Efficient Synthesis of Optically Pure (4*R*,6*S*)-4-(*tert*-Butyldimethylsilyloxy)-6-(hydroxymethyl)tetrahydropyran-2-one and Its Enantiomer

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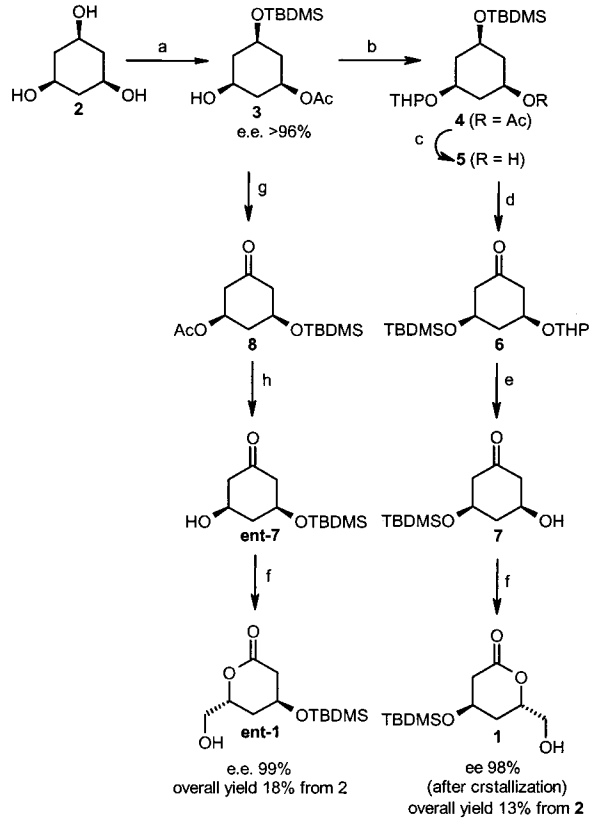
After the discovery of compactin,[1] a potent competitive inhibitor of HMG CoA reductase, the statin group of drugs, e.g. atorvastatin, lovastatin, and fluvastatin, have emerged as leading antihyperlipoproteinemic agents. All these drugs have (4*R*,6*S*)-*β*-hydroxy-*δ*-lactone (**1**) or its open chain acid as a common essential structural feature. Even though various chemical and chemoenzymatic approaches have been reported for the synthesis of **1** and its analogues,[2] development of efficient, cost-effective synthesis of this lactone moiety would be the major task toward an industrial process for these drugs. As a part of our chemoenzymatic process development program for various commercially valuable drugs and intermediates,[3] we planned to develop a cost-effective process for lactone **1**.

Sakai and co-workers have reported a chemoenzymatic route for lactone **1** analogue starting from phloroglucitol (**2**) wherein they have attempted Baeyer−Villiger oxidation of diprotected 3,5-dihydroxycyclohexanone to obtain the desired lactone, but almost equal quantities of two regioisomers were obtained; hence, a lengthier and low-yielding route based on ozonolysis was followed (overall yield 1.73%).[4] We decided to study this phloroglucitol approach for synthesis of lactone **1**, wherein a regioselective Baeyer−Villiger oxidation was desired to achieve shorter and more efficient process. Here we describe our preliminary successful results toward the synthesis of (4*R*,6*S*) 4-(*tert*-butyldimethylsilyloxy)-6-(hydroxymethyl)-tetrahydropyran-2-one involving Baeyer−Villiger oxidation as the key step.

Scheme 1. Chemoenzymatic Synthesis of 1 and ent-1 from Phloroglucitol 2[a]



[a] Key: (a) chemoenzymatic route; (b) DHP, dry CH_2Cl_2, 0 °C, 99%; (c) K_2CO_3, MeOH, 96%; (d) PCC, CH_2Cl_2, 80%; (e) $MgBr_2$ etherate, dry ether, 3 h, 90%; (f) 2 equiv of 3-chloroperbenzoic acid, RT, 45%; (g) PCC, CH_2Cl_2, 95%; (h) PLE, buffer pH 6.5, 75%.

It was desired to obtain an optically pure 3-hydroxycyclohexanone derivative from phloroglucitol to study the Baeyer−Villiger oxidation. We have developed efficient chemoenzymatic synthesis of 3-hydroxy-5-(*tert*-butyldimethylsilyloxy)-(1*S*,3*R*,5*R*)-cyclohexyl acetate (**3**, ee > 96%) from phloroglucitol through the enzymatic desymmetrization method.[5] We planned to utilize this chiral intermediate (**3**) for the synthesis of desired hydroxycyclohexanone. Compound **3** of >96% ee was subjected to further chemical transformations as shown in Scheme 1. Free −OH in **3** was protected as THP ether **4** at 0 °C, which on solvolysis in methanol, followed by PCC oxidation, afforded 3,5-disubstituted cyclohexanone **6**. Magnesium bromide assisted selective deprotection of the OTHP group[6] afforded the desired 3-hydroxycyclohexanone derivative **7** in 76% yield from compound **3**. The next important step was efficient Baeyer−Villiger oxidation of **7**.

Cyclohexanone **7** was subjected to Baeyer−Villiger oxidation under standard conditions using 3-chloroperbenzoic acid in dichloromethane for several hours, but

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the substrate **7** was found to be unreactive under these conditions. Various reaction conditions were attempted, but hydroxycyclohexanone **7** was either unreactive or unstable under conditions attempted. But fortunately when it was mixed with 3-chloroperbenzoic acid under neat conditions and kept for few hours, it reacted to afford lactone **1** as a single isomer in 45% yield. ^{1}H NMR, ^{13}C NMR, and ^{1}H NOE data for **1** matched exactly with that of literature reported values.[7] No traces of the regioisomeric lactone arising out of oxygen insertion from other side of the ring could be detected by NMR of the crude reaction mixture. Thus, our speculation of affecting a Baeyer−Villiger oxidation was found to be correct where the corresponding 7-membered lactone underwent rearrangement to the thermodynamically more stable 6-membered lactone **1** under our reaction conditions. The optical rotation of the lactone obtained was found to be +3 (c = 1, $CHCl_3$), whereas the reported value is −7 (c = 1, $CHCl_3$).[7] To clear the ambiguity, which perhaps arose out of impurity in the sample(s) or inadequate purification methods employed, we prepared its tosyl derivative. The rotation of the pure tosyl derivative {$[\alpha]_D$ = +7 (c =2, $CHCl_3$)} matched well with the reported value of +5 (c = 1, $CHCl_3$)[7] (our material was even purer optically). Thus, our configuration assignment was found to be correct. Enatiomeric excess of the lactone **1** was determined to be 86% by the chiral HPLC of its benzoate [Lichrocart (*R*, *R*) Whelk-O1 (5μm) column]. There could have been epimerization during the −OTHP deprotection stage, resulting in deterioration of ee. Enantiomeric excess could be improved up to 98% by a single recrystallization from petroleum ether + chloroform mixture (yield 75%). The specific rotation of this recrystallized lactone **1** was found to be +1.9 (c = 1, $CHCl_3$)! There could have been some diastereomeric impurity responsible for the higher rotation value (epimerization possible at THP deprotection stage; vide infra), which was removed during recrystallization. Thus, synthesis of enantiopure lactone **1** was achieved in overall 13% yield.

Since the epimerization encountered in the above-discussed scheme demands extra purification measures to improve ee with concomitant loss of yield, a route wherein a protection−deprotection sequence and subsequent epimerization can be avoided was sought. As shown in Scheme 1, compound **3** was oxidized efficiently with PCC to afford β-ketoacetate **8**. Now a mild hydrolytic condition for hydrolysis of **8** was required to avoid β-elimination. It could not be achieved by chemical methods, e.g. methanol−K_2CO_3, methanol−NH_3, etc. Therefore, enzymatic hydrolysis under neutral pH condition was attempted using PLE as catalyst. When hydrolysis was carried out in buffer media containing 10% DMSO, the desired hydroxyketone **ent-7** was isolated in 50% yield. Its optical rotation was found to be −22.5 (c = 1, $CHCl_3$), whereas that of **7** obtained in the earlier route was only +16.8 (c = 1, $CHCl_3$). This indicates that enzymatic hydrolysis is not only mild enough to minimize β-elimination and avoid epimerization but possibly helped achieve higher optical purity by kinetic resolution of **8**. This assumption was confirmed by carrying out hydrolysis of racemic **8** under the same reaction conditions wherein we could isolate **ent-7** showing optical rotation of −20 (c = 1, $CHCl_3$). To further minimize β-elimination, enzymatic hydrolysis was carried under slightly acidic conditions (pH 6.5), and **ent-7** of the same enantiopurity could be isolated in 75% yield. **ent-7** reacted with 3-chloroperbenzoic acid under neat conditions to afford lactone **ent-1** in 45% isolated yield. The optical rotation of **ent-1** was −1.96 (c = 1, $CHCl_3$), and its ee was found to be 99% by chiral HPLC analysis. The structure of **ent-1** was also confirmed by single-crystal X-ray analysis. Thus, this route affords **ent-1** in less steps more efficiently in 18% overall yield and more importantly avoids epimerization, obviating the need for extra purification. Therefore, the process to achieve **ent-3** by this route would afford lactone **1** much more efficiently.[8]

Thus, a much shorter and efficient chemoenzymatic synthesis of optically pure (4*R*,6*S*)-4-(*tert*-butyldimethylsilyloxy)-6-(hydroxymethyl)-tetrahydropyran-2-one (**1**) and its enantiomer was advantageously carried out from *cis*-phloroglucitol through effective Baeyer−Villiger oxidation as compared to the earlier phloroglucitol route based on ozonolysis. We hope a good chemoenzymatic route for lactone **1** is established, and addressing further some of the key cost factors, viz. cost of enzyme and oxidizing agent, would lead to a commercially viable route for lactone **1**.

Experimental Section

General Methods. All the reagents were purchased from Aldrich and were used without further purification. NMR spectra were recorded on a Brucker NMR (200 MHz) spectrometer. IR spectra were recorded on a Research Series FTIR spectrometer. Optical rotations were recorded on a Jasco Dip-181 and Jasco P-1020 polarimeter using a sodium vapor lamp. Enantiomeric excess (ee) was determined by comparing the specific rotation value $[\alpha]_D$ with the literature value. PPL and PLE were purchased from Sigma.

Preparation of 3-Tetrahydro-2*H*-2-(pyranyloxy)-5-(*tert*-butyldimethylsilyloxy)-(1*S*,3*R*,5*R*)-cyclohexyl Acetate (4). 3-Hydroxy-5-(*tert*-butyldimethylsilyloxy)-(1*S*,3*R*,5*R*)-cyclohexyl acetate (**3**, 2.9 g, 9.73 mmol) was dissolved in dry dichloromethane (30 mL). The solution was cooled below 0 °C in an ice−salt bath. To the stirred solution, dihydropyran (1 g, 12 mmol) was added and *p*-toluenesulfonic acid monohydrate (0.1 g) was added as catalyst. The reaction mixture was stirred at −10 °C for 2 h. The reaction was quenched by adding aqueous sodium bicarbonate solution. Both the layers were separated. The aqueous layer was extracted with dichloromethane (2 × 10 mL). The organic layers were combined and washed with water followed by brine. The solution was then dried on anhydrous sodium sulfate, and the solvent was removed under vacuum. The residue was purified by flash column chromatography to yield 3-tetrahydro-2*H*-2-(pyranyloxy)-5-(*tert*-butyldimethylsilyloxy)-(1*S*,3*R*,5*R*)-cyclohexyl acetate (**4**) (yield 3.7 g, 99.5%) as an oily liquid.

^{1}H NMR ($CDCl_3$): δ 0.05 (s, 6H), 0.87 (s, 9H), 1.25−1.90 (m, 9H), 2.04 (s, 3H), 2.05−2.40 (m, 3H), 3.40−3.75 (m, 3H), 3.86 (m, 1H), 4.55−4.80 (m, 2H). ^{13}C NMR ($CDCl_3$): δ −4.90, 18.00, 19.40, 19.50, 25.20, 25.80, 30.90, 36.80, 40.70, 41.00, 42.80, 62.00, 62.50, 66.00, 68.00, 69.70, 95.00, 96.80, 169.90.

IR ($CHCl_3$): 752.08, 768.22, 838.35, 1029.76, 1114.56, 1215.63, 1251.94, 1727.19, 2858.86, 2950.80, 3016.74 cm^{-1}. Mass: base *m*/*e* = 85; other *m*/*e* 231, 211, 171, 159, 129, 117, 105, 101, 85, 79, 75, 67, 55. Anal. Calcd for $C_{19}H_{36}O_5Si$: C, 61.29; H, 9.68. Found: C, 61.37; H, 10.03. Specific rotation: $[\alpha]_D$ = +1.39 (c = 1, $CHCl_3$).

Preparation of 3-Tetrahydro-2*H*-2-(pyranyloxy)-5-(*tert*-butyldimethylsilyloxy)-(1*S*,3*R*,5*S*)-cyclohexan-1-ol (5). 3-Tet-

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rahydro-2*H*-2-(pyranyloxy)-5-(*tert*-butyldimethylsilyloxy)-(1*S*,3*R*,5*R*)-cyclohexyl acetate (**4**, 3.5 g, 9.16 mmol) was dissolved in dry methanol (25 mL). To the solution anhydrous potassium carbonate (0.828 g, 6 mmol) was added, and the mixture was stirred at room temperature for 2 h. Methanol was removed under vacuum, and the residue was extracted with dichloromethane (3 × 10 mL). The dichloromethane layers were combined and washed with water followed by brine wash. The solution was dried on anhydrous sodium sulfate. Solvent was removed under vacuum, and the residue was purified by flash column chromatography to yield 3-tetrahydro-2*H*-2-(pyranyloxy)-5-(*tert*-butyldimethylsilyloxy)-(1*S*,3*R*,5*S*)-cyclohexan-1-ol (**5**, yield 3 g, 96%) as a viscous liquid.

^{1}H NMR ($CDCl_3$): δ 0.06 (s, 6H), 0.87 (s, 9H), 1.35−1.90 (m, 10H), 2.05−2.35 (m, 3H), 3.40−3.75 (m, 4H), 3.80−3.98 (m, 1H), 4.73 (s, 1H). ^{13}C NMR ($CDCl_3$): δ −4.90, 18.00, 19.50, 25.20, 25.80, 30.90, 40.00, 40.70, 42.00, 42.30, 44.70, 62.00, 62.50, 65.80, 66.90, 69.50, 70.00, 96.40, 96.80. IR ($CHCl_3$): 753.06, 766.83, 838.54, 867.39, 1020.84, 1048.02, 1114.23, 1215.02, 1253.72, 2858.73, 2884.47, 2947.49, 3013.80, 3418.48 cm^{-1}. Mass: base *m*/*e* = 75; other *m*/*e* 309, 189, 171, 129, 119, 101, 85, 79, 75, 67, 55. Anal. Calcd for $C_{17}H_{34}O_4Si$: C, 61.82; H, 10.30. Found: C, 61.83; H, 11.00. Specific rotation: $[\alpha]_D = +0.93$ (*c* = 1, $CHCl_3$).

Preparation of 3-Tetrahydro-2*H*-2-(pyranyloxy)-5-(*tert*-butyldimethylsilyloxy)-(3*S*,5*R*)-cyclohexan-1- one (6). 3-Tetrahydro-2*H*-2-(pyranyloxy)-5-(*tert*-butyldimethylsilyloxy)-(1*S*,3*R*,5*S*)-cyclohexan-1-ol (**5**, 2.85 g, 8.38 mmol) was dissolved in dry dichloromethane (25 mL) under argon atmosphere. To the solutiom were added anhydrous sodium acetate (0.2 g) and pyridinium chlorochromate (13 g, 12.6 mmol) in one portion, and the mixture was stirred under argon atmosphere for 8 h. Then reaction mixture was diluted with diethyl ether (30 mL) and stirred well. The solution was decanted, and the remaining black tar was extracted with diethyl ether (3 × 15 mL). The organic layers were combined and were filtered through a small Celite bed. Then, the organic layer was washed with water (3 × 20 mL) followed by brine. It was dried on anhydrous sodium sulfate, and solvent was removed under vacuum. The residue was purified by flash column chromatography to afford 3-tetrahydro-2*H*-2-(pyranyloxy)-5-(*tert*-butyldimethylsilyloxy)-(3*S*,5*R*)-cyclohexan-1-one (**6**, 2.24 g, 80%) as an oily liquid.

^{1}H NMR ($CDCl_3$): δ 0.07 (s, 6H), 0.87 (s, 9H), 1.35−1.95 (m, 8H), 2.2−2.8 (m, 4H), 3.50 (m, 1H), 3.85 (m, 3H), 4.60 & 4.75 (2s, 1H). ^{13}C NMR ($CDCl_3$): δ −4.9, 18.0, 19.5, 19.9, 25.8, 26.0, 30.9, 41.0, 42.5, 47.0, 48.5, 51.5, 62.5, 63.0, 69.0, 69.8, 97.5, 206.5, 207.0. IR ($CHCl_3$): 858.87, 980.49, 1028.79, 1053.00, 1254.14, 1360.70, 1377.86, 1462.85, 1717.24, 2857.60, 2892.24 cm^{-1}. Mass: base *m*/*e* = 187, 85; other *m*/*e* 271, 227, 169, 159, 143, 127, 95, 75, 67. Anal. Calcd for $C_{17}H_{32}O_4Si$: C, 62.19; H, 9.75. Found: C, 61.90; H, 10.10. Specific rotation: $[\alpha]_D = +3.71$ (*c* = 1, $CHCl_3$).

Preparation of 3-Hydroxy-5-(*tert*-butyldimethylsilyloxy)-(3*S*,5*R*)-cyclohexan-1-one (7). 3-Tetrahydro-2*H*-2-(pyranyloxy)-5-(*tert*-butyldimethylsilyloxy)-(3*S*,5*R*)-cyclohexan-1-one (**6**, 1 g, 2.96 mmol) was placed in a 50 mL two-necked round-bottom flask equipped with a two-way stopcock and rubber septum. The flask was evacuated and flushed with argon. To it was added dry ether (10 mL), and the resulting solution was stirred vigorously. To the stirred solution magnesium bromide etherate (2.3 g, 8.9 mmol) was added, and the mixture was stirred for 3 h. The reaction mixture was cooled in an ice bath, and the reaction was quenched by adding saturated ammonium chloride solution. Both the layers were separated. The aqueous layer was extracted with ether (3 × 10 mL). The organic layers were combined and washed with brine. Then the solution was dried on anhydrous sodium sulfate and solvent was removed under vacuum. The residue was purified to yield 3-hydroxy-5-(*tert*-butyldimethylsilyloxy)-(3*S*,5*R*)-cyclohexan-1-one (**7**, yield 0.69 g, 90%) as a viscous liquid.

^{1}H NMR ($CDCl_3$): δ 0.10 (s, 6H), 0.88 (s, 9H), 1.95−2.30 (m, 2H), 2.45−2.78 (m, 4H), 3.95 (d, 1H), 4.36 (m, 1H), 4.56 (m, 1H). ^{13}C NMR ($CDCl_3$): δ −5.50, −5.28, 17.55, 25.34, 38.24, 49.56, 49.89, 68.86, 70.48, 206.78. IR ($CHCl_3$): 777.13, 835.81, 1010.66, 1045.71, 1095.81, 1254.55, 1381.17, 1413.71, 1464.09, 1715.72, 2857.70, 2892.64, 2932.26, 2951.84, 3439.28 cm^{-1}. Mass: base *m*/*e* = 75; other *m*/*e* 187, 169, 145, 129, 101, 95, 75, 69, 59. Anal. Calcd for $C_{12}H_{24}O_3Si$: C, 59.01; H, 9.83. Found: C, 58.85; H, 10.18. Specific rotation: $[\alpha]_D = +16.20$ (*c* = 1, $CHCl_3$).

Preparation of (4*R*,6*S*)-4-(*tert*-butyldimethylsilyloxy)-6-(hydroxymethyl)tetrahydropyran-2-one (1). 3-Hydroxy-5-(*tert*-butyldimethylsilyloxy)-(3*S*,5*R*)-cyclohexan-1-one (**7**, 0.1 g, 0.394 mmol) and 50% 3-chloroperbenzoic acid (0.275 g, 0.79 mmol) were mixed and kept in the dark for 15 h. The reaction mixture was dissolved in ethyl acetate (5 mL) and washed successively with cold sodium metabisulfite solution and sodium bicarbonate solution followed by a brine wash. It was then dried on anhydrous sodium sulfate, and solvent was removed under vacuum. The residue was purified by flash column chromatography to yield white, crystalline (4*R*,6*S*)-4-(*tert*-butyldimethylsilyloxy)-6-(hydroxymethyl)tetrahydropyran-2-one (**1,** yield 0.048 g, 45%, mp 91 °C). It was recrystallized from petroleum ether (2 mL) containing 5% chloroform (yield = 0.036 g, 75%, mp 95 °C).

^{1}H NMR ($CDCl_3$): δ 0.09, 0.07 (2s, 6H), 0.89 (s, 9H), 1.64 (bs, 1H), 1.74−1.92 (m, 2H), 2.60 (d, 2H, *J* = 3), 3.65 (dd, 1H, *J* = 12), 3.88 (dd, 1H, *J* = 12), 4.39 (m, 1H), 4.81 (m, 1H). ^{13}C NMR ($CDCl_3$): δ −4.93, 17.93, 25.68, 32.15, 39.26, 63.61, 64.59, 76.86, 170.10. IR ($CHCl_3$): 666.31, 898.12, 1021.88, 1061.06, 1086.17, 1118.98, 1390.84, 1463.17, 1729.43, 2857.28, 3418.25 cm^{-1}. Mass: base *m*/*e* = 75; other *m*/*e* 260, 229, 203, 185, 161, 143, 129, 111, 101, 69, 59. Anal. Calcd for $C_{12}H_{24}O_4Si$: C, 55.38; H, 9.20. Found: C, 55.42; H, 9.03. Specific rotation: $[\alpha]_D = +3.0$ (*c* = 1, $CHCl_3$) before recrystallization, ee 86%; $[\alpha]_D = +1.9$ (*c* = 1, $CHCl_3$) after recrystallization, ee 98% (ee determined by chiral HPLC of corresponding benzoate derivative, column-Whelk-O1 [4.0 mm i.d. × 25 cm] AT-256; λ =254 nm, flow rate 1 mL/min; mobile phase hexane:2-propanol, 92:08; retention time for benzoate of **1** = 13.78 and for benzoate of **ent-1** = 15.72).

Preparation of 3-Oxo-5-(*tert*-butyldimethylsilyloxy)-(1*R*,5*S*)-cyclohexyl Acetate (8). *cis*,*cis*-3-Hydroxy-5-(*tert*-butyldimethylsilyloxy)-(1*S*,3*R*,5*R*)-cyclohexyl acetate (**3**, 1.40 g, 2.78 mmol) was dissolved in dichloromethane (5 mL). To the solution were added sodium acetate (0.1 g) and pyridinium chlorochromate (1.57 g, 7.3 mmol). The mixture was stirred for 5 h at RT (room temperature). The residue was extracted with ether (3 × 10 mL). The organic extracts were combined and filtered through Celite. The filtrate was washed with brine + water (1:1) and finally with brine. The organic layer was dried on anhydrous sodium sulfate and concentrated under vacuum. The residue was filtered through silica gel column to afford 3-oxo-5-(*tert*-butyldimethylsilyloxy)-(1*R*,5*S*)-cyclohexyl acetate (**8**, 1.30 g, 94%) as an oily liquid.

^{1}H NMR ($CDCl_3$): δ 0.07 (d, 6H), 0.88 (d, 9H), 2.06 (s, 3H), 2.41 (m, 4H), 2.65 (m, 2H), 4.01 (m, 1H), 5.00 (m, 1H). ^{13}C NMR ($CDCl_3$): δ −4.96, 17.80, 20.95, 25.56, 39.32, 45.91, 50.28, 65.96, 67.21, 169.85, 205.25. IR ($CHCl_3$): 442.57, 756.83, 1218.50, 1244.99, 1723.00, 2857.44, 2932.80, 2953.64, 3019.98 cm^{-1}. Mass: base *m*/*e* = 163; other *m*/*e* 185, 169, 145, 127, 117, 111, 101, 95, 75, 59. Anal. Calcd for $C_{14}H_{26}O_4Si$: C, 58.74; 9.09. Found: C, 58.60; H, 9.28. Specific rotation: $[\alpha]_D = -11.54$ (*c* = 1, $CHCl_3$).

Preparation of 3-Hydroxy-5-(*tert*-butyldimethylsilyloxy)-(3*R*,5*S*)-cyclohexan-1-one (ent-7). 3-Oxo-5-(*tert*-butyldimethylsilyloxy)-(1*R*,5*S*)-cyclohexyl acetate (**8**, 1.2 g, 4.2 mmol) was dissolved in DMSO (10 mL) and 0.1 M phosphate buffer (pH 6.5, 90 mL). To the mixture was added PLE (0.1 g), and the reaction mixture was shaken for 48 h. It was filtered through Celite, and the filtrate was extracted with ethyl acetate (3 × 100 mL). The organic extracts were combined and washed with brine. The organic layer was dried on anhydrous sodium sulfate and concentrated under vacuum. The residue was chromatographed on silica gel to afford 3-hydroxy-5-(*tert*-butyldimethylsilyloxy)-(3*R*,5*S*)-cyclohexan-1-one (**ent-7**, 0.77 g, 75%) as a viscous liquid.

^{1}H NMR ($CDCl_3$): δ 0.10 (s, 6H), 0.87 (s, 9H), 1.95−2.4 (m, 2H), 2.45−2.78 (m, 4H), 3.98 (bs, 1H), 4.39 (m, 1H), 4.58 (m, 1H). ^{13}C NMR ($CDCl_3$): δ −5.50, −5.28, 17.55, 25.34, 38.24, 49.56, 49.89, 68.86, 70.48, 206.78. IR ($CHCl_3$): 668.15, 759.18, 837.70, 1216.14, 1255.02, 1676.48, 1712.47, 2930.89, 2955.00, 3018.43, 3387.52, 3406.91. Mass: base *m*/*e* = 75; other *m*/*e* 187, 169, 145, 129, 101, 95, 75, 69, 59. Anal. Calcd for $C_{12}H_{24}O_3Si$:

C, 59.01; H, 9.83. Found: C, 59.1; H, 9.98. Specific rotation: $[\alpha]_D = -22.06$ ($c = 1$, $CHCl_3$).

Preparation of (4*S*,6*R*)-4-(*tert*-Butyldimethylsilyloxy)-6-(hydroxymethyl)tetrahydropyran-2-one (ent-1). 3-Hydroxy-5-(*tert*-butyldimethylsilyloxy)-(3*R*,5*S*)-cyclohexan-1-one (**ent-7**, 0.1 g, 0.394 mmol) and 50% 3-chloroperbenzoic acid (0.275 g, 0.79 mmol) were mixed and kept in the dark for 15 h. The reaction mixture was dissolved in ethyl acetate (5 mL) and washed successively with cold sodium metabisulfite solution and sodium bicarbonate solution followed by brine wash. It was then dried on anhydrous sodium sulfate, and solvent was removed under vacuum. The residue was purified by flash column chromatography to yield white, crystalline (4*S*,6*R*)-4-(*tert*-butyldimethylsilyloxy)-6-(hydroxymethyl)tetrahydropyran-2-one (**ent-1**, yield 0.047 g, 45%; mp 95 °C).

^{1}H NMR ($CDCl_3$): δ 0.08, 0.09 (2s, 6H), 0.89 (s, 9H), 1.55−2.00 (m + bs, 3H), 2.60 (d, 2H, $J = 3$), 3.66 (dd, 1H, $J = 12$), 3.90 (dd, 1H, $J = 12$), 4.38 (m, 1H), 4.80 (m, 1H). ^{13}C NMR ($CDCl_3$): δ −5.17, 17.66, 25.41, 31.59, 38.90, 63.24, 64.19, 76.73, 170.31. IR ($CHCl_3$): 666.31, 898.12, 1021.88, 1061.06, 1086.17, 1118.98, 1390.84, 1463.17, 1729.43, 2857.28, 3418.25 cm^{-1}. Mass: base *m/e* = 101; other *m/e* 260, 229, 203, 185, 161, 143, 129, 111, 75, 68, 59. Anal. Calcd for $C_{12}H_{24}O_4Si$: C, 55.38; H, 9.20. Found: C, 55.40; H, 9.30. Specific rotation: $[\alpha]_D = -1.96$ (*c* 1, $CHCl_3$); ee 99% (determined by chiral HPLC of corresponding benzoate derivative, column-Whelk-O1 [4.0 mm i.d. × 25 cm] AT-256; λ =254 nm, flow rate 1 mL/min; mobile phase hexane: 2-propanol, 92:08; retention time for benzoate of **1** = 17.96 and for benzoate of **ent-1** = 19.97).

Preparation of (4*R*,6*S*)-4-(*tert*-Butyldimethylsilyloxy)-6-(p-tolylsulfonylmethyl)tetrahydropyran-2-one and Its Enantiomer. (4*R*,6*S*)-4-(*tert*-butyldimethylsilyloxy)-6-(hydroxymethyl)tetrahydropyran-2-one (**1**, 0.02 g, 0.077 mmol) was dissolved in dry pyridine (0.2 mL). The solution was cooled to 0 °C in an ice−salt mixture. To the cold solution was added *p*-toluenesulfonyl chloride (0.025 g, 0.13 mmol), and the reaction mixture was stirred at RT for 12 h. The reaction mixture was diluted with ether (5 mL). The ether layer was washed with dilute hydrochloric acid followed by washings with brine + water, aqueous $NaHCO_3$, and finally brine. The organic layer was dried on anhydrous sodium sulfate, and the solvent was removed under vacuum. The residue was purified on silica gel column (20% ethyl acetate in petroleum ether) to afford the tosyl of lactone **1** (yield 0.27 g). The same procedure was followed for preparation of the tosyl of **ent-1**.

^{1}H NMR data for both the tosyl derivatives were identical and were as follows:

^{1}H NMR ($CDCl_3$) δ 0.06, 0.07 (2s, 6H), 0.86 (s, 9H), 1.76−2 (m, 2H), 2.46 (s, 3H), 2.54 (d, 2H, $J = 3$), 4.18 (m, 2H), 4.36 (m, 1H), 7.36 (d, 2H, $J = 12$), 7.80 (d, 2H, $J = 12$). Specific rotation for the tosyl of **1**: $[\alpha]_D = +6.85$ ($c = 1.94$, $CHCl_3$) {lit.[7] $[\alpha]_D = +5$ ($c = 0.82$, $CHCl_3$)}. Specific rotation for the tosyl of **ent-1:** $[\alpha]_D = -6.61$ ($c = 1.87$, $CHCl_3$).

Preparation of Racemic 4-(*tert*-Butyldimethylsilyloxy)-6-(hydroxymethyl)tetrahydropyran-2-one [(±)-1]. Racemic 3-hydroxy-5-(*tert*-butyldimethylsilyloxy)cyclohexyl acetate [(±)-**3**] was processed as mentioned earlier for the preparation of (+)-**1** to afford a racemic sample of 4-(*tert*-butyldimethylsilyloxy)-6-(hydroxymethyl)tetrahydropyran-2-one [(±)-**1**].

Preparation of Benzoates of Lactones 1, ent-1, and Racemic 1. Lactone **1** (0.01 g, 0.038 mmol) was dissolved in dichloromethane (1 mL). To the solution was added triethylamine (0.014 g, 0.02 mL, 0.138 mmol), and the resulting solution was cooled to 0 °C in an ice−salt bath. To the cold reaction mixture was added a solution of benzoyl chloride (0.008 g, 0.057 mmol) in dry dichloromethane (0.5 mL). The reaction mixture was stirred at RT for 10 h. The reaction was quenched by adding cold, dilute hydrochloric acid. The organic layer was separated and washed with dilute hydrochloric acid followed by washing with brine + water, aqueous $NaHCO_3$, and finally brine. The organic layer was dried on anhydrous sodium sulfate, and solvent was removed under vacuum to afford the benzoate of lactone **1** (yield 0.01 g). The same procedure was followed for the other two lactones.

^{1}H NMR data for the benzoate were as follows:

^{1}H NMR ($CDCl_3$) δ 0.07 (s, 6H), 0.90 (s, 9H), 1.93 (m, 2H), 2.64 (d, 2H), 4.40 (m, 1H), 4.53 (d, 2H), 5.00 (m, 1H), 7.45 (t, 2H), 7.59 (t, 1H), 8.06 (d, 2H).

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Supporting Information Available: Experimental procedures and detailed spectral data of all the compounds, a few representative spectra, chiral HPLC charts, and an ORTEP diagram for the single-crystal structure of **ent-1** and its crystallographic data. This material is available free of charge via the Internet http//pubs.acs.org.

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