

Note

Synthesis of 1,3-di-*O*-benzyl-D-*glycero*-tetrulose

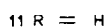
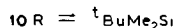
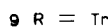
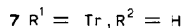
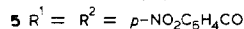
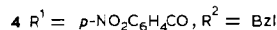
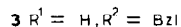
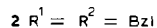
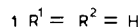
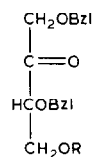
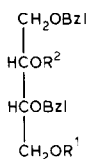
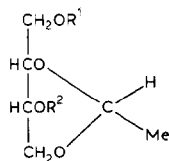
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In connection with studies of the synthesis of phosphocarbohydrates¹, large quantities of 1,3-di-*O*-protected D-(or L)-*glycero*-tetrulose were required. Although D-*glycero*-tetrulose is easily obtained², its di-*O*-substituted derivatives have not been described. The synthesis of 1,3-di-*O*-benzyl-D-*glycero*-tetrulose (**11**), a new four-carbon chiron^{3,4} containing a β -hydroxy ketone moiety is now reported.

1,3-*O*-Ethylidene-L-erythritol⁵ (**1**) was treated with benzyl bromide–tetrahydrofuran in the presence of a catalytic amount of tetrabutylammonium iodide⁶, to afford 1,3-di-*O*-benzyl-2,4-*O*-ethylidene-D-erythritol (**2**) in almost quantitative yield. When insufficient tetrahydrofuran was used, benzylation was incomplete and a mixture of mono-*O*-benzyl derivatives of **1** could be isolated by column chromatography. The major (~85%) component (**3**) of this mixture could be isolated, after *p*-nitrobenzylation, as 3-*O*-benzyl-2,4-*O*-ethylidene-1-*O*-(*p*-nitrobenzoyl)-D-erythritol (**4**). The structure **4** was assigned on the basis of a comparison of ¹H-n.m.r. data with those of 2,4-*O*-ethylidene-1,3-di-*O*-(*p*-nitrobenzoyl)-D-erythritol (**5**).



Hydrolysis of **2** with aqueous sulfuric acid^{7,8} gave a high yield of 1,3-di-*O*-benzyl-D-erythritol (**6**), which was purified by chromatography on silica gel. Although **6** has been reported^{9,10}, no physical properties were recorded.

The primary hydroxyl group in **6** was quantitatively substituted on reaction with trityl chloride in pyridine at room temperature¹¹, and the crude ether **7** was oxidised with pyridinium dichromate¹² in the presence of molecular sieve¹³ to afford 1,3-di-*O*-benzyl-4-*O*-trityl-D-*glycero*-tetrulose (**9**, 95%). Treatment of **9** with hydrogen bromide–acetic acid¹⁴ below 10° gave 1,3-di-*O*-benzyl-D-*glycero*-tetrulose (**11**) of high purity. Other reagents commonly used for detritylation, for example, boiling aqueous 80% acetic acid¹⁵ or 1% trifluoroacetic acid in dichloromethane¹⁶, completely removed the trityl group from **9** but also caused substantial decomposition and partial racemisation of **11**. Detritylation of **9** with zinc bromide¹⁷ was not only incomplete but substantial racemisation of **11** also occurred.

Alternatively, selective protection of **6** with *tert*-butyldimethylsilyl chloride catalysed by 4-dimethylaminopyridine¹⁸ was readily achieved to give **8**. Oxidation of **8** to 1,3-di-*O*-benzyl-4-*O*-(*tert*-butyldimethylsilyl)-D-*glycero*-tetrulose (**10**, 86%) was accomplished as for **7**. The *tert*-butyldimethylsilyl group was removed from **10** with hydrofluoric acid in aqueous acetonitrile (a procedure recommended for compounds containing β -hydroxy ketone moieties¹⁹) to form **11**. The optical activity of **11** diminished very slowly when traces of acidic impurities were present.

EXPERIMENTAL

General methods. — Evaporations were performed under diminished pressure at 35° (bath) and finally at 0.01 mmHg. Optical rotations were measured with a Perkin–Elmer 241 MC polarimeter. ¹H-N.m.r. spectra were recorded with Bruker HX-72 (90 MHz), Tesla BS-487C (80 MHz), and Tesla BS-467 (60 MHz) instruments for solutions in CDCl₃ (internal Me₄Si) unless stated otherwise. I.r. spectra were recorded with a Specord 71 IR spectrophotometer. The purity of products was monitored by t.l.c. on Silica Gel 60 F 254 (Merck) with chloroform–methanol mixtures A, 50:1; B, 100:1; and C, 200:1. Silica gel 60 (Merck, 0.063–0.200 mm) was used for column chromatography.

Benzylation of 1,3-O-ethylidene-L-erythritol (1). — (a) To a stirred suspension of sodium hydride (5.52 g, 0.23 mol) in tetrahydrofuran (300 mL) was added dropwise at 30–35° a solution of **1** (15.6 g, 0.105 mol) in tetrahydrofuran (50 mL). When the evolution of hydrogen ceased, tetrabutylammonium iodide (3.9 g, 10.5 mmol) was added followed by dropwise addition of benzyl bromide (26.3 mL, 0.221 mol). The mixture was kept at 40° for 6 h and then left at room temperature overnight. After removal of tetrahydrofuran, the residue was added portionwise to ice–water. The organic layer was extracted with ether (3 × 100 mL), and the combined extracts were washed with water until neutral, dried, and concentrated. The crude product was freed from non-polar impurities by chromatography on a column of silica gel (150 g). Elution with chloroform gave 1,3-di-*O*-benzyl-2,4-*O*-ethylidene-D-erythritol (**2**) as a colorless oil (33.6 g, 91%), *R*_F 0.75 (solvent A). ¹H-n.m.r. data (80 MHz): δ 1.32 (d, 3 H, *J* 5 Hz, CH₃CH), 3.2–3.8 (m, 5 H, H-

1,1',2,4,4'), 4.1–4.3 (m, 1 H, H-3), 4.44 (s, 2 H, OCH₂Ph), 4.59 (s, 2 H, OCH₂Ph), 4.68 (q, 1 H, *J* 5 Hz, CH₃CH), 7.23 and 7.30 (2 s, 10 H, 2 Ph).

A sample of this material, after further chromatography, had $[\alpha]_D^{20} - 41^\circ$ (*c* 5.9, chloroform).

Anal. Calc. for C₂₀H₂₄O₄: C, 73.14; H, 7.37. Found: C, 72.97; H, 7.06.

(b) To a stirred suspension of sodium hydride (1.59 g, 66 mmol) in tetrahydrofuran (80 mL) was added **1** (4.14 g, 0.03 mol) portionwise in a stream of argon at room temperature. After 1 h, tetrabutylammonium iodide (1.16 g, 3 mmol) was added followed by dropwise addition of benzyl bromide (7.6 mL, 63 mmol). The mixture was stirred at room temperature for 3 h followed by evaporation of tetrahydrofuran, and was further worked-up as in (a). Column chromatography of the crude product on silica gel (160 g) with chloroform–methanol (100:1) gave **2** (5.52 g, 56%) and a mixture of mono-*O*-benzyl derivatives as an oil (2.43 g, 34%), $[\alpha]_D^{18} - 49^\circ$ (*c* 4.8, chloroform) (*cf.* $[\alpha]_D^{27} - 52.5^\circ$ for crystalline 2-*O*-benzyl-1,3-*O*-ethylidene-L-erythritol²⁰).

Anal. Calc. for C₁₃H₁₈O₄: C, 65.53; H, 7.61. Found: C, 65.61; H, 7.57.

To a stirred solution of *p*-nitrobenzoyl chloride (172 mg, 0.93 mmol) in dichloromethane (0.5 mL) was added a solution of the foregoing mixture (185 mg, 0.77 mmol) in dichloromethane (1 mL) followed by dropwise addition of pyridine (0.1 mL). The mixture was left at room temperature overnight and then concentrated. The semi-solid residue was subjected to chromatography on silica gel, and the appropriate fractions were recrystallised from chloroform–hexane (1:6) to give 3-*O*-benzyl-2,4-*O*-ethylidene-1-*O*-(*p*-nitrobenzoyl)-D-erythritol (**4**) as yellowish needles (253 mg, 85%), m.p. 78–79°, $[\alpha]_D^{18} - 58^\circ$ (*c* 1, chloroform), *R*_F 0.60 (solvent *B*); ν_{\max}^{KBr} 1720 cm⁻¹ (C=O). ¹H-N.m.r. data (90 MHz): in CDCl₃, δ 1.34 (d, 3 H, *J* 5.1 Hz, CH₃CH), 3.3–3.8 (m, 3 H, H-2,4*a*,4*e*), 4.2–4.4 (m, 1 H, H-3), 4.48 and 4.59 (AB-system, 2 H, *J* 11.9 Hz, OCH₂Ph), 4.45–4.6 (m, 2 H, H-1,1'), 4.73 (q, 1 H, *J* 5.1 Hz, CH₃CH), 7.25 (m, 5 H, Ph), and ~8.2 (AA'BB'-system, 4 H, C₆H₄); in C₆D₆, δ 1.30 (d, 3 H, *J* 5.1 Hz, CH₃CH), 3.1–3.7 (m, 3 H, H-2,4*a*,4*e*), 4.06 and 4.18 (AB-system, 2 H, *J* 11.9 Hz, OCH₂Ph), 4.40 (q, 1 H, *J* 5.1 Hz, CH₃CH), and 4.48–4.54 (m, 2 H, H-1,1').

Anal. Calc. for C₂₀H₂₁NO₇: C, 62.01; H, 5.46; N, 3.62. Found: C, 61.92; H, 5.20; N, 3.66.

2,4-*O*-Ethylidene-1,3-di-*O*-(*p*-nitrobenzoyl)-D-erythritol (**5**). — Conventional *p*-nitrobenzoylation of **1** gave **5** (82%), m.p. 151–152° (from chloroform–hexane), $[\alpha]_D^{22} - 100^\circ$ (*c* 3.3, chloroform), *R*_F 0.58 (solvent *C*). ¹H-n.m.r. data (90 MHz): δ 1.43 (d, 3 H, *J* 5.1 Hz, CH₃CH), 3.64 (t, 1 H, *J* 10.3 Hz, H-4*a*), 4.13 (ddd, 1 H, *J*_{1,2} 4.6, *J*_{1',2} 3.1, *J*_{2,3} 9.9, Hz, H-2), 4.42 (dd, *J*_{4*a*,4*e*} 10.3, *J*_{3,4*e*} 5.5 Hz, H-4*e*), 4.49 (dAB-system, *J*_{1,1'} 12.1, *J*_{1,2} 4.6 Hz, H-1), 4.63 (dAB-system, *J*_{1',2} 3.1 Hz, H-1'), 4.84 (q, 1 H, *J* 5.1 Hz, CH₃CH), 5.21 (dt, 1 H, *J*_{2,3} ≈ *J*_{3,4*a*} = 10.1, *J*_{3,4*e*} 5.5 Hz, H-3), and 8.0–8.5 (m, 8 H, aromatic protons).

Anal. Calc. for C₂₀H₁₈N₂O₁₀: C, 53.81; H, 4.06; N, 6.28. Found: C, 53.80; H, 4.24; N, 6.40.

1,3-Di-O-benzyl-D-erythritol (6). — Compound **2** (33.6 g, 0.102 mol) was vigorously stirred with 62.5mM sulfuric acid (440 mL) at 95–100° until **2** was not detected by t.l.c. (solvent *A*). The mixture was extracted with ether (5 × 100 mL), and the combined extracts were washed with potassium hydrogencarbonate and water, dried, and eluted from silica gel (60 g) with chloroform to remove traces of **2**, and with chloroform–methanol (40:1) to give **6** as a colorless oil (26.4 g, 86%), R_F 0.40 (solvent *A*). $^1\text{H-N.m.r.}$ data (80 MHz): δ 3.8 (bs, 2 H, 2 HO), 3.4–4.1 (m, 6 H, H-1,1',2,3,4,4'), 4.50 (s, 2 H, OCH_2Ph), 4.51 and 4.63 (AB-system, 2 H, J 11.5 Hz, OCH_2Ph), and 7.2–7.4 (m, 10 H, 2 Ph). This material was sufficiently pure for the next step, but a sample was subjected to rechromatography to give pure **6**, $[\alpha]_D^{20} -27^\circ$ (c 7.3, chloroform).

Anal. Calc. for $\text{C}_{18}\text{H}_{22}\text{O}_4$: C, 71.50; H, 7.34. Found: C, 71.35; H, 7.40.

1,3-Di-O-benzyl-4-O-trityl-D-glycero-tetrol (9). — To a cooled solution of **6** (2.01 g, 6.6 mmol) in pyridine (5 mL) was added trityl chloride (1.95 g, 7.0 mmol). The suspension was stirred until a clear solution was obtained, and this was then left at room temperature for 1 week. The solvent was evaporated, and toluene (20 mL) was evaporated from the residue, a solution of which in dichloromethane was then washed with cold dilute hydrochloric acid, sodium hydrogencarbonate, and water, dried, and concentrated, to give syrupy **7** which was pure by t.l.c. (R_F 0.49, solvent *C*).

To a suspension of crude **7** and molecular sieve 3A (6.7 g) in dichloromethane (26 mL) was added pyridinium dichromate (5.0 g, 13.3 mmol) in 1 portion, and the progress of the reaction was monitored by t.l.c. When **7** had disappeared (8 h), ether (50 mL) was added, the solids were collected and washed with ether (2 × 50 mL), and the combined filtrate and washings were concentrated. The brownish, oily residue was eluted from silica gel (26 g) with chloroform, to give **9** (3.45 g, 95%) as a colorless syrup, $[\alpha]_D^{20} +10.5^\circ$ (c 4.8, chloroform), R_F 0.70 (solvent *C*); $\nu_{\text{max}}^{\text{film}}$ 1735 cm^{-1} (C=O). $^1\text{H-N.m.r.}$ data (CCl_4 , 80 MHz): δ 3.25–3.5 (m, 2 H, H-4,4'), 3.9–4.1 (m, 1 H, H-3), 4.3 (s, 2 H, H-1,1'), 4.43 and 4.47 (2 s, 4 H, 2 OCH_2Ph), and 7.0–7.5 (m, 25 H, 5 Ph).

Anal. Calc. for $\text{C}_{37}\text{H}_{34}\text{O}_4$: C, 81.89; H, 6.32. Found: C, 81.65; H, 6.35.

2,4-Di-O-benzyl-1-O-(tert-butyldimethylsilyl)-L-erythritol (8). — To a cooled (water bath) solution of **6** (5.685 g, 18.8 mmol), *tert*-butyldimethylsilyl chloride (3.074 g, 20.4 mmol), and triethylamine (2.9 mL, 20.7 mmol) in dichloromethane (60 mL) was added 4-dimethylaminopyridine (92 mg, 0.75 mmol), and the mixture was stirred at room temperature overnight. After dilution with dichloromethane, the mixture was washed with water, aqueous ammonium chloride, and water, and dried. The crude product was filtered through silica gel (30 g), to give **8** (6.23 g, 80%) as a colorless oil, $[\alpha]_D^{20} -21^\circ$ (c 6.1, chloroform), R_F 0.53 (solvent *B*); $\nu_{\text{max}}^{\text{film}}$ 3450 cm^{-1} (OH). $^1\text{H-N.m.r.}$ data (CCl_4 , 60 MHz): δ 0.1 (s, 6 H, SiMe_2), 0.9 (s, 9 H, CMe_3), 2.9 (bs, 1 H, OH), 3.6–4.1 (m, 6 H, H-1,1',2,3,4,4'), 4.5 (s, 2 H, OCH_2Ph), 4.55 and 4.70 (AB-system, 2 H, J 12 Hz, OCH_2Ph), and 7.3 (m, 10 H, 2 Ph).

Anal. Calc. for $C_{24}H_{36}O_4Si$: C, 69.19; H, 8.71. Found: C, 68.98; H, 8.77.

1,3-Di-O-benzyl-4-O-(tert-butyltrimethylsilyl)-D-glycero-tetralose (10). — To a cooled suspension of molecular sieve 3A (15 g) and pyridinium dichromate (11.2 g, 29.7 mmol) in dichloromethane (60 mL) was added a solution of **8** (6.18 g, 14.8 mmol) in dichloromethane (15 mL), and the oxidation was monitored by t.l.c. When **8** had disappeared (8 h), ether (140 mL) was added, the solids were collected and washed with ether (2×100 mL), and the combined filtrate and washings were concentrated. The brownish oil was twice eluted from silica gel (60 g) with chloroform, to give **10** (5.26 g, 86%) as a colorless oil, $[\alpha]_D^{20} +18^\circ$ (c 5.9, benzene), R_F 0.70 (solvent B); ν_{\max}^{film} 1730 cm^{-1} (C=O). $^1\text{H-N.m.r.}$ data (CDCl_3 , 60 MHz): δ 0.0 (s, 6 H, SiMe_2), 0.88 (s, 9 H, CMe_3), 3.7–4.1 (m, 3 H, H-3,4,4'), 4.4 (s, 2 H, H-1,1'), 4.5 (s, 4 H, 2 OCH_2Ph), and 7.3 (m, 10 H, 2 Ph).

Anal. Calc. for $C_{24}H_{34}O_4Si$: C, 69.52; H, 8.27. Found: C, 69.84; H, 8.30.

1,3-Di-O-benzyl-D-glycero-tetralose (11). — (a) To an ice-cold and efficiently stirred solution of **9** (14.0 g, 25.8 mmol) in glacial acetic acid (20 mL) was rapidly added 45% hydrogen bromide in acetic acid (4.6 mL). After 3 min, the mixture was filtered onto crushed ice, and the solid was washed with glacial acetic acid (15 mL). The cold solution was extracted with ether (5×50 mL), and the combined extracts were washed with cold aqueous potassium hydrogencarbonate and ice–water, and dried. The crude product was eluted from a column of silica gel with chloroform–methanol (100:1), to give **11** (3.53 g, 45%) as a colorless oil, $[\alpha]_D^{21} +24^\circ$ (c 5.6, benzene), R_F 0.37 (solvent A); ν_{\max}^{film} 3430 (OH) and 1725 cm^{-1} (C=O). $^1\text{H-N.m.r.}$ data (80 MHz): δ 3.3 (bs, 1 H, OH), 3.78 (d, 2 H, J 4 Hz, H-4,4'), 4.03 (t, 1 H, J 4 Hz, H-3), 4.3 (s, 2 H, H-1,1'), 4.48 (s, 4 H, 2 OCH_2Ph), and 7.2–7.3 (m, 10 H, 2 Ph).

Anal. Calc. for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. Found: C, 71.60; H, 7.00.

(b) Compound **9** (695 mg, 1.3 mmol) was warmed to reflux with aqueous 80% acetic acid (2 mL) and maintained at 100° for 2 min. The mixture was then left at room temperature for 5 h, triphenylmethanol (270 mg, 81%) was removed, and the filtrate was concentrated. A solution of the residue in chloroform was dried and subjected to chromatography on silica gel (8 g), to give **11** (158 mg, 41%) as a colorless oil, $[\alpha]_D^{22} +12^\circ$ (c 2.4, benzene).

(c) To a suspension of zinc bromide (2.0 g) in dichloromethane (2 mL) was added a solution of **9** (895 mg, 1.6 mmol) in dichloromethane (2 mL), and the mixture was stirred at room temperature for 21 h. After the addition of water, the crude product was extracted with chloroform and purified on silica gel (8 g), to give **11** (73 mg, 15%) as a colorless oil, $[\alpha]_D^{20} +13^\circ$ (c 1.4, benzene). Unreacted **9** (620 mg, 69%) was also recovered.

(d) A mixture of **10** (1.978 g, 4.8 mmol), aqueous 40% hydrofluoric acid (0.25 mL), and acetonitrile (4.75 mL) was stirred at room temperature and the reaction was monitored by t.l.c. After 1 h, barium carbonate (1 g) and magnesium sulfate (1 g) were added, the mixture was stirred for 30 min and then concentrated, and the residue was chromatographed on silica gel (25 g) with chloroform, to give **11** (875 mg, 61%) as a colorless oil, $[\alpha]_D^{22} +23.5^\circ$ (c 4.2, benzene).

ACKNOWLEDGMENTS

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