Organic Syntheses

A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

The procedures described in *Organic Syntheses* are provided as published and are conducted at one's own risk. *Organic Syntheses, Inc.*, its Editors, and its Board of Directors do not warrant or guarantee the safety of individuals using these procedures and hereby disclaim any liability for any injuries or damages claimed to have resulted from or related in any way to the procedures herein.

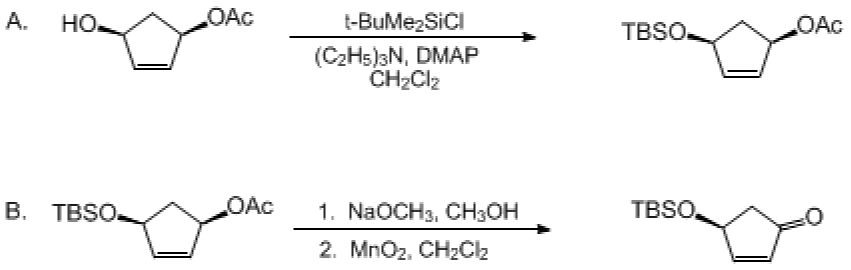
September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

DOI:10.15227/orgsyn.073.0044

Organic Syntheses, Coll. Vol. 9, p.136 (1998); Vol. 73, p.44 (1996).

(4S)-(−)-tert-BUTYLDIMETHYLSILOXY-2-CYCLOPENTEN-1-ONE

[(4S)-(−)-tert-Butyldimethylsiloxy-2-cyclopenten-1-one]



Submitted by Leo A. Paquette and Todd M. Heidelbaugh[1].
Checked by Thomas Kirrane and Albert I. Meyers.

1. Procedure

A. *(1R,4S)-(−)-4-tert-Butyldimethylsiloxy-2-cyclopentenyl acetate*. A dry, 500-mL, three-necked, round-bottomed flask, equipped with a Teflon-coated magnetic stirring bar, rubber septum, and nitrogen inlet, is purged with nitrogen and charged with 7.67 g (54 mmol) of (1R,4S)-(+)-4-hydroxy-2-cyclopentenyl acetate (Note 1), 660 mg (5.4 mmol) of 4-dimethylaminopyridine (Note 2), 17 mL (122 mmol) of triethylamine (Note 3), and 175 mL of dichloromethane (Note 3). The reaction mixture is cooled to 0°C in an ice-water bath, and tert-butyldimethylsilyl chloride (10.24 g, 68 mmol) (Note 2) is introduced in one portion. The ice-water bath is removed and the mixture is allowed to warm to room temperature and stir for 3 hr. At this point, more silyl chloride is added if necessary (Note 4). After 5 hr, 200 mL of water is added, the mixture is transferred to a separatory funnel and the organic phase separated. The aqueous phase is extracted with three 100-mL portions of dichloromethane. The combined organic layers are washed with 100 mL of saturated sodium bicarbonate solution and 100 mL of brine prior to drying over anhydrous magnesium sulfate. After filtration and solvent removal with a rotary evaporator, the residual solids are removed by filtration (Note 5), and the resulting yellow oil is purified by bulb-to-bulb distillation at 0.4–0.6 mm (pot temperature 80–100°C) to give 10.67–11.08 g (77–80%) of (1R,4S)-(−)-4-tert-butyldimethylsiloxy-2-cyclopentenyl acetate as a colorless liquid, $[\alpha]^{20}_{D}$ −1.32° (CH$_3$OH, *c* 1.52) (Note 6).

B. *(4S)-(−)-tert-Butyldimethylsiloxy-2-cyclopenten-1-one*. A dry, 500-mL, one-necked, round-bottomed flask, equipped with a Teflon-coated magnetic stirring bar, is purged with nitrogen and charged with 11.7 g (45.6 mmol) of (1R,4S)-(−)-tert-butyldimethylsiloxy-2-cyclopentenyl acetate and 250 mL of anhydrous methanol (Note 7) to which 4.94 g (91.5 mmol) of powdered sodium methoxide (Note 8) is added. The reaction mixture is stirred for 15 min at ambient temperature, freed of most of the methanol using a rotary evaporator, and taken up in 400 mL of dichloromethane. The solution is washed with three 200-mL portions of water, dried over anhydrous magnesium sulfate, filtered, and concentrated using a rotary evaporator, giving 11.2 g of crude allylic alcohol which is carried into the next reaction without further purification.

A 500-mL, round-bottomed flask, equipped with a Teflon-coated magnetic stirring bar, is charged with the 11.2 g of crude allylic alcohol obtained above and 300 mL of dichloromethane, and the resulting vigorously stirred solution is treated with 33 g of active manganese dioxide (380 mmol) (Note 9). Additional 2–5 g lots of the oxidant are added every 2–3 hr until the reaction is complete (Note 10). The reaction mixture is vacuum-filtered through a pad of diatomaceous earth, and the pad is washed with 200 mL of dichloromethane. The resulting clear filtrate is concentrated carefully using a rotary evaporator, and the residual oil is purified by bulb-to-bulb distillation at 0.3 mm (pot temperature 100°C) affording 8.43–8.71 g (87–90%) of enone as a pale yellow oil that solidifies when cooled below 15°C. Crystallization of the crude product from pentane at −70°C gives (4S)-(−)-tert-butyldimethylsiloxy-2-cyclopenten-1-one as colorless needles having mp 32–33°C, $[\alpha]^{23}_{D}$ −65.1° (CH$_3$OH, *c* 0.94) (Note

11).

2. Notes

1. High purity (≥99% ee) (1R,4S)-4-hydroxy-2-cyclopentenyl acetate exhibiting $[\alpha]_D^{20}$ values of +71.1 to +71.3° in $CHCl_3$ can be obtained by enzymatic hydrolysis of the racemic diacetate[2,3,4] either with electric eel cholinesterase[2] or with A.K. lipase (Amano International Enzyme Company).[5] The checkers employed the EEAC procedure.[2]
2. 4-Dimethylaminopyridine and tert-butyldimethylsilyl chloride were purchased from the Aldrich Chemical Company, Inc. and used without further purification.
3. Triethylamine and dichloromethane were distilled from calcium hydride before use.
4. The progress of the reaction is easily monitored by TLC analysis. Silyl chloride is added until the starting hydroxy acetate is no longer detected.
5. Filtration is performed only to prevent bumping during the ensuing distillation.
6. The spectral data are as follows: ^1H NMR (300 MHz, $CDCl_3$) δ: 0.09 (s, 6 H), 0.90 (s, 9 H), 1.57–1.65 (m, 1 H), 2.04 (s, 3 H), 2.75–2.85 (dt, 1 H, J = 7.3, 3.8), 4.69–4.73 (m, 1 H), 5.44–5.48 (m, 1 H), 5.87–5.98 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: −4.7, −4.6, 18.2, 21.1, 25.9, 41.2, 74.9, 77.4, 131.2, 138.9, 170.9; IR (neat) cm^{-1}: 2940, 2870, 1740, 1610, 1375, 1250.
7. The methanol was refluxed over magnesium turnings and a crystal of iodine under nitrogen for 3 hr prior to use.
8. Sodium methoxide was freshly prepared by adding sodium metal to methanol (*Caution: hydrogen evolution*), evaporation of the solvent, and vacuum drying of the white solid.
9. Manganese dioxide was prepared as described.[6]
10. The time required to achieve complete reaction varies from 20–48 hr depending on the activity of the manganese dioxide. The progress of the oxidation is easily monitored by TLC analysis on silica gel.
11. The spectral data are identical to those reported for the (4R) enantiomer.[7]

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

Although (1R,4S)-(+)- and (1S,4R)-(−)-4-hydroxy-2-cyclopentenyl acetate are both available by enzyme-promoted enantioselective hydrolysis,[8,9] different enzymes are, of course, required to achieve this stereochemical divergence. Economy would be realized if one of these enantiomeric products could serve as the starting point for the preparation of both antipodal forms of structurally more advanced intermediates. The importance of (4R)-(+)-[10,11] and (4S)-(−)-tert-butyldimethylsiloxy-2-cyclopenten-1-one[12] to prostaglandin synthesis is well established. The latent potential of these highly functionalized building blocks for the enantiospecific synthesis of other natural products is beginning to emerge.[13,14,15] Use of the present procedure makes possible the direct, efficient acquisition of the 4S enantiomer from the same hydroxy acetate that serves as a convenient progenitor to the 4R isomer.[7] The synthetic route is closely similar to that outlined earlier by Danishefsky, Cabal, and Chow.[13]

References and Notes

1. Evans Chemical Laboratories, The Ohio State University, Columbus, OH 43210.
2. Deardorff, D. R.; Windham, C. Q.; Craney, C. L. *Org. Synth., Coll. Vol. IX* **1998**, 487.
3. Korach, M.; Nielson, D. R.; Rideout, W. H. *Org. Synth., Coll. Vol. V* **1973**, 414.
4. Deardorff, D. R.; Myles, D. C. *Org. Synth., Coll. Vol. VIII* **1993**, 13.
5. Smith, G. F.; Earle, M. J., unpublished results.
6. Attenburrow, J.; Cameron, A. F. B.; Chapman, J. H.; Evans, R. M.; Hems, B. A.; Jansen, A. B. A.; Walker, T. *J. Chem. Soc.* **1952**, 1094.
7. Paquette, L. A.; Earle, M. J.; Smith, G. F. *Org. Synth., Coll. Vol. IX* **1998**, 132.

8. Schneider, M.; Laumen, K. *Ger. Offen.* DE 3 620 646 (1987); *Chem. Abstr.* **1988**, *109*, 21633t.
9. Babiak, K. A.; Ng, J. S.; Dygos, J. H.; Weyker, C. L.; Wang, Y.-F.; Wong, C.-H. *J. Org. Chem.* **1990**, *55*, 3377 and relevant references cited therein.
10. Johnson, C. R.; Bis, S. J. *Tetrahedron Lett.* **1992**, *33*, 7287 and relevant references cited therein.
11. Kitamura, M.; Kasahara, I.; Manabe, K.; Noyori, R.; Takaya, H. *J. Org. Chem.* **1988**, *53*, 708.
12. Kitano, Y.; Okamoto, S.; Sato, F. *Chem. Lett.* **1989**, 2163.
13. Danishefsky, S. J.; Cabal, M. P.; Chow, K. *J. Am. Chem. Soc.* **1989**, *111*, 3456.
14. Paquette, L. A.; Ni, Z.; Smith, G. F.; Earle, M. J. unpublished work.
15. Paquette, L. A.; Heidelbaugh, T. M. unpublished results.

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

brine

(4S)-(−)-tert-BUTYLDIMETHYLSILOXY-2-CYCLOPENTEN-1-ONE

(1R,4S)-(−)-4-tert-Butyldimethylsiloxy-2-cyclopentenyl acetate

(1R,4S)-(−)-tert-butyldimethylsiloxy-2-cyclopentenyl acetate

(1R,4S)-(+)- and (1S,4R)-(−)-4-hydroxy-2-cyclopentenyl acetate

methanol (67-56-1)

hydrogen (1333-74-0)

sodium bicarbonate (144-55-8)

magnesium turnings (7439-95-4)

nitrogen (7727-37-9)

iodine (7553-56-2)

sodium methoxide (124-41-4)

sodium (13966-32-0)

manganese dioxide (1313-13-9)

Pentane (109-66-0)

dichloromethane (75-09-2)

magnesium sulfate (7487-88-9)

triethylamine (121-44-8)

calcium hydride (7789-78-8)

4-dimethylaminopyridine (1122-58-3)

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

tert-butyldimethylsilyl chloride (18162-48-6)