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

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Received April 17, 2003; Accepted May 21, 2003

(R) and (S)-Aldehydes 2, which are intermediates for the synthesis of (5R) and (5S)-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

(5S)-HETE 1 is a precursor of the potent inflammatory mediator, 5-oxo-ETE, but has less activity than that of 5-oxo-ETE. It has recently been reported that (5S)-HETE stimulated DNA synthesis which induced expression of the basic fibroblast growth factor. 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 (5R) and (5S)-HETE have been reported.

In previous work using aldehyde 2 as an intermediate for the synthesis of 5-HETE, the lower optical purity of (+)-(R)-2 resulted in a lower enantiomeric excess (95% ee) of (5R)-HETE 1 than that of (5S)-HETE 1 (99% ee). In this present study, the respective transformation of yeast-mediated reduction products 3 and 4 to (+)-(R)-2 and (-)-(S)-2 by employing Baeyer-Villiger 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 MoOPH11) 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 methoxyethoxy ether 10 in 83% yield. Subsequent LiAlH4 reduction (66% yield) and selective protection of the resulting primary hydroxy group by using tert-butylchlorodiphenylsilane, triethyamine, and 4-dimethylaminopyridine gave (2S)-cyclcopentanol.

Scheme 1.
derivative 12 in 81% yield. This (2S)-cyclopentanol derivative 12 was converted to (2R)-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 hydroxy group (91% yield) followed by methoxymethyl protection of the secondary hydroxy group as a trityl ether by treatment with trityl chloride and pyridine in 88% 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 trisopropylsilyl enol ether by employing triisopropylsilyl triflate, 1,8-diazabicyclo[5.4.0]undec-7-ene, and 4-dimethylaminopyridine. Subsequent osmium oxidation and treatment with silica gel resulted in a polymer of α-hydroxy aldehyde, which was exposed to NaBH₄ 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 disobutylaluminum hydride, providing (2R)-cyclopentanol derivative 12 in 88% yield, which was transformed to (2S)-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 (2R)-13 by using $m$-chloroperbenzoic acid in a phosphate buffer at pH 8⁴⁰ and CHCl₃ afforded (5R,6R)-heptanolide 20 (52% yield) and (5R,6S)-heptanolide 20 (35% yield). Treatment of (5R,6R) and (5R,6S)-heptanolide 20 with K₂CO₃ in ethanol produced corresponding unstable hydroxy ethyl esters, respectively. Subsequent exposure to benzoyl chloride and pyridine gave (5R,6R)-ester 21 (82% yield) and (5R,6S)-ester 21 (92% yield), respectively.

The absolute configurations of (5R,6R) and (5R,6S)-21 were proven by a comparison with those compounds derived from 2-deoxyribose.¹⁹ The enantiomeric excesses of (5R,6R) and (5R,6S)-21 were each determined to be 99% ee by using chiralpak chromatography.

Desilylation of (5R,6R) and (5R,6S)-21 by treatment with (n-Bu)₃NF in the presence of acetic acid was successful to give 22 (98% yield) and 22 (92% yield), respectively. Cleavage of the methoxymethyl ethers of (5R,6R) and (5R,6S)-22 by using trimethylsilyl bromide provided corresponding glycols, which underwent oxidative cleavage by periodate to give (R)-aldehyde 2 ((α)D = +48.3) in 76% and 74% yields, respectively. The [α]D²⁰ value of synthesized (R)-2 was higher than that in the literature ([α]D²⁰ = +35).⁷ (S)-Aldehyde 2 ([α]D²⁰ = −48.3) was also obtained from (2S)-cyclopentanone derivative 13 via (5S,6S)- and 23 via (5R,6R)- and 24 via (5S,6R)- and
Scheme 3. Conversion to \((2R)\)- and \((2S)\)-Ketone 13.

(a) BzCl, Et3N, CH2Cl2, r.t., 18 h (93\%). (b) LDA, MoOPH, THF, \(-23^\circ C\), 20 min (54\% yield). (c) MOMCl, N,N-(iso-Pr)2NEt, CH2Cl2, r.t., 18 h (83\% yield). (d) LiAlH4, ether, \(-10^\circ C\), 3.5 h (92\% yield). (e) MOMCl, N,N-(iso-Pr)2NEt, CH2Cl2, r.t., 18 h (83\% yield). (f) LiAlH4, ether, \(-10^\circ C\), 3.5 h (92\% yield). (g) TBDPSCl, Et3N, DMAP, CH2Cl2, r.t., 3 h (81\% yield). (h) PCC, NaOAc, MS 4A, CH2Cl2, 0\(^\circ C\), 18 h (88\% yield).

(5S,6R)-ester 21, respectively. The enantiomeric excesses of (5S,6S)- and (5S,6R)-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, \((2R)\)-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). \((2R)\)-23 was recovered in 37\% yield. After conversion to benzoate 25 and separation of \((5R,6R)\) and \((5R,6S)\) 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 \(\text{erythro}\) isomer was higher than that of \(\text{threo}\) isomer. In this experiment, the \(\text{tertiarybuthydroaryl}silyl\) 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 \(\text{cis}\)-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 \((2R)\) and \((2S)\)-cyclopentanone derivative 13 as substrates resulted in complete retention of the enantiomeric excess, giving optically pure \((5R,6R)\), \((5R,6S)\), \((5S,6S)\) and \((5S,6R)\)-21. This synthetic process demonstrates a new application 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, CHCl₃, 0°C, 18 h [(5R,6R): 52% yield; (5R,6S): 35% yield]. (b) (1) K₂CO₃, EtOH, r.t., 18 h; (2) BzCl, pyridine, r.t., 18 h [(5R,6R): 82% yield, 2 steps; (5R,6S): 92% yield, 2 steps]. (c) (n-Bu)₄NF, AcOH, THF, r.t., 60 h [(5R,6R): 98% yield; (5R,6S): 92% yield]. (d) (1) TMSBr, CH₂Cl₂, 0°C, 1 h; (2) NaIO₄, MeOH, r.t., 2 h [from (5R,6R): 76% yield, 2 steps; from (5R,6S): 74% yield, 2 steps].

Scheme 5. Baeyer-Villiger Oxidation of Cyclopentanone Derivative 23.
(a) MCPBA, phosphate buffer, pH 8, CHCl₃, 0°C, 18 h (44% yield). (b) (1) K₂CO₃, EtOH, r.t., 18 h; (2) BzCl, pyridine, r.t., 18 h [(5R,6R): 31% yield, 2 steps; (5R,6S): 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 Et₃N (9.24 ml, 0.066 mol) in CH₂Cl₂ (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. NaHCO₃ solution and CH₂Cl₂ were added. The organic solution was separated, washed with brine, and dried (Na₂SO₄). 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. [α]D²₀ = +58.0 (c 1.00, CHCl₃). NMR δH (CDCl₃): 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, CH₂CO₂Me), 2.54 (1H, m, CH₂CH₂CO₂Me), 2.61 (1H, dd, J = 14.7, 5.9 Hz, CH₂CO₂Me), 3.63 (3H, s, OCH₃), 5.05 (1H, m, CHOBz), 7.41–7.45 (2H, m, ArH), 7.55 (1H, m, ArH), 8.01–8.03 (2H, m, ArH). NMR δC (CDCl₃): 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 νmax (CHCl₃): 2955, 1732, 1713, 1453, 1439, 1316, 1279, 1202, 1177, 1119 cm⁻¹. Anal. Found: C, 68.81; H, 7.08%. Calcd. for C₁₅H₁₈O₄: C, 68.68; H, 6.92%.

(R/S)-Methyl [(1R,2S)-2-benzoyloxycyclopentyl]-hydroxyacetate (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 Na₂SO₄ solution and EtOAc were added. The organic solution was separated, washed with 10%aq. HCl solution, sat. aq. NaHCO₃ solution, and brine, and dried (Na₂SO₄). 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 δH (CDCl₃): 1.50–1.68 (1H, m), 1.70–1.85 (2H, m), 2.04–2.20 (2H, m), 2.35 (1H, dd, J = 14.7, 8.3 Hz, CH₂CO₂Me), 2.61 (1H, dd, J = 14.7, 5.9 Hz, CH₂CO₂Me), 3.63 (3H, s, OCH₃), 5.05 (1H, m, CHOBz), 7.41–7.45 (2H, m, ArH), 7.55 (1H, m, ArH), 8.01–8.03 (2H, m, ArH). NMR δC (CDCl₃): 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 νmax (CHCl₃): 2955, 1732, 1713, 1453, 1439, 1316, 1279, 1202, 1177, 1119 cm⁻¹. Anal. Found: C, 68.81; H, 7.08%. Calcd. for C₁₅H₁₈O₄: C, 68.68; H, 6.92%. 

Methyl [(1R,2S)-2-Benzoyloxycyclopentyl]acetate (8). To an ice-cooled solution of hydroxy ester 3
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7.54–7.55 (1H, m, ArH), 7.98–8.04 (2H, m, ArH).
NMR δc (CDCl3): 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 νmax (CHCl3): 3525, 2959, 1732, 1713, 1279, 1316, 1119, 922, 897 cm⁻¹. Anal. Found: C, 64.94; H, 6.73%. Calcd. for C15H18O5: C, 64.74; H, 6.52%.

(R/S)-Methyl [(1S,2S)-2-benzyloxyxycyclopentyl]- (methoxymethoxy)acetate (10). To a solution of alcohol 9 (3.35 g, 0.012 mol) and N-N-(iso-Pr2)3NET (16.7 ml, 0.096 mol) in CH2Cl2 (5 ml) was added MOMCI (3.65 ml, 0.048 mol). After the reaction mixture was stirred at room temperature for 18 h, MeOH and CH2Cl2 were added. The organic solution was separated, washed with 1 M aq. HCl solution, sat. aq. NaHCO3 solution, and brine, and dried (Na2SO4). 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 δc (CDCl3): 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, CH(OMOM)CO2 Me), 2.64 (0.6H, m, CHCH(OMOM)CO2 Me), 3.38 (1.8H, s, OCH3), 3.40 (1.2H, s, OCH3), 3.67 (1.8H, s, OCH3), 3.68 (1.2H, s, OCH3), 4.15 (0.6H, d, J = 5.4 Hz, CH(OMOM)CO2 Me), 4.38 (0.4H, d, J = 4.9 Hz, CHOMOM), 4.65 (0.6H, d, J = 7.1 Hz, CH3O), 4.68 (0.6H, d, J = 7.1 Hz, OCH2OMe), 4.70 (0.4H, d, J = 7.1 Hz, OCH3OMe), 4.74 (0.4H, d, J = 7.1 Hz, OCH3OMe), 5.29 (0.4H, CHOBz), 5.41 (0.6H, m, CHOBz), 7.40–7.46 (2H, m, ArH), 7.55 (1H, m, ArH), 7.99–8.04 (2H, m, ArH). NMR δh (CDCl3): 23.2, 23.4, 25.4, 27.2, 32.6, 32.9, 48.0, 48.3, 51.9, 56.2, 75.3, 75.6, 77.4, 78.1, 79.6, 96.4, 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 νmax (CHCl3): 2955, 2974, 1713, 1279, 914, 903 cm⁻¹. Anal. Found: C, 63.34; H, 6.89%. Calcd. for C17H18O5Si: C, 63.34; H, 6.88%.

(1S,2S)-2-[(1R / S)-2-Hydroxy-1-(methoxymethoxy)ethyl]cyclopentanol (11). To an ice-cooled solution of diol 11 (1.69 g, 8.89 mmol), Et3N (1.49 ml, 10.7 mmol), and 4-DMAP (43 mg, 0.35 mmol) in CH2Cl2 (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. NaHCO3 solution and CH2Cl2 were added. The organic solution was separated, washed with brine, and dried (Na2SO4). Concentration followed by silica gel column chromatography (EtOAc/hexane = 1/9) gave (2S)-cyclopentanol derivative 12 (3.10 g, 7.23 mmol, 81%) as a colorless oil. NMR δh (CDCl3): 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, OCH3), 3.57–3.79 (3H, m, 1-H, CH2OSi), 4.04 (1H, m, CHOMOM), 4.49 (0.6H, d, J = 6.8 Hz, OCH2OMe), 4.60 (0.6H, d, J = 6.8 Hz, OCHOMe), 4.63 (0.4H, d, J = 6.8 Hz, OCHOMe), 4.86 (0.4H, d, J = 6.8 Hz, OCHOMe), 5.77–7.43 (6H, m, ArH), 7.65–7.69 (4H, m, ArH). NMR δc (CDCl3): 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, 75.9, 82.2, 96.3, 96.5, 127.69, 127.71, 127.74, 129.73, 129.75, 133.0, 133.19, 133.24, 135.57, 135.59, 135.63. IR νmax (CHCl3): 3500, 2961, 1146, 1113, 1030 cm⁻¹. Anal. Found: C, 70.08; H, 8.49%. Calcd. for C25H36O4Si: C, 70.05; H, 8.47%.

(1S,2S)-2-(2-Trityloxyethyl)cyclopentanol (14). To a suspension of LiAlH4 (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. MgSO4 and K2CO3. 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 H2O and EtOAc. The organic solution was separated, washed with sat. aq. CuSO4, sat. aq. NaHCO3, and brine, and dried (Na2SO4). 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. [α]D = −21.0 (c 1.02, CHCl₃).

NMR δH (CDCl₃): 1.35 (1H, m), 1.49 (1H, m), 1.60–1.85 (7H, m), 2.11 (1H, s, OH), 3.07 (1H, m, CH(OH)Tr), 3.31 (1H, m, CH(OH)Tr), 4.11 (1H, m, CH(OH)), 7.20–7.31 (9H, m), 7.42–7.44 (6H, m).

NMR δC (CDCl₃): 21.2, 29.50, 29.52, 34.4, 44.3, 63.5, 74.2, 87.2, 126.9, 127.8, 128.6, 141.1. IR νmax (CHCl₃): 3500, 2936, 1493, 1449, 1071, 1049, 1003, 982, 909 cm⁻¹. Anal. Found: C, 83.35; H, 7.64%.

Calcd. for C₂₆H₂₈O₂: C, 83.83; H, 7.58%.

(IS,2S)-2-(2-Trityloxyethyl)cyclopentyl benzoate (15). To an ice-cooled solution of alcohol 14 (29.7 g, 0.080 mol) and Et₃N (29.7 ml, 0.21 mol) in CH₂Cl₂ (25 ml) was added a solution of BzCl (10.2 ml, 0.088 mol). The reaction mixture 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 a unstable aldehyde (10.5 g, 0.045 mol, 78%). NMR δH (CDCl₃): 1.57 (1H, m), 1.71 (1H, m), 1.80–2.10 (5H, m), 2.40–2.57 (2H, m, CH₂ CHO), 5.47 (1H, m, CHOBz), 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 δC (CDCl₃): 22.1, 29.8, 32.4, 32.8, 38.2, 41.4, 78.2, 128.3, 132.8, 166.0. IR νmax (CHCl₃): 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 CH₂Cl₂ (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. NaHCO₃ solution was added. The organic solution was separated, washed with brine, and dried (Na₂SO₄). 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 OsO₄ (2% in H₂O, 2 ml) in acetone (100 ml), tert-BuOH (25 ml) and H₂O (25 ml) was stirred at room temperature for 18 h before addition of Na₂S₂O₄. After the mixture was concentrated, the residue was dissolved in EtOAc and H₂O. The organic solution was separated, washed with brine, and dried (Na₂SO₄). 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 NaBH₄ (1.25 g, 0.03 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. NaHCO₃ solution, the mixture was concentrated. The residue was dissolved in EtOAc and H₂O. The organic solution was separated, washed with brine, and dried (Na₂SO₄). Concentration followed by silica gel column chromatography (EtOAc/hexane = 1/1) gave a diastereomeric mixture of glycol (1.5 g, 0.014 mol, 54% from TIPS ether) as a colorless oil. NMR δH (CDCl₃): 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, CH(OH)OH), 3.63 (0.4H, m, CH(OH)), 3.66–3.72 (1H, m, CH(OH)OH), 3.90 (0.6H, m, CH(OH)), 5.42 (0.4H, m, CH(OBz)), 5.60 (0.6H, m, CH(OBz)), 7.41–7.46 (2H, m, ArH), 7.75 (1H, m, ArH), 7.97–8.02 (2H, m, ArH). NMR δC (CDCl₃): 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,
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133.0, 133.3, 166.0, 167.6. IR $\nu_{\text{max}}$ (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%.

$\text{(1S,2S)-2-[(1R / S)-2-(tert-Butyldiphenylsilyloxy)-1-hydroxyethyl}$$
\text{cyclopentenyl benzene (18). To an ice-cooled solution of glycol}$
\text{17 (2.52 g, 0.010 mol), Et$_3$N (1.68 ml, 0.012 mol) and DMAP (0.049 g,}
\text{0.40 mmol) in CH$_2$Cl$_2$ (10 ml) was added TBDPSCl (2.62 ml,}
\text{0.010 mol). The reaction mixture was stirred at room temperature for 1 h before additions}
\text{of sat. aq. NaHCO$_3$ and CH$_3$Cl$_2$. The organic solution was separated, washed with}
\text{brine, and dried (Na$_2$SO$_4$). Concentration followed by silica gel column}
\text{chromatography (EtOAc/hexane = 1/9) gave a diastereomeric mixture of silyl ether 18 (4.89 g,}
\text{0.010 mol, 100%) as a colorless oil. NMR $\delta$ (CDCl$_3$): 1.02 (5.4H, s, tBu), 1.05 (3.6H, s, tBu),
\text{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,}
\text{OH), 2.93 (0.4H, d, $J = 3.9$ Hz, OH), 3.56–3.60 (1H, m, CH/HOSi), 3.70 (0.4H, m, CH/OH), 3.74–3.80
\text{(1H, m, CH/OH), 3.97 (0.6H, m, CH/OH), 5.22 (0.6H, m, CHO/Bz), 5.65 (0.4H, m, CHO/Bz),}
\text{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 $\delta$ (CDCl$_3$):}
\text{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,
\text{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,}
\text{130.7, 130.72, 132.82, 132.9, 133.0, 133.1, 133.2, 133.4, 135.3, 135.4, 135.5, 135.6, 165.7. IR $\nu_{\text{max}}$
\text{(CHCl$_3$): 2878, 1713, 1279, 1115 cm$^{-1}$. Anal. Found: C, 73.79; H, 7.70%. Calcd. for C$_{38}$H$_{56}$O$_4$Si: C,}
\text{73.73; H, 7.42%.}

$\text{(1S,2R)-2-[(1R / S)-2-(tert-Butyldiphenylsilyloxy)-1-methoxy}
\text{methylcyclopentanol (2R)-12). To a solution of benzene 19 (5.33 g, 10.0 mmol) in}
\text{toluene (80 ml) was added DIBAL (18.9 ml, 1M in}
\text{toluene, 18.9 mmol) at ~75°C. After the reaction solution was stirred at ~75°C for 30 min, 1 M aq. HCl}
\text{solution was added. The organic solution was separated}
\text{washed with sat. aq. NaHCO$_3$ solution and}
\text{brine, and dried (Na$_2$SO$_4$). Concentration followed by}
\text{silica gel column chromatography (EtOAc/hexane = 1/9) gave (2R)-12 (3.77 g, 8.50 mmol, 88%) as a}
\text{colorless oil. NMR $\delta$ (CDCl$_3$): 1.05 (5.4H, s, tBu), 1.06 (3.6H, s, tBu), 1.35–1.46 (1H, m), 1.50–1.60
\text{(1H, m), 1.61–1.76 (3H, m), 1.76–1.92 (2H, m), 2.58 (0.4H, br, s, OH), 3.30 (1.2H, s, OCH$_3$), 3.44 (1.8H,}
\text{s, OCH$_3$), 3.54 (0.6H, br, s, OH), 3.63–3.78 (2.6H, m, CH$_2$OSi, CHOMOM), 3.91 (0.4H, ddd, $J = 6.4$
\text{, 6.4, 4.9 Hz, CHOMOM), 4.30–4.37 (1H, m, CH/OH), 4.58 (0.4H, d, $J = 6.8$ Hz, OCH/HOME), 4.67 (0.4H, d,}
\text{$J = 6.8$ Hz, OCH/HOME), 4.70 (0.6H, d, $J = 6.8$ Hz, CH/HOME), 4.99 (0.6H, d, $J = 6.8$ Hz, OCH/HOME)
\text{7.36–7.44 (6H, m, ArH), 7.66–7.70 (4H, m, ArH). NMR $\delta$ (CDCl$_3$): 19.06, 19.14, 21.9, 22.7, 25.7, 26.0, 26.8,
\text{33.3, 34.8, 47.7, 49.0, 55.7, 55.9, 63.5, 66.5, 67.1, 73.1, 74.1, 79.1, 81.1, 96.5, 98.3, 126.9, 127.7, 128.5, 129.5,}
\text{129.7, 129.9, 132.8, 133.3, 135.5, 135.6. IR $\nu_{\text{max}}$ (CHCl$_3$): 3500, 2934, 1429, 1113, 1073, 1030 cm$^{-1}$.
Anal. Found: C, 69.83; H, 8.73%. Calcd. for C$_{38}$H$_{56}$O$_4$Si: C, 70.05; H, 8.47%.

$\text{(2R)-2-[(1R / S)-2-(tert-Butyldiphenylsilyloxy)-1-}
\text{(methoxy)methylcyclopentanone (13). A reaction mixture of (2S)-cyclopentanol}
\text{derivative 12 (3.87 g, 9.03 mmol), PCC (2.14 g, 9.39 mmol),}
\text{NaOAc (0.81 g, 8.97 mmol) and MS 4A (1.5 g) in}
\text{CH$_2$Cl$_2$ (80 ml) was stirred at 0°C for 18 h before}
\text{addition of dry ether. After the mixture was filtered, the filtrate was concentrated. The residue was applied}
\text{to silica gel column chromatography (3% EtOAc/ benzene) to give a diastereomeric mixture of (2R)-}
\text{cyclopentanone derivative 13 (3.39 g, 7.95 mmol,}
\text{88%) as a colorless oil. NMR $\delta$ (CDCl$_3$): 1.03 (3.6H, s, tBu), 1.04 (5.4H, s, tBu), 1.65–1.79 (1H, m),}
\text{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,}$
\text{$J = 10.3$, 7.3 Hz, CH/HOSi), 3.76–3.85 (1.4H, m, CH$_2$OSi), 4.00 (0.6H, ddd,}$
\text{$J = 5.9$, 5.9, 3.4 Hz,
(5R,6R) and (5R,6S)-ethyl 5-benzoxyloxy-7-(tert-butylidiphenylsilyloxy)-6-(methoxymethylsilyloxy)-5-heptanolide (20). A reaction mixture of (2R)-cyclopentanone derivative 13 (2.92 g, 6.84 mmol), MCBPA (2.06 g, 11.9 mmol) in a phosphate buffer at pH 8 (50 ml) and CHCl₃ (50 ml) was stirred at 0°C for 18 h before addition of Na₂SO₄. The organic solution was separated, washed with sat. aq. NaHCO₃ solution and brine, and dried (Na₂SO₄). Concentration followed by silica gel column chromatography (10% EtOAc/benzene) gave (5R,6R)-heptanolide 20 (1.58 g, 5.37 mmol, 52%) as a colorless oil, [α]D²⁰ = −9.5 (c 0.36, CHCl₃), and (5R,6S)-heptanolide 20 (1.05 g, 2.37 mmol, 35%) as a colorless oil, [α]D²⁰ = −16.6 (c 0.30, CHCl₃). (5R,6R)-heptanolide 20. NMR δH (CDCl₃): 1.05 (9H, s, tBu), 1.21 (3H, t, J = 7.3 Hz, tBu), 1.69–1.77 (3H, m), 1.89 (1H, m). 2.58 (1H, d, J = 18.1, 5.4, 5.4 Hz, 2-ΗΗ), 3.33 (3H, s, OCH₃), 3.68 (1H, m, 6-Η), 3.80 (1H, dd, J = 10.7, 4.9 Hz, 7-ΗH), 3.89 (1H, dd, J = 10.7, 5.4 Hz, 7-ΗH), 4.57 (1H, d, J = 6.8 Hz, OCH₂OMe), 4.70 (1H, d, J = 6.8 Hz, OCH₂OMe), 5.40 (1H, d, J = 7.8, 4.4, 4.4 Hz, 5-Η), 7.20 (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 δC (CDCl₃): 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, 129.6, 129.7, 130.2, 132.9, 133.0, 133.2, 135.5, 165.9, 173.2. 1H IR νmax (CHCl₃): 2949, 1720, 1717, 1275, 1133, 1036, 1026 cm⁻¹. Anal. Found: C, 69.06; H, 7.66%. Calcd. for C₁₄H₁₃O₅Si: C, 68.89; H, 7.48%. (5R,6S)-ester 21, 92% yield, [α]D²⁰ = −9.9 (c 1.00, CHCl₃). NMR δH (CDCl₃): 1.05 (9H, s, tBu), 1.21 (3H, t, J = 7.3 Hz, OCH₂CH₃), 1.68–1.85 (4H, m, 3-Η, 4-Η), 2.28–2.35 (2H, m, 2-Η), 3.30 (3H, s, OCH₃), 3.75–3.82 (2H, m, 7-Η), 3.97 (1H, m, 6-Η), 4.09 (2H, q, J = 7.3 Hz, OCH₂CH₃), 4.67 (1H, d, J = 6.6 Hz, OCH₂OMe), 4.67 (1H, d, J = 6.6 Hz, OCH₂OMe), 5.36 (1H, d, J = 7.8 Hz, 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).
**Synthetic Study of 5-HETE**

**5-HETE (5S,5R,6S,6R)-ester 21.** To an ice-cooled solution of (5S,5R)-alcohol 22 (0.60 g, 1.69 mmol) in CH₂Cl₂ (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. NaHCO₃ solution was added. The organic solution was separated, washed with brine, and dried (Na₂SO₄). Concentration gave crude glycol. The reaction mixture of the crude glycol and NaIO₄ (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 H₂O. The organic solution was separated, washed with brine, and dried (Na₂SO₄). Concentration followed by silica gel column chromatography (10% EtOAc/toluene) gave (5R)-aldehyde 2 (0.36 g, 1.29 mmol, 76%) as a colorless oil. From (5R,6S)-alcohol 22, (5R)-aldehyde 2 was also obtained in 74% yield. [α]D²⁰ = +48.3 (c 0.15, CHCl₃), [α]D²⁰ = +35 in lit.¹⁹ NMR δC (CDCl₃): 1.25 (3H, t, J = 7.3 Hz, OCH₂CH₃), 1.83–1.92 (2H, m), 1.92–2.04 (2H, m), 2.40 (2H, t, J = 7.3 Hz, 2-CH₂), 4.13 (2H, q, J = 7.3 Hz, OCH₂CH₃), 5.24 (1H, d, J = 3.0 Hz, 5-H), 6.77–7.40 (5H, m, ArH). NMR δH (CDCl₃): 0.88 (3H, t, J = 7.3 Hz, 2-CH₃), 1.23–1.80 (2H, m, 2-H₂), 3.91 (1H, d, J = 2.0 Hz, OCH₂CH₃), 6.87–7.47 (5H, m, ArH). Anal. Found: C, 75.66; H, 7.65%. Calculated for C₂₈H₃₀O₅: C, 75.31; H, 7.39%. 

**Baeyer-Villiger oxidation of (2R)-cyclohexane derivative 23 and determination of the enantiomeric excess.** A reaction mixture of (2R)-cyclopentanone 23 (1.08 g, 2.52 mmol, a diasteromeric mixture of 1:1), MCPBA (0.87 g, 5.04 mmol) in a phosphate buffer at pH 8 (10 ml) and CHCl₃ (10 ml) was stirred at 0°C for 18 h before addition of Na₂S₂O₅. The organic solution was separated, washed with sat. aq. NaHCO₃ solution and brine, and dried (Na₂SO₄). Concentration followed by silica gel column chromatography (EtOAc/hexane = 1/3) gave recovered 22 (0.40 g, 0.93 mmol, 37%) and (5R,6R/S)-24 (0.50 g, 1.12 mmol, 44%), a diasteromeric mixture of 1:1 as a colorless oil. Anal. Found: C, 75.23; H, 7.65%. Calculated for C₂₈H₃₀O₅: C, 75.31; H, 7.39%. A reaction mixture of (5R,6R/S)-24 (5.28 g, 5.80 mmol) in CH₂Cl₂ (60 ml) was stirred at 20°C for 18 h before concentration. The residue was dissolved in EtOAc and H₂O. The organic solution was separated, washed with brine, and dried (Na₂SO₄). 

**Determination of the enantiomeric excess of (5S,5R,6S,6R)-ester 21.** The enantiomeric excess was determined by using DİCEL AD-H [(5S,6S)-ester 21, 99% ee, (5S,6R)-ester 21, 99% ee]. The reaction solution was stirred at 0°C for 1 h, sat. aq. NaHCO₃ solution was added. The organic solution was separated, washed with brine, and dried (Na₂SO₄). Concentration followed by silica gel column chromatography (EtOAc) gave crude glycol. The reaction mixture of the crude glycol and NaIO₄ (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 H₂O. The organic solution was separated, washed with brine, and dried (Na₂SO₄). Concentration followed by silica gel column chromatography (10% EtOAc/toluene) gave (5R)-aldehyde 2 (0.36 g, 1.29 mmol, 76%) as a colorless oil. From (5R,6S)-alcohol 22, (5R)-aldehyde 2 was also obtained in 74% yield. [α]D²⁰ = +48.3 (c 0.15, CHCl₃), [α]D²⁰ = +35 in lit.¹⁹ NMR δC (CDCl₃): 1.25 (3H, t, J = 7.3 Hz, OCH₂CH₃), 1.83–1.92 (2H, m), 1.92–2.04 (2H, m), 2.40 (2H, t, J = 7.3 Hz, 2-CH₂), 4.13 (2H, q, J = 7.3 Hz, OCH₂CH₃), 5.24 (1H, d, J = 8.1 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 δC (CDCl₃): 14.2, 20.5, 28.2, 33.6, 60.5, 78.3, 128.5, 129.0, 129.8, 133.6, 166.1, 172.8, 198.1. IR νmax (CHCl₃): 3031, 2988, 2932, 1725, 1271, 1125, 1113, 1026 cm⁻¹. HRMS (FAB) m/z (M⁺+H): Calcd. for C₃₉H₄₂O₅: 729.2132; found, 729.2136. (5S)-aldehyde 2, [α]D²⁰ = −48.3 (c 0.35, CHCl₃), [α]D²⁰ = −46 in lit.¹⁵
aq. NaHCO₃ solution and CH₂Cl₂. The organic solution was separated, washed with brine, and dried (Na₂SO₄). 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 concentration. The residue was dissolved in EtOH (10 ml) was stirred at room temperature for 1968 2134–2143 (1993).


References

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