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Synthesis of optically active 3-alkoxy-6-hydroxymethyl-6-methyl-2-cyclohexenone

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Abstract

Optically active 3-alkoxy-6-hydroxymethyl-6-methyl-2-cyclohexenone and 6-acetoxymethyl-3-alkoxy-6-methyl-2-cyclohexenone were efficiently obtained by lipase-catalyzed kinetic resolution. (*R*)-6-Acetoxymethyl-3-(methoxymethoxy)-6-methyl-2-cyclohexenone was converted to the synthetic intermediate of cassiol.

1. Introduction

Optically active cyclohexenone **I** possessing an asymmetric quaternary carbon has been found useful as a starting material for synthesizing natural products, such as terpenoids. The syntheses of sesquiterpenoid cassiol[1,2] and diterpenoid trisporol B[3,4] from cyclohexenone **I** have been reported, however, only limited means are available for the synthesis of optically active cyclohexenone **I**. The authors are presently engaged in the synthesis of sesterterpenoid dysidiolide, a potent inhibitor of protein phosphatase cdc25A,[5,6] for optically active cyclohexenones **I** (R^1=H or protecting group, R^2=H, R^3=alkoxy) are prerequisite to the synthesis as starting materials. The enzymatic kinetic resolution of the primary alcohol attached to the asymmetric quaternary carbon appears only slightly in the literature,[7,8] although the enzymatic asymmetrization of prochiral diols has been extensively reported.[9] In this study, an efficient method was established for synthesizing optically active cyclohexenones **I** (R^1=H or Ac, R^2=H, R^3=OMe or OMOM), equivalent to (+)-**3**, (+)-**4**, (−)-**5** and (−)-**6**, by lipase-catalytic kinetic resolutions. (*R*)-6-Acetoxymethyl-3-(methoxymethoxy)-6-methyl-2-cyclohexenone (−)-**6**, obtained by lipase-catalytic kinetic resolution, was converted to a synthetic intermediate of cassiol (Fig. 1).

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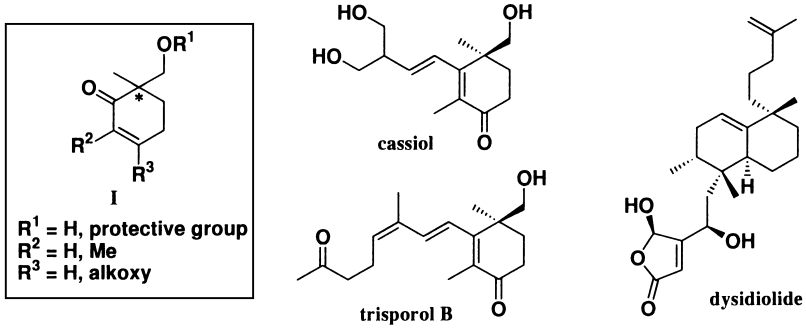
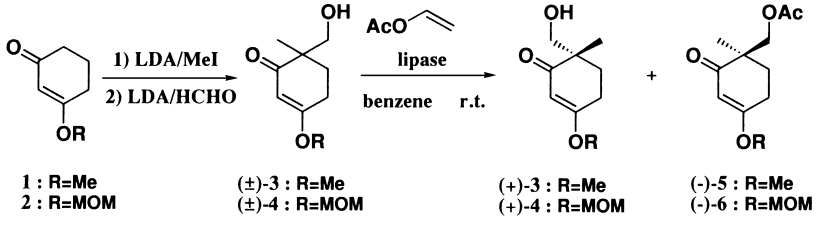


Figure 1.

2. Results and discussion

Alcohols (±)-**3** and (±)-**4** were prepared from cyclohexenone **1** and **2**,[10] respectively, in two steps: 1) methylation with lithium diisopropylamide (LDA) and iodomethane and 2) hydroxymethylation with LDA and formaldehyde (Scheme 1). Table 1 shows the results of enantioselective acetylation of alcohols (±)-**3** and (±)-**4**. Alcohol (±)-**3** was treated with vinyl acetate in benzene at room temperature in the presence of lipase AY (from *Candida rugosa*) to give alcohol (+)-**3** and acetate (−)-**5**, but the reaction rate and enantiomeric excesses were low (entry 1). Acetylation of (±)-**3** with lipase PS (from *Pseudomonas cepacia*) gave alcohol (+)-**3** (69% ee) and acetate (−)-**5** (90% ee) (entry 2). On using lipase AK (from *Pseudomonas fluorescens*), the acetylation of (±)-**3** gave alcohol (+)-**3** (96% ee) and acetate (−)-**5** (90% ee) (entry 3). Alcohol (±)-**4** was acetylated with lipase AY, PS and AK (entries 4–6) and satisfactory results were obtained on using lipase AK. Treatment of (±)-**4** with vinyl acetate in the presence of lipase AK in benzene at room temperature gave alcohol (+)-**4** (99% ee) and acetate (−)-**6** (97% ee) (entry 6). Enantiomeric excesses of (+)-**3** and (+)-**4** were determined by HPLC analysis, using a column packed with CHIRALPAK AS (hexane:isopropanol 9:1). Enantiomeric excesses of (−)-**5** and (−)-**6** were determined by HPLC analysis of (−)-**4**, prepared by the methanolysis of (−)-**5** and (−)-**6** under the above conditions.



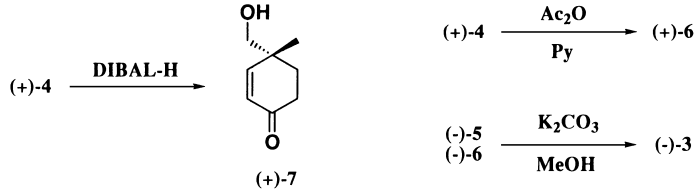
Scheme 1.

Absolute configurations of alcohol (+)-**3**, alcohol (+)-**4**, acetate (−)-**5** and acetate (−)-**6** were determined based on chemical conversions (Scheme 2). Alcohol (+)-**4** was reduced with DIBAL-H to give enone (+)-**7** ($[\alpha]_D^{26}$ +31.2 (*c* 0.84, $CHCl_3$)), the antipode of the known enone (−)-**7** ($[\alpha]_D^{26}$ +28.0 (*c* 1.85, $CHCl_3$), 85% ee).[11] Acetylation of (+)-**4** gave acetate (+)-**6** ($[\alpha]_D^{26}$ +66.2 (*c* 1.25, $CHCl_3$)). Methanolysis of acetates (−)-**5** and (−)-**6** afforded alcohol (−)-**3** in either case. The absolute configurations of (+)-**3**, (+)-**4**, (−)-**5** and (−)-**6** at C-6 position were thus concluded to be *S*, *S*, *R* and *R*, respectively.

For assessment of the optically active cyclohexenone derivatives (+)-**4** and (−)-**6** as potential chiral building blocks, cyclohexenone derivative (−)-**6** was converted to a synthetic intermediate of cassiol (Scheme 3). Hydrogenation of (−)-**6** in the presence of 10% Pd–C and K_2CO_3 in MeOH gave alcohol **8**

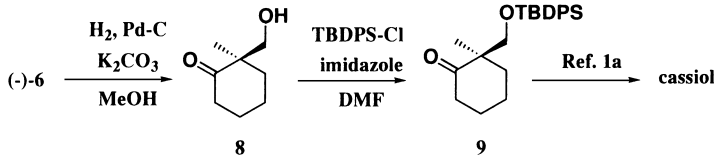
Table 1

				alcohol			acetate		
entries	substrate	lipase	reaction time (d)	alcohol	yield (%)	ee (%)	acetate	yield (%)	ee (%)
1	(±)-**3**	AY	10	(+)-**3**	62	22	(-)-**5**	26	49
2	(±)-**3**	PS	14	(+)-**3**	54	69	(-)-**5**	36	90
3	(±)-**3**	AK	3	(+)-**3**	45	96	(-)-**5**	38	90
4	(±)-**4**	AY	7	(+)-**4**	68	14	(-)-**6**	25	45
5	(±)-**4**	PS	5	(+)-**4**	51	75	(-)-**6**	40	94
6	(±)-**4**	AK	1	(+)-**4**	48	99	(-)-**6**	46	97



Scheme 2.

in 76% yield. The hydroxyl group in **8** was protected as TBDPS ether so as to afford cyclohexanone **9**, a synthetic intermediate of cassiol.[3a]



Scheme 3.

The lipase-catalyzed method for synthesizing the optically active primary alcohol adjacent to a quaternary carbon was established. Cyclohexenone derivatives (+)-**4** and (−)-**6** were clearly shown to be useful as chiral building blocks in the synthesis of natural products. The total synthesis of dysidiolide starting from cyclohexenone (+)-**4** is now being carried out.

3. Experimental

3.1. General

Optical rotation was measured with a JASCO DIP-360 automatic polarimeter. Infrared (IR) spectra were recorded with a Perkin–Elmer FT-IR 1710 spectrometer or JASCO FT-IR 620 spectrometer. Ultraviolet (UV) spectra were recorded with a JASCO V-550 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker DPX-400 or Varian Gemini-300. Chemical shifts were expressed on a δ (ppm) scale with tetramethylsilane (TMS) as the internal standard (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad). Electron impact mass spectra (EIMS) and high resolution electron impact mass spectra (HREIMS) were obtained using Hitachi M-80 or VG Auto Spec spectrometer. Elemental analysis was conducted using a Perkin–Elmer 242. Column chromatography was carried out on Merck silica gel 60 (70–230 mesh).

3.2. (±)-6-Hydroxymethyl-3-methoxy-6-methyl-2-cyclohexenone (±)-**3**

To a cold (−78°C) solution of lithium diisopropylamide [prepared from diisopropylamine (25.6 mL, 182 mmol) and butyllithium (1.48 M in hexane, 104 mL, 154 mmol)] in THF (470 mL) was added dropwise a solution of the 3-methoxycyclohexenone **1** (17.6 g, 140 mmol) in THF (10 mL). After the mixture had been stirred at −78°C for 30 min, iodomethane (12.2 mL, 196 mmol) was added and the mixture was warmed to room temperature over 1 h. The reaction mixture was poured into ether and saturated NH_4Cl solution. The organic layer was washed with water and saturated NaCl solution, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluted with hexane:AcOEt 1:1) to give methylcyclohexenone derivative (17.6 g, 90% yield) as a colorless oil.

EIMS m/z (relative intensity) 140 (M^+, 80), 98 (100); HREIMS: calcd for $C_8H_{12}O_2$ (M^+) 140.0837; found: 140.0829; IR (neat) 2962, 1661, 1613 cm^{-1}; UV (EtOH) λ_{max} 246 nm (ε 7900); ^1H NMR (300 MHz, $CDCl_3$) δ 1.14 (3H, d, *J*=6.9 Hz), 1.70 (1H, m), 2.04 (1H, dq, *J*=13.2, 4.7 Hz), 2.30 (1H, m), 2.39 (1H, ddd, *J*=4.6, 5.5, 17.6 Hz), 2.47 (1H, dddd, *J*=1.2, 5.2, 10.0, 17.6 Hz), 3.67 (3H, s), 5.33 (1H, d, *J*=1.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.3, 28.1, 29.2, 40.1, 55.6, 101.6, 177.7, 201.9.

To a cold (−78°C) solution of lithium diisopropylamide [prepared from diisopropylamine (23.2 mL, 166 mmol) and butyllithium (1.54 M in hexane, 98.2 mL, 151 mmol)] in THF (230 mL) was added dropwise a solution of the above methylcyclohexenone derivative (6.43 g, 45.9 mmol) in THF (10 mL). The mixture was stirred at −78°C for 30 min and formaldehyde gas [prepared from paraformaldehyde (36.7 g) by heating at 180°C] was then introduced during a 30 min period. The reaction mixture was poured into ether and saturated NH_4Cl solution. The organic layer was washed with water and saturated NaCl solution, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluted with hexane:AcOEt 1:2) to give alcohol (±)-**3** (3.73 g, 48% yield) as a colorless oil.

EIMS m/z (relative intensity) 170 (M^+, 46), 98 (100); HREIMS: calcd for $C_9H_{14}O_3$ (M^+) 170.0943; found: 170.0935; IR (neat) 3419, 2938, 1636, 1606 cm^{-1}; UV (EtOH) λ_{max} 246 nm (ε 13300); ^1H NMR (400 MHz, $CDCl_3$) δ 1.16 (3H, s), 1.44 (1H, ddd, *J*=3.2, 5.4, 13.4 Hz), 2.03 (1H, ddd, *J*=5.5, 12.0, 13.4 Hz), 2.39 (1H, ddd, *J*=3.2, 5.5, 18.0 Hz), 2.61 (1H, dddd, *J*=1.0, 5.4, 12.0, 18.0 Hz), 3.04 (1H, br t, *J*=5.5 Hz), 3.70 (3H, s), 3.56 (2H, m), 5.28 (1H, d, *J*=1.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.9, 25.5, 29.8, 44.6, 55.8, 69.1, 101.1, 177.8, 205.5.

3.3. (±)-6-Hydroxymethyl-3-(methoxymethoxy)-6-methyl-2-cyclohexenone (±)-**4**

To a cold (−78°C) solution of lithium diisopropylamide [prepared from diisopropylamine (15.5 mL, 110 mmol) and butyllithium (1.56 M in hexane, 66.0 mL, 103 mmol)] in THF (355 mL) was added dropwise a solution of the 3-(methoxymethoxy)-2-cyclohexenone (**2**) (11.5 g, 73.4 mmol) in THF (10 mL). The mixture was stirred at −78°C for 30 min, followed by the addition of iodomethane (6.40 mL, 103 mmol). The mixture was warmed to room temperature over 1 h. The reaction mixture was poured into ether and saturated NH_4Cl solution. The organic layer was washed with water and saturated NaCl solution, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluted with hexane:AcOEt 1:1) to give methylcyclohexenone derivative (12.3 g, 91% yield) as a colorless oil.

EIMS m/z (relative intensity) 170 (M^+, 20), 45 (100). Anal. calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.36; H, 8.21. IR (neat) 2936, 1661, 1614 cm^{-1}; UV (EtOH) λ_{max} 245 nm (ε 9600); ^1H NMR (400 MHz, $CDCl_3$) δ 1.15 (3H, d, *J*=6.9 Hz), 1.71 (1H, m), 2.06 (1H, dq, *J*=13.2, 4.8 Hz), 2.28 (1H, m),

2.42 (1H, dt, *J*=4.8, 17.4 Hz), 2.50 (1H, dddd, *J*=1.3, 5.1, 10.3, 17.4 Hz), 3.46 (3H, s), 5.03 (1H, d, *J*=6.1 Hz), 5.05 (1H, d, J=6.1 Hz), 5.45 (1H, d, *J*=1.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.3, 28.0, 29.1, 40.0, 57.0, 94.0, 104.2, 174.5, 201.9.

To a cold (−78°C) solution of lithium diisopropylamide [prepared from diisopropylamine (5.91 mL, 42.0 mmol) and butyllithium (1.56 M in hexane, 89.0 mL, 139 mmol)] in THF (60.0 mL) was added dropwise a solution of the above methylcyclohexenone derivative (2.04 g, 12.0 mmol) in THF (10 mL). The mixture was stirred at −78°C for 30 min and formaldehyde gas [prepared from paraformaldehyde (9.0 g) by heating at 180°C] was then introduced during 30 min. The reaction mixture was poured into ether and saturated NH_4Cl solution. The organic layer was washed with water and saturated NaCl solution, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluted with hexane:AcOEt 1:2) to give alcohol (±)-**4** (1.44 g, 60% yield) as a colorless oil.

EIMS m/z (relative intensity) 200 (M^+, 25), 45 (100); HREIMS: calcd for $C_{10}H_{16}O_4$ (M^+) 200.1049; found: 200.1045; IR (neat) 3436, 2934, 1646, 1614 cm^{-1}; UV (EtOH) λ_{max} 247 nm (ε 12000); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.15 (3H, s), 1.57 (1H, ddd, *J*=3.1, 5.4, 13.5 Hz), 2.05 (1H, ddd, *J*=5.6, 11.6, 13.5 Hz), 2.40 (1H, ddd, *J*=3.1, 5.6, 18.2 Hz), 2.60 (1H, dddd, *J*=1.5, 5.4, 11.6, 18.2 Hz), 3.03 (1H, s), 3.45 (3H, s), 3.55 (2H, m), 5.04 (1H, d, *J*=6.2 Hz), 5.07 (1H, d, *J*=6.2 Hz), 5.40 (1H, d, *J*=1.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.8, 25.2, 29.5, 44.5, 57.0, 68.8, 94.1, 103.5, 174.6, 205.2.

*3.4. Lipase-catalyzed acetylation of alcohols (±)-**3** and (±)-**4***

3.4.1. Typical procedure

To a solution of alcohol (±)-**4** (195 mg, 0.988 mmol) and vinyl acetate (270 μL, 2.93 mmol) in benzene (4.9 mL), lipase AK (99 mg) was added, followed by stirring for one day at room temperature. The reaction mixture was diluted with Et_2O, filtered using a Kiriyama funnel and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluted with hexane:AcOEt 1:2) to give alcohol (+)-**4** (96.4 mg, 48% yield, 99% ee) and acetate (−)-**6** (109 mg, 46% yield, 97% ee) as a colorless oil, respectively.

*3.5. (S)-6-Hydroxymethyl-3-methoxy-6-methyl-2-cyclohexenone (+)-**3***

$[\alpha]_D^{26}$ +80.5 (*c* 1.19, $CHCl_3$).

*3.6. (R)-6-Acetoxymethyl-3-methoxy-6-methyl-2-cyclohexenone (−)-**5***

$[\alpha]_D^{26}$ −59.5 (*c* 1.26, $CHCl_3$); EIMS m/z (relative intensity) 212 (M^+, 15), 152 (20), 98 (100). Anal. calcd for $C_9H_{14}O_3$: C, 62.25; H, 7.60. Found: C, 62.35; H, 7.47. IR (neat) 2942, 1741, 1653, 1611 cm^{-1}; UV (EtOH) λ_{max} 248 nm (ε 11800); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10 (3H, s), 1.72 (1H, dt, *J*=13.6, 5.1 Hz), 2.02 (3H, s), 2.09 (1H, ddd, *J*=5.6, 9.9, 13.6 Hz), 2.41 (1H, dt, *J*=18.0, 5.6 Hz), 2.51 (1H, dddd, *J*=0.9, 5.1, 9.9, 18.0 Hz), 3.68 (3H, s), 3.97 (1H, d, *J*=10.9 Hz), 4.31 (1H, d, *J*=10.9 Hz), 5.31 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.9, 25.5, 29.8, 44.6, 55.8, 69.1, 101.1, 177.8, 205.5.

*3.7. (S)-6-Hydroxymethyl-3-(methoxymethoxy)-6-methyl-2-cyclohexenone (+)-**4***

$[\alpha]_D^{27}$ +91.8 (*c* 1.36, $CHCl_3$).

3.8. (R)-6-Acetoxymethyl-3-(methoxymethoxy)-6-methyl-2-cyclohexenone (−)-**6**

$[\alpha]_D^{26}$ −63.6 (*c* 1.33, $CHCl_3$); EIMS m/z (relative intensity) 242 (M^+, 10), 138 (18), 45 (100). Anal. calcd for $C_{12}H_{18}O_5$: C, 59.49; H, 7.49. Found: C, 59.19; H, 7.51. IR (neat) 2940, 1740, 1655, 1614 cm^{-1}; UV (EtOH) λ_{max} 248 nm (ε 16300); ^1H NMR (300 MHz, $CDCl_3$) δ 1.12 (3H, s), 1.75 (1H, dt, *J*=13.5, 5.5 Hz), 2.04 (3H, s), 2.12 (1H, ddd, *J*=5.5, 9.6, 13.5 Hz), 2.44 (1H, dt, *J*=18.3, 5.5 Hz), 2.55 (1H, dddd, *J*=1.1, 5.5, 9.6, 18.3 Hz), 3.47 (3H, s), 3.98 (1H, d, *J*=10.9 Hz), 4.32 (1H, d, *J*=10.9 Hz), 5.05 (1H, d, *J*=5.7 Hz), 5.07 (1H, d, *J*=5.7 Hz), 5.31 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.6, 20.9, 25.3, 29.5, 43.7, 57.1, 68.2, 77.2, 94.1, 103.7, 173.8, 200.6.

3.9. (R)-4-Hydroxymethyl-4-methyl-2-cyclohexenone (+)-**7**

To a cold (−78°C) solution of cyclohexenone (+)-**4** (52.7 mg, 264 μmol, 99% ee) in toluene (2.6 mL), DIBAL-H (0.95 M in hexane, 584 μL, 555 μmol) was added dropwise and the mixture was stirred at the same temperature for 30 min. The reaction mixture was diluted with Et_2O, treated with saturated NaCl solution and stirred for 6 h at room temperature. The organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluted with hexane:AcOEt 1:1) to give cyclohexenone (+)-**7** (25.3 mg, 69% yield) as a colorless oil.

$[\alpha]_D^{26}$ +31.2 (*c* 0.84, $CHCl_3$); EIMS m/z (relative intensity) 240 (M^+, 10), 110 (100); HREIMS: calcd for $C_8H_{12}O_2$ (M^+) 140.0837; found: 140.0817; IR (neat) 3427, 2931, 1676 cm^{-1}; UV (EtOH) λ_{max} 227 nm (ε 6400); ^1H NMR (300 MHz, $CDCl_3$) δ 1.14 (3H, s), 1.74 (1H, dddd, *J*=1.0, 5.6, 6.8, 13.7 Hz), 2.08 (1H, ddd, *J*=6.8, 8.3, 13.7 Hz), 2.48 (2H, m), 3.48 (1H, d, *J*=10.5 Hz), 3.56 (1H, d, *J*=10.5 Hz), 5.94 (1H, d, *J*=10.2 Hz), 6.73 (1H, dd, *J*=1.0, 10.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.9, 30.8, 33.9, 38.2, 69.8, 129.0, 156.1, 199.8.

3.10. Acetylation of alcohol (+)-**4** to acetate (+)-**6**

To a solution of alcohol (+)-**4** (14.6 mg, 73.0 μmol, 99% ee) in pyridine (1.0 mL), Ac_2O (1.0 mL) was added and stirred at room temperature for 10 h. The reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluted with hexane:AcOEt 1:2) to give acetate (+)-**6** (16.5 mg, 93% yield) as a colorless oil.

$[\alpha]_D^{26}$ +66.2 (*c* 1.25, $CHCl_3$).

3.11. Methanolysis of acetate (−)-**5** to alcohol (−)-**3**

To a solution of acetate (−)-**5** (32.9 mg, 155 μmol, 90% ee) in MeOH (1.55 mL), K_2CO_3 (107 mg, 775 μmol) was added, followed by stirring at room temperature for 3 h. The reaction mixture was diluted with AcOEt, filtered through silica gel. The filtrate was concentrated under reduced pressure to give alcohol (−)-**3** (22.9 mg, 87% yield) as a colorless oil.

$[\alpha]_D^{27}$ −76.1 (*c* 1.45, $CHCl_3$).

3.12. Methanolysis of acetate (−)-**6** to alcohol (−)-**3**

To a solution of acetate (−)-**6** (11.8 mg, 48.4 μmol, 97% ee) in MeOH (500 μL), K_2CO_3 (33.4 mg, 242 μmol) was added and stirred at room temperature for 3 h. The reaction mixture was diluted with AcOEt

and filtered through silica gel. The filtrate was concentrated under reduced pressure to give alcohol (−)-**3** (7.5 mg, 91% yield) as a colorless oil.

$[\alpha]_D^{24}$ −64.4 (*c* 0.63, $CHCl_3$).

3.13. (R)-2-Hydroxymethyl-2-methylcyclohexanone *8*

A solution of cyclohexenone (−)-**6** (419 mg, 1.73 mmol, 97% ee) in MeOH (30.0 mL) in the presence of 10% Pd–C (164 mg) and K_2CO_3 (196 mg) was stirred at room temperature for 1 h under H_2 atmosphere and then diluted with Et_2O and filtered through Celite. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluted with hexane:AcOEt 4:1) to give cyclohexanone **8** (184 mg, 76% yield) as a colorless oil.

$[\alpha]_D^{26}$ −98.4 (*c* 1.06, $CHCl_3$); EIMS m/z (relative intensity) 142 (M^+, 3), 124 (60), 82 (100); HREIMS: calcd for $C_8H_{14}O_2$ (M^+) 142.0994; found: 142.0995; IR (neat) 3422, 2936, 1700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.18 (3H, s), 1.57 (1H, m), 1.65 (1H, m), 1.75 (1H, m), 1.81 (1H, m), 2.03 (1H, m), 2.27 (1H, dddd, *J*=1.4, 3.2, 4.6, 14.4 Hz), 2.51 (1H, ddd, *J*=6.1, 12.9, 14.4 Hz), 2.56 (1H, t, *J*=7.1 Hz), 3.47 (1H, dd, *J*=6.7, 11.4 Hz), 3.51 (1H, dd, *J*=7.3, 11.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.2, 20.7, 27.3, 35.6, 39.0, 50.1, 69.1, 218.1.

3.14. (R)-2-(tert-Butyldiphenylsiloxymethyl)-2-methylcyclohexanone *9*

To a solution of alcohol **8** (77.9 mg, 550 μmol) in DMF (600 μL) was added imidazole (112 mg, 1.65 mmol) and *tert*-butyldiphenylsilyl chloride (357 μL, 1.38 mmol). The mixture was stirred at room temperature for 1 h and diluted with ether. The organic layer was washed with water and saturated NaCl solution, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluted with hexane:AcOEt 5:1) to give TBDPS ether **9** (139 mg, 66% yield) as a colorless oil.

$[\alpha]_D^{27}$ +10.9 (*c* 1.39, $CHCl_3$); EIMS m/z (relative intensity) 323 ($M^+-{}^t$Bu, 100); HREIMS: calcd for $C_{20}H_{23}O_2Si$ ($M^+-{}^t$Bu) 323.1467; found: 323.1474; IR (neat) 2932, 2858, 1709 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.04 (9H, s), 1.14 (3H, s), 1.6–2.0 (6H, m), 2.30 (1H, dt, *J*=6.5, 14.5 Hz), 2.37 (1H, dt, *J*=6.9, 14.5 Hz), 3.69 (1H, d, *J*=9.8 Hz), 3.71 (1H, d, *J*=9.8 Hz), 7.35–7.45 (6H, m), 7.66 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.3, 20.8, 21.2, 26.8, 27.0, 36.0, 39.2, 50.8, 68.8, 127.6, 129.6, 133.3, 135.7, 214.5.

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