

Attempts towards Synthesis of Piperidine Derived Aza Sugars: Glycosidase Inhibitors

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Abstract— In this paper attempts towards the synthesis of some poly hydroxylated derivatives of aza heterocycles *viz.*, piperidine analogs which could act as glycosidase inhibitors have been demonstrated. Two different approaches were followed using the chemistry of glycals. However, the advanced intermediates obtained during these approaches could not be cyclized to the final products.

Keywords— Azasugars, glycosidase inhibitors, poly hydroxylated piperidine.

I. INTRODUCTION

Azasugars (also known as imino sugars) are sugar analogues containing an imino group instead of an oxygen atom in the ring¹. In 1966 nojirimycin (a polyhydroxylated piperidine), an azasugar, was discovered as the first alkaloid, obtained from the filtrate of streptomycin². Many such alkaloids found in nature and their analogues have aroused a great deal of synthetic interest in recent years because of their ability to inhibit oligosaccharides processing enzymes such as glycosidases³ and glycosyltransferases^{4,5}. Glycosidases are ubiquitous enzymes that are involved not only in the degradation of carbohydrates foodstuff⁶ but also in the processing of eukaryotic glycoproteins⁷ and glycolipids⁸. These enzymes inhibitors are useful in the treatment of variety of carbohydrates mediated diseases such as diabetics⁹, viral infections¹⁰, HIV¹¹, cancer metastases¹², hepatitis and gaucher disease¹³. Thus, azasugars has attracted considerable attention from synthetic and medicinal chemist, biologist and clinical researchers in recent years. Among the natural occurring azasugars the most important ones are nojirimycin¹⁴, 1-deoxynojirimycin¹⁵ and 1-deoxymannojirimycin¹⁶.

Azasugars undoubtedly constitute the most remarkable class of ‘glycomimetics’ designed by nature. Many structural variations have led to the development of number of useful

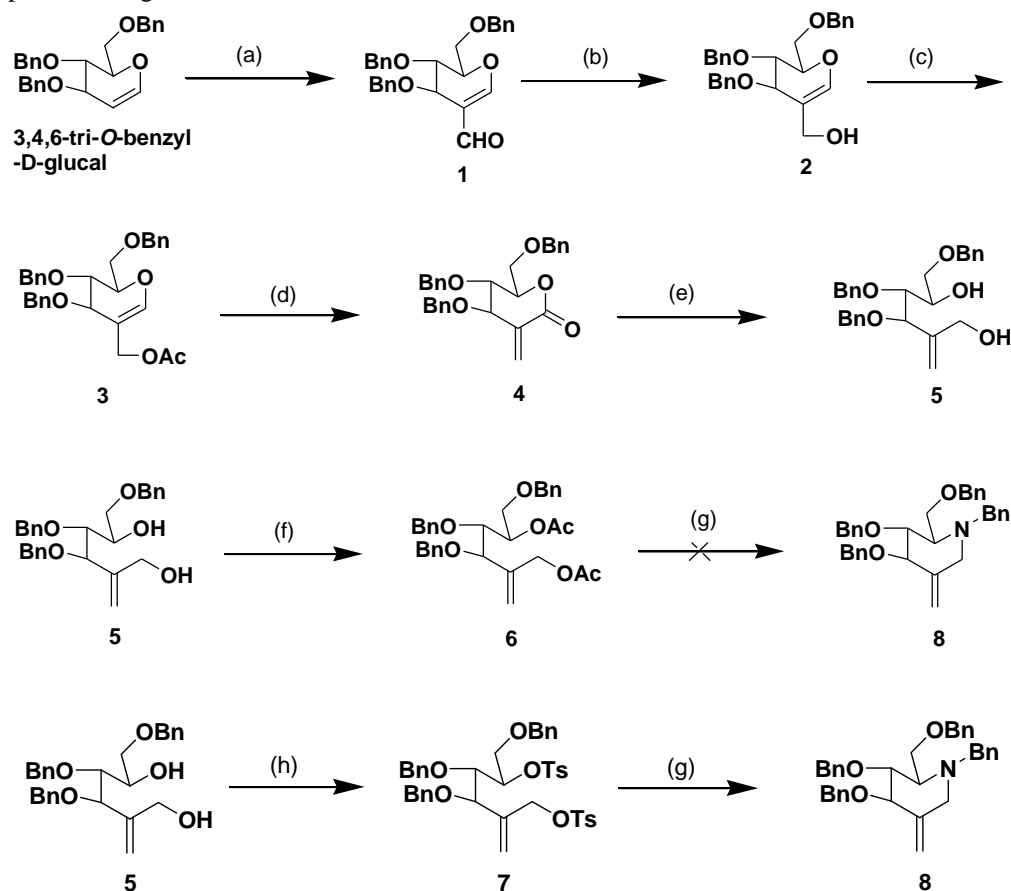
glycosidase inhibitors. The impressive biological activity profile of azasugars and their potential for therapeutic application has stimulated interest in the synthesis of six membered azasugars and their analogues through manipulation of the number and stereochemical disposition of the hydroxyl groups.

II. RESULTS AND DISCUSSION

Keeping in view the promising enzyme inhibitory activity, we planned to synthesize a six membered azasugar from sugar lactone **4** which was prepared from 3,4,6-tri-*O*-benzyl-D-glucal by the known literature procedure. Lactone **4** on reduction with LiAlH₄ in ether formed a diol **5** in 67% yield. Its ¹H NMR spectrum showed a doublet at δ: 4.29-4.33 for C-1 protons. The IR spectrum of the compound **5** showed a broad peak at 3417 cm⁻¹ and -OH bending at 1085 cm⁻¹. The exomethylene protons appeared as a doublet at δ: 5.22-5.28. Diol **5** was confirmed from its corresponding diacylated product **6**. Its ¹H NMR showed two singlets at δ: 1.89 and 2.07 for the two -COCH₃ groups. Compound **6** on treatment with benzylamine in presence of Et₃N and THF didn't cyclize to form an aza derivative **8** (Scheme 1).

However, the diol **5** on treatment with tosyl chloride in presence of triethylamine formed a ditosylated compound **7**, which in its ¹H NMR

spectrum showed a singlet at δ : 1.94 for the two methyl protons of the tosyl group. The ditosylate **7** on treatment with benzylamine in presence of Et_3N also did not cyclize to form expected azasugar **8**.



Scheme 1

Reagents and conditions: (a) POCl_3 , DMF, 0 °C to rt, 5h; (b) NaBH_4 , MeOH, 1h; (c) Ac_2O , Et_3N , rt; (d) m-CPBA, $\text{BF}_3\text{-Et}_2\text{O}$, DCM, -65 °C, 1h (e) LiAlH_4 , ether, 4h (f) Ac_2O (2eq.), Et_3N (2eq.), rt (g) BnNH_2 , NaH, THF, 2.5h; (h) TsCl , Et_3N , DCM, 28h.

Thus, in conclusion, we tried to synthesize piperidine analogue of aza heterocycles which could act as glycosidase inhibitors *via* different approaches could not be cyclized to the final product.

III. EXPERIMENTAL SECTION

General:

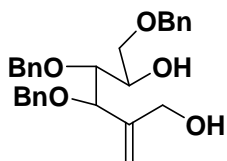
All the experiments were performed in oven dried glass apparatus and under nitrogen atmosphere. Commercial grade solvents were distilled before use. Dichloromethane was dried with activated CaCl_2 and distilled over CaH_2 . $\text{BF}_3\text{.Et}_2\text{O}$ was distilled over

P_2O_5 under vacuum. Thin layer chromatography was performed on prepared thin layers of Acme silica gel on microscopic slides or precoated plates (E-Merck, Germany). The visualization of spots on TLC plates was effected by exposure to iodine and spraying with 10% H_2SO_4 followed by charring. Column chromatography was performed over Acme silica gel (100-200 mesh) using hexane and ethyl acetate as eluent.

Infrared spectra were recorded on Bruker Vector 22 FT-IR spectrometer. The rotation values were recorded on Autopot II automatic polarimeter at the wavelength of the sodium D-line (589 nm) at 25 °C.

^1H , ^{13}C , COSY, NOESY spectra were recorded on JEOL JNM-LA 400 spectrometer in the solution of CDCl_3 using tetramethylsilane as the internal standard. Chemical shifts are reported in ppm downfield to tetramethylsilane. Coupling constants are reported and expressed in Hz, splitting patterns are designated as br (broad), s (singlet), d (doublet), dd (double doublet), ddd (doublet of a doublet of a doublet), q (quartet), dt (doublet of a triplet), m (multiplet). Elemental analyses (C, H, N, S and O) were done using thermoquest CE-instruments EA-1110 automatic elemental analyzer. The mass spectra were recorded on a microscopical II triple quadrupole mass spectrometer using electrospray technique. Melting points were determined using a PEW (Pathak Electrical Works, Bombay, India) melting point apparatus.

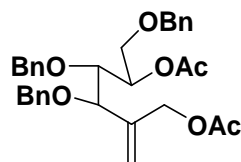
Compound 5



To a stirred suspension of LiAlH_4 (239 mg, 6.28 mmol) in ether at 0°C was added compound **4** (700 mg, 1.57 mmol) in small portions. The reaction mixture was refluxed at 30°C - 40°C for 7h. The completion of the reaction was monitored by TLC. The reaction mixture was cooled to 0°C and then ethyl acetate and water was added to it. The mixture was neutralized by 1N NaOH and the solution was stirred for 10-15 min at room temperature. The solution was filtered on a pad of celite in order to remove the white precipitate. The filtrate was extracted with ethyl acetate (2 x 25 mL), washed with water, brine and dried over anhydrous Na_2SO_4 . The crude product was purified by column chromatography to obtain 473 mg of compound **5** as a white solid.

$R_f = 0.27$ (7:3 hexane:EtOAc); Yield = 67%; $[\alpha]_D^{25} = +1.82$ ($c=2.30$, CHCl_3); IR (CH_2Cl_2) $\nu_{\text{max}} = 3417\text{ cm}^{-1}$; ^1H NMR (400 MHz, CDCl_3): δ : 1.90 (brs, 2H), 3.48-3.52 (m, 1H), 3.59-3.60 (m, 1H), 3.70-3.82 (m, 3H), 4.09-4.20 (m, 3H), 4.29-4.33 (m, 1H), 4.50-4.65 (m, 4H), 5.22-5.28 (m, 2H), 7.24-7.33 (m, 15 H); ^{13}C NMR (100 MHz, CDCl_3) δ : 29.6, 69.3, 70.9, 71.1, 73.1, 73.3, 73.5, 74.2, 78.0, 78.2, 127.7-128.3m, 137.7, 137.9; MS (ESI): $m/z = 471(\text{M}+\text{Na}^+)$; Anal. Calcd. for $\text{C}_{28}\text{H}_{32}\text{O}_5$ (448.55): C, 74.97%, H, 7.19%; Found: C, 74.96% H, 7.17%.

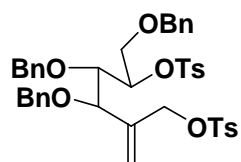
Compound 6



To a stirred solution of compound **5** (100 mg, 0.22 mmol) in dry DCM (1 mL) was added acetic anhydride (0.05 mL, 0.55 mmol) and triethyl amine (0.04 mL, 0.33 mmol) at room temperature. The reaction mixture was stirred for 2h. After the completion of the reaction (TLC monitoring), the organic layer was extracted with DCM (2 x 30 mL), washed with water and brine and dried over anhydrous Na_2SO_4 . The crude product was purified by column chromatography to get 107mg of compound **6** as a white solid.

$R_f = 0.70$ (7:3 hexane:EtOAc); Yield = 90%; IR (CH_2Cl_2) $\nu_{\text{max}} = 1740\text{ cm}^{-1}$; ^1H NMR (400 MHz, CDCl_3): δ : 1.89 (s, 3H), 2.07 (s, 3H), 3.71-3.79 (m, 2H), 3.86-3.88 (m, $J = 5.6$ Hz, 1H), 3.99-4.01 (d, $J = 5.6$ Hz, 1H), 4.26-4.29 (d, $J = 11.7$ Hz, 1H), 4.46 (brs, 2H), 4.56-4.74 (m, 5H), 5.07-5.10 (m, 1H), 5.27 (brs, 1H), 5.34 (brs, 1H), 7.25-7.33 (m, 15H); ^{13}C NMR (100 MHz, CDCl_3) δ : 29.6, 69.8, (two peaks), 69.3, 70.9, 71.1, 71.8, 72.6, 72.9, 73.1, 74.4, 75.1, 77.8, 78.7, 127.6-128.3, 137.8-138.1, 170, 170.6; MS (ESI): $m/z = 555(\text{M}+\text{Na}^+)$; Anal. Calcd. for $\text{C}_{32}\text{H}_{36}\text{O}_7$ (532.25): C, 72.16% H, 6.81%; Found: C, 72.15% H, 6.80%.

Compound 7



To a stirred solution of compound **5** (100 mg, 0.22 mmol) in dry DCM (2 mL) was added triethyl amine (0.11 mL, 0.77 mmol) at 0°C . The reaction mixture was stirred for 10-15 min and then tosyl chloride (104 mg, 0.55 mmol) was added to it. The reaction mixture was heated to 30°C - 40°C for 28h. After the completion of the reaction (TLC monitoring), the organic layer was extracted with DCM (2 x 30 mL), washed with water, brine and dried

over anhydrous Na_2SO_4 . The crude product was purified by column chromatography to get 68 mg of ditosylated compound **7** as a viscous liquid.

$R_f = 0.65$ (7:3 hexane:EtoAc); Yield = 40%; $[\alpha]_D^{25} = -24.3$ (c1.15, CHCl_3); IR (CH_2Cl_2) $\nu_{\text{max}} = 1104\text{cm}^{-1}$; ^1H NMR (400 MHz, CDCl_3): δ : 1.93 (s, 6H), 3.51-3.59 (m, 3H), 3.88-3.91 (m, 3H), 4.10-4.13 (m, 1H), 4.16-4.20 (d, $J = 5.6$ Hz, 1H), 4.33-4.36 (d, $J = 11.9$ Hz, 2H), 4.51 (s, 2H), 4.54-4.55 (m, 1H), 5.42-5.44 (d, $J = 9.5$ Hz, 2H), 7.24-7.35 (m, 23H); ^{13}C NMR (100 MHz, CDCl_3) δ : 69.2, 71.0, 73.4, 73.5, 75.0, 79.5, 79.9, 83.9, 109.9, 127.5-128.4, 138.1, 141.7; MS (ESI): $m/z = 779$ ($\text{M} + \text{Na}^+$); Anal. Calcd. for $\text{C}_{42}\text{H}_{44}\text{O}_9\text{S}_2$ (756.24): C, 66.64% H, 5.86 % S, 8.47% Found: C, 66.63% H, 5.85% S, 8.45 %.

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