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# Efficient Synthesis of Enantiomerically Pure 5,5-Dimethyl-4-hydroxy-2-cyclopentenone

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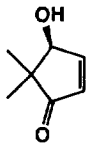
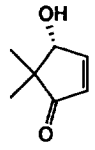
***Abstract:*** (+)- and (-)-5,5-Dimethyl-4-hydroxy-2-cyclopentenone **1** were efficiently synthesized by the dissymmetrization of *meso* diol **2** with lipase-catalyzed acetylation as a key step. The synthesis of (+)-5,5-dimethyl-4-hydroxy-2-cyclopentenone was also carried out by the chemical conversion of (-)-pantolactone **6**.

The development of versatile chiral building blocks is essential to the synthesis of optically active compounds. The efficient synthesis of optically active cyclohexenone derivatives as chiral building blocks for the synthesis of natural products was recently reported.[2]




(+)-1

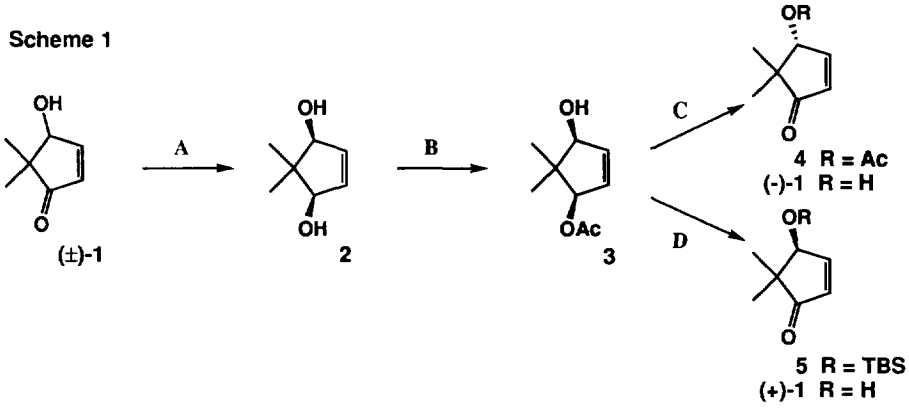



(-)-1

Optically active 5,5-dimethyl-4-hydroxy-2-cyclopentenone **1** is very useful for the synthesis of natural products[3] and drugs (prostaglandin derivatives)[4] as a starting material. Methods for the synthesis of optically active **1** are limited. One such method consists in the separation of diastereomers, prepared by reaction of racemic **1** and (1*R*, 4*R*, 5*S*)-6,6-dimethyl-4-hydroxy-3-oxabicyclo[3.1.0]hexane-2-one.[5] Another method is the lipase-catalyzed enantioselective hydrolysis of racemic 4-acetoxy-5,5-dimethyl-2-cyclopentenone.[6] However, these methods are inefficient, since only one enantiomer can be utilized and the enantiomeric excess is low (93.6% ee)[6]. In this study, we have devised two methods for the efficient synthesis of enantiomerically pure (+)- and (-)-5,5-dimethyl-4-hydroxy-2-cyclopentenone by lipase-catalyzed dissymmetrization of *meso* diol **2** and the chemical conversion of (-)-pantolactone **6**.

The lipase-catalyzed dissymmetrization of *meso* diol **2** was successfully conducted. *Meso* diol **2** was prepared from (±)-**1**[7] by diastereoselective reduction with sodium borohydride in the presence of cerium (III) chloride at 0°C in 95% yield, as shown in Scheme 1. It was then treated with vinyl acetate in the presence of immobilized[8] lipase PS[9] (from *Pseudomonas* sp.) in acetonitrile for 7 days at room temperature to obtain monoacetate **3** $[\alpha]_D$ -93.4 (*c* 0.70, $CHCl_3$) in 89% yield. The enantiomeric excess of monoacetate **3** was

**Scheme 1**

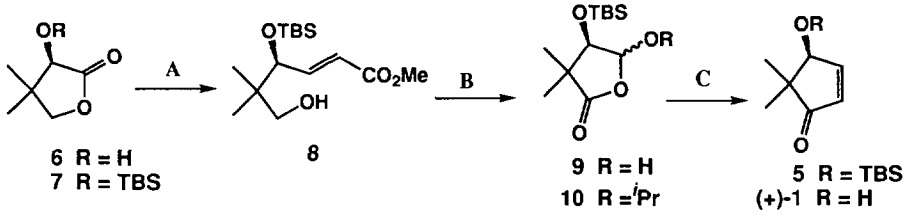



***Reagents***: A. $NaBH_4$, $CeCl_3$, MeOH, 0°C, 95%; **B**. lipase PS, vinyl acetate, $CH_3CN$, r.t., 89%; **C**. i) PDC, 4ÅMS, $CH_2Cl_2$, r.t., 98%, ii) LiOH, DME, 0°C, 89%; **D**. i) TBS-Cl, imidazole, DMF, r.t., 98%, ii) DIBAL-H, toluene, -78°C, quant., iii) PDC, 4ÅMS, $CH_2Cl_2$, r.t., 92%, iv) 80% AcOH, 40°C, 83%.

>99% as determined by $^1$H-NMR analysis of the (*S*)-MTPA ester.[10] (+)-**1** and (-)-**1** were both obtained from monoacetate **3**. The oxidation of **3** with pyridinium dichromate (PDC) gave cyclopentenone **4** in 98% yield, whose hydrolysis with 1*N* LiOH in dimethoxyethane (DME) at 0 °C afforded (-)-**1** $[\alpha]_D$ -86.8 (*c* 0.65, MeOH)(lit.[5] $[\alpha]_D$ -84.2 (*c* 0.5, MeOH)) in 89% yield. The alcohol **3** was converted to cyclopentenone **5** as follows: 1) protection of the hydroxy group as the *tert*-butyldimethylsilyl (TBS) ether (98% yield), 2) reduction of acetate with diisobutyl aluminium hydride (DIBAL-H) (quantitative yield) and 3) oxidation of the hydroxy group with PDC (92% yield). Deprotection of the TBS ether of **5** with 80% acetic acid afforded (+)-**1** $[\alpha]_D$ +87.5 (*c* 0.20, MeOH)(lit.[5] $[\alpha]_D$ +85.1 (*c* 0.5, MeOH)) in 83% yield.

(+)-**1** was efficiently converted from (-)-pantolactone **6**, as shown in Scheme 2. (-)-Pantolactone **6** was converted to α, β-unsaturated ester **8** *via* **7** as follows: 1) protection of the hydroxy group as the TBS ether to give **7** (95% yield), 2) reduction of the lactone to the hemiacetal with DIBAL-H at -78°C (92% yield) and 3) Wittig reaction (94% yield). The hydroxy group of **8** was oxidized stepwise to carboxylic acid with PDC and $NaClO_2$.[11] The olefin was oxidized with ozone to give hemiacetal **9** in 86% (3 steps). Treatment of **9** with a

**Scheme 2**




***Reagents***: A. i) TBS-Cl, imidazole, DMF, r.t., 95%, ii) DIBAL-H, toluene, -78°C, then 2*N* $H_2SO_4$, 92%, iii) $Ph_3P{=}CHCO_2Me$, $CH_2ClCH_2Cl$, 70°C, 94%; **B**. i) PDC, 4ÅMS, $CH_2Cl_2$, r.t., ii) $NaClO_2$, $NaHPO_4$, 2-methyl-2-butene, $^t$BuOH-$H_2O$, 0°C, iii) $O_3$, $CH_2Cl_2$-MeOH(1:1), -78°C, then $Me_2S$, r.t., 86% (3 steps), iv) PPTS, $^i$PrOH, r.t., 92%; C. i) $(MeO)_2P(O)CH_2Li$, THF, -78°C ~ 0°C, 63%, ii) 80% AcOH, 40°C, 83%.

catalytic amount of pyridinium *p*-toluenesulfonate (PPTS) in 2-propanol provided a diastereomeric mixture of acetal **10** in a 2:3 ratio in 92% yield. Without separating the isomers, acetal **10** was allowed to react with lithium dimethyl methylphosphonate at -78°C to give cyclopentenone **5** in 63% yield.[12] The TBS ether of **5** was deprotected by treatment with 80% acetic acid to give (+)-**1** $[\alpha]_D$ +87.2 (*c* 1.31, MeOH)[5] in 83% yield.

In this study, the synthesis of enantiomerically pure (+)-**1** and (-)-**1** has been achieved using lipase catalysis dissymmetrization of *meso* diol **2** as the key reaction and facile synthesis of (+)-**1** from (-)-pantolactone **6**.

## Experimental

Melting points were measured on a Yazawa BY-2 micro melting point apparatus and uncorrected. Optical rotations were measured with a JASCO DIP-360 automatic polarimeter. Infrared (IR) spectra were recorded with a Perkin-Elmer FT-IR 1710 spectrometer. $^1$H-NMR spectra were recorded with Varian Gemini-300 (300 MHz) or Bruker AM-400 (400 MHz). Chemical shifts are given 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 (EIMS) spectra and high resolution mass spectra (HRMS) were obtained with Hitachi M-80 spectrometer 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). Preparative thin layer chromatography (PTLC) was carried out on Merck Silica gel 60 $F_{254}$ TLC plates. Ether, tetrahydrofuran (THF) and benzene were distilled from sodium-benzophenone ketyl under argon. Dichloromethane ($CH_2Cl_2$) was distilled from $P_2O_5$ under argon and *N, N*-Dimethylformamide (DMF), from calcium hydride under reduced pressure.

### (1*R**, 4*S**)-5,5-Dimethyl-2-cyclopentene-1,4-diol, 2.

To a cold (0°C) solution of hydroxyenone (±)-**1** (1.96 g, 15.6 mmol) and $CeCl_3 \cdot 7H_2O$ (8.70 g, 23.3 mmol) in MeOH (50 ml), $NaBH_4$ (440 mg, 11.7 mmol) was added portionwise and stirred for 20 min at the same temperature. The reaction mixture was diluted with AcOEt and washed with saturated $NH_4Cl$ solution, $H_2O$ and saturated NaCl solution, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed on a silica gel column (eluted with AcOEt only) to give 1.90 g (95% yield) of *meso* diol **2** as colorless crystals: m.p. 84 - 85°C; IR (KBr) 3269, 2955 cm$^{-1}$; $^1$H-NMR (400MHz, $CDCl_3$) δ 1.03 (6H, s), 1.61 (2H, d, J = 6.9 Hz), 4.09 (2H, d, J = 6.9 Hz), 6.02 (2H, s); EIMS m/z (relative intensity): 128 ($M^+$, 1.6), 95 (100); Anal. Calcd for $C_7H_{12}O_2$: C, 65.59; H, 9.44. Found: C, 65.92; H, 9.24.

### (1*S*, 4*R*)-4-Acetoxy-5,5-dimethyl-2-cyclopentene-1-ol, 3.

To a solution of *meso* diol **2** (760 mg, 5.94 mmol) and vinyl acetate (3.30 ml, 35.6 mmol) in acetonitrile (33 ml), immobilized lipase on celite (760 mg) was added and stirred for 7 days at room temperature. The reaction mixture was diluted with $CH_2Cl_2$, filtered through a plug of celite and the filtrate was concentrated under reduced pressure. The residue was chromatographed on a silica gel column (eluted with hexane-AcOEt = 3:1) to give 898 mg (89% yield) of mono acetate **3** as a colorless oil : $[\alpha]_D$ -93.4 (*c* 0.70, $CHCl_3$); IR (neat) 3446, 2960, 1733 cm$^{-1}$; $^1$H-NMR (300MHz, $CDCl_3$) δ 0.96 (3H, s), 1.08 (3H, s), 2.04 (3H, s), 4.07 (1H, brs),

5.18 (1H, brs), 5.90 (1H, dd, J = 5.5, 2.3 Hz), 6.08 (1H, dd, J = 5.5, 2.4 Hz); EIMS m/z (relative intensity): 128 ($M^+$-Ac, 20), 95 (100); HRMS: Calcd for $C_7H_{12}O_2$ ($M^+$-Ac): 128.0837. Found: 128.0844.

**Preparation of the (*S*)-MTPA ester of 3.**

To a solution of alcohol **3** (6.3 mg, 37 μmol) in $CH_2Cl_2$ (500 μl), (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (19 μl, 74 μmol) and 4-dimethylaminopyridine (23 mg, 185 μmol) were added and stirred for 1 h at room temperature. The reaction mixture was diluted with ether, washed with water and saturated NaCl solution, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed on silica gel column (eluted with hexane-ether = 15:1) to give 14.1 mg (99% yield) of MTPA ester as a single compound. The enantiomeric excess of alcohol **3** was >99% based on $^1$H-NMR analysis of this MTPA ester: $^1$H-NMR (400MHz, $CDCl_3$) δ 0.97 (3H, s),1.21 (3H, s), 2.00 (3H, s), 3.52 (3H, s), 5.21 (1H, d, J = 1.8 Hz), 5.30 (1H, d, J = 1.7 Hz), 6.08 (1H, dd, J = 6.5. 1.8 Hz), 6.09 (1H, dd, J = 6.5. 1.7 Hz), 7.37 - 7.40 (3H, m), 7.51 - 7.57 (2H, m).

**(*R*)-4-Acetoxy-5,5-dimethyl-2-cyclopentenone, 4.**

To a solution of the alcohol **3** (90 mg, 0.529 mmol) in $CH_2Cl_2$ (5.0 ml), 4 Å molecular sieves (MS) (240 mg) and PDC (240 mg, 0.635 mmol) were added and stirred for 3 h at room temperature. The reaction mixture was diluted with ether and filtered through a plug of silica gel and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column (eluted with hexane-ether = 2:1) to give 87 mg (98% yield) of cyclopentenone **4** as a colorless oil: $[\alpha]_D$ -61.6 (*c* 1.75, $CHCl_3$), IR (neat) 2977, 1740, 1719 $cm^{-1}$; $^1$H-NMR (300MHz, $CDCl_3$) δ 1.01 (3H, s), 1.21 (3H, s), 2.13 (3H, s), 5.57 (1H, dd, J = 2.4, 1.4 Hz), 6.28 (1H, dd, J = 5.9. 1.4 Hz), 7.40 (1H, dd, J = 5.9, 2.4 Hz); EIMS m/z (relative intensity): 168 ($M^+$, 10), 111 (100); HRMS: Calcd for $C_9H_{12}O_3$ ($M^+$): 168.0786. Found: 168.0793.

**(*R*)-5,5-Dimethyl-4-hydroxy-2-cyclopentenone, (-)-1[5].**

To a cold (0°C) solution of acetate **4** (15 mg, 89 μmol) in DME (8.6 ml), aqueous 1*N* LiOH (8.6 ml) was added and stirred for 5 min at the same temperature. The reaction mixture was diluted with AcOEt and washed with saturated $NH_4Cl$ solution, $H_2O$ and saturated NaCl solution, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed on silica gel column (eluted with hexane-AcOEt = 3:1) to give 10 mg (89% yield) of enone (-)-**1** as a colorless crystal: m.p. 64 - 65 °C; $[\alpha]_D$ -86.8 (*c* 0.65, MeOH); IR (KBr) 3475, 2923, 1723, 1690 $cm^{-1}$; $^1$H-NMR (400MHz, $CDCl_3$) δ 1.07 (3H, s), 1.16 (3H, s), 1.83 (1H, d, J = 7.7 Hz), 4.58 (1H, m), 6.20 (1H, dd, J = 5.9, 1.4 Hz), 7.45 (1H, dd, J = 5.9, 2.3 Hz); EIMS m/z (relative intensity): 126 ($M^+$, 20), 82 (100); Anal. Calcd for $C_7H_{10}O_2$: C, 66.65; H, 7.99. Found: C, 66.38; H, 7.92.

**(*S*)-4-((*tert*-Butyldimethylsilyl)oxy)-5,5-dimethyl-2-cyclopentenone, 5.**

To a solution of the alcohol **3** (1.62 g, 9.53 mmol) in DMF (9.5 ml), imidazole (1.30 ml, 19.1 mmol) and *tert*-buthyldimethylsilyl chloride (1.72 g, 11.4 mmol) were added portionwise and stirred for 6 h at room temperature. The reaction mixture was diluted with ether, washed with water and saturated NaCl solution, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed on silica gel column (eluted with hexane-ether =10:1) to give 2.66 g (98% yield) of silyl ether as a colorless oil:

$[\alpha]_D$ +19.2 (*c* 1.36, $CHCl_3$), IR (neat) 2957, 1741 $cm^{-1}$; $^1$H-NMR (300MHz, $CDCl_3$) δ 0.07 (6H, s), 0.86 (3H, s), 0.90 (9H, s), 1.11 (3H, s), 2.06 (3H, s), 4.18 (1H, dd, J = 1.9, 1.1 Hz), 5.22 (1H, dd, J = 2.0, 1.6 Hz), 5.76 (1H, ddd, J = 5.8, 2.0, 1.1 Hz), 5.87 (1H, ddd, J = 5.8, 1.9, 1.6 Hz); EIMS m/z (relative intensity): 284 ($M^+$, 5.7), 225 (100); HRMS: Calcd for $C_{15}H_{28}O_4Si$ ($M^+$): 284.1807. Found: 284.1797.

To a cold (-78°C) solution of above silyl ether (4.11 g, 14.5 mmol) in toluene (140 ml), DIBAL-H (34.3 ml, 31.9 mmol, 0.93 M in hexane) was added dropwise and stirred at the same temperature for 1 h. Following the addition of MeOH (0.6 ml), the reaction mixture was diluted with ether (500 ml), treated with saturated NaCl solution (20 ml) and stirred for 30 min. The organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed on a silica gel column (eluted with hexane-ether =4:1) to give 3.50 g (quantitative yield) of alcohol as colorless crystals: m.p. 53 - 54 °C; $[\alpha]_D$ +56.0 (*c* 1.21, $CHCl_3$); IR (KBr) 3294, 2957 $cm^{-1}$; $^1$H-NMR (300MHz, $CDCl_3$) δ 0.06 (3H, s), 0.07 (3H, s), 0.88 (9H, s), 0.96 (3H, s), 1.01 (3H, s), 1.36 (1H, d, J = 10.5 Hz), 4.00 (1H, brd, J = 10.5 Hz), 4.08 (1H, d, J = 1.0 Hz), 5.86 (1H, dd, J = 6.0, 1.0 Hz), 5.95 (1H, dd, J = 6.0, 1.0 Hz); EIMS m/z (relative intensity): 242 ($M^+$, 1.3), 185 (100); HRMS: Calcd for $C_{13}H_{26}O_2Si$ ($M^+$): 242.1702. Found: 242.1694.

To a solution of the alcohol (3.50 g, 14.5 mmol) obtained above in $CH_2Cl_2$ (70 ml), PDC (6.55 g, 17.4 mmol) and 4 Å MS (3.5 g) were added and stirred for 2 h at room temperature. The reaction mixture was diluted with ether and filtered through a plug of silica gel and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column (eluted with hexane-ether = 20:1) to give 3.19 g (92% yield) of cyclopentenone **5** as a colorless oil: $[\alpha]_D$ +93.6 (*c* 1.01, $CHCl_3$), IR (neat) 2958, 1719 $cm^{-1}$; $^1$H-NMR (400MHz, $CDCl_3$) δ 0.13 (3H, s), 0.14 (3H, s), 0.93 (9H, s), 1.00 (3H, s), 1.12 (3H, s), 4.50 (1H, dd, J = 2.1, 1.3 Hz), 6.13 (1H, dd, J = 5.9, 1.3 Hz), 7.29 (1H, dd, J = 5.9, 2.1 Hz); EIMS m/z (relative intensity): 240 ($M^+$, 3.2), 183 (100); HRMS: Calcd for $C_{13}H_{24}O_2Si$ ($M^+$): 240.1545. Found: 240.1544.

**(*S*)-5,5-Dimethyl-4-hydroxy-2-cyclopentenone, (+)-1**[5].

A solution of silyl ether **5** (5.0 mg, 21 μmol) in 80% acetic acid (0.5 ml) was stirred at 40°C for 1 day. The reaction mixture was concentrated under reduced pressure. The residue was chromatographed on PTLC (developed with hexane-AcOEt = 1:3) to give 2.2 mg (83% yield) of enone (+)-**1** as a colorless crystal: m.p. 64 - 65 °C; $[\alpha]_D$ +87.0 (*c* 0.20, MeOH).

**(*R*)-2-((*tert*-Butyldimethylsilyl)oxy)-3,3-dimethyl-4-butanolide, 7.**

To a solution of the (-)-pantolactone (commercially available) **6** (25.0 g, 192 mmol) and imidazole (27.2 g, 384 mmol) in DMF (33 ml), *tert*-buthyldimethylsilyl chloride (36.2 g, 230 mmol) was added portionwise and stirred for 1 h at room temperature. The reaction mixture was diluted with ether, washed with water and saturated NaCl solution, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed on a silica gel column (eluted with hexane-ether = 1:1) to give 41.0 g (95% yield) of silyl ether **7** as a colorless crystal: m.p. 96 - 97 °C; $[\alpha]_D$ +31.5 (*c* 1.29, $CHCl_3$), IR (KBr) 2932, 1796 $cm^{-1}$; $^1$H-NMR (400MHz, $CDCl_3$) δ 0.13 (3H, s), 0.20 (3H, s), 0.93 (9H, s), 1.05 (3H, s), 1.14 (3H, s), 3.87 (1H, d, J = 8.9 Hz), 3.98 (1H, d, J = 8.9 Hz), 3.98 (1H, s); EIMS m/z (relative intensity): 229 ($M^+$-Me, 1.7), 187 (100); Anal. Calcd for $C_{12}H_{24}O_3Si$: C, 58.97; H, 9.90. Found: C, 58.97; H, 9.82.

**(*E*)-(*S*) Methyl 4-((*tert*-butyldimethylsilyl)oxy)-5,5-dimethy-6-hydroxy-2-hexenoate, 8.**
To a cold (-78°C) solution of lactone **7** (9.40 g, 38.2 mmol) in $CH_2Cl_2$ (210 ml), DIBAL-H (49.3 ml, 45.9 mmol, 0.93 M in hexane) was added dropwise and stirred for 30 min at the same temperature. To the reaction mixture, ether - 2*N* $H_2SO_4$ (1:1, 200 ml) was added and extracted with AcOEt. The organic layer was washed with saturated $NaHCO_3$ solution, water and saturated NaCl solution, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed on a silica gel column (eluted with hexane-ether = 1:2) to give 9.50 g (92% yield) of hemiacetal as a mixture of anomers (5 : 1): IR (neat) 3392, 2957 $cm^{-1}$; $^1$H-NMR (300MHz, $CDCl_3$) δ 0.09, 0.10 and 0.11, 0.13 (5:1, 3Hx2, all s), 0.91 and 0.95 (5:1, 9H, both s), 1.00, 1.01 and 1.05, 1.06 (5:1, 3Hx2, all s), 5.14 (5/6H,dd, J = 4.2, 2.9 Hz) and 5.37 (1/6H,dd, J = 9.7, 4.3 Hz); EIMS m/z (relative intensity): 229 ($M^+$-OH, 4.5), 189 (100); HRMS: Calcd for $C_{12}H_{25}O_2Si$ ($M^+$-OH): 229.1623. Found: 229.1626.

To a solution of the above hemiacetal (9.40 g, 38.2 mmol) in 1,2-dichloroethane (42 ml), methyl (triphenyphosphoranylidene)acetate (83.9 g, 251 mmol) was added and stirred at 70 °C for 6 h. The reaction mixture was concentrated under reduced pressure. The residue was chromatographed on a silica gel column (eluted with hexane-ether = 1:1) to give 25.1 g (94% yield) of α, β - unsaturated ester **8** as a colorless oil: $[\alpha]_D$ +13.1 (*c* 0.72, $CHCl_3$); IR (neat) 3476, 2956,1729,1658 $cm^{-1}$; $^1$H-NMR (400MHz, $CDCl_3$) δ 0.01 (3H, s), 0.09 (3H, s), 0.84 (3H, s), 0.92 (9H, s), 0.98 (3H, s), 2.23 (1H, dd, J = 6.7, 4.5 Hz), 3.30 (1H, dd, J = 10.8, 6.7 Hz), 3.57 (1H, dd, J = 10.8, 4.5 Hz), 3.76 (3H, s), 4.14 (1H, dd, J = 6.4, 1.4 Hz), 5.97 (1H, dd, J = 15.7, 1.4 Hz), and 6.99 (1H, dd, J = 15.7, 6.4 Hz); EIMS m/z (relative intensity): 287 ($M^+$-Me, 2.0), 229 (100); HRMS: Calcd for $C_{14}H_{27}O_4Si$ ($M^+$-Me): 287.1678. Found: 287.1675.

**(3*R*, 4*R*)- and (3*R*, 4*S*)-3-((*tert*-Butyldimethylsilyl)oxy)-2,2-dimethyl-4-hydroxy-4-butanolide, 9.**
To a solution of alcohol **8** (16.4 g, 54.3 mmol) in $CH_2Cl_2$ (200 ml), 4 Å MS (47 g) and PDC (23.3 g, 65.2 mmol) were added and stirred for 5 h at room temperature. The reaction mixture was diluted with ether and filtered through a plug of silica gel and the filtrate was concentrated under reduced pressure. The crude aldehyde was used in the next without purification: IR (neat) 2956, 1729, 1660 $cm^{-1}$; $^1$H-NMR (400MHz, $CDCl_3$) δ 0.00 (3H, s), 0.04 (3H, s), 0.89 (9H, s), 1.01 (3H, s), 1.07 (3H, s), 3.75 (3H, s), 4.37 (1H, dd, J = 6.3, 1.4 Hz), 5.99 (1H, dd, J = 15.7, 1.4 Hz), 6.89 (1H, dd, J = 15.7, 6.3 Hz), 9.57 (1H, s).

To a solution of the above aldehyde in 2-methyl-2-propanol (200 ml) and 2-methyl-2-butene (20 ml), an aqueous solution (44 ml) of $NaClO_2$ (8.10 g, 89.6 mmol) and $NaH_2PO_4$ (8.1 g) was added dropwise and stirred for 30 min at room temperature. The reaction mixture was diluted with AcOEt, washed with 30% $NaH_2PO_4$ aqueous solution and saturated NaCl solution, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude carboxylic acid was used in the next without purification: IR (neat) 3150, 2955, 1730, 1708, 1660 $cm^{-1}$; $^1$H-NMR (400MHz, $CDCl_3$) δ 0.01 (3H, s), 0.06 (3H, s), 0.90 (9H, s), 1.15 (3H, s), 1.18 (3H, s), 3.75 (3H, s), 4.46 (1H, dd, J = 6.5, 1.3 Hz), 5.99 (1H, dd, J = 15.7, 1.3 Hz), 6.89 (1H, dd, J = 15.7, 6.5 Hz).

A cold (-78°C) solution of the crude carboxylic acid obtained above in $CH_2Cl_2$ (100 ml) and MeOH (100 ml), was treated with ozone until blue color persisted. Excess ozone was removed by a flow of argon. The reaction mixture was treated with $Me_2S$ (5 ml), allowed to warm slowly to room temperature over 2 h, stirred for 5 h at the same temperature and concentrated under reduced pressure. The residue was chromatographed on a silica gel column (eluted with hexane-ether = 5:1) to give 4.7 g (86% yield, 3 steps) of hemiacetal **9** as a mixture of anomer (2:3): IR (neat) 3392, 2956, 1750 $cm^{-1}$; $^1$H-NMR (400MHz, $CDCl_3$) δ 0.11, 0.13 and 0.14, 0.15 (2:3, 3Hx2, all s), 0.91 and 0.95 (2:3, 9H, both s), 1.16, 1.30 and 1.22, 1.25 (2:3, 3Hx2, all s), 5.46 (2/5H,dd, J = 3.7, 3.3 Hz) and 5.31 (2/5H,dd, J = 11.2, 4.0 Hz); EIMS m/z (relative intensity): 231 ($M^+$-CHO, 3.8), 158 (100); HRMS: Calcd for $C_{11}H_{23}O_3Si$ ($M^+$-CHO): 231.1416. Found: 231.1420.

**(3*R*, 4*R*)-and (3*R*, 4*S*)-3-((*tert*-Butyldimethylsilyl)oxy)-2,2-dimethyl-4-isopropoxy-4-butanolide, 10.**

To hemiacetal **9** (1.36 g, 5.20 mol), 0.1% PPTS in 2-propanol (26 ml) was added and stirred at 70°C for 4 days. Following the addition of pyridine (2.0 ml), the reaction mixture was concentrated under reduced pressure. The residue was chromatographed on a silica gel column (eluted with hexane-ether = 3:1) to give 640 mg (92% yield based on recovered hemiacetal **9**) of isopropylacetal **10** as a mixture of anomer (2:3) and 778 mg hemiacetal **9** recovered: IR (neat) 2932, 1786 $cm^{-1}$; $^1$H-NMR (400MHz, $CDCl_3$) δ 0.08 and 0.09 (2:3, 6H, all s), 0.90 and 0.92 (2:3, 9H, both s), 3.82 (2/5H, d, J = 3.5 Hz), 3.96 (3/5H, d, J = 4.8 Hz), 5.19 (2/5H, d, J = 3.5 Hz) and 5.34 (2/5H, d, J = 4.8 Hz); EIMS m/z (relative intensity): 243 ($M^+$-$^i$PrO, 8.8), 158 (100); HRMS: Calcd for $C_{12}H_{23}O_3Si$ ($M^+$-$^i$PrO): 243.1416. Found: 243.1418.

**(*S*)-4-((*tert*-Butyldimethylsilyl)oxy)-5,5-dimethyl-2-cyclopentenone, 5.**

To a cold (-78°C) solution of dimethyl methylphosphonate (690 μl, 6.30 mmol) in THF (7.0 ml), butyl lithium (1.80 ml, 2.50 mmol, 1.45 M in hexane) was added dropwise and stirred for 20 min at same temperature. To the mixture, a solution of acetal **10** (640 mg, 2.10 mmol) in THF (3.5 ml) was added dropwise and stirred for 5 h at same temperature and reaction temperature was raised to 0°C and stirred for 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 chromatographed on silica gel column (eluted with hexane-ether = 2:1) to give 320 mg (63% yield) of cyclopentenone **5** as a colorless oil: $[\alpha]_D$ +92.3 (*c* 1.53, $CHCl_3$).

**(*S*)-5,5-Dimethyl-4-hydroxy-2-cyclopentenone, (+)-1[5].**

A solution of the silyl ether **5** (87 mg, 0.360 mol) in 80% acetic acid (2.0 ml) was stirred at 40°C for 1 day. The reaction mixture was concentrated under reduced pressure. The crude crystals were recrystalized from ether-hexane to give 38 mg (83% yield) of (+)-**1** as a colorless crystal: m.p. 64 - 65 °C; $[\alpha]_D$ +87.2 (*c* 1.31, MeOH).

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## References and Notes


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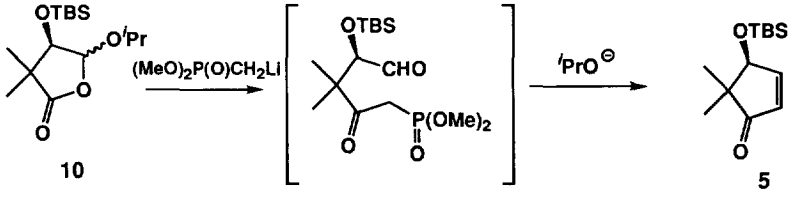
Formation of **5** can be rationalized as follows.

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