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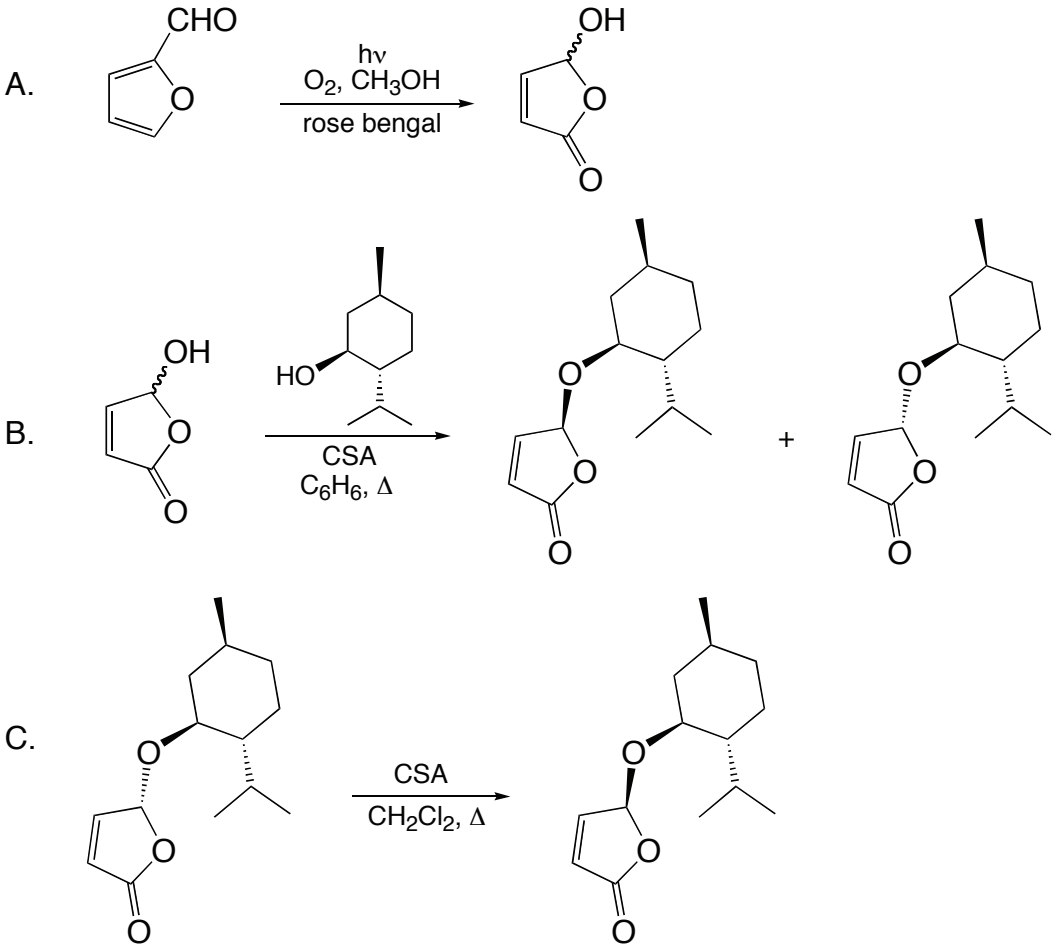
September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

DOI:10.15227/orgsyn.080.0066
Organic Syntheses, Vol. 80, p. 66-74 (2003); Coll. Vol. 11, p. 128-134 (2009).

(5*S*)-(d-MENTHYLOXY)-2(5*H*)-FURANONE [(2(5*H*)-Furanone, 5[[(1*S*,2*R*,5*S*)-5-methyl-2-(1-methylethyl)cyclohexyl]oxy]-, (5*S*)-)]



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1. Procedure

A. 5-Hydroxy-2(5H)-furanone. A solution consisting of freshly distilled furfural (85.84 g, 0.893 mol) (Note 1) and rose bengal (1.82 g, 1.8 mmol, 0.2% mol/eq) (Note 2) in dry methanol (450 mL) is placed in a 600-

mL Pyrex photochemical reactor. The outer vessel, which is fitted at its base with a fritted disc, is also equipped with a thermometer, magnetic stirring bar, and reflux condenser. With oxygen bubbling from the bottom of the reactor (Note 3) and appropriate (water) cooling in the reactor well, the stirred solution is irradiated with a tungsten halogen lamp (Note 4). The reaction temperature is maintained at or below 33 °C at all times. After 18-22 h, when no residual furfural can be detected by thin layer chromatography (TLC) (Note 5), the solution is carefully concentrated at 35-38 °C (bath temperature) (Note 6). Following standing overnight, the orange solid that forms is taken up in 70 mL of cold (−78 °C) chloroform and the resulting crystals are collected by vacuum filtration, washed once with 70 mL of chloroform, and dried under high vacuum to afford 72.70-75.65 g (81-85%) of 5-hydroxy-2(5*H*)-furanone as sticky, yellowish crystals, mp 52 °C (Note 7).

B. (5S)-(d-Menthyloxy)-2(5H)-furanone. A 500-mL, round-bottomed flask equipped with a magnetic stirring bar, 10-mL Dean-Stark trap, and reflux condenser is charged with d-menthol (51.9 g, 0.330 mol), 5-hydroxy-2(5*H*)-furanone (37.3 g, 0.370 mol), D-(+)-camphorsulfonic acid (3.96 g, 0.170 mol), and 190 mL of dry benzene (Note 8). The stirred suspension is heated to reflux under argon with an oil bath preheated to 100 °C (Note 9). After 1-2 h, a total of 5.1 mL of water is collected and no residual menthol is apparent by TLC analysis (Note 10). The reaction mixture is cooled in an ice bath and treated carefully with 100 mL of saturated sodium bicarbonate solution. After completion of the addition, stirring is maintained for 90 min as the mixture is allowed to warm to room temperature. The product is extracted with dichloromethane (300 mL) and the organic phase is washed with three 70-mL portions of brine, dried over anhydrous magnesium sulfate, filtered and concentrated by rotary evaporation to provide 66.7 g (85%) of a 1:1 diastereomeric mixture of the menthyloxybutenolides (Note 11). This mixture is dissolved in 400 mL of hot petroleum ether (bp 35-60 °C) and subsequently cooled to room temperature and eventually to −10 °C (Note 12). Two additional recrystallizations from petroleum ether (200 mL on each occasion) with slow cooling affords 10.7-17.33 g (14-22%) of pure (5*S*)-(d-menthyloxy)-2(5*H*)-furanone, mp 79-80 °C (Note 13).

C. Acid-catalyzed epimerization. The combined mother liquors from Step B are concentrated to dryness, dissolved in 50 mL of benzene, and

concentrated again under reduced pressure. The resulting solid is dissolved in 150 mL of dichloromethane, treated with D-(+)-camphorsulfonic acid (2.0 g, 8.6 mmol) and the mixture is heated to reflux under argon with magnetic stirring for 19 h. The resulting solution is cooled to 0 °C and saturated sodium bicarbonate solution (40 mL) is carefully added. The mixture is stirred for 2 h at 20 °C. The organic phase is separated and washed with two 50-mL portions of water, dried over anhydrous magnesium sulfate, filtered, and concentrated by rotary evaporation. The residue is crystallized three times from petroleum ether as described in Step B to give an additional 13.04-17.60 g (17-22%) of furanone. The total yield of pure (5*S*)-(d-menthyloxy)-2(5*H*)-furanone (based on the menthol used in Step B) is 24.75-34.93 g (32-44%) (Note 14).

2. Notes

1. Furfural was purchased from Alfa Aesar and was distilled at reduced pressure (47 mm) from hydroquinone before use.

2. Rose bengal was obtained by the submitters from Acros (certified 80%) and by the checkers from the Aldrich Chemical Company, Inc. (certified 89%) and used as received. Anhydrous methanol was obtained from Malinckrodt and used as received.

3. A gentle flow of oxygen is sufficient. A vigorous stream of the gas results in rapid loss of solvent, followed by an undesirable increase in temperature and decomposition of the product.

4. The submitters used a conventional slide projector bulb (Radiac DYS/SYV/BHC 120V, 600W) and the checkers employed a General Electric DYS 600W/120V bulb. The bulb was welded to lead wires contained within porcelain tubing that set properly within the inner well of the photoreactor. The bulb was attached to a Variac at full power (the checkers used a Variac set at 480W). Importantly, the bulb was additionally cooled with a strong flow of air that was introduced two-thirds of the way down in the well by means of Tygon tubing appropriately fastened to the porcelain.

5. TLC was carried out by the checkers on silica gel plates using 50:1 chloroform:methanol as eluent and $KMnO_4$ for visualization. Under these conditions, the R_fs of furfural and the furanone are 0.6 and 0.0, respectively.

6. It is convenient to divide the reaction mixture into three portions (ca. 170 mL each) and to transfer them into three 1-L, round-bottomed flasks to effect concentration separately. In each case, some chloroform was introduced and concentration was carried out at 35-38 °C. This process was repeated a second time and the residual oils were combined in a 300-mL beaker, this transfer being effected with the aid of a minimum amount of chloroform.

7. The submitters, starting with 266.3 g (2.77 mol) of furfural, obtained the product as colorless crystals, mp 57-59 °C and found that, upon stirring the mother liquors at −78 °C and seeding, an additional 70.3 g (total yield of 77%) of the butenolide could be obtained. The checkers noted that their product could be decolorized by charcoal treatment (twice) of a chloroform solution heated at reflux to furnish an analytically pure sample of the furanone with mp 54 °C. The product displays the following spectral data: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.24 (br s, 1H), 6.23 (dd, *J*= 1.2, 5.4, 1H), 6.27 (m, 1H), 7.33 (dd, *J* = 1.2, 5.4, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 99.4, 124.7, 152.5, 172.0; IR (NaCl) cm^{-1}: 3363, 3114, 2929, 2739, 1792, 1756, 1611, 1583, 1442, 1341, 1283, 1183, 1131, 1083, 996; Anal. Calcd for $C_4H_4O_3$: C, 48.01; H, 4.03. Found: C, 48.11; H, 4.15.

8. The submitters purchased d-menthol from TCI and the checkers obtained this compound (99%, 98% ee) from Aldrich Chemical Company, Inc. Menthol was used as received. D-(+)-camphorsulfonic acid (99%) was purchased from Avocado and used as received. Benzene was purchased from EM Science and used as received.

9. The submitters observed that the two liquid phases that are present when refluxing begins form a homogeneous solution within a few minutes.

10. The theoretical amount of water is 5.9 mL. TLC analysis was conducted by the checkers on silica gel plates using 50:1 chloroform:methanol as eluent and iodine and $KMnO_4$ for visualization. Under these conditions, the R_fs of the product ($KMnO_4$) and menthol (I_2) are 0.59 and 0.46, respectively.

11. This mixture solidifies spontaneously on standing. ^{1}H NMR analysis (in $CDCl_3$ solution) clearly shows the α- (δ 3.53) and β-diastereomers (δ 3.66) to be present in equal amounts.

12. In order to maximize the purity of the product, rapid cooling should be avoided. The submitters allowed the solution to cool slowly to

room temperature in an open beaker in the hood, followed by storage in a refrigerator at +5 °C and ultimately at −10 °C.

13. The product exhibits the following spectral data: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.79 (d, *J*= 7.0, 3H), 0.84 (d, *J* = 7.0 Hz, 3H), 0.94 (d, *J* = 6.5, 3H), 0.96-1.50 (m, 3H), 1.61-1.72 (m, 2H), 2.08-2.17 (m, 2H), 3.66 (dt, *J* = 4.5, 10.8, 1H), 6.09 (t, *J* = 1.2, 1H), 6.20 (dd, *J* = 1.2, 5.9, 1H), 7.17 (dd, *J* = 1.2, 5.9, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 15.9, 21.1, 22.4, 23.3, 25.5, 31.7, 34.4, 40.5, 47.9, 79.3, 100.7, 125.0, 151.1, 171.0; IR (NaCl) cm^{-1}: 2930, 1795, 1752, 1451, 1387, 1347, 1312, 1173, 1132, 1016, 923, 825; Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.56; H, 9.30. Found: C, 70.52: H, 9.16. The submitters found $[\alpha]_D^{20}$ +136.9 (EtOH, c 8.2) and the checkers observed $[\alpha]_D^{20}$ +135.12 ($CHCl_3$, c 8.2).

14. The submitters obtained 14.2 g of product in Step C. Based on the amount of furanone theoretically present in the mother liquors subjected to Step C, this represents a 35% yield of the desired diastereomer in the epimerization step.

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 synthetic utility of (5*S*)- and (5*R*)-menthyloxy-2(5*H*)-furanones has been extensively explored and is well documented. The ready availability of these enantiomerically pure butenolides via the singlet photooxygenation of furfural[2] and their wide range of reactivity contribute to their popularity as chiral building blocks. The present procedure for the preparation of the title compound and the useful epimerization step are modifications of methods originally reported by Feringa and co-workers.[3]

The double bond of these enantiomerically pure butenolides participates readily in asymmetric Diels-Alder reactions,[4,5,6] 1,4-conjugate additions,[7,8,9,10,11,12,13,14,15] [2+2] photochemical reactions,[16,17,18] 1,3-dipolar cycloadditions,[3,19,20] diastereoselective dihydroxylation,[21] and tandem double Michael addition/intramolecular nucleophilic substitution processes.[22,23] As a consequence, they have played a key strategic role in the total syntheses of such structurally varied enantiopure targets as dibenzylbutyrolactone[24,25,26,27] and aryltetralin lignans,[28] podophyllotoxin[29,30,31] and isomers thereof,[32,33] β-lactams,[34] grandisol,[17] terebic acid,[35] isostegane derivatives,[36] and chiral nitronic esters[37] among others.

The current procedure provides material of high enantiomeric purity (>98% ee) starting with inexpensive and easily handled reagents. The two steps proceed in reasonable overall yield and require no chromatographic separation.

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

2(5*H*)-(d-Menthyloxy)-2(5*H*)-furanone: 2(5*H*)-Furanone, 5-[[(1*S*,2*R*,5*S*)-5-methyl-2-(1-methyethyl)cyclohexyl]oxy]-, (5*S*)- (9); (122079-41-8)

2-Hydroxy-2(5*H*)-furanone: 2(5*H*)-Furanone, 5-hydroxy-(8, 9); (14032-66-7)

Furfural: 2-Furancarboxaldehyde (9); (98-01-1)

Rose Bengal (9); (11121-48-5)

D-(+)-Camphorsulfonic acid: Bicyclo[2.2.1]heptane-1-methanesulfonic acid, 7,7-dimethyl-2-oxo-, (1*S*,4*R*)-(9); (3144-16-9)