PERKIN 1

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

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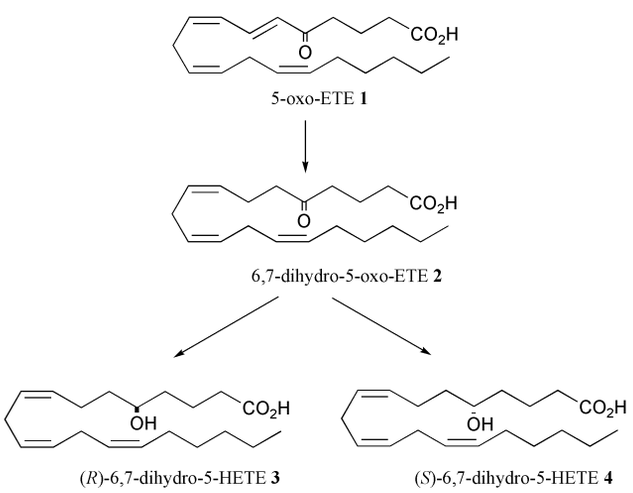
Novel yeast reduction which gave (1*R*,2*S*)-hydroxy ester **10** and (1*S*,5*S*)-lactone **11** from racemic ketoester **12** was discovered. After **10** and **11** were converted to lactone **15** and **17**, enantiomeric excesses were determined as 99% and 95%, respectively. This novel yeast reduction was applied to synthetic study of metabolites of 5-oxo-ETE **1**. (*R*)-6,7-Dihydro-5-HETE lactone **5** and (*S*)-6,7-dihydro-5-HETE lactone **6** were synthesized from **15** and **17**, respectively.

Introduction

The metabolites of polyunsaturated fatty acid (PUFA) play an important role in organisms. However, their isolation is very difficult because they are present in very small quantities. Synthetic studies of PUFA metabolite are important for biological research and many synthetic efforts of PUFA have been carried out.[1]

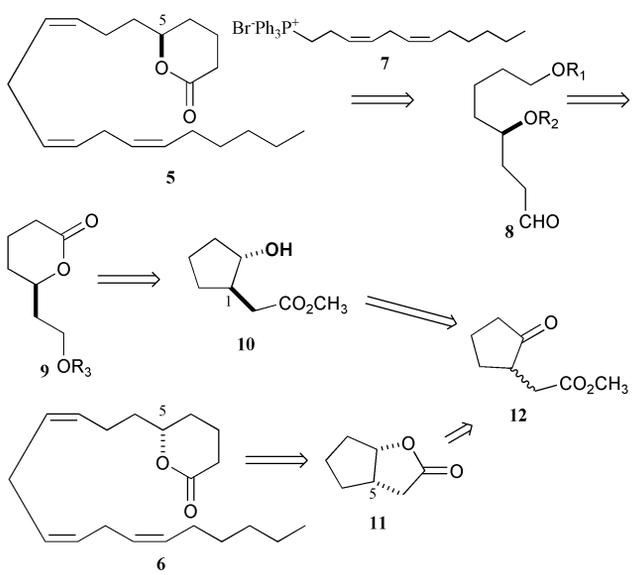
5-Oxo-ETE **1** is a metabolite of arachidonic acid and has a potent chemotactic agent for human neutrophiles. 5-Oxo-ETE **1** is reduced to (*R*) and (*S*)-6,7-dihydro-5-HETE **3** and **4** *via* 6,7-dihydro-5-oxo-ETE **2** (Scheme 1). Though the synthesis and



Scheme 1 Biosynthesis of (*R*)-6,7-dihydro-5-HETE **3** and (*S*)-6,7-dihydro-5-HETE **4**.

biological activity of 6,7-dihydro-5-oxo-ETE **2** has been reported,[2] there is no report about 6,7-dihydro-5-HETE **3** and **4**. The synthetic study of both enantiomers is valuable for biological research and the construction of the one chiral center is interesting for synthetic research. A microbiological reduction is one of the effective methods to construct the chiral center.[3,4] This report describes the synthesis of (*R*)-6,7-dihydro-5-HETE lactone **5** and (*S*)-6,7-dihydro-5-HETE lactone **6** using a new yeast reduction as a key reaction.

Scheme 2 shows the retrosynthetic analysis of (*R*)-6,7-dihydro-5-HETE lactone **5** and (*S*)-6,7-dihydro-5-HETE lactone **6**. Aldehyde **8** could be converted to target compound **5** by employing *cis* selective Wittig reaction with Wittig reagent



Scheme 2 Retrosynthetic analysis of (*R*)-6,7-dihydro-5-HETE lactone **5** and (*S*)-6,7-dihydro-5-HETE lactone **6**.

7.[2] This aldehyde **8** would be obtained from lactone **9** by one carbon homologation. Hydroxy ester **10** could be converted to lactone **9** by oxidation to the ketone followed by Baeyer–Villiger oxidation, that proceeds with retention of configuration. In this way the stereogenic center at position 5 could be introduced stereospecifically. The planned starting materials for the two enantiomers are (1*R*,2*S*)-hydroxy ester **10** and (1*S*,5*S*)-lactone **11**, obtained by a novel yeast reduction of racemic ketoester **12**. The stereogenic center at C5 of (*R*)-**5** or (*S*)-**6** derives from C1 carbon of **10** or from C5 carbon of **11**. Therefore, it is necessary to obtain these adducts in high enantiomeric excess. As an example of bioreduction of cyclopentanone bearing a carboxylate group, the reduction of ethyl 2-oxocyclopentanecarboxylate has been previously reported.[5] Our substrate has a longer carboxylate bearing side chain.

Results and discussion

At first, the yeast reduction of racemic ketoester **12** was examined in the preparation of the two optically active reductive products, which were expected to be the starting materials for this project. The incubation of racemic substrate **12** with

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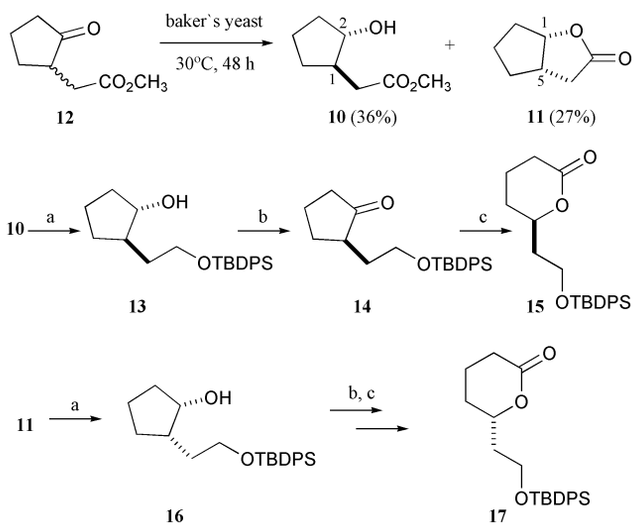
baker's yeast gave (1*R*,2*S*)-hydroxy ester **10**[6] (36%) and (1*S*,5*S*)-latone **11**[7] (27%). It is worth noting that two optically active products were obtained in this yeast reduction using our substrate. The enantiomeric excess was determined after Baeyer–Villiger oxidation. The yeast reductions of the substrates with longer side chain, 3-(2-oxocyclopentyl)propionic acid, 2-(2-methoxy/ethoxycarbonylethyl)cyclopentanone, did not proceed, recovering racemic substrates.

After $LiAlH_4$ reduction of **10**, the primary hydroxy group of the resulting diol was selectively protected as TBDPS ether by using TBDPSCl, Et_3N, and 4-DMAP in CH_2Cl_2[8] to give **13** in 69% yield. This alcohol **13** was subjected to subsequent PCC oxidation (99%) and Baeyer–Villiger oxidation with MCPBA in $CHCl_3$ and phosphate buffer pH 8[9] to give (*R*)-lactone **15** in 84% yield (Scheme 3). By the same procedure, (1*S*,5*S*)-lactone **11** was transformed to (*S*)-lactone **17**.



12 **10** (36%) **11** (27%)

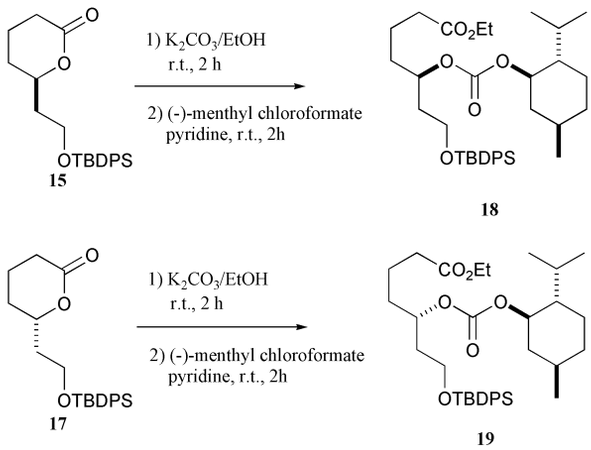
13 **14** **15**

16 **17**

Scheme 3 *Reagents and conditions (yields)*: (a) i) $LiAlH_4$, diethyl ether, −10 °C, 1 h; ii) TBDPSCl, Et_3N, 4-DMAP, CH_2Cl_2, rt, 2 h (69%); (b) PCC, AcONa, CH_2Cl_2, −10 °C, 17 h (99%); (c) MCPBA, phosphate buffer pH 8, $CHCl_3$, 0 °C, 17 h (84%).

To determine the enantiomeric excess, (*R*)-lactone **15** was converted to **18** by subsequent ethanolysis and reaction with (−)-menthyl chloroformate. HPLC analysis showed that diastereomeric excess was 99%. Diastereomeric excess of (*S*)-lactone **17** was also determined as 95% by the same method. These facts indicate that the 1 position of **10** and the 5 position of **11**, which are the new yeast reductive products of **12**, had high enantiomeric purity (Scheme 4).

Since desilylation of **15** gave many by-products, the lactone ring was opened at this stage. The lactone ring of **15** was reduced by subsequent DIBAL-H and $NaBH_4$ reductions, giving diol **20** in 96% yield. After the primary and secondary hydroxy groups were protected as trityl ethers by using trityl chloride in pyridine (89%) and MOM ether by using MOMCl and iso-Pr_2NEt (88%), respectively, the silyl ether of the resulting fully protected compound **22** was cleaved by *n*-Bu_4NF in 100% yield. The resulting alcohol **23** was treated with TsCl and KOH in diethyl ether to give tosylate **24** in 92% yield, and then conversion to nitrile **25** by using NaCN in DMF was performed in 100% yield. DIBAL-H reduction of nitrile **25** in ether gave aldehyde **26** in 76% yield. This resulting aldehyde **26** was subjected to *cis*-selective Wittig reaction with Wittig reagent **7** by using LHMDS and HMPA,[2] giving triene **27** in 68% yield. Cleavage of trityl ether in HCO_2H–diethyl ether (71%) following Swern and $NaClO_2$ oxidations gave carboxylic acid **29** in 73% yield. Finally, cleavage of MOM ether in acidic condition gave (*R*)-6,7-dihydro-5-HETE lactone **5** in 92% yield (Scheme 5). By the same procedure, (*S*)-6,7-dihydro-5-HETE lactone **6** was synthesized from lactone **17**.



15 **18**

17 **19**

Scheme 4 Determination of enantiomeric excess of **15** and **17**.

As the synthetic study of the metabolites of 5-oxo-ETE **1**, (*R*)-6,7-dihydro-5-HETE lactone **5** and (*S*)-6,7-dihydro-5-HETE lactone **6** were synthesized. A new yeast reduction which gave (1*R*,2*S*)-hydroxyester **10** and (1*S*,5*S*)-lactone **11** from racemic ketoester **12** was discovered in this project. These compounds **10** and **11** were transformed to lactone **15** and **17**, which were 99% ee and 95% ee, respectively.

(*R*)-6,7-Dihydro-5-HETE lactone **5** and (*S*)-6,7-dihydro-5-HETE lactone **6** were synthesized from lactone **15** and **17**, respectively.

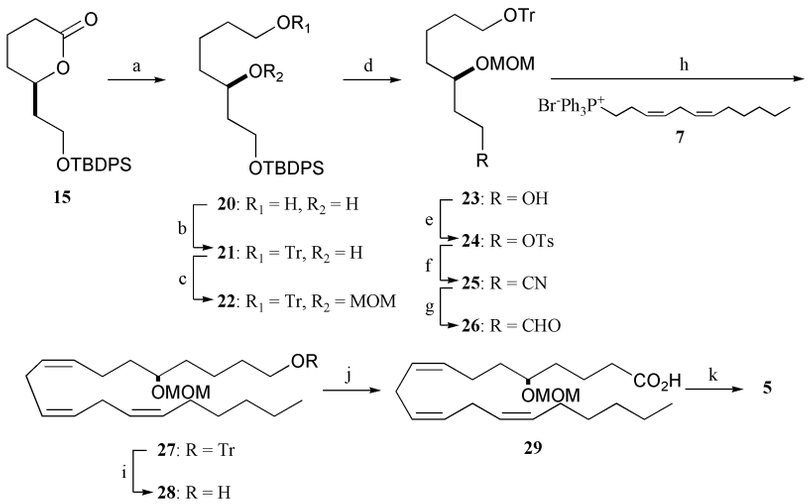
Experimental

Melting-point (mp) data are uncorrected. NMR data were measured by a JNM-EX 400 spectrometer. FABMS data were measured with JEOL HX-110 spectrometers and optical rotations were evaluated with Horiba SEPA-200, $[\alpha]_D$-values are in units of 10^{-1} deg cm^2 g^{-1}. The silica gel used was Wakogel C-300 (Wako, 200–300 mesh). HPLC analysis was performed by Shimadzu LC-6AD and SPD-6AV.

Yeast reduction of racemic ketoester 12

A mixture of (±)-ketoester **12** (4.69 g, 0.030 mol), sucrose (30 g), baker's yeast (14 g) in H_2O (250 ml) was shaken at 30 °C for 48 h. After the mixture was filtered, the filtrate was extracted with diethyl ether. The ether solution was washed with brine, dried (Na_2SO_4) and evaporated. The residue was purified with silica gel column chromatography (10% EtOAc in benzene) to give (1*R*,2*S*)-hydroxy ester **10** (1.69 g, 36%) as a colorless oil and (1*S*,5*S*)-lactone **11** as a colorless oil (1.02 g, 27%). **10**: $[\alpha]_D^{20}$ = +40.6, *c* 3.23, MeOH (lit.,[6] $[\alpha]_D^{23}$ = +43.1, *c* 1.08, MeOH). **11**: $[\alpha]_D^{20}$ = −59.4, *c* 4.90, MeOH (lit.,[7] $[\alpha]_D^{25}$ = −59.0, *c* 1.00, MeOH).

(1*S*,2*R*)-2-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]cyclopentanol 13. To a suspension of $LiAlH_4$ (3.80 g, 0.10 mol) in diethyl ether (50 ml) was added a solution of (1*R*,2*S*)-hydroxy ester **10** (17.2 g, 0.11 mol) in diethyl ether (50 ml) at −10 °C. After stirring at −10 °C for 1 h, sat. aq. $MgSO_4$ (*ca.* 3 ml) and K_2CO_3 (0.1 g) were added. The mixture was stirred at room temperature for 1 h and filtered. The filtrate was concentrated to give crude diol. To a solution of the crude diol, Et_3N (17.1 ml, 0.12 mol), and 4-DMAP (0.50 g, 0.0041 mol) in CH_2Cl_2 (10 ml) was added TBDPSCl (26.5 ml, 0.10 mol). The resulting reaction solution was stirred at room temperature for 2 h before additions of H_2O and CH_2Cl_2. The organic solution was separated, washed with brine, and dried (Na_2SO_4). After concentration, the residue was applied to silica gel column chromatography (10% EtOAc–hexane) to give silyl ether **13** (28.1 g, 0.076 mol, 69%) as a colorless oil. $[\alpha]_D^{20}$ = +21.9 (*c* 1.56, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3428, 2876, 1472, 1429, 1113, 1076, 1015; $\delta_H(CDCl_3)$ 1.06 (9H, s, $C(CH_3)_3$), 1.18 (1H, m, C*H*HCH$_2$OTBDPS), 1.58–1.72 (5H,



Scheme 5 *Reagents and conditions (yields)*: (a) i) DIBAL-H, CH_2Cl_2, −75 °C, 30 min; ii) $NaBH_4$, EtOH, 0 °C, 30 min (96%); (b) TrCl, pyridine, rt, 2 h (89%); (c) MOMCl, DIPEA, CH_2Cl_2, rt, 16 h (88%); (d) *n*-Bu_4NF, THF, 0 °C, 1 h (100%); (e) TsCl, KOH, diethyl ether, rt, 2.5 h (92%); (f) NaCN, DMF, 50 °C, 2 h (100%); (g) DIBAL-H, ether, −10 °C, 1 h (76%); (h) **7**, LHMDS, HMPA, THF, from −75 °C (30 min) to rt (30 min) (68%); (i) HCO_2H, diethyl ether, 0 °C, 30 min (71%); (j) i) $(COCl)_2$, DMSO, CH_2Cl_2, −45 °C, 1 h, and then Et_3N, 0 °C, 1 h; ii) 2-methylbut-2-ene, NaH_2PO_4, $NaClO_2$, aq. *tert*-BuOH, rt, 1 h (73%); (k) 6 M aq. HCl, THF, rt, 2 h (92%).

m, 3-H_2, 4-H_2, CH*H*CH_2OTBDPS), 1.72–1.86 (2H, m, 5-H_2), 1.97 (1H, m, 2-H), 3.31 (1H, s, OH), 3.73–3.80 (2H, m, C*H*$_2$OTBDPS), 3.82 (1H, m, 1-H), 7.38–7.44 (6H, m, ArH), 7.67–7.68 (4H, m, ArH); δ_C($CDCl_3$) 19.1, 21.3, 26.8, 30.8, 33.7, 36.6, 47.1, 64.2, 78.9, 127.7, 129.8, 133.2, 135.6 (Found: C, 74.77; H, 8.98. $C_{23}H_{32}O_2Si$ requires C, 74.95; H, 8.75%).

(1*S*,2*S*)-2-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]cyclopentanol 16. To a suspension of $LiAlH_4$ (3.0 0 g, 0.079 mol) in diethyl ether (50 ml) was added a solution of (1*S*,5*S*)-lactone **11** (11.1 g, 0.079 mol) in diethyl ether (50 ml) at −10 °C. After stirring at −10 °C for 1 h, sat. aq. $MgSO_4$ (*ca.* 2 ml) and K_2CO_3 (0.1 g) were added. The mixture was stirred at room temperature for 1 h and filtered. The filtrate was concentrated to give crude diol. To a solution of the crude diol, Et_3N (13.2 ml, 0.095 mol), and 4-DMAP (0.39 g, 0.0032 mol) in CH_2Cl_2 (10 ml) was added TBDPSCl (20.6 ml, 0.079 mol). The resulting reaction mixture was stirred at room temperature for 2 h before additions of H_2O and CH_2Cl_2. The organic solution was separated, washed with brine, and dried (Na_2SO_4). After concentration, the residue was applied to silica gel column chromatography (10% EtOAc–hexane) to give silyl ether **16** (23.7 g, 0.064 mol, 81%) as a colorless oil. $[\alpha]_D^{20}$ = +8.73 (*c* 1.03, $CHCl_3$); ν_{max}($CHCl_3$)/cm^{-1} 3460, 2934, 1472, 1429, 1113, 1084, 1035, 990; δ_H($CDCl_3$) 1.06 (9H, s, C(CH_3)$_3$), 1.41 (1H, m, C*H*HCH_2-OTBDPS), 1.52 (1H, m, CH*H*CH_2OTBDPS), 1.61–1.74 (3H, m), 1.76–1.92 (4H, m), 2.51 (1H, s, OH), 3.67 (1H, m, C*H*HOTBDPS), 3.76 (1H, m, CH*H*OTBDPS), 4.28 (1H, m, 1-H), 7.39–7.44 (6H, m, ArH), 7.66–7.69 (4H, m, ArH); δ_C($CDCl_3$) 19.0, 22.4, 26.8, 29.9, 32.0, 34.4, 44.8, 64.2, 74.1, 127.7, 129.7, 133.2, 133.3, 135.6 (Found: C, 75.13; H, 8.96. $C_{23}H_{32}O_2Si$ requires C, 74.95; H, 8.75%).

(*R*)-2-[(2-*tert*-Butyldiphenylsilyloxy)ethyl]cyclopentanone 14. A reaction mixture of alcohol **13** (27.0 g, 0.073 mol), PCC (19.1 g, 0.089 mol), CH_3CO_2Na (6.65 g, 0.081 mol) in CH_2Cl_2 (200 ml) was stirred at −10 °C for 17 h. After addition of dry diethyl ether, the mixture was filtered. The filtrate was concentrated. The residue was applied to silica gel column chromatography (EtOAc–hexane 1 : 10) to give ketone **14** (26.4 g, 0.072 mol, 99%) as a colorless oil, $[\alpha]_D^{20}$ = +59.4 (*c* 1.01, $CHCl_3$); ν_{max}($CHCl_3$)/cm^{-1} 2934, 1732, 1429, 1111; δ_H($CDCl_3$) 1.04 (9H, s, C(CH_3)$_3$), 1.41–1.52 (2H, m, C*H*$_2$$CH_2$OTBDPS), 1.75 (1H, m), 1.98 (1H, m), 2.07–2.33 (5H, m), 3.69 (1H, ddd, *J* 10.3, 7.6, 5.6 Hz, C*H*HOTBDPS), 3.77 (1H, ddd, *J* 10.3, 6.4, 6.4 Hz, CH*H*OTBDPS), 7.36–7.44 (6H, m, ArH), 7.65–7.67 (4H, m, ArH); δ_C($CDCl_3$) 19.2, 20.8, 26.8, 29.7, 32.5, 37.9, 46.3, 62.1, 127.6, 129.6, 133.8, 135.5, 221.3 (Found: C, 75.27; H, 8.48. $C_{23}H_{30}O_2Si$ requires C, 75.36; H, 8.25%). (*S*)-isomer: $[\alpha]_D^{20}$ = −59.6 (*c* 1.34, $CHCl_3$).

(*R*)-7-(*tert*-Butyldiphenylsilyloxy)heptan-5-olide 15. To an ice-cooled mixture of ketone **14** (24.6 g, 0.067 mol) in $CHCl_3$ (50 ml) and phosphate buffer pH 8 (100 ml) was added MCPBA (23.3 g, 0.14 mol) in $CHCl_3$ (50 ml). The resulting reaction mixture was stirred in an ice-bath for 17 h before additions of sat. aq. sodium thiosulfate and sat. aq. $NaHCO_3$ soln. After the mixture was filtered, the organic solution was separated from the filtrate, washed with brine, and dried (Na_2SO_4). After concentration, the residue was applied to silica gel column chromatography (EtOAc–hexane 1 : 8) to give lactone **15** (21.5 g, 0.056 mol, 84%) as a colorless oil, $[\alpha]_D^{20}$ = −28.2 (*c* 1.70, $CHCl_3$); ν_{max}($CHCl_3$)/cm^{-1} 2932, 1727, 1429, 1246, 1113, 1094, 1057; δ_H($CDCl_3$) 1.05 (9H, s, C(CH_3)$_3$), 1.53 (1*H*, 6-*H*H), 1.77–1.98 (5H, m, 3-H_2, 4-H_2, 6-H*H*), 2.42 (1H, ddd, *J* 17.6, 8.3, 8.3 Hz, 2-*H*H), 2.56 (1H, ddd, *J* 17.6, 7.3, 7.3 Hz, 2-H*H*), 3.78 (1H, ddd, *J* 10.3, 5.9, 5.9 Hz, 7-*H*H), 3.90 (1H, ddd, *J* 10.3, 7.1, 4.9 Hz, 7-H*H*), 4.52 (1H, m, 5-H), 7.36–7.44 (6H, m, ArH), 7.63–7.67 (4H, m, ArH); δ_C($CDCl_3$) 18.5, 19.2, 26.9, 27.9, 29.4, 38.6, 59.6, 77.4, 127.7, 129.7, 133.5, 133.7, 135.5, 171.8 (Found: C, 71.86; H, 8.04. $C_{23}H_{30}O_3Si$ requires C, 72.21; H, 7.90%). (*S*)-isomer **17**: $[\alpha]_D^{20}$ = +28.3 (*c* 1.10, $CHCl_3$).

Determination of enantiomeric excess

A reaction mixture of lactone **15** (50 mg, 0.13 mmol) and K_2CO_3 (18 mg, 0.13 mmol) in EtOH (5 ml) was stirred at room temperature for 2 h before additions of H_2O and EtOAc. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Evaporation gave crude ethyl ester. To an ice-cooled solution of the crude ethyl ester in pyridine (0.2 ml) was added (−)-menthyl chloroformate (0.030 ml, 0.14 mmol). The resulting reaction solution was stirred at room temperature for 2 h before addition of H_2O and EtOAc. The organic solution was separated, washed with brine, dried (Na_2SO_4), and concentrated to give crude **18**, which was applied to HPLC (LiChrospher Si 60 of Cica-MERK, 3% EtOAc in hexane, 2 ml min^{-1}, detected at 270 nm): retention time was 12.3 min, diastereomeric excess was 99%. Lactone **17** was converted to **19** by the same procedure and applied to HPLC: retention time was 11.1 min, diastereomeric excess was 95%.

(*R*)-7-(*tert*-Butyldiphenylsilyloxy)heptane-1,5-diol 20. To a solution of lactone **15** (10.0 g, 0.026 mol) in CH_2Cl_2 (150 ml) was added DIBAL-H (1 M in toluene, 44.6 ml, 0.045 mol) at −75 °C. After the reaction solution was stirred at −75 °C for 30 min, 6 M aq. HCl soln. was added. The organic solution was separated, washed with sat. aq. $NaHCO_3$ and brine, dried (Na_2SO_4), and evaporated to give crude hemiacetal. To an ice-cooled solution of the hemiacetal in EtOH (150 ml) was added $NaBH_4$ (0.75 g, 0.020 mol). The reaction mixture was stirred in an ice-bath for 30 min before addition of 6 M aq. HCl solution. After neutralization with sat. aq. $NaHCO_3$, the mixture was concentrated. The residue was dissolved in H_2O and EtOAc. The organic solution was separated, washed with brine, dried (Na_2SO_4), and concentrated. The residue was applied to silica gel column chromatography (EtOAc–hexane 1 : 1) to give diol **20** (9.59 g, 0.025 mol, 96%) as colorless crystals, mp 88–89 °C (iso-Pr_2O), $[\alpha]_D^{20} = +5.3$ (*c* 0.75, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3500, 2934, 1429, 1113, 1078; $\delta_H(CDCl_3)$ 1.05 (9H, s, $C(CH_3)_3$), 1.46–1.59 (6H, m, 2-H_2, 3-H_2, 4-H_2), 1.60–1.69 (2H, m, 6-H_2), 3.34 (2H, br s, OH × 2), 3.64–3.67 (2H, m, 1-H_2), 3.84–3.89 (3H, m, 5-H, 7-H_2), 7.40–7.44 (6H, m, ArH), 7.66–7.68 (4H, m, ArH); $\delta_C(CDCl_3)$ 19.0, 21.7, 26.8, 32.7, 37.1, 38.3, 62.8, 63.6, 71.8, 127.8, 129.8, 132.9, 135.5 (Found: C, 71.23; H, 8.74. $C_{23}H_{34}O_3Si$ requires C, 71.46; H, 8.86%). (*S*)-isomer: $[\alpha]_D^{20} = -5.3$ (*c* 1.12, $CHCl_3$).

(*R*)-1-(*tert*-Butyldiphenylsilyloxy)-7-trityloxyheptan-3-ol 21. A solution of diol **20** (6.77 g, 0.018 mol) and TrCl (4.90 g, 0.018 mol) in pyridine (10 ml) was stirred at room temperature for 2 h before additions of H_2O and EtOAc. The organic solution was separated, washed with sat. aq. $CuSO_4$, $NaHCO_3$, and brine, dried (Na_2SO_4), and evaporated. The residue was purified with silica gel column chromatography (5% EtOAc–hexane) to give trityl ether **21** (10.1 g, 0.016 mol, 89%) as a colorless oil, $[\alpha]_D^{20} = +3.5$ (*c* 1.14, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3500, 3073, 2934, 1449, 1429, 1113, 1078; $\delta_H(CDCl_3)$ 1.05 (9H, s, $C(CH_3)_3$), 1.38–1.42 (2H, m, 5-H_2), 1.45–1.57 (2H, m, 4-H_2), 1.63–1.74 (4H, m, 2-H_2, 6-H_2), 3.06 (2H, t, *J* 6.6 Hz, 7-H_2), 3.18 (1H, s, OH), 3.82–3.88 (3H, m, 1-H_2, 3-H), 7.19–7.29 (9H, m, ArH), 7.37–7.45 (12H, m, ArH), 7.66–7.68 (4H, m, ArH); $\delta_C(CDCl_3)$ 19.0, 22.3, 26.8, 30.1, 37.4, 38.3, 63.6, 71.7, 86.3, 126.8, 127.7, 127.8, 129.8, 133.1, 135.5, 135.6, 144.5 (Found: C, 79.97; H, 7.92. $C_{42}H_{48}O_3Si$ requires C, 80.21; H, 7.69%). (*S*)-isomer: $[\alpha]_D^{20} = -3.6$ (*c* 1.10, $CHCl_3$).

(*R*)-1-(*tert*-Butyldiphenylsilyloxy)-3-methoxymethoxy-7-trityloxyheptane 22. To a mixture of alcohol **21** (10.1 g, 0.016 mol) and DIPEA (11.2 ml, 0.064 mol) in CH_2Cl_2 (10 ml) was added MOMCl (2.44 ml, 0.032 mol). After the reaction mixture was stirred at room temperature for 16 h, MeOH and CH_2Cl_2 were added. The organic solution was separated, washed with 6 M aq. HCl, $NaHCO_3$, and brine, dried (Na_2SO_4), and evaporated. The residue was purified with silica gel column chromatography (5% EtOAc–hexane) to give MOM ether **22** (9.40 g, 0.014 mol, 88%) as a colorless oil, $[\alpha]_D^{20} = -2.8$ (*c* 1.08, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3071, 2934, 1491, 1474, 1462, 1449, 1429, 1111, 1090, 1036; $\delta_H(CDCl_3)$ 1.04 (9H, s, $C(CH_3)_3$), 1.30–1.50 (4H, m, 4-H_2, 5-H_2), 1.59–1.64 (2H, m, 6-H_2), 1.68–1.73 (2H, m, 2-H_2), 3.04 (2H, t, *J* 6.6 Hz, 7-H_2), 3.28 (3H, s, OCH_3), 3.68–3.78 (3H, m, 1-H_2, 3-H), 4.56 (1H, d, *J* 6.8 Hz, OC*H*HOCH$_3$), 4.59 (1H, d, *J* 6.8 Hz, OCH*H*OCH$_3$), 7.19–7.30 (9H, m, ArH), 7.34–7.40 (6H, m, ArH), 7.43–7.45 (6H, m, ArH), 7.63–7.66 (4H, m, ArH); $\delta_C(CDCl_3)$ 19.2, 22.0, 26.9, 30.2, 34.6, 37.3, 55.4, 60.6, 63.5, 74.7, 86.3, 95.6, 126.8, 127.6, 127.7, 128.7, 129.6, 133.9, 135.5, 144.5 (Found: C, 78.70; H, 8.01. $C_{44}H_{52}O_4Si$ requires C, 78.53; H, 7.79%). (*S*)-isomer: $[\alpha]_D^{20} = +2.8$ (*c* 2.58, $CHCl_3$).

(*R*)-3-Methoxymethoxy-7-trityloxyheptan-1-ol 23. To an ice-cooled solution of silyl ether **22** (9.40 g, 0.014 mol) in THF (80 ml) was added *n*-Bu_4NF (1 M THF, 15.4 ml, 0.015 mol). The resulting reaction solution was stirred in an ice-bath for 1 h before additions of sat. aq. NH_4Cl and EtOAc. The organic solution was separated, washed with brine, dried (Na_2SO_4), and evaporated. The residue was applied to silica gel column chromatography (EtOAc–hexane 1 : 7) to give alcohol **23** (6.00 g, 0.014 mol, 100%) as a colorless oil, $[\alpha]_D^{20} = -28.0$ (*c* 1.07, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3500, 2943, 1491, 1449, 1151, 1090, 1075, 1032, 920; $\delta_H(CDCl_3)$ 1.37–1.49 (3H, m, 4-*H*H, 5-H_2), 1.51–1.70 (4H, m, 2-*H*H, 4-H*H*, 6-H_2), 1.80 (1H, m, 2-H*H*), 2.37 (1H, br s, OH), 3.06 (2H, t, *J* 6.3 Hz, 7-H_2), 3.38 (3H, s, OCH_3), 3.60–3.83 (3H, m, 1-H_2, 3-H), 4.63 (1H, d, *J* 6.8 Hz, OC*H*HOCH$_3$), 4.66 (1H, d, *J* 6.8 Hz, OCH*H*OCH$_3$), 7.20–7.31 (9H, m, ArH), 7.42–7.44 (6H, m, ArH); $\delta_C(CDCl_3)$ 22.0, 30.1, 34.4, 36.6, 55.8, 59.9, 63.3, 76.4, 86.3, 95.9, 126.8, 127.7, 128.7, 144.4 (Found: C, 77.57; H, 8.03. $C_{28}H_{34}O_4$ requires C, 77.39; H, 7.89%). (*S*)-isomer: $[\alpha]_D^{20} = +28.0$ (*c* 1.00, $CHCl_3$).

(*R*)-3-Methoxymethoxy-1-(*p*-tolylsulfonyloxy)-7-trityloxyheptane 24. A reaction mixture of alcohol **23** (5.15 g, 0.012 mol), TsCl (2.71 g, 0.014 mol), and pulverized KOH (1.33 g, 0.024 mol) in diethyl ether (50 ml) was stirred at room temperature for 2.5 h before addition of H_2O. The organic solution was separated, washed with brine, and dried (Na_2SO_4). After concentration, the residue was applied to silica gel column chromatography (EtOAc–hexane 1 : 5) to give tosylate **24** (6.67 g, 0.011 mol, 92%) as a colorless oil, $[\alpha]_D^{20} = -7.9$ (*c* 1.01, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3063, 2942, 1599, 1491, 1449, 1360, 1190, 1177, 1098, 1036, 960, 920; $\delta_H(CDCl_3)$ 1.30–1.41 (3H, m, 5-H_2, 4-*H*H), 1.45 (1H, m, 4-H*H*), 1.55–1.62 (2H, m, 6-H_2), 1.77 (1H, m, 2-*H*H), 1.84 (1H, m, 2-H*H*), 2.42 (3H, s, OSO_2-$C_6H_4CH_3$), 3.04 (2H, t, *J* 6.8 Hz, 7-H_2), 3.26 (3H, s, OCH_3), 3.57 (1H, m, 3-H), 4.08–4.18 (2H, m, 1-H_2), 4.50 (1H, d, *J* 6.8 Hz, OC*H*HOCH$_3$), 4.53 (1H, d, *J* 6.8 Hz, OCH*H*OCH$_3$), 7.20–7.33 (11H, m, ArH), 7.41–7.44 (6H, m, ArH), 7.78 (2H, d, *J* 8.3 Hz, ArH); $\delta_C(CDCl_3)$ 21.6, 21.7, 30.0, 33.8, 34.3, 55.6, 63.3, 67.5, 74.1, 86.3, 95.8, 126.8, 127.7, 127.9, 128.6, 129.8, 133.2, 144.4, 144.7 (Found: C, 71.23; H, 7.02. $C_{35}H_{40}O_6S$ requires C, 71.40; H, 6.85%). (*S*)-isomer: $[\alpha]_D^{20} = +7.9$ (*c* 1.00, $CHCl_3$).

(*R*)-4-Methoxymethoxy-8-trityloxyoctanenitrile 25. A reaction mixture of tosylate **24** (6.67 g, 0.011 mol) and NaCN (1.67 g, 0.034 mol) in DMSO (5 ml) was heated at 50 °C for 2 h before additions of EtOAc and H_2O. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Evaporation and silica gel column chromatography (EtOAc–hexane 1 : 5) gave nitrile **25** (4.68 g, 0.011 mol, 100%) as a colorless oil, $[\alpha]_D^{20} = -20.6$ (*c* 1.07, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3063, 2940, 1491, 1449, 1219, 1152, 1090, 1076, 1036; $\delta_H(CDCl_3)$ 1.35–1.46 (3H, m, 5-*H*H, 6-H_2), 1.50–1.58 (1H, m, 5-H*H*), 1.59–1.66 (2H, m, 7-H_2), 1.77 (1H, m, 3-*H*H), 1.87 (1H, m, 3-H*H*), 2.41 (2H, t, *J* 7.8 Hz, 2-H_2), 3.06 (2H, t, *J* 6.6 Hz, 8-H_2), 3.36 (3H, s, OCH_3), 3.60 (1H, m, 4-H), 4.60 (1H, d, *J* 6.8 Hz, OC*H*HOCH$_3$), 4.64 (1H, d, *J* 6.8 Hz, OCH*H*OCH$_3$), 7.20–7.31 (9H, m, ArH), 7.42–7.44 (6H, m, ArH); $\delta_C(CDCl_3)$ 13.2, 21.8, 30.0, 30.1, 33.7, 55.8, 63.1, 75.8, 86.4, 95.8, 119.8, 126.9, 127.7, 128.6, 144.4 (Found: C, 78.55; H, 7.65; N, 2.87. $C_{29}H_{33}O_3N$ requires C, 78.52; H, 7.50; N, 3.16%). (*S*)-isomer: $[\alpha]_D^{20} = +20.5$ (*c* 1.12, $CHCl_3$).

(*R*)-4-Methoxymethoxy-8-trityloxyoctanal 26. To a solution of nitrile **25** (3.23 g, 7.28 mmol) in diethyl ether (10 ml) was added DIBAL-H (1 M toluene, 16.7 ml, 16.7 mmol) at −10 °C. After stirring at −10 °C for 1 h, MeOH (2 ml), a few drops of H_2O, and toluene (3 ml) were added, and then the mixture was stirred at room temperature for 30 min before filtration. The filtrate was concentrated. The residue was applied to silica gel column chromatography (EtOAc–hexane 1 : 5) to give aldehyde **26** (2.48 g, 5.55 mmol, 76%) as a colorless oil, $[\alpha]_D^{20} = -19.9$ (*c* 1.01, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3063, 2940, 1725, 1491, 1449, 1152, 1090, 1076, 1036; $\delta_H(CDCl_3)$ 1.35–1.48 (3H, m,

5-*H*H, 6-H_2), 1.48–1.57 (1H, m, 5-H*H*), 1.58–1.68 (2H, m, 7-H_2), 1.75 (1H, m, 3-*H*H), 1.88 (1H, m, 3-H*H*), 2.49 (2H, t, *J* 7.3 Hz, 2-H_2), 3.06 (2H, t, *J* 6.3 Hz, 8-H_2), 3.34 (3H, s, OCH_3), 3.55 (1H, m, 4-H), 4.59 (2H, s, OCH_2OCH_3), 7.20–7.36 (9H, m, ArH), 7.42–7.44 (6H, m, ArH), 9.76 (1H, s, CHO); $\delta_C(CDCl_3)$ 22.0, 26.5, 30.0, 34.1, 39.8, 55.7, 63.3, 76.5, 86.3, 95.5, 126.8, 127.7, 128.7, 144.4, 202.2 (Found: C, 77.88; H, 7.82. $C_{29}H_{34}O_4$ requires C, 78.00; H, 7.67%). (*S*)-isomer: $[\alpha]_D^{20}$ = +20.0 (*c* 0.90, $CHCl_3$).

(6*Z*,9*Z*,12*Z*,16*R*)-16-Methoxymethoxy-20-trityloxyicosa-6,9,12-triene 27. To a solution of Wittig reagent **7** (6.82 g, 13.4 mmol) in THF (120 ml) was added LHMDS (1 M THF, 9.00 ml, 9.00 mmol) at −75 °C, and then the reaction solution was stirred at −75 °C for 2 h before additions of HMPA (7 ml) and aldehyde **26** (2.00 g, 4.48 mmol) in THF (50 ml). The reaction solution was stirred at −75 °C for 30 min and gradually warmed to room temperature. After stirring at rt for 30 min, THF–H_2O (1 : 1) and $CHCl_3$ were added. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Evaporation and silica gel column chromatography (5% EtOAc–hexane) gave triene **27** (1.82 g, 3.06 mmol, 68%) as a colorless oil, $[\alpha]_D^{20}$ = −4.6 (*c* 1.09, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 2932, 1491, 1449, 1150, 1090, 1075, 1038; $\delta_H(CDCl_3)$ 0.88 (3H, t, *J* 6.8 Hz, 1-H_3), 1.22–1.40 (6H, m, 2-H_2, 3-H_2, 4-H_2), 1.40–1.58 (4H, m, 17-H_2, 18-H_2), 1.50–1.58 (2H, m, 15-H_2), 1.60–1.67 (2H, m, 19-H_2), 2.02–2.07 (2H, m, 5-H_2), 2.09–2.13 (2H, m, 14-H_2), 2.77–2.83 (4H, m, 8-H_2, 11-H_2), 3.06 (2H, t, *J* 6.3 Hz, 20-H_2), 3.35 (3H, s, OCH_3), 3.53 (1H, m, 16-H), 4.64 (2H, s, OCH_2OCH_3), 5.34–5.37 (6H, m, 6-H, 7-H, 9-H, 10-H, 12-H, 13-H), 7.19–7.30 (9H, m, ArH), 7.42–7.44 (6H, m, ArH); $\delta_C(CDCl_3)$ 14.1, 22.1, 22.6, 23.1, 25.6, 27.2, 29.3, 30.2, 31.5, 34.2, 34.3, 55.5, 63.5, 77.1, 86.3, 95.5, 126.8, 127.6, 127.7, 128.1, 128.5, 128.7, 129.8, 130.5, 144.5 (Found: C, 82.45; H, 9.08. $C_{41}H_{54}O_3$ requires C, 82.78; H, 9.15%). (*S*)-isomer: $[\alpha]_D^{20}$ = +4.7 (*c* 1.07, $CHCl_3$).

(5*R*,8*Z*,11*Z*,14*Z*)-5-Methoxymethoxyicosa-8,11,14-trien-1-ol 28. To an ice-cooled solution of trityl ether **27** (0.85 g, 1.43 mmol) in diethyl ether (20 ml) was added HCO_2H (15 ml). After the reaction solution was stirred in an ice-bath for 30 min, diethyl ether and H_2O were added. The organic solution was separated, washed with sat. aq. $NaHCO_3$ and brine, dried (Na_2SO_4), and evaporated. The residue was purified with silica gel column (EtOAc–hexane 1 : 4) to give alcohol **28** (0.36 g, 1.02 mmol, 71%) as a colorless oil, $[\alpha]_D^{20}$ = −6.9 (*c* 1.16, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3715, 2874, 1460, 1453, 1148, 1100, 1038; $\delta_H(CDCl_3)$ 0.89 (3H, t, *J* 6.8 Hz, 20-H_3), 1.24–1.40 (6H, m, 17-H_2, 18-H_2, 19-H_2), 1.40–1.47 (3H, m, 3-H_2, 4-*H*H), 1.50–1.62 (5H, m, 2-H_2, 4-H*H*, 6-H_2), 2.03–2.08 (2H, m, 16-H_2), 2.12–2.15 (2H, m, 7-H_2), 2.77–2.83 (4H, m, 10-H_2, 13-H_2), 3.39 (3H, s, OCH_3), 3.56 (1H, m, 5-H), 3.65 (2H, t, *J* 6.6 Hz, 1-H_2), 4.66 (2H, s, OCH_2OCH_3), 5.33–5.43 (6H, m, 8-H, 9-H, 11-H, 12-H, 14-H, 15-H); $\delta_C(CDCl_3)$ 14.0, 21.4, 22.5, 23.1, 25.6, 27.2, 29.3, 31.5, 32.8, 34.1, 34.3, 55.5, 62.8, 77.2, 95.6, 127.6, 128.0, 128.2, 128.5, 129.7, 130.5; *m*/*z* (FAB) 375 (M + Na^+, 100), 173 (53) [Found (HRMS): M + Na^+, 375.2869. $C_{22}H_{40}O_3Na$ requires M + Na^+, 375.2875]. (*S*)-isomer: $[\alpha]_D^{20}$ = −7.0 (*c* 1.01, $CHCl_3$).

(5*R*,8*Z*,11*Z*,14*Z*,)-5-Methoxymethoxyicosa-8,11,14-trienoic acid 29. To a solution of $(COCl)_2$ (0.19 ml, 2.18 mmol) in CH_2Cl_2 (15 ml) was added DMSO (0.21 ml, 2.96 mmol) in CH_2Cl_2 (0.2 ml) and alcohol **28** (0.36 g, 1.02 mmol) in CH_2Cl_2 (1 ml) at −75 °C. The reaction solution was warmed to −45 °C, and then stirred for 1 h before addition of Et_3N (1.03 ml, 7.39 mmol). After the reaction solution was stirred at 0 °C for 1 h, sat. aq. NH_4Cl and CH_2Cl_2 were added. The organic solution was separated, washed with brine, dried (Na_2SO_4), and concentrated to give crude aldehyde. A reaction mixture of the crude aldehyde, 2-methylbut-2-ene (0.47 ml, 4.44 mmol), $NaH_2PO_4 \cdot 2H_2O$ (0.16 g, 1.01 mmol), and $NaClO_2$ (0.31 g, 3.44 mmol) in *tert*-BuOH (2 ml) and H_2O (0.5 ml) was stirred at room temperature for 1 h before additions of sat. aq. NH_4Cl and EtOAc. The organic solution was separated, washed with brine, and dried (Na_2SO_4). After evaporation, the residue was purified with silica gel column chromatography (EtOAc–hexane 1 : 3) to give carboxylic acid **29** (0.27 g, 0.74 mmol, 73%) as a colorless oil, $[\alpha]_D^{20}$ = +7.7 (*c* 1.55, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3510, 2930, 1709, 1456, 1148, 1102, 1036; $\delta_H(CDCl_3)$ 0.89 (3H, t, *J* 6.4 Hz, 20-H_3), 1.25–1.40 (6H, m, 17-H_2, 18-H_2, 19-H_2), 1.51–1.62 (4H, m, 4-H_2, 6-H_2), 1.65–1.80 (2H, m, 3-H_2), 2.00–2.08 (2H, m, 16-H_2), 2.08–2.18 (2H, m, 7-H_2), 2.38 (2H, t, *J* 7.3 Hz, 2-H_2), 2.77–2.83 (4H, m, 10-H_2, 13-H_2), 3.38 (3H, s, OCH_3), 3.57 (1H, m, 5-H), 4.65 (2H, s, OCH_2OCH_3), 5.28–5.43 (6H, m, 8-H, 9-H, 11-H, 12-H, 14-H, 15-H); $\delta_C(CDCl_3)$ 14.0, 20.5, 22.5, 23.1, 25.6, 27.2, 28.3, 29.3, 31.5, 33.6, 33.8, 34.2, 55.6, 77.2, 95.6, 127.6, 128.0, 128.3, 128.5, 129.5, 130.5, 178.2; *m*/*z* (FAB) 389 (M + Na^+, 100), 365 (79) [Found (HRMS): M + Na^+, 389.2670. $C_{22}H_{38}O_4Na$ requires M + Na^+, 389.2668]. (*S*)-isomer: $[\alpha]_D^{20}$ = −7.6 (*c* 1.06, $CHCl_3$).

(5*R*,8*Z*,11*Z*,14*Z*)-Icosa-8,11,14-trien-5-olide ((*R*)-6,7-dihydro-5-HETE lactone) 5. A reaction solution of MOM ether **29** (43 mg, 0.12 mmol) in THF (3 ml) and 6 M aq. HCl (3 ml) was stirred at room temperature for 2 h. After additions of H_2O and EtOAc, the organic solution was separated, washed with sat. aq. $NaHCO_3$ and brine, and dried (Na_2SO_4). After concentration, the residue was applied to silica gel column chromatography (EtOAc–hexane 1 : 5) to give lactone **5** (33 mg, 0.11 mmol, 92%) as a colorless oil, $[\alpha]_D^{20}$ = −36.0 (*c* 0.75, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 2930, 1728, 1464, 1445, 1375, 1345, 1329, 1248, 1178, 1053, 909; $\delta_H(CDCl_3)$ 0.89 (3H, t, *J* 6.8 Hz, 20-H_3), 1.24–1.40 (6H, m, 17-H_2, 18-H_2, 19-H_2), 1.54 (1H, m, 4-*H*H), 1.63 (1H, m, 4-H*H*), 1.75–1.86 (2H, m, 6-H_2), 1.87–1.93 (2H, m, 3-H_2), 2.03–2.08 (2H, m, 16-H_2), 2.21–2.26 (2H, m, 7-H_2), 2.44 (1H, ddd, *J* 17.6, 8.8, 6.8 Hz, 2-*H*H), 2.58 (1H, m, 2-H*H*), 2.79–2.84 (4H, m, 10-H_2, 13-H_2), 4.29 (1H, m, 5-H), 5.30–5.45 (6H, m, 8-H, 9-H, 11-H, 12-H, 14-H, 15-H); $\delta_C(CDCl_3)$ 14.0, 18.5, 22.5, 22.7, 25.6, 27.2, 27.8, 29.3, 29.4, 31.5, 35.6, 79.7, 127.5, 127.8, 128.5, 128.6, 129.1, 130.5, 171.6; *m*/*z* (FAB) 327 (M + Na^+, 100), 305 (90) [Found (HRMS): M + Na^+, 327.2301. $C_{20}H_{32}O_2Na$ requires M + Na^+, 327.2300]. (*S*)-isomer **6**: $[\alpha]_D^{20}$ = +36.0 (*c* 1.03, $CHCl_3$).

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