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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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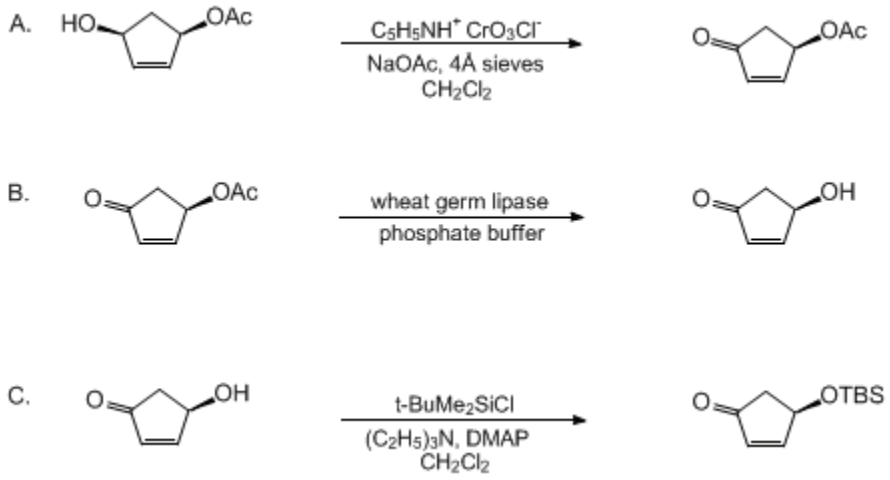
(4R)-(+)-tert-BUTYLDIMETHYLSILOXY-2-CYCLOPENTEN-1-ONE

[2-Cyclopenten-1-one, 4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-, (R)-]



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1. Procedure

A. *(4R)-(+)-Acetoxy-2-cyclopenten-1-one*. A flame-dried, 2-L, three-necked, round-bottomed flask, equipped with a Teflon-coated magnetic stirring bar, is purged with nitrogen and charged with 1.0 L of dry dichloromethane (Note 1), 1.5 g of anhydrous sodium acetate (Note 2), 70 g of 4 Å molecular sieves (Note 3), and 23 g (162 mmol) of (1R,4S)-(+)-4-hydroxy-2-cyclopentenyl acetate (Note 4). Finely powdered pyridinium chlorochromate (50 g, 240 mmol) is added portionwise over a period of 5 min, and the mixture is stirred at room temperature for 3 hr (Note 5), then filtered through a pad of Florisil. The filtrate is concentrated on a rotary evaporator, and the residual dark oil is purified by flash chromatography on silica gel with elution by 20% ethyl acetate in petroleum ether (bp 35–60°C) (Note 6) to give 18.9 g (83%) of (4R)-(+)-acetoxy-2-cyclopenten-1-one as a colorless oil (Note 7).

B. *(4R)-(+)-Hydroxy-2-cyclopenten-1-one*. A 2-L, one-necked, round-bottomed flask, fitted with a Teflon-coated magnetic stirring bar, is charged with 1.5 L of 0.05 M phosphate buffer (Note 8) and 18.8 g (134 mmol) of (4R)-(+)-acetoxy-2-cyclopenten-1-one. A 4.0-g lot of wheat germ lipase (Note 9) is added slowly with rapid stirring. Once the enzyme is dispersed, the speed of the stirrer is reduced and the flask is sealed with a glass stopper prior to being stirred at room temperature for 7 days (Note 10). The stopper is removed and the contents of the flask are transferred to the body of a lighter than water continuous extraction apparatus whose pot is charged with 1 L of ethyl acetate. After extraction for 3 days, the ethyl acetate solution is concentrated on a rotary evaporator, and the residue is subjected to flash chromatography on silica gel using 30% ethyl acetate in petroleum ether (bp 35–60°C) as eluent (Note 11). After recovery of 4.60 g (25%) of the less polar, unreacted acetoxy ketone (Note 12), 7.80 g (60%) of the colorless, oily (R)-(+)-hydroxy ketone is obtained (Note 13).

C. *(4R)-(+)-tert-Butyldimethylsiloxy-2-cyclopenten-1-one*. A 500-mL, three-necked, round-bottomed flask equipped with a Teflon-coated magnetic stirring bar, pressure-equalizing addition funnel, and nitrogen inlet, is flame-dried under a stream of dry nitrogen. The apparatus is charged with 7.7 g (78 mmol) of (4R)-(+)-hydroxy-2-cyclopenten-1-one, 0.96 g (10 mol %) of 4-dimethylaminopyridine (Note 14), 20 g (200 mmol) of triethylamine (Note 2), and 150 mL of dry dichloromethane (Note 1). The dropping funnel is charged with a solution of 14.2 g (94 mmol) of tert-butyldimethylsilyl chloride (Note 14) in 50 mL of dry dichloromethane. Magnetic stirring is initiated, the reaction mixture is cooled in an ice-water bath, and the silyl chloride solution is added dropwise

during 10 min. The ice-water bath is removed, and the mixture is stirred at room temperature for 3 hr; then 100 mL of deionized water is added with stirring. After the organic layer is separated, the aqueous phase is extracted three times with 50 mL of dichloromethane and the combined organic solutions are dried over anhydrous magnesium sulfate, filtered, and concentrated on a rotary evaporator. The residue is filtered through a short column of silica gel with elution by 5% ethyl acetate in petroleum ether (bp 35–60°C). After concentration of the fractions containing the product, the resulting oil is distilled in a short path distillation apparatus (bp 60°C at 0.1 mm) to give 13.2 g of a colorless oil. Crystallization of this material from pentane with cooling by an acetone-dry ice bath gives 10.6 g (64%) of colorless needles, mp 27–28°C, $[\alpha]_D^{20}$ +65.3° (CH_3OH, *c* 0.4) (Note 15) and (Note 16).

2. Notes

1. Dichloromethane is distilled from calcium hydride prior to use.
2. Sodium acetate and triethylamine were purchased from the J. T. Baker Chemical Company. Sodium acetate is used without further purification; triethylamine is distilled from calcium hydride prior to use.
3. The 4 Å molecular sieves were purchased from the Aldrich Chemical Company, Inc., and activated by drying in a vacuum oven at 150°C for 24 hr prior to storing in an oven at 140°C. Both powdered and pelletized forms of the sieve were used without affecting the yield of product.
4. High purity (≥99% ee) (1R,4S)-4-hydroxy-2-cyclopentenyl acetate exhibiting $[\alpha]_D^{23}$ values of +71.1° to +71.3° in $CHCl_3$ can be obtained by enzymatic hydrolysis of the racemic diacetate (*Org. Synth., Coll. Vol. IX* **1998**, 487)[2,3,4] with electric eel acetyl cholinesterase[4] or with A.K. lipase (Amano International Enzyme Company).[5]
5. The progress of this reaction is conveniently monitored by TLC. The silica gel plates are eluted with 50% ethyl acetate in petroleum ether (bp 35–60°C). Under these conditions, the alcohol exhibits an R_f of 0.45 and the acetate an R_f of 0.80.
6. The column consists of 300 g of silica gel; 100-mL sized fractions are collected. Since release of the product from the chromium salts occurs slowly, fractions 5–20 are found to contain the acetoxy ketone and are combined.
7. The spectral data for (4R)-(+)-acetoxy-2-cyclopenten-1-one are as follows: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.06 (s, 3 H), 2.29 (dd, 1 H, J = 2.2, 18.7), 2.78 (dd, 1 H, J = 6.4, 18.7), 5.81 (m, 1 H), 6.29 (dd, 1 H, J = 1.3, 5.7), 7.53 (dd, 1 H, J = 2.4, 5.7); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 20.7, 40.9, 71.9, 136.9, 158.8, 170.3, 204.7; IR ($CHCl_3$) cm^{-1}: 2950, 1740, 1720, 1600, 1375, 1355, 1190, 795; $[\alpha]_D^{20}$ +96.1° (CH_3OH, *c* 0.17) [lit.[6] $[\alpha]_D^{22}$ +97° (CH_3OH, *c* 0.1].
8. The buffer is prepared by dissolving 27.2 g of potassium dihydrogen phosphate in 4.0 L of deionized water and titrating with 1 M sodium hydroxide until pH 5.0 is reached.
9. Wheat germ lipase was purchased from the Sigma Chemical Company.
10. The reaction rate decreased significantly toward the end of the hydrolysis. The level of conversion can be improved either by increasing the amount of enzyme or by lengthening the reaction time. The course of the reaction can be monitored by TLC on silica gel (elution with 50% ethyl acetate in petroleum ether). The product has an R_f of 0.20 and the starting material an R_f of 0.40.
11. The column consists of 200 g of silica gel; 100-mL sized fractions are collected. The starting material was recovered in fractions 2–5 while the product was recovered from fractions 7–20.
12. This material can be recycled in future reactions.
13. The spectral data for (4R)-(+)-hydroxy-2-cyclopenten-1-one are as follows: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.27 (dd, 1 H, J = 3.0, 18.0), 2.78 (dd, 1 H, J = 6.0, 18.0), 3.27 (br s, 1 H), 4.88–5.22 (m, 1 H), 6.25 (d, 1 H, J = 6.0), 7.60 (dd, 1 H, J = 2.0, 6.0); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 44.1, 70.1, 134.7, 164.0, 207.3; $[\alpha]_D^{20}$ +78.1° (CH_3OH, *c* 2.03).
14. 4-Dimethylaminopyridine and tert-butyldimethylsilyl chloride were purchased from the Aldrich Chemical Company, Inc., and used without purification.
15. The spectral data for (4R)-(+)-tert-butyldimethylsiloxy-2-cyclopenten-1-one are as follows: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.12 (s, 3 H), 0.13 (s, 3 H), 0.91 (s, 9 H), 2.23 (dd, 1 H, J = 2.3, 18.2), 2.69 (dd, 1 H, J = 6.0, 18.2), 4.98 (m, 1 H), 6.17 (dd, 1 H, J = 1.2, 5.7), 7.44 (dd, 1 H, J = 2.3, 5.7); ^{13}C NMR (75 MHz, $CDCl_3$) δ: −4.76, −4.74, 18.0, 25.7, 44.9, 70.9, 134.4, 163.7, 206.3.
16. The reported optical rotations are $[\alpha]_D^{21}$ +66.6° (CH_3OH, *c* 1.0),[7] $[\alpha]_D^{21}$ +67.0° (CH_3OH, *c* 0.12),[6] and $[\alpha]_D^{21}$ +67.3° (CH_3OH, *c* 0.82).[8]

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

As a direct consequence of the quest for optically active prostaglandins,[9] derivatives of (R)-4-hydroxy-2-cyclopenten-1-one have come to be regarded as important chiral building blocks. Initial efforts to obtain these compounds in enantiomerically pure form involved the chemical modification of D-tartaric acid,[10] degradation of the fungal metabolite terrein,[11] ring contraction of 2,4,6-trichlorophenol with resolution,[9,12] chromatography of diastereomeric[13] or racemic hydroxy-protected derivatives,[14] and a multi-step conversion from glucose.[15] Subsequent discoveries that excellent kinetic resolution can be achieved either by asymmetric BINAL-H reduction of 4-cyclopentene-1,3-dione[16] or by enzymatic hydrolysis of the acetate[17] proved to be major advances.

More recently, the desymmetrization of cis-3,5-diacetoxycyclopent-1-ene by enantioselective monohydrolysis in the presence of various enzymes has been intensively investigated.[18,19,20,21,22,23] This approach is readily adaptable to a laboratory setting, is inexpensive, and is capable of straightforwardly delivering multigram quantities of high quality (>99% ee) product.

The reaction sequence shown here, which has been adapted from earlier literature reports, permits the convenient acquisition of (4R)-(+)-tert-butyldimethylsiloxy-2-cyclopenten-1-one, perhaps the most useful of the possible derivatives for further synthetic elaboration.[24] The companion synthesis of the useful (4S) enantiomer from the same starting material is also described.[25]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 9, 136

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

petroleum ether

ethyl acetate (141-78-6)

sodium acetate (127-09-3)

sodium hydroxide (1310-73-2)

nitrogen (7727-37-9)

acetate

Pentane (109-66-0)

glucose (492-62-6)

dichloromethane (75-09-2)

magnesium sulfate (7487-88-9)

potassium dihydrogen phosphate (7778-77-0)

triethylamine (121-44-8)

calcium hydride (7789-78-8)

phosphate

4-cyclopentene-1,3-dione (930-60-9)

pyridinium chlorochromate (26299-14-9)

4-dimethylaminopyridine (1122-58-3)

(4R)-(+)-tert-BUTYLDIMETHYLSILOXY-2-CYCLOPENTEN-1-ONE (61305-35-9)

2-Cyclopenten-1-one, 4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-, (R)-

(4R)-(+)-Acetoxy-2-cyclopenten-1-one (59995-48-1)

(1R,4S)-(+)-4-Hydroxy-2-cyclopentenyl acetate (60410-16-4)

(4R)-(+)-Hydroxy-2-cyclopenten-1-one

acetoxy ketone

tert-butyldimethylsilyl chloride (18162-48-6)

(R)-4-hydroxy-2-cyclopenten-1-one

D-tartaric acid (147-71-7)

2,4,6-trichlorophenol (88-06-2)

cis-3,5-diacetoxycyclopent-1-ene (54664-61-8)