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Working with Hazardous Chemicals

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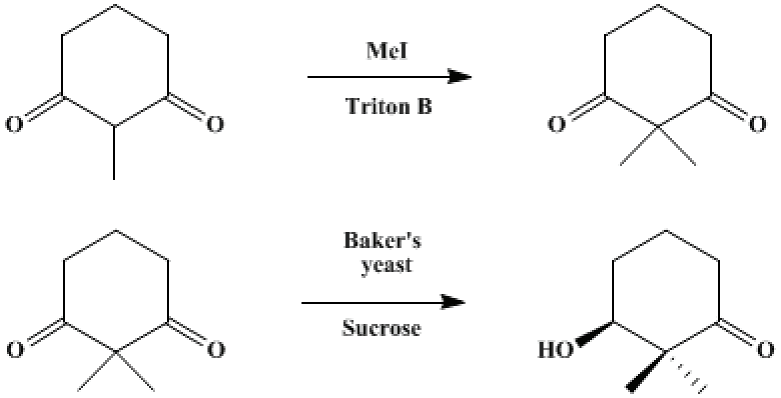
These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

DOI:10.15227/orgsyn.068.0056

Organic Syntheses, Coll. Vol. 8, p.312 (1993); Vol. 68, p.56 (1990).

YEAST REDUCTION OF 2,2-DIMETHYLCYCLOHEXANE-1,3-DIONE: (*S*)-(+)-3-HYDROXY-2,2-DIMETHYLCYCLOHEXANONE)

[Cyclohexanone, 3-hydroxy-2,2-dimethyl-, (*S*)-]



Submitted by Kenji Mori and Hideto Mori[1].
Checked by Mark Hopkins and Larry E. Overman.

1. Procedure

A. *2,2-Dimethylcyclohexane-1,3-dione*. In a 1-L, three-necked, round-bottomed flask equipped with a magnetic stirrer, a 200-mL pressure-equalizing dropping funnel, and a reflux condenser (the top of which is connected to a calcium chloride drying tube) are placed 50.4 g (0.4 mol) of 2-methylcyclohexane-1,3-dione[2] and 500 mL of dry methanol. To this stirred solution is added dropwise 168 mL of commercial Triton B (40% in methanol) (Note 1) and (Note 2). After the additional is complete, the resulting solution is stirred at room temperature for 10 min and 60.0 g (0.423 mol) of methyl iodide is added portionwise. This solution is then stirred and heated under reflux for 16–20 hr (Note 3). After the reaction mixture is cooled to room temperature, about 400 mL of methanol is removed by rotary evaporation. The residue is poured into a mixture of 100 mL (1.2 mol) of concentrated hydrochloric acid and about 100 g of ice to decompose the O-alkylated product (Note 4), and the mixture is stirred for 30 min. The precipitated solid (recovered starting material) is collected by filtration and the filtrate is extracted 4 times with 100 mL of ethyl acetate. The combined ethyl acetate extracts are washed with 5% sodium thiosulfate solution (4 × 100 mL), saturated sodium hydrogen carbonate solution (2 × 100 mL) and saturated sodium chloride solution (100 mL), dried over anhydrous magnesium sulfate, and filtered. Ethyl acetate is removed by rotary evaporation and the residue is distilled to give 30–32 g (54–57%) of 2,2-dimethylcyclohexane-1,3-dione bp 92–97°C (4 mm) as a glassy solid (Note 5) and (Note 6).

B. *(S)-(+)-3-Hydroxy-2,2-dimethylcyclohexanone*. In a 5-L, three-necked, round-bottomed flask equipped with a mechanical stirrer, a thermometer, and an air-reflux condenser are placed 3 L of tap water and 450 g of sucrose (Note 7). The mixture is stirred at 30°C, and 200 g of dry baker's yeast (Note 8) is added with stirring, whereupon brisk fermentation takes place (Note 2). This fermenting mixture is stirred at 30°C for 10 min and a solution of 15 g (0.107 mol) of 2,2-dimethylcyclohexane-1,3-dione in 95% ethanol (30 mL) and 0.2% Triton X-100 (120 mL) is added portionwise (Note 9). The mixture is stirred at 30°C for 40–48 hr (Note 10). Diethyl ether (about 200 mL) and Celite (about 50 g) are then added to the mixture and it is left to stand overnight. After the flocculated yeast cells are precipitated, the mixture is filtered through a pad of Celite (Note 11). The filter cake is washed with ethyl acetate (2 × 100 mL) and the combined filtrate and washings are saturated with sodium chloride and extracted 4 times with 100 mL of ethyl acetate. The combined ethyl acetate extracts are washed with saturated sodium hydrogen carbonate solution (200 mL) and saturated sodium chloride solution (200 mL), dried over anhydrous magnesium sulfate, and filtered. Ethyl acetate is removed by rotary evaporation and the residue (about 20 g) is chromatographed over 200 g of silica gel (Fuji Davison 820 MH gel) (Note 12). Elution with hexane–ethyl acetate (10 : 1–5 : 1) gives 5–6 g of recovered starting material. Further elution with hexane-ethyl acetate (5 : 1–1 : 2) gives 7.7–7.9 g (47–52%) of (*S*)-3-hydroxy-2,2-dimethylcyclohexanone. An analytical sample can be obtained by distillation, bp 85–87°C at 3.7 mm, $[\alpha]_D^{21}$ + 23.0° ($CHCl_3$, *c* 2.0) (Note 13),(Note 14),(Note 15).

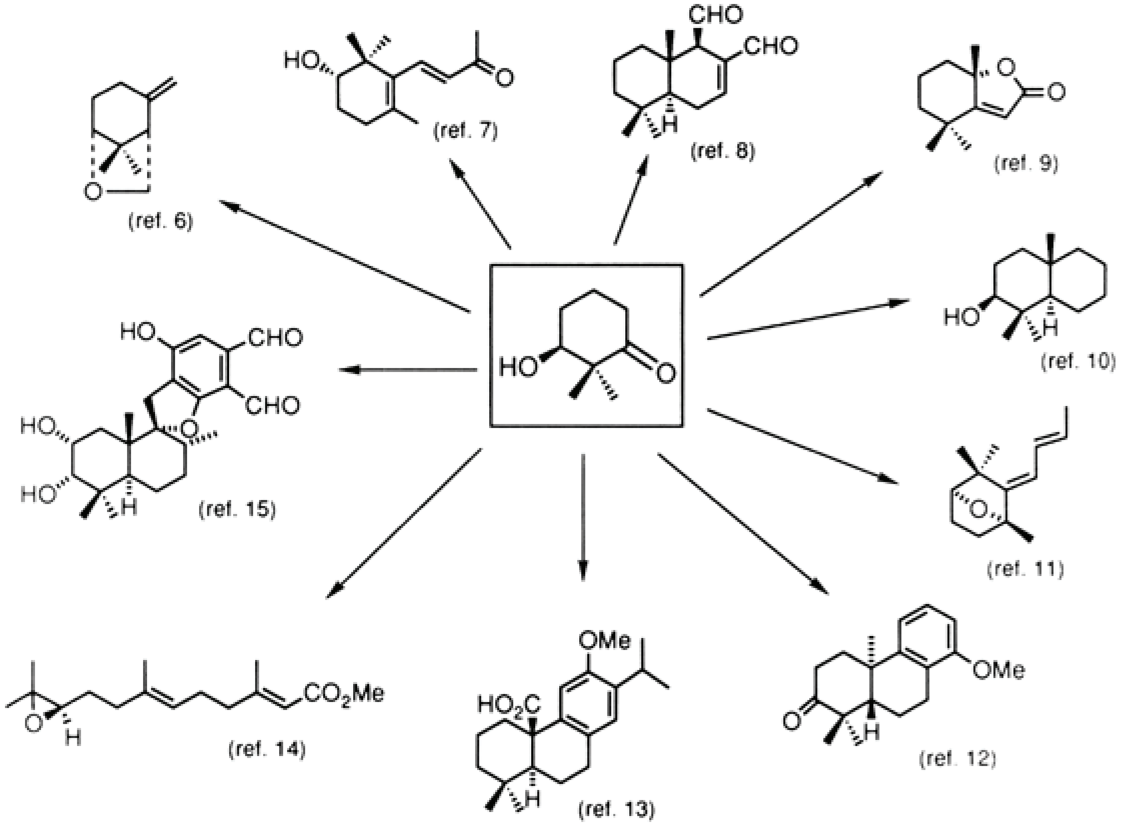
2. Notes

1. The submitters used Triton B purchased from Tokyo Kasei Co., Ltd., whereas the checkers used material purchased from Aldrich Chemical Company, Inc. A rigorously moisture-free condition is not necessary. Even with ordinary methanol, the same result was obtained.
2. No temperature control is required because of the nonexothermic nature of this reaction.
3. The checkers found (GLC analysis using a 12.5-m, 5% methyl silicone capillary column) that the reaction was complete within 4–6 hr.
4. To ensure the complete decomposition of the O-alkylated product, this amount of hydrochloric acid is used. A smaller amount may result in incomplete decomposition of the by-product.
5. This material is sufficiently pure for use in the next step. Analysis by ^{13}C NMR indicates that 2–4% of an unknown impurity is present. Recrystallization from hexane–methylene chloride gives pure product melting at 37–38°C.
6. The spectra are as follows: ^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.29 (s, 6 H), 1.93 (5 lines, 2 H, $J = 6.5$), 2.67 (t, 4 H, $J = 6.9$); ^{13}C NMR (76 MHz, $CDCl_3$) δ: 18.1, 22.3, 37.4, 61.8, 210.6.
7. Commercially available sucrose is used. The checkers employed deionized water.
8. The submitters used yeast purchased from the Oriental Yeast Co., Ltd., whereas the checkers used Fleischman's Dry Active Yeast.
9. The submitters used Triton X-100 purchased from Tokyo Kasei Co., Ltd., whereas the checkers used material purchased from Rohm & Haas Co.
10. To keep the temperature at 30°C, the flask is gently heated on a large water bath.
11. The checkers found that the use of coarse filter paper and a Büchner funnel was preferable to a sintered glass funnel.
12. The checkers found that the chromatography was best accomplished using 450 g of silica gel (E. Merck).
13. The spectral properties of (*S*)-(+)-3-hydroxy-2,2-dimethylcyclohexanone are as follows: IR ν_{max} (film) cm^{-1}: 3470 (s), 1705 (s), 1120 (m), 1055 (s), 985 (s), 965 (m); ^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.11 (s, 3 H), 1.15 (s, 3 H), 1.60–1.71 (m, 1 H), 1.76–1.86 (m, 1 H), 1.96–2.05 (m, 2 H), 2.16 (br s, 1 H), 2.35–2.45 (m, 2 H), 3.69 (dd, 1 H, $J = 7.6, 2.9$); ^{13}C NMR (76 MHz, $CDCl_3$) δ: 19.7, 20.7, 22.9, 29.0, 37.3, 51.3, 77.8, 215.3.
14. The optical purity of (*S*)-(+)-3-hydroxy-2,2-dimethylcyclohexanone can be determined by HPLC analysis. The (*S*)-α-methoxy-α-trifluoromethylphenylacetate (MTPA ester) is prepared according to the reported procedure:[3] HPLC analysis (Column, Nucleosil® 50-5, 25 cm × 4.6 mm; eluant, hexane : THF = 30 : 1, 1.03 mL/min; detected at UV 256 nm) retention time 35.6 min (98.0–99.4%) and 29.6 min (0.6–(2.0%). Therefore, the optical purity is determined to be 96.0–98.8% ee.
15. Analysis of the MTPA ester of this product by 250 MHz ^{1}H NMR and capillary GLC (12.5 m, 5% methyl silicone column) failed to detect any more of the minor diastereomer than would have been expected from the purity (98% ee) of the MTPA-Cl employed.

3. Discussion

Microbial reduction of prochiral cyclopentane- and cyclohexane-1,3-diones was extensively studied during the 1960s in connection with steroid total synthesis.[4] Kieslich, Djerassi, and their coworkers reported the reduction of 2,2-dimethylcyclohexane-1,3-dione with *Kloeckera magna* ATCC 20109, and obtained (*S*)-3-hydroxy-2,2-dimethyl-cyclohexanone.[5] We found that the reduction of the 1,3-diketone can also be effected with conventional baker's yeast, and secured the hydroxy ketone of 98–99% ee as determined by an HPLC analysis of the corresponding (*S*)-α-methoxy-αtrifluoromethyl-phenylacetate (MTPA ester).[6,7] (*S*)-3-Hydroxy-2,2-dimethylcyclohexanone has been proved to be a versatile chiral nonracemic building block in terpene synthesis as shown in Figure 1.

Figure 1. Natural products synthesized from (*S*)-3-hydroxy-2,2-dimethylcyclohexanone



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References and Notes

1. Department of Agricultural Chemistry, The University of Tokyo, Yayoi 1-1-1, Bunkyo-Ku, Tokyo 113, Japan.
2. Mekler, A. B.; Ramachandran, S.; Swaminathan, S.; Newman, M. S. *Org. Synth., Coll. Vol. V* **1973**, 743, *3*.
3. Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.
4. Kieslich, K. "Microbial Transformations of Non-Steroid Cyclic Compounds;" Georg Thieme; Stuttgart, 1976, pp. 28–31.
5. Lu, Y.; Barth, G.; Kieslich, K.; Strong, P. D.; Duax, W. L.; Djerassi, C. *J. Org. Chem.* **1983**, *48*, 4549.
6. Mori, K.; Mori, H. *Tetrahedron* **1985**, *41*, 5487.
7. Yanai, M.; Sugai, T.; Mori, K. *Agric. Biol. Chem.* **1985**, *49*, 2373.
8. Mori, K.; Watanabe, H. *Tetrahedron* **1986**, *42*, 273.
9. Mori, K.; Nakazono, Y. *Tetrahedron* **1986**, *42*, 283.
10. Mori, K.; Mori, H.; Yanai, M. *Tetrahedron* **1986**, *42*, 291.
11. Mori, K.; Tamura, H. *Tetrahedron* **1986**, *42*, 2643.
12. Sugai, T.; Tojo, H.; Mori, K. *Agric. Biol. Chem.* **1986**, *50*, 3127.
13. Mori, K.; Mori, H. *Tetrahedron* **1986**, *42*, 5531.
14. Mori, K.; Mori, H. *Tetrahedron* **1987**, *43*, 4097.
15. Mori, K.; Komatsu, M. *Liebigs Ann. Chem.* **1988**, 107.

Appendix
Chemical Abstracts Nomenclature (Collective Index Number);

(Registry Number)

silica gel

Triton B

Triton X-100

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

ethyl acetate (141-78-6)

methanol (67-56-1)

diethyl ether (60-29-7)

sodium hydrogen carbonate (144-55-8)

sodium chloride (7647-14-5)

sodium thiosulfate (7772-98-7)

sucrose

Methyl iodide (74-88-4)

methylene chloride (75-09-2)

magnesium sulfate (7487-88-9)

THF (109-99-9)

hexane (110-54-3)

2-methylcyclohexane-1,3-dione (1193-55-1)

2,2-Dimethylcyclohexane-1,3-dione (562-13-0)

(S)-(+)-3-Hydroxy-2,2-dimethylcyclohexanone,
Cyclohexanone, 3-hydroxy-2,2-dimethyl-, (S)-,
(S)-3-hydroxy-2,2-dimethylcyclohexanone,
(S)-3-hydroxy-2,2-dimethyl-cyclohexanone (87655-21-8)

(S)-α-methoxy-α-trifluoromethylphenylacetate,
(S)-α-methoxy-αtrifluoromethyl-phenylacetate