



A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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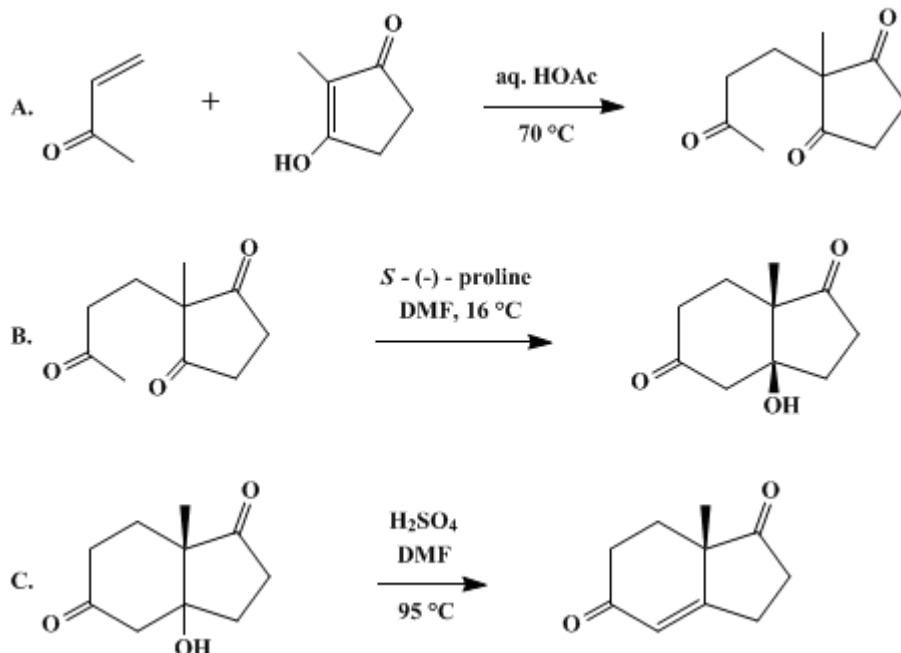
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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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(+)-(7*aS*)-7*a*-METHYL-2,3,7,7*a*-TETRAHYDRO-1 *H*-INDENE-1,5-(6*H*-DIONE

[1 *H*-Indene-1,5(6 *H*)-dione, 2,3,7,7*a*-tetrahydro-7*a*-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-cyclopentanedione*. A 1.0-L, three-necked, round-bottomed flask equipped with a condenser, magnetic stirring bar, and thermometer is charged with 112.1 g (1.0 mol) of *2-methyl-1,3-cyclopentanedione* (Note 1), 230 mL of deionized water, 3.0 mL of glacial acetic acid, and 140 mL (120.96 g, 1.72 mol) of methyl vinyl ketone (Note 2). The system is shielded from light with aluminum foil and placed under a slight positive pressure of nitrogen. The flask is placed in an oil bath and the temperature is raised to 70 °C. The reaction is monitored by gas chromatography (GLC, (Note 3)) until complete (1–2 hr). The mixture is cooled, transferred to a separatory funnel, and extracted with 500 mL and then two 100-mL portions of dichloromethane. The combined extracts are washed with 500 and 100 mL of saturated brine. The combined brine wash is extracted with a further two 100-mL portions of dichloromethane. The total dichloromethane extract is dried over sodium sulfate and filtered. The solvent is removed on a rotary evaporator at 45 °C (70 mm). Drying on the rotary evaporator at 40–45 °C (0.03 mm) for 16 hr gives 181.8 g (100%) of the desired triketone as an orange oil (Note 4) and (Note 5).

B. *(+)-(3*aS*,7*aS*)-2,3,3*a*,4,7,7*a*-Hexahydro-3*a*-hydroxy-7*a*-methyl-1 *H*-indene-1,5(6*H*)-dione*. A 500-mL, three-necked, round-bottomed flask equipped with a magnetic stirring bar and a nitrogen inlet is charged with 188 mL of *N,N*-dimethyl-formamide (Note 6) and 863 mg (7.5 mmol) of *S*-(-)-proline (Note 7) and (Note 8). The mixture is degassed four times by alternate evacuation and refilling with nitrogen. The system is shielded from light with aluminum foil and the contents of the flask are stirred in a 15–16 °C bath (Note 9) for 1.0 hr. To the resultant suspension is added 45.5 g (0.25 mol) of the 2-

methyl-2-(3-oxobutyl)-1,3-cyclopentanedione prepared in Step A. A total of 62.5 mL of *N,N*-dimethylformamide is used to ensure complete transfer. The degassing procedure is repeated four times and stirring at 15–16°C (Note 10) is continued for 40–120 (Note 11) as the mixture becomes yellow and then brown. The reaction is monitored for completeness by TLC (Note 12). The solution of the desired ketol (Note 13) is used directly in Step C.

C. (+)-(7*aS*)-7*a*-Methyl-2,3,7,7*a*-tetrahydro-1*H*-indene-1,5(6*H*)-dione. A 100-mL, three-necked, round-bottomed flask equipped with a magnetic stirring bar, pressure-equalizing dropping funnel, and nitrogen inlet is charged with 50 mL of *N,N*-dimethylformamide (Note 6). The contents of the flask are cooled to –20°C with a dry ice–acetone bath and 2.70 mL (4.97 g, 48.6 mmol) of concentrated sulfuric acid is added over 5–10 min at a rate to maintain a temperature of –15 to –20°C (Note 14).

The flask containing the solution of the (+)-(3*aS*,7*aS*)-2,3,3*a*,4,7,7*a*-hexahydro-3*a*-hydroxy-7*a*-methyl-1*H*-indene-1,5(6*H*)-dione in *N,N*-dimethylformamide is placed in an oil bath and heated to 95°C. When the temperature reaches 70–75°C, an 18.8-mL aliquot of the concd sulfuric acid in *N,N*-dimethylformamide solution is added in one portion. The reaction mixture is heated to 95°C for 3.0 hr. After 1.0 hr, an additional 7.5-mL aliquot of the concd sulfuric acid in *N,N*-dimethylformamide solution is added in one portion. The reaction is monitored for completeness by GLC (Note 15) and cooled. The solvent is removed on a rotary evaporator at 45°C (0.3–0.5 mm) to give a brown oil. The material is taken up in 375 mL of dichloromethane. The solution is washed with two 190-mL portions of 2.0 *N* sulfuric acid solution that have been saturated with sodium chloride, two 190-mL portions of saturated sodium bicarbonate solution that have been saturated with sodium chloride, and 190 mL of saturated brine. Each aqueous wash is extracted, in turn, with the same two 190-mL portions of dichloromethane. The combined dichloromethane solutions are dried over sodium sulfate and filtered, and the solvent is removed on a rotary evaporator at 40°C (70 mm) to give 38.8–39.6 g of oily, brown semisolid. This material is taken up in 78 mL of ethyl acetate and the solution is applied to a dry column of 78 g of silica gel (Note 16). The column is eluted with 600 mL of ethyl acetate, and the total eluate is stripped of solvent on a rotary evaporator at 40°C (70 mm) to give 37.2–38.8 g of tan crystalline solid. The solid is subjected to bulb-to-bulb distillation³ (Note 17) at 120–135°C (0.1 mm) to give 35.9–36.9 g of a slightly yellowish (cream white) solid, mp 56–61°C, $[\alpha]_{\text{D}}^{25} +324\text{--}329^\circ$ (toluene, *c* 1.0) (Note 18),(Note 19),(Note 20). This material is taken up in 74 mL of ether at reflux. The solution is brought at reflux to the point of turbidity with 19 mL of hexanes. The mixture is seeded, allowed to stand at ambient temperature for 2 hr, and then chilled in a 17°C water bath for 30 min (Note 21). The solid is collected by filtration on medium porosity sintered glass, washed with two 12-mL portions of cold (3°C) 1 : 1 v/v ether : hexanes and dried at 20°C (70 mm) to give 28.7–31.3 g (70–76%) of white crystalline solid (Note 22), mp 64–66°C, $[\alpha]_{\text{D}}^{25} +347.5\text{--}349^\circ$ (toluene, *c* 1.0) (Note 23), purity by GLC 99.4–99.5% (Note 24),(Note 25),(Note 26).

2. Notes

1. 2-Methyl-1,3-cyclopentanedione, 98%, purchased from the Aldrich Chemical Company, Inc., was used. Material prepared according to Hengartner, U.; Chu, V. *Org. Synth., Coll. Vol. VI* **1988**, 774 was determined by the checkers to be equally satisfactory.
2. Methyl vinyl ketone, technical grade, purchased from the Aldrich Chemical Company, Inc., was fractionally distilled into ca. 1% w/v hydroquinone shortly before use. The fraction boiling at 33–36°C (120 mm) was used.
3. Analyses were carried out on a Hewlett Packard HP 5840 A gas chromatograph operated isothermally at 150°C. A 25-m capillary column packed with cross-linked phenylmethylsilicone was employed. 2-Methyl-1,3-cyclopentanedione and 2-methyl-2-(3-oxobutyl)-1,3-cyclopentanedione had retention times of ca. 7 min 12.5 min, respectively.
4. If desired, pure triketone can be isolated by distillation of the crude triketone through a Vigreux column. The yield of light yellow oil, bp 115–120°C (0.2–0.3 mm), is 80–89%.
5. The triketone has the following spectral properties: IR (neat) cm^{-1} : 1770, 1725; ¹H NMR (CDCl₃) δ : 1.12 (s, 3 H, CH₃), 2.22 (s, 3 H, CH₃CO), 2.8 (m, 4 H, COCH₂CH₂CO).
6. *N,N*-Dimethylformamide, purchased from the Fisher Scientific Co., was mixed with 10% v/v toluene and distilled at atmospheric pressure. After all of the toluene had been distilled (head temperature to 148°C), vacuum was cautiously applied. The fraction of *N,N*-dimethylformamide that distilled at 78–

82°C (56–65 mm) was collected and stored under nitrogen prior to use.

7. L-(-)-Proline [(*S*)-configuration], 99+%, purchased from the Aldrich Chemical Company, Inc., was employed. The material was finely ground in a mortar and pestle immediately before use.

8. The L-(-)-proline was established by the checkers to be of >99.8% (estimated level of detection) enantiomeric purity by conversion to *N*-pentafluoropropionyl-L-(-)-proline isopropyl ester and GLC analysis on a 50-m glass capillary column containing the chiral phase, Chirasil-Val (Quadrex, Inc.). Analyses were performed on a Hewlett-Packard HP 5710 A instrument operated isothermally at 140°C. Racemic proline was used as a control.

9. The checkers used a flask with a built-in jacket. Water at 15–16°C was continuously circulated through the jacket.

10. Temperature control in this reaction is critical. At higher temperatures, the enantioselectivity of the reaction drops off significantly, while at lower temperatures, the reaction time becomes unacceptably long.

11. The reaction time varied substantially from run to run, but generally complete conversion was observed in 48–72 hr.

12. E. Merck silica gel F-254 plates were used, with 20 : 1 v/v dichloromethane : methanol as eluent. The plates were developed by drying, spraying with 9 : 1 v/v deionized water : concentrated sulfuric acid, light drying with a hot air gun, spraying with 3% w/v vanillin solution in ethanol, and strong heating with the hot air gun. The approximate R_f values observed were 0.67 (starting triketone) and 0.37 (product ketol). In addition, a minor spot at R_f 0.59 (enone arising from dehydration of the ketol) was seen.

13. If desired, the ketol can be isolated as follows. The reaction mixture from 18.0 g of distilled 2-methyl-2-(3-oxobutyl)-1,3-cyclopentanedione is evaporated on a rotary evaporator at 45°C (0.3 mm) to give 22.0 g of brown oil. A solution of this material in 200 mL of ethyl acetate is filtered through 80 g of J. T. Baker silica gel. Elution with ca. 1.3 L of ethyl acetate in 200-mL fractions is monitored by TLC (Note 12). The fractions containing the desired product are combined and stripped of solvent on a rotary evaporator at 45°C (70 mm). Final drying on the rotary evaporator at 45°C (0.3 mm) gives 18.0 g (100%) of crude ketol as a slightly oily, brown solid having the following spectral properties: IR (CHCl₃) cm^{-1} : 3600, 3500–3300, 1742, 1722; ¹H NMR (CDCl₃) δ : 1.26 (s, 3 H, CH₃), 2.63 (s, 2 H, COCH₂COH). Further purification of the compound by crystallization from ether (ca. 50% recovery) gives material of mp 118–119°C, $[\alpha]_D^{25}$ +59.8° (lit.⁴ mp 119–119.5°C, $[\alpha]_D^{25}$ +60.4°).

14. The solution is prepared immediately before use and kept at –20°C.

15. The GLC system described in (Note 3) was employed. The intermediate ketol and product enone had retention times of ca. 23 and 16.5 min, respectively. A trace of ketol (<1%) is observed at the end of the reaction.

16. E. Merck silica gel 60 (70–230 mesh) was used. The column dimensions were 3.2 cm × 60 cm.

17. A Kugelrohr apparatus purchased from the Aldrich Chemical Company, Inc. was used. The receiving bulb was cooled with an ice–water bath. The temperature indicated is that of the oven air bath.

18. The ratio of rotations obtained in toluene and benzene has been determined to be 1.00 : 1.03. The rotation of enantiomerically pure material in toluene, based on the accepted⁵ value of +362° in benzene, is 351°. The enantiomeric purity at this stage is thus 92–94% (Note 19).

19. Attempts by both the submitters and checkers to find a method other than optical rotation to determine the enantiomeric purity have been unsuccessful.

20. Material of this purity is satisfactory for many synthetic purposes; see ³.

21. Further cooling results in a higher recovery of material. However, the melting point and rotation of the samples thus obtained are lower.

22. The compound is somewhat unstable. It is best stored in an amber bottle under nitrogen at 3°C.

23. The enantiomeric purity of the purified material is thus 99.0–99.4% (see (Note 18)).

24. GLC analysis was carried out on a Hewlett Packard HP 5710 A gas chromatograph operated isothermally at 155°C. A 50-m capillary column of OV-17 on fused silica was employed. The enone had a retention time of ca. 14.5 min.

25. The material has the following spectral properties: UV (CH₃OH) λ 235 nm (ϵ = 11,200); IR (CHCl₃) cm^{-1} : 1746, 1665; ¹NMR (CDCl₃) δ : 1.31 (s, 3 H), 7a-CH₃, 5.97 (broad, s, 1 H, vinylic-H).

26. Steps B and C have been scaled up to the 2.0-mol level with no loss in yield or enantiomeric purity.

3. Discussion

The (*S*)-(–)-proline-catalyzed asymmetric aldol cyclization of the triketone to the optically active bicyclic aldol product, followed by dehydration to the optically active enedione, (+)-7a-methyl-(7*aS*)-2,3,7,7*a*-tetrahydro-1*H*-indene-1,5(6*H*)-dione, has been described, and two alternative reaction mechanisms have been suggested by the submitters.⁴ The exact mechanism of the extremely high asymmetric induction in the crucial conversion of the prochiral triketone to the optically active ketol still needs to be clarified.^{6 7 8}

The synthesis of the triketone has been included (Step A of the procedure), since identification of the crystalline compound originally claimed⁹ to be the triketone has been shown to be in error.¹⁰ After completion of our work, the triketone was correctly characterized by another research group.¹¹

Asymmetric aldol cyclization of the triketone with (*S*)-(–)-proline can also be effected in solvents other than *N,N*-dimethylformamide; acetonitrile is outstanding.⁴

Of the asymmetric amino acid reagents investigated, (*S*)-(–)-proline gave the highest optical yield (93.4%); (–)-*trans*-4-hydroxyproline gave 73.1%, and (*S*)-(–)-azetidincarboxylic acid gave 63.9% optical yields in the asymmetric synthesis of the optically active bicyclic ketol.

The use of (*R*)-(+)–proline in acetonitrile induced the asymmetric aldol cyclization of the triketone to the enantiomeric ketol, (–)-(3*aR*,7*aR*)-2,3,3*a*,4,7,7*a*-hexahydro-3*a*-hydroxy-7*a*-methyl-1*H*-indene-1,5(6*H*)-dione.¹²

The ethyl homolog of the triketone, 2-ethyl-2-(3-oxobutyl)-1,3-cyclopentanedione, has been converted with (*S*)-(–)-proline in *N,N*-dimethylformamide to (+)-(3*aS*, 7*aS*)-7*a*-ethyl-2,3,3*a*,4,7,7*a*-hexahydro-3*a*-hydroxy-1*H*-indene-1,5(6*H*)-dione in good yield.⁴ This, in turn, could be dehydrated to the homologous bicyclic enedione, (+)-(7*aS*)-7*a*-ethyl-2,3,7,7*a*-tetrahydro-1*H*-indene-1,5(6*H*)-dione.⁴

Circular dichroism studies of the 7*a*-methyl bicyclic ketol suggested, and a single-crystal X-ray diffraction study of the racemic compound confirmed, the *cis* conformation with an axial 7*a*-methyl and an equatorial 3*a*-hydroxy group in the six-membered ring of the bicyclic system. On the other hand, similar measurements of the 7*a*-ethyl bicyclic keto established the alternate possible *cis* conformation to avoid the 1,3-diaxial inter-actions between the angular ethyl group and the C-4 and C-6 axial hydrogens.

Dehydration of the optically active bicyclic ketols in refluxing benzene with a little *p*-toluenesulfonic acid could readily be effected without loss of optical purity.⁴ It has been shown by a research group at Schering A. G., Berlin, Germany that the triketone can be converted directly to the optically active enedione with 0.5 eq. of (*S*)-(–)-proline and 0.25 equiv. of 1 *N* aqueous HClO₄ in refluxing acetonitrile.¹³

The optically active bicyclic enedione, (+)-7a-methyl-(7*aS*)-2,3,7,7*a*-tetrahydro-1*H*-indene-1,5(6*H*)-dione, was prepared first by microbiological means,⁵ and its absolute stereochemistry has been established.¹⁴ The compound was later prepared by optical resolution.¹⁵

The products of this highly efficient asymmetric synthesis are important intermediates in natural product chemistry, such as the total synthesis of steroids and prostaglandins.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 7, 368

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

silica gel

hexanes

brine

(+)-(7aS)-7a-METHYL-2,3,7,7a-TETRAHYDRO-1 H-INDENE-1,5-(6H-DIONE

phenylmethylsilicone

HClO₄

ethanol (64-17-5)

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

Benzene (71-43-2)

ethyl acetate (141-78-6)

methanol (67-56-1)

ether (60-29-7)

acetonitrile (75-05-8)

hydroquinone (123-31-9)

sodium bicarbonate (144-55-8)

sodium chloride (7647-14-5)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

toluene (108-88-3)

dichloromethane (75-09-2)

vanillin (121-33-5)

triketone

proline,

,

,

(147-85-3)

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

methyl vinyl ketone (78-94-4)

2-Methyl-1,3-cyclopentanedione (765-69-5)

p-toluenesulfonic acid (104-15-4)

2-Methyl-2-(3-oxobutyl)-1,3-cyclopentanedione (25112-78-1)

2-ethyl-2-(3-oxobutyl)-1,3-cyclopentanedione

(R)-(+)-proline (344-25-2)

1 H-Indene-1,5(6 H)-dione, 2,3,7,7a-tetrahydro-7a-methyl-, (S)-,
(+)-(7aS)-7a-Methyl-2,3,7,7a-tetrahydro-1H-indene-1,5(6H)-dione,
(+)-7a-methyl-(7aS)-2,3,7,7a-tetrahydro-1H-indene-1,5(6H)-dione (17553-86-5)

(+)-(3aS,7aS)-2,3,3a,4,7,7a-Hexahydro-3a-hydroxy-7a-methyl-1 H-indene-1,5(6H)-dione,
(+)-(3aS,7aS)-2,3,3a,4,7,7a-hexahydro-3a-hydroxy-7a-methyl-1H-indene-1,5(6H)-dione,
(33879-04-8)

(+)-(3aS, 7aS)-7a-ethyl-2,3,3a,4,7,7a-hexahydro-3a-hydroxy-1H-indene-1,5(6H)-dione

(+)-(7aS)-7a-ethyl-2,3,7,7a-tetrahydro-1H-indene-1,5(6H)-dione