



A Publication  
of Reliable Methods  
for the Preparation  
of Organic Compounds

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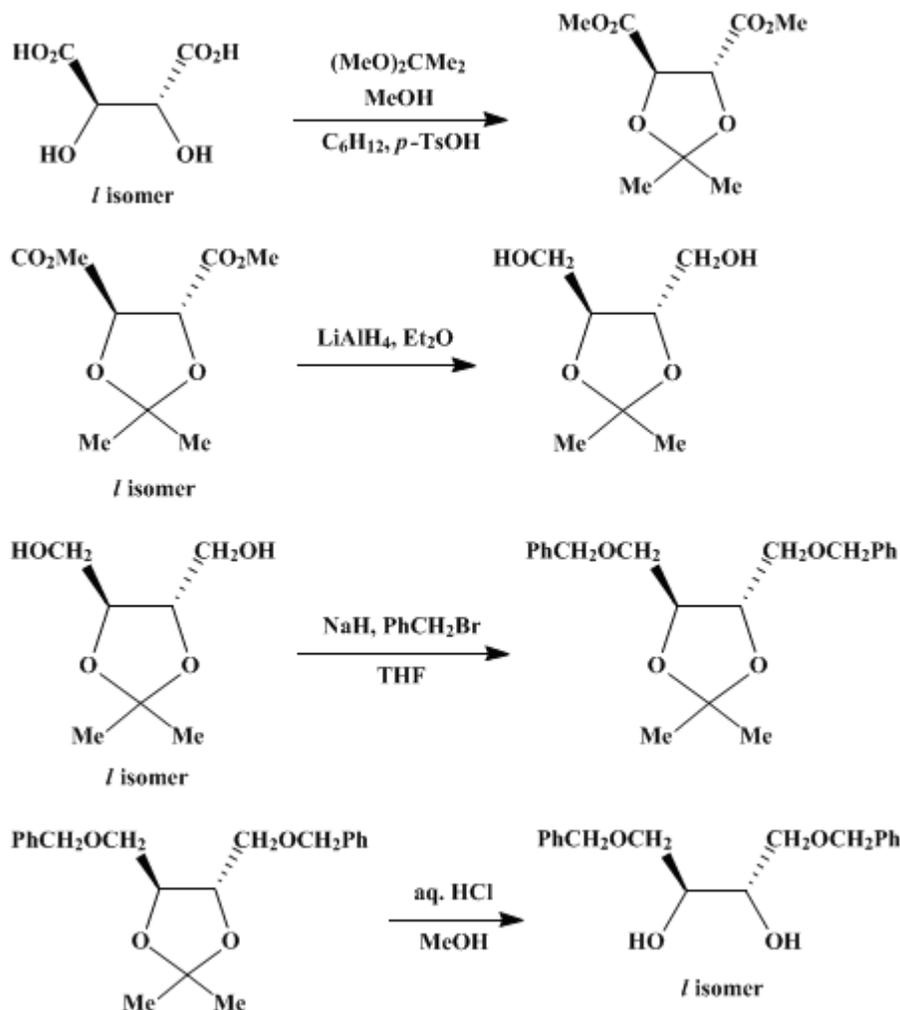
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*These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.*

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## 1,4-DI-O-ALKYL THREITOLS FROM TARTARIC ACID: 1,4-DI-O-BENZYL-L-THREITOL

[2,3-Butanediol, 1,4-bis(phenylmethoxy)- [*S*-(*R*<sup>\*</sup>,*R*<sup>\*</sup>)]-]



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### 1. Procedure

A. *Dimethyl 2,3-O-isopropylidene-L-tartrate*. (See (Note 1).) In a 1-L, one-necked, round-bottomed flask fitted with a reflux condenser and a large magnetic stirring bar under argon, a mixture of L-tartaric acid (101 g, 0.673 mol) (Note 2), 2,2-dimethoxypropane (190 mL, 1.54 mol) (Note 3), methanol (40 mL) (Note 4), and *p*-toluenesulfonic acid monohydrate (0.4 g, 2.1 mmol) (Note 5) is warmed on a steam bath with occasional swirling until a dark-red homogeneous solution is obtained (Note 6). Additional 2,2-dimethoxypropane (95 mL, 80.5 g, 0.77 mol) and cyclohexane (450 mL) (Note 7) are added and the flask is fitted with a 30-cm Vigreux column and a variable reflux distilling head. The mixture is heated to reflux with internal stirring and the acetone-cyclohexane and methanol-cyclohexane azeotropes are slowly removed (Note 8). Additional 2,2-dimethoxypropane (6 mL, 5.1 g, 49 mmol) is then added and the mixture heated under reflux for 15 min (Note 9). After the mixture has cooled to room temperature, anhydrous potassium carbonate (1 g, 7.2 mmol) is added and the mixture is stirred until the reddish color has abated (Note 10). Volatile material is removed under reduced pressure

(water aspirator) and the residue is fractionally distilled under vacuum to afford the product as a pale-yellow oil, bp 94–101°C (0.5 mm); 125–135 g (0.57–0.62 mmol, 85–92% yield) (Note 11) and (Note 12).

B. *2,3-Di-O-isopropylidene-L-threitol*. (See (Note 13).) In a dry, 2-L, three-necked, round-bottomed flask equipped with a 500-mL pressure-equalized addition funnel, a reflux condenser, a thermometer, and a large magnetic stirring bar is suspended lithium aluminum hydride (36 g, 0.95 mol) (Note 14) in diethyl ether (600 mL) (Note 15) under argon. The mixture is stirred and heated to reflux for 30 min. Heating is discontinued while a solution of dimethyl 2,3-*O*-isopropylidene-*L*-tartrate (123 g, 0.564 mol) in diethyl ether (300 mL) (Note 15) is added dropwise over 2 hr. Heating is then resumed and the mixture is refluxed for an additional 3 hr. The mixture is cooled to 0–5°C (Note 16) and cautiously treated with water (36 mL), 4 *N* sodium hydroxide solution (36 mL), and water (112 mL) (Note 17). The mixture is then stirred at room temperature until the gray color of unquenched lithium aluminum hydride has completely disappeared (Note 18). The mixture is filtered on a Büchner funnel and the inorganic precipitate is extracted with ether in a Soxhlet apparatus (Note 19). The combined ethereal extracts are dried over anhydrous magnesium sulfate and filtered, and volatile material is removed under reduced pressure (water aspirator). The residue is fractionally distilled under vacuum to afford the product as a colorless to pale-yellow oil, bp 94–106°C (0.4 mm); 50.2–60.3 g (0.31–0.37 mmol, 54–66% yield) (Note 20) and (Note 21).

C. *1,4-Di-O-benzyl-2,3-O-isopropylidene-L-threitol*. In a 2-L, three-necked, round-bottomed flask equipped with a large magnetic stirring bar under argon is placed fresh sodium hydride (33.6 g of a 55% dispersion in oil; 18.5 g, 0.77 mol) (Note 22). The oil is removed by washing with hexanes (3 × 100 mL) (Note 23) and (Note 24). The flask is fitted with a 500-mL pressure-equalized addition funnel, a reflux condenser, and a stopper. Tetrahydrofuran (250 mL) (Note 25) is added under argon. A solution of 2,3-*O*-isopropylidene-*L*-threitol (55 g, 0.34 mol) in tetrahydrofuran (250 mL) is then added dropwise with stirring at room temperature (Note 26). Benzyl bromide (91 mL, 130.8 g, 0.76 mol) (Note 27) is then added dropwise via the addition funnel (Note 28). After stirring for 12 hr at room temperature, the mixture is heated at reflux for 2 hr, cooled in an ice bath, and quenched by addition of water until a clear solution results. Tetrahydrofuran is removed under reduced pressure (water aspirator); the residue is diluted with water (500 mL) and extracted with diethyl ether (3 × 500 mL). The extracts are combined, dried over anhydrous magnesium sulfate, and filtered. Removal of volatile material under reduced pressure (water aspirator) gives crude 1,4-*di-O*-benzyl-2,3-*O*-isopropylidene-*L*-threitol as an oil (115–116 g).

D. *1,4-Di-O-benzyl-L-threitol*. The crude ketal is dissolved in methanol (300 mL), 0.5 *N* hydrochloric acid (30 mL) is added, and the resulting mixture is heated to reflux. Acetone and methanol are slowly distilled off (Note 29). Additional methanol (50 mL) and 0.5 *N* hydrochloric acid (20 mL) are added and the mixture is kept at room temperature until ketal hydrolysis is complete. The mixture is diluted with saturated sodium bicarbonate solution (500 mL) and extracted with ether (3 × 500 mL). The ether extracts are combined, dried over anhydrous magnesium sulfate, and filtered. Removal of volatile material under reduced pressure gives crude 1,4-*di-O*-benzyl-*L*-threitol as a pale-yellow solid. This solid is recrystallized twice from chloroform/hexanes to provide 59–65 g (195–215 mmol, 57–63% yield) of pure diol, mp 54–55°C (Note 30) and (Note 31). Concentration of the mother liquors from the recrystallizations gives a yellow solid that is chromatographed on 70–230-mesh silica gel 60 (500 g) (Note 32), and eluted with 50% ethyl acetate/hexanes, to provide an additional 20–26 g (66–86 mmol, 19–25% yield) of diol, mp 56–57°C (Note 33).

## 2. Notes

1. Dimethyl 2,3-*O*-isopropylidene-*L*-tartrate is also commercially available from Fluka Chemical Corporation.
2. *L*-tartaric acid, 99 + %, mp 170–172°C,  $[\alpha]_D^{20} + 12.4^\circ$  (water, *c* 20), from Aldrich Chemical Company, Inc., was used as obtained.
3. 2,2-Dimethoxypropane, 98%, from Aldrich Chemical Company, Inc., was distilled before use. The checkers used this material directly from the bottle without adverse effects.
4. Methanol was distilled from sodium methoxide before use. The checkers used absolute methanol

from Fisher Chemical Company directly from the bottle without adverse effects.

5. *p*-Toluenesulfonic acid monohydrate, 99%, from Aldrich Chemical Company, Inc., was used as obtained.

6. This procedure normally requires 1–2 hr.

7. Reagent-grade cyclohexane, from MCB Manufacturing Chemists Inc., was used as obtained.

8. Removal over a 2-day period (10–15 mL/hr) is satisfactory. After approximately 600 mL of distillate has been collected, the temperature at the solvent head is approximately 79°C.

9. The checkers omitted this final addition and 15-min reflux period without adverse effects.

10. This normally occurs within 1–2 hr, leaving a yellow solution.

11. This product was ≥88% pure based on recovery of an analytical sample from chromatography on silica gel 60 eluted with 30% ethyl acetate/hexanes. Physical properties and spectral data are as follows:  $[\alpha]_D^{24}$   $-42.6^\circ$  (CHCl<sub>3</sub>, *c* 5.1), lit.  $[\alpha]_D^{20}$   $-49.4^\circ$  (neat);<sup>2</sup> IR (neat) cm<sup>-1</sup>: 2992, 2956, 1759, 1438, 1384, 1213, 1111, 1013, 858, 749; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$ : 1.49 (s, 6 H), 3.83 (s, 6 H), 4.81 (s, 2 H); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$ : 25.98, 52.42, 76.68, 113.49, 169.75. The checkers found this material to be 91–94% pure by gas chromatography.

12. Dimethyl 2,3-*O*-isopropylidene-*D*-threitol was prepared similarly.

13. 2,3-*O*-Isopropylidene-*L*-threitol is also commercially available from Aldrich Chemical Company Inc. and from Fluka Chemical Corporation.

14. Lithium aluminum hydride, ≥95%, from Aldrich Chemical Company, Inc., was used as obtained.

15. Diethyl ether was distilled from sodium immediately prior to use.

16. An ice–salt or ice–acetone bath is employed.

17. Dropwise addition via a funnel is recommended. During the quenching procedure, stirring becomes difficult for a time and manual swirling may be necessary. Use of a stirrer with a powerful magnet is recommended.

18. *Cautious* scraping of the sides of the flask to expose isolated pockets of unquenched lithium aluminum hydride may be expeditious at this point.

19. The checkers obtained a greater yield by carrying out the Soxhlet extraction with tetrahydrofuran instead of ether.

20. This product was ≥80% pure based on recovery of an analytical sample from chromatography on silica gel 60 eluted with 80% ethyl acetate/hexanes. Physical properties and spectral data are as follows:  $[\alpha]_D^{24}$   $+2.78^\circ$  (CHCl<sub>3</sub>, *c* 4.67), lit.  $[\alpha]_D^{20}$   $+4.1^\circ$  (CHCl<sub>3</sub>, *c* 5);<sup>3</sup> IR (neat) cm<sup>-1</sup>: 3413, 2987, 2934, 1455, 1372, 1218, 1166, 1057, 986, 882, 844, 801, 756; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$ : 1.42 (s, 6 H), 3.73 (m, 6 H), 3.94 (m, 2 H); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$ : 26.75, 62.06, 78.32, 109.08. The checkers found this material to be 95–97% pure by gas chromatography.

21. 2,3-Di-*O*-isopropylidene-*D*-threitol was prepared similarly.

22. Sodium hydride, 55–60% dispersion in mineral oil, from Alfa Products, Morton/Thiokol, Inc., was used as obtained.

23. Hexanes were distilled from calcium hydride prior to use.

24. The hexane washes can be decanted into a larger beaker containing isopropyl alcohol and dry ice. The last traces of hexanes can be removed under vacuum, followed by reintroduction of an argon atmosphere.

25. Tetrahydrofuran was distilled from sodium immediately prior to use.

26. Toward the end of this addition stirring becomes increasingly difficult. Use of a stirrer with a powerful magnet is recommended.

27. Benzyl bromide from Fluka Chemical Corporation was used as obtained.

28. If magnetic stirring is impossible at this point, manual swirling of the flask may be necessary for a time. As the alkylation proceeds, the mixture becomes less viscous.

29. This procedure requires 3–5 hr. Progress of this hydrolysis can be monitored by thin-layer chromatography on 0.25-mm silica gel 60 plates eluted with 50% ethyl acetate/hexanes; *R*<sub>f</sub> ketal 0.59, *R*<sub>f</sub> diol 0.21.

30. Physical properties and spectral data for 1,4-di-*O*-benzyl-*L*-threitol are as follows:  $[\alpha]_D^{24}$   $-5.85^\circ$  (CHCl<sub>3</sub>, *c*, 5.15), lit.  $[\alpha]_D^{25}$   $-5.0$  (CHCl<sub>3</sub>, *c* 5);<sup>4</sup> IR (CHCl<sub>3</sub>) cm<sup>-1</sup>: 3562, 3065, 3014, 2867, 1495, 1453, 1361, 1233, 1101, 1027; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$ : 2.93 (br s, 2 H), 3.54–3.60 (m, 4 H), 3.83–3.87 (m, 2 H), 4.47–4.57 (m, 4 H), 7.23–7.36 (m, 10 H); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$ : 70.45, 71.85, 73.45, 127.70, 128.37, 137.66.

31. 1,4-Di-*O*-benzyl-*D*-threitol was prepared similarly;  $[\alpha]_D^{24}$   $+6.16^\circ$  (CHCl<sub>3</sub>, *c* 3.83).

32. E. Merck 70–230-mesh silica gel 60 from Curtin-Matheson Scientific was employed.

33. The checkers found that the solid obtained by recrystallization from chloroform/hexanes occludes a large amount of solvent. To obtain pure, dry material, it is necessary to press the moist solid while it is still on the Büchner funnel and then to dry it under vacuum (room temperature, 0.05 mm, 12–18 hr). Only 35 g of pure material was obtained in this manner. Repetition of the process with the mother liquors yielded another 35 g of material. The remaining product (ca. 20 g) was obtained by chromatography. Recrystallization from ethyl acetate/hexanes gave a product that is easier to dry.

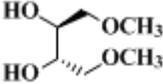
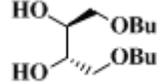
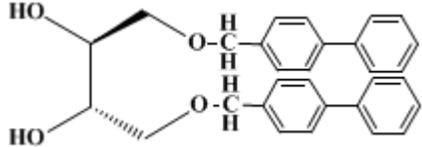
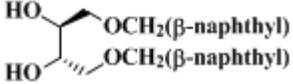
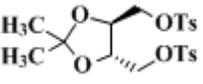
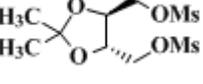
### 3. Discussion

Homochiral molecules readily available from inexpensive sources are useful synthetic building blocks and chiral auxiliaries. 1,4-Di-*O*-benzyl-*L*-threitol has been used in construction of homochiral crown ethers that are useful as enzyme model systems.<sup>5 6 7</sup> Topologically controlled diastereoselective delivery of the Simmons–Smith reagent for 2-cycloalken-1-one 1,4-di-*O*-benzyl-*L*-threitol ketals was recently reported.<sup>8 9 10</sup>

A number of other enantioselective processes are known to depend on homochiral acetal or ketal participation.<sup>11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26</sup> Diols used in these reactions include tartrate esters, tartramides, propanediols, butanediols, and pentanediols. 1,4-Di-*O*-benzyl-*L*-threitol may prove superior to other diols since it (a) can be produced inexpensively in quantity in either enantiomeric form; (b) is an amorphous solid; (c) contains a UV chromophore, making derivatives easy to monitor; (d) can be introduced directly or via transketalization; and (e) provides "functionalized arms" which can be chemically manipulated after ketalization.

The preparation of 1,4-di-*O*-benzyl-*L*-threitol described here from *L*-tartaric acid via 2,3-*O*-isopropylidene-*L*-threitol is adapted from work by Carmack,<sup>2</sup> Feit,<sup>3</sup> and Inouye.<sup>4</sup> This general route has been employed by the submitters and by others for the production of a number of synthetically useful *L*-threitol derivatives (Table I). The corresponding *D*-threitol derivatives are as easily prepared from commercially available *D*-tartaric acid.

TABLE I

Electrophile	Threitol Derivative	Yield, % <sup>a</sup>	Reference
Methyl iodide		62	27
Butyl iodide		37	27
4-(Chloromethyl)biphenyl		53	28
2-(Bromomethyl)naphthalene		83	28
<i>p</i> -Toluenesulfonyl chloride		82–90	1,27,29
Methanesulfonyl chloride		75–82	2,30

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This preparation is referenced from:

- *Org. Syn. Coll. Vol. 10*, 349
- *Org. Syn. Coll. Vol. 10*, 297

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## Appendix

### Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

2,3-Butanediol, 1,4-bis(phenylmethoxy)- [S-(R\*,R\*)]-

hexanes

2-cycloalken-1-one 1,4-di-O-benzyl-L-threitol

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

ethyl acetate (141-78-6)

methanol (67-56-1)

ether,  
diethyl ether (60-29-7)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

sodium bicarbonate (144-55-8)

cyclohexane (110-82-7)

acetone (67-64-1)

sodium methoxide (124-41-4)

sodium (13966-32-0)

isopropyl alcohol (67-63-0)

tartaric acid,  
L-tartaric acid (87-69-4)

Methyl iodide (74-88-4)

magnesium sulfate (7487-88-9)

benzyl bromide (100-39-0)

Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

sodium hydride (7646-69-7)

hexane (110-54-3)

2-(Bromomethyl)naphthalene (939-26-4)

argon (7440-37-1)

calcium hydride (7789-78-8)

Methanesulfonyl chloride (124-63-0)

2,2-dimethoxypropane (77-76-9)

p-Toluenesulfonyl chloride (98-59-9)

THREITOL,  
D-threitol (6968-16-7)

Butyl iodide (542-69-8)

4-(Chloromethyl)biphenyl (1667-11-4)

p-toluenesulfonic acid monohydrate (6192-52-5)

D-tartaric acid (147-71-7)

2,3-O-isopropylidene-L-threitol (50622-09-8)

2,3-Di-O-isopropylidene-L-threitol (50622-09-8)

Dimethyl 2,3-O-isopropylidene-L-tartrate

1,4-Di-O-benzyl-L-threitol (17401-06-8)

1,4-di-O-benzyl-2,3-O-isopropylidene-L-threitol (68394-39-8)

Dimethyl 2,3-O-isopropylidene-D-threitol

2,3-Di-O-isopropylidene-D-threitol

1,4-Di-O-benzyl-D-threitol

L-threitol