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Concise and practical route to tri- and tetra-hydroxy seven-membered iminocyclitols as glycosidase inhibitors from D-(+)-glucurono-γ-lactone

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ABSTRACT

An efficient and short total synthesis of tetrahydroxy-**1c** and trihydroxy-azepane **1d** is reported in 72% and 57% overall yields, respectively, from D-(+)-glucurono-γ-lactone. Thus, D-glucuronolactone **2** on acetonide protection, DIBAL-H reduction and one-pot intermolecular reductive amination followed by −*N*Cbz protection afforded 6-(*N*-benzyl-*N*-benzyloxycarbonyl) amino-6-deoxy-1,2-*O*-isopropylidene-α-D-*gluco*-1,4-furanose **5a**. 1,2-Acetonide hydrolysis in **5a** and Pd-mediated intramolecular reductive aminocyclization afforded tetrahydroxyazepane **1c**. An analogous pathway with 5-deoxy-1,2-*O*-isopropylidene-α-D-glucurono-6,3-lactone **3b** gave trihydroxy-azepane **1d**. Glycosidase inhibitory activity of **1c**/**1d** was studied and **1d** was found to be potent inhibitor of α-mannosidase and β-galactosidase.

1. Introduction

Iminosugars are known for their potential therapeutic applications in the treatment of cancer,[1] diabetes,[2] Gaucher's disease,[3] and the viral infections including HIV[4] due to their glycosidase inhibitory activity. Amongst monocyclic iminosugars[5] the seven-membered iminocyclitols, commonly known as azaseptanoses or polyhydroxy azepanes,[6] also demonstrate potent glycosidase[7] and glycosyltransferase inhibitory activity.[8] Due to flexibility of seven-membered ring (compared with five and six-membered-ring) polyhydroxylated azepanes **1** (Fig. 1) adopt different pseudo-half-chair conformations, required to mimic the putative oxo-carbenium ion like TS with minimum energetic demand, thus favoring binding to the enzyme active site in the glycosidase process.[9] As a result, polyhydroxylated azepanes were found to be potent glycosidase inhibitors and in some cases proven to be more active than their lower ring analogues. For example, tetrahydroxy azepane **1a** is a better inhibitor of β-*N*-acetylglucosaminidase than 1-deoxy-*N*-acetylnojirimycin and **1b** is exhibiting higher α-mannosidase and β-galactosidase inhibitory activity than its six-membered ring analogues 1-deoxymannojirimycin and 1-deoxygalactonojirimycin, respectively.[10] In addition the high water solubility and flexibility of iminocycloheptitols allow the hydroxyl groups to adopt a variety of positions increasing the probability of them forming hydrogen bonds with the purine and pyrimidine bases, hence that make them potentially useful as DNA minor groove binding ligands (MGBL's).[11]

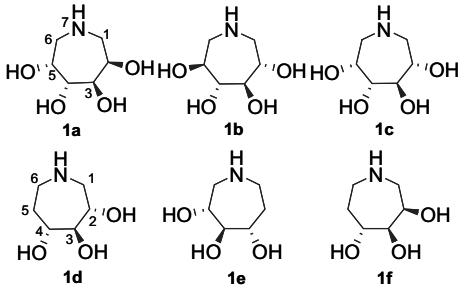

Fig. 1. Azepane iminocyclitols.

A number of syntheses for trihydroxy-[12,14a] and tetrahydroxy-azepanes[13,14b,c] along with their hydroxymethyl/acetamido analogues[15] are known in the literature. In general, chiron approaches to iminocycloheptitols make use of starting materials, such as *chiro*-inositols, L-serine, D-mannitol, *trans*-4-hydroxy-L-proline, D-glucose, and D-quinic acid. etc., whereas, in asymmetric approaches Prinzbach et al. illustrated a cyclooctatetraene route and Mehta and Lakshminath reported a norbornyl route toward the synthesis of novel polyhydroxylated azepanes.[15h,i] A chemo-enzymatic approach to various polyhydroxy azepanes has been reported independently by Wong and Wang groups.[10,13d]

As a part of our ongoing efforts in syntheses and investigation of biological activity of polyhydroxy azepanes and azocanes,[14] we

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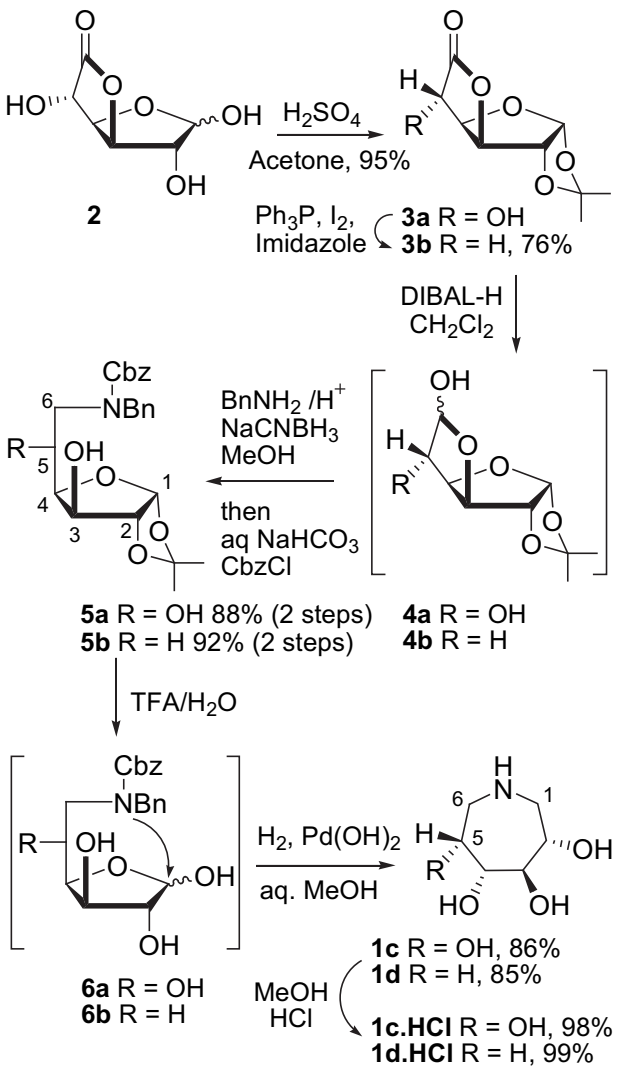
thought of exploiting D-glucurono lactone **2** (easily available by oxidation of amylose and commercially cheap as compared to diacetone D-glucose)[16] as a substrate in the synthesis of iminocyclitols **1c** and **1d**. The only one example reported, by Dax et al. using glucuronolactone derivative in the synthesis of tetrahydroxy azepane **1c** via the key step S_N2 displacement by an azide nucleophile, on 5-chloro-5-deoxy-1,2-*O*-isopropylidene-β-L-*ido*-furanose[13h] leading to the mixture of regio-isomeric products with low yields of target molecules. Here we report the short, high yielding and stereospecific synthesis, of D-*gluco*-configured tetrahydroxy-**1c** and D-*xylo*-configured trihydroxy-azepanes **1d** from D-glucurono-γ-lactone, and evaluation of their glycosidase inhibitory activity.

2. Result and discussion

As shown in Scheme 1, D-(+)-glucurono-6,3-lactone **2** was treated with acetone and concentrated H_2SO_4 to get the l,2-*O*-isopropylidene-α-D-glucofuranurono-6,3-lactone **3a** in 95% yield.[17] Reaction of γ-lactone **3a** with DIBAL-H in dichloromethane at −78 °C afforded lactol **4a** that was directly (without purification) subjected to the intermolecular reductive amination with benzyl amine, acetic acid (cat.) and $NaBH_3CN$ in methanol. The amine thus generated was treated, in the same pot, with aq sodium bicarbonate and benzyl chloroformate to give *N*-Cbz protected C-6 amino compound **5a**. (88% yield in two steps after column chromatography). Finally, hydrolysis of 1,2-acetonide functionality in **5a** using TFA/water (3:2) at 25 °C furnished C-1 anomeric mixture **6a** that was directly subjected to intramolecular reductive aminocyclization using 10% $Pd(OH)_2/C$ in aq methanol at 90 psi to afford tetrahydroxy azepane **1c** (86% in two steps) as a yellowish sticky solid. This one-pot three-step process involves hydrogenolysis of *N*-benzyl and *N*-Cbz functionalities, in situ formation of seven-membered cyclic-imine and concomitant reduction under hydrogenation conditions to give tetrahydroxy azepane **1c**. The specific rotation and spectral data of **1c** were found to be in agreement with that reported; $[\alpha]_D^{25}$ −24.2 (*c* 0.85, H_2O) [lit.[13h] $[\alpha]_D^{20}$ −23.0 (*c* 0.85, H_2O). Treatment of **1c** with methanol-HCl afforded hydrochloride salt **1c·HCl** (98%) whose spectral and analytical data was also found to be in consonance with that reported.[13h]



Scheme 1. Synthesis of **1c** and **1d**.

While targeting the synthesis of trihydroxy-azepane **1d**, we were in need of 5-deoxy-1,2-*O*-isopropylidene-glucuronolactone. Although different methods are known for the deoxygenation of **3a** to **3b**,[18] we adopted one-step process reported by Rauter et al.[18a] Thus lactone **3a** was reacted with triphenylphosphine, imidazole, and iodine at 60 °C for 3.5 h to give 5-deoxy-1,2-*O*-isopropylidene-D-glucurono-6,3-lactone **3b** as a crystalline solid in 76% yield. Reaction of lactone **3b** with DIBAL-H in anhydrous CH_2Cl_2 at −78 °C afforded lactol **4b**, as an anomeric mixture, that on reductive amination using benzyl amine and $NaBH_3CN$ in cat acetic acid afforded amine, which was (in same pot) treated with benzyl chloroformate and aq $NaHCO_3$ to get −*N*Cbz protected aminol **5b** in 93% yield in two steps after column chromatography. The −*N*Cbz protected aminol **5b** on treatment with 60% aq TFA and hydrogenation using 10% $Pd(OH)_2/C$ in methanol/H_2O (9:1) afforded trihydroxy-azepane **1d** in 85% yield in two steps. The spectral data were found to be in agreement that with reported by us and 'that with its enatiomer'.[12b,14a] The hydrochloride salt of **1d** is not known, therefore we treated **1d** with methanol/HCl that afforded hydrochloride salt **1d·HCl** in 98% yield whose spectral and analytical data were found to be in agreement with the structure.

2.1. Biological evaluation

Iminocyclitols **1c** and **1d** thus obtained as free bases were tested for their inhibitory activity against various glycosidases namely α-galactosidase, β-galactosidase, β-glucosidase, α-mannosidase, *N*-acetyl-β-glucosaminidase (all isolated from almond seeds), α-galactosidase (from *Geobacillus toebii* BK1), and α-glucosidase (from Baker's yeast-Sigma Chemical Co.). Thus, tetrahydroxy azepane **1c** showed a strong inhibitoin against α-galactosidase (K_i=5 μM) isolated from the green coffee beans.[10] Inhibition against β-glucosidase (inhibition=9%) isolated from almond seeds and α-glucosidase (inhibition=21%) from bakers yeast was insignificant[10] while, no significant inhibition was observed for **1c** against the other enzymes studied. Trihydroxy-azepane **1d** was found to be a potent competitive inhibitor of α-mannosidase and β-

Table 1
Glycosidase inhibition study of **1d** (as free base)[a,b]

Enzyme	IC_{50}	K_i
α-Galactosidase	NI	NI
β-Galactosidase	147	161
α-Glucosidase	NI	NI
β-Glucosidase	142	485
α-Mannosidase	775	100
N-Acetyl-β-glucosaminidase	NI	NI
α-Galactosidase (*G. toebii* BK1)	NI	NI

[a] IC_{50} and K_i Values are in μM.
[b] NI=No inhibition at 1 mM concentration of Inhibitor.

galactosidase with K_i values of 100 and 161 μM, respectively (Table 1). Compound **1d** also showed moderate inhibition against β-glucosidase (K_i=485 μM and IC_{50}=142 μM) and was noticed to be a better inhibitor of β-glucosidase than its enantiomer **1e** (IC_{50}=250 μM)[12b] and its C2 epimer **1f**[12c] (Fig. 1).

3. Conclusions

In summary, we have developed a new, short, and straightforward total synthesis of tetrahydroxy-**1c** and trihydroxy-azepanes **1d** starting from readily available and cheap D-(+)-glucurono-γ-lactone in five and six steps in overall 72% and 57% yields, respectively. The practicability of our method lies with the fact that: (a) apart from protection and de-protection steps (three) the other two steps involve routine reactions such as DIBAL-H reduction, reductive amination and hydrogenation (b) column chromatography was applied at only two stages-one for the purification of *N*-Cbz aminol compounds **5a**/**5b** and other for the purification of iminocyclitols **1c**/**1d** thus making the synthetic route workable on multigram scale. From the literature values of other iminosugars,[12b,c] it is better to say that trihydroxy-azepane **1d** showed moderate to weak inhibitory properties against α-mannosidase, β-galactosidase and β-glucosidase. The methodology could be further extended in the syntheses of different other iminosugars and polyhydroxylated azepanes, using other readily available sugar γ-lactones,[19] and work in this direction is in progress.

4. Experimental

4.1. General methods

Melting points were recorded with Thomas Hoover Capillary 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}. ^1H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded with Varian Mercury instrument using $CDCl_3$, D_2O or CD_3OD as a solvent. Elemental analyses were carried out with Thermo-Electron Corporation CHNS analyzer Flash-EA 1112 at Department of Chemistry, University of Pune, Pune. Optical rotations were measured using Bellingham Stanley-ADP 220 digital polarimeter with sodium light (589.3 nm) at 25 °C. Thin layer chromatography was performed on pre-coated plates (0.25 mm, silica gel 60 F_{254}). Visualization was made by absorption of UV light or by thermal development after spraying with 3.5% solution of 2,4-dinitrophenylhydrazine in ethanol/H_2SO_4 and with basic aqueous potassium permanganate solution. Column chromatography was carried out with silica gel (100–200 mesh). Unless not mention the reactions were carried out in oven-dried glasswares under dry N_2. Acetone, dichloromethane, toluene, and methanol were purified and dried before use. Distilled *n*-hexane, ethyl acetate, CH_2Cl_2, and methanol were used for column chromatography. 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 using rotary evaporator.

*4.1.1. 1,2-O-Isopropylidene-α-D-glucofuranurono-6,3-lactone (**2**).* It was prepared by the slightly modified procedure of Klemer et al.[17] To a stirred suspension of α-D-glucurono-γ-lactone (20.0 g, 0.17 mmol) in dry acetone (500 mL) concentrated sulfuric acid (10 mL) was added drop wise over the period of 20 min at room temperature, the reaction mixture was then vigorously stirred for further 4 h. The resulting clear yellow solution was neutralized with slow of addition of solid sodium carbonate (27 g). Solution was filtered through Celite and residue washed with acetone (200 mL×3) the combine filtrate was concentrated, dissolved in chloroform (500 mL), and washed with water (100 mL). Organic layer was dried on sodium sulfate and concentrated under vacuum, the residue was recrystallised ($CHCl_3$/*n*-hexane) to give **2** (23.54 g) as white solid, mp 119–121 °C [lit.[17] 119–120 °C]; $[\alpha]_D^{25}$ 52.0 (*c* 1.95, $CHCl_3$) [lit.[17] $[\alpha]_D^{20}$ 52.5 (*c* 1.95, $CHCl_3$)].

*4.1.2. 1,2-O-Isopropylidene-6-(N-benzyl,N-benzyloxycarbonyl) amino-6-deoxy-α-D-gluco-1,4-furanose (**5a**).* To a cooled solution of **3a** (2 g, 9.25 mmol) in dry CH_2Cl_2 (100 mL) at −78 °C was added 1 M solution of DIBAL-H in toluene (10.12 mL, 10.18 mmol). After stirring for 0.5 h at −78 °C, reaction mixture was quenched by aq ammonium chloride (20 mL) and stirred for 2 h at 0 °C. The solution was filtered through Celite, and residue was washed with dichloromethane (20 mL×4). Evaporation of solvent under reduced pressure afforded lactol **4a** (1.93 g, 96% crude yield) as a sticky solid. To the solution of crude lactol **4a** (1.71 g) at −20°C in dry methanol (15 mL) was added an ice cold solution of benzyl amine (0.94 mL, 8.62 mmol) and glacial acetic acid (0.07 mL 1.17 mmol) in dry methanol (2 mL) over a period of 10 min and solution was stirred at −20 °C for 1 h. Sodium cyanoborohydride (1.21 g, 19.61 mmol) was added in three portions (20 min) at −20 °C, and the solution was warmed to 0 °C and stirred for 2 h. To the above ice cold solution was added aq $NaHCO_3$ (3.29 g, 39.15 mmol in 10 mL water) followed by addition of 50% solution of benzyl chloroformate in toluene (3.95 mL 23.5 mmol). The reaction mixture was allowed to attain room temperature and stirred for 3 h. Methanol was evaporated under reduced pressure and the residue was extracted with chloroform (25 mL×3). The combined organic layer was dried (Na_2SO_4) and concentrated. Purification by column chromatography using *n*-hexane/ethyl acetate=7/3 gave **5a** (3.19 g, 88% over two steps) as a colorless sticky solid. Found: C, 65.15; H, 6.70. $C_{24}H_{29}NO_7$ requires: C, 65.00; H, 6.59; R_f 0.40 (*n*-hexane/ethyl acetate=1/1); $[\alpha]_D^{25}$ −1.2 (*c* 4.68, $CHCl_3$); IR (CH_2Cl_2) 3429 (broad), 1678, 1244, 1076 cm^{-1}; ^1H NMR 300 MHz ($CDCl_3$+D_2O) δ 1.25 (3H, s, CH_3), 1.42 (3H, s, CH_3), 3.41–3.60 (2H, br s, *N*–CH_2Ph), 3.97 (1H, dd, *J*=5.7 and 1.5 Hz, H-4), 4.00–4.10 (1H, m, H-5), 4.32 (1H, br s, H-3), 4.46 (1H, d, *J*=3.5Hz, H-2), 4.54 (1H, br s, 6-H), 4.62–4.70 (1H, m, 6-H), 5.16 (2H, s, *O*-CH_2Ph) 5.94 (1H, d, *J*=3.5Hz, H-1), 7.02–7.42 (10H, m, Ar–H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.1 (CH_3), 26.8 (CH_3), 51.7 (C-6), 52.1 (*N*–CH_2Ph), 68.0 (*O*-CH_2Ph) 70.4 (C-5), 75.1, 80.6, 85.1 (C-2, C-3, C-4), 105.1 (C-1), 111.6 (isopropylidene), 127.4, 127.5, 127.9, 128.2, 128.5, 128.6, 130.9, 140.0 (Ar), 159.0 (NCOO).[20]

*4.1.3. 1,6-Dideoxy-1,6-imino-D-glucitol (**1c**).* A solution of **5a** (0.43 g, 2.63 mmol) in TFA/H_2O (3:2, 8 mL) was stirred at 0 °C for 30 min and at 25 °C for 4 h. Solvent was co-evaporated with toluene at rotary evaporator using high vacuum to furnish sticky solid. A solution of the above product and 10% $Pd(OH)_2$/C (0.06 g) in aq methanol (5 mL, 9:1) was hydrogenated at 90 psi for 48 h at 25 °C. The catalyst was filtered through Celite and solvent was evaporated to afford thick liquid. Purification by column chromatography (CH_2Cl_2/MeOH/25% NH_4OH=2/2/0.2) yielded **1c** (136 mg, 86%) as a semi solid: R_f 0.4 (CH_2Cl_2/MeOH/25% NH_4OH=2/7/1); $[\alpha]_D^{25}$ −24.2 (*c* 0.85, H_2O) [lit.[13h] $[\alpha]_D^{20}$ −23.0 (*c* 0.85, H_2O).

*4.1.4. 1,6-Dideoxy-1,6-imino-D-glucitol, hydrochloride salt (**1c**·**HCl**).* To an ice cold solution of **1c** (15 mg, 0.092 mmol) in methanol (1 mL) was added concentrated HCl (0.1 mL) and the reaction mixture was stirred at 25 °C for 12 h. The solvent was evaporated to dryness and the residue was dissolved in distilled water (1 mL) and extracted with chloroform (1 mL×3). The aqueous layer was concentrated to afford hydrochloride salt of **1c** (17 mg, 98%) as a gummy solid. Found: C, 36.40; H, 7.35. $C_6H_{14}ClNO_4$ requires: C,

36.10; H, 7.07; R_f 0.3 (CH_2Cl_2/MeOH/25% NH_4OH=2/7/1); $[\alpha]_D^{25}$ −12.6 (*c* 1.3, MeOH) [lit.[13f] $[\alpha]_D^{26}$ −15.0 (*c* 1, H_2O)].

*4.1.5. 5,6-Dideoxy-6-(N-benzyl,N-benzyloxycarbonyl)amino-1,2-O-isopropylidene-α-D-gluco-1,4-furanose (**5b**).* Reaction of **3b** (1.7 g, 8.5 mmol) in dry CH_2Cl_2 (90 mL) with 1 M solution of DIBAL-H in toluene (9.33 mL, 9.35 mmol) as stated for **4a** furnished lactol **4b** (1.66 g, 97% crude yield) as a sticky solid. Reaction of **4b** (1.2 g 5.94 mmol) with benzyl amine (0.71 mL, 6.53 mmol), sodium cyanoborohydride (0.92 g, 14.8 mmol) and glacial acetic acid (0.05 mL 0.9 mmol) in dry methanol (2 mL) followed by reaction with benzyl chloroformate in toluene (2.98 mL 17.81 mmol) and aq $NaHCO_3$ (2.5 g, 29.7 mmol, 8 mL water) as described for **5a** and column chromatography using *n*-hexane/ethyl acetate=4/1 yielded **5b** (2.43 g, 92% in two steps) as a colorless thick liquid. Found: C, 67.21; H, 7.12. $C_{24}H_{29}NO_6$ requires: C, 67.43; H, 6.84; R_f 0.56 (*n*-hexane/ethyl acetate=1/1); $[\alpha]_D^{25}$ −2.3 (*c* 2.54, $CHCl_3$); IR (CH_2Cl_2) 3443 (broad), 1693, 1220, 1076 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.29 (3H, s, CH_3), 1.45 (3H, s, CH_3), 1.54–2.0 (2H, m, H-5), 3.10–3.40 (2H, m, H-6), 3.80–4.20 (3H, m, H-3, H-4, OH), 4.38–4.6 (3H, m, *N*–CH_2Ph, H-2), 5.20 (2H, s, *O*-CH_2Ph), 5.82 (1H, d, *J*=3.57, 1-H), 7.10–7.40 (10H, m, Ar–H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.0 (CH_3), 26.5 (CH_3), 43.5 (C-5), 44.0 (C-6) 50.7 (*N*–CH_2Ph), 67.3 (*O*-CH_2Ph) 74.9 (C-4), 78.0 (C-3), 85.1 (C-2), 104.2 (C-1), 111.1 (isopropylidene), 127.3, 127.7, 127.9, 128.3, 128.4, 136.2, 137.3 (Ar), 156.4 (NCOO).[21]

*4.1.6. 1,5,6-Trideoxy-1,6-imino-D-xylo-hexitol (**1d**).* Reaction of **5b** (0.61 g, 1.42 mmol) with TFA/H_2O (3:2, 12 mL) followed by hydrogenation with 10% $Pd(OH)_2$/C (0.08 g) in aq methanol (10 mL, 9:1) as described for **1c** and column chromatography purification using CH_2Cl_2/MeOH/25% NH_4OH 3/2/0.2 afforded **1d** (178 mg, 85%) as a sticky solid: R_f 0.4 (CH_2Cl_2/MeOH/25% NH_4OH=3/6/1); $[\alpha]_D^{25}$ 18.1 (*c* 0.95, MeOH) [lit.[14a] $[\alpha]_D^{26}$ 16.36 (*c* 0.33, MeOH)].

*4.1.7. 1,5,6-Trideoxy-1,6-imino-D-xylo-hexitol, hydrochloride salt (**1d·HCl**).* Compound **1d** (40 mg, 0.27 mmol) in methanol (3 mL) was reacted with concentrated HCl (0.3 mL) as described for **1c·HCl** to afford hydrochloride salt **1d·HCl** (49 mg, 99%) as a yellow gummy solid. Found: C, 39.53; H, 7.91. $C_6H_{14}ClNO_3$ requires C, 39.24; H, 7.68; R_f 0.3 (CH_2Cl_2/MeOH/25% NH_4OH=2/6/1); $[\alpha]_D^{22}$ 4.0 (*c* 2.4, H_2O). IR (KBr) 3331–2833 (broad), 1579, 1053 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 2.12–2.25 (2H, m, H-5), 3.16–3.30 (1H, m, H-6), 3.32–3.58 (3H, m, H-1/H-6), 3.68 (1H, dd, *J*=7.2 and 5.2 Hz, H-3), 3.84 (1H, dt, *J*=7.2 and 3.6 Hz, H-4), 4.10 (1H, dt, *J*=5.2 and 2.3 Hz, H-2); ^{13}C NMR (75 MHz, D_2O) δ 27.6 (C-5), 42.2 (C-6), 45.3 (C-1) 68.2 (C-4), 72.5 (C-2), 78.4 (C-3).

4.2. Procedure for the inhibition assay

The enzymes α-galactosidase, β-galactosidase, β-glucosidase, α-mannosidase, and *N*-acetyl-β-D-glucosaminidase were isolated from almond seeds; α-galactosidase was isolated from *G. toebii* BK1 and α-glucosidase was procured from Sigma Chemical Co. were used for glycosidase inhibitory activity. Inhibition potencies of **1c** and **1d** were determined by measuring the residual hydrolytic activities of the glycosidases. The substrates *p*-nitrophenyl-β-D-glucopyranoside, *p*-nitrophenyl-α-D-glucopyranoside, *p*-nitrophenyl-α-D-galactopyranoside and *p*-nitrophenyl-β-D-galactopyranoside, *p*-nitrophenyl-*N*-acetyl-β-D-glucopyranoside, and *p*-nitrophenyl-α-D-mannopyranoside (all of Sigma Chemicals Co., USA) of 2 mM concentration, were prepared in 0.025 M citrate buffer with pH 4.0 and used for assay. The test compound (of various concentrations from 20 μM to 1000 μM) was pre-incubated with the enzyme, buffered at its optimal pH, for 1 h at 37 °C. The enzyme reaction was initiated by the addition of 100 μL of substrate. Reaction was terminated at the end of 90 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 with a UV–visible Spectrophotometer. Controls were run simultaneously in the absence of test compound. One unit of glycosidase activity is defined as the amount of enzyme that hydrolyzed 1 μmol of *p*-nitrophenol per minute at 37 °C. The inhibition constants (K_i) and the nature of the inhibition were determined from Lineweaver–Burk plots.

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Supplementary data

Copies of ^1H and ^{13}C NMR spectra of **5a**, **5b**, **1c**, **1c·HCl**, **1d**, **1d·HCl** and Lineweaver–Burk plots of **1d** against glycosidase. Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.08.060. These data include MOL files and InChIKeys of the most important compounds described in this article.

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