A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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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.

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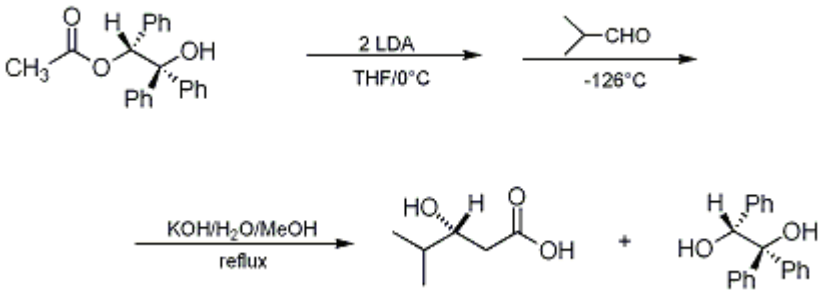
Organic Syntheses, Coll. Vol. 9, p.497 (1998); Vol. 72, p.38 (1995).

STEREOSELECTIVE ALDOL REACTION OF DOUBLY DEPROTONATED (R)-(+)-2-HYDROXY-1,2,2-TRIPHENYLETHYL ACETATE (HYTRA): (R)-3-HYDROXY-4-METHYLPENTANOIC ACID

[Pentanoic acid, 3-hydroxy-4-methyl-, (R)-]



Submitted by Manfred Braun and Silke Gräf[1].
Checked by K. Ryan, J. Lynch, and I. Shinkai.

1. Procedure

A 500-mL, two-necked, round-bottomed flask is equipped with a magnetic stirrer, septum, and a connection to a combined vacuum/nitrogen line (Note 1). The air in the flask is replaced by nitrogen by repeated evacuation and flushing with nitrogen, the pressure of which is maintained during the reaction at ca. 70 mm above atmospheric pressure with a mercury bubbler. Dry tetrahydrofuran (100 mL) (Note 2) and 38.4 mL (0.269 mol) of diisopropylamine (Note 3) are injected with syringes through the septum. The mixture is cooled to −78°C by means of a dry ice/acetone bath and treated with stirring with 165 mL (0.264 mol) of a 15% solution of butyllithium in hexane. The dry ice/acetone bath is replaced with an ice bath, and stirring is continued for 30 min. A 2-L, three-necked, round-bottomed flask equipped with a mechanical stirrer, septum, and a connection to the combined vacuum/nitrogen line (Note 1) is charged with 40.0 g (0.120 mol) of (R)-(+)-2-hydroxy-1,2,2-triphenylethyl acetate [(R)-HYTRA].[2] The air in the flask is replaced with nitrogen, and 400 mL of dry tetrahydrofuran is added via a cannula with 1.2 mm inside diameter, whereby the flask is slightly evacuated. The suspension is stirred at −78°C in a dry ice/acetone bath. The ice-cold solution of lithium diisopropylamide, prepared as described above, is added via a cannula under vigorous stirring, whereby the 2-L flask is slightly evacuated. The reaction mixture is stirred at 0°C for 60 min to complete the double deprotonation. A clear orange solution forms that is cooled, below −70°C (dry ice/acetone bath). Thereafter, 900 mL of dry 2-methylbutane (Note 4) is added via a cannula. A thermocouple, connected to a resistance thermometer (Note 5), is introduced via the septum. The reaction flask is plunged into a bath of liquid nitrogen, the depth of immersion being 0.5–1 cm (Note 6). When the temperature of the suspension has reached −128°C, a solution of 18.3 mL (0.200 mol) of 2-methylpropanal in 5 mL of dry tetrahydrofuran is added dropwise via syringe through the septum at such a rate that the temperature does not rise above −126°C. Stirring is continued for 90 min at −128°C to −106°C (Note 7). The mixture is treated with 500 mL of a saturated aqueous solution of ammonium chloride and allowed to reach room temperature.

The organic layer is separated and washed twice with a total of 200 mL of water. The aqueous reaction layer is extracted five times with a total of 600 mL of chloroform. The organic extracts are washed twice with a total amount of 250 mL of water. The combined organic layers are dried with magnesium sulfate and evaporated to dryness. The residual solid product is carefully dried under reduced pressure to yield 48–50 g (≥ 100%) (Note 8).

The crude product is transferred to a 2-L, round-bottomed flask equipped with a magnetic stirrer and a condenser. Methanol (1.4 L), water (0.4 L), and 66.6 g of potassium hydroxide are added and the

mixture is refluxed for 3 hr. After the solution is cooled to room temperature, the organic solvent is removed on a rotary evaporator. The residual aqueous alkaline suspension is filtered through a suction filter. The solid (Note 9) is washed carefully with 250 mL of water. In a separatory funnel the combined aqueous layers are washed three times with a total of 300 mL of methylene chloride. The aqueous solution is transferred to a 2-L, round-bottomed flask, immersed in an ice bath, and acidified to pH 2.5 by cautious addition of 6 N hydrochloric acid. The mixture is stirred vigorously with a magnetic stirrer, and the pH is controlled carefully to avoid over-acidification. The clear solution is again poured into a separatory funnel, saturated with sodium chloride, and extracted with five 100-mL portions of diethyl ether. The pH of the aqueous layer is controlled and readjusted to pH 2.5 by addition of 6 N hydrochloric acid, if necessary. The combined organic layers are dried with magnesium sulfate and concentrated in a rotary evaporator without heating. The yellow syrupy residue is dried carefully at room temperature under reduced pressure (10^{-3} mm) to yield 9.7–12.4 g (61–78%) (76 mmol; 63%) of (R)-(+)-3-hydroxy-4-methylpentanoic acid in 86–92% optical purity (Note 10), $[\alpha]_D^{20}$ +32° to +37° (99% chloroform, *c* 0.11) [lit.[2] $[\alpha]_D^{20}$ +40.5° (chloroform, *c* 0.0063); lit.[3] $[\alpha]_D^{20}$ +40.14° (chloroform, *c* 1.22)].

2. Notes

1. Alternatively, the flask can be closed with a three-way stop-cock to maintain connections to a vacuum pump and to a nitrogen line.
2. Tetrahydrofuran is distilled first from sodium wire and then under nitrogen from lithium aluminum hydride. 2-Methylbutane (purchased from Aldrich Chemical Company, Inc.) and petroleum ether (low-boiling fraction, bp 30–37°C) are distilled from lithium aluminum hydride under nitrogen. The solvents are stored under nitrogen, and can be taken from the receiving flasks, closed with septa, with syringes or cannulas.
3. Diisopropylamine (Merck AG, D-Darmstadt) is distilled from calcium hydride and stored over molecular sieves (3 Å). Butyllithium (15% solution in hexane) was purchased from Merck AG, D-Darmstadt.
4. Instead of 2-methylbutane, a low-boiling fraction of petroleum ether (bp 30–37°C), but not pure pentane, can be used (cf. (Note 2)).
5. Because of the inaccuracy of alcohol thermometers it is strongly recommended that one monitor those reactions that are run below −80°C with a resistance thermometer. The submitters used an apparatus purchased from Ebro, D-Ingolstadt.
6. The submitters used a 2-L Dewar cylinder of 20 cm inner depth, covered with aluminum foil. The mixture should be stirred very vigorously to avoid solidification.
7. When the addition of the aldehyde is complete, liquid nitrogen is removed from the Dewar cylinder.
8. ^{1}H NMR ($CDCl_3$/TMS/300 MHz) δ: 0.82 (d, 3 H, J = 6.9, CH_3), 0.83 (d, 3 H, J = 6.7, CH_3), 1.53 (m, 1 H, $CH(CH_3)_2$), 2.35 (m, 2 H, CH_2), 3.56 (m, 1 H, CH(OH), 6.72 (s, 1 H, CHPh), 7.11 (m, 10 H, Ar-H), 7.32 (m, 3 H, Ar-H); 7.63 (m, 2 H, Ar-H); $[\alpha]_D^{20}$ +159° to 171° (99% chloroform, *c* 1); mp 178° to 190° C. The optical rotation is influenced by the diastereomeric ratio and by traces of HYTRA, if present. Those traces can be detected by TLC on silica gel (R_f = 0.2, chloroform).
9. Colorless, crystalline, optically pure (R)-(+)-1,1,2-triphenyl-1,2-ethanediol can be recovered in >95% yield after recrystallization from methanol,[2] mp 124°C, $[\alpha]_D^{20}$ +224° (95% aqueous ethanol, *c* 0.984).
10. The optical purity of 3-hydroxy-4-methylpentanoic acid is determined by shift measurements on the methyl ester. Chemical purity exceeds 98% according to GC. The submitters report consistent ee of 92–94%; the checker's experience is recorded in the procedure.

Waste Disposal Information

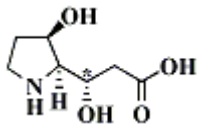
All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

The addition of doubly deprotonated HYTRA to achiral[4,5] as well as to enantiomerically pure aldehydes[6] enables one to obtain non-racemic β-hydroxycarboxylic acids. Thus, the method provides a practical solution for the stereoselective aldol addition of α-unsubstituted enolates, a long-standing

synthetic problem.[7] As opposed to some other chiral acetate reagents,[7] both enantiomers of HYTRA are readily available. Furthermore, the chiral auxiliary reagent, 1,1,2-triphenyl-1,2-ethanediol, can be recovered easily. Aldol additions of HYTRA have been used in syntheses of natural products and biological active compounds, and some of those applications are given in Table I. (The chiral center, introduced by a stereoselective aldol addition with HYTRA, is marked by an asterisk.)

TABLE I
NATURAL PRODUCTS AND BIOLOGICALLY ACTIVE ANALOGUES PREPARED BY STEREOSELECTIVE ALDOL ADDITION OF DOUBLY DEPROTONATED (R)- AND (S)-HYTRA



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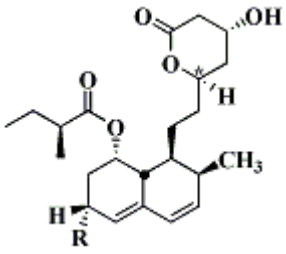

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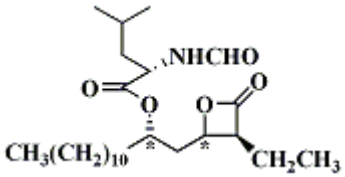

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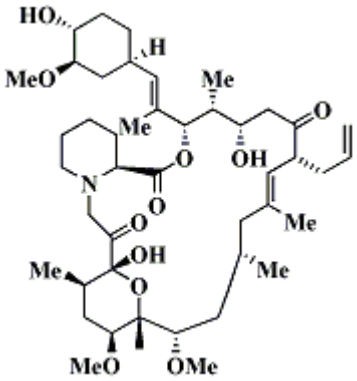

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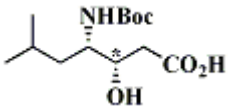

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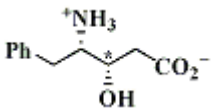

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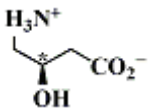

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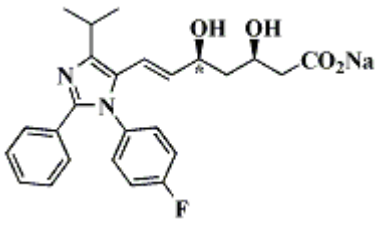

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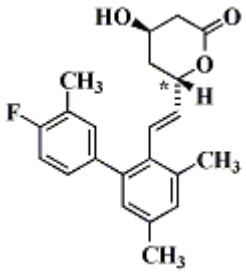

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Preparation of (R)-(+)-3-hydroxy-4-methylpentanoic acid has been reported previously by the submitters.[5] Alternative syntheses of (R)-(+)- or (S)-(−)-3-hydroxy-4-methylpentanoic acid rely on aldol reactions of chiral ketone, ester, or amide enolates,[3,18,19,20] or Lewis-acid mediated additions of chiral

silyl ketene acetals to isobutyraldehyde.[21,22] Since both enantiomers of HYTRA are readily available this method enables one to prepare (S)-3-hydroxy-4-methylpentanoic acid as well.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 10, 464

References and Notes

1. Institut für Organische und Makromolekulare Chemie, Heinrich-Heine Universität, Universitätstrasse 1, D-40225 Düsseldorf, Germany.
2. Braun, M.; Gräf, S.; Herzog, S. *Org. Synth., Coll. Vol. IX* **1998**, 507
3. Evans, D. A.; Taber, T. R. *Tetrahedron Lett.* **1980**, *21*, 4675–4678.
4. Braun, M.; Devant, R. *Tetrahedron Lett.* **1984**, *25*, 5031–5034.
5. Devant, R.; Mahler, U.; Braun, M. *Chem. Ber.* **1988**, *121*, 397–406.
6. Mahler, U.; Devant, R. M.; Braun, M. *Chem. Ber.* **1988**, *121*, 2035–2044.
7. For a review see: Braun, M. *Angew. Chem.* **1987**, *99*, 24–37; *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 24–37.
8. Ewing, W. R.; Harris, B. D.; Bhat, K. L.; Joullié, M. M. *Tetrahedron* **1986**, *42*, 2421–2428.
9. Lynch, J. E.; Shinkai, I.; Volante, R. P. US Patent 4 611 081, 1985; *Chem. Abstr.* **1987**, *106*, 18119n.
10. Barbier, P.; Schneider, F.; Widmer, U. *Helv. Chim. Acta* **1987**, *70*, 1412–1418.
11. Mills, S.; Desmond, R.; Reamer, R. A.; Volante, R. P.; Shinkai, I. *Tetrahedron Lett.* **1988**, *29*, 281–284.
12. Wuts, P. G. M.; Putt, S. R. *Synthesis* **1989**, 951–953. For a recent application of HYTRA in a synthesis of a fluoroolefin dipeptide mimic, see: Allmendinger, T.; Felder, E.; Hungerbühler, E. *Tetrahedron Lett.* **1990**, *31*, 7301–7304.
13. Devant, R. M.; Radunz, H.-E. *Tetrahedron Lett.* **1988**, *29*, 2307–2310.
14. Braun, M.; Waldmüller, D. *Synthesis* **1989**, 856–858.
15. Prasad, K.; Chen, K.-M.; Repic, O.; Hardtmann, G. E. *Tetrahedron: Asymmetry* **1990**, *1*, 703–706.
16. Lynch, J. E.; Volante, R. P.; Wattley, R. V.; Shinkai, I. *Tetrahedron Lett.* **1987**, *28*, 1385–1388.
17. For more recent applications of HYTRA in syntheses of HMG CoA reductase inhibitors, see: Jendralla, H.; Baader, E.; Bartmann, W.; Beck, G.; Bergmann, A.; Granzer, E.; von Kerekjarto, B.; Kesseler, K.; Krause, R.; Schubert, W.; Wess, G. *J. Med. Chem.* **1990**, *33*, 61–70; Jendralla, H.; Granzer, E.; von Kerekjarto, B.; Krause, R.; Schacht, U.; Baader, E.; Bartmann, W.; Beck, G.; Bergmann, A.; Kesseler, K.; Wess, G.; Chen, L.-J.; Granata, S.; Herchen, J.; Kleine, H.; Schüssler, H.; Wagner, K. *J. Med. Chem.* **1991**, *34*, 2962–2983; Roth, B. D.; Blankley, C. J.; Chucholowski, A. W.; Ferguson, E.; Hoefle, M. L.; Ortwine, D. F.; Newton, R. S.; Sekerke, C. S.; Sliskovic, D. R.; Stratton, C. D.; Wilson, M. W. *J. Med. Chem.* **1991**, *34*, 357–366.
18. Trost, B. M.; Urabe, H. *J. Org. Chem.* **1990**, *55*, 3982–3983.
19. Duthaler, R. O.; Herold, P.; Lottenbach, W.; Oertle, K.; Riediker, M. *Angew. Chem.* **1989**, *101*, 490–491; *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 495.
20. Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127–2129.
21. Helmchen, G.; Leikauf, V.; Taufer-Knöpfel, I. *Angew. Chem.* **1985**, *97*, 874–875; *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 874–875.
22. Oppolzer, W.; Marco-Contelles, J. *Helv. Chim. Acta* **1986**, *69*, 1699–1703.

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

silica gel

petroleum ether

(R)-(+)- or (S)-(−)-3-hydroxy-4-methylpentanoic acid

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

methanol (67-56-1)

diethyl ether (60-29-7)

ammonium chloride (12125-02-9)

chloroform (67-66-3)

sodium chloride (7647-14-5)

nitrogen (7727-37-9)

aluminum (7429-90-5)

potassium hydroxide (1310-58-3)

sodium (13966-32-0)

Pentane (109-66-0)

methylene chloride (75-09-2)

magnesium sulfate (7487-88-9)

isobutyraldehyde,
2-methylpropanal (78-84-2)

2-methylbutane (78-78-4)

butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

hexane (110-54-3)

calcium hydride (7789-78-8)

lithium diisopropylamide (4111-54-0)

diisopropylamine (108-18-9)

(R)-3-Hydroxy-4-methylpentanoic acid,
(R)-(+)-3-hydroxy-4-methylpentanoic acid,
Pentanoic acid, 3-hydroxy-4-methyl-, (R)- (77981-87-4)

(R)-(+)-1,1,2-triphenyl-1,2-ethanediol (95061-46-4)

3-hydroxy-4-methylpentanoic acid

1,1,2-triphenyl-1,2-ethanediol

(S)-3-hydroxy-4-methylpentanoic acid

(R)-(+)-2-Hydroxy-1,2,2-triphenylethyl acetate (95061-47-5)