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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.

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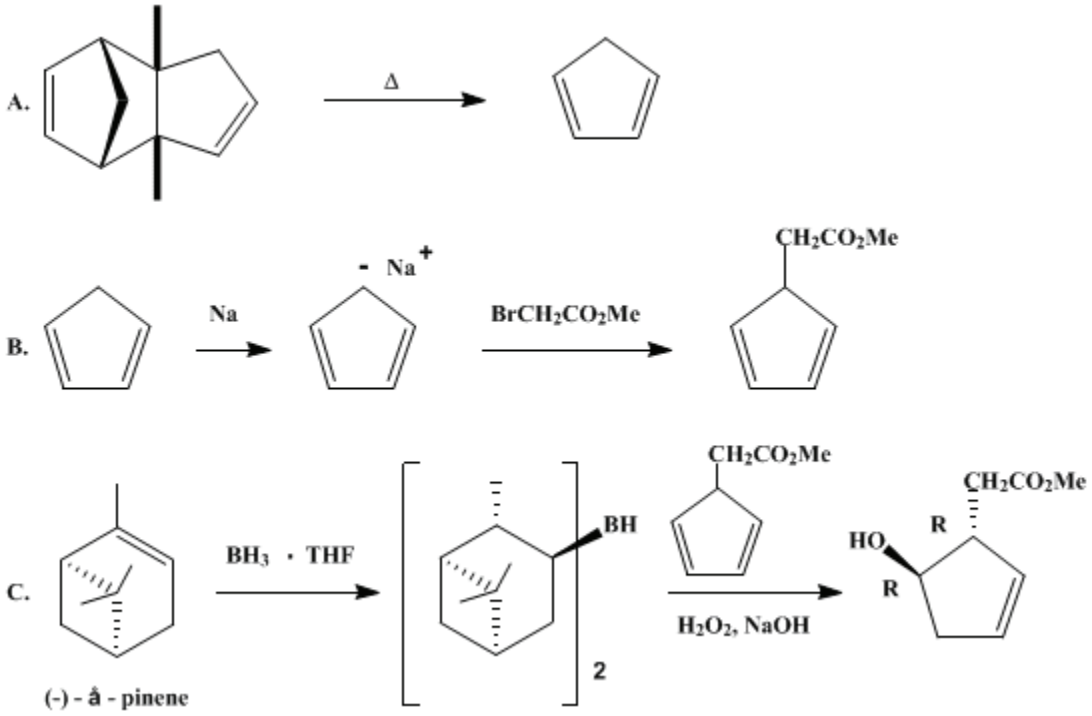
ASYMMETRIC HYDROBORATION OF 5-SUBSTITUTED CYCLOPENTADIENES: SYNTHESIS OF METHYL (1 *R*,5*R*)-5-HYDROXY-2-CYCLOPENTENE-1-ACETATE

[2-Cyclopentene-1-acetic acid, 5-hydroxy-, methyl ester, (1*R-trans*)-]



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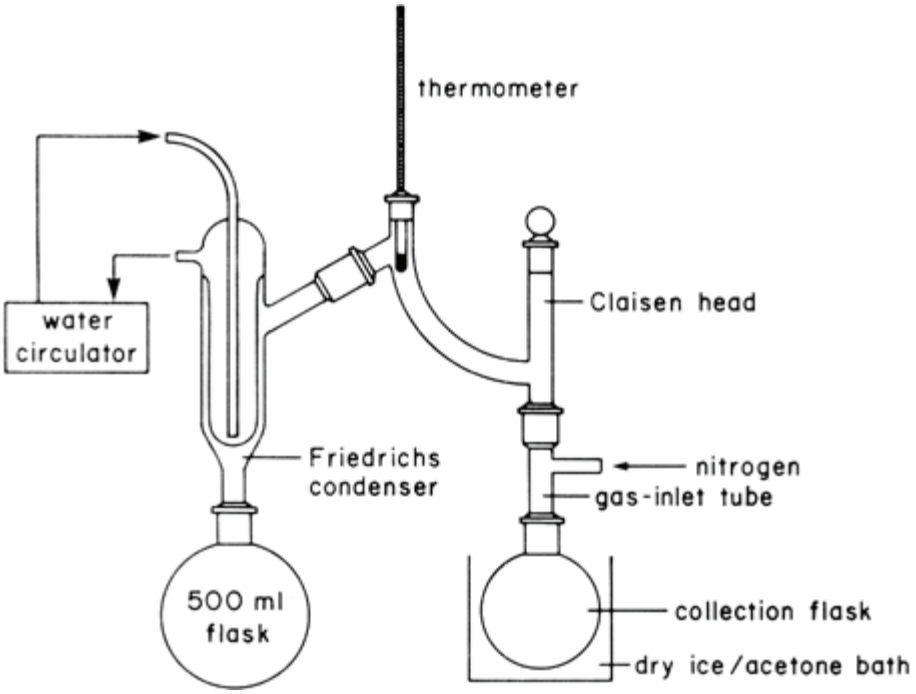
Checked by Bai Dong-Lu and Clayton H. Heathcock.

1. Procedure

Caution! Methyl bromoacetate, used in Step B, is intensely irritating to eyes and skin. The preparation of the ester should be carried out in an efficient hood.

A. *Pyrolysis of dicyclopentadiene to form cyclopentadiene*. Cyclopentadiene is prepared from its dimeric form by distillation according to the method of Moffett.[2] The apparatus for the distillation is assembled as shown in Figure 1. The equipment consists of a 250-mL flask, a Friedrichs condenser fitted with a Haake Model FE hot water circulator, a Claisen head, a thermometer, a gas inlet tube, and a collection receiver that is cooled to −78°C in a dry ice–acetone bath.

Figure 1. Apparatus for producing cyclopentadiene.



In the 250-mL flask is placed 100 mL of dicyclopentadiene (Note 1). The material is heated at reflux (bath temperature 200–210°C) under a nitrogen atmosphere (Note 2). After a 5-mL forerun is collected and discarded, the collection receiver is cooled to −78°C and 25 mL (0.30 mol) of cyclopentadiene is rapidly distilled at bp 36–42°C. A slight positive pressure of nitrogen is maintained throughout the distillation to prevent moisture from entering the system.

The distilled cyclopentadiene is stored at −78°C until it is used (Note 3). Residual dicyclopentadiene can be reused until it solidifies on cooling.

B. *Preparation in situ of methyl 2,4-cyclopentadiene-1-acetate (Note 4)*. Cyclopentadienylsodium is prepared by modification of the methods of King[3] and Hafner[4] (Note 5).

In a 500-mL, three-necked Morton flask fitted with a condenser, mechanical stirrer, and gas inlet tube is placed 8.6 g (0.375 g-atom) of sodium and 75 mL of dry xylene (Note 6); the unstirred mixture is heated at reflux under a nitrogen atmosphere. After the xylene has reached its boiling point and the sodium has melted, the solution is rapidly stirred to produce a very fine-grained sodium sand. Quickly the heating mantle is removed and stirring stopped (Note 7). After cooling, the xylene is pipetted or siphoned away from the sodium sand and stored for future use.

The sand is washed with 3 × 25 mL of dry tetrahydrofuran (Note 8) and then is layered with 100 mL of dry tetrahydrofuran, and the mixture is cooled to −10°C (Note 9) under a nitrogen atmosphere. A solution of 25 mL (0.30 mol) of cyclopentadiene in 25 mL of tetrahydrofuran is added dropwise using a dropping funnel. After the addition is complete, the mixture is stirred overnight at room temperature, by which time hydrogen evolution has ceased. In the absence of air, the solution ranges from near colorless to bright pink (Note 10).

In a 1-L, three-necked flask fitted with a 200-mL pressure-equalizing dropping funnel, mechanical stirrer, and a gas inlet tube is placed 45.9 g (0.30 mol) of methyl bromoacetate (Note 11) and 75 mL of tetrahydrofuran and the mixture is cooled to −78°C in an inert atmosphere.

The solution of ca. 0.30 mol of cyclopentadienylsodium is decanted from residual sodium sand with a U-tube into the dropping funnel (Note 12) and is added dropwise over a 2-hr period (Note 13). A white precipitate of sodium bromide forms during the addition. The heterogeneous solution is stirred overnight at −78°C to ensure complete formation of methyl 2,4-cyclopentadiene-1-acetate.

C. *Asymmetric hydroboration with (+)-di-3-pinanylborane to form methyl (1R,5R)-5-hydroxy-2-cyclopentene-1-acetate (Note 4)*. The (+)-di-3-pinanylborane is prepared from (−)-α-pinene by a modification[5,6] of the method of Brown[7] (Note 14).

In a 2-L, three-necked flask fitted with a condenser, mechanical stirrer, and a gas inlet tube is placed 90.0 g (0.66 mol) of (−)-α-pinene (Note 15). The flask is cooled to 0°C and under an inert atmosphere a total of 300 mL (0.30 mol) of 1 *M* borane in tetrahydrofuran (Note 16) is added dropwise over a 1-hr period. The solution is stirred for 18 hr at 0°C, during which time a white precipitate of (+)-di-3-pinanylborane forms. This solution is then cooled to −78°C. The ca. 0.30 mol solution of methyl 2,4-cyclo-pentadiene-1-acetate (Section B) is transferred at −78°C to a 500-mL pressure-equalizing dropping funnel through a U-tube in an inert atmosphere and is added rapidly, in one portion, to the stirring solution of di-3-pinanylborane at −78°C. After this mixture is stirred for 6 hr at −78°C, the bath temperature is allowed to rise to 0°C and the mixture is stirred for 16 hr at 0°C to complete the hydroboration reaction.

To the reaction mixture is added dropwise 90 mL of 3 *N* aqueous sodium hydroxide, followed by 90 mL of 30% hydrogen peroxide (Note 17). The mixture is stirred for 30 min to complete the oxidation process. A total of 3 g of sodium bisulfite, 5 g of sodium chloride, and 125 mL of ether are added and the mixture is stirred for 10 min (Note 18). On standing, the reaction mixture separates into two layers, which are separated with a 1-L separatory funnel. The organic layer is washed with brine (2 × 50 mL). The water layer and the brine washes are combined and extracted with ether (3 × 125 mL). All the organic layers are then combined and dried over anhydrous magnesium sulfate. Filtration and removal of solvent under reduced pressure yield 110 g of a pale-yellow oil containing the desired product as well as (+)-isopinocampheol, and (−)-α-pinene (Note 19). The product mixture is dissolved in 250 mL of ether and is extracted with 1 *M* aqueous silver nitrate solution (3 × 100 mL). The aqueous layers are combined and back-extracted once with 50 mL of ether. The ether layers containing (+)-isopinocampheol are discarded.

The aqueous layers containing the silver(I) complex of methyl (1*R*,5*R*)-5-hydroxy-2-cyclopentene-1-acetate are then treated with an excess of saturated brine to precipitate silver chloride and free the desired product. After precipitation is complete, the water layer is decanted from the solid silver chloride. The solids are washed with ether (4 × 100 mL) and each ether layer is used to extract the water layer (Note 20). The combined ether layers are washed with 50 mL of brine and dried over anhydrous magnesium sulfate. Filtration and removal of solvent under reduced pressure yield 16–19 g of crude product. The product is distilled through a 4-in.-Vigreux column at 0.1 mm pressure to yield 12.8–14.7 g (27–31%) of methyl (1*R*,5*R*)-5-hydroxy-2-cyclopentene-1-acetate, bp 74–78°C at 0.1 mm, $[\alpha]_D^{25}$ −132° (CH_3OH, *c* 1.06) (Note 21) and (Note 22).

2. Notes

1. Dicyclopentadiene was obtained from Ace Scientific (TX 315), practical grade, 95%.
2. The Haake water circulator was employed with the circulating water temperature at 50°C. This allows only cyclopentadiene to distill.
3. Cyclopentadiene is stable at −78°C but dimerizes readily at room temperature.
4. Steps B and C must be run concurrently.
5. The efficient formation of cyclopentadienylsodium is of paramount importance for the entire reaction sequence. Variations in the yield of methyl 2,4-cyclopentadiene-1-acetate have been traced to the degree of efficiency in producing a fine sodium sand that is used to produce cyclopentadienylsodium. In the alkylation reaction of cyclopentadienylsodium with methyl bromoacetate, the entire process must be carried out in an inert dry atmosphere at −78°C. At higher temperatures, the desired product can undergo undesired dimerization and double-bond migration side reactions. Methyl 2,4-cyclopentadiene-1-acetate, once formed, is used immediately.
6. Xylene was obtained from Fisher Scientific Company. The xylene is initially dried over sodium and is saved and reused in making additional batches of sodium sand.
7. If stirring continues while the xylene cools, the sodium sand coagulates into a large lump.
8. Tetrahydrofuran was obtained from Fisher Scientific Company. The tetrahydrofuran employed was freshly distilled from lithium aluminum hydride. Care should be exercised in drying tetrahydrofuran; cf.

Org. Synth., Coll. Vol. V **1973**, 976. The checkers also examined the use of tetrahydrofuran that had been dried by distillation from sodium–benzophenone ketyl. When material that has been purified in this manner is used, the fine sodium sand coagulates, giving small porous lumps. No such coagulation occurs when tetrahydrofuran that has been dried by distillation from lithium aluminum hydride is used. However, the method of drying had no effect on overall yield of final product.
9. A bath of carbon tetrachloride containing a little dry ice is used for cooling.
10. The efficient formation of cyclopentadienylsodium was found to be the product-limiting step for the reaction sequence. *If air is present or if the sodium sand is not fine-grained, quantitative formation of cyclopentadienylsodium cannot be assumed.* Residual sodium sand may be washed with tetrahydrofuran, dried in a nitrogen atmosphere, and weighed to determine approximately the extent of cyclopentadienylsodium formation.
11. Methyl bromoacetate was obtained from Ace Scientific (MX 755).
12. Care must be taken during this transfer to minimize exposure of the cyclopentadienylsodium to air. Trace amounts of oxygen cause the formation of a dark brown color and brown solid in the solution.
13. The drip rate should be adjusted so that the dropping funnel is not plugged by crystalline cyclopentadienylsodium.
14. After the asymmetric hydroboration–oxidation sequence is completed, the desired product is separated via its silver(I) complex from (+)-isopinocampheol. The desired product can also be isolated by column chromatography.
15. (−)-α-Pinene was obtained from Chemical Samples Company. The (−)-α-pinene was distilled from sodium metal: bp 155–156°C; $[\alpha]_D^{25}$ −47° (neat).
16. Borane–tetrahydrofuran was obtained from Alfa Products, Morton Thiokol Inc.
17. The hydrogen peroxide oxidation is a very exothermic process and efficient cooling and stirring are necessary.
18. After the addition of ether, some inorganic salts precipitate. The checkers found it advantageous to remove this solid by suction filtration. The solid was washed with ether, which was combined with the organic solution.
19. Vacuum distillation does not effectively purify the desired product from the other impurities.
20. Methyl (1*R*,5*R*)-5-hydroxy-2-cyclopentene-1-acetate is found in both the aqueous layer and occluded with the solid silver chloride.
21. In like manner and employing (+)-α-pinene [bp 155–156°C; $[\alpha]_D^{25}$ +47° (neat)], the sequence affords the methyl (1*S*,5*S*)-5-hydroxy-2-cyclopentene-1-acetate, bp 74–77°C (0.1 mm); $[\alpha]_D^{25}$ +131° (CH_3OH, *c* 1.03).
22. The checkers used (−)-α-pinene (bp 155°C, $[\alpha]_D^{22}$ −42° (neat)) from Aldrich Chemical Company, Inc. and obtained a product having bp 75–80°C (0.15 mm) and $[\alpha]_D^{21}$ −126° (CH_3OH, *c* 0.039).

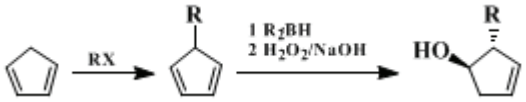
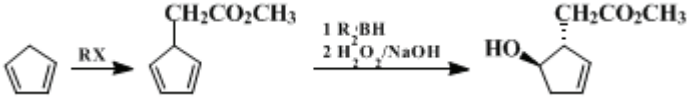
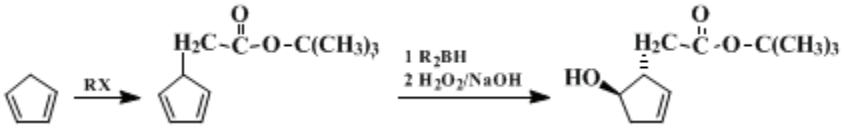
3. Discussion

Several highly enantioselective asymmetric hydroboration reactions with prochiral olefins have been reported[8] with the di-3-pinanylborane reagents (diisopinocamphenyl-boranes) discovered by Brown and Zweifel.[9] Recently, alternative reagents such as the mono-3-pinanylboranes (monoisopinocamphenyl boranes)[10,11] and (+)-dilongifolyl-borane[12] have been used in effecting asymmetric hydroborations on prochiral olefins. With the di-3-pinanylborane reagents, the cis-disubstituted olefins[8,9] and 5-substituted cyclopentadienes[5,6] yield alcohols of high optical purity (80–95% e.e.). Lower asymmetric inductions (20–40% e.e.) occur when 1,1-disubstituted, trans-disubstituted, or trisubstituted olefins are employed as substrates. However, significantly higher enantioselective hydroborations occur when these olefins are treated with the mono-3-pinanylboranes[10,11] and (+)-longifolylborane.[12] Tetrasubstituted olefins have not successfully been asymmetrically hydroborated with any of these reagents.

Several racemic *cis*- or *trans*-2-alkyl-3-cyclopenten-1-ols have been prepared by multistep sequences from cyclopentadiene[13,14,15,16] or from substituted 1,3-dienes.[17] However, optically active *cis*- and *trans*-2-alkyl-3-cyclopenten-1-ols have been prepared directly by asymmetric hydroboration reactions using prochiral 5-substituted cyclopentadienes as substrates.[5,6] This asymmetric hydroboration method, described above, gives moderate yields of highly optically active *trans*-2-alkyl-3-cyclopenten-1-ols (94–96% e.e.), which are readily converted into the corresponding cis isomers.[5,6] Several of these substances are intermediates in the synthesis of such natural products as the monoterpene glycoside

loganin,[5] the carbohydrate daunosamine,[18] and the prostaglandins such as $PGF_{2\alpha}$[6]

TABLE I
ASYMMETRIC HYDROBORATION OF 5-SUBSTITUTED CYCLOPEN

Substituent	Alkylating Agent	Hydroborating Agent
 R = CH_3	CH_3I	(+)-Di-3-pinanylborane
	CH_3I	(−)-Di-3-pinanylborane
	$(CH_3)_2SO_4$	(+)-Di-3-pinanylborane
 R = $CH_2CO_2CH_3$	$BrCH_2CO_2CH_3$	(+)-Di-3-pinanylborane
	$BrCH_2CO_2CH_3$	(−)-Di-3-pinanylborane
	$ClCH_2CO_2CH_3$	(+)-Di-3-pinanylborane
 R = CH_2CO_2-*t*-Bu	$BrCH_2CO_2$-*t*-Bu	(+)-Di-3-pinanylborane

[a]The percent enantiomeric excess was determined by HPLC analysis of products esterifie trifluoromethylphenylacetyl chloride (Mosher Reagent).[19,20]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 9, 186

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

benzophenone ketyl

brine

silver(I) complex of methyl (1R,5R)-5-hydroxy-2-cyclopentene-1-acetate

diisopinocamphenyl-boranes

mono-3-pinanylboranes

monoisopinocamphenyl boranes

(+)-dilongifolyl-borane

(+)-longifolylborane

METHYL (1 R,5R)-5-HYDROXY-2-CYCLOPENTENE-1-ACETATE

ether (60-29-7)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

sodium chloride (7647-14-5)

silver chloride (7783-90-6)

silver nitrate (7761-88-8)

sodium bromide (7647-15-6)

oxygen (7782-44-7)

nitrogen (7727-37-9)

sodium bisulfite (7631-90-5)

sodium (13966-32-0)

hydrogen peroxide (7722-84-1)

xylene (106-42-3)

magnesium sulfate (7487-88-9)

borane (7440-42-8)

Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

CYCLOPENTADIENE (542-92-7)

dicyclopentadiene (77-73-6)

cyclopentadienylsodium

methyl bromoacetate (96-32-2)

(+)-isopinocampheol (27779-29-9)

(+)-α-pinene,
(7785-70-8)

Di-3-pinanylborane,
(+)-di-3-pinanylborane,
(+)-di-3-pinanylborane (21947-87-5)

methyl 2,4-cyclopentadiene-1-acetate,
methyl 2,4-cyclo-pentadiene-1-acetate (37455-98-4)

Methyl (1R,5R)-5-hydroxy-2-cyclopentene-1-acetate,
2-Cyclopentene-1-acetic acid, 5-hydroxy-, methyl ester, (1R-trans)- (49825-99-2)

methyl (1S,5S)-5-hydroxy-2-cyclopentene-1-acetate

(S)-α-methoxy-α-trifluoromethylphenylacetyl chloride (20445-33-4)