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of Reliable Methods  
for the Preparation  
of Organic Compounds

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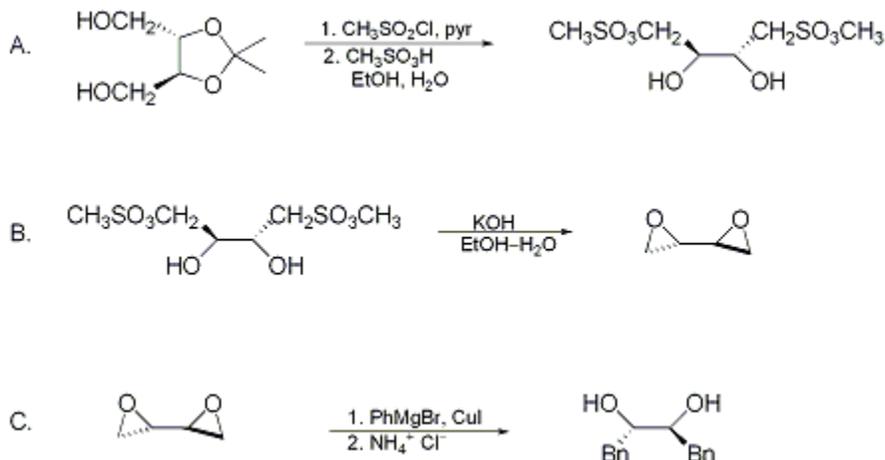
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*September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.*

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## SYNTHESIS OF CHIRAL NON-RACEMIC DIOLS FROM (S,S)-1,2,3,4-DIEPOXYBUTANE: (2S,3S)-DIHYDROXY-1,4-DIPHENYLBUTANE

[ 2,2'-Bioxirane, [S-(R,R)]- and 2,3-Butanediol, 1,4-diphenyl-, [S-(R,R)]- ]



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### 1. Procedure

*A. L-Threitol 1,4-bismethanesulfonate.* A dry, 1-L, round-bottomed flask equipped with a magnetic stirring bar, vacuum adapter, rubber septum, and a nitrogen line (Note 1) is charged with 2,3-O-isopropylidene-L-threitol (25.0 g, 0.154 mol) (Note 2), pumped under high vacuum for 10 min, and a nitrogen atmosphere is introduced. Methylene chloride (308 mL) (Note 3) and pyridine (37.4 mL, 0.462 mol) (Note 4) are added, and the stirred solution is cooled to 0°C with an ice-water bath. Methanesulfonyl chloride (29.8 mL, 0.385 mol) (Note 5) is added dropwise via a 50-mL glass syringe over a period of 10 min. After an additional 30 min, the ice-water bath is removed, and the stirred solution is allowed to warm to room temperature. After an additional 6 hr a precipitate forms (pyridinium chloride); 300 mL of an aqueous saturated solution of sodium bicarbonate (NaHCO<sub>3</sub>) is added slowly, dissolving the precipitate. The solution is stirred for a further 30 min and then transferred to a 1-L separatory funnel. The layers are separated, and the aqueous layer is extracted with methylene chloride (3 × 100 mL). The organic layers are combined, dried with anhydrous sodium sulfate, and the drying agent is removed by filtration. The solvent is removed by rotary evaporation to give a tan solid that can be used as such or recrystallized (Note 6) from 1:1 chloroform-diethyl ether to give the product as a crystalline white solid, mp 77-78°C, 43 g (88% yield) (Note 7).

A 1-L, one-necked, round-bottomed flask equipped with a heating mantle, magnetic stirring bar, and a reflux condenser is charged with 2,3-O-isopropylidene-L-threitol 1,4-bismethanesulfonate (40 g, 0.126 mol), 95% ethanol (250 mL) (Note 8) and methanesulfonic acid (0.204 mL, 3.14 mmol) (Note 9), and brought to a gentle reflux. The solution is refluxed for 10 hr and then cooled to 0°C with an ice-water bath resulting in the formation of crystals. The crystals are collected by suction filtration, washed with cold ethanol (2 × 50 mL) and diethyl ether (2 × 50 mL), and dried in a vacuum desiccator at 60°C under full vacuum for 4 hr to give the product as white crystals, mp 101-102°C, 29.6 g, (84% yield) (Note 10).

*B. (S,S)-1,2,3,4-Diepoxybutane.* A 250-mL, two-necked, round-bottomed flask equipped with a magnetic stirring bar, nitrogen line, and a 125-mL pressure-equalizing addition funnel is charged with L-threitol 1,4-bismethanesulfonate (25.0 g, 0.0898 moles) and diethyl ether (180 mL). The mixture is

stirred vigorously to form a suspension, and a solution of **potassium hydroxide** (11.6 g, 0.207 mol) (Note 11) in water (35 mL) is added dropwise via the addition funnel over a period of 15 min. The clear mixture is stirred for an additional 45 min at room temperature, and the **ether** layer is decanted. The aqueous layer is transferred to a 500-mL separatory funnel and extracted with **methylene chloride** (3 × 50 mL). The combined **ether** and **methylene chloride** extracts are dried with anhydrous **sodium sulfate**, the **sodium sulfate** is removed by filtration, and the solution is concentrated to approximately 50 mL total volume by rotary evaporation. The concentrate is fractionally distilled through a 13-cm Vigreux distillation column at atmospheric pressure to give the product as a clear oil, bp 138-140°C, 6.3 g (81%) (Note 12) and (Note 13).

C. *(2S,3S)*-Dihydroxy-1,4-diphenylbutane . A 500-mL, one-necked, round-bottomed flask is equipped with a vacuum adapter, septum, magnetic stirring bar and an argon line (Note 14). The flask is flame-dried under reduced pressure, an **argon** atmosphere is reintroduced, and **copper iodide** (CuI) (1.89 g, 9.9 mmol) (Note 15) is added. The flask with CuI is pumped under reduced pressure for 10 min, and the **argon** atmosphere is reintroduced. Then 30 mL of **tetrahydrofuran** (THF) (Note 16) is added to the flask, stirring is initiated, and the slurry is cooled to -30°C with a dry ice-bromobenzene bath. **Phenylmagnesium bromide** in THF (18.0 g, 0.099 mol, 99 mL of a 1 M solution in THF) (Note 17) is added via a 50-mL syringe over a period of 10 min, and the stirred slurry is aged a further 10 min. (S,S)-1,2,3,4-Diepoxybutane (2.84 g, 0.033 mol, 11 mL of a 3 M solution in THF) is added dropwise via syringe over a period of 10 min. After an additional 10 min at -30°C, the reaction mixture is warmed to 0°C with an ice-water bath. After an additional 2.5 hr at 0°C, the reaction is quenched by the slow addition of 200 mL of an aqueous saturated **ammonium chloride** solution, the ice-water bath is removed, and the quenched reaction is stirred for 15 min yielding a deep blue color. The reaction mixture is transferred to a 1-L separatory funnel, and the layers are separated. The aqueous layer is extracted with **methylene chloride** (4 × 50 mL), the combined organic layers are dried with **magnesium sulfate** the drying agent is removed by filtration, and solvent is removed by rotary evaporation to give 7.1 g of a light yellow solid. The solid is dissolved in 225 mL of **toluene** with heat (heating mantle) then cooled to 0°C with an ice-water bath resulting in the formation of fine needles. The needles are collected via suction filtration and dried in a vacuum desiccator at 40°C under full vacuum for 6 hr to yield 6.0 g of a white solid. The filtrate is evaporated to dryness via rotary evaporation to yield 1.1 g of a yellow solid. The yellow solid is flash-chromatographed on 30 g of Merck 230-400 mesh silica gel with 1:1 hexanes-**ethyl acetate** to give 1.0 g of a white solid (Note 18). The combined recrystallized and chromatographed product yields a total of 7.0 g of diol (88%) (Note 19).

## 2. Notes

1. The reaction was maintained under a positive pressure of dry **nitrogen** except during the quenching process. All glassware was dried in a 150°C oven for 30 min and cooled in a desiccator prior to use.
2. The submitters used **2,3-O-isopropylidene-L-threitol** prepared according to the procedure in *Org. Synth., Coll. Vol. VIII 1993*, 155-161. The diol was recrystallized from 1:1 hexanes-**diethyl ether** prior to use. Alternatively, **2,3-O-isopropylidene-L-threitol** can be purchased from Aldrich Chemical Company, Inc.
3. **Methylene chloride** was distilled from **calcium hydride** under **nitrogen** immediately prior to use. The **methylene chloride** was transferred from the still to the reaction flask in two portions via a dry 250-mL pressure-equalizing addition funnel.
4. **Pyridine** was distilled from **calcium hydride** and stored over **KOH** until needed. The **pyridine** was added via a 50-mL glass syringe.
5. **Methanesulfonyl chloride** was obtained from Aldrich Chemical Company, Inc. , distilled under reduced pressure and stored under **nitrogen** at 0°C (freezer) until needed.
6. The tan solid is recrystallized as follows. It is dissolved in approximately 250 mL of 1:1 chloroform-diethyl ether with heat (heating mantle). Upon cooling to 0°C with an ice-water bath, a solid precipitates that is collected by suction filtration. The solid is washed twice with cold 50-mL portions of **diethyl ether** and dried in a vacuum desiccator at 40°C under full vacuum to give the product as a white crystalline solid.
7. This product was found to be greater than 98% pure by <sup>1</sup>H and <sup>13</sup>C NMR. Physical properties and spectral data are as follows:  $[\alpha]_D -22.1$  ( **acetone** , *c* 1.9, ), lit.<sup>3</sup>  $[\alpha]_D -21.3$  ( **acetone** , *c* 2.0); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$ : 1.49 (s, 6 H), 3.10 (s, 6 H), 4.20 (q, 2 H), 4.39 (q, 4 H) ; <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$ : 27.1, 37.9,

67.9, 75.7, 111.4 .

8. 95% ethanol from Pharmco Products Inc. was used as obtained.

9. Methanesulfonic acid, from Aldrich Chemical Company, Inc. , was used as obtained. Methanesulfonic acid was measured and added with a 1-mL syringe.

10. This product was found to be greater than 98% pure by <sup>1</sup>H and <sup>13</sup>C NMR. Physical properties and spectral data are as follows:  $[\alpha]_D -5.2$  (acetone, *c* 1.85), lit.<sup>3</sup>  $[\alpha]_D -5.5$  (acetone, *c* 2); <sup>1</sup>H NMR (CDCl<sub>3</sub> + DMSO-d<sub>6</sub>)  $\delta$ : 2.80 (s, 6 H), 3.62 (m, 2 H), 3.79 (br s, 2 H), 4.00 (m, 4 H) ; <sup>13</sup>C NMR (CDCl<sub>3</sub> + DMSO)  $\Delta$ : 36.5, 67.5, 70.1 .

11. Potassium hydroxide, from J.T. Baker Inc. , was used as obtained.

12. This product was found to be greater than 98% pure by <sup>1</sup>H and <sup>13</sup>C NMR. Physical properties and spectral data are as follows  $[\alpha]_D +25.7$  (CHCl<sub>3</sub>, *c* 2.1), lit.<sup>4</sup>  $[\alpha]_D +23.6$  (CHCl<sub>3</sub>, *c* 2); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$ : 2.56 (m, 2 H), 2.68 (m, 4 H) ; <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$ : 44.4, 51.0 .

13. The product was stored in a dry, round-bottomed flask under argon in a freezer until needed.

14. The reaction was maintained under a positive pressure of dry argon except during the quenching process. All glassware was dried in a 150°C oven for 30 min and cooled in a desiccator prior to use.

15. Copper iodide, from Aldrich Chemical Company, Inc. , was purified by Soxhlet extraction in THF followed by drying under full vacuum overnight.

16. THF was distilled from potassium under nitrogen immediately prior to use.

17. Phenylmagnesium bromide was prepared immediately prior to use according to established procedures. Phenylmagnesium bromide, 1.0 M in THF, can be purchased from Aldrich Chemical Company, Inc.

18. The diol elutes at an  $R_f = 0.64$ , (SiO<sub>2</sub>, 1:1, hexanes-ethyl acetate).

19. This product was found to be greater than 98% pure by <sup>1</sup>H and <sup>13</sup>C NMR. Physical properties and spectral data are as follows:  $[\alpha]_D +6.2$  (chloroform, *c* 1.7); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$ : 2.07 (bd, 2 H), 2.88 (m, 4 H), 3.75 (m, 2 H), 7.23 (m, 6 H), 7.31 (m, 4 H) ; <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$ : 40.3, 74.0, 126.6, 128.6, 129.4, 138.0 . The checkers recrystallized the product in hexane-ethyl acetate (1:1).

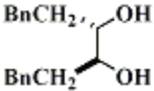
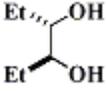
### Waste Disposal Information

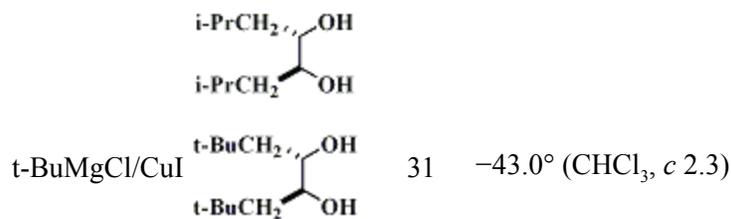
All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

### 3. Discussion

The present approach provides a general method for the preparation of optically active diols. The Table illustrates the preparation of several diols.<sup>5 6</sup> The procedures are simple, and there is no possibility of racemization in any of the steps. This method does not require any difficult-to-handle or disposal of metals, which makes it a good alternative to osmium-catalyzed dihydroxylation.<sup>7</sup> A variety of diols can be prepared from the one diepoxide substrate. The optically active epoxides and diols are highly useful in organic synthesis.<sup>8 9 10</sup> A variety of diols have been useful as chiral ligands in asymmetric catalyst.<sup>11</sup>

TABLE<sup>3</sup>  
OPENING OF THE DIEPOXIDE

Nucleophile	Product	Yield(%)	$[\alpha]_D^{23}$
BnMgBr/CuI		80	-35.0° (CHCl <sub>3</sub> , <i>c</i> 2.2)
MeMgBr/CuI		89	-23° (CHCl <sub>3</sub> , <i>c</i> 5.0)
i-PrMgCl/CuI		66	-53.2° (CHCl <sub>3</sub> , <i>c</i> 3.8)



## References and Notes

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  2. Department of Chemistry, California State University, Northridge, CA 91330-8200.
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  7. For a review of osmium-catalyzed dihydroxylation, see: Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, 94, 2483.
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  11. Whitesell, J. K. *Chem. Rev.* **1989**, 89, 1581.
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## Appendix Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

(S,S)-1,2,3,4-Diepoxybutane:  
 Butane, 1,2:3,4-diepoxy-, (2S,3S)- (8);  
 2,2'-Bioxirane, [S-(R,R)]- (9); (30031-64-2)

L-Threitol 1,4-methanesulfonate:  
 1,2,3,4-Butanetetrol, 1,4-dimethanesulfonate, [S-(R,R)]- (9); (299-75-2)

2,3-Di-O-isopropylidene-L-threitol: Aldrich:  
 (+)-2,3-O-Isopropylidene-L-threitol:  
 1,3-Dioxolane-4,5-dimethanol, 2,2-dimethyl-, (4S-trans)- (9); (50622-09-8)

Pyridine (8,9); (110-86-1)

Methanesulfonyl chloride (8,9); (124-63-0)

Pyridinium chloride:  
 Pyridinium hydrochloride (8,9); (628-13-7)

Methanesulfonic acid (8,9); (75-75-2)

(2S,3S)-Dihydroxy-1,4-diphenylbutane:  
2,3-Butanediol, 1,4-diphenyl-, [S-(R,R)]- (12); (133644-99-2)

Copper iodide (8,9); (7681-65-4)

Phenylmagnesium bromide:  
Magnesium, bromophenyl- (8,9); (100-58-3)