Total Synthesis of Potent Antitumor Macrolides Pladienolides B and D

Regina M. Kanada, Daisuke Itoh, Mitsuo Nagai, Jun Niijima, Naoki Asai, Yoshiharu Mizui, Shinya Abe, Yoshihiko Kotake*

Discovery Research Laboratories II, Eisai Co., Ltd.
5-1-3 Tokodai, Tsukuba, Ibaraki, 300-2635, Japan

Supplementary Figures

Figure S1. Proposed mechanism of epoxide opening by neighboring acetoxy group.

Figure S2. NOESY correlations in bicyclic acetals 31a and 31b. Vicinal J-Value in Hz, 31a: H18/H19=10, H19/H20=0, H20/H21=2, 31b: H18/H19=4, H19/H20=10.
Experimental Section

General

Dry THF and dry CH<sub>2</sub>C1<sub>2</sub> were used during this synthesis (Kanto Chemical (Cat.-No. 40993) and Kanto Chemical (Cat.-No. 11338), respectively), unless otherwise stated. Other solvents and reagents were reagent grade and were used without purification unless otherwise stated. Silica gels for column chromatography were purchased from Kanto Chemical (Kanto Chemical Co., Inc., Silica gel 60N, spherical neutral, 0.040-0.100 mm, Cat.-No.37561) and Merck (Silica Gel 60, 0.040-0.063 mm, Cat.-No. 109385) unless otherwise stated.

Melting points (m.p.) were measured by Yanaco micro melting point apparatus and are not corrected. Unless otherwise stated, infrared (IR) spectra were recorded as films on NaCl plates on JASCO FT/IR 620 spectrometer. ¹H-NMR spectra were recorded at 400 MHz or 600 MHz and ¹³C-NMR spectra were recorded at 100 MHz or 150 MHz, on Varian Mercury Plus 400 or Bruker AVANCE 600 spectrometer. The chemical shifts are expressed in ppm downfield from internal tetramethylsilane or internal solvent peaks CHCl<sub>3</sub> (7.24 ppm, ¹H-NMR), CD<sub>3</sub>OD (3.35 ppm, ¹H-NMR), CHCl<sub>3</sub> (77.0 ppm, ¹³C-NMR), CD<sub>3</sub>OD (49.0 ppm, ¹³C-NMR) or Acetone-­‐d₆ (29.3 ppm, ¹³C-NMR) and J values are given in hertz. High resolution mass spectra (HRMS) were recorded on Micromass Q-TOF Ultima Global spectrometer. Optical rotations were measured by JASCO DIP 1000 digital polarimeter.

Abbreviations

PMB = p-­‐methoxybenzyl, TBAI = tetrabutylammonium iodide, TMS = trimethylsilyl, TBS = tert-­‐butyl-­‐dimethylsilyl, PPTS = pyridinium p-­‐toluenesulfonate, DDQ = 2,3-­‐dichloro-­‐5,6-­‐dicyano-­‐1,4-­‐benzoquinone, DMP = Dess-­‐Martin periodinane, Bz = benzoyl, Cy = cyclohexyl, Tf = trifluoromethanesulfonyl, DMAP = 4-­‐dimethylaminopyridine, 2nd generation Hoveyda-­‐Grubbs catalyst = [1,3-­‐bis(2,4,6-­‐trimethylphenyl)-­‐2-­‐imidazolidinylidene]dichloro[O-­‐isopropoxyphenylmethylidene] rutenium, BHT = 2,6-­‐di-­‐ tert-­‐butyl-­‐4-­‐methylphenol, DIBAL = diisobutylaluminum hydride, Bn = benzyl, DIAD = diisopropyl azodicarboxylate, TES = triethylsilyl, KHMDS = potassium hexamethyldisilazide, EDTA = ethylenediaminetetraacetic acid, DEIPS = diethylisopropylsilyl, TBAF = tetrabutylammonium fluoride, LAH = lithium aluminum hydride, de = diastereomeric excess, CSA = camphorsulfonic acid, DME = 1,2-­‐dimethoxyethane, DET = diethyl tartrate, Ts = p-­‐toluenesulfonyl, Tebbe reagent = μ-­‐chloro-­‐μ-­‐methylene[ bis(cyclopentadienyl) titanium] dimethylaluminum, 2nd generation Grubbs catalyst = tricyclohexylphosphine[1,3-­‐bis(2,4,6-­‐trimethylphenyl)-­‐2-­‐imidazolidinylidene] [benzylidene] ruthenium(IV) dichloride.
Experimental Procedures and Compounds Characterization

Total synthesis of pladienolide B

< Synthesis of C1-C8 unit >

1-(((2Z)-3,7-dimethylocta-2,6-dien-1-y]oxy)methyl)-4-methoxybenzene (S1)

Nerol (150 g, 972 mmol) was added dropwise to a stirred suspension of NaH (60% oil dispersion, 38.9 g, 973 mmol) in DMF (1.5 L), and the mixture was stirred under nitrogen stream at RT for 1 hr. After the reaction mixture was cooled to 0°C, TBAH (35.9 g, 97.2 mmol) was added in a portion and then PMBCl (148 g, 926 mmol) was added dropwise. The reaction mixture was stirred at 0°C for 4 hr and then at RT for 6 hr. Water was added to the reaction mixture, which was then extracted with heptane. The organic layer was washed with water and brine sequentially, dried over MgSO₄, and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (Kanto Chemical; heptane : EtOAc = 1 : 0 → 30 : 1 → 25 : 1) to give S1 (246.7 g, 97%) as a colorless oil. 400 MHz ¹H-NMR (CDCl₃) δ (ppm) 1.58 (s, 3H), 1.67 (s, 3H), 1.75 (d, J = 1.2 Hz, 3H), 2.00-2.12 (m, 4H), 3.80 (s, 3H), 3.97 (dd, J = 1.0, 7.0 Hz, 1H), 4.43 (s, 2H), 5.04-5.12 (m, 1H), 5.40 (dt, J = 1.2, 6.8 Hz, 2H), 6.85-6.89 (m, 2H), 7.25-7.28 (m, 2H); 100 MHz ¹³C-NMR (CDCl₃) δ (ppm) 17.49, 23.36, 25.56, 26.59, 32.13, 55.06, 65.96, 71.62, 113.59, 121.82, 123.79, 129.24, 130.55, 131.69, 140.31, 159.00; IR (film) 2964, 2913, 2855, 1612, 1512, 1247, 1093, 1067, 1037, 819 cm⁻¹; HRMS C₁₈H₂₇O₂ (M+H⁺) Calcd : 275.2011, Found : 275.2003.

(4Z)-6-[(4-Methoxybenzyl)oxy]-4-methylhex-4-enal (5)[][]

O₂ was bubbled into a stirred solution of S1 (75.0 g, 273 mmol) in CH₂Cl₂ (1.13 L) and pyridine (11.3 mL) for 170 min (flow rate 2 L/min, electric voltage 90 V) at −78°C. Dimethylsulfide (80.3 mL, 1.09 mol) was added to the solution and allowed to warm to RT with stirring overnight. The reaction mixture was concentrated under reduced pressure and the obtained residue was purified by silica gel column chromatography (Kanto Chemical; heptane : EtOAc = 4 : 1) to give 5 (36.9 g, 67%, based on recovery) as a colorless oil and recovered S1 (14.1 g). 400 MHz ¹H-NMR (CDCl₃) δ (ppm) 1.75 (s, 3H), 2.36 (t, J = 7.6 Hz, 2H), 2.47-2.55 (m, 2H), 3.81 (s, 3H), 3.98 (d, J = 6.7 Hz, 2H), 4.43 (s, 2H), 5.46 (brt, J = 6.7 Hz, 1H), 6.86-6.90 (m, 2H), 7.25-7.27 (m, 2H), 9.75 (t, J = 1.2 Hz, 1H); 100 MHz ¹³C-NMR (CDCl₃) δ (ppm) 22.99, 24.34, 42.11, 55.09, 65.61, 71.82, 113.62, 122.97, 129.29, 130.25, 138.43, 159.04, 201.63; IR (film) 2935, 2835, 2727, 1722, 1612, 1514, 1249, 1072, 1035, 819 cm⁻¹; HRMS C₁₈H₂₉NaO₃ (M+Na⁺) Calcd : 271.1310, Found : 271.1322.

(4R)-3-[3R,6Z]-3-Hydroxy-8-[(4-methoxybenzyl)oxy-6-methyloct-6-enoyl]-4-isopropyl-1,3-oxazolidin-2-one (7)[][]

CH₂Cl₂ (1.20 mL, 14.9 mmol) was added to a suspension of SM powder (45.0 g, 299 mmol) in dry THF (200 mL, freshly distilled from LAH before use) at RT under nitrogen atmosphere, and a solution of CH₂Cl₂ (21.0 mL, 261
mmol) in dry THF (700 mL) was added dropwise to the mixture over 100 min. The reaction mixture was stirred at RT for 2 hr and then cooled to −78°C. A mixture of 5 (28.4 g, 115 mmol) and (R)-N-bromoacetyl-4-isopropyl-2-oxazolidinone 6 (30.1 g, 120 mmol) in dry THF (280 mL) was added dropwise to the reaction mixture at such a rate that the reaction mixture temperature was kept below −72°C. After the reaction mixture was stirred at −78°C for additional 1 hr and then warmed to RT. The reaction was quenched by adding 0.5N HCl (300 mL) with stirring. Additional 0.5N HCl (700 mL) was added and the reaction mixture was extracted with EtOAc. The organic layer was washed with 5% aq. Na2SO3 solution, water and brine sequentially, dried over MgSO4 and evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (Kanto Chemical; heptane : EtOAc = 3 : 1 → 2 : 1 → 3 : 2 → 3 : 2 → 1 : 1) to give 7 (43.4 g, 90%, >98% de) as a yellow oil. The de was determined by HPLC (DAICEL CHEMICHAL INDUSTRIES, CHIRALCEL OD; hexane : isopropyl alcohol = 4 : 1). 400 MHz 1H-NMR (CDCl3) δ (ppm) 0.87 (d, J = 7.2 Hz, 3H), 0.92 (d, J = 7.2 Hz, 3H), 1.56-1.64 (m, 2H), 1.76 (s, 3H), 2.08-2.18 (m, 1H), 2.30-2.40 (m, 2H), 2.98 (dd, J = 9.2, 16.9 Hz, 1H), 3.13 (dd, J = 2.9, 16.9 Hz, 1H), 3.26 (d, J = 4.4 Hz, 1H), 3.80 (s, 3H), 3.93 (dd, J = 7.2, 10.8 Hz, 1H), 4.01-4.08 (m, 2H), 4.21 (dd, J = 3.2, 9.2 Hz, 1H), 4.27 (t, J = 9.2 Hz, 1H), 4.40-4.49 (m, 1H), 4.44 (s, 2H), 5.46 (brt, J = 6.6 Hz, 1H), 6.86-6.89 (m, 2H), 7.26-7.29 (m, 2H); 100 MHz 13C-NMR (CDCl3) δ (ppm) 14.55, 17.79, 23.09, 27.73, 28.34, 34.38, 42.58, 55.10, 58.25, 63.37, 65.59, 66.76, 71.75, 113.59, 122.02, 129.39, 130.26, 140.64, 153.95, 159.01, 172.18; IR (film) 3455, 2963, 1781, 1699, 1514, 1388, 1303, 1248, 1207, 1061, 1034 cm⁻¹; HRMS C23H34N2NaO3 (M+Na⁺) Calcd : 442.2206, Found : 442.2197; [α]D22 −60.2 (c 1.06, CHCl3).

Methyl (3R,6Z)-3-[[4-tert-butyl(dimethyl)silyl]oxy]-8-[[4-methoxybenzyl]oxy]-6-methyloct-6-enoate (8)

To a stirred solution of 7 (14.6 g, 34.8 mmol) in THF (175 mL), LiOH (2.50 g, 104 mmol) and 30% H2O2 (11.8 mL) in water (43.0 mL) was added at 0°C, and the mixture was stirred at RT for 13 hr. LiOH (3.75 g, 156 mmol) and 30% H2O2 (17.7 mL) in water (20.0 mL) was further added, and the reaction mixture was stirred for additonal 2 hr. Na2SO3 (21.0 g, 165 mmol) was added at 0°C and the mixture was stirred at RT for 5 min. The reaction mixture was diluted with water and then washed with CHCl3. The aqueous layer was acidified with 2N HCl and extracted with EtOAc. The EtOAc layer was washed with water and brine sequentially, dried over MgSO4, and evaporated under reduced pressure. The obtained residue was dissolved in THF (220 mL)-MeOH (22.0 mL) and cooled to 0°C. TMS diazomethane (2M hexane solution, 22.6 mL, 45.1 mmol) was added to the solution and stirred at 0°C for 40 min and then at RT for 30 min. Acetic acid (1.0 mL) was added to the mixture and stirred at RT for 30 min. The reaction mixture was concentrated under reduced pressure. The obtained residue was dissolved in DMF (80 mL), imidazole (7.09 g, 104 mmol) and TBSCI (7.85 g, 52.1 mmol) were added and the mixture was stirred at RT for 14 hr. The reaction mixture was poured into water, and extracted with EtOAc. The organic layer was washed with water and brine sequentially, dried over MgSO4, and evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (Kanto Chemical; heptane : EtOAc = 6 : 1) to give 8 (12.9 g, 85%, 3 steps) as a colorless oil. 400 MHz 1H-NMR (CDCl3) δ (ppm) 0.03 (s, 3H), 0.06 (s, 3H), 0.87 (s, 9H), 1.51-1.58 (m, 2H), 1.74 (brs, 3H), 1.96-2.05 (m, 1H), 2.08-2.18 (m, 1H), 2.39 (dd, J = 5.6, 14.1 Hz, 1H), 2.46 (dd, J = 7.2, 14.4 Hz, 1H), 3.66 (s,
Methyl 3-O-[tert-butyl (dimethyl)silyl]-2,4,5-trideoxy-8-O-(4-methoxybenzyl)-6-C-methyl-1-arabino-octonate (S2)

A mixture of AD-mix-α (181 g) and methanesulfonylimide (12.4 g, 130 mmol) in rBuOH (700 mL)-water (700 mL) was stirred at 0°C for 30 min. To this mixture was added 8 (56.8 g, 130 mmol) in rBuOH (150 mL) - water (150 mL) and stirred at 0°C for 11 hr. Na₂SO₃ (197 g, 1.56 mol) was added to the reaction mixture and stirred at RT. The mixture was diluted with water and then extracted with EtOAc. The organic layer was washed with water and brine sequentially, dried over MgSO₄, and evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (Kanto Chemical; heptane : EtOAc = 3 : 1) to give S2 (56.3 g, 92%, 76% de) as a colorless oil. The de was determined by HPLC (DAICEL CHEMICAL INDUSTRIES, CHIRALCEL OD; hexane : isopropyl alcohol = 95 : 5). Data of the major product: 400 MHz ¹H-NMR (CDCl₃) δ (ppm) 0.04 (s, 3H), 0.06 (s, 3H), 0.87 (s, 3H), 1.17 (s, 3H), 1.24-1.40 (m, 3H), 1.46-1.68 (m, 3H), 1.46-1.68 (m, 3H), 2.39 (dd, J = 5.6, 14.8 Hz, 1H), 2.45 (dd, J = 6.8, 14.8 Hz, 1H), 2.66 (s, 1H), 2.73 (d, J = 4.8 Hz, 1H), 3.54-3.66 (m, 3H), 3.66 (s, 3H), 3.81 (s, 1H), 4.09-4.18 (m, 1H), 4.46 (d, J = 11.2 Hz, 1H), 4.50 (d, J = 11.2 Hz, 1H), 6.87-6.91 (m, 2H), 7.23-7.27 (m, 2H); 100 MHz ¹³C-NMR (CDCl₃) δ (ppm) -4.99, -4.57, 17.85, 23.03, 25.66, 30.94, 32.86, 42.00, 51.40, 55.14, 69.40, 70.81, 73.24, 73.39, 74.78, 113.81, 129.41, 129.50, 159.32, 172.02; IR (film) 3481, 2953, 2931, 1739, 1514, 1251, 1173, 1084, 1038, 835, 777 cm⁻¹; HRMS C₂₉H₄₄NaO₇Si (M+Na⁺) Calcd : 493.2598, Found : 493.2556.

Methyl 6,7-O-benzylidene-3-O-[tert-butyl (dimethyl)silyl]-2,4,5-trideoxy-8-O-(4-methoxybenzyl)-6-C-methyl-1-arabino-octonate (S3)

To a stirred solution of S2 (5.00 g, 10.6 mmol) in CH₂Cl₂ (90 mL), benzaldehyde dimethyl acetal (9.55 mL, 63.6 mmol) and PPTS (133 mg, 0.53 mmol) were added and stirred at RT for 23 hr. The reaction mixture was poured into saturated aq. NaHCO₃ solution and then extracted with CH₂Cl₂. The organic layer was washed with water and brine sequentially, dried over MgSO₄, and evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (Kanto Chemical; heptane : EtOAc = 5 : 1 → 2 : 1) to give S3 (5.92 g, 98%) as a colorless oil. Data of the major product: 400 MHz ¹H-NMR (CDCl₃) δ (ppm) 0.00 (s, 3H), 0.01 (s, 3H), 0.85 (s, 3H), 1.19-1.38 (m, 1H), 1.35 (s, 3H), 1.56-1.83 (m, 3H), 2.30 (dd, J = 5.2, 14.5 Hz, 1H), 2.40 (dd, J = 7.7, 14.5 Hz, 1H), 3.58 (dd, J = 5.6, 9.9 Hz, 1H), 3.64 (s, 3H), 3.68 (dd, J = 7.1, 9.9 Hz, 1H), 3.81 (s, 3H), 4.06 (dd, J = 5.0, 7.1 Hz, 1H), 4.07-4.13 (m, 1H), 4.46 (d, J = 11.4 Hz, 1H), 4.56 (d, J = 11.4 Hz, 1H), 5.88 (s, 1H), 6.86-6.90 (m, 2H), 7.25-7.28 (m, 2H), 7.33-7.37 (m, 3H), 7.43-7.47 (m, 2H); 100 MHz ¹³C-NMR (CDCl₃) δ (ppm) -5.04, -4.61, 17.84, 22.73, 25.65, 30.53, 31.18, 42.18, 51.34, 55.12, 67.74,
69.47, 73.17, 81.23, 84.81, 102.27, 113.74, 126.60, 128.14, 129.02, 129.38, 129.71, 137.84, 159.23, 172.03; IR
(film) 2953, 2930, 2857, 1739, 1514, 1250, 1092, 835, 776 cm⁻¹; HRMS C₉H₁₄O₄Si (M+Na⁺) Calcd : 

**Methyl 6,7-O-benzylidene-3-O-[tert-butyldimethylsilyl]-2,4,5-trideoxy-6-C-methyl-L-arabino-octonate (9)**

To a stirred solution of S₃ (8.80 g, 15.7 mmol) in CH₂Cl₂ (176 mL)-water (17.6 mL), DDQ (5.38 g, 23.7 mmol) was added at 0°C and stirred for 1 hr. Additional water (17.6 mL) and DDQ (2.70 g, 11.9 mmol) were added and stirred at 0°C for additional 5.5 hr. The reaction mixture was poured into aq. NaHCO₃ solution and then extracted with CH₂Cl₂. The organic layer was washed with water and brine sequentially, dried over MgSO₄, and evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (Kanto Chemical; heptane : EtOAc = 5 : 1 → 4 : 1 → 2 : 1) to give 9 (4.76 g) as a white solid. Pure 9 (4.44 g, 65%) was obtained as a colorless crystal by recrystallization from hexane. 400 MHz ¹H-NMR (CDCl₃) δ (ppm) 0.02 (s, 3H), 0.05 (s, 3H), 0.86 (s, 9H), 1.32-1.41 (m, 1H), 1.38 (s, 3H), 1.59-1.82 (m, 3H), 1.88 (dd, J = 4.0, 8.4 Hz, 1H), 2.38 (dd, J = 5.6, 14.6 Hz, 1H), 2.46 (dd, J = 7.2, 14.6 Hz, 1H), 3.65 (s, 3H), 3.73 (dd, J = 3.6, 8.4, 11.8 Hz, 1H), 3.84 (dddd, J = 4.0, 7.6, 11.8 Hz, 1H), 3.98 (dd, J = 3.6, 7.6 Hz, 1H), 4.10-4.18 (m, 1H), 5.91 (s, 1H), 7.36-7.40 (m, 3H), 7.45-7.49 (m, 2H); 100 MHz ¹³C-NMR (CDCl₃) δ (ppm) −4.94, −4.56, 17.91, 22.66, 25.71, 30.71, 31.38, 42.25, 51.47, 61.42, 69.40, 81.33, 86.38, 102.20, 126.60, 128.36, 129.29, 137.69, 172.07; IR (KBr) 3489, 2951, 2856, 1746, 1087, 1024, 836, 768, 704 cm⁻¹; HRMS C₂₉H₄₄NaO₄Si (M+Na⁺) Calcd : 461.2335, Found : 461.2368; [α]D° = 12 (c 1.21, CHCl₃); m.p. 86.0-87.0°C.

**Methyl (3R)-3-[tert-butyldimethylsilyloxy]-5-[(2S,4R,5S)-4-methyl-2-phenyl-5-vinyl-1,3-dioxolan-4-yl]pentanoate (S₄)**

To a stirred solution of 9 (10.2 g, 23.3 mmol) in CH₂Cl₂ (300 mL), DMP (12.8 g, 30.3 mmol) was added and stirred at RT for 1 hr. The reaction mixture was diluted with ether, washed with saturated aq. NaHCO₃ solution containing Na₂SO₃ and brine sequentially, dried over MgSO₄, and concentrated under reduced pressure. The obtained residue was dissolved in THF (50 mL) and added dropwise to a solution of methylene triphenylphosphorane, prepared by a conventional procedure from methyltriphenylphosphonium iodide (10.4 g, 25.7 mmol) and nBuLi (2.59M hexane solution 9.94 mL, 25.7 mmol), in dry THF (100 mL) at −15°C under nitrogen atmosphere. The reaction mixture was stirred at −15°C for 20 min and then at RT for 30 min. The reaction mixture was poured into saturated aq. NH₄Cl solution and extracted with EtOAc. The organic layer was washed with water and brine sequentially, dried over MgSO₄, and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (Kanto Chemical; heptane : EtOAc = 19 : 1 → 9 : 1) to give S₄ (7.91 g, 78%, 2 steps) as a colorless oil. 400 MHz ¹H-NMR (CDCl₃) δ (ppm) 0.00 (s, 3H), 0.02 (s, 3H), 0.85 (s, 9H), 1.25-1.36 (m, 1H), 1.35 (s, 3H), 1.55-1.72 (m, 3H), 2.34 (dd, J = 5.4, 14.6 Hz, 1H), 2.42 (dd, J = 7.4, 14.6 Hz, 1H), 3.64 (s, 3H), 4.06-4.14 (m, 1H), 4.28 (ddd, J = 1.2, 1.2, 6.8 Hz, 1H), 5.31 (ddd, J = 1.2, 1.2, 10.6 Hz, 1H), 5.42 (ddd, J = 1.2, 1.2, 17.2 Hz, 1H), 5.90 (ddd, J = 6.8, 10.6, 17.2 Hz, 1H), 5.92 (s, 1H), 7.35-7.38 (m, 3H), 7.46-7.50 (m, 2H); 100 MHz ¹³C-NMR (CDCl₃) δ (ppm) −5.05, −4.66,
(3R)-3-[(tert-Butyl(dimethyl)silyloxy)-5-[(2S,4R,5S)-4-methyl-2-phenyl-5-vinyl-1,3-dioxolan-4-yl]-pentanoic acid (10)

To a stirred solution of S4 (14.6 g, 33.6 mmol) in THF (140 mL)-MeOH (140 mL)-water (70.0 mL), LiOH (4.02 g, 168 mmol) was added and stirred at RT for 4.5 hr. The reaction mixture was poured into 0.5N HCl and extracted with EtOAc. The organic layer was washed with water and brine sequentially, dried over MgSO₄, and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (Kanto Chemical; heptane : EtOAc = 4 : 1 → 2 : 1) to give 10 (14.1 g, 82%) as a colorless oil. 400 MHz ¹H-NMR (CDCl₃) δ (ppm) 0.05 (s, 6H), 0.87 (s, 9H), 1.26-1.34 (m, 1H), 1.35 (s, 3H), 1.50-1.68 (m, 2H), 1.73-1.79 (m, 1H), 2.44 (dd, J = 5.4, 15.4 Hz, 1H), 2.48 (dd, J = 5.4, 15.4 Hz, 1H), 4.00-4.06 (m, 1H), 4.29 (dd, J = 1.2, 1.2, 6.8 Hz, 1H), 5.32 (dd, J = 1.2, 1.2, 10.1 Hz, 1H), 5.44 (dd, J = 1.2, 1.2, 17.2 Hz, 1H), 5.88 (dd, J = 6.8, 10.8, 17.2 Hz, 1H), 5.93 (s, 1H), 7.35-7.38 (m, 3H), 7.47-7.49 (m, 2H); 100 MHz ¹³C-NMR (CDCl₃) δ (ppm) −5.00, −4.63, 17.88, 22.38, 25.69, 31.18, 32.03, 41.99, 69.40, 82.18, 87.77, 102.17, 118.88, 126.59, 128.25, 129.10, 132.51, 137.90, 177.39; IR (film) 3036, 2956, 2930, 2886, 2857, 1712, 1254, 1090, 1065, 836, 776 cm⁻¹; HRMS C₂₃H₃₈NaO₅Si (M+Na⁺) Calcd : 457.2386, Found : 457.2394; [α]D²² −11.5 (c 2.26, CHCl₃).

< Synthesis of C9-C14 unit >

1-[[2E]-4,4-Dimethoxy-3-methylbut-2-en-1-yl]oxy)methyl]-4-methoxybenzene (S5)³⁵

NaH (60% oil dispersion, 407 mg, 10.2 mmol) was added to a stirred solution of triethyl phosphonoacetate (2.28 g, 10.2 mmol) in THF (20 mL) at 0°C under nitrogen atmosphere and stirred at 0°C for 15 min. Pyruvic aldehyde dimethyl acetal (1.00 g, 8.47 mmol) was added to the mixture and stirred at 0°C for 30 min and then at RT for 10 min. The reaction mixture was poured into water and extracted with hexane. The organic layer was washed with brine, and dried over MgSO₄, and concentrated under reduced pressure. The obtained residue was dissolved in THF (3.20 mL) and cooled to −78°C under nitrogen atmosphere. DIBAL (0.95M toluene solution, 21.3 mL, 20.3 mmol) was added dropwise to this solution and the mixture was stirred at −78°C for 10 min and then at RT for 30 min. The reaction mixture was ice cooled and 20% Rochelle salt solution was added and stirred vigorously for 1 hr. The mixture was extracted with EtOAc and the organic layer was washed with water and brine sequentially, dried over MgSO₄, and concentrated under reduced pressure. The obtained residue was dissolved in DME (12.0 mL) and cooled to 0°C under nitrogen atmosphere. NaH (60%, 394 mg, 9.85 mmol) was added to this solution and stirred at 0°C for 20 min. PMBCl (1.00 mL, 7.39 mmol) and NaI (1.11 g, 7.39 mmol) were added to the mixture and stirred and at RT for 45 min. Then the reaction mixture was poured into water and extracted with hexane. The organic layer washed with aq. Na₂SO₃ solution and brine sequentially, dried over MgSO₄, and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (Kanto Chemical; heptane : EtOAc = 19 : 1 → 9 : 1 → 5 : 1) to give S5 (1.52 g, 70%, 3 steps) as a colorless oil. The
geometric ratio of S5 was determined to be E/Z = 18 : 7 by $^1$H-NMR. 400 MHz $^1$H-NMR (CDCl$_3$) δ (ppm) 1.62 (d, J = 0.8 Hz, 2.1H), 1.74 (d, J = 1.2 Hz, 0.84H), 3.30 (s, 1.68H), 3.31 (s, 4.32H), 3.81 (s, 2.16H), 3.82 (s, 0.84H), 4.09 (d, J = 6, 0 Hz, 2H), 4.45 (s, 2H), 4.49 (s, 0.72H), 4.87 (s, 0.28H), 5.66 (brt, J = 6.6 Hz, 0.28H), 5.78 (brt, J = 6.2 Hz, 0.72H), 6.86-6.91 (m, 2H), 7.25-7.28 (m, 2H); 100 MHz $^{13}$C-NMR (CDCl$_3$) δ (ppm) 11.40, 17.86, 53.48, 53.68, 55.04, 65.07, 65.66, 71.75, 101.96, 106.92, 113.61, 125.84, 127.08, 129.20, 129.23, 130.18, 134.98, 135.97, 159.05; IR (film) 2934, 2834, 1514, 1249, 1112, 1072, 1036, 820 cm$^{-1}$; HRMS C$_{15}$H$_{22}$AgO$_4$ (M+Ag$^+$) Calcd : 373.0569, Found : 373.0552.

(2E)-4-[(4-Methoxybenzyl)oxy]-2-methylbut-2-enal (11)$^{[35]}$

To a stirred solution of S5 (1.52 g, 5.71 mmol) in MeCN (16.0 mL), 1N HCl (4.0 mL) was added and stirred at RT for 1 h. Subsequently, 2N HCl (4.0 mL) was added and the mixture was further stirred for 4 h. The reaction mixture was poured into saturated aq. NaHCO$_3$ solution and extracted with ether. The organic layer was washed with water and brine sequentially, dried over MgSO$_4$, and concentrated under reduced pressure to give 11 (1.52 g, 95%) as a colorless oil (During the reaction, the isomerization of olefin was occurred).$^{[35]}$ 400 MHz $^1$H-NMR (CDCl$_3$) δ (ppm) 1.73 (dt, J = 1.2, 1.2 Hz, 3H), 3.82 (s, 3H), 4.32 (dq, J = 1.2, 5.6 Hz, 2H), 4.52 (s, 2H), 6.60 (tq, J = 1.2, 5.6 Hz, 1H), 6.88-6.92 (m, 2H), 7.26-7.30 (m, 2H), 9.44 (s, 1H); 100 MHz $^{13}$C-NMR (CDCl$_3$) δ (ppm) 9.20, 54.94, 66.17, 72.45, 113.63, 129.24, 129.32, 139.04, 149.47, 159.18, 194.10; IR (film) 2837, 1688, 1612, 1512, 1249, 1074, 1033, 820 cm$^{-1}$; HRMS C$_{14}$H$_{18}$NaO$_3$ (M+Na$^+$) Calcd : 243.0997, Found : 243.1044.

(1S,3R,4S,5E)-4-Hydroxy-7-[(4-methoxybenzyl)oxy]-1,3,5-trimethyl-2-oxohept-5-en-1-yl benzoate (S6)$^{[14]}$

N,N-dimethylethylamine (24.0 mL, 221 mmol) was added to a stirred solution of Cy$_2$BCl (38.8 mL, 177 mmol)$^{[36]}$ in dry ether (500 mL, freshly distilled from LAH before use) under nitrogen atmosphere at −78°C and the mixture was stirred for 15 min. Then a solution of 12 (30.4 g, 148 mmol) in dry ether (400 mL) was added dropwise over 35 min, and the mixture was stirred at −78°C for 10 min and then at 0°C for 2 h. Then the reaction mixture was cooled to −78°C again and a solution of 11 (27.0 g, 123 mmol) in dry ether (400 mL) was added dropwise over 20 min, and the mixture was stirred at −78°C for 2 h and then at −26°C for overnight. The reaction mixture was warmed to 0°C, MeOH (400 mL), phosphate buffer (pH = 7, 400 mL) and 30% H$_2$O$_2$ (350 mL) were added sequentially, and the resulting mixture was stirred at 0°C for 1 h. The reaction mixture was poured into water and extracted with EtOAc. The organic layer was washed with water and brine sequentially, dried over MgSO$_4$, and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (Kanto Chemical; heptane : EtOAc = 4 : 1 → 2 : 1). The obtained white solid was purified by recrystallization (hexane/EtOAc) to give S6 (42.6 g, 81%, >99% de) as a colorless needle. The de was determined by HPLC (DAICEL CHEMICAL INDUSTRIES, CHIRALCEL OD; hexane : isopropyl alcohol = 95 : 5). 400 MHz $^1$H-NMR (CDCl$_3$) δ (ppm) 1.07 (d, J = 7.2 Hz, 3H), 1.57 (d, J = 7.2 Hz, 3H), 1.63 (s, 3H), 2.02 (d, J = 3.8 Hz, 1H), 3.04 (dq, J = 7.2, 9.2 Hz, 1H), 3.81 (s, 3H), 3.80-4.10 (m, 2H), 4.24 (dd, J = 3.8, 9.2 Hz, 1H), 4.44 (s, 2H), 5.45 (q, J = 7.2 Hz, 1H), 5.65 (brt, J = 6.4 Hz, 1H), 6.86-6.90 (m, 2H), 7.24-7.28 (m, 2H), 7.44-7.47 (m, 2H), 7.56-7.61 (m, 1H), 8.07-8.10 (m, 2H); 100 MHz $^{13}$C-NMR (CDCl$_3$) δ (ppm) 11.07,
To a stirred solution of S6 (70.0 g, 164 mmol) and 2,6-lutidine (38.2 mL, 328 mmoll) in dry CH₂Cl₂ (1.0 L), TBSOTf (56.5 mL, 246 mmol) was added dropwise for 10 min at −78°C under nitrogen atmosphere and stirred for 1.5 hr. After addition of saturated aq. NaHCO₃ solution, the mixture was warmed to RT and then extracted with CH₂Cl₂. The organic layer was washed with water and brine sequentially, dried over MgSO₄, and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (Kanto Chemical; heptane : EtOAc = 8 : 1) to afford 13 (89.0 g, quant.) as a colorless oil. 400 MHz ¹H-NMR (CDCl₃) δ (ppm) −0.02 (s, 3H), −0.01 (s, 3H), 0.82 (s, 9H), 0.97 (d, J = 7.2 Hz, 3H), 1.54 (d, J = 7.2 Hz, 3H), 1.58 (s, 3H), 3.00 (dq, J = 7.2, 9.6 Hz, 1H), 3.81 (s, 3H), 4.04 (d, J = 6.0 Hz, 2H), 4.28 (d, J = 9.6 Hz, 1H), 4.43 (s, 2H), 5.43 (q, J = 7.2 Hz, 1H), 5.59 (brt, J = 6.0 Hz, 1H), 6.86-6.90 (m, 2H), 7.24-7.27 (m, 2H), 7.43-7.47 (m, 2H), 7.56-7.60 (m, 1H), 8.07-8.09 (m, 2H); 100 MHz ¹³C-NMR (CDCl₃) δ (ppm) −5.17, −4.78, 10.79, 14.54, 15.17, 18.01, 25.75, 46.17, 55.21, 65.83, 71.72, 75.20, 80.54, 113.75, 126.24, 128.36, 129.22, 129.66, 129.76, 130.35, 133.16, 138.11, 159.15, 165.68, 209.02; IR (film) 2954, 2931, 2856, 1721, 1512, 1453, 1301, 1250, 1117, 1070, 1040, 837, 778, 713 cm⁻¹; HRMS C₃₅H₃₉NaO₇Si (M+Na⁺) Calcd : 563.2805, Found : 563.2786; [α]D²⁵ +12.6 (c 1.01, CHCl₃).

tert-Butyl[(1S,2E)-4-[(4-methoxybenzyl)oxy]-2-methyl-1-[(1S)-1-methylprop-2-en-1-yl]but-2-en-1-yl]oxy)-dimethylsilane (S7)[¹⁴]

To a stirred solution of 13 (1.00 g, 1.85 mmol) in THF (10.0 mL), LiBH₄ (2M THF solution, 18.5 mL, 37.0 mmol) was added at −78°C under nitrogen atmosphere and stirred overnight at an ambient temperature. The reaction mixture was ice cooled, added water, and extracted with EtOAc. The organic layer was washed with water and brine sequentially, dried over MgSO₄, and concentrated under reduced pressure to obtain a white solid (611 mg). The obtained white solid (300 mg) was dissolved in THF-water (4 : 1, 6.0 mL), and NaI₂O₄ (438 mg, 2.05 mmol) was added to the solution and stirred at RT for 1.5 hr. The reaction mixture was poured into water and extracted with EtOAc. The organic layer was washed with water and brine sequentially, dried over MgSO₄, and concentrated under reduced pressure. The obtained residue was dissolved in THF (4.0 mL) and added dropwise to a solution of methylenetriphenylphosphorane in THF (4.0 mL), prepared by a conventional procedure from methyltriphenylphosphonium iodide (415 mg, 1.02 mmol) and nBuLi (2.59M hexane solution, 397 µL, 1.03 mmol), under nitrogen atmosphere at −15°C. The reaction mixture was stirred at −15°C for 1 hr and poured into water, and extracted with EtOAc. The organic layer was washed with water and brine sequentially, dried over MgSO₄, and concentrated under reduced pressure. The obtained residue was purified by silica gel column
chromatography (Kanto Chemical; heptane : EtOAc = 19 : 1) to give S7 (258 mg, 73%, 3 steps) as a colorless oil. 400 MHz $^1$H-NMR (CDCl$_3$) $\delta$ (ppm) = 0.03 (s, 3H), 0.02 (s, 3H), 0.87 (d, $J = 7.2$ Hz, 3H), 0.88 (s, 9H), 1.58 (s, 3H), 2.24-2.33 (m, 1H), 3.72 (d, $J = 7.2$ Hz, 1H), 3.81 (s, 3H), 4.05 (d, $J = 6.4$ Hz, 2H), 4.42 (s, 2H), 4.98 (brd, $J = 10.4$ Hz, 1H), 4.99 (brd, $J = 17.4$ Hz, 1H), 5.50 (brt, $J = 6.4$ Hz, 1H), 5.84 (dd, $J = 7.6$, 10.4, 17.4 Hz, 1H), 6.87-6.89 (m, 2H), 7.25-7.27 (m, 2H); 100 MHz $^{13}$C-NMR (CDCl$_3$) $\delta$ (ppm) = 5.02, -4.55, 11.74, 16.65, 18.16, 25.81, 42.07, 55.12, 65.84, 71.32, 82.35, 113.68, 113.91, 123.76, 129.19, 130.55, 140.26, 141.67, 159.07; IR (film) 2956, 2929, 2856, 1514, 1249, 1065, 1040, 836, 775 cm$^{-1}$; HRMS C$_{32}$H$_{38}$NaO$_3$Si (M+Na$^+$) Calcd : 413.2488, Found : 413.2504; $[\alpha]_D^{26}$ = -2.26 (c 1.02, CHCl$_3$).

(3S,4S,5E)-7-[(4-Methoxybenzyl)oxy]-3,5-dimethylhepta-1,5-dien-4-ol (14)

To a stirred solution of S7 (41.8 g, 107 mmol) in MeCN (300 mL), 1N HCl (100 mL) was added and stirred at RT for 10.5 hr. The mixture was poured into brine and extracted with EtOAc. The organic layer was washed with brine, dried over MgSO$_4$, and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (Kanto Chemical; heptane : EtOAc = 4 : 1 → 3 : 1 → 2 : 1) and 14 was obtained (26.8 g, 99%) as a colorless oil. 400 MHz $^1$H-NMR (CDCl$_3$) $\delta$ (ppm) = 0.93 (d, $J = 6.4$ Hz, 3H), 1.64 (s, 3H), 1.77 (brs, 1H), 2.28-2.39 (m, 1H), 3.71 (d, $J = 8.0$ Hz, 1H), 3.81 (s, 3H), 4.07 (d, $J = 6.4$ Hz, 2H), 4.45 (s, 2H), 5.15 (brd, $J = 10.4$ Hz, 1H), 5.16 (brd, $J = 17.1$ Hz, 1H), 5.62 (brt, $J = 6.4$ Hz, 1H), 5.75 (ddt, $J = 8.4, 10.4, 17.1$ Hz, 1H), 6.86-6.90 (m, 2H), 7.25-7.29 (m, 2H); 100 MHz $^{13}$C-NMR (CDCl$_3$) $\delta$ (ppm) = 11.44, 16.62, 41.60, 55.04, 65.74, 71.58, 80.52, 113.59, 116.10, 124.73, 129.19, 130.24, 138.94, 140.67, 159.00; IR (film) 3443, 2962, 2931, 2862, 1613, 1513, 1456, 1301, 1249, 1174, 1065, 1035, 913, 820 cm$^{-1}$; HRMS C$_{17}$H$_{34}$NaO$_3$ (M+Na$^+$) Calcd : 299.1623, Found : 299.1612; $[\alpha]_D^{26}$ = -14.1 (c 1.02, CHCl$_3$).

---

< Synthesis of macrolide part >

(1S,2E)-4-[(4-Methoxybenzyl)oxy]-2-methyl-1-[(1S)-1-methylprop-2-en-1-yl]but-2-en-1-yl-3-{{[tert-butyl-(dimethyl)silyl)oxy]-5-[(2S,4R,5S)-4-methyl-2-phenyl-5-vinyl-1,3-dioxolan-4-yl] pentanoate (15)}

To a stirred solution of 10 (6.50 g, 15.5 mmol) and Et$_3$N (2.80 mL, 20.2 mmol) in THF (130 mL), 2,4,6-trichlorobenzoyl chloride (2.65 mL, 17.0 mmol) was added at 0°C under nitrogen atmosphere and stirred at 0°C for 10 min and then at RT for 2 hr. The reaction mixture was filtered with Celite®, and the filtrate was concentrated under reduced pressure. To the obtained residue, a solution of 14 (4.71 g, 17.0 mmol) and DMAP (2.46 g of 20.2 mmol) in dry toluene (130 mL) were added and stirred at RT for 2 hr under nitrogen atmosphere. The reaction mixture was poured into 0.5N HCl and extracted with EtOAc. The organic layer was washed with saturated aq. NaHCO$_3$ solution, water and brine sequentially, dried over MgSO$_4$, and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (Kanto Chemical; heptane : EtOAc = 10 : 1 → 5 : 1) to give 15 (9.81 g, 93%) as a colorless oil. 400 MHz $^1$H-NMR (CDCl$_3$) $\delta$ (ppm) = 0.01 (s, 3H), 0.02 (s, 3H), 0.86 (s, 9H), 0.94 (d, $J = 6.8$ Hz, 3H), 1.22-1.32 (m, 1H), 1.32 (s, 3H), 1.57-1.65 (m, 2H), 1.60 (s, 3H), 1.65-1.79 (m, 1H), 2.32 (dd, $J = 6.0, 15.2$ Hz, 1H), 2.43 (dd, $J = 6.0, 15.2$ Hz, 1H), 2.42-2.52 (m, 1H), 3.80 (s,
3H), 4.02 (d, J = 6.4 Hz, 2H), 4.01-4.08 (m, 1H), 4.26 (dt, J = 1.0, 7.0 Hz, 1H), 4.40 (s, 2H), 4.96-5.05 (m, 3H), 5.29 (ddd, J = 1.0, 1.6, 10.5 Hz, 1H), 5.41 (dt, J = 1.6, 17.5 Hz, 1H), 5.62 (brt, J = 6.2 Hz, 1H), 5.69 (ddd, J = 8.0, 10.4, 17.2 Hz, 1H), 5.88 (ddd, J = 7.0, 10.5, 17.5 Hz, 1H), 5.90 (s, 1H), 6.85-6.89 (m, 2H), 7.23-7.26 (m, 2H), 7.26-7.37 (m, 3H), 7.48-7.52 (m, 2H); 100 MHz $^{13}$C-NMR (CDCl$_3$) δ (ppm) −4.83, −4.76, 12.65, 16.63, 17.85, 22.32, 25.73, 31.21, 32.28, 39.94, 42.72, 55.09, 65.60, 69.21, 71.53, 81.37, 82.18, 82.72, 102.16, 113.65, 115.17, 118.64, 126.03, 126.67, 128.14, 129.00, 129.27, 130.25, 132.66, 135.53, 137.90, 139.83, 159.08, 170.36; IR (film) 2957, 2931, 2856, 1736, 1612, 1250, 1173, 1090, 1065, 1036, 836 cm$^{-1}$; HRMS C$_{49}$H$_{50}$NaO$_5$Si (M+Na$^+$) Calcd: 701.3849, Found: 701.3824; [α]$_D^{23}$ = −2.69 (c 1.09, CHCl$_3$).

(2S,3aS,4E,6S,7S,13aR)-11-[(tert-Butyl(dimethyl)silyloxy)-7-[(1E)-3-[(4-methoxybenzyloxy)-1-methylprop-1-en-1-yl]-6,13a-dimethyl-2-phenyl-3a,6,7,10,11,12,13,13a-octahydro-9H-[1,3]dioxolo[4,5-f]oxacyclododecin-9-one (16)$^{[16d]}$

A solution of 15 (1.10 g, 1.63 mmol) and BHT (35.9 mg, 0.16 mmol) in dry toluene (freshly distilled from sodium metal/benzophenone under argon atmosphere) was heated at reflux for 1 hr under argon atmosphere. Then a solution of 2nd generation Hoveyda-Grubbs catalyst (102 mg, 0.16 mmol) in dry toluene (330 mL) was added to the mixture and heated at reflux for 5 hr. The mixture was cooled to RT and filtered with silica gel (Fuji Silysia Chemical, Chromatorex, NH, 200-350 mesh) pad. The filtrate was concentrated under reduced pressure and the obtained residue was purified by silica gel column chromatography (Kanto Chemical; heptane : EtOAc = 8 : 1) to give 16 (486.1 mg, 46%) as a white solid. Analytical sample of 16 was obtained as a colorless needle by recrystallization (hexane/EtOAc). 400 MHz $^1$H-NMR (CDCl$_3$) δ (ppm) 0.07 (s, 3H), 0.09 (s, 3H), 0.88 (s, 9H), 0.91 (d, J = 6.8 Hz, 3H), 1.38 (s, 3H), 1.38-1.46 (m, 1H), 1.48-1.56 (m, 1H), 1.61 (s, 3H), 1.62-1.68 (m, 1H), 1.99-2.10 (m, 1H), 2.31 (ddd, J = 10.4, 14.7 Hz, 1H), 2.52-2.58 (m, 1H), 2.58 (dd, J = 4.4, 14.7 Hz, 1H), 3.81 (s, 3H), 3.92-4.01 (m, 1H), 4.04 (d, J = 6.4 Hz, 2H), 4.19 (d, J = 9.4 Hz, 1H), 4.42 (s, 2H), 4.97 (d, J = 10.8 Hz, 1H), 5.41 (ddd, J = 9.8, 15.2 Hz, 1H), 5.63 (dd, J = 9.4, 15.2 Hz, 1H), 5.74 (brt, J = 6.4 Hz, 1H), 5.91 (s, 1H), 6.87-6.90 (m, 2H), 7.24-7.26 (m, 2H), 7.36-7.40 (m, 3H), 7.49-7.51 (m, 2H); 100 MHz $^{13}$C-NMR (CDCl$_3$) δ (ppm) −4.73, −4.61, 11.50, 16.72, 17.80, 22.69, 25.62, 31.44, 34.31, 39.97, 43.98, 55.02, 65.45, 71.51, 71.69, 81.55, 83.44, 85.18, 101.07, 113.61, 126.62, 128.18, 128.41, 129.12, 129.21, 129.47, 130.05, 134.39, 137.55, 137.63, 159.05, 168.89; IR (film) 2932, 2856, 1735, 1513, 1460, 1247, 1066, 1034, 1006, 978, 836 cm$^{-1}$; HRMS C$_{49}$H$_{50}$NaO$_5$Si (M+Na$^+$) Calcd: 673.3536, Found: 673.3505; [α]$_D^{28}$ = −14.8 (c 1.03, CHCl$_3$); m.p. 118.0-119.0°C.

(2S,3aS,4E,6S,7S,13aR)-11-[(tert-Butyl(dimethyl)silyloxy)-7-[(1E)-3-hydroxy-1-methylprop-1-en-1-yl]-6,13a-dimethyl-2-phenyl-3a,6,7,10,11,12,13,13a-octahydro-9H-[1,3]dioxolo[4,5-f]oxacyclododecin-9-one (S8)

Phosphate buffer (pH = 7, 1.40 mL) was added to a solution of 16 (710 mg, 1.09 mmol) in CH$_2$Cl$_2$ (14.0 mL) and DDQ (297 mg, 1.31 mmol) was added to the reaction mixture at 0°C and stirred for 3 hr. Additional DDQ (74.3 mg, 0.33 mmol) was added and the reaction mixture was stirred at 0°C for 1.5 hr. Further DDQ (74.3 mg, 0.33 mmol) was added again and the mixture was
stirred at 0°C for additional 30 min and then the mixture was passed through silica gel short column (Fuji Silysia Chemical, Chromatorex, NH, 200-350 mesh). The filtrate was washed with saturated aq. NaHCO₃ solution, water and brine sequentially, dried over MgSO₄, and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (Kanto Chemical; heptane : EtOAc = 4 : 1 → 3 : 1) to give S8 (460 mg, 80%) as a colorless needle. 400 MHz ¹H-NMR (CDCl₃) δ (ppm) 0.08 (s, 3H), 0.09 (s, 3H), 0.88 (s, 9H), 0.90 (d, J = 6.8 Hz, 3H), 1.25 (t, J = 5.6 Hz, 1H), 1.38-1.46 (m, 2H), 1.39 (s, 3H), 1.60-1.68 (m, 1H), 1.65 (s, 3H), 2.00-2.09 (m, 1H), 2.32 (dd, J = 10.2, 14.6 Hz, 1H), 2.52-2.59 (m, 1H), 2.59 (dd, J = 4.2, 14.6 Hz, 1H), 3.92-4.01 (m, 1H), 4.16-4.27 (m, 3H), 4.95 (d, J = 10.4 Hz, 1H), 5.41 (dd, J = 9.8, 15.2 Hz, 1H), 5.64 (dd, J = 9.6, 15.2 Hz, 1H), 5.75 (br, J = 5.8 Hz, 1H), 5.91 (s, 1H), 7.36-7.41 (m, 3H), 7.49-7.52 (m, 2H); 100 MHz ¹³C-NMR (CDCl₃) δ (ppm) −4.67, −4.56, 11.24, 16.69, 17.88, 22.75, 25.67, 31.50, 34.33, 39.92, 43.98, 58.64, 71.49, 81.86, 83.55, 85.25, 101.15, 126.70, 128.28, 129.25, 129.56, 130.77, 133.52, 137.58, 169.25; IR (KBr) 3232, 2937, 2858, 1730, 1243, 1107, 1082, 1067, 1007, 973, 836, 776, 700 cm⁻¹; HRMS C₃₀H₄₆NaO₉Si (M+Na⁺) Calc’d : 553.2961, Found : 553.2948; [α]D²⁵ +11.5 (c 1.02, CHCl₃); m.p. 161.0-162.0°C.

\[(\text{25,3aS,4E,6S,7S,13aR})-11-[(\text{ tert-Butyl(dimethyl)silyl}o\text{xy})-7-[(\text{E})-2-formyl-1-methyleth-1-en-1-yl]-6,13a-dimethyl-2-phenyl-3a,6,7,10,11,12,13,13a-octahydro-9H-[1,3]dioxolo[4,5-f]oxacyclocodocin-9-one} (17)\]

DMP (565 mg, 1.33 mmol) was added to a solution of S8 (587 mg, 1.11 mmol) in CH₂Cl₂ (12.0 mL) and stirred at RT for 30 min. The reaction mixture was diluted with ether, washed with a saturated aq. NaHCO₃ solution containing Na₂SO₄, water and brine sequentially, dried over MgSO₄, and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (Kanto Chemical; heptane : EtOAc = 10 : 1 → 8 : 1 → 6 : 1) to give 17 (587 mg, quant.) as a white solid. 17 was obtained as a colorless crystal by recrystallization (hexane/EtOAc). 400 MHz ¹H-NMR (CDCl₃) δ (ppm) 0.09 (s, 3H), 0.10 (s, 3H), 0.89 (s, 9H), 0.95 (d, J = 6.8 Hz, 3H), 1.38-1.50 (m, 2H), 1.40 (s, 3H), 1.63-1.70 (m, 1H), 1.96-2.10 (m, 1H), 2.17 (d, J = 1.2 Hz, 3H), 2.37 (dd, J = 9.6, 14.4 Hz, 1H), 2.60 (dd, J = 4.0, 14.4 Hz, 1H), 2.61 (m, 1H), 3.93-4.03 (m, 1H), 4.20 (d, J = 9.6 Hz, 1H), 4.92 (d, J = 10.4 Hz, 1H), 5.41 (dd, J = 9.2, 15.2 Hz, 1H), 5.69 (dd, J = 9.6, 15.2 Hz, 1H), 5.92 (s, 1H), 6.07 (dd, J = 1.2, 7.6 Hz, 1H), 7.34-7.42 (m, 1H), 7.48-7.52 (m, 2H), 10.0 (d, J = 7.6 Hz, 1H); 100 MHz ¹³C-NMR (CDCl₃) δ (ppm) −4.70, −4.60, 13.20, 16.31, 17.87, 22.66, 25.64, 31.46, 34.14, 40.40, 43.19, 71.13, 80.52, 83.52, 85.00, 101.22, 126.63, 128.28, 129.25, 129.84, 130.58, 136.19, 137.59, 155.92, 168.80, 190.56; IR (KBr) 2954, 2935, 2880, 2858, 2787, 2755, 1739, 1674, 1461, 1401, 1240, 1224, 1101, 1004, 980, 830, 775, 698 cm⁻¹; HRMS C₃₂H₄₄NaO₉Si (M+Na⁺) Calc’d : 551.2805, Found : 551.2803; [α]D²⁵ +4.00 (c 1.06, CHCl₃); m.p. 127.5-128.5°C.

< Synthesis of C15-C18 unit >
Scheme S1. Synthetic scheme of C15-C18 unit 20.

**Methyl (2R)-3-(benzzyloxy)-2-methylpropanoate (S9)**

To a stirred solution of methyl (R)-3-hydroxy isobutyrate (6.30 g, 53.3 mmol) and benzyl 2,2,2-trichloro-acetimidate (12.0 mL, 64.6 mmol) in CH₂Cl₂-cyclohexane (180 mL, 1 : 1), trifluoromethanesulfonic acid (0.80 mL, 5.40 mmol) was added dropwise and stirred at RT for 3 hr. The reaction mixture was diluted with CH₂Cl₂, washed with aq. NaHCO₃ solution and brine sequentially, dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (Merck; hexane : EtOAc = 30 : 1) and S9 (9.79 g, 88%) was obtained as a colorless oil. 400 MHz ¹H-NMR (CDCl₃) δ (ppm) 1.19 (d, J = 7.2 Hz, 3H), 2.74-2.84 (m, 1H), 3.50 (dd, J = 6.0, 9.2 Hz, 1H), 3.66 (dd, J = 7.2, 9.2 Hz, 1H), 3.69 (s, 3H), 4.52 (s, 2H), 7.20-7.37 (m, 5H); 100 MHz ¹³C-NMR (CDCl₃) δ (ppm) 13.91, 40.12, 51.65, 71.89, 73.02, 127.51, 127.53, 128.28, 138.09, 175.24; IR (film) 2977, 2946, 2862, 2362, 2323, 1738, 1458, 1202 cm⁻¹; HRMS C₁₂H₁₈NaO₃ (M+Na⁺) Calcd : 231.0997, Found : 231.0989; [α]D²⁸ −10.9 (c 2.10, CHCl₃).

**([(2S)-4-Methoxy-2-methylbut-3-en-1-yl]oxy)methyl]benzene (S10)**

DIBAL (1.0M toluene solution, 3.78 mL, 3.78 mmol) was added dropwise to a solution of S9 (0.81 g, 3.88 mmol) in toluene (32 mL) at −78°C and stirred at the same temperature for 1.5 hr. MeOH (0.5 mL, 12.3 mmol) was added to the mixture and warmed to RT and then stirred for further 2 hr. The reaction mixture was passed through Celite® pad, dried over Na₂SO₄, and evaporated under reduced pressure to afford crude aldehyde. To a stirred solution of (methoxymethyl)triphenylphosphonium chloride (2.54 g, 7.40 mmol) in THF (20 mL), tert-ButOK (0.76 g, 6.76 mmol) was added with cooling on ice and the mixture was stirred at RT for 30 min. Subsequently, a solution of the crude aldehyde in THF (5 mL) was added dropwise to this reaction mixture at RT and stirred for 12 hr. The reaction mixture was diluted with EtOAc, washed with water and brine sequentially, dried over MgSO₄, and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (Merck; hexane : EtOAc = 100 : 1) to give S10 (0.44 g, 55%, 2 steps) as a colorless oil. The obtained S10 was determined to be a mixture of E/Z = 2 : 1 by ¹H-NMR. 400 MHz ¹H-NMR (CDCl₃) δ (ppm) 1.01 (d, J = 6.8 Hz, 0.9H), 1.04 (d, J = 6.8 Hz, 2.1H), 2.36-2.47 (m, 0.7H), 2.92-3.00 (m, 0.3H), 3.22-3.37 (m, 2H), 3.50 (s, 2.1H), 3.58 (s, 0.9H), 4.23 (dd, J = 6.4, 9.2 Hz, 0.3H), 4.52 (s, 2.0H), 4.65 (dd, J = 8.0, 12.8 Hz, 0.7H), 5.89 (dd, J = 0.8, 6.4 Hz, 0.3H), 6.35 (dd, J = 0.8, 12.8 Hz, 0.7H), 7.25-7.36 (m, 5H); 100 MHz ¹³C-NMR (CDCl₃) δ (ppm) 17.97, 18.43, 29.60, 33.22, 55.67, 59.50, 72.67, 72.88, 75.24, 76.16, 105.60, 109.51, 127.34, 127.45, 127.53,
128.25, 128.31, 138.72, 138.92, 146.35, 147.31; IR (film) 3060, 3033, 2956, 2935, 2856, 1655, 1454, 1207, 1098, 737 cm$^{-1}$; HRMS C$_{13}$H$_{18}$NaO$_2$ (M+Na$^+$) Calcd : 229.1204, Found : 229.1207.

(3S)-4-(Benzyloxy)-3-methylbutan-1-ol (S11)$^{[38c]}$

Water (10 mL) and formic acid (1 mL) were added to S10 (3.73 g, 18 mmol) and the mixture was stirred at RT for 10 min. The reaction mixture was diluted with EtOAc, washed with water, aq. NaHCO$_3$ solution and brine sequentially, dried over Na$_2$SO$_4$, and concentrated under reduced pressure. The residue was dissolved in MeOH (40 mL) and NaBH$_4$ (0.68 g, 18 mmol) was added to the solution with ice cooling. The reaction mixture was stirred at the same temperature for 10 min and then acetone was added thereto. The mixture was diluted with EtOAc, washed with brine, dried over Na$_2$SO$_4$, and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (Merck; hexane : EtOAc = 5 : 1) to give S11 (3.30 g, 94%, 2 steps) as a colorless oil. 400 MHz $^1$H-NMR (CDCl$_3$) $\delta$ (ppm) 0.95 (d, J = 7.2 Hz, 3H), 1.51-1.68 (m, 2H), 1.89-1.99 (m, 1H), 3.31 (dd, J = 7.6, 9.2 Hz, 1H), 3.39 (dd, J = 4.8, 9.2 Hz, 1H), 3.61-3.75 (m, 2H), 4.52 (s, 2H), 7.26-7.37 (m, 5H); 100 MHz $^{13}$C-NMR (CDCl$_3$) $\delta$ (ppm) 17.51, 31.18, 37.74, 60.88, 73.08, 75.96, 127.57, 127.58, 128.31, 137.99; IR (film) 3389, 3086, 3058, 3030, 2951, 2929, 2872, 1454, 1363, 1205, 1095, 738, 698 cm$^{-1}$; HRMS C$_{13}$H$_{18}$NaO$_2$ (M+Na$^+$) Calcd : 217.1204, Found : 217.1190; [$\alpha$]$_D^{29}$ = -4.52 (c 2.41, CHCl$_3$).

5-[[3S]-4-(Benzyloxy)-3-methylbutyl]thio]-1-phenyl-1H-tetrazole (S12)$^{[29]}$

To a stirred solution of S11 (2.76 g, 14.2 mmol) in THF (60 mL), 5-mercapto-1-phenyltetrazole (3.03 g, 17 mmol), Ph,P (4.47 g, 17 mmol) and DIAD (40% toluene solution, 8.04 mL, 18 mmol) were added with ice cooling and then the reaction mixture was stirred at RT for 3 hr. Then the reaction mixture was diluted with EtOAc, washed with water and brine sequentially, dried over Na$_2$SO$_4$, and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (Merck; hexane : EtOAc = 15 : 1 → 5 : 1) to give S12 (5.38 g, 86%) as a colorless oil. 400 MHz $^1$H-NMR (CDCl$_3$) $\delta$ (ppm) 0.99 (d, J = 6.8 Hz, 3H), 1.65-1.74 (m, 1H), 1.92-2.03 (m, 2H), 3.26-3.52 (m, 4H), 4.49 (s, 2H), 7.21-7.35 (m, 5H), 7.49-7.58 (m, 5H); 100 MHz $^{13}$C-NMR (CDCl$_3$) $\delta$ (ppm) 16.72, 31.23, 32.82, 33.13, 73.02, 75.07, 123.78, 127.48, 128.30, 129.70, 129.99, 133.67, 138.39, 154.37; IR (film) 3067, 3036, 2956, 2925, 2858, 1598, 1499, 1386, 1092, 761, 696 cm$^{-1}$; HRMS C$_{19}$H$_{22}$N$_5$O$_5$S (M+H$^+$) Calcd : 355.1593, Found : 355.1583; [$\alpha$]$_D^{27}$ = -2.62 (c 1.56, CHCl$_3$).

5-[[3S]-4-(Benzyloxy)-3-methylbutyl]sulfonyl]-1-phenyl-1H-tetrazole (20)$^{[30]}$

A solution of hexaammonium heptamolybdate tetrahydrate (1.80 g, 1.46 mmol) in 30% H$_2$O$_2$ (16.5 mL) was added to a solution of S12 (5.17 g, 14.6 mmol) in EtOH (20 mL) at RT and stirred for 24 hr. The reaction mixture was diluted with EtOAc, washed with water and brine sequentially, dried over Na$_2$SO$_4$, and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (Merck; hexane : EtOAc = 10 : 1) to give 20 (5.68 g, quant.) as a colorless oil. 400 MHz $^1$H-NMR (CDCl$_3$) $\delta$ (ppm) 0.98 (d, J = 6.8 Hz, 3H), 1.83-2.13 (m, 3H), 3.29 (dd, J = 6.8, 9.6 Hz, 1H), 3.40 (dd, J = 4.8, 9.6 Hz, 1H), 3.74-3.87 (m, 2H), 4.49 (s, 2H), 7.25-7.36 (m, 5H),
7.55-7.68 (m, 5H); 100 MHz $^{13}$C-NMR (CDCl$_3$) $\delta$ (ppm) 16.72, 26.23, 32.49, 54.30, 73.11, 74.70, 125.05, 127.55, 127.62, 128.39, 129.63, 131.37, 132.99, 138.09, 153.38; HRMS C$_{19}$H$_{23}$N$_4$O$_3$(M+H$^+$) Calcd : 387.1491, Found : 387.1468; $[\alpha]_D^{25}$ $-$5.28 (c 1.00, CHCl$_3$).

< Synthesis of C18-C23 unit >

(2R,3S)-3-hydroxy-N-methoxy-N,2-dimethylpentamide (S13)$^{[39]}$

Me$_3$Al (2M toluene solution, 90 mL, 180 mmol) was added to a stirred suspension of $N,O$-dimethylhydroxamine hydrochloride (18.3 g, 187.6 mmol) in THF (180 mL) at $-10^\circ$C and then warmed to 0°C and stirred for 10 min. The mixture was warmed to RT and further stirred for 30 min. Then the reaction mixture was cooled to $-10^\circ$C again, and a solution of 18 (21.85 g, 75 mmol)$^{[18]}$ in THF-CH$_2$Cl$_2$ (4 : 5, 180 mL) was added dropwise and warmed to 0°C. After stirring for 2 hr, a mixture of CH$_2$Cl$_2$-0.5N HCl (1 : 1, 80 mL) was added slowly and stirred for 1 hr at 0°C. The mixture was passed through Celite$^\circledR$ pad, and the filtrate was dried over Na$_2$SO$_4$, and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (Merck; heptane : EtOAc = 3 : 2) to give S13 (13.0 g, quant.) as a colorless oil. 400 MHz $^1$H-NMR (CDCl$_3$) $\delta$ (ppm) 0.96 (t, $J$ = 7.2 Hz, 3H), 1.16 (d, $J$ = 7.2 Hz, 3H), 1.34-1.45 (m, 1H), 1.53-2.04 (m, 1H), 2.84-2.94 (m, 1H), 3.19 (s, 3H), 3.71 (s, 3H), 3.74-3.80 (m, 1H); 100 MHz $^{13}$C-NMR (CDCl$_3$) $\delta$ (ppm) 10.08, 10.21, 26.64, 31.73, 38.09, 61.35, 72.95, 177.21; IR (film) 3433, 2971, 2943, 2881, 2361, 2337, 1638, 1461, 993 cm$^{-1}$; HRMS C$_{19}$H$_{23}$N$_4$O$_3$ (M+Na$^+$) Calcd : 198.1106, Found : 198.1100; $[\alpha]_D^{25}$ $-$17.3 (c 1.11, CHCl$_3$).

(2R,3S)-N-Methoxy-N,2-dimethyl-3-[(triethylyl)silyloxy]pentanamide (S14)$^{[39]}$

To a stirred solution of S13 (7.3 g, 41.7 mmol) in CH$_2$Cl$_2$ (150 mL), 2.6-lutidine (10.2 mL, 87 mmol) and TESOTf (14.1 mL, 62 mmol) was added with ice cooling and stirred for 5 hr. The reaction mixture was diluted with CH$_2$Cl$_2$, washed with saturated aq. NH$_4$Cl solution and brine sequentially, dried over Na$_2$SO$_4$, and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (Merck; hexane : EtOAc = 10 : 1) to give S14 (11.95 g, 99%) as a colorless oil. 400 MHz $^1$H-NMR (CDCl$_3$) $\delta$ (ppm) 0.62 (q, $J$ = 8.0 Hz, 6H), 0.90 (t, $J$ = 7.2 Hz, 3H), 0.98 (t, $J$ = 8.0 Hz, 9H), 1.17 (d, $J$ = 6.8 Hz, 3H), 1.40-1.59 (m, 2H), 2.90-3.08 (m, 1H), 3.18 (s, 3H), 3.69 (s, 3H), 3.90 (dt, $J$ = 4.8, 8.4 Hz, 1H); 100 MHz $^{13}$C-NMR (CDCl$_3$) $\delta$ (ppm) 4.96, 6.74, 8.60, 14.35, 28.25, 31.86, 40.21, 61.16, 74.50, 176.51; IR (film) 3483, 2958, 2918, 2879, 1743, 1663, 1460, 1384, 1118, 1049, 1007, 857, 741 cm$^{-1}$; HRMS C$_{19}$H$_{23}$N$_4$O$_3$Si (M+H$^+$) Calcd : 290.2151, Found : 290.2150; $[\alpha]_D^{27}$ $-$7.39 (c 1.04, CHCl$_3$).

(2R,3S)-2-Methyl-3-[(triethylyl)silyloxy]pentanal (19)$^{[39]}$

To a stirred solution of S14 (1.06 g, 3.66 mmol) in THF (20 mL), DIBAL (1M toluene solution, 18.0 mL, 18.0 mmol) was added dropwise at $-78^\circ$C and stirred for 1 hr. After an addition of 5% HCl-MeOH solution (2 mL), the mixture was warmed to RT and stirred for 1 hr. The reaction mixture was passed through Celite$^\circledR$ pad and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (Merck; hexane : EtOAc = 40 : 1) to give 19 (0.75 g, 89%) as a colorless oil. 400 MHz $^1$H-NMR (CDCl$_3$) $\delta$ (ppm) 0.60 (q, $J$ = 8.0 Hz, 6H), 0.89 (t, $J$
= 7.2 Hz, 3H), 0.94 (t, J = 8.0 Hz, 9H), 1.06 (d, J = 6.8 Hz, 3H), 1.43-1.62 (m, 2H), 2.40-2.49 (m, 1H), 4.05 (ddd, J = 3.4, 6.4, 9.6 Hz, 1H), 9.77 (s, 1H); 100 MHz $^{13}$C-NMR (CDCl$_3$) $\delta$ (ppm) 5.01, 6.74, 7.43, 10.01, 27.47, 50.82, 73.33, 205.26; IR (film) 3455, 2958, 2914, 2872, 2715, 2356, 2341, 1726, 1460, 1239, 1011, 740 cm$^{-1}$; HRMS C$_{17}$H$_{36}$NaO$_5$Si (M+Na$^+$) Calcd : 253.1600, Found : 253.1596; [$\alpha$]$_{D}^{25}$ −55.3 (c 1.19, CHCl$_3$).

**< Synthesis of side chain part >**

\[ ((1S,2S,3E,6S)-7-(Benzylloxy)-1-ethyl-2,6-dimethylhept-3-en-1-yl)oxy(triethysilyl)silane (21) \]

KHMDMS (15% toluene solution, 0.65 mL, 0.428 mmol) was added dropwise to a solution of 20 (100 mg, 0.244 mmol) in dry THF (2.0 mL, freshly distilled from LAH before use) at −78°C and stirred at the same temperature for 1 hr. Subsequently a solution of 19 (112 mg, 0.49 mmol) in THF (0.5 mL) was added dropwise to the reaction mixture at −78°C and stirred for 1 hr. After the reaction mixture was warmed to RT, the reaction was quenched by adding an appropriate amount of water and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over Na$_2$SO$_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (Merck; hexane : ether = 100 : 1) to give 21 (66 mg, 68%) as a colorless oil. 400 MHz $^1$H-NMR (CDCl$_3$) $\delta$ (ppm) 0.60 (q, J = 8.0 Hz, 6H), 0.86 (t, J = 7.2 Hz, 3H), 0.91 (d, J = 6.4 Hz, 3H), 0.94 (d, J = 6.8 Hz, 3H), 0.96 (t, J = 8.0 Hz, 9H), 1.34-1.49 (m, 2H), 1.78-1.93 (m, 2H), 2.11-2.19 (m, 1H), 2.20-2.27 (m, 1H), 3.24 (dd, J = 6.0, 8.8 Hz, 1H), 3.33 (dd, J = 6.0, 8.8 Hz, 1H), 3.42 (dt, J = 5.2, 5.6 Hz, 1H), 4.49 (s, 2H), 5.31-5.41 (m, 2H), 7.26-7.36 (m, 5H); 100 MHz $^{13}$C-NMR (CDCl$_3$) $\delta$ (ppm); 5.18, 6.97, 9.35, 16.15, 16.84, 26.81, 33.80, 36.83, 41.73, 72.92, 75.33, 77.44, 127.34, 127.44, 127.48, 128.23, 134.81, 138.77; IR (film) 3086, 3067, 3033, 2958, 2903, 2879, 1500, 1456, 1102, 1011, 737 cm$^{-1}$; HRMS C$_{25}$H$_{42}$AgO$_5$Si (M+Ag$^+$) Calcd : 497.205, Found : 497.1981; [$\alpha$]$_{D}^{25}$ −16.1 (c 1.28, CHCl$_3$).

(2S,4E,6S,7S)-2-Dimethyl-7-[(triethysilyl)oxy]non-4-en-1-ol (S15) \]

Lithium (39.4 mg, 5.62 mmol) was added to a stirred solution of di-tert-butyl-biphenyl (1.87 g, 7.02 mmol) in THF (25 mL) with ice cooling and stirred at RT for 3 hr. Then the mixture turned dark green solution during the stirring. The solution was added dropwise slowly (at such a rate that green color of the reaction mixture was maintained) to a stirred solution of 21 (500 mg, 1.28 mmol) in THF (5 mL) at −78°C. The mixture was stirred at −78°C for 3 hr, added saturated aq. NH$_4$Cl solution, and warmed to RT. The reaction mixture was diluted with EtOAc, washed with brine, dried over Na$_2$SO$_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (Merck; hexane : EtOAc = 15 : 1) to give S15 (296 mg, 77%) as a colorless oil. 400 MHz $^1$H-NMR (CDCl$_3$) $\delta$ (ppm) 0.60 (q, J = 8.0 Hz, 6H), 0.87 (t, J = 7.6 Hz, 3H), 0.90 (d, J = 6.8 Hz, 3H), 0.95 (d, J = 7.6 Hz, 3H), 0.96 (t, J = 8.0 Hz, 9H), 1.34-1.50 (m, 2H), 1.65-1.76 (m, 1H), 1.87-1.94 (m, 1H), 2.09 (ddd, J = 5.6, 5.6, 14.0 Hz, 1H), 2.21-2.29 (m, 1H), 3.42-3.48 (m, 2H), 3.51 (dd, J = 6.0, 10.4 Hz, 1H), 5.30-5.46 (m, 2H); 100 MHz $^{13}$C-NMR (CDCl$_3$) $\delta$ (ppm); 5.11, 6.90, 9.39, 16.05, 16.37, 26.67, 35.96, 36.69, 41.71, 67.81, 77.46, 127.57, 134.84; IR (film) 3342, 2958, 2916, 2877, 1459, 1415, 1380, 1013, 741 cm$^{-1}$; HRMS C$_{17}$H$_{36}$AgO$_5$Si (M+Ag$^+$) Calcd : 407.1536, Found : 407.1512; [$\alpha$]$_{D}^{25}$ −24.7 (c 1.36, CHCl$_3$).
5-[(2S,4E,6S,7S)-2,6-Dimethyl-7-[(triethylsilyloxy)non-4-en-1-yl]thio]-1-phenyl-1H-tetrazole (S16)[29]

DIAD (40% toluene solution, 0.63 mL, 1.44 mmol) was added dropwise to a stirred solution of 5-mercapto-1-phenyltetrazole (237 mg, 1.33 mmol), Ph₃P (350 mg, 1.11 mmol), and S15 (334 mg, 1.11 mmol) in THF (10 mL) with ice cooling and then stirred at RT for 3 hr. The mixture was diluted with EtOAc, washed with water and brine sequentially, dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (Merck; hexane : EtOAc = 40 : 1) to give S16 (457 mg, 91%) as a colorless oil. 400 MHz ¹H-NMR (CDCl₃) δ (ppm) 0.59 (q, J = 8.0 Hz, 6H), 0.85 (t, J = 7.6 Hz, 3H), 0.95 (d, J = 6.8 Hz, 3H), 0.95 (t, J = 8.0 Hz, 9H), 1.03 (d, J = 6.0 Hz, 3H), 1.32-1.52 (m, 2H), 1.97-2.06 (m, 2H), 2.18-2.29 (m, 2H), 3.28 (dd, J = 6.4, 12.8 Hz, 1H), 3.41-3.45 (m, 2H), 5.3-5.39 (m, 1H), 5.45 (dd, J = 7.2, 15.2 Hz, 1H), 7.52-7.60 (m, 5H); 100 MHz ¹³C-NMR (CDCl₃) δ (ppm): 5.09, 6.90, 9.40, 16.05, 15.86, 18.80, 26.64, 33.09, 38.84, 39.71, 41.68, 77.29, 123.75, 126.09, 129.66, 129.95, 133.68, 135.96, 154.56; IR (film) 2958, 2883, 1594, 1500, 1459, 1383, 1240, 1013, 742 cm⁻¹; HRMS C₂₅H₁₇N₅OSSi (M+H⁺) Calcd : 461.2770, Found : 461.2787; [α]D⁺²⁴ = 22.0 (c 1.51, CHCl₃).

(3S,4S,5E,8S)-4,8-Dimethyl-9-[(1-phenyl-1H-tetrazol-5-yl)sulfonyl]non-5-en-3-ol (22)[30]

A solution of hexaammonium heptamolybdate tetrahydrate (140 mg, 0.12 mmol) in 30% H₂O₂ (1.29 mL) was added to a stirred solution of S16 (444 mg, 1.14 mmol) in EtOH (10 mL) at RT and stirred for 24 hr. The reaction mixture was diluted with EtOAc, washed with water and brine sequentially, dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (Merck; hexane : EtOAc = 5 : 1→1 : 1) to give 22 (300 mg, 81%) as a white solid. 400 MHz ¹H-NMR (CDCl₃) δ (ppm) 0.95 (t, J = 7.3 Hz, 3H), 1.01 (d, J = 6.8 Hz, 3H), 1.16 (d, J = 6.6 Hz, 3H), 1.31-1.42 (m, 1H), 1.42-1.49 (m, 1H), 1.49-1.59 (m, 1H), 2.20 (dd, J = 6.2, 6.4 Hz, 2H), 2.23-2.31 (m, 1H), 2.37-2.47 (m, 1H), 3.34-3.42 (m, 1H), 3.53 (dd, J = 7.4, 14.5 Hz, 1H), 3.88 (dd, J = 4.8, 14.5 Hz, 1H), 5.39-5.47 (m, 1H), 5.50 (dd, J = 7.2, 15.6 Hz, 1H), 7.57-7.70 (m, 5H); 100 MHz ¹³C-NMR (CDCl₃) δ (ppm) 10.24, 14.79, 19.60, 26.92, 28.25, 39.35, 42.14, 60.73, 76.35, 125.02, 126.09, 129.55, 131.34, 132.92, 137.02, 153.88; IR (KBr) 3384, 3351, 3316, 2961, 2939, 2879, 2356, 2338, 1593, 1499, 1459, 1332, 1156, 1098, 1019, 967, 840, 768, 691, 633 cm⁻¹; HRMS C₂₅H₂₁N₂O₅Si (M+H⁺) Calcd : 379.1804, Found : 379.1806; [α]D⁺²⁴ = -29.5 (c 1.20, CHCl₃); m.p. 64.0-65.0°C.

(2R,3S)-2-((2R,3R)-3-[(2S)-2-Methyl-3-[(1-phenyl-1H-tetrazol-5-yl)sulfonyl]propyl]oxiran-2-yl) pentane-3-ol (23)[9]

To a stirred solution of 22 (190 mg, 0.50 mmol) in MeCN (7.5 mL) and 0.05M sodium tetraborate decahydrate-0.4mM Na₂EDTA solution (5 mL), 1,2:4,5-di-O-isopropylidene-d-erythro-2,3-hexadioxo-2,6-pyranose (450 mg, 1.74 mmol) was added with ice cooling. Subsequently, a mixed powder of K₂CO₃ (0.85 mg, 6.16 mmol) and Ozone (1.27 g, 2.06 mmol) was added to the mixture in several portions at the same temperature over 1 hr and stirred for additional 1 hr. The reaction mixture was diluted with EtOAc, washed with water and brine sequentially, dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified by silica gel
column chromatography (Kanto Chemical, Silica Gel 60N, spherical, 40-100 µm; heptane : EtOAc = 3 : 1) to give 23 (160 mg, 81%, 94% de) as a colorless oil. The de was determined by HPLC (DAICEL CHEMICHAL INDUSTRIES, CHIRALCEL OD; hexane : isopropyl alcohol = 75 : 25). The residue 23 was crystallized from hexane at −78°C, and the obtained crystals were recrystallized (hexane/EtOAc) to give pure 23 as a colorless prism (140 mg, 70%, >99% de). 400 MHz 1H-NMR (CD2OD) δ (ppm) 0.98 (d, J = 7.1 Hz, 3H), 0.99 (t, J = 7.3 Hz, 3H), 1.26 (d, J = 6.8 Hz, 3H), 1.29-1.37 (m, 1H), 1.45-1.63 (m, 3H), 1.89(ddd, J = 4.6, 5.8, 14.3 Hz, 1H), 2.45-2.57 (m, 1H), 2.69 (ddd, J = 2.2, 7.9 Hz, 1H), 2.86 (ddd, J = 2.2, 4.6, 6.9 Hz, 1H), 3.57 (dt, J = 4.6, 8.8 Hz, 1H), 3.69 (dd, J = 7.3, 14.8 Hz, 1H), 3.91 (dd, J = 5.2, 14.8 Hz, 1H), 7.66-7.77 (m, 5H); 100 MHZ 13C-NMR (CD2OD) δ (ppm) 10.54, 10.87, 20.29, 28.32, 28.57, 39.26, 42.23, 56.63, 61.67, 62.23, 75.15, 126.94, 130.58, 132.54, 134.54, 155.41; IR (KBr) 3336, 3245, 2961, 2925, 2900, 2869, 1779, 1594, 1460, 1334, 1154, 1109, 1071, 981, 955, 828, 765, 688, 634, 524, 456 cm⁻¹; HRMS C18H27N2O2S (M+H⁺) Calcd : 395.1753, Found : 395.1721; [α]b²⁰ +21.0 (c 1.00, MeOH); m.p. 65.0-66.0°C.


Imidazole (345 mg, 5.07 mmol) and DEIPSCI (418 mg, 2.54 mmol) were added to a solution of 23 (200 mg, 0.507 mmol) in DMF (4 mL) and stirred at RT for 1 hr. The reaction mixture was diluted with EtOAc, washed with water and brine sequentially, dried over Na2SO4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (Kanto Chemical, Silica Gel 60N, spherical, 40-100 µm; heptane : EtOAc = 20 : 1 → 10 : 1) to give 24 (265 mg, quant.) as a colorless oil. 400 MHz 1H-NMR (CD2OD) δ (ppm) 0.67-0.74 (m, 4H), 0.88 (t, J = 7.2 Hz, 3H), 0.95 (d, J = 6.8 Hz, 3H), 0.90-0.98 (m, 1H), 1.04 (t, J = 7.6 Hz, 3H), 1.05 (t, J = 7.6 Hz, 3H), 1.06 (d, J = 5.6 Hz, 6H), 1.26 (d, J = 6.8 Hz, 3H), 1.32-1.43 (m, 1H), 1.52-1.63 (m, 3H), 1.92 (ddd, J = 4.4, 6.0, 14.0 Hz, 1H), 2.45-2.56 (m, 1H), 2.71 (dd, J = 2.4, 7.6 Hz, 1H), 2.86 (ddd, J = 2.4, 4.4, 6.8 Hz, 1H), 3.70 (dd, J = 7.6, 14.8 Hz, 1H), 3.80-3.86 (m, 1H), 3.90 (dd, J = 5.2, 14.8 Hz, 1H), 7.65-7.75 (m, 5H); 100 MHZ 13C-NMR (CD2OD) δ (ppm) 5.00, 5.17, 7.65, 10.02, 10.11, 14.40, 17.93, 20.31, 28.46, 28.64, 39.40, 40.84, 57.28, 61.58, 62.28, 75.78, 126.99, 130.63, 132.58, 134.71, 155.54; IR (film) 2961, 2881, 1596, 1498, 1462, 1339, 1153, 1014, 823, 763, 723, 633 cm⁻¹; HRMS C25H32N2O2Ss (M+H⁺) Calcd : 523.2774, Found : 523.2766; [α]b²¹ +19.3 (c 1.09, MeOH).

< Completion of the total synthesis of pladienolide B >

6,7-O-[(S)-Benzyldiene]-3-O-[[tert-butyl(dimethyl)silyl]oxy]-21-O-[[diethyl(isopropyl)silyl]oxy]-pladienolide A (25)[8]

KHMDMS (15% toluene solution, 0.317 mL, 0.208 mmol) was added dropwise to a stirred solution of 24 (62 mg, 0.119 mmol) in dry THF (1 mL, freshly distilled from LAH before use) at −78°C and stirred for 30 min. Then a solution of 17 (94.0 mg, 0.179 mmol) in dry THF (1 mL) was added dropwise at −78°C and stirred for 1 hr. The reaction mixture
was warmed to RT and partitioned between EtOAc and water. The organic layer was washed with brine, dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (Kanto Chemical, Silica Gel 60N, spherical, 40-100 μm, heptane : EtOAc = 25 : 1 → 15 : 1) to give 25 (65 mg, 64%) as a colorless oil. 400 MHz ¹H-NMR (CD₃OD) δ (ppm) 0.15 (s, 3H), 0.17 (s, 3H), 0.66-0.75 (m, 4H), 0.86 (t, J = 7.6 Hz, 3H), 0.90 (d, J = 6.8 Hz, 3H), 0.93 (d, J = 6.8 Hz, 3H), 0.95 (s, 9H), 0.94-1.03 (m, 1H), 1.05 (t, J = 8.4 Hz, 6H), 1.07 (d, J = 6.4 Hz, 6H), 1.12 (d, J = 6.8 Hz, 3H), 1.24-1.35 (m, 1H), 1.38-1.50 (m, 3H), 1.42 (s, 3H), 1.58 (dq, J = 7.6, 14.4 Hz, 2H), 1.69-1.78 (m, 2H), 1.78 (s, 3H), 1.96-2.05 (m, 1H), 2.28 (dd, J = 10.2, 14.8 Hz, 1H), 2.44-2.58 (m, 1H), 2.64-2.72 (m, 3H), 2.78 (dt, J = 2.4, 6.0 Hz, 1H), 3.80-3.86 (m, 1H), 4.05-4.13 (m, 1H), 4.28 (d, J = 9.6 Hz, 1H), 4.96 (d, J = 10.8 Hz, 1H), 5.50 (dd, J = 9.6, 15.2 Hz, 1H), 5.68 (dd, J = 9.6, 14.4 Hz, 1H), 5.70 (dd, J = 9.6, 15.2 Hz, 1H), 5.94 (s, 1H), 6.12 (d, 10.8 Hz, 1H), 6.36 (dd, J = 10.8, 14.4 Hz, 1H), 7.40-7.44 (m, 3H), 7.52-7.54 (m, 2H); 100 MHz ¹³C-NMR (Acetone-d₆) δ (ppm) −4.94, −4.85, 4.06, 4.24, 7.02, 7.05, 9.44, 9.76, 11.17, 13.33, 16.70, 17.32, 19.72, 21.07, 22.61, 25.64, 27.74 31.69, 34.80, 35.51, 40.00, 40.08, 40.19, 44.08, 56.95, 60.92, 71.89, 74.66, 82.34, 83.54, 85.35, 101.21, 124.75, 127.09, 128.24, 129.11, 130.29, 130.76, 131.79, 137.63, 139.00, 141.19, 168.35; IR (film) = 2959, 1732, 1462, 1376, 1276, 1247, 1064, 1008, 971, 881, 836, 775, 760, 722, 564, 536, 463 cm⁻¹; HRMS Cₘ₋₈₈Hₙ₉₀NaOₙ₇₈Si₂ (M+Na⁺) Calcd : 847.5340, Found : 847.5323; [α]D²⁶ +21.3 (c 1.09, CH₂Cl₂).

6,7-O-[(S)-Benzyldiene]pladienolide A (26)

TBAF (1M THF solution, 3.80 mL, 696 μmol) was added to a stirred solution of 25 (191 mg, 232 μmol) in THF (3.80 mL) at RT and stirred for 1.5 hr. The reaction mixture was poured into saturated aq. NH₄Cl solution and then extracted with EtOAc. The organic layer was washed with water and brine sequentially, dried over MgSO₄, and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (Kanto Chemical; heptane : EtOAc = 2 : 1 → 1 : 1) to give 26 (135 mg, quant.) as a colorless oil. 400 MHz ¹H-NMR (CD₃OD) δ (ppm) 0.93 (d, J = 7.2 Hz, 3H), 0.94 (d, J = 7.2 Hz, 3H), 0.97 (t, J = 7.4 Hz, 3H), 0.98 (d, J = 6.8 Hz, 3H), 1.13 (d, J = 6.8 Hz, 3H), 1.18-1.29 (m, 1H), 1.44 (s, 3H), 1.44-1.60 (m, 6H), 1.64-1.72 (m, 1H), 1.79 (d, J = 1.2 Hz, 3H), 2.00-2.10 (m, 1H), 2.33 (dd, J = 9.8, 14.6 Hz, 1H), 2.46-2.56 (m, 1H), 2.62-2.78 (m, 3H), 3.55 (dt, J = 4.8, 8.0 Hz, 1H), 3.93-4.01 (m, 1H), 4.28 (d, J = 9, 2 Hz, 1H), 4.97 (d, J = 10.4 Hz, 1H), 5.49 (dd, J = 9.6, 14.8 Hz, 1H), 5.69 (dd, J = 9.2, 14.8 Hz, 2H), 5.94 (s, 1H), 6.13 (brd, J = 11.0 Hz, 1H), 6.36 (dd, J = 11.0, 14.8 Hz, 1H), 7.40-7.43 (m, 3H), 7.51-7.34 (m, 2H); 100 MHz ¹³C-NMR (Acetone-d₆) δ (ppm) 10.20, 10.30, 11.26, 16.48, 20.87, 22.33, 27.88, 31.04, 34.09, 35.51, 39.80, 40.20, 41.53, 42.71, 56.45, 61.31, 70.01, 73.62, 82.39, 83.66, 85.21, 101.20, 124.65, 127.09, 128.30, 129.14, 130.49, 130.86, 131.74, 137.37, 139.11, 141.32, 169.85; IR (film) 3502, 2965, 2931, 2874, 1711, 1456, 1377, 1246, 1221, 1178, 1092, 1064, 971, 761 cm⁻¹; HRMS Cₘ₋₉₀H₉₀NaO₇₈Si₂ (M+Na⁺) Calcd : 605.3454, Found : 605.3449; [α]D²⁶ +13.0 (c 1.05, CH₂Cl₂).

6,7-O-[(S)-Benzyldiene]-3,21-O-bis(dichloroacetyl) pladienolide A (27)
Et$_3$N (686 µL, 4.92 mmol), dichloroacetic anhydride (375 µL, 2.46 mmol), and DMAP (15 mg, 123 µmol) were added to a stirred solution of 26 (144 mg, 2.46 mmol) in CH$_2$Cl$_2$ (7.20 mL) at 0°C and stirred at 0°C for 40 min. Additional DMAP (15 mg, 123 µmol) was added and stirred at 0°C for additional 1.5 hr. The reaction mixture was poured into water and then extracted with EtOAc. The organic layer was washed with water and brine sequentially, dried over MgSO$_4$, concentrated under reduced pressure. The residue was purified by silica gel column chromatography (Merck; heptane : EtOAc = 8 : 1 → 6 : 1 → 4 : 1) to give 27 (198 mg, quant.) as a yellow oil. 400 MHz $^1$H-NMR (CDCl$_3$) δ (ppm) 0.88 (d, $J = 6.8$ Hz, 3H), 0.93 (t, $J = 7.6$ Hz, 3H), 0.95 (d, $J = 6.8$ Hz, 3H), 1.07 (d, $J = 6.8$ Hz, 3H), 1.41 (s, 3H), 1.46-1.60 (m, 3H), 1.62-1.68 (m, 1H), 1.68-1.81 (m, 4H), 1.73 (s, 3H), 1.94-2.05 (m, 1H), 2.40-2.56 (m, 3H), 2.56-2.78 (m, 2H), 2.83 (dd, $J = 4.2$, 15.0 Hz, 1H), 4.21 (d, $J = 9.2$ Hz, 1H), 4.92 (d, $J = 10.4$ Hz, 1H), 5.02-5.08 (m, 1H), 5.12-5.22 (m, 1H), 5.42 (dd, $J = 9.6$, 15.2 Hz, 1H), 5.62 (dd, $J = 8.4$, 14.8 Hz, 1H), 5.67 (dd, $J = 9.6$, 15.2 Hz, 1H), 5.92 (s, 1H), 5.93 (s, 1H), 5.96 (s, 1H), 6.09 (d, $J = 10.8$ Hz, 1H), 6.24 (dd, $J = 10.8$, 14.8 Hz, 1H), 7.37-7.42 (m, 3H), 7.49-7.52 (m, 2H); 100 MHz $^{13}$C-NMR (CDCl$_3$) δ (ppm) 9.62, 10.96, 11.73, 16.48, 21.04, 22.62, 24.79, 27.87, 32.99, 35.31, 38.87, 39.30, 39.55, 40.13, 56.41, 60.03, 64.14, 64.58, 75.78, 80.54, 83.02, 83.19, 85.06, 101.26, 124.45, 126.61, 128.33, 129.31, 129.64, 130.86, 131.04, 137.74, 141.03, 164.06, 167.56; IR (film) 3015, 2972, 2931, 2877, 1759, 1739, 1576, 1457, 1377, 1281, 1248, 1171, 1092, 1066, 1004, 968, 911, 816, 758,699 cm$^{-1}$; HRMS C$_{39}$H$_{56}$Cl$_{5}$O$_{10}$Na (M+Na$^+$) Calcd : 825.2107; Found : 825.2120; [α]$_D^{23}$ +15.0 (c 1.02, CH$_2$Cl$_2$).

3.21-O-Bis(dichloroacetyl) pladienolide A (28) PPTS (70.5 mg, 280 µmol) was added to a solution of 27 (112 mg, 140 µmol) in MeOH (4.48 mL) and stirred at RT for 46 hr. The reaction mixture was poured into brine and then extracted with EtOAc. The organic layer was washed with water and brine sequentially, dried over MgSO$_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (Merck; heptane : EtOAc = 8 : 1 → 6 : 1 → 3 : 1 → 3 : 2 → 1 : 1) to give 28 (32.2 mg, 32%, 64% based on recovery) as a colorless oil and recovered 27 (55.9 mg). 400 MHz $^1$H-NMR (CDCl$_3$) δ (ppm) 0.90 (d, $J = 7.2$ Hz, 3H), 0.93 (t, $J = 7.2$ Hz, 3H), 0.96 (d, $J = 7.2$ Hz, 3H), 1.06 (d, $J = 6.8$ Hz, 3H), 1.32 (s, 3H), 1.43-1.62 (m, 5H), 1.63-1.69 (m, 2H), 1.72 (s, 3H), 1.72-1.79 (m, 2H), 2.00 (brs, 1H), 2.41-2.48 (m, 1H), 2.51-2.58 (m, 3H), 2.61 (dd, $J = 3.2$, 15.2 Hz, 1H), 2.66-2.70 (m, 1H), 2.74 (dd, $J = 4.0$, 15.2 Hz, 1H), 3.80 (dd, $J = 2.6$, 9.8 Hz, 1H), 4.93-4.97 (m, 1H), 5.01-5.05 (m, 1H), 5.05 (d, $J = 10.4$ Hz, 1H), 5.47 (dd, $J = 9.8$, 15.3 Hz, 1H), 5.61 (dd, $J = 8.0$, 15.1 Hz, 1H), 5.74 (dd, $J = 9.6$, 15.3 Hz, 1H), 5.97 (s, 1H), 5.98 (s, 1H), 6.07 (brd, $J = 10.4$ Hz, 1H), 6.24 (dd, $J = 10.4$, 15.1 Hz, 1H); 100 MHz $^{13}$C-NMR (CDCl$_3$) δ (ppm) 9.68, 11.00, 11.77, 16.51, 21.08, 24.60, 24.83, 25.61, 34.76, 35.35, 36.17, 39.34, 39.61, 40.47, 56.48, 60.07, 64.27, 64.61, 73.28, 74.59, 80.60, 83.08, 124.52, 129.71, 130.86, 131.11, 137.79, 141.06, 163.91, 164.17, 168.05; IR (film) 3526, 2971, 2929, 1759, 1745, 1456, 1377, 1281, 1217, 1171, 1092, 1008, 964, 927, 816, 757 cm$^{-1}$; HRMS C$_{39}$H$_{56}$Cl$_{5}$NaO$_9$
Pladenolide A (1)

K$_2$CO$_3$ (13.5 mg, 97.5 μmol) was added to a solution of 28 (69.9 mg, 97.5 μmol) in MeOH (2.50 mL) and stirred at RT for 20 min. The mixture was poured into brine and then extracted with EtOAc. The organic layer was dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (Kanto Chemical; heptane : acetone = 3 : 2 → 1 : 1) to give I (46.2 mg, 96%) as a colorless oil. Further purification by HPLC (Shiseido, CAPCELL PAK C18SG120; MeCN : water = 37 : 63) followed by lyophilization gave I as a white amorphous residue. 600 MHz $^1$H-NMR (CD$_3$OD) δ (ppm) 0.95 (d, J = 7.0 Hz, 3H), 0.95 (d, J = 6.7 Hz, 3H), 0.98 (t, J = 7.4 Hz, 3H), 1.13 (d, J = 6.8 Hz, 3H), 1.24 (m, 1H), 1.31 (s, 3H), 1.38 (m, 2H), 1.50 (m, 1H), 1.53 (m, 2H), 1.57 (m, 1H), 1.61 (m, 1H), 1.68 (ddd, J = 5.5, 5.9, 14.0 Hz, 1H), 1.79 (brs, 3H), 2.52 (m, 2H), 2.56 (m, 2H), 2.61 (ddq, J = 7.0, 9.8, 10.7 Hz, 1H), 2.70 (dd, J = 2.2, 8.2 Hz, 1H), 2.77 (ddd, J = 2.2, 5.9, 5.9 Hz, 1H), 3.56 (ddd, J = 4.5, 4.5, 8.7 Hz, 1H), 3.74 (d, J = 9.8 Hz, 1H), 3.81 (m, 1H), 5.07 (d, J = 10.7 Hz, 1H), 5.42 (dd, J = 9.8, 15.0 Hz, 1H), 5.70 (dd, J = 8.4, 15.0 Hz, 1H), 5.76 (dd, J = 9.8, 15.0 Hz, 1H), 6.13 (brd, J = 10.8 Hz, 1H), 6.37 (dd, J = 10.8, 15.0 Hz, 1H); 150 MHz $^{13}$C-NMR (CD$_3$OD) δ (ppm) 10.8, 10.9, 11.9, 17.1, 21.7, 24.4, 28.6, 30.5, 36.7, 36.7, 40.1, 40.7, 41.8, 42.8, 58.5, 65.3, 70.7, 74.7, 75.3, 78.2, 84.4, 125.9, 131.6, 132.1, 132.6, 137.7, 142.3, 171.9; IR (KBr) 3403, 2966, 2935, 2876, 1708, 1458, 1371, 1256, 1177, 1060, 1021, 977, 903, 789 cm$^{-1}$; HRMS C$_2$H$_{14}$NaO$_5$ (M+Na$^+$) Calcd : 517.3141, Found : 517.3134; [α]$_D^{27}$ -1.54 (c 1.02, MeOH).

Pladenolide B (2)

Et$_3$N (17.2 μL, 123 μmol), acetic anhydride (5.83 μL, 616 μmol), and DMAP (1.50 mg, 12.3 μmol) were added to a stirred solution of 1 (30.5 mg, 61.6 μmol) in CH$_3$Cl$_2$ (2.0 mL) at 0°C and stirred for 1 hr. The mixture was poured into a saturated aq. NaHCO$_3$ solution and then extracted with EtOAc. The organic layer was washed with brine, dried over MgSO$_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (Kanto Chemical; heptane : acetone = 3 : 1 → 2 : 1) to give 2 (27.2 mg, 82%) as a colorless oil. Further purification by HPLC (Shiseido, CAPCELL PAK C18SG120; MeCN : water = 45 : 55) followed by lyophilization gave 2 as a white amorphous residue. 600 MHz $^1$H-NMR (CD$_3$OD) δ (ppm) 0.93 (d, J = 6.8 Hz, 3H), 0.95 (d, J = 7.0 Hz, 3H), 0.98 (t, J = 7.4 Hz, 3H), 1.13 (d, J = 6.8 Hz, 3H), 1.23 (s, 3H), 1.24 (m, 1H), 1.41 (m, 1H), 1.42 (m, 1H), 1.51 (m, 1H), 1.53 (m, 2H), 1.61 (m, 1H), 1.67 (m, 1H), 1.68 (m, 1H), 1.79 (brs, 3H), 2.10 (s, 3H), 2.52 (m, 1H), 2.57 (m, 2H), 2.61 (ddq, J = 6.8, 9.9, 10.1 Hz, 1H), 2.70 (dd, J = 2.2, 8.2 Hz, 1H), 2.77 (ddd, J = 2.2, 5.9, 5.9 Hz, 1H), 3.55 (ddd, J = 4.5, 4.5, 8.7 Hz, 1H), 3.82 (m, 1H), 5.09 (d, J = 9.8 Hz, 1H), 5.09 (d, J = 10.1 Hz, 1H), 5.61 (dd, J = 9.9, 15.2 Hz, 1H), 5.70 (dd, J = 8.4, 15.0 Hz, 1H), 5.74 (dd, J = 9.8, 15.2 Hz, 1H), 6.13 (brd, J = 10.8 Hz, 1H), 6.37 (dd, J = 10.8, 15.0 Hz, 1H); 150 MHz $^{13}$C-NMR (CD$_3$OD) δ (ppm) 10.8, 10.9, 11.9, 16.9, 21.1,
21.7, 24.2, 28.6, 30.4, 36.7, 37.5, 40.1, 40.7, 41.7, 42.8, 58.5, 63.0, 70.4, 74.1, 75.3, 80.3, 84.3, 125.8, 127.0, 132.2, 132.4, 141.6, 142.3, 171.8, 172.2; IR (KBr) 3447, 2966, 2935, 2875, 1735, 1720, 1458, 1372, 1244, 1175, 1022, 978, 910, 551, 478 cm⁻¹; HRMS C₃₀H₄₈NaO₈ (M+Na⁺) Calcd : 559.3247, Found : 559.3227; [α]D²⁷ +7.90 (c 1.10, MeOH).

Chemical degradation and derivatization of pladienolide D

3,16,21- O-Tris(triethylsilyl)pladienolide D (S17)

To a stirred solution of natural pladienolide D (3) (200 mg, 0.298 mmol) in CH₂Cl₂ (4 mL), Et₃N (151 µL, 0.149 mmol), TESCl (500 µL, 2.98 mmol), and DMAP (15 mg, 0.123 mmol) were added at RT and stirred overnight. The reaction mixture was diluted with EtOAc, washed with water and brine sequentially, dried over Na₂SO₄, and concentrated. The obtained residue was purified by silica gel column chromatography (Kanto Chemical, Silica Gel 60N, spherical, 40-100 µm, hexane : EtOAc = 20 : 1 → 5 : 1) to give S17 (220 mg, 82%) as a colorless oil. 400 MHz ¹H-NMR (CD₃OD) δ (ppm) 0.56-0.72 (m, 18H), 0.80-0.88 (m, 6H), 0.89 (t, J = 6.8 Hz, 3H), 0.90-1.06 (m, 27H), 1.17 (s, 3H), 1.16-1.26 (m, 1H), 1.30-1.40 (m, 2H), 1.42 (s, 3H), 1.38-1.74 (m, 5H), 1.75 (brs, 3H), 1.93 (dd, J = 4.8, 14.0 Hz, 1H), 2.05 (s, 3H), 2.39 (dd, J = 4.4, 13.6 Hz, 1H), 2.52 (dd, J = 3.2, 14.0 Hz, 1H), 2.52-2.60 (m, 1H), 2.61 (dd, J = 2.0, 8.0 Hz, 1H), 2.84-2.92 (m, 1H), 3.65-3.80 (m, 1H), 3.75-3.98 (m, 1H), 4.93 (d, J = 10.8 Hz, 1H), 5.02 (d, J = 10.0 Hz, 1H), 5.56 (dd, J = 9.6, 15.2 Hz, 1H), 5.70 (dd, J = 9.2, 15.2 Hz, 1H), 5.82 (d, J = 15.2 Hz, 1H), 6.12 (dd, J = 10.8 Hz, 1H), 6.50 (dd, J = 11.2, 15.2 Hz, 1H); 150 MHz ¹³C-NMR (CD₃OD) δ (ppm) 5.6, 6.2, 7.3, 7.5, 7.6, 7.8, 10.3, 10.5, 12.2, 17.0, 21.2, 24.4, 28.7, 29.2, 31.6, 37.5, 41.5, 41.5, 41.6, 47.7, 56.6, 62.3, 71.6, 74.1, 75.7, 76.0, 80.2, 84.1, 124.2, 127.0, 131.3, 134.2, 141.4, 143.0, 170.2, 171.8; [α]D²⁵ +3.43 (c 1.66, CH₂Cl₂).

5,6-Anhydro-1,2,4,7-tetrae deoxy-4-methyl-8-C-methyl-3,8-bis-O-(triethylsilyl)-1-L-glycer o-D-galacto-nonitol (29), (1R)-1,2-Anhydro-3,5-dideoxy-4-C-{[(1E)-3-hydroxyprop-1-en-1-yl]-1-{[(1S,2S)-1-methyl-2-[(triethyl silyl)oxy]butyl]-4-O-(triethylsilyl)-D-erythro-pentitol (S18), (2S,3S,4E,6S,7R,10R)-7-hydroxy-2-(1-hydroxyethyl)-3,7-dimethyl-12-oxo-10-[(triethylsilyl)oxy]oxacyclododec-4-en-6-yl acetate (S19) and (2S,3S,4E,6S,7R,10R)-7-Hydroxy-2-{[(1E)-3-hydroxy-1-methylprop-1-en-1-yl]-3,7-dimethyl-12-oxo-10-[(triethylsilyl)oxy]oxacyclododec-4-en-6-yl acetate (S20)

To a stirred solution of 3,16,21-O-tri s(triethylsilyl)pladienolide D (S17) (210 mg, 0.235 mmol) in CH₂Cl₂ - MeOH (25 mL - 25 mL), O₃ was bubbled (flow rate 2 L/min, electric voltage 90 V) for 3 min with stirring at −78°C. After addition of NaBH₄ (88.9 mg, 2.35 mmol), the mixture was allowed to warm to 0°C and stirred for 1.5 hr. The reaction mixture was
diluted with EtOAc, washed with brine, dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (Merck; heptane : EtOAc = 10 : 1 → 3 : 2 → 1 : 2) to give S29 (77.3 mg, 38%) as a colorless oil, S18 (17.3 mg, 9%) as a colorless oil, S19 (49.1 mg, 36%) as a colorless oil, and S20 (38.5 mg, 25%) as a colorless oil. S29: 400 MHz ¹H-NMR (CD₂OD) δ (ppm) 0.64-0.72 (m, 1H), 0.89 (t, J = 7.2 Hz, 3H), 0.98 (d, J = 7.6 Hz, 3H), 1.03 (t, J = 8.0 Hz, 9H), 1.04 (t, J = 8.0 Hz, 9H), 1.26 (s, 3H), 1.28-1.40 (m, 1H), 1.52-1.65 (m, 2H), 1.68 (dd, J = 6.4, 14.4 Hz, 1H), 1.77 (dd, J = 5.2, 14.4 Hz, 1H), 2.71 (dd, J = 2.4, 8.0 Hz, 1H), 2.95-3.02 (m, 1H), 3.48 (d, J = 9.6 Hz, 1H), 3.55 (d, J = 9.6 Hz, 1H), 3.79 (dt, J = 3.2, 6.4 Hz, 1H); MS C₂₃H₉₀NaO₆Si₂ (M+Na⁺) Calcd : 469.31, Found : 469.16. S18: 400 MHz ¹H-NMR (CD₂OD) δ (ppm) 0.69 (q, J = 8.0 Hz, 6H), 0.70 (q, J = 8.0 Hz, 6H), 0.89 (t, J = 7.2 Hz, 3H), 1.02 (t, J = 8.0 Hz, 9H), 1.03 (t, J = 8.0 Hz, 9H), 1.28-1.40 (m, 1H), 1.46 (s, 3H), 1.52-1.66 (m, 2H), 1.70-1.84 (m, 2H), 2.69 (dd, J = 2.4, 8.4 Hz, 1H), 2.95 (dt, J = 2.4, 5.6 Hz, 1H), 3.81 (dt, J = 3.2, 6.4 Hz, 1H), 4.12 (d, J = 4.0 Hz, 2H), 5.78-5.88 (m, 2H); MS C₂₃H₉₀NaO₆Si₂ (M+Na⁺) Calcd : 495.33, Found : 495.31. S19: 400 MHz ¹H-NMR (CDCl₃) δ (ppm) 0.62 (q, J = 8.0 Hz, 6H), 0.97 (t, J = 8.0 Hz, 9H), 1.06 (d, J = 6.8 Hz, 3H), 1.15 (d, J = 6.4 Hz, 3H), 1.18 (s, 3H), 1.32-1.68 (m, 4H), 2.08 (s, 3H), 2.42-2.64 (m, 2H), 2.68-2.80 (m, 1H), 3.80-3.90 (m, 1H), 3.95-4.07 (m, 1H), 4.71 (d, J = 10.4 Hz, 1H), 5.08 (d, J = 9.2, 1H), 5.60-5.72 (m, 2H); MS C₂₃H₉₀NaO₆Si (M+Na⁺) Calcd : 481.26, Found : 481.22. S20: MS C₂₃H₉₀NaO₆Si (M+Na⁺) Calcd : 507.28, Found : 507.27.

5,6-Anhydro-1,2,4,7-tetrahydroxy-4-methyl-8-C-methyl-L-glycero-D-galacto-nonitol (S21)

![Image](image-url)

To a stirred solution of alcohol S29 (23.0 mg, 51.5 μmol) in THF (2 mL), TBAF (1M THF solution, 129 μL, 129 μmol) was added and stirred at RT for 2 hr. The reaction mixture was diluted with EtOAc, washed with water and brine sequentially, dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (Kanto Chemical, Silica Gel 60N, spherical, 40-100 μm, EtOAc) to give alcohol S21 (10.0 mg, 89%) as a colorless oil. 400 MHz ¹H-NMR (CD₂OD) δ (ppm) 0.99 (d, J = 7.2 Hz, 3H), 0.99 (t, J = 7.6 Hz, 3H), 1.26 (s, 3H), 1.33-1.64 (m, 3H), 1.67 (dd, J = 6.8, 14.4 Hz, 1H), 1.77 (dd, J = 5.2, 14.4 Hz, 1H), 2.74 (dd, J = 2.4, 7.6 Hz, 1H), 2.95-3.02 (m, 1H), 3.36-3.50 (m, 2H), 3.60 (dt, J = 4.0, 8.0 Hz, 1H).

1,4-Anhydro-3,6,8,9-tetrahydroxy-6-methyl-2-C-methyl-L-glycero-D-allo-nonitol (30)

![Image](image-url)

To a stirred solution of alcohol S21 (10.0 mg, 45.8 μmol) in MeOH (1 mL, distilled over CaH₂), tBuOK (60.0 mg, 53.5 μmol) was added and stirred at RT for 6 hr. Water was added to the reaction mixture and then extracted with EtOAc. The organic layer was washed with water and brine sequentially, dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (Merck; EtOAc) to give triol 30 (7.3 mg, 73%) as a colorless oil. 400 MHz ¹H-NMR (CDCl₃) δ (ppm) 0.90 (d, J = 7.2 Hz, 3H), 0.98 (t, J = 7.6 Hz, 3H), 1.43 (s, 3H), 1.40-1.60 (m, 2H), 1.65-1.80 (m, 1H), 1.95 (d, J = 8.0 Hz, 2H), 3.65-3.80 (m, 1H), 3.70 (d, J = 9.2 Hz, 1H), 3.76 (d, J = 9.2 Hz, 1H), 3.81 (dd, J = 4.8, 8.0 Hz, 1H), 4.34 (dt, J = 4.8, 8.0 Hz, 1H).
1,4-Anhydro-5,7-O-(4-bromobenzylidene)-3,6,8,9-tetra(oxy-6-methyl-2-C-methyl-L-glycero-D-allo-nonitol (31a) and (31b)

![Chemical Structures](image)

To a stirred solution of triol 30 (7.3 mg, 33.4 µmol) in CH₂Cl₂ (1 mL), CSA (1.5 mg, 6.5 µmol) and 4-bromobenzaldehyde dimethyl acetal (15.0 mg, 64.9 µmol) were added and stirred at RT for 24 hr. The reaction mixture was diluted with EtOAc, washed with water and brine sequentially, dried over MgSO₄, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (Merck; EtOAc) to give α-benzylidene acetal 31a (7.0 mg, 54%) as a colorless oil and β-benzylidene acetal 31b (3.6 mg, 28%) as a colorless oil. 31a: 600 MHz 1H-NMR (CDCl₃) δ (ppm) 0.86 (t, J = 7.4 Hz, 3H), 1.00 (s, 3H), 1.19 (d, J = 7.1 Hz, 3H), 1.24 (ddq, J = 5.3, 7.4, 13.9 Hz, 1H), 1.55 (dd, J = 9.6, 13.0 Hz, 1H), 1.62 (ddq, J = 7.4, 8.0, 13.9 Hz, 1H), 1.91, (ddd, J = 1.2, 5.9, 13.0 Hz, 1H), 1.98 (qdd, J = 0.8, 2.4, 7.1 Hz, 1H), 3.40 (d, J = 9.0 Hz, 1H), 3.55 (dd, J = 1.2, 9.0 Hz, 1H), 3.57 (brd, J = 9.3 Hz, 1H), 3.87 (ddd, J = 2.4, 5.3, 8.0 Hz, 1H), 4.82 (ddd, J = 5.9, 9.3, 9.6 Hz, 1H), 5.44 (s, 1H), 7.28 (d, J = 8.5 Hz, 2H), 7.33 (d, J = 8.5 Hz, 2H); 150 MHz ¹³C-NMR (CDCl₃) δ (ppm); 10.0, 13.1, 24.4, 25.9, 31.4, 45.2, 76.0, 76.8, 78.4, 79.8, 83.2, 96.2, 122.8, 128.4, 131.4, 139.2; HRMS C₁₅H₂₅⁷⁹BrNaO₄ (M+Na⁺) Calcd : 407.0834, Found : 407.0856. 31b: 600 MHz ¹H-NMR (CDCl₃) δ (ppm) 0.53 (d, J = 7.1 Hz, 3H), 0.85 (t, J = 7.4 Hz, 3H), 1.07 (s, 3H), 1.05 (ddq, J = 4.0, 7.4, 11.8 Hz, 1H), 1.60 (ddq, J = 7.4, 11.7, 11.8 Hz, 1H), 1.72 (ddd, J = 1.3, 6.6, 12.8 Hz, 1H), 1.92 (ddq, J = 5.4, 7.1, 10.4 Hz, 1H), 1.96, (dd, J = 9.3, 12.8 Hz, 1H), 3.60 (dd, J = 1.3, 8.8 Hz, 1H), 3.63 (d, J = 8.8 Hz, 1H), 3.65 (ddd, J = 4.0, 5.4, 11.7 Hz, 1H), 3.82 (dd, J = 4.0, 10.4 Hz, 1H), 4.32 (ddd, J = 4.0, 6.6, 9.3 Hz, 1H), 5.50 (s, 1H), 7.32 (m, 4H); 150 MHz ¹³C-NMR (CDCl₃) δ (ppm); 10.3, 12.6, 18.0, 23.9, 35.5, 41.1, 77.7, 78.4, 79.2, 79.8, 80.2, 92.9, 122.7, 128.3, 131.4, 139.2; HRMS C₁₅H₂₅⁷⁹BrNaO₄ (M+Na⁺) Calcd : 407.0834, Found : 407.0824.

**Total synthesis of pladienolide D**

< Synthesis of macroside part >

(2S,3aS,4E,6S,7S,11R,13aR)-11-[(tert-Butyl(dimethyl)silyl)oxy]-6,13a-dimethyl-7-[(1E)-1-methylbuta-1,3-diene-1-yl]-2-phenyl-3a,6,7,10,11,12,13,13a-octahydro-9H-[1,3]dioxolo[4,5-f]oxacyclodecacin-9-one (S22)

To a stirred solution of aldehyde 17 (50.0 mg, 0.09 mmol) in THF-toluene (0.4 mL - 2.8 mL), pyridine (0.38 mL, 4.73 mmol) and Tebbe reagent (0.5M toluene solution, 1.14 mL, 0.57 mmol) were added at -40°C and stirred for 30 min. The mixture was warmed to RT and stirred for additional 1 hr. After the reaction was quenched by adding water (1 mL), the reaction mixture was diluted with EtOAc, washed with water and brine sequentially, dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (Merck; hexane : diethyl ether = 4 : 1) to obtain the diene S22 (36.3 mg, 75%) as a colorless
amorphous residue. 400 MHz $^{1}$H-NMR (CDCl$_3$) $\delta$ (ppm) 0.07 (s, 3H), 0.09 (s, 3H), 0.88 (s, 9H), 0.89 (d, $J = 6.0$ Hz, 3H), 1.35-1.47 (m, 2H), 1.38 (s, 3H), 1.59-1.67 (m, 1H), 1.74 (d, $J = 0.8$ Hz, 3H), 2.01-2.09 (m, 1H), 2.31 (dd, $J = 10.4$, 14.4 Hz, 1H), 2.58 (dd, $J = 4.4$, 14.4 Hz, 1H), 2.54-2.63 (m, 1H), 3.94-4.02 (m, 1H), 4.19 (d, $J = 9.2$ Hz, 1H), 4.97 (d, $J = 10.4$ Hz, 1H), 5.18 (dd, $J = 1.6$, 17.6 Hz, 1H), 5.27 (dd, $J = 1.6$, 17.2 Hz, 1H), 5.40 (dd, $J = 9.6$, 15.2 Hz, 1H), 5.64 (dd, $J = 9.6$, 15.2 Hz, 1H), 5.91 (s, 1H), 6.13 (d, $J = 10.8$ Hz, 1H), 6.54 (dt, $J = 10.4$, 17.2 Hz, 1H), 7.34-7.41 (m, 3H), 7.48-7.52 (m, 2H); 100 MHz $^{13}$C-NMR (CDCl$_3$) $\delta$ (ppm) -4.63, -4.51, 11.63, 16.72, 17.93, 22.82, 25.72, 31.59, 34.42, 40.24, 44.11, 71.62, 82.07, 83.61, 85.32, 101.21, 118.83, 126.75, 128.32, 129.28, 129.57, 131.26, 131.87, 133.41, 137.69, 137.76, 169.18; IR (KBr) = 2957, 2931, 2857, 1735, 1459, 1375, 1275, 1244, 1174, 1078, 1005, 975, 908, 877, 835, 735, 759, 698 cm$^{-1}$; HRMS $C_{31}H_{46}AgO_3Si (M+Ag^+)$ Calcd : 633.2165, Found : 633.2189; $[\alpha]_D^{23} +19.5$ (c 0.90, CHCl$_3$).

(4R,7R,8S,9E,11S,12S)-4,7,8-Trihydroxy-7,11-dimethyl-12-[(1E)-1-methylbuta-1,3-dien-1-yl]oxacyclo-dodec-9-en-2-one (S23)

PPTS (68.2 mg, 271 $\mu$mol) were added to a stirred solution of diene S22 (36.0 mg, 0.07 mmol) in MeOH (1.22 mL) and stirred at RT for 4 days. Distilled water (1 mL) was added to the reaction mixture. The mixture was diluted with EtOAc, washed with water and brine sequentially, dried over Na$_2$SO$_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (Merck; hexane : diethyl ether = 1 : 3) to give S23 (18.3 mg, 77%) as a white solid. 400 MHz $^{1}$H-NMR (CDCl$_3$) $\delta$ (ppm) 0.92 (d, $J = 6.9$ Hz, 3H), 1.24-1.32 (m, 1H), 1.31 (s, 3H), 1.36-1.72 (m, 3H), 1.76 (d, $J = 1.0$ Hz, 3H), 2.51-2.65 (m, 3H), 3.72-3.77 (m, 1H), 3.82 (d, $J = 9.6$ Hz, 1H), 5.17 (d, $J = 10.8$ Hz, 1H), 5.20 (d, $J = 11.2$ Hz, 1H), 5.28 (dd, $J = 1.6$, 16.8 Hz, 1H), 5.43 (dd, $J = 10.0$, 15.2 Hz, 1H), 5.73 (dd, $J = 10.0$, 15.2 Hz, 1H), 6.12 (d, $J = 11.6$ Hz, 1H), 6.55 (dt, $J = 10.4$, 16.8 Hz, 1H); 100 MHz $^{13}$C-NMR (CDCl$_3$) $\delta$ (ppm) 11.75, 16.52, 24.45, 29.72, 35.57, 38.23, 40.66, 69.23, 73.39, 77.12, 82.45, 119.17, 130.19, 131.61, 131.81, 132.94, 137.18, 172.16; IR (KBr) = 3473, 3336, 2960, 2928, 2872, 1729, 1604, 1580, 1460, 1274, 1122, 1028, 959, 743, 420 cm$^{-1}$; HRMS $C_{18}H_{26}AgO_5 (M+Ag^+)$ Calcd : 431.0988, Found : 431.0960; $[\alpha]_D^{22} +7.01$ (c 1.09, CHCl$_3$); m.p. 146.0-148.0$^\circ$C.

(2S,3S,4E,6S,7R,10R)-7,10-Dihydroxy-3,7-dimethyl-2-[(1E)-1-methylbuta-1,3-dien-1-yl]-12-oxooxacyclo-dodec-4-en-6-yl acetate (32)

Et$_3$N (35.6 $\mu$L, 246 $\mu$mol), acetic anhydride (11.6 $\mu$L, 123 $\mu$mol), and DMAP (3.0 mg, 24.6 $\mu$mol) were added to a solution of triol S22 (40.0 mg, 123 $\mu$mol) in CH$_2$Cl$_2$ (2 mL) at 0$^\circ$C and stirred for 1 hr. The solution was poured into a saturated aq. NaHCO$_3$ solution and then extracted with EtOAc. The organic layer was washed with water and brine sequentially, dried over Na$_2$SO$_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (Merck; hexane : ether = 1 : 2) to give 32 (42.0 mg, 93%) as a white solid. 400 MHz $^{1}$H-NMR (CDCl$_3$) $\delta$ (ppm) 0.90 (d, $J = 6.8$ Hz, 3H), 1.21 (s, 3H), 1.25-1.42 (m, 2H), 1.51-1.74 (m, 2H), 1.75 (s, 3H), 2.09 (s, 3H), 2.16 (s, 1H), 2.46-2.67 (m, 3H), 3.54 (d, $J = 11.2$ Hz, 1H), 3.70-3.80 (m, 1H), 5.09 (d, $J = 8.8$ Hz, 1H), 5.17 (d, $J = 10.8$ Hz, 1H), 5.18 (d, $J = 11.0$ Hz, 1H), 6.53 (d, $J = 8.0$ Hz, 1H), 6.93 (s, 1H), 7.21 (d, $J = 8.0$ Hz, 1H), 7.32 (s, 1H), 7.45 (d, $J = 8.0$ Hz, 1H), 7.89 (d, $J = 8.0$ Hz, 1H), 8.02 (d, $J = 8.0$ Hz, 1H), 8.19 (d, $J = 8.0$ Hz, 1H), 8.28 (d, $J = 8.0$ Hz, 1H), 8.38 (d, $J = 8.0$ Hz, 1H), 8.48 (d, $J = 8.0$ Hz, 1H), 8.58 (d, $J = 8.0$ Hz, 1H), 8.68 (d, $J = 8.0$ Hz, 1H), 8.78 (d, $J = 8.0$ Hz, 1H), 8.88 (d, $J = 8.0$ Hz, 1H), 8.98 (d, $J = 8.0$ Hz, 1H), 9.08 (d, $J = 8.0$ Hz, 1H).
10.0 Hz, 1H), 5.28 (d, J = 16.8 Hz, 1H), 5.61 (dd, J = 9.6, 15.2 Hz, 1H), 5.68 (dd, J = 9.6, 15.2 Hz, 1H), 6.12 (d, J = 10.8 Hz, 1H), 6.55 (dt, J = 10.4, 16.8 Hz, 1H); 100 MHz 13C-NMR (CDCl3) δ (ppm) 11.75, 16.40, 21.24, 24.57, 29.75, 35.15, 38.26, 40.71, 69.11, 73.35, 78.85, 82.39, 119.19, 125.57, 131.65, 131.79, 132.88, 140.39, 169.61, 172.00; IR (KBr) = 3513, 3404, 2970, 2948, 2876, 1734, 1705, 1454, 1429, 1405, 1361, 1248, 1175, 1051, 1023, 968, 921, 652, 550, 508 cm⁻¹; HRMS C20H19O6Na (M+Na⁺) Calcd: 389.1940, Found: 389.1927; [α]D²² +22.2 (c 1.21, CHCl₃); m.p. 156.0-158.0°C.

< Synthesis of side chain part >

Methyl-(2E)-3-methyl-5-[(1-phenyl-1-H-tetrazol-5-yl)thio]pent-2-enoate (S24)[29]

To a stirred solution of alcohol S3 (1.16 g, 7.31 mmol)[28] in THF (36.8 mL), 5-mercapto-1-phenyltetrazole (2.62 g, 14.60 mmol), Ph3P (3.83 g, 14.6 mmol), and DIAD (95%, 2.96 g, 14.6 mmol) were added at 0°C and stirred at ambient temperature for 2 hr. The mixture was diluted with EtOAc, washed with water and brine sequentially, dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (Merck; hexane : EtOAc = 5:1) to give S24 (2.33 g, quant.) as a white solid. Analytical sample was further purified by recrystallization (EtOAc/hexane). 400 MHz 1H-NMR (CDCl₃) δ (ppm) 2.22 (d, J = 1.2 Hz, 3H), 2.70 (t, J = 7.2 Hz, 2H), 3.54 (t, J = 7.2 Hz, 2H), 3.70 (s, 3H), 5.70-5.74 (q, J = 1.2 Hz, 1H), 7.52-7.59 (m, 5H); 100 MHz 13C-NMR (CDCl₃) δ (ppm) 18.41, 30.75, 39.68, 50.94, 117.30, 123.73, 129.81, 130.18, 133.46, 153.79, 155.84, 166.49; IR (KBr) = 3071, 2991, 2948, 1707, 1648, 1593, 1499, 1437, 1412, 1380, 1226, 1153, 1057, 877, 761, 693, 559, 485, 407 cm⁻¹; HRMS C₁₄H₁₆AgₙO₄S (M+Ag⁺) Calcd : 411.0045, Found : 411.0073; m.p. 53.0-54.0°C.

Methyl-(2E)-3-methyl-5-[(1-phenyl-1-H-tetrazol-5-yl)sulfonyl]pent-2-enoate (34)[30]

To a stirred solution of S24 (7.53 g, 24.70 mmol) in EtOH (150 mL), a solution of hexaammonium heptamolybdate tetrahydrate (2.91 g, 2.35 mmol) in 30% H₂O₂ (26.7 mL) was added and stirred at RT for 12 hr. The reaction mixture was diluted with EtOAc, washed with water and brine sequentially, dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (Merck; hexane : EtOAc = 4:1) to give 34 (8.24 g, quant.) as a white solid. Analytical sample was further purified by recrystallization (EtOAc/hexane). 400 MHz 1H-NMR (CDCl₃) δ (ppm) 2.24 (d, J = 1.2 Hz, 3H), 2.79-2.83 (m, 2H), 3.71 (s, 3H), 3.88-3.92 (m, 2H), 5.78 (q, J = 1.2 Hz, 1H), 7.60-7.71 (m, 5H); 100 MHz 13C-NMR (CDCl₃) δ (ppm) 18.25, 32.44, 50.90, 53.59, 117.67, 124.83, 129.51, 131.30, 132.66, 152.97, 165.99; IR (KBr) = 3102, 3075, 2952, 2913, 1703, 1651, 1495, 1439, 1346, 1238, 1160, 1047, 998, 923, 882, 764, 689, 593, 550, 507, 456, 420 cm⁻¹; HRMS C₁₄H₁₆AgₙO₄S (M+Ag⁺) Calcd : 442.9943, Found : 442.9929; m.p. 65.0-67.0°C.

Methyl-(2E,5E,7S,8S)-3,7-dimethyl-8-[(triethylsilyloxy)deca-2,5-dienoate (35)[38]

KHMDMS (0.5M toluene solution, 8.48 mL, 4.24 mmol) was added dropwise to a stirred solution of sulfone 34 (1.19 g, 3.53 mmol) in dry DME (40 mL, freshly distilled from LAH before use) at −60°C and stirred for 30 min.
Subsequently, a solution of aldehyde 19 (1.63 g, 7.06 mmol) in dry THF (5 mL, freshly distilled from LAH before use) was added dropwise at −78°C and stirred for 2 hr. The mixture was warmed to RT and water was added. The mixture was diluted with EtOAc, washed with brine, dried over Na₂SO₄, and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (Merck; hexane : diethyl ether = 50 : 1) to afford 35 (1.17 g, 97%) as a colorless oil. The obtained 35 was determined to be a mixture of E/Z = 17:1 by ¹H-NMR, 400 MHz ¹H-NMR (CDCl₃) δ (ppm) 0.60 (q, J = 8.0 Hz, 6H), 0.87 (t, J = 7.2 Hz, 3H), 0.95 (t, J = 8.0 Hz, 9H), 0.96 (d, J = 6.8 Hz, 3H), 1.35-1.50 (m, 2H), 2.14 (d, J = 1.2 Hz, 3H), 2.25-2.31 (m, 1H), 2.82 (d, J = 6.4 Hz, 2H), 3.44-3.48 (m, 1H), 3.69 (s, 3H), 5.36 (ddd, J = 6.8, 13.6, 15.6 Hz, 1H), 5.51 (dd, J = 7.6, 15.2 Hz, 1H), 5.68 (q, J = 1.2 Hz, 1H); 100 MHz ¹³C-NMR (CDCl₃) δ (ppm) 5.04, 6.78, 9.35, 15.41, 18.57, 26.65, 41.50, 43.86, 50.48, 77.18, 115.38, 124.80, 136.84, 158.86, 166.97; IR (film) = 2958, 2879, 2352, 2330, 1723, 1651, 1435, 1219, 1147, 1013, 740 cm⁻¹; HRMS C₁₉H₃₆AgO₄Si (M+Ag⁺) Calcd: 447.1485, Found: 447.1461; [α]D²¹ = -22.1 (c 1.10, CHCl₃).

*(2E,5E,7S,8S)-3,7-Dimethyl-8-[(triethylysilyl)oxy]deca-2,5-dien-1-ol (S25)*

DIBAL (1M toluene solution, 1.76 mL, 1.76 mmol) was added dropwise to a stirred solution of 35 (0.22 g, 0.64 mmol) in toluene (6 mL) at −78°C and stirred for 30 minutes. The reaction mixture was diluted with diethyl ether, followed by an addition of a saturated Rochelle salt solution (1.0 mL). The mixture was stirred at ambient temperature for 2 hr. The organic layer was dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (Merck; hexane : diethyl ether = 8:1) to give S25 (150 mg, 74%) as a colorless oil. 400 MHz ¹H-NMR (CDCl₃) δ (ppm) 0.60 (q, J = 7.6 Hz, 6H), 0.87 (t, J = 7.6 Hz, 3H), 0.95 (d, J = 14.0 Hz, 3H), 0.96 (t, J = 7.6 Hz, 9H), 1.35-1.50 (m, 2H), 1.65 (brs, 3H), 2.24-2.29 (m, 1H), 2.70 (d, J = 6.4 Hz, 2H), 3.45 (dd, J = 5.6 Hz, 1H), 4.16 (d, J = 7.2 Hz, 2H), 5.32-5.48 (m, 3H); 100 MHz ¹³C-NMR (CDCl₃) δ (ppm) 5.08, 6.85, 9.37, 15.73, 16.08, 26.72, 41.50, 42.82, 59.10, 77.39, 123.82, 126.73, 135.25, 138.53; IR (film) = 3330, 2959, 2875, 1671, 1459, 1419, 1009, 740 cm⁻¹; HRMS C₁₉H₃₆AgO₂Si (M+Ag⁺) Calcd: 419.1536, Found: 419.1572; [α]D²¹ = -23.4 (c 1.45, CHCl₃).

*(2R,3R)-3-Methyl-3-[(2E,4S,5S)-4-methyl-5-[(triethylysilyl)oxy]hept-2-en-1-yl]oxiran-2-yl)methanol (36)*

To a stirred suspension of activated molecular sieves 4Å powder (880 mg) in dry CH₂Cl₂ (22 mL, freshly distilled over CaH₂), (−)-DET (2.01 mL, 11.7 mmol) and Ti(OiPr)₄ (2.32 mL, 7.89 mmol) were added at −30°C under argon atmosphere and stirred for 5 min. Subsequently, a solution of S25 (1.76 g, 5.63 mmol) in dry CH₂Cl₂ (4 mL) was added dropwise to the mixture and stirred for 30 min. To the mixture, tert-butyl hydroperoxide (5M decane solution, 2.26 mL, 11.20 mmol) was added dropwise over 15 min and stirred for further 1.5 hr at the same temperature. Distilled water (5 mL) was added to the mixture and then the mixture was filtered through Celite® pad. The filtrate was diluted with EtOAc, washed with water and brine sequentially, dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (Kanto Chemical, Silica Gel 60N, spherical, 40-100 µm, heptane : EtOAc = 5 : 1) to afford 36 (1.69 g, 91%, 90% de) as a colorless oil. The optical purity of 36 was determined by HPLC (DAICEL CHEMICAL INDUSTRIES,
CHIRALPAK AD-H, hexane : isopropyl alcohol = 90 : 10) of the corresponding tosylate 37. 400 MHz $^1$H-NMR (CD$_3$OD) $\delta$ (ppm) 0.67 (q, J = 8.0 Hz, 6H), 0.93 (t, J = 7.6 Hz, 3H), 1.02 (d, J = 6.8 Hz, 3H), 1.03 (t, J = 8.0 Hz, 9H), 1.29 (s, 3H), 1.45-1.58 (m, 2H), 2.23-2.35 (m, 3H), 2.97 (dd, J = 4.8, 6.4 Hz, 1H), 3.56 (dt, J = 5.6, 6.0 Hz, 1H), 3.63 (dd, J = 6.0, 12.0 Hz, 1H), 3.75 (dd, J = 4.8, 12.0 Hz, 1H), 5.13 (dt, J = 7.2, 15.6 Hz, 1H), 5.57 (dd, J = 7.6, 15.6 Hz, 1H); 100 MHz $^{13}$C-NMR (CD$_3$OD) $\delta$ (ppm) 6.14, 7.43, 9.85, 16.39, 17.05, 27.91, 42.79, 42.99, 61.68, 61.72, 63.68, 78.70, 125.23, 138.18; IR (film) = 3422, 2959, 2877, 1459, 1239, 1103, 1016, 740 cm$^{-1}$; HRMS C$_{18}$H$_{38}$AgO$_5$Si (M+Ag$^+$) Calcd: 435.1485, Found: 435.1492; [\alpha]_D$^{21}$ +15.1 (c 2.14, MeOH) (90% de).

$(2R,3R)$-3-Methyl-3-[(2E,4S,5S)-4-methyl-5-[(triethylsilyl)oxy]hept-2-en-1-yl]oxiran-2-yl)methyl 4-methylbenzenesulfonate (S26)

(2) Et$_3$N (1.86 mL, 12.90 mmol), DMAP (23.7 mg, 0.19 mmol), and TsCl (493 mg, 2.59 mmol) were added to a stirred solution 36 (425 mg, 1.29 mmol, 90% de) in CH$_2$Cl$_2$ (9 mL) at RT and stirred for 2 hr. The reaction mixture was diluted with EtOAc, washed with water and brine sequentially, dried over Na$_2$SO$_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (Kanto Chemical, Silica Gel 60N, spherical, 40-100 μm, heptane : EtOAc = 15:1) to give S26 (641 mg, quant., 90% de) as a colorless oil. The optical purity of S26 was determined by HPLC (DAICEL CHEMICAL INDUSTRIES, CHIRALPAK AD-H, hexane : isopropyl alcohol = 90 : 10) of the corresponding tosylate 37. 400 MHz $^1$H-NMR (CD$_3$OD) $\delta$ (ppm) 0.66 (q, J=8.0Hz, 6H), 0.91 (t, J=7.6Hz, 3H), 0.99 (d, J=7.2Hz, 3H), 1.02 (t, J = 8.0 Hz, 9H), 1.21 (s, 3H), 1.40-1.56 (m, 2H), 2.15-2.35 (m, 3H), 2.50 (s, 3H), 3.02 (dd, J = 4.8, 6.8 Hz, 1H), 3.54 (dt, J = 5.2, 6.0 Hz, 1H), 4.10 (dd, J = 6.8, 11.2 Hz, 1H), 4.27 (dd, J = 4.8, 11.2 Hz, 1H), 5.37 (dt, J = 8.0, 15.6 Hz, 1H), 5.53 (dd, J = 8.0, 15.6 Hz, 1H), 7.50 (dd, J = 1.0, 2.0, 6.8 Hz, 2H), 7.85 (dd, J = 1.6, 6.8 Hz, 2H); 100 MHz $^{13}$C-NMR (CD$_3$OD) $\delta$ (ppm) 6.11, 7.51, 9.90, 16.44, 17.20, 21.73, 27.87, 42.11, 42.92, 59.45, 61.85, 70.33, 78.54, 124.60, 128.97, 131.07, 134.19, 138.53, 146.44; [\alpha]_D$^{21}$ +2.70 (c 2.10, MeOH) (90% de).

$[{2R,3R}]-[{2E,4S,5S}]-5$-Hydroxy-4-methylhept-2-en-1-yl]-3-methyloxiran-2-yl)methyl 4-methylbenzenesulfonate (37)

To a stirred solution of tosylate S26 (440 mg, 0.91 mmol, 90% de) in THF (2 mL), 1N HCl (0.1 mL) was added and stirred at RT for 1 hr. The reaction mixture was diluted with EtOAc, washed with water and brine sequentially, dried over Na$_2$SO$_4$, and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (Kanto Chemical, Silica Gel 60N, spherical, 40-100 μm, heptane : EtOAc = 2 : 1) to give 37 (334 mg, quant., 90% de) as a colorless oil. The optical purity was determined by HPLC (DAICEL CHEMICAL INDUSTRIES, CHIRALPAK AD-H, hexane : isopropyl alcohol = 90 : 10). 400 MHz $^1$H-NMR (CD$_3$OD) $\delta$ (ppm) 0.97 (t, J = 7.6 Hz, 3H), 1.04 (d, J = 6.8 Hz, 3H), 1.21 (s, 3H), 1.29-1.38 (m, 1H), 1.53-1.63 (m, 1H), 2.14-2.30 (m, 3H), 2.50 (s, 3H), 3.03 (dd, J = 4.4, 6.8 Hz, 1H), 3.25-3.29 (m, 1H), 4.10 (dd, J = 6.8, 11.2 Hz, 1H), 4.28 (dd, J = 4.4, 11.2 Hz, 1H), 5.38 (dt, J = 6.8, 15.6 Hz, 1H), 5.49 (dd, J = 8.0, 15.6 Hz, 1H), 7.50 (dd, J = 1.0, 8.4 Hz, 2H), 7.85 (dd, J = 2.0, 2.0, 8.4 Hz, 2H); 100 MHz $^{13}$C-NMR (CD$_3$OD) $\delta$ (ppm) 10.64,
16.58, 17.10, 21.62, 28.31, 41.96, 44.21, 59.51, 62.01, 70.43, 77.63, 124.85, 129.00, 131.13, 134.15, 138.80, 146.65; IR (film) = 3386, 2976, 2958, 2924, 2502, 1933, 1599, 1454, 1359, 1173, 1095, 967, 866, 782, 667, 554 cm⁻¹; HRMS C₁₀H₂₈NaO₃S (M+Na⁺) Calcd : 391.1555, Found : 391.1550; [α]D° +2.82 (c1.04, MeOH) (90% de).

5,6,8,9-Dianhydro-1,2,4,7-tetraoxo-4,8-dimethyl-10-O-[(4-methylphenyl)sulfonyl]-D-threo-D-galacto-decitol (38)[30]

The tosylate 37 (2.82 g, 7.64 mmol, 89% de) was dissolved in a mixture of MeCN (80.8 mL) and 0.4mM Na₂EDTA solution in 0.05M sodium tetraborate decahydrate (pH 9, 53.4 mL). To this stirred solution, 1,2,4,5-Di-O-isopropylidene-D-erythro-2,3-hexodiuro-2,6-pyranose (1.97 g, 7.64 mmol) was added to at 0°C, followed by an addition of a mixture of potassium carbonate (12.70 g, 91.80 mmol) and Oxone® (14.10 g, 22.93 mmol) in several portions over 4 hr. The reaction mixture was stirred at 0°C for additional 1 hr and diluted with EtOAc. The organic layer was washed with water and brine sequentially, dried over Na₂SO₄, and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (Kanto Chemical, Silica Gel 60N, spherical, 40-100 μm, heptane : EtOAc = 3 : 1 → 2 : 1) to give 38 (2.57 g, 87%, 81% de) as a colorless oil. The optical purity was determined by HPLC (DACEL CHEMICAL INDUSTRIES, CHIRALPAK AD-H, hexane : isopropyl alcohol = 80 : 20). The product was recrystallized (hexane/diethyl ether) to afford 38 (1.52 g, 51%) as a colorless prism (>99% de). 400 MHz ¹H-NMR (CD₃OD) δ (ppm) 0.98 (d, J = 7.2 Hz, 3H), 0.99 (t, J = 7.6 Hz, 3H), 1.27-1.36 (m, 1H), 1.32 (s, 3H), 1.48-1.61 (m, 2H), 1.67 (dd, J = 6.8, 14.4 Hz, 1H), 1.80 (dd, J = 4.8, 14.4 Hz, 1H), 2.50 (s, 3H), 2.71 (dd, J = 6.4, 8.0 Hz, 1H), 2.85-2.89 (m, 1H), 3.10 (dd, J = 4.4, 6.4 Hz, 1H), 3.57 (dt, J = 4.8, 8.0 Hz, 1H), 4.12 (dd, J = 6.4, 11.2 Hz, 1H), 4.31 (dd, J = 4.4, 11.6 Hz, 1H), 7.44 (dd, J = 1.0, 8.0 Hz, 2H), 7.86 (dd, J = 2.0, 8.4 Hz, 1H), 7.87 (dd, J = 2.0, 8.4 Hz, 1H); 100 MHz ¹³C-NMR (CD₃OD) δ (ppm) 10.55, 10.85, 17.41, 21.62, 28.55, 41.82, 42.36, 55.43, 60.18, 60.63, 61.63, 70.17, 75.15, 129.00, 131.13, 134.04, 146.66; IR (KBr) = 3389, 2976, 2957, 2873, 1923, 1598, 1454, 1359, 1188, 1173, 1099, 969, 866, 815, 569, 557, 507 cm⁻¹; HRMS C₁₀H₂₈AgO₃S (M+Ag⁺) Calcd: 491.0658, Found: 491.0638; [α]D° +42.7 (c 1.00, MeOH) (>99% de); m.p. 58.0-59.0°C.

(1R)-1,2-Anhydro-3,5-dideoxy-1-[(1R,2S)-2-hydroxy-1-methylbutyl]-4-C-vinyl-D-erythro-pentitol (39)[32]

To a stirred solution of 38 (200 mg, 0.52 mmol) in aceton - DMF (5 mL - 1 mL), KI (303 mg, 1.83 mmol) was added and heated at reflux for 2 hr. Then the mixture was cooled to 0°C and an aq. solution of 5% NaHCO₃ and 5% Na₂SO₃ was added and stirred for 10 min. The mixture was diluted with EtOAc, washed with water and brine sequentially, dried over Na₂SO₄, and concentrated to afford iodide compound. This was used in the next step without further purification. To a stirred suspension of activated zinc powder (102 mg, 1.56 mmol) in MeOH - distilled water (0.5 mL - 0.75 mL), CuI (99.0 mg, 0.52 mmol) was added and sonicated for 5 min at RT. To this reaction mixture, a solution of crude iodide in MeOH (0.5 mL) was added and sonicated at RT for 1.5 hr. The mixture was diluted with EtOAc and filtered through Celite® pad. The filtrate was washed with water and brine
sequentially, dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (Kanto Chemical, Silica Gel 60N, spherical, 40-100 µm, heptane : EtOAc = 2.5 : 1) to give 39 (110 mg, 99%) as a colorless oil. 400 MHz ¹H-NMR (CD₂OD) δ (ppm) 0.98 (d, J = 7.2 Hz, 3H), 0.99 (t, J = 7.6 Hz, 3H), 1.29-1.37 (m, 1H), 1.36 (s, 3H), 1.48-1.61 (m, 2H), 1.73 (dd, J = 6.0, 14.0 Hz, 1H), 1.80 (dd, J = 6.0, 14.0 Hz, 1H), 2.72 (dd, J = 2.4, 7.6 Hz, 1H), 2.95 (dt, J = 2.4, 6.0 Hz, 1H), 3.38 (s, 1H), 3.58 (dt, J = 4.8, 8.0 Hz, 1H), 5.08 (dd, J = 1.6, 10.8 Hz, 1H), 5.29 (dd, J = 1.6, 17.6 Hz, 1H), 6.02 (dd, J = 10.8, 17.6 Hz, 1H); 100 MHz ¹³C-NMR (CD₂OD) δ (ppm) 10.28, 10.92, 27.88, 28.54, 42.39, 45.54, 55.74, 62.10, 73.17, 75.18, 112.21, 146.27; IR (film) = 3418, 3088, 2970, 2935, 2879, 1647, 1455, 1416, 925 cm⁻¹; HRMS C₁₂H₂₂O₅Ag (M+Ag⁺) Calcd : 321.0620, Found : 321.0667; [α]₀²⁴ +13.5 (c 1.67, MeOH).

< Completion of the total synthesis of pladienolide D >

**Pladienolide D (3)**[26,33,34]

![Pladienolide D (3)](image)

To a solution of 32 (10.0 mg, 27.3 µmol) and allyl alcohol 39 (11.7 mg, 54.6 µmol) in CH₂Cl₂ (2.5 mL), the 2nd generation Grubbs catalyst (1.16 mg, 1.4 µmol) was added and heated at refluxed for 1 hr under argon atmosphere. The reaction mixture was cooled to RT and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (Kanto Chemical, Silica Gel 60N, spherical, 40-100 µm, heptane : EtOAc = 2.5 : 1 → 1 : 2 → 0 : 1) to afford pladienolide D (3) (9.5 mg, 64%) as a colorless amorphous residue. Further purification by HPLC (Shiseido, CAPCELL PAK C18SG120; MeCN : water = 32 : 68) followed by lyophilization gave pure 3 as a white amorphous residue. 600 MHz ¹H-NMR (CD₂OD) δ (ppm) 0.93 (d, J = 6.8 Hz, 3H), 0.94 (d, J = 7.0 Hz, 3H), 0.98 (t, J = 7.4 Hz, 3H), 1.23 (s, 3H), 1.30 (m, 1H), 1.38 (s, 3H), 1.40 (m, 1H), 1.42 (m, 1H), 1.54 (m, 2H), 1.62 (m, 1H), 1.66 (m, 1H), 1.70 (dd, J = 6.3, 14.1 Hz, 1H), 1.82 (d, J = 0.9 Hz, 3H), 1.91 (dd, J = 5.5, 14.0 Hz, 1H), 2.10 (s, 3H), 2.57 (m, 2H), 2.62 (ddq, J = 6.8, 9.8, 10.6 Hz, 1H), 2.71 (dd, J = 2.2, 7.9 Hz, 1H), 2.93 (ddd, J = 2.2, 6.3, 6.3 Hz, 1H), 3.57 (ddd, J = 4.5, 4.5, 8.3 Hz, 1H), 3.83 (m, 1H), 5.09 (d, J = 9.8 Hz, 1H), 5.11 (d, J = 10.6 Hz, 1H), 5.61 (dd, J = 9.9, 15.2 Hz, 1H), 5.75 (dd, J = 9.8, 15.2 Hz, 1H), 5.92 (d, J = 15.3 Hz, 1H), 6.18 (d, J = 11.0 Hz, 1H), 6.57 (dd, J = 11.0, 15.3 Hz, 1H)); 150 MHz ¹³C-NMR (CD₂OD) δ (ppm) 10.5, 10.8, 12.0, 16.9, 21.1, 24.2, 28.6, 28.8, 30.5, 37.5, 40.1, 41.8, 42.6, 46.0, 56.0, 62.5, 70.4, 73.1, 74.1, 75.3, 80.3, 84.2, 123.7, 127.1, 131.8, 133.8, 141.6, 143.2, 171.7, 172.2; IR (KBr) = 3438, 2968, 2939, 2879, 1733, 1720, 1458, 1371, 1244, 1176, 1021, 977, 832, 789, 747, 612, 551, 474, 433, 420, 409 cm⁻¹; HRMS: C₃₀H₆₆NaO₇ (M+Na⁺), Calcd : 575.3196, Found : 575.3168; [α]₀²⁵ ~14.7 (c 1.10, MeOH).
References


Comparison between $^1$H- and $^{13}$C-NMR Spectra of Synthetic and Natural Pladienolides