Simple, Efficient Chemoenzymatic Synthesis of (*S*)-5-(*tert*-Butyldimethylsilyloxy)-2-cyclohexenone and Enantiomeric Ketone Intermediates of 19-Nor-1α,25-dihydroxyvitamin D_3

Uttam R. Kalkote,* Sandeep R. Ghorpade, Subhash P. Chavan, and T. Ravindranathan

Division of Organic Chemistry: Technology, National Chemical Laboratory, Pune, India − 411 008

kalkote@dalton.ncl.res.in

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1α,25-Dihydroxyvitamin D_3 (**1**), the bioactive metabolite of vitamin D, and its various analogues have high potential for application as drugs in a diverse range of disease conditions.[1] Among various A-ring modifications, deletion of the 19-exomethylene function has been shown to induce interesting biological activities. 19-Nor-1α,25-dihydroxyvitamin D_3 **2** displays reduced calcemic effects (<10%) while retaining good cell-differentiating properties.[2] Several synthetic approaches toward the synthesis of the hormone 1α,25-D_3 and its various analogues have been developed.[3] Among all these approaches, the phosphine oxide coupling approach, first developed by Lythgoe,[4] is probably the most useful method for producing side-chain and other analogues, wherein the phosphine oxide **4** is directly coupled to a Grundmann's ketone derivative of type **3** producing the 1α,25-D_3 skeleton (Scheme 1). The shortcoming of this route is that the synthesis of the A-ring fragment **4** is somewhat tedious. While there are good syntheses of **4**, more simple and efficient syntheses are still required. Phosphine oxide fragments **4a** and **4b** can be easily accessed from cyclohexylidene esters **5a** and **5b**, respectively,[2b,4c,f] which in turn are obtained from 3,5-trans-disubstituted cyclohexanones **6** and **7**, respectively, through Peterson's olefination in good yields.[2b] The quinic acid method developed by De Luca et al.[2b] for the preparation of cyclohexanone **7** is an efficient method but involves the use of costlier DIBALH, Bu_3SnH, etc. Also, the chemoenzymatic synthesis of **2** described by Vandewalle et al. involves very lengthy chemoenzymatic procedures (5−10 days) and, hence, is not practical.[5] Therefore, a shorter and simpler method would be desirable. Recently, we have demonstrated[6] that the compound 3-hydroxy-5-(*tert*-butyldimethylsilyoxy)-(1*S*,3*R*,5*R*)-cyclohexyl acetate (**8**, ee >95%) is a key synthon for compactin lactone starting from phloroglucitol. We planned to utilize this chiral intermediate **8** for the synthesis of (*S*)-5-(*tert*-butyldimethylsilyloxy)-2-cylcopentenone (**13)** and both the enantiomeric forms of chiral ketone **7** (Scheme 1). A recent report[7] on the utility of **13** toward a vitamin D_3 analogue prompts us to report our findings.

The key chiral intermediate **8** was synthesized as shown in Scheme 2.[8] While the SAM lipase-catalyzed transesterification of **9** affords the diacetate **11** in good yields (78%), the reaction is very lengthy (10 days, 35 °C).[5] Thus, we sought to develop a much more convenient method through enzymatic hydrolysis of triacetate **10**, which is easily made in quantitative yield from **9**. Very recently, the multiselective enzymatic hydrolysis of the triacetate of *trans*-phloroglucitol was reported,[9] but to the best of our knowledge, there is no report on the selective enzymatic hydrolysis of *cis*-triacetate **10** to **11**. We screened a few commercial enzymes for the hydrolysis of **10** in phosphate buffer at pH 7 with PLE, and the most efficient conversion was observed within 12 h to diacetate **11** (90%). The reaction was successfully scaled up to a 25 g scale (Scheme 2).

Diacetate **11** was protected as the TBDMS ether to give *meso*-diacetate **12**. Compound **12** was subjected to desymmetrization through enzymatic hydrolysis. Compound **8** with $[\alpha]_D = -4$ (*c* 1, $CHCl_3$) could be obtained using PPL, but the reaction was slow and was not reproducible on a large scale. On the other hand, with PLE as a catalyst, the reaction was quite rapid but nonselective affording mainly completely hydrolyzed diol. There are few reports where the enantioselectivity of PLE-catalyzed reactions have been improved considerably through optimization, i.e., optimization of reaction media by adding organic cosolvents.[10] The same approach was applied for optimization of the hydrolysis of **12** using PLE as the catalyst. After a few solvents at 10% v/v concentration were screened, the best yield of **8** could be obtained using *tert*-butyl alcohol as a cosolvent. The enantiopurity of **8** was established by HPLC analysis of its Mosher ester on an (R,R) Whelk-O1 (5 μm) chiral column. In addition, the desymmetrization reaction was standardized on an 8 g scale to afford product **8** with an ee > 96% in 70% isolated yield at pH 8 using 8% v/v *tert*-butyl alcohol as a cosolvent. The configuration of **8** at C5 was established to be R by converting it to enone **13** and comparing the rotation with the reported value {compound **13** $[\alpha]_D = +9.4$ (*c* 1, $CHCl_3$) (lit.[11] $[\alpha]_D = +9.8$ (*c* 1, $CHCl_3$) for (*S*)-**13**)}. Therefore, the absolute configuration at centers C1 and C3 are automatically fixed as 1S and

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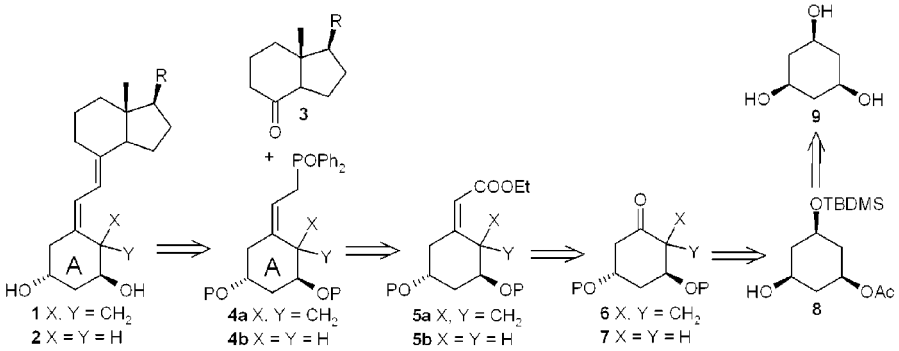
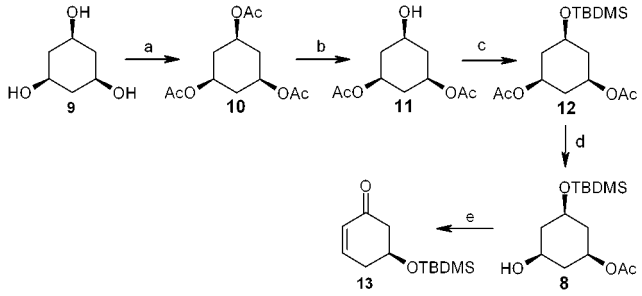
Scheme 1

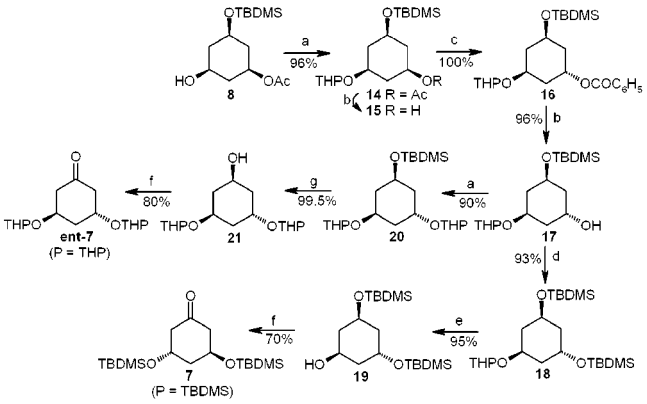


Scheme 2[a]



[a] Key: (a) acetic anhydride, pyridine, 0 °C−RT, 8 h, 100%; (b) PLE, pH 7, 12 h, 90%; (c) TBDMSCl, Et_3N, DMAP, CH_2Cl_2, 0 °C−RT, 90%; (d) PLE, pH 8, buffer with 8% *tert*-butyl alcohol, 30 °C, 48 h, 70%; (e) (i) PCC, CH_2Cl_2, RT, 2 h, 95%, (ii) DBU, CH_2Cl_2, RT, 10 min, 90%.

Scheme 3[a]



[a] Key: (a) DHP, PTSA, 0 °C, 2 h; (b) K_2CO_3, methanol, RT, 2−12 h; (c) PPh_3, benzoic acid, DEAD, 0 °C, 2 h; (d) TBDMSCl, Et_3N, DMAP, CH_2Cl_2, 0 °C−RT, 12 h; (e) $MgBr_2$, etherate, dry ether, RT, 3 h; (f) PCC, NaOAc, CH_2Cl_2, RT, 1 h; (g) TBAF, THF, 1 h.

3R as the compound is all cis, being derived from *cis*-phloroglucitol (Scheme 2). This was further supported by the recently published synthesis of **ent-8** {Compound **8** $[\alpha]_D = -4.8$ (*c* 1, $CHCl_3$), **ent-8** $[\alpha]_D = +5$ (*c* 1, $CHCl_3$)}.[9] It is pertinent to note that, very recently, Sato[7] has demonstrated the utility of the same intermediate **13** toward the synthesis of Vitamin D_3 intermediates.

Compound **8** (ee > 96%) was subjected to further chemical transformations as shown in Scheme 3.

The synthesis of ketone **7** from **8** would require Mitsunobu inversion[12] and functional group interchange as critical steps to achieve the correct stereochemistry. The symmetric nature of intermediate **8** offers an opportunity for selective manipulation of functional groups to obtain both enantiomeric forms of the desired compound. Since Mitsunobu inversion directly on compound **8** would further create problems due to hydrolysis of the acetate group, compound **8** was protected as the THP ether **14**, which on solvolysis with methanol−K_2CO_3 afforded cyclohexanol derivative **15** in 96% yield (Scheme 3). Inversion of the cyclohexanol **15** was accomplished quantitatively under Mitsunobu conditions (0 °C, DEAD, benzoic acid) to affoard **16**.[12] Methanolysis of **16** with methanol−K_2CO_3 afforded cyclohexanol **17** possessing the required trans substitution pattern in 96% yield. Compound **17** was protected as its TBDMS derivative (TBDMSCl, Et_3N, DMAP, 93%) followed by selective THP deprotection using anhydrous $MgBr_2$ in dry ether[13] to afford *trans*-3,5-disilyloxycyclo-hexanol **19** (95% yield). Finally, PCC oxidation of **19** afforded the required ketone **7** (P = TBDMS) in good yield (70%). Thus, an efficient chiral synthesis of ketone **7** was achieved starting from phloroglucitol (**9**) in 57% overall yield.

In a similar procedure, **ent-7** (P = THP) was obtained from **17**. In this case, free −OH in **17** was protected as the THP ether **20** (DHP, PTSA, 0 °C, 90%) followed by selective TBDMS deprotection using tetrabutylammonium fluoride to afford compound **21** (99.5%) enantiomerically related to **19**. The compound **21** on PCC oxidation afforded **ent-7** (P = THP) in 66% overall yield from **9**. Enantiomeric excess of **ent-7** (P = THP) was determined to be 96% by HPLC analysis using a chiral column [Lichrocart (*R*,*R*) Whelk- O 1 (5μm) column]. Since all the reactions were carried out under nonracemizing conditions (even in the conversion of compound **21** to **ent-7**), the ee of **7** was also assumed to be nearly 96% similar to that of **ent-7** (P = THP).

In conclusion, we have demonstrated a simple and efficient chemoenzymatic chiral synthesis of 2-cylcohexenone (**13**) and both enantiomeric forms of diprotected *trans*-3,5-dihydroxy cyclohexanone (**7**) starting from phloroglucitol (**9**), which are useful intermediates of 19-nor-1α,25-dihydroxyvitamin D_3 (**2**).

Experimental Section

Preparation of *cis,cis*-3,5-Di(methylcarbonyloxy)cyclohexyl Acetate (10). Phloroglucitol (**9**, dried at 110 °C to remove water of crystallization, 6.6 g, 50 mmol) was mixed with pyridine in a 100 mL two-necked round-bottom flask fitted with a pressure-equalizing dropping funnel and a calcium chloride guard tube. The mixture was cooled to 0 °C in an ice−salt

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mixture. To the cold, stirred mixture was added acetic anhydride (17.34 g, 0.17 mol) dropwise while maintaining the temperature below 0 °C. After the addition was over, the reaction mixture was stirred at room temperature (RT) for 10 h. Then, it was cooled to 0 °C in an ice−salt mixture, and the reaction was quenched by slowly adding ice-cold, dilute HCl. The mixture was taken up in a separating funnel and was extracted with ethyl acetate (3 × 50 mL). Organic extracts were mixed and washed several times with cold, dilute HCl until free from pyridine, followed by an aqueous $NaHCO_3$ wash and a final brine wash. The organic layer was then dried on anhydrous sodium sulfate, and solvent was evaporated under vacuum. Residue was crushed and dried under high vacuum to afford pure, crystalline *cis*,*cis*-3,5-di(methylcarbonyloxy)cyclohexyl acetate (**10**, yield 12.9 g, 100%, mp 78 °C). ^{1}H NMR ($CDCl_3$): δ 1.33−1.51 (dd, 3H), 2.03 (s, 9H), 2.33 (m, 3H), 4.79 (m, 3H). ^{13}C NMR ($CDCl_3$): δ 21, 36, 67, 169. IR (KBr): cm^{-1} 759, 1023, 1235, 1436, 1740, 2094, 2252, 2874, 2946. Mass: base *m*/*e* = 139, 96; other *m*/*e* = 238, 198, 156, 78, 67, 61. Anal. Calcd for $C_{12}H_{18}O_6$: C, 55.81%; H, 6.98%. Found: C, 55.63%; H 7.01%.

Preparation of *cis*,*cis*-3-Hydroxy-5-methylcarbonyloxycyclohexyl Acetate (11). Finely powdered *cis*,*cis*-3,5-di(methylcarbonyloxy)cyclohexyl acetate (**10**, 6.5 g, 25.19 mmol) was suspended in 0.1 M sodium phosphate buffer (pH 7) (135 mL) and stirred vigorously. To the stirred suspension was added Porcine Liver Esterase (0.110 g), and reaction mixture was stirred vigorously at 30 °C for 12 h. The pH of the reaction mixture was monitored every 2 h and was maintained at pH 7 using 1 N NaOH solution. After completion of the reaction (12 h), the mixture was extracted with ethyl acetate (3 × 150 mL). The organic layers were combined, washed with brine, dried on anhydrous sodium sulfate, and concentrated under vacuum to yield *cis*,*cis*-3-hydroxy-5-methylcarbonyloxycyclohexyl acetate (**11**, yield 4.92 g, 90%) as a semisolid. ^{1}H NMR ($CDCl_3$): δ 1.43 (qn, 3H), 2.01 (s, 6H), 2.24 (m, 3H), 2.71 (bs, 1H), 3.72 (m, 1H), 4.72 (m, 2H). ^{13}C NMR (CDCl3): δ 20.76, 35.99, 39.59, 64.83, 67.31, 170.04. IR (KBr): cm^{-1} 755, 884, 1029, 1140, 1250, 1368, 1739, 2871, 2953, 3445. Mass: base *m*/*e* = 96; other *m*/*e* = 156, 138, 114, 73, 67, 67, 60, 55. Anal. Calcd for $C_{10}H_{16}O_5$: C, 55.56%; H, 7.40%. Found: C, 55.40%; H, 7.56%.

Preparation of *cis*,*cis*-3-(Methylcarbonyloxy)-5-(*tert*-butyldimethylsilyloxy)-cyclohexyl Acetate (12). *cis*,*cis*-3-Hydroxy-5-methylcarbonyloxycyclohexyl acetate (**11**, 2 g, 9.26 mmol) and DMAP (0.113 g, 0.926 mmol) were placed in a 100 mL two-necked round-bottom flask equipped with a dropping funnel and a two-way stopcock. The vessel was evacuated and flushed with argon. Dry dichloromethane (10 mL) was added, and the solution was cooled to −10 °C with stirring. A solution of *tert*-butyldimethylsilyl chloride in dry dichloromethane (10 mL) was added dropwise while maintaining temperature below 0 °C. The reaction mixture was stirred for 15 min, and dry triethylamine (2.02 g, 20 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 12 h. It was then transferred to a separating funnel and washed successively with cold, dilute HCl water, aqueous $NaHCO_3$, and then brine. The organic layer was dried on anhydrous sodium sulfate, and solvent was removed under vacuum. The residue was purified by flash column chromatography (eluent 2−4% ethyl acetate in petroleum ether) to yield *cis*,*cis*-3-(methylcarbonyloxy)-5-(*tert*-butyldimethylsilyloxy)cyclohexyl acetate (**12,** yield 2.85 g, 90%) as an oily liquid. ^{1}H NMR ($CDCl_3$): δ 0.06 (s, 9H), 0.87 (s, 6H), 1.20−1.45 (m, 3H), 2.03 (s, 6H), 2.2 (m, 3H), 3.38 (m, 1H), 4.73 (m, 2H). ^{13}C NMR ($CDCl_3$): δ −5.07, 17.61, 20.73, 25.40, 36.17, 40.40, 65.43, 67.01, 169.64. IR ($CHCl_3$): cm^{-1} 759, 838, 1035, 1106, 1249, 1369, 1734, 2859, 2955. Mass: base *m*/*e* = 117; other *m*/*e* = 273, 213, 171, 159, 129, 117, 97, 79, 75, 57. Anal. Calcd for $C_{16}H_{30}O_5Si$: C, 58.18%; H, 9.10%. Found: C, 58.19%; H, 9.29%.

Preparation of 3-Hydroxy-5-(*tert*-butyldimethylsilyloxy)−(1*S*,3*R*,5*R*)-cyclohexyl Acetate (8). *cis*,*cis*-3-(Methylcarbonyloxy)-5-(*tert*-butyldimethylsilyloxy)cyclohexyl acetate (**12**, 8 g, 242 mmol) was dissolved in *tert*-butyl alcohol (32 mL). To the solution was added 0.1 M sodium phosphate buffer (368 mL, pH 8), and the mixture was stirred vigorously. To the stirred emulsion was added Porcine Liver Esterase (0.30 g), and the mixture was stirred vigorously at 30 °C for 48 h. During the reaction, the pH was maintained at 8 using 1 N sodium hydroxide solution. The reaction mixture was extracted with ethyl acetate (3 × 200 mL). Organic layers were combined and washed with brine. They were then dried on anhydrous sodium sulfate, and solvent was removed under vacuum. The oily residue contained 3-hydroxy-5-(*tert*-butyldimethylsilyloxy)-(1*S*,3*R*,5*R*)-cyclohexyl acetate **8** along with unreacted **12**. These were separated by flash column chromatography. *cis*,*cis*-3-(Methylcarbonyloxy)-5-(*tert*-butyldimethylsilyloxy) cyclohexyl acetate (**12**) was recovered: 2.04 g. 3-Hydroxy-5-(*tert*.butyldimethylsilyloxy)−(1*S*,3*R*,5*R*)-cyclohexyl acetate was recovered as a viscous liquid (**8**, yield 3.7 g, 70% based on recovered starting material). ^{1}H NMR ($CDCl_3$): δ 0.06 (s, 9H), 0.87 (s, 6H), 1.35−1.60, (m, 3H), 2.05 (s, 3H), 2.15 (m, 3H), 3.74 (m, 2H), 4.77 (m, 1H). ^{13}C NMR ($CDCl_3$): −4.99, 17.68, 20.89, 25.49, 39.66, 40.11, 43.71, 64.80, 65.96, 67.83, 170.16. IR ($CHCl_3$): cm^{-1} 758, 839, 1049, 1109, 1218, 1254, 1370, 1725, 2860, 2888, 2952, 3017. Mass: base *m*/*e* = 75; other *m*/*e* = 231, 171, 129, 117, 105, 97, 79, 75, 67, 59. Anal. Calcd for $C_{14}H_{28}O_4Si$: C, 58.33%; H, 9.72%. Found: C, 58.15%; H, 9.91%. $[\alpha]_D = -4.8$ (*c* 1, $CHCl_3$). ee > 96% (determined by chiral HPLC of corresponding Mosher ester. Column: (*R*,*R*) Whelk-O1 [4.0 mm Id x 25 cm] AT-256; λ = 254 nm; flow rate = 1 mL/min; mobile phase = hexane:2-propanol 98:02; retention time for Mosher ester of **8** = 4.59, for Mosher ester of **ent-8** = 4.34).

Synthesis of 3-Tetrahydro-2*H*-2-pyranyloxy-5-(*tert*-butyldimethylsilyloxy)−(1*S*,3*R*,5*R*)-cyclohexyl Acetate (14). 3-Hydroxy-5-(*tert*-butyldimethylsilyloxy)-(1*S*,3*R*,5*R*)-cyclohexyl acetate (**8**, 2.9 g, 9.73 mmol) was dissolved in dry dichloromethane (30 mL). The solution was cooled to below 0 °C in an ice−salt bath. To the stirred solution was added dihydropyran (1 g, 12 mmol), and *p*-toluenesulfonic acid monohydrate (0.1 g) was added as a catalyst. The reaction mixture was stirred at −10 °C for 2 h. The reaction was quenched with aqueous sodium bicarbonate solution. Both of the layers were separated. The aqueous layer was extracted with dichloromethane (10 mL). Organic layers were combined and washed with water followed by brine. They were then dried on anhydrous sodium sulfate, and 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 (**14**, 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 ($CHCl_3$): cm^{-1} 752, 768, 838, 1030, 1115, 1216, 1252, 1727, 2859, 2951, 3017. 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, 9.84%. $[\alpha]_D = +1.39$ (*c* 1, $CHCl_3$).

Synthesis of 3-Tetrahydro-2*H*-2-pyranyloxy-5-(*tert*-butyldimethylsilyloxy)-(1*S*,3*R*,5*S*)-cyclohexan-1-ol (15). 3-Tetrahydro-2*H*-2-pyranyloxy-5-(*tert*-butyldimethylsilyloxy)-(1*S*,3*R*,5*R*)-cyclohexyl acetate (**14**, 3.5 g, 9.16 mmol) was dissolved in dry methanol (25 mL). To the solution was added anhydrous potassium carbonate (0.828 g, 6 mmol), 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). Dichloromethane layers were combined and washed with water followed by brine. They were 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 (**15**, yield 3 g, 96%) as a viscous oil. ^{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 ($CHCl_3$): cm^{-1} 753, 767, 838, 867, 1021, 1048, 1114, 1215, 1254, 2859, 2884, 2948, 3014, 3419. 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, 10.74%. $[\alpha]_D = +0.93$ (*c* 1, $CHCl_3$).

Synthesis of 1-Phenylcarbonyloxy-3-tetrahydro-2*H*-2-pyranyloxy-5-(*tert*-butyldimethylsilyloxy)-(1*R*,3*R*,5*R*)-cyclohexane (16). 3-Tetrahydro-2*H*-2-pyranyloxy-5-(*tert*-butyldimethylsilyloxy)-(1*S*,*3R*,5*S*)-cyclohexan-1-ol **(15**, 1.2 g, 3.64

mmol), benzoic acid (0.61 g, 5 mmol), and triphenylphosphine (1.31 g, 5 mmol) were placed in 50 mL two-necked round-bottomed flask equipped with a two-way stopcock and a sidearm addition funnel. The assembly was evacuated and flushed with argon. Anhydrous THF (10 mL) was added, and the solution was cooled to −10 °C in an ice−salt mixture with magnetic stirring. To the cold, stirred solution was added diethylazodicarboxylate (0.87 g, 5 mmol) in anhydrous THF (5 mL) dropwise over a period of 30 min. while maintaining the temperature well below 0 °C. The reaction mixture was stirred at 0 °C for 2 h. Then, it was filtered through a silica gel bed and solvent was evaporated under vacuum. The residue was purified on a silica gel column (8% ethyl acetate in pet. ether) to afford 1-phenylcarbonyloxy-3-tetrahydro-2*H*-2-pyranyloxy-5-(*tert*-butyldimethylsilyloxy)-(1*R*,3*R*, 5*R*)-cyclohexane (**16**, yield 1.57 g, 100%) as a viscous liquid. ^{1}H NMR ($CDCl_3$): δ 0.06 (s, 6H), 0.88 (s, 9H), 1.20−1.95 (m, 9H), 2.05−2.60 (m, 3H), 3.51 (m, 1H), 4.00 (m, 2H), 4.69, 4.80 (2m, 1H), 5.52 (m, 1H), 7.40−7.65 (m, 3H), 8.00 (md, 2H). ^{13}C NMR ($CDCl_3$): δ −4.50, 18.18, 20.00, 25.80, 25.93, 31.00, 35.80, 37.00, 39.46, 41.70, 43.58, 62.32, 66.18, 69.50, 70.45, 96.54, 97.61, 128.49, 129.59, 130.80, 132.93, 165.58. IR ($CHCl_3$): cm^{-1} 418, 440, 470, 668, 748, 770, 1026, 1098, 1215, 1275, 1712, 2857, 1712, 2857, 2951, 3017. Mass: base *m*/*e* = 105; other *m*/*e* = 293, 179, 171, 159, 135, 129, 122, 105, 85, 67, 55. Anal. Calcd for $C_{24}H_{38}O_5Si$: C, 66.36%; H, 8.76%. Found: C, 66.24%; H, 8.91%. $[\alpha]_D$ = +3.71 (*c* 1.3, $CHCl_3$).

Synthesis of 3-Tetrahydro-2*H*-2-pyranyloxy-5-(*tert*-butyldimethylsilyloxy)−(1*R*,3*R*,5*S*)-cyclohexan-1-ol (17). 1-Phenylcarbonyloxy-3-tetrahydro-2*H*-2-pyranyloxy-5-(*tert*-butyldimethylsilyloxy)-(1*R*,3*R*,5*R*)-cyclohexane (**16**,1.7 g, 3.92 mmol) was dissolved in dry methanol (15 mL). To the solution was added anhydrous potassium carbonate (0.5 g, 3.6 mmol), and the reaction mixture was stirred at RT for 12 h. Methanol was removed under vacuum, and the residue was extracted with ethyl acetate (3 × 10 mL). Organic extracts were combined, washed with brine, and dried on anhydrous sodium sulfate. Solvent was removed under vacuum, and the residue was purified on a silica gel column (20% ethyl acetate in pet. ether) to afford 3-tetrahydro-2*H*-2-pyranyloxy-5-(*tert*-butyldimethylsilyloxy)-(1*R*,3*R*,5*S*)-cyclohexan-1-ol (**17**, yield 1.24 g, 96%) as a viscous liquid. ^{1}H NMR ($CDCl_3$): δ 0.05 (s, 6H), 0.86 (s, 9H), 1.20−2.35 (m, 13H), 3.49 (m, 1H), 3.90 (m, 1H), 4.00 (m, 2H), 4.26 (m, 1H), 4.69 (m, 1H). ^{13}C NMR ($CDCl_3$): δ −4.66, 16.00, 19.70, 25.40, 25.80, 31.14, 37.82, 39.78, 41.73, 41.91, 43.53, 62.55, 62.67, 65.75, 66.36, 69.41, 70.02, 96.82, 97.34. IR ($CHCl_3$): cm^{-1} 435, 471, 668, 751, 770, 835, 1025, 1099, 1124, 1214, 1252, 2857, 2892, 2948, 3013, 3450. Mass: base *m*/*e* = 85; other *m*/*e* = 309, 229, 213, 187, 171, 159, 145, 119, 97, 79, 75, 69, 55. Anal. Calcd for $C_{17}H_{34}O_4Si$: C, 61.82%; H, 10.30%. Found: C, 61.76%; H, 10.56%. $[\alpha]_D$ = +1.59 (*c* 1, $CHCl_3$).

Synthesis of 2-[3,5-Di(*tert*-butyldimethylsilyloxy)cyclohexyloxy]tetrhydro-2*H*-pyran (18). 3-Tetrahydro-2*H*-2-pyranyloxy-5-(*tert*-butyldimethylsilyloxy)-(1*R*,3*R*,5*S*)-cyclohexan-1-ol (**17**, 0.5 g, 1.5 mmol) was dissolved in dry dichloromethane (5 mL) and dry HMPA (0.5 mL) under an argon atmosphere. The solution was cooled to 0 °C in an ice−salt mixture. To the cold, stirred solution was added *tert*-butyldimethylsilyl chloride (0.35 g, 2.3 mmol), and DMAP (0.02 g, 0.16 mmol) dissolved in dry dichloromethane (2 mL) was added dropwise while maintaining a temperature below 0 °C. The reaction mixture was stirred for 5 min. To the cold reaction mixture was added triethylamine (0.3 g, 2.97 mmol, 0.41 mL) dropwise while maintaining a temperature below 0 °C. After the addition was over, the reaction mixture was stirred at RT for 12 h. The reaction was quenched by adding ice-cold, dilute hydrochloric acid. The organic layer was separated. The aqueous layer was extracted with dichloromethane. Organic layers were combined and washed with dilute hydrochloric acid, brine−water, 10% sodium bicarbonate solution, and finally with brine. The organic layer was dried on anhydrous sodium sulfate, and solvent was evaporated under vacuum. The residue was purified on a silica gel column (2% ethyl acetate in pet. ether) to afford pure 2-[3,5-di(*tert*-butyldimethylsilyloxy)cyclohexyloxy]tetrhydro-2*H*-pyran (**18**, yield 0.625 g, 93%) as an oily liquid. ^{1}H NMR ($CDCl_3$): δ 0.05, 0.06 (2s, 12H), 0.88 (s, 18H), 1.20−2.35 (m, 12H), 3.51 (m, 1H), 4.01 (m, 3H), 4.19(m, 1H), 4.26 (m, 1H), 4.65,4.73 (2m, 1H). ^{13}C NMR ($CDCl_3$): δ −5.02, −4.66, 17.96, 18.20, 19.82, 20.06, 25.53, 25.71, 25.92, 31.11, 31.29, 38.74, 40.33, 41.94, 42.80, 43.65, 62.36, 62.79, 66.06, 67.12, 67.25, 69.81, 70.24, 96.85, 97.37. IR ($CHCl_3$): cm^{-1} 419, 450, 475, 668, 755, 769, 835, 1026, 1214, 2856, 2891, 2950, 3018. Mass: base *m*/*e* = 85; other *m*/*e* = 303, 285, 211, 185, 171, 159, 145, 129, 115, 101, 75. Anal. Calcd for $C_{23}H_{48}O_4Si_2$: C, 62.16%; H, 10.81%. Found: C, 62.29%; H, 11.01%. $[\alpha]_D$ = +3.98 (*c* 1, $CHCl_3$).

Synthesis of 3,5-Di(*tert*-butyldimethylsilyloxy)cyclohexan-1-ol (19). 2-[3,5-Di(*tert*-butyldimethylsilyloxy)cyclohexyloxy]tetrahydro-2*H*-pyran (**18**, 0.3 g, 676 mmol) was dissolved in dry ether under an argon atmosphere. To the solution was added magnesium bromide etherate (0.524 g, 2.03 mmol), and the reaction mixture was stirred for 3 h at RT. The reaction was quenched by adding cold, saturated ammonium chloride solution. The ether layer was separated, and the aqueous layer was extracted with ether (ether 3 × 5 mL). Organic extracts were combined, washed with brine, and dried on anhydrous sodium sulfate. Solvent was evaporated under vacuum, and the residue was purified on a silica gel column (10% ethyl acetate in pet. ether) to afford 3,5-di(*tert*-butyldimethylsilyloxy)cyclohexan-1-ol (**19**, yield 0.23 g, 95%) as an oily liquid. ^{1}H NMR ($CDCl_3$): δ 0.09 (s, 12H), 0.91 (s, 18H), 1.48−2.05 (m, 7H), 4.10 (m, 1H), 4.27 (m, 2H). ^{13}C NMR ($CDCl_3$): δ −4.93, −4.75, 17.96, 18.08, 25.77, 42.68, 64.50, 67.55, 68.89. IR ($CHCl_3$): cm^{-1} 436, 457, 753, 769, 834, 1039, 1060, 1092, 1117, 1215, 1254, 2859, 2892, 2934, 2950, 3014, 3482. Mass: base *m*/*e* = 145; other *m*/*e* = 303, 227, 211, 185, 171, 133, 129, 115, 101, 79, 72, 59. Anal. Calcd for $C_{18}H_{40}O_3Si_2$: C, 60.00%; H, 11.11%. Found: C, 60.12%; H, 11.34%. $[\alpha]_D$ = +2.98 (*c* 1.17, $CHCl_3$).

Synthesis of 3,5-Di(*tert*-butyldimethylsilyloxy)-(3*S*,5*S*)-cyclohexan-1-one (7, P = TBDMS). 3,5-Di(*tert*-butyldimethylsilyloxy)cyclohexan-1-ol (**19**, 0.15 g, 0.41 mmol) was dissolved in dichloromethane (3 mL). To the solution were added pyridinium chlorochromate (0.153 g, 0.71 mmol) and anhydrous sodium acetate (0.02 g), and the reaction was stirred for 1 h. The reaction mixture was diluted with ether (5 mL), and solvent was decanted. A sticky residue was extracted with ether (3 × 5 mL). Ether extracts were combined, washed successively with brine−water and brine. The organic layer was dried on anhydrous sodium sulfate, and solvent was removed under vacuum. The residue was purified on a silica gel column (1% ethyl acetate in pet. ether) to afford 3,5-di(*tert*-butyldimethylsilyloxy)-(3*S*, 5*S*)-cyclohexan-1-one (**7**, yield 0.10 g, 70%) as an oily liquid. ^{1}H NMR ($CDCl_3$): δ 0.05 (s, 12H), 0.86 (s, 18H), 1.94 (t, 2H, *J* = 9), 2.38 (dd, 2H, *J* = 12), 2.55 (dd, 2H, *J* = 6), 4.34 (qn, 2H, *J* = 6). ^{13}C NMR ($CDCl_3$): δ −4.94, −4.88, 17.94, 25.71, 42.13, 50.25, 66.83, 207.84. IR ($CHCl_3$): cm^{-1} 411, 434, 452, 461, 478, 767, 806, 837, 868, 902, 1035, 1064, 1100, 1216, 1255, 1719, 2858, 2955, 3019. Mass: base *m*/*e* = 143; other *m*/*e* = 301, 101. Anal. Calcd for $C_{18}H_{38}O_3Si_2$: C, 60.33%; H, 10.61%. Found: C, 60.21%; H, 10.82%. $[\alpha]_D$ = −14.62 (*c* 1.1, $CHCl_3$).

Synthesis of 2-[3-Tetrahydro-2*H*-2-pyranyloxy-5-(*tert*-butyldimethylsilyloxy)cyclohexyloxy]-tetrahydro-2*H*-pyran (20). 3-Tetrahydro-2*H*-2-pyranyloxy-5-(*tert*-butyldimethylsilyloxy)-(1*R*,3*R*,5*S*)-cyclohexan-1-ol (**17**, 0.30 g, 9.09 mmol) was dissolved in dry dichloromethane (5 mL) under a nitrogen atmosphere. To the solution was added 3,4-dihydropyran (0.115 g, 1.36 mmol). The solution was cooled to below 0 °C in an ice−salt mixture. To the cold, stirred solution was added PTSA (0.01 g), and the mixture was stirred at 0 °C for 2 h. The reaction was quenched by adding aqueous sodium bicarbonate solution. The organic layer was separated, and the aqueous layer was extracted with dichloromethane (2 × 3 mL). Combined organic extracts were washed with brine−water and dried on anhydrous sodium sulfate. Solvent was evaporated under vacuum, and the residue was purified on a silica gel column (5% ethyl acetate in pet. ether) to afford 2-[3-tetrahydro-2*H*-2-pyranyloxy-5-(*tert*-butyldimethylsilyloxy)cyclohexyloxy]-tetrahydro-2*H*-pyran (20, yield 0.34 g, 90%) as an oily liquid. ^{1}H NMR ($CDCl_3$): δ 0.06, 0.07 (2s, 6H), 0.89 (s, 9H), 1.15−2.38 (m, 18H), 3.5 (m, 2H), 3.8 (m, 4H), 4.14 (m, 1H), 4.72 (m, 2H). ^{13}C NMR ($CDCl_3$): δ −4.84, 17.88, 19.31, 19.53, 25.30, 25.63, 30.93, 34.49, 35.82, 36.81, 38.00, 38.43, 40.52, 41.44, 43.31, 43.50, 62.10, 62.39, 65.70, 65.96, 69.45, 70.29, 70.70, 96.50, 97.05. IR ($CHCl_3$): cm^{-1} 437, 478, 747, 771, 1024, 1076, 1121, 1213, 1250, 2856, 2944, 3011. Mass: base *m*/*e* = 84; other *m*/*e* = 272, 255, 210, 171, 128. Anal.

Calcd for $C_{22}H_{42}O_5Si$: C, 63.77%; H, 10.14%. Found: C, 63.71%; H, 10.31%. $[\alpha]_D = -0.55$ (*c* 1.11, $CHCl_3$).

Synthesis of 3,5-Di(tetrahydro-2*H*-2-pyraynyloxy)-1-cyclohexanol (21). 2-[3-Tetrahydro-2*H*-2-pyranyloxy-5-*tert*-butyldimethylsilyloxy)cyclohexyloxy]-tetrahydro-2*H*-pyran (**20**, 0.25 g, 0.60 mmol) was dissolved in THF (3 mL). To the solution was added 1 M tetrabutylammonium fluoride solution (0.9 mL, 0.235 g, 0.9 mmol), and the reaction was stirred for 1 h. Solvent was evaporated under vacuum, and the residue was purified on a silica gel column (20% ethyl acetate in pet. ether) to afford compound 3,5-di(tetrahydro-2*H*-2-pyraynyloxy)-1-cyclohexanol (**21**, yield 0.18 g, 99.5%). ^{1}H NMR ($CDCl_3$): δ 1.4−2.15 (m, 19H), 3.52 (m, 2H), 3.90 (m, 2H), 4.13 (m, 3H), 4.72 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 19.23, 19.33, 19.50, 25.10, 30.76, 34.41, 35.98, 36.42, 38.04, 38.79, 40.02, 40.18, 62.06, 62.20, 62.32, 62.41, 65.51, 65.78, 69.18, 69.34, 69.60, 70.66, 71.01, 71.21, 96.51, 96.65, 96.80, 96.96. IR ($CHCl_3$): cm^{-1} 667, 754, 1022, 1067, 1120, 1350, 1448, 2858, 2943, 3009, 3453. Mass: base *m*/*e* = 85; other *m*/*e* = 263, 215, 199, 185, 175, 115, 97. Anal. Calcd for $C_{16}H_{28}O_5$: C, 64.00%; H, 9.33%. Found: C, 64.07%; H, 9.41%. $[\alpha]_D = +2.58$ (*c* 1.18, $CHCl_3$).

Synthesis of 3,5-Di(tetrahydro-2*H*-2-pyraynyloxy)-(3*R*, 5*R*)-cyclohexan-1-one (ent-7, P = THP). 3,5-Di(tetrahydro-2*H*-2-pyranyloxy)-1-cyclohexanol (**21**, 0.1 g, 0.33 mmol) was dissolved in dichloromethane (2 mL). To the solution were added sodium acetate (0.02 g) and pyridinium chlorochromate (0.108 g, 0.5 mmol) . The reaction mixture was stirred for 1 h and diluted with ether (2 mL). Solvent was decanted, and the residue was extracted with ether (3 × 2 mL). Organic extracts were combined and washed with a 1:1 brine−water mixture followed by brine. The organic layer was dried on anhydrous sodium sulfate, and solvent was evaporated under vacuum. The residue was purified on a silica gel column (10% ethyl acetate in pet. ether) to afford 3,5-di(tetrahydro-2*H*-2-pyraynyloxy)-(3*R*,5*R*)-cyclohexan-1-one (**ent-7**, P = THP, yield = 0.080, g 80%). ee = 96% {determined by HPLC on a chiral column: (*R*,*R*) Whelk-O1 [4.0 mm Id x 25 cm] AT-256; λ =210 nm; flow rate = 1 mL/min; mobile phase = hexane:2-propanol 97:03; retention time for **ent-7** = 13.09 and 15.33 (diastereomeric pair), for enantiomer of **ent-7** = 13.70 and 15.76 (diastereomeric pair)}. ^{1}H NMR ($CDCl_3$): δ 1.35−1.95 (m, 12H), 2.00−2.33 (m, 2H), 2.38−2.85 (m, 4H), 3.50 (m, 2H), 3.85 (m, 2H), 4.30 (m, 2H), 4.68 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 18.86, 19.12, 19.26, 25.04, 30.51, 34.33, 36.06, 37.72, 45.80, 46.06, 47.94, 48.16, 61.79, 61.94, 62.12, 62.42, 69.70, 70.03, 70.28, 70.61, 96.46, 96.97, 159.46, 206.95, 207.10, 207.32. IR ($CHCl_3$): cm^{-1} 436, 668, 756, 1214, 2947, 3018. Mass: base *m*/*e* = 85; other *m*/*e* = 213, 197, 113, 101, 95, 67, 55. Anal. Calcd for $C_{16}H_{26}O_5$: C, 64.43%; H, 8.72%. Found: C, 64.48%; H, 8.91%. $[\alpha]_D = +16.36$ (*c* 1.12, $CHCl_3$).

Preparation 5-*tert*-Butyldimethylsilyloxy-(5*S*)-2-cyclohexenone (13). *cis*,*cis*-3-Hydroxy-5-*tert*-butyldimethylsilyloxy-(1*S*,3*R*,5*R*)-cyclohexyl acetate (**8**, 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. The residue was extracted with ether (3 × 10 mL). Organic extracts were combined and filtered through Celite. The filtrate was washed with 1:1 brine−water and finally with brine. The organic layer was dried on anhydrous sodium sulfate and concentrated under vacuum. The residue was filtered through a silica gel column to afford 3-oxo-5-*tert*-butyldimethylsilyloxy-(1*R*,5*S*)-cyclohexyl acetate (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 ($CHCl_3$): cm^{-1} 442, 756, 1218, 1245, 1723, 2857, 2933, 2954, 3020. 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%; H, 9.09%. Found: C, 58.60%; H, 9.28%. $[\alpha]_D = -11.54$ (*c* 1, $CHCl_3$).

3-Oxo-5-*tert*-butyldimethylsilyloxy-(1*R*,5*S*)-cyclohexyl acetate (0.30 g, 1 mmol) was dissolved in dichloromethane (5 mL). To the solution was added DBU (0.150 g, 1 mmol), and the reaction mixture was stirred for 2 h. The reaction was quenched by adding cold ammonium chloride solution. Both layers were separated. The organic layer was washed with ammonium chloride solution and was dried on anhydrous sodium sulfate. Solvent was removed under vacuum, and the residue was purified on a silica gel column to afford 5-*tert*-butyldimethylsilyloxy-(5*S*)-2-cyclohexanone (**13**, yield 0.224 g, 95%) as an oily liquid. ^{1}H NMR ($CDCl_3$): δ 0.07 (s, 6H), 0.87 (s, 9H), 2.25−2.75 (m, 4H), 4.23 (m, 1H), 6.05 (dm, 1H), 6.9 (m, 1H). ^{13}C NMR ($CDCl_3$): δ −5.10, 17.62, 25.38, 35.23, 47.69, 67.32, 129.77, 146.27, 197.92. IR ($CHCl_3$): cm^{-1} 757, 834, 869, 1102, 1218, 1254, 1386, 1678, 2857, 2892, 2934, 2953, 3015. Mass: base *m*/*e* = 74; other *m*/*e* = 211, 169, 151, 127, 110, 94, 66, 58. Anal. Calcd for $C_{12}H_{22}O_2Si$: C, 63.72%; H, 9.73%. Found: C, 63.65%; H, 9.91%. $[\alpha]_D = +9.41$ (*c* 1, $CHCl_3$) (lit.[11] $[\alpha]_D = +9.8$ (*c* 1, $CHCl_3$)).

Preparation of Racemic 3-Hydroxy-5-*tert*-butyldimethylsilyloxycyclohexyl Acetate (+) 8. *cis*,*cis*-3-(Methylcarbonyloxy)-5-(*tert*-butyldimethylsilyloxy)cyclohexyl acetate (**12**, 1.0 g mmol) was dissolved in THF (30 mL). To the solution was added methanol (5 mL) and K_2CO_3 (0.250 g), and the reaction mixture was stirred at RT for 3 h. The reaction mixture was concentrated under vacuum. The residue was extracted with dichloromethane (3 × 5 mL). Organic extracts were combined, washed with brine, and dried over anhydrous sodium sulfate. They were concentrated under vacuum. The residue was chromatographed on a silica gel column to afford racemic 3-hydroxy-5-*tert*-butyldimethylsilyloxy cyclohexyl acetate **(+) 8**, yielding 0.65 g (84.4%) on the basis of recovered starting material along with unreacted starting material **12** (0.25 g). Spectral data for racemic **8** was the same as that obtained for **(−) 8**.

Preparation of Racemic Samples for Ketone 7 (P = TBDMS) and ent-7 (P = THP). Racemic ketones **7** (P = TBDMS) and **ent-7** (P = THP) were prepared from racemic **8** following the same procedure described for optically pure samples.

Preparation of Mosher Esters of Racemic 8 and Optically Enriched 3-Hydroxy-5-*tert*-butyldimethylsilyloxycyclohexyl acetate (−) 8. 3-Hydroxy-5-*tert*-butyldimethylsilyloxycyclohexyl acetate (**8**, 0.020 g, 0.0694 mmol) was dissolved in dry dichloromethane (1 mL). To the solution was added pyridine (0.01 g, 0.126 mmol), and the solution was cooled to 0 °C in an ice−salt bath. To the cold solution was added a solution of (*S*)-Mosher acid chloride (0.023 g, 0.09 mmol) in dry dichloromethane (0.5 mL). The reaction mixture was stirred at RT for 5 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 Mosher ester of 171 (0.025 g). ^{1}H NMR ($CDCl_3$): δ 0.09 (s, 6H), 0.88 (s, 9H), 1.43 (m, 3H), 2.05, 2.07 (2s, 3H), 2.25 (m, 3H), 3.54, 3.55 (2s, 3H), 3.73 (m, 1H), 4.77 (m, 1H), 5.00 (m, 1H), 7.45 (m, 5H).

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Supporting Information Available: Detailed spectral data of all the compounds, some representative spectra, and chiral HPLC charts. This material is available free of charge via the Internet at http://pubs.acs.org.

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