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# Simple and Practical Routes to Enantiomerically Pure 5-(Trialkylsilyl)-2-cyclohexenones

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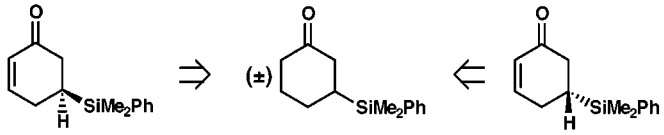
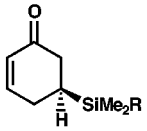
## ABSTRACT

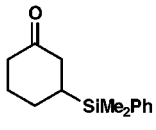



**Enantiomerically pure chiral 5-silylated 2-cyclohexenones are easily prepared in high yield using as a key step kinetic resolution with a commercially available lipase. Fully active enzyme can be recovered very efficiently for reuse. The synthetic steps are outlined in Schemes 1 and 3. Enantiomerically pure 2-cyclohexenones such as 1 and 2 are versatile intermediates for the synthesis of a multitude of chiral targets by means of a variety of diastereoselective reactions such as those illustrated in Scheme 2.**

Chiral 2-cyclohexenones such as pulegone and carvone have been utilized as starting materials for the total synthesis of a large and structurally diverse collection of natural products.[1] This note describes a very convenient method for the synthesis of both enantiomers of 5-(dimethylphenylsilanyl)-cyclohex-2-enone (**1**) and 5-(trimethylsilanyl)cyclohex-2-enone (**2**) which makes these chiral enones readily available.




(*S*)-**1** R = Ph
(*S*)-**2** R = $CH_3$




(±)-**3**

The stereocenter in **1** and **2** is strategically placed for the elaboration of these substrates to a wide variety of chiral multisubstituted cyclohexanone derivatives with control of stereochemistry, and the $\beta$-silyl substituent is a useful and more stable equivalent of the hydroxyl core functional group.[2] Asaoka and co-workers have already described a preparation of chiral **2** and its application to the synthesis of several terpenoids (for example, chiral curcumone and methyl citronellate).[3,4] However, possibly because of the cumbersome and inefficient mode of synthesis of chiral **2**,[3] this starting material has not seen further use.

The starting material for the synthesis of (*S*)-**1** and the enantiomer uses (±)-3-(dimethylphenylsilanyl)cyclohexanone (**3**), which is available in 96% yield from 2-cyclohexenone by reaction with $(Me_2PhSi)Et_2ZnLi$.[5]

(1) Ho, T.-L. *Enantioselective Synthesis: Natural Products from Chiral Terpenes*; Wiley: New York, 1992.

(2) By Tamao-Fleming oxidation; for a review of silyl groups as masked hydroxyl equivalents see: Fleming, I.; Henning, R.; Parker, D. C.; Plaut, H. E.; Sanderson, P. E. J. *J. Chem. Soc., Perkin Trans. 1* **1995**, 317.

(3) Asaoka, M.; Shima, K.; Takei, H. *Tetrahedron Lett.* **1987**, *28*, 5669.

(4) (a) Asaoka, M.; Shima, K.; Fujii, N.; Takei, H. *Tetrahedron* **1988**, *44*, 4757. (b) Asaoka, M.; Sonoda, S.; Fujii, N.; Takei, H. *Tetrahedron* **1990**, *46*, 1541. (c) Asaoka, M.; Sakurai, M.; Takei, H. *Tetrahedron Lett.* **1990**, *31*, 4159. (d) Asoako, M.; Hayashibe, S.; Sonoda, S.; Takei, H. *Tetrahedron Lett.* **1990**, *31*, 4761. (e) Takano, S.; Higashi, Y.; Kamikubo, T.; Moriya, M.; Ogasawora, K. *Synth.* **1993**, 948.

(5) Crump, R. A. N. C.; Fleming, I.; Urch, C. J. *J. Chem. Soc., Perkin Trans. 1* **1994**, 701.

(6) Determined by $^1H$ NMR analysis of **4** in $CDCl_3$ solution.

(7) For other resolutions of cyclohexanol derivatives by enantioselective acetylation under lipase catalysis see: (a) Tanikaga, R.; Morita, A. *Tetrahedron Lett.* **1998**, *39*, 635. (b) Fujisawa, T.; Yamanaka, K.; Mobele, B. I.; Shimizu, M. *Tetrahedron Lett.* **1991**, *32*, 399. (c) Fukazawa, T.; Hashimoto, T. *Tetrahedron: Asymmetry* **1993**, *4*, 2323. (d) Hiratake, J.; Inagaki, M.; Nishioka, T.; Oda, J. *J. Org. Chem.* **1988**, *53*, 6130. (e) Weissfloch, A. N. E.; Kazlauskas, R. J. *J. Org. Chem.* **1995**, *60*, 6959.

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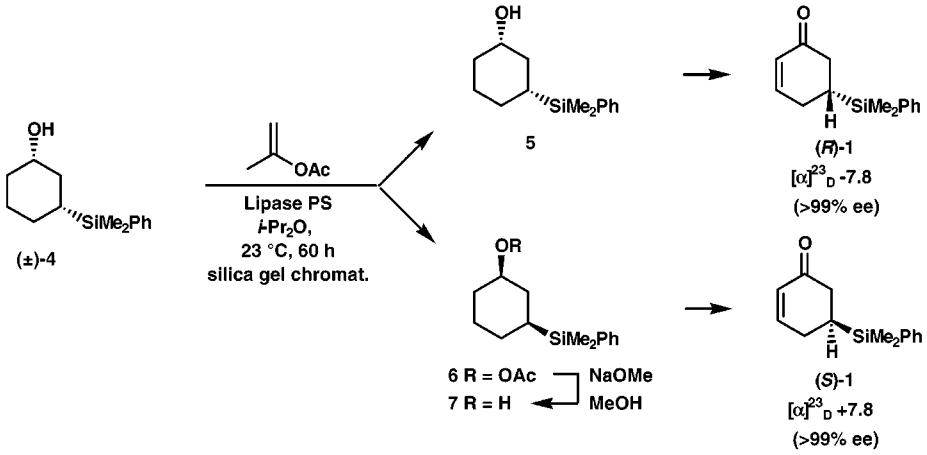
**Scheme 1**




Reduction of **3** with LiAl(*t*-BuO)$_3$H in tetrahydrofuran (THF) at −60 °C for 16 h afforded the *cis* alcohol (±)-**4** in 99% yield with >14:1 *cis/trans* selectivity. After two recrystallizations from pentane at −60 °C, the *cis* alcohol (±)-**4** in 99% stereochemical purity was obtained,[6] mp 42.5−44 °C.

Racemic **4** underwent highly enantioselective acetylation when treated in diisopropyl ether solution with isopropenyl acetate in the presence of Amano Lipase PS powder (essentially insoluble in *i*-Pr$_2$O) for 60 h at 23 °C. At the end of this period, the fully active enzyme was recovered for reuse by filtration. Concentration of the filtrate and chromatographic separation on silica gel afforded 96% of the theoretical yield of the (*R*)-alcohol **5** (>99% ee) and 99% yield of the acetate of the enantiomer **6** (>99% ee), as outlined in Scheme 1.[7,8] Proof of absolute configurations is provided below. Methoxide-catalyzed methanolysis of **6** provided the (*S*)-alcohol **7** in 99% yield.[9] The (*R*)-alcohol **5** was readily transformed to enantiomerically pure (*R*)-**1** by the following three-step sequence: (1) oxidation of the alcohol **5** by pyridinium dichromate (PDC) in $CH_2Cl_2$ at 23 °C for 26 h in the presence of 4 Å molecular sieves to form the corresponding ketone (93%), (2) addition of this ketone to a solution of lithium hexamethyldisilazane (LHMDS) and trimethylchlorosilane (TMSCl) in THF at −78 °C to form 2-((trimethylsilyl)oxy)-4-(dimethylphenylsilanyl)cyclohexene (with ca. 40:1 position selectivity in the deprotonation step),[10] and (3) oxidation of this silyl enol ether in dimethyl

(8) A stirred solution of (±)-**4** (4.88 g, 20.8 mmol, 99% *cis*) in *i*-Pr$_2$O (83 mL, Aldrich) at 23 °C was treated with Lipase PS powder (1.12 g, Amano Pharmaceutical Co., Inc.) and isopropenyl acetate (2.27 mL, 20.6 mmol, Aldrich). The progress of the reaction was monitored by chiral phase analytical HPLC, using a Chiralcel OJ column (Daicel Chemical Industries, Ltd.), until one enantiomer of the starting material was completely consumed. After a total time of 60 h, the insoluble enzyme was removed by filtration, washed with several portions of ether, dried in air for 5−10 min, and stored at −20 °C under $N_2$ for reuse. Concentration of the filtrate in vacuo and silica gel flash chromatography (ethyl acetate−hexanes gradient) afforded the unreacted alcohol **5** (2.38 g, 98% of theoretical yield, ca. 98% *cis*, oil) and the acetate ester **6** (2.82 g, 98% of theoretical yield, oil). For **5**, >99% ee, determined by chiral phase HPLC using a Daicel OJ column, 5% *i*-PrOH in hexanes as eluent at a flow rate of 0.6 mL/min, detection at 215 nm with elution times $t_{minor}$ = 11 min, $t_{major}$ = 14 min. For **6**, $[\alpha]^{24}_D$ = +36.4° (*c* 4.38, $CHCl_3$); >99% ee, determined by chiral phase HPLC using an *S,S* Whelk O1 column (Regis Chemical Co.), 0.25% *i*-PrOH in hexanes as eluent at a flow rate of 1 mL/min, detection at 215 nm with elution times $t_{major}$ = 14.5 min, $t_{minor}$ = 18.0 min.

(9) Found for **7**, >99% ee, determined as above for **5**.

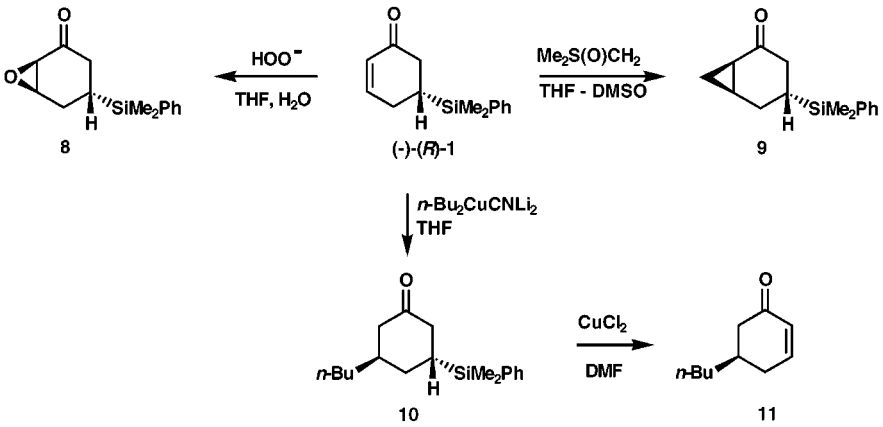
(10) Corey, E. J.; Gross, A. W. *Tetrahedron Lett.* **1984**, *25*, 495.

(11) Larock, R. C.; Hightower, T. R.; Kraus, G. A.; Hahn, P.; Zheng, D. *Tetrahedron Lett.* **1995**, *36*, 2423.

(12) A stirred solution of dry hexamethyldisilazane (6.165 mL, 29.22 mmol) in hexanes (24 mL) at −5 to −10 °C was treated with a solution of *n*-butyllithium in hexanes (3.90 M, 6.94 mL, 27.1 mmol, Alfa). Within 10 min a precipitate appeared. The mixture was stirred for an additional period of 15 min, THF (90 mL) was introduced, and the solution was cooled to −78 °C. To this cold solution was added neat, dry TMSCl (6.865 mL, 54.11 mmol) down the walls of the flask, followed by **5** (2.514 g, 10.82 mmol) as a precooled (−78 °C) solution in THF (10 mL). The reaction mixture was stirred for 30 min and treated with dry $Et_3N$ (12 mL) and then saturated aqueous $NaHCO_3$ (200 mL). The mixture was warmed to room temperature, and the solvents were removed in vacuo. The residue was extracted with ether (2 × 150 mL), and the combined organic layers were washed with water (2 × 150 mL) and brine (150 mL) and dried over anhydrous $K_2CO_3$. After filtration and evaporation of the solvent in vacuo, the crude residue (a 97.5:2.5 mixture of regioisomeric enol ethers, determined by GC using a J&W DB1701 capillary column) was dried azeotropically with benzene (2 × 20 mL) at 80 mmHg and 40−50 °C. A solution of this crude product and $Pd(OAc)_2$ (243.0 mg, 1.082 mmol, 0.10 equiv based on **5**, Aldrich) in dry DMSO (90 mL) in a 500 mL flask was placed under 1 atm of oxygen (balloon). The orange solution turned dark within min. After the mixture was stirred for 11 h at 23 °C, additional $Pd(OAc)_2$ (24.3 mg, 0.108 mmol, 0.01 equiv) was added. After a total time of 14 h, the reaction mixture was poured into water (600 mL) and the products were extracted into 1:1 ether−pentane (250 mL + 150 mL). The combined organic layers were washed, dried ($K_2CO_3$), and concentrated in vacuo. The oily residue was dissolved in pentane (25 mL), filtered through Celite, and crystallized by cooling to −20 °C (seeding was sometimes necessary). The product **(−)-1** (2.131 g, 85% yield based on **5**) was obtained as pale yellow crystals: $[\alpha]^{23}_D$ = −7.8 ± 0.1° (*c* 1.08, $CHCl_3$); mp 35−35.5 °C; $R_f$ = 0.31 (ether−pentane 1:3); FTIR (film) $\nu$ 2955, 1682, 1675, 1427, 1384, 1249, 1166, 1152, 1115, 900, 873, 833, 815 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ 7.49−7.47 (m, 2H), 7.39−7.35 (m, 3H), 6.98 (ddd, *J* = 2.4, 5.6, 10.1 Hz, 1H), 5.98−5.96 (m, 1H), 2.44 (dd, *J* = 3.5, 16.3 Hz, 1H), 2.31−2.14 (m, 3H), 1.65 (tdd, *J* = 11.7, 4.4, 3.7 Hz, 1H), 0.33 (s, 6H); $^{13}$C NMR ($CDCl_3$, 101 MHz) $\delta$ 199.9, 151.4, 136.2, 133.9, 129.5, 129.4, 128.0, 38.6, 26.9, 22.9, −5.3, −5.5; HRMS (EI+) *m/z* calcd for $[C_{14}H_{18}OSi]^+$ 230.1127, found 230.1131; >99% ee as determined by HPLC using a Chiralpak AS column (Daicel Chemical Industries, Ltd.), 4% *i*-PrOH in hexanes as eluent at a flow rate of 1 mL/min, detection of 220 nm with elution times $t_{major}$ = 15 min, $t_{minor}$ = 20 min. The enantiomer, (+)-**1**, was prepared similarly in >99% ee; $[\alpha]^{22}_D$ = +7.8 ± 0.1° (*c* 1.21, $CHCl_3$).

(13) (a) X-ray data for (1*R*,4*R*,6*R*)-(+)-**8**: $C_{14}H_{18}O_2Si$; monoclinic; $P2_1$; *a* = 6.5347(11) Å, *b* = 17.880(3) Å, *c* = 11.411(2) Å; α = 90°, $\beta$ = 93.175(17)°, $\gamma$ = 90°; *Z* = 4; R1($I > 2\sigma(I)$) = 0.0380. (b) Detailed X-ray crystallographic data are available from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, U.K.

**Scheme 2**




sulfoxide solution with 1 atm of $O_2$ and 11 mol % of Pd(OAc)$_2$ at 23 °C for 14 h to form the enone (*R*)-**1** (85% yield over two steps).[11,12] The enantiomer (*S*)-**1** was prepared by a parallel sequence of three steps in a similar yield (ca. 80% overall from **7**).

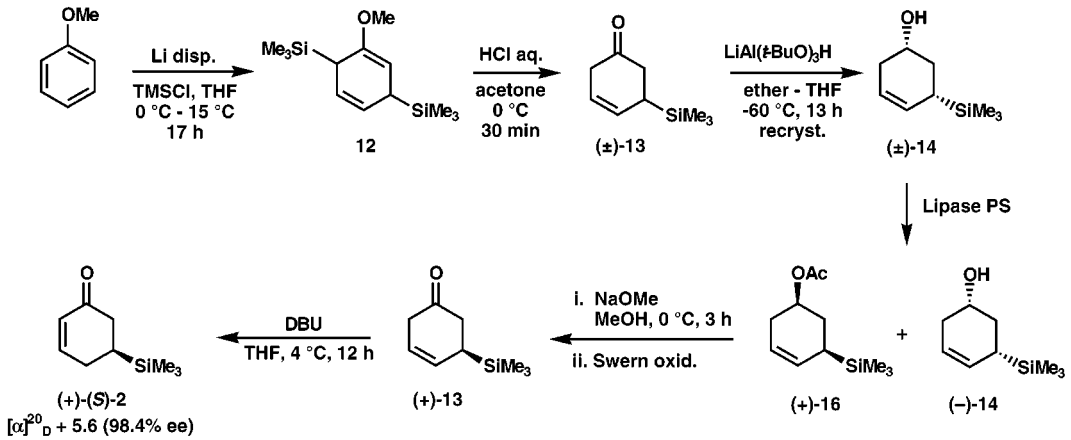
The absolute configuration of the chiral cyclohexanol **5** and compounds derived therefrom was proven by X-ray crystallographic analysis of the crystalline product **8** (Scheme 2), obtained by epoxidation of the levorotatory enone (*R*)-**1** with $H_2O_2$ and LiOH in aqueous THF at 0 °C for 45 min (99:1 *trans/cis* ratio).[13] Highly *trans*-selective (96:4) α,*β*-methylene addition to (*R*)-**1** to form **9** was also observed in the reaction with dimethyloxosulfonium methylide $Me_2S(O)CH_2$, as shown in Scheme 2.[14] The *cis* relationship between the *endo* proton of the cyclopropyl methylene group and the cyclohexyl C−H α to the $SiMe_2Ph$ group of **9** was established by the observation of a 13% NOE effect in the $^1$H NMR spectrum.

Reaction of (−)-(*R*)-**1** with lithium di-*n*-butylcyanocopper[15] in THF at −78 °C for 30 min afforded, as expected, the *trans* conjugate adduct **10**, as outlined in Scheme 2 (50:1 *trans/cis* selectivity). Reaction of **10** with cupric chloride in DMF at 55 °C for 1 h[16] gave the known (*R*)-α,*β*-enone **11**[17] in 75% yield, in accord with expectations.

For the preparation of (*S*)-**2**, racemic *β*,*γ*-unsaturated ketone **13** was synthesized from anisole, lithium (dispersion in mineral oil), and TMSCl in 63% overall yield, according to the known literature procedures (Scheme 3).[3,18] Reduction of **13** with LiAl(*t*-BuO)$_3$H in 3:1 ether−THF at −60 °C for 13 h afforded a 97:3 mixture of *cis/trans* alcohols **14** in 94% yield. The *cis* alcohol was easily purified after one recrystallization from pentane at −15 °C in 77% yield based on **13**. Enantioselective lipase catalyzed acetylation of **14** with isopropenyl acetate in *i*-Pr$_2$O at 23 °C for 64 h produced the optically pure alcohol (−)-**14** and acetate ester (+)-**16**, each in 98% of the theoretical yield after silica gel chromatography. Both products were obtained in >99% ee, as determined by chiral HPLC.[19]

The ester (+)-**16** underwent methanolysis by NaOMe in MeOH at 0 °C for 3 h, and the resulting alcohol was oxidized under Swern conditions to the dextro ketone (+)-**13** ($[\alpha]^{21}_D$ = +219.3° (*c* 1.31, $CHCl_3$)) in quantitative yield. Isomerization of (+)-**13** to the desired enone (+)-**2** was effected using 2.3 equiv of 1,8-diazabicyclo[5.4.0]undec-7-ene in the

**Scheme 3**



presence of a minimum amount of THF at 4 °C for 12 h (79% yield after workup and silica gel chromatography).[20] The ee of (+)-**2** was 98.4%, as determined by enantioselective HPLC analysis.[21] The known *S* absolute configuration of (+)-**2** agrees with the expected sense of asymmetric induction of the lipase-catalyzed acetylation.

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(15) See: Lipshutz, B. H. In *Organocopper Reagents: a Practical Approach*; Taylor, R. J. K., Ed.; Oxford University Press: New York, 1994; pp 105−128.
(16) Asaoka, M.; Shima, K.; Takei, H. *J. Chem. Soc., Chem. Commun.* **1988**, 430.
(17) Asaoka, M.; Takenouchi, K.; Takei, H. *Chem. Lett.* **1988**, 921.
(18) Bennetau, B.; Rajarison, F.; Dunogués, J.; Babin, P. *Tetrahedron* **1994**, *50*, 1179.
(19) For determination of ee, (−)-**14** was converted to (−)-**16** and the ee's of both (+)- and (−)-**16** were measured by enantioselective HPLC analysis using an *S,S* Whelk O1 column, 0.25% *i*-PrOH in hexanes as eluent at a flow rate of 0.7 mL/min and detection at 215 nm with elution times $t_{(+)} = 14.5$ min, $t_{(-)} = 17.0$ min.
(20) $[\alpha]^{20}_D = +5.6°$ (*c* 0.61, $CHCl_3$); lit.[3] $[\alpha]^{20}_D = +9.40°$ (*c* 2.19, $CHCl_3$).
(21) Chiralcel OJ column, 0.2% *i*-PrOH in hexanes as eluent at a flow rate of 1 mL/min, detection at 215 nm with elution times $t_{minor} = 10$ min, $t_{major} = 11$ min.