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Improved synthesis of 6-amino-6-deoxy-D-galactono-1,6-lactam and D-mannono-1,6-lactam from corresponding unprotected D-hexono-1,4-lactones

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Abstract—Regioselective bromination of unprotected D-galactono-1,4-lactone and D-mannono-1,4-lactone with PPh_3/CBr_4 led to 6-bromo-6-deoxy derivatives. These intermediates were treated with LiN_3 and hydrogenated to give 6-amino-6-deoxy-D-galactono-1,6-lactam (**8**) and 6-amino-6-deoxy-D-mannono-1,6-lactam (**13**) in 74 and 67% overall yield, respectively.

1. Introduction

The discovery of the glycosidase inhibitor activity of the natural product nojirimycin **1** initiated the synthesis of various polyhydroxylated piperidine and pyrrolidine derivatives (azasugars).[1] This group of inhibitors is potentially useful for treating metabolic disorders such as diabetes,[2] cancer[3] and AIDS.[4] Seven-member azasugars (polyhydroxyazepanes **2**, **3**, **4**) have also shown to possess potent inhibitory activities.[5] (Fig. 1) The hydroxyl groups, in azepanes, adopt different spatial disposition due to the flexibility of the seven-member ring, therefore increasing the formation of hydrogen bonds to make contact with the enzyme.

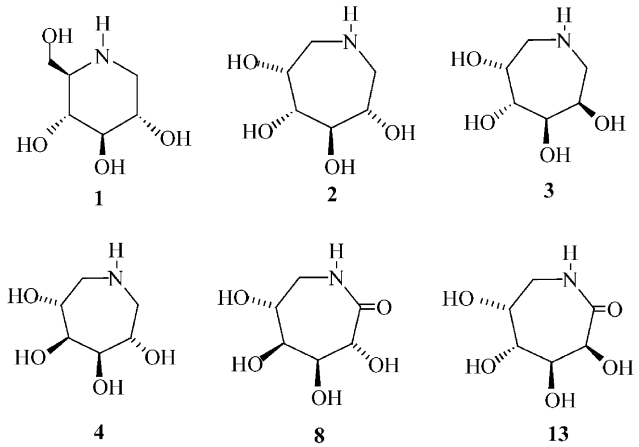

Figure 1. Examples of azasugars.

However, only a few reports have appeared on the synthesis of seven-member iminosugars. In some of those reported they have been obtained in admixture with their corresponding six-member ring derivatives, requiring separation.[6]

The use of protected D-galactono-1,4-lactone and D-mannono-1,4-lactone for preparing the corresponding lactams **8**[7] and **13**[8] has been described. The title compounds were obtained in 54 and 27% overall yield, respectively.

In the continuation of our interest in the synthesis of azasugars,[9] we now describe a direct and improved synthetic route to 6-amino-6-deoxy-D-1,6-galactonolactam (**8**) and 6-amino-6-deoxy-D-mannono-1,6-lactam (**13**) from unprotected D-galactono-1,4-lactone and D-mannono-1,4-lactone, in three steps.

2. Results and discussion

The selective bromination of the primary hydroxyl group in D-galactono-1,4-lactone (**5**) using triphenylphosphine (PPh_3)-carbon tetra-bromide (CBr_4) in pyridine gave the 6-bromo-6-deoxy-D-galactono-1,4-lactone (**6**) in 82% yield as the key starting material for the synthesis of lactam **8**. The introduction of an azide function at the C-6 position was achieved using lithium azide (LiN_3) to give 6-azido-6-deoxy-D-galactono-1,4-lactone (**7**) in 91% yield. A one-pot procedure for the azidation of (**5**), was attempted: either by using a mixture of PPh_3-CBr_4 and lithium azide in (DMF)

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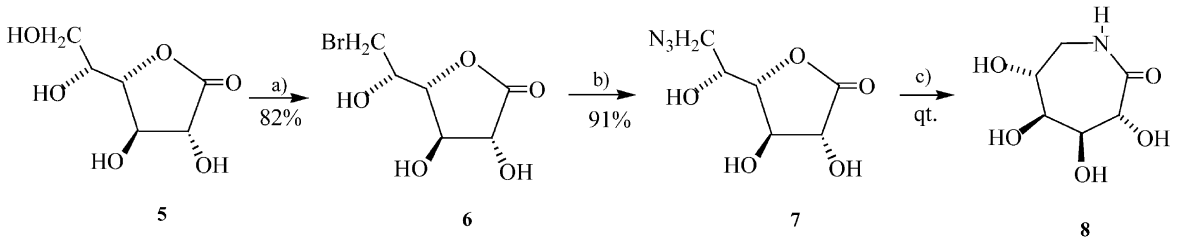


Scheme 1. Conditions: (a) PPh_3, CBr_4; (b) LiN_3; (c) H_2, Pd/C.

to give compound **7** but in only 11% yield, or by using Mitsunobu reaction (PPh_3-diethyl azodicarboxylate-diphenylphosphoryl azide in DMF) to give **7** in 40% yield.

Catalytic hydrogenation of **7** over palladium on charcoal (10%), at room temperature, produced quantitatively the desired 6-amino-6-deoxy-D-galactono-1,6-lactam (**8**) (Scheme 1).

D-mannono-1,4-lactone was used as the key starting material for the synthesis of lactam **13** (Scheme 2). For synthesis of D-mannono-1,4-lactone (**10**), which was not commercially available, we have used two procedures. First, we have hydrogenated the double bound of D-isoascorbic acid as describe in literature[8] but the yield of this reaction was lower than 50%. In a second time oxidation, of D-mannose (**9**), using bromine and barium carbonate in water[10] afforded a mixture of D-mannono-1,4-lactone (**10**) and D-mannono-1,5-lactone. Isolation of compound **10** was very difficult and lead to substantially lower yield.

However, when sodium hydrogencarbonate was used instead of barium carbonate, D-mannono-1,4-lactone (**10**) was isolated in quantitative yield.

Treatment of D-mannono-1,4-lactone (**10**) with PPh_3–CBr_4 in pyridine gave the 6-bromo-6-deoxy-D-mannono-1,4-lactone (**11**) in 69% yield. The reaction of the brominated derivative **11** with LiN_3 afforded the 6-azido-6-deoxy-D-mannono-1,4-lactone (**12**) in 98% yield. Hydrogenation of **12** with H_2–Pd/C produced quantitatively 6-amino-6-deoxy-D-mannono-1,6-lactam (**13**) (Scheme 2).

Overall yields for the transformation of unprotected D-galactono and D-mannono-1,4-lactones into corresponding 6-amino-6-deoxy-D-hexono-1,6-lactams are 74 and 67%, respectively.

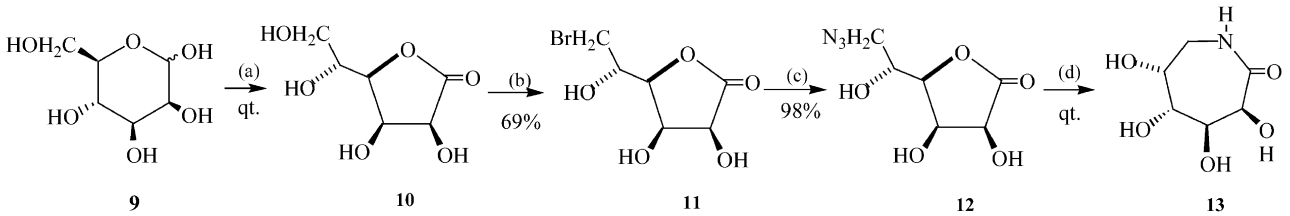
3. Experimental

3.1. General

Melting points were determined on a Buchi 535 apparatus and are uncorrected. Optical rotations were measured with a JASCO DIP-370 digital polarimeter, using a sodium lamp (λ=589 nm) at 24 °C. ^1H and ^{13}C NMR spectra were recorded in D_2O, in MeOD or in DMSO-d_6. Me_4Si was used as an internal standard on a Bruker 300 MHz spectrometer.

Thin-layer chromatography (TLC) was performed on E. Merck glass plates silica gel sheets (SilicaGel F_{254}) and visualised under UV light and/or stained with phosphomolybdic acid-aqueous H_2SO_4 solution. Column chromatography was carried out on silica gel (E. Merck 230–400 mesh). All solvents were distilled before use.

3.1.1. 6-Bromo-6-deoxy-D-galactono-1,4-lactone (6). To a solution of D-galactono-1,4-lactone (**5**) (10 g, 56.2 mmol) in pyridine (200 mL) was added triphenylphosphine (30 g, 2 equiv.) and carbon tetra-bromide (3×6 g, 1 equiv.) at 20 min intervals. The mixture was stirred, under an inert atmosphere, at room temperature for 18 h. Methanol was added and the solution was kept for 10 min at room temperature and concentrated in vacuo. The toluene (50 mL) was added to the crude material. After concentration, the residue was diluted with water and washed with CH_2Cl_2. The water extracts were concentrated in vacuo and the obtained residue was chromatographed on silica gel. Elution with EtOAc–hexanes (9:1) to give **6** (11.2 g, 82%) as white solid: R_f 0.6 (EtOAc–MeOH 9:1); mp 126–127 °C; $[\alpha]_D^{24}$ −100 (*c* 1.0, H_2O). Anal. calcd % for $C_6H_9BrO_5$: C, 29.90; H, 3.76; Br, 33.15. Found % C, 30.4; H, 3.70; Br 33.02; ^1H NMR (300 MHz, MeOD) δ 4.42 (d, 1H, *J*=8.4 Hz), 4.32 (m, 2H), 3.98 (m, 1H), 3.62 (dd, 1H, *J*=6.9, 10.3 Hz), 3.50 (dd, 1H, *J*=6.7, 10.2 Hz). ^{13}C NMR (75 MHz, MeOD) δ 174.9, 80.3, 74.7, 73.8, 69.0, 32.5.



Scheme 2. Conditions: (a) Br_2, H_2O, $NaHCO_3$; (b) PPh_3, CBr_4; (c) LiN_3; (d) H_2, Pd/C.

3.1.2. 6-Azido-6-deoxy-D-galactono-1,4-lactone (7). A stirred solution of 6-bromo-6-deoxy-D-galactono-1,4-lactone (**6**) (1 g, 4.15 mmol) in DMF (10 mL) was treated with lithium azide (20% in H_2O) (12 mL, 1.3 equiv.) and set aside at 80 °C for 1 h. The mixture was poured into ice-water (15 mL) and the product extracted with ethyl acetate. The organic layer was concentrated in vacuo and the obtained residue was chromatographed on silica gel. Elution with EtOAc–hexanes (7:3) to give **7** (0.74 g, 91%) as yellow oil: R_f 0.7 (EtOAc–MeOH 9:1); $[\alpha]_D^{24}$ −65 (*c* 1.0, MeOH). Lit.[7] $[\alpha]_D^{23}$ −70.6 (*c* 1.0, MeOH); ^{1}H NMR (300 MHz, MeOD) δ 4.40 (d, 1H, *J*=8.8 Hz), 4.27 (dd, 1H, *J*=8.2, 8.8 Hz), 4.11 (dd, 1H, *J*=2.8, 8.1 Hz), 3.91 (m, 1H), 3.51 (dd, 1H, *J*=7.7, 12.7 Hz), 3.41 (dd, 1H, *J*=5.0, 12.7 Hz); ^{13}C NMR (75 MHz, MeOD) δ 175.0, 80.8, 74.6, 73.6, 68.5, 53.4.

3.1.3. 6-Amino-6-deoxy-D-galactono-1,6-lactam (8). A solution of compound **7** (0.35 g, 1.72 mmol) in ethanol (8 mL) was treated with palladium on charcoal (10%, 0.035 g) and then hydrogenated for 18 h at room temperature. The mixture was filtered through a layer of celite and the filtrate was concentrated in vacuo to give **8** as white solid: R_f 0.4 (EtOAc–MeOH 3:2); mp 168–170 °C; $[\alpha]_D^{24}$ −13 (*c* 1.0, H_2O). Lit.[7] $[\alpha]_D^{25}$ −16.3 (*c* 1.0, H_2O); mp 175–176 °C; ^{1}H NMR (300 MHz, D_2O) δ 4.43 (d, 1H, *J*=9.3 Hz), 3.91 (m, 1H), 3.71 (m, 2H), 3.50 (dd, 1H, *J*=4.6, 15.8 Hz), 3.21 (dd, 1H, *J*=2.9, 15.8 Hz); ^{13}C NMR (75 MHz, D_2O) δ 176.4, 73.3, 69.1, 40.6.

3.1.4. D-mannono-1,4-lactone (10). To a solution of D-mannose (**9**) (5 g, 2.8 mmol) and sodium hydrogencarbonate (3.35 g, 4 mmol) in distilled water (50 mL) cooled at 0 °C, bromine (3×1 mL, 58.5 mmol) was added at 20 min intervals. The reaction mixture was stirred at this temperature for 1 h and then for 4 days at room temperature. Sodium thiosulfate was added to destroy the excess of bromine and the solvent was removed in vacuo to give a white solid. The obtained solid was chromatographed on silica gel. Elution with EtOAc–MeOH (9:1) and recrystallized from 2-propanol to give quantitatively compound **10** as white solid: R_f 0.5 (EtOAc–MeOH 7:3); mp 145–146 °C; $[\alpha]_D^{24}$ +53 (*c* 1.0, H_2O). Lit.[11] mp 151 °C; $[\alpha]_D^{20}$ +51.2 (*c* 2, H_2O); ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.55 (d, 1H, *J*=4.6 Hz), 4.50 (dd, 1H, *J*=2.7, 4.6 Hz), 4.31 (dd, 1H, *J*=8.9, 2.8 Hz), 3.96 (m, 1H), 3.80 (dd, 1H, *J*=2.8, 11.7 Hz), 3.67 (dd, 1H, *J*=5.1, 11.7 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 177.1, 78.6, 71.2, 69.8, 68.5, 63.2.

3.1.5. 6-Bromo-6-deoxy-D-mannono-1,4-lactone (11). Reaction of **10** (2.15 g, 12 mmol) with triphenylphosphine and carbon tetra-bromide in pyridine, as in case of **5** gave **11** (2 g, 69%) as white solid: R_f 0.44 (EtOAc–MeOH 9:1); mp 136–137 °C; $[\alpha]_D^{24}$ +55 (*c* 1.0, H_2O). Lit.[12] mp 136–139 °C; $[\alpha]_D^{20}$ +54.7 (*c* 1.1, H_2O). ^{1}H NMR (300 MHz, MeOD) δ 4.61 (d, 1H, *J*=4.6 Hz), 4.47 (dd, 1H, *J*=2.7, 4.6 Hz), 4.32 (dd, 1H, *J*=2.7, 9.0 Hz), 4.13 (m, 1H), 3.75 (dd, 1H, *J*=2.8, 11.6 Hz), 3.63 (dd, 1H, *J*=5.1, 11.6 Hz). ^{13}C NMR (75 MHz, MeOD) δ 177.3, 80.6, 71.8, 70.1, 67.5, 37.4.

3.1.6. 6-Azido-6-deoxy-D-mannono-1,4-lactone (12). Reaction of **11** (0.7 g, 2.9 mmol) in DMF with lithium azide, as in case of **6** gave **12** (0.58 g, 98%) as yellow oil: R_f 0.6 (EtOAc–MeOH 9:1); $[\alpha]_D^{24}$ +20 (*c* 1.0, MeOH). Anal. calcd % for $C_6H_9N_3O_5$: C, 35.47; H, 4.47. Found % C, 35.42; H, 4.42; ^{1}H NMR (300 MHz, MeOD) δ 4.68 (d, 1H, *J*=4.5 Hz), 4.57 (dd, 1H, *J*=2.7, 4.4 Hz), 4.52 (dd, 1H, *J*=2.7, 8.9 Hz), 4.15 (m, 1H), 3.55 (dd, 1H, *J*=2.2, 12.8 Hz), 3.39 (dd, 1H, *J*=4.9, 12.8 Hz). ^{13}C NMR (75 MHz, MeOD) δ 176.6, 79.2, 71.3, 69.6, 67.4, 54.2.

3.1.7. 6-Amino-6-deoxy-D-mannono-1,6-lactam (13). Compound **12** (0.3 g, 1.48 mmol) in ethanol was treated with palladium on charcoal and then hydrogenated for 18 h, as in case of **7**, to give **13**, in quantitative yield, as white solid: R_f 0.4 (EtOAc–MeOH 3:2); mp 150–152 °C; $[\alpha]_D^{24}$ +47 (*c* 1.0, H_2O). Anal. calcd % for $C_6H_{11}NO_5$: C, 40.68; H, 6.26. Found % C, 40.60; H, 6.12; ^{1}H NMR (300 MHz, D_2O) δ 4.71 (d, 1H, *J*=5.6 Hz), 3.98 (m, 2H), 3.74 (m, 1H), 3.52 (dd, 1H, *J*=6.8, 13.4 Hz), 2.84 (m, 1H). ^{13}C NMR (75 MHz, D_2O) δ 175.9, 75.1, 72.2, 75.1, 68.8, 67.4, 39.7.

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