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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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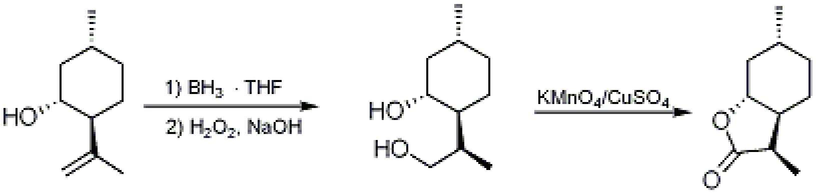
A SELECTIVE, HETEROGENEOUS OXIDATION USING A MIXTURE OF POTASSIUM PERMANGANATE AND CUPRIC SULFATE: (3aS,7aR)-HEXAHYDRO-(3S,6R)-DIMETHYL-2(3H)-BENZOFURANONE

[2(3H)-Benzofuranone, hexahydro-3,6-dimethyl-, [3R-(3α,3aβ,6β,7aα)]-]



Submitted by Charles W. Jefford, Yun Li, and Ying Wang[1].
Checked by Timothy J. Watson and Leo A. Paquette.

1. Procedure

A. *(−)-(1R,3R,4S,8R)-p-Menthane-3,9-diol*. To a dry, 2-L, three-necked flask equipped with a gas outlet, an overhead stirrer, and a 500-mL pressure-equalizing dropping funnel with a gas inlet, is added a solution of 31 g (0.20 mol) of isopulegol (Note 1) in 550 mL of tetrahydrofuran (THF) (Note 2) under nitrogen. From the funnel, 230 mL of a 1.0 M diborane solution (Note 3) is added dropwise with stirring at room temperature at such a rate to insure that gas evolution is not violent. When the addition is complete, the clear solution is stirred for 3 hr at room temperature. The dropping funnel is removed and 100 mL of aqueous 3 N sodium hydroxide is added slowly; the solution is then warmed to 60°C on the steam bath for 2 hr. The gas outlet is replaced by a thermometer and the septum is replaced by another dropping funnel charged with 120 mL of aqueous 30% hydrogen peroxide and the reaction flask is placed in an ice bath. Hydrogen peroxide is then added and the reaction temperature is maintained between 30–50°C by carefully controlling the rate of addition (the reaction is strongly exothermic at the beginning). When the addition is complete, the ice bath is removed and the reaction mixture is stirred at 50°C for 2 hr. The bulk of the THF is removed under reduced pressure and the residue is diluted with 200 mL of ether and washed with brine. The aqueous layer is extracted with two 50-mL portions of ether; the resulting extracts are combined and dried over anhydrous sodium sulfate for several hours and filtered. The filtrate is concentrated using a rotary evaporator. The resulting oil is dissolved in 100 mL of hot hexane, allowed to cool slowly, and stored at 0°C for 2 days. The supernatant mother liquor is decanted, 100 mL of fresh hexane is added, the crystalline mass is swirled for 2–3 min and the product is separated by filtration. After vacuum drying, 17.6 g (51%) of (−)-(1R,3R,4S,8R)-p-menthane-3,9-diol is obtained as colorless crystals, mp 105–107°C (Note 4).

B. *(+)-(3aS,7aR)-Hexahydro-(3S,6R)-dimethyl-2(3H)-benzofuranone*. To a 1-L round-bottomed flask equipped with an efficient magnetic stirrer is added 10 g (58 mmol) of (−)-(1R,3R,4S,8R)-p-menthane-3,9-diol and 400 mL of dichloromethane. The resulting suspension is stirred until all the solid dissolves at which time a mixture of powdered potassium permanganate and copper sulfate ($CuSO_4 \cdot 5H_2O$) (Note 5) is added in one portion. The reaction mixture is then stirred at 25°C between 6 and 8 hr depending upon the quality of the oxidant (Note 6), 400 mL of ether is added, and stirring is continued for an additional 20 min. The suspension is transferred with the aid of a small amount of ether onto a fritted-disk Büchner funnel containing 50 g of silica gel and a little ether. The spent manganese salt is mixed with some of the silica gel, using a spatula, to insure that all the solution is absorbed. The resulting filter-cake is washed with 500 mL of ether (Note 7). Upon removal of the solvent, the crude product is obtained as a clear, colorless oil. More product is recovered by taking the filter-cake from the funnel and placing it in a 2-L beaker containing 100 mL of ether and a solution of 270 g of sodium metabisulfite in 1 L of water that is cooled in an ice bath (Note 8). The cake is broken up with a glass rod and stirred. To the resulting slurry, 150 mL of aqueous 10% hydrochloric acid is added in portions with stirring until the color turns from dark gray to pale yellow and all the solid material, except the silica, is dissolved. The resulting mixture is filtered and the filtrate is extracted with three 150-mL portions of ether. The ether extracts are combined and washed twice with water and once with brine. The ethereal solution is dried by shaking with 30 g of anhydrous sodium sulfate and filtered. The filtrate is concentrated to about 150 mL and stirred with 10 g of Amberlyst-15 for 3 hr (Note 9). After another filtration, the solvent is evaporated and the residual oil is combined with that previously obtained. Purification by vacuum distillation gives 4.8–5.0 g (49–51% yield) of 3aS,7aR-hexahydro-3S,6R-dimethyl-2(3H)-benzofuranone as a colorless oil, bp 110°C (0.05 mm) (Note 10).

2. Notes

1. Isopulegol (Tech. as obtained from Aldrich-Chemie GmbH & Company KG, D-7924 Steinheim, Federal Republic of Germany) contains about 65–70% (−)-isopulegol according to its NMR spectrum. It has an optical rotation of $[\alpha]_D^{20}$ −4.6° (neat), while $[\alpha]_D^{20}$ −22° is reported[2] for the pure material. The technical grade product was used without further purification. Pure (−)-isopulegol can be prepared in a highly stereoselective manner from (+)-citronellal.[3]

2. Tetrahydrofuran (THF) was dried with and distilled from sodium in the presence of benzophenone.

3. Diborane was obtained as a 1.0 M THF solution from Aldrich Chemical Company, Inc.

4. The NMR spectrum of the diol obtained was identical to that already reported:[2] ^{1}H NMR (360 MHz, $CDCl_3$) δ: 0.86–0.99 (m, 2 H), 0.92 (d, 3 H, J = 6.6), 0.96 (d, 3 H, J = 7.5), 1.17–1.29 (m, 1 H), 1.32–1.49 (m, 2 H), 1.57 (m, 1 H), 1.64 (m, 1 H), 1.85 (m, 1 H), 1.96 (m, 1 H), 3.29 (br, s, 2 H), 3.47 (t, d, 1 H, J = 10.4, 4.2), 3.60 (dd, 1 H, J = 10.6, 3.5), 3.66 (dd, 1 H, J = 10.6, 5.4). Its optical rotation ($[\alpha]_D^{20}$ −18.7° ($CHCl_3$, *c* 10)) was identical to that reported.[2] The checkers recorded an $[\alpha]_D^{20}$ of −20.7° ($CHCl_3$, *c* 10).

5. The oxidant was prepared from 130 g of crystalline potassium permanganate ($KMnO_4$) and 25 g of $CuSO_4 \cdot 5H_2O$ by grinding them together in a mortar until a fine powder was obtained.

6. The progress of the oxidation can be monitored by the disappearance of the diol using TLC (eluent, hexane:ethyl acetate, 2:7).

7. It is essential to mix thoroughly the spent oxidant and the silica gel with a spatula while washing. This process does not cause any manganese salt to pass into the filtrate.

8. The quality of the $KMnO_4$ and $CuSO_4 \cdot 5H_2O$ varies with the supplier and affects the yield. Consequently, some hydroxy acid, instead of the lactone, may be formed. In such a case, treatment with sodium metabisulfite solution followed by acidification converts any free acid retained on the filter cake into lactone.

9. Amberlyst-15, a cation exchange resin, was supplied by Fluka Chemical Corporation.

10. The lactone is identical to that previously reported[4] and has the following spectral data: IR (neat) cm^{-1}: 1770, 1453, 1375, 1290, 1190, 1096, 847; ^{1}H NMR (360 MHz, $CDCl_3$) δ: 0.99–1.38 (m, 3 H), 1.02 (d, 3 H, J = 6.5), 1.15 (d, 3 H, J = 7.6), 1.59 (m, 1 H), 1.78 (m, 2 H), 1.92 (m, 1 H), 2.25 (m, 1 H), 2.64 (quint., 1 H, J = 7.6), 4.00 (dt, 1 H, J = 11, 4); ^{13}C NMR (360 MHz, $CDCl_3$) δ: 9.57, 21.99, 23.77, 31.25, 34.15, 38.72 (2 carbons), 47.09, 81.38, 180.27. It has $[\alpha]_D^{20}$ +106.2° ($CHCl_3$, *c* 0.6). The checkers recorded $[\alpha]_D^{25}$ of +72 to +88° ($CHCl_3$, *c* 0.6). If the temperature of the distillation exceeds 110°C, a decrease in $[\alpha]_D$ might be observed because of epimerization α to the lactone carbonyl. If the pure diastereomer is required, it is recommended that purification be effected by column chromatography over silica gel (eluent, pentane:ethyl acetate 20:1). Typically, the lactone is obtained in a yield of 55% with an $[\alpha]_D^{20}$ +149° ($CHCl_3$, *c* 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

There are few oxidants that oxidize primary alcohols faster than secondary ones. We have demonstrated that a solid mixture of $KMnO_4$ and $CuSO_4 \cdot 5H_2O$ treated with base can bring about such selectivity.[4] The present procedure illustrates a general and convenient method for the oxidation of α,ω-diols to give lactones, that is typified by procedure B, where base is not necessary since ideally no acid is produced. When conducted on a 1-g scale and using pure (−)-isopulegol, overall yields were as high as 89%. In the present instance, starting with pure diol in 10-g lots, maximum yields of only 55% were attained. The reason for the lower yield on larger scale is unclear, although the formation of hydroxy acid rather than lactone may account for some loss. Nonetheless, the procedure has undeniable advantages, including, the formation of a single lactone retaining the initial stereochemistry at C(3). Although Jones oxidation of the diol[5] is reported to give the product lactone in 89% yield, repetition of the experiment reveals that only 38% is found in practice, the balance of material being two other related, but different products.[4] Other routes[6,7] to this lactone, because of the conditions, give most probably the 3R epimer as evidenced by the NMR spectral data.

References and Notes

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

sodium metabisulfite

brine

diborane

(−)-(1R,3R,4S,8R)-p-Menthane-3,9-diol

(−)-isopulegol

$KMnO_4$

$CuSO_4 \cdot 5H_2O$

hydrochloric acid (7647-01-0)

ethyl acetate (141-78-6)

ether (60-29-7)

sodium hydroxide (1310-73-2)

potassium permanganate (7722-64-7)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

copper sulfate,
cupric sulfate (7758-98-7)

Benzophenone (119-61-9)

sodium (13966-32-0)

hydrogen peroxide (7722-84-1)

Pentane (109-66-0)

dichloromethane (75-09-2)

Tetrahydrofuran,
THF (109-99-9)

hexane (110-54-3)

(+)-citronellal (106-23-0)

(3aS,7aR)-HEXAHYDRO-(3S,6R)-DIMETHYL-2(3H)-BENZOFURANONE,
3aS,7aR-hexahydro-3S,6R-dimethyl-2(3H)-benzofuranone,
(+)-(3aS,7aR)-Hexahydro-(3S,6R)-dimethyl-2(3H)-benzofuranone (79726-51-5)

isopulegol (89-79-2)

2(3H)-Benzofuranone, hexahydro-3,6-dimethyl-, [3R-(3α,3aβ,6β,7aα)]-