



A Publication  
of Reliable Methods  
for the Preparation  
of Organic Compounds

## Working with Hazardous Chemicals

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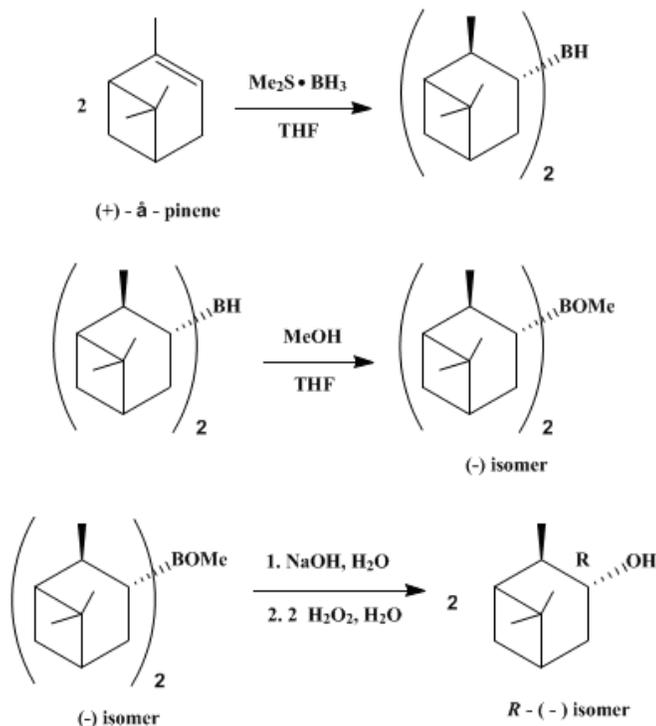
*These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.*

*Organic Syntheses, Coll. Vol. 6, p.719 (1988); Vol. 52, p.59 (1972).*

## (-)-ISOPINOCAMPHEOL

### [Bicyclo[3.1.1]heptan-3-ol, 2,6,6-trimethyl-, [1*R*-(1*α*,2*β*,3*α*,5*α*)-]

The article that follows immediately below is the article that appeared in *Collective Volume 6 (1988)* of *Organic Syntheses*. This article provides an improved procedure for the preparation of isopinocampheol as well as (-)-diisopinocampheylborane. The original procedure for the preparation of these compounds appeared in *Organic Syntheses Annual Volume 52 (1972)* and follows within this file.



Submitted by C. F. Lane and J. J. Daniels<sup>1</sup>.

Checked by D. M. Ryckman and R. V. Stevens.

### 1. Procedure

A 300-ml., three-necked flask (Note 1), equipped with a magnetic stirring bar, thermometer, pressure-equalizing dropping funnel fitted with septum inlet adapter (Note 2), and reflux condenser fitted with a hose adapter leading to a mineral oil bubbler (Note 3), is charged with 10.0 ml. (0.100 mole) of borane–methyl sulfide complex (Note 4) and 30 ml. of tetrahydrofuran (Note 5) and (Note 6). The flask is immersed in an ice-water bath as 27.2 g. (31.7 ml., 0.200 mole) of (+)- $\alpha$ -pinene (Note 7) is added dropwise at 0–3° to the well-stirred reaction mixture over a period of 15 minutes. The (-)-diisopinocampheylborane [(-)-di-3-pinanylborane] precipitates as a white solid as the reaction proceeds. Following addition, the reaction mixture is stirred for 3.5 hours at 0°. Under a slow stream of nitrogen, the outlet hose adapter on the reflux condenser is connected with rubber vacuum hose to a vacuum trap which is then cooled in an acetone–dry ice bath. The dimethyl sulfide and tetrahydrofuran are bulb-to-bulb vacuum-distilled (0.1 mm.) with the reaction flask in a room temperature water bath. When only a dry, white solid residue remains, the vacuum is released with nitrogen. The flask is again placed under a slight positive pressure of nitrogen. The solid is slurried in 36 ml. of tetrahydrofuran (Note 5) at room temperature. An additional 4.08 g. (4.76 ml., 0.030 mole) of (+)- $\alpha$ -pinene (Note 7) is added. The resulting slurry is stirred at room temperature for 5 minutes and then stored under nitrogen in a closed system in a cold room at 4° for 3 days (Note 8). The flask is then removed from the cold room and immersed in an ice-water bath. Under a slow stream of nitrogen, the outlet adapter on the reflux

condenser is again connected to the mineral oil bubbler. The excess hydride is destroyed by the slow, dropwise addition of 8 ml. of **methanol** (Note 9), followed by the addition in one portion of 36.6 ml. of 3 M aqueous **sodium hydroxide**. The borinic acid intermediate is now oxidized by the dropwise addition of 24 ml. of 30% aqueous **hydrogen peroxide** (Note 10) to the well-stirred reaction mixture at  $35^{\circ} \pm 3^{\circ}$  (Note 11). After the **hydrogen peroxide** addition is complete, the ice-water bath is replaced with a warm-water bath and the reaction mixture is stirred for one hour at  $50\text{--}55^{\circ}$  (Note 12) and then cooled to room temperature. The aqueous layer is saturated with **sodium chloride** and 50 ml. of **diethyl ether** is added. The upper organic layer is removed, and the aqueous layer is extracted with two 100-ml. portions of **ether**. The organic layer and extracts are combined, dried over anhydrous **potassium carbonate**, filtered, and concentrated to an oil on a rotary evaporator at  $60^{\circ}$  (15 mm.) (Note 13). The crude product is fractionally distilled using a 30-cm. column packed with glass helices, giving 24.7 g. (80%) of (–)-isopinocampheol, b.p.  $60\text{--}65^{\circ}$  (0.1 mm.) (Note 14). The distillate crystallizes completely in the receiver, m.p.  $49\text{--}55^{\circ}$ , 97.5% purity by GC,  $[\alpha]_D^{25} -34.3^{\circ}$  (C, 20 in **ethanol**) (Note 15). Slurrying 4.7 g. in 2.3 ml. of **pentane** at room temperature, cooling to  $-78^{\circ}$ , collecting on a filter, and air drying gives 3.8 g. of crystalline (–)-isopinocampheol, m.p.  $52\text{--}55^{\circ}$ , purity 99.2% by GC,  $[\alpha]_D^{25} -34.9^{\circ}$  (C, 20 in **ethanol**).

## 2. Notes

1. The apparatus is dried in an oven and assembled hot while being flushed with **nitrogen**. A slow stream of **nitrogen** is continued until the apparatus is cool. Alternatively, the apparatus can be assembled and then flame-dried while flushing with **nitrogen**.
  2. A suitable septum inlet adapter is available from Aldrich Chemical Company (product number Z10, 130-3).
  3. A suitable bubbler is available from Aldrich (product number Z10, 121-4) and used to maintain a slight positive pressure of **nitrogen** in the reaction vessel.
  4. **Borane–methyl sulfide** complex was obtained from Aldrich and used as received.
  5. An anhydrous grade of **tetrahydrofuran** was obtained from Aldrich and used as received.
  6. **Borane–methyl sulfide** and anhydrous **tetrahydrofuran** are extremely moisture-sensitive. All transfers must be done under a **nitrogen** atmosphere, with syringe techniques being the most convenient.<sup>2</sup>
  7. (+)- **$\alpha$ -Pinene** ( $[\alpha]_D^{25} +47.1^{\circ}$ ) was obtained from Aldrich and was short-path vacuum-distilled under **nitrogen** from a small amount of **lithium aluminum hydride**.
  8. The equilibrated (–)-diisopinocampheylborane obtained at this point can be utilized directly for asymmetric hydroboration.<sup>3</sup>
  9. Since the **pinene** is hydroborated only to the dialkylborane stage ( $R_2BH$ ), methanolysis liberates a large amount of **hydrogen**. The rate of evolution is controlled by the slow addition of **methanol**, and some foaming is observed. *The hydrogen must be vented to an efficient hood.* Water can be used to destroy the hydride, but **methanol** addition is easier to control and the final mixture is homogenous once methanolysis is complete.
  10. Thirty percent aqueous **hydrogen peroxide** was obtained from Aldrich and used as received.
  11. The oxidation is exothermic and can be quite vigorous. It should be controlled by the slow, dropwise addition of **hydrogen peroxide**. Cooling in an ice-water bath is necessary. However, a reaction temperature of around  $35^{\circ}$  must be maintained.
  12. The additional one hour of heating is necessary to destroy excess **hydrogen peroxide**. **Oxygen** is evolved and some foaming occurs.
  13. The oil solidifies upon cooling but can be easily remelted in a warm-water bath for transfer to a small distillation flask.
  14. An air-cooled condenser is used for the distillation of **isopinocampheol**.
  15. The enantiomeric excess of (–)-isopinocampheol was determined to be greater than 95% by 200 MHz  $^1H$  NMR using the chiral shift reagent, tris[3-heptafluoropropylhydroxymethylene]-d-camphorato], europium(III). Addition of the lanthanide reagent (40 mg., 0.034 mmol.) to the chiral alcohol (30 mg., 0.21 mmol.) produced a shift of 7.5 p.p.m. in the peak centered around  $\delta$  4.05. Only one broad peak was observed.
- Treatment of ( $\pm$ )-isopinocampheol in a similar manner gave two broad singlets of equal intensity centered around  $\delta$  10.75 (separated by 0.15 p.p.m.), attributable to the diastereomeric protons.

### 3. Discussion

Isopinocampheol has been prepared by hydroboration of  $\alpha$ -pinene using *in situ* generated diborane with diglyme as the solvent.<sup>4</sup>

The present procedure employs a recently developed method which provides a product of greatly improved enantiomeric purity (>99%).<sup>5</sup> Also, this preparation utilizes commercially available borane–methyl sulfide and  $\alpha$ -pinene of 92% enantiomeric purity. An equilibration is used to improve the optical purity of the intermediate dialkylborane.

Isopinocampheol is only of limited interest. More importantly this procedure provides optically pure (–)-diisopinocampheylborane, a very versatile reagent which has been used widely for the synthesis of many chiral products.<sup>3</sup>

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 943
- Org. Syn. Coll. Vol. 7, 339
- Org. Syn. Coll. Vol. 9, 522

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### References and Notes

1. Aldrich-Boranes, Inc., Sheboygan Falls, Wisconsin 53085.
  2. C. F. Lane, *Aldrichimica Acta*, **10**, 11 (1977).
  3. For a review of asymmetric syntheses using chiral organoboranes, see H. C. Brown, P. K. Jadhav, and A. K. Mandal, *Tetrahedron*, **37**, 3547 (1981).
  4. G. Zweifel and H. C. Brown, *Org. Synth.*, **52**, 59 (1972).
  5. H. C. Brown, M. C. Desai, and P. K. Jadhav, *J. Org. Chem.*, **47**, 5065 (1982).
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### Appendix

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

diborane

(–)-ISOPINOCAMPHEOL

(–)-diisopinocampheylborane

(–)-di-3-pinanylborane

tris[3-heptafluoropropylhydroxymethylene]-d-camphorato], europium(III)

ethanol (64-17-5)

potassium carbonate (584-08-7)

methanol (67-56-1)

ether,

diethyl ether (60-29-7)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

sodium chloride (7647-14-5)

oxygen (7782-44-7)

nitrogen (7727-37-9)

hydrogen peroxide (7722-84-1)

Pentane (109-66-0)

borane (7440-42-8)

methyl sulfide,  
dimethyl sulfide (75-18-3)

Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

diglyme (111-96-6)

Isopinocampheol (27779-29-9)

(+)- $\alpha$ -pinene,  
 $\alpha$ -pinene (7785-70-8)

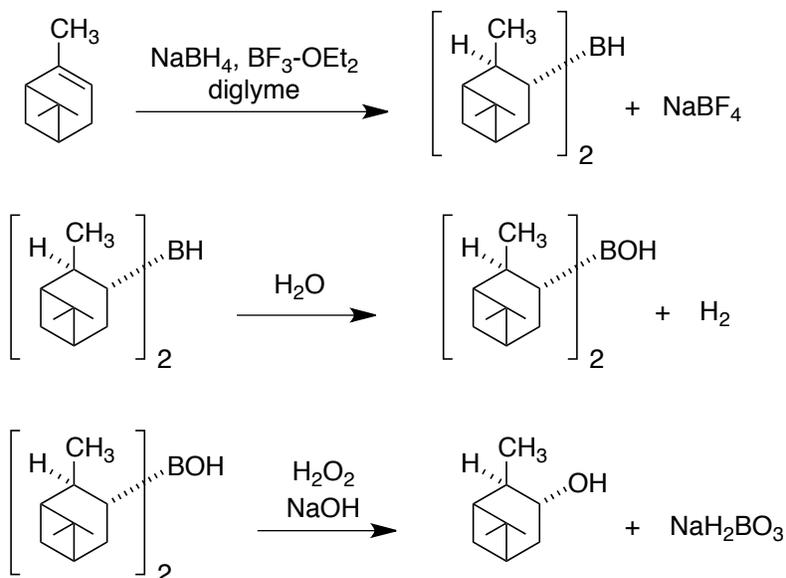
pinene (18172-67-3)

Bicyclo[3.1.1]heptan-3-ol, 2,6,6-trimethyl-, [1R-(1 $\alpha$ ,2 $\beta$ ,3 $\alpha$ ,5 $\alpha$ )]- (1196-00-5)

# HYDROBORATION OF OLEFINS: (+)-ISOPINOCAMPHEOL

## [(+)-3-Pinanol]

The following is the original version of the article that was published in *Organic Syntheses* **1972**, 52, 59-62.



Submitted by G. Zweifel<sup>1</sup> and H. C. Brown

Checked by E. J. Corey, D. Shore, and Ravi K. Varma

### 1. Procedure

In a 300-ml. three-necked flask equipped with a condenser fitted with a calcium chloride tube, a pressure-equalizing dropping funnel, a thermometer, and a mechanical stirrer (Note 1) are placed 3.1 g. (0.080 mole) of sodium borohydride, 100 ml. of diglyme (Note 2), and 27.2 g. (0.200 mole) of (—)- $\alpha$ -pinene (Note 3) diluted with 20 ml. of diglyme. The flask is immersed in a water bath (20—25°). Diborane is generated by dropwise addition of 14 ml. (0.11 mole,  $D^{20}$  1.125) of boron trifluoride etherate (Note 4) to the well-stirred reaction mixture over a period of 15 minutes. The diisopinocampheylborane precipitates as white solid as the reaction proceeds. The mixture is maintained for an additional hour at room temperature. The excess hydride is then decomposed by dropwise addition of 20 ml. of water (Note 5). The organoborane formed ( $\text{R}_2\text{BOH}$ ) is oxidized a 30—50° (water bath) by adding in one portion of 22 ml. of aqueous 3M sodium hydroxide, followed by the dropwise addition of 22 ml. of aqueous 30% hydrogen peroxide to the well stirred reaction mixture. The flask is kept for an additional 30 minutes at room temperature.

The alcohol reaction mixture is extracted with 200 ml. of ether and the ether extract is washed five times with equal volumes of ice water to remove the diglyme. The ether extract is dried over anhydrous magnesium sulfate and the ether is removed by distillation through a short Vigreux column. The residue is distilled under reduced pressure to separate 26.2 g. (85%) of isopinocampheol, b.p. 80—82° (2 mm.). The distillate crystallizes immediately in the collection flask (Note 6). The crystals melt at 50—52° (Note 7). Recrystallization from about 10 ml. of petroleum ether (b.p. 35—37°) affords pure isopinocampheol as needles, m.p. 55-57°,  $[\alpha]_{20}^D +32.8^\circ$  (*c*, 10 in benzene).

## 2. Notes

1. The apparatus is dried in an oven and assembled under dry nitrogen. Alternatively it can be flamed dry in a stream of dry nitrogen. A magnetic stirrer can be utilized for small scale experiments.

2. Diglyme (dimethyl ether of diethylene glycol, b.p. 162° at 760 mm.) from Ansul Chemical Company, Marinette, Wisconsin, is purified in the following way. Diglyme (1 l.) is stored over 10 g. of granular calcium hydride for 12 hours. The diglyme is decanted into a distilling flask and sufficient lithium aluminum hydride is added to ensure an excess of active hydride. The solvent is distilled at 62—63° (15 mm.).

3. (—)- $\alpha$ -Pinene ( $[\alpha]_{20}^D -47.9^\circ$ ) was obtained by the submitters from the Glidden Co., Jacksonville, Florida. Alternatively (—)- $\beta$ -pinene ( $[\alpha]_{20}^D -21.1^\circ$ ) is readily available and can be isomerized to (—)- $\alpha$ -pinene by shaking with a palladium hydrogenation catalyst in the presence of hydrogen.<sup>2</sup> The checkers used (—)- $\alpha$ -pinene ( $[\alpha]_{28}^D -52.2^\circ$ ) supplied by Chemical Samples Co., 4692 Kenny Road, Columbus, Ohio, 43220.

4. Commercial boron trifluoride ethyl etherate (from Matheson Coleman and Bell) is distilled in an all glass apparatus at 46° (10 mm.) from a few pieces of granular calcium hydride. The latter serves to remove small quantities of volatile acids and greatly reduces bumping during distillation.

5. Since the olefin is hydroborated to the dialkylborane stage ( $R_2BH$ ), a large amount of hydrogen is evolved on hydrolysis. Consequently, the addition of water should be carried out slowly (dropwise) and adequate ventilation is recommended.

6. For distillation of the isopinocampheol the Vigreux column is attached to an air condenser. The receiver is immersed in an ice bath.

7. The checkers obtained from (—)- $\alpha$ -pinene, after distillation, (+)-isopinocampheol, m.p. 51—53° (corr.),  $[\alpha]_{28}^D +32.1^\circ$ .

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

### 3. Discussion

(—)-Isopinocampheol has been prepared by hydrogenation of *trans*-pinocarveol with a neutral nickel catalyst at 70—100°.<sup>3</sup>

The hydroboration reaction provides a convenient procedure for the conversion of olefins to alcohols without rearrangement and with a predictable stereochemistry. The reaction has been applied to a number of olefins of widely different structures.<sup>4,5</sup> The results obtained support the proposed generalization that hydroboration involves *anti*-Markownikoff, *cis*-addition of borane from the less hindered side of the double bond.<sup>6</sup>

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### References and Notes

1. Department of Chemistry, University of California, Davis, California.
2. I. Richter and W. Wolff, *Ber.*, **59**, 1733 (1926).
3. H. Schmidt, *Ber.*, **77**, 544 (1944).
4. H. C. Brown, "Hydroboration," W. A. Benjamin, Inc., New York, 1962.
5. G. Zweifel and H. C. Brown, *Org. React.*, **13**, 1 (1963).
6. H. C. Brown and G. Zweifel, *J. Amer. Chem. Soc.*, **83**, 2544 (1961).