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Synthesis and evaluation of glycosidase inhibitory activity of octahydro-2*H*-pyrido[1,2-*a*]pyrimidine and octahydro-imidazo[1,2-*a*]pyridine bicyclic diazasugars

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Abstract—An efficient chiron approach for the synthesis of bicyclic diazasugars **4a** and **4b** having both –CH_2OH and –OH functionality at the same carbon atom (C-6) is reported. Thus, easily available α-D-xylo-pentodialdo-1,4-furanose **5**, obtained from D-glucose, on aldol-crossed Cannizzaro reaction followed by hydrogenolysis afforded **7**. The regio-selective β- and α-sulfonylation of hydroxymethyl groups in **7** afforded **8a** (β-sulfonylation) and **11** (α-sulfonylation) in good yields. The cleavage of the 1,2-acetonide functionality, individually in **8a** and **11**, followed by reaction with ethylenediamine gave in situ formation of sugar aminals that undergo concomitant nucleophilic displacement of the sulfonyloxy group, by amino functionality, to give hitherto unknown bicyclic diazasugars **4a** and **4b**, respectively. The inhibitory potency of the earlier reported bicyclic diazasugars **3a**,**b** and **4a**,**b** was evaluated against α- and β-glycosidases and they were found to be potent and specific against the β-glycosidases with IC_{50} and K_i values in the micro molar range.

1. Introduction

Glycosidase inhibitors play a crucial role in biological processes involving breakdown of edible carbohydrates,[1] eukaryotic glycoprotein processing,[2] glycoconjugate anabolism and catabolism[3] and therefore are potential drug candidates in the treatment of a variety of carbohydrate mediated diseases such as diabetes,[4] cancer,[5] HIV,[6] hepatitis[7] and Gaucher's disease.[8] Polyhydroxylated piperidine, pyrrolizidine and indolizidine alkaloids, commonly called as azasugars, are known to be the promising glycosidase inhibitors.[9] In recent years, the discovery of specific and promising glycosidase inhibitors, in particular anomer-selective β-glycosidases, led to the development of a new class of bicyclic azasugars wherein the nitrogen atom is present at the glycosidic position. Naturally occurring kifunensine **1**[10] and nagstatin **2**[11] (Fig. 1) are the bicyclic diazasugars (containing a glycosidic nitrogen atom), which showed selectivity in enzyme inhibition, for example, mannosidase I and β-*N*-acetyl-glucosaminidase (NAG-ase), respectively, enabling us to understand the processes of intractable diseases such as nephritis, cancer and immune disorders.[12] Berges and co-workers have reported the synthesis of a number of new analogues of bicyclic diazasugars with different stereochemical

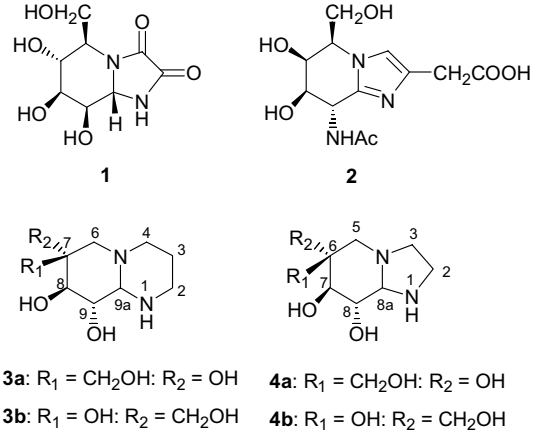

Figure 1. Bicyclic diazasugars.

Keywords: Alkaloids; Azasugars; Glycosides; Enzyme inhibitors.
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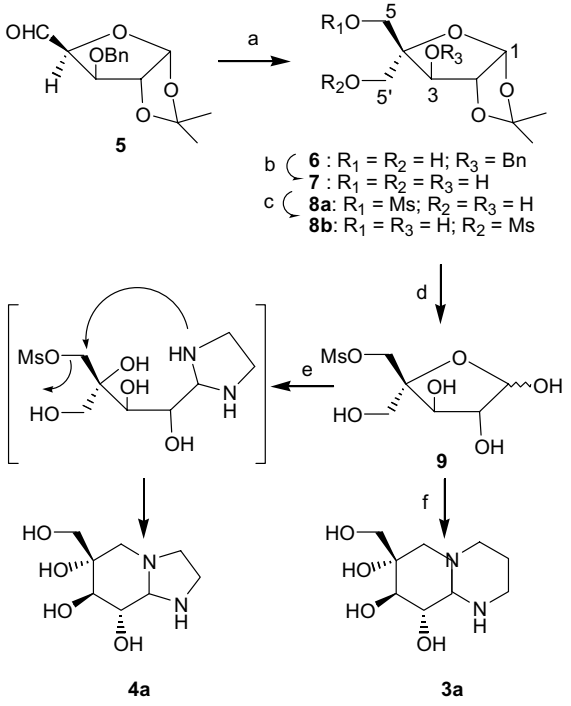
orientation of the –OH functionality at C-6/C-7/C-8/C-9 as well as presence or absence of hydroxymethyl substituent at C-6 and observed that the hydroxymethyl substituent at C-6 of diazasugars had a significant effect on enzyme substrate activity.[13,14]

Inspired with this observation and as a part of our interest in the synthesis of azasugars,[15] we have recently reported an efficient route for the synthesis of octahydro-2*H*-pyrido[1,2-*a*]pyrimidine (six to six ring fused) bicyclic diazasugars **3a** and **3b** (Fig. 1) with hydroxyl and hydroxymethyl substituent at C-7.[16] In the course of evaluation of glycosidase inhibitory activities of **3a** and **3b**, we were particularly interested in examining the effect of ring size on the activity relationship. This has led to the synthesis of hitherto unknown octahydroimidazo[1,2-*a*]pyridine (six to five ring fused) bicyclic diazasugar **4a** and **4b** (Fig. 1) with hydroxyl and hydroxymethyl substituent at C-6. Our results towards the synthesis of **4a** and **4b** and evaluation of glycosidase inhibitory activity of compounds **3a**, **3b**, **4a** and **4b** are reported herein.

2. Results and discussion

2.1. Synthesis of bicyclic diazasugar 4a

As shown in Scheme 1, D-glucose was converted to 1,2-*O*-isopropylidene-3-*O*-benzyl-α-D-xylo-pentodialdo-1,4-furanose (**5**) as per the reported procedure.[17] The aldol-crossed Cannizzaro reaction of **5** with excess formaldehyde and sodium hydroxide in THF–water afforded diol **6**, which on hydrogenolysis using 10% Pd/C in methanol afforded triol **7**.[18] Treatment of **7** with methanesulfonyl chloride (0.95 equiv) in pyridine at −10 °C gave a mixture of mono-mesylated products **8a** and **8b** in the 3:1 ratio. The major product **8a** was crystallized out from the binary solvent system (chloroform/hexane = 1:1) on keeping the solution at 0 °C for 24 h.[19] The formation of the mono-mesylated product **8a** was evident from the ^{1}H NMR spectrum. The assignment of the α- or β-mesylated product was established by the 1D-NOSEY spectrum wherein irradiation of a signal at δ 3.59 for methylene protons of –CH_2OH (C-5′) showed NOE for the methylene protons at δ 4.33 for –CH_2OMs group (C-5) and for a singlet at δ 4.19 corresponding to the α-orientated protons at C-3. This indicated that the mesylation had occurred at the β-orientated CH_2OH group (C-5) resulting in (*S*) absolute configuration at C-4. The good selectivity in the favour of **8a** could be attributed to the presence of α-orientated 1,2-acetonide functionality that hindered the mesylation of α-CH_2OH group (C-5′).



Scheme 1. Reagents and conditions: (a) HCHO, NaOH, THF–H_2O, rt, 10 h, (**6**, 41%), (**7**, 21%); (b) 10% Pd/C, MeOH, H_2, rt, 24 h, 93%; (c) MsCl, pyridine, −10 °C, 4 h, (**8a**, 44%); (d) TFA–H_2O, 0 °C to rt, 3 h, 93%; (e) $NH_2(CH_2)_2NH_2$, MeOH–H_2O, rt, 12 h, 78%; (f) $NH_2(CH_2)_3NH_2$, MeOH–H_2O, rt, 12 h, 81%.

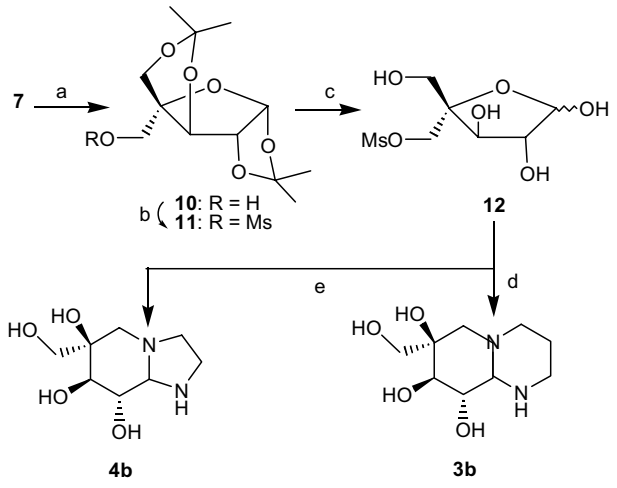
The utility of **8a** in the synthesis of bicyclic diazasugar **3a** was demonstrated earlier wherein the de-protection of the 1,2-acetonide functionality in **8a** (TFA/water 3:2) afforded hemiacetal **9**, which on reaction with 1,3-propanediamine (1 equiv) in methanol–water for 12 h afforded octahydro-2*H*-pyrido[1,2-*a*]pyrimidine **3a**.[16] Similarly, the reaction of the hemiacetal **9** with ethylenediamine (1 equiv) gave octahydro-imidazo[1,2-*a*]pyridine **4a** as a semi-solid, wherein the six-membered azasugar ring skeleton is fused to the five-membered ring.

2.2. Synthesis of bicyclic diazasugar 4b

For the synthesis of bicyclic diazasugars **3b** and **4b** (C7 epimer of **3a** and C6 epimer of **4a**), it was necessary to have α-sulfonyloxy methylene group at C-4 of triol **7**. For this reason, we have planned to selectively protect the β-orientated OH groups at C-3 and C-5 as an acetonide group followed by protection of C4α-hydroxymethelene group as mesyl derivative. Thus, treatment of **7** with 2,2-dimethoxy propane using *p*-TSA (catalytic) in methanol gave exclusively 3,5-*O*-isopropylidene derivative **10** that on mesylation afforded the mesylated product **11** (Scheme 2). In the next step, reaction of **11** with TFA/water (3:2) furnished hemiacetal **12**, which on reaction with 1,3-propanediamine in aqueous methanol gave octahydro-2*H*-pyrido[1,2-*a*]pyrimidine **3b**[16] while; the reaction with ethylenediamine afforded octahydroimidazo[1,2-*a*]pyridine **4b**.

2.3. Conformational assignment of 4a,b

The azasugars with a singly bonded glycosidic heteroatom and having preferred α- or β-anomeric configuration are very selective glycosidase inhibitors. For



Scheme 2. Reagents and conditions: (a) 2,2-dimethoxy-propane, MeOH, *p*-TSA, 25 °C, 5 min, 97%; (b) MsCl, pyridine, 0 °C, 4 h, 92%; (c) TFA–H_2O (3:2), 0 °C to rt, 3 h, 97%; (d) $NH_2(CH_2)_3NH_2$, MeOH–H_2O, rt, 12 h, 79%; (e) $NH_2(CH_2)_2NH_2$, MeOH–H_2O, rt, 12 h, 75%.

example, α-anomeric diazasugars are α-glycosidase inhibitors and β-anomer configurated cleave β-glycosides while diazasugars with anomeric mixture are not selective and inhibit both α- and β-glycosidases.[14e] In order to correlate such structure–activity relationship, it is imperative to know the conformations of bicyclic diazasugars **4a**,**b**. In this respect, we have earlier noticed that the bicyclic diazasugars **3a** and **3b** exist in $^4C_1$ conformations **A** and **B**, respectively, with β-orientated glycosidic nitrogen atom (Fig. 2).[16] In compounds **4a** and **4b**, the presence α/β orientated –CH_2OH and –OH groups on the same carbon atom (C-6), is expected to alter the conformation. Therefore, four structures **W**, **X**, **Y** and **Z** and **W′**, **X′**, **Y′** and **Z′** for compounds **4a** and **4b**, respectively, were considered. The conformational assignment was studied using ^{1}H NMR wherein the

Table 1. ^{1}H–^{1}H coupling constants of compounds **4a** and **4b**

Compound	*J* Hz			
	$J_{2a,2e}$	$J_{5a,5e}$	$J_{7,8}$	$J_{8,8a}$
4a	5.5[a]	12.3	9.0	8.5
4b	5.6[a]	12.6	9.1	8.9

[a] This value has been calculated by decoupling experiments.

coupling constant information was confirmed from the decoupling experiments and are given in Table 1. In case of **4a**, appearance of a doublet of doublet at δ 3.57 ($J_{8,8a} = 8.5$ Hz and $J_{8,7} = 9.0$ Hz) for H-8 and a doublet at δ 3.32 ($J_{7,8} = 9.0$ Hz) for H-7, clearly indicated the *trans*-diaxial relationship between the H-7, H-8 and H-8a and thus ruled out the possibility of structure **Y** with $^1C_4$ conformation. The coupling constant $J_{8,8a}$ was informative for the determination of the configuration at C-8a and the appearance of a doublet at δ 2.40, corresponding to H-8a, with large coupling constant ($J_{8,8a} = 8.5$ Hz) indicated β-anomeric configuration of the singly bonded glycosidic nitrogen atom. The initial geometry in the precursor **8a** ensures that, in the product **4a** the –OH substituents at C-8, C-7 and C-7, C-6 should be *trans* and therefore the –CH_2OH substituent was assigned the axial orientation with (6*S*) absolute configuration. Therefore, conformations **W** and **Z**, with $^4C_1$ conformation, were assigned to compound **4a** (Fig. 2). The conformations **W** and **Z** are interconvertible by inversion at nitrogen and are in dynamic equilibrium. As the *trans* conformer **W** is more stable than the *cis* conformer **Z**,[20] we believe that the compound **4a** exists in conformation **W**. The predominance of equatorial orientation of *N*1 of bicyclic diazasugars was also demonstrated by Berges and co-workers.[14] Furthermore, the intra-molecular hydrogen bonding between –CH_2OH and a lone pair of electrons on a fused ring nitrogen atom, in a six-membered transition state, stabilize the conformation **W** for compound **4a**.

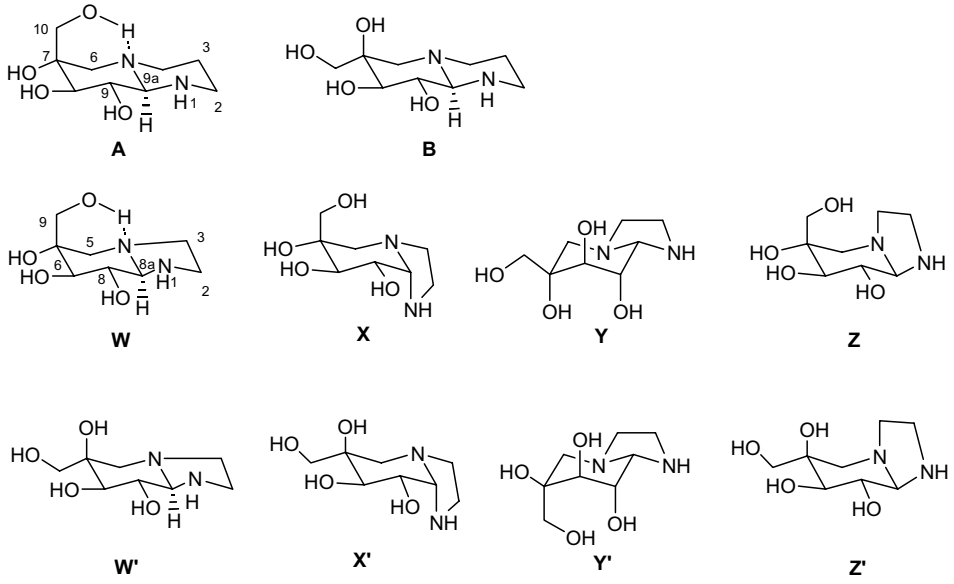


Figure 2. Conformational structures of **3a**, **3b**, **4a** and **4b**.

Since the ^{1}H NMR spectrum of **4b** is different from **4a**, it was thought that **4b** could exist in different conformation. However, the appearance of one doublet of doublet at δ 3.47 ($J_{8,8a} = 8.5$ Hz and $J_{8,7} = 9.1$ Hz) and a doublet at δ 3.32 ($J_{7,8} = 9.1$ Hz) for H-8 and H-7, respectively, indicated the *trans*-diaxial relationship of H-7, H-8 and H-8a. In addition, the appearance of a doublet at δ 2.74 for H-8a with large coupling constant ($J_{8a,8} = 8.9$ Hz) indicated the β-anomeric position for glycosidic nitrogen atom. Since the relative stereochemistry of substituents at C-8, C-7 and C-6 in precursor **11** is retained in the product formation, the –CH_2OH substituent was assigned the equatorial orientation with (6*R*) absolute configuration. Therefore, structure **W′** with conformation $^4C_1$ as shown in Figure 2, was assigned to compound **4b** (the *cis* conformer **Z′** is less stable than the *trans* conformer **W′**).[20]

2.4. Biological activity

Glycosidases namely β-glucosidase (E.C. 3.2.1.21), α-galactosidase (E.C. 3.2.1.22), β-galactosidase (E.C. 3.2.1.23) and α-mannosidase (E.C. 3.2.1.24) are abundantly present in sweet almonds. Therefore inhibitory potency of **3a**, **3b**, **4a** and **4b** was evaluated using glycosidases extracted from sweet almonds. Glycosidases were partially purified using Sephadex G-100 column chromatography. α-Glucosidase from yeast was purchased from Sigma Chemicals. However, no inhibition by these compounds was observed towards α-glucosidase. The IC_{50} values obtained for the above mentioned compounds are summarized in Table 2.

IC_{50} values indicate that compounds **3b**, **4a** and **4b** are potent inhibitors of glycosidase. Compound **3a** showed no inhibition towards any glycosidase. While comparing the inhibitory potency of compounds **3b**, **4a** and **4b**, it can be observed from the Table 2 that **4b** is most potent followed by **4a**. When C-7 CH_2OH group is axial in pyrido-pyrimidine as in **3a** there is complete loss of inhibition. Lowest IC_{50} values obtained among the four compounds studied are by compound **4b** in which C-7 CH_2OH group is equatorial in imidazo-pyridine ring system. Thus, it can be concluded that for best binding to active site of the enzymes and thus acting as good competitive inhibitors, C-7 CH_2OH should be equatorial (α) in imidazo-pyridine ring system. In general compounds inhibited β-galactosidase more effectively than other glycosidases assayed. Probable reason for

Table 2. Inhibitory potencies of bicyclic diazasugars

Compd	IC_{50} (μM)				
	α-Glucosidase	β-Glucosidase	β-Galactosidase	α-Galactosidase	α-Mannosidase
3a	NI	NI	NI	NI	NI
3b	NI	5.54	5.17	9.71	5.61
4a	NI	3.78	3.30	NI	4.65
4b	NI	2.50	2.67	2.71	NI

NI—inhibition not observed under assay conditions.
All above values are an average of three sets of assay performed.

Table 3. K_i values against β-galactosidase

Compd	K_i, μM (β-galactosidase)
3b	0.74
4a	0.46
4b	0.23

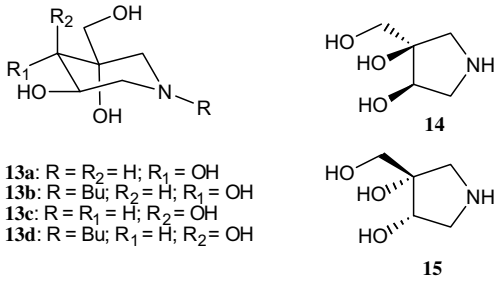


Figure 3. Structure of compounds **13**–**15**.

such specificity towards β-glycosidases is due to the presence of β-orientated glycosidic nitrogen atom, which has been confirmed by conformational assignment of these compounds using spectroscopic technique. Hence in addition to IC_{50}, K_i values against β-galactosidase have also been determined (Table 3).

It has been reported that in some isofagomine (1-*N*-iminosugar **13** with $^1C_4$ conformation)[21] and pyrrolidine azasugar analogues (**14** and **15**) (Fig. 3) the presence of –CH_2OH and –OH functionality on the same carbon atom decreased the inhibitory activity, however, these compounds demonstrated some inhibition of glycolipid biosynthesis.[21] Interestingly, in compounds **3b**, **4a** and **4b**, the presence of –CH_2OH and –OH groups on the same carbon atom in a bicyclic diazasugar ($^4C_1$ conformation) system showed considerable potency in β-glycosidase inhibition.

3. Conclusion

In conclusion, we have described the synthesis of a new type of bicyclic diazasugar **4a** and **4b** with –CH_2OH and –OH groups at C-6 position. The present approach involves a highly selective and efficient strategy using D-glucose as a substrate. The diazasugars **3a**,**b** and **4a**,**b** showed good inhibitory activities against glycosidases. The relatively low IC_{50} and K_i values for inhibition of β-glycosidases suggest their inhibitory selectivity towards β-glycosidases.

4. Experimental

4.1. General methods

Melting points were recorded with Thomas Hoover melting point apparatus and are uncorrected. Elemental analyses were carried out with C,H-analyzer. Optical

rotations were measured using a Bellingham Stanley-ADP digital polarimeter using sodium light (D line 589.3 nm) at 25 °C. IR spectra were recorded with FTIR 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 using D_2O as a solvent. Chemical shifts were reported in δ unit (ppm) with reference to TMS as an external standard and J values are given in Hz. The assignments of the signals were confirmed by decoupling and DEPT experiments. Thin layer chromatography was performed on pre-coated plates (0.25 mm, silica gel 60 F_{254}). Column chromatography was carried out with silica gel (100–200 mesh) and in some cases with ammonia solution. Amberlite A-21 anion exchange resin (OH^- form, weak base) was used for neutralization. Ethylenediamine and 10% Pd–C was purchased from Aldrich and/or Fluka. 1,2-*O*-Isopropylidene-3-*O*-benzyl-α-D-xylo-petodialdo-1,4-furanose (**5**) was prepared according to reported procedure.[17] The preparation of compounds **6**, **7**, **8a**, **10** and **11** were reported from our laboratory.[16]

4.2. (6*S*,7*R*,8*S*,8a*R*)-Octahydro-6-hydroxymethyl-6,7,8-trihydroxy-imidazo-[1,2-*a*]-pyridine (4a)

A solution of **8a** (0.45 g, 1.508 mmol) in TFA/H_2O (5 mL, 3:2) was stirred at 25 °C for 3 h. TFA was evaporated in vacuum and co-evaporated with water (2×2 mL). The hemiacetal **9** thus obtained (0.374 g, 96%) was dissolved in water (6 mL) and ethylenediamine (0.044 g, 0.728 mmol; 0.5 equiv) was added carefully with stirring. After 30 min a second lot of ethylenediamine (0.044 g, 0.5 equiv) in MeOH (10 mL) was added dropwise at room temperature. After 12 h amberlite A-21 anion exchange resin (OH^- form, weak base) was added to neutralize methanesulfonic acid. The solution was filtered and the solvent was evaporated to give a gum that was dissolved in ethanol (1 mL) and precipitated with diethyl ether (15 mL). The precipitate thus obtained was filtered, washed with diethyl ether and dried. Chromatographic purification of the residue with chloroform/methanol/ammonia (80:19:1) afforded **4a** (0.213 g, 78%) as a semi-solid [found: C, 47.19; H, 8.01. $C_8H_{16}N_2O_4$ requires C, 47.05; H, 7.89]; R_f (66% methanol/chloroform) 0.10; $[\alpha]_D$ +24.2 (*c* 0.66, MeOH); ν_{max} (Nujol) 3560–3150 (br), 2926 and 2858 cm^{-1}; δ_H (300 MHz, D_2O) 2.29 (1H, d, *J* 12.3 Hz, *H*5a), 2.40 (1H, d, *J* 8.5 Hz, *H*8a), 2.93 (1H, d, *J* 12.3 Hz, *H*5e), 2.99–3.19 (4H, m, *H*2, *H*3), 3.32 (1H, d, *J* 9.0 Hz, *H*7), 3.40 (2H, br s, CH_2OH), 3.57 (1H, dd, *J* 8.5 and 9.0 Hz, *H*8); δ_C (75 MHz, D_2O) 42.7, 50.1, 53.4 (*C*-2/*C*-3/*C*-5), 63.8 (*C*H_2OH), 70.8, 73.2, 73.8 (*C*-6/*C*-7/*C*-8), 79.1 (*C*-8a).

4.3. (6*R*,7*R*,8*S*,8a*R*)-Octahydro-6-hydroxymethyl-6,7,8-trihydroxy-imidazo-[1,2-*a*]-pyridine (4b)

To a solution of **11** (0.5 g, 2.955 mmol) was added TFA/H_2O (5 mL, 3:2) at 0 °C and stirred at 25 °C for 3 h. TFA was evaporated in vacuum and co-evaporated with water (3×2 mL). The hemiacetal **12** thus obtained (0.37 g, 97%) was dissolved in water (7 mL) and ethylenediamine (0.043 g, 0.715 mmol; 0.5 equiv) was added carefully with stirring. After 0.5 h extra 0.5 equiv of ethylenediamine (0.043 g, 0.715 mmol) in MeOH (4 mL) was added dropwise at room temperature. Stirring was continued for 10 h and the solution was treated with amberlite A-21 anion exchange resin (OH^- form, weak base) to remove methanesulfonic acid. The solvent was evaporated to give a gum that was dissolved in ethanol (1 mL) and then ether was added with shaking. The precipitate thus obtained again washed with ether and dried. Column chromatographic purification of the residue with chloroform/methanol/ammonia (Merck, 25% solution) = 70:29:1 afforded **4b** (0.219 g, 75%) as semi-solid mass [found: C, 47.19; H, 7.96. $C_8H_{16}N_2O_4$ requires C, 47.05; H, 7.89]; R_f (66% methanol/chloroform) 0.11; $[\alpha]_D$ +15 (*c* 0.4, MeOH); ν_{max} (Nujol) 3550–3200 (br band) cm^{-1}; δ_H (300 MHz, D_2O) 2.25 (1H, d, *J* 12.6 Hz, *H*5a), 2.74 (1H, d, *J* 8.9 Hz, *H*8a), 2.88–3.60 (5H, m, *H*2a, *H*3a, *H*3e, *H*5e), 3.16 (1H, dd, *J* 5.6 and 5.8 Hz, *H*2e), 3.32 (1H, d, *J* 9.1 Hz, *H*7), 3.43 (2 H, br s, CH_2OH), 3.47 (1H, dd, *J* 8.9 and 9.1 Hz, *H*8); δ_C (75 MHz, D_2O) 42.6, 51.1, 53.8 (*C*-2/*C*-3/*C*-5), 64.2 (*C*H_2OH), 72.5, 73.6, 74.1 (*C*-6/*C*-7/*C*-8), 80.1 (*C*-8a).

4.4. General procedure for inhibition assay

Inhibition potencies of the bicyclic diazasugars **3a**,**b** and **4a**,**b** were determined by measuring the residual hydrolytic activities of the glycosidases. The substrates (purchased from Sigma Chemicals Co.) namely *p*-nitrophenyl-α-D-glucopyranoside, *p*-nitrophenyl-β-D-glucopyranoside, *p*-nitrophenyl-β-D-galactopyranoside, *p*-nitrophenyl-α-D-galactopyranoside and *p*-nitrophenyl-α-D-mannopyranoside of 2 mM concentration was prepared in 0.025 M citrate buffer with pH 4.0. The test compound was preincubated with the enzyme (almond seed extract) for 1 h at 37 °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 420 nm using Shimadzu Spectrophotometer UV-1601. 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.[22] K_i was determined using Lineweaver–Burk plot method using formula: X-intercept = $Vm/Km(1+[I]/K_i)$.[23] For determination of K_i effective inhibitor concentration in assay mixture was 1.26 μM and various effective substrate concentrations of 1.25–6.25 mM were used.

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