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SYNTHESIS OF 3-*C*-(HYDROXYMETHYL)ERYTHRITOL AND 3-*C*-METHYLERYTHRITOL*

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ABSTRACT

3-*C*-(Hydroxymethyl)erythritol was prepared from 3-*C*-(hydroxymethyl)-2,3-*O*-isopropylidene-D-*erythro*-tetrofuranose (**4**) by hydrolysis followed by reduction, or by reduction followed by hydrolysis. Monotosylation of **4**, followed by reduction with lithium aluminum hydride and hydrolysis, afforded 3-*C*-methylerythritol.

INTRODUCTION

In connection with a program to develop noncariogenic sweeteners according to the structure–sweetness correlation method of Daniel and Whistler[1], a convenient synthesis of 3-deoxy-D-*erythro*-pentitol has been described[2]. We have now initiated an extended study of branched-chain alditols from the D-apiose group. This led to the preparation of 3-*C*-(hydroxymethyl)erythritol (**12**) (D-apitol) and 3-*C*-methylerythritol (3-deoxy-D-apitol) (**14**) which may have increased sweetness according to the increase of the calculated ^3X_m value by the aforementioned correlation method[1]. The starting product for this approach could be naturally occurring apiose, which may be obtained either by extraction of a cell-wall polysaccharide present in several marine and fresh water plants, *e.g.*, *Zostera marina L.*[3], *Posidonia australis L.*[4], and *Lemna minor*[5], or by several synthetic methods[6], or by photochemical cycloaddition[7]. One of the synthetic methods used 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranose (**1**) as starting material[8].

RESULTS AND DISCUSSION

The synthesis of D-apiose started from D-mannose[8] and proceeded through 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranose[9] (**1**). Condensation of **1** with formaldehyde in methanol in the presence of potassium carbonate at pH 10, under

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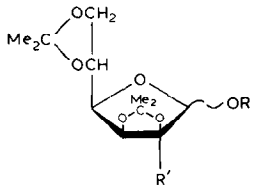
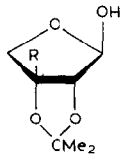


1 R = R′ = H
2 R = H, R′ = CH_2OH
3 R = Bz, R′ = CH_2OBz



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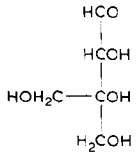
5 R = CHO
6 R = CH_2OTs



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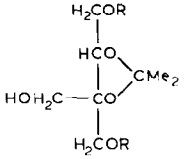
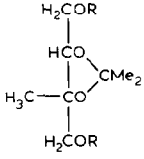


8 R = H
9 R = Bz



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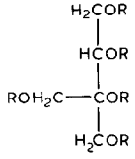
11 R = Bz



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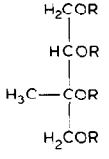
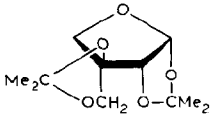
13 R = Bz



14 R = H
15 R = Bz



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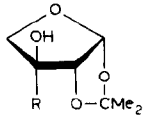
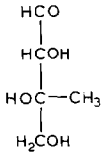


17 R = CH_2OH
18 R = CH_2OTs
19 R = CH_3



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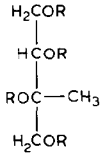

21 R = H
22 R = Bz

conditions given by Ho[8], led to a mixture of **2** and a few polymerized products, from which **2** was isolated by column chromatography as a crystalline derivative in 80% yield. Conversion of 2-*C*-(hydroxymethyl)-2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranose (**2**) in a one-pot reaction into 3-*C*-(hydroxymethyl)-2,3-*O*-isopropylidene-β-D-*erythro*-furanose (**4**) according to Ho[8] afforded a mixture of **4** and oxidation product **5** in the ratio 3:2, which were separated by column chromatography in 32 and 25% yield, respectively. Hydrolysis of **4** according to the method of Ho[8], and Williams and Jones[3] gave syrupy D-apiose (**7**). However, the product was not homogenous on t.l.c., and required double purification by column chromatography.

During concentration of its solutions chromatographically homogenous **7** was converted into another product moving slower on t.l.c. In slightly acid solution, pH 5.5–6, the conversion was not detectable and **7** was stable. Reduction of **7** with sodium borohydride in water at 25–30° for 24 h according to Wolfrom and

Thompson[10] gave syrupy 3-*C*-(hydroxymethyl)erythritol[11] (**12**). Because of the poor overall yield and difficulties in purification, an alternative method of preparation of **12** was developed. Reduction of **4** with sodium borohydride using the same procedure as for the preparation of **12** directly from D-apiose (**7**) gave crystalline 3-*C*-(hydroxymethyl)-2,3-*O*-isopropylideneerythritol (**8**). Hydrolysis of **8** with 90% aqueous trifluoroacetic acid[12] gave syrupy **12**, chromatographically identical with that prepared by direct reduction of D-apiose (**7**).

Analogous to the aforementioned procedure of preparation of **12**, we attempted a new method for the preparation of 3-*C*-methylerythritol (**14**). This reaction sequence also started from **4**, which was monotosylated to give crystalline tosyl derivative **6** in 62% yield; the ^{1}H-n.m.r. spectrum of **6** exhibited a characteristic singlet signal for the tosyl-CH_3 group at δ 2.45, as well as for H-1 as a doublet at δ 4.94 ($J_{1,2}$ 2.5 Hz), and two singlet signals at δ 1.24 and 1.4 for isopropylidene groups, in agreement with structure **6**. Reduction of the tosyl group of **6** with lithium aluminum hydride afforded only one product, 2,3-*O*-isopropylidene-3-*C*-methylerythritol (**10**) in 72% yield. Compound **10** was characterized as the crystalline dibenzoyl derivative (**11**). Hydrolysis of **10** with 90% aqueous trifluoroacetic acid afforded syrupy **14** in 65% yield.

To compare the physicochemical properties of **14** with those of the possible configurational isomer, *i.e.*, 3-*C*-methyl-L-threitol (**21**), we attempted a new method of preparation of **21** by reduction of 3-*C*-methyl-L-*threo*-tetrose (3-deoxy-D-apiose) (**20**) with lithium aluminum hydride. The synthetic approach for the preparation of **21** started from 1,2:3,5-di-*O*-isopropylidene-3-*C*-methyl-β-L-*threo*-tetrofuranose[13] (**16**) which was obtained by acetonation of **7** according to Ball *et al.*[14]. Hydrolysis of **16** according to the procedure of Carey *et al.*[13] using 60% acetic acid for 48 h afforded crystalline 3-*C*-(hydroxymethyl)-1,2-*O*-isopropylidene-β-L-*threo*-tetrofuranose (**17**) in 75% yield. Monotosylation of **17** in anhydrous pyridine afforded crystalline 1,2-*O*-isopropylidene-3-*C*-(*p*-tolylsulfonyloxymethyl)-β-L-*threo*-tetrofuranose[15] (**18**) in 80% yield. Reduction of **18** with lithium aluminum

TABLE I

^{13}C-N M R DATA (δ) OF THE TETRITOLS

Compound	*C-1*	*C-2*	*C-3*	*C-3'*	*C-4*	$(CH_3)_2C$	CH_3
Erythritol[a]	64.0	73.3	73.3		64.0		
Threitol[a]	63.9	72.9	72.9		63.9		
Erythritol[b]	63.2	72.4	72.4		63.2		
Threitol[b]	63.0	71.8	71.8		63.0		
8[a]	64.2	82.6	82.1	62.5	63.9	108.7	26.3, 27.6
10[a]	64.5	82.7	83.9	21.4	59.7	109.3	26.4, 27.9
12[a]	62.9	73.7	76.4	62.5	62.7		
14[a]	62.7	74.8	75.7	19.9	67.0		
21[a]	62.9	74.5	75.2	20.1	67.1		

[a]For solutions in D_2O; signals downfield from signal of external Me_4Si in D_2O. [b]For solutions in $(CD_3)_2SO_2$; signals downfield from signal of external Me_4Si in $(CD_3)_2SO_2$.

TABLE II

^{13}C-N.M R DATA[a] (δ) OF THE COMPOUNDS **4, 5, 6, 18** AND **19**[a]

Compound	*C-1*	*C-2*	*C-3*	*C-3'*	*C-4*	$(CH_3)_2C$	CH_3
4	101.5	91.6	86.8	64.1	76.3	113.4	27.3, 27.5
5	101.6	90.8	80.3	201.6	76.0	113.8	27.2, 27.6
6[b]	101.7	89.5	86.6	70.7	76.3	114.2	27.0, 27.4
17 (ref. 20)	106.1	84.3	82.2	62.3	73.2	112.6	26.9, 26.4
18[c]	106.8	84.6	80.6	71.7	73.5	112.5	26.2, 26.7
19	105.8	85.8	79.3	17.5	75.7	112.2	26.2, 26.8

[a]For solutions in $CDCl_3$; signal downfield from signal of internal Me_4Si in $CDCl_3$. [b]Additional signals were observed at δ 145.1, 130.0, 129.8, 128.0 (aromatic), and 21.6 (CH_3). [c]For a solution in CD_3COCD_3, signals downfield from signal of internal Me_4Si in CD_3COCD_3; additional signals were observed at δ 130.4, 129.9, 128.6, 128.0 (aromatic), and 21.2 (CH_3).

hydride according to Ball *et al.*[15] gave 1,2-*O*-isopropylidene-3-*C*-methyl-β-L-*threo*-tetrofuranose (**19**) in 56% yield. Hydrolysis of **19** in the same manner as for **10** gave **20** which was reduced with sodium borohydride [by use of the same procedure as for the preparation of **12** directly from D-apiose (**7**)] to give syrupy **21** in 62% yield. Compound **21** was characterized as its crystalline tetra-*O*-benzoyl derivative **22**.

Because the ^{1}H-n.m.r. spectra of free tetritols are uninformative, as most of the proton signals coincide, ^{13}C-n.m.r. spectra were recorded for assignment of the structures as well as determination of the conformations. The ^{13}C-n.m.r. spectra of several alditols (among them erythritol and threitol) have already been reported[16–19].

The ^{13}C-n.m.r. spectra of the synthesized tetritols **8, 10, 12, 14,** and **21**, as compared with those of the model erythritol and threitol, were in agreement with the structural assignments (Table I). In the case of compounds **4, 5, 6, 17, 18,** and **19**, the ^{13}C-n.m.r. chemical-shift data are related to those described in the literature[17,18] (Table II) and in agreement with the structural assignments.

Interestingly, in the spectrum of **21** the C-3 signal was shifted downfield (2.3 p.p.m.), relative to the corresponding signal in the spectrum of L-threitol[17]. The C-3 signals of **12** and **8** were shifted downfield (3.1 and 8.2 p.p.m.) with respect to the corresponding signal in the spectrum of erythritol[18]. However, the remaining assignments are consistent with those reported by Schnar *et al.*[17], as well as Angyal and LeFur[18]. It is noteworthy that comparison of the chemical shift data for the C-3 signal of two isomeric compounds, 3-*C*-methylerythritol (**14**) and 3-*C*-methyl-L-threitol (**21**), showed practically no distinction (downfield shift 0.2 p.p.m.) between the vicinal *erythro* and *threo* substituents.

EXPERIMENTAL

General methods. — 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) and D_2O (internal standard, sodium 4,4-dimethyl-4-silapentane-1-sulfonate) with a Varian T-60A spectrometer. ^{13}C-N.m.r. spectra were recorded at 50.3 MHz for solution in $CDCl_3$, CD_3COCD_3, and D_2O (internal standard Me_4Si) with a Nicolet NT-200 N.m.r. spectrometer. Mass spectra were determined for samples that were introduced by direct insertion or from a g.l.c. capillary column of silicone DB5-15N attached by a jet separator to a Finnigan 4000 GC/MS mass spectrometer equipped with an INCOS data system; the ion-source temperature was 250° and the ion-source voltage 70 eV and electron-multiplier voltage 1500 V. The purity of products was determined by t.l.c. on silica gel plates GF_{254} (Merck), and the components were detected by spraying with 5% sulfuric acid in ethanol and charring. The following chromatographic solvent systems were used (v/v): 7:2:1 ethyl acetate–dichloromethane–methanol (solvent *A*), 3:1 methanol–chloroform (solvent *B*), 2:1:1 propyl alcohol–ethyl acetate–methanol (solvent *C*), 4:1 hexane–acetone (solvent *D*), and 3:1:1 butanone–methanol–acetic acid (solvent *E*). Column chromatography was performed on silica gel (60–200 mesh), Davidson, Grade 62-Baker Analytical Reagents. Flash chromatography was performed on silica gel (240–400 mesh) EM9385-Baker Analytical Reagents, according to Still *et al.*[21].

All organic solutions were dried with sodium sulfate and evaporated (generally <40°) under reduced pressure. Starting 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranose (**1**) was prepared according to Schmidt[9] and 1,2:3,5-di-*O*-isopropylidene-3-*C*-methyl-β-L-*threo*-tetrofuranose (**16**) according to Ball *et al.*[14], as well as purchased from Pfanstiehl Laboratories Inc. Microanalyses were performed in the Chemistry Department, Purdue University.

2-C-(Hydroxymethyl)-2,3:5,6-di-O-isopropylidene-D-mannofuranose (**2**). — Compound **1** (15.4 g, 63 mmol) and potassium carbonate (11.2 g, 81 mmol) were dissolved in methanol (200 mL) and then 37% aqueous formaldehyde (120 mL) was added. The solution was heated to 85° under a N_2 atmosphere. The condensation reaction was monitored by t.l.c. (solvent *A*) which after two days indicated the formation of a new product (R_F 0.52) and a small amount of a by-product (R_F 0.33). The solution was made neutral with 10% aqueous H_2SO_4. Evaporation of the solvent gave a residue which was extracted with chloroform, and the extracts were dried and evaporated to a syrup. Chromatography of the crude product on silica gel by elution with solvent *A* gave **2** as a chromatographically homogenous syrup (R_F 0.52). Crystallization from ether–hexane gave crystalline **2** (yield 13.0 g, 76%), m.p. 116–118°, $[\alpha]_D^{20}$ +11.2° (*c* 1.0, methanol); lit.[8] $[\alpha]_D^{20}$ +11° (*c* 1.2, methanol); ^{1}H-n.m.r. ($CDCl_3$): δ 1.3–1.56 (m, 12 H, 4 CH_3), 3.83 (m, 2 H, CH_2-2′), 4.7 (d, 1 H, H-3), and 5.46 (s, 1 H, H-1); ^{13}C-n.m.r. ($CDCl_3$): δ 113.6, 109.1 [$C(Me)_2$], 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 Me).

1-O-Benzoyl-2-C-(benzoyloxymethyl)-2,3,5,6-di-O-isopropylidene-D-mannofuranose (**3**). — 2-*C*-(Hydroxymethyl)-2,3,5,6-di-*O*-isopropylidene-D-mannofuranose

(**2**) (0.2 g, 0.7 mmol) was benzoylated with benzoyl chloride (2 mL) in dry pyridine (5 mL) at room temperature for 12 h, and then poured into ice–water and extracted with ether. The ether layer was washed with aqueous $NaHCO_3$, water, and then dried and evaporated. The syrupy residue crystallized from ethanol (yield 0.27 g, 78%), m.p. 98–100°, $[\alpha]_D^{20}$ +36.2° (*c* 1.2, chloroform); ^{1}H-n.m.r. ($CDCl_3$): δ 1.4 (s, 3 H, CH_3), 1.53 (s, 3 H, CH_3), 4.3 (s, 2 H, CH_2-2', 4.8 (d, 1 H, H-3), 6.26 (s 1 H, H-1), and 7.23–7 8 (m, 10 H, arom.).

Anal. Calc. for $C_{27}H_{30}O_9$: C, 65.04; H, 6.06. Found: C, 64.88; H, 6.21.

*3-C-Formyl-2,3-O-isopropylidene-β-*D-erythro-*tetrofuranose* (**5**) *and 3-C-(hydroxymethyl)-2,3-O-isopropylidene-β-*D-erythro-*tetrofuranose* (**4**). — A solution of **2** (20 g, 72 mmol) in 10% aqueous methanol (200 mL) with conc. H_2SO_4 (0.25 mL) was stirred at room temperature for 12 h and then made neutral to pH 7 with a solution of $NaHCO_3$. A solution of $NaBH_4$ (8 g, 21 mmol) in water (50 mL) was added, dropwise, during 30–45 min. After 12 h at room temperature, acetic acid was added until the pH of the solution was 7. To the stirred solution at 0°, $NaIO_4$ (24 g, 11 mmol) in water (200 mL) was added in portions, and the stirring continued for 1 h at room temperature. After filtration of precipitated NaI, the mixture was concentrated to 100 mL (at 35°) and extracted with hot chloroform (5 × 80 mL). The extract was dried (Na_2SO_4) and evaporated to dryness, The residual syrupy product was purified by silica gel column chromatography (elution with solvent *A*). Fractions containing the faster-moving by-product (**5**, R_F 0.59) were collected and evaporated to give a syrup (yield 5.6 g, 32%), $[\alpha]_D^{20}$ −36° (*c* 1.2, chloroform); ^{1}H-n.m.r. ($CDCl_3$): δ 1.39 (s, 3 H, CH_3), 1.49 (s, 3 H, CH_3), 3.3 (t, 1 H, OH), 3.76–3.95 (m, 2 H, H-4), 4.26 (s, 1 H, H-2), 5.36 (d, 1 H, H-1), and 8.36 (s, 1 H, CHO).

Anal. Calc for $C_8H_{12}O_5$: C, 51.10; H, 6.43. Found: C, 50.96; H, 6.32.

Fractions containing the slower-moving component **4** (R_F 0.42) were collected and evaporated to give a syrup (4.2 g, 25%), $[\alpha]_D^{20}$ −39.2° (*c* 1.2, chloroform); lit.[8] $[\alpha]_D^{20}$ −40° (*c* 1.5, chloroform). Crystallization from ether–hexane gave a crystalline product, m.p. 72–74° (lit.[8] m.p. 72°); ^{1}H-n.m.r. ($CDCl_3$): δ 1.39 (s, 3 H, CH_3), 1.43 (s, 3 H, CH_3), 3.3 (t, 1 H, OH), 3.76 (d, 2 H, H-3), 3.93 (s, 2 H, H_2-4), 4.1 (d, 1 H, OH), 4.26 (s. 1 H, H-2), and 5.3 (d, 1 H, H-1).

*2,3-O-Isopropylidene-3-C-(p-tolylsulfonyloxymethyl)-β-*D-erythro-*tetrofuranose* (**6**). — To a solution of **4** (9.5 g, 50 mmol) in dry pyridine (35 mL) was added *p*-toluenesulfonyl chloride (9.52 g, 50 mmol). The solution was kept overnight at room temperature, after which t.l.c. indicated complete reaction. Pyridine was removed by evaporation followed by coevaporation with toluene (50 mL). The crude syrupy product was purified by silica gel column chromatography (elution with solvent *A*) to give a syrup (R_F 0.48) which crystallized from ether–hexane (yield 10.6 g, 62%), m.p. 113–115°, $[\alpha]_D^{20}$ −38.6° (*c* 2, chloroform); ^{1}H-n.m.r. ($CDCl_3$): δ 1.24 (s, 3 H, CH_3 of CMe_2), 1.4 (s, 3 H, CH_3 of CMe_2), 2.4 (s, 3 H, $CH_3C_6H_4$), 3.42 (d, 2 H, H-3'), 3.84 (s, 2 H, CH_2-4), 4.2 (s, 1 H, H-2), 4.24 (d, 1 H, OH), 4.94 (d, 1 H, $J_{1,2}$ 2.5 Hz, H-1), and 7.18–7.78 (m, 4 H, arom.); m.s. (70 eV): *m/z* (%) M^+, 329 (5.1) (M − 15; 344 − 15), 173 (9.4), 172 (11.9), 157 (10), 155 (37), 126 (13.6),

114 (5.6), 113 (9.1), 97 (18.6), 92 (8), 91 (49), 85 (37.5), 71 (20.9), 69 (11.9), 68 (27.6), 63 (11.3), 59 (32.6), 57 (16.8), 44 (43.8), 43 (50.8), 42 (5.15), 47 (73.7), and 40 (100).

Anal. Calc. for $C_{15}H_{20}O_7S$: C, 52.31; H, 5.85; S, 9.31. Found: C, 52.40; H, 6.08; S, 9.43.

*3-C-(Hydroxymethyl)-*D-glycero-*tetrose (*D-*apiose)* (**7**). — (*a*) A mixture of **4** (2 g, 13 mmol) and 90% aqueous trifluoroacetic acid (20 mL) was stirred at room temperature for 12 h. The reaction was monitored by t.l.c. (solvent *A*) and, after this time, indicated complete hydrolysis. The solution was evaporated and the residue, treated by addition and evaporation of toluene (3 × 15 mL) to remove traces of trifluoroacetic acid, was dissolved in water (15 mL) and passed through a column of Amberlite IR-45 (OH^-) ion-exchange resin. The eluate was evaporated, and the residue purified by column chromatography on silica gel (elution with solvent *E*) and finally by flash chromatography[21] (elution with the same solvent) to give a pure syrup (yield 1.29, 76%), R_F 0.47, $[\alpha]_D^{20}$ +6° (*c* 1, water); lit.[8] $[\alpha]_D^{20}$ +5.2° (*c* 1.1, water).

(*b*) A mixture of **4** (2 g, 13 mmol) and M H_2SO_4 (50 mL) was heated at 70° (on an oil bath) for 4 h. The reaction was monitored by t.l.c. (solvent *A*). The solution was made neutral with $BaCO_3$, the suspension filtered, and the filtrate evaporated to give a yellow syrup that was purified by silica gel column chromatography (elution with solvent *C*), yield 0.76 (46%). During concentration of the solution, the chromatographically homogenous product (R_F 0.4) was converted into another product which gave a second spot on t.l.c. (slower-moving component), R_F 0.22. In slightly acid solution, pH 5.5–6, the conversion was not detectable and the sugar stable; m.s. (70 eV): *m/z* (%) 150 (8.0) (M^+), 149 (100) ($M^+ - 1$), 137 (7.31), 136 (5.5), 123 (6.8), 121 (8.3), 109 (6.8), 97 (8.8), 95 (13.1), 93 (10.6), 84 (11.7), 82 (18.3), 81 (42.9), 73 (9.9), 70 (19.5), 69 (74.2), 68 (10.4), 60 (9.3), 57 (20.2), 55 (19.8), and 43 (19.1).

*3-C-(Hydroxymethyl)-2,3-*O*-isopropylidene-erythritol* (**8**). — Compound **4** (9.5 g, 50 mmol) was dissolved in water (100 mL) and a solution of $NaBH_4$ (2.1 g, 52 mmol) in water (50 mL) was added dropwise with stirring for 30 min, the temperature not being allowed to rise >50°. After 24 h, acetic acid was added to bring the pH to 5, and the solution was de-ionized with Amberlite IR-120 (H^+) ion-exchange resin. The solution was evaporated and methanol (8 × 50 mL) and toluene (5 × 50 mL) were successively added to, and evaporated from, the residue. The crude syrup was purified by column chromatography (elution with solvent *B*). T.l.c. showed that the product was homogenous (R_F 0.58). Crystallization from chloroform gave pure **8** (yield 7.5 g, 78.9%), m.p. 86–88°, $[\alpha]_D^{20}$ 0° (*c* 1.2, methanol); ^{1}H-n.m.r. ($CDCl_3$): δ 1.36 (s, 3 H CH_3CO), 1.52 (s, 3 H, CH_3CO), 3.12 (s, 2 H, CH_2-5), 3.4–3.66 (m, 4 H, 2 CH_2), and 4.0 (s, 1 H, H-2).

Anal. Calc. for $C_8H_{16}O_5$: C, 49.98; H, 10.60. Found: C, 49.86; H, 10.53.

*1,4-Di-*O*-benzoyl-3-C-(benzyloxymethyl)-2,3-*O*-isopropylidene-erythritol (***9***).* — Compound **8** (0.5 g, 2.6 mmol) was benzoylated in the same manner as **3** to give

a crystalline derivative (1.5 g, 76.5%), m.p. 102–104° (ether–ethanol); ^{1}H-n.m.r. ($CDCl_3$): δ 3.46–3.83 (m, 7 H, 3 CH_2, H-2), and 7.16–7.83 (m, 15 H, arom.).

Anal. Calc. for $C_{29}H_{28}O_8$: C, 69.03; H, 5.59. Found: C, 69.16; H, 5.41.

2,3-O-Isopropylidene-3-C-methylerythritol (**10**). — To a solution of **6** (3 g, 8 mmol) in dry ether was added $LiAlH_4$ (1.09 g, 2.6 mmol) in portions and the suspension was boiled under reflux for 24 h. T.l.c. (solvent *A*) showed the absence of starting product **6** and formation of a new product having R_F 0.4. Excess $LiAlH_4$ was eliminated by addition of ethyl acetate (3 mL) and then water, and the gelatinous mixture was filtered. Concentration of the filtrate gave a syrupy mixture that was purified by column chromatography (elution with solvent *A*). Fractions containing the product having R_F 0.4 were collected and evaporated. The syrup crystallized from ethyl acetate–hexane (yield 1.0 g, 72%), m.p. 70–72°; ^{1}H-n.m.r. ($CDCl_3$): δ 1.2 (s, 3 H, CH_3 of CMe_2), 1.4 (s, 3 H, CH_3 of CMe_2), 1.46 (s, 3 H, CH_3), and 3.4–3.8 (m, 4 H, 2 CH_2OH).

Anal. Calc. for $C_8H_{16}O_4$: C, 54.47; H, 9.24. Found: C, 54.28; H, 9.12.

1,4-Di-O-benzoyl-2,3-O-isopropylidene-3-C-methylerythritol (**11**). — Compound **10** (0.75 g. 3 mmol) was benzoylated, in the same manner as compounds **3** and **9**, to give a crystalline product (1.59 g, 75%), m.p. 92–94°; ^{1}H-n.m.r. ($CDCl_3$): δ 1.2 (s, 3 H, CH_3 of CMe_2), 1.4 (s, 3 H, CH_3 of CMe_2), 1.46 (s, 3 H, CH_3), 3.4–3.86 (m, 4 H, 2 CH_2), 4.1 (s, 1 H, H-2), and 7.26–7.8 (m, 10 H, arom.).

Anal. Calc. for $C_{22}H_{24}O_6$: C, 68.73; H, 6.29. Found: C, 68.58; H, 6.12.

3-C-(Hydroxymethyl)erythritol (**12**). — (*a*) Compound **8** (1.0 g, 7.2 mmol) was dissolved in 90% aqueous trifluoroacetic acid (20 mL), and the mixture kept for 3 h at room temperature. The solvent was evaporated, and the residue treated with toluene (2 × 20 mL) to remove traces of trifluoroacetic acid and 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 column chromatography on silica gel (elution with solvent *D*) to give a pure syrupy product (yield 0.65 g, 82%), R_F 0.67.

(*b*) Compound **7** (10.0 g, 66 mmol) (D-apiose) was dissolved in water (30 mL) and then a solution of $NaBH_4$ (2.0 g, 52 mmol) was added dropwise with stirring. The time of addition was 30 min and the temperature was not allowed to rise >50°. After 24 h, acetic acid was added to bring the pH to 5, and the solution de-ionized with Amberlite IR-120 (H^+) ion-exchange resin. The solution was evaporated and methanol (8 × 50 mL) and toluene (5 × 50 mL) were successively added to, and evaporated from, the residue. The crude syrup was purified by column chromatography (elution with solvent *D*) to give a pure syrup (yield 7.6 g, 75%), R_F 0.67; ^{1}H-n.m.r. (D_2O): δ 3.48 (s, 2 H, CH_2-3), 3.82 (m, 1 H, H-2), and 4.82 (s, 4 H, H_2-1,4); m.s. (70 eV): *m/z* (%) M^+, 151 (3.27) (M − 1) (152 − 1), 150 (26.8), (M − 2), 148 (100) (M − 4), 121 (11), 104 (72.8), 95 (10.6), 93 (11.6), 82 (10.8), 71 (12.5), 69 (34.9), 57 (27), 56 (11), 55 (12.7), 43 (12.7), and 41 (21.9).

Anal. Calc. for $C_5H_{12}O_5$: C, 39.46; H, 7.95. Found: C, 39.21; H, 8.12.

1,2,3,4-Tetra-O-benzoyl-3-C-(benzoyloxymethyl)erythritol (**13**). — Com-

pound **12** (0.75 g, 5 mmol) was benzoylated, in the same manner as compounds **3, 9,** and **11**, to give a crystalline product (1.65 g, 80%), m.p. 66–68° (ethanol); ^{1}H-n.m.r. ($CDCl_3$: δ 3.46–3.96 (m, 6 H, 3 CH_2), 4.2 (s, 1 H, H-2), and 7.36–7.93 (m, 25 H, arom.).

Anal. Calc. for $C_{40}H_{32}O_{10}$: C, 71.41; H, 4.79. Found: C, 71.25; H, 4.62.

3-C-Methylerythritol (**14**). — Compound **10** (1.0 g, 7.2 mmol) was dissolved in 90% aqueous (v/v) trifluoroacetic acid (1 mL) and the mixture kept for 8 h at room temperature. The product was recovered in the same manner as **12** to give syrupy **14** (0.5 g, 65%) which was purified by flash-column chromatography[21] on silica gel (elution with solvent *B*), R_F 0.6; ^{1}H-n.m.r. (D_2O): δ 1.4 (s, 3 H, CH_3), 3.43–3.76 (m, 4 H, 2 CH_2), and 3.9 (d, 1 H, H-2); m.s. (70 eV): *m/z* (%) 137 (1.2) (M^+ + 1, 136 + 1), 105 (20.4) (M^+ − CH_2OH, 136 − 31), 87 (12.4), 75 (100), 73 (5.9), 70 (6.5), 69 (5.7), 61 (22.4), 59 (18.2), 58 (18.1), 57 (68.3), 55 (13.0), 45 (28.4), 44 (50.6), 43 (93.5), 42 (16.3), and 41 (37.5).

Anal. Calc. for $C_5H_{12}O_4$: C, 44.10; H, 8.88. Found: C, 43.89; H, 8.95.

1,2,3,4-Tetra-O-benzoyl-3-C-methylerythritol (**15**). — Compound **14** (0.75 g, 5.4 mmol) was benzoylated in the same manner as compounds **3, 9,** and **11** to give a crystalline product (2.38 g, 78%), m.p. 81–83° (methanol); ^{1}H-n.m.r. ($CDCl_3$): δ 1.36 (s, 3 H, CH_3), and 3.46–3.9 (m, 5 H, 2 CH_2, H-2).

Anal. Calc. for $C_{33}H_{32}O_8$: C, 71.20; H, 5.79. Found: C, 71.06; H, 5.90.

*1,2-O-Isopropylidene-3-C-(p-tolylsulfonyloxymethyl)-β-*L-threo-*tetrofuranose* (**18**). — Commercially available 1,2:3,5-di-*O*-isopropylidene-3-*C*-methyl-*β*-L-*threo*-tetrofuranose[14] (**16**) (5 g, 21 mmol) was dissolved in 60% (v/v) aqueous acetic acid (75 mL) and the solution stirred for 60 h at room temperature. Acetic acid was evaporated and the residue crystallized from dichloromethane–hexane to yield 3-*C*-(hydroxymethyl)-1,2-*O*-isopropylidene-*β*-L-*threo*-tetrofuranose[14] (**17**) (2.96 g, 70%), m.p. 123–125°, $[\alpha]_D^{20}$ +43.6° (*c* 0.8, methanol); lit.[14] m.p. 123–125°, $[\alpha]_D^{20}$ 44° (*c* 1, ethanol).

To a solution of **17** (2.5 g, 13 mmol) in anhydrous pyridine (25 mL) was added *p*-toluenesulfonyl chloride (3.0 g, 15 mmol), and the solution kept overnight at 25°. Pyridine was removed by evaporation and coevaporation with toluene (50 mL), and the residue chromatographed on a silica gel column (solvent *A*). Fractions containing the product were combined and evaporated to give a crystalline solid. Recrystallization from dry ether gave **18** (3.5 g, 78%), m.p. 137–138°, $[\alpha]_D^{20}$ +42.8° (*c* 2, chloroform); lit.[14] m.p. 137–138°, $[\alpha]_D^{20}$ +43.2° (*c* 4.4, chloroform).

*1,2-O-Isopropylidene-3-C-methyl-β-*L-threo-*tetrofuranose* (**19**). — To a stirred solution of **18** (1.7 g, 10 mmol) in dry ether (40 mL) and dry oxolane (15 mL) was added $LiAlH_4$ (0.3 g, 70 mmol), and the suspension was boiled under reflux for 20 h. T.l.c. (solvent *A*) indicated one product and the absence of **18**. Excess $LiAlH_4$ was eliminated by the addition of ethyl acetate and then water, and the white gelatinuous mixture was filtered. Concentration of the colorless filtrate gave a syrup (0.75 g, 85%), $[\alpha]_D^{20}$ +29° (*c* 1.3, chloroform). Crystallization from hexane gave **19**, m.p. 60–62° (lit.[15] m.p. 57–60°), $[\alpha]_D^{20}$ +29.8° (*c* 1.5, chloroform).

*3-C-Methyl-*L-threo-*tetrofuranose (3-deoxy-*D-*apiose)* (**20**). — A solution of **19** (3.0 g, 17 mmol) in 90% trifluoroacetic acid (25 mL) was stirred for 12 h at room temperature, and the solvent evaporated. The residue was treated with hot hexane (3 × 20 mL) to remove traces of trifluoroacetic acid. The syrupy residue was dissolved in water (10 mL) and passed through a column of anion-exchange resin (Amberlite IR-45; OH^-). The eluate was evaporated and the syrupy residue was dried under reduced pressure (yield 1.8 g, 86%), $[\alpha]_D^{20}$ +12.1° (*c* 1, methanol); ^{1}H-n.m.r. (D_2O): δ 1.4 (s, 3 H, CH_3), 3.63–3.96 (m, 3 H, H_2-4, H-2); m.s. (70 eV): *m/z* (%) 135 (16.7) (M + 1), 119 (4.8), 111 (6.2), 97 (8.2), 85 (7.1), 83 (9.0), 69 (14.1), 60 (21.4), 57 (18.2), 44 (100), and 43 (54.6).

Anal. Calc. for $C_5H_{10}O_4$: C, 44.77; H, 7.44. Found: C, 45.08; H, 7.61.

*3-C-Methyl-*L-*threitol* (**21**). — To a solution of 3-C-methyl-L-*threo*-tetrofuranose (**20**) (0.5 g, 63 mmol) in water (50 mL) was added dropwise a solution of $NaBH_4$ (0.95 g, 25 mmol) in water (15 mL), and the mixture was stirred for 24 h at room temperature. The product was recovered in the same manner as compound **12**, to give a syrup (0.6 g, 80%), $[\alpha]_D^{20}$ −7° (*c* 2.0, methanol); ^{1}H-n.m.r. (D_2O): δ 1.36 (s, 3 H, CH_3), and 3.4–3.83 (m, 4 H, 2 CH_2); m.s. (70 eV): *m/z* (%) 137 (2.1), (M^+ + 1; 136 + 1), 105 (30.6) (M^+ − CH_2OH; 136 − 31), 87 (10.1), 75 (100), 70 (5.3), 61 (26.1), 59 (12.1), 58 (19.2), 57 (65.5), 55 (12.6), 45 (26.1), 44 (52.0), 43 (95.6), 42 (14.1), and 41 (37.3).

Anal. Calc. for $C_5H_{12}O_4$: C, 44.10; H, 8.88. Found: C, 43.91; H, 8.99.

*1,2,3,4-Tetra-*O*-benzoyl-3-C-methyl-*L-*threitol* (**22**). — Compound **21** (0.5 g, 36 mmol) was benzoylated in the same manner as compounds **9** and **11** to give a crystalline derivative (1.25 g, 75%), m.p. 90–92°, $[\alpha]_D^{20}$ −11.2° (*c* 2, chloroform); ^{1}H-n.m.r. ($CDCl_3$): δ 1.36 (s, 3 H, CH_3), 3.46–3.86 (m, 4 H, 2 CH_2), and 7.16–7.73 (m, 16 H, arom.).

Anal. Calc for $C_{32}H_{28}O_8$: C, 71.09; H, 7.34. Found: C, 69.87; H, 7.51.

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