azasugars or iminosugars, are of great importance as they often exhibit significant glycosidase inhibitory activity. Among these, the polyhydroxylated piperidine[14] (*e.g.*, 1-deoxynojirimycin **1a**) and pyrrolidine[15] (*e.g.*, 1,4-dideoxy-1,4-imino-L-arabinitol **2a**) alkaloids selectively inhibit glycosidase that modify glycoconjugates by hydrolyzing glycosidic linkages and are therefore potential candidates as antiviral, antibacterial or, antimetastatic agents[16] (Fig. 2). In the search for structure–activity relationship, a number of six and five membered azasugar analogues of **1a** and **2a** were synthesized and evaluated for their biological activities. In the continuation of our work in the area of azasugars,[17] we thought of exploiting aziridine carboxylate **A** (R^1 = D-*gluco*-furanose) in

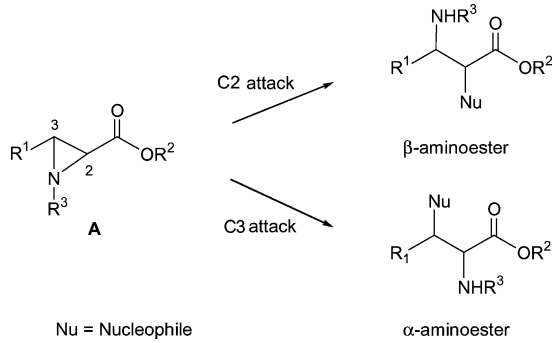

Fig. 1 Nucleophilic ring-opening of aziridine esters.

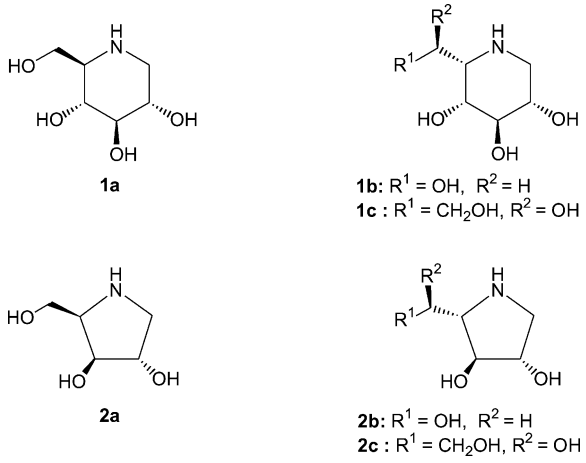

Fig. 2 Piperidine and pyrrolidine alkaloids.

† Electronic supplementary information (ESI) available: General experimental methods, crystallographic data for **5** and copies of ^1H and ^{13}C NMR spectra of compounds **1b**, **1c**, **2b**, **2b**.**HCl**, **2c**, **4**, **5**, **6**, **7**, **8**, **9**, **10**. See http://dx.doi.org/10.1039/b509216g

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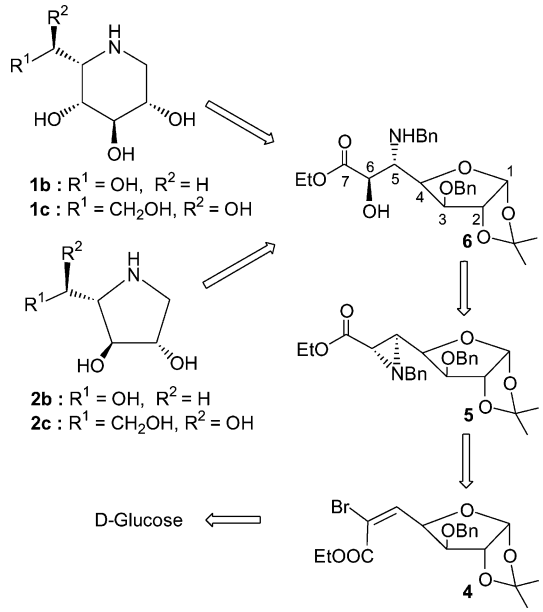
the synthesis of 1-deoxy-L-*ido*-nojirimycin **1b**, 1,4-dideoxy-1,4-imino-L-*xylitol* **2b** and one-carbon homologated 1,5-dideoxy-1,5-imino-6-hydroxy-β-L-*glycero*-L-*ido*-heptitol **1c**, 1,4-dideoxy-1,4-imino-5-hydroxy-L-iditol **2c**, with hydroxyl functionality at the homologated carbon. Although compounds **1b** and **2b** are known in the literature, compounds **1c** and **2c**, to the best of our knowledge, are not reported so far.

We realized that the six membered piperidine alkaloids **1b** and **1c** could be prepared from sugar aminal **6** by joining the C5 amino group to carbon C1 by reductive amination, while chopping of C1 and joining the C5 amino group to C2 will give an access to the five membered pyrrolidine alkaloids **2b** and **2c** (Scheme 1). Thus, the key intermediate for all four target molecules is the α-hydroxy-β-amino ester **6** that could be prepared from the aziridinyl precursor **5** following a regioselective ring opening under acidic condition, using water as a nucleophile. The main feature of this strategy lies in the evolution of a masked nucleophilic center at C6 carbon through aziridine ring formation that could be achieved by intermolecular conjugate addition of benzylamine and concomitant S_N2 displacement of bromine. Our efforts in the successful implementation of this method for the formation of piperidine **1b**/**1c** and pyrrolidine alkaloids **2b**/**2c** are reported herein.



Scheme 1 Retrosynthetic analysis.

Results and discussion

The Wittig olefination of α-D-*xylo*-pentodialdose **3** using $Ph_3PCBrCOOEt$ in dichloromethane afforded the required bromocarboxylate **4** in 77% yield.[18,19] The exclusive formation of *E*-isomer **4** was confirmed by ^1H NMR spectra in which the vinylic proton H5 appeared at downfield position (δ 7.50)[20] as well as the H4 proton showed a considerable downfield shift and appeared at δ 5.05 (as compared to the normal position of $\delta \sim 4.0$) due to the diamagnetic anisotropic deshielding effect induced by the ester carbonyl functionality,[21] indicating the *cis* relative orientation of carboxylate group and sugar moiety. In the next step, compound **4** was treated with benzylamine (15 equiv.) to give aziridine carboxylic ester **5** in 70% yield.[22] The *trans*-aziridine geometry of **5** was established by ^1H NMR analysis which showed a small vicinal coupling constant of H5 and H6 ($J_{5,6} = 2.9$ Hz) against the large J_{vic} (~7.0 Hz) known for the *cis*-aziridine derivative.[23] Compound **5** was isolated as a colorless solid and the single crystal X-ray analysis (Fig. 3) firmly established the *trans* relative configuration, 5*S* and 6*S*, of the carboxylate group and the sugar functionality respectively. This one-pot two-step reaction of **4** probably involves *in situ* generation of β-aminoester, by the *Re* face attack of benzylamine at the prochiral C5, that concomitantly undergoes S_N2 type nucleophilic displacement of the bromine (by rotation around C5–C6 bond) to give the more stable *trans*-aziridine as the only isolable product.[24]

Subsequently, the aziridine ring-opening of **5** with water in the presence of TFA (1 equiv.) in acetone afforded α-hydroxy-β-aminoester **6** as the only product in 82% yield. The use of other acids like $HClO_4$ and H_2SO_4 afforded a mixture of products probably due to the hydrolysis of the 1,2-acetonide functionality.

The formation of **6** with regioselective S_N2-type aziridine ring opening α to the carboxylate group in **5** is unusual, as a nucleophilic solvent like water is known to afford essentially α-aminoesters resulting from an attack at the β-position of the carboxylate group. The observed regioselectivity in favour of β-amino-α-hydroxy ester **8**, with 5*S*, 6*R* absolute stereochemistry could be explained by the preferential β-attack at the C6 carbon atom, rather than at the C5 which is hindered due to the β-oriented C3-*O*Bn group.[25] Although the spectral data of **6** were in

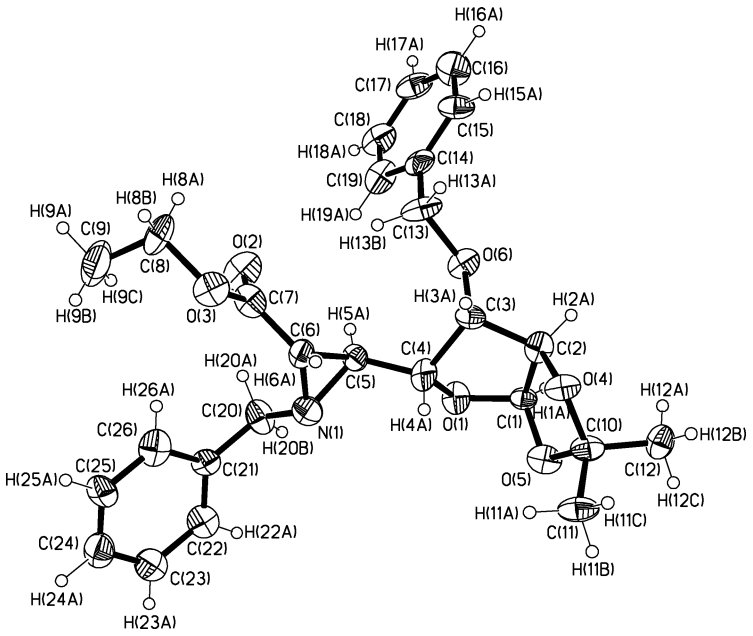
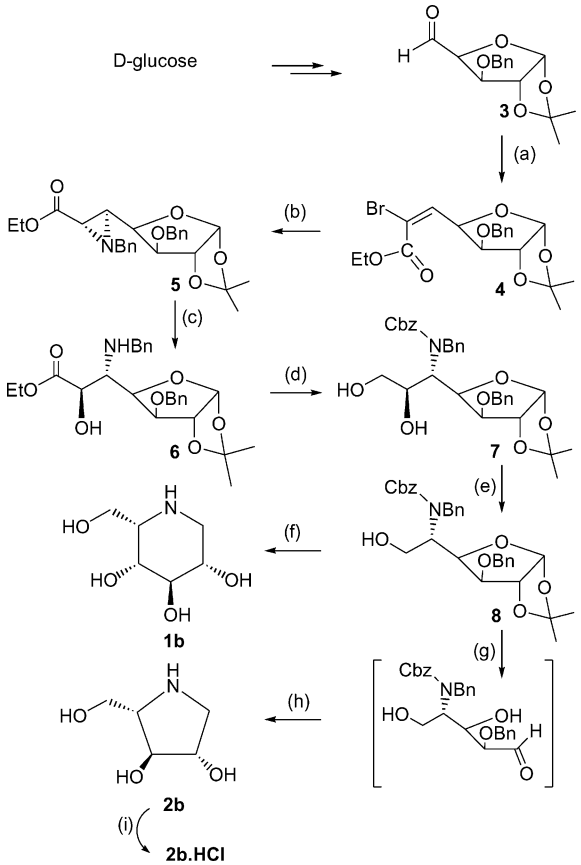


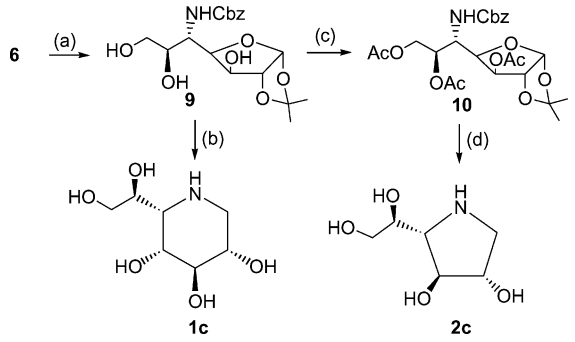
Fig. 3 ORTEP drawing of compound **5**.

agreement with the β-aminoester structure, further evidence was obtained by converting **6** to the known azasugars 1-deoxy-L-*ido*-nojirimycin **1b** and 1,4-dideoxy-1,4-imino-L-xylitol **2b**. Thus, as shown in (Scheme 2), the reduction of the ester group by LAH in **6** followed by selective amine protection by benzylchloroformate afforded the *N*-Cbz protected diol **7**. The oxidative cleavage of diol **7** with sodium periodate furnished an unstable aldehyde, which was subjected to sodium borohydride reduction to yield primary alcohol **8**. The compounds **4** to **8** were obtained in good yield and characterized by spectral/analytical techniques, which were found to be in agreement with the structures.[26] The hydrolysis of the 1,2-acetonide functionality in **8** with TFA–water followed by treatment with ammonium formate and 10% Pd/C in MeOH gave 1-deoxy-L-*ido*-nojirimycin **1b** as a thick liquid. The analytical and spectral data of **1b** were found to be identical with those reported in the literature (observed $[a]_D$ + 7.91 (*c* 0.25, MeOH), lit.,[14s] $[a]_D$ + 8.49 (*c* 0.5, MeOH)). Compound **8** proved to be a valuable precursor for the five membered pyrrolidine alkaloid 1,4-dideoxy-1,4-imino-L-xylitol **2b**. Thus, cleavage of the 1,2-acetonide functionality in **8** by TFA–water and treatment with sodium metaperiodate afforded the one carbon degraded aminal that was directly subjected to hydrogenation with 10% Pd/C in methanol to give 1,4-dideoxy-1,4-imino-L-xylitol **2b** as a viscous liquid. The reaction of **2b** with MeOH.HCl afforded the hydrochloride salt of **2b** as a sticky solid. The spectral and analytical data of **2b**.**HCl** was in agreement with that reported (observed $[a]_D$ −9.40 (*c* 0.74, H_2O), lit.,[15b,d] $[a]_D$ −9.9 (*c* 0.71, H_2O)).



Scheme 2 *Reagents and conditions*: (a) PPh_3=CBrCOOEt, CH_2Cl_2, 25 °C, 12 h, 77%; (b) $BnNH_2$, benzene, 10 to 20 °C, 6 h, 70%; (c) TFA (1 equiv.), acetone–water (2 : 1), 25 °C, 24 h, 82%; (d) (i) LAH, THF, 0 to 25 °C, 2 h,; (ii) CbzCl, $NaHCO_3$, MeOH–water, 0 to 25 °C, 6 h, 82%; (e) (i) $NaIO_4$, acetone–water (3 : 1), 0 to 15 °C, 1.5 h; (ii) $NaBH_4$, EtOH, 15 °C, 15 min, 93%. (f) (i) TFA–water (6 : 4), 0 to 25 °C, 3 h; (ii) $HCOONH_4$, 10% Pd/C, MeOH, reflux, 1.5 h, 58%; (g) (i) TFA–water (9.5 : 0.5), 0 °C, 4 h; (ii) $NaIO_4$, acetone–water (8 : 2), 0 °C, 2 h. (h) $HCOONH_4$, 10% Pd/C, reflux, 3 h, 46%; (i) MeOH.HCl, 0 to 25 °C, 3 h, 98%.

The utility of α-hydroxy-β-aminoester **6** was also demonstrated by the synthesis of the new azasugar analogues **1c** and **2c** (Scheme 3). Thus, the reduction of the ester functionality in **6** with LAH in THF followed by treatment with ammonium formate in the presence of 10% Pd/C, in methanol, afforded an aminotriol that was reacted with benzylchloroformate to give the *N*-Cbz protected triol **9**. The cleavage of 1,2-acetonide group and hydrogenation afforded 1,5-dideoxy-1,5-imino-6-hydroxy-β-L-*glycero*-L-*ido*-heptitol **1c** as a thick oil. In order to prepare the new pyrrolidine alkaloid 1,4-dideoxy-1,4-imino-5-hydroxy-L-iditol **2c** the same protocol as in the synthesis of **2b** was followed. Thus, the *N*-Cbz protected triol **9** was reacted with acetic anhydride in pyridine to give the tri-acetylated compound **10**. The careful cleavage of 1,2-acetonide functionality in **10**, at 0 °C with 95% TFA–water followed by oxidative cleavage of the C1–C2 bond and treatment with ammonium formate and 10% Pd/C in methanol yielded a product[27] which on treatment with sodium methoxide in methanol at 0 °C afforded 1,4-dideoxy-1,4-imino-5-hydroxy-L-iditol **2c** as a white solid.



Scheme 3 *Reagents and conditions*: (a) (i) LAH, THF, 0 to 25 °C, 2 h; (ii) $HCOONH_4$, 10% Pd/C, MeOH, reflux, 2 h; (iii) CbzCl, MeOH–H_2O (9 : 1), 0 to 25 °C, 3.5 h, 82%; (b) (i) TFA–H_2O (2 : 1), 0 to 25 °C, 4 h; (ii) H_2, 10% Pd/C, 80 psi, 24 h, 75%; (c) Ac_2O, py, DMAP, 0 to 25 °C, 6 h, 86%; (d) (i) TFA–H_2O (9.5 : 0.5), 0 °C, 2.5 h; (ii) $NaIO_4$, acetone–water (5 : 1), 0 °C, 1.5 h; (iii) $HCOONH_4$, 10% Pd/C, MeOH, reflux, 3 h; (iv) NaOMe, MeOH, 25 °C, 3 h, 45%.

Conformational analysis

We have recently reported that the D-*gluco*-homo-1-deoxynojirimycin and L-*ido*-homo-1-deoxynojirimycin exist in $^4C_1$ and $^1C_4$ conformations, respectively.[17d,e] The conformational aspect of hitherto unknown **1c** was studied by using ^{1}H NMR data wherein the assignment of signals and coupling constant information were obtained from decoupling experiments. In the ^{1}H NMR spectrum of **1c**, the appearance of a doublet of doublets corresponding to the H1a proton with one large geminal ($J_{1a,1e}$ = 14.3 Hz) and an other small vicinal ($J_{1a,2}$ = 3.2 Hz) coupling indicated a *cis* axial–equatorial relationship with the H2 proton. The initial geometry in the precursor **9** ensures that in the product **1c** the substituent at C2/C3 should be *trans*. Therefore, the proton at H3 should be equatorial. The coupling constant value between H4 and H5 was evident from the decoupling experiments and was found to be ($J_{4,5}$ = 2.0 Hz). The low coupling constant corresponds to the equatorial–axial relationship between H4 and H5 protons, thus indicating the $^1C_4$ conformation.

Glycosidase inhibitory study

The IC_{50} values were determined for the compounds **1b**, **c** and **2b**, **c** and are summarized in Table 1. All the compounds showed inhibitory potencies in millimolar range. These results are in consonance with the IC_{50} value reported by Kato *et al.* for compound **1b** wherein it shows no inhibition in micromolar range.[14s] The compound **2b** showed selectivity towards α-glycosidases while compound **1c** is selective towards α-galactosidase.

Table 1 Inhibitory potencies of piperidine (**1b/c**) and Pyrrolidine (**2b/c**) analogues

	IC_{50}/mM			
Enzyme	**1b**	**1c**	**2b**	**2c**
α – *Glucosidase*(*yeast*)	NI[a]	NI[a]	22.6	NI
β-Glucosidase (almond)	2.57	51.8	NI	85.22
α-Galactosidase (almond)	3.19	2.88	5.89	NI[a]
α-Mannosidase (jack bean)	4.72	10.31	9.96	187.5

[a] NI: Inhibition not observed under assay conditions. Data is average of three sets of assay performed.

Conclusion

In conclusion, we have reported a new aziridine carboxylate chiron synthon **5** from D-glucose and demonstrated that the aziridine ring opening takes place α to the carboxylate although the ring nitrogen is not activated with electron withdrawing group. The utility of **5** is demonstrated in the synthesis of six membered piperidine alkaloids **1b**, **c** and five membered pyrrolidine alkaloids **2b**, **c**. The target molecules showed poor glycosidase inhibition indicating that the L-azasugars with hydroxyl functionality at the C6 side chain are not good candidates for inhibition study.

Experimental

Single crystals of compound **5** suitable for X-ray diffraction were selected directly from the analytical samples.

Crystal structure determination of compound 5

Crystal data‡. $C_{26}H_{31}N_1O_6$, $M = 453.52$, monoclinic, $a = 9.934(4)$ Å, $b = 5.408(2)$ Å, $c = 22.042(1)$, $U = 1176.3(8)$ Å^3, $T = 293(2)$ K, space group $P2_1$, $Z = 2$, μ(Mo Kα) $= 0.091$ mm^{-1}, 5045 reflections measured, unique ($R_{int} = 0.0408$) which were used in all calculations. The final w$R(F^2)$ was 0.1554 (all data). The Flack parameter −0.6555 (with esd 3.0219) is inconclusive and therefore no conclusions on the absolute structure can be drawn

General methods

Melting points were recorded with Thomas Hoover melting point apparatus and are uncorrected. IR spectra were recorded with Shimadzu FTIR-8400 as a thin film or in nujol mull or using KBr pellets and are expressed in cm^{-1}. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded with Varian Mercury 300 using $CDCl_3$ or D_2O as a solvent. Chemical shifts were reported in δ unit (ppm) with reference to TMS as an internal standard and J values are given in Hz. Elemental analysis were carried out with Elemental Analyser Flash 1112. Optical rotations were measured using a Bellingham Stanley-ADP digital polarimeter with sodium light (589.3 nm) at 25 °C. Thin layer chromatography was performed on Merck pre-coated plates (0.25 mm, silica gel 60 F_{254}). Column chromatography was carried out with silica gel (100–200 mesh). The reactions were carried out in oven-dried glassware under dry N_2. Methanol, DMF, THF were purified and dried before use. Petroleum ether (PE) that was used is a distillation fraction between 40–60 °C. LAH, CbzCl, 10% Pd–C were purchased from Aldrich and/or Fluka. After decomposition of the reaction with water, the work-up involves washing of combined organic layer with water, brine, drying over anhydrous sodium sulfate and evaporation of solvent at reduced pressure. For enzyme inhibition studies substrates were purchased from Sigma Chemicals Co., USA. α-Glucosidase from yeast and α-mannosidase from jack bean were purchased from Sigma Chemicals Co. USA. α-Glucosidase and β-galactosidase were extracted and purified from sweet almonds and used.

‡ CCDC reference numbers 276962. See http://dx.doi.org/10.1039/b509216g for crystallographic data in CIF format.

(*E*)-6-Bromo-ethyl-3-*O*-benzyl-5-deoxy-1,2-*O*-isopropylidene-hept-5-eno-furanuronate 4. To the solution of α-D-*xylo*-pentodialdose **3** (10 g, 35 mmol) in dry dichloromethane (250 cm^3) was added bromophosphorane, $PPh_3CBrCOOEt$ (17.72 g, 43 mmol) and stirred at 25 °C for 12 h. The reaction mixture was concentrated on vacuum and purified by column chromatography on silica (*n*-hexane–ethyl acetate = 95 : 5) to afford alkene **4** (11 g, 77%) as a thick liquid (Found: C, 53.52; H, 5.32. Calc. for $C_{19}H_{23}O_6Br$: C, 53.41; H, 5.43); R_f 0.67 (30% ethyl acetate–*n*-hexane); $[\alpha]_D$ −103.0 (*c* 11.77, $CHCl_3$); ν_{max} (neat)/cm^{-1}1741, 1230, 1637, 866 and 740. δ_H (300 MHz, $CDCl_3$) 1.36 (3H, t, $J = 7.0$ Hz, CH_2CH_3), 1.37 (3H, s, CH_3) 1.55 (3H, s, CH_3), 4.28 (1H, d, $J = 3.2$ Hz, *H*3), 4.34 (2H, q, $J = 7.0$ Hz, CH_2CH_3), 4.50 (1H, d, $J = 11.8$ Hz, OCH_2Ph), 4.65 (1H, d, $J = 11.8$ Hz, OCH_2Ph), 4.68 (1H, d, $J = 3.6$ Hz, *H*2), 5.05 (1H, dd, $J = 6.5$ and 3.2 Hz, *H*4), 6.06 (1H, d, $J = 3.6$ Hz, *H*1), 7.23–7.44 (5H, m, Ar–*H*), 7.50 (1H, d, $J = 6.5$ Hz, *H*5); δ_C (75 MHz, $CDCl_3$) 14.2 (CH_2CH_3), 26.3, 26.9 (2 × CH_3), 62.7 (OCH_2CH_3), 72.4 (OCH_2), 80.5, 82.4, 82.7 (*C*2/*C*3/*C*4), 105.1 (*C*1), 111.9 (*OC*O), 116.6 (*C*6), 127.6 (strong), 127.8, 128.3 (strong), 136.8 (Ar–*C*), 141.3 (*C*5), 161.3 (*C*O).

Ethyl-3-*O*-benzyl-5,6-*N*-benzyl-*E*-aziridine-1,2-*O*-isopropylidene-5,6-dideoxy-*β*-L-*ido*-heptofuranuronate 5. To a cooled solution of **4** (0.4 g, 0.94 mmol) in dry benzene (0.4 cm^3) was added benzylamine (1.37 cm^3, 1.4 mmol) drop by drop at 10 °C and allowed to stirred well at 25 °C for 6 h, the excess of benzyl amine was removed on vacuum and the reaction mixture was diluted with ether and filtered. The filtrate was concentrated and purified by column chromatography on silica (*n*-hexane–ethyl acetate, 9 : 1) to afford **5** (0.29 g, 70%) as a white solid, mp 95–97 °C (Found: C, 68.80; H, 6.79. Calc. for $C_{26}H_{31}NO_6$: C, 68.86; H, 6.89); R_f 0.52 (30% ethyl acetate–*n*-hexane); $[\alpha]_D$ −71.69 (*c* 0.27, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 1720.4, 1458.1 and 1242; δ_H (300 MHz, $CDCl_3$) 1.18 (3H, t, $J = 7.0$ Hz, CH_2CH_3), 1.35 (3H, s, CH_3), 1.48 (3H, s, CH_3) 2.62 (1H, d, $J = 2.9$ Hz, *H*6), 2.90 (1H, dd, $J = 7.0$, 2.9 Hz, *H*5), 3.60–4.00 (3H, m, *H*3, *H*4, NCH_2Ph), 4.06–4.20 (2H, m, CH_2), 4.29 (1H, d, $J = 13.7$ Hz, NCH_2Ph), 4.54 (1H, d, $J = 12.0$ Hz, OCH_2Ph), 4.67 (1H, d, $J = 3.8$ Hz, *H*2), 4.75 (1H, d, $J = 12.0$ Hz, OCH_2Ph), 6.04 (1H, d, $J = 3.8$ Hz, *H*1), 7.24–7.39 (10H, m, Ar–*H*); δ_C (75 MHz, $CDCl_3$) 13.9 (CH_2CH_3), 26.2, 26.8 (2 × CH_3), 37.1 (*C*5), 45.0 (*C*6), 54.9 (NCH_2Ph), 61.1(OCH_2CH_3), 71.8 (OCH_2Ph), 82.1 (strong) (*C*2/*C*3/*C*4), 105.3 (*C*1), 111.7 (*OC*O), 126.8 (strong), 127.6, 127.9 (strong), 128.1, 128.2, 128.4, 137.2, 138.8 (Ar–*C*), 168.5 (*C*O).

Ethyl-3-*O*-benzyl-5-(*N*-benzyl)amino-1,2-*O*-isopropylidene-*β*-L-*glycero*-L-*ido*-heptofuranuronate 6. To a solution of **5** (1 g, 2.20 mmol) in acetone–water (2 : 1, 20 cm^3) at 10 °C was added TFA (0.17 cm^3, 2.20 mmol) and stirred well for 24 h at 25 °C. After neutralization of TFA with sat. sodium bicarbonate solution, reaction mixture was concentrated on rotavapor, extracted with dichloromethane (3 × 10 cm^3). The combined organic layer was concentrated to afford a pale yellow liquid, which was purified by column chromatography on silica (*n*-hexane–ethyl acetate = 4 : 1) to give **6** (0.82 g, 82.0%) as a thick liquid (Found: C, 66.38; H, 7.10. Calc. for $C_{26}H_{33}NO_7$: C, 66.22; H, 7.05); R_f 0.56 (30% ethyl acetate–*n*-hexane); $[\alpha]_D$ −48.65 (*c* 0.19, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3050–3700 (broad), 2925, 1739, 1213; δ_H (300 MHz, $CDCl_3$) 1.25 (3H, t, $J = 7.0$ Hz, CH_3), 1.36 (3H, s, CH_3), 1.51 (3H, s, CH_3), 2.20–3.20 (2H, b s, N*H*/O*H* exchangeable with D_2O,), 3.55 (1H, dd, $J = 8.7$, 3.5 Hz, *H*5), 3.86 (1H, d, $J = 12.8$ Hz, N–CH_2Ph), 4.06 (1H, d, $J = 12.8$ Hz, NCH_2Ph), 4.08 (1H, d, $J = 3.2$ Hz, *H*3), 4.10–4.22 (3H, m, O–CH_2CH_3, *H*6), 4.30 (1H, dd, $J = 8.7$ and 3.2 Hz, *H*4), 4.52 (1H, d, $J = 11.7$ Hz, OCH_2Ph), 4.68 (1H, d,

J = 3.9 Hz, $H2$), 4.74 (1H, d, J = 11.7 Hz, OCH_2Ph), 5.99 (1H, d, J = 3.9 Hz, $H1$), 7.27–7.42 (10H, m, Ar–H); δ_C (75 MHz, $CDCl_3$) 14.0, 26.2, 26.6 (CH_3), 52.8 (N–CH_2Ph), 59.3 ($C5$), 61.3 (O–CH_2CH_3), 70.1 (O–CH_2Ph), 71.4 ($C6$), 80.8, 81.7 (strong) ($C2/C3/C4$), 104.5 ($C1$), 111.5 (OCO), 127.0 (strong), 127.1, 127.8, 128.1, 128.3, 128.4, 128.5, 136.8, 138.8 (Ar–C), 172.8 (COOEt).

5-(N-Benzyl-benzoxycarbonyl)amino-3-O-benzyl-6,7-dihydroxy-5deoxy-1,2-O-isopropylidene-β-L-glycero-L-*ido*-hepto-1,4-furanose 7. A solution of **6** (0.6 g, 0.24 mmol) in tetrahydrofuran (2 cm^3) was added cautiously drop by drop over 5 min to a stirred solution of lithium aluminum hydride (0.19 g, 4.88 mmol) in THF (3 cm^3) at 0 °C. The mixture was stirred in an atmosphere of nitrogen for 2 h at 25 °C, and quenched by careful addition of ethyl acetate and saturated aqueous ammonium chloride, filtered, concentrated and dried. To this reduced product (0.41 g, 0.93 mmol) in methanol–water (4 : 1) at 10 °C, sodium bicarbonate (0.22 g, 2.6 mmol) and benzylchloroformate (0.16 cm^3, 1.12 mmol) were added and stirred for 6 h at 25 °C. The reaction mixture was concentrated under vacuum and then extracted with dichloromethane (4 × 10 cm^3). The combined organic layers were dried and evaporated under reduced pressure to leave a viscous liquid, which was purified by column chromatography (*n*-hexane–ethyl acetate = 7 : 3) afforded **7** (0.48 g, 88.88%) as a thick liquid (Found: C, 68.00; H, 6.25. Calc. for $C_{32}H_{37}NO_8$: C, 68.19; H, 6.62); R_f 0.50 (50% ethyl acetate–*n*-hexane); $[\alpha]_D$ −18.88 (*c* 1.69, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3150–3600 (broad), 2929, 1685, 1232; the ^{1}H and ^{13}C NMR of this compound showed a doubling of signals due to restricted rotation around the C–N bond of urethane hence only relatively high intensity signals are given. δ_H (300 MHz, $CDCl_3$) 1.34 (6H, s, CH_3), 1.52 (3H, s, CH_3), 1.60–2.20 (2H, b s, 2–OH, exchangeable with D_2O), 3.10 (1H, dd, J = 11.2 and 3.2 Hz, $H5$), 3.24–3.38 (1H, m, N–CH_2Ph), 3.90–3.99 (1H, m, NCH_2Ph), 4.14 (2H, m, $H3$, $H4$), 4.47 (2H, d, J = 11.7 Hz, O–CH_2Ph, $H6$), 4.67 (1H, d, J = 11.7 Hz, O–CH_2Ph), 4.70 (1H, d, J = 3.5 Hz, $H2$), 4.78 (2H, b s, $H7$), 5.18 (2H, m, N–COOCH_2Ph), 5.57 (1H, d, J = 3.5 Hz, $H1$), 7.17–7.34 (15H, m, Ar–H); δ_C (75 MHz, $CDCl_3$) 26.3, 26.5 (CH_3), 54.9, 55.0 (N–CH_2Ph/$C5$), 62.8 (O–CH_2Ph), 67.3 ($C6$), 71.0 ($C7$), 81.8, 82.1(strong) ($C2/C3/C4$), 103.6 ($C1$), 111.4(OCO), 127.2, 127.4, 127.5, 127.6, 127.7, 128.2, 129.5, 136.0, 137.1, 137.4 (Ar–C), 157.1 (N–COOCH$_2$Ph).

Preparation of 5-(N-benzyl-benzoxycarbonyl)amino-3-O-benzyl-5-deoxy-6-hydroxy-1,2-O-isopropylidene-β-L-*ido*-hexo-1,4-furanose 8. *1. Conversion of diol 7 to 6-aldehydo-5-(*N*-benzyl-benzoxycarbonyl)amino-3-*O*-benzyl-5-deoxy-1,2-*O*-isopropylidene-β-L-*ido*-hexo-1,4-furanose* To the Cbz protected product **7** (0.25 g, 0.36 mmol) in acetone–water (3 : 1, 5 cm^3) was added metaperiodate (0.09 g, 0.44 mmol) at 15 °C and stirred well for 1 h. Excess metaperiodate was decomposed by using ethylene glycol (0.01 cm^3), concentrated under vacuum extracted with chloroform (4 × 10 cm^3) and concentrated to afford a thick liquid, which was purified by column chromatography on silica (*n*-hexane–ethyl acetate, 4 : 1) to give aldehyde (0.17 g, 70%) in the form of a thick liquid (Found: C, 70.02; H, 6.22. Calc. for $C_{31}H_{33}NO_7$: C, 70.04; H, 6.26.); R_f 0.56 (30% ethyl acetate–*n*-hexane); $[\alpha]_D$ + 12.21 (*c* 0.65, $CDCl_3$); ν_{max}(nujol)/cm^{-1} 3200–3600 (broad); δ_H (300 MHz, $CDCl_3$) and δ_C (75 MHz, $CDCl_3$) Both ^{1}H NMR and ^{13}C NMR spectra were very complicated due to doubling of signals.

*2. Convertion of aldehyde to 5-(*N*-benzyl-benzoxycarbonyl)-amino-3-*O*-benzyl-5-deoxy-6-hydroxy-1,2-*O*-isopropylidene-β-L-*ido*-hexo-1,4-furanose **8**.* To the solution of aldehyde (0.12 g, 0.28 mmol) in ethanol–water (2 : 1, 3 cm^3) was added sodium borohydride (0.01 g, 0.28 mmol) at 15 °C and stirred well for 15 min. Excess borohydride was quenched using sat. NH_4Cl solution, concentrated and extracted with chloroform and purified by column chromatography (*n*-hexane–ethyl acetate = 9 : 1) to yield alcohol **8** (0.11 g, 93%) in the form of white solid; mp 97–99 °C (Found: C, 69.77; H, 6.59. Calc. for $C_{31}H_{35}NO_7$: C, 69.78; H, 6.61); R_f 0.34 (30% ethyl acetate–*n*-hexane); $[\alpha]_D$ +13.33 (*c* 0.15, $CDCl_3$); ν_{max}(KBr)/cm^{-1} 3502 (broad), 2904, 1676, 1253; δ_H (300 MHz, $CDCl_3$) 1.32 (3H, s, CH_3), 1.49 (3H, s, CH_3), 3.58–3.74 (3H, m, 2 × $H6$, $H5$), 4.15 (1H, d, J = 1.9 Hz, $H3$), 4.22 (1H, d, J = 15.8 Hz, NCH_2Ph), 4.47 (1H, d, J = 11.7 Hz, OCH_2Ph), 4.62 (1H, d, J = 3.5 Hz, $H2$), 4.65 (1H, d, J = 11.7 Hz, OCH_2Ph), 4.86 (1H, dd, J = 9.0 and 1.9 Hz, $H4$), 4.98 (1H, d, J = 15.8 Hz, NCH_2Ph), 5.16 (2H, ABq, J = 12.6 Hz, N–COOCH_2Ph), 5.99 (1H, d, J = 3.5 Hz, $H1$), 7.20–7.30 (15H, m, Ar–H); δ_C (75 MHz, $CDCl_3$) 26.3, 26.7 (CH_3), 53.7 (C5), 60.8 (NCH_2Ph), 63.3 (N–COOCH_2Ph), 67.4 ($C6$), 71.8 (O–CH_2Ph), 77.7, 81.6, 81.9 ($C2/C3/C4$), 104.5 ($C1$), 111.7 (OCO), 127.2, 127.5, 127.6, 127.7, 127.9, 128.4, 136.1, 137.1, 137.9 (Ar–C), 157.6 (N–COOCH$_2$Ph).

1,5-Dideoxy-1,5-imino-(2*S*, 3*R*, 4*R*, 5*S*)-L-iditol (1-deoxy-L-*ido*-nojirimycin) 1b. A cooled solution of **8** (0.18 g, 0.33 mmol) in TFA–water (2 : 1, 3 mL) was stirred for 3 h at 25 °C. TFA was co-evaporated with benzene to furnish a thick liquid, which was treated with ammonium formate and 10% Pd/C in methanol at reflux for 1.5 h. The reaction mixture was filtered, concentrated and purified by column chromatography on silica (chloroform–methanol, 1 : 1) to give **1b** (0.032 g, 58.1%) as a thick liquid (Found: C, 44.23; H, 8.00. Calc. for $C_6H_{13}NO_4$: C, 44.16; H, 8.03); R_f 0.20 (60% methanol–chloroform); $[\alpha]_D$ +7.9 (*c* 0.25, MeOH), lit.[14s] $[\alpha]_D$ +8.49 (*c* 0.5, MeOH)]; ν_{max}(nujol)/cm^{-1} 3200–3600 (broad band); δ_H (300 MHz, D_2O) 2.72 (1H, dd, J = 13.1 and 7.3 Hz, $H1$a), 2.91 (1H, dd, J = 13.1 and 3.3 Hz, $H1$e), 3.08–3.14 (1H, m, $H5$) 3.50–3.58 (2H, m, $H6$), 3.60–3.69 (3H, m, $H2/H3/H4$); δ_C (75 MHz, D_2O) 44.0 ($C1$), 56.3 ($C5$), 57.7 ($C6$), 69.2, 69.8, 71.3 ($C2/C3/C4$).

1,4-Dideoxy-1,4-imino-L-xylitol 2b. A solution of **8** (0.45 g, 0.84 mmol) in TFA–water (3 : 2, 5 cm^3) was stirred for 4 h at 25 °C. TFA was co-evaporated with benzene to furnish hemiacetal as a thick liquid. To the cooled solution of hemiacetal in acetone–water (5 : 1, 10 cm^3) was added sodium metaperiodate (0.17 g, 1.04 mmol). After stirring the reaction mixture for 2 h at 20 °C the excess sodium metaperiodate was neutralized using ethylene glycol (0.2 cm^3). The reaction mixture was concentrated and the residue was extracted with chloroform (3 × 15 cm^3). The combined organic layer was concentrated to afford a yellow liquid, which was purified by column chromatography on silica (*n*-hexane–ethyl acetate, 4 : 1) to give aldehyde as a thick liquid. The aldehyde was directly subjected for ammonium formate treatment in methanol (8 cm^3) and 10% Pd/C (0.10 g). After refluxing for 3 h the reaction mixture was filtered and purified by column chromatography (chloroform–methanol, 1 : 1) to give **2b** (0.049 g, 45.53%) as a thick liquid (Found: C, 44.90; H, 8.23. Calc. for $C_5H_{11}NO_3$: C, 45.1; H, 8.33); R_f 0.25 (60% methanol–chloroform); $[\alpha]_D$ −7.4 (*c* 0.54, MeOH); ν_{max}(neat)/cm^{-1} 3200–3600 (broad); δ_H (300 MHz, D_2O) 3.29 (1H, d, J = 12.9, 4.1 Hz, $H1$a), 3.65 (1H, dd, J = 12.9 and 4.1 Hz, $H1$e), 3.85–3.95 (2H, m, $H4$, $H5$a), 3.96–4.08 (1H, m, $H5$b), 4.33 (1H, m, $H3$), 4.34–4.42 (1H, m, $H2$); δ_C (75 MHz, D_2O) 50.4 ($C1$), 57.1 ($C4$), 62.9 ($C5$), 74.1, 74.2 ($C2/C3$).

1,4-Dideoxy-1,4-imino-L-xylitol hydrochloride 2b·HCl. A solution of **2b** (0.012 g, 0.09 mmol) in methanolic hydrochloric acid (5 cm^3) was stirred under nitrogen at 0 °C and stirred for 3 h at 25 °C. The reaction mixture was concentrated on vacuum to afford **2b·HCl** (0.015 g, 98%) as a semi solid (Found: C, 36.5; H, 7.4. Calc. for $C_5H_{12}NO_3Cl$: C, 36.1; H, 7.3); $[\alpha]_D$ −9.4 (*c* 0.74, H_2O), lit. $[\alpha]_D$ −9.9 (*c* 0.71, H_2O);[15b,d] ν_{max}(nujol)/cm^{-1} 3200–3600 (broad); δ_H (300 MHz, D_2O) 3.32 (1H, d, J = 12.9 Hz, $H1$a), 3.68 (1H, dd, J = 12.9 and 4.4 Hz, $H1$b), 3.88–3.98 (2H, m, $H4$, $H5$a), 4.05 (1H, dd, J = 15.4 and 8.5 Hz, $H5$b), 4.34 (1H, m, $H3$), 4.41 (1H, m, $H2$); δ_C (75 MHz, D_2O) 52.7 ($C1$), 59.5 ($C5$), 65.2 ($C4$), 76.5, 76.6 ($C2/C3$).

5-(*N*-Benzoxycarbonyl)amino-3,6,7-trihydroxy-5-deoxy-1,2-*O*-isopropylidene-β-L-glycero-L-*ido*-hepto-1,4-furanose 9. A solution of **6** (0.6 g, 0.24 mmol) in tetrahydrofuran (2 cm^3) was added cautiously drop by drop over 5 min to a stirred solution of lithium aluminum hydride (0.19 g, 4.88 mmol) in THF (3 cm^3) at 0 °C. The mixture was stirred in an atmosphere of nitrogen for 2 h at 25 °C, and quenched by careful addition of ethyl acetate and saturated aqueous ammonium chloride, filtered, concentrated and dried. To it dry ethanol (5 cm^3), followed by 10% Pd/C (0.1 g) and ammonium formate (0.055 g, 6.96 mmol), was added and refluxed for 2 h under nitrogen. The reaction mixture was filtered through celite-540, concentrated and dried to afford an amino triol. The amino triol was dissolved in ethanol–water (4 : 1) at 10 °C, sodium bicarbonate (0.056 g, 0.67 mmol) and benzylchloroformate (0.041 cm^3, 0.29 mmol) were added and stirred for 3.5 h at 25 °C. The reaction mixture was concentrated under vacuum and extracted with dichloromethane (4 × 10 cm^3). The combined organic layers were dried and evaporated under reduced pressure to leave a viscous liquid, which was purified by column chromatography on silica (*n*-hexane–ethyl acetate, 7 : 3), afforded **9** (0.76 g, 82.6%) as a white solid, mp 132–135 °C (Found: C, 56.22; H, 6.28. Calc. for $C_{18}H_{25}NO_8$: C, 56.39; H, 6.57); R_f 0.37 (50% ethyl acetate–*n*-hexane); $[a]_D$ −13.33 (*c* 0.15, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3523–3477 (broad), 3413, 1706, 1521, 1238 and 1083; δ_H (300 MHz, CD_3OD) 1.23 (3H, s, CH_3), 1.42 (3H, s, CH_3), 3.59 (1H, dd, *J* = 11.7 and 5.8 Hz, *H*7a), 3.65 (1H, dd, *J* = 11.7 and 3.2 Hz, *H*7b), 3.74 (1H, ddd, *J* = 7.3, 5.8 and 3.2 Hz, *H*6), 4.07 (1H, t, *J* = 7.3 Hz, *H*5), 4.22 (1H, d, *J* = 2.6 Hz, *H*3), 4.34 (1H, dd, *J* = 7.3 and 2.6 Hz, *H*4), 4.55 (1H, d, *J* = 3.8 Hz, *H*2), 5.12 (2H, s, N-COOCH_2Ph), 5.91 (1H, d, *J* = 3.8 Hz, *H*1), 7.23–7.45 (5H, m, Ar–*H*); δ_C NMR (75 MHz, CD_3OD) 26.4, 27.0 (*C*H_3), 53.5 (*C*5), 64.6 (NCOO*C*H_2Ph), 67.6 (*C*7), 73.3 (*C*6), 76.3, 81.1, 87.0 (*C*2/*C*3/*C*4), 105.3(*C*1), 112.6 (O*C*O), 128.7, 128.8, 128.9, 129.4, 129.5, 138.3 (Ar–*C*), 159.0 (N*C*OOCH$_2$Ph).

1,5-Dideoxy-1, 5-imino-6-hydroxy-β-L-*glycero*-L-*ido*-heptitol 1c. To the Cbz protected amino triol **9** (0.04 g, 0.10 mmol), TFA–water (2 : 1, 3 cm^3) was added at 0 °C and stirred well for 4 h at 25 °C. TFA was co-evaporated with benzene to furnish a thick liquid. To a solution of above product in methanol (5 cm^3) was added 10% Pd/C (0.05 g) and hydrogenated at 80 psi for 24 h. The reaction mixture was filtered through celite-540 and filtrate was concentrated under vacuum to afford product **1c** (0.027 g, 75%) as thick liquid (Found: C, 44.01; H, 7.73. Calc. for $C_7H_{15}NO_5$: C, 43.52; H, 7.83); R_f 0.20 (80% methanol–chloroform); $[a]_D$ +1.28 (*c* 1.56, MeOH); ν_{max}(nujol)/cm^{-1} 3200–3600 (broad); δ_H (300 MHz, D_2O) 2.75 (1H, dd, *J* = 14.3 and 3.2 Hz, *H*1a), 2.87 (1H, dd, *J* = 7.9 and 2.0 Hz, *H*5), 2.91 (1H, dd, *J* = 14.3 and 2.9 Hz, *H*1e), 3.49 (1H, dd, *J* = 12.0 and 6.4 Hz, *H*7a), 3.53–3.59 (1H, m, *H*2), 3.63 (1H, dd, *J* = 12.0 and 3.5 Hz, *H*7b), 3.71 (1H, ddd, *J* = 7.9, 6.4 and 3.5 Hz, *H*6), 3.74–3.80 (2H, m, *H*3, *H*4); δ_C NMR (75 MHz, D_2O) 45.6 (*C*1), 54.3 (*C*5), 63.2 (*C*7), 67.7, 68.2, 68.9 (*C*2/*C*3/*C*4), 70.3 (*C*6).

3,6,7-Tri-*O*-acetyl-5-(*N*-benzoxycarbonylamino)-5-deoxy-1,2-*O*-isopropylidine-β-L-*glycero*-L-*ido*-heptofuranose 10. To an ice-cold solution of triol **9** (0.32 g, 0.83 mmol) in pyridine (5 cm^3), acetic anhydride (0.51 cm^3, 4.98 mmol) was added and stirred well for 6 h at 25 °C. The excess of pyridine and acetic anhydride was removed under vacuum and purified by column chromatography on silica (*n*-hexane–ethyl acetate, 4 : 1) to afford triacetate **10** (0.36 g, 86%) as a white solid; mp 109–111 °C (Found: C, 56.22; H, 6.28. Calc. for $C_{19}H_{25}N_3O_7$: C, 56.01; H, 6.18); R_f 0.38 (30% ethyl acetate–*n*-hexane); $[a]_D$ −24.77 (*c* 0.56, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3338, 1728, 1537 and 1234; δ_H (300 MHz, $CDCl_3$) 1.32 (3H, s, CH_3), 1.50 (3H, s, CH_3), 1.93 (3H, s, COCH_3), 2.08 (6H, s, COCH_3), 4.18 (1H, dd, *J* = 12.0 and 5.5 Hz, *H*5), 4.28–4.54 (4H, m, *H*4, *H*6, *H*7, *H*2), 4.95–5.40 (5H, m, *H*3, *H*7, NCOOCH_2Ph, N*H*), 5.93 (1H, d, *J* = 3.5 Hz, *H*1), 7.29–7.37 (5H, m, Ar–*H*); δ_C (75 MHz, $CDCl_3$) 20.2, 20.4, 20.5 (CO*C*H_3), 25.8, 26.3 (*C*H_3), 48.9 (*C*5), 61.7 (NCOO*C*H_2Ph), 66.6 (*C*6), 71.4 (*C*7), 75.3, 76.5, 83.1 (*C*2/*C*3/*C*4), 104.0 (*C*1), 111.9 (O*C*O), 127.8, 128.2, 135.9 (Ar–*C*), 155.8 (N*C*OOCH$_2$Ph), 169.6, 169.7, 170.3 (*C*OCH$_3$).

1,4-Dideoxy-1,4-imino-5-hydroxy-L-iditol 2c. A solution of triacetate **10** (0.63 g, 1.13 mmol) in TFA–water (9.5 : 0.5, 5 cm^3) was stirred at 0 °C for 3 h. TFA was co-evaporated with benzene to furnish a hemiacetal as a thick liquid. To the ice-cooled solution of hemiacetal in acetone–water (5 : 1, 10 cm^3) was added $NaIO_4$ (0.34 g, 1.59 mmol) and stirred well for 1.5 h at 15 °C. Work up as usual and purified by column chromatography on silica afforded aldehyde which was directly treated with ammonium formate in the presence of catalytic amount of 10% Pd/C in methanol and refluxed for 3 h to yield mixture of acetylated product that was deacetylated using sodium methoxide in methanol at 25 °C for 3 h and purified by column chromatography (chloroform–methanol, 1 : 1) afforded **2c** (0.038 g, 45.23%) as a white solid; mp 118–120 °C (Found: C, 43.9; H, 8.02. Calc. for $C_6H_{13}NO_4$: C, 44.1; H, 8.03); R_f 0.20 (60% methanol–chloroform); $[a]_D$ +8.75 (*c* 0.8, MeOH); ν_{max}(neat)/cm^{-1}3200–3600 (broad); δ_H (300 MHz, D_2O) 2.66 (1H, dd, *J* = 12.8 and 1.0 Hz, *H*1a), 3.06 (1H, dd, *J* = 9.3 and 3.3 Hz, *H*4), 3.18 (1H, dd, *J* = 12.8 and 4.8 Hz, *H*1b), 3.44 (1H, dd, *J* = 11.9 and 6.5 Hz, *H*6a), 3.62 (1H, dd, *J* = 11.9 and 3.0 Hz, *H*6b), 3.69 (1H, ddd, *J* = 9.3, 6.5 and 3.3 Hz, *H*5), 4.00–4.06 (2H, m, *H*2, *H*3); δ_C (75 MHz, D_2O) 51.2 (*C*1), 60.9 (*C*4), 63.9 (*C*6), 69.3 (*C*5), 75.9, 76.0 (*C*2/*C*3).

General procedure for inhibition assay

Inhibition potencies of **1b/1c** and **2b/2c** were determined by measuring the residual hydrolytic activities of the glycosidases. The substrates (Purchased from Sigma Chemicals Co. USA.) namely *p*-nitrophenyl-α-D-glucopyranoside, *p*-nitrophenyl-β-D-glucopyranoside and *p*-nitrophenyl-α-D-galactopyranoside, of 2 mM concentration were prepared in 0.025 M citrate buffer with pH 6.0. *p*-Nitrophenyl-α-D-mannopyranoside of 2 mM was prepared in 0.025 M citrate buffer with pH 4.0. The test compound was preincubated with the respective enzyme buffered at their optimal pH, for 1 h at 25 °C. The enzyme reaction was initiated by the addition of 100 μL substrate. Controls were run simultaneously in absence of test compound. The reaction was terminated at the end of 10 min by the addition of 0.05 M borate buffer (pH 9.8) and absorbance of the liberated *p*-nitrophenol was measured at 405 nm using Shimadzu Spectrophotometer UV-1601.[28] One unit of glycosidase activity is defined as the amount of enzyme that hydrolyzed 1 μmol of *p*-nitrophenyl pyranoside per minute at 25 °C.

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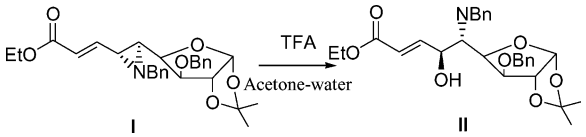
25 The effect of –*O*Bn substituent at C3 was also noticed with substrate **I** which under similar reaction conditions resulted into the regio-selective ring opening at C6 carbon leading to the formation of product **II**.



I II

26 The ^{1}H and ^{13}C NMR spectra of the compounds **7** and **8** showed doubling of signals due to the restricted rotation around C–N bond of urethane functionality. This type of phenomenon is general with *N*-Cbz protected compounds.[17].

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