Total Synthesis of (+)-Macquarimicin A

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Supporting Information

1. Experimental Section

General

Specific rotations were measured in a 10 mm cell. ^1H NMR spectra were recorded at 270 MHz or at 300 MHz with tetramethylsilane as an internal standard. ^{13}C NMR spectra were recorded at 68 MHz or at 75 MHz. All spectra were recorded in CDCl_3 as solvent. High-resolution mass spectra (HRMS) were measured by the EI method (70 eV) unless otherwise noted. Thin-layer chromatography (TLC) was performed with a glass plate coated with Kieselgel 60 F_{254} (Merck). The crude reaction mixtures and extractive materials were purified by chromatography on silica gel Daisogel IR-60 (Daiso Co., Ltd.) or Wakogel C300 (Wako Pure Chemical Industries). Unless otherwise described, reactions were carried out at ambient temperature. Combined organic extracts were dried over anhydrous Na_2SO_4 . Solvents were removed from reaction mixture or combined organic extracts by concentration under reduced pressure using an evaporator with a water bath at 35–45 °C.

(1Z,3S,4R,6E)-1-Bromo-8-(*t*-butyldiphenylsilyloxy)-3-[(4-methoxyphenyl)methoxy]-4-methyl-1,6-octadiene (10)

The following reaction was carried out under argon. To a stirred solution of PPh_3 (764 mg, 2.91 mmol) in degassed toluene (160 mL) was added $\text{Pd}(\text{OAc})_2$ (163 mg, 0.724 mmol). The mixture was stirred for 40 min and then **9**¹ (12.2 g, 18.1 mmol) in degassed toluene (80 mL) and Bu_3SnH (5.4 mL, 20.1 mmol) were added. The mixture was stirred for 30 min and then diluted with EtOAc (250 mL). This was washed with saturated brine. The combined aqueous layers were extracted with EtOAc. The combined organic layers were dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (Et_3N /hexane, 1:100 then EtOAc/hexane, 1:70) to provide 9.19 g (85%) of **10** as a colorless oil; TLC, R_f 0.68 (EtOAc/hexane, 1:3); $[\alpha]_D^{24} +3.00$ (c 1.72, CHCl_3); ^1H NMR (270 MHz) δ 0.95 (d, J = 6.6 Hz, 3H), 1.05 (s, 9H), 1.75 (m, 1H), 1.87 (m, 1H), 2.24 (m, 1H), 3.78 (s, 3H), 4.14 (d, J = 4.4 Hz, 2H), 4.17 (dd, J = 5.9, 8.8 Hz, 1H), 4.28, 4.50

¹ Munakata, R.; Ueki, T.; Katakai, H.; Takao, K.; Tadano, K. *Org. Lett.* **2001**, *3*, 3029.

(2d, $J = 11.5$ Hz, 1H $\times$ 2), 5.52 (dt, $J = 15.4, 4.4$ Hz, 1H), 5.63 (dt, $J = 15.4, 6.4$ Hz, 1H), 6.14 (dd, $J = 7.3, 8.8$ Hz, 1H), 6.42 (dd, $J = 0.7, 7.3$ Hz, 1H), 6.86 (m, 2H), 7.26 (m, 2H), 7.36-7.40 (m, 6H), 7.66-7.70 (m, 4H); ^{13}C NMR (68 MHz) δ 14.94, 19.21, 26.81 $\times$ 3, 35.39, 37.78, 55.20, 64.45, 70.38, 79.28, 110.58, 113.63 $\times$ 2, 127.60 $\times$ 4, 128.98, 129.41 $\times$ 2, 129.53 $\times$ 2, 130.53, 130.68, 133.85 $\times$ 2, 135.11, 135.52 $\times$ 4, 159.04; IR (neat) 3080, 2940, 1615, 1515 cm^{-1} ; HRMS calcd for $\text{C}_{29}\text{H}_{32}\text{O}_3\text{Si}^{81}\text{Br}$ ($\text{M}^+ - t\text{-Bu}$) m/z 537.1284, found 537.1287.

(1Z,3S,4R,6E)-8-(*t*-Butyldiphenylsilyloxy)-3-[(4-methoxyphenyl)methoxy]-4-methyl-1-tributylstannyl-1,6-octadiene (7)

The following reaction was carried out under argon. To a cooled (-78 $^{\circ}\text{C}$), stirred solution of **10** (9.19 g, 15.5 mmol) in Et_2O (180 mL) was added $t\text{-BuLi}$ (27 mL of 1.40 M in pentane, 37 mmol). The mixture was stirred at -78 $^{\circ}\text{C}$ for 1 h and then Bu_3SnCl (5.1 mL, 18.6 mmol) was added. The mixture was stirred at -78 $^{\circ}\text{C}$ for 2 h and then quenched with H_2O . This was diluted with EtOAc (250 mL), and washed with H_2O . The organic layer was dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel ($\text{Et}_3\text{N}/\text{hexane}$, 1:100 then $\text{EtOAc}/\text{hexane}$, 1:100) to provide 9.96 g (80%) of **7** as a colorless oil; TLC, R_f 0.77 ($\text{EtOAc}/\text{hexane}$, 1:5); $[\alpha]_D^{24} +5.23$ (c 1.99, CHCl_3); ^1H NMR (300 MHz) δ 0.85-0.91 (m, 15H), 0.96 (d, $J = 6.8$ Hz, 3H), 1.05 (s, 9H), 1.25-1.33 (m, 6H), 1.42-1.50 (m, 6H), 1.67 (m, 1H), 1.86 (m, 1H), 2.30 (m, 1H), 3.45 (dd, $J = 4.9, 8.8$ Hz, 1H), 3.79 (s, 3H), 4.15 (d, $J = 3.9$ Hz, 2H), 4.22, 4.51 (2d, $J = 11.4$ Hz, 1H $\times$ 2), 5.51-5.68 (m, 2H), 6.15 (d, $J = 13.1, ^2J_{\text{Sn-H}} = 62.7$ Hz, 1H), 6.42 (dd, $J = 8.8, 13.1$ Hz, 1H), 6.86 (m, 2H), 7.24 (m, 2H), 7.33-7.42 (m, 6H), 7.66-7.70 (m, 4H); ^{13}C NMR (75 MHz) δ 10.51 $\times$ 3, 13.68 $\times$ 3, 14.59, 19.20, 26.80 $\times$ 3, 27.34 $\times$ 3, 29.15 $\times$ 3, 36.32, 38.95, 55.24, 64.61, 69.73, 86.15, 113.65 $\times$ 2, 127.57 $\times$ 4, 128.78 $\times$ 2, 129.52 $\times$ 2, 129.95, 130.21, 131.25, 132.81, 133.85 $\times$ 2, 135.53 $\times$ 4, 148.49, 158.87; IR (neat) 3080, 2960, 1615, 1515 cm^{-1} ; HRMS calcd for $\text{C}_{41}\text{H}_{59}\text{O}_3\text{Si}^{118}\text{Sn}$ ($\text{M}^+ - \text{Bu}$) m/z 745.3252, found 745.3241.

(2R)-1-Chloro-5-trimethylsilyl-4-pentyn-2-ol (12)²

The following reaction was carried out under argon. To a cooled (-78 $^{\circ}\text{C}$), stirred solution of trimethylsilylacetylene (5.0 mL, 35 mmol) in THF (45 mL) was added $n\text{-BuLi}$ (13 mL of 2.66 M in hexane, 35 mmol). The mixture was stirred at -78 $^{\circ}\text{C}$ for 10 min and then (*R*)-epichlorohydrin (**11**) (2.3 mL, 30 mmol) was added. The mixture was stirred at -78 $^{\circ}\text{C}$ for 10 min and then $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (4.9 mL, 35 mmol) was added. The mixture was stirred while gradually warmed to -30 $^{\circ}\text{C}$ over 2 h and at -30 $^{\circ}\text{C}$ for 19 h. The mixture was quenched with saturated aqueous NH_4Cl . This was diluted with saturated aqueous NH_4Cl (200 mL), and extracted with EtOAc . The combined organic layers were dried and concentrated in vacuo to give crude **12**, which was used in the next step without purification. In a small-scale experiment, pure **12** was

² Takano, S.; Kamikubo, T.; Sugihara, T.; Suzuki, M.; Ogasawara, K. *Tetrahedron: Asymmetry* **1993**, 4, 201.

obtained by column chromatography on silica gel (EtOAc/hexane, 1:20) as a colorless oil; TLC, R_f 0.60 (EtOAc/hexane, 1:2); $[\alpha]_D^{19}$ -10.7 (c 1.69, CHCl_3); ^1H NMR (270 MHz) δ 0.16 (s, 9H), 2.54 (dd, J = 6.6, 16.9 Hz, 1H), 2.55 (m, 1H), 2.62 (dd, J = 5.9, 16.9 Hz, 1H), 3.62 (dd, J = 6.0, 11.4 Hz, 1H), 3.72 (dd, J = 4.4, 11.4 Hz, 1H), 3.98 (m, 1H); ^{13}C NMR (68 MHz) δ -0.03 $\times$ 3, 25.74, 48.23, 69.60, 88.26, 101.22; IR (neat) 3400, 2960, 2180 cm^{-1} .

(3*R*)-3-Hydroxy-6-trimethylsilyl-5-hexynenitrile and (3*R*)-3-Hydroxy-5-hexynenitrile

To a stirred solution of the crude **12** obtained above in DMSO- H_2O (10:1, 44 mL) were added KCN (2.88 g, 44.3 mmol) and NaI (13.2 g, 88.5 mmol). The mixture was stirred at 80 $^\circ\text{C}$ for 5 h and then diluted with EtOAc (250 mL). This was washed with saturated brine. The combined aqueous layers were extracted with EtOAc. The combined organic layers were dried and concentrated in vacuo to give crude mixture of the nitriles, which were used in the next step without purification. In a small-scale experiment, pure products were obtained by column chromatography on silica gel (EtOAc/hexane, 1:15 to 1:3) as a colorless oil; (3*R*)-3-Hydroxy-6-trimethylsilyl-5-hexynenitrile: TLC, R_f 0.30 (EtOAc/hexane, 1:3); ^1H NMR (300 MHz) δ 0.17 (s, 9H), 2.39 (d, J = 5.8 Hz, 1H), 2.59 (d, J = 6.0 Hz, 2H), 2.66 (m, 2H), 4.11 (m, 1H); ^{13}C NMR (68 MHz) δ -0.12 $\times$ 3, 24.73, 28.02, 66.09, 89.56, 100.18, 117.11; IR (neat) 3450, 2960, 2250, 2180 cm^{-1} ; (3*R*)-3-Hydroxy-5-hexynenitrile: TLC, R_f 0.16 (EtOAc/hexane, 1:3); $[\alpha]_D^{23}$ -22.0 (c 2.06, CHCl_3); ^1H NMR (270 MHz) δ 2.15 (t, J = 2.6 Hz, 1H), 2.39 (d, J = 5.5 Hz, 1H), 2.57 (dd, J = 2.6, 5.9 Hz, 2H), 2.65 (dd, J = 6.4, 16.8 Hz, 1H), 2.72 (dd, J = 5.5, 16.8 Hz, 1H), 4.15 (m, 1H); ^{13}C NMR (68 MHz) δ 24.62, 26.38, 65.88, 72.19, 78.56, 117.32; IR (neat) 3450, 3300, 2920, 2250, 2120 cm^{-1} ; HRMS calcd for $\text{C}_6\text{H}_8\text{NO}$ ($\text{M}^+ + \text{H}$) m/z 110.0606, found 110.0628.

(3*R*)-3-Hydroxy-5-hexynenitrile

To a cooled (0 $^\circ\text{C}$), stirred solution of the crude mixture obtained above in MeOH (26 mL) was added K_2CO_3 (395 mg, 2.86 mmol). The mixture was stirred for 4.5 h and then Amberlite IR 120 [H^+] was added at 0 $^\circ\text{C}$ until the pH of the mixture showed 6. The resin was filtered off and the filtrate was concentrated in vacuo to give the crude nitrile, which was used in the next step without purification.

(3*R*)-3-(*t*-Butyldimethylsilyloxy)-5-hexynenitrile

To a cooled (0 $^\circ\text{C}$), stirred solution of the crude (3*R*)-3-hydroxy-5-hexynenitrile obtained above in DMF (25 mL) were added imidazole (8.02 g, 118 mmol) and TBSCl (8.92 g, 59.2 mmol). The mixture was stirred for 13.5 h and then diluted with H_2O (300 mL). This was extracted with CH_2Cl_2 . The combined organic layers

were dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:40) to provide 5.62 g (84%, 4 steps from **11**) of the TBS ether as a colorless oil; TLC, R_f 0.67 (EtOAc/hexane, 1:2); $[\alpha]_D^{23}$ -16.7 (c 2.06, CHCl_3); ^1H NMR (270 MHz) δ 0.12, 0.15 (2s, 3H $\times$ 2), 0.91 (s, 9H), 2.07 (t, J = 2.6 Hz, 1H), 2.43 (ddd, J = 2.6, 7.3, 16.9 Hz, 1H), 2.51 (ddd, J = 2.6, 5.1, 16.9 Hz, 1H), 2.61 (dd, J = 6.2, 16.5 Hz, 1H), 2.71 (dd, J = 4.4, 16.5 Hz, 1H), 4.09 (m, 1H); ^{13}C NMR (75 MHz) δ -4.94, -4.79, 17.88, 25.46, 25.56 $\times$ 3, 27.11, 67.23, 71.67, 79.09, 117.35; IR (neat) 3300, 2930, 2250, 2120 cm^{-1} ; HRMS calcd for $\text{C}_{12}\text{H}_{21}\text{NOSi}$ (M^+) m/z 223.1392, found 223.1373.

(3R)-3-(*t*-Butyldimethylsilyloxy)-5-hexynal (13**)**

The following reaction was carried out under argon. To a cooled ($-52\text{ }^\circ\text{C}$), stirred solution of (3R)-3-(*t*-butyldimethylsilyloxy)-5-hexynenitrile (5.49 g, 24.6 mmol) in toluene (100 mL) was added Dibal-H (35 mL of 1.04 M solution in toluene, 37 mmol). The mixture was stirred at $-52\text{ }^\circ\text{C}$ for 2 h and then quenched with EtOH. This was diluted with 0.2 M aqueous HCl (200 mL), and extracted with hexane. The combined organic layers were washed with saturated brine-saturated aqueous NaHCO_3 (1:1). The organic layer was dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:40) to provide 5.56 g (quant.) of **13** as a colorless oil; TLC, R_f 0.69 (EtOAc/hexane, 1:5); $[\alpha]_D^{21}$ -27.1 (c 1.11, CHCl_3); ^1H NMR (270 MHz) δ 0.08, 0.11 (2s, 3H $\times$ 2), 0.87 (s, 9H), 2.04 (t, J = 2.8 Hz, 1H), 2.39 (ddd, J = 2.8, 7.2, 16.7 Hz, 1H), 2.47 (ddd, J = 2.8, 5.0, 16.7 Hz, 1H), 2.67 (ddd, J = 2.4, 6.8, 16.1 Hz, 1H), 2.77 (ddd, J = 1.7, 4.6, 16.1 Hz, 1H), 4.36 (m, 1H), 9.82 (dd, J = 1.7, 2.4 Hz, 1H); ^{13}C NMR (68 MHz) δ -4.93, -4.55, 17.91, 25.63 $\times$ 3, 27.64, 50.19, 66.66, 71.10, 80.17, 201.23; IR (neat) 3300, 2930, 2120, 1730 cm^{-1} ; HRMS calcd for $\text{C}_8\text{H}_{13}\text{O}_2\text{Si}$ ($\text{M}^+ - t\text{-Bu}$) m/z 169.0685, found 169.0685.

(2RS,4R)-4-(*t*-Butyldimethylsilyloxy)-1-(2,2-dimethyl-1,3-dioxin-4-one-6-yl)-6-heptyn-2-ol (ca. 1:1 diastereomeric mixture)

The following reaction was carried out under argon. To a cooled ($-78\text{ }^\circ\text{C}$), stirred solution of **13** (5.56 g, 24.6 mmol) in CH_2Cl_2 (100 mL) were added $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (3.3 mL, 26 mmol) and 2,2-dimethyl-6-methylene-4-(trimethylsilyloxy)-1,3-dioxin (6.90 g, 32.2 mmol). The mixture was stirred at $-78\text{ }^\circ\text{C}$ for 45 min and then quenched with saturated aqueous NaHCO_3 . This was diluted with saturated aqueous NaHCO_3 (200 mL), and extracted with CH_2Cl_2 . The combined organic layers were dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:3) to provide 6.65 g (73%) of the secondary alcohol as a colorless oil; TLC, R_f 0.28 (EtOAc/hexane, 1:2); ^1H NMR (270 MHz) δ 0.12, 0.14, 0.15 (3s, total 6H) 0.90, 0.91 (2s, total 9H), 1.70 (s, 6H), 1.72-2.04 (m, 3H), 2.30-2.48 (m, 4H), 3.05 (d, J = 2.9 Hz, 1H $\times$ 1/2), 3.20 (d, J = 1.1 Hz, 1H $\times$ 1/2), 4.00-4.30 (m, 2H), 5.34, 5.35 (2s, total 1H); IR (neat) 3450, 3300, 2930, 2120, 1720, 1635 cm^{-1} ; HRMS calcd for $\text{C}_{18}\text{H}_{29}\text{O}_5\text{Si}$ ($\text{M}^+ - \text{CH}_3$) m/z 353.1784, found 353.1810.

(4R)-4-(*t*-Butyldimethylsilyloxy)-1-(2,2-dimethyl-1,3-dioxin-4-one-6-yl)-6-heptyn-2-one

To a cooled (0 °C), stirred solution of (2*RS*,4*R*)-4-(*t*-butyldimethylsilyloxy)-1-(2,2-dimethyl-1,3-dioxin-4-one-6-yl)-6-heptyn-2-ol (12.58 g, 34.13 mmol) in CH₂Cl₂ (250 mL) was added Dess-Martin periodinane (17.4 g, 40.9 mmol). The mixture was stirred for 1.5 h and then Dess-Martin periodinane (33.3 g, 78.5 mmol) was added at 0 °C. The mixture was stirred for 5 h and then diluted with saturated aqueous NaHCO₃–20% aqueous Na₂S₂O₃ (1:1, 400 mL) and CH₂Cl₂ (200 mL) at 0 °C. The mixture was stirred for 20 min and then the organic layer was separated. The aqueous layer was extracted with CH₂Cl₂. The combined organic layers were dried and concentrated in vacuo to give the crude ketone, which was used in the next step without purification. In a small-scale experiment, the pure ketone was obtained by column chromatography on silica gel (EtOAc/hexane, 1:10) as a colorless oil; TLC, *R*_f 0.40 (EtOAc/hexane, 1:2); [α]²¹_D –46.9 (*c* 1.56, CHCl₃); ¹H NMR (270 MHz) δ 0.05, 0.10 (2s, 3H ×2), 0.87 (s, 9H), 1.72 (s, 6H), 2.03 (t, *J* = 2.7 Hz, 1H), 2.34 (ddd, *J* = 2.7, 7.0, 16.7 Hz, 1H), 2.42 (ddd, *J* = 2.7, 4.8, 16.7 Hz, 1H), 2.78 (m, 2H), 3.34 (d, *J* = 16.9 Hz, 1H), 3.41 (d, *J* = 16.9 Hz, 1H), 4.31 (m, 1H), 5.33 (s, 1H); ¹³C NMR (68 MHz) δ –4.96, –4.73, 17.91, 24.96, 25.05, 25.68 ×3, 27.36, 48.64, 49.18, 67.24, 71.13, 80.08, 96.73, 107.21, 160.68, 164.25, 201.69; IR (neat) 3300, 2930, 2120, 1730, 1640 cm^{–1}; HRMS calcd for C₁₅H₂₁O₅Si (M⁺–*t*-Bu) *m/z* 309.1158, found 309.1169.

(4R)-1-(2,2-Dimethyl-1,3-dioxin-4-one-6-yl)-4-hydroxy-6-heptyn-2-one (15)

To a cooled (0 °C), stirred solution of the crude ketone obtained above in MeCN (250 mL) was added 48% aq. HF (12 mL). The mixture was stirred at room temperature for 8 h and then quenched with saturated aqueous NaHCO₃. This was diluted with saturated aqueous NaHCO₃ (400 mL), and extracted with CH₂Cl₂. The combined organic layers were dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:2) to provide **15** (7.95 g, 92%, 2 steps) as a colorless oil; TLC, *R*_f 0.15 (EtOAc/hexane, 1:1); [α]²²_D –38.3 (*c* 1.21, CHCl₃); ¹H NMR (270 MHz) δ 1.72 (s, 6H), 2.09 (t, *J* = 2.6 Hz, 1H), 2.42 (ddd, *J* = 2.6, 6.6, 16.9 Hz, 1H), 2.49 (ddd, *J* = 2.6, 5.9, 16.9 Hz, 1H), 2.77 (dd, *J* = 8.1, 17.6 Hz, 1H), 2.87 (dd, *J* = 3.7, 17.6 Hz, 1H), 2.93 (d, *J* = 4.4 Hz, 1H), 3.41 (s, 2H), 4.25 (m, 1H), 5.37 (s, 1H); ¹³C NMR (68 MHz) δ 24.96 ×2, 26.26, 47.74, 48.09, 65.77, 71.41, 79.71, 96.87, 107.27, 160.57, 163.82, 203.16; IR (neat) 3430, 3300, 2920, 2120, 1720, 1640 cm^{–1}; HRMS calcd for C₁₃H₁₇O₅ (M⁺+H) *m/z* 253.1076, found 253.1075.

(2*R*,4*R*)-1-(2,2-Dimethyl-1,3-dioxin-4-one-6-yl)-6-heptyn-2,4-diol

The following reaction was carried out under argon. To a cooled (–78 °C), stirred solution of **15** (7.95 g, 31.5 mmol) in THF–MeOH (150 mL) was added Et₂BOMe (38 mL of 1.0 M solution in THF, 38 mmol). The

mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 30 min and then NaBH_4 (1.70 g, 44.9 mmol) was added. The mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 8 h. This was quenched with AcOH and diluted with saturated aqueous NaHCO_3 (300 mL), and extracted with EtOAc. The combined organic layers were dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 2:3) to provide 8.01 g (quant.) of the diol as a colorless oil; TLC, R_f 0.10 (EtOAc/hexane, 1:1); $[\alpha]_D^{22}$ -14.8 (c 1.11, CHCl_3); ^1H NMR (270 MHz) δ 1.71 (s, 6H), 1.60–1.86 (m, 2H), 2.09 (t, $J = 2.6$ Hz, 1H), 2.34–2.49 (m, 4H), 3.29 (brd, $J = 10.6$ Hz, 1H), 3.68 (brd, $J = 7.7$ Hz, 1H), 4.05 (m, 1H), 4.18 (m, 1H), 5.35 (s, 1H); ^{13}C NMR (68 MHz) δ 24.82, 25.20, 27.79, 41.47, 41.90, 69.00, 70.55, 71.27, 80.05, 95.20, 106.69, 161.26, 168.72; IR (neat) 3410, 3300, 2910, 2120, 1720, 1640 cm^{-1} ; HRMS calcd for $\text{C}_{13}\text{H}_{19}\text{O}_5$ ($\text{M}^+ + \text{H}$) m/z 255.1233, found 255.1234.

(2*R*,4*R*)-2,4-Bis(*t*-butyldimethylsilyloxy)-1-(2,2-dimethyl-1,3-dioxin-4-one-6-yl)-6-heptyne

To a cooled ($0\text{ }^{\circ}\text{C}$), stirred solution of (2*R*,4*R*)-1-(2,2-dimethyl-1,3-dioxin-4-one-6-yl)-6-heptyn-2,4-diol (4.87 g, 19.2 mmol) in DMF (40 mL) were added imidazole (5.49 g, 80.6 mmol) and TBSCl (6.06 g, 40.2 mmol). The mixture was stirred for 5 h and then diluted with saturated aqueous NaHCO_3 (250 mL). This was extracted with CH_2Cl_2 . The combined organic layers were dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:10) to provide 8.58 g (93%) of the bisTBS ether as a colorless oil; TLC, R_f 0.48 (EtOAc/toluene, 1:10); $[\alpha]_D^{22}$ -40.9 (c 1.58, CHCl_3); ^1H NMR (270 MHz) δ 0.05, 0.07, 0.09, 0.10 (4s, 3H $\times$ 4), 0.88, 0.90 (2s, 9H $\times$ 2), 1.69 $\times$ 2 (2s, 3H $\times$ 2), 1.79 (ddd, $J = 5.1, 7.7, 13.9$ Hz, 1H), 1.88 (ddd, $J = 4.4, 8.1, 13.9$ Hz, 1H), 2.00 (t, $J = 2.6$ Hz, 1H), 2.31 (dd, $J = 7.3, 13.6$ Hz, 1H), 2.34 (m, 2H), 2.44 (dd, $J = 4.2, 13.6$ Hz, 1H), 3.86 (m, 1H), 4.13 (m, 1H), 5.29 (s, 1H); ^{13}C NMR (68 MHz) δ : $-4.73, -4.44, -4.29 \times 2, 17.94 \times 2, 24.30, 25.74 \times 6, 25.89, 27.70, 41.58, 44.26, 66.46, 67.93, 70.64, 80.74, 95.66, 106.32, 161.00, 169.12$; IR (neat) 3310, 2930, 2120, 1730, 1640 cm^{-1} ; HRMS calcd for $\text{C}_{21}\text{H}_{37}\text{O}_5\text{Si}_2$ ($\text{M}^+ - t\text{-Bu}$) m/z 425.2180, found 425.2191.

(2*R*,4*R*)-7-Bromo-2,4-bis(*t*-butyldimethylsilyloxy)-1-(2,2-dimethyl-1,3-dioxin-4-one-6-yl)-6-heptyne (16)

To a cooled ($0\text{ }^{\circ}\text{C}$), stirred solution of (2*R*,4*R*)-2,4-bis(*t*-butyldimethylsilyloxy)-1-(2,2-dimethyl-1,3-dioxin-4-one-6-yl)-6-heptyne (8.58 g, 17.8 mmol) in acetone (180 mL) were added AgNO_3 (0.30 g, 1.8 mmol) and NBS (3.81 g, 21.4 mmol). The mixture was stirred at room temperature for 30 min and then diluted with saturated aqueous NaHCO_3 (200 mL). This was extracted with CH_2Cl_2 . The combined organic layers were dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:8) to provide 9.72 g (97%) of **16** as a colorless oil; TLC, R_f 0.52 (EtOAc/toluene, 1:10); $[\alpha]_D^{21}$ -36.3 (c 1.38, CHCl_3); ^1H NMR (300 MHz) δ 0.05, 0.08 $\times$ 2, 0.10 (4s, 3H $\times$ 4), 0.88, 0.90 (2s, 9H $\times$ 2), 1.69, 1.70 (2s, 3H $\times$ 2), 1.80 (m, 2H), 2.32 (dd, $J = 7.1, 13.9$ Hz, 1H), 2.36 (m, 2H), 2.44 (dd, $J = 4.4, 13.9$ Hz,

1H), 3.87 (m, 1H), 4.13 (m, 1H), 5.29 (s, 1H); ^{13}C NMR (75 MHz) δ -4.77, -4.71, -4.49, -4.36, 17.91 $\times$ 2, 24.28, 25.73 $\times$ 6, 25.92, 28.84, 40.28, 41.63, 44.50, 66.42, 67.77, 76.84, 95.65, 106.35, 160.98, 169.02; IR (neat) 2930, 1730, 1640 cm^{-1} ; HRMS calcd for $\text{C}_{21}\text{H}_{36}\text{O}_5\text{Si}_2\text{Br}^{79}$ ($\text{M}^+ - t\text{-Bu}$) m/z 503.1284, found 503.1288.

(2R,4R,6E)-2,4-Bis(*t*-butyldimethylsilyloxy)-1-(2,2-dimethyl-1,3-dioxin-4-one-6-yl)-7-iodo-6-heptene (8)

The following reaction was carried out under argon. To a stirred solution of **16** (9.72 g, 17.3 mmol) in argon-bubbled THF (200 mL) were added $\text{Pd}_2(\text{dba})_3$ (79.2 mg, 0.0865 mmol) and PPh_3 (181.5 mg, 0.692 mmol). Then a solution of Bu_3SnH (14 mL, 52 mmol) in THF (50 mL) was slowly added over 20 min. The mixture was stirred for 2 h and then concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (200 mL) and stirred at 0 $^\circ\text{C}$. To the solution I_2 (9.66 g, 38.1 mmol) was added. The mixture was stirred for 1 h and then diluted with 10% aqueous $\text{Na}_2\text{S}_2\text{O}_3$ (200 mL). This was extracted with CH_2Cl_2 . The combined organic layers were dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:20) to provide 8.82 g (84%) of **8** as a colorless oil; TLC, R_f 0.29 (EtOAc/hexane, 1:5); $[\alpha]_D^{21}$ -16.4 (c 1.58, CHCl_3); ^1H NMR (270 MHz) δ 0.05, 0.06, 0.07 (3s, total 12H), 0.88, 0.90 (2s, 9H $\times$ 2), 1.58 (m, 1H), 1.68, 1.70 (2s, 3H $\times$ 2), 1.73 (m, 1H), 2.21 (m, 2H), 2.30 (dd, J = 6.8, 13.9 Hz, 1H), 2.40 (dd, J = 4.9, 13.9 Hz, 1H), 3.79 (m, 1H), 4.05 (m, 1H), 5.27 (s, 1H), 6.06 (d, J = 14.3 Hz, 1H), 6.48 (dt, J = 14.3, 7.4 Hz, 1H); ^{13}C NMR (68 MHz) -4.58 $\times$ 2, -4.44, -4.21, 17.94 $\times$ 2, 24.42, 25.74 $\times$ 3, 25.80 $\times$ 3, 25.89, 41.84, 43.86, 44.66, 66.49, 67.96, 77.14, 95.66, 106.37, 142.34, 160.91, 168.86; IR (neat) 2930, 1730, 1640 cm^{-1} ; HRMS calcd for $\text{C}_{21}\text{H}_{38}\text{O}_5\text{Si}_2\text{I}$ ($\text{M}^+ - t\text{-Bu}$) m/z 553.1303, found 553.1297.

(2E,5R,6S,7Z,9E,12R,14R)-12,14-Bis(*t*-butyldimethylsilyloxy)-1-(*t*-butyldiphenylsilyloxy)-15-(2,2-dimethyl-1,3-dioxin-4-one-6-yl)-6-[(4-methoxyphenyl)methoxy]-5-methyl-2,7,9-pentadecatriene

The following reaction was carried out under argon. To a stirred solution of **7** (1.69 g, 2.10 mmol) and **8** (1.06 g, 1.74 mmol) in degassed DMSO-THF (1:1, 40 mL) was added CuCl (254 mg, 2.57 mmol). Then a solution of $\text{Pd}(\text{PPh}_3)_4$ (101 mg, 0.0877 mmol) in degassed THF (3 mL) was added. The mixture was stirred for 1 h and then $\text{Pd}(\text{PPh}_3)_4$ (10.5 mg, 0.00909 mmol) was added. The mixture was stirred for 1 h and then diluted with saturated brine-saturated aqueous NaHCO_3 (1:1, 300 mL). This was extracted with Et_2O . The combined organic layers were dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:10) to provide 1.68 g (97%) of the triene as a colorless oil; TLC, R_f 0.57

(EtOAc/hexane, 1:3); $[\alpha]_D^{21}$ -25.9 (*c* 1.36, CHCl₃); ¹H-NMR (300 MHz) δ 0.04×2, 0.06 (3s, total 12H), 0.86, 0.89 (2s, 9H×2), 0.93 (d, *J* = 6.3 Hz, 3H), 1.04 (s, 9H), 1.66, 1.68 (2s, 3H×2), 1.59-1.79 (m, 4H), 2.17-2.34 (m, 4H), 2.41 (dd, *J* = 4.3, 13.8 Hz, 1H) 3.79 (s, 3H), 3.79 (m, 1H), 4.01 (dd, *J* = 5.9, 9.3 Hz, 1H), 4.09 (m, 1H), 4.14 (d, *J* = 4.2 Hz, 2H), 4.21, 4.49 (2d, *J* = 11.5 Hz, 1H×2), 5.27 (s, 1H), 5.30 (t, *J* = 9.3 Hz, 1H), 5.47-5.72 (m, 3H), 6.18-6.29 (m, 2H), 6.85 (m, 2H), 7.23 (m, 2H), 7.33-7.41 (m, 6H), 7.66-7.69 (m, 4H); ¹³C-NMR (75 MHz) δ -4.71, -4.59, -4.43, -4.08, 15.15, 17.88, 17.95, 19.16, 24.30, 25.71×3, 25.81×4, 26.78×3, 35.42, 38.46, 41.12, 41.68, 44.87, 55.15, 64.47, 66.60, 68.96, 69.58, 77.59, 95.60, 106.26, 113.57×2, 127.55×4, 128.06, 129.20×2, 129.43, 129.51×3, 130.25, 130.96, 131.96, 132.06, 133.82×2, 135.46×4, 158.94, 160.89, 169.04; IR (neat) 2930, 1730, 1640, 1615, 1515 cm⁻¹; HRMS (FAB) calcd for C₅₅H₈₃O₇Si₃ (M⁺-acetone +H) *m/z* 939.5447, found 939.5452.

(2*E*,5*R*,6*S*,7*Z*,9*E*,12*R*,14*R*)-12,14-Bis(*t*-butyldimethylsilyloxy)-15-(2,2-dimethyl-1,3-dioxin-4-one-6-yl)-6-[(4-methoxyphenyl)methoxy]-5-methyl-2,7,9-pentadecatrien-1-ol (17)

To a cooled (0 °C), stirred solution of (2*E*,5*R*,6*S*,7*Z*,9*E*,12*R*,14*R*)-12,14-bis(*t*-butyldimethylsilyloxy)-1-(*t*-butyldiphenylsilyloxy)-15-(2,2-dimethyl-1,3-dioxin-4-one-6-yl)-6-[(4-methoxyphenyl)methoxy]-5-methyl-2,7,9-pentadecatriene (1.68 g, 1.68 mmol) in MeOH (35 mL) was added NH₄F (351 mg, 9.48 mmol). The mixture was stirred for 14 h and then NH₄F (35.5 mg, 0.958 mmol) was added. The mixture was stirred for 10 h and quenched with saturated aqueous NaHCO₃. This was diluted with saturated aqueous NaHCO₃ (200 mL), and extracted with CH₂Cl₂. The combined organic layers were dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:8 to 1:3) to provide 1.20 g (94%) of **17** as a colorless oil, and 28.8 mg (2%) of the TBDPS ether was recovered; TLC, *R_f* 0.53 (EtOAc/hexane, 1:1); $[\alpha]_D^{20}$ -22.8 (*c* 1.17, CHCl₃); ¹H-NMR (300 MHz) δ 0.04, 0.05, 0.07 (3s, total 12H), 0.86, 0.90 (2s, 9H×2), 0.94 (d, *J* = 6.6 Hz, 3H), 1.67, 1.68 (2s, 3H×2), 1.55-1.81 (m, 4H), 2.23-2.32 (m, 4H), 2.41 (dd, *J* = 4.2, 13.8 Hz, 1H), 3.80 (s, 3H), 3.80 (m, 1H), 3.99-4.09 (m, 4H), 4.21, 4.49 (2d, *J* = 11.6 Hz, 1H×2), 5.27 (s, 1H), 5.30 (t, *J* = 9.5 Hz, 1H), 5.52-5.73 (m, 3H), 6.18-6.28 (m, 2H), 6.86 (m, 2H), 7.23 (m, 2H); ¹³C-NMR (68 MHz) δ -4.70, -4.58, -4.44, -4.09, 15.20, 17.88, 17.97, 24.33, 25.71×4, 25.83×3, 35.39, 38.33, 41.18, 41.70, 44.86, 55.20, 63.61, 66.63, 68.97, 69.57, 77.32, 95.57, 106.32, 113.57×2, 128.06, 129.27×2, 129.41, 130.50, 130.91, 131.37, 132.06, 132.12, 158.96, 160.97, 169.06; IR (neat) 3500, 2930, 1730, 1640, 1615, 1515 cm⁻¹; HRMS calcd for C₃₉H₆₄O₇Si₂ (M⁺-acetone) *m/z* 700.4191, found 700.4191.

(2*E*,5*R*,6*S*,7*Z*,9*E*,12*R*,14*R*)-12,14-Bis(*t*-butyldimethylsilyloxy)-15-(2,2-dimethyl-1,3-dioxin-4-one-6-yl)-1-methoxycarbonyloxy-6-[(4-methoxyphenyl)methoxy]-5-methyl-2,7,9-pentadecatriene

To a cooled (0 °C), stirred solution of **17** (1.21 g, 1.59 mmol) in CH₂Cl₂ (24 mL) were added pyridine (0.70 mL, 9.7 mmol) and methyl chloroformate (0.40 mL, 5.1 mmol). The mixture was stirred for 2 h, and this was concentrated in vacuo. The residue was purified by column chromatography on silica gel (Et₃N/hexane, 1:100 to EtOAc/hexane, 1:5) to provide 1.29 g (quant.) of the carbonate as a colorless oil; TLC, R_f 0.63 (EtOAc/hexane, 1:1); [α]²⁵_D −23.9 (*c* 1.77, CHCl₃); ¹H-NMR (270 MHz) δ 0.04, 0.05, 0.07 (3s, total 12H), 0.86, 0.90 (2s, 9H×2), 0.92 (d, *J* = 6.6 Hz, 3H), 1.67, 1.68 (2s, 3H×2), 1.54-1.83 (m, 4H), 2.17-2.32 (m, 4H), 2.43 (dd, *J* = 4.4, 13.9 Hz, 1H), 3.77 (s, 3H), 3.77 (m, 1H), 3.80 (s, 3H), 4.02 (dd, *J* = 5.7, 9.5 Hz, 1H), 4.10 (m, 1H), 4.20, 4.49 (2d, *J* = 11.7 Hz, 1H×2), 4.54 (d, *J* = 6.2 Hz, 2H), 5.27 (s, 1H), 5.28 (t, *J* = 9.5 Hz, 1H), 5.53 (dt, *J* = 15.0, 6.2 Hz, 1H), 5.63-5.78 (m, 2H), 6.17-6.25 (m, 2H), 6.86 (m, 2H), 7.22 (m, 2H); ¹³C-NMR (68 MHz) δ −4.67, −4.55, −4.41, −4.06, 15.15, 17.91, 18.00, 24.36, 25.74×3, 25.83×4, 35.45, 38.21, 41.18, 41.75, 44.92, 54.65, 55.23, 66.63, 68.53, 69.00, 69.60, 77.29, 95.63, 106.32, 113.63×2, 124.69, 127.97, 129.27×3, 130.88, 132.23×2, 135.75, 155.64, 158.98, 160.97, 169.09; IR (neat) 2930, 1750, 1730, 1640, 1615, 1515 cm^{−1}; HRMS calcd for C₄₀H₆₃O₁₀Si₂ (M⁺−*t*-Bu) *m/z* 759.3960, found 759.3974.

Methyl (5*R*,7*R*,9*E*,11*Z*,13*S*,14*R*,16*E*)-5,7-Bis(*t*-butyldimethylsilyloxy)-18-(methoxycarbonyloxy)-13-[(4-methoxyphenyl)methoxy]-14-methyl-3-oxo-9,11,16-octadecatriene-1-carboxylate (6**)**

(2*E*,5*R*,6*S*,7*Z*,9*E*,12*R*,14*R*)-12,14-bis(*t*-butyldimethylsilyloxy)-15-(2,2-dimethyl-1,3-dioxin-4-one-6-yl)-1-methoxycarbonyloxy-6-[(4-methoxyphenyl)methoxy]-5-methyl-2,7,9-pentadecatriene (1.29 g 1.59 mmol) was dissolved in degassed toluene–MeOH (8:1, 25 mL). The solution was transferred into three 20 mL sealed tubes equipped with a screwed stopper, and the tubes were filled with argon. The tubes were heated to 110 °C for 3 h. After being cooled to ambient temperature, the solution was concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:5) to provide 1.23 g (98%) of **6** as a colorless oil; TLC, R_f 0.74 (EtOAc/hexane, 1:2); [α]²⁶_D −22.3 (*c* 1.11, CHCl₃); ¹H-NMR (270 MHz) δ 0.03,

0.05, 0.06 (3s, total 12H), 0.86, 0.89 (2s, 9H×2), 0.92 (d, $J = 6.7$ Hz, 3H), 1.52-1.86 (m, 4H), 2.17-2.37 (m, 3H + 2H×1/7, enol form), 2.67-2.69 (m, 2H×6/7, keto form), 3.48 (s, 2H×6/7, keto form), 3.72 (s, 3H), 3.77 (s, 3H), 3.78 (m, 1H), 3.80 (s, 3H), 4.01 (dd, $J = 5.5, 9.2$ Hz, 1H), 4.21, 4.49 (2d, $J = 11.6$ Hz, 1H×2), 4.28 (m, 1H), 4.55 (d, $J = 6.1$ Hz, 2H), 5.01 (s, 1H×1/7, enol form), 5.29 (t, $J = 9.2$ Hz, 1H), 5.51 (dt, $J = 15.3, 6.1$ Hz, 1H), 5.65-5.79 (m, 2H), 6.21-6.25 (m, 2H), 6.86 (m, 2H), 7.23 (m, 2H), 11.94 (s, 1H×1/7, enol form); ^{13}C -NMR (68 MHz, keto form) δ -4.81, -4.52×2, -4.21, 15.17, 17.88, 17.97, 25.83×6, 35.48, 38.21, 40.92, 44.78, 50.05, 50.68, 52.21, 54.65, 55.23, 66.49, 68.56, 68.91, 69.56, 77.29, 113.60×2, 124.63, 127.86, 129.01, 129.30×2, 130.97, 132.43, 132.55, 135.80, 155.64, 158.98, 167.45, 201.60 (derived from enol form δ 43.57, 45.09, 51.08, 67.01, 91.17, 12.74, 128.92, 132.78, 172.81, 175.66); IR (neat) 2930, 1750, 1615, 1515 cm^{-1} ; HRMS (FAB) calcd for $\text{C}_{42}\text{H}_{70}\text{O}_{10}\text{Si}_2\text{Na}$ ($\text{M}^+ + \text{Na}$) m/z 813.4406, found 813.4416.

(2*RS*,4*E*,7*R*,8*S*,9*Z*,11*E*,14*R*,16*R*)-14,16-Bis(*t*-butyldimethylsilyloxy)-2-methoxycarbonyl-8-[(4-methoxyphenyl)methoxy]-7-methyl-4,9,11-cycloheptadecatrien-1-one (18, *ca.* 3:2 diastereomeric mixture)

To a stirred solution of $\text{Pd}(\text{PPh}_3)_4$ (113 mg, 0.0976 mmol) and 1,2-bis(diphenylphosphino)ethane (40.1 mg, 0.101 mmol) in THF (100 mL) was added a solution of **6** (400 mg, 0.489 mmol) in THF (80 mL) over 1 h. The mixture was stirred for 21 h, and then concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:50 to 1:15) to provide 293 mg (84%) of **18** as a colorless oil; TLC, R_f 0.66 (EtOAc/hexane, 1:4); $[\alpha]_D^{24} +28.8$ (c 1.48, CHCl_3); ^1H -NMR (270 MHz) δ -0.03, 0.03, 0.05, 0.06, 0.07 (5s, total 12H), 0.86, 0.87, 0.89, 0.90 (4s, total 18H), 0.95, 0.98 (2d, $J = 6.7$ Hz, total 3H), 1.43-1.76 (m, 3H), 1.89 (m, 1H), 2.14 (m, 1H), 2.31-2.46 (m, 3H), 2.46-2.80 (m, 3H), 3.49 (m, 1H), 3.70, 3.73 (2s, total 3H), 3.81 (s, 3H), 3.87 (m, 1H), 4.03 (dd, $J = 5.2, 8.9$ Hz, 1H×3/5), 4.18, 4.22 (2d, $J = 11.6$ Hz, total 1H), 4.20-4.29 (m, 1H+1H×2/5), 4.49, 4.50 (2d, $J = 11.6$ Hz, total 1H), 5.22 (m, 1H), 5.34-5.48 (m, 2H), 5.76 (m, 1H), 6.11-6.26 (m, 1H+1H×3/5), 6.48 (dd, $J = 11.3, 15.0$ Hz, 1H×2/5), 6.88 (m, 2H), 7.25 (m, 2H); ^{13}C -NMR (68 MHz) δ -4.67, -4.61, -4.52, -4.35, 14.80, 15.92, 17.82, 17.91, 18.00, 18.14, 25.74, 25.80, 25.89, 30.72, 30.78, 36.34, 36.86, 38.56, 39.65, 39.74, 42.04, 44.32, 46.97, 50.39, 50.85, 52.35, 52.41, 55.20, 55.26, 57.65, 58.37, 65.05, 65.86, 68.88, 69.08, 69.48, 69.80, 74.01, 75.30, 113.63, 126.65, 127.57, 128.00, 128.09, 129.30, 129.38, 130.79, 130.85, 131.08, 131.20, 131.25, 131.31, 132.03, 132.12, 132.23, 133.24, 158.96, 169.44, 169.75, 202.35, 202.76; IR (neat) 2930, 1750, 1650, 1615, 1585, 1515 cm^{-1} ; HRMS calcd for $\text{C}_{40}\text{H}_{66}\text{O}_7\text{Si}_2$ (M^+) m/z 714.4347, found 714.4342.

**(2*RS*,4*E*,7*R*,8*S*,9*Z*,11*E*,14*R*,16*R*)-14,16-Dihydroxy-2-methoxycarbonyl-8-[(4-methoxyphenyl)methoxy]-
(2*RS*,4*E*,7*R*,8*S*,9*Z*,11*E*,14*R*,16*R*)-14,16-Dihydroxy-2-methoxycarbonyl-8-[(4-methoxy-phenyl)methoxy]-
7-methyl-4,9,11-cycloheptadecatrien-1-one**

To a cooled (0 °C), stirred solution of **18** (73.6 mg, 0.103 mmol) in pyridine (5 mL) was added HF-pyridine complex (0.5 mL). The mixture was stirred for 30 h, and quenched with saturated aqueous NaHCO₃. This was diluted with saturated aqueous NaHCO₃ (60 mL), and extracted with CH₂Cl₂. The combined organic layers were dried and concentrated in vacuo to give the crude diol, which was used in the next step without purification. In a small-scale experiment, a pure sample was obtained by column chromatography on silica gel (EtOAc/hexane, 2:3 to 1:1) as an amorphous solid; TLC, R_f 0.37 (acetone/toluene, 1:2), HRMS calcd for C₂₈H₃₈O₇ (M⁺) m/z 486.2618, found 486.2618.

**(1*RS*,3*E*,6*R*,7*S*,8*Z*,10*E*,13*R*,15*R*)-13-Hydroxy-7-[(4-methoxyphenyl)methoxy]-6-methyl-16-oxabicyclo-
[13.2.2]nonadeca-3,8,10-triene-17,18-dione**

To a cooled (0 °C), stirred solution of the crude diol obtained above in MeOH (5 mL) was added *i*Pr₂NEt (0.5 mL). The mixture was stirred for 24 h, and then azeotroped with toluene to give the crude lactone, which was used in the next step without purification. In a small-scale experiment, a pure sample was obtained by column chromatography on silica gel (acetone/toluene, 1:3 to 1:1) as an amorphous solid; TLC, R_f 0.27 (acetone/toluene, 1:1), HRMS calcd for C₂₇H₃₄O₆ (M⁺) m/z 454.2355, found 454.2353.

**(1*RS*,3*E*,6*R*,7*S*,8*Z*,10*E*,13*R*,15*R*)-13-Hydroxy-7-[(4-methoxyphenyl)methoxy]-6-methyl-1-phenylselenyl-
16-oxabicyclo[13.2.2]nonadeca-3,8,10-triene-17,18-dione**

The following reaction was carried out under argon. To a stirred solution of the crude lactone obtained above in CH₂Cl₂ (2 mL) was added Et₃N (0.057 mL, 0.41 mmol). The mixture was stirred for 10 min, and a solution

of PhSeCl (41.2 mg, 0.215 mmol) in CH₂Cl₂ (0.2 mL) was added at –78 °C. The mixture was stirred for 30 min at –78 °C, and then a solution of PhSeCl (9.9 mg, 0.052 mmol) in CH₂Cl₂ (0.2 mL) was added. The mixture was stirred for 30 min, and then diluted with toluene (4 mL) at –78 °C. The mixture cooled to –78 °C was directly transferred into a short column packed with silica gel. The column was eluted with the following cooling (dry ice–acetone bath) solvents (toluene, CH₂Cl₂, then EtOAc) successively, to prevent the decomposition of the selenide. The elute was concentrated in vacuo to provide 55.7 mg (89%, 3 steps from **18**) of the phenylselenide as an amorphous solid; TLC, *R_f* 0.57 (acetone/toluene, 1:2), HRMS calcd for C₃₃H₃₈O₆Se (M⁺) *m/z* 610.1833, found 610.1842.

(1*EZ*,3*E*,6*R*,7*S*,8*Z*,10*E*,13*R*,15*R*)-13-Hydroxy-7-[(4-methoxyphenyl)methoxy]-6-methyl-16-oxabicyclo-[13.2.2]nonadeca-1,3,8,10-tetraene-17,18-dione (5)

The following reaction was carried out under argon. To a cooled (–50 °C) stirred solution of (1*RS*,3*E*,6*R*,7*S*,8*Z*,10*E*,13*R*,15*R*)-13-hydroxy-7-[(4-methoxyphenyl)methoxy]-6-methyl-1-phenylselenyl-16-oxa-bicyclo[13.2.2]nonadeca-3,8,10-triene-17,18-dione (159 mg, 0.260 mol) in CH₂Cl₂ (5mL) was added mCPBA (125 mg, 0.724 mmol). The mixture was stirred for 3.5 h at –50 °C, and quenched with Me₂S. The mixture was stirred for 0.5 h, and then diluted with saturated aqueous NaHCO₃ (20 mL). This was extracted with CH₂Cl₂, and the combined organic layers were dried and concentrated in vacuo. The residue was filtered through silica gel to provide 118 mg of **5** as a pale yellow oil, which was used in the next step immediately.; TLC, *R_f* 0.31 (acetone/toluene, 1:2), HRMS calcd for C₂₇H₃₂O₆ (M⁺) *m/z* 452.2199, found 452.2195.

(1*Z*,3*R*,4*R*,6*R*,7*S*,8*S*,9*Z*,11*S*,13*R*,15*R*)-13-Hydroxy-7-[(4-methoxyphenyl)methoxy]-6-methyl-16-oxatetracyclo[13.2.2.0^{3,11}.0^{4,8}]nonadeca-1,9-diene-17,18-dione (4)

The compound **5** (118 mg, 0.260 mmol) was dissolved in degassed toluene (16 mL), and a crystal of BHT was added. The solution was divided into two 20 mL sealed tubes equipped with a screwed stopper, and the tubes were filled with argon. The tubes were heated to 130 °C for 26 h. After being cooled to ambient temperature, the combined solution was concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/toluene, 1:2) to provide 62.1 mg (53%, 2 steps from the

phenylselenide) of **4** as a colorless oil; TLC, R_f 0.31 (acetone/toluene, 1:2); $[\alpha]_D^{23} +37.5$ (c 0.625, CHCl_3); $^1\text{H-NMR}$ (270 MHz) δ 1.08 (d, $J = 6.6$ Hz, 3H), 1.48 (q, $J = 12.1$ Hz, 1H), 1.64-1.87 (m, 3H), 1.90-2.06 (m, 2H), 2.42-2.57 (m, 2H), 2.66 (dd, $J = 0.7, 18.7$ Hz, 1H), 2.70-2.83 (m, 2H), 3.12 (ddd, $J = 0.7, 7.3, 18.7$ Hz, 1H), 3.26 (dd, $J = 2.7, 6.8$ Hz, 1H), 3.32 (m, 1H), 3.65 (m, 1H), 3.81 (s, 3H), 4.44, 4.57 (2d, $J = 11.2$ Hz, 1H $\times$ 2), 4.89 (m, 1H), 5.68 (d, $J = 10.4$ Hz, 1H), 5.73 (d, $J = 10.4$ Hz, 1H), 6.86-6.91 (m, 3H), 7.29 (m, 2H); $^{13}\text{C-NMR}$ (68 MHz) δ 18.69, 35.22, 35.53, 37.61, 39.62, 39.88, 41.26, 41.32, 41.75, 45.61, 55.29, 66.86, 71.53, 72.71, 92.38, 113.83 $\times$ 2, 124.83, 129.27 $\times$ 2, 130.50, 131.02, 135.95, 157.03, 159.16, 165.72, 194.23; IR (neat) 3450, 2950, 1735, 1705, 1620, 1515 cm^{-1} ; HRMS calcd for $\text{C}_{27}\text{H}_{32}\text{O}_6$ (M^+) m/z 452.2199, found 452.2195.

(1Z,3R,4R,6R,7S,8S,9Z,11S,13R,15R)-7-[(4-Methoxyphenyl)methoxy]-6-methyl-13-triethylsilyloxy-16-oxatetracyclo[13.2.2.0^{3,11}.0^{4,8}]nonadeca-1,9-diene-17,18-dione

The following reaction was carried out under argon. To a cooled (-78 °C), stirred solution of **4** (38.6 mg, 0.0853 mmol) in CH_2Cl_2 (4 mL) were added 2,6-lutidine (0.10 mL, 0.85 mmol) and TESOTf (0.10 mL, 0.43 mmol). The mixture was stirred at -78 °C for 0.5 h, and quenched with saturated aqueous NaHCO_3 . This was diluted with saturated aqueous NaHCO_3 (10 mL), and extracted with CH_2Cl_2 . The combined organic layers were dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:4) to provide 35.9 mg (78%) of the TES ether as a colorless oil; TLC, R_f 0.33 (EtOAc/hexane, 1:2); $[\alpha]_D^{23} +47.1$ (c 0.40, CHCl_3); $^1\text{H-NMR}$ (270 MHz) δ 0.49-0.56 (m, 6H), 0.90-0.10 (m, 9H), 1.07 (d, $J = 6.6$ Hz, 3H), 1.25 (q, $J = 11.7$ Hz, 1H), 1.62 (m, 1H), 1.72 (m, 1H), 1.82 (m, 1H), 1.95-2.12 (m, 2H), 2.39-2.54 (m, 2H), 2.62 (dd, $J = 0.7, 18.5$ Hz, 1H), 2.77-2.89 (m, 2H), 3.12 (dd, $J = 7.2, 18.5$ Hz, 1H), 3.27 (dd, $J = 2.6, 6.6$ Hz, 1H), 3.31 (m, 1H), 3.68 (m, 1H), 3.81 (s, 3H), 4.45, 4.57 (2d, $J = 11.2$ Hz, 1H $\times$ 2), 4.87 (m, 1H), 5.65 (d, $J = 10.4$ Hz, 1H), 5.71 (d, $J = 10.4$ Hz, 1H), 6.90 (d, $J = 11.4$ Hz, 1H), 6.90 (m, 2H), 7.30 (m, 2H); $^{13}\text{C-NMR}$ (68 MHz) δ 5.35 $\times$ 3, 6.88 $\times$ 3, 18.86, 35.56 $\times$ 2, 37.64, 39.65, 39.82, 41.47, 41.81, 42.30, 45.61, 55.26, 67.79, 71.59, 72.77, 92.61, 113.80 $\times$ 2, 125.52, 129.27 $\times$ 2, 130.27, 130.59, 135.86, 157.23, 159.16, 165.75, 194.03; IR (neat) 2950, 1740, 1715, 1615, 1515 cm^{-1} ; HRMS calcd for $\text{C}_{33}\text{H}_{46}\text{O}_6\text{Si}$ (M^+) m/z 566.3064, found 566.3061.

(1Z,3R,4R,6R,7S,8S,9Z,11S,13R,15R)-7-Hydroxy-6-methyl-13-triethylsilyloxy-16-oxatetracyclo[13.2.2.0^{3,11}.0^{4,8}]nonadeca-1,9-diene-17,18-dione

To a stirred solution of (1Z,3R,4R,6R,7S,8S,9Z,11S,13R,15R)-7-[(4-methoxyphenyl)methoxy]-6-methyl-13-triethylsilyloxy-16-oxatetracyclo[13.2.2.0^{3,11}.0^{4,8}]nonadeca-1,9-diene-17,18-dione (35.9 mg, 0.0633 mmol) in CH₂Cl₂ (4 mL) was added aqueous phosphate buffer (0.4 mL, pH 7). This was stirred for 30 min and then DDQ (22.4 mg, 0.0985 mmol) was added at 0 °C. The mixture was stirred for 3.5 h and then DDQ (18.9 mg, 0.0831 mmol) was added at 0 °C. The mixture was stirred for 2 h and then quenched with saturated aqueous NaHCO₃. This was diluted with saturated aqueous NaHCO₃ (15 mL), and extracted with CH₂Cl₂. The combined organic layers were dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:3 to 1:1) to provide 26.1 mg (92%) of the secondary alcohol as a colorless oil; TLC, R_f 0.30 (EtOAc/hexane, 1:1); [α]_D²² +65.9 (c 0.33, CHCl₃); ¹H-NMR (270 MHz) δ 0.49-0.58 (m, 6H), 0.89-0.95 (m, 9H), 1.07 (d, *J* = 6.6 Hz, 3H), 1.25 (m, 1H), 1.61-1.87 (m, 3H), 2.08 (m, 1H), 2.40-2.66 (m, 4H), 2.62 (dd, *J* = 0.7, 18.7 Hz, 1H), 2.80 (m, 1H), 3.12 (ddd, *J* = 0.7, 7.3, 18.7 Hz, 1H), 3.28 (ddd, *J* = 1.5, 5.9, 11.4 Hz, 1H), 3.44 (dd, *J* = 4.0, 6.6 Hz, 1H), 3.69 (m, 1H), 4.87 (m, 1H), 5.74 (d, *J* = 10.4 Hz, 1H), 5.85 (dt, *J* = 10.4, 2.9 Hz, 1H), 6.86 (d, *J* = 11.4 Hz, 1H); ¹³C-NMR (68 MHz) δ 5.35 ×3, 6.88 ×3, 17.94, 35.53, 35.73, 36.69, 40.20, 41.41, 41.81, 42.33, 44.29, 45.64, 67.81, 72.80, 86.47, 125.18, 125.44, 129.90, 157.11, 165.75, 193.97; IR (neat) 3440, 2950, 1730, 1715, 1615 cm⁻¹; HRMS calcd for C₂₅H₃₈O₅Si (M⁺) *m/z* 446.2489, found 446.2497.

(1Z,3R,4R,6R,8S,9Z,11S,13R,15R)-6-methyl-13-triethylsilyloxy-16-oxatetracyclo[13.2.2.0^{3,11}.0^{4,8}]nonadeca-1,9-diene-7,17,18-trione

To a cooled (0 °C), stirred solution of (1Z,3R,4R,6R,7S,8S,9Z,11S,13R,15R)-7-hydroxy-6-methyl-13-triethylsilyloxy-16-oxatetracyclo[13.2.2.0^{3,11}.0^{4,8}]nonadeca-1,9-diene-17,18-dione (23.5 mg, 0.0526 mmol) in CH₂Cl₂ (3 mL) were added NaHCO₃ (14.4 mg, 0.171 mmol) and Dess-Martin periodinane (34.4 mg, 0.0810 mmol). The mixture was stirred for 1.5 h and then diluted with saturated aqueous NaHCO₃-20% aqueous Na₂S₂O₃ (1:1, 10 mL) and CH₂Cl₂ (5 mL) at 0 °C. The mixture was stirred for 30 min and then the organic layer was separated. The aqueous layer was extracted with CH₂Cl₂. The combined organic layers were dried

and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:3) to provide 22.0 mg (94%) of the ketone as a colorless oil; TLC, R_f 0.55 (EtOAc/hexane, 1:1); $[\alpha]_D^{23} +182$ (c 0.26, CHCl_3); $^1\text{H-NMR}$ (270 MHz) δ 0.47-0.56 (m, 6H), 0.88-0.94 (m, 9H), 1.11 (d, J = 6.6 Hz, 3H), 1.47 (q, J = 12.1 Hz 1H), 1.68-1.74 (m, 2H), 2.12 (dt, J = 16.5, 6.6 Hz, 1H), 2.21-2.35 (m, 2H), 2.46 (ddd, J = 4.2, 11.5, 15.6 Hz, 1H), 2.63 (m, 1H), 2.64 (dd, J = 0.7, 18.7 Hz, 1H), 2.88 (m, 1H), 3.14 (ddd, J = 0.7, 7.3, 18.7 Hz, 1H), 3.15 (m, 1H), 3.44 (ddd, J = 2.2, 6.2, 11.7 Hz, 1H), 3.67 (m, 1H), 4.89 (m, 1H), 5.66 (dt, J = 10.3, 3.1 Hz, 1H), 5.88 (dt, J = 10.3, 2.2 Hz, 1H), 6.81 (d, J = 11.7 Hz, 1H); $^{13}\text{C-NMR}$ (68 MHz) δ 5.33 $\times$ 3, 6.85 $\times$ 3, 13.96, 33.17, 34.67, 35.53, 38.56, 41.47, 41.98, 43.88, 45.53, 45.67, 67.70, 72.85, 123.02, 128.32, 136.32, 155.36, 165.67, 193.91, 217.13; IR (neat) 2960, 1740, 1700, 1620 cm^{-1} ; HRMS calcd for $\text{C}_{25}\text{H}_{36}\text{O}_5\text{Si}$ (M^+) m/z 444.2332, found 444.2331.

(+)-Macquarimicin A (1)

To a cooled (0 °C), stirred solution of (1Z,3R,4R,6R,8S,9Z,11S,13R,15R)-6-methyl-13-triethylsilyloxy-16-oxatetracyclo[13.2.2.0^{3,11}.0^{4,8}]nonadeca-1,9-diene-7,17,18-trione (22.0 mg, 0.0495 mmol) in MeOH (3 mL) was added PPTS (1.0 mg, 0.0040 mmol). The mixture was stirred for 2 h and then NaHCO_3 (6.0 mg, 0.071 mmol) was added at 0 °C. This was azeotroped with EtOAc and the residue was purified by column chromatography on silica gel (EtOAc/toluene, 1:1) to provide 15.8 mg (97%) of macquarimicin A (**1**) as an amorphous solid; TLC, R_f 0.45 (acetone/toluene, 2:3); $[\alpha]_D^{23} +270$ (c 0.20, MeOH), $[\alpha]_D^{23} +285$ (c 0.780, MeOH); $^1\text{H-NMR}$ (270 MHz) δ 1.11 (d, J = 6.6 Hz, 3H), 1.48 (q, J = 12.1 Hz, 1H), 1.75-1.81 (m, 2H), 2.01 (dt, J = 16.9, 6.6 Hz, 1H), 2.19-2.36 (m, 2H), 2.51 (ddd, J = 4.0, 11.7, 15.4 Hz, 1H), 2.64 (m, 1H), 2.68 (dd, J = 0.7, 19.1 Hz, 1H), 2.90 (m, 1H), 3.15 (ddd, J = 0.9, 7.5, 19.1 Hz, 1H), 3.15 (m, 1H), 3.46 (ddd, J = 2.3, 6.0, 11.4 Hz, 1H), 3.65 (m, 1H), 4.92 (m, 1H), 5.67 (dt, J = 10.3, 2.9 Hz, 1H), 5.91 (dt, J = 10.3, 2.0 Hz, 1H), 6.80 (d, J = 11.4 Hz, 1H); $^{13}\text{C-NMR}$ (68 MHz) δ 13.91, 33.17, 34.67, 35.25, 38.64, 40.86, 41.26, 43.88, 45.64, 45.70, 66.81, 72.77, 123.68, 127.57, 136.44, 155.15, 165.64, 194.12, 217.04; IR (neat) 3450, 2930, 1735, 1705, 1620 cm^{-1} ; HRMS calcd for $\text{C}_{19}\text{H}_{22}\text{O}_5$ (M^+) m/z 330.1467, found 330.1457.

2. Determination of the geometry of the C(2)–C(3) double bond

The relative configuration of macquarimicin A (**1**) was originally assigned based on that of macquarimicin B, which was determined by a single crystal X-ray experiment (Fig. S1).³ Since the C(2)–C(3) double bond does not exist in macquarimicin B, there are no experimental data that support the reported *E* geometry of the double bond. Considering the structural and spectroscopic similarity of **1** to cochleamycin A (**2**), whose C(4)–C(5) geometry (cochleamycin numbering) was determined by a ¹³C–{¹H} NOE experiment,⁴ it is expected that the C(2)–C(3) geometry of **1** may be *Z*. To establish the stereochemistry and C(2)–C(3) geometry of **1** unambiguously, we conducted the throughout NOE experiments on our synthetic sample, which lead to the confirmation of the relative configuration of **1** and the revision of C(2)–C(3) geometry to be *Z* (Fig. S2). The observed NOEs and *J* values are completely in accordance with the conformation depicted in Fig. S2. None of other diastereomeric or geometrical isomers, including **1'** (Fig. S3), can explain these results.

Fig. S1. Structures of macquarimicins A and B, and cochleamycin A.

Fig. S2. NOE experiments on macquarimicin A.

³ Hochlowski, J. E.; Mullally, M. M.; Henry, R.; Whittern, D. M.; McAlpine, J. B. *J. Antibiot.* **1995**, *48*, 467.

⁴ Shindo, K.; Iijima, H.; Kawai, H. *J. Antibiot.* **1996**, *49*, 244.

Fig. S3. Two possible conformers of (*E*)-macquarimicin A (**1'**).