Total Synthesis of (+)-Mayolide A. Absolute Structure of Mayolide A, a Secocembrane Diterpenoid from the Soft Coral *Sinularia mayi*

Hiroto NAGAOKA, Makoto IWASHIMA, Haruyasu ABE, Kazuo IGUCHI and Yasuji YAMADA*

Tokyo College of Pharmacy, Horinouchi, Hachioji, Tokyo 192-03, Japan. *Received December 25, 1991*

The stereoselective total synthesis of (+)-mayolide A (1) was achieved starting from D-mannitol *via* two crucial steps: stereoselective introduction of a two-carbon unit into the β-position of the butenolide 5 and repeated Claisen rearrangement to produce the side chain. The absolute structure of natural mayolide A from the Okinawan soft coral *Sinularia mayi* was determined as 2 by the present synthesis.

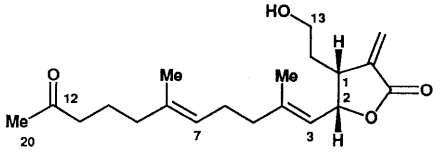
Keywords total synthesis; mayolide A; secocembrane; diterpenoid; absolute structure; Claisen rearrangement; D-mannitol

Mayolide A, recently isolated from the Okinawan soft coral *Sinularia mayi*,[1] is the first secocembrane-type diterpenoid. It has a unique skeleton in which the bond between the C-12 and C-13 positions of the 14-membered carbocyclic skeleton of usually encountered cembranolides is cleaved. The structure of mayolide A has been elucidated by nuclear magnetic resonance (NMR) studies,[1] but the absolute configurations remain to be determined. We have now achieved the stereoselective total synthesis of (+)-mayolide A (**1**) starting from D-mannitol; it involved two crucial steps of stereoselective introduction of a two carbon unit into the β-position of the butenolide **5**, and repeated Claisen rearrangement to produce the side chain. Based on this synthesis, the absolute structure of natural mayolide A was clearly shown to be **2**. A part of this work has appeared in a previous communication.[2] In the present peper, we discuss the synthesis in detail.

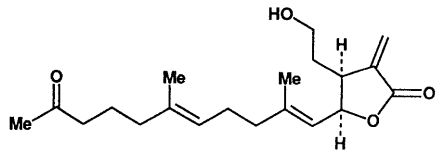
Methyl (2*Z*,4*S*)-4,5-di-*O*-isopropylidenepent-2-enoate (**3**),[3] which is readily available from D-mannitol, was converted to butenolide **5** *via* **4**[4] by acid-catalyzed lactonization (99% yield) and protection of the hydroxyl group as the tetrahydropyranyl (THP) ether (95% yield), as shown in Chart 1. Michael reaction of **5** with the lithium enolate of *tert*-butyl acetate in tetrahydrofuran (THF) at −78 °C gave with highly stereoselectivity the lactone **6** in 82% yield.[5] The *trans* stereochemistry of the substituents at the C-3 and -4 positions on the lactone **6** was strongly suggested by preferential attack of the enolate from the less-hindered side. Confirmation of this point was obtained by analysis of the two-dimensional nuclear Overhauser effect spectrum (2D NOESY) of the alcohol **7** obtained by acid treatment of **6**. NOEs were observed between the methine proton [δ 4.28 (ddd)] at C-4 and the methylene protons [δ 2.31 (dd), 2.83 (m)] at the α-position to the *tert*-butoxycarbonyl group. Selective reduction of the lactone carbonyl in **6** with diisobutylaluminum hydride (DIBAH) in THF at −78 °C, followed by treatment with sodium borohydride gave the diol **8** with the requisite side chain at the C-3 position in 35% overall yield.

The diol **8** was converted to the aldehyde **9** in three steps: 1) protection of two hydroxyl groups as the methoxymethyl (MOM) ether by treatment with chloromethyl methyl ether in the presence of diisopropylethylamine; 2) deprotection of the tetrahedyropyranyloxy group with pyridinium *p*-toluenesulfonate (PPTS) (85% yield, two steps) and 3) Swern oxidation[6] (quantitative yield). Grignard reaction of the aldehyde with 1-methylvinylmagnesium bromide in THF at −78 °C gave a diastereomeric mixture of the alcohols **10** at a ratio of 5:2 in 85% yield. Without separating the isomers, **10** was reduced with lithium aluminum hydride in ether to give a mixture of diols which were subsequently converted to the *tert*-butyldimethylsilyl (TBDMS) ether **11** in 81% yield (two steps), and this compound was subjected to Claisen rearrangement.[7] A mixture of the alcohols in ethyl vinyl ether and mercury(II) acetate was heated at 135 °C in a sealed tube for 48 h to give the desired *E*-olefin **12a** along with its *Z*-isomer (*E*:*Z*=5:1) in 62% yield. Following their separation, the major product **12a** was treated with 1-methylvinylmagnesium bromide to give **13a** (72% yield, 1:1 diastereomeric mixture), which was then subjected to Claisen rearrangement under reaction conditions similar to those used for **11** to give the dienals **14a** (8*E*:8*Z*=12:1) in 66% yield.

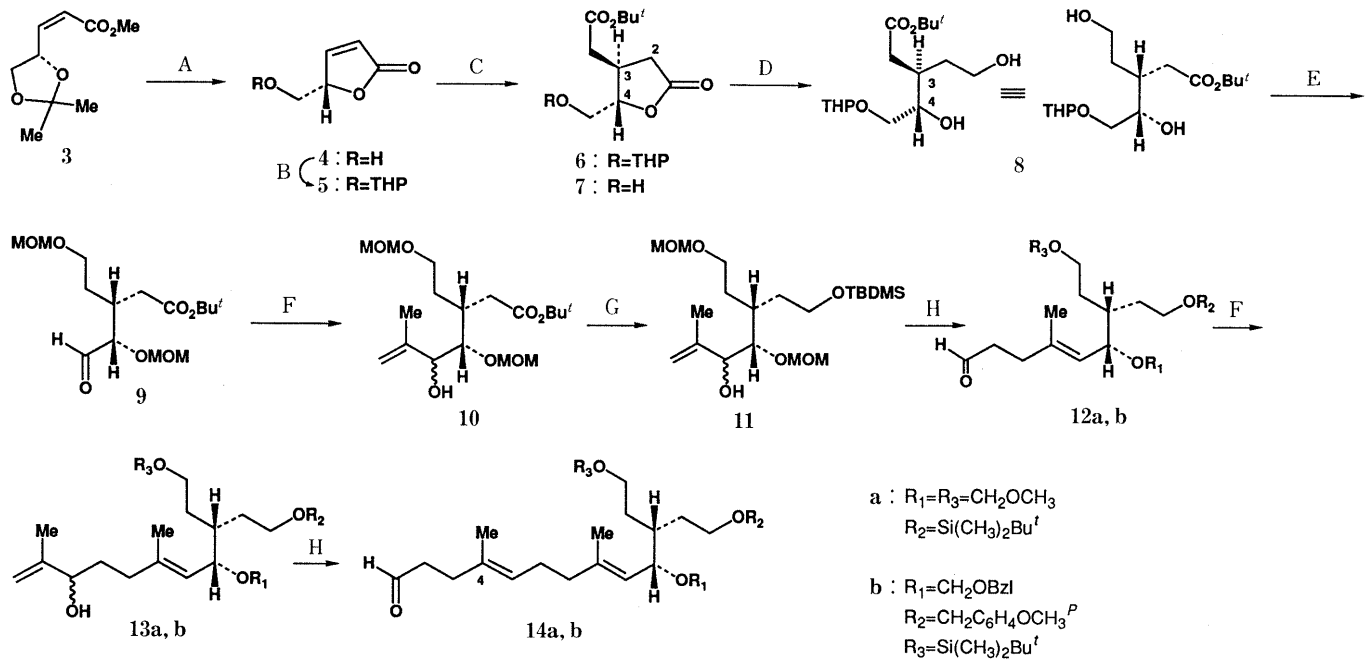
Further extension with a two carbon unit on the aldehyde **14a** produced the methyl ketone **16a** with the side chain (C-3 to -20) of mayolide A in 85% overall yield through the following steps (Chart 2): 1) reduction of the aldehyde with sodium borohydride; 2) methanesulfonylation of the resulting hydroxyl group; 3) iodination with sodium iodide in acetone to give the iodide **15a** (87% yield, three steps); 4) treatment with 1-ethoxyvinyllithium in THF at −78 °C and 5) selective hydrolysis of the resulting vinyl ether with acetic acid–water (2:1) (97% yield, two steps). Experiments were then conducted to obtain the γ-butyrololactone moiety, as follows. Treatment of **16a** with tetrabutylammonium fluoride gave the primary alcohol **17** in quantitative yield, and this was oxidized with Jones reagent to give the corresponding carboxylic acid. Treatment of the carboxylic



1

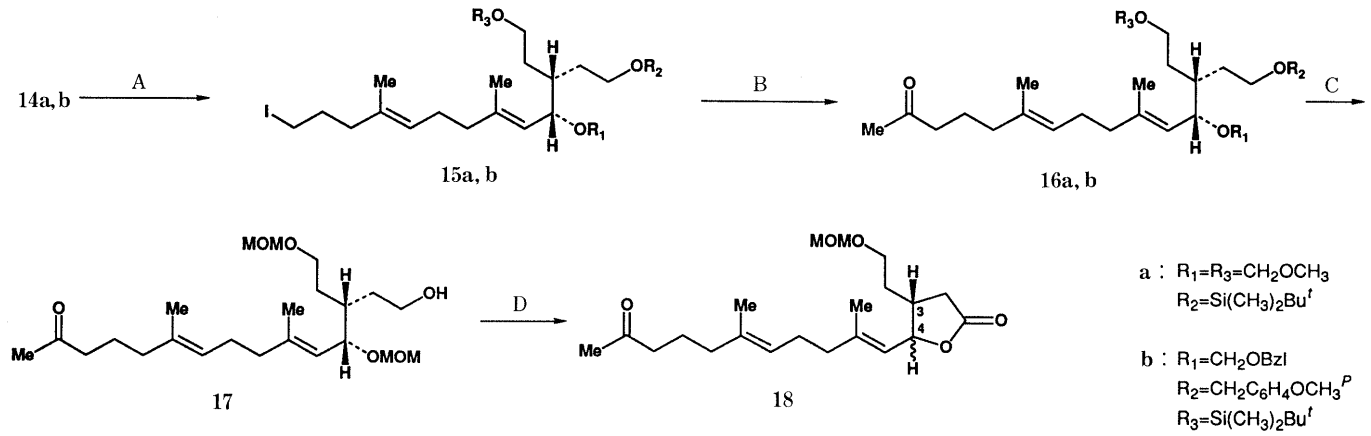


2 mayolide A



reagents: (A) CSA, MeOH; (B) DHP, CSA; (C) *tert*-BuOAc, LDA, THF, -78°C; (D) i) DIBAH, THF, ii) $NaBH_4$; (E) i) $MeOCH_2Cl$, iso-Pr_2NEt, ii) PPTS, MeOH, iii) DMSO, $(COCl)_2$ then Et_3N; (F) CH_2=C(Me)MgBr, THF, -78°C; (G) i) $LiAlH_4$, ii) *tert*-$BuMe_2SiCl$, imidazole; (H) CH_2=CHOEt, $Hg(OAc)_2$, 135°C

Chart 1



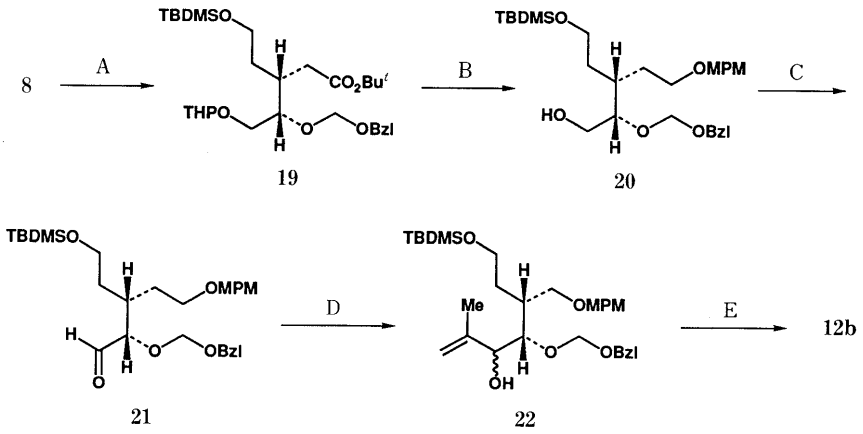
reagents: (A) i) $NaBH_4$, ii) MsCl, Et_3N, iii) NaI; (B) i) CH_2=CHOEt, *tert*-BuLi, ii) AcOH-H_2O (2:1); (C) Bu_4NF; (D) i) Jones oxid., ii) AcOH-H_2O (4:1), 60°C

Chart 2

acid with acetic acid–water (4:1) at 60 °C gave an inseparable mixture of two lactones **18** [infrared (IR) spectrum 1779, 1714 cm^{-1}). The ^{1}H-NMR spectrum of the mixture showed two methine signals due to H-4 [δ 4.81 (t, J=8.6 Hz) and 5.28 (dd, J=7.0, 9.6 Hz) ppm] at a ratio of 2:1. Epimerization is thus clearly shown to occur at the allylic C-4 position during reaction under acidic conditions. So, to protect the hydroxyl groups, a group other than the methoxymethyl group should be considered, such as a benzyloxymethyl group which can be removed under non-acidic conditions.

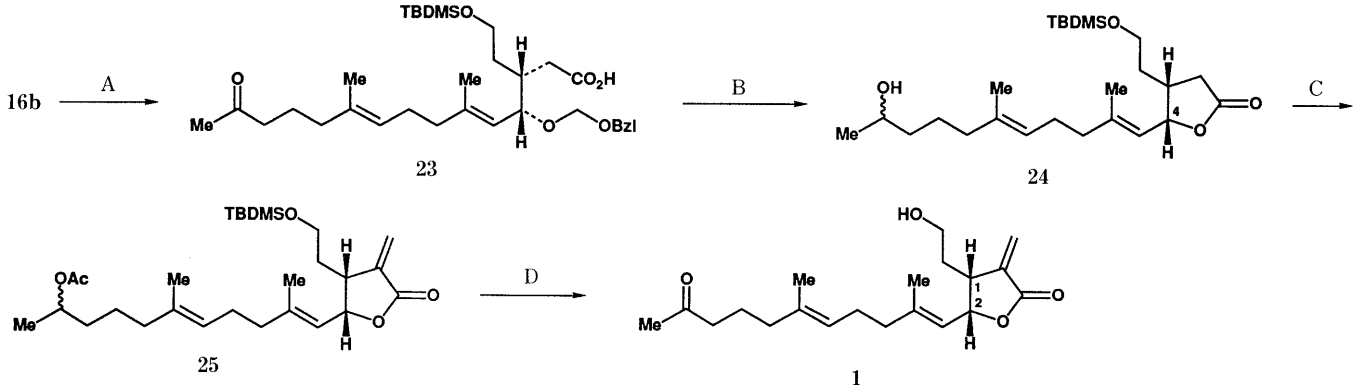
As shown in Chart 3, the primary hydroxyl group in **8** was first protected selectively as the TBDMS ether, and then the secondary hydroxyl group at C-4 was protected as a benzyloxymethyl group to give **19** in 88% overall yield. Compound **19** was converted to the aldehyde **21** *via* **20** as follows in 63% overall yield: 1) reduction of *tert*-butyl ester with lithium aluminum hydride; 2) protection of the resultant primary hydroxyl group as a *p*-methoxyphenylmethyl (MPM) ether; 3) selective deprotection of the tetrahydropyranyl group with magnesium bromide in ether at 20 °C to give **20** and 4) oxidation of the hydroxyl group by Swern's procedure. Grignard reaction of **21** with 1-methylvinylmagnesium bromide in THF at −78 °C gave the allylic alcohol **22** as a diastereomeric mixture (5:2) in 85% yield. Claisen rearrangement of **22** gave the aldehyde **12b** in 66% yield (E:Z=5:1).

Compound **12b** was similarly converted to the aldehyde **14b** *via* **13b** in 48% overall yield as shown in Chart 1. The aldehyde **14b** was then converted to **16** in 90% overall yield as shown in Chart 2. Removal of the MPM group in **16b** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)[8]



reagents: (A) i) *tert*-$BuMe_2SiCl$, imidazole, ii) $PhCH_2OCH_2Cl$, iso-Pr_2NEt; (B) i) $LiAlH_4$, ii) *p*-$MeOC_6H_4CH_2Br$, NaH, iii) $MgBr_2$, Et_2O; (C) DMSO, $(COCl)_2$ then Et_3N; (D) CH_2=C(Me)MgBr, THF; (E) CH_2=CHOEt, $Hg(OAc)_2$, 135°C

Chart 3



reagents: (A) i) DDQ, ii) PDC, iii) $NaClO_2$; (B) i) Li, liq.NH_3, THF, ii) CSA; (C) i) LDA, CH_2O, ii) Ac_2O, C_5H_5N,DMAP, iii) DBU; (D) i) DIBAH, ii) PDC, iii) Bu_4NF

Chart 4

in dichloromethane containing a small amount of water at 25 °C followed by stepwise oxidation [pyridinium dichromate (PDC) and sodium chlorite oxidation[9]] gave the carboxylic acid **23** in 71% overall yield as shown in Chart 4. Deprotection of the benzyloxymethyl group in **23** with lithium in liquid ammonia, followed by treatment with a catalytic amount of *dl*-camphorsulfonic acid (CSA) in ethyl acetate at 60 °C gave the lactone alcohol **24** without epimerization at the C-4 position in 93% yield from **23**. The *cis* configuration between the C-3 and -4 positions in **24** was confirmed by nuclear Overhauser effect (NOE) measurement; a 6.3% NOE was observed between H-3 [δ 2.75 (m)] and H-4 [δ 5.27 (dd)].

An exomethylene group was introduced into the α-position to the lactone carbonyl in **24** to give **25** by way of the following reactions: 1) reaction of the enolate generated from **24** with 2.1 eq of lithium diisopropylamide, with formaldehyde in THF at −78 °C to −30 °C (70% yield), 2) acetylation with acetic anhydride in pyridine in the presence of 4-dimethylaminopyridine at 25 °C, and 3) elimination of acetic acid with 1,8-diazabicyclo[5.4.0]undecene (DBU) in benzene at 50 °C (95% yield, two steps).

By adjustment of the functional groups in **25**, the synthesis of **1** was achieved. Reaction of **25** with DIBAH in THF at −78 °C gave the corresponding hydroxy hemiacetal (concomitant reduction of the lactone). Oxidation of the hydroxy hemiacetal with PDC in the presence of 4 Å molecular sieves in dichloromethane at 25 °C, followed by removal of the silyl group with tetrabutylammonium fluoride in THF furnished compound **1** (1*R*,2*R*) in 47% overall yield. ^{1}H-NMR, IR, and thin-layer chromatographic (TLC) behavior were identical with those of the natural mayolide A, though the optical rotation of **1**, observed as ($[\alpha]_D$ +56.4°, $CHCl_3$), was opposite to that of the natural form ($[\alpha]_D$ −52°, $CHCl_3$). The present synthesis of the antipodal (+)-mayolide A (**1**) has clearly established the absolute configuration of the natural mayolide A as shown in **2** (1*S*,2*S*).

Experimental

Melting points were measured on a kofler block and are uncorrected. Optical rotations were measured with a JASCO DIP-360 automatic polarimeter. IR spectra were recorded with a Perkin-Elmer FTIR 1710 spectrophotometer. ^{1}H- and ^{13}C-NMR spectra were recorded with a Bruker AM-400 (400 MHz for ^{1}H and 100 MHz for ^{13}C) spectrometer. Chemical shifts are given on a δ (ppm) scale with tetramethylsilane (TMS) as an internal standard (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad). Electron impact mass (EIMS) and chemical ionization mass (CIMS) spectra were taken with a Hitachi M-80 spectrometer. Column chromatography was carried out on Fuji-Davison BW 820-MH (silica gel, 70—200 mesh), and preparative thin layer chromatography (PTLC) was carried out on Merck Kieselgel 60 F_{254} TLC plates.

(4*S*)-4-Hydroxy-5-tetrahydropyranyloxy-2-pentenoic Acid γ-Lactone (5) CSA (1.23 g) was added to a cold (0 °C) solution of **4**[4] (30.3 g) and 3,4-dihydro-2*H*-pyran (49 ml) in dry THF (300 ml) under an argon atmosphere. After 15 h at 10 °C, pyridine (3 ml) was added to the reaction mixture. Then the whole was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (hexane : EtOAc = 4 : 1 as an eluent) to give **5** (49.9 g, 95% yield). Colorless oil. IR (film) cm^{-1}: 1780, 1757. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 5.19 (1H, m), 6.15 (0.5H, dd, *J* = 1.9, 5.7 Hz), 6.16 (0.5H, dd, *J* = 1.9, 5.7 Hz), 7.50 (0.5H, dd, *J* = 1.4, 5.7 Hz), 7.51 (0.5H, dd, *J* = dd, *J* = 1.4, 5.7 Hz). CIMS *m/z*: 199 ($M^+ + 1$). *Anal.* Calcd for $C_{10}H_{14}O_4$: C, 60.58; H, 7.12. Found: C, 60.40; H, 7.05.

(3*R*,4*S*)-3-*tert*-Butyloxycarbonylmethyl-4-hydroxy-5-tetrahydropyranyloxypentanoic Acid γ-Lactone (6) A 1.70 M solution of butyllithium in hexane (11.6 ml) was added to a cold (0 °C) solution of diisopropylamine (3.2 ml) in dry THF (30 ml) under an argon atmosphere, then the mixture was stirred for 10 min at 0 °C and cooled to −78 °C. *tert*-Butyl acetate (3.0 ml) was added and the mixture was stirred for 40 min at −78 °C.

Next a solution of the α,β-unsaturated lactone **5** (3.0 g) in dry THF (5 ml) was added. After being stirred for 30 min at −78 °C, the reaction mixture was diluted with ether, washed with saturated NH_4Cl solution and saturated NaCl solution, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane : CH_2Cl_2 : ether = 3 : 1 : 2 as an eluent) to give **6** (3.9 g, 82% yield). Colorless oil. IR (film) cm^{-1}: 1783, 1727. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.45 (9H, s), 4.37 (1H, m), 4.60 (0.5H, br t, *J* = 3.5 Hz), 4.67 (0.5H, br t, *J* = 3.5 Hz). *Anal.* Calcd for $C_{16}H_{26}O_6$: C, 61.11; H, 8.34. Found: C, 61.04; H, 8.32.

(3*R*,4*S*)-3-*tert*-Butyloxycarbonylmethyl-4,5-dihydroxypentanoic Acid γ-Lactone (7) A mixture of **6** (50 mg), PPTS (10 mg) and MeOH (1 ml) was stirred at 40 °C for 5 h. After addition of pyridine (0.1 ml), the mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane : EtOAc = 2 : 1 as an eluent) to give **7** (34 mg, 93% yield). Colorless needles: mp 54 °C, $[\alpha]_D$ +24.2° (*c* = 0.94, $CHCl_3$). IR (KBr) cm^{-1}: 3452, 1779, 1724. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.38 (9H, s), 2.31 (1H, dd, *J* = 4.9, 15.5 Hz), 2.40 (1H, dd, *J* = 7.0, 16.2 Hz), 2.49 (1H, dd, *J* = 6.9, 16.2 Hz), 2.83 (1H, m), 2.86 (1H, dd, *J* = 9.2, 15.5 Hz), 3.72 (1H, dd, *J* = 4.0, 12.5 Hz), 3.92 (1H, dd, *J* = 3.0, 12.5 Hz), 4.28 (1H, ddd, *J* = 3.0, 4.0, 6.0 Hz). *Anal.* Calcd for $C_{11}H_{18}O_5$: C, 57.36; H, 7.88. Found: C, 57.66; H, 7.92.

***tert*-Butyl (3*R*,4*S*)-3-(2-Hydroxy)ethyl-4-hydroxy-5-tetrahydropyranyloxypentanoate (8)** A 1.0 M solution of DIBAH (47.0 ml) in hexane was added to a cold (−78 °C) solution of **6** (10.6 g) in dry THF (200 ml) under an argon atmosphere, and the mixture was stirred for 30 min. MeOH was added and the reaction mixture was stirred for 10 min, then diluted with ether (700 ml). Saturated NaCl solution (50 ml) was added, and the whole was stirred for 1 h at room temperature. The ether layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give a hemiacetal (5.6 g, 53% yield) along with **6**. IR (film) cm^{-1}: 3486, 1729.

Sodium borohydride (2.3 g) was added to a cold (0 °C) solution of the hemiacetal (15.0 g) in MeOH (100 ml) and the mixture was stirred for 20 min at 0 °C. After addition of saturated NH_4Cl solution, the mixture was concentrated under reduced pressure. The residue was diluted with a 3 : 1 mixture of ether and CH_2Cl_2, washed with water and saturated NaCl solution, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane : EtOAc = 3 : 1 as an eluent) to give **8** (9.9 g, 66% yield). Colorless oil. IR (film) cm^{-1}: 3426, 1728. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.43 (9H, s), 4.56 (1H, m). EIMS *m/z*: 283 ($M^+ + 1 - 2H_2O$). High-resolution MS Calcd for $C_{12}H_{19}O_5$ ($M^+ - C_4H_9 - H_2O$): 243.1232. Found: 243.1222.

***tert*-Butyl (3*R*,4*S*)-3-(2-Methoxymethyloxyethyl)-4-methoxymethyloxy-5-oxopentanoate (9)** Diisopropylethylamine (5.1 ml) and chloromethyl methyl ether (1.8 ml) were added to a solution of **8** (1.87 g) in dry 1,2-dichloroethane (15 ml). After being stirred for 1 h at 60 °C, the reaction mixture was diluted with ether, washed with water and saturated NaCl solution, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane : EtOAc = 5 : 1 as an eluent) to give the bismethoxymethyl ether (2.2 g, 93% yield).

PPTS (237 mg) was added in one portion to a solution of the bismethoxymethyl ether (12.4 g) in MeOH (200 ml) and the mixture was stirred at 40 °C for 8 h. After addition of pyridine (3 ml), the mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give an alcohol (8.9 g, 91% yield).

Dimethyl sulfoxide (DMSO) (5.08 ml) was added dropwise to a cold (−70 °C) solution of oxalyl chloride (4.68 ml) in dry CH_2Cl_2 (200 ml) under an argon atmosphere. The mixture was stirred for 5 min at −70 °C, then a solution of the above alcohol (5.76 g) in dry CH_2Cl_2 (30 ml) was added dropwise with stirring. After 15 min at −70 °C, triethylamine (12.5 ml) was further added and stirring was continued for 20 min at this temperature. The mixture was allowed to warm to 0 °C over 20 min with stirring, then diluted with a 5 : 1 mixture of benzene and ether, and filtered. The filtrate was washed with water and saturated NaCl solution, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane : AcOEt = 5 : 1 as an eluent) to give **9** in quantitative yield. Colorless oil. $[\alpha]_D$ −19.6° (*c* = 0.5, $CHCl_3$). IR (film) cm^{-1}: 1730. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.45 (9H, s), 2.37 (1H, dd, *J* = 5.9, 16.0 Hz), 2.43 (1H, dd, *J* = 8.2, 16.0 Hz), 2.62 (1H, m), 3.34 (3H, s), 3.41 (3H, s), 3.53 (2H, t, *J* = 6.5 Hz), 4.07 (1H, dd, *J* = 1.0, 3.7 Hz), 4.59 (2H, s), 4.70 (1H, d, *J* = 6.7 Hz), 4.73 (1H, d, *J* = 6.7 Hz), 9.67 (1H, d, *J* = 3.7 Hz). EIMS *m/z*: 263 ($M^+ - C_4H_9$). High-resolution MS Calcd for $C_{11}H_{19}O_7$ ($M^+ - C_4H_9$): 263.1131. Found: 263.1167.

***tert*-Butyl (3*R*,4*S*)-5-Hydroxy-6-methyl-4-methoxymethyloxy-3-(2-methoxymethyloxyethyl)-6-heptenoate (10)** A 1.0 M solution of 1-methylvinylmagnesium bromide in THF solution (22.6 ml) was added to a cold (−78 °C) solution of **9** (6.0 g) in dry THF (130 ml) under an argon atmosphere. After being stirred for 1 h at this temperature, the reaction mixture was diluted with ether, and washed with diluted HCl, water, and saturated NaCl solution, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane : EtOAc = 8 : 1 as an eluent) to give **10** as a diastereomeric mixture (5 : 2, 5.53 g 85% yield). Colorless oil. IR (film) cm^{-1}: 3458, 1727. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.44 (9H, s), 1.77 (2.1H, br s), 1.79 (0.9H, br s), 4.11 (0.7H, dd, *J* = 2.8, 7.0 Hz), 4.18 (0.29H, br t, *J* = 5.2 Hz), 4.95 (1H, br d, *J* = 0.8 Hz), 5.04 (0.71H, br d, *J* = 0.9 Hz), 5.08 (0.29H, br s). EIMS *m/z*: 256 ($M^+ - CH_3OH - C_4H_9OH$). High-resolution MS Calcd for $C_{13}H_{20}O_5$ ($M^+ - CH_3OH - C_4H_9OH$): 256.1311. Found: 256.1244.

(4*S*,5*R*)-7-*O*-*tert*-Butyldimethylsilyl-2-methyl-4-*O*-methoxymethyl-5-(2-methoxymethyloxyethyl)-1-heptene-3,4,5-triol (11) Lithium aluminum hydride (1.20 g) was added portionwise to a cold (0 °C) solution of **10** (5.53 g) in dry ether (300 ml) under an argon atmosphere. After being stirred for 30 min at 0 °C, the mixture was diluted with ether. Then saturated NaCl solution (1 ml) was added and the reaction mixture was stirred for 30 min at room temperature. The ether layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane : AcOEt = 2 : 1 as an eluent) to give a diol (4.46 g, quantitative yield).

Imidazole (315 mg) and *tert*-butyldimethylsilychlorosilane (604 mg) were added to a solution of the diol (0.91 g) in dry *N*,*N*-dimethylformamide (DMF) (13 ml) under an argon atmosphere. After being stirred for 20 h at room temperature, the reaction mixture was diluted with ether, washed with water and saturated NaCl solution, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane : AcOEt = 7 : 1 as an eluent) to give **11** (1.02 g, 81% yield). Colorless oil. IR (film) cm^{-1}: 3462. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.04 (6H, s), 0.88 (9H, s), 1.70 (2.1H, br s), 1.79 (0.9H, br s). EIMS *m/z*; 313 ($M^+ - CH_3OCH_2OH - CH_3OH$).

(4*E*,6*S*,7*R*)-9-*tert*-Butyldimethylsilyloxy-4-methyl-6-methoxymethyloxy-7-(2-methoxymethyloxyethyl)-4-nonen-1-al (12a) A mixture of **11** (1.02 g), dry ethyl vinyl ether (18 ml), and mercury(II) acetate (400 mg) in a sealed tube was heated at 135 °C for 2 d. After dilution with a 3 : 1 mixture of hexane and ether, potassium carbonate (1 g) was added and the mixture was stirred at room temperature for 20 min. The mixture was passed through a short silica gel column, and the filtrate was concentrated under reduced pressure. The residue was subjected to silica gel column chromatography and elution with hexane–EtOAc (15 : 1, 8 : 1, and 4 : 1 in this order) gave the *E*-olefin **12a** (610 mg, 56% yield) and a mixture of **12a** and its *Z*-isomer (2 : 1, 123 mg, 11% yield).

12a: Colorless oil. $[\alpha]_D$ −48.1° (*c* = 0.265, $CHCl_3$). IR (film) cm^{-1}: 1728, 1668. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.03 (6H, s), 0.88 (9H, s), 1.69 (3H, d, *J* = 1.2 Hz), 2.37 (2H, t, *J* = 7.4 Hz), 2.55 (2H, td, *J* = 1.7, 7.6 Hz), 3.33 (3H, s), 3.35 (3H, s), 3.56 (2H, td, *J* = 2.1, 7.1 Hz), 3.65 (2H, t, *J* = 6.7 Hz), 4.28 (1H, dd, *J* = 5.3, 9.4 Hz), 4.44 (1H, d, *J* = 6.7 Hz), 4.57 (1H, d, *J* = 6.7 Hz), 4.60 (2H, s), 5.11 (1H, dd, *J* = 1.2, 9.4 Hz), 9.76 (1H, t, *J* = 1.7 Hz). EIMS *m/z*: 387 ($M^+ - CH_2OCH_3$). High-resolution MS Calcd for $C_{20}H_{39}O_5Si$ ($M^+ - CH_3OCH_2$): 387.2567. Found: 387.2565.

(6*E*,8*S*,9*R*)-11-*O*-*tert*-Butyldimethylsilyl-2,6-dimethyl-8-*O*-methoxy-

methyl-9-(2-methoxymethyloxyethyl)-1,6-undecadiene-3,8,11-triol (13a) A 1.02 M solution of isopropenylmagnesium bromide in THF (4.4 ml) was added to a cold (−40 °C) solution of **12a** (1.66 g) in dry THF (50 ml) under an argon atmosphere, and the reaction mixture was stirred for 1 h. Similar work-up and purification to those described for **10** gave **13a** (1.31 g, 72% yield). Colorless oil. IR (film) cm^{-1}: 3473, 1651, 919.

(4*E*,8*E*,10*S*,11*R*)-13-*tert*-Butyldimethylsilyloxy-4,8-dimethyl-10-methoxymethyloxy-11-(2-methoxymethyloxyethyl)-4,8-tridecadien-1-al (14a) A mixture of **13a** (330 mg), dry ethyl vinyl ether (1.5 ml), and mercury(II) acetate (108 mg) was heated in a sealed tube at 135 °C for 2 d. Similar work-up and purification to those described for **12a** gave the *E*-olefin **14a** (229 mg, 66% yield) and a mixture of **14a** and its *Z*-isomer (1 : 5, 10 mg, 3% yield).

14a: Colorless oil. $[\alpha]_D$ −51.6° (c=0.49, $CHCl_3$). IR (film) cm^{-1}: 1728. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.03 (6H, s), 0.88 (9H, s), 1.61 (3H, s), 1.67 (3H, d, J=1.2 Hz), 2.30 (2H, t, J=7.5 Hz), 2.50 (2H, td, J=1.9, 7.5 Hz), 3.34 (3H, s), 3.35 (3H, s), 3.58 (2H, t, J=6.4 Hz), 3.66 (2H, t, J=6.7 Hz), 4.28 (1H, dd, J=5.1, 9.6 Hz), 4.45 (1H, d, J=6.6 Hz), 4.61 (2H, s), 4.62 (1H, d, J=6.6 Hz), 5.05 (1H, dd, J=1.0, 9.6 Hz), 5.13 (1H, td, J=1.2, 6.8 Hz), 9.75 (1H, t, J=1.9 Hz). EIMS m/z: 455 ($M^+ - CH_3OCH_2$). High-resolution MS Calcd for $C_{23}H_{41}O_3Si$ ($M^+ - CH_3OCH_2OH - CH_3OCH_2$): 393.2825. Found: 393.2826.

(4*E*,8*E*,10*S*,11*R*)-13-*tert*-Butyldimethylsilyloxy-4,8-dimethyl-1-iodo-10-methoxymethyloxy-11-(2-methoxymethyloxyethyl)-4,8-tridecadiene (15a) Sodium borohydride (10 mg) was added to a cold (0 °C) solution of **14a** (78 mg) in MeOH (1 ml), and the reaction mixture was stirred for 30 min at 0 °C. After addition of saturated NH_4Cl solution, the mixture was concentrated under reduced pressure. The residue was diluted with a 3 : 1 mixture of ether and CH_2Cl_2, washed with water and saturated NaCl solution, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. This residue was purified by silica gel column chromatography (hexane : EtOAc = 8 : 1 as an eluent) to give an alcohol (75 mg, 96% yield).

Triethylamine (0.88 ml) and methanesulfonyl chloride (0.36 ml) were added to a cold (0 °C) solution of the alcohol (790 mg) in dry CH_2Cl_2 (5 ml) under an argon atmosphere. After being stirred for 30 min at 0 °C, the mixture was diluted with ether, washed with water and saturated NaCl solution, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was used for the next reaction without further purification.

A solution of the crude methanesulfonate (900 mg) in dry acetone (10 ml) was treated with sodium iodide (710 mg). After being stirred for 16 h at room temperature, the mixture was diluted with hexane and filtered. The filtrate was concentrated to 20 ml and diluted with a 1 : 1 mixture of hexane–ether. The solution was washed with water and saturated NaCl solution, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane : EtOAc = 8 : 1 as an eluent) to give **15a** (833 mg, 91% yield, 2 steps from the alcohol). Pale yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.05 (6H, s), 0.88 (9H, s), 1.60 (3H, d, J=3.0 Hz), 1.67 (3H, d, J=3.0 Hz), 3.13 (1H, t, J=7.0 Hz), 3.35 (3H, s), 3.36 (3H, s), 3.49 (1H, t, J=6.7 Hz), 3.58 (2H, t, J=6.6 Hz), 3.66 (2H, t, J=6.6 Hz), 4.28 (1H, dd, J=5.1, 9.6 Hz), 4.45 (1H, d, J=6.6 Hz), 4.61 (2H, s), 4.62 (1H, d, J=6.6 Hz), 5.06 (1H, br d, J=9.6 Hz), 5.16 (1H, br t, J=6.5 Hz).

(6*E*,10*E*,12*S*,13*R*)-15-*tert*-Butyldimethylsilyloxy-6,10-dimethyl-12-methoxymethyloxy-13-(2-methoxymethyloxyethyl)-6.10-pentadecadien-2-one (16a) A 1.0 M solution of *tert*-butyllithium in pentane (2.5 ml) was added to a cold (−78 °C) solution of ethyl vinyl ether (0.86 ml) in dry THF (9 ml) and the mixture was warmed to 0 °C. After addition of hexamethylphosphoramide (HMPA, 0.424 ml), the mixture was cooled to −78 °C. Then a solution of the iodide **15a** (780 mg) in dry THF (2 ml) was added, and the resulting mixture was stirred for 20 min at −78 °C and warmed to 0 °C. The mixture was diluted with ether, washed with saturated NH_4Cl solution, water and saturated NaCl solution, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to give a crude enol ether (900 mg).

A mixture of the crude enol ether (900 mg), AcOH (2 ml) and water (1 ml) in THF (7 ml) was stirred for 1 h at room temperature. After concentration of the mixture, the residue was purified by silica gel column chromatography (hexane : EtOAc = 8 : 1 as an eluent) to give a methylketone **16a** (650 mg, 97% yield, 2 steps). Colorless oil. $[\alpha]_D$ −52.4° (c=0.34, $CHCl_3$). IR (film) cm^{-1}: 1719. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.03 (6H, s), 0.88 (9H, s), 1.58 (3H, s), 1.67 (3H, s), 1.96 (2H, t, J=7.4 Hz), 2.12 (3H, s), 2.37 (2H, t, J=7.3 Hz), 3.35 (6H, s), 3.58 (2H, t, J=6.6 Hz), 3.66 (2H, t, J=6.9 Hz), 4.28 (1H, dd, J=5.0, 9.6 Hz), 4.44 (1H, d, J=6.6 Hz), 4.60 (2H, s), 4.62 (1H, d, J=6.6 Hz), 5.05 (1H, br d, J=9.6 Hz), 5.09 (1H, br s). EIMS m/z: 483 ($M^+ - CH_3OCH_2$).

(6*E*,10*E*,12*S*,13*R*)-6,10-Dimethyl-15-hydroxy-12-methoxymethyloxy-13-(2-methoxymethyloxyethyl)-6,10-pentadecadien-2-one (17) A mixture of **16a** (650 mg) and tetrabutylammonium fluoride (1.0 M solution in THF, 2 ml) in THF (1.5 ml) was stirred for 1 h at room temperature. The mixture was diluted with ether, washed with water and saturated NaCl solution, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane : EtOAc = 3 : 1 as an eluent) to give **17** (508 mg, quantitative yield). Colorless oil. $[\alpha]_D$ −58.6° (c=0.15, $CHCl_3$). IR (film) cm^{-1}: 3474, 1715. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.58 (3H, s), 1.69 (3H, s), 2.13 (3H, s), 3.35 (6H, s), 3.60 (2H, t, J=6.6 Hz), 3.63—3.77 (2H, m), 4.36 (1H, dd, J=5.0, 9.6 Hz), 4.47 (1H, d, J=6.6 Hz), 4.63 (2H, s), 4.65 (1H, d, J=6.6 Hz), 5.07 (1H, br s), 5.12 (1H, br d, J=9.6 Hz). EIMS m/z: 414 (M^+).

Diastereomeric Mixture of (3*S*,5*E*,9*E*)-6,10-Dimethyl-4-hydroxy-3-(2-methoxymethyloxyethyl)-14-oxo-5,9-pentadecadienoic Acid γ-Lactone (18) Jones reagent (about 0.3 ml) was added dropwise to a cold (0 °C) solution of **17** (105 mg) in acetone (5 ml), until the color of the reagent remained, and then 2-propanol was added. After being stirred for 10 min, the mixture was diluted with ether, washed with water and saturated NaCl solution, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to give a crude carboxylic acid (110 mg). IR (film) cm^{-1}: 3500—2500, 1733, 1713.

A mixture of the crude carboxylic acid (18 mg), AcOH (0.8 ml) and water (0.2 ml) was stirred for 2 h at 60 °C. The mixture was concentrated under reduced pressure and the resulting residue was purified by silica gel column chromatography (hexane : EtOAc = 1 : 1 as an eluent) to give an inseparable diastereomeric mixture of **18** (8 mg, 52% yield). The ratio of 4*R* and 4*S* isomers (1 : 2) was determined based on the ^{1}H-NMR spectrum. Colorless oil. IR (film) cm^{-1}: 1779, 1714. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.72 (0.33H, d, J=1.1 Hz), 1.75 (0.67H, d, J=1.1 Hz), 4.81 (0.33H, dd, J=7.0, 9.6 Hz), 5.28 (0.67H, t, J=8.6 Hz). EIMS m/z: 366 (M^+). High-resolution MS Calcd for $C_{19}H_{29}O_4$ ($M^+ - CH_3OCH_2$): 321.2066. Found: 321.2062.

***tert*-Butyl (3*R*,4*S*)-4-Benzyloxymethyloxy-3-(2-*tert*-butyldimethylsilyloxyethyl)-5-tetrahydropyranyloxypentanoate (19)** Imidazole (389 mg) and *tert*-butyldimethylchlorosilane (730 mg) were added sequentially to a solution of **8** (1.40 g) in dry THF (7 ml) and the mixture was stirred for 20 h at room temperature under an argon atmosphere. The mixture was diluted with ether, washed with water and saturated NaCl solution, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane : EtOAc = 5 : 1 as an eluent) to give *tert*-butyl (3*R*,4*S*)-3-(2-*tert*-butyldimethylsilyloxyethyl)-4-hydroxy-5-tetrahydropyranyloxypentanoate (1.65 g, 88% yield). Colorless oil. IR (film) cm^{-1}: 3446, 1729. EIMS m/z: 359 (M^+ − *tert*-BuO). *Anal.* Calcd for $C_{22}H_{44}O_6Si$: C, 61.07; H, 10.25. Found: C, 60.94; H, 10.27.

Diisopropylethylamine (2.65 ml) and benzyl chloromethyl ether (1.6 ml) were added sequentially to a solution of the compound obtained above (1.65 g) in dry 1,2-dichloroethane (8 ml). After being stirred for 5 h at 60 °C, the mixture was diluted with ether, washed with water and saturated NaCl solution, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane : EtOAc = 4 : 1 as an eluent) to give **19** (2.11 g, quantitative yield). Colorless oil. IR (film) cm^{-1}: 1729. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.06 (6H, s), 0.90 (9H, s), 1.43 (9H, s), 4.62 (2H, s), 7.27—7.38 (5H, m). EIMS m/z: 480 ($M^+ + 1$ − *tert*-BuO).

(2*S*,3*S*)-2-*O*-Benzyloxymethyloxy-5-*O*-*tert*-butyldimethylsilyl-3-[2-(*p*-methoxyphenyl)methyloxyethyl]pentane-1,2,5-triol (20) Lithium aluminum hydride (290 mg) was added portionwise to a cold (0 °C) solution of **19** (2.11 g) in dry ether 840 ml), and the mixture was stirred at 0 °C for 30 min, then diluted with ether. Saturated NaCl solution (2 ml) was added and the mixture was stirred for 30 min. The ethereal layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to give a crude alcohol (1.89 g), which was used for the next reaction without further purification.

p-Methoxybenzyl bromide (1.44 ml) and sodium hydride (240 mg) were added sequentially to a cold (0 °C) solution of the alcohol (1.89 g) in a 4 : 1 mixture of THF and DMF (30 ml) under an argon atmosphere, and the mixture was stirred for 5 h at room temperature. After addition of MeOH (1 ml), the mixture was stirred for 3 h. The resulting mixture was diluted with ether, washed with water and saturated NaCl solution, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was dissolved in a 10 : 1 mixture of hexane and EtOAc and the

solution was passed through a short silica gel column. The filtrate was concentrated under reduced pressure to give a *p*-methoxybenzyl ether (2.39 g), which was used for the next reaction without further purification.

A mixture of magnesium bromide (2.93 g) and the *p*-methoxybenzyl ether (2.39 g) in dry ether (200 ml) was stirred for 7 h at room temperature under an argon atmosphere. The mixture was diluted with ether, washed with diluted HCl, water, and saturated NaCl solution, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane : EtOAc = 8 : 1 as an eluent) to give **20** (1.32 g, 64% yield, 3 steps). Colorless oil $[\alpha]_D$ +21.9° (c = 0.32, $CHCl_3$). IR (film) cm^{-1}: 3461. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.05 (6H, s), 0.89 (9H, s), 3.24 (1H, dd, J = 3.6, 9.0 Hz), 3.47 (1H, dt, J = 3.6, 9.0 Hz), 3.59—3.71 (4H, m), 3.79 (3H, s), 4.41 (2H, s), 4.58 (1H, d, J = 11.6 Hz), 4.71 (1H, d, J = 11.6 Hz), 4.73 (1H, d, J = 7.0 Hz), 4.88 (1H, d, J = 7.0 Hz), 6.87 (2H, dd, J = 1.9, 8.3 Hz), 7.24 (2H, dd, J = 1.9, 8.3 Hz), 7.28—7.38 (5H, m). EIMS m/z: 397 ($M^+ - p$-MeO$-C_6H_4CH_2$). *Anal.* Calcd for $C_{29}H_{46}O_6Si$: C, 67.14; H, 8.94. Found: C, 67.20; H, 8.99.

(2*S*,3*S*)-2-Benzyloxymethyloxy-5-*tert*-butyldimethylsilyloxy-3-[2-(*p*-methoxyphenyl)methyloxyethyl]pentan-1-al (21) DMSO (4.93 ml) was added dropwise to a cold (−70 °C) solution of oxalyl chloride (4.54 ml) in dry CH_2Cl_2 (180 ml) under an argon atmosphere. The mixture was stirred for 5 min at −70 °C, then a solution of **20** (9.0 g) in anhydrous CH_2Cl_2 (15 ml) was added dropwise with stirring. After 15 min at −70 °C, triethylamine (12.1 ml) was added and stirring was continued for 20 min at this temperature. The mixture was allowed to warm to 0 °C over 30 min with stirring, diluted with a 5 : 1 mixture of benzene and ether, and filtered. The filtrate was washed with water and saturated NaCl solution, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane : AcOEt = 5 : 1 as an eluent) to give **21** (9.0 g, 99% yield). Pale yellow oil. $[\alpha]_D$ −5.9° (c = 0.99, $CHCl_3$). IR (film) cm^{-1}: 1732. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.04 (6H, s), 0.88 (9H, s), 2.30 (1H, br s), 3.45—3.58 (2H, m), 3.59—3.68 (2H, m), 3.79 (3H, s), 4.12 (1H, d, J = 3.2 Hz), 4.39 (1H, d, J = 11.0 Hz), 4.42 (1H, d, J = 11.0 Hz), 4.63 (1H, d, J = 11.8 Hz), 4.67 (1H, d, J = 11.8 Hz), 4.80 (1H, d, J = 7.1 Hz), 4.84 (1H, d, J = 7.1 Hz), 6.87 (2H, d, J = 8.3 Hz), 7.24 (2H, d, J = 8.3 Hz), 7.28—7.38 (5H, m), 9.67 (1H, br s). EIMS m/z: 395 ($M^+ - p$-MeO$-C_6H_4CH_2$). High-resolution MS Calcd for $C_{21}H_{35}O_5Si$ ($M^+ - p$-MeO$-C_6H_4CH_2$): 395.2254. Found: 395.2230.

Diastereomeric Mixture of (4*S*,5*S*)-4-*O*-Benzyloxymethyl-7-*O*-*tert*-butyldimethylsilyl-2-methyl-5-[2-(*p*-methoxyphenyl)methyloxyethyl]-1-heptene-3,4,7-triol (22) A 1.0 M solution of 1-methylvinylmagnesium bromide in THF (24.4 ml) was added to a cold (−78 °C) solution of **21** (9.0 g) in dry THF (100 ml) under an argon atmosphere, and the mixture was stirred for 1 h. Similar work-up and purification to those described for **10** gave **22** (7.2 g, 85% yield) as a diastereomeric mixture (5 : 2). Colorless oil. IR (film) cm^{-1}: 3476. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.71 (2.1H, s), 1.78 (0.9H, s), 4.14 (0.71H, d, J = 8.0 Hz), 4.20 (0.29H, d, J = 6.4 Hz), 5.06 (0.71H, br s), 5.10 (0.29H, br s). EIMS m/z: 437 ($M^+ - p$-MeO$-C_6H_4CH_2$).

(4*E*,6*S*,7*S*)-6-Benzyloxymethyloxy-9-*tert*-Butyldimethylsilyloxy-4-methyl-7-[2-(*p*-methoxyphenyl)methyloxyethyl]-4-nonen-1-al (12b) A mixture of **22** (8.3 g), dry ethyl vinyl ether (50 ml) and mercury(II) acetate (2.4 g) was heated in a sealed tube at 135 °C for 2 d. After dilution of the mixture with a 3 : 1 mixture of hexane and ether, potassium carbonate (1 g) was added and the mixture was stirred at room temperature for 20 min. The mixture was passed through a short silica gel column and the filtrate was concentrated under reduced pressure. The residue was subjected to silica gel column chromatography with hexane–EtOAc (15 : 1, 8 : 1, and 4 : 1 in that order) to give the *E*-olefin **12b** (5.4 g, 66% yield) and its *Z*-isomer (1.1 g, 13% yield).

12b: Colorless oil. $[\alpha]_D$ −49.3° (c = 1.45, $CHCl_3$). IR (film) cm^{-1}: 1726. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.03 (6H, s), 0.88 (9H, s), 1.67 (3H, d, J = 1.2 Hz), 2.34 (2H, t, J = 7.5 Hz), 2.51 (2H, dt, J = 1.6, 7.5 Hz), 3.49 (2H, t, J = 7.0 Hz), 3.64 (2H, t, J = 6.9 Hz), 3.79 (3H, s), 4.36 (1H, dd, J = 5.1, 9.4 Hz), 4.41 (2H, s), 4.50 (1H, d, J = 11.9 Hz), 4.63 (1H, d, J = 6.9 Hz), 4.67 (1H, d, J = 11.9 Hz), 4.68 (1H, d, J = 6.9 Hz), 5.13 (1H, dd, J = 1.2, 9.4 Hz), 6.87 (2H, td, J = 2.0, 8.7 Hz), 7.24 (2H, td, J = 2.0, 8.7 Hz), 7.28—7.38 (5H, m), 9.74 (1H, t, J = 1.6 Hz). EIMS m/z: 446 ($M^+ - p$-MeOH$-C_6H_4CH_2$). High-resolution MS Calcd for $C_{26}H_{42}O_4Si$ ($M^+ - p$-MeO$-C_6H_4CH_2$): 446.2852. Found: 446.2846.

Z-Isomer of **12b**: $[\alpha]_D$ −67.6° (c = 0.19, $CHCl_3$). IR (film) cm^{-1}: 1725. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.03 (6H, s), 0.89 (9H, s), 1.72 (3H, d, J = 1.3 Hz), 3.51 (2H, td, J = 2.0, 7.0 Hz), 3.64 (2H, t, J = 6.9 Hz), 3.79 (3H, s), 4.37 (1H, dd, J = 4.7, 9.7 Hz), 4.41 (2H, s), 4.50 (1H, d, J = 11.9 Hz), 4.63 (1H, d, J = 6.9 Hz), 4.67 (1H, d, J = 11.9 Hz), 4.71 (1H, d, J = 6.9 Hz), 5.15 (1H, br d, J = 9.6 Hz), 6.86 (2H, td, J = 2.0, 8.7 Hz), 7.23 (2H, td, J = 2.0, 8.7 Hz), 7.28—7.38 (5H, m), 9.63 (1H, t, J = 1.4 Hz).

(6*E*,8*S*,9*S*)-8-*O*-Benzyloxymethyl-11-*O*-(*tert*-butyldimethylsilyl)-2,6-dimethyl-9-[2-(*p*-methoxyphenyl)methyloxyethyl]-1,6-undecadiene-3,8,11-triol (13b) A 1.0 M soltuion of 1-methylvinylmagnesium bromide in THF (16.1 ml) was added to a cold (−78 °C) solution of **12b** (5.40 g) in dry THF (100 ml) under an argon atmosphere, and the mixture was stirred for 1 h. Similar work-up and purification to those described for **10** gave **13b** (4.4 g, 76% yield) as a diastereomeric mixture (1 : 1). Colorless oil. IR (film) cm^{-1}: 3447. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.04 (6H, s), 0.89 (9H, s), 1.67 (3H, d, J = 1.3 Hz), 4.02 (1H, m), 4.84 (1H, br s), 4.94 (1H, br s). EIMS m/z: 489 ($M^+ - p$-MeO$-C_6H_4CH_2$). High-resolution MS Calcd for $C_{29}H_{48}O_4Si$ ($M^+ - p$-MeO$-C_6H_4CH_2$): 488.3322. Found: 488.3309.

(4*E*,8*E*,10*S*,11*S*)-10-Benzyloxymethyloxy-11-[2-(*tert*-butyldimethylsilyloxy)ethyl]-4,8-dimethyl-13-(*p*-methoxyphenyl)methyloxy-4,8-tridecadien-1-al (14b) A mixture of **13b** (4.40 g), dry ethyl vinyl ether (30 ml) and mercury(II) acetate (1.1 g) in a sealed tube was heated at 135 °C for 2 d. After dilution with a 3 : 1 mixture of hexane and ether, potassium carbonate (1 g) was added and the mixture was stirred at room temperature for 20 min. The mixture was passed through a silica gel short column (hexane : EtOAc = 1 : 1 as an eluent) and the filtrate was concentrated under reduced pressure. The residue was subjected to silica gel column chromatography with hexane–EtOAc (15 : 1, 10 : 1, and 5 : 1, in that order) to give the *E*-olefin **14b** (2.9 g, 63% yield) and a mixture of **14b** and its *Z*-isomer (7 : 1, 856 mg, 19% yield).

14b: Colorless oil. $[\alpha]_D$ −53.5° (c = 0.23, $CHCl_3$). IR (film) cm^{-1}: 1726. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.03 (6H, s), 0.88 (9H, s), 1.60 (3H, s), 1.64 (3H, s), 2.29 (2H, t, J = 7.5 Hz), 2.49 (2H, dt, J = 1.8, 7.5 Hz), 3.50 (2H, t, J = 7.0 Hz), 3.64 (2H, t, J = 6.9 Hz), 3.79 (3H, s), 4.37 (1H, dd, J = 5.3, 9.5 Hz), 4.41 (2H, s), 4.50 (1H, d, J = 11.9 Hz), 4.63 (1H, d, J = 6.8 Hz), 4.67 (1H, d, J = 11.9 Hz), 4.71 (1H, d, J = 6.8 Hz), 5.08 (1H, d, J = 9.8 Hz), 5.11 (1H, t, J = 6.5 Hz), 6.87 (2H, d, J = 8.5 Hz), 7.24 (2H, d, J = 8.5 Hz), 7.28—7.38 (5H, m), 9.72 (1H, t, J = 1.8 Hz). EIMS m/z: 531 ($M^+ - p$-MeO$-C_6H_4CH_2$). High-resolution MS Calcd for $C_{31}H_{50}O_4Si$ ($M^+ - p$-MeO$-C_6H_4CH_2OH$): 514.3478. Found: 514.3473.

(4*E*,8*E*,10*S*,11*S*)-10-Benzyloxymethyloxy-11-[2-(*tert*-butyldimethylsilyloxy)ethyl]-4,8-dimethyl-1-iodo-13-(*p*-methoxyphenyl)methoxy-4,8-tridecadiene (15b) Sodium borohydride (70 mg) was added to a solution of **14b** (970 mg) in MeOH (15 ml) at 0 °C, and the mixture was stirred at 0 °C for 30 min. Similar work-up and purification to those described for **15a** gave the corresponding alcohol (970 mg, 99% yield). Colorless oil. $[\alpha]_D$ −49.5° (c = 0.37, $CHCl_3$). IR (film) cm^{-1}: 3453, 1613. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.04 (6H, s), 0.89 (9H, s), 1.59 (3H, s), 1.64 (3H, d, J = 1.0 Hz), 3.50 (2H, t, J = 7.0 Hz), 3.58 (2H, t, J = 6.8 Hz), 3.62 (2H, t, J = 6.9 Hz), 3.78 (3H, s), 4.33 (1H, m), 4.41 (2H, s), 4.53 (1H, br s), 4.62 (1H, d, J = 6.2 Hz), 4.64 (1H, br s), 4.70 (1H, d, J = 6.2 Hz), 5.08 (1H, br s), 5.12 (1H, br s), 6.87 (2H, d, J = 8.7 Hz), 7.24 (2H, d, J = 8.7 Hz), 7.28—7.38 (5H, br s). EIMS m/z: 516 ($M^+ - p$-MeO$-C_6H_4CH_2OH$). High-resolution MS Calcd for $C_{31}H_{52}O_4Si$ ($M^+ - p$-MeO$-C_6H_4CH_2OH$): 516.3635. Found: 516.3628.

Triethylamine (0.41 ml) and methanesulfonyl chloride (0.173 ml) were added sequentially to a cold (0 °C) solution of the alcohol (960 mg) in dry CH_2Cl_2 (5 ml) under an argon atmosphere. After reaction for 30 min at 0 °C, similar work-up and purification to those described for **15a** gave a methanesulfonate, which was used for the next reaction without further purification.

Sodium iodide (430 mg) was added to a solution of the crude methanesulfonate (420 mg) in dry acetone (8 ml), and the mixture was stirred for 20 h at room temperature. Similar work-up and purification to those described for **15a** gave **15b** (406 mg, 93% yield) from the alcohol. Colorless oil. $[\alpha]_D$ −45.7° (c = 1.66, $CHCl_3$). IR (film) cm^{-1}: 1613, 1513. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.05 (6H, s), 0.90 (9H, s), 1.59 (3H, s), 1.66 (3H, s), 3.12 (2H, t, J = 7.0 Hz), 3.52 (1H, t, J = 7.0 Hz), 3.66 (2H, t, J = 7.0 Hz), 3.80 (3H, s), 4.38 (1H, dd, J = 5.3, 9.5 Hz), 4.42 (2H, s), 4.51 (1H, d, J = 11.9 Hz), 4.65 (1H, d, J = 6.7 Hz), 4.72 (1H, d, J = 6.7 Hz), 5.10 (1H, d, J = 9.5 Hz), 5.16 (1H, br t, J = 6.7 Hz), 6.87 (2H, dd, J = 2.0, 8.6 Hz), 7.24 (2H, dd, J = 2.0, 8.6 Hz), 7.28—7.38 (5H, br s). EIMS m/z: 626 ($M^+ - p$-MeO$-C_6H_4CH_2 - H_2O$).

(6*E*,10*E*,12*S*,13*S*)-12-Benzyloxymethyloxy-13-(2-*tert*-butyldimethylsilyloxyethyl)-6,10-dimethyl-15-(*p*-methoxyphenyl)methyloxy-6,10-pentadecadien-2-one (16b) A 1.0 M solution of *tert*-butyllithium in pentane (1.6 ml) was added to a cold (−78 °C) solution of ethyl vinyl ether (0.6 ml) in dry THF (8 ml) and the reaction mixture was warmed to 0 °C. After

addition of HMPA (0.274 ml), the mixture was cooled to −78 °C. Then a solution of the iodide **15b** (390 mg) in dry THF (1.5 ml) was added to the mixture. Similar work-up to that described for **16a** gave a crude enol ether.

A mixture of the crude enol ether, AcOH (1.3 ml) and water (0.67 ml) in THF (4 ml) was stirred for 2 h at room temperature. After concentration of the mixture, the residue was purified by silica gel column chromatography (hexane : EtOAc = 8 : 1 as an eluent) to give **16b** (340 mg, 98% yield, 2 steps). Colorless oil. $[\alpha]_D$ −54.0° (c = 0.4, $CHCl_3$). IR (film) cm^{-1}: 1717. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.03 (6H, s), 0.88 (9H, s), 1.58 (3H, s), 1.66 (3H, s), 2.11 (3H, s), 2.36 (2H, t, J = 7.4 Hz), 3.51 (2H, t, J = 7.0 Hz), 3.66 (2H, t, J = 7.0 Hz), 3.79 (3H, s), 4.37 (1H, dd, J = 5.3, 9.6 Hz), 4.42 (2H, s), 4.51 (1H, d, J = 11.9 Hz), 4.63 (1H, d, J = 6.6 Hz), 4.68 (1H, d, J = 6.2 Hz), 4.72 (1H, d, J = 6.6 Hz), 5.09 (1H, br t, J = 5.8 Hz), 5.09 (1H, dd, J = 1.1, 9.6 Hz), 6.86 (2H, dd, J = 2.0, 7.8 Hz), 7.242 (2H, dd, J = 2.0, 7.8 Hz), 7.28—7.38 (5H, br s). EIMS m/z: 542 (M^+ − p-MeO−$C_6H_4CH_2$). High-resolution MS Calcd for $C_{25}H_{45}O_3Si$ (M^+ − p-MeO−$C_6H_4CH_2$−$C_6H_5CH_2OCH_2$): 421.3138. Found: 421.3140.

(3*R*,4*S*,5*E*,9*E*)-4-Benzyloxymethyloxy-3-(2-*tert*-butyldimethylsilyloxyethyl)-6,10-dimethyl-14-oxo-5,9-pentadecadienoic Acid (23) A mixture of the methyl ketone **16b** (100 mg), DDQ (56 mg) and water (0.1 ml) in CH_2Cl_2 (2 ml) was stirred for 1.5 h at room temperature. Saturated $NaHCO_3$ solution (1 ml) was then added and the mixture was stirred for 30 min. The mixture was diluted with a 3 : 1 mixture of ether and CH_2Cl_2, washed with water and saturated NaCl solution, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane : EtOAc = 10 : 1 as an eluent) to give an alcohol (73 mg, 89% yield). Colorless oil. $[\alpha]_D$ −58.5° (c = 0.61, $CHCl_3$). IR (film) cm^{-1}: 3464, 1715. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.04 (6H, s), 0.88 (9H, s), 1.57 (3H, s), 1.67 (3H, s), 2.10 (3H, s), 2.35 (2H, t, J = 7.4 Hz), 3.68 (4H, m), 4.38 (1H, dd, J = 5.0, 9.7 Hz), 4.51 (1H, d, J = 11.9 Hz), 4.64 (1H, d, J = 6.8 Hz), 4.66 (1H, d, J = 11.9 Hz), 4.72 (1H, d, J = 6.8 Hz), 5.08 (1H, br t, J = 6.6 Hz), 5.11 (1H, dd, J = 1.1, 9.7 Hz), 7.28—7.38 (5H, br s). EIMS m/z: 422 (M^+ − $C_6H_5CH_2OCH_2OH$).

Powdered molecular sieves (4 Å, 100 mg) and PDC (98 mg) were added sequentially to a solution of the alcohol (73 mg) in dry CH_2Cl_2 (10 ml), and the mixture was stirred for 2 h at room temperature under an argon atmosphere. The mixture was diluted with dry ether and passed through a short silica gel column (ether as an eluent). The eluate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane : EtOAc = 10 : 1 as an eluent) to give an aldehyde (58 mg, 80% yield). Colorless oil. $[\alpha]_D$ −58.9° (c = 0.98, $CHCl_3$). IR (film) cm^{-1}: 1719. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.03 (6H, s), 0.88 (9H, s), 1.57 (3H, s), 1.67 (3H, s), 2.11 (3H, s), 2.34 (1H, ddd, J = 2.2, 6.1, 15.9 Hz), 2.35 (2H, t, J = 7.4 Hz), 2.53 (1H, ddd, J = 2.2, 6.1, 15.9 Hz), 3.64 (2H, t, J = 6.5 Hz), 4.42 (1H, dd, J = 5.4, 9.7 Hz), 4.51 (1H, d, J = 11.9 Hz), 4.62 (1H, d, J = 6.7 Hz), 4.64 (1H, d, J = 11.9 Hz), 4.69 (1H, d, J = 6.7 Hz), 5.03 (1H, dd, J = 1.0, 9.7 Hz), 5.07 (1H, br t, J = 6.5 Hz), 7.28—7.38 (5H, br s), 9.71 (1H, t, J = 2.2 Hz). EIMS m/z: 558 (M^+).

2-Methyl-2-butene (0.1 ml) a solution of sodium chlorite (47 mg) in water (0.3 ml) and a solution of sodium dihydrogen phosphate (65 mg) in water (0.4 ml) were added sequentially to a solution of the above aldehyde (58 mg) in *tert*-BuOH (3 ml). After being stirred for 30 min at room temperature, the mixture was diluted with a 3 : 1 mixture of EtOAc and CH_2Cl_2, washed with water and saturated NaCl solution, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane : EtOAc = 1 : 1 as an eluent) to give **23** (60 mg, quantitative yield). Colorless oil. $[\alpha]_D$ −61.2° (c = 0.311, $CHCl_3$). IR (film) cm^{-1}: 3500—2500, 1720, 1710. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.05 (6H, s), 0.89 (9H, s), 1.58 (3H, s), 1.66 (3H, s), 2.12 (3H, s), 2.37 (2H, t, J = 7.3 Hz), 2.59 (1H, dd, J = 6.2, 15.8 Hz), 3.67—3.73 (2H, m), 4.45 (1H, dd, J = 5.7, 9.5 Hz), 4.52 (1H, d, J = 11.9 Hz), 4.65 (1H, d, J = 6.8 Hz), 4.67 (1H, d, J = 11.9 Hz), 4.72 (1H, d, J = 6.8 Hz), 5.07 (1H, br d, J = 9.5 Hz), 5.08 (1H, br t, J = 6.7 Hz), 7.26—7.34 (5H, m). CIMS m/z: 575 (M^+ + 1).

(3*R*,4*S*,5*E*,9*E*)-3-(2-*tert*-Butyldimethylsilyloxyethyl)-6,10-dimethyl-4,14-dihydroxy-5,9-pentadecadienoic Acid γ-Lactone (24) Lithium (about 200 mg) was added portionwise to a cold (−78 °C) solution of **23** (205 mg) in a mixture of THF (2 ml) and liquid ammonia (30 ml), and the mixture was stirred for 30 min at −78 °C. After addition of NH_4Cl (0.5 g), ammonia was evaporated off at room temperature. To the residue, sodium dihydrogen phosphate solution (3 ml) was added, and the mixture was extracted with a mixture of EtOAc and CH_2Cl_2. The solution was washed with water and saturated NaCl solution, dried over anhydrous $MgSO_4$, and concentrated undeer reduced pressure. The residue was dissolved in EtOAc (40 ml), and CSA (2 mg) was added to the solution. The mixture was stirred for 1 h at 60 °C, and pyridine (0.3 ml) was then added. The mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane : EtOAc = 4 : 1 as an eluent) to give **24** (145 mg, 93% yield) as a diastereomeric mixture at C-14. Colorless oil. IR (film) cm^{-1}: 3450, 1776. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.03 (6H, s), 0.88 (9H, s), 1.18 (3H, d, J = 6.2 Hz), 3.79 (1H, m), 5.27 (1H, dd, J = 7.0, 9.5 Hz). EIMS m/z: 438 (M^+). High-resolution MS Calcd for $C_{25}H_{45}O_4Si$ (M^+ − 1): 437.3087. Found: 437.3037.

(3*R*,4*S*,5*E*,9*E*)-14-Acetyloxy-3-(2-*tert*-butyldimethylsilyloxyethyl)-6,10-dimethyl-4-hydroxy-2-methylene-5,9-pentadecadienoic Acid γ-Lactone (25) A 1.33 M solution of butyllithium in hexane (0.536 ml) was added dropwise to a cold (0 °C) solution of diisopropylamine (77 μl) in dry THF (3 ml) under an argon atmosphere, the mixture was stirred for 10 min at 0 °C and cooled to −78 °C. Then the lactone **24** (52 mg) was added to the mixture. After 40 min at −78 °C, gaseous formaldehyde was passed through the mixture at −30 °C and the mixture was further stirred for 5 min at this temperature, then diluted with ether, washed with saturated NH_4Cl solution and saturated NaCl solution, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane : EtOAc = 4 : 1 as an eluent) to give a β-hydroxylactone (41 mg, 71% yield).

Acetic anhydride (0.15 ml), 4-dimethylaminopyridine (5 mg) and pyridine (0.2 ml) were added to a solution of the β-hydroxylactone (30 mg) in dry CH_2Cl_2 (0.5 ml). After being stirred for 1 h at room temperature the mixture was concentrated under reduced pressure. The residue was dissolved in an 8 : 1 mixture of hexane and EtOAc and passed through a short silica gel column. The eluate was concentrated under reduced pressure to give a crude acetate (17 mg).

The mixture of the crude acetate (17 mg) and DBU (20 μl) in dry benzene was stirred for 1 h at 50 °C, then diluted with ether, washed with water and saturated NaCl solution, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane : EtOAc = 6 : 1 as an eluent) to give α-methylene-γ-lactone **25** (14 mg, 95% yield) as a diastereomeric mixture. Colorless oil. IR (film) cm^{-1}: 1769, 1736, 1667. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.03 (6H, s), 0.87 (9H, s), 1.18 (3H, d, J = 6.3 Hz), 1.55 (3H, s), 1.72 (3H, d, J = 1.2 Hz), 2.00 (3H, s), 3.60 (2H, m), 4.87 (1H, m), 5.05 (1H, br t, J = 6.8 Hz), 5.11 (1H, br d, J = 9.5 Hz), 5.28 (1H, dd, J = 7.5, 9.5 Hz), 5.55 (1H, d, J = 2.4 Hz), 6.23 (1H, d, J = 2.7 Hz). EIMS m/z: 493 (M^+ + 1).

(+)-Mayolide A (1) A 1.0 M solution of DIBAH in hexane (0.036 ml) was added to a cold (−78 °C) solution of **25** (12 mg) in dry THF (0.8 ml) under an argon atmosphere, and the mixture was stirred at −78 °C for 20 min. After addition of three drops of MeOH, the mixture was stirred for 10 min. The resulting mixture was diluted with ether and saturated NaCl solution (1 ml), and stirred for 45 min at room temperature, then the ethereal layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue (10.2 mg) was used for the next reaction without further purification.

Powdered molecular sieves (4 Å, 11 mg) and PDC (11 mg) were added sequentially to a solution of the residue (6 mg) obtained above in CH_2Cl_2 (1 ml), and the mixture was stirred at room temperature for 1.5 h under an argon atmosphere. The mixture was diluted with ether and passed through a short silica gel column. The eluate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane : EtOAc = 5 : 1 as an eluent) to give a keto lactone (4.3 mg, 67% yield from **25**).

A 1.0 M solution of tetrabutylammonium fluoride in THF–H_2O (9 : 1) (0.02 ml) was added to a solution of the keto lactone (3.5 mg) in THF (0.015 ml). After being stirred for 15 min at room temperature, the mixture was diluted with ether, washed with water and saturated NaCl solution, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel PTLC (hexane : CH_2Cl_2 : EtOAc = 2 : 2 : 5 as a development solvent) to give (+)-mayolide A (**1**) (1.8 mg, 69% yield). Colorless oil. $[\alpha]_D$ −56.4° (c = 0.075, $CHCl_3$). IR (film) cm^{-1}: 3475, 1763, 1714, 1667, 956. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.58 (3H, br s), 1.74 (3H, s), 1.95 (2H, t, J = 7.7 Hz), 2.14 (3H, s), 2.39 (2H, t, J = 7.7 Hz), 3.30 (1H, m), 3.70 (2H, m), 5.05 (1H, dt, J = 1.0, 6.7 Hz), 5.13 (1H, dd, J = 1.1, 9.6 Hz), 5.34 (1H, dd, J = 7.4, 9.6 Hz), 5.59 (1H, d, J = 2.4 Hz), 6.27 (1H, d, J = 2.7 Hz). EIMS m/z: 334 (M^+), 316 (M^+ − H_2O). High-resolution MS Calcd for $C_{20}H_{28}O_3$ (M^+ − H_2O): 316.2038. Found: 316.2041.

Acknowledgement We thank Dr. M. Kobayashi, Hokkaido University, for providing a sample of natural mayolide A.

References and Notes

1) M. Kobayashi, *Chem. Pharm. Bull.*, **36**, 488 (1988).
2) H. Nagaoka, M. Iwashima, H. Abe and Y. Yamada, *Tetrahedron Lett.*, **30**, 5911 (1989).
3) N. Minami, S. S. Ko and Y. Kishi, *J. Am. Chem. Soc.*, **104**, 1109 (1982); J. A. Marshall, J. D. Trometer, and D. G. Crealy, *Tetrahedron*, **45**, 391 (1989); H. Matsunaga, T. Sakamaki, H. Nagaoka and Y. Yamada, *Tetrahedron Lett.*, **24**, 3009 (1983).
4) K. Ohsawa, H. Abe, Y. Hashiura, H. Nagaoka and Y. Yamada, 103rd Annual Meeting of the Pharmaceutical Society of Japan, Tokyo Abstracts of Papers, April 1983, p. 160; B. Hafele and V. Jager, *Justus Liebigs Ann. Chem.*, **1987**, 86.
5) Similar stereoselective reactions have been reported. For example: K. Tomioka, T. Ishiguro and K. Koga, *Tetrahedron Lett.*, **21**, 2973 (1980); J. P. Vigneron, R. Meric, M. Larcheveque, A. Debal, G. Kunesch, P. Zagatti and M. Gallois, *ibid.*, **25**, 5051 (1982); S. Hanessian and P. J. Murray, *J. Org. Chem.*, **52**, 1170 (1987).
6) D. Swern, A. J. Mancuso and S. L. Hung, *J. Org. Chem.*, **43**, 2480 (1978).
7) R. E. Ireland and D. J. Dawson, "Organic Syntheses," Coll. Vol. VI, ed. by W. E. Nolant, John Wiley and Sons, Inc., New York, 1988, p. 298.
8) Y. Oikawa, T. Yoshida and O. Yonemitsu, *Tetrahedron Lett.*, **23**, 885 (1982).
9) B. S. Bal, W. E. Childers, Jr. and H. W. Pinnick, *Tetrahedron*, **37**, 2091 (1981).