# Enantioselective Synthesis of (*R*)- and (*S*)-4-Benzyloxy-2-cyclohexen-1-one

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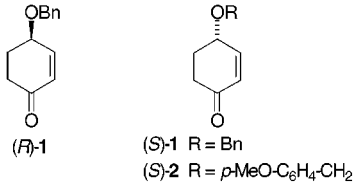
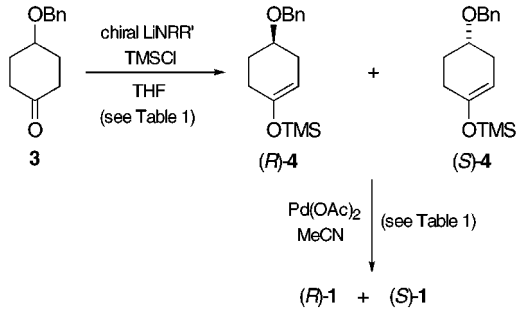
In connection with our work on natural product synthesis, we required a general synthesis of both enantiomers of 4-benzyloxy-2-cyclohexen-1-one (**1**). Inspection of the literature revealed that the asymmetric synthesis of the *S* enantiomer of **1** can be attained via diastereoselective reduction of a chiral ketosulfoxide.[1] On the other hand, the conversion of (−)-quinic acid into the *S* enantiomer of [(4-methoxybenzyl)oxy]-2-cyclohexen-1-one (**2**) has been reported in the context of the total synthesis of the immunosuppressive FK-506.[2] In this paper, we report the development of a simple and efficient enantioselective synthesis of both enantiomeric enones (*R*)-**1** and (*S*)-**1** based on a tandem asymmetric deprotonation−palladium(II)-induced dehydrosilylation reaction sequence.

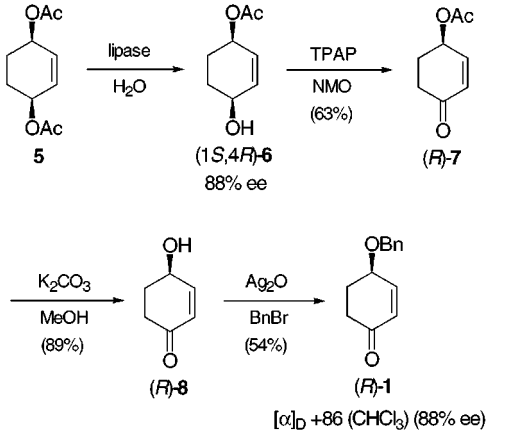



A number of recent studies pointed out the utility of asymmetric deprotonation with chiral bases for desymmetrization of prochiral cyclic ketones.[3] It is envisioned that this asymmetric tactic could serve for a convenient enantioselective access to both enantiomers of the enones, (*R*)-**1** and (*S*)-**1**, involving the formation of chiral enol derivatives by $\sigma$ symmetry-breaking deprotonation of the cyclic ketone 4-(benzyloxy)cyclohexanone (**3**) under the influence of both enantiomers of chiral lithium amide bases. Thus, the Corey in situ quench technique[4] was applied to the cyclic ketone **3** for chiral base-mediated enolization, followed by in situ conversion to the enol silane **4** as shown in Scheme 1: In a typical experiment, the chiral lithium amide and $Me_3SiCl$ were premixed in THF and the cyclic ketone **3** was added to this at −78 °C. The resulting enantiomerically enriched enol silane **4** was subjected to palladium(II)-catalyzed dehydrosilylation (0.5 molar equiv of $Pd(OAc)_2$ in the presence of 0.5 molar equiv of *p*-benzoquinone) according to the procedure developed by Saegusa et al.[5] to yield the optically active cyclic enone **1**. In this case, however, since

**Scheme 1**




**Scheme 2**




the reaction was rather sluggish and **1** was obtained in moderate yield (55%) along with the recovered starting material (34%), a stoichiometric amount of $Pd(OAc)_2$ was used, leading to a remarkable improvement in the yield of **1** (98%).

For the purpose of the assignment of the absolute configuration of the obtained chiral enone **1** and determination of its enantiomeric purity by chiral HPLC analysis, the *R* enantiomer of the enone, (*R*)-**1**, was then synthesized by an alternative route outlined in Scheme 2. Thus, *meso*-1,4-(diacetyloxy)cyclohex-2-ene (**5**) was subjected to hydrolase-catalyzed resolution with *Pseudomonas cepacia* lipase (Amano) based on a reported procedure,[6] which delivered the enantiomerically enriched alcohol (1*S*,4*R*)-**6** with 88% ee (by chiral HPLC analysis). Oxidation of the latter with tetrapropylammonium perruthenate (TPAP)/4-methylmorpholine *N*-oxide (NMO) produced the enone (*R*)-**7**, which was converted via acetate hydrolysis followed by O-benzylation to (*R*)-**1**. Comparison of the $^1$H NMR data of synthetic (*R*)-**1** with those for (*S*)-**1** reported by Carreño et al.[1] proved that the chemical structures of these compounds are identical. However, to our surprise, the sign of the optical rotation of synthetic (*R*)-**1** ($[\alpha]^{24}_D$ +86 (*c* 1.2, $CHCl_3$)) was found to be the same as that reported[1] for (*S*)-**1** ($[\alpha]_D$ +66 (*c* 0.4, $CHCl_3$)). Furthermore, the sample of (*S*)-**1** obtained by following the exactly same reaction sequence reported

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(6) (a) Harris, K. J.; Shih, Y.-E.; Girdaukas, G.; Sih, C. J. *Tetrahedron Lett.* **1991**, *32*, 3941−3944. (b) Kazlauskas, R. J.; Weissfloch, A. N. E.; Rappaport, A. T.; Cuccia, L. A. *J. Org. Chem.* **1991**, *56*, 2656−2665.

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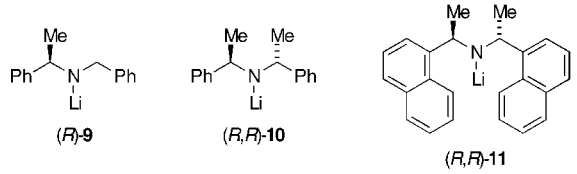


**Figure 1.** Chiral lithium dialkylamides (represented by one enantiomer in each case).

**Table 1. Enantioselective Synthesis of Cyclic Enones (*R*)-1 and (*S*)-1 via Enol Silanes (*R*)-4 and (*S*)-4 Formed by Lithium Amide-Mediated Deprotonation[a]**

| | enol silane (*R*)-**4**/(*S*)-**4** | | | cyclic enone[c] | |
|---|---|---|---|---|---|
| entry | lithium amide | temp (°C) | yield (%)[b] | compound[d] | ee (%)[e] |
| 1 | (*R*)-**9** | −78 | 76 | (*S*)-**1** | 24 |
| 2 | (*S*)-**9** | −78 | 79 | (*R*)-**1** | 26 |
| 3 | (*R,R*)-**10** | −78 | 87 | (*S*)-**1** | 80 |
| 4 | (*R,R*)-**10** | −95 | 65 | (*S*)-**1** | 82 |
| 5 | (*S,S*)-**10** | −78 | 84 | (*R*)-**1** | 81 |
| 6 | (*R,R*)-**11** | −78 | 57 | (*S*)-**1** | 82 |
| 7 | (*S,S*)-**11** | −78 | 56 | (*R*)-**1** | 82 |

[a] Cf. Scheme 1. [b] Isolated yield of the enantiomeric mixture of (*R*)-**4** and (*S*)-**4** after silica gel chromatography. [c] Converted from the enantiomeric mixture of **4** by Pd(II)-induced dehydrosilylation in 96−98% yield as the enantiomeric mixture. [d] Major enantiomer formed. [e] Determined by chiral HPLC using a Chiralcel OD column.

by the same authors[1] was found to have the optical rotation value ($[\alpha]^{23}_D$ −96 (*c* 1.2, $CHCl_3$)) being not only significantly larger but also of the opposite sign from the reported value. These facts led to the conclusion that the positive sign of the optical rotation given for (*S*)-**1** ($[\alpha]_D$ +66 (*c* 0.4, $CHCl_3$)) is erroneous and should be corrected to the negative sign. Therefore, the correct value of $[\alpha]_D$ −98 ($CHCl_3$) should be adopted for enantiomerically pure (*S*)-**1**, which was estimated from the observed value $[\alpha]^{24}_D$ +86 (*c* 1.2, $CHCl_3$) for the above-described 88% ee material of (*R*)-**1**).

Having established the absolute stereochemistry and the optical rotation value of the enones (*R*)-**1** and (*S*)-**1**, we examined the effect of chiral lithium amide bases on enantioselectivity in asymmetric synthesis of these enones based on the asymmetric deprotection−dehydrosilylation protocol described above. We chose a series of the chiral arylethylamine-based lithium amides **9**−**11** for the reason of their commercial availability in both enantiomeric forms (Figure 1). The results from these experiments are depicted in Table 1. Within the range of our experiments, these results proved that the *R* (or *S*) chirality of the arylethylamino moiety in the chiral lithium amides induces the formation of the enone **1** having the *S* (or *R*) absolute configuration. As can be seen in Table 1, the use of the lithium amide **9** for the asymmetric deprotonation of the cyclic ketone **3** resulted in poor asymmetric induction (24% and 26% ee) in the formation of the chiral cyclic enone **1** (entries 1, 2). However, the use of the $C_2$-symmetrical lithium amides **10** (entries 3, 5) and **11** (entries 6, 7) led to good enantioselectivity (80−82% ee), though in the latter case the chemical yields of **4** were rather low (57% and 56%). When the deprotonation of **3** using (*R,R*)-**10** was carried out at lower temperature (−95 °C), the yield of the enol silane **4** decreased to 65% with no change in the enantioselectivity (entry 4).

In conclusion, application of the tandem asymmetric deprotonation−palladium(II)-induced dehydrosilylation reaction sequence to the $\sigma$-symmetrical cyclic enone **3** has allowed the successful preparation of both enantiomers of cyclic enones **1**. Additionally, our synthesis and chiral HPLC analysis of **1** led to the conclusion that the positive sign of the specific rotation reported for (*S*)-**1** should be corrected to the negative sign.

## Experimental Section

**General Methods.** $^1$H NMR spectra were recorded at 400 MHz using residual $CHCl_3$ (7.26 ppm) as reference. $^{13}$C NMR spectra were recorded at 100.6 MHz with $CDCl_3$ (77.05 ppm) as reference. IR spectra were taken with an FTIR instrument. Mass spectra were measured at an ionizing voltage of 70 eV. Organic solvents used were dried by standard methods. Unless otherwise noted, silica gel 60 (230−400 mesh, Merck) was used for column chromatography, and precoated silica gel $60F_{254}$ plates (0.25 mm, Merck) were used for TLC. All enantiomeric excesses were determined by chiral HPLC on a solid stationary phase Chiralpak AD or Chiralcel OD column using hexane-2-propanol mixtures as eluents.

**4-(Benzyloxy)-1-trimethylsilyloxycyclohex-1-ene (4).** In a typical procedure, a solution of the chiral lithium amide (*R,R*)-**10** was prepared by treatment of a solution of the corresponding secondary amine (121 mg, 0.54 mmol) in THF (2 mL) at −78 °C under Ar with a solution (1.54 M) of BuLi (350 $\mu$L, 0.54 mmol) in hexane. After 30 min, $Me_3SiCl$ (310 $\mu$L, 2.45 mmol) was added to it via a microsyringe with stirring. After being stirred for 2 min, a solution of **3**[7] (100 mg, 0.49 mmol) in THF (0.5 mL) was added, and the mixture was stirred at −78 °C for 10 min. The mixture was quenched by addition of saturated $NaHCO_3$ solution (5 mL) and extracted with $Et_2O$ (3 × 20 mL). The combined organic extracts were washed with water (20 mL) and brine (20 mL), dried ($MgSO_4$), and concentrated. Chromatography (hexane−AcOEt, 50:1) of the crude residue gave an enantiomeric mixture of **4** (118 mg, 87%) as a colorless oil: $^1$H NMR ($CDCl_3$) $\delta$ 0.20 (9H, s), 1.65−1.81 (1H, m), 1.95−2.01 (1H, m), 2.11−2.18 (3H, m), 2.30−2.42 (1H, m), 3.61−3.68 (1H, m), 4.58 (2H, s), 4.74−4.76 (1H, m), 7.26−7.38 (5H, m); $^{13}$C NMR ($CDCl_3$) $\delta$ 0.3 (3 carbons), 28.1 (2 carbons), 29.8, 70.1, 73.5, 100.8, 127.3, 127.4 (2 carbons), 128.3 (2 carbons), 139.0, 149.9; IR (neat) 1670, 1372, 1252, 1189, 1099, 888, 845 cm$^{-1}$; EIMS *m*/*z* (relative intensity) 276 ($M^+$, 0.8), 204 (1.0), 170 (12), 155 (20), 104 (24), 91 (100).

**4-Benzyloxy-2-cyclohexen-1-one (1). Method A.** To a solution of $Pd(OAc)_2$ (224 mg, 1 mmol) and *p*-benzoquinone (108 mg, 1 mmol) in acetonitrile (4 mL) was added the enantiomeric mixture of **4** (552 mg, 2 mmol) with stirring under Ar at room temperature. After being stirred at room temperature for 10 h, the mixture was filtered through Celite and concentrated in vacuo. Chromatography of the residue gave the unreacted starting material **4** (188 mg, 45%) and an enantiomeric mixture of **1** (222 mg, 55% or 83% based on recovered starting material) as a colorless oil: $^1$H NMR ($CDCl_3$) $\delta$ 2.01−2.11 (1H, m), 2.30−2.39 (2H, m), 2.58−2.65 (1H, m), 4.25−4.29 (1H, m), 4.66 (1H, ABq, $J$ = 11.8 Hz), 5.55 (1H, ddd, $J$ = 10.3, 1.8, 0.9 Hz), 6.99 (1H, ddd, $J$ = 10.3, 2.3, 1.5 Hz), 7.30−7.37 (5H, m); $^{13}$C NMR ($CDCl_3$) $\delta$ 26.2, 35.3, 70.9, 72.5, 127.7 (2 carbons), 127.9, 128.6 (2 carbons), 137.8, 150.5, 198.7; IR (neat) 1682, 1094 cm$^{-1}$; EIMS *m*/*z* (relative intensity) 202 ($M^+$, 0.2), 174 (0.5), 142 (0.6), 124 (1.1), 104 (1.7), 91 (100). Anal. Calcd for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 76.9; H, 6.97.

The enantiomeric excess of **1** (see Table 1) was determined by chiral HPLC analysis using a Chiralcel OD column (hexane−2-propanol (90:10, v/v), 0.5 mL/min, detection at 254 nm, (*S*)-**1**: 27.04 min, (*R*)-**1**: 31.23 min).

**Method B.** A solution of the enantiomeric mixture of **4** (118 mg, 0.43 mmol) and $Pd(OAc)_2$ (96 mg, 0.43 mmol) in acetonitrile (4 mL) was stirred at room temperature under Ar for 10 h. The mixture was filtered through Celite and concentrated in vacuo. Purification of the residue by chromatography (hexane−AcOEt, 9:1) afforded an enantiomeric mixture of **1** (85 mg, 98%).

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**Lipase-Catalyzed Hydrolysis of 5.** To a stirred solution of the diacetate **5**[8] (5.00 g, 25.2 mmol) in toluene (100 mL) were added 0.1 M phosphate buffer solution (pH 7.5, 400 mL) and then *Pseudomonas cepacia* lipase (Amano) (5.0 g) at room temperature. The suspension was stirred at room temperature for 2 days, extracted with $Et_2O$ (3 × 200 mL), and filtered through Celite. The filtrate was dried ($MgSO_4$) and concentrated. The residue was chromatographed (hexane−AcOEt, 20:1) to give the monoacetate (1*S*,4*R*)-**6** (0.96 g, 25% or 64% based on recovered starting material (3.50 g)) in 88% ee as determined by HPLC using a Chiralpak AD column (hexane−2-propanol (95:5, v/v), 0.5 mL/min, RI detection, (1*S*,4*R*)-**6**: 22.86 min, (1*R*,4*S*)-**6**: 23.86 min): $^1$H NMR ($CDCl_3$) $\delta$ 1.51−1.62 (1H, br m), 1.70−1.95 (4H, m), 2.07 (3H, s), 4.15−4.23 (1H, br m), 5.17−5.20 (1H, m), 5.80 (1H, ddd, $J$ = 10.1, 3.5, 0.8 Hz), 5.97 (1H, ddd, $J$ = 10.1, 2.8, 0.9 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 21.3, 25.0, 28.2, 65.4, 67.3, 128.0, 134.8, 170.7.

**(*R*)-4-Acetoxy-2-cyclohexen-1-one ((*R*)-7).** To a stirred solution of (1*S*,4*R*)-**6** (88% ee, 2.0 g, 12.8 mmol) in $CH_2Cl_2$ (120 mL) were added powdered 4 Å molecular sieves (200 mg) and NMO (2.59 g, 19.2 mmol). After the mixture was stirred at room temperature for 30 min, TPAP (225 mg, 0.64 mmol) was added and stirring was continued. After 10 min, the mixture was diluted with $CHCl_3$ (120 mL) and washed with 10% $Na_2CO_3$ solution (100 mL), 10% $CuSO_4$ solution (100 mL), and brine (100 mL). Drying ($MgSO_4$) and concentration in vacuo left a residue which was purified by chromatography (hexane−AcOEt, 5:1) to give (*R*)-**7** (1.24 g, 63%) as a colorless oil: $[\alpha]^{26}_D$ +113 (*c* 1.48, $CHCl_3$); $^1$H NMR ($CDCl_3$) $\delta$ 2.10 (3H, s), 2.04−12.13 (1H, m), 2.31−2.38 (1H, m), 2.44 (1H, ddd, $J$ = 16.8, 11.6, 5.0 Hz), 2.61 (1H, dt, $J$ = 16.8, 5.0 Hz), 5.53−5.58 (1H, m), 6.05 (1H, ddd, $J$ = 10.3, 1.9, 0.7 Hz), 6.84 (1H, ddd, $J$ = 10.3, 2.7, 1.4 Hz), 7.29−7.59 (5H, m); $^{13}$C NMR ($CDCl_3$) $\delta$ 21.0, 28.7, 34.9, 67.7, 130.8, 147.6, 170.3, 197.8; IR (neat) 1740, 1688, 1373, 1237, 1038 cm$^{-1}$; EIMS *m*/*z* (relative intensity) 154 ($M^+$, 21), 126 (9), 112 (50), 94 (39), 84 (88), 43 (100); HRMS (EI) calcd for $C_8H_{10}O_3$ ($M^+$) 154.0630, found 154.0634.

**(*R*)-4-Hydroxy-2-cyclohexen-1-one ((*R*)-8).** To a solution of above-described (*R*)-**7** (200 mg, 1.29 mmol) in MeOH (4 mL) was added $K_2CO_3$ (180 mg, 1.30 mmol). After being stirred at room temperature for 10 min, the mixture was diluted with brine (4 mL) and extracted with $CHCl_3$ (3 × 8 mL). The combined organic layers were washed with brine (5 mL), dried ($MgSO_4$), and concentrated in vacuo. The resulting residue was purified by chromatography (hexane−AcOEt, 1:1) to give (*R*)-**8** (129 mg, 89%) as a colorless oil, which had spectral data (NMR and IR) in agreement with those previously reported[2a] for (*S*)-**8**.

**Preparation of (*R*)-1 by *O*-Benzylation of (*R*)-8.** To a solution of above-described (*R*)-**8** (400 mg, 3.57 mmol) in $CH_2Cl_2$ (7 mL) were added $Ag_2O$ (993 mg, 4.28 mmol) and benzyl bromide (855 mg, 5.00 mmol). The mixture was stirred at room temperature for 24 h, filtered through Celite, and concentrated in vacuo. After rapid chromatography of the residue on neutral alumina (hexane−AcOEt, 4:1) to remove the resulting benzyl alcohol, silica gel chromatography (hexane−AcOEt, 4:1) was performed to give (*R*)-**1** (390 mg, 54%) as a colorless oil: $[\alpha]^{24}_D$ +86 (*c* 1.2, $CHCl_3$).

**Supporting Information Available:** Copies of $^1$H and $^{13}$C NMR spectra for compounds (*R*)-**4**, (1*S*,4*R*)-**6**, and (*R*)-**7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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