



A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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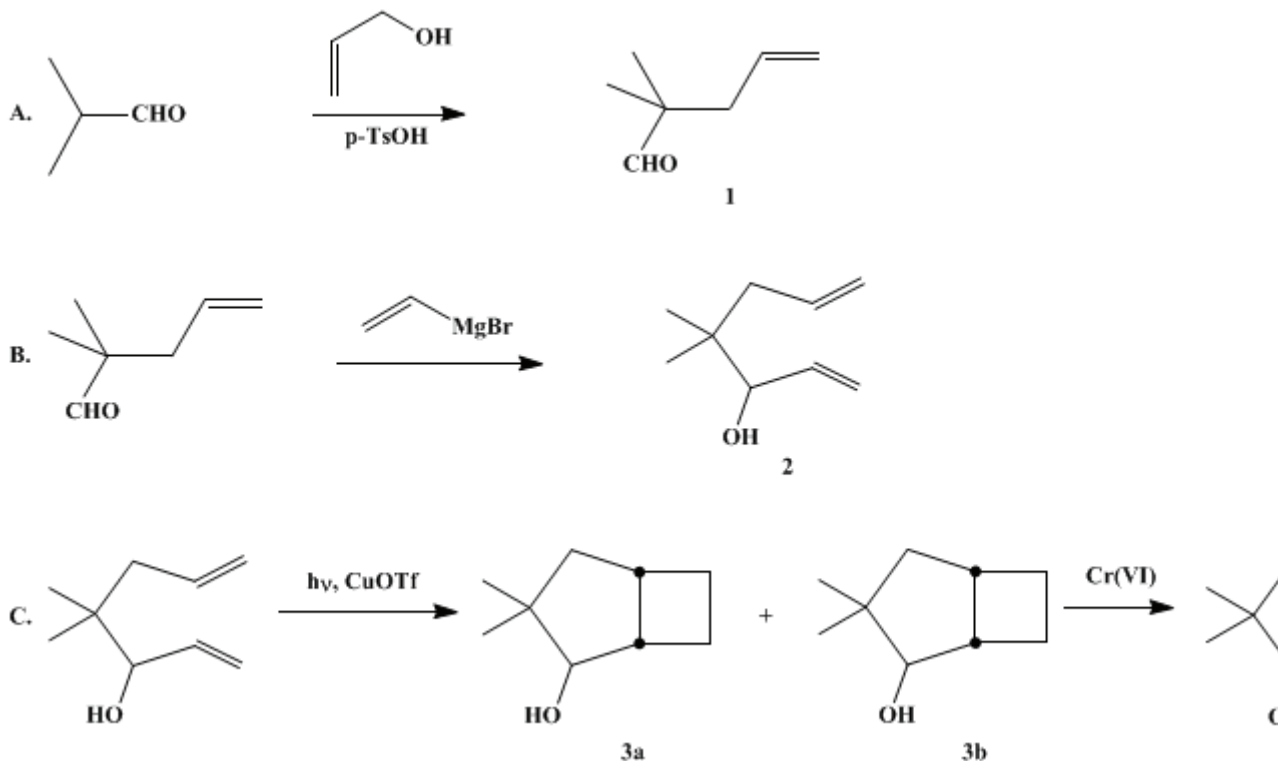
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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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COPPER(I)-CATALYZED PHOTOCYCLOADDITION: 3,3-DIMETHYL-*cis*-BICYCLO[3.2.0]HEPTAN-2-ONE

[Bicyclo[3.2.0]heptan-2-one, 3,3-dimethyl-]



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1. Procedure

A. *2,2-Dimethyl-4-pentenal*. In a 500-mL, one-necked, round-bottomed flask that contains a magnetic stirring bar are placed 108 g (1.5 mol) of *isobutyraldehyde* (Note 1), 58 g (1.0 mol) of *allyl alcohol* (Note 1), 230 mL of *p-cymene* (Note 1), and 0.4 g (2 mmol) of *p-toluenesulfonic acid monohydrate* (Note 1). The mixture is heated with a mantle with stirring for 32 hr under a 50-cm fractionating column packed with 6-mm glass beads and topped by a Dean-Stark trap. The reaction mixture is then distilled through the packed column. The fraction that boils at 120–126°C is collected. The yield is 86.0–87.3 g (77–78%) of *2,2-dimethyl-4-pentenal* (1) as a clear, colorless oil, n_D^{25} 1.4216 (Note 2).

B. *4,4-Dimethyl-1,6-heptadien-3-ol*. In a 1-L, three-necked, round-bottomed flask, fitted with mechanical stirrer, 500-mL pressure-equalizing addition funnel, and condenser topped with a gas inlet for maintaining an atmosphere of dry *nitrogen*, is placed 17 g (0.7 g-atom) of *magnesium turnings* (Note 3). The system is flushed with *nitrogen*, and *methanol* maintained at –20°C is circulated through the condenser (Note 4). From a solution of 70 g (0.65 mol) of *vinyl bromide* (Note 5) in 400 mL of *tetrahydrofuran* (Note 6), a 50-mL quantity is added by means of the addition funnel, and the resulting mixture is stirred mechanically. After a few minutes an exothermic reaction ensues, which subsides after several minutes of vigorous boiling (Note 7). The remainder of the *vinyl bromide* solution is added at such a rate as to maintain a gentle reflux. After stirring at room temperature for 12 hr, the resulting mixture is cooled with an ice–water bath, and 62 g (0.55 mol) of *2,2-dimethyl-4-pentenal* (1) is added dropwise over 25–30 min through the addition funnel, which is then rinsed with 10 mL of dry

tetrahydrofuran. The resulting mixture is stirred for 1 hr at 23°C and then poured into a mixture of 1 kg of ice, 200 mL of concentrated **hydrochloric acid**, and 400 mL of water. The resulting mixture is extracted with three 500-mL portions of **ether**. The combined extracts are washed successively with 400 mL of water, 400 mL of saturated aqueous **sodium bicarbonate**, and 400 mL of saturated aqueous **sodium chloride** and then dried over anhydrous **sodium sulfate**. The drying agent is removed by filtration and the **ether** is removed with a rotary evaporator. Distillation of the product through a 15-cm vacuum-jacketed Vigreux column gives 63.4–63.8 g (82–83% yield) of **4,4-dimethyl-1,6-heptadien-3-ol (2)**, bp 76–79°C (20 mm), n_D^{24} 1.4562 (Note 8).

C. **3,3-Dimethyl-cis-bicyclo[3.2.0]heptan-2-ol**. A 25-mL test tube is charged with 0.3–0.4 g (0.6–0.8 mmol) of bis(copper trifluoromethanesulfonate)benzene complex (Note 9) and sealed with a rubber septum under an atmosphere of dry **nitrogen**. A solution of 5 mL (4.3 g, 0.031 mol) of **4,4-dimethyl-1,6-heptadien-3-ol** in 10 mL of **ether** (Note 10) is added by means of a syringe. The resulting solution is poured (Note 11) into a nitrogen-flushed Pyrex 250-mL annular reactor fitted with a magnetic stirrer, an internal concentric water-jacketed quartz immersion well, and a water-cooled reflux condenser topped with a gas inlet for maintaining an atmosphere of dry **nitrogen**. An additional 20 mL (17.4 g, 0.124 mol) of the hydroxydiene **2** in 200 mL of dry **ether** is added. The resulting solution is stirred and irradiated for 15 hr with a 450-W medium-pressure Hanovia mercury arc (Note 12) that is suspended in the immersion well. At the end of that time an opaque film of **copper** is wiped from the immersion well, and irradiation is then continued for an additional 7 hr. The resulting solution is shaken in a separatory funnel with a mixture of 100 g of ice and 100 mL of concentrated aqueous **ammonium hydroxide**. The organic phase is separated and the aqueous phase is extracted with 100 mL of **ether**. The organic phases are combined and washed with 100 mL of saturated aqueous **sodium chloride** and dried over anhydrous **sodium sulfate**. The solvent is removed by distillation using a rotary evaporator and the product is distilled through a 15-cm vacuum-jacketed Vigreux column to give 19.0–19.9 g (88–92% yield) of **3,3-dimethyl-cis-bicyclo[3.2.0]heptan-2-ol (3)**, bp 80–84°C (12 mm), n_D^{25} 1.4761–1.4783 (Note 13).

D. **3,3-Dimethyl-cis-bicyclo[3.2.0]heptan-2-one**. In a 500-mL Erlenmeyer flask containing a magnetic stirring bar is placed 35.1 g (0.25 mol) of **3,3-dimethyl-cis-2-bicyclo[3.2.0]heptanol** and 200 mL of **acetone** (Note 14). The solution is cooled with an ice-water bath while 100 mL of 2.7 M Jones reagent (Note 15) is added in small portions over 15 min with vigorous stirring (Note 16). The ice-water bath is removed and the reaction mixture is stirred at 5–20°C for 2 hr. Then 400 mL of saturated aqueous **sodium chloride** is added, and the resulting mixture is extracted with three 500-mL portions of **ether**. The extractions are combined and washed successively with 400 mL of saturated aqueous **sodium chloride** and 200 mL of saturated aqueous **sodium bicarbonate**. The solvent is removed by means of a rotary evaporator, and the resulting product is transferred to a separatory funnel and separated from the water. The aqueous layer is extracted with 50 mL of **ether**. The product and the **ether** layer are combined and dried over anhydrous **sodium sulfate**. The **ether** is removed by distillation using a rotary evaporator and the product is distilled through a 15-cm vacuum-jacketed Vigreux column to give 28.7–32.2 g (83–93% yield) of **3,3-dimethyl-cis-bicyclo[3.2.0]heptan-2-one (4)**, bp 72–75°C (12 mm), n_D^{20} 1.4622 (Note 17).

2. Notes

1. **Isobutyraldehyde**, **allyl alcohol**, **p-cymene**, and **p-toluenesulfonic acid monohydrate** were purchased from Aldrich Chemical Company, Inc., and used as received.
2. The submitters state that the distilled product was about 97% pure as shown by GLC analysis on a 6.4-mm × 1.4-m column packed with 15% FFAP on Chromosorb W, 60–80 mesh, and operated at 140°C. The retention time is about 1.40 min. Two minor impurities with retention times of about 0.95 and 1.15 min were detected in roughly equal amounts. The product has the following spectral properties: IR (neat) cm^{-1} : 2965 (m), 2925 (m), 1725 (vs), 1465 (m), and 915 (m), together with numerous weaker absorption bands; $^1\text{H NMR}$ (CDCl_3) δ : 1.04 (s, 6 H), 2.22 (d, 2 H, $J = 7.0$), 4.9–5.3 (m, 2 H), 5.4–6.2 (m, 1 H), 9.40 (s, 1 H).
3. Reagent available from Fisher Scientific Company was used.
4. A Neslab ULT-80 refrigerated circulating bath was used. Alternatively, a Dewar condenser cooled with acetone–dry ice can be used.
5. **Vinyl bromide**, available from Aldrich Chemical Company, Inc., was used as received.

6. **Tetrahydrofuran**, anhydrous, 99.9% (water content <0.006%), was purchased from Aldrich Chemical Company, Inc., and used as received. The **vinyl bromide** solution was prepared in a 500-mL, round-bottomed flask fitted with a glass stopper. The stoppered flask containing the **tetrahydrofuran** was chilled to about 5°C and weighed. The **vinyl bromide**, also chilled to about 5°C, was rapidly poured into the **tetrahydrofuran** until the desired amount had been added. The flask was stoppered, the contents mixed by shaking, allowed to warm to about 16°C, and then added to the pressure-equalizing addition funnel.
7. The checkers found it necessary to initiate the reaction with a crystal of **iodine**.
8. The submitters state that the purity of the product is greater than 98% by gas chromatographic analysis on a 6.4-mm × 1.4-m column packed with 15% FFAP on Chromosorb W, 60–80 mesh, and operated at 140°C. The retention time is about 4.7 min. An impurity with a retention time of about 2.9 min was detected. The product has the following spectral properties: ¹H NMR (CDCl₃) δ: 0.84 (s, 3 H), 0.88, (s, 3 H), 1.80–2.30 (m, 2 H), 2.69 (s, 1 H), 3.78 (d, 1 H, *J* = 6), 4.87–5.33 (m, 4 H), 5.57–6.13 (m, 2 H).
9. The copper complex is available from Strem Chemicals, Inc., under the name "**cuprous triflate**" (benzene complex). The checkers recommend handling the material in a dry box because of its high sensitivity to moisture and air.
10. Anhydrous ether was distilled from **lithium aluminum hydride** under dry **nitrogen** immediately before use.
11. The submitters state that the **copper(I) triflate** is quite air-stable in solution in the presence of the allylic alcohol.
12. The checkers recommend the use of a relatively new arc lamp. Substantially higher conversions were obtained with a new lamp because of an apparent bathochromic shift in the frequency of the light emitted as the lamp ages, thus lessening the intensity of light in the important absorption region for the reaction.
13. The submitters state that the purity of the product is greater than 97% by GLC analysis on a 6.4-mm × 1.4-m column packed with 15% FFAP on Chromosorb W, 60–80 mesh, and operated at 140°C. The retention time is about 8.0 min. The only impurity is unreacted diene with a retention time of about 4.7 min. The product is an epimeric mixture. TLC analysis by the submitters on 0.25-mm silica gel with 20% **ethyl acetate** in **hexane** shows major (>90%) and minor (<10%) epimers with *R_f* 0.32 and 0.23, respectively. The epimers are separable by column chromatography on silica gel with **ethyl acetate–hexane** mixtures as eluting solvents. A 3.1-g portion of the distilled isomer mixture was chromatographed by the checkers on 475 g of silica gel (Silica Woelm TSC—activity III/30 mm) using 5% **ethyl acetate–hexane** as eluent. The elution proceeded as follows: 1520 mL, nil; 1440 mL, 2.7 g of endo isomer; 1400 mL, nil; 2010 mL, 0.20 g of exo isomer. Analysis of the ¹H NMR spectrum of the distilled product confirms that the reaction is greater than 90% stereoselective in favor of the endo epimer. The major epimer, **3,3-dimethyl-endo-cis-bicyclo[3.2.0]heptan-2-ol**, has the following spectral properties: ¹H NMR (CDCl₃) δ: 0.81 (s, 3 H), 1.13 (s, 3 H), 1.4–3.2 (m, 9 H), 3.66 (d, 1 H), *J* = 6.7; ¹³CMR (CDCl₃) δ: 16.3 (t), 22.5 (q, CH₃), 26.0 (t), 27.8 (q, CH₃), 36.0 (d), 42.8 (d), 45.5 (t), 45.8 (s, C-3), 80.9 (d, C-2). The minor epimer, **3,3-dimethyl-exo-cis-bicyclo[3.2.0]heptan-2-ol**, has the following spectral properties: ¹H NMR (CDCl₃) δ: 0.77 (s, 3 H), 1.08 (s, 3 H), 1.2–2.9 (m, 9 H), 3.80 (d, 1 H, *J* = 4.6); ¹³CMR (CDCl₃) δ: 20.7 (q, CH₃), 24.0 (t), 26.5 (q, CH₃), 27.1 (t), 34.6 (d), 45.6 (s, C-3), 45.8 (d), 46.7 (t), 88.7 (d, C-2).
14. Certified ACS-grade **acetone** purchased from Fisher Scientific Company was used as received.
15. Eisenbraun, E. J. *Org. Synth., Coll. Vol. V* **1973**, 310–314.
16. Initially a gummy green precipitate is formed that is difficult to stir magnetically. Eventually, however, the inorganic by-products become more fluid. The use of a mechanical stirrer may be desirable.
17. The submitters state that the distilled product is <98% pure by GLC on a 6.4-mm × 1.4-m column packed with 15% FFAP on Chromosorb W, 60–80 mesh, operated at 140°C. The relative retention time is 2.3 versus an unidentified impurity at 1.0. The distilled product has the following spectral properties: IR (neat) cm⁻¹: 2960 (vs), 2940 (vs) and 1735 (vs), and other weaker bands. ¹H NMR (CCl₄) δ: 0.92 (s, 3 H), 1.12 (s, 3 H), 1.4–3.0 (m, 8 H); ¹³CMR (CDCl₃) δ: 22.7, 24.1, 25.6, 26.4, 31.0, 43.9, 44.2, 48.4, 224.7.

3. Discussion

This procedure illustrates a general method for the preparation of 2-hydroxybicyclo[3.2.0]heptanes by copper(I)-catalyzed photobicyclization of 3-hydroxy-1,6-heptadienes² and a general route to the requisite dienes from allyl alcohols by conversion to 4-pentenal and treatment of the latter with vinyl Grignard reagents.

Compound **1**, [2,2-dimethyl-4-pental](#), has been prepared by the Claisen rearrangement route³ described above and by reaction of [isobutyraldehyde](#) with [allyl chloride](#) in the presence of aqueous [sodium hydroxide](#) and a phase-transfer catalyst.⁴ Both routes are applicable to the synthesis of a variety of substituted 4-pententials.

cis-Bicyclo[3.2.0]heptan-2-ols have been prepared by reduction⁵ of the corresponding *cis*-bicyclo[3.2.0]-heptan-2-ones, which have been prepared by photocycloaddition of alkenes with 2-cyclopentenones.⁶ The synthetic strategy of the present procedure is complementary.

This preparation is referenced from:

- [Org. Syn. Coll. Vol. 8, 208](#)

References and Notes

1. Department of Chemistry, Case Western Reserve University, Cleveland, OH 44106.
2. Salomon, R. G.; Coughlin, D. J.; Easler, E. M. *J. Am. Chem. Soc.* **1979**, *101*, 3961–3963.
3. Brannock, K. C. *J. Am. Chem. Soc.* **1959**, *81*, 3379–3383.
4. Dietl, H. K.; Brannock, K. C. *Tetrahedron Lett.* **1973**, 1273–1275.
5. Svensson, T. *Chem. Scr.* **1973**, *3*, 171–175.
6. For reviews, see the following: Eaton, P. E. *Acc. Chem. Res.* **1968**, *1*, 50–57; Bauslaugh, P. G. *Synthesis* **1970**, 287–300; de Mayo, P. *Acc. Chem. Res.* **1971**, *4*, 41–47.

Appendix

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

bis(copper trifluoromethanesulfonate)benzene complex

2-hydroxybicyclo[3.2.0]heptanes

3-hydroxy-1,6-heptadienes

allyl alcohols

cis-Bicyclo[3.2.0]heptan-2-ols

cis-bicyclo[3.2.0]-heptan-2-ones

2-cyclopentenones

[hydrochloric acid](#) (7647-01-0)

[ethyl acetate](#) (141-78-6)

methanol (67-56-1)

ether (60-29-7)

sodium hydroxide (1310-73-2)

sodium bicarbonate (144-55-8)

magnesium turnings (7439-95-4)

sodium chloride (7647-14-5)

ethyl (2025-56-1)

Allyl alcohol (107-18-6)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

allyl chloride (107-05-1)

copper (7440-50-8)

iodine (7553-56-2)

acetone (67-64-1)

ammonium hydroxide (1336-21-6)

vinyl bromide (593-60-2)

p-cymene (99-87-6)

isobutyraldehyde (78-84-2)

Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

hexane (110-54-3)

²⁴_D (94-75-7)

copper(I) triflate,
cuprous triflate

Bicyclo[3.2.0]heptan-2-one, 3,3-dimethyl- (71221-70-0)

2,2-Dimethyl-4-pentenal (5497-67-6)

4,4-Dimethyl-1,6-heptadien-3-ol (58144-16-4)

p-toluenesulfonic acid monohydrate (6192-52-5)

3,3-Dimethyl-cis-bicyclo[3.2.0]heptan-2-one

3,3-Dimethyl-cis-bicyclo[3.2.0]heptan-2-ol,
3,3-dimethyl-cis-2-bicyclo[3.2.0]heptanol,
3,3-dimethyl-endo-cis-bicyclo[3.2.0]heptan-2-ol,
3,3-dimethyl-exo-cis-bicyclo[3.2.0]heptan-2-ol (71221-67-5)