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Note

A new practical synthesis of (2*S*,3*R*,4*R*,5*S*)-3,4-dihydroxy-2,5-bis(hydroxymethyl)pyrrolidine

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Many aza sugars, compounds formed by substitution of the ring oxygen of pyranoses and furanoses by nitrogen, are powerful inhibitors of glycosidases and enzymes responsible for glycoprotein processing, and some have shown anti-HIV activity[1–6]. In addition to polyhydroxylated piperidines, polyhydroxylated pyrrolidines are still of interest from a synthetic point of view[7–14]. (2*R*, 3*R*, 4*R*, 5*R*)-3,4-Dihydroxy-2,5-bis(hydroxymethyl)pyrrolidine is a natural inhibitor of many glycosidases; a diastereoisomer, namely, (2*S*, 3*R*, 4*R*, 5*S*)-3,4-dihydroxy-2,5-bis(hydroxymethyl)pyrrolidine (**5**), has not been isolated from Nature; however, it has been synthesized by others[7–10], three of the routes being from D-mannitol derivatives by way of a double S_N2-type reaction[7–9]. We describe herein a more practical method for the synthesis of **5** (Scheme 1).

Reductive amination is a very useful method to prepare an amine from an aldehyde or ketone[15]. Reitz and Baxter[11] reported a double reductive amination of D-*threo*-2,5-hexodiulose (5-keto-D-fructose) using benzhydrylamine–sodium cyanoborohydride to yield three pyrrolidine stereoisomers. We believed that the low stereoselectivity could be improved by using a rigid substrate, for example, 1,3:4,6-di-*O*-benzylidene-5-keto-D-fructose[16] (see hydrate **2**). Compound **2** was prepared in 59% yield from 1,3:4,6-di-*O*-benzylidene-D-mannitol[17] (**1**) by oxidation with pyridinium chlorochromate–sodium acetate in acetonitrile–dichloromethane. Both of the secondary hydroxyl groups were oxidized to give a product which existed as a C_2-symmetric, cyclic hydrate; the two hemiketal centers were established to have the same configuration by ^1H and ^{13}C NMR spectroscopy. The absolute configurations of C-2 and C-5 were presumed to be *S* in both cases to afford a more flexible and stable fused-ring system. A double reductive amination of **2** with 2.5 equiv of sodium cyanoborohydride and benzylamine in oxolane–methanol gave, in an absolutely stereocontrolled manner, the less strained product, *N*-benzyl-1,3:4,6-di-*O*-benzylidene-2,5-dideoxy-2,5-imino-L-iditol (**3**), in 82% yield. Compound **3** also possesses C_2 symmetry, a feature which facilitated the structural assignment by NMR spectroscopy. The result obtained from the reaction indicated

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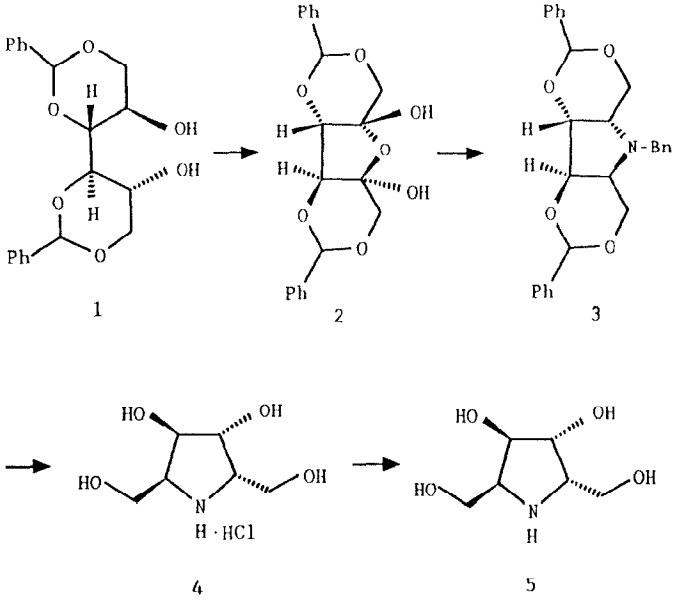

Scheme 1.

that the reduction of the imines, formed by reaction of the ketones with the amine, was under thermodynamic control.

Deprotection of **3** by hydrogenolysis over palladium-on-charcoal under acidic conditions afforded compound **4**, an ammonium salt, in 81% yield. The title compound **5** was obtained from **4** in 91% yield. The overall yield of **5** from **1** was ~ 38%.

EXPERIMENTAL

General methods.—Melting points were determined on a Fisher–Johns apparatus and are uncorrected. Optical rotations were measured with a Perkin–Elmer 241 automatic polarimeter for solutions in a 0.1-dm cell at room temperature. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker AC-F200 (200 MHz) spectrometer. Tetramethylsilane (Me_4Si) was used as the internal standard, and chemical shifts (δ) are given in ppm downfield from the signal of Me_4Si. Thin-layer chromatography (TLC) was performed using glass plates precoated with E. Merck Silica Gel 60F-254 as the adsorbent (layer thickness, 0.25 mm). The developed plates were air-dried and sprayed with a solution of cerium(IV) sulfate (1%) and molybdic acid (1.5%) in 10% aq H_2SO_4, and heated at 150°C. Column chromatography was performed on E. Merck no. 7734 Silica Gel 60 (70–230 mesh). Solvents were evaporated under reduced pressure at < 40°C.

*1,3:4,6-Di-O-benzylidene-*D*-threo-2,5-hexodiulose hydrate* (**2**).—To a solution of 1,3:4,6-di-*O*-benzylidene-D-mannitol[14] (**1**; 5.0 g, 14.0 mmol) in 3:1 CH_3CN–CH_2Cl_2 (80 mL) were added NaOAc (6.5 g) and 4A molecular sieves (15 g). The

mixture was stirred for 10 min at room temperature, and then pyridinium chlorochromate (14 g) was added; the mixture was heated for 4 h at reflux temperature. The mixture was cooled to room temperature, diethyl ether (100 mL) was added, and the mixture was filtered; the filtrate was concentrated to give a residue, which was subjected to column chromatography (EtOAc) to give **2** as needles (2.9 g, 59%) which were recrystallized from EtOAc–hexane; mp 170–172°C; $[\alpha]_D$ +60° (*c* 2.73, $CHCl_3$); {lit.[16] mp 144–145°C; $[\alpha]_D$ +58.5° (*c* 1.04, 1:1 $CHCl_3$–MeOH)}; ^1H NMR ($CDCl_3$): δ 3.95 (s, 2 H, 2- and 5-OH), 4.03 (d, 2 H, $J_{a,e}$ 12 Hz, H-1a,6a), 4.40 (d, 2 H, $J_{e,a}$ 12 Hz, H-1e,6c), 4.46 (s, 2 H, H-3,4), 5.60 (s, 2 H, 2 PhC*H*), 7.40 (m, 6 H, *o*- and *p*-aromatic H), and 7.45 (m, 4 H, *m*-aromatic H); ^{13}C NMR ($CDCl_3$): δ 70.11 (C-1,6), 82.85 (C-3,4), 99.17 (C-2,5), 100.09 (2 Ph*C*H), 125.97, 128.60, 129.61, and 136.37 (aromatic C). *Anal.* Calcd for $C_{20}H_{20}O_7$: C, 64.51; H, 5.41. Found: C, 64.44; H, 5.44.

N-*Benzyl-1,3:4,6-di*-O-*benzylidene-2,5-dideoxy-2,5-imino*-L-*iditol* (**3**).—To a solution of **2** (0.93 g, 2.5 mmol) in 1:1 oxolane–MeOH (20 mL) containing 4A molecular sieves was added benzylamine (285 μL), and the mixture was stirred at room temperature for 3 h. Sodium cyanoborohydride (0.4 g) and acetic acid (300 uL) were added, and the mixture was stirred at room temperature for 4 h. The mixture was filtered, and the filtrate was concentrated to give a residue, which was dissolved in $CHCl_3$ (50 mL). The solution was washed with aq $NaHCO_3$ and then with water, dried over anhyd Na_2SO_4, and concentrated to give **3** (0.94 g, 88%), which was recrystallized from hexane; mp 105°C; $[\alpha]_D$ +91° (*c* 1.18, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 3.55 (br, 2 H, H-2,5), 3.96 (dd, 2 H, $J_{1a,1e} = J_{6a,6e} = 12.8$, $J_{1a,2} = J_{5,6a} = 2.1$ Hz, H-1a,6a), 4.09 (d, 1 H, J_{gem} 16 Hz, N-CH_2Ph), 4.26 (br d, 2 H, $J_{1e,1a} = J_{6e,6a} = 12.8$, $J_{1e,2} = J_{5,6e} \approx 0$ Hz, H-1e,6e), 4.41 (d, 2 H, $J_{2,3} = J_{4,5} = 2.1$ Hz, H-3,4), 4.50 (d, 1 H, J_{gem} 16 Hz, N-CH_2Ph), and 7.20–7.57 (m, 15 H, 3 Ph); ^{13}C NMR ($CDCl_3$): δ 51.91 (N-CH_2Ph), 57.77 (C-2,5), 66.89 (C-1,6), 79.52 (C-3,4), 99.77 (Ph*C*H), 126.35, 128.41, 129.16, and 138.46 (*Ph*CH), 126.66, 127.42, 128.51, and 141.82 (N-CH$_2$*Ph*). *Anal.* Calcd for $C_{27}H_{27}NO_4$: C, 75.50; H, 6.34; N, 3.26. Found: C, 75.76; H, 6.33; N, 3.29.

(*2S,3R,4R,5S*)-3,4-Dihydroxy-2,5-bis(hydroxymethyl)pyrrolidine hydrochloride (**4**) *and the free base* (**5**).—To a solution of **3** (0.44 g, 1.02 mmol) in hot MeOH (5 mL) were added 10% Pd–C (200 mg) and concd HCl (3 drops). The mixture was kept under H_2 (50 psig) for 24 h. The mixture was filtered, and the filtrate was concentrated to a crystalline mass, which was recrystallized from MeOH–EtOAc to give **4** (0.17 g, 81%); mp 193–195°C; $[\alpha]_D$ -15° (*c* 0.67, H_2O); ^1H NMR (D_2O): δ 3.74–3.95 (m, 6 H, H-1, 1′, 2, 5, 6, 6′), and 4.25 (d, 2 H, $J_{2,3} = J_{5,4} = 2.35$ Hz, H-3,4); ^{13}C NMR (D_2O): δ 61.19 (C-1,6), 66.61 (C-2,5), and 78.36 (C-3,4). *Anal.* Calcd for $C_6H_{14}ClNO_4$: C, 36.10; H, 7.07; N, 7.02. Found: C, 35.95; H, 6.90; N, 6.89.

A solution of **4** (0.05 g) in water (0.5 mL) was deionized using Amberlite CG-400 resin (OH^- form, 1 × 6 cm). Evaporation of the water gave a residue, which was crystallized from MeOH–EtOAc to give **5** (35 mg, 90%); mp 160–161°C;

[lit.[7] 161–162°C; lit.[9] 167°C]; $[\alpha]_D$ +9.6° (*c* 0.57, H_2O); [lit.[7] +14.3° (*c* 0.93, H_2O); lit.[9] +16.2° (*c* 1.0, H_2O)]; ^1H NMR (D_2O): δ 3.02 (dt, 2 H, $J_{1,2} = J_{1',2} = J_{5,6} = J_{5,6'} = 6.0$, $J_{3,2} = J_{4,5} = 3.4$ Hz, H-2,5), 3.36 (dd, 2 H, $J_{2,1} = J_{5,6} = 6.0$, $J_{1,1'} = J_{6,6'} = 10.9$ Hz, H-1,6), 3.43 (dd, 2 H, $J_{2,1'} = J_{5,6'} = 6.0$, $J_{1,1'} = J_{6,6'} = 10.9$ Hz, H-1′,6′), and 3.76 (d, 2 H, $J_{2,3} = J_{5,4} = 3.4$ Hz, H-3,4); ^{13}C NMR (D_2O): δ 63.33 (C-1,6), 64.41 (C-2,5), and 79.93 (C-3,4).

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