Organic Syntheses

A Publication
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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.

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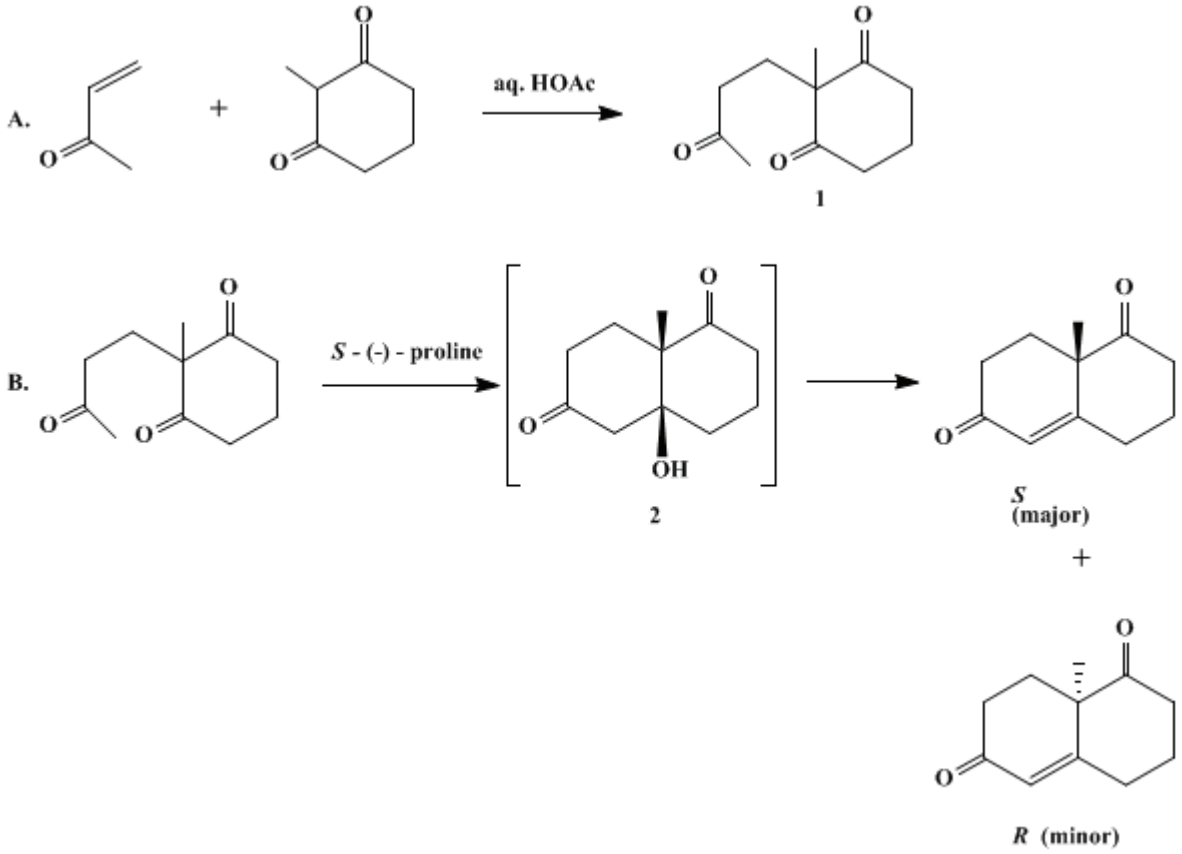
(*S*)-8a-METHYL-3,4,8,8a-TETRAHYDRO-1,6(2*H*, 7*H*)-NAPHTHALENEDIONE

[1,6(2*H*, 7*H*)-Naphthalenedione, 3,4,8,8a-tetrahydro-8a-methyl-, (*S*)-]



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1. Procedure

Caution! Part A should be performed in a well-ventilated hood because methyl vinyl ketone is a lachrymator.

A. *2-Methyl-2-(3-oxobutyl)-1,3-cyclohexanedione*. A 1-L, round-bottomed flask equipped with a thermometer and a reflux condenser capped with an argon-inlet tube is charged with 126.1 g (1 mol) of 2-methyl-1,3-cyclohexanedione (Note 1) and 300 mL of distilled water. To the well-stirred suspension are added 3 mL of acetic acid, 1.1 g of hydroquinone, and 142 g (167 mL, 2 mol) of freshly distilled methyl vinyl ketone (Note 2). The reaction mixture is stirred under argon at 72–75°C for 1 hr, cooled to room temperature, treated with sodium chloride (103 g), and poured into a separatory funnel containing ethyl acetate (400 mL). The organic phase is collected and the aqueous phase is reextracted twice with ethyl acetate (150 mL each time). The combined extracts are washed with two 200-mL portions of saturated brine, dried over anhydrous magnesium sulfate, and filtered, and the filtrate is evaporated at 40°C under reduced pressure (water aspirator) on a rotary evaporator. The residue is kept under high vacuum (1.0 mm) at 40°C for 30 min to give 210.8 g of crude 2-methyl-2-(3-oxobutyl)-1,3-cyclohexanedione (**1**, "trione") as a pale-yellow oil, homogeneous by thin-layer chromatography (Note 3). This crude material is used in Step B.

B. *(S)-8a-Methyl-3,4,8,8a-tetrahydro-1,6(2H, 7H)-naphthalenedione (3-S)*. A 3-L, one-necked, round-bottomed flask, equipped with an argon-inlet tube and containing a magnetic stirrer, is charged with 5.75 g (0.05 mol) of finely ground L-proline (Note 4) and a solution of 210.8 g of crude trione **1** (from Step A) in 1 L of anhydrous dimethyl sulfoxide (Note 5). The mixture is stirred at room temperature (ca. 25°C) under argon for 120 hr, the magnetic bar is removed, and the solvent is removed under high vacuum (1.0 mm) at 65°C (Note 6) on a rotary evaporator to give 206.9 g of a dark reddish-violet oil. The oil is dissolved in toluene (100 mL) and is absorbed on a column (9 cm X 60 cm) of silica gel (1.5 kg, 70–230 mesh) (Note 7), which was previously packed in hexane. Elution is carried out under a slight positive pressure of argon (ca. 1 atm) (Note 8) initially with 1 L of hexane: ethyl acetate (5 : 1) and then with a 3 : 2 mixture of hexane : ethyl acetate taking 300-mL fractions. The progress of the purification is monitored by thin-layer chromatography (Note 9): no product is observed until ca. 5 L of eluant is collected. Fractions containing the product are combined, and the solvents are removed under reduced pressure (water aspirator) at 45–50°C. The residue is then kept under high vacuum (0.1 mm) at 40°C for 30 min to give 154.2 g of an orange-colored oil, which became glassy and sometimes crystalline on standing at room temperature, $[\alpha]_D^{25}$ + 68° (toluene, *c* 1.5) (Note 10). This material is dissolved in 535 mL of ether and is filtered through a fluted filter paper to remove small particles. The flask is rinsed with 500 mL of ether, and this is passed through the filter paper. After cooling to 3°C, the combined filtrates are seeded with a few crystals of pure 3-S (Note 11), and the mixture is left undisturbed at −20°C for 18 hr. Most of the supernatant liquid is carefully decanted without agitation, and the crystals are collected by filtration. The flask is rinsed with cold (0°C) 50% ether in hexane and the rinse is used to wash the crystals. The crystals are dried for 16 hr under high vacuum at room temperature to yield 85.9 g of (*S*)-enedione (first crop), mp 49–50°C, $[\alpha]_D^{25}$ + 96.9° (toluene, *c* 1.2). The combined filtrate and washings are evaporated to give 67.1 g of an orange-colored oil, which is dissolved in 604 mL of ether, cooled to 3°C, and seeded with (*R,S*)-enedione (Note 12). The mixture is left at −20°C for 18 hr, and the supernatant liquid is carefully decanted (no agitation). The wet crystals are then collected by filtration, washed with cold (0°C) 50% ether in hexane, and dried under reduced pressure at room temperature to give 36.3 g of racemic material (3*R* + 3*S*). The filtrate and washing are evaporated to give 30.6 g of an oil, which is dissolved in 100 mL of ether, and filtered through a fluted filter paper. The flask is rinsed with 114 mL of ether, and filtered through the fluted filter paper, and the combined filtrates are cooled to 3°C and seeded with crystals of the pure 3-S. The mixture is left at −20° C overnight, the supernatant liquid is carefully decanted without much agitation and the wet crystals are collected by filtration and washed with cold (0°C) 50% hexane in ether. After drying 15.3 g of light amber-colored crystals (second crop), (mp 49–50°C, (or $[\alpha]_D^{25}$ + 97.3° (toluene, *c* 1.0). The total yield of (*S*)-enedione is 101.2 g (56.8%) (Note 13).

2. Notes

1. 2-Methyl-1,3-cyclohexanedione[2] was obtained from Aldrich Chemical Company, Inc. or Fluka and had mp 208–210°C.
2. Methyl vinyl ketone, bp 34°C/120 mm, was obtained from Aldrich Chemical Company, Inc. or Fluka.
3. Thin-layer chromatography was performed on silica gel with ethyl acetate : hexane (3 : 2). Visualization of the spots was achieved by spraying the plates with 10% ceric sulfate in 10% sulfuric acid, heating the plates to ca. 120°C, and spraying again with 10% phosphomolybdic acid in isopropyl alcohol. The product has R_f 0.50; 2-methyl-1,3-cyclohexanedione has R_f 0.30.
4. *S*-(−) Proline was obtained from Aldrich Chemical Company, Inc. It is also available from Ajinomoto GmbH or Degussa.
5. Dimethyl sulfoxide was dried over Linde 4A molecular sieves. Anhydrous, deaerated *N,N*-dimethylformamide was preferred by the submitters (Note 14).[3]
6. The temperature should be kept below 70°C.
7. Silica gel was purchased from EM Reagents, E. Merck, Darmstadt, Germany. The submitters preferred to do the preliminary purification by fractional vacuum distillation using a Hickman-type short-path distillation head. The main fraction distills as a light orange oil, bp 126–130°C (0.02 mm) (Note 14).
8. The procedure of W. C. Still[4] is used.
9. Silica gel and 60% ethyl acetate in hexane were used. The product, R_f 0.40, is visible under short-wavelength UV light, whereas the starting trione, also R_f 0.40, is not. Visualization is achieved as

described in (Note 3).
10. The material was melted at 55°C under reduced pressure (12 mm) on a rotary evaporator prior to sampling in order to measure the optical rotation on a homogeneous sample.
11. Compound 3-S was obtained from material having (or $[\alpha]_D^{25}$ + 68° (toluene, *c* 1.5) that was prepared in another experiment. Thus, 28.2 g of this (*S*)-enedione is dissolved in 90 mL of ether and the solution is left at −20°C for 18 hr. The crystals are collected by filtration without much agitation, washed with 30 mL of cold (0°C) 50% ether in hexane, and redissolved in 117 mL of ether. The solution is left at −20°C for 18 hr, and the crystals are collected by filtration, washed with 30 mL of cold (0°C) 50% ether in hexane, and dried under reduced pressure (1.0 mm) at room temperature to give 12.0 g of (*S*)-enedione, mp 50°C, $[\alpha]_D^{25}$ + 100° (benzene, *c* 1.5); $[\alpha]_D^{25}$ + 97° (toluene, *c* 1.0). It should be possible to prepare seed crystals from a small aliquot, but this was not attempted by the checkers.
12. Racemic Wieland-Miescher ketone was obtained from Aldrich Chemical Company, Inc. or prepared according to the procedure of Ramachandran and Newman.[5]
13. ^{1}H NMR studies (100 MHz, $CDCl_3$) using the shift reagent tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato] europium(III) (purchased from Aldrich Chemical Company, Inc.) indicated that the two crops were enantiomerically pure. Under identical conditions (10 mg of reagent per 9.6 mg of substrate), absorption due to the vinyl proton at 5.86 in the racemate appeared as two peaks (1-Hz separation) of equal intensity.
14. The submitters' procedure using dimethylformamide in Step B and using distillation for isolation of the enantiomerically enriched ketone was checked by K. Job, A. K. Beck, and D. Seebach and proved equally satisfactory.

3. Discussion

Racemic 8a-methyl-3,4,8,8a-tetrahydro-1,6(2*H*, 7*H*)-naphthalenedione (the Wieland-Miescher ketone)[5,6] is a versatile building block for the synthesis of steroids[7] and terpenoids.[8] The (*S*)-enantiomer, 3-S, was first obtained by microbiological means[9] and by classical resolution via a derived hemiphthalate.[10] The present synthesis[3] of 3-S is based[11 12] on the asymmetric intramolecular aldolization of the prochiral triketone 1 using *S*-(−)-proline catalytically. The product is obtained in 56% yield (from **2**) and is enantiomerically pure on the basis of optical rotation and NMR spectroscopy determined in the presence of a chiral shift reagent. Despite numerous synthetic investigations and modifications of this asymmetric Robinson annulation,[13 14 15] the mechanism of enantio-differentiation is still not fully understood;[16 17 18] see discussion in this volume, p. 367, relating to the asymmetric synthesis of the corresponding *S*-(+)-tetrahydro-7-methylindenedione.

References and Notes

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

brine

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

Wieland-Miescher ketone

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

ethyl acetate (141-78-6)

ether (60-29-7)

hydroquinone (123-31-9)

sodium chloride (7647-14-5)

toluene (108-88-3)

isopropyl alcohol (67-63-0)

magnesium sulfate (7487-88-9)

triketone

S-(−)-proline,
L-proline,
S-(−) Proline (147-85-3)

N,N-dimethylformamide,
dimethylformamide (68-12-2)

hexane (110-54-3)

methyl vinyl ketone (78-94-4)

vinyl (2669-89-8)

dimethyl sulfoxide (67-68-5)

ceric sulfate (13590-82-4)

argon (7440-37-1)

8a-methyl-3,4,8,8a-tetrahydro-1,6(2H, 7H)-naphthalenedione (20007-72-1)

2-Methyl-1,3-cyclohexanedione (1193-55-1)

2-Methyl-2-(3-oxobutyl)-1,3-cyclohexanedione (5073-65-4)

phosphomolybdic acid (51429-74-4)

(S)-8a-METHYL-3,4,8,8a-TETRAHYDRO-1,6(2H, 7H)-NAPHTHALENEDIONE,
(S)-8a-Methyl-3,4,8,8a-tetrahydro-1,6(2H, 7H)-naphthalenedione (3-S),
1,6(2H, 7H)-Naphthalenedione, 3,4,8,8a-tetrahydro-8a-methyl-, (S)- (33878-99-8)

S-(+)-tetrahydro-7-methylindenedione