Bioscience, Biotechnology, and Biochemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/tbbb20

New Method for Synthesizing the Intermediates to 5-HETE from Yeast-mediated Reduction Products by Employing Baeyer-Villiger Oxidation with Complete Retention of Enantiomeric Excess

Satoshi YAMAUCHI[a], Yoshihiro KINOSHITA[a] & Yoshiro KINOSHITA[a]
[a] Faculty of Agriculture, Ehime UniversityTarumi 3-5-7, Matsuyama, Ehime 790-8566, Japan
Published online: 22 May 2014.

Biosci. Biotechnol. Biochem., **67** (9), 1959–1969, 2003

New Method for Synthesizing the Intermediates to 5-HETE from Yeast-mediated Reduction Products by Employing Baeyer-Villiger Oxidation with Complete Retention of Enantiomeric Excess

Satoshi YAMAUCHI,† Yoshihiro KINOSHITA, and Yoshiro KINOSHITA

Faculty of Agriculture, Ehime University, Tarumi 3-5-7, Matsuyama, Ehime 790-8566, Japan

Received April 17, 2003; Accepted May 21, 2003

(*R*) and (*S*)-Aldehydes 2, which are intermediates for the synthesis of (5*R*) and (5*S*)-HETE, were respectively synthesized from the yeast-mediated reductive products, hydroxy ester 3 and *cis*-lactone 4, through Baeyer-Villiger oxidation with complete retention of enantiomeric excess.

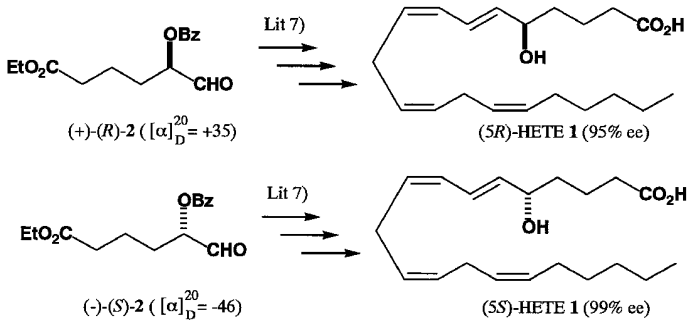
Key words: 5-HETE; yeast reduction

(5*S*)-HETE **1** is a precursor of the potent inflammatory mediator, 5-oxo-ETE, but has less activity than that of 5-oxo-ETE.[1] It has recently been reported that (5*S*)-HETE stimulated DNA synthesis which induced expression of the basic fibroblast growth factor.[2] Fatty acid metabolites play important roles in the living body, although their amounts are very small. This is the reason why synthetic studies of fatty acid metabolites have been continued and the syntheses of (5*R*) and (5*S*)-HETE have been reported.[3–9] In previous work using aldehyde **2** as an intermediate for the synthesis of 5-HETE,[7] the lower optical purity of (+)-(*R*)-**2** resulted in a lower enantiomeric excess (95% ee) of (5*R*)-HETE **1** than that of (5*S*)-HETE **1** (99% ee). In this present study, the respective transformation of yeast-mediated reduction products **3** and **4**[10] to (+)-(*R*)-**2** and (−)-(*S*)-**2** by employing Baeyer-Viliiger oxidation with complete retention of the enantiomeric excess is described (Schemes 1 and 2).

The retrosynthetic analysis is shown in Scheme 2. (+)-(*R*)-Aldehyde **2** could be obtained from glycol **5** by oxidative cleavage. Lactone **6** would be converted to glycol **5**. This lactone **6** could be obtained by Baeyer-Villiger oxidation of ketone **7**. The most important reaction in this experiment is the Baeyer-Villiger oxidation of cyclopentanone derivative **7**. The complete retention of enantiomeric excess is required in this project. Hydroxy ester **3** would be converted to cyclopentanone derivative **7** in a few steps involving α-hydroxylation. According to the same process, (−)-(*S*)-aldehyde **2** could be obtained from *cis*-lactone **4**.

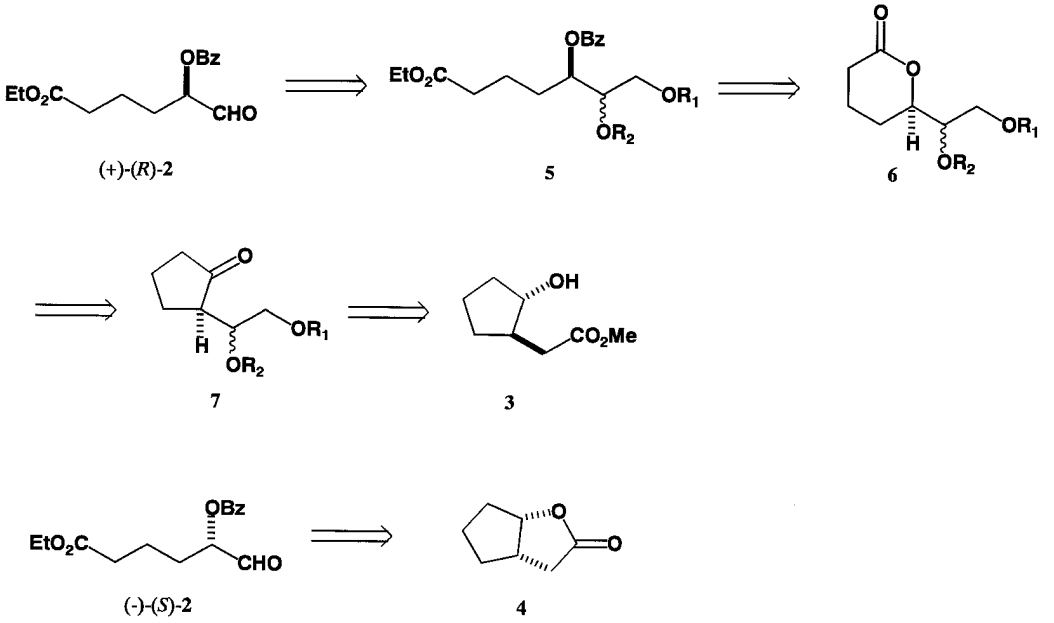
Results and Discussion

After the hydroxy group of hydroxy ester **3** was protected as a benzoate by treatment with benzoyl chloride and triethylamine in 93% yield, α-hydroxylation was tried. Exposure of ester **8** to MoOPH[11] and lithium diisopropylamide gave alcohol **9** in 54% yield as a 3:2 mixture of diastereomers. Methoxymethylation by using chloromethyl methyl ether and *N*,*N*-diisopropylethylamine afforded methoxymethoxy ether **10** in 83% yield. Subsequent $LiAlH_4$ reduction (66% yield) and selective protection of the resulting primary hydroxy group by using *tert*-butylchlorodiphenylsilane, triethylamine, and 4-dimethylaminopyridine[12] gave (2*S*)-cyclopentanol



Scheme 1.

† To whom correspondence should be addressed. Fax: +81-89-977-4364; E-mail: syamauch@agr.ehime-u.ac.jp



Scheme 2. Retrosynthetic Analysis of (+)-(*R*) and (−)-(*S*)-Aldehyde **2**.

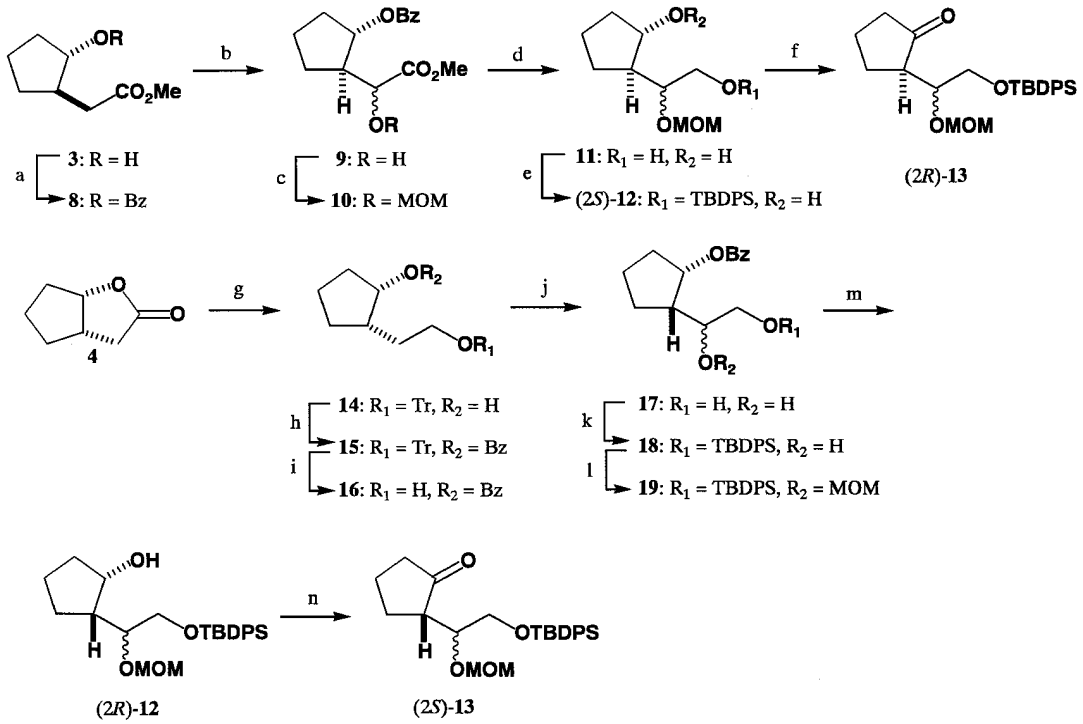
derivative **12** in 81% yield. This (2*S*)-cyclopentanol derivative **12** was converted to (2*R*)-cyclopentanone derivative **13** by pyridinium chlorochromate oxidation in 88% yield.

Since direct α-hydroxylation to *cis*-lactone **4** proved unproductive, this lactone ring was opened to alcohol **16**. $LiAlH_4$ reduction of *cis*-lactone **4**, and subsequent selective protection of the resulting primary hydroxy group as a trityl ether by treatment with trityl chloride and pyridine gave trityl ether **14** in 69% yield. After the secondary hydroxy group present in **14** was converted to a benzoate by using benzoyl chloride and triethylamine in 84% yield, cleavage of the trityl ether was carried out in refluxing methanol containing a catalytic amount of pyridinium *p*-toluenesulfonate in 92% yield. To achieve hydroxylation, this alcohol **16** was subjected to pyridinium chlorochromate oxidation to give an unstable corresponding aldehyde, which was converted to a triisopropylsilyl enol ether by employing triisopropylsilyl triflate, 1,8-diazabicyclo[5.4.0]undec-7-ene, and 4-dimethylaminopyridine.[13] Subsequent osmium oxidation and treatment with silica gel resulted in a polymer of α-hydroxy aldehyde, which was exposed to $NaBH_4$ reduction to give desired glycol **17** as a 2:3 mixture of diastereomers in 31% yield from alcohol **16**. *tert*-Butyldiphenylsilyl protection of the primary hydroxy group (100% yield) followed by methoxymethyl protection of the secondary hydroxy group (91% yield) gave fully protected compound **19**. The benzoate function was then cleaved through the action of diisobutylaluminum hydride, providing (2*R*)-cyclopentanol derivative **12** in 88% yield, which was transformed to (2*S*)-cyclopentanone derivative **13** by pyridinium chlorochromate oxidation in 93% yield. At this stage, all preparations of the substrates for the Baeyer-Villiger oxidation, which is the key reaction in this project, had been accomplished (Scheme 3).

Baeyer-Villiger oxidation of (2*R*)-**13** by using *m*-chloroperbenzoic acid in a phosphate buffer at pH 8[14] and $CHCl_3$ afforded (5*R*,6*R*)-heptanolide **20** (52% yield) and (5*R*,6*S*)-heptanolide **20** (35% yield). Treatment of (5*R*,6*R*) and (5*R*,6*S*)-heptanolide **20** with K_2CO_3 in ethanol produced corresponding unstable hydroxy ethyl esters, respectively. Subsequent exposure to benzoyl chloride and pyridine gave (5*R*,6*R*)-ester **21** (82% yield) and (5*R*,6*S*)-ester **21** (92% yield), respectively.

The absolute configurations of (5*R*,6*R*) and (5*R*,6*S*)-**21** were proven by a comparison with those compounds derived from 2-deoxyribose.[15] The enantiomeric excesses of (5*R*,6*R*) and (5*R*,6*S*)-**21** were each determined to be 99% ee by using chiralpak chromatography.

Desilylation of (5*R*,6*R*) and (5*R*,6*S*)-**21** by treatment with $(n\text{-Bu})_4NF$ in the presence of acetic acid[16] was successful to give (5*R*,6*R*)-alcohol **22** (98% yield) and (5*R*,6*S*)-alcohol **22** (92% yield), respectively. Cleavage of the methoxymethyl ethers of (5*R*,6*R*) and (5*R*,6*S*)-**22** by using trimethylsilyl bromide[17] provided corresponding glycols, which underwent oxidative cleavage by periodate to give (*R*)-aldehyde **2** ($[\alpha]_D^{20} = +48.3$) in 76% and 74% yields, respectively. The $[\alpha]_D^{20}$ value of synthesized (*R*)-**2** was higher than that in the literature ($[\alpha]_D^{20} = +35$).[7] (*S*)-Aldehyde **2** ($[\alpha]_D^{20} = -48.3$) was also obtained from (2*S*)-cyclopentanone derivative **13** *via* (5*S*,6*S*)- and



Scheme 3. Conversion to (2*R*) and (2*S*)-Ketone **13**.

(a) BzCl, Et_3N, CH_2Cl_2, r.t., 18 h (93%). (b) LDA, MoOPH, THF, −23°C, 20 min (54% yield). (c) MOMCl, *N*,*N*-(*iso*-Pr)$_2$NEt, CH_2Cl_2, r.t., 18 h (83% yield). (d) $LiAlH_4$, ether, −10°C, 3.5 h (66% yield). (e) TBDPSCl, Et_3N, DMAP, CH_2Cl_2, r.t., 3 h (81% yield). (f) PCC, NaOAc, MS 4A, CH_2Cl_2, 0°C, 18 h (88% yield). (g) (1) $LiAlH_4$, ether, −10°C, 30 min; (2) TrCl, pyridine, r.t., 2.5 h (69% yield, 2 steps). (h) BzCl, Et_3N, CH_2Cl_2, r.t., 18 h (84%). (i) PPTS, MeOH, reflux, 1 h (92% yield). (j) (1) PCC, NaOAc, MS 4A, CH_2Cl_2, r.t., 18 h; (2) TIPSOTf, DBU, DMAP, 0°C, 1 h; (3) OsO_4, NMO, aq. *tert*-BuOH, acetone, r.t., 18 h; (4) silica gel; (5) $NaBH_4$, EtOH, r.t., 3 h (31% yield, 5 steps). (k) TBDPSCl, Et_3N, DMAP, CH_2Cl_2, r.t., 1 h (100% yield). (l) MOMCl, *N*,*N*-(*iso*-Pr)$_2$NEt, CH_2Cl_2, r.t., 18 h (91% yield). (m) DIBAL, toluene, −75°C, 30 min (88% yield). (n) PCC, NaOAc, MS 4A, CH_2Cl_2, 0°C, 18 h (93% yield).

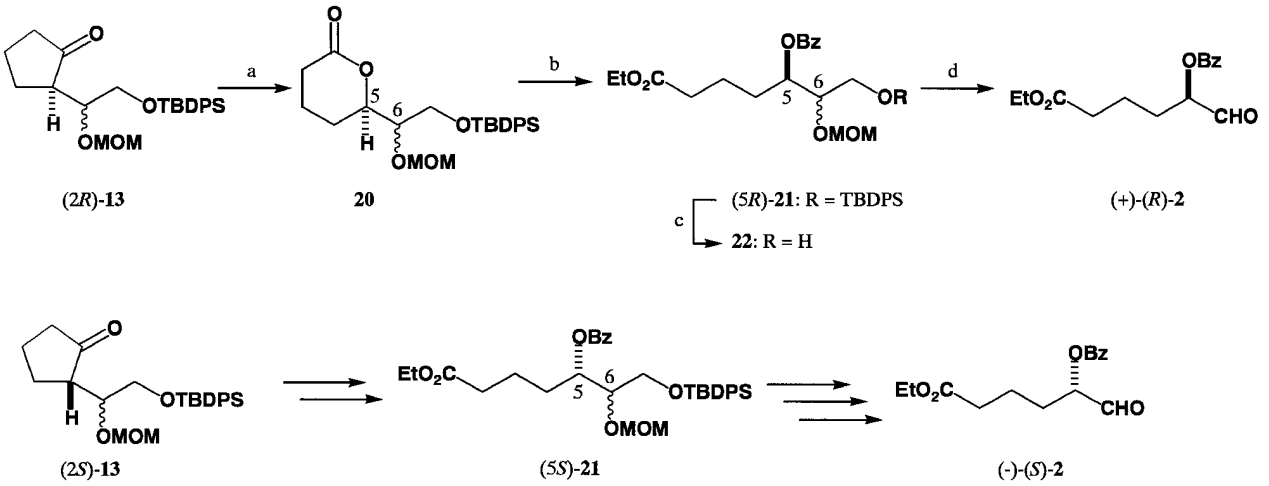
(5*S*,6*R*)-ester **21**, respectively. The enantiomeric excesses of (5*S*,6*S*)- and (5*S*,6*R*)-ester **21** were each determined to be 99% ee by chiralpak chromatography (Scheme 4).

To examine the retention of enantiomeric excess in the Baeyer-Villiger oxidation, a different substrate, (2*R*)-**23** (a diastereomeric mixture of 1:1), was subjected to Baeyer-Villiger oxidation. Lactone **24** was obtained in a lower yield (44%) as a diastereomeric mixture (1:1). (2*R*)-**23** was recovered in 37% yield. After conversion to benzoate **25** and separation of (5*R*,6*R*) and (5*R*,6*S*) isomers, the enantiomeric excesses were determined as 83% ee and 96% ee, respectively (Scheme 5). This fact showed that the trityl group had reduced the yield of the Baeyer-Villiger oxidation products and their enantiomeric excess. When the trityl group was present, the enantiomeric excess of the *erythro* isomer was higher than that of *threo* isomer. In this experiment, the *tert*-butyldiphenylsilyl group was better than the trityl group to achieve complete retention of the enantiomeric excess in the Baeyer-Villiger oxidation.

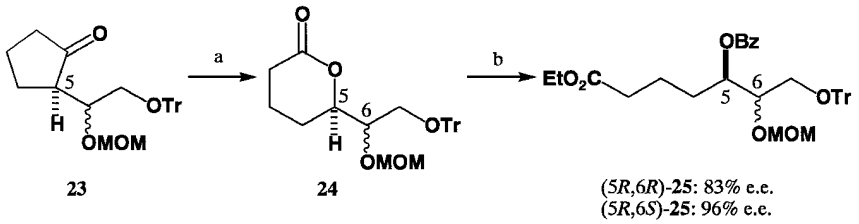
(*R*) and (*S*)-Aldehydes **2**, which were intermediates for the synthesis of 5-HETE, were synthesized from the yeast-mediated reduction products, hydroxy ester **3** and *cis*-lactone **4**, in 12 and 18 steps with 10% and 7% overall yields, respectively. In this synthesis, the stereogenic centers of (*R*) and (*S*)-aldehyde **2** were respectively introduced from yeast reductive products **3** and **4** and Baeyer-Villiger oxidation with (2*R*) and (2*S*)-cyclopentanone derivative **13** as substrates resulted in complete retention of the enantiomeric excess, giving optically pure (5*R*,6*R*), (5*R*,6*S*), (5*S*,6*S*) and (5*S*,6*R*)-**21**. This synthetic process demonstrates a new applicatipon of yeast reductive products **3** and **4**.

Experiment

NMR data were measured by a JNM-EX400 spectrometer, IR spectra were determined with a Shimadzu FTIR-8100 spectrophotometer, FABMS data were measured with a JMS-MS700V spectrometer, and optical rotation values were evaluated with a HORIBA SEPA-200 instrument. The silica gel used was Wakogel C-300 (Wako, 200–300 mesh). HPLC analysis was performed by Shimadzu LC-6AD and SPD-6AV instruments.



Scheme 4. Conversion to (+)-(*R*) and (−)-(*S*)-**2**.
(a) MCPBA, phosphate buffer, pH 8, $CHCl_3$, 0°C, 18 h [(5R,6*R*): 52% yield; (5*R*,6*S*): 35% yield]. (b) (1) K_2CO_3, EtOH, r.t., 18 h; (2) BzCl, pyridine, r.t., 18 h [(5*R*,6*R*): 82% yield, 2 steps; (5*R*,6*S*): 92% yield, 2 steps]. (c) (*n*-Bu)$_4$NF, AcOH, THF, r.t., 60 h [(5*R*,6*R*): 98% yield; (5*R*,6*S*): 92% yield]. (d) (1) TMSBr, CH_2Cl_2, 0°C, 1 h; (2) $NaIO_4$, MeOH, r.t., 2 h [from (5*R*,6*R*): 76% yield, 2 steps; from (5*R*,6*S*): 74% yield, 2 steps].



Scheme 5. Baeyer-Villiger Oxidation of Cyclopentanone Derivative **23**.
(a) MCPBA, phosphate buffer, pH 8, $CHCl_3$, 0°C, 18 h (44% yield). (b) (1) K_2CO_3, EtOH, r.t., 18 h; (2) BzCl, pyridine, r.t., 18 h [(5*R*,6*R*): 31% yield, 2 steps; (5*R*,6*S*): 35% yield, 2 steps].

Methyl [(1R,2S)-2-Benzoyloxycyclopentyl]acetate (8). To an ice-cooled solution of hydroxy ester **3** (9.53 g, 0.055 mol) and Et_3N (9.24 ml, 0.066 mol) in CH_2Cl_2 (10 ml) was added BzCl (7.69 ml, 0.066 mol). After the reaction mixture was stirred at room temperature for 18 h, sat. aq. $NaHCO_3$ solution and CH_2Cl_2 were added. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (1% EtOAc/benzene) gave benzoyl ester **8** (13.3 g, 0.051 mol, 93%) as a colorless oil. $[\alpha]_D^{20} = +58.0$ (*c* 1.00, $CHCl_3$). NMR δ_H ($CDCl_3$): 1.34 (1H, m), 1.70–1.85 (3H, m), 2.04–2.20 (2H, m), 2.35 (1H, dd, $J = 14.7$, 8.3 Hz, C*H*HCO_2Me), 2.54 (1H, m, C*H*CH_2CO_2Me), 2.61 (1H, dd, $J = 14.7$, 5.9 Hz, CH*H*CO_2Me), 3.63 (3H, s, OCH_3), 5.05 (1H, m, C*H*OBz), 7.41–7.45 (2H, m, ArH), 7.55 (1H, m, ArH), 8.01–8.03 (2H, m, ArH). NMR δ_C ($CDCl_3$): 22.5, 30.1, 31.6, 37.7, 42.2, 51.5, 80.7, 128.3, 129.5, 129.6, 130.4, 132.8, 132.9, 166.4, 172.9. IR ν_{max} ($CHCl_3$): 2955, 1732, 1713, 1453, 1439, 1316, 1279, 1202, 1177, 1119 cm^{-1}. *Anal.* Found: C, 68.81; H, 7.08%. Calcd. for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92%.

(R/S)-Methyl [(1R,2S)-2-benzoyloxycyclopentyl]-(hydroxy)acetate (9). To a solution of LDA (0.029 mol) in THF (150 ml) was added a solution of ester **8** (6.76 g, 0.026 mol) in THF (50 ml) at −75°C. After the mixture was stirred at −75°C for 30 min, MoOPH (16.8 g, 0.039 mol) was added. The reaction mixture was stirred at −23°C for 20 min, and then sat. aq Na_2SO_3 solution and EtOAc were added. The organic solution was separated, washed with 10% aq. HCl solution, sat. aq. $NaHCO_3$ solution, and brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (EtOAc/hexane = 1/6, 1/4 and 1/3) gave a diastereomeric mixture of hydroxy ester **9** (3.90 g, 0.014 mol, 54%) as a colorless oil. NMR δ_H ($CDCl_3$): 1.50–1.68 (1H, m), 1.70–1.86 (4H, m), 1.93–2.10 (1H, m), 2.51 (0.6H, m, C*H*CH(OH)CO_2Me), 2.58 (0.4H, m, C*H*CH(OH)CO_2Me), 3.04 (0.6H, br. s, OH), 3.30 (0.4H, br. s, OH), 3.70 (1.2H, s, OCH_3), 3.75 (1.8H, s, OCH_3), 4.24 (0.4H, br. d, $J = 4.4$ Hz, C*H*(OH)CO_2Me), 4.54 (0.6H, br. s, C*H*(OH)CO_2Me), 5.33 (0.4H, m, C*H*OBz), 5.37 (0.6H, m, C*H*OBz), 7.41–7.46 (2H, m, ArH),

7.54–7.55 (1H, m, ArH), 7.98–8.04 (2H, m, ArH). NMR δ_C ($CDCl_3$): 23.5, 24.3, 27.6, 32.7, 32.9, 49.4, 52.5, 70.4, 71.2, 78.5, 127.9, 128.3, 129.5, 130.3, 130.4, 132.9, 166.3, 166.6, 174.5, 174.8. IR ν_{max} ($CHCl_3$): 3525, 2959, 1732, 1713, 1279, 1316, 1119, 922, 897 cm^{-1}. *Anal.* Found: C, 64.94; H, 6.73%. Calcd. for $C_{15}H_{18}O_5$: C, 64.74; H, 6.52%.

*(R/S)-Methyl [(1S,2S)-2-benzoyloxycyclopentyl]-(methoxymethoxy)acetate (**10**).* To a solution of alcohol **9** (3.35 g, 0.012 mol) and *N,N*-(*iso*-Pr)$_2$NEt (16.7 ml, 0.096 mol) in CH_2Cl_2 (5 ml) was added MOMCl (3.65 ml, 0.048 mol). After the reaction mixture was stirred at room temperature for 18 h, MeOH and CH_2Cl_2 were added. The organic solution was separated, washed with 1 M aq. HCl solution, sat. aq. $NaHCO_3$ solution, and brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (EtOAc/hexane = 1/5) gave a diastereomeric mixture of MOM ether **10** (3.31 g, 0.010 mol, 83%) as a colorless oil. NMR δ_H ($CDCl_3$): 1.57 (0.4H, m), 1.66–1.90 (4.6H, m), 1.97 (0.4H, m), 2.08 (0.6H, m), 2.58 (0.4H, m, C*H*CH(OMOM)CO_2Me), 2.64 (0.6H, m, C*H*CH(OMOM)CO_2Me), 3.38 (1.8H, s, OCH_3), 3.40 (1.2H, s, OCH_3), 3.67 (1.8H, s, OCH_3), 3.68 (1.2H, s, OCH_3), 4.15 (0.6H, d, J = 5.4 Hz, C*H*(OMOM)CO_2Me), 4.38 (0.4H, d, J = 4.9 Hz, C*H*(OMOM)CO_2Me), 4.65 (0.6H, d, J = 7.1 Hz, OC*H*HOMe), 4.68 (0.6H, d, J = 7.1 Hz, OC*H*HOMe), 4.70 (0.4H, d, J = 7.1 Hz, OCH*H*OMe), 4.73 (0.4H, d, J = 7.1 Hz, OCH*H*OMe), 5.29 (0.4H, m, C*H*OBz), 5.41 (0.6H, m, C*H*OBz), 7.40–7.46 (2H, m, ArH), 7.55 (1H, m, ArH), 7.99–8.04 (2H, m, ArH). NMR δ_C ($CDCl_3$): 23.2, 23.4, 25.4, 27.2, 32.6, 32.9, 48.0, 48.3, 51.9, 56.2, 56.3, 75.6, 76.5, 77.4, 78.1, 96.46, 96.52, 128.2, 128.3, 129.49, 129.53, 130.3, 130.5, 132.7, 132.9, 165.9, 166.3, 172.1, 172.3. IR ν_{max} ($CHCl_3$): 2955, 1748, 1713, 1279, 914, 903 cm^{-1}. *Anal.* Found: C, 63.34; H, 6.89%. Calcd. for $C_{17}H_{22}O_6$: C, 63.34; H, 6.88%.

*(1S,2S)-2-[(1R / S)-2-Hydroxy-1-(methoxymethoxy)ethyl]cyclopentanol (**11**).* To an ice-cooled suspension of $LiAlH_4$ (0.43 g, 0.011 mol) in ether (10 ml) was added a solution of ester **10** (3.31 g, 0.010 mol) in ether (20 ml). The reaction mixture was stirred at 0°C for 3.5 h before additions of sat. aq. $MgSO_4$ solution and K_2CO_3. The mixture was stirred at room temperature for 30 min and filtered. The filtrate was concentrated. The residue was applied to silica gel column chromatography (EtOAc/hexane = 1/1 and 3/1) to give diol **11** (1.26 g, 6.62 mmol, 66%) as a colorless oil. NMR δ_H ($CDCl_3$): 1.32 (0.4H, m), 1.44 (0.6H, m), 1.53–1.63 (2H, m), 1.67–1.77 (1H, m), 1.80–2.00 (3H, m), 3.42 (1.8H, s, OCH_3), 3.45 (1.2H, s, OCH_3), 3.50–3.58 (1.4H, m, C*H*OH and CH_2OH), 3.67–3.75 (1.6H, m, C*H*OH and CH_2OH), 3.98 (0.6H, m, C*H*OMOM), 4.11 (0.4H, m, C*H*OMOM), 4.66 (0.6H, d, J = 6.8 Hz, OC*H*HOMe), 4.71 (0.4H, d, J = 6.8 Hz, OCH*H*OMe), 4.76 (0.6H, d, J = 6.8 Hz, OC*H*HOMe), 4.81 (0.4H, d, J = 6.8 Hz, OCH*H*OMe). NMR δ_C ($CDCl_3$): 21.7, 21.8, 26.6, 27.6, 33.8, 34.8, 49.0, 50.2, 55.6, 55.8, 64.35, 64.39, 75.1, 76.0, 83.0, 85.2, 96.90, 96.93. IR ν_{max} ($CHCl_3$): 3425, 2961, 1034, 909 cm^{-1}. *Anal.* Found: C, 56.61; H, 9.36%. Calcd. for $C_9H_{18}O_4$: C, 56.82; H, 9.54%.

*(1S,2S)-2-[(1R / S)-2-(tert-Butyldiphenylsilyloxy)-1-(methoxymethoxy)ethyl]cyclopentanol ((2S)-**12**).* To an ice-cooled solution of diol **11** (1.69 g, 8.88 mmol), Et_3N (1.49 ml, 10.7 mmol), and 4-DMAP (43 mg, 0.35 mmol) in CH_2Cl_2 (10 ml) was added TBDPSCl (2.31 ml, 8.88 mmol). After the reaction mixture was stirred at room temperature for 3 h, sat. aq. $NaHCO_3$ solution and CH_2Cl_2 were added. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (EtOAc/hexane = 1/9) gave (2*S*)-cyclopentanol derivative **12** (3.10 g, 7.23 mmol, 81%) as a colorless oil. NMR δ_H ($CDCl_3$): 1.06 (9H, s, tBu), 1.41 (0.6H, m), 1.50–1.74 (3.8H, m), 1.82 (0.6H, m), 1.90–2.00 (2H, m), 2.85 (0.6H, br. s, OH), 3.02 (0.4H, br. s, OH), 3.29 (1.8H, s, OCH_3), 3.39 (1.2H, s, OCH_3), 3.57–3.79 (3H, m, 1-H, CH_2OSi), 4.04 (1H, m, C*H*OMOM), 4.49 (0.6H, d, J = 6.8 Hz, OC*H*HOMe), 4.60 (0.6H, d, J = 6.8 Hz, OC*H*HOMe), 4.63 (0.4H, d, J = 6.8 Hz, OCH*H*OMe), 4.86 (0.4H, d, J = 6.8 Hz, OCH*H*OMe), 7.37–7.43 (6H, m, ArH), 7.65–7.69 (4H, m, ArH). NMR δ_C ($CDCl_3$): 19.1, 19.2, 21.5, 21.7, 26.2, 26.79, 26.81, 27.5, 33.5, 34.1, 48.8, 50.7, 55.7, 55.9, 65.6, 65.8, 75.0, 79.5, 82.2, 96.3, 96.5, 127.69, 127.71, 127.74, 129.73, 129.75, 129.8, 133.0, 133.19, 133.24, 135.57, 135.59, 135.63. IR ν_{max} ($CHCl_3$): 3500, 2961, 1146, 1113, 1030 cm^{-1}. *Anal.* Found: C, 70.08; H, 8.49%. Calcd. for $C_{25}H_{36}O_4Si$: C, 70.05; H, 8.47%.

*(1S,2S)-2-(2-Trityloxyethyl)cyclopentanol (**14**).* To a suspension of $LiAlH_4$ (2.85 g, 0.075 mol) in ether (40 ml) was added a solution of *cis* lactone **4** (9.45 g, 0.075 mol) in ether (80 ml) at −10°C. The reaction mixture was stirred at −10°C for 30 min before additions of sat. aq. $MgSO_4$ and K_2CO_3. The mixture was stirred at room temperature for 30 min and then filtered. The filtrate was concentrated to give a crude diol. To a solution of this crude diol in pyridine (20 ml) was added TrCl (20.9 g, 0.075 mol) in pyridine (20 ml). The reaction mixture was stirred at room temperature for 2.5 h before additions of H_2O and EtOAc. The organic solution was separated, washed with sat. aq. $CuSO_4$, sat. aq. $NaHCO_3$, and brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (EtOAc/hexane = 1/9) gave trityl ether **14** (19.3 g, 0.052 mol, 69%)

as a colorless oil. $[\alpha]_D^{20} = -21.0$ (*c* 1.02, $CHCl_3$). NMR δ_H ($CDCl_3$): 1.35 (1H, m), 1.49 (1H, m), 1.60–1.85 (7H, m), 2.11 (1H, s, OH), 3.07 (1H, m, C*H*HOTr), 3.31 (1H, m, CH*H*OTr), 4.11 (1H, m, C*H*OH), 7.20–7.31 (9H, m), 7.42–7.44 (6H, m). NMR δ_C ($CDCl_3$): 22.1, 29.50, 29.52, 34.4, 44.3, 63.5, 74.2, 87.2, 126.9, 127.8, 128.6, 144.1. IR ν_{max} ($CHCl_3$): 3500, 2936, 1493, 1449, 1071, 1032, 1003, 982, 909 cm^{-1}. *Anal.* Found: C, 83.35; H, 7.64%. Calcd. for $C_{26}H_{28}O_2$: C, 83.83; H, 7.58%.

(1S,2S)-2-(2-Trityloxyethyl)cyclopentyl benzoate (15). To an ice-cooled solution of alcohol **14** (29.7 g, 0.080 mol) and Et_3N (29.7 ml, 0.21 mol) in CH_2Cl_2 (25 ml) was added a solution of BzCl (10.2 ml, 0.088 mol). After the reaction mixture was stirred at room temperature for 18 h, sat. aq. $NaHCO_3$ solution and CH_2Cl_2 were added. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (3% EtOAc/hexane) gave benzoate **15** (31.9 g, 0.067 mol, 84%) as a colorless oil. $[\alpha]_D^{20} = +30.9$ (*c* 1.03, $CHCl_3$). NMR δ_H ($CDCl_3$): 1.46 (1H, m), 1.58–1.72 (2H, m), 1.74–1.88 (3H, m), 1.94–2.03 (2H, m), 2.09 (1H, m), 3.07–3.15 (2H, m, C*H*$_2$OTr), 5.30 (1H, m, C*H*OBz), 7.16–7.33 (11H, m, ArH), 7.40–7.42 (6H, m, ArH), 7.54 (1H, dd, *J* = 7.3, 7.3 Hz, ArH), 7.99 (2H, d, *J* = 7.9 Hz). NMR δ_C ($CDCl_3$): 22.1, 29.75, 29.82, 32.6, 41.6, 62.5, 78.8, 86.4, 126.8, 127.2, 127.7, 127.89, 127.91, 128.3, 128.4, 128.6, 129.5, 130.9, 132.7, 144.3, 146.9, 166.0. IR ν_{max} ($CHCl_3$): 2961, 1709, 1491, 1449, 1316, 1279, 1119, 1071, 1028 cm^{-1}. *Anal.* Found: C, 83.08; H, 6.84%. Calcd. for $C_{33}H_{32}O_3$: C, 83.16; H, 6.77%.

(1S,2S)-2-(2-Hydroxyethyl)cyclopentyl benzoate (16). A reaction solution of trityl ether **15** (28.8 g, 0.060 mol) and PPTS (20 mg, 0.080 mmol) in MeOH (500 ml) was heated under reflux for 1 h. After addition of a few drops of Et_3N, the mixture was concentrated. The residue was applied to silica gel column chromatography (EtOAc/hexane = 1/5) to give alcohol **16** (13.0 g, 0.055 mol, 92%) as a colorless oil. $[\alpha]_D^{20} = +64.2$ (*c* 1.93, $CHCl_3$). NMR δ_H ($CDCl_3$): 1.55–1.60 (2H, m), 1.60–1.72 (2H, m), 1.79–1.97 (3H, m), 2.02 (1H, m), 2.10 (1H, m), 3.64–3.75 (2H, m, C*H*$_2$OH), 5.46 (1H, m, C*H*OBz), 7.43 (2H, dd, *J* = 7.8, 7.3 Hz, ArH), 7.55 (1H, dd, *J* = 7.3, 7.3 Hz, ArH), 8.02 (2H, d, *J* = 7.8 Hz, ArH). NMR δ_C ($CDCl_3$): 22.0, 29.8, 32.4, 32.6, 41.4, 62.0, 78.6, 128.3, 129.5, 130.7, 132.8, 166.3. IR ν_{max} ($CHCl_3$): 3500, 2948, 1709, 1279, 1119 cm^{-1}. *Anal.* Found: C, 71.83; H, 7.71%. Calcd. for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74%.

(1S,2S)-2-[(1R/S)-1,2-Dihydroxyethyl]cyclopentyl benzoate (17). A reaction mixture of alcohol **16** (13.6 g, 0.058 mol), PCC (13.8 g, 0.064 mol), NaOAc (5.24 g, 0.064 mol), and MS 4A (3 g) in CH_2Cl_2 (200 m) was stirred at room temperature for 18 h before addition of dry ether. After the mixture was filtered, the filtrate was concentrated. The residue was applied to silica gel column chromatography (EtOAc/hexane = 1/5) to give an unstable aldehyde (10.5 g, 0.045 mol, 78%). NMR δ_H ($CDCl_3$): 1.57 (1H, m), 1.71 (1H, m), 1.80–2.10 (5H, m), 2.40–2.57 (2H, m, C*H*$_2$CHO), 5.47 (1H, m, C*H*OBz), 7.43–7.46 (2H, m, ArH), 7.55 (1H, m, ArH), 7.99–8.01 (2H, d, *J* = 7.8 Hz, ArH), 9.84 (1H, s, CHO). NMR δ_C ($CDCl_3$): 22.1, 29.8, 32.4, 38.2, 44.1, 78.2, 128.35, 128.40, 129.5, 129.6, 132.9, 133.0, 166.0, 201.4. IR ν_{max} ($CHCl_3$): 2963, 1717, 1277, 1117 cm^{-1}.

To an ice-cooled solution of the resulting aldehyde (10.5 g, 0.045 mol), DBU (14.8 ml, 0.099 mol), and 4-DMAP (4.89 g, 0.040 mol) in CH_2Cl_2 (150 ml) was added TIPSOTf (13.4 ml, 0.050 mol). After the reaction solution was stirred at 0°C for 1 h, sat. aq. $NaHCO_3$ solution was added. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (3% EtOAc/hexane) gave an unstable TIPS enol ether (9.98 g, 0.033 mol, 74%) as a colorless oil.

The reaction solution of the resulting silyl enol ether (9.98 g, 0.026 mol), NMO (3.87 g, 0.033 mol) and OsO_4 (2% in H_2O, 2 ml) in acetone (100 ml), *tert*-BuOH (25 ml) and H_2O (25 ml) was stirred at room temperature for 18 h before addition of $Na_2S_2O_3$. After the mixture was concentrated, the residue was dissolved in EtOAc and H_2O. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (EtOAc/hexane = 1/1) gave polymer of α-hydroxy aldehyde (7.96 g).

To an ice-cooled solution of this polymer (7.96 g) in EtOH (150 ml) was added $NaBH_4$ (1.25 g, 0.033 mol). The reaction mixture was stirred at room temperature for 3 h before addition of 1 M aq. HCl solution. After neutralized with sat. aq. $NaHCO_3$ solution, the mixture was concentrated. The residue was dissolved in EtOAc and H_2O. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (EtOAc/hexane = 1/2) gave a diastereomeric mixture of glycol **17** (3.50 g, 0.014 mol, 54% from TIPS ether) as a colorless oil. NMR δ_H ($CDCl_3$): 1.48 (0.6H, m), 1.60–2.20 (6.4H, m), 2.37–2.90 (2H, br., OH × 2), 3.47–3.55 (1H, m, C*H*HOH), 3.63 (0.4H, m, C*H*OH), 3.66–3.72 (1H, m, CH*H*OH), 3.90 (0.6H, m, C*H*OH), 5.42 (0.4H, m, C*H*OBz), 5.60 (0.6H, m, C*H*OBz), 7.41–7.46 (2H, m, ArH), 7.57 (1H, m, ArH), 7.97–8.02 (2H, m, ArH). NMR δ_C ($CDCl_3$): 21.9, 22.0, 25.0, 26.6, 31.9, 33.3, 46.6, 49.2, 65.3, 65.6, 71.3, 72.4, 77.9, 78.5, 128.3, 128.4, 129.4, 129.6, 129.7, 129.8, 130.4,

133.0, 133.3, 166.0, 167.6. IR ν_{max} ($CHCl_3$): 3313, 2971, 1709, 1283, 1121 cm^{-1}. *Anal.* Found: C, 66.89; H, 7.43%. Calcd. for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25%.

(1S,2S)-2-[(1R / S)-2-(tert-Butyldiphenylsilyloxy)-1-hydroxyethyl]cyclopentyl benzoate (18). To an ice-cooled solution of glycol **17** (2.52 g, 0.010 mol), Et_3N (1.68 ml, 0.012 mol) and 4-DMAP (0.049 g, 0.40 mmol) in CH_2Cl_2 (10 ml) was added TBDPSCl (2.62 ml, 0.010 mol). The reaction mixture was stirred at room temperature for 1 h before additions of sat. aq. $NaHCO_3$ and CH_2Cl_2. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (EtOAc/hexane = 1/9) gave a diastereomeric mixture of silyl ether **18** (4.89 g, 0.010 mol, 100%) as a colorless oil. NMR δ_H ($CDCl_3$): 1.02 (5.4H, s, tBu), 1.05 (3.6H, s, tBu), 1.41 (0.4H, m), 1.58–1.75 (1.6H, m), 1.80–2.00 (3H, m), 2.00–2.19 (2H, m), 2.64 (0.6H, d, J = 3.9 Hz, OH), 2.93 (0.4H, d, J = 3.9 Hz, OH), 3.56–3.60 (1H, m, C*H*HOSi), 3.70 (0.4H, m, C*H*OH), 3.74–3.80 (1H, m, CH*H*OSi), 3.97 (0.6H, m, C*H*OH), 5.22 (0.6H, m, C*H*OBz), 5.65 (0.4H, m, C*H*OBz), 7.17–7.20 (1H, m), 7.28–7.45 (8H, m), 7.53–7.68 (4H, m), 7.94–8.01 (2H, m). NMR δ_C ($CDCl_3$): 19.18, 19.24, 21.9, 22.2, 25.4, 26.8, 26.9, 27.0, 32.2, 33.3, 46.6, 48.2, 66.8, 67.1, 71.4, 72.2, 77.5, 77.8, 127.65, 127.69, 127.71, 127.75, 128.2, 128.3, 128.4, 129.5, 129.6, 129.71, 129.72, 129.74, 129.8, 130.5, 130.7, 132.75, 132.82, 132.9, 133.0, 133.1, 133.2, 134.8, 135.3, 135.4, 135.5, 135.6, 165.7. IR ν_{max} ($CHCl_3$): 2878, 1713, 1279, 1115 cm^{-1}. *Anal.* Found: C, 73.79; H, 7.70%. Calcd. for $C_{30}H_{36}O_4Si$: C, 73.73; H, 7.42%.

(1S,2R)-2-[(1R / S)-2-(tert-Butyldiphenylsilyloxy)-1-(methoxymethoxy)ethyl]cyclopentyl benzoate (19). A reaction mixture of alcohol **18** (5.21 g, 0.011 mol), *N*,*N*-(*iso*-Pr)$_2$NEt (14.9 ml, 0.086 mol) and MOMCl (3.24 ml, 0.043 mol) in CH_2Cl_2 (15 ml) was stirred at room temperature for 18 h before additions of MeOH and CH_2Cl_2. The organic solution was washed with 1 M HCl solution, sat. aq. $NaHCO_3$ solution, and brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (EtOAc/hexane = 1/9) gave a diastereomeric mixture of MOM ether **19** (5.53 g, 0.010 mol, 91%) as a colorless oil. NMR δ_H ($CDCl_3$): 1.00 (5.4H, s, tBu), 1.07 (3.6H, s, tBu), 1.55–2.09 (5.4H, m), 2.13 (0.6H, m), 2.28–2.38 (1H, m), 3.10 (1.2H, s, OCH_3), 3.37 (1.8H, s, OCH_3), 3.64–3.85 (2H, m), 3.85–3.90 (1H, m), 4.49 (0.4H, d, J = 6.8 Hz, OC*H*HOMe), 4.64 (1H, d, J = 6.8 Hz, OCH*H*OMe), 4.83 (0.6H, d, J = 6.8 Hz, OC*H*HOMe), 5.34 (0.6H, m, C*H*OBz), 5.53 (0.4H, m, C*H*OBz), 7.20–7.24 (1H, m, ArH), 7.31–7.45 (6H, m, ArH), 7.52–7.64 (4H, m, ArH), 7.68–7.70 (2H, m, ArH), 7.97–8.01 (2H, m ArH). NMR δ_C ($CDCl_3$): 19.3, 21.8, 21.9, 26.1, 26.5, 26.8, 26.9, 28.0, 32.3, 33.3, 45.8, 46.8, 55.6, 55.7, 65.35, 65.44, 77.5, 77.8, 78.8, 96.1, 96.4, 127.56, 127.64, 127.67, 127.69, 128.3, 128.4, 129.4, 129.5, 129.56, 129.61, 129.7, 130.6, 132.7, 132.9, 133.1, 133.2, 133.4, 134.8, 135.49, 135.53, 135.6, 135.7, 165.8. IR ν_{max} ($CHCl_3$): 2946, 1711, 1279, 1115, 1036, 1028, 909 cm^{-1}. *Anal.* Found: C, 72.43; H, 7.87%. Calcd. for $C_{32}H_{40}O_5Si$: C, 72.14; H, 7.57%.

(1S,2R)-2-[(1R / S)-2-(tert-Butyldiphenylsilyloxy)-1-(methoxymethoxy)ethyl]cyclopentanol ((2R)-12). To a solution of benzoate **19** (5.33 g, 10.0 mmol) in toluene (80 ml) was added DIBAL (18.9 ml, 1 M in toluene, 18.9 mmol) at −75°C. After the reaction solution was stirred at −75°C for 30 min, 1 M aq. HCl solution was added. The organic solution was separated washed with sat. aq. $NaHCO_3$ solution and brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (EtOAc/hexane = 1/9) gave (2*R*)-**12** (3.77 g, 8.80 mmol, 88%) as a colorless oil. NMR δ_H ($CDCl_3$): 1.05 (5.4H, s, tBu), 1.06 (3.6H, s, tBu), 1.35–1.46 (1H, m), 1.50–1.60 (1H, m), 1.61–1.76 (3H, m), 1.76–1.92 (2H, m), 2.85 (0.4H, br. s, OH), 3.30 (1.2H, s, OCH_3), 3.44 (1.8H, s, OCH_3), 3.54 (0.6H, br. s, OH), 3.63–3.78 (2.6H, m, CH_2OSi, C*H*OMOM), 3.91 (0.4H, ddd, J = 6.4, 6.4, 4.9 Hz, C*H*OMOM), 4.30–4.37 (1H, m, C*H*OH), 4.58 (0.4H, d, J = 6.8 Hz, OC*H*HOMe), 4.67 (0.4H, d, J = 6.8 Hz, OC*H*HOMe), 4.70 (0.6H, d, J = 6.8 Hz, CH*H*OMe), 4.99 (0.6H, d, J = 6.8 Hz, OCH*H*OMe), 7.36–7.44 (6H, m, ArH), 7.66–7.70 (4H, m, ArH). NMR δ_C ($CDCl_3$): 19.06, 19.14, 21.9, 22.7, 25.7, 26.0, 26.8, 33.3, 34.8, 47.7, 49.0, 55.7, 55.9, 65.3, 66.5, 67.1, 73.1, 74.1, 79.1, 81.1, 96.5, 98.3, 126.9, 127.7, 127.8, 128.5, 129.68, 129.72, 129.9, 132.8, 133.3, 135.5, 135.6. IR ν_{max} ($CHCl_3$): 3500, 2934, 1429, 1113, 1073, 1030 cm^{-1}. *Anal.* Found: C, 69.83; H, 8.73%. Calcd. for $C_{25}H_{36}O_4Si$: C, 70.05; H, 8.47%.

(2R)-2-[(1R / S)-2-(tert-Butyldiphenylsilyloxy)-1-(methoxymethoxy)ethyl]cyclopentanone (13). A reaction mixture of (2*S*)-cyclopentanol derivative **12** (3.87 g, 9.03 mmol), PCC (2.14 g, 9.93 mmol), NaOAc (0.81 g, 9.87 mmol) and MS 4A (1.5 g) in CH_2Cl_2 (80 ml) was stirred at 0°C for 18 h before addition of dry ether. After the mixture was filtered, the filtrate was concentrated. The residue was applied to silica gel column chromatography (3% EtOAc/benzene) to give a diastereomeric mixture of (2*R*)-cyclopentanone derivative **13** (3.39 g, 7.95 mmol, 88%) as a colorless oil. NMR δ_H ($CDCl_3$): 1.03 (3.6H, s, tBu), 1.04 (5.4H, s, tBu), 1.65–1.79 (1H, m), 1.81–2.35 (5H, m), 2.43–2.54 (1H, m), 3.20 (1.8H, s, OCH_3), 3.29 (1.2H, s, OCH_3), 3.55 (0.6H, dd, J = 10.3, 7.3 Hz, C*H*HOSi), 3.76–3.85 (1.4H, m, CH_2OSi), 4.00 (0.6H, ddd, J = 5.9, 5.9, 3.4 Hz,

C*H*OMOM), 4.20 (0.4H, ddd, J=5.9, 5.9, 2.4 Hz, C*H*OMOM), 4.55 (0.6H, d, J=6.3 Hz, OC*H*HOMe), 4.57 (0.6H, d, J=6.3 Hz, OCH*H*OMe), 4.61 (0.4H, d, J=6.3 Hz, OC*H*HOMe), 4.69 (0.4H, d, J=6.3 Hz, OCH*H*OMe), 7.37–7.45 (6H, m, ArH), 7.65–7.68 (4H, m, ArH). NMR δ_C ($CDCl_3$): 19.1, 19.2, 20.87, 20.94, 23.0, 25.7, 26.7, 26.8, 39.0, 39.1, 50.2, 50.5, 55.5, 55.6, 64.1, 64.5, 76.2, 77.9, 96.7, 97.1, 127.67, 127.70, 129.66, 129.72, 133.21, 133.24, 133.28, 133.33, 135.5, 135.6, 217.9, 220.0. IR ν_{max} ($CHCl_3$): 2932, 1736, 1113, 1036, 909 cm^{-1}. *Anal.* Found: C, 70.61; H, 8.14%. Calcd. for $C_{25}H_{34}O_4Si$: C, 70.38; H, 8.03%. *2S*-**13**: 93% yield. NMR δ_H ($CDCl_3$): 1.03 (5.4H, s, tBu), 1.04 (3.6H, s, tBu), 1.65–1.79 (1H, m), 1.81–2.35 (5H, m), 2.43–2.54 (1H, m), 3.20 (1.2H, s, OCH_3), 3.29 (1.8H, s, OCH_3), 3.55 (0.4H, dd, J=10.3, 7.3 Hz, C*H*HOSi), 3.76–3.85 (1.6H, m, CH_2OSi), 4.00 (0.4H, ddd, J=5.9, 5.9, 3.4 Hz, C*H*OMOM), 4.20 (0.6H, ddd, J=5.9, 5.9, 2.4 Hz, C*H*OMOM), 4.55 (0.4H, d, J=6.3 Hz, OC*H*HOMe), 4.57 (0.4H, d, J=6.3 Hz, OCH*H*OMe), 4.61 (0.6H, d, J=6.3 Hz, OC*H*HOMe), 4.69 (0.6H, d, J=6.3 Hz, OCH*H*OMe), 7.37–7.45 (6H, m, ArH), 7.65–7.68 (4H, m, ArH).

(5R,6R) and (5R,6S)-7-(tert-Butyldiphenylsilyloxy)-6-(methoxymethoxy)-5-heptanolide (20). A reaction mixture of (2*R*)-cyclopentanone derivative **13** (2.92 g, 6.84 mmol), MCPBA (2.06 g, 11.9 mmol) in a phosphate buffer at pH 8 (50 ml) and $CHCl_3$ (50 ml) was stirred at 0°C for 18 h before addition of $Na_2S_2O_3$. The organic solution was separated, washed with sat. aq. $NaHCO_3$ solution and brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (10% EtOAc/benzene) gave (5*R*,6*R*)-heptanolide **20** (1.58 g, 3.57 mmol, 52%) as a colorless oil, $[\alpha]_D^{20}=-19.5$ (*c* 0.36, $CHCl_3$), and (5*R*,6*S*)-heptanolide **20** (1.05 g, 2.37 mmol, 35%) as a colorless oil, $[\alpha]_D^{20}=-16.6$ (*c* 0.30, $CHCl_3$). (5*R*,6*R*)-heptanolide **20**. NMR δ_H ($CDCl_3$): 1.05 (9H, s, tBu), 1.71–1.98 (4H, m, 3-H_2, 4-H_2), 2.42 (1H, ddd, J=18.1, 8.3, 7.3 Hz, 2-*H*H), 2.58 (1H, ddd, J=18.1, 5.4, 5.4 Hz, 2-H*H*), 3.33 (3H, s, OCH_3), 3.68 (1H, m, 6-H), 3.80 (1H, dd, J=10.7, 4.9 Hz, 7-*H*H), 3.89 (1H, dd, J=10.7, 5.4 Hz, 7-H*H*), 4.57 (1H, ddd, J=11.2, 3.9, 3.9 Hz, 5-H), 4.64 (1H, d, J=6.8 Hz, OC*H*HOMe), 4.70 (1H, d, J=6.8 Hz, OCH*H*OMe), 7.37–7.43 (6H, m, ArH), 7.65–7.69 (4H, m, ArH). NMR δ_C ($CDCl_3$): 18.6, 19.2, 24.0, 26.8, 29.6, 55.8, 62.7, 78.6, 79.4, 96.8, 127.7, 129.8, 133.0, 133.2, 135.5, 135.6, 171.1. IR ν_{max} ($CHCl_3$): 2948, 1728, 1244, 1107, 1053, 1030, 911 cm^{-1}. *Anal.* Found: C, 67.74; H, 7.91%. Calcd. for $C_{25}H_{34}O_5Si$: C, 67.84; H, 7.74%. (5*R*,6*S*)-heptanolide **20**. NMR δ_H ($CDCl_3$): 1.05 (9H, s, tBu), 1.72–1.85 (3H, m), 1.91 (1H, m), 2.42 (1H, ddd, J=16.0, 9.3, 6.8 Hz, 2-*H*H), 2.58 (1H, ddd, J=16.0, 6.0, 5.4 Hz, 2-H*H*), 3.29 (3H, s, OCH_3), 3.67 (1H, dd, J=10.7, 6.6 Hz, 7-*H*H), 3.83 (1H, dd, J=10.7, 5.4 Hz, 7-H*H*), 3.88 (1H, m, C*H*OMOM), 4.58 (1H, ddd, J=10.3, 3.9, 3.9 Hz, 5-H), 4.63 (1H, d, J=6.6 Hz, OC*H*HOMe), 4.66 (1H, d, J=6.6 Hz, OCH*H*OMe), 7.36–7.46 (6H, m, ArH), 7.64–7.66 (4H, m, ArH). NMR δ_C ($CDCl_3$): 18.4, 19.2, 22.0, 26.8, 29.8, 55.7, 62.6, 78.2, 79.8, 96.8, 127.78, 127.80, 129.9, 133.0, 133.1, 135.53, 135.55, 135.60, 171.3. IR ν_{max} ($CHCl_3$): 2948, 1728, 1244, 1113, 1107, 1053, 1030, 911 cm^{-1}. *Anal.* Found: C, 68.07; H, 7.92%. Calcd. for $C_{25}H_{34}O_5Si$: C, 67.84; H, 7.74%. (5*S*,6*S*)-*heptanolide* **20**, $[\alpha]_D^{20}=+19.5$ (*c* 0.20, $CHCl_3$). (5*S*,6*R*)-*heptanolide* **20**, $[\alpha]_D^{20}=+16.6$ (*c* 0.42, $CHCl_3$).

(5R,6R) and (5R,6S)-Ethyl 5-benzoyloxy-7-(tert-butyldiphenylsilyloxy)-6-(methoxymethoxy)heptanoate (21). A reaction mixture of (5*R*,6*R*)-heptanolide **20** (1.03 g, 2.33 mmol) and K_2CO_3 (0.32 g, 2.32 mmol) in EtOH (10 ml) was stirred at room temperature for 18 h before its concentration. The residue was dissolved in H_2O and EtOAc. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration gave a crude unstable hydroxy ester. To an ice-cooled solution of this hydroxy ester in pyridine (10 ml) was added BzCl (0.30 ml, 2.58 mmol). The reaction mixture was stirred at room temperature for 18 h before additions of sat. aq. $NaHCO_3$ solution and CH_2Cl_2. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (1% EtOAc/toluene) gave (5*R*,6*R*)-ester **21** (1.14 g, 1.92 mmol, 82%) as a colorless oil. $[\alpha]_D^{20}=-9.3$ (*c* 1.18, $CHCl_3$). NMR δ_H ($CDCl_3$): 1.03 (9H, s, tBu), 1.21 (3H, t, J=6.8 Hz, OCH_2CH_3), 1.69–1.77 (3H, m), 1.89 (1H, m), 2.26–2.38 (2H, m, 2-H_2), 3.30 (3H, s, OCH_3), 3.75–3.82 (2H, m, 7-H_2), 3.87 (1H, m, 6-H), 4.09 (2H, q, J=6.8 Hz, OCH_2CH_3), 4.67 (1H, d, J=6.6 Hz, OC*H*HOMe), 4.73 (1H, d, J=6.6 Hz, OCH*H*OMe), 5.40 (1H, ddd, J=7.8, 4.4, 4.4 Hz, 5-H), 7.22 (2H, d, J=7.3 Hz, ArH), 7.30–7.43 (6H, m, ArH), 7.55 (1H, dd, J=7.3, 7.3 Hz, ArH), 7.60 (2H, d, J=7.8 Hz), 7.66 (2H, d, J=7.8 Hz, ArH), 8.00 (2H, d, J=7.3 Hz, ArH). NMR δ_C ($CDCl_3$): 14.2, 19.1, 21.0, 26.7, 29.6, 34.0, 55.8, 60.2, 63.2, 73.3, 78.2, 96.8, 127.6, 127.7, 128.3, 129.6, 129.69, 129.72, 130.2, 132.9, 133.0, 133.20, 135.5, 165.9, 173.2. IR ν_{max} ($CHCl_3$): 2934, 1720, 1717, 1275, 1113, 1036, 1026 cm^{-1}. *Anal.* Found: C, 69.06; H, 7.66%. Calcd. for $C_{34}H_{44}O_7Si$: C, 68.89; H, 7.48%. (5*R*,6*S*)-ester **21**, 92% yield, $[\alpha]_D^{20}=+9.9$ (*c* 1.00, $CHCl_3$). NMR δ_H ($CDCl_3$): 1.05 (9H, s, tBu), 1.21 (3H, t, J=7.3 Hz, OCH_2CH_3), 1.68–1.85 (4H, m, 3-H_2, 4-H_2), 2.28–2.35 (2H, m, 2-H_2), 3.30 (3H, s, OCH_3), 3.75–3.82 (2H, m, 7-H_2), 3.97 (1H, m, 6-H), 4.09 (2H, q, J=7.3 Hz, OCH_2CH_3), 4.67 (1H, d, J=6.6 Hz, OC*H*HOMe), 4.72 (1H, d, J=6.6 Hz,

OCH*H*OMe), 5.39 (1H, ddd, J=8.8, 3.4, 3.4 Hz, 5-H), 7.31–7.44 (8H, m, ArH), 7.55 (1H, dd, J=7.3, 7.3 Hz, ArH), 7.64–7.70 (4H, m, ArH), 8.00 (2H, d, J=7.3 Hz, ArH). NMR δ_C ($CDCl_3$): 14.2, 19.1, 21.1, 26.7, 29.0, 34.0, 55.7, 60.2, 63.4, 73.8, 78.2, 96.4, 127.69, 127.73, 128.3, 129.65, 129.69, 129.8, 130.3, 132.9, 133.1, 133.2, 135.59, 135.62, 165.9, 173.2. IR ν_{max} ($CHCl_3$): 2934, 1721, 1717, 1273, 1113, 1034, 1028 cm^{-1}. *Anal.* Found: C, 69.11; H, 7.65%. Calcd. for $C_{34}H_{44}O_7Si$: C, 68.89; H, 7.48%. (5*S*,6*S*)-*ester* **21**, $[\alpha]_D^{20}$ = +9.3 (*c* 1.09, $CHCl_3$). (5*S*,6*R*)-*ester* **21**, $[\alpha]_D^{20}$ = −9.9 (*c* 1.02, $CHCl_3$).

Determination of the enantiomeric excess of (5S,6S), (5S,6R), (5R,6R) and (5R,6S)-ester 21. The enantiomeric excess was determined by using DICEL CHIRALPAC AD-H [(5*S*,6*S*) and (5*R*,6*R*)-ester **21**, 2% EtOH/hexane, (5*S*,6*R*) and (5*R*,6*S*)-ester **21**, 2% 2-propanol/hexane, 1.0 ml/min, detected at 254 nm]. (5*S*,6*S*)-ester **21**, retention time 5.9 min, 99% ee (5*S*,6*R*)-ester **21**, retention time 6.5 min, 99% ee (5*R*,5*R*)-ester **21**, retention time 6.9 min, 99% ee (5*R*,6*S*)-ester **21**, retention time 9.8 min, 99% ee.

(5R,6R) and (5R,6S)-Ethyl 5-benzoyloxy-7-hydroxy-6-(methoxymethoxy)heptanoate (22). To an ice-cooled solution of (5*R*,6*R*)-silyl ether **21** (0.52 g, 0.88 mmol) and AcOH (56 μl, 0.98 mmol) in THF (10 ml) was added (n-Bu)$_4$NF (0.88 ml, 1 M in THF, 0.88 mmol). The reaction solution was stirred at room temperature for 60 h before additions of sat. aq. $NaHCO_3$ solution and EtOAc. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (5% EtOAc/toluene) gave (5*R*,6*R*)-alcohol **22** (0.31 g, 0.87 mmol, 98%) as a colorless oil. $[\alpha]_D^{20}$ = +34.2 (*c* 0.15, $CHCl_3$). NMR δ_H ($CDCl_3$): 1.23 (3H, t, J=7.3 Hz, OCH_2CH_3), 1.68–1.77 (2H, m), 1.80–1.86 (2H, m), 2.33–2.36 (2H, m, 2-H_2), 3.05 (1H, dd, J=6.8, 6.8 Hz, OH), 3.41 (3H, s, OCH_3), 3.66–3.71 (2H, m, 7-H_2), 3.77 (1H, m, 6-H), 4.11 (2H, q, J=7.3 Hz, OCH_2CH_3), 4.71 (1H, d, J=6.8 Hz, OC*H*HOMe), 4.76 (1H, dd, J=6.8 Hz, OCH*H*OMe), 5.33 (1H, m, 5-H), 7.43–7.47 (2H, m, ArH), 7.58 (1H, m, ArH), 8.05–8.07 (2H, m, ArH). NMR δ_C ($CDCl_3$): 14.2, 21.0, 29.6, 33.8, 55.9, 60.3, 62.0, 73.4, 81.5, 97.5, 127.7, 128.4, 129.8, 133.2, 166.5, 173.1. IR ν_{max} ($CHCl_3$): 3500, 2955, 1721, 1275, 1113, 1026 cm^{-1}. *Anal.* Found: C, 61.50; H, 7.63%. Calcd. for $C_{18}H_{26}O_7$: C, 61.00; H, 7.39%. (5*R*,6*S*)-*alcohol* **22**, 92% yield. $[\alpha]_D^{20}$ = −9.7 (*c* 0.21, $CHCl_3$). NMR δ_H ($CDCl_3$): 1.23 (3H, t, J=7.3 Hz, OCH_2CH_3), 1.65–1.89 (4H, m, 3-H_2, 4-H_2), 2.33–2.36 (2H, m, 2-H_2), 2.90 (1H, m, OH), 3.42 (3H, s, OCH_3), 3.68 (1H, m, 5-H), 3.75–3.80 (2H, m, 7-H_2), 4.11 (2H, q, J=7.3 Hz, OCH_2CH_3), 4.74 (1H, d, J=6.8 Hz, OC*H*HOMe), 4.77 (1H, d, J=6.8 Hz, OCH*H*OMe), 5.28 (1H, m, 5-H), 7.43–7.47 (2H, m, ArH), 7.58 (1H, m, ArH), 8.03–8.04 (2H, m, ArH). NMR δ_C ($CDCl_3$): 14.2, 20.8, 29.7, 33.8, 55.9, 60.3, 62.0, 73.0, 81.3, 97.0, 128.4, 129.7, 129.8, 133.2, 166.2, 173.1. IR ν_{max} ($CHCl_3$): 3503, 2896, 1721, 1273, 1115, 1026 cm^{-1}. *Anal.* Found: C, 61.17; H, 7.53%. Calcd. for $C_{18}H_{26}O_7$: C, 61.00; H, 7.39%. (5*S*,6*S*)-*alcohol* **22**, $[\alpha]_D^{20}$ = −34.2 (*c* 1.00, $CHCl_3$). (5*S*,6*R*)-*alcohol* **22**, $[\alpha]_D^{20}$ = +9.7 (*c*, 1.54, $CHCl_3$).

(5R)-Ethyl 5-benzoyloxy-5-formylpentanoate (2). To an ice-cooled solution of (5*R*,6*R*)-alcohol **22** (0.60 g, 1.69 mmol) in CH_2Cl_2 (20 ml) was added TMSBr (0.24 ml, 1.82 mmol). After the reaction solution was stirred at 0°C for 1 h, sat. aq. $NaHCO_3$ solution was added. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration gave crude glycol. The reaction mixture of the crude glycol and $NaIO_4$ (0.39 g, 1.82 mmol) in MeOH (15 ml) was stirred at room temperature for 2 h before concentration. The residue was dissolved in EtOAc and H_2O. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (10% EtOAc/toluene) gave (5*R*)-aldehyde **2** (0.36 g, 1.29 mmol, 76%) as a colorless oil. From (5*R*,6*S*)-alcohol **22**, (5*R*)-aldehyde **2** was also obtained in 74% yield. $[\alpha]_D^{20}$ = +48.3 (*c* 0.15, $CHCl_3$), $[\alpha]_D^{20}$ = +35 in lit.[7] NMR δ_H ($CDCl_3$): 1.25 (3H, t, J=7.3 Hz, OCH_2CH_3), 1.83–1.92 (2H, m), 1.92–2.04 (2H, m), 2.40 (2H, t, J=7.3 Hz, 2-H_2), 4.13 (2H, q, J=7.3 Hz, OCH_2CH_3), 5.24 (1H, dd, J=8.1, 4.7 Hz, 5-H), 7.46–7.50 (2H, m, ArH), 7.62 (1H, m, ArH), 8.09–8.11 (2H, m, ArH), 9.64 (1H, s, CHO). NMR δ_C ($CDCl_3$): 14.2, 20.5, 28.2, 33.6, 60.5, 78.3, 128.5, 129.0, 129.8, 129.9, 133.6, 166.1, 172.8, 198.1. IR ν_{max} ($CHCl_3$): 3031, 2988, 2932, 1725, 1271, 1113, 1098, 1071, 1026, 909 cm^{-1}. HRMS (FAB) m/z (M^++H): Calcd. for $C_{15}H_{19}O_5$, 279.1232; found, 279.1236. (5*S*)-*aldehyde* **2**, $[\alpha]_D^{20}$ = −48.3 (*c* 0.35, $CHCl_3$), $[\alpha]_D^{20}$ = −46 in lit.[15]

Baeyer-Villiger oxidation of (2R)-cyclohexanone derivative 23 and determination of the enantiomeric excess. A reaction mixture of (2*R*)-cyclopentanone derivative *23* (1.08 g, 2.52 mmol, a diastereomeric mixture of 1:1), MCPBA (0.87 g, 5.04 mmol) in a phosphate buffer at pH 8 (10 ml) and $CHCl_3$ (10 ml) was stirred at 0°C for 18 h before addition of $Na_2S_2O_3$. The organic solution was separated, washed with sat. aq. $NaHCO_3$ solution and brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (EtOAc/hexane=1/3) gave recovered **22** (0.40 g, 0.93 mmol, 37%) and (5*R*,6*R*/*S*)-**24** (0.50 g, 1.12 mmol, 44%, a diastereomeric mixture of 1:1) as a colorless oil. *Anal.* Found: C, 75.23; H, 7.65%. Calcd. for $C_{28}H_{30}O_5$: C, 75.31; H, 6.77%. A reaction mixture of (5*R*,6*R*/*S*)-**24**

(0.50 g, 1.12 mmol) and K_2CO_3 (0.19 g, 1.37 mmol) in EtOH (10 ml) was stirred at room temperature for 18 h before concentration. The residue was dissolved in H_2O and EtOAc. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration gave a crude unstable hydroxy ester. To an ice-cooled solution of this hydroxy ester in pyridine (10 ml) was added BzCl (0.16 ml, 1.38 mmol). The reaction mixture was stirred at room temperature for 18 h before additions of sat. aq. $NaHCO_3$ solution and CH_2Cl_2. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (EtOAc/hexane = 1/3) gave (5*R*,6*R*)-**25** (0.21 g, 0.35 mmol, 31%) as a colorless oil and (5*R*,6*S*)-**25** (0.23 g, 0.39 mmol, 35%) as a colorless oil. (5*R*,6*R*)-**25**. NMR δ_H ($CDCl_3$): 1.20 (3H, t, J = 7.3 Hz, OCH_2CH_3), 1.57–1.72 (4H, m, 3-H_2, 4-H_2), 2.21–2.31 (2H, m, 2-H_2), 3.23 (1H, dd, J = 10.3, 5.9 Hz, 7-*H*H), 3.31 (3H, s, OCH_3), 3.33 (1H, dd, J = 10.3, 4.9 Hz, 7-H*H*), 3.91 (1H, m, 6-H), 4.07 (2H, q, J = 7.3 Hz, OCH_2CH_3), 4.70 (1H, d, J = 6.8 Hz, OC*H*$HOCH_3$), 4.76 (1H, d, J = 6.8 Hz, OCH*H*OCH_3), 5.39 (1H, m, 5-H), 7.16–7.26 (11H, m, ArH), 7.38–7.44 (6H, m, ArH), 7.55 (1H, m, ArH), 7.93–7.95 (2H, m, ArH). *Anal.* Found: C, 74.58; H, 7.77%. Calcd. for $C_{37}H_{40}O_7$: C, 74.47; H, 6.76%. 83% ee determined by DICEL CHIRALPAC AD-H, 1.0 ml/min, detected at 254 nm, 5% 2-PrOH /hexane. (5*R*,6*S*)-**25**. NMR δ_H ($CDCl_3$): 1.20 (3H, t, J = 7.3 Hz, OCH_2CH_3), 1.54–1.63 (4H, m, 3-H_2, 4-H_2), 2.25–2.28 (2H, m, 2-H_2), 3.26 (1H, dd, J = 4.9, 3.7 Hz, 7-*H*H), 3.30–3.33 (1H, m, 7-H*H*), 3.32 (3H, s, OCH_3), 4.03–4.10 (3H, m, OCH_2CH_3, 6-H), 4.67 (1H, d, J = 6.6 Hz, OC*H*$HOCH_3$), 4.74 (1H, d, J = 6.6 Hz, OCH*H*OCH_3), 5.37 (1H, m, 5-H), 7.18–7.28 (11H, m, ArH), 7.38–7.44 (6H, m, ArH), 7.53 (1H, m, ArH), 7.91–7.93 (2H, m, ArH). *Anal.* Found: C, 74.27; H, 7.60%. Calcd. for $C_{37}H_{40}O_7$: C, 74.47; H, 6.76%. 96% ee determined by DICEL CHIRALPAC AD-H, 1.0 ml/min, detected at 254 nm, 5% 2-PrOH/hexane.

Acknowledgments

We measured the 400 MHz NMR data in Advanced Instrumentation Center For Chemical Analysis Ehime University. We thank the staff of this center for the FAB measurements. We are grateful to Marutomo Co. for financial support.

References

1) Powell, W. S., Gravel, S., MacLeod, R. J., Mills, E., and Hashefi, M., Stimulation of human neutrophils by 5-oxo-6,8,11,14-eicosatetraenoic acid by a mechanism independent of the leukotriene B_4 receptor. *J. Biol. Chem.*, **268**, 9280–9286 (1993).
2) Zeng, Z.-Z., Yellaturu, C. R., Neeli, I., and Rao, G. N., 5(*S*)-Hydroxyeicosatetraenoic acid stimulates DNA synthesis in human microvascular endothelial cells *via* activation of jak/STAT and phosphatidylinositol 3-kinase/akt signaling, leading to induction of expression of basic fibroblast growth factor 2. *J. Biol. Chem.*, **277**, 41213–41219 (2002).
3) Gueugnot, S., Alami, M., Linstrumelle, G., Mambu, L., Petit, Y., and Larcheveque, M., An efficient total synthesis of 5-(*S*)-HETE. *Tetrahedron*, **52**, 6635–6646 (1996).
4) Tao, C., and Donaldson, W. A., Reactivity of tricarbonyl(pentadienyl)iron(1+) cations: enantioselective synthesis of 5-HETE methyl ester. *J. Org. Chem.*, **58**, 2134–2143 (1993).
5) Shimazaki, T., Kobayashi, Y., and Sato, F., Stereospecific total synthesis of dimorphecolic acid, 5(*S*)-HETE, and 12(*S*)-HETE. *Chem. Lett.*, 1785–1788 (1988).
6) Nicolaou, K. C., Ladduwahetty, T., Taffer, I. M., and Zipkin, R. E., A general strategy for the synthesis of monohydroxyeicosatetraenoic acids. Total synthesis of 5(*S*)-hydroxy-6(*E*),8,11,14(*Z*)-eicosatetraenoic acid (5-HETE) and 12(*S*)-hydroxy-5,8,14(*Z*),10(*E*)-eicosatetraenoic acid (12-HETE). *Synthesis*, 344–347 (1986).
7) Zamboni, R., and Rokach, J., Stereospecific synthesis of 5*S*-HETE, 5*R*-HETE, and their transformation to 5-(±)-HPETE. *Tetrahedron Lett.*, **24**, 999–1002 (1983).
8) Corey, E. J., and Hashimoto, S., A practical process for large-scale synthesis of (*S*)-5-hydroxy-6-*trans*-8,11,14-*cis*-eicosatetraenoic acid (5-HETE). *Tetrahedron Lett.*, **22**, 299–302 (1981).
9) Corey, E. J., Albright, J. O., Barton, A. E., and Hashimoto, S., Chemical and enzymic syntheses of 5-HPETE, a key biological precursor of slow-reacting substance of anaphylaxis (SRS), and 5-HETE. *J. Am. Chem. Soc.*, **102**, 1435–1436 (1980).
10) Yamauchi, S., Takeda, K., Ganaha, M., and Kinoshita, Y., Synthesis of (*R*)-6,7-dihydro-5-HETE lactone and (*S*)-6,7-dihydro-5-HETE lactone by using novel yeast reduction as a key reaction. *J. Chem. Soc. Perkin Trans. 1*, 2156–2160 (2002).
11) Vedejs, E., and Larsen, S., Hydroxylation of enolates with oxodiperoxymolybdenum(pyridine)(hexamethylphosphoric triamide), $MoO_5 \cdot Py \cdot HMPA$ (MoOPH): 3-hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one. *Org. Synth., Coll. Vol. VII*, 277–282 (1990).
12) Chaudhary, S. K., and Hernandez, O., 4-Dimethylaminopyridine: an efficient and selective catalyst for the silylation of alcohols. *Tetrahedron Lett.*, 99–102 (1979).
13) Kusama, H., Hara, R., Kawahara, S., Nishimori, T., Kashima, H., Nakamura, N., Morihira, K., and Kuwajima, I., Enantioselective total synthesis of (−)-taxol. *J. Am. Chem. Soc.*, **122**, 3811–3820 (2000).
14) Delay, F., and Ohloff, G., Synthesis of (*R*)- and (*S*)-*p*-mentha-1,8-dien-4-ols from (*R*)-limonene. *Helv. Chem. Acta*, **62**, 2168–2173 (1979).
15) Guindon, Y., Zamboni, R., Lau, C.-K., and Rokach, J., Stereospecific synthesis of leukotriene B_4 (LTB_4).

Tetrahedron Lett., **23**, 739–742 (1982).
16) Smith III, A. B., and Ott, G. R., Total synthesis of (−)-macrolactin A. *J. Am. Chem. Soc.*, **118**, 13095–13096 (1996).
17) Hanessian, S., Delorme, D., and Dufresne, Y., Mild cleavage of methoxymethyl (MOM) ethers with trimethylsilyl bromide. *Tetrahedron Lett.*, **25**, 2515–2518 (1984).