A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

The procedures described in *Organic Syntheses* are provided as published and are conducted at one's own risk. *Organic Syntheses, Inc.*, its Editors, and its Board of Directors do not warrant or guarantee the safety of individuals using these procedures and hereby disclaim any liability for any injuries or damages claimed to have resulted from or related in any way to the procedures herein.

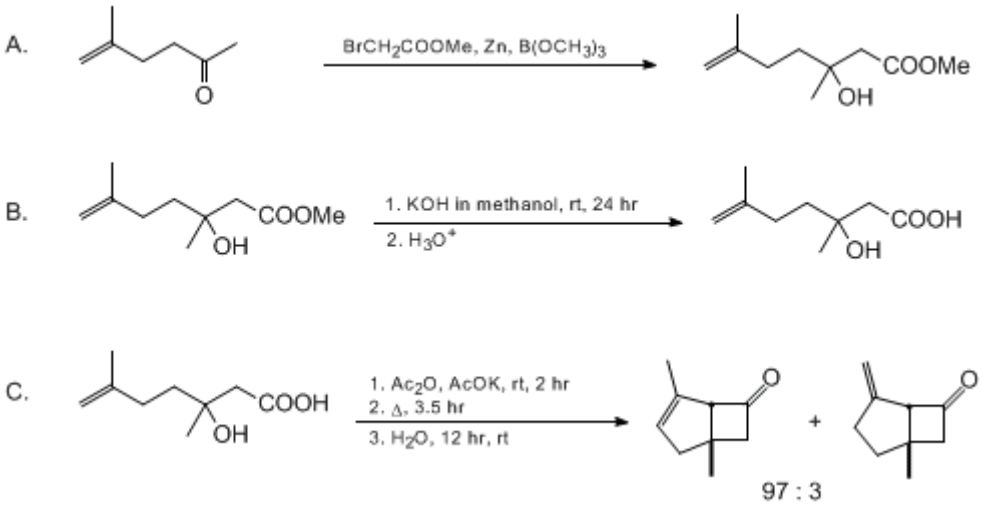
September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

DOI:10.15227/orgsyn.074.0158

Organic Syntheses, Coll. Vol. 9, p.275 (1998); Vol. 74, p.158 (1997).

PREPARATION OF BICYCLO[3.2.0]HEPT-3-EN-6-ONES: 1,4-DIMETHYLBICYCLO[3.2.0]HEPT-3-EN-6-ONE

[Bicyclo[3.2.0]hept-3-en-6-one, 1,4-dimethyl-, cis-(±)-]



Submitted by Goffredo Rosini[1], Giovanni Confalonieri[2], Emanuela Marotta[1], Franco Rama[2], and Paolo Righi[1].
Checked by Jian-Ping Chao and Robert K. Boeckman, Jr..

1. Procedure

A. *Methyl 3,6-dimethyl-3-hydroxy-6-heptenoate* (Note 1). An oven-dried, three-necked, 500-mL, round-bottomed flask, is fitted with an efficient mechanical stirrer, a Claisen adapter bearing a reflux condenser with a nitrogen inlet and rubber septum, and a thermometer. The flask is maintained under a static nitrogen pressure and charged with 5-methyl-5-hexen-2-one (24.20 g, 0.216 mol) (Note 2), trimethyl borate (60 mL) (Note 3), tetrahydrofuran (60 mL) (THF) (Note 4), and freshly activated 20-mesh zinc granules (16.96 g, 0.259 g-atom) (Note 5). The reaction flask is immersed in an oil bath at 25°C. Stirring is initiated and methyl bromoacetate (39.65 g, 0.259 mol) (Note 6) is added in a single portion through the septum. After an induction time (Note 7), a white precipitate starts to form and an increase of the internal temperature, up to reflux, is observed (Note 8). The mixture is stirred for 3 hr, after which time starting material is completely consumed (Note 9). The reaction is quenched by the sequential addition of glycerol (60 mL) and saturated aqueous ammonium chloride (60 mL), then is transferred to a separatory funnel using 120 mL of diethyl ether. The aqueous layer is separated and extracted again with diethyl ether (3 × 60 mL). The combined ether extracts are washed with aqueous 30% ammonium hydroxide solution (3 × 30 mL) and then with saturated sodium chloride solution (2 × 30 mL). The organic extracts are dried over magnesium sulfate ($MgSO_4$) and concentrated at reduced pressure with a rotary evaporator to afford 37.32–38.92 g of crude β-hydroxy ester (93–97% yield) (Note 10).

B. *3,6-Dimethyl-3-hydroxy-6-heptenoic acid*. In a 500-mL flask, the crude ester prepared in Part A (37.00 g, 0.199 mol) is dissolved in a 2 N solution of potassium hydroxide (KOH) in methanol (130 mL, 0.260 mol). The solution is stirred at 25°C and disappearance of the starting material is monitored by GLC (Note 9). After 5 hr saponification is complete and the methanol is evaporated at reduced pressure (Note 11). The residue is taken up with water (500 mL), extracted with diethyl ether (3 × 100 mL), and the organic phase is discarded. The aqueous phase is acidified (pH 2.5 on universal pH indicator paper) with ~6 N hydrochloric acid (about 60 mL) and extracted with diethyl ether (5 × 100 mL). These latter ethereal extracts are washed with water (2 × 30 mL) and then with saturated sodium chloride (2 × 30 mL). The organic phase is dried over sodium sulfate, and filtered. Evaporation at reduced pressure

affords crude 3,6-dimethyl-3-hydroxy-6-heptenoic acid as a viscous yellow oil that can be used in Part C without further purification. Evacuation at 0.5 mm at room temperature with internal magnetic stirring for 24 hr gives 28.07–29.40 g (82–86% yield) of a solvent-free material (Note 12) and (Note 13).

C. *1,4-Dimethylbicyclo[3.2.0]hept-3-en-6-one*. A three-necked, 500-mL, round-bottomed flask, equipped with a condenser fitted with a calcium chloride tube, an efficient mechanical stirrer, and an immersion thermometer, is charged with crude 3,6-dimethyl-3-hydroxy-6-heptenoic acid (29.40 g, 0.171 mol), acetic anhydride (185 mL) (Note 14) and potassium acetate (40.28 g, 0.410 mol). The reaction mixture is stirred for 2 hr at room temperature. During this time, an exotherm is observed (up to 50°C) followed by a slow return to room temperature, and the suspension becomes thicker. The reaction is brought to reflux (in ca. 20 min) by means of a heating mantle and stirring is continued for another 3.5 hr. A two-necked, 2-L, round-bottomed flask fitted with a condenser and magnetic stirrer is charged with crushed ice (400 g) and water (100 g), and the hot mixture is added carefully with good stirring. Light petroleum ether (500 mL) is added and the mixture is stirred for 12 hr at room temperature. The reaction mixture is transferred into a 2-L separatory funnel and the aqueous layer is separated and extracted with light petroleum ether (4 × 100 mL). The combined organic layers are washed with saturated sodium bicarbonate solution (3 × 50 mL) and saturated sodium chloride solution (2 × 30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated at ambient pressure to give the crude product as a dark oil. Final purification is achieved by distillation under reduced pressure (Note 15) affording 17.70–18.86 g (76–81% yield) of a 99% pure mixture (97:3) of the keto olefin isomers as a colorless oil, bp 84–85°C/26–28 mm (Note 16).

2. Notes

1. This procedure is essentially that of Rathke and Lindert.[3]
2. The submitters used freshly distilled ketone prepared according to the *Organic Syntheses* procedure.[4] 5-Methyl-5-hexen-2-one is also available from Aldrich Chemical Company, Inc., and can be used as purchased.
3. Trimethyl borate was distilled from calcium hydride and stored under nitrogen.
4. Tetrahydrofuran (reagent grade) was dried by distillation from sodium/benzophenone ketyl and freshly distilled before use.
5. Zinc granules (20-mesh, 99.8%, A.C.S. reagent grade, Pb ≤ 0.01%, Fe ≤ 0.01%) obtained from Aldrich Chemical Company, Inc., were activated according to the procedure of Newman and Evans.[5] About 25 g of 20-mesh zinc was covered with 5% hydrochloric acid (30 mL) and stirred vigorously for 3 min. The zinc was washed by decantation with distilled water (3 × 30 mL), with acetone (2 × 20 mL), with diethyl ether (2 × 20 mL), and finally dried and stored in a vacuum desiccator.
6. Methyl bromoacetate was distilled and stored under nitrogen. Ethyl bromoacetate can also be used: in this case a mixture of ethyl and methyl esters is obtained.
7. Induction times from 15 to 45 min have been observed. In one instance, the reaction did not start even after 1.5 hr, and required the mixture to be heated to 60°C for several minutes until a white precipitate began to form. The checkers observed induction periods of 25–35 min.
8. On some occasions, the exotherm induced a vigorous reflux that was difficult to control. In such cases, stirring had to be stopped occasionally to control the reflux rate. Although the use of 20-mesh zinc granules reduces the possibility of hard-to-control exotherms, a cold water bath was kept ready to provide cooling if needed. The checkers did not observe an uncontrollable exotherm, but this type of reaction is well-known to be susceptible to such a problem. The checkers recommend that the mesh size not be reduced further without first testing the procedure on smaller scale. The checkers successfully performed this reaction at twice the reported scale without event and obtained the same yield (93%).
9. Progress of the reactions and analysis of the products was monitored by GLC using a Hewlett Packard 5890 Series II gas chromatograph equipped with an HP 3396 Series II Integrator and a Quadrex 007 Series bonded-phase fused silica capillary column (methyl 5% phenyl silicone; length 25 m; internal diameter 0.25 mm; film thickness 0.25 μm; carrier gas: nitrogen 75 kPa). Injector: 200°C; detector (FID): 250°C; Temperature program: 75°C (2 min); 15°/min, 250°C (3 min). Retention times (min): methyl bromoacetate, 2.24 (2.54); 5-methyl-5-hexen-2-one, 2.68 (2.94); 1,4-dimethylbicyclo [3.2.0]hept-3-en-6-one, 4.42 (4.77); 1-methyl-4-methylidenebicyclo[3.2.0]heptan-6-one, 4.73 (5.08); methyl 3,6-dimethyl-3-hydroxy-6-heptenoate, 7.05 (7.44). The checkers employed a similar column 30

m in length with the same stationary phase and observed the retention times shown above in parentheses.
10. The crude ester so obtained is greater than 97% pure by GLC analysis and is used in the next step without further purification. The checkers determined that the remainder of the material (~3%) is unreacted methyl bromoacetate. Spectral data for the crude ester are as follows: IR (neat) cm^{-1}: 3516, 2951, 1735, 1649, 1439, 1216; ^1H NMR (200 MHz, $CDCl_3$) δ: 1.22 (s, 3 H), 1.70 (m, 2 H), 1.75 (s, 3 H), 2.11 (m, 2 H), 2.48 (d, 1 H, J = 17.2), 2.54 (d, 1 H, J = 17.2), 3.52 (s, 1 H, disappears after D_2O exchange), 3.73 (s, 3 H), 4.70 (s, 2 H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ: 23.07 (CH_3), 27.04 (CH_3), 32.43 (CH_2), 40.33 (CH_2), 45.16 (CH_2), 52.12 (CH_3), 71.26 (C), 110.2 (CH_2), 146.2 (C), 173.8 (C).
11. The submitters employed a 1 N solution of KOH in methanol and observed the saponification to be complete in 24 hr. The checkers observed that the saponification required ~48 hr for completion under these conditions. The checkers employed a 2 N solution of KOH in methanol and observed that saponification was complete in 5 hr.
12. The submitters reported 87–92% yields of the acid. In the hands of the checkers, the yield of this reaction appears to be scale dependent. At one half the reported scale, the yield was reduced by 10–12%. This variation appears to result from losses during the isolation procedure. The acid has a very disagreeable butyric acid-like odor. The checkers recommend that all manipulations of this material be performed in a good hood, and that all apparatus employed be kept in the hood until base washed.
13. Spectral data for the crude acid are as follows: IR (neat) cm^{-1}: 3380, 2971, 1707, 1646, 1222, 888; ^1H NMR (200 MHz, $CDCl_3$) δ: 1.30 (s, 3 H), 1.67 (m, 2 H), 1.72 (s, 3 H), 2.10 (m, 2 H), 2.55 (d, 1 H, J = 17.1), 2.60 (d, 1 H, J = 17.1), 4.70 (s, 2 H), 6.61 [s (broad), 2 H]; ^{13}C NMR (50.3 MHz, $CDCl_3$) δ: 23.11 (CH_3), 26.33 (CH_3), 32.40 (CH_2), 40.18 (CH_2), 45.13 (CH_2), 71.84 (C), 110.5 (CH_2), 146.0 (C), 177.9 (C).
14. Acetic anhydride was distilled from anhydrous sodium acetate and stored under nitrogen.
15. To control foaming, the submitters recommend the use of a distillation flask larger than usual. In this instance, they used a 250-mL flask fitted with a Claisen adapter.
16. The product is about 99% pure by GLC analysis (Note 9), containing about 1% of an unknown impurity having a retention time of 8.01 min. The ratio of the olefin isomers, 1,4-dimethylbicyclo[3.2.0]hept-3-en-6-one and 1-methyl-4-methylenebicyclo-[3.2.0]heptan-6-one, was determined to be 97:3. Spectral data for the major isomer are as follows: IR (neat) cm^{-1}: 1770; ^1H NMR (200 MHz, $CDCl_3$) δ: 1.35 (s, 3 H), 1.73 (s, 3 H), 2.55 (m, 2 H), 2.87 (dd, 1 H, J = 17.8, 4.7), 3.03 (dd, 1 H, J = 17.8, 2.9), 3.58 (m, 1 H), 5.45 (m, 1 H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ: 15.34 (CH_3), 24.03 (CH_3), 35.35 (C), 47.08 (CH_2), 58.81 (CH_2), 79.94 (CH), 126.8 (CH), 135.2 (C), 207.9 (C).

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

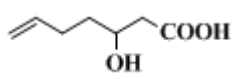
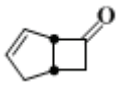
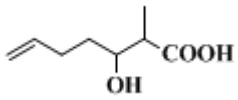
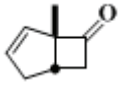
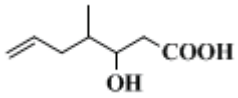
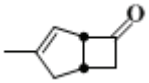
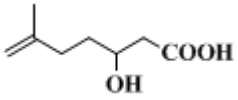
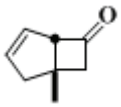
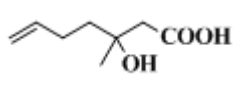
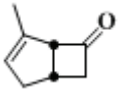
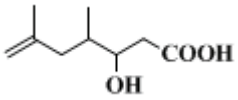
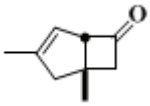
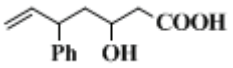
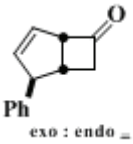
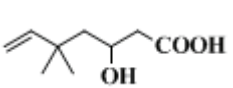
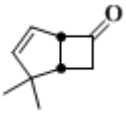
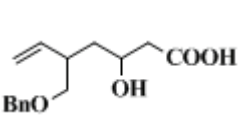
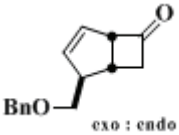
3. Discussion

Bicyclo[3.2.0]hept-3-en-6-ones are fused ring compounds that offer different functionalities in each ring, and have different ring size. They are suitable for chemo-, regio- and stereo-controlled manipulations and are useful for the assembly of more complex structures in a predictable fashion. The preparation reported here illustrates the simplicity of the procedure and the selectivity by which the thermodynamically more stable isomer can be prepared in high purity and good yield. Both yield and stereoselectivity are superior to those observed in the syntheses of 1,4-dimethylbicyclo[3.2.0]hept-3-en-6-one previously reported in the literature.[6,7] This process involves the generation of an α,β-unsaturated ketene intermediate that undergoes intramolecular [2+2] cyclization to give a bicyclo[3.2.0]hept-3-en-6-one. An equilibrium among the possible isomers of the α,β-unsaturated ketene intermediate could account for the good yield as well as the high selectivity in generating the thermodynamically more stable endo-ene isomer.[8]

This foregoing procedure is rather general as demonstrated by the preparation of a number of bicyclo[3.2.0]hept-3-en-6-ones by the bicyclization of a variety of secondary and tertiary 3-hydroxy-6-alkenoic acids (Table). The use of bicyclo[3.2.0]hept-3-en-6-ones as starting materials has been reported in the synthesis of racemic grandisol,[9] lineatin,[1,2,4] filifolone,[10] and several intermediates[5,11] in Curran's

synthesis of linear condensed sesquiterpenes such as hirsutene,[12,13] δ²-capnellene,[14] hypnophilin[15] and coriolin.[15] The successful use of these intermediates in the previously mentioned applications, and their unusual reactivity,[16] suggest the broad usefulness of the bicyclo[3.2.0]hept-3-en-6-ones made readily available by the present procedure. Some bicyclo[3.2.0]hept-3-en-6-ones have been obtained enantiomerically pure[17] by the oxidation of the enantiomers of bicyclo[3.2.0]hept-3-en-6-endo-ols, resolved using (−)-(1S,4R)-camphanic acid chloride.[18]

TABLE I
PREPARATION OF BICYCLO[3.2.0]HEPT-3-EN-6-ONES

Starting Material	Product	Yield (%)
		62
		63
		63
		78
		79
		55
	 exo : endo = 3:1	60
		48
	 exo : endo = 3:1	70

References and Notes

1. Dipartimento di Chimica Organica "A. Mangini" dell'Università di Bologna, Viale Risorgimento n.4, I-40136 Bologna, Italy.
2. ISAGRO Ricerca s.r.l. — Via Fauser n.4, I-28100 Novara, Italy.
3. Rathke, M. W.; Lindert, A. *J. Org. Chem.* **1970**, *35*, 3966–3967.
4. Boatman, S.; Hauser, C. R. *Org. Synth., Coll. Vol. V* **1973**, 767.
5. Newman, M. S.; Evans, F. J., Jr. *J. Am. Chem. Soc.* **1955**, *77*, 946–947.
6. Baeckström, P.; Li, L.; Polec, I.; Unelius, C. R.; Wimalasiri, W. R. *J. Org. Chem.* **1991**, *56*, 3358–3362.
7. Snider, B. B.; Ron, E.; Burbaum, B. W. *J. Org. Chem.* **1987**, *52*, 5413–5419.
8. Marotta, E.; Medici, M.; Righi, P.; Rosini, G. *J. Org. Chem.* **1994**, *59*, 7529–7531.
9. Confalonieri, G.; Marotta, E.; Rama, F.; Righi, P.; Rosini, G.; Serra, R.; Venturelli, F. *Tetrahedron* **1994**, *50*, 3235–3250.
10. Marotta, E.; Pagani, I.; Righi, P.; Rosini, G. *Tetrahedron* **1994**, *50*, 7645–7656.
11. Marotta, E.; Righi, P.; Rosini, G. *Tetrahedron Lett.* **1994**, *35*, 2949–2950.
12. Curran, D. P.; Rakiewicsz, D. M. *Tetrahedron* **1985**, *41*, 3943–3958.
13. Curran, D. P.; Rakiewicz, D. *J. Am. Chem. Soc.* **1985**, *107*, 1448–1449
14. Curran, D. P.; Chen, M.-H. *Tetrahedron Lett.* **1985**, *26*, 4991–4994.
15. Fevig, T. L.; Elliott, R. L.; Curran, D. P. *J. Am. Chem. Soc.* **1988**, *110*, 5064–5067.
16. Marotta, E.; Piombi, B.; Righi, P.; Rosini, G. *J. Org. Chem.* **1994**, *59*, 7526–7528.
17. Marotta, E.; Pagani, I.; Righi, P.; Rosini, G.; Bertolasi, V.; Medici, A. *Tetrahedron: Asymmetry* **1995**, *6*, 2319–2328.
18. Gerlach, H.; Kappes, D.; Boeckman, R. K., Jr.; Maw, B. N. *Org. Synth., Coll. Vol. IX* **1998**, 151.

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

petroleum ether

sodium/benzophenone ketyl

coriolin

grandisol

lineatin

filifolone

hirsutene

δ^2-capnellene

hypnophilin

(−)-(1S,4R)-camphanic acid chloride

hydrochloric acid (7647-01-0)

methanol (67-56-1)

ether,
diethyl ether (60-29-7)

acetic anhydride (108-24-7)

ammonium chloride (12125-02-9)

sodium acetate (127-09-3)

glycerol (56-81-5)

sodium bicarbonate (144-55-8)

sodium chloride (7647-14-5)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

acetone (67-64-1)

potassium hydroxide,
KOH (1310-58-3)

zinc (7440-66-6)

ammonium hydroxide (1336-21-6)

magnesium sulfate (7487-88-9)

potassium acetate (127-08-2)

Ethyl bromoacetate (105-36-2)

Tetrahydrofuran (109-99-9)

calcium hydride (7789-78-8)

5-Methyl-5-hexen-2-one (3240-09-3)

trimethyl borate (121-43-7)

methyl bromoacetate (96-32-2)

1,4-Dimethylbicyclo[3.2.0]hept-3-en-6-one (133700-21-7)

3,6-Dimethyl-3-hydroxy-6-heptenoic acid

1-methyl-4-methylidenebicyclo[3.2.0]heptan-6-one,
1-methyl-4-methylenebicyclo-[3.2.0]heptan-6-one

Methyl 3,6-dimethyl-3-hydroxy-6-heptenoate

Bicyclo[3.2.0]hept-3-en-6-one, 1,4-dimethyl-, cis-(±)-