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1-Aza-sugars from D-Glucose. Preparation of 1-Deoxy-5-dehydroxymethyl-Nojirimycin, Its Analogues and Evaluation of Glycosidase Inhibitory Activity

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Abstract—D-Glucose derived pentodialdoses **11a–c** on reduction followed by tosylation, azide displacement, hydrogenation and protection with -Cbz group gave *N*-Cbz protected compounds **14a–c**, respectively, which on removal of 1,2-acetonide functionality and hydrogenation afforded corresponding 1-aza-sugars **3**, **9** and **10** in good overall yields. The glycosidase inhibition activity of these 1-aza-sugars was tested with sweet almond as a rich source of different glycosidases.

In the last two decades, glycosidase inhibitors such as aza-sugars have been attractive target molecules for synthetic as well as bio-chemists not only because they serve as a useful tool for studying the biological function of oligosachorides[1] but also because they may have great potential as drugs in the treatment of a variety of carbohydrate mediated diseases.[2] Amongst these aza-sugars, nojirimycin (**1**) and 1-deoxy nojirimycin (**2**) are the first naturally occurring alkaloids with promising biological activity.[3] In recent years, improved glycosidase inhibition is being examined for each hydroxyl substituent in **1** or **2** and systematic data in the inhibition of β-glucosidases is documented in the literature.[4] In this aspect, it has been noted that the removal of the hydroxymethyl substituent at C-5 in **2** had very little effect on enzyme substrate activity.[5] In view of this, Ganem et al. have first reported the synthesis of piperidine triols **3**, **4** and **5** and referred these compounds as 1-aza-sugars or 1-*N*-imino sugars wherein the nitrogen atom is considered to be at one position.[5] Later on, Genjiro and coworkers have isolated 1-aza-sugars **3** and **4** from *Eupatorium fortunei Turz*.[6] Since then a number of new derivatives of 5-de(hydroxymethyl)-1-deoxy-nojirimycin **3** with different stereochemical orientation of the –OH functionality at C-3/C-4/C-5 (e.g., **3**, **4** and **5**) as well as the replacement of one of the –OH functionality at C-3/C-5 with hydroxymethyl substituent (e.g., **6**, **7** and **8**) have been synthesised and evaluated for glycosidase inhibition.[7] As a part of our continuing interest in the synthesis of nojirimycin analogues,[8] we are now reporting an efficient route for the synthesis of 3*S*, 4*R*, 5*R* piperidine triol (**3**), 3*S*, 4*S*, 5*R* piperidine triol (**9**), and 3*S*,4*S*(2-hydroxyethyl), 5*R* piperidine triol (**10**) and discuss their glycosidase inhibitory activity.

Results and Discussion

Synthesis of 3*S*, 4*R*, 5*R* piperidine triol (3) and 3*S*, 4*S*, 5*R* piperidine triol (9)

As shown in Scheme 1, D-glucose was converted to 1,2-*O*-isopropylidene-3-*O*-benzyl-α-D-*xylo*-pentodialdose **11a** in 68% overall yield as reported earlier by us.[8] The pentodialdose **11a** was reduced with sodium borohydride in methanol to give an alcohol which on tosylation afforded 5-*O*-tosyl 1,2-*O*-isopropylidene-3-*O*-benzyl α-D-*xylo*furanose **12a** in good yield. The nucleophilic displacement of the tosyl group by NaN_3 in DMF led to the formation of an azido compound **13a**.[9] Subsequently, **13a** was subjected to catalytic hydrogenation and the amino alcohol thus obtained was directly treated with benzylchloroformate in the presence of sodium bicarbonate in ethanol to give 5-(*N*-benzoxy-

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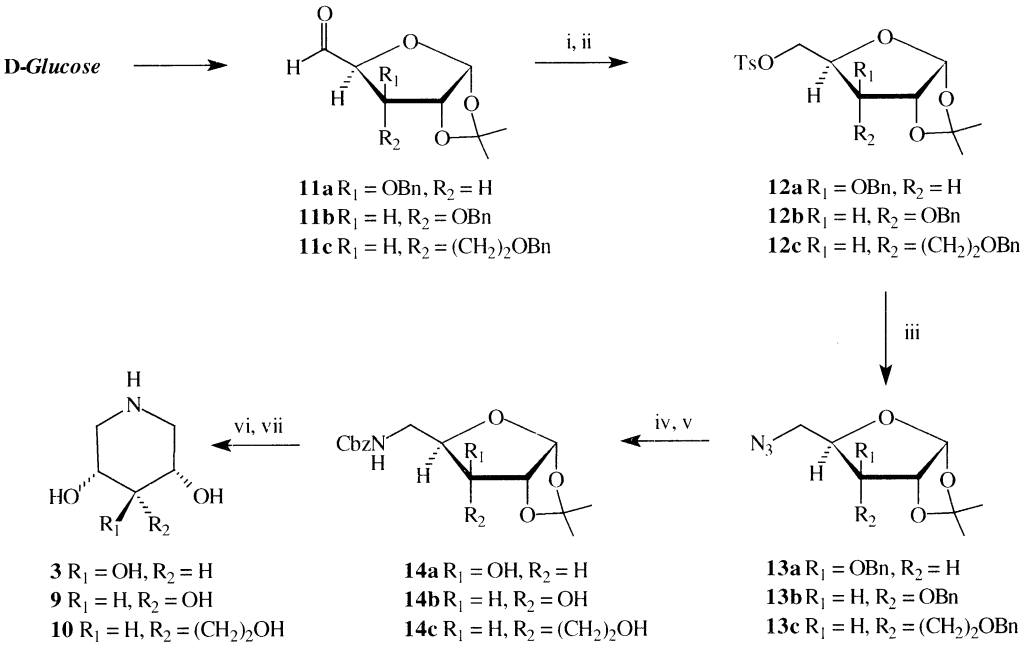

Scheme 1. Reagents and conditions: (i) $NaBH_4$, MeOH, rt, 15 min; (ii) TsCl, pyridine, rt, 12 h; (iii) NaN_3, DMSO, 100 °C, 6 h; (iv) 10% Pd/C, H_2, 80 psi, MeOH, 12 h; (v) CbzCl, NaHCO3, EtOH-H_2O (8:2), rt, 2 h; (vi) TFA-H_2O (3:2), rt, 2 h; (vii) 10% Pd/C, H_2, 8 psi, MeOH, 12 h.

carbonylamino)-5-deoxy 1,2-*O*-isopropylidene-3-*O*-benzyl-α-D-*xylo*furanose **14a**. Treatment of **14a** with TFA-water followed by catalytic hydrogenation afforded **3**. The spectral and analytical data of **3** was found to be in good agreement with that reported.[5] The same sequence of reactions was repeated using D-glucose derived 1,2-*O*-isopropylidene-3-*O*-benzyl-α-D-*ribo*-pentodialdose **11b** and 3*S*, 4*S*, 5*R* piperidine triol **9** was synthesised in overall 62% yield. Compound **9** was treated with MeOH-HCl and amine-hydrochloride salt **9**·HCl was isolated as a solid. The spectral and analytical data of **9**·HCl was in consonance with that reported [mp = 162–163 °C (reported mp = 161–163 °C)].[7l]

Synthesis of 3*S*, 4*S*(2-hydroxyethyl), 5*R* piperidine triol (10):

The literature survey indicates that different analogues of **3** wherein –OH group at C-3 and C-5 is replaced with a hydroxymethyl group are known. However, substitution of C-4 hydroxy with either $-CH_2OH$ or $-CH_2CH_2OH$ group is not reported so far. In the present study, we thought of synthesising a new analogue wherein C-4 hydroxyl group in **3** is substituted by $-CH_2CH_2OH$ functionality with inversion of orientation of the group. Thus, D-glucose was converted to known aldehyde **11c** with α-oriented $-CH_2CH_2OH$ functionality at C-3 by a known method.[10] The aldehyde group in **11c** was subjected to $NaBH_4$ reduction in methanol and the product thus obtained on tosylation and nucleophilic displacement with NaN_3 afforded azido compound **13c** (Scheme 1). Catalytic hydrogenation of **13c** followed by Cbz protection afforded **14c** as a thick oil in 90% yield. Treatment of **14c** with TFA-H_2O and catalytic hydrogenation afforded a compound that on purification with amberlite IR 400A (OH^-) resin gave a piperidine triol **10** in 95% yield.

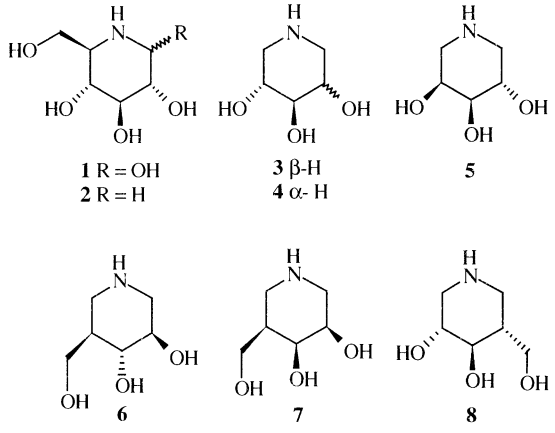

Figure 1.

Conformational Assignment of 3, 9 and 10

Nojirimycin (**1**) and 1-deoxy-nojirimycin (**2**) are known to exist in $^4C_1$ conformation. Recently,[8d] we have described the conformational study of 1-deoxy-D-*gluco*-homonojirimycin **15a** and 1-deoxy-L-*ido*-homonojirimycin **15b** and shown that both the compounds exist in $^4C_1$ conformations although, in **15b** the bulky $-CH2CH_2OH$ group at C-5 is axially oriented (Fig. 2). The assignment of conformation is based on the ^1H NMR spectra and coupling constant information between H-1, H-2, H-3, H-4 and H-5. In the case of 1-aza-sugars **3**, **9** and **10**, we have observed a dramatic differences in the ^1H NMR spectra which we would like to attribute to the conformational changes of these molecules. Thus, in case of compound **3** two conformations $^5C_2$ (**3a**) and $^2C_5$ (**3b**) are possible. In conformation **3a**, it is expected that the coupling constant $J_{2a,3a}$, $J_{3a,4a}$ and $J_{4a,5a}$ should be large (*J*aa = 7–9 Hz) while in the case of **3b** coupling constants should be small as

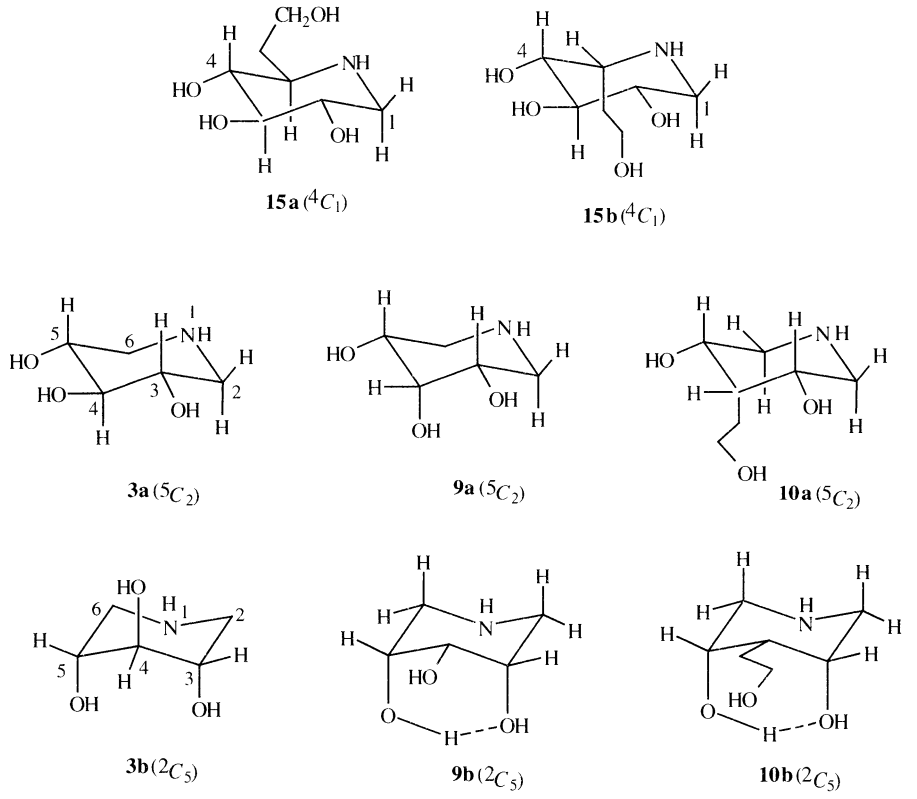

Figure 2. Different conformations of **3**, **9** and **10**.

Table 1. Inhibitory potencies of 1-aza-sugars (IC_{50}, CM) of **3**, **9** and **10**

Enzyme	**3**	**9**	**10**
β-Glucosidase	1.40×10^{-3}	3.18×10^{-6}	4.97×10^{-6}
α-Glucosidase	—	—	—
β-Galactosidase	3.6×10^{-6}	3.27×10^{-6}	
α-Galactosidase	4.44×10^{-6}	—	—
α-Mannosidase	—	—	—

H-3, H-4 and H-5 are equatorially oriented. In **3**, the appearance of triplet at 3.37 ($J_{3,4}=8.9$ Hz), a doublet of doublet at 3.32 ($J_{2e,2a}=12.5$, $J_{2e,3a}=4.8$ Hz), and another doublet of doublet at 2.80 ($J_{2e,2a}=12.7$, $J_{2a,3a}=12.2$ Hz) clearly indicated the *trans*-diaxial relationship between the H-2a, H-3a, and H-3a, H-4a confirming $^5C_2$ conformation **3a**. However, in the case of compound **9**, the ^{1}H NMR showed small coupling constant values ($W_H=5$ Hz) for H-2, H-3 and H-3, H-4 protons indicating $^2C_5$ conformation **9b**. In the ^{1}H NMR spectra of **10**, two broad doublets at 2.50 and 2.74 ($J_{2e,2a}=13.5$ Hz) corresponding to protons H-2a and H-2e suggested that H-3 is equatorially oriented and bisecting the H-2 protons (dihedral angle ~55°). The H-3 and H-5 protons also appeared as narrow multiplets thus indicating $^2C_5$ conformation **10b**. The conformation **9b** and **10b** is stabilised by intramolecular hydrogen bonding (Fig. 2). In addition, in the case of **10b**, the CH_2CH_2OH is equatorial while in **10a** it is axial. This further stabilises **10b** in relation to **10a**.

Biological Activity

Almond seeds are known to be a rich source of glycosidases namely α-glucosidases (E.C. 3.2.1.23), β-glucosidases (E.C. 3.2.1.2.4), α-galactosidases (E.C. 3.2.1.2.2), β-galactosidases (E.C. 3.2.1.2.3), and α-mannosidases (E.C. 3.2.1.2.4). Therefore, the potency of 1-aza-sugars **3**, **9** and **10** as glycosidase inhibitors was evaluated using almond seed extract as a glycosidase source. The IC_{50} values obtained are summarised in Table 1.

In the case of **3**, the observed IC_{50} value for β-glucosidase inhibition is found to be comparable to that reported.[5] The glycosidases inhibition activity of **9**, although known in the literature as **9**·HCl, is not reported. Our results demonstrate that **9** is a potent β-glucosidase inhibitor than **3**. This indicates that inversion of configuration at C-4 in piperidine triol, with –OH substituent, has a significant increase in β-glucosidase inhibition activity. Biological activities of **3** and **10** (wherein β-hydroxy functionality at C-4 was replaced by α-CH_2CH_2OH functionality) were compared. The comparative study demonstrates that the replacement of C4-OH with α-oriented –CH_2CH_2OH functionality resulted in increased potency towards β-glucosidases with high specificity.

In conclusion, we have demonstrated an efficient and straightforward methodology for the synthesis of 1-aza-sugars that can be reproduced on multigram scale. The concept that we have demonstrated herein clearly

indicates a design strategy for the development of new analogues of 1-aza-sugars. The synthesised compounds were tested for inhibition of glycosidases and are found to be good β-glucosidase inhibitors.

Experimental

^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded using $CDCl_3$ as a solvent unless otherwise stated. Chemical shifts are reported in ppm (δ) relative to internal standard Me_4Si. IR spectra (ν, cm^{-1}) were measured as thin films or Nujol mulls or KBr pellets. Optical rotations were recorded at 25 °C. Whenever required the reactions were carried out in oven-dried glassware under dry N2. On workup, reaction mixture was extracted with organic solvents, evaporated at reduced pressure with rotary evaporator. Thin layer chromatography was performed on 0.25 mm precoated silica gel, flash chromatography was carried out on silica gel 200–400 mesh and column chromatography on silica gel 100–200 mesh. The organic solvents such as *n*-hexane, THF, diethyl ether, chloroform, petroleum ether (pet. ether, 60–70 °C fraction), ethyl acetate and methanol were purified and dried before use. LAH, Cbz-Cl were purchased from Aldrich and/or Fluka. 1,2-*O*-Isopropylidene-3-[2-benzyloxyethyl]-α-D-*ribo*-pentodialdo-1,4-furanose **11c** and azido compounds **13a**,**b** were prepared as per literature procedure and characterisedby spectral methods.

Assay method

The substrates (2 mM in 0.025 M citrate buffer, pH 4.0) used were *p*-nitrophenyl *N*-acetyl-β-glucosaminide, *p*-nitrophenyl β-D-galactoside, *p*-nitrophenyl α-D-galactoside, *p*-nitrophenyl α-D-glucoside, *p*-nitrophenyl α-D-mannoside, respectively. The test compound was pre-incubated 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 the absence of the test compound. The reaction was terminated at the end of 90 min by the addition of borate buffer (0.05 M, pH = 9.8) and absorbance of the liberated *p*-nitrophenol was measured at 420 nm. The IC_{50} values were determined (IC_{50} value is the concentration of inhibitor at 50% ofenzyme activity). One unit of glycosidase activity is defined as the amount of enzyme that hydrolysed 1 μmole of *p*-nitrophenyl pyranoside per min at 25 °C.

1,2-*O*-Isopropylidene-3(2-benyloxyethyl)-5-*O*-tosyl-α-D-*ribo*furanose (12c). To an ice cooled solution of **11c** (0.8 g, 2.61 mmol) in methanol–water (4:1, 10 mL) was added $NaBH_4$ (0.118 g, 3.13 mmol) over a period of 10 min. The reaction mixture was warmed to room temperature and stirred for 0.5 h. Methanol was evaporated and resulting reaction mixture was extracted with ethyl acetate (10 mL×3). The organic layer was dried over sodium sulphate and evaporated to obtain product as a thick liquid. The product thus obtained was dissolved in pyridine (1.05 mL, 13.05 mmol), cooled to 0 °C and tosyl chloride (0.597 g, 3.13 mmol) was added. The reaction mixture was warmed to room temperature and stirred for 12 h. Water was added and resulting reaction mixture was extracted with ethyl acetate (10 mL×3). The organic layer was washed with cooled dil HCl, water and dried. Evaporation of organic layer afforded tosyl derivative **12c** (1.02 g, 85%) as a thick liquid.

R_f = 0.65 (*n*-hexane/ethyl acetate = 7/3); $[\alpha]_D$ = +21.5 (c, 0.6, $CHCl_3$); IR ν_{max} (neat) = 1656; ^{1}H NMR ($CDCl_3$, 300 MHz): 1.35 (3H, s, CH_3), 1.51 (3H, s, CH_3), 1.64–1.80 (1H,m, CH_2/H-3), 1.88–2.00 (1H, m, CH_2/H-3), 2.10–2.22 (1H, m, CH_2/H-3), 2.49 (3H, m, CH_3), 3.58–3.70 (2H, m, CH_2OBn), 3.98–4.06 (1H, m, H-4), 4.14 (1H, dd, J = 4.2, 11.1 Hz, H-5), 4.32 (1H, dd, J = 2.7, 11.1 Hz, H-5), 4.7 (2H, bs, *O*-CH_2Ph), 4.62 (1H, dd, J = 3.9, 4.2 Hz, H-2), 5.74 (1H, d, J = 3.9 Hz, H-1), 7.2 (7H, Ar–H), 7.85 (2H, d, J = 8 Hz, Ar–H); ^{13}C NMR ($CDCl_3$, 75 MHz): 25.0 (CH_3), 26.2 (CH_3), 40.8 (CH_2), 42.9 (CH_2), 51.7 (*O*-CH_2), 67.2 (*O*-CH_2Ph), 73.9, 75.5, 81.8 (C-2, C-3, C-4), 104.5 (C-1), 111.3 (O–C–O), 127.6, 128.4, 129, 138.3, 144 (Ar–C); Anal. calcd for $C_{24}H_{30}SO_7$: C, 62.87; H, 6.60. Found C, 62.90; H, 6.80.

1,2-*O*-Isopropylidene-3(2-benyloxyethyl)-5-azido-5-deoxy-α-D-*ribo*furanose (13c). A mixture of **12c** (0.6 g, 1.298 mmol) and NaN_3 (0.42 g, 6.49 mmol) in anhydrous DMF was stirred at 100 °C for 6 h. The reaction mixture was cooled to room temperature. After adding water the reaction mixture was extracted with ethyl acetate. The organic layer was dried and concentrated to furnish azido compound **13c** (0.37 g, 86%) as a thick liquid.

R_f = 0.72 (*n*-hexane/ethyl acetate = 7/3); $[\alpha]_D$ = +31.00 (*c*, 0.6, $CHCl_3$); IR ν_{max} (neat) = 2102; ^{1}H NMR ($CDCl_3$, 300MHz): 1.32 (3H, s, CH_3), 1.54–2.02 (3H, m, CH_2 and H-3), 3.48 (2H, narrow multiplet, N_3CH_2), 3.65–3.78 (2H, m, *O*–CH_2), 3.80–3.85 (1H, m, H-4), 4.67 (1H, dd, J = 3.6, 3.5 Hz, H-2), 5.11 (2H, ABq, J = 12.3 Hz, CH_2Ph), 5.76 (1H, d, J = 3.5 Hz, H-1), 7.2 (5H, s, Ar–H); ^{13}C NMR ($CDCl_3$, 75 MHz): 24.9 (CH_3), 26.3 (CH_3), 26.8 (CH_2), 42.6 (CH_2), 51.7 (OCH_2), 68.2 (CH_2Ph), 72.9, 80.5, 81.2 (C-2, C-3, C-4), 104.8 (C-1), 111.7 (O–C–O), 127.6, 128.4, 138.3 (Ar–C); Anal. calcd for $C_{17}H_{23}N_3O_4$: C, 61.24; H, 6.95. Found C, 61.34; H, 7.01.

General procedure for hydrogenation and *N*-Cbz protection. A mixture of azido compounds (1 mmol) and 10% Pd/C (10% w/w of the starting) in methanol was subjected to hydrogenation at 80 psi for 12 h. The catalyst was filtered through Celite and washed with methanol (5 mL). To the filtrate, sodium bicarbonate (4 mmol) and benzyloxycarbonyl chloride (1.2 mmol) was added at 0 °C. The mixture was stirred at 25 °C for 1 h. The methanol was evaporated and water (2 mL) was added. The reaction mixture was extracted with chloroform (3×10 mL), washed with water, dried and the organic layer was evaporated to give a thick liquid. Purification by column chromatography afforded *N*-Cbz compound.

1,2-*O*-Isopropylidene-3-*O*-benzyl-5-(*N*-benzoxycarbonylamino)-5-deoxy-α-D-xylofuranose (14a). White solid; mp = 119–121 °C; yield = 95%; R_f = 0.36 (*n*-hexane/ethyl acetate = 7/3); $[\alpha]_D$ = 31.25 (c, 0.8, $CHCl_3$);IR ν_{max} (neat) = 1687, 3350–3150 (broad band); ^{1}H NMR ($CDCl_3$ + D_2O, 300 MHz): 1.23 (3H, s, CH_3), 1.45 (3H, s, CH_3), 3.20–3.25 (1H, dd, *J* = 3.3, 14.0 Hz), 3.60–3.68 (1H, dd, *J* = 9.3, 14.0 Hz), 4.0–4.06 (2H, m, H-3, H-4), 4.60 (1H, d, *J* = 3.6 Hz, H-2), 5.05 (2H, s, *O*-CH_2), 5.85 (1H, d, *J* = 3.6 Hz, H-1), 7.17–7.22 (5H, m, Ar–H); ^{13}C NMR ($CDCl_3$ + D_2O, 75 MHz): 26.1 (CH_3), 26.8 (CH_3), 38.3 (*N*–CH_2), 67.5 (*O*–CH_2), 73.9, 80.1, 84.9 (C-2/C-3/C-4), 104.7 (C-1), 111.5 (O–C–O), 128.16, 128.4, 128.6, 135.8 (Ar–C), 157.9 (NCO); Anal. calcd for $C_{16}H_{21}NO_6$: C, 59.43; H, 6.55. Found C, 59.60; H, 6.60.

1,2-*O*-Isopropylidene-3-*O*-benzyl-5-(*N*-benzoxycarbonylamino)-5-deoxy-α-D-*ribo*furanose (14b). Thick liquid; yield = 93%; R_f = 0.18 (*n*-hexane/ethyl acetate = 7/3); $[\alpha]_D$ = 25.33 (c, 0.9, $CHCl_3$); IR ν_{max} (neat) = 1685, 3360–3100 (broad band); ^{1}H NMR ($CDCl_3$ + D_2O, 300 MHz): 1.36 (3H, s, CH_3), 1.56 (3H, s, CH_3), 3.47–3.6 (2H, m, *N*–CH_2), 3.7 (1H, dd, *J* = 5.1, 8.8 Hz, H-3), 3.85 (1H, m, H-4), 4.57 (1H, dd, *J* = 3.6, 5.1 Hz, H-2), 5.1 (2H, bs, $COCH_2$), 7.75 (d, *J* = 3.6 Hz, H-1); ^{13}C NMR ($CDCl_3$ + D_2O, 75 MHz): 26.31 (CH_3), 26.34 (CH_3), 41.1 (*N*-CH_2), 66.88 (*O*-CH_2), 72.50, 78.58, 78.64 (C-2/C-3/C-4), 103. 62 (C-1), 112.72 (O–C–O), 128.08, 128.43, 136.21 (Ar–C), 156.9 NCO); Anal. calcd for $C_{16}H_{21}NO_6$: C, 59.43; H, 6.55. Found C, 59.53; H, 6.72.

1,2-*O*-Isopropylidene-3(2-benzyloxyethyl)-5-(*N*-benzoxycarbonylamino)-5-deoxy-α-D-*ribo*furanose (14c). White solid; yield = 90%; R_f = 0.25 (*n*-hexane/ethyl acetate = 7/3); $[\alpha]_D$ = +31.00 (c, 0.6, $CHCl_3$); IR ν_{max} (neat) = 1680, 3400–3100 (broad band); ^{1}H NMR ($CDCl_3$ + D_2O, 300 MHz): 1.31 (3H, s, CH_3), 1.49 (3H, s, CH_3), 1.56–1.7 (1H, m, CH_2), 1.82–1.95 (1H, m, CH_2), 2.08–2.19 (1H, m, *N*-CH_2), 2.22 (1H, dd, *J* = 4.8, 12.9 Hz, *N*-CH_2), 3.56–3.64 (3H, m, H-3, *O*-CH_2), 3.95–4.01 (1H, m, H-4), 4.6 (1H, t, *J* = 4.2 Hz, H-2), 5.8 (1H, d, *J* = 4.2 Hz, H-1); ^{13}C NMR ($CDCl_3$ + D_2O, 75 MHz): 26.3 (CH_3), 26.7 (CH_3), 27.7 (CH_2), 41.4 (*N*-CH_2/*O*-CH_2) 41.6 (*N*-CH_2/*O*-CH_2), 60.7 ($COCH_2$), 60.7, 80.6, 81.4 (C-2, C-3, C-4), 104.8 (C-1), 111.6 (O–C–O), 128.2, 128.5, 136.2 (Ar–C), 157.1 (NCO); Anal. calcd for $C_{18}H_{25}NO_6$: C, 61.52; H, 7.17. Found C, 61.54; H, 7.21.

General procedure for acid hydrolysis and hydrogenation. A solution of *N*-Cbz compound (1 mmol) in TFA-H_2O (3/2, 2 mL) was stirred at 25 °C for 2 h. Trifluroacetic acid was co-evaporated with benzene to furnish a thick liquid, which was directly used in the next reaction. To a solution of the above product in methanol was added 10% Pd/C (10% w/w of the starting) and solution was hydrogenated at 80 psi for 12 h. The catalyst was filtered through Celite, washed with methanol and the filtrate concentrated to get crude compound. The crude compound was washed with chloroform (which was discarded) and thick oil thus obtained was dissolved in methanol and stirred with basic ion-exchange resin IRA 400 for 10 min. Filtration through Celite and concentration of the methanol under reduced pressure afforded 1-aza-sugar.

(3*S*, 4*R*, 5*R*) 3,4,5-Piperidine triol (3). Semi solid; yield = 92%; R_f = 0.18 (chloroform/methanol = 1/1); $[\alpha]_D$ = 0.0 (c 0.9, MeOH); IR ν_{max} (KBr pellet) = 3300–3250 (broad band); ^{1}H NMR ($CDCl_3$ + D_2O, 300 MHz): 2.80 (1H, dd, *J* = 12.8, 12.3 Hz, H2a/H6a) 3.32 (1H, dd, *J* = 12.8, 4.8 Hz, H-2e/H-6e), 3.37 (1H, t, *J* = 8.95 Hz, H-4), 3.64 (1H, m, H-3/H-5); ^{13}C NMR ($CDCl_3$ + D_2O, 75 MHz): 46.3 (C-2, C-6), 66.9 (C-3, C-5), 74.76 (C-4); Anal. calcd for $C_5H_{11}NO_3$: C, 45.10; H, 8.33. Found C, 45.32; H, 8.55.

(3*S*, 4*S*, 5*R*) 3,4,5-piperidine triol (9). Semi solid; yield = 94%; R_f = 0.18 (chloroform/methanol = 1/1); $[\alpha]_D$ = 0.0 (c 0.8, MeOH); IR ν_{max} (KBr pellet) = 3300–3200 (broad band); ^{1}H NMR ($CDCl_3$ + D_2O, 300 MHz): 3.0–3.04 (4H, m, H-2, H-6), 3.81–3.85 (3H, m, H-3,H-4, H-5); ^{13}C NMR ($CDCl_3$ + D_2O, 75 MHz): 44.29 (C-2, C-6), 65.55 (C-3, C-5), 68.35 (C-4); Anal. calcd for $C_5H_{11}NO_3$: C, 45.10; H, 8.33. Found C, 45.20; H, 8.50.

To a stirred solution of compound **9** (0.2 g, 1.50 mmol) in dry methanol was added HCl (0.1 mL) under dry N_2. The reaction mixture was stirred at room temperature for 2 h. After 2 h, the solvent was evaporated under reduced pressure to give **9**·HCl (0.23 g, 95%) as crystal which was crystallized from DMF–EtOH.

White solid; mp = 162–163 °C (reported mp = 161–163 °C); yield = 95%; $[\alpha]_D$ = 0.0 (c 0.8, MeOH); IR ν_{max} (KBr pellet) = 3300–3200 (broad band); ^{1}H NMR ($CDCl_3$ + D_2O, 300 MHz): 3.12–3.31 (4H, m, H-2, H-6), 4.05–4.10 (3H, m, H-3, H-4, H-5); ^{13}C NMR ($CDCl_3$ + D_2O, 75 MHz): 44.20 (C-2, C-6), 65.45 (C-3, C-5), 69.30 (C-4).

3*S*, 4*S* (2-Hydroxyethyl), 5*R* piperidine triol (10). Semi solid; yield = 95%; R_f = 0.15 (chloroform/methanol = 1/1); $[\alpha]_D$ = 0.0 (c 0.1, MeOH); IR ν_{max} (KBr pellet) = 3300–3260 (broad band); ^{1}H NMR (D_2O, 300 MHz): 1.05–1.30 (3H, m, CH_2, H-4), 2.50 (2H, bd, *J* = 13.5 Hz, H-2a, H-6a, 2.74 (2H, d, *J* = 13.5 Hz, H-2e, H-6e), 2.90–3.10 (2H, m, CH_2), 3.4 (2H, bs, H-3, H-5); ^{13}C NMR (D_2O, 75 MHz): 30.0 (CH_2), 36.3 (C-1/CH_2), 49.8 (C-1/CH_2), 58.6 (C-4), 65.30 (C-3); Anal. calcd for $C_7H_{15}NO_3$: C, 52.15; H, 9.38. Found C, 52.20; H, 9.49.

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