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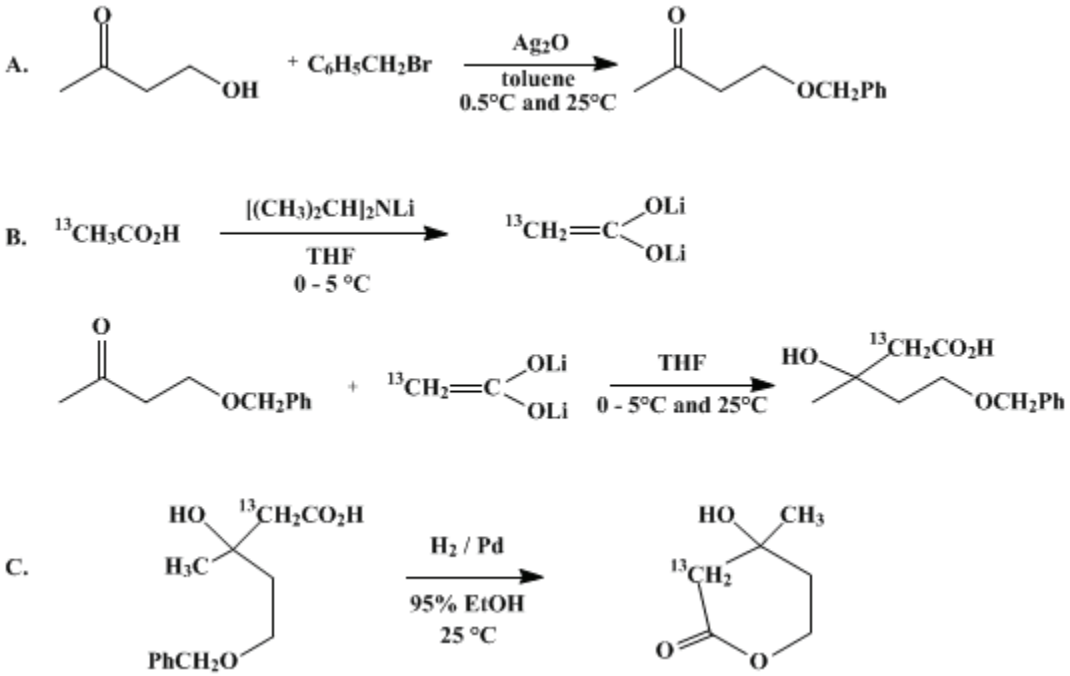
(*R,S*)-MEVALONOLACTONE-2-^{13}C

[2*H*-Pyran-2-one-^{13}C, tetrahydro-4-hydroxy-4-methyl-]



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Checked by Paula M. Roach, Sung W. Rhee, and Robert M. Coates.

1. Procedure

Benzyl bromide is a lachrymator. This procedure should be conducted in a ventilated hood.

A. *4-Benzyloxy-2-butanone*. A 100-mL, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, a condenser mounted with a nitrogen inlet, and a pressure-equalizing dropping funnel (Note 1). The flask is charged with 4.40 g (0.050 mol) of 4-hydroxy-2-butanone (Note 2), 50 mL of dry toluene (Note 3), and 13.9 g (0.060 mol) of freshly prepared silver oxide (Note 4). The suspension is stirred and cooled in an ice bath while 12.0 g (0.070 mol) of benzyl bromide (Note 5) is added over ca. 5 min. The ice bath is removed, and the mixture is allowed to stir for 18 hr at room temperature (Note 6). The suspension is filtered through Celite, the filter cake is washed with two 50-mL portions of toluene, and the combined filtrates are evaporated under reduced pressure. The remaining liquid, which weighs 9.6–10.4 g, is dissolved in 15 mL of 5% tetrahydrofuran in hexane. The cloudy solution is applied to a 5-cm × 47.5-cm column prepared with 380–385 g of silica gel (Note 7) packed in 5% tetrahydrofuran in hexane. The column is eluted with 5% tetrahydrofuran in hexane, and 250-mL fractions are collected and analyzed by TLC (Note 8). A total of 12 or 13 fractions (3–3.25 L) is collected first to separate benzyl bromide, dibenzyl ether, and other minor by-products. The product is then eluted with 0.5–1.0 L of tetrahydrofuran, the solvent is evaporated, and the remaining 6.0–6.5 g of liquid is distilled under reduced pressure. After separation of a 0.7–1.0 g forerun, bp 30–68°C (0.2 mm), consisting mainly of benzyl alcohol, 3.87–4.33 g (43–49%) of 4-benzyloxy-2-butanone, bp 77–79°C (0.2 mm), n_D^{25} 1.5018 is collected (Note 9).

B. *5-Benzyloxy-3-hydroxy-3-methylpentanoic-2-^{13}C acid*. A 50-mL, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, a rubber septum, a condenser connected to a nitrogen inlet, and a pressure-equalizing dropping funnel. The apparatus is purged with nitrogen and dried (Note

1), and the flask is charged with 1.79 g (2.4 mL, 0.0177 mol) of freshly distilled diisopropylamine and 6.5 mL of dry tetrahydrofuran (Note 10). The solution is stirred and cooled in an ice bath while 7.22 mL (0.0169 mol) of 2.34 *M* butyllithium in hexane (Note 11) is added from the dropping funnel over 30 min. After 30 min a solution of 0.439 g (0.00720 mol) of acetic acid-2-^{13}C (Note 12) in 3 mL of tetrahydrofuran is added by syringe over ca. 10 min. The solution is stirred and cooled in an ice bath for 3.5 hr, after which 1.30 g (0.0073 mol) of 4-benzyloxy-2-butanone in 4 mL of tetrahydrofuran is added by syringe over 15 min. Stirring is continued for 2 hr at 0°C and 18 hr at room temperature. The reaction mixture is cooled in an ice bath, hydrolyzed by adding 4.5 mL of water, and concentrated under reduced pressure to remove most of the tetrahydrofuran. The remaining aqueous suspension is basified by addition of 6 mL of aqueous 4% sodium hydroxide and extracted with 30 mL of diethyl ether. The ethereal layer is extracted with 40 mL of 4% sodium hydroxide, the combined alkaline extracts are cooled and acidified to pH 3 with ca. 10 mL of 18% hydrochloric acid, and the aqueous mixture is extracted with three 25-mL portions of ether. The combined ethereal extracts are dried over anhydrous sodium sulfate and evaporated. The remaining viscous, yellow liquid weighs 0.95–1.01 g (55–59%) and is used in part C without further purification (Note 13).

C. *Mevalonolactone-2-^{13}C*. In a 250-mL Parr hydrogenation bottle are placed 50 mL of 95% ethanol, 0.107 g (0.001 mol) of palladium black (Note 14), and 0.519 g (0.00217 mol) of 5-benzyloxy-3-hydroxy-3-methylpentanoic acid-2-^{13}C. The bottle is attached to a Parr hydrogenation apparatus (Note 15), charged to 50 psig with hydrogen and shaken at room temperature for 2 hr. The hydrogen is flushed from the bottle with nitrogen, and the suspension is filtered by gravity through a layer of Celite with a medium-porosity sintered-glass Büchner funnel to separate the catalyst. *The palladium is pyrophoric and must always be kept wet with ethanol during filtration to prevent contact with air* (Note 16). The bed of Celite and adhering catalyst is rinsed with three 5-mL portions of ethanol. The combined filtrates are returned to the Parr bottle, 0.107 g (0.001 mol) of fresh palladium black is added, and the hydrogenation is continued for another 8 hr. The catalyst is separated by filtration as previously described, and the combined filtrates are evaporated under reduced pressure. Distillation of the residual liquid with a Kugelrohr apparatus at 90–100°C and 0.01 mm affords 0.235–0.249 g (83–88%) of mevalonolactone-2-^{13}C as a slightly yellow oil (Note 17).

2. Notes

1. The apparatus was dried in an oven at 125°C and allowed to cool while a stream of nitrogen was passed through the condenser and out the dropping funnel. Alternatively the apparatus may be flushed with nitrogen and flamed dry. A nitrogen atmosphere was maintained within the apparatus during the subsequent operations.
2. 4-Hydroxy-2-butanone was purchased from Chemical Samples Company by the checkers and distilled, bp 56–58°C (5.0 mm). The submitters obtained the material from BASF Wyandotte Corporation, Parsippany, NJ 07054.
3. Toluene was dried over sodium wire for 36 hr.
4. The silver oxide was prepared by the following procedure. A solution of 6.9 g (0.172 mol) of sodium hydroxide in 200 mL of water was heated to 80–90°C and added to a solution of 30 g (0.177 mol) of silver nitrate in 200 mL of water, also heated to 80–90°C. The resulting hot suspension was quickly filtered, and the filter cake was washed with 200 mL of hot water, 200 mL of 95% ethanol, and 200 mL of absolute ethanol. The silver oxide was dried at 1 mm and weighed 17.8–18.3 g (87–89%).
5. Benzyl bromide was distilled before use, bp 89°C (14 mm).
6. The reaction is mildly exothermic, and the mixture becomes warm after the ice bath is removed. The checkers monitored the progress of the reaction by TLC on silica gel with 5% methanol in chloroform as developing solvent. After 2 hr the spot at R_f 0.42 for the starting alcohol has disappeared, and the formation of the spots at R_f 0.70 and 0.47 for the product and benzyl alcohol, respectively, appeared to be complete.
7. The checkers used silica gel 60 having particle sizes from 0.05 to 0.2 mm (70–270-mesh ASTM), supplied by Brinkmann Instruments, Inc., Westbury, NY. The submitters used 450 g of silica gel with 90–200 mesh purchased from Gallard-Schlesinger Chemical Manufacturing Corp., Carle Place, NY 11514.
8. Thin-layer chromatograms were performed by the checkers on plates coated with silica gel using chloroform as developing solvent. The R_f values for benzyl bromide, dibenzyl ether, 4-benzyloxy-2-

butanone, and benzyl alcohol were 0.72, 0.61, 0.20, and 0.09, respectively. Chromatograms of the crude product showed spots for these four components and in addition three minor spots at R_f 0.44, 0.40, and 0.36. The first six fractions (1.5 L) were combined and evaporated, affording 0.6–1.5 g of material judged to be mainly benzyl bromide. The following six or seven fractions (1.5–1.75 L) provided 1.6–3.2 g of material composed largely of dibenzyl ether.

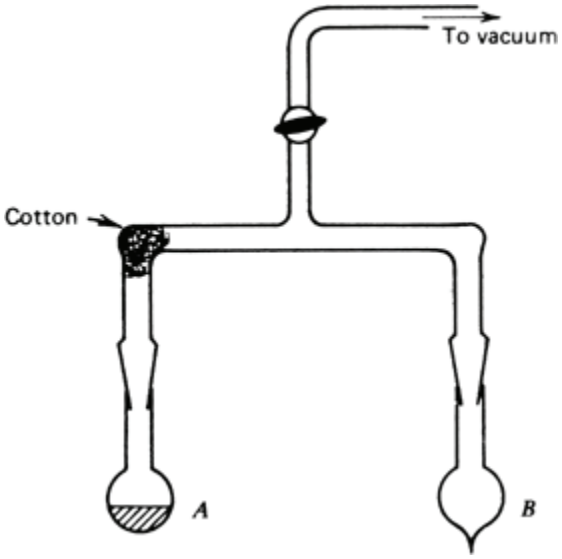
9. The submitters obtained 4.5 g (51%) of product, bp 95°C (0.8 mm), n_D^{27} 1.5029. A boiling point of 88–91°C (0.5 mm) and a refractive index of n_D^{28} 1.5040 are reported for 4-benzyloxy-2-butanone.[2] The product was analyzed by the checkers. Anal. calcd. for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 73.87; H, 8.09. The product has the following spectral characteristics: IR (liquid film) cm^{-1}: 1725 and 1710 (split C=O), 1360, 1175, 1110, 1090, 740, 700; ^1H NMR ($CDCl_3$) δ: 2.17 (singlet, 3, CH_3), 2.70 (triplet, 2, J = 6, CH_2CH_2O), 3.78 (triplet, 2, J = 6, CH_2CH_2O), 4.50 (singlet, 2, $CH_2C_6H_5$), 7.32 (singlet, 5, C_6H_5).

10. Diisopropylamine was dried over potassium hydroxide pellets and distilled from barium oxide before use. The submitters purified tetrahydrofuran by distillation from lithium aluminum hydride. For a warning concerning the potential hazards of this procedure, see *Org. Synth., Coll. Vol. V*, **1973**, 976. The checkers distilled the solvent from the sodium ketyl of benzophenone.

11. Butyllithium in hexane is available from Alfa Products, Morton Thiokol, Inc. The submitters standardized the butyllithium solution by titration of diphenylacetic acid in tetrahydrofuran.[3] The concentration of the butyllithium solution was determined by the checkers by titration of a 1-mL aliquot in 10 mL of benzene with 1 *M* 2-butanol in xylene using 1,10-phenanthroline as indicator.[4]

12. Acetic acid-2-^{13}C of 90% isotopic purity was purchased by the checkers from Stohler Isotope Chemicals, Rutherford, NJ, and dried by distillation from phosphorus pentoxide in the following manner. A 0.5-g portion of the labeled acetic acid was transferred to a 5-mL flask containing 0.1 g of phosphorus pentoxide. The flask (A) was attached to a vacuum system (see Figure 1), chilled with a dry ice-acetone bath until the mixture solidified, and evacuated to 0.01 mm. The stopcock was closed, the cooling bath was moved to the receiver (flask B), and flask A was allowed to warm to room temperature. The distillation was completed by heating flask A to 60°C. Nitrogen was introduced into the system and flask B removed and stoppered. The recovery of acetic acid-2-^{13}C was 0.42–0.44 g (84–86%).

Figure 1



13. The submitters carried out the procedure in Section B at five times the scale described with 1.96 g (0.0321 mol) of acetic acid-2-^{13}C and obtained 4.01 g (56%) of product. The spectral properties of the product are as follows: IR (liquid film) cm^{-1}: 1710 (C=O); ^1H NMR ($CDCl_3$) δ: 1.31 (doublet, ca. 2.4, J = 4.5, $^{13}CH_2CCH_3$), 1.31 (singlet, ca. 0.6, $^{12}CH_2CCH_3$), 1.89 (multiplet, 2, CH_2CH_2O), 2.55 (doublet, ca. 1.6, J = 128, $^{13}CH_2CO_2H$), 2.55 (singlet, ca. 0.4, $^{12}CH_2CO_2H$), 3.70 (triplet, 2, J = 6, CH_2CH_2O), 4.52 (singlet, 2, $C_6H_5CH_2$), 7.35 (singlet, 5, C_6H_5). The product may be purified further by Kugelrohr distillation with an oven temperature of 100–110°C (0.015 mm).

14. The palladium black was purchased from Engelhard Industries Division, Engelhard Minerals and

Chemicals Corporation, Iselin, NJ 08830. The checkers found that the hydrogenolysis may also be effected with 5% palladium on carbon, although 20 hr was required to achieve complete reaction.
15. The hydrogenation apparatus is available from Parr Instrument Company, Inc., Moline, IL 61265.
16. As a further precaution the checkers chilled the suspension in an ice bath prior to filtration.
17. The product was further purified by the checkers by recrystallization from ca. 1.5 mL of ether at 0° C. The recovery of white, crystalline mevalonolactone-2-^{13}C, mp 24–26°C, was 90–92%. The reported[2] melting point is 27–28°C. The spectral properties of the product are as follows: IR (liquid film) cm^{-1}: 3300 (OH), 1730 (C=O); 220–MHz ^{1}H NMR ($CDCl_3$) δ: 1.40 (doublet, ca. 2.4, J = 4.5, $^{13}CH_2CCH_3$), 1.40 (singlet, ca. 0.6, $^{12}CH_2CCH_3$), 1.90 (multiplet, 2, CH_2CH_2O), 2.54 and 2.67 (eight-line *ABX* multiplet, ca. 1.6, J_{AB} = 17, J_{AX} = 132, J_{BX} = 127, $^{13}CH_AH_B$), 2.54 and 2.67 (*AB* doublet, 0.4, J = 17, $^{12}CH_AH_B$), 4.47 (multiplet, 2, CH_2CH_2O).

3. Discussion

The important role of mevalonate is the biosynthesis of terpenes and sterols has been the impetus for the development of numerous syntheses of the parent mevalonolactone[5,6,7,8,9,10,11] and a host of labeled analogs.[7,8,9,10,11] Mevalonolactone has been prepared by reduction of dimethyl or diethyl 3-hydroxy-3-methylglutarate in two stages with lithium aluminum hydride and hydrogen[12] or sodium borohydride[13 14]; by reduction of monomethyl 3-hydroxy-3-methylglutarate with lithium borohydride[15,16] or sodium in liquid ammonia[16]; by reduction of mevaldic acid or its esters with borohydride,[13,17 18,19] hydrogen,[18] or NADPH in enzyme preparations[20 21 22]; by reduction of *N*-(diphenylmethyl)-3,4-epoxy-5-hydroxy-3-methylpentanamide with lithium borohydride followed by hydrolysis;[23] by oxidation of 3,5-dihydroxy-3-methylpentanal and its derivatives with hydrogen peroxide in acetic acid,[24 25] or formic acid,[8] or with aqueous bromine;[26] by oxidation of 3-methyl-1,3,5-pentanetriol with chromium trioxide[27] or silver carbonate;[28] by ozonolysis of 3-methyl-1-tetrahydropyranyloxy-5-hexen-3-ol;[6,29] by hydrolysis of 3,5-dihydroxy-3-methylpentanenitrile;[30] by degradation of linalool;[31] and by Reformatsky reactions of acetate with a variety of 4-substituted 2-butanones.

The Reformatsky reactions of methyl or ethyl bromoacetate with 4-acetoxy-,[2,32 33] 4-benzyloxy-,[2] 4-tetrahydropyranyloxy-,[2] 4-chloro-,[6] and 4,4-dimethoxy-2-butanone[17,18,24,25] have been carried out. The adducts were converted to mevalonolactone by hydrolysis and, in the case of the acetal reactant, by appropriate reduction and oxidation procedures. The same Reformatsky-type syntheses of mevalonolactone have also been performed using the lithium and magnesium carbanions of acetate esters[5,26,34,35] and the dianion of acetic acid[35,36] instead of the usual zinc reagent. The intramolecular Reformatsky reaction of 4-(bromoacetoxy)-2-butanone gives mevalonolactone directly.[37] A related route to mevalonolactone involves boron trifluoride-catalyzed cycloaddition of ketene to 4-acetoxy-2-butanone followed by hydrolysis.[24]

Many of the procedures given above have been utilized for the preparation of mevalonolactone labeled with isotopes of carbon, hydrogen, and oxygen.[7,8,9,10,11] Mevalonolactone-^{14}C has been prepared with the label at all six positions: 1-,[7,38] 2-,[7,17,32,33] 3-,[14] 3'-,[27,39] 4-,[7,24] and 5-^{14}C.[26] Preparations of singly and doubly labeled mevalonolactone-^{13}C have been reported recently: 2-,[35,40] 3-,[41] 4-,[42 43] 3',4-,[7,24] 3,4-,[35,43] and 4,5-^{13}C.[44] The procedure described here[35] for the preparation of mevalonolactone-2-^{13}C is both convenient and economical compared to the usual Reformatsky methods since acetic acid-2-^{13}C is utilized directly in the condensation reaction, rather than methyl or ethyl bromoacetate. The overall yield of mevalonolactone-2-^{13}C is 46–52% based on acetic acid-2-^{13}C.

References and Notes

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

silica gel

palladium black

sodium ketyl of benzophenone

dimethyl or diethyl 3-hydroxy-3-methylglutarate

methyl or ethyl bromoacetate

2H-Pyran-2-one-^{13}C, tetrahydro-4-hydroxy-4-methyl-

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ammonia (7664-41-7)

Benzene (71-43-2)

methanol (67-56-1)

ether,
diethyl ether (60-29-7)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

silver oxide (20667-12-3)

silver nitrate (7761-88-8)

bromine (7726-95-6)

sodium sulfate (7757-82-6)

oxygen (7782-44-7)

formic acid (64-18-6)

barium oxide

nitrogen (7727-37-9)

carbon (7782-42-5)

potassium hydroxide pellets (1310-58-3)

toluene (108-88-3)

zinc (7440-66-6)

sodium,
sodium wire (13966-32-0)

palladium (7440-05-3)

Benzyl alcohol (100-51-6)

Dibenzyl ether (103-50-4)

hydrogen peroxide (7722-84-1)

xylene (106-42-3)

Diphenylacetic acid (117-34-0)

chromium trioxide (1333-82-0)

boron trifluoride (7637-07-2)

benzyl bromide (100-39-0)

butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

4-hydroxy-2-butanone (590-90-9)

silver carbonate (534-16-7)

hexane (110-54-3)

4,4-dimethoxy-2-butanone (5436-21-5)

sodium borohydride (16940-66-2)

2-Butanol (78-92-2)

1,10-phenanthroline (66-71-7)

diisopropylamine (108-18-9)

Linalool (78-70-6)

phosphorus pentoxide (1314-56-3)

4-Benzyloxy-2-butanone (6278-91-7)

mevalonolactone

monomethyl 3-hydroxy-3-methylglutarate

lithium borohydride (16949-15-8)

3,5-dihydroxy-3-methylpentanal

3-methyl-1,3,5-pentanetriol (7564-64-9)

3-methyl-1-tetrahydropyranyloxy-5-hexen-3-ol

3,5-dihydroxy-3-methylpentanenitrile

4-(bromoacetoxy)-2-butanone

4-acetoxy-2-butanone (10150-87-5)

N-(diphenylmethyl)-3,4-epoxy-5-hydroxy-3-methylpentanamide

5-Benzyloxy-3-hydroxy-3-methylpentanoic-2-^{13}C acid,
5-benzyloxy-3-hydroxy-3-methylpentanoic acid-2-^{13}C (57830-65-6)

acetic acid-2-^{13}C

Mevalonolactone-2-^{13}C

Mevalonolactone-^{14}C

(R,S)-Mevalonolactone-2-^{13}C