Approaches towards the synthesis of Pyrrolidine derived Aza-sugars

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Introduction

Iminosugars or aza-sugars[1]are compounds in which the ring oxygen of a monosaccharide has been replaced by an imino group. Many polyhydroxylated pyrimidine alkaloids have attracted considerable attention due to their ability to inhibit glycosidases[2]**.** Because glycosidases are involved in several important biological processes, these polyhydroxylatedalkaloids have stimulated interest in the development of specific glycosidase inhibitors such as diabetes[3]or as antiviral, antibacterial and anticancer agents[4]. In particulars, glycosidase inhibitors have shown potential as therapeutic agent for type II diabetes[5]and HIV-I infection[6].In this direction various glycosidase inhibitors have been synthesized such as amidines[7], imidazoles[8], trizoles[9] and tetrazoles[10].

Results and discussion

Due to the emerging importance of hybrid molecules[11] we tried to synthesizepyrrolidineanalog of azaheterocycles, which could act as glycosidase inhibitors from tri-*O*-bengyl-D-glucal. Two approaches were followed using the chemistry of D-glycal.

Approach-1

In this approach,3,4,6-tri-*O*-benzyl-D-glucal was converted to tri-benzylatedallylic alcohol **1** by the known literature procedure[12]*via*two steps viz., formylation followed by $NaBH_4$ reduction. Compound **1** on benzylation with benzyl bromide inpresence of NaH in DMSO forms benzylatedcompound **2** in 89% yield, which was characterized from its ^{1}H NMR data, ^{13}C NMR data and by mass spectral data. Compound **2** on dihydroxylation with OsO_4-NMO formed a diol**3**in 94% yields, which in its ^{1}H NMR spectrum showed a singlet for anomeric proton at δ 5.36-5.39. IR spectrum of the compound **3** showed the absorption peak for -OH group at 3408 cm^{-1}. Compound **3** on oxidative cleavage with $NaIO_4$ in acetonitrile formed compound **4** in 83% yield. Compound **4** was directly obtained from compound **2** by ozonolysis process.

Reagents and conditions

(a) BnBr, NaH, DMSO, rt, 5 h; (b) OsO_4-NMO, Acetone:H_2O :^{t}BuOH (1:1:0.5), $Na_2S_2O_5$, rt, 2.5 h; (c) $NaIO_4$, CH_3CN/H_2O, 0 °C to 10 °C, 2 h; (d) O_3, DCM, 15 min; (e) $LiAlH_4$, THF, rt, 1 h; (f) IBX, EtOAc, 80 °C, reflux, 4 h; (g) K_2CO_3, MeOH, rt, 1 h; (h) $NaCNBH_3$/AcOH, 0 ºC to rt; (i) MsCl, Et_3N, DCM, 2 h. (j) $BnNH_2$, NaH, CH_2Cl_2, 0 ºC to rt.

Scheme 1

Compound **4** in its ^{1}H NMR spectrum showed a peak at δ 7.78 for -OCO<u>H</u> group. A multiplet at δ 5.15-5.17 was seen for C-5 proton. IR spectrum of compound **4** showed a peak at 1726 cm^{-1} for -OCHO group. Compound **4** on hydrolysis with K_2CO_3/ MeOH[13] formed compound **6**, which on oxidation with IBX formed compound **7**.However, compound **4** on $LiAlH_4$ reduction formed a diol**5** in 70% yield, which was confirmed from its ^{1}H NMR spectrum. IR spectrum of compound **5** showed a peak for the hydroxy group at 3437cm^{-1} (Scheme1). Diol**5** was also confirmed from its corresponding diacetate, which in its ^{1}H NMR spectrum

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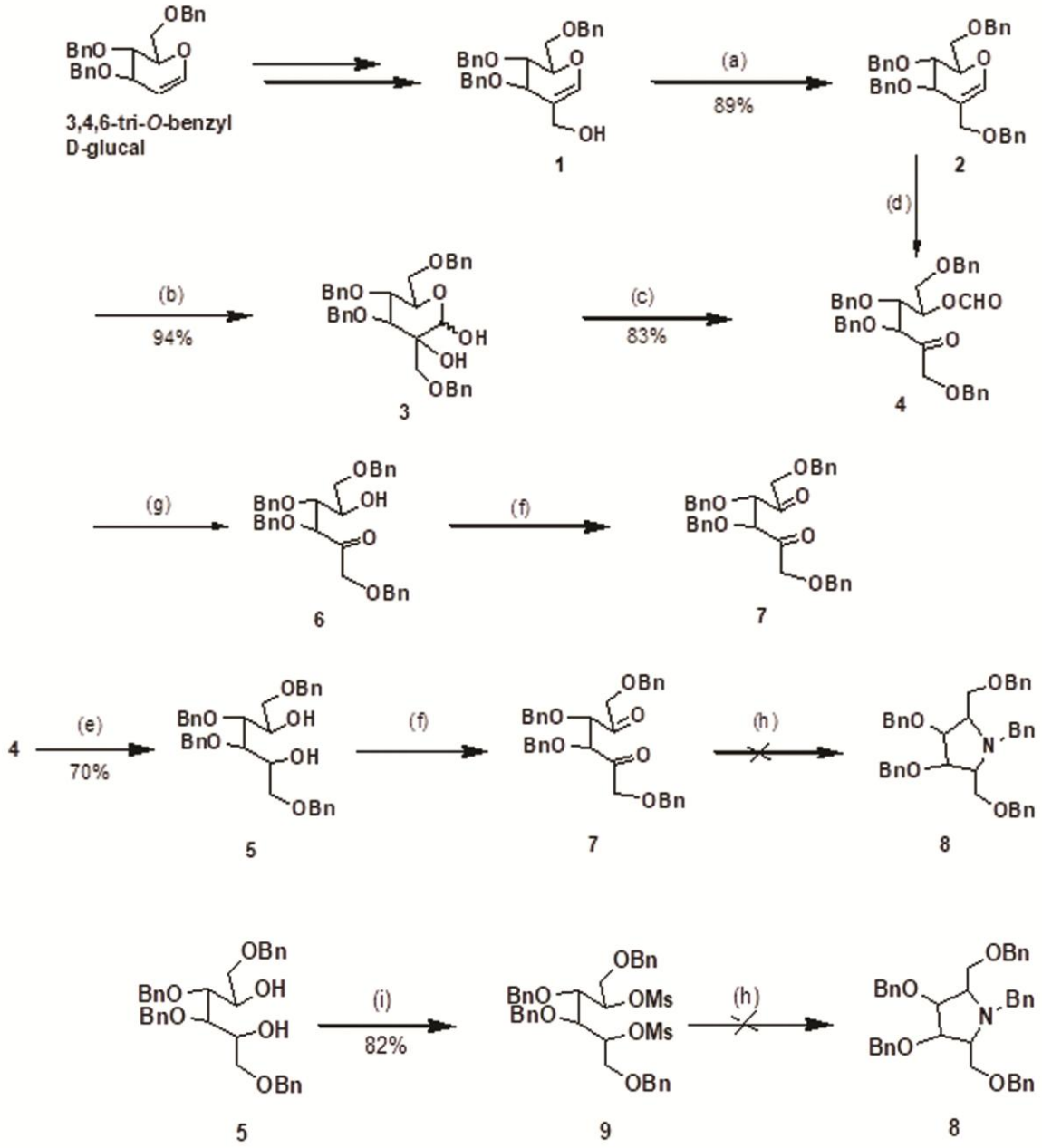
showed two singlets at δ 1.92 and 1.98 cm^{-1} for the two –$COCH_3$groups.

Diol**5** on oxidation with IBX in ethyl acetate forms a diketo derivative **7**. Diol**5** was also oxidized by CrO_3/H_2SO_4 to form a diketo product **7**. Compound **7** on treatment with $BnNH_2$ in presence of $NaCNBH_3/AcOH$[14] didn't form a cyclized aza product **8**(Scheme 1).

However, the diol**5** was mesylated with MsCl to form a dimesylated product **9** in 82 % yield**,** which in its ^1H NMR spectrum showed a singlet at δ 2.96 for the mesyl group. Compound **9** on treatment with $BnNH_2$/NaH didn't form a cyclized product **8.**

The extension of this work to other six membered aza-sugars is under progress and soon will be published soon.



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