Organic Syntheses

A Publication
of Reliable Methods
for the Preparation
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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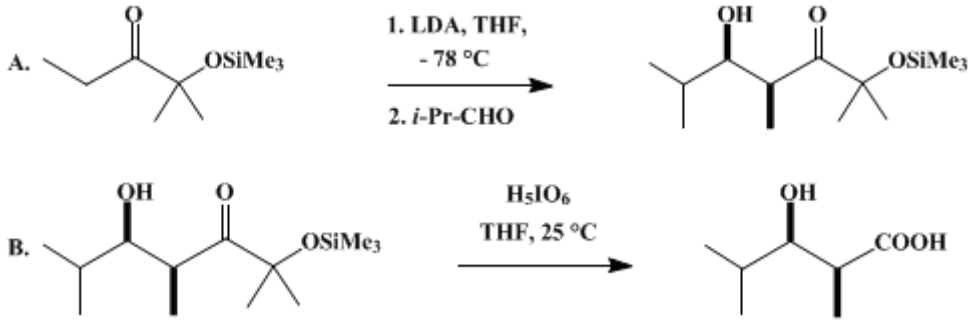
Organic Syntheses, Coll. Vol. 7, p.185 (1990); Vol. 63, p.89 (1985).

(2*SR*,3*RS*)-2,4-DIMETHYL-3-HYDROXYPENTANOIC ACID

[Pentanoic acid, 3-hydroxy-2,4-dimethyl-, (*R**,*S**)-(±)-]



Submitted by B. Bal, C. T. Buse, K. Smith, and Clayton H. Heathcock[1].
Checked by Joseph R. Flisak, Stan S. Hall, Hugh W. Thompson, and Gabriel Saucy.

1. Procedure

A. *5-Hydroxy-2,4,6-trimethyl-2-(trimethylsiloxy)heptan-3-one*. A dry, 1-L, four-necked (including a thermometer well), round-bottomed flask equipped with an efficient mechanical stirrer, thermometer, graduated 250-mL pressure-equalizing addition funnel sealed with a rubber septum, and a nitrogen inlet is charged with 125 mL of dry tetrahydrofuran (Note 1) and 31 mL (0.22 mol) of diisopropylamine (Note 2). The stirrer is started and 137 mL (0.20 mol) of 1.5 *M* butyllithium in hexane is transferred to the addition funnel by means of a 16-gauge cannula and argon pressure (Note 3). The reaction flask and its contents are cooled to below −5°C by immersion in a dry ice–acetone bath that is maintained at −10 to −15°C by the occasional addition of dry ice. The butyllithium is added dropwise over a period of 20 min. After the addition is complete 10 mL of dry tetrahydrofuran is added to the addition funnel with a syringe to rinse the walls of the funnel, and the rinse is then added to the pale-yellow solution. After the addition is complete, the solution is stirred for an additional 15 min and is then cooled to below −70°C (dry ice–acetone bath). While the reaction solution is cooling, a solution of 37.7 g (0.20 mol) of 2-methyl-2-(trimethylsiloxy)pentan-3-one (Note 4) in 10 mL of dry tetrahydrofuran is introduced through the septum into the addition funnel. When the lithium diisopropylamide (LDA) solution has cooled to below −70°C, the ketone is slowly added to the solution over a period of 20–25 min to ensure that the reaction temperature is maintained below −70°C. After the addition is complete 10 mL of dry tetrahydrofuran is added to rinse the walls of the addition funnel, the rinse is added, and the stirred reaction solution is maintained below −70°C for an additional 30–40 min. During this time the addition funnel is charged through the septum with a solution of 14.4 g (0.20 mol) of 2-methylpropanal (Note 5) in 10 mL of dry tetrahydrofuran. The aldehyde solution is added dropwise to the vigorously stirring yellow enolate solution at −70°C over a 15-min period, and then the addition funnel is again rinsed with 10 mL of dry tetrahydrofuran and the rinse added to the reaction mixture. After 10–15 min 200 mL of a saturated aqueous ammonium chloride solution is added to the vigorously stirring, −70°C reaction mixture. At this point stirring is discontinued, the cooling bath is removed, and the partially frozen mixture is allowed to warm to room temperature. The contents of the reaction flask are introduced into a 2-L separatory funnel, 200 mL of ether is added to the flask, and the ether rinse is then transferred to the separatory funnel. The layers are shaken and then separated, and the aqueous phase is extracted again with 200 mL of ether. The combined organic phase is washed with 200 mL of water and 200 mL of saturated brine and then dried over magnesium sulfate. After removal of the drying agent by filtration the solvents are removed with a rotary evaporator at aspirator pressure to give 52.1–52.4 g of a pale-yellow oil that is a 63 : 37 mixture of the expected product and the starting material. Most of the starting material is then selectively removed by stirring (magnetic stirring bar) at 25°C at reduced pressure (vacuum pump, 0.1–0.08 mm) for 19 hr to yield 35.2 g of a 90 : 10 mixture (31.7 g, 61%), which is used without further purification for Step B (Note 6) and (Note 7).

B. *(2SR,3RS)-2,4-Dimethyl-3-hydroxypentanoic acid*. A dry, 500-mL, three-necked, round-bottomed flask equipped with a mechanical stirrer, thermometer, and a nitrogen inlet is flushed with nitrogen, charged with 12.5 g (55 mmol) of periodic acid (Note 8) and 150 mL of dry tetrahydrofuran (Note 1), and then sealed with a stoppered, 25-mL, pressure-equalizing addition funnel. The solution is stirred vigorously and cooled to 0–5°C with an ice–salt bath. During this time the addition funnel is charged with a solution of 12.0 g of 5-hydroxy-2,4,6-trimethyl-2-(trimethylsiloxy)heptan-3-one (10.8 g, 41 mmol of ketone from a 90 : 10 mixture from Part A) in 10 mL of dry tetrahydrofuran, which is then rapidly introduced (1 min) to the cold, stirring solution. After the addition is complete 5 mL of dry tetrahydrofuran is added to the addition funnel to rinse the walls of the funnel, and the rinse is then added to the reaction solution. The cooling bath is removed after 15 min and stirring is continued for 1.5 hr, during which time a white precipitate forms. In the meantime, 52 g (0.5 mol) of sodium bisulfite is mixed with 100 mL of distilled water in a 500-mL filtering flask with a side hose connection and cooled to 0–5°C with an ice–salt bath. The reaction mixture is filtered directly through filter paper with suction into the cold slurry of sodium bisulfite. The residue is rinsed with 50 mL of dry ether (Note 9), which is added to the filter funnel and drawn by suction into the yellow solution. After magnetic stirring of the cold mixture for 20 min the contents of the flask are introduced into a 500-mL separatory funnel and the layers are separated. The aqueous layer (pH 4.3) is extracted twice with 100 mL of ether and the combined yellow organic layer is washed with 125 mL of distilled water and separated (the pH of the wash is 2.6–3.5). The organic layer is dried over magnesium sulfate for 1 hr and filtered to remove the drying agent, and the solvents are removed with a rotary evaporator at aspirator pressure. Distillation of the dark-yellow oil affords 4.9–5.4 g (82–89%) of (2*SR*,3*RS*)-2,4-dimethyl-3-hydroxypentanoic acid, bp 85–89°C (0.01 mm), as a viscous, yellow–green liquid (Note 10). Crystallization from hexane using decolorizing carbon provides 4.6–5.0 g (77–83%) of pure hydroxy acid, mp 75–76°C, as white crystals (Note 11).

2. Notes

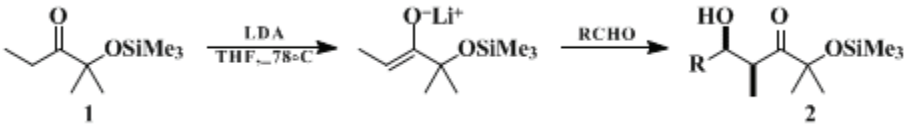
1. Tetrahydrofuran was distilled under a nitrogen atmosphere from sodium–benzophenone immediately prior to use.
2. Diisopropylamine was distilled, bp 85°C, under a nitrogen atmosphere from calcium hydride immediately prior to use.
3. *Caution! Concentrated butyllithium may ignite spontaneously on exposure to air or moisture. Manipulations with this reagent should be performed with care.* The submitters used fresh butyllithium from Foote Mineral Company, Johnsonville, Tennessee. The checkers used fresh butyllithium, 1.6 *M* in hexane under argon, from Aldrich Chemical Company, Inc. The butyllithium solutions may be standardized;[2] [3] however, both the submitters and the checkers chose to use fresh reagents and forego the titration. Stainless-steel cannulas with deflected points (double-tip syringe needles) are available from Ace Glass, Inc. and Aldrich Chemical Company, Inc.
4. 2-Methyl-2-(trimethylsiloxy)pentan-3-one was prepared by the method of Young, Buse, and Heathcock, *Org. Synth., Coll. Vol. VII* **1990**, 381.
5. 2-Methylpropanal was freshly distilled; bp 64–65°C.
6. The submitters report that the starting material can be removed within 4 hr to give 38–42 g of the 90 : 10 mixture if the concentration is continued with the rotary evaporator rather than a stationary flask at 0.5–0.1 mm.
7. The ^{1}H NMR (200 MHz, $CDCl_3$) spectrum of the product (taken from a spectrum of a 90 : 10 mixture) is as follows δ: 0.18 (s, 9 H), 0.89 (d, 3 H, J = 6.7), 1.02 (d, 3 H, J = 6.5), 1.08 (d, 3 H, J = 7.1), 1.36 (s, 3 H), 1.37 (s, 3 H), 1.68 (d of septets, 1 H, J = 8.4 and 6.6), 2.95 (d, 1 H, J = 2.6, OH), 3.42 (dt, 1 H, J = 8.5, 2.6, and 2.6), 3.59 (dq, 1 H, J = 7.0 and 2.6). The IR spectrum (film) of a 93 : 7 mixture shows absorptions at 1700 and 3600–3300 cm^{-1}.
8. Fresh periodic acid was obtained from Aldrich Chemical Company, Inc. and stored in a desiccator.
9. Reagent-grade diethyl ether from a freshly opened container was used without further drying.
10. The checkers discovered that the desired hydroxy acid is sensitive to strong acid and heat. Early runs of Step B by the checkers using the original conditions recommended by the submitters involved stirring the bisulfite slurry at room temperature for 3–4 hr, simple partitioning without an aqueous backwash, and drying of the bisulfite oxidation mixture, and distillation of the product at 0.8 mm reduced pressure. These runs consistently resulted in acid-catalyzed transformation in either the workup or in distillation and led to mixtures contaminated with 2-methylpropanal produced by a retroaldol reaction, as well as

with other unsaturated materials. Distillation of one of these runs, which had used a crude 58 : 42 mixture from Step A as starting material, afforded 13.4 g (53%) of α,γ,γ-trimethylbutyrolactone, bp 85–105°C (0.8 mm), as a yellow–green liquid by dehydration–lactonization. Crystallization from hexane provided 10.1 g (40%) of pure lactone, mp 50–51°C, as white crystals. The lactone had the following spectral properties: ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.28 (d, 3 H, J = 7.1), 1.38 (s, 3 H), 1.46 (s, 3 H), 1.71 (superficial t, 1 H, J = ca. 12), 2.30 (dd, 1 H, J = 12.6 and 8.9), 2.83 (16-line m; 1 H, J = 11.2, 8.9, and 7.1); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 15.6, 27.0, 29.0, 35.6, 43.5, 81.8, 179.1; IR (CCl_4) cm^{-1}: 1780; mass spectrum, *m/z* (relative intensity): 129 (M^+ + 1, 1), 113 (33), 84 (16), 69 (30), 59 (34), 43 (100).

11. The hydroxy acid showed the following spectral properties: ^{1}H NMR (200 MHz, $CDCl_3$) δ: 0.89 (d, 3 H, J = 6.6), 1.02 (d, 3 H, J = 6.6), 1.21 (d, 3 H, J = 7.1), 1.71 (octet, 1 H, J = 6.7), 2.71 (dq, 1 H, J = 7.3 and 3.4), 3.64 (dd, 1 H, J = 8.1 and 3.4), 6.7 (br s, 2 H, OH and CO_2H); IR (CCl_4) cm^{-1}: 1700, 3600–2500.

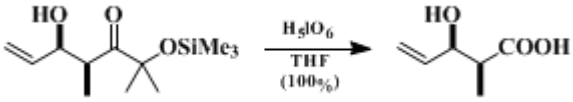
3. Discussion

The stereochemistry of the aldol addition reaction has been actively investigated in recent years, and several methods for achieving high stereoselectivity have been developed.[4 5 6] One of these utilizes the preformed lithium enolates of compounds such **1**.[7] Compound **1** gives a single enolate, which has the *Z*-configuration. This enolate reacts with aldehydes to give β-hydroxy ketones **(2)** with high stereoselectivity:

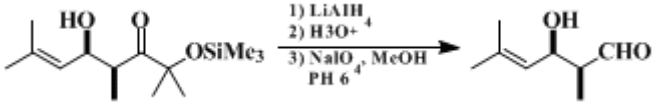


1 2

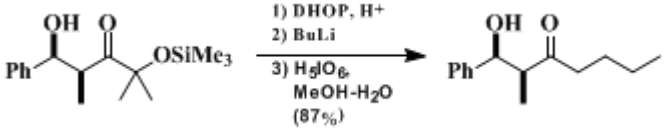
Compounds **2** may be directly cleaved with periodic acid to obtain β-hydroxy acids; for example:[7,8]



Alternatively, the carbonyl group may be reduced, the silyl group hydrolyzed, and the resulting vicinal diol cleaved with buffered sodium periodate to obtain the β-hydroxy aldehyde; for instance:[9,10]

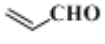


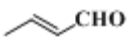
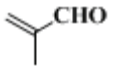
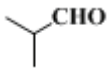
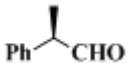
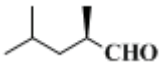
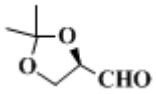
Finally, the hydroxy group may be protected as the tetrahydropyranyl ether, an aryl or alkyllithium reagent added to the carbonyl, and the resulting vicinal diol cleaved to obtain the corresponding β-hydroxy ketone; for example:[11]



Selected examples of the addition of ketone **1** to a variety of aldehydes are collected in Table I.

TABLE I
CONDENSATION OF KETONE **1** WITH ALDEHYDES (Equation 1)

Aldehyde	β-Hydroxy Ketone	β-Hydroxy Acid	Yield (%)	mp	Yield (%)	mp	Ref.
	80	oil	100	oil			[8,12] 9

	97	oil	62	oil	[12]
	99	oil	97	oil	[12]
	43	oil	–	–	[10]
	93	oil	61	73–75°C	[7]
	51	oil	76	119–120°C	[7]
PhCHO	78	oil	87	oil	[7]
	100[a]	oil	65	134–135°C[d]	[7]
	61[b]	oil	–	–	[10]
	75[c]	oil	–	–	[9]

[a]This is a 4 : 1 mixture of Cram : anti-Cram isomers.
[b]Major isomer.
[c]This is a 15 : 1 mixture of Cram : anti-Cram isomers.
[d]This is a 1.3 : 1 mixture of Cram : anti-Cram isomers.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 8, 326

References and Notes

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

(2SR,3RS)-2,4-Dimethyl-3-hydroxypentanoic acid

Pentanoic acid, 3-hydroxy-2,4-dimethyl-, (R^*,S^*)-(±)-

lithium diisopropylamide (LDA)

ether,
diethyl ether (60-29-7)

ammonium chloride (12125-02-9)

nitrogen (7727-37-9)

sodium bisulfite (7631-90-5)

decolorizing carbon (7782-42-5)

Benzophenone (119-61-9)

sodium (13966-32-0)

magnesium sulfate (7487-88-9)

2-methylpropanal (78-84-2)

butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

hexane (110-54-3)

periodic acid

argon (7440-37-1)

calcium hydride (7789-78-8)

Sodium periodate (7790-28-5)

diisopropylamine (108-18-9)

2-methyl-2-(trimethylsiloxy)pentan-3-one (72507-50-7)

5-hydroxy-2,4,6-trimethyl-2-(trimethylsiloxy)heptan-3-one (64869-24-5)

α,γ,γ-trimethylbutyrolactone

tetrahydropyranyl ether