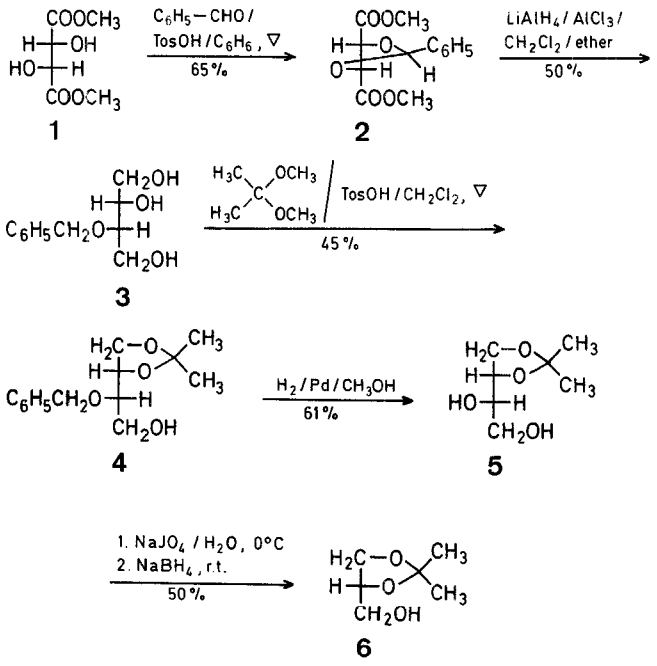
Synthesis of 1,2-*O*-Isopropylidene-L-threitol and its Conversion to (*R*)-1,2-*O*-Isopropylideneglycerol

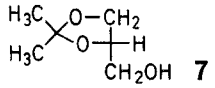
Ali H. Al-Hakim, Alan H. Haines*, Christopher Morley

School of Chemical Sciences, University of East Anglia, Norwich NR4 7TJ, England

The selective protection of hydroxy groups in carbohydrates and related polyols is often achieved through formation of cyclic acetal derivatives[1,2,3]. Although a very large number of such derivatives have been prepared, there remain potentially useful members of this class of compounds for which no convenient synthesis has been described. 1,2-*O*-Isopropylidene-L-threitol **(5)**, which is obtained[4,5] in only low yield by the acid-catalysed reaction of L-threitol with acetone, and which is an obvious precursor of the synthetically useful (*R*)-1,2-*O*-isopropylideneglycerol **(6)**, is such a compound. We report the preparation of **5** by hydrogenolysis of the known[6], 3-*O*-benzyl-1,2-*O*-isopropylidene-L-threitol **(4)**, which is itself prepared from the readily available (2*R*,3*R*)-dimethyl tartrate **(1)**, and the conversion of **5** through sequential application of periodate cleavage and borohydride reduction to the chiral glycerol derivative **6**.



(2*R*,3*R*)-Dimethyl tartrate (**1**) was converted[7] by acid-catalysed reaction with benzaldehyde in benzene into (2*R*,3*R*)-dimethyl 2,3-*O*-benzylidenetartrate (**2**). Acetal **2** was then transformed into **4** by the published procedure[6] involving reductive cleavage with lithium aluminium hydride/aluminium trichloride to give 2-*O*-benzyl-L-threitol (**3**), followed by reaction of the latter with 2,2-dimethoxypropane under acidic catalysis. Benzyl ether **4** was subjected to palladium-catalysed hydrogenolysis, affording **5** in 61% yield. The chemical shift of the acetal carbon in **5** is 109.5 ppm, confirming the presence of the 5-membered acetal ring[8]. Glycol cleavage of **5** with aqueous sodium metaperiodate, followed by immediate reduction of the product with aqueous sodium borohydride gave **6**.



7

Although (*S*)-1,2-*O*-isopropylideneglycerol (**7**), which has found widespread synthetic use, is readily prepared[9] from the inexpensive D-mannitol, (*R*)-isomer **6** has, until recently, been a relatively inaccessible compound. An analogous route to that used for the preparation of the (*S*)-isomer requires L-mannitol, that is the unnatural isomer, as a starting material[10], but a useful synthesis of **6** has been reported recently[11], based on degradation of L-ascorbic acid. Our new synthesis offers an alternative, cheap, and convenient route to **6** based on (2*R*,3*R*)-tartaric acid, which is currently of considerable interest[12] as a source of chiral building blocks for organic synthesis.

(2*R*,3*R*)-Dimethyl 2,3-*O*-Benzylidenetartrate (2):
A solution containing (2*R*,3*R*)-dimethyl tartrate (**1**; 50 g, 0.281 mmol), benzaldehye (30 ml, 0.295 mol), and *p*-toluenesulphonic acid monohydrate (0.1 g) in benzene (300 ml) is heated under reflux, with provision for azeotropic removal of water, for 12 h. The solution is then washed with aqueous sodium carbonate (50 ml), water (50 ml), and is then dried. Concentration of the filtered solution and crystallisation of the residue from ethanol gives **2**; yield: 48.4 g (65%); m.p. 72–73°C; $[\alpha]_D$: −43.4° (*c* 1.0, C_2H_5OH) [Lit.[7], m.p. 70–71°C; $[\alpha]_D$: −44° (C_6H_6); Lit.[13], m.p. 74°C; $[\alpha]_D$: −44.2° (*c* 1.74, C_2H_5OH)].

2-*O*-Benzyl-L-threitol (3):
To a stirred suspension of lithium aluminium hydride (5.7 g, 150 mmol) in 1:1 (v/v) diethyl ether/dichloromethane (250 ml) is added **2** (13.3 g, 50 mmol) followed by a solution of aluminium trichloride (20 g, 150 mmol) in diethyl ether (110 ml). The mixture is stirred for 1 h at room temperature, then heated under reflux for 1 h. After cooling the solution, water (11 ml) is added carefully to destroy the excess hydride, and then a further quantity (120 ml) is added. The organic layer is separated and the aqueous layer is extracted with diethyl ether (2 × 75 ml) and dichloromethane (2 × 75 ml). The combined organic extracts are dried, concentrated, and the residue recrystallised from ethyl acetate/light petroleum to give **3**; yield: 5.3 g (50%); m.p. 75–76°C; $[\alpha]_D$: +15.6° (*c* 0.34, CH_3OH) [Lit.[6], m.p. 73–76°C; $[\alpha]_D$: +15.7° (*c* 1.0, CH_3OH)].

3-*O*-Benzyl-1,2-*O*-isopropylidene-L-threitol (4):
A solution of **3** (5.3 g, 25 mmol), 2,2-dimethoxypropane 3.9 g, 37.5 mmol), and *p*-toluenesulphonic acid monohydrate (0.11 g) in dichloromethane (125 ml) is heated under reflux under a Soxhlet extractor containing 4A molecular seives for 2 h. The sieves are then replaced by a fresh batch and heating is continued for a further 2 h. The mixture is cooled, washed with saturated aqueous sodium hydrogen carbonate (50 ml), dried, and the material (3.86 g) so obtained is purified by column chromatography on Merck kieselgel (70–230 mesh) using toluene/ethyl acetate 4:1 v/v as eluent, to give the chromatographically homogeneous product; yield: 2.82 g (45%). Distillation of this material gives the analytical sample of **4**; b.p. 140–145°C (bath)/0.05 torr; $[\alpha]_D$: −14.1° (*c* 0.6, $CHCl_3$) [Lit.[6], $[\alpha]_D$ +16.8° (*c* 1.63, $CHCl_3$)][14].

$C_{14}H_{20}O_4$ calc. C 66.65 H 7.99
(252.31) found 66.56 8.20

^{1}H-N.M.R. ($CDCl_3$): δ = 1.34, 1.42 (2 × s, 2 × 3H, 2 × CH_3); 2.74 (br. s, 1H, OH); 3.40–4.60 (complex, 6H, 4 × O—CH_2, 2 × O—CH); 4.68 (s, 2H, O—$CH_2C_6H_5$); 7.28 ppm (br. s, 5H, Ar—H).

^{13}C-N.M.R. ($CDCl_3$): δ = 25.4; 26.4; 61.7; 65.6; 72.7; 76.6; 79.5; 109.3; 127.7; 127.8; 128.3; 138.3 ppm.

1,2-*O*-Isopropylidene-L-threitol (5):
A solution of **4** (2.006 g, 7.96 mmol) in methanol (150 ml) is shaken under a slight overpressure of hydrogen in the presence of 5% palladium-charcoal catalyst, at room temperature, until hydrogen uptake ceases (uptake, 1.04 mol equivalents). The filtered solution is concentrated and the crude product is purified by column chromatography (Merck kieselgel, ethyl acetate) to give **5**; yield: 0.784 g, (61%); b.p. 115–120°C (bath)/0.05 torr; $[\alpha]_D$: +3.9° (*c* 1.4, CH_3OH).

$C_7H_{14}O_4$ calc. C 51.84 H 8.70
(162.2) found 51.73 8.79

^{1}H-N.M.R. ($CDCl_3$): δ = 1.36, 1.44 (2 × s, 2 × 3H, 2 × CH_3); 3.40–4.40 ppm (complex, 8H, 4 × O—CH_2, 2 × O—CH, 2 × OH).

^{13}C-N.M.R. ($CDCl_3$): δ = 25.2, 26.4, 63.9, 65.8, 72.2, 76.5, 109.5 ppm [$C(CH_3)_2$].

(*R*)-1,2-*O*-Isopropylideneglycerol (6):
To a stirred solution of **5** (0.64 g, 4 mmol) in water (10 ml), cooled in ice, is added, dropwise, a solution of sodium metaperiodate (0.85 g, 4 mmol) in water (10 ml). After 15 min, a solution of barium chloride dihydrate (1.24 g, 5 mmol) in water (10 ml) is added, and after a further 5 min the mixture is filtered through kieselguhr. Sodium hydrogen carbonate (0.1 g) is added to the filtrate, followed by sodium borohydride (1.4 g, 37 mmol). The mixture is stored for 24 h at room temperature and excess borohydride is destroyed by addition of glacial acetic acid (~ 5 ml). The solution is then brought to pH 8 by addition of sodium hydrogen carbonate, and is extracted with dichloromethane (4 × 50 ml). The combined extracts are dried, then concentrated to give **6**; yield: 0.26 g (50%); $[\alpha]_D$: −10.6°; $[\alpha]_{546}$: −12.9° (*c* 4, CH_3OH) [Lit.[10], $[\alpha]_D$: −10.76°; $[\alpha]_{546}$: −12.99° (*c* 16.9, CH_3OH)].

$C_6H_{12}O_3$ calc. C 54.53 H 9.15
(132.2) found 54.34 9.43

The ^{1}H-N.M.R. spectrum and I.R. spectrum of **6** were indistinguishable from those of the (*S*)-isomer **7**, prepared[9] from D-mannitol.

Received: September 13, 1984

[1] A.B. Foster, in *The Carbohydrates: Chemistry and Biochemistry*, W. Pigman, D. Horton, Eds., Academic Press, New York, 1972, Vol. 1A, pp. 391–402.
[2] A.N. de Belder, *Adv. Carbohydr. Chem.* **20**, 219 (1965); *Adv. Carbohydr. Chem. Biochem.* **34**, 179 (1977).
[3] S.A. Barker, E.J. Bourne, *Adv. Carbohydr. Chem.* **7**, 137 (1952).
[4] A.B. Foster, A.H. Olavesen, J.M. Webber, *J. Chem. Soc.* **1961**, 5095.
[5] P.W. Feit, *Chem. Ber.* **96**, 712 (1963).
[6] K. Fujita et al., *Tetrahedron Lett.* **23**, 3507 (1982).
[7] M. Farines, J. Soulier, R. Soulier, *Bull. Soc. Chim. Fr.* **1972**, 1066.
[8] J.G. Buchanan et al. *Carbohydr. Res.* **100**, 75 (1982).
[9] E. Baer, H.O.L. Fischer, *J. Biol. Chem.* **128**, 463 (1939).
[10] E. Baer, H.O.L. Fischer, *J. Am. Chem. Soc.* **61**, 761 (1939).
[11] M.E. Jung, T.J. Shaw, *J. Am. Chem. Soc.* **102**, 6304 (1980).
[12] D. Seebach, E. Hungerbühler, in *Modern Synthetic Methods*, R. Scheffold, Ed., Salle and Sauerländer, Frankfurt and Aarau, 1980, pp. 91–171.
[13] H.O.L. Fischer, H. Appel, *Helv. Chim. Acta* **17**, 1574 (1934).
[14] The same authors[6] report $[\alpha]_D$: −16.6° (*c* 1.5, $CHCl_3$) for the enantiomer of **4**; it appears there was an error in assignment of the measured rotations to the enantiomers.