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Note

Branched-chain alditols. A convenient synthesis of 6-deoxy-2-*O*-methyl-D-mannitol and 2-*C*-(hydroxymethyl)-D-mannitol

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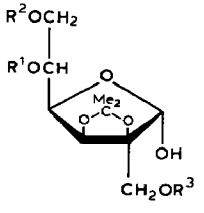
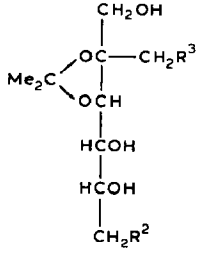
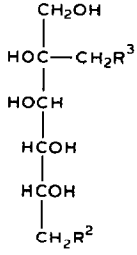
Branched-chain sugars are useful compounds in carbohydrate chemistry[1,2], assuming key roles in the synthesis of modified sugars and complex natural products, including antibiotics from microorganisms and higher plants[2]. Branched-chain alditols should have a relatively high degree of sweetness according to correlations by Daniel and Whistler[3]. To test one projection for sweetness we prepared 3-deoxy-D-*erythro*-pentitol[4], 3-*C*-(hydroxymethyl)-erythritol, and 3-*C*-methylerythritol[5] and found convenient syntheses for 6-deoxy-2-*C*-methyl-D-mannitol (**5**) and 2-*C*-(hydroxymethyl)-D-mannitol (**7**) giving overall yields of 35 and 66%, respectively, calculated from the starting 2-*C*-(hydroxymethyl)-2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranose[5,6] (**1**). The ^{1}H-n.m.r. spectrum (200 MHz) of **1** indicated the α-D configuration at C-1 (sharp singlet at δ 6.28) and the location of the hydroxymethyl group at C-2 (δ 3.86 m, 2 H, 2′-CH_2). The α-D-anomeric configuration of **1** was confirmed from its ^{13}C-n.m.r. spectrum (C-1 singlet at δ 103.4, characteristic for the α-D-*manno* configuration). Selective hydrolysis of **1** with dilute sulfuric acid[6,7] afforded syrupy 2-*C*-(hydroxymethyl)-2,3-*O*-isopropylidene-α-D-mannofuranose (**2**) in 82% yield.



1 $R^1 + R^2 = >CMe_2, R^3 = H$
2 $R^1 = R^2 = H, R^3 = H$
3 $R^1 = H, R^2 = R^3 = Ts$



4 $R^2 = R^3 = H$
6 $R^2 = R^3 = OH$



5 $R^2 = R^3 = H$
7 $R^2 = R^3 = OH$

*Dedicated to Dr. R. Stuart Tipson.

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Reaction of **2** with two equivalents of *p*-toluenesulfonyl chloride for 12 h at 25° yielded, after purification by column chromatography on silica gel, crystalline 2,3-*O*-isopropylidene-6-*O*-(*p*-tolylsulfonyl)-2-*C*-(*p*-tolylsulfonyloxymethyl)-α-D-mannofuranose (**3**) in 88% yield.

Reduction of **3** with lithium triethylborohydride[8] in tetrahydrofuran at ambient temperature, according to improved literature recommendations[9–14], produced 6-deoxy-2,3-*O*-isopropylidene-2-*C*-methyl-D-mannitol (**4**) in 78% yield, after crystallization from hexane–ether. The advantage of this reduction of primary tosyl groups over reduction by lithium aluminum hydride is the high yield and purity of product. Deacetonation of **4** with 90% aqueous trifluoroacetic acid[15] afforded the crystalline 6-deoxy-2-*C*-methyl-D-mannitol (**5**) in 42% overall yield.

Reduction of **1** with sodium borohydride at 25° gave crystalline 2,3:5,6-di-*O*-isopropylidene-2-*C*-(hydroxymethyl)-D-mannitol (**6**) in 51% yield. Hydrolysis of **6** with 90% aqueous trifluoroacetic acid[15] give crystalline 2-*C*-(hydroxymethyl)-D-mannitol (**7**) in 41% overall yield.

The ^{13}C-n.m.r. spectra of **5**, **7** and their isopropylidene precursors **4** and **6** exhibit characteristic signals for C-2 and C-6 (Table I). It is noteworthy that the C-2 signal of **4** is shifted upfield (0.5 p.p.m.) relative to the corresponding signal in the spectrum of **5**. However, the remaining assignments are practically unchanged, and the shifts for C-3, C-4, and C-5 are in agreement with the chemical shifts of other alditols reported[16,17]. Preliminary examination indicates that compounds **5** and **7** are sweet; however no noticeable enhancement of sweetness over that of sucrose is observed.

TABLE I

^{13}C CHEMICAL-SHIFT DATA FOR COMPOUNDS **2–5**

Compound	*C-1*	*C-2*	*C-2'*	*C-3*	*C-4*	*C-5*	*C-6*	*–OCO–*	*Me*
								26.6	
2[a]	103.4	93.5	63.2	82.0[d]	80.4[d]	70.2	65.4	113.1	26.2
									26.4
3[a,b]	103.1	93.2	70.7	81.8[d]	80.2[d]	70.6	68.3	112.9	26.1
									27.4
4[c]	64.4	79.8	17.6	70.6	70.6	74.0	17.9	108.9	26.3
5[c]	64.6	79.3	17.3	70.6	70.6	74.0	18.0		
								109.3	25.3, 24.6
6[a]	64.8	79.6	64.6	70.8	70.6	74.2	65.2	108.6	25.8, 24.2
7[c]	65.4	79.8	64.8	70.6	70.6	74.0	65.0		
Mannitol[17]	64.6	72.2		70.7	70.7	72.2	64.6		

[a]In p.p.m. downfield from internal Me_4Si in $CDCl_3$. [b]Additional signals were observed at δ 145.1, 145.2, 131.9, 132.0, 129.81, 129.85, 127, 89, 127.61 (aromatic), and 21.41, 21.45 (CH_3). [c]In p.p.m. downfield from internal 1,4-($^2H_4$)dioxane in D_2O. [d]Assignments for these peak positions may be reversed.

EXPERIMENTAL

General methods. — The purity of products was determined by t.l.c. on silica gel GT_{254} (Merck), and detection was effected by charring with 5% H_2SO_4. Column chromatography was performed on Davison Grade 62 silica gel (60–200 mesh, Baker Analytical Reagents). Melting points were determined with a Fisher–Johns apparatus and are uncorrected. Optical rotations were measured with a Perkin–Elmer Model 141 polarimeter. ^{1}H-N.m.r. spectra were recorded for solutions in $CDCl_3$ (internal standard Me_4Si) with Varian T-60A and XL-200 spectrometers. ^{13}C-N.m.r. spectra were recorded at 50.3 MHz with a Nicolet NT-200 n.m.r. spectrometer, for solutions in $CDCl_3$ (internal standard Me_4Si) and D_2O, with 1,4-($^2H_4$)dioxane added as the internal reference. Chemical shifts relative to the signal for Me_4Si were obtained by adding 66.487 p.p.m. [the chemical shift of 1,4-($^2H_4$)dioxane relative to that of Me_4Si] to the values experimentally obtained.

Mass spectra were recorded with a Finnigan 400 GC/MS spectrometer equipped with an INCOS data system. The ion-source temperature was 250° the ion-source voltage 70 eV, and the electron-multiplier voltage 1500 V. Microanalyses were peformed in the Chemistry Department, Purdue University. All organic solutions were dried with Na_2SO_4 and evaporated, generally <40°, under diminished pressure.

*2-C-(Hydroxymethyl)-2,3:5,6-di-O-isopropylidene-α-*D*-mannofuranose* (**1**). — Compound **1** was prepared earlier[5,6] and has now been examined by ^{1}H-n.m.r. as well as ^{13}C-n.m.r. spectra to confirm the α-D- configuration of the hydroxy group at C-1: ^{1}H-n.m.r. ($CDCl_3$): δ 1.34, 1.39, 1.46 (3 s, 12 H, CH_3), 3.86 (m, 2 H, 2′-CH_2), 4.0–4.16 (AB part of an ABX spectrum, $J_{5,6}$ 4.6, $J_{5,6'}$ 6.2, $J_{6,6'}$ 9 Hz, H-6,6), 4.24 (dd, $J_{1,4}$ 1.0, $J_{3,4}$ 3.5, $J_{4,5}$ 8.0 Hz, H-4), 4.45 (dd, H-5), 4.86 (d, H-3), and 6.28 (s, H-1); ^{13}C-n.m.r. (50.3 MHz, $CDCl_3$): δ 113.6, 109.1 (CMe_2), 103.4 (C-1), 93.5 (C-2), 82.6 (C-3), 80.6 (C-4), 73.0 (C-5), 66.4 (C-6), 63.4 (C-2′), 27.4, 27.1, 26.7, and 25.1 (4 CH_3).

*2-C-Hydroxymethyl-2,3-*O*-isopropylidene-α-*D*-mannofuranose* (**2**). — To a solution of compound **1** (2.9 g, 10 mmol), prepared according to the literature procedure[5,6] in 30% aq. MeOH was added ~1.5 mL of 20% H_2SO_4 to adjust the pH to 4.5. The solution was stirred for 12 h at room temperature, when t.l.c. [7:2:1 (v/v) EtOAc–$CHCl_2$–MeOH] indicated complete reaction, with the formation of new product, R_F 0.24. The solution was made neutral with $NaHCO_3$ and evaporated to a syrup. The syrupy residue was purified by flash column chromatography on silica gel by elution with the same solvent as for t.l.c. Fractions containing product having R_F 0.24 were collected and evaporated to a syrup; yield 2.3 g (96%), $[\alpha]_D^{20}$ +16.6° (*c* 2, Me_2CO) [lit.[6] $[\alpha]_D^{20}$ +16.3° (*c* 3.2, Me_2CO)]; ^{1}H-n.m.r. ($CDCl_3$: δ 1.4 (s, 3 H, CH_3), 1.46 (s, 3 H, CH_3), 3.82 (m, 2 H, 2′-CH_2), 4.0–4.13 (AB part of an ABX spectrum; $J_{5,6}$ 4.6, $J_{5,6'}$ 6.1, $J_{6,6}$ 9.2 Hz, H-6,6), 4.22 (dd, $J_{1,4}$ 1.0, $J_{3,4}$ 3.6, $J_{4,5}$ 8.0 Hz, H-4), 4.45 (dd, H-5), 4.88 (d, $J_{2,3}$ 5.5 Hz, H-3), and 6.28 (s, H-1).

*2,3-*O*-Isopropylidene-6-*O*-(*p*-tolylsulfonyl)-2-*C*-(*p*-tolylsulfonyloxymethyl)-*

α-D-*mannofuranose* (**3**). — To a solution of compound **2** (2.5 g, 10 mmol) in 35 mL of dry C_5H_5N was added TsCl (in portions, 3.81 g, 20 mmol). The solution was kept overnight at room temperature, after which time t.l.c., [7:2:1 (v/v) EtOAc–$CH_{21}Cl_2$–MeOH] indicated complete reaction. The C_5H_5N was removed by evaporation and 50 mL of PhMe was evaporated from the residue. The crude syrupy product was purified by column chromatography on silica gel by elution with the same solvent as for t.l.c. The fractions containing product of R_F 0.32 were collected and evaporated to a syrup and finally purified by crystallization from Et_2O–hexane; yield 3.4 g (61%), m.p. 121–123°, $[\alpha]_D^{20}$ +24.2° (*c* 2.0, $CHCl_3$); ^{1}H-n.m.r. ($CDCl_3$): δ 1.41 (s, 3 H, CH_3), 1.46 (s, 3 H, CH_3), 2.41 (s, 3 H, $ArCH_3$), 2.46 (s, 3 H, $ArCH_3$), 3.86 (m, 2 H, 2′-CH_2), 4.0–4.18 (AB part of an ABX spectrum), 4.26 (dd, $J_{1,4}$ 1.0, $J_{3,4}$ 3.8, $J_{4,5}$ 8.2 Hz, H-6,6′), 4.48 (dd, H-5), 4.92 (d, $J_{2,3}$ 5.8 Hz, H-3), 5.18 (s, H-1), and 7.28–7.76 (m, 8 H, aromatic).

Anal. Calc. for $C_{24}H_{30}S_2O_{11}$: C, 51.59; H, 5.41; S, 11.48. Found: C, 51.02; H, 5.95; S, 11.32.

*6-Deoxy-2,3-*O-*isopropylidene-2-*C-*methyl-*D-*mannitol* (**4**). — To a solution of the ditosyl derivative **3** (5.5 g, 10 mmol) in 1,4-dioxane (12 mL) an M solution of lithium triethylborohydride in tetrahydrofuran (22 mL) was added, and the mixture was kept for 12 h at room temperature, at which time t.l.c. [7:2:1 (v/v) EtOAc–CH_2Cl_2–MeOH] showed no remaining starting material, and the formation of a new product, R_F 0.43. The excess of hydride was decomposed with water (2 mL) and the organoborane oxidized with 30% H_2O_2 (18 mL) and 3M aq. NaOH (18 mL). After 2 h at room temperature the mixture was extracted with $CHCl_3$. The organic layer was separated, and the aqueous layer was extracted further with $CHCl_3$ (3 × 30 mL). The combined extracts were washed with water (92 × 30 mL), dried, and evaporated to a syrup that was crystallized from Et_2O–hexane; yield 1.7 g, (78%), m.p. 89–93°, $[\alpha]_D^{20}$ +2.9° (*c* 2.3, $CHCl_3$); *m/z* (%): M^+, 205 (10.1, M − 15), 187 (23.5), 166 (10.1), 149 (13.1), 147 (10.1), 129 (10.8), 113 (5.9), 91 (7.9), 81 (10.1), 55 (10.8), and 53 (7.1).

Anal. Calc. for $C_{10}H_{20}O_5$: C, 54.52; H, 9.15. Found: C, 54.22; H, 9.58.

*6-Deoxy-2-*C-*methyl-*D-*mannitol* (**5**). — Compound **4** (2.2 g, 0.10 mmol) was stirred in aq. 90% CF_3CO_2H (10 mL) for 12 h at room temperature, and the solvent was evaporated. The residue was treated with PhMe (2 × 25 mL) to remove traces of CF_3CO_2H and finally dissolved in 30 mL of water and passed through a column of Amberlite IR-45 (OH^-). The eluate was evaporated and the residue purified by column chromatography on silica gel by elution with 3:1:1 (v/v) butanone–MeOH–AcOH. Fractions containing the product having R_F 0.56 were collected and evaporated. The syrupy product was crystallized from Me_2CO–hexane; yield 1.47 g (82%), m.p. 141–143°, $[\alpha]_D^{20}$ +101° (*c* 1.2 H_2O); *m/z* (%): M^+, 181 (1.9, M + H), 164 (10.5, $M^+ - H_2O$), 147 (9.1), 128 (15.1), 111 (5.1), 99 (5.5), 98 (6.1), 85 (9.1) 83 (7.2), 73 (6.5), 69 (21.0), and 61 (7.3).

Anal. Calc. for $C_7H_{16}O_5$: C, 46.65; H, 8.95. Found: C, 46.14; H, 8.31.

*2,3:5,6-Di-*O-*isopropylidene-2-*C-*(hydroxymethyl)-*D-*mannitol* (**6**). — To a

solution of **1** (2.9 g, 10 mmol) in aq. 80% MeOH (200 mL) was added dropwise a solution of $NaBH_4$ (0.93 g, 25 mmol) in water (30 mL). The mixture was stirred overnight at room temperature. Acetic acid was added to bring the pH to 5, and the solution was decationized with Amberlite IR-120 (H^+) resin. The solution was evaporated, and MeOH (8 × 50 mL) and PhMe (5 × 50 mL) were successively added to and evaporated from the residue. The crude, syrupy product was homogenous by t.l.c. [R_F 0.48, 7:2:1 (v/v) EtOAc–CH_2Cl_2–MeOH].

Crystallization from Et_2O–hexane gave pure **6**; yield 1.95 g (67%) m.p. 104–106°, $[\alpha]_D^{20}$ +2.3° (*c* 1.2, chloroform); *m/z* (%): M^+, 293 (1.1, M + H), 263 [100, (M + H) − 30], 205 (67.3), 187 (5.4), 167 (11.5), 147 (33.7), 137 (32.6), 135 (10.1), 129 (11.2), 113 (5.9), 107 (50.2), 81 (7.6), 77 (23.6), 71 (10.8), 69 (10.9), and 61 (13.1).

Anal. Calc. for $C_{13}H_{25}O_7$: C, 53.22; H, 8.59. Found: C, 53.29; H, 8.92.

2-C-(Hydroxymethyl)-D-mannitol (**7**). — Compound **6** (2.92 g, 10 mmol) was dissolved in 90% aq. CF_3CO_2H (20 mL), and the mixture was kept for 18 h at room temperature. The solvent was evaporated, the residue was treated with PhMe (2 × 20 mL) to remove traces of CF_3CO_2H, and it was finally dissolved in water (20 mL) and passed through a column of Amberlite IR-45 (OH^-) ion-exchange resin. The eluate was evaporated and the residue purified by flash column chromatography on silica gel by elution with 1:1 (v/v) MeOH–$CHCl_3$. Fractions containing the product having R_F 0.21 were collected and evaporated. The syrup crystallized from ethanol; yield 1.89 g, (89%), m.p. 128–130°, $[\alpha]_D^{20}$ +144° (*c* 1.2, H_2O); *m/z* (%): M^+ 213 (4.9, M + H), 195 (15.4, M^+ − H), 183 (100), 166 (10.2), 165 816), 147 (9.3), 129 (15.6), 111 (5.8), 99 (6.3), 85 (8.5), 73 (7.3), 69 (30.3), and 61 (8.1).

Anal. Calc. for $C_7H_{16}O_7$: C, 39.61; H, 7.60. Found: C, 39.12; H, 7.22.

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